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KIDNEYWEEK 2015

Abstract Publication

More than 4,300 abstracts are published in this supplement. Abstracts are arranged by the abstract type**, then by presentation date*, and then by chronological publication number. Abstracts with a "PUB" number will not be presented at the ASN Annual Meeting.

* TH = Thursday, FR = Friday, SA = Saturday

** OR = Oral, PO = Poster, PUB = Publication Only

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- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
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TH-OR001

Dapagliflozin Reduces Albuminuria Over 2 Years in Diabetic Patients with Renal Impairment Bergur V. Stefansson,² Paola Fioretto,¹ Eva K.A. Johnsson,² Valerie A. Cain,³ David Sjostrom.² ¹Univ of Padova, Italy; ²AZ, Mölndal, Sweden; ³AZ, Wilmington.

Background: Pooled clinical data has shown reductions in albuminuria during dapagliflozin (DAPA) treatment. This analysis explored the long term effect of DAPA on albuminuria and renal safety.

Methods: This is a post hoc analysis of patients with CKD3 and albuminuria (≥ 30 mg/g) from study NCT00663260. Percent change in urinary albumin:creatinine ratio (UACR) was evaluated up to 104 weeks. At baseline 57 placebo (PBO), 53 DAPA 5 mg and 56 DAPA 10 mg patients were identified.

Results: The baseline (BL) median (range) values for UACR, mg/g, were: PBO: 180 (30 to 9262), DAPA 5 mg: 397 (31 to 4970) and DAPA 10 mg: 179 (32 to 4792). The corresponding mean (SD) values for eGFR, mL/min/1.73 m², were: 45.1 (9.37), 43.9 (8.96) and 44.1 (11.1), respectively. A reduction in UACR was already evident at Week 1. At 104 weeks the mean (95% CI) PBO-corrected reduction in UACR was -44% (-71, 9.0) and -57% (-77, -20) for DAPA 5 and 10 mg, respectively. After adjusting for changes in blood pressure, HbA1c and eGFR, the reductions were largely maintained. During the 104 week study period 7% of PBO patients regressed to normoalbuminuria, the corresponding numbers for DAPA 5 and 10 mg were 19 and 18%, respectively. After a transient decrease in eGFR in DAPA-treated patients, the DAPA 5 and 10 mg groups showed PBO-corrected 104 week changes of 2.1 (-1.3, 5.5) and -0.7 (-4.0, 2.6) mL/min/1.73 m². Renal adverse events (AEs) were more common in DAPA 10 mg treated subjects (10.7%) than in DAPA 5 mg (1.9%) or PBO treated (3.5%) subjects, many were due to increased creatinine. There was no increase in serious AEs related to renal impairment in the DAPA 10 mg group (1.8%) compared with the PBO group (1.8%).

Conclusions: Dapagliflozin reduces UACR for up to 2 years in subjects with CKD3, without increases in serious renal AEs. The UACR reduction remained present after adjustments for changes in blood pressure, HbA1c and eGFR, indicating a direct renal effect independent of changes in these variables.

Funding: Pharmaceutical Company Support - AstraZeneca

TH-OR002

Structural Predictors of Loss of Renal Function in Type 2 Diabetes Gudeta D. Fufaa,¹ E. Jennifer Weil,¹ Kevin V. Lemley,² William Knowler,¹ Frank C. Brosius,³ Berne Yee,⁴ Michael Mauer,⁵ Robert G. Nelson.¹ ¹NIDDK; ²Univ of Southern California; ³Univ of Michigan; ⁴Southwest Kidney Inst; ⁵Univ of Minnesota.

Background: Diabetes is the leading cause of kidney failure in the US, but the early structural determinants of renal function loss in type 2 diabetes are poorly defined. We examined the association between morphometrically-determined renal structural variables and renal function loss in 111 Pima Indians with type 2 diabetes who volunteered for a research kidney biopsy and for annual measurement of glomerular filtration rate (GFR, iothalamate).

Methods: Renal function loss was defined as $\geq 40\%$ loss of GFR from baseline. Associations with renal function loss were evaluated by Cox proportional-hazards regression. Hazard ratios (HR) were reported per 1 SD increment for each morphometric variable.

Results: Of the 111 participants (82% women, baseline mean age 46 years, diabetes duration 16 years, HbA1c 9.4%, GFR 147 ml/min, and median albumin/creatinine ratio [ACR] 41 mg/g), 51 (46%) developed renal function loss during a median follow-up of 6.6 years (IQR=3.1-9.0). Higher mesangial fractional volume (HR=2.33, 95% CI 1.63-3.33), percent global sclerosis (HR=1.57, 95% CI 1.18-2.09), non-podocyte cell number per glomerulus (HR=1.49, 95% CI 1.08-2.05), GBM width (HR=1.45, 95% CI 1.04-2.04), lower glomerular filtration surface density (HR=0.61, 95% CI 0.41-0.93), and reduced endothelial fenestrations (HR=0.67, 95% CI 0.47-0.94) were each associated with loss of renal function after adjustment for baseline age, sex, duration of diabetes, HbA1c and GFR. Although power was reduced when 14 participants with baseline GFR <90 ml/min were excluded from the analysis, baseline structure still predicted renal function loss.

Conclusions: Quantitative measures of glomerular structure predict loss of renal function in type 2 diabetes.

Funding: NIDDK Support

TH-OR003

Mitotic Catastrophe in Diabetic Nephropathy Masanori Hara,¹ Helen Liapis.² ¹Dept of Pediatrics, Yoshida Hospital, Tsubame, Niigata, Japan; ²Nephropathy, Little Rock, AR.

Background: Podocytopenia is involved in the progression of diabetic nephropathy. Apoptosis is thought to be a major mechanism for loss of podocytes. However, apoptotic podocytes (Podo) are not seen in renal biopsy specimens with diabetes. Instead mitotic catastrophe (MC) is a newly recognized form of podocyte death characterized by Podo multinucleation, aberrant mitotic spindles and micronucleoli. Because injured podocytes may die and released in the urine, in this study we sought to quantitate MC in urine samples from diabetic patients.

Methods: Urine samples from patients with diabetes type 2 (n=41, microalbuminuria 8, macroalbuminuria 33) were used. All samples were evaluated for the presence of urinary Podo by immunofluorescence (IF) using anti-podocalyxin (PCX) antibody and the only PCX positive Podo (PCX-podo) were selected for further immunohistochemical study.

Urine sediments were double or triple stained by IF using antibodies against various podocyte antigens such as 1) PCX, nephrin, podocin and GLEPP1 (podocyte markers), 2) macrophages, and panleucocytes (leucocyte markers), 3) cytokeratin 8 (parietal epithelial marker), 4) Annexin V, cleaved caspase-3 and Tunel assay (apoptosis markers), and 5) phosphorylated vimentin (cell mitosis marker). Nucleus was stained with hematoxylin or DAPI.

Results: The PCX-podo showed various nuclear morphology such as 1) mononucleated, normal shape (8.7%), 2) mononucleated, large and abnormal shape (3.8%), 3) multinucleated with or without micronucleoli (40.2%) 4) single nucleus and fragmented nuclei (10.9%) and 5) numerous fragmented nuclei (31.0%). We considered 2) and 3) as definitive MC, and 4) and 5) suspected MC. Apoptotic bodies were not found. 50% of PCX-podo were positive for GLEPP 1, while none of PCX-podo were positive for nephrin and podocin. None of PCX-podo were positive for leucocyte and parietal epithelial cell markers, annexin V, cleaved caspase-3 and Tunel assay. 10% of PCX-podo were positive for phosphorylated vimentin.

Conclusions: Urine from diabetic patients contains a significant number of urinary Podo with MC and no Podos with apoptotic bodies. Our results indicate that the majority of urine podocytes in diabetic patients may be due to MC and not to apoptosis.

TH-OR004

Advanced Glycation End Products Predict Loss of Renal Function and Correlate with Diabetic Nephropathy Lesions in Type 2 Diabetes Pierre Jean Saulnier,¹ Kevin M. Wheelock,¹ William Knowler,¹ Robert G. Nelson,¹ Paul James Beisswenger,² Scott K. Howell.² ¹NIDDK; ²PreventAGE Healthcare.

Background: We examined the associations of serum advanced glycation end-products (AGEs) with loss of renal function and with the structural lesions of diabetic nephropathy in a post-hoc analysis of a clinical trial of renoprotection with losartan in Pima Indians with type 2 diabetes (ClinicalTrials.gov number, NCT00340678).

Methods: Free AGEs were measured at baseline in 168 subjects by LC triple quadrupole mass spectrometry. Glomerular filtration rate (GFR, iothalamate) was measured annually, and kidney biopsies were performed in 109 of the subjects 6 years later. Loss of renal function was defined as $\geq 40\%$ loss of GFR from baseline. Multivariable associations between AGEs and loss of renal function were examined by Cox proportional-hazards regression, and between AGEs and morphometric variables by linear regression, after adjustment for age, sex, diabetes duration, HbA1c, treatment, albumin/creatinine ratio (ACR), and GFR. Hazard ratios (HR) were reported per doubling for each AGE. Linear regression results were reported as the difference in the structural measurement in SD units per doubling of AGE.

Results: Of the 168 subjects (73% women, mean age 41 \pm 11 years, diabetes duration 11 \pm 6 years, HbA1c 9.2 \pm 2.3%, median GFR=165 ml/min (IQR=135-190), and median ACR=31 mg/g (IQR=14-76)), 104 (62%) lost $\geq 40\%$ of their renal function during a median follow-up of 8.0 years (IQR=4.9-13.1). After multivariable adjustment, higher concentrations of carboxyethyllysine (CEL) and methylglyoxal hydroimidazolones (MGH1) were associated with loss of renal function (HR for CEL=1.7, 95% CI 1.1-2.5; HR for MGH1=1.3, 95% CI 1.1-1.7). MGH1 (β =0.23, P=0.018) and CEL (β =0.36, P=0.033) were also positively associated with mesangial fractional volume, and MGH1 (β =-0.27, P=0.009) and 3DG hydroimidazolone (3DGH) (β =-0.27, P=0.047) were inversely associated with total filtration surface per glomerulus.

Conclusions: Higher baseline dicarbonyl-derived AGEs are associated with loss of renal function and its structural correlates, including increased mesangial fractional volume and the corresponding loss of total filtration surface per glomerulus.

Funding: NIDDK Support

TH-OR005

Serum Amyloid A and Increased Risk of End-Stage Renal Disease and Death in Diabetic Kidney Disease Brad Dieter,¹ Sterling Mcpherson,² Maryam Afkarian,³ Ian H. De Boer,³ Rajnish Mehrotra,³ Rick L. Meek,³ Katherine R. Tuttle.^{1,3} ¹Providence Health Care, Spokane, WA; ²Washington State Univ, Spokane, WA; ³Univ of Washington, Seattle, WA.

Background: Serum amyloid A (SAA) activates inflammation and apoptosis in kidney cells. SAA is also increased in the blood, urine, and kidneys of mice and people with DKD. The objective of this study was to determine if SAA adds to risk prediction models for death and end-stage renal disease (ESRD) in DKD.

Methods: Serum SAA was measured in a longitudinal cohort with type 2 diabetes and prevalent DKD, defined by urine protein-to-creatinine ratio >0.5 g/g (n=135). Cox-proportional hazard models tested whether SAA was associated with a composite primary outcome of death and ESRD, adjusting for age, sex, race, hemoglobin A1c, diabetes duration, body mass index, renin-angiotensin system inhibitor use, systolic and diastolic blood pressure, albuminuria and estimated glomerular filtration rate (eGFR). Improvement in risk prediction was assessed by receiver-operating curves (ROC), goodness-of-fit, and Akaike's Information Criterion (AIC).

Results: Participants were 73% Mexican-American (99/135) with mean (SD) age of 57 (7.4) years, 55% male (75/135), mean eGFR 56 (22) ml/min/1.73m², and median (IQR) urine albumin-to-creatinine of 1.9 (0.7-3.9) g/g. The incident rate for the primary outcome was 44% (60/135). Risk of the composite primary outcome was higher in the 3rd tertile of SAA (>1.0 ug/ml) compared to the 1st tertile (<0.55 ug/ml): adjusted HR=3.7, 95% CI 1.7-8.3, p<0.001. The risk of death was markedly increased in the 3rd versus 1st tertile of SAA: adjusted HR 8.2, 95% CI 2.7-24.2, p<0.001. The C-statistic, generated from ROC curves, improved predictive ability of the model for the primary outcome (0.71 and 0.74, without versus with SAA). Goodness-of-fit and AIC also improved with inclusion of SAA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: In DKD, higher serumSAA concentration is associated with increased risk of death and ESRD. SAA improves risk prediction when added to traditional risk factors. SAA is a candidate biomarker that may advance DKD risk assessment and is a potential therapeutic target.

Funding: Private Foundation Support

TH-OR006

Biomarkers of Early Decline in Renal Function: A Translational Study in Type 2 Diabetes Jennifer W. Xu,¹ Carla Cavallin,¹ Sona Haku,^{1,2} Michael S. Simonson.¹ ¹*Nephrology and Hypertension, Univ Hospitals Case Medical Center and CWRU School of Medicine, Cleveland, OH;* ²*Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.*

Background: Kidney disease in type 2 diabetes (DKD) is the leading cause of end-stage renal disease. Early detection and treatment of DKD can prevent or slow progression to end-stage disease, but identifying early decline in renal function can be problematic because albuminuria is insensitive. In a Phase I preclinical exploratory study we measured the performance of candidate biomarkers from mouse models of early renal function decline.

Methods: Patients with type 2 diabetes (median baseline eGFR = 80.3 + 29.5 ml/min/1.73m²) were recruited into training (n=56) and independent, non-overlapping test (n=37) groups. Biomarkers were measured in spot urine collections by ELISA, and performance was assessed as area under the receiver operating characteristic curve (AUC) with adjustment for clinical covariates of DKD.

Results: For classifying participants with baseline early renal function decline (eGFR 90 – 60) vs normal function (i.e., >90), the highest performing biomarkers were: transforming growth factor b (TGFb, AUC + SD, 0.827 + 0.070), interleukin-6 (IL-6, 0.815 + 0.065) and endothelin-1 (ET-1, 0.720 + 0.082; all *P* < 0.01 compared to ACR, 0.465 + 0.093 and angiotensinogen 0.465 ± 0.090). Performance was validated in the independent test group. AUCs were unchanged after multivariate adjustment for age, sex, race, duration of diabetes, HbA1c, hypertension, cardiovascular disease, body mass index, and use of angiotensin converting enzyme inhibitors or receptor blockers. In participants with eGFR 90 – 60 at baseline, TGFb, IL-6 and ET-1 predicted a composite renal outcome at 5 years (eGFR < 60 OR ESRD) better than ACR (0.769 ± 0.105, 0.690 ± 0.128, and 0.793 ± 0.091, all *P* < 0.05 versus ACR, 0.520 ± 0.119).

Conclusions: Urine levels of TGFb, IL-6 or ET-1 may identify patients with early renal function decline and aid development of novel therapeutics.

Funding: Other NIH Support - R01DK096549

TH-OR007

Primary Prevention of Albuminuria Using Renin-Angiotensin-System Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis Frederik I. Persson,¹ Bianca Hemmingsen,² Morten Lindhardt,¹ Peter Rossing,^{1,3,4} Hans-Henrik Parving.^{3,5} ¹*Steno Diabetes Center, Gentofte, Denmark;* ²*Copenhagen Trial Unit, Copenhagen Univ Hospital, Copenhagen, Denmark;* ³*HEALTH, Univ of Aarhus, Aarhus, Denmark;* ⁴*Novo Nordisk Foundation for Basic and Metabolic Research, Univ of Copenhagen, Copenhagen, Denmark;* ⁵*Dept of Medical Endocrinology, Rigshospitalet, Copenhagen Univ Hospital, Copenhagen, Denmark.*

Background: Early prevention of diabetic nephropathy by way of blocking the renin angiotensin system (RAS) in patients with normoalbuminuria seems rational, but trials have so far shown conflicting results. The present meta-analysis was undertaken to investigate if such treatment can prevent development of microalbuminuria and also to assess whether available trials can provide sufficient information for such conclusions.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library for double-masked randomised controlled trials, with a population of patients with type 2 diabetes and normoalbuminuria, comparing angiotensin enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) to placebo. At least one year of follow-up was considered reasonable for the development of micro- or macroalbuminuria, and studies had to have at least 50 participants in each arm. Random and fixed effect models were performed as well as trial sequential analysis.

Results: Six trials were identified and included in the analysis (n=16921). Overall risk of bias was low. In a fixed model analysis ACE or ARB treatment was superior to placebo in relation to development of microalbuminuria, relative risk 0.84 (95% CI 0.79, 0.88) *p*<0.001, I² 23%, risk difference -0.04 (-0.05, -0.03), *p*= 0.001. Similar results were seen with the random model approach. Trial sequential analysis revealed a Z-value of 6.53 and an information size of 4163 patients (O'Brien twosided 5% boundaries).

Conclusions: Sufficient trial data are available for the meta-analysis to conclude that in patients with type 2 diabetes and normoalbuminuria, ACEinhibitors or ARBs reduces the risk for development of microalbuminuria.

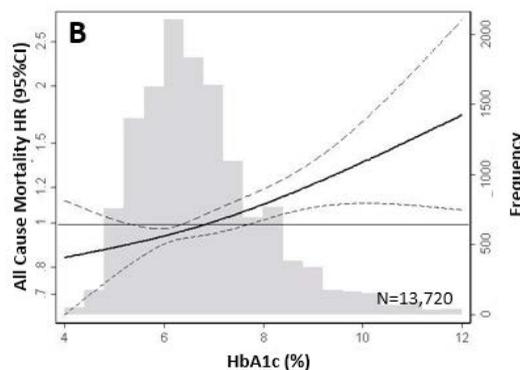
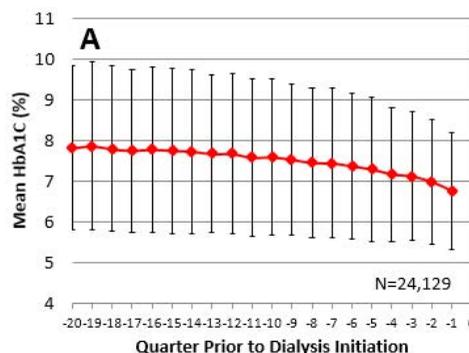
TH-OR008

The Impact of Pre-ESRD Glycemic Status on Early Post-ESRD Mortality Among U.S. Veterans: A Transition of Care in CKD Study Connie Rhee,¹ Elani Streja,¹ Melissa Soohoo,¹ Jennie Jing,¹ Danh V. Nguyen,¹ Steven M. Brunelli,² Gregory Brent,³ Csaba P. Kovessy,⁴ Kamyar Kalantar-Zadeh.¹ ¹*UC Irvine;* ²*DaVita Clinical Research;* ³*UCLA;* ⁴*UTHSC.*

Background: In the general population randomized controlled trials show no benefit and possible harm with intensive glycemic targets in diabetics. Non-dialysis dependent (NDD) CKD and ESRD patients experience both hypo- and hyperglycemia through multifactorial pathways, and studies of glycemic status and mortality in dialysis patients have shown mixed findings. Little is known about the net effect of kidney dysfunction on glucose homeostasis in NDD-CKD patients transitioning to dialysis, and how pre-ESRD glycemic status impacts early post-ESRD mortality.

Methods: We first examined the longitudinal trajectory of glycemic status defined by HbA1c during the 5-year pre-ESRD prelude period among veterans with NDD-CKD transitioning to dialysis from 10/2007-9/2011. In a subcohort of patients with at least one HbA1c measure during the 6 month prelude period, we then examined HbA1c levels averaged over 6 months as a continuous predictor of all-cause mortality using restricted cubic spline analysis. Associations with mortality in the first 3 months of ESRD were estimated using Cox models adjusted for age, sex, race, ethnicity, ESRD cause, and geographic region.

Results: Among 24,129 veterans transitioning to dialysis, there was a decline in mean HbA1c over the 5 year prelude period. Among 13,720 patients with at least one HbA1c in the 6 month prelude period, higher HbA1c was monotonically associated with a higher risk of post-ESRD death.



Conclusions: In veterans transitioning to dialysis there is a steady decline in HbA1c as they approach ESRD. Higher HbA1c levels in the pre-ESRD period are associated with higher early post-ESRD mortality. Further studies are needed to determine if glycemic-lowering strategies in the pre-ESRD period improves post-ESRD outcomes.

Funding: NIDDK Support, Veterans Administration Support

TH-OR009

Glycemic Markers and 2-Year Diabetic Hemodialysis Outcomes from the Glycemic Indices in Dialysis Evaluation Study Mark E. Williams,¹ Neal Mittman,² Lin Ma,³ Julia I. Brennan,⁴ Chinu M. Jani,⁴ Curtis D. Johnson,⁴ Franklin W. Maddux,³ Eduardo K. Lacson.^{3,5} ¹*Joslin Diabetes Center, Boston, MA;* ²*Kidney Care of Brooklyn and Queens, Brooklyn, NY;* ³*Fresenius Medical Care North America, Waltham, MA;* ⁴*Spectra Laboratories, Rockleigh, NJ;* ⁵*Physician, Lexington, MA.*

Background: Initial results from the GIDE (Glycemic Indices in Dialysis Evaluation) Study have added to concerns about sole reliance on hemoglobin (Hgb) A1c in patients with diabetes on hemodialysis (HD). We reported correlations of HgbA1c with nontraditional glycemic markers [albumin-adjusted and unadjusted fructosamine (AlbF; F) and glycated albumin (GA) or percent GA (%GA)]. One-year results indicated a potential association only with high AlbF and outcomes. We report here two-year outcomes.

Methods: 1,424 active HD patients with DM from 26 FMCNA facilities with glycemic markers from Jan-March 2013 were followed until April, 2015. Poor glycemic control was based on: HgbA1c >7% (sensitivity analysis>8%), AlbF ≥ 974 μmol/g, F > 285 μmol/L, %GA>15.7%, and GA> 300 μmol/L. Standard and Time-dependent (TD) Cox models with adjustment for age, sex, race, ethnicity, vintage, BMI, HD catheter, and baseline comorbid illnesses were utilized to determine associations between each dichotomized glycemic index and hospitalization/death outcomes.

Results: Poor glycemic control was found in 28% according to HgbA1c>7% (13% for HgbA1c>8%), but 35% by AlbF, 87% by F, 81% by %GA, and 68% by GA. Elevated AlbF was significantly associated with 2-year hospitalization [Standard Cox: Hazard Ratio (HR)=1.66, 95% CI (1.28,2.15), p=0.0001; TD Cox: HR=1.83, 95% CI (1.37,2.44), p<0.0001] and mortality [Standard Cox: HR=1.53, 95% CI (1.21,1.93), p=0.0004; TD Cox: HR=1.65, 95% CI (1.28,2.13), p=0.0001]. For all other glycemic indices, there were no such associations, at the proposed thresholds for glycemic control.

Conclusions: A strong association between poor glycemic control, determined by elevated AlbF, and worse 2-year hospitalization and mortality risks has emerged from the GIDE study data. Future analyses will include longer follow-up, use of continuous values for glycemic indices, and cardiovascular mortality outcomes.

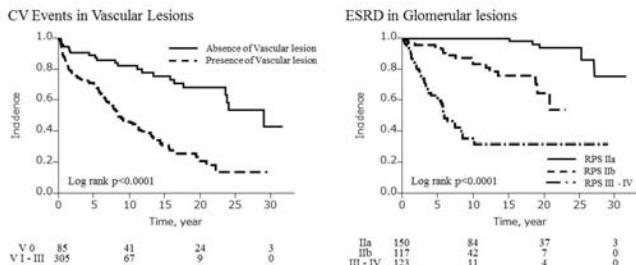
TH-OR010

Renal Biopsy for Diabetic Nephropathy Is Useful for the Prediction of Cardiovascular Events – 10-Year Follow Up Katsuhiko Morimoto, Ken-ichi Samejima, Masaru Matsui, Yasuhiro Akai, Miho Tagawa, Yoshihiko Saito. *First Dept of Internal Medicine, Nara Medical Univ, Kashihara, Japan.*

Background: Diabetic nephropathy has a higher risk of cardiovascular (CV) events and end-stage renal disease (ESRD). However, the association between renal histopathology, especially vascular lesion, and CV risk in diabetic nephropathy remains to be elucidated. We investigated the relationship between the glomerular or vascular lesions of renal specimen and CV events or ESRD in the patients with biopsy-proven diabetic nephropathy.

Methods: Three hundred ninety patients with biopsy-proven diabetic nephropathy with type 2 diabetes were enrolled in this retrospective study. According to the Renal Pathological Society (RPS) classification, the glomerular lesions were divided into three groups as Iia, Iib, and III – IV and vascular lesions were classified into 2 groups according to the absence or presence of vascular involvement.

Results: The background features were as follows: mean age of 57.7 ± 11.3 years old, the average observation period of 9.3 ± 8.0 years. During the observation period 164 patients had outcome of CV events and 71 patients reached ESRD. In Kaplan-Meier survival analysis, significant difference among different glomerular lesion class and vascular class was observed in terms of CV events and ESRD, respectively.



In Cox proportional hazard analysis, presence of vascular lesion in the renal tissue was an independent risk factor for the development of CV events (HR 2.12 [1.27 to 3.70]) and glomerular lesion was NOT associated with CV events. Glomerular lesions in the renal tissue was an independent risk factor for the development of ESRD (Iib vs. Iia, HR 6.44 [2.39 to 20.7]; III – IV vs. Iia, HR 12.1 [4.46 to 39.2]) and vascular lesion was NOT associated with renal outcome.

Conclusions: Vascular lesion of renal tissue had predictive value for the development of CV events.

TH-OR011

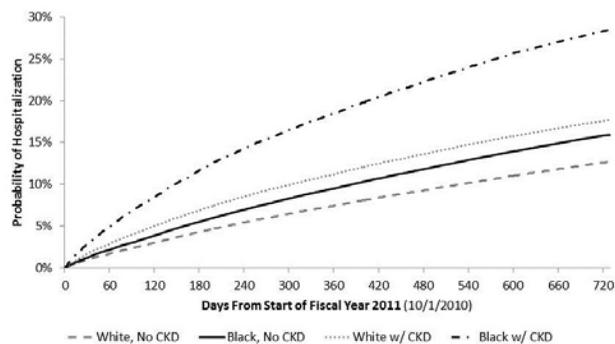
Racial Differences in Hospitalization Rates Among U.S. Veterans with and without Chronic Kidney Disease Jennifer L. Bragg-Gresham,¹ Hal Morgenstern,¹ Neil R. Powe,² Deidra C. Crews,³ Nilka Rios Burrows,⁴ Sharon Saydah,⁴ Kara Zivin,¹ Rajiv Saran.¹ ¹KECC & SPH, Univ of Michigan, Ann Arbor, MI; ²Univ of California, San Francisco, CA; ³Johns Hopkins Univ, Baltimore, MD; ⁴Centers for Disease Control and Prevention, Atlanta, GA.

Background: To elucidate potential racial disparities, we examined hospitalization rates for black and white veterans with and without CKD, utilizing the Veterans Affairs Health System.

Methods: This cohort study included 2.6 million black and white veterans who attended ³¹ outpatient visit, had a serum creatinine value during the baseline period (10/1/09-9/31/10), and had no indication of ESRD on 9/31/10. Cox regression was used to estimate the combined effects of race and CKD status on first hospitalization during the next 2 years, adjusting for age, gender, comorbidities, and prior hospitalization during the baseline period. CKD was defined by clinical diagnosis or eGFR <60 ml/min/1.73m².

Results: Black patients were younger with a higher prevalence of diabetes, but lower prevalence other comorbidities, including hypertension. Although the overall prevalence of CKD at baseline was higher in whites (21.0% vs. 15.8%), the prevalence of a clinical

diagnosis was higher in blacks (11.8% vs. 9.4%). The rate of first hospitalization was greater for blacks in both persons with and without CKD (HR=1.30, 95% CI: 1.29-1.31 & HR=1.16, 95% CI: 1.15-1.17, respectively). The 2-year risk of hospitalization was greatest (27.9%) in black patients with CKD, compared with the other groups (figure; p for interaction <0.001).



Conclusions: In an integrated health-care system with presumably less disparity in access to care between racial groups, the 2-year risk of hospitalization was greater for blacks than for whites, especially among patients with CKD. Further research is warranted to better understand these differences.

Funding: Other U.S. Government Support

TH-OR012

Optimal Endpoint Definition for Transition in Albuminuria Stage in Clinical Trials Tobias Felix Kröpelin,¹ Dick de Zeeuw,¹ Rudolf W. Bilous,² Giuseppe Remuzzi,³ Hans-Henrik Parving,⁴ Hiddo Jan Lambers Heerspink.¹ ¹Clinical Pharmacy and Pharmacology, UMCG, Groningen; ²Newcastle Univ, United Kingdom; ³IRCCS Mario Negri Inst for Pharmacological Research, Ospedale Papa Giovanni XXIII, Bergamo, Italy; ⁴Medical Endocrinology, Univ of Copenhagen, Denmark.

Background: Albuminuria transition (normo- to micro- to macroalbuminuria) is used as an endpoint in clinical trials that assess renoprotective drug efficacy. Current definitions vary between trials in: number of urine collections, requirement of a confirmation visit, if yes at what time, and the requirement of an additional percentage albuminuria change when transitions occur. We assessed the impact of these variations.

Methods: We used 3 clinical trials that tested the effect of RAS intervention on albuminuria class transition in diabetic patients (BENEDICT, DIRECT, IRMA 2). We assessed the drug effect per trial using varying transition definitions: 1) class transition based on either 1, 2, or 3 consecutively collected urine samples prior to each study visit, 2) based on a single urine sample confirmed by a next visit (within 2 - 8 weeks, next planned visit), 3) class transition and 10 - 40% increase in albuminuria.

Results: Neither increasing the number of urines collected at a visit, nor the inclusion of a confirmation visit, nor the time to the confirmation visit, nor the addition of a percentage albuminuria change altered the average drug effect or standard error.

	Single visit			Single urine +
	One urine	Two urines	Three urines	confirmation visit
	HR (SE) [95% CI]	HR (SE) [95% CI]	HR (SE) [95% CI]	HR (SE) [95% CI]
BENEDICT	0.75 (0.21) [0.50 - 1.12]	0.73 (0.22) [0.48 - 1.12]	0.66 (0.23) [0.42 - 1.04]	0.68 (0.34) [0.35 - 1.32]
DIRECT	0.95 (0.06) [0.84 - 1.07]	0.96 (0.07) [0.84 - 1.10]		0.95 (0.14) [0.73 - 1.24]
IRMA 2	0.55 (0.20) [0.37 - 0.82]			0.64 (0.38) [0.30 - 1.35]

Conclusions: Our results suggest that the optimal transition endpoint for a clinical trial measuring a drug effect can use a single urine collection per study visit. It needs to be tested whether more frequent study visits with albuminuria measurement would improve precision of the drug effect, as suggested in our previous work on quantitative albuminuria change (Kropelin 2014).

TH-OR013

CKD and Risk for Gastrointestinal Bleeding: The Atherosclerosis Risk in Communities (ARIC) Study Junichi Ishigami, Morgan Grams, Rakhi Naik, Josef Coresh, Kunihiko Matsushita. *Johns Hopkins Univ.*

Background: Patients on dialysis have increased risk for gastrointestinal (GI) bleeding. However, GI bleeding risk across the full spectrum of CKD has not been comprehensively investigated.

Methods: We studied 11,143 participants in the ARIC Study, a bi-ethnic community-based cohort. Baseline CKD measures (eGFR and ACR) were assessed at visit 4 (1996-

1998), and follow-up was continued through 2011. The primary outcome was hospitalization with relevant ICD codes of upper- or lower-GI bleeding. Cox regression models were used to estimate incident rate and hazard ratios of GI bleeding, respectively.

Results: A total of 693 hospitalizations related to GI bleeding was observed during a median follow-up of 13.9 years (incident rate 4.9 per 1,000 person-years). After adjusting for potential confounders, both lower eGFR and higher ACR were independently associated with increased risk of GI bleeding (Table). Compared to eGFR ≥ 90 ml/min/1.73m², the association was particularly strong in eGFR <30 ml/min/1.73m² (HR 8.37 [5.04-13.88] in Model 2), but eGFR between 30-60 also reached significance (HR 1.55 [1.16-2.06]). Compared to ACR <10 mg/g, both microalbuminuria (30-299 mg/g) and macroalbuminuria (≥ 300 mg/g) were associated with 2-2.5 greater hazard of GI bleeding (HR 2.14 [1.69-2.72] and 2.40 [1.59-3.62], respectively, in Model 2). Of note, high-normal albuminuria (10-29 mg/g) was also significantly associated with GI bleeding (HR 1.36 [1.09-1.70]). These results were largely consistent even after adjusting for each of kidney measures (Model 3) or accounting for cardiovascular events and incident dialysis during follow-up.

Conclusions: Both low eGFR (<60 but especially <30 ml/min/1.73m²) and high ACR (particularly ≥ 30 but also ≥ 10 mg/g), were associated with incidence of GI bleeding, warranting clinical attention for GI bleeding risk among persons with even mild to moderate CKD.

Table: Hazard ratios of GI bleeding events according to eGFR and ACR categories

	Model1	Model2	Model3
eGFR category (ml/min/1.73m ²)			
Events/N		226/4703	
90-	reference	reference	reference
Events/N		378/5648	
60-89	1.23 (1.03-1.46)	1.19 (1.00-1.42)	1.18 (0.99-1.41)
Events/N		72/735	
30-59	1.92 (1.45-2.53)	1.55 (1.16-2.06)	1.42 (1.06-1.91)
Events/N		17/57	
0-30	12.15 (7.39-19.97)	8.37 (5.04-13.88)	6.40 (3.49-11.77)
ACR category (mg/gCre)			
Events/N		460/8798	
0-9	reference	reference	reference
Events/N		101/1307	
10-29	1.53 (1.23-1.90)	1.36 (1.09-1.70)	1.37 (1.10-1.71)
Events/N		91/730	
30-299	2.56 (2.04-3.21)	2.14 (1.69-2.72)	2.05 (1.61-2.61)
Events/N		28/197	
300-	3.63 (2.47-5.34)	2.40 (1.59-3.62)	1.57 (0.98-2.52)

Model 1 was adjusted for age, race and gender. Model 2 was adjusted for Model 1 plus aspirin use, anticoagulant agents use, hypertension, diabetes, BMI, history of CVD, alcohol consumption, smoking status and education level. Model 3 was adjusted for ACR/eGFR in addition to Model 2.

Funding: Other NIH Support - NHLBI

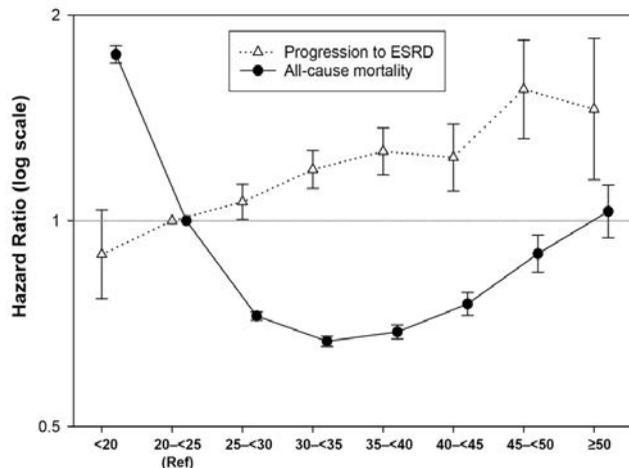
TH-OR014

Association of Body Mass Index with Clinical Outcomes in Non Dialysis Dependent Chronic Kidney Disease: A Systematic Review and Meta-Analysis Seyed-foad Ahmadi,¹ Golar Zahmatkesh,¹ Emad Ahmadi,¹ Elani Streja,⁵ Connie Rhee,¹ Luca De Nicola,³ Roberto Minutolo,³ Ana C. Ricardo,⁴ Csaba P. Kovessy,² Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC; ³Second Univ Napoli, Italy; ⁴Univ Illinois, Chicago; ⁵Harvard.

Background: Previous studies have not shown a consistent link between body mass index (BMI) and outcomes such as mortality and kidney disease progression in non-dialysis dependent (NDD) CKD patients. We therefore aimed to complete a systematic review and meta-analysis on this subject.

Methods: We searched MEDLINE, EMBASE, Web of Science, CINAHL, and Cochrane CENTRAL, and screened 7,123 retrieved studies for inclusion. Two investigators independently selected studies using predefined criteria and assessed each study's quality using the Newcastle-Ottawa Quality Assessment Scale. We meta-analyzed the results based on BMI classification by WHO.

Results: Ten studies with a total sample size of 484,906 were included in the systematic review presenting generally heterogeneous results. Through re-analysis of the largest reported study and quantitative data synthesis, we observed that in Stages 3-5 CKD, being underweight was associated with higher death risk while being overweight or obese class I was associated with lower death risk; however, obesity classes II or III were not associated with death risk. In addition, re-analysis of the largest available study showed that higher BMI was associated with incrementally higher risk of kidney disease progression; however, this association was attenuated in our pooled results. For earlier stages of CKD, we could not complete meta-analyses as the studies were sparse and had heterogeneous BMI classifications and/or referent BMI groups.



Conclusions: Patients with stage 3-5 CKD have a differential association between obesity classes I-III and mortality compared with the general population, indicating an obesity paradox in the CKD population.

Funding: NIDDK Support

TH-OR015

Risk Factors for Cognitive Impairment in Chronic Kidney Disease – The Brain in Kidney Disease Study Anne M. Murray,^{1,6} Elizabeth J. Bell,¹ David S. Knopman,² Yelena Slinin,^{3,4} Robert N. Foley,³ David Tupper.⁵ ¹Minneapolis Medical Research Foundation; ²Dept of Neurology, Mayo Clinic; ³Nephrology Div, U of Minnesota; ⁴VA Medical Center; ⁵Neuropsychology Section, Hennepin County Medical Center (HCMC); ⁶Geriatrics Div, HCMC.

Background: Cognitive impairment (CI) in patients with chronic kidney disease (CKD) poses a substantial public health burden. The extent that factors beyond estimated glomerular filtration rate (eGFR) contribute to the increased risk of CI in CKD has not been adequately measured.

Methods: We used cross-sectional data from the baseline exam (2011-2015) of the BRAIN IN Kidney disease study. Level of CI was determined using an algorithm based on neuropsychological tests that incorporates the DSM-IV dementia criteria. We assessed the relation between baseline characteristics and moderate to severe CI (yes/no) using logistic regression, controlling for potential confounding variables: age, gender, race, education, diabetes, hypertension, smoking status, cholesterol, BMI, and eGFR.

Results: The CKD cohort includes 422 community-dwelling participants (mean age=70, mean eGFR=34) with eGFR <60 ml/min/1.73 m² but not on dialysis. Of these, 149 had CI at baseline. Prior stroke, phosphorus ≥ 4.5 mg/dL and African American race were associated with a higher risk of CI. EGFR, markers of inflammation (TNF α and IL-6) and microalbuminuria (UACR), cholesterol and hemoglobin were not associated with CI.

Conclusions: We identified elevated phosphorus, prior stroke and African American race as potential risk factors for CI in community-dwelling CKD patients. Phosphorus is a potentially modifiable risk factor. Longitudinal analyses are needed to confirm these findings and identify potential preventive interventions against CI.

Adjusted odds ratios for CI		
Characteristics	Unit change	Odd ratios (95% confidence intervals)
EGFR	-10 ml/min/1.73 m ²	1.19 (0.99-1.44)
Prior stroke	Yes vs no	1.89 (1.09-3.27)
UACR	100 mg/g	1.01 (0.99-1.03)
TNF α	3 pg/mL	1.02 (0.87-1.20)
IL-6	6 pg/mL	1.17 (0.94-1.44)
Phosphorus	≥ 4.5 mg/dL vs <4.5	2.42 (1.15-5.10)
Cholesterol	-45 mg/dL	1.26 (0.99-1.61)
Hemoglobin	<10.5 g/dL vs ≥ 10.5	1.56 (0.64-3.82)
African American	Yes vs no	4.86 (2.44-9.64)

Funding: Other NIH Support - National Institute on Aging, Pharmaceutical Company Support - Satellite Healthcare Research Foundation

TH-OR016

Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease and Mortality in Diabetic Patients with Comorbid Depression

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Background: Depressed patients with diabetes have worse diabetes self-care and worse clinical outcomes. Here we aimed to determine the association of depression and the risk of incident CKD, cardio-vascular (CV) outcomes and all-cause mortality in a population of US veterans with diabetes mellitus (DM).

Methods: From a nationally representative prospective cohort of over 3 million US veterans with baseline estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73m², we identified 933,211 diabetic patients. The associations between depression and outcomes 1) incident CKD; 2) incident coronary heart disease [CHD]; 3) incident ischemic stroke; 4) all-cause mortality were assessed using the Kaplan-Meier method, and Cox proportional hazard models.

Results: Mean age was 64 \pm 11 years, 97% were male and 18% African-American. Depression was present in 340,806 patients at enrollment. Depressed patients were somewhat younger (61 \pm 11 versus 65 \pm 11 years), had slightly higher eGFR (84 \pm 15 versus 81 \pm 14 ml/min/1.73m²) but had somewhat more comorbidities at baseline. During a median follow-up of 7.3 years, 180,343 patients (19%) developed CKD. The presence of depression at enrollment was associated with 20% higher risk of incident CKD (adjusted hazard ratio [aHR] and 95% confidence interval [CI]: 1.20 (1.19-1.21)). Similarly, depression was associated with 35% higher risk of incident stroke (aHR and 95% CI: 1.35 (1.32-1.39)), 24% higher risk of incident CHD (aHR and 95% CI: 1.24 (1.22-1.27)) and 25% higher risk of all cause mortality (aHR and 95% CI: 1.25 (1.24-1.26)) during the follow-up.

Conclusions: Comorbid depression is associated with increased risk of developing CKD in diabetic patients. Similarly, the presence of depression is associated with worse CV outcomes. Appropriate intervention studies are needed to determine if treating depression in patients with diabetes would prevent CKD and CV disease.

Funding: Veterans Administration Support

TH-OR017

Cardiorespiratory Fitness and Neurocognitive Function in Older Adults with Chronic Kidney Disease

Daniel E. Weiner,³ Lindsay J. Lajoie,^{1,2} Eamon F. Fleming,³ Dylan R. Kirm,² Shari R. Waldstein,⁴ Jason Kissler,⁴ Kieran Reid,² Roger A. Fielding,² Stephen L. Seliger.⁵ ¹Friedman School of Nutrition, Tufts Univ; ²Human Nutrition Research Center on Aging, Tufts Univ; ³Tufts Medical Center; ⁴Univ of Maryland Baltimore County; ⁵Univ of Maryland School of Medicine.

Background: Chronic kidney disease (CKD) is associated with an increased risk for neurocognitive impairment in older adults, while greater cardiorespiratory fitness (CRF) is associated with better neurocognitive function among healthy older adults. This relationship has not been adequately explored in patients with CKD. This study examines whether CRF, as measured by VO₂peak, is associated with neurocognitive function in older adults with CKD stage 3b-4.

Methods: Baseline data from a multi-center randomized controlled trial of exercise training was used. The Mini-Mental State Exam (MMSE), Digit Symbol Substitution Test (DSST), Montreal Cognitive Assessment (MoCA), Trail Making Test Part A (TMT-Part A), and Trail Making Test Part B (TMT-Part B) were utilized to quantify neurocognitive function. The association between VO₂peak and neurocognitive function was assessed using multiple linear regression, adjusted for age, sex, and education level.

Results: Among 71 participants, with mean age 68.4 \pm 7.74 years and mean eGFR=33.2 \pm 10.6 ml/min/1.73m², higher VO₂peak was associated with better performance on the MMSE ($\beta=0.08$, $p=0.04$), and DSST ($\beta=0.75$, $p=0.03$). While not statistically significant, directionality was similar for other cognitive tests, including the MoCA ($\beta=0.12$, $p=0.20$), TMT-Part A ($\beta=-0.47$, $p=0.30$) and TMT-Part B ($\beta=-1.39$, $p=0.38$).

Conclusions: Better cardiorespiratory fitness, as assessed by VO₂peak, is associated with better performance on several neurocognitive tests in older adults with advanced CKD. Further research is needed to better understand the underlying mechanisms of this relationship and whether improved fitness can modify cognitive performance.

Funding: NIDDK Support

TH-OR018

Low Birth Weight and Risk of Progression to End Stage Renal Disease in IgA Nephropathy

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Background: Low Birth Weight (LBW) is a surrogate for fetal undernutrition and is associated with impaired nephron development in utero. Low birth weight is associated with fewer and larger glomeruli and increased risk of hypertension and renal disease in later life. In this study, we investigate whether low birth weight (LBW) and low birth weight for gestational age (LBW-GA) predict progression to ESRD in IgAN patients.

Methods: The Medical Birth Registry has recorded medical data for all births in Norway since 1967 and the Norwegian Renal Registry has recorded all patients With ESRD since

1980. From the Norwegian Kidney Biopsy Registry we retrieved all patients who had been diagnosed with IgAN from 1988-2013. These registries were linked and we analysed risk of progression to ESRD associated with LBW (defined as less than the 10th percentile of gender-specific birth weight) and/or LBW-GA (defined as less than the 10th percentile of birth weight for gestational age) by regression statistics.

Results: We included 471 patients, of whom 74 (15.7%) developed ESRD. As compared to patients without LBW, patients with LBW had a hazard ratio (HR) of 2.0 (95% confidence interval 1.0-3.7) for the total cohort, HR 2.2 (1.1-4.4) for males and HR 1.3 (0.30-5.8) for females. Corresponding HRs for LBW-GA were 2.2 (1.1-4.2), 2.7 (1.4-5.5) and 0.8 (0.10-5.9). After adjustments for eGFR at time of diagnosis, the association was lost. Further analyses showed that as compared to patients who were neither LBW nor LBW-GA, patients who were LBW-GA but not LBW had a HR of 1.3 (0.39-4.0), patients who were LBW but not LBW-GA had a HR of 1.4 (0.51-3.9) and patients who were both LBW and LBW-GA had a HR of 3.2 (1.5-6.8).

Conclusions: Among IgAN patients, having had low birth weight or low birth weight for gestational age predicted progression to ESRD. The association was only significant in male patients.

TH-OR019

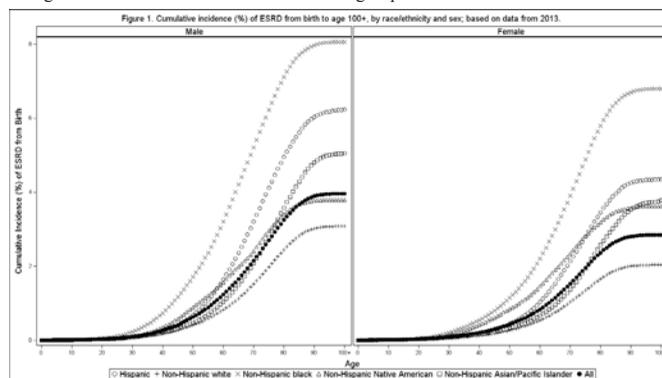
Risks of End-Stage Renal Disease (ESRD) in the United States

Patrick J. Albertus,¹ Hal Morgenstern,¹ Bruce M. Robinson,^{1,2} Rajiv Saran.¹ ¹Univ of Michigan; ²Arbor Research Collaborative for Health.

Background: Although incidence rates of ESRD are reported routinely by the USRDS, these are not directly relevant for individuals or providers. The objective of this study was to utilize incidence rate information to estimate the short- and long-term risk of ESRD by age, sex and race/ethnicity.

Methods: Using data from 2000 and 2013, risks/cumulative incidences were estimated using DevCan software developed principally to estimate risk of cancer diagnosis. This method uses a competing-risk framework by constructing a hypothetical cohort followed from birth to death. Incidence and mortality rates of ESRD were obtained from the USRDS and all-cause mortality rates from CDC-Wonder.

Results: Among males, the lifetime risk of ESRD from birth using 2013 data was 3.08% for non-Hispanic (NH) whites, 8.06% for NH blacks, 3.80% for NH Native Americans, 5.05% for NH Asians/Pacific Islanders, and 6.23% for Hispanics. Among females, the lifetime risks were 2.03% for NH whites, 6.80% for NH blacks, 3.63% for NH Native Americans, 3.78% for NH Asian/Pacific Islanders, and 4.34% for Hispanics. The 10-year risk was highest at age 70 at 1.52% for males and 1.03% for females. Comparing risk estimates based on 2013 data to 2000 data, the lifetime risk of ESRD from birth increased from 3.53% to 3.96% in males and decreased from 2.96% to 2.85% in females, but these changes were not uniform across racial/ethnic groups.



Conclusions: The risk of ESRD in the U.S. varies substantially among racial/ethnic groups for both sexes. Lifetime risks increased a little during the previous decade in males, but decreased slightly in females. The statistical approach used in this study could be applied routinely to USRDS data to estimate the probability of individuals being diagnosed with ESRD. To be most useful in clinical practice, this application will require additional data elements (e.g., comorbidities, CKD stage).

Funding: NIDDK Support

TH-OR020

The Relevance of Systolic Blood Pressure to Renal Progression: Observations from the Study of Heart and Renal Protection (SHARP)

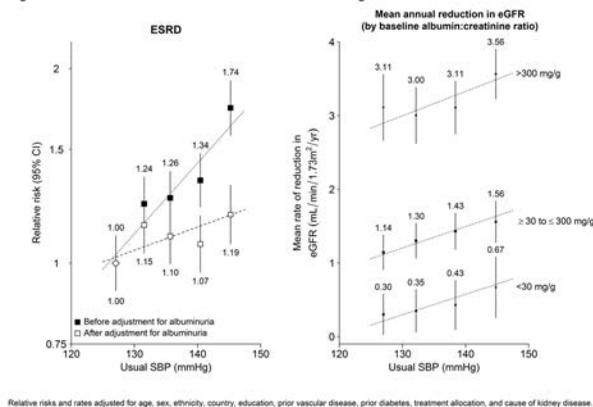
Natalie Staplin, William G. Herrington. On behalf of the SHARP Collaborative Group. CTSU, Univ of Oxford.

Background: Meta-analysis of intensive versus standard blood pressure (BP) lowering trials has demonstrated that lower BP reduces the risk of end-stage renal disease (ESRD), but there is uncertainty about optimal BP targets in chronic kidney disease (CKD), particularly in those without albuminuria.

Methods: Systolic blood pressure (SBP), creatinine and renal outcomes were assessed 6 monthly for 5 years among 6245 SHARP participants not on dialysis at baseline of whom 2137 (33%) developed ESRD. Regression models adjusted for confounders assessed the relevance of usual SBP to ESRD and to annual rate of change in CKD-EPI eGFR. High BP may cause or be caused by albuminuric CKD, so analyses were performed with and without adjustment for albuminuria.

Results: Each 20 mmHg higher usual SBP was associated with an average increase of 71% in the risk of ESRD (adjusted hazard ratio [HR] 1.71, 95% CI 1.50-1.95). The risk of ESRD was substantially attenuated, but remained statistically significant, after adjustment for albuminuria (HR 1.18, 1.02-1.35). Among those with at least 3 creatinine measurements, each 20 mmHg higher usual SBP was associated with a 1.3 (95% CI 1.0-1.6) mL/min/1.73m²/year greater mean decline in eGFR, which reduced to 0.7 (0.4-1.0) after adjustment for albuminuria. Mean rate of reduction in eGFR was similar irrespective of baseline albuminuria (macroalbuminuria 0.7 [0.1-1.3]; microalbuminuria 0.6 [0.2-1.0]; normoalbuminuria 0.6 [0.1-1.1]).

Figure: Relevance of SBP to ESRD and annual rate of change in eGFR



Conclusions: In CKD, the true relevance of SBP to renal progression is difficult to quantify precisely as the relative risks are substantially attenuated by adjustment for albuminuria (which may not be appropriate if this is on the causal pathway). Nevertheless, after such adjustment, higher SBP is significantly associated with renal progression irrespective of the presence or absence of albuminuria.

Funding: Pharmaceutical Company Support - Merck/Schering-Plough Pharmaceuticals (North Wales, PA, USA), Government Support - Non-U.S.

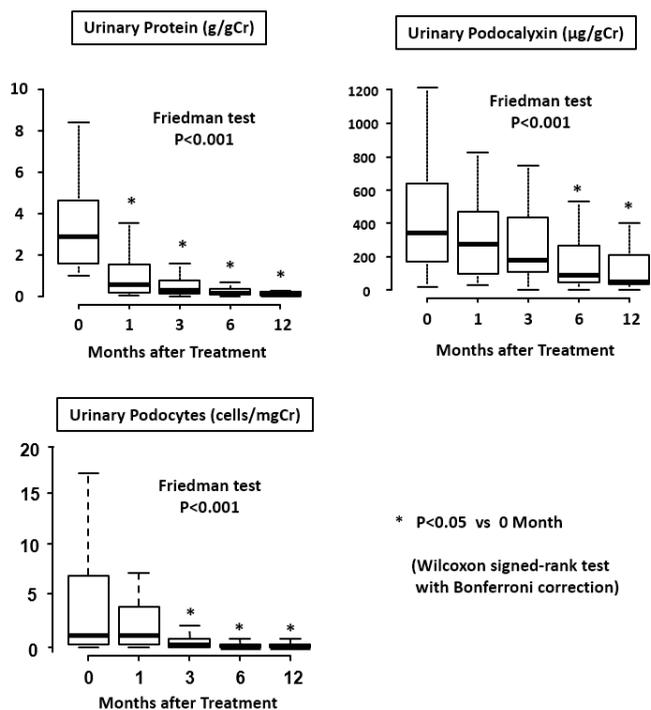
TH-OR021

The Significance of Urinary Podocalyxin Level and Urinary Podocyte Number in Lupus Nephritis: A Longitudinal Study Keiju Hiromura,¹ Hiroshi Kajiyama,² Hidekazu Ikeuchi,¹ Junya Suwa,¹ Daisuke Ikuma,² Toru Sakairi,¹ Yoriaki Kaneko,¹ Akito Maeshima,¹ Hiroyuki Kurosawa,³ Yoshiaki Hirayama,³ Masanori Hara,⁴ Toshihide Mimura,² Yoshihisa Nojima.¹ ¹Dept of Medicine and Clinical Science, Gunma Univ, Japan; ²Dept of Rheumatology and Applied Immunology, Saitama Medical Univ, Japan; ³Denki Kagaku Kogyo K.K., Japan; ⁴Dept of Pediatrics, Yoshida Hospital, Japan.

Background: Podocalyxin sheds in urine from injured podocytes. We have previously reported that urinary podocalyxin levels (U-PCX) and urinary podocytes numbers (U-POD) were highly elevated in active lupus nephritis (LN) before treatment (Arthritis Rheum, 2013, 65:10 S377). In the current study, we examined the changes of U-PCX and U-POD levels after treatment and the impact of baseline U-PCX and U-POD on the response to treatment.

Methods: Patients with active LN (n=37), whose urinary protein levels (U-Prot) >1.0 g/gCr and who required initiation or intensification of treatment, were examined. Early proteinuric remission was defined as U-Prot <0.3g/gCr at 3 months, which was observed in 15 patients.

Results: Although the significant improvement of U-Prot was observed at 1 month after treatment, U-PCX and U-POD decreased more gradually (Fig). A weakly positive correlation was found between U-PCX and U-POD (R=0.363, P=0.027), but not between U-Prot and U-PCX or U-POD. Multivariate logistic regression analysis showed that U-Prot >3g/gCr, U-PCX >600 mg/gCr and U-POD >1cell/mgCr at baseline were risk factors for not achieving early proteinuric remission (OR32.4, 95%CI 2.8-373.2, P=0.005; OR 24.9, 95%CI 1.3-455.2, P=0.030; OR 13.9, 1.2-161.2, P=0.036; respectively). The combination of U-Prot <3g/gCr and U-PCX <600mg/gCr at baseline predicted early proteinuric remission (sensitivity 80%, specificity 86%, PPV 80%, NPV 86%).



Conclusions: U-PCX and U-POD would be novel biomarkers of podocyte injury in LN. **Funding:** Government Support - Non-U.S.

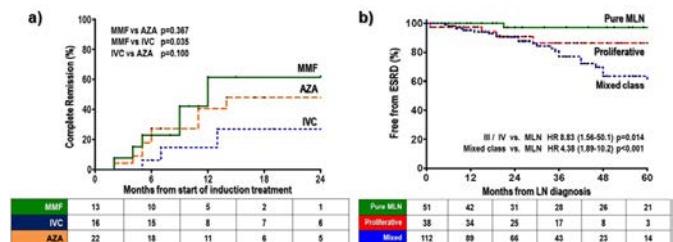
TH-OR022

Mycophenolate Mofetil, Azathioprine and Intravenous Cyclophosphamide Are Effective for Treatment of Pure Membranous Lupus Nephritis in Hispanic Population Juan M. Mejia-Vilet, Ricardo Correa-Rotter. Dept of Nephrology, National Science and Nutrition Inst Salvador Zubirán, Mexico City, Distrito Federal, Mexico.

Background: Membranous lupus nephritis (MLN) accounts for 10-20% of renal biopsy diagnosis in SLE patients. Its optimal treatment remains uncertain.

Methods: Treatment of 51 patients with biopsy proven MLN was retrospectively evaluated. Response to therapy and outcome were compared to those with proliferative (III or IV, n=38) and mixed-class LN (III+V / IV+V, n=112).

Results: Fifty one patients with MLN were distributed by induction drug in 3 groups: MMF (mean 2.6±0.4g/day), IV cyclophosphamide (5.4g/m²BSA accumulative dose), azathioprine (mean 2.1±0.6 mg/kg/d). Median follow-up was 44 months (IQR 15-94). At presentation, patients in IVC group had a trend to worse urinary protein to creatinine ratio (uPCR) and a longer time from symptoms to start of treatment. Complete remission rates at 6, 12 and 24 months were 23.1, 61.5 and 61.5% for MMF, 6.2, 14.8 and 26.9% for IVC and 27.3, 40.5 and 47.9% for AZA. MMF induction was superior to IVC on Kaplan-Meier analysis (HR 5.42, 95% CI 1.38-21.2, p=0.03), but after Cox multivariate analysis there was only a trend to a better complete remission with MMF (HR 3.65, 95% CI 0.94-14.2, p=0.061). There were no differences between groups in adverse effects and thrombotic events. Only two MLN patients developed ESRD on follow-up. When compared with an historical cohort, patients with proliferative (HR 8.83, 1.56-50.1, p=0.014) and mixed histological classes (HR 4.38, 1.89-10.2, p<0.001) were more likely to develop ESRD.



Conclusions: Mycophenolate mofetil, IVC and AZA are effective for induction treatment of MLN. At our center, there is a trend to treat severe nephrotic patients with IVC and less severe cases with MMF or AZA. MLN has a similar rate of response to treatment and better long-term outcome than proliferative and mixed classes.

TH-OR023

Impact of Tabalumab on the Kidney in Lupus: Results from Two Phase 3 Clinical Trials Brad H. Rovin,¹ Mary Anne Dooley,² Jai Radhakrishnan,³ Ellen M. Ginzler,⁴ Tammy Forrester,⁵ Pamela W. Anderson.⁵ ¹Ohio State Univ, Columbus, OH; ²Univ of North Carolina, Chapel Hill, NC; ³Columbia Univ, New York, NY; ⁴SUNY Downstate, Brooklyn, NY; ⁵Eli Lilly & Company, Indianapolis, IN; ⁶Eli Lilly & Company, Indianapolis, IN.

Background: Tabalumab (TAB) is a monoclonal antibody that neutralizes membrane and soluble B-cell activating factor. Two 52-week, randomized, double-blinded, placebo (PBO)-controlled Phase 3 trials evaluated the safety and efficacy of TAB for non-renal disease in lupus.

Methods: Patients with moderate-severe active lupus, but without severe active lupus nephritis (ie, urine protein/creatinine ratio [uPCR] of >200 mg/mmol or estimated creatinine clearance of <30 mL/min) were randomized 1:1:1 to TAB (120 mg subcutaneously [SC] every 4 weeks [Q4W] or 120 mg SC every 2 weeks [Q2W]) or PBO for 52 weeks. Serum creatinine (SCr), glomerular filtration rate (GFR), uPCR, and renal adverse events were determined monthly. Data were analyzed for the intent-to-treat (ITT) population and for ITT patients with a baseline uPCR >20 mg/mmol (ITT+uPCR) using an ANCOVA model.

Results: The trials enrolled 2262 patients. Baseline demographics, lupus disease activity, use of lupus drugs, SCr, GFR, and uPCR were similar among treatment arms. In the ITT and ITT+uPCR populations, there were no differences between treatment arms in baseline-to-endpoint change in SCr, GFR, or uPCR. Renal adverse events were not different among treatment arms.

ITT	Tab Q2W N=597	Tab Q4W N=583	PBO N=575
ΔSCr	.54±10.7	.11±9.8	.31±11.4
p-value vs PBO	.549	.897	
ΔGFR	.17±17.6	.63±14.8	.38±16.6
p-value vs PBO	.622	.805	
ΔuPCR	.44±53.4	-.30±51.6	1.87±44.4
p-value vs PBO	.718	.517	
ITT+uPCR			
ΔSCr	1.68±13.0	1.42±12.1	2.73±14.4
p-value vs PBO	.471	.655	
ΔGFR	-.87±18.9	.29±16.0	-2.14±20.7
p-value vs PBO	.604	.559	
ΔuPCR	-12.52±85.8	-9.08±111.8	-7.53±102.9
p-value vs PBO	.383	.434	

Conclusions: Compared to PBO, TAB did not significantly affect SCr, GFR, or uPCR over 52 weeks in ITT or ITT+uPCR patients. There were no significant renal safety signals.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

TH-OR024

Evaluation and Validation of a Biomarker Panel in ANCA-Associated Renal Vasculitis Andreas Kronbichler, Julia Kerschbaum, Georg Gründlinger, Johannes Leierer, Gert J. Mayer, Michael Rudnicki. *Internal Medicine IV, Nephrology and Hypertension, Innsbruck, Austria.*

Background: Emerging studies in ANCA-associated vasculitis revealed markers of disease activity. The aim of the study was to evaluate and validate encouraging markers identified by literature search and the creation of respective panels.

Methods: 161 marker molecules were identified by a systematic literature review. ELISA assays were performed to validate a panel of biomarkers in an independent cross-sectional cohort of patients with renal involvement. Active vasculitis as assessed by BVAS v3 was defined as BVAS v3 ≥ 1 and inactive disease as BVAS v3 of 0. Statistical analysis was performed with SPSS 21 ® and the Salford Predictive Modeler 7.0® was used to generate a biomarker panel.

Results: Our review indicated increased expression of monocyte chemoattractant protein (MCP)-1, sC5bC9, C3a and C5a in urine, whereas GM-CSF, sFlt1, CRP, IL-17A, C5a, hyaluronan, C3a and IL-18 bp were identified to be diversely regulated in active and inactive disease in blood samples. Our cross-sectional analysis revealed increased expression of CRP, C5a, C3a, IL-18 bp in blood and C5a and MCP-1 in urine samples during active AAV (all p<0.05).

	Units	Active	Remission	p-value
CRP	mg/l	18.7	6.4	<0.001
sFlt1	ng/ml	0.8	0.8	0.737
C3a	ng/ml	253	135	<0.001
C5a	ng/ml	10.2	6.2	0.006
IL-17A	pg/ml	0.8	0.3	0.115
IL-18 bp	ng/ml	8.5	5.2	0.007
Hyaluronan	ng/ml	43.3	46.3	0.894
MCP-1 urine	ng/ml	2.4	0.4	<0.001
C5a urine	ng/ml	0.4	0.0	0.010
sC5bC9 urine	ng/ml	0.0	0.0	0.639
C3a urine	ng/ml	0.0	0.0	0.384

Table 1. The respective biomarker with a mean expression is given in active and inactive disease. CRP, C3a, C5a, IL-18 bp in plasma as well as MCP-1 and C5a in urine yielded significance (all p<0.05).

Creation of a biomarker panel yielded a sensitivity and specificity of 76% (AUC 0.89) when CRP and urinary MCP-1 were added.

Conclusions: We could find a significant increase in CRP, C3a, C5a, IL-18 bp in blood and MCP-1 and C5a in urine samples. Moreover, we propose a biomarker panel comprising CRP and urinary MCP-1 in patients with ANCA-associated renal vasculitis. Further investigations to confirm our results are desired, including the reliability to predict renal relapses.

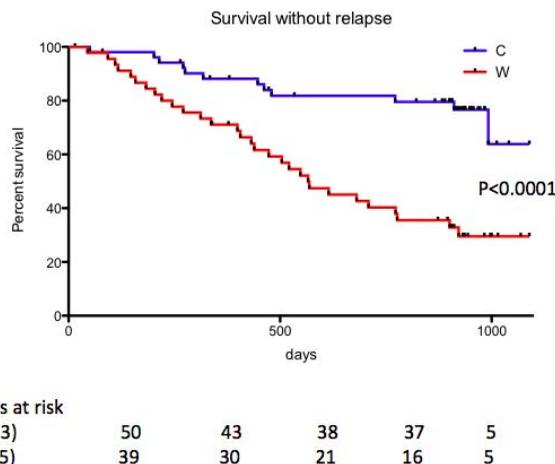
TH-OR025

Randomized Controlled Trial of Treatment Withdrawal in the Remission Phase of ANCA Vasculitis: The REMAIN Study Alexandre Karras,^{1,4} Marten Segelmark,^{3,4} David R.W. Jayne.^{2,4} ¹Nephrology, HEGP Hospital, Paris, France; ²Nephrology, Addenbrooke's Hospital, Cambridge, United Kingdom; ³Dept of Nephrology, Linköping Univ, Sweden; ⁴On behalf of the EUVAS Study Group.

Background: After induction of remission, continuation of immunosuppressive and glucocorticoid therapy is recommended in ANCA-associated vasculitis (AAV), to reduce the risk of relapse. The optimal duration of immunosuppression (IS) for maintenance of remission is unknown.

Methods: The REMAIN study is a prospective, randomized trial conducted by the European Vasculitis Study (EUVAS) group. AAV patients were included after induction of remission with Cyclophosphamide/Prednisone (PRED) and initiation of remission maintenance therapy with azathioprine (AZA). They were randomized (1:1) at month 18, to receive either AZA/PRED until 48 months from onset of therapy (continuation group, C) or to discontinue IS by 24 months (withdrawal group, W). The primary endpoint was the rate of relapses during 30-months follow-up.

Results: 121 patients were included, 45% had antiMPO ANCA. At randomization, median SCreat was 15 mg/l, ANCA remained detectable in 56%, median AZA dose was 98 mg/day, median PRED dose 5.5 mg/day. The rate of relapse was higher in the W than in the C group (66% vs 22%, p<0.0001, OR 6.83, CI 2.79-16.69).



ANCA positivity at randomization was associated with higher relapse risk (51% vs 31%, p=0.04, OR 2.31, CI 1.02-5.29). Renal function, ANCA specificity (MPO vs PR3) or age were not predictive of relapse. IS-related severe adverse events were more frequent in the C group (9 vs 2) but this group had better renal outcome (0 vs 5 ESRD cases).

Conclusions: Prolonged remission maintenance therapy with AZA/PRED beyond 24 months after diagnosis reduced relapse rate. Continuation of immunosuppression was associated with better renal survival but not with improvement of overall patient survival.

TH-OR026

Pharmacogenetics of Rituximab in ANCA Associated Vasculitis

Federico Alberici,¹ Rona M. Smith,¹ Mariana G. Fonseca,¹ Lisa C. Willcocks,¹ Rachel B. Jones,¹ James E. Peters,¹ Augusto Vaglio,² Renato Alberto Sinico,⁴ Julia U. Holle,¹¹ Bo Baslund,⁶ Annette Bruchfeld,³ Iva Gunnarsson,³ Sophie Ohlsson,⁷ Vladimir Tesar,⁸ Zdenka Hruskova,⁸ Maria C. Cid,⁹ Thomas Neumann,¹⁰ Paul Anthony Lyons,¹ Kenneth GC Smith,¹ David R.W. Jayne.¹
¹Dept of Medicine, Univ of Cambridge, United Kingdom; ²Univ Hospital of Parma, Italy; ³Karolinska Inst, Sweden; ⁴AO San Carlo Borromeo, Milano, Italy; ⁵Rigshospitalet, Denmark; ⁶Lund Univ, Sweden; ⁷Charles Univ, Czech Republic; ⁸Hospital Clinic of Barcelona, Spain; ⁹Univ of Jena, Germany; ¹⁰Klinikum Bad Bramstedt, Germany.

Background: Rituximab(RTX) is effective for induction and maintenance of remission in ANCA associated vasculitis(AAV); however optimal dosing approach is still unclear, relapse is common after discontinuation and predictors of response do not exist. This study assesses potential genetic determinants of response to RTX in AAV.

Methods: We included AAV-patients treated with RTX from European centers (primary cohort) and UK(replication cohort). Genotyping of 18 single nucleotide polymorphisms(SNPs) identified according to a biological rationale was performed using TaqMan and Sequenom platforms. End points were treatment failure rate(TF) 6 months after RTX and time to TF or relapse(TTR). Bonferroni correction was applied.

Results: 213 patients were enrolled in the primary and 109 in the replication cohorts. A SNP in the *TNFSF13B* gene region(BAFF) was associated to TTR in the primary (HR12.4,p=7x10⁻⁰⁴) and replication cohorts (HR5.4,p=0.0024). Meta-analyses showed an association with both end-points.

	Primary cohort		Replication cohort		Meta-analysis	
	OR-HR	p	OR	p	OR-HR	p
TF at 6 months	8	0.07	9.8	0.009	9.2	0.006
TTR	12.4	7x10 ⁻⁰⁴	5.4	0.002	7.3	5.2x10 ⁻⁰⁶

Carriers of the risk genotype had higher rate of detectable B cells 6 months after RTX (50%vs14%,p=0.0146). The association was restricted to patients historically PR3-ANCA positive (TF risk-OR 9,p=0.0141;TTR-HR 8.2,p=8.7x10⁻⁰⁶) while in the MPO-ANCA subgroup an association with a SNP in chromosome 4 was identified (TF risk,p=0.03;TTR,p=0.0238).

Conclusions: We have identified a SNP that may predict response to RTX in AAV. Our results may suggest a role for this SNP in modulating BAFF levels.

TH-OR027

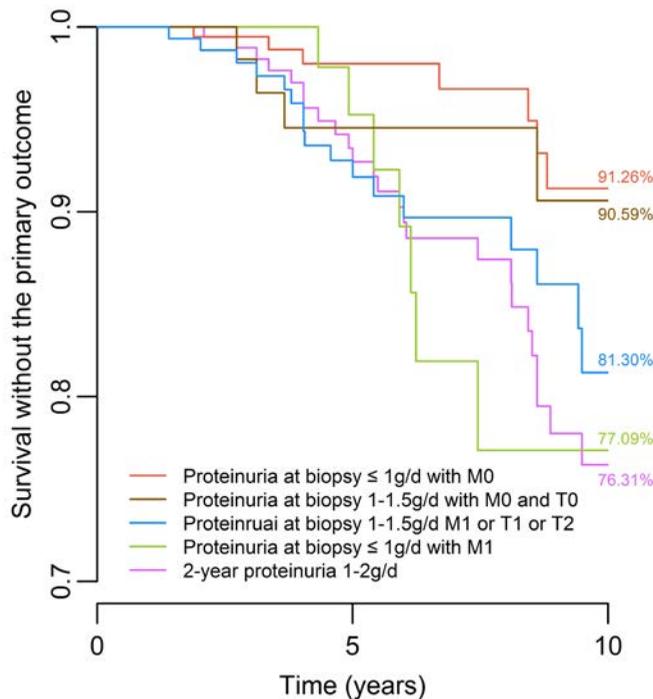
The MEST Score in IgA Nephropathy: Implications for Clinical Management

Sean Barbour,^{1,2,7} Gabriela Espino-Hernandez,^{2,7} Heather N. Reich,^{3,7} Rosanna Coppo,^{4,7} Ian Roberts,^{5,7} John Feehally,^{6,7} Daniel C. Catran.^{3,7}
¹Univ of BC; ²BC Renal Agency; ³Univ of Toronto; ⁴Univ of Turin; ⁵Oxford Univ; ⁶Leicester General Hospital; ⁷For the Oxford Derivation, North American Validation and VALIGA Consortia.

Background: The MEST score from the Oxford classification of IgA nephropathy (IgAN) is independently associated with renal outcome. Current risk stratification in IgAN requires clinical data over 2 years of follow-up. Using modern prediction tools, we examined whether combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods that use 2 years of follow-up data.

Methods: We used a cohort of 901 adults with IgAN from the Oxford derivation, North American validation and VALIGA studies to analyze the risk of a 50% decrease in eGFR or ESRD using Cox regression models. Median follow-up was 5.6yrs. We considered the following covariates: clinical data at biopsy (eGFR, proteinuria, MAP) with or without MEST, and 2-year clinical data alone (2-year average of proteinuria/MAP, eGFR at biopsy). Prediction was assessed using the AIC, R², NRI, IDI, C-statistic and calibration curves.

Results: There was significant improvement in prediction by adding MEST to clinical data at biopsy, and the combination predicted the outcome as well as using 2-year clinical data alone. Results did not change in subgroups treated or not with RAS blockade or immunosuppression. The figure provides examples of how using MEST with clinical data at biopsy can identify high or low risk groups compared to using 2-year clinical data alone.



Conclusions: These results demonstrate that combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods, and should allow modification of treatment based on risk assessment using data readily available at the time of biopsy.

TH-OR028

Effects of Tonsillectomy Combined with Steroid Pulse Therapy upon IgA Nephropathy Depending on Proteinuria Status at Diagnosis

Hirofumi Komatsu,¹ Shouchi Fujimoto,¹ Yuji Sato,¹ Akihiro Fukuda,¹ Yoshinari Yasuda,² Takashi Yasuda,³ Tetsuya Kawamura,⁴ Seiichi Matsuo.²
¹Univ of Miyazaki, Miyazaki, Japan; ²Univ of Nagoya, Nagoya, Aichi, Japan; ³St. Marianna Univ School of Medicine, Kanagawa, Japan; ⁴Jikei Univ School of Medicine, Tokyo, Japan.

Background: Little is known about the effects of tonsillectomy combined with steroid pulse therapy on IgA nephropathy (IgAN) with a hard end-point and long-term observation. We therefore examined the effects of the combined therapy on renal outcomes of IgAN in a large, nationwide cohort study in Japan.

Methods: We divided 669 of 1,174 patients who were diagnosed with IgAN between 2002 and 2004 into three groups based on their having mild (0.50 - 0.99 g/day; n = 258), moderate (1.00 - 1.99 g/day, n = 225), or severe (≥ 2.00 g/day; n = 186) proteinuria at diagnosis. Ratios of decline in renal function and urinary remission were compared among the three groups after receiving combined, steroid or conservative therapy during a mean follow-up of 6.2 ± 3.4 years.

Results: The ratio of urinary remission at final observation was significantly higher in the groups given combined, than steroid or conservative therapy (mild proteinuria: 63% vs. 46% and 42%; moderate proteinuria, 52% vs. 44% and 23%; severe proteinuria, 43% vs. 33% and 16%, respectively). In contrast, the ratio of a 50% increase in serum creatinine decreased more groups given combined, than steroid or conservative therapy (mild proteinuria, 3.7% vs. 10.8% and 14.6%; moderate proteinuria, 7.6% vs. 6.5% and 19.8%; severe proteinuria, 16.7% vs. 25.0% and 36.8%, respectively). Cox proportional hazards models revealed that the combined therapy significantly prevented a 50% increase in serum creatinine compared with conventional therapy in the groups with moderate and severe proteinuria (hazards ratio, 3.64 and 3.09, respectively).

Conclusions: Tonsillectomy combined with steroid pulse therapy induces urinary remission and prevents the decline in renal function in patients with moderate and severe proteinuria.

TH-OR029

Pregnancy and IgA Nephropathy: Renal, Maternal and Fetal Outcomes

Sehoon Park, Kyung Don Yoo, Dong Ki Kim, Kwon Wook Joo, Chun Soo Lim, Yon Su Kim, Hajeong Lee. Dept of Internal Medicine, Seoul National Univ Hospital.

Background: Impact of pregnancy on long term renal prognosis of IgA nephropathy (IgAN) remains controversial. Also, there are few information about maternal and fetal outcomes of pregnancy in IgAN women.

Methods: This study included women with biopsy proven IgAN from 1979 to 2013 and all mothers with delivery record from 1999 to 2014 in Seoul National University Hospital.

A survey was done by medical chart review and telephone poll. Primary outcome for kidney was end-stage renal disease (ESRD) progression and doubling of serum creatinine. Maternal outcomes were preeclampsia, gestational hypertension, and proteinuria. Fetal outcomes were preterm birth, fetal death and fetal growth restriction (FGR). Matched analysis was done by 2:1 propensity score matching (PSM).

Results: A total of 803 IgAN women were enrolled including 88 patients with 166 pregnancy experiences. In addition, 15,028 women with 17,432 pregnancies were enrolled as control. After PSM, no significant difference of baseline parameters was found between matched groups. For renal outcome, pregnancy affect neither ESRD progression nor creatinine doubling in overall IgAN women. However, renal progression was accelerated by pregnancy (HR, 2.90; 95% CI, 1.171–7.179, $P=0.023$) in IgAN women with moderate kidney dysfunction (eGFR <60). In maternal outcome, pregnancy of IgAN showed more proteinuria, gestational hypertension, and preeclampsia than normal pregnancies. Moreover, risks of fetal death and FGR were elevated. We found that this adverse pregnancy outcomes of IgAN patients occurred inversely to their pregestational kidney function. Unexpectedly, this trend started even from preserved pregestational renal function (eGFR <75), not from advanced renal dysfunction.

Conclusions: We demonstrated pregnancy accelerated renal progression in IgAN women with impaired kidney function. Moreover, we found that IgAN women suffered from a substantial burden of pregnancy even in those with relatively preserved pregestational renal function.

TH-OR030

Semaphorin 3F (SEMA3F) Expression Is Reduced in Pregnancy Complicated by Preeclampsia (PE) Giovanni Stallone, Adelaide Di Lorenzo, Giuseppe S. Nettì, Barbara Infante, Francesca Bruno, Pantaleo Greco, Maria Matteo, Stefania Carlucci, Federica Trezza, Giuseppe Grandaliano. *Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.*

Background: PE, characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation, affects 2-10% of pregnancies worldwide. It is characterized by an ineffective remodeling of maternal vessels perfusing the placenta. SEMA3F is a well-known anti-angiogenic mediator. We aimed to investigate whether SEMA3F placenta expression and serum and amniotic levels are modulated in PE.

Methods: To this purpose, we performed an observational single center, cohort study in the period from March 2013 to July 2014. We enrolled 132 consecutive pregnant women (PE n=13), undergoing an elective cesarean section (cross-sectional study) and 150 consecutive pregnant women undergoing amniocentesis for routine clinical indications at 16-18 week of gestation (perspective study). SEMA3F concentration was evaluated in maternal peripheral blood, venous umbilical blood and amniotic fluid at the time of delivery in the first group. In addition, in this group we examined placental SEMA3F protein expression. We then investigated amniotic fluid SEMA3F level at 16-18 weeks of gestation in the second group of pregnant.

Results: SEMA3F placenta expression was significantly reduced in PE (Control 3.2 ± 3 vs. PE 1.3 ± 6 AU, $p=0.01$). In addition, SEMA3F level at the time of delivery was significantly lower in serum (2.0 ± 4 vs 2.9 ± 6 ng/mL, $p=0.04$), amniotic fluid (133.6 ± 41.9 vs 202.4 ± 102.2 ng/mL, $p=0.01$) and cord blood (58 ± 27 vs 92 ± 20 ng/mL, $p=0.02$) of PE patients compared with normal pregnant women. SEMA3F level in maternal serum was significantly associated with placental weight ($R^2=0.802$; $p<0.001$) and newborn weight ($R^2=0.532$; $p<0.001$) at birth. In the prospective cohort study 14 women developed PE. In this setting, SEMA3F level in the amniotic fluid was lower in women developing PE compared to women with a normal pregnancy (12.9 ± 8.1 vs 30.1 ± 8.0 ng/mL, $p<0.01$).

Conclusions: Our findings demonstrate, for the first time, that SEMA3F expression is significantly reduced in PE and support the hypothesis that SEMA3F amniotic fluid levels might represent a biomarker of PE.

Funding: Government Support - Non-U.S.

TH-OR031

Efficacy in Diabetic Nephropathy in a Phase 2 Clinical Trial of Chemokine Receptor 2 Inhibitor CCX140-B Richard J. Glasscock,¹ Elena Henkel,² Heidrun Mehling,³ Christoph Hasslacher,⁴ Ioanna Gouni-Berthold,⁵ Vladimir Tesar,⁶ Antonia Potarca,⁷ Pirow Bekker,⁷ Thomas J. Schall.⁷ ¹David Geffen School of Med; ²Technical Univ; ³Free Univ; ⁴Univ Heidelberg; ⁵Univ of Cologne; ⁶Charles Univ; ⁷ChemoCentryx.

Background: The orally administered inhibitor of C-C chemokine receptor 2 (CCR2) CCX140-B blocks the deleterious effects of monocyte chemoattractant protein-1, including macrophage infiltration, podocyte injury and dysfunction. The aim was to test CCX140-B in diabetic nephropathy (DN).

Methods: This is a randomized, one-year clinical trial. Primary efficacy measure: change in urinary albumin:creatinine ratio (UACR) over 52 wks. Eligible patients were on stable ACE inhibitor or ARB, and anti-diabetic treatment for ≥ 8 wks prior to entry, with UACR 100-3000 mg/g creatinine, HbA1c 6-10%, and eGFR ≥ 25 mL/min/1.73 m². Patients were stratified based on baseline UACR and eGFR, and then randomized to receive placebo, 5 mg, or 10 mg CCX140-B once daily (QD) plus standard of care (SOC) for 52 wks.

Results: 332 pts were enrolled. Baseline characteristics (mean \pm SD): 63 \pm 8 yrs, 77% males, BMI 33 \pm 5 kg/m², duration of diabetes 16 \pm 8 yrs, UACR (geo mean) 461 (range 77-2922) mg/g, eGFR 60 \pm 24 mL/min/1.73 m². The primary endpoint was met: 5 mg CCX140-B QD plus SOC showed a statistically significant ($p=0.01$) reduction in UACR compared to SOC alone. The maximum effect (24% reduction) was at 12 wks, with sustained reduction in UACR over the full year. 10 mg CCX140-B QD did not provide further improvement in UACR vs. 5 mg. CCX140-B treatment showed an improvement in fasting plasma glucose (-1.12 mmol/L). In a covariate analysis, CCX140-B was effective on UACR across patient

groups. In a pre-specified subgroup with high baseline UACR (>800 mg/g creatinine), CCX140-B resulted in a placebo-corrected 28% improvement in albuminuria over 52 wks, and a slower rate of decline in eGFR. CCX140-B did not affect systemic BP or body weight, and appeared to be well tolerated with a low overall dropout rate (10%).

Conclusions: CCX140-B improved albuminuria over 52 weeks in a broad patient population. Patients with high baseline UACR may benefit most from CCX140-B treatment, relevant for design of a renal endpoint study.

Funding: Pharmaceutical Company Support - ChemoCentryx, Inc.

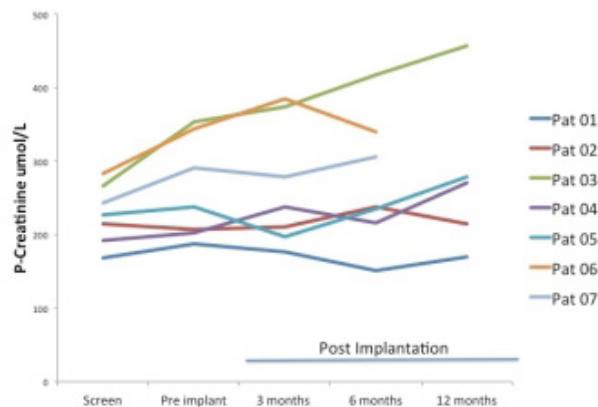
TH-OR032

A First in Human Study of Implantation of Neo-Kidney Augment, an Autologous Selected Renal Cell Population, in Type-2 Diabetic CKD Stage 3-4 Patients Peter Stenvinkel,¹ Torbjörn Lundgren,¹ Jonas Wadstrom,¹ Pontus Blomberg,¹ Torkel Brismar,¹ Randal K. Detwiler,² ¹Karolinska Univ Hospital, Sweden; ²Univ of North Carolina.

Background: Animal models of CKD show that a selected population of bioactive renal cells (Selected Renal Cells; SRC) can be delivered to the kidney through intra-parenchymal injection resulting in a decrease in disease progression. We have used a laparoscopic technique to perform the first-in-human study with Neo-Kidney Augment (NKA).

Methods: 7 male type-2 diabetic (108 \pm 11kg) patients (63 \pm 6yrs) with CKD were selected. After evaluation of renal function and radiology they underwent renal biopsy. Two cores were shipped to the manufacturing plant for cell isolation, culture and product preparation. NKA was shipped back to the clinical centre (44-87d after biopsy) and injected into the left kidney.

Results: Implantation of 8 mL NKA was uneventful. 1 postop complication was observed (ileocecal volvulus). Infectious complications were observed in 3 patients during the first 3 months. Antihypertensive medication has been reduced in 3/7 during the first 6 months. Creatinine has remained stable at 6 and 12 months after autologous renal cell implantation in 6/7 patients. In one patient a rise in s-creatinine has, at least partly, been due to prostatic hypertrophy. 2 patients have only been followed for 6 months. Kidney volume was stable at 3, 6, and 12 m (n5).



Conclusions: NKA was safely implanted in 7 diabetic CKD patients. Complications after the implantations in this population were found to be related to the surgical procedure. Longer follow-up and a larger number of patients is needed to reveal if this novel technique can arrest progression of CKD and delay the start of renal replacement therapy. Perioperative findings indicate that image-guided percutaneous techniques ("reversed biopsy") could facilitate the procedure in this patient group.

TH-OR033

Selective Inhibition of CCR2/5 Chemokine Receptors Reduces Macroalbuminuria in Subjects with Type 2 Diabetes and Overt Nephropathy Jeremy D. Gale,¹ Steven A. Gilbert,¹ Samuel S. Blumenthal,² Tom Elliott,⁴ Pablo E. Pergola,³ Kosalarum Goteti,¹ Douglas Girgenti,¹ Willem H. Scheele,¹ Robert Webster,¹ Christelle Huguet Perros.¹ ¹Pfizer Inc, Cambridge, MA; ²Zablocki VAMC, Milwaukee, WI; ³Renal Associates PA, San Antonio, TX; ⁴BCDiabetes, Vancouver, Canada.

Background: Recruitment, infiltration and activation of inflammatory cells appears important in diabetic nephropathy (DN). Inhibition of MCP-1/CCR2 receptor pathways may have renoprotective effects in DN and clinical data support a potential protective role of CCR5 receptors. Our hypothesis was that combined blockade of CCR2 and CCR5 receptors could decrease proteinuria in subjects with nephropathy.

Methods: The effect on albuminuria of the novel and specific dual CCR2/5 receptor antagonist, PF-04634817, was assessed in a multinational, randomized, double-blind, placebo-controlled, parallel group trial of subjects with Type 2 diabetes and overt nephropathy already receiving ACEi and/or ARB. Subjects with eGFR 20-75 mL/min/1.73m² and urinary albumin creatinine ratio (UACR) >300 mg/g (33.9 mg/mmol) at baseline were assigned to receive PF-04634817 200mg (150mg if baseline eGFR <30 mL/min/1.73m²) or placebo (3:1), orally, once daily for 12 weeks.

Results: 226 subjects (mean UACR of 180.78 \pm 160.53 mg/mmol Cr and mean eGFR of 41.46 \pm 12.64 mL/min/1.73 m² at baseline) were randomized. A modest placebo-adjusted

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

reduction in UACR of 8% (95% CI -9% to 23%) was observed in response to treatment with PF-04634817 using the pre-defined primary assessment of efficacy (Bayesian analysis with informative prior). Ad hoc analysis, of those with eGFR <60 mL/min/1.73m² at baseline, showed a placebo-adjusted reduction of UACR approaching 19%. However, interpretation of subgroups are difficult due to the 3:1 randomization and the presence of data outliers. Adverse events (AEs) were mostly mild, the most common treatment-related AEs being nausea, acne and diarrhoea.

Conclusions: The efficacy of PF-04634817 to reduce UACR in this study appears modest, although may be greater in a subset of subjects with more advanced disease. This profile combined with good safety supports further investigation of its potential as a novel therapeutic strategy to improve renal outcome in DN.

Funding: Pharmaceutical Company Support - Pfizer

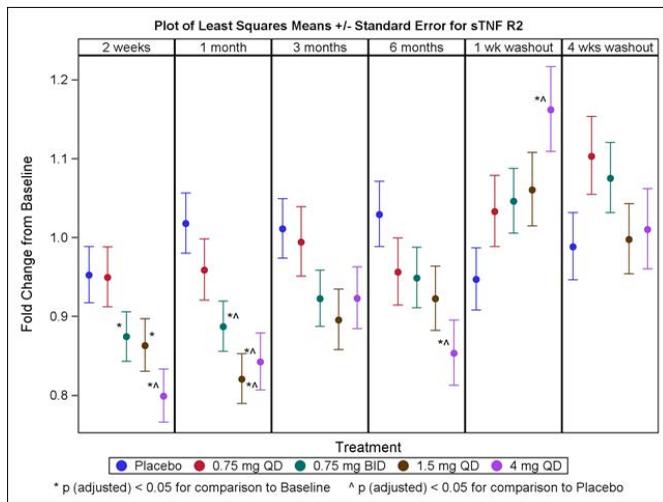
TH-OR034

Baricitinib in Diabetic Kidney Disease: Biomarker Analysis from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Frank C. Brosius,¹ Katherine R. Tuttle,² Sharon G. Adler,³ Matthias Kretzler,¹ Ravindra L. Mehta,⁴ James A. Tumlin,⁵ Kevin L. Duffin,⁶ Joseph V. Haas,⁶ Jiajun Liu,⁶ Maria E. Silk,⁶ William Macias,⁶ Jonathan M. Janes.⁶ ¹Univ MI Med Sch, Ann Arbor; ²Univ WA Sch Med, Spokane; ³LA BioMed, Torrance; ⁴Univ CA, San Diego; ⁵Univ TN Coll Med, Chattanooga; ⁶Eli Lilly & Co, IN.

Background: New therapies for diabetic kidney disease (DKD) are needed as standard care (SC) fails to prevent progressive DKD. Baricitinib (bari) is an oral Janus Kinase (JAK)1/JAK2 inhibitor. The study met its primary endpoint of significantly reduced urine albumin/creatinine ratio (UACR) at 6 months (mo) in diabetics with albuminuria despite SC.^a

Methods: To examine effects of bari treatment (tx) on key secondary endpoints: 24h urine protein; ³⁰% UACR decrease; inflammatory biomarkers: urinary interferon gamma-induced protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), and plasma soluble tumor necrosis factor receptor (sTNFR) 1&2. Type 2 diabetics at high-risk for progressive DKD on SC were randomized to bari 0.75mg QD (n=25), 0.75mg BID (n=26), 1.5mg QD (n=26), 4mg QD (n=25), or placebo (PBO;n=27) for 6 mo.

Results: Reductions in 24h proteinuria compared with PBO were observed at 6 mo of bari tx (LSM ratio vs PBO for 0.75mg BID, 1.5mg QD, 4mg QD; 0.59, 0.58, 0.60, resp. p<.05). Benefits were maintained during a 1-2 mo washout period. The proportion with ³⁰% UACR decline was increased by bari tx. IP-10, MCP-1, and sTNFR 1&2 decreased in a numerically dose-dependent manner. Estimated glomerular filtration rate by cystatin C was unchanged. At 6 mo, only 4mg bari had decreased hemoglobin vs PBO (-1.0±0.35 g/dL). No other safety concerns were observed.



Conclusions: Analysis of proteinuria and inflammatory biomarkers supports efficacy of bari in high-risk DKD. Data suggest an anti-inflammatory tx response encouraging further study of bari in DKD. ^aTuttle et al, ADA Jun 2015, Post. 114-LB.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

TH-OR035

Patiromer Lowers Serum K⁺ and Prevents Recurrent Hyperkalemia in CKD Patients ≥65 Years of Age on RAAS Inhibitors Matthew R. Weir,¹ David A. Bushinsky,² Martha Mayo,³ Dahlia Garza,³ Yuri Stasiv,³ Daniel J. Wilson,³ Susan Arthur,³ Lance Berman,³ George L. Bakris.⁴ ¹Univ of Maryland; ²Univ of Rochester; ³Relypsa, Inc; ⁴Univ of Chicago.

Background: Older pts are at risk for hyperkalemia (HK) due to comorbid diseases and K⁺-altering medications. The active moiety of patiromer is a nonabsorbed K⁺-binder. We present a prespecified subgroup analysis in pts ≥65 yr with CKD and HK on RAASi from a 2-part, single-blind, phase 3 patiromer trial (OPAL-HK).

Methods: Pts (n=243) with baseline (BL) serum K⁺ (s-K⁺) 5.1 to <6.5 mEq/L received patiromer (4.2 or 8.4 g BID) in a 4-wk treatment phase (part A); then pts with BL s-K⁺ 5.5

to <6.5 mEq/L by central lab (n=107) were randomized to continue patiromer or switch to placebo (PBO) in an 8-wk withdrawal phase (part B). Primary endpoints were Ds-K⁺ from BL at 4 wk in part A and between-group difference in Ds-K⁺ from part B BL to part B wk 4.

Results: 131 (54%) pts were ≥65 yr at BL. Consistent with overall results, primary endpoints were significant for pts ≥65 yr (Table). Overall and in pts ≥65 yr, 76% and 73%, respectively, had s-K⁺ 3.8 to <5.1 mEq/L (2nd endpoint) at part A wk 4. More PBO pts (p<0.001) developed recurrent HK in part B. In all pts, mild-moderate constipation was the most common AE in part A (11%).

Conclusions: Patiromer significantly reduced s-K⁺ in pts ≥65 yr and, vs. PBO, maintained control of s-K⁺.

Table. Primary Endpoint Results (mEq/L)			
Treatment Phase			
	Mean±SE BL S-K ⁺	Mean ΔS-K ⁺ ±SE (95% CI)	
Overall (n=237) ^a	5.58±0.03	-1.01±0.03 (-1.07, -0.95) p<0.001	
≥65 yr (n=126) ^a	5.56±0.04	-1.01±0.05 (-1.10, -0.92) p<0.001	
Withdrawal Phase			
	Median ΔS-K ⁺ (25 th , 75 th Percentile) from BL to Wk 4 ^b		Between-Group Difference in Median ΔS-K ⁺ (95% CI)
	PBO	Patiromer	
Overall (n=107)	0.72 (0.22, 1.22) n=52	0.00 (-0.30, 0.30) n=55	0.72 (0.46, 0.99) p<0.001 ^c
≥65 yr (n=60)	0.81 (0.51, 1.48) n=31	0.00 (-0.35, 0.30) n=29	0.81 (0.49, 1.14) p<0.001 ^c

^aExcludes 6 (overall) and 5 (≥65 yr) pts with no s-K⁺ value at wkly visit after Day 3. ^bOr earlier timepoint if pt first had s-K⁺ <3.8 mEq/L or ≥5.5 mEq/L. ^cBetween-group difference in mean ranks of change.

Funding: Pharmaceutical Company Support - Relypsa, Inc

TH-OR036

The Microalbuminuria Intervention Study: Effects of Different Losartan Combination Antihypertensive Therapy in Patients with CKD, MIDLAND-COMBID Yoshinari Yasuda,¹ Takeyuki Hiramatsu,² Seiichi Matsuo,¹ Shoichi Maruyama.¹ ¹CKD Initiatives/Nephrol/CAMCR, Nagoya Univ, Nagoya, Aichi, Japan; ²Nephrol, Konankosei Hosp, Konan, Aichi, Japan.

Background: GUARD study reported that ACEI with a diuretic resulted in a greater reduction in albuminuria compared to ACEI and calcium channel blocker (CCB), however GFR significantly declined in ACEI and diuretic group and superiority between diuretics and CCB in combination with ACEI remains controversial. In addition the effect of combination antihypertensive therapy with ARB has not been fully evaluated. Thus the effect to reduce albuminuria were studied between amlodipine and HCTZ in combination with losartan, ARB.

Methods: Study design was randomized control trial. Eligible subjects were hypertensive CKD patients (aged 20-79) treated with ACEI or ARB more than 2 months, BP 140/90 mmHg and above, and suspected albuminuria. Suspected albuminuria was defined as albuminuria creatinine ratio (ACR) greater than 30 mg/gCr in a single spot urinalysis, or ± and above in urine dipstick test more than 2 times within 1 year. Exclusion criteria were renal insufficiency, prescription of CCB/diuretics, cardiovascular events within 6 months, abnormal liver function, and uncontrolled diabetes/hyperuricemia within 3 months. Written informed consent were obtained from all patients. This study was approved by the ethical committee and registered to UMIN (ID: 000004062). Patients were randomly assigned to group A (losartan and amlodipine) or B (compounding agent of losartan and HCTZ 12.5mg) for 6 months.

Results: 48 and 46 patients were assigned to group A and B. There was no significant difference in patient characteristics between 2 groups at baseline, and BP were well controlled in both groups. ACR were decreased in both groups at 3 and 6 months without statistical significance. Among patients with ACR 30mg/gCr and above, ACR was significantly decreased in group B compared to A at 3 and 6 months (-17.5 ± 77.4 vs -56.3 ± 37.3 %, p<0.01 and -27.8 ± 63.4 vs -63.8 ± 34.0 %, p<0.01). DeGFR were not significantly different in 2 groups.

Conclusions: Compounding agent of losartan and HCTZ was superior to losartan and amlodipine treatment in hypertensive CKD patients with albuminuria.

Funding: Private Foundation Support

TH-OR037

Blood Pressure and Renal Outcomes in Diabetic Kidney Disease: Results from the VA NEPHRON-D Trial David J. Leehey,¹ Jane Hongyuan Zhang,² Nicholas Emanuele,¹ Adam Whaley-Connell,³ Paul M. Palevsky,⁴ Robert F. Reilly,⁵ Peter Guarino,² Linda F. Fried,⁴ Edward Hines, Jr. Veterans Affairs (VA) Hospital, Hines, IL; ²Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT; ³Harry S. Truman Memorial VA Hospital, Columbia, MO; ⁴VA Pittsburgh Healthcare System, Pittsburgh, PA; ⁵VA North Texas Healthcare System, Dallas, TX; ⁶VA NEPHRON-D Study Group.

Background: Proteinuric diabetic kidney disease (DKD) frequently progresses to end-stage renal disease (ESRD). Control of blood pressure (BP) delays progression, but the optimal BP to improve outcomes remains unclear. The objective of this analysis was to evaluate the relationship between BP and renal outcomes in proteinuric DKD.

Methods: BP data from all 1448 randomized participants in the VANEPHRON-D study were included in a post-hoc analysis. The effects of mean on-treatment BP on the primary endpoint (decline in the estimated GFR (eGFR), ESRD, or death), renal endpoint (decline in eGFR or ESRD), rate of eGFR decline, and mortality were measured.

Results: In univariate analyses, both mean systolic BP (SBP) and mean diastolic BP (DBP) were strongly associated (p < 0.001) with the primary endpoint. After multivariate adjustment, the hazard of developing the primary endpoint increased as mean SBP rose from < 120 to > 150 mmHg (p=0.018); a significant increase in hazard ratio was seen when mean SBP was > 140 mmHg. There was also a significant effect of mean DBP on the hazard of developing the primary endpoint (p=0.005), with an increase in hazard ratio when mean DBP was > 80 mmHg. Associations between BP and both renal endpoint and rate of eGFR decline were similar to those with the primary endpoint. No effect of BP on mortality was observed, possibly because of the limited number of mortality events.

Conclusions: In patients with proteinuric DKD, mean SBP > 140 mmHg and mean DBP > 80 mmHg were associated with worse renal outcomes.

Funding: Veterans Administration Support

TH-OR038

Hemoglobin (HGB) Response in a Phase 2b Study of AKB-6548 for the Treatment of Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Bruce S. Spinowitz,¹ Pablo E. Pergola,² Volker H. Haase,³ Tasha M. Farmer,⁴ Charlotte S. Hartman,⁴ Bradley J. Maroni,⁴ New York Hospital Queens, Flushing, NY; ²Renal Associates PA and Univ of Texas Health Sciences Center, San Antonio, TX; ³Vanderbilt Univ, Nashville, TN; ⁴Akebia Therapeutics, Inc., Cambridge, MA.

Background: AKB-6548 is a novel, once-daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) that preferentially stabilizes HIF-2α. Studies have shown AKB-6548 produces physiologic increases in erythropoietin, enhances iron mobilization and utilization, and produces a dose dependent increase in HGB.

Methods: A randomized, double-blind, placebo-controlled study assessed HGB response of AKB-6548 over 20 weeks in CKD subjects with anemia. 210 subjects were enrolled into one of 3 groups: 1) ESA naïve with HGB \leq 10.5 g/dL, 2) previously treated with ESA with HGB \leq 10.5 g/dL, or 3) actively treated with ESA with HGB \geq 9.5 and \leq 12.0 g/dL, and randomized (2:1) to once daily AKB-6548 or placebo. Primary endpoint was percent of subjects with mean HGB of \geq 11.0 g/dL or increase in HGB by \geq 1.2 g/dL from baseline.

Results: Overall, 54.9% of AKB-6548 vs. 10.3% of placebo subjects met the primary endpoint (p=0.0001) and mean change in HGB at end of treatment was 0.84 g/dL in the AKB-6548 group as compared to 0.02 g/dL in the placebo group (p=0.0054 at Week 2, p<0.0001 all time points Week 4 and beyond). HGB responses in the Naïve and Previously Treated groups were similar to each other and the overall group. In subjects converting from active ESA, AKB-6548 maintained a stable HGB throughout the study. HGB response with AKB-6548 was associated with an increase in reticulocytes and TIBC, and a decrease in serum hepcidin and ferritin across all three treatment groups. AKB-6548 was generally well tolerated and overall adverse events were balanced between treatment groups (74.6% vs. 73.6%).

Conclusions: AKB-6548, a novel HIF-PHI being developed for the treatment of anemia of CKD, raised and maintained HGB, while increasing iron mobilization and utilization, providing a more physiologic approach to the treatment of renal anemia. This study forms the basis for future Phase 3 studies.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

TH-OR039

Anemia Correction with Roxadustat Improves Health Related Quality of Life (HRQOL) in Chronic Kidney Disease (CKD) Patients Lynda Szczech, Stefan Hemmerich, Anatole Besarab, Khalil Georges Saikali, Lona Poole, Kin-Hung Peony Yu, Thomas B. Neff. FibroGen, San Francisco, CA.

Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat is being developed for treatment of CKD anemia. This analysis of two phase 2 trials was undertaken to assess the effect of roxadustat on HRQOL in non-dialysis (NDD) and dialysis dependent (DD) CKD.

Methods: HRQOL was assessed by SF-36 and FACT-An questionnaires in efficacy-evaluable populations in 2 open-label studies, CKD-NDD (041) and ESA-naïve incident

CKD-DD (053). HRQOL was assessed at baseline (BL), 8 and 16 wks [end of treatment (EOT)] in 041 and at BL, 8 and 12 wks (EOT) in 053 [mean±SE change from BL (Δ)]. Missing data were imputed by last observation carried forward.

Results: Data from 141 subjects with CKD-NDD and 55 subjects with CKD-DD were available. In both populations, SF-36 physical component summary and FACT-An scores improved compared to BL (p=0.005 & 0.001, CKD-NDD; p=0.01 & 0.02, CKD-DD). SF-36 vitality norm-based domain scores (NBDS) and FACT-An anemia score increased by an average of >4 points. Benefits were seen particularly among those with low BL scores. In Study 053, subjects with BL SF-36 Physical Functioning NBDS <35 experienced a mean increase of 8.7 (p=0.005) and those with BL Vitality NBDS <50 increased by 6.7 (p<0.0001). Subjects with BL FACT-An Anemia score <55 increased 10.3 (p=0.0001), and those with BL FACT-An Total Score <135 increased 16.0 (p=0.0005).

Population (Study) (n)	Instrument	HRQOL Domains	Baseline	Δ at EOT	P-value
NDD (041) (n=141)	SF-36	Physical Functioning NBDS Vitality NBDS	37.7±1.0 48.1±1.1	1.4±0.7 4.3±0.9	0.04 <0.0001
	FACT-An	Physical Well Being Anemia	21.7±0.4 54.8±1.3	1.0±0.3 4.3±1.0	0.0004 <0.0001
DD (053) (n=55)	SF-36	Physical Functioning NBDS Vitality NBDS	40.0±1.4 47.3±1.5	3.9±1.0 3.7±1.2	0.0002 0.003
	FACT-An	Physical Well Being Anemia	19.3±0.8 52.4±2.1	1.6±0.7 4.9±1.6	0.03 0.003

Conclusions: Roxadustat consistently improved mean HRQOL sub- and summary scores. Improvements were greatest in subjects with low BL scores. Roxadustat is currently being evaluated in phase 3 trials in which HRQOL is further explored.

Funding: Pharmaceutical Company Support - FibroGen

TH-OR040

Hepcidin Response to Intravenous (IV) or Oral Iron in the Randomized FIND-CKD Trial of Patients with Non-Dialysis Dependent CKD (ND-CKD) Carlo A. Gaillard,¹ Andreas H. Bock,² Fernando Carrera,³ Kai-Uwe Eckardt,⁴ David B. Van Wyck,⁵ Sukhvinder Singh Bansal,⁶ Bernard Roubert,⁷ Maureen Cronin,⁷ Simon D. Roger,⁸ Iain C. Macdougall,⁶ Uni. of Groningen, Groningen, Netherlands; ²Kantonsspital, Aarau, Switzerland; ³Eurodial, Leiria, Portugal; ⁴Uni. of Erlangen-Nuremberg, Erlangen, Germany; ⁵Davita Healthcare Partners, Denver, CO; ⁶King's College Hospital, London, United Kingdom; ⁷Vifor Pharma Ltd, Glattbrugg, Switzerland; ⁸Renal Research, Gosford, NSW, Australia.

Background: Hepcidin is the key regulator of iron homeostasis but its temporal response to iron therapy, and response to IV vs oral iron therapy, are unexplored.

Methods: In the 56-week, open-label, multicenter, prospective, randomized FIND-CKD study, 626 anemic patients with ND-CKD and iron deficiency not receiving ESA therapy were randomized (1:1:2) to IV ferric carboxymaltose (FCM), targeting higher (400–600µg/L) or lower (100–200µg/L) ferritin, or oral iron. In a subset of patients enrolled in the UK, serum hepcidin was measured centrally by a validated liquid chromatography tandem mass spectrometry assay.

Results: 61 patients provided baseline and ³¹P post-baseline hepcidin values. Mean (SD) baseline hepcidin level was 4.0(3.5), 7.3(6.4) and 6.5(5.6) ng/mL in the high ferritin FCM, low ferritin FCM and oral iron groups. The mean (SD) endpoint value (i.e. the last post-baseline value) was 26.0(9.1), 15.7(7.7) and 16.3(11.0) ng/mL, respectively. The increase in hepcidin from baseline was smaller with low ferritin FCM and with oral iron vs high ferritin FCM up to week 52 (all p<0.05). Correlations were significant between the post-baseline increases in hepcidin and ferritin (r=0.70, p<0.0001), TSAT (r=0.42, p=0.0008) or hemoglobin (r=0.30, p=0.0295) using endpoint values across all groups. The increase in hepcidin levels over the 12-month study generally mirrored the cumulative iron dose in all groups.

Conclusions: These prospective, 1-year data from a randomized trial show that hepcidin levels rose in response to either IV or oral iron therapy, but that the speed and extent of the rise was greatest with IV iron targeting a higher ferritin level. Oral iron and IV iron targeting a lower ferritin level resulted in similar hepcidin levels.

Funding: Pharmaceutical Company Support - Vifor Pharma, Glattbrugg, Switzerland

TH-OR041

Isolation of Live Nephron Progenitors Cells Expressing Six2+ and Cited1+ from Human Embryonic Kidneys and Amniotic Fluid Laura Perin,¹ Stefano Da Sacco,¹ Astgik Petrosyan,¹ Matthew Edward Thornton,² Brendan Grubbs,² Roger E. De Filippo.¹ ¹Urology, Children's Hospital Los Angeles, Los Angeles, CA; ²Univ of Southern California, Los Angeles, CA.

Background: In the developing kidney, formation of new nephrons relies on a small population of self renewing progenitors co-expressing Six2 and Cited1. Unfortunately, despite their essential role in the renal formation, direct isolation and expansion of human nephrogenic progenitor cells has not been successfully achieved and our knowledge is mostly based on rodent models. We have identified a small niche of Six2+Cited1+ cells within human amniotic fluid (hAF) and in this project we report for the first time the isolation and characterization of this population from both hAF and human embryonic kidneys (hEK).

Methods: Six2+ Cited1+ live cells from hAF and hEK were sorted using Smartflair RNA probes. RNAseq on positive and negative selections was performed immediately after sorting to evaluate their genetic profile without the confounding effects of cell culture. Integration into developing renal structures was assessed. Potential for a glomerular fate was tested by differentiation toward podocyte lineage.

Results: Six2+Cited1+ cells were successfully isolated from hEK (0.17%) and hAF (0.2%). RNASeq confirmed expression of genes such as Six2, Cited1, Osr1, suggesting a nephrogenic signature. Clones and subclones were derived and expanded for many passages in specific nephrogenic media maintaining Six2 and Cited1 expression. These populations were able to integrate in developing renal structures when co-cultured with dissociated/re-aggregated hEK. Differentiation into podocyte-like cells was evaluated by expression of specific markers including WT1 and nephrin, deposition of collagen IV alpha3-4-5 and functional response to angiotensin II.

Conclusions: Our preliminary results suggest the possibility of deriving and expanding for the first time, Six2+Cited1+ cells from hEK as well as from an exogenous source of cells like hAF without genetic manipulation. This system might represent an accessible and novel source of nephron progenitors that can guide studies of renal cell specification, thus increasing our knowledge on human renal development.

Funding: Private Foundation Support

TH-OR042

Novel Noninvasive Source of Kidney Progenitor Cells with Potential to Differentiate into Podocytes Fanny Oliveira Arcolino,¹ Silvia Zia,¹ Katharina Held,¹ Joris Vriens,¹ Elli Papadimitriou,³ Benedetta Bussolati,³ Anke Raaijmakers,^{1,2} Karel Allegaert,¹ Jan A. DePreest,¹ Jaan Toelen,^{1,2} Lambertus P.W.J. Van den Heuvel,^{1,4} Elena N. Levchenko.^{1,2} ¹Development and Regeneration, Catholic Univ Leuven, Leuven, Belgium; ²Dept of Pediatrics, Univ Hospitals Leuven, Leuven, Belgium; ³Dept of Molecular Biotechnology and Health Sciences, Univ of Turin, Turin, Italy; ⁴Dept of Pediatric Nephrology, Raaboud UMC, Nijmegen, Netherlands.

Background: Recently, subpopulations of cells from amniotic fluid (AF) and adult urine were shown to express kidney progenitor cell features with multipotential of differentiation. We aimed to study urine of preterm neonates born before the completion of nephrogenesis for the presence of kidney neonatal stem/progenitor cells (nKSPC) and the ability of these cells to differentiate into functional podocytes.

Methods: Clonal cell lines were characterized as KSPC and KSPC-derived podocytes by gene expression analyses using quantitative rt-PCR and protein expression by flow cytometry and immunofluorescence. Podocytes differentiation was induced by incubation of cells in medium containing retinoic acid and vitamin D. Function of podocytes was assessed by albumin endocytosis and calcium influx assays. Results were compared to conditionally immortalized podocytes (ciPodocytes) and podocytes differentiated from amniotic fluid stem cells (AFSC) and adult urine progenitor cells (aUPC).

Results: nKSPCs expressed mesenchymal stem cell markers and kidney progenitor cell markers as SIX2, CD24, CD133, Vimentin and CITED1 maintaining these characteristics up to passage 17. nKSPC-derived podocytes presented mesenchymal-to-epithelial transition and acquired arborized cytoplasm comparable to ciPodocytes. Cells presented up-regulation of podocyte-specific genes and proteins and were able to endocytose albumin and uptake calcium via transient receptor potential cation channel, subfamily C, member 6 (TRPC6).

Conclusions: Preterm neonatal urine represents a novel noninvasive source of self-renewing kidney progenitor cells with potential to differentiate into functional podocytes and may be a promising tool for regenerative medicine aiming kidney repair and a model for studying renal disease.

TH-OR043

Pluripotent, Non-Tumorigenic, Human Muse Cells Integrate into Glomerulus to Recover Function in a Chronic Kidney Disease Mouse Model Nao Uchida,¹ Naonori Kumagai,¹ Yoshiaki Kondo,² Shigeo Kure.¹ ¹Pediatrics, Tohoku Univ School of Medicine, Sendai, Miyagi, Japan; ²Healthcare Services Management, Nihon Univ School of Medicine, Tokyo, Japan.

Background: As availability of transplantable kidneys is limited, stem/progenitor cell therapy replenishing new glomerular cells may be helpful; several pluripotent stem cell types have been studied, including non-tumorigenic Muse cells, collectable from the bone marrow as stage-specific embryonic antigen (SSEA)-3(+) cells. Here the effect of intravenously injected human Muse cells on a chronic kidney disease (CKD) mice model was evaluated.

Methods: Muse SSEA-3(+) and non-Muse SSEA-3(-) cells were isolated from bone marrow-derived mesenchymal stem cells (MSCs) using fluorescence-activated cell sorter. CKD was induced by intravenously injecting doxorubicin into severe combined immunodeficient (SCID), Balb/c mice, mimicking human focal segmental glomerulosclerosis. A week later, 2×10^4 cells of Muse, or non-Muse cells, or sterile vehicle were infused via the tail vein.

Results: In vitro, Muse cells showed specific migration activity toward the serum from CKD mice. After three weeks of renal lineage induction, Muse cells expressed WT1, while no signals were detected in non-Muse cells. In CKD-SCID mice, intravenously injected Muse cells migrated and integrated into the glomerulus, replacing a certain number of glomerular cells by differentiating into WT1-, podocin-, megsin-, and CD31-positive cells. This led to functional recovery, particularly in creatinine clearance at 7 weeks. In CKD-Balb/c mice, WT1(+) and CD31(+) Muse cells were recognized in the glomerulus at 5 weeks without immunosuppressant, whereas majority of these were rejected by 7 weeks. Significant functional recovery was observed for urine protein, creatinine clearance, and plasma creatinine compared with the vehicle group at 5 weeks. Attenuated glomerular sclerosis, interstitial fibrosis, and podocyte loss was noted in both models.

Conclusions: Muse cells are unique from other pluripotent stem cells in their high integration rate into the damaged glomerulus simply by intravenous injection, non-tumorigenicity, and differentiation in vivo into glomerular cells that mediate functional recovery.

Funding: Pharmaceutical Company Support - Clio inc., Government Support - Non-U.S.

TH-OR044

Patient-Derived Induced Pluripotent Stem Cell (iPSC) Modeling of Genetic Renal Disease (GRD) Andrew John Mallett,^{1,3,4} Barbara Maier,^{1,2} Pei Xuan Er,^{1,2} Minoru Takasato,^{1,2} Jane Sun,⁵ Ernst J. Wolvetang,⁵ Stephen I. Alexander,⁶ Cas Simons,¹ Melissa H. Little.^{1,2,7} ¹Inst for Molecular Bioscience, The Univ of Queensland, Brisbane, Australia; ²Murdoch Children's Research Inst, Melbourne, Australia; ³Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane and Women's Hospital, Australia; ⁴School of Medicine, UQ, Australia; ⁵Australian Inst of Bioengineering and Nanotechnology, UQ, Australia; ⁶Dept of Nephrology, Children's Hospital at Westmead, Australia.

Background: The reprogramming of somatic cells into iPSCs provides potential to model human diseases in vitro, as has been demonstrated in the cardiac and neuronal fields. Nephrology has not yet benefited from these advancements primarily due to lack of a robust kidney differentiation protocol.

Methods: We aimed to generate and characterize iPSCs from patients with different GRDs. Families with clinically diagnosed GRD were recruited from a Renal Genetics Clinic for concurrent research-based massively parallel sequencing (MPS) and iPSC generation. One affected and unaffected member of each family was recruited. To establish transgene-free iPSC lines, fibroblasts were isolated via skin biopsy and reprogrammed using non-integrating Sendai virus (21day protocol).

Results: 7 families (14 participants) were recruited with a variety of GRD diagnoses. Fibroblast culture was successful in 6 families. Established iPSC lines have typical hESC-like morphology and express pluripotency markers after 4 (TRA1-60) and 15 passages (NANOG). Moreover, iPSC lines have cleared the Sendai virus vectors, as confirmed by RT-PCR after only 7 passages. G-band analysis of 2 lines from each isolation confirmed that each of the derived lines had maintained the normal karyotype after reprogramming. Paired patient and control iPSC are being redifferentiated towards kidney employing an established protocol. Renal organoids will be analyzed using IF, FACS and transcriptional profiling.

Conclusions: Patient derived iPSC have been generated and renal redifferentiation commenced. We hope to uncover the biological consequences of novel genetic variants causing GRD as identified via MPS, thereby beginning to explain patient phenotypes and disease pathogenesis.

Funding: Private Foundation Support

TH-OR045

Multi-Segmented Nephron Organoids Derived from Human Pluripotent Stem Cells Model Kidney Development and Injury Ryujii Morizane, Albert Q. Lam, Benjamin S. Freedman, Seiji Kishi, M. Todd Valerius, Joseph V. Bonventre. *Medicine, Brigham and Women's Hospital, Boston, MA.*

Background: Kidney differentiation from human pluripotent stem cells (hPSCs) is limited by the inability to generate complete nephrons, which has inhibited efforts to model kidney development and disease. One important problem is the low efficiency of SIX2+ nephron progenitor cell (NPC) generation by published protocols. We hypothesized that more precise recapitulation of the stages of *in vivo* metanephric development with hPSCs would result in the generation of more pure populations of NPCs with the capacity to form nephrons.

Methods: We developed a chemically defined protocol to direct the differentiation of hPSCs into NPCs that form multi-segmented nephron structures in 2D and 3D organoids, mimicking the stages of *in vivo* nephrogenesis: late primitive streak (PS), posterior intermediate mesoderm (IM), SIX2+ metanephric mesenchyme (NPCs), renal vesicles (RVs), and nephrons. hPSC-derived nephron organoids were tested for the ability to model kidney development and injury.

Results: Efficient differentiation of hPSCs into late PS followed by WT1+HOXD11+ posterior IM enabled the induction of SIX2+SALL1+WT1+PAX2+ NPCs with ~90% efficiency within 9 days. Treatment with Wnt and FGF signals induced differentiation into PAX8+LHX1+ RVs, which spontaneously differentiated into multi-segmented nephron

structures containing podocytes (Nephrin+PODXL+WT1+, foot process formation shown by EM), proximal tubules (LTL+CDH6+AQP1+), loops of Henle (CDH1+THP+), and distal tubules (CDH1+BRN1+) in an organized, contiguous arrangement in both 2D and 3D culture. Inhibition of Notch signaling during organoid formation resulted in specific defects in proximal tubules, indicating that nephron organoids model kidney development. Moreover, treatment with the nephrotoxins, gentamicin or cisplatin, induced KIM-1 expression in LTL+ tubules in a dose dependent manner.

Conclusions: We developed a novel method to differentiate hPSCs into NPCs with ~90% efficiency within 9 days of differentiation. NPCs formed organized, contiguous, multi-segmented nephron structures in 2D and 3D organoids, which could be used to model kidney development and injury.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR046

A Developmentally Plastic Adult Mouse Kidney Cell Line Spontaneously Generates Multiple Adult Kidney Structures Tomoko Obara. *Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) in the US. Although the precise causes are not well understood, DN is characterized by fibrosis within the glomeruli and tubular interstitium. Dialysis and kidney transplantation are currently the only successful therapies for ESRD. The renal transplantation approach suffers from donor shortages and complications of immune rejection. New therapies for renal replacement are needed. At this time the derivation of kidney lineage cells from either mouse or human induced pluripotent stem cells leads to limited nephron-like structures. To date, no one has been able to regenerate or model functional nephrons from normal or diseased kidneys.

Methods: In this study, we explored the utility of the absence of the epigenetic regulator ARID3a in an adult mouse kidney cell line (KKPS5) for generating nephron structures in both *in vitro* and *in vivo* model systems.

Results: We discovered that KKPS5 acquires renal progenitor surface markers as an alternative cell source and further develop into multicellular nephron-like structures within a few days in 3-D matrigel. Moreover, when these cells are engrafted into immunocompromised medaka adult kidney they formed mouse nephron structures. We are unaware of the existence of other cell lines that exhibit this unique multipotent property.

Conclusions: These data implicate KKPS5 cells provide a unique advantage for exploring kidney development. Moreover, we predict our findings will be relevant for future therapeutic manipulations in kidney disease.

Funding: Private Foundation Support

TH-OR047

Decellularized Renal Extracellular Matrix Scaffolds Serve as 3D Biological Templates for Regeneration of Nephron Structures by Human Kidney Cells Joseph S. Uzarski,¹ Carol Ann Deaton,² Heather Hilary Ward,² Angela Wandinger-Ness,³ Jason Wertheim.¹ ¹Dept of Surgery, Northwestern Univ Feinberg School of Medicine, Chicago, IL; ²Dept of Internal Medicine, Univ of New Mexico HSC, Albuquerque, NM; ³Dept of Pathology, Univ of New Mexico HSC, Albuquerque, NM.

Background: An alternative to current renal replacement therapy options aims to utilize renal tissues developed *ex vivo* using patient-derived cells for implantation to augment or replace failing kidneys. Our objective was to characterize the phenotypic effects of culturing particular populations of human nephron-derived cells within 3D decellularized renal extracellular matrix scaffolds (ECMs) as a step toward regenerating functional nephrons.

Methods: Rat kidneys were perfused antegrade with detergents to completely remove the autologous cells. The resultant renal ECMs were injected arterially with select populations of immortalized or primary human renal epithelial or progenitor cells (RPC) and cultured using specialized perfusion bioreactors. We compared proliferation, metabolism, gene expression, and morphological adaptation in cells derived from different nephron components.

Results: Epithelial cells infused into ECMs dispersed in periglomerular tubules. Distal tubule-derived RCTE cells formed patent, polarized E-cadherin+ tubular structures, and steadily proliferated over 1 week of perfusion culture. Proximal tubule-derived RPTE cells similarly distributed in the tubular space, with some cells found in glomeruli and Bowman's capsules. Both epithelial lines showed downregulation of EMT markers S100A4 and vimentin after culture within renal ECMs. After 7 days, kidney-specific-cadherin was upregulated in RPTE cells. Injury markers KIM-1 and CD24 were downregulated in RCTE cells alone. Cadaver-derived CD133/1+ RPC formed tubular structures within renal ECMs, and gradually decreased proteolytic KIM-1 shedding over 7 days.

Conclusions: We conclude that renal ECMs have inductive properties that may eventually be used in concert with exogenous biological or chemical stimuli to promote differentiation of stem or progenitor cells into mature, functional nephron-specific epithelial cells.

Funding: Private Foundation Support

TH-OR048

Systems Biology of Polycystic Kidney Disease Suggests It Is a Metabolic Disease Luis F. Menezes, Fang Zhou, Gregory G. Germino. *NIDDK, National Insts of Health, Bethesda, MD.*

Background: The major gene mutated in autosomal dominant polycystic kidney disease was identified over 20 years ago yet its function remains poorly understood. We have used a systems-based approach to examine the effects of acquired loss of *Pkd1* in an orthologous mouse model of human ADPKD as the kidneys transition from normal to cystic state.

Methods: A total of 135 *Pkd1*^{cko};Tg(Cre/Esr1) mice animals in which *Pkd1* knockout was induced by tamoxifen at P40 were harvested between P100 and P210 and kidney/body weight curves were fitted for males and females separately. Gene expression in 80 kidneys was analyzed with Illumina arrays, followed by differential gene expression and network analysis. Predictions were tested using: 1) metabolite and complex lipids profiling in 14 male kidneys; 2) diet manipulations in 33 *Pkd1*^{cko};Tg(Cre/Esr1) mice induced at P7 and harvested at P21 and in 52 *Pkd1*^{cko}; Tg(Cdh16-cre) mice harvested at P14.

Results: We found in the P40-induction model that females were significantly protected from cystic kidney disease but had more severe cystic liver disease. Furthermore, the transcriptional profiles of normal male and female kidneys differed almost as much as those of normal and cystic kidneys and the differentially expressed gene modules were enriched for genes involved in lipid metabolism. Gene ontology of the differentially expressed genes common to both sexes showed enrichment for metabolic pathways. Metabolic and lipid profiling confirmed differences in cystic kidneys. We also found that the P7- and P40-induced mice share common transcriptional signatures, suggesting similar mechanisms of cyst initiation and growth. Finally, we showed that a modest change in the lipid composition of diet could significantly affect the progression of disease.

Conclusions: Gene expression and network analysis accompanied by global metabolites and complex lipid profiling suggested that metabolic status could be a major regulator of disease susceptibility. By manipulating the lipid content of mouse diets we corroborate this hypothesis and suggest that metabolic pathways are a major component of polycystic kidney disease, possibly underlying some of the sex effects.

Funding: NIDDK Support

TH-OR049

Smyd2 Synergistically Activates STAT3 and NF-κB and Represses p53 to Promote Cyst Growth Xiaoyan Li, Lucy Fan, Xia Zhou, James P. Calvet, Xiaogang Li. *Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: Protein methylation has emerged as a post-translational modification that exerts key roles in defining protein functions, at the level of signaling mediators and at the level of epigenetic regulation of transcription, in polycystic kidney disease (PKD). Smyd2, as a SET-domain-containing histone (lysine) methyltransferase, methylates both histone and non-histone proteins, including PKD associated p53, Rb and HSP90. However, the roles and underlying mechanisms of Smyd2 in regulating cyst development remain unknown.

Methods: To understand the role of Smyd2 in cyst growth *in vivo*, we generated *Pkd1* and *Smyd2* double conditional knockout mice (*Pkd1*^{fllox/fllox}; *Smyd2*^{fllox/fllox}; *Ksp-Cre*), and we treated *Pkd1*^{int/mt} mutant mice with the Smyd2 specific inhibitor, AZ505. To identify novel Smyd2 target genes involved in cystogenesis, we performed ChIP-seq analysis.

Results: We found that knockout of Smyd2 or inhibition of Smyd2 with AZ505 delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in *Pkd1* mutant mice (all *p* < 0.01). We further found that *Pkd1* and *Smyd2* double knockout mice lived longer, to a mean age of 25 days, while *Pkd1* knockout mice died at a mean age of 17 days (*p* < 0.001). We found that STAT3 and the p65 subunit of NF-κB are novel non-histone substrates of Smyd2, which methylates and activates them leading to increased cystic epithelial cell proliferation and survival. Smyd2 also regulates cystic epithelial cell apoptosis by repressing p53 activity and expression. Further, we identified novel Smyd2 target genes, including the primary cilia associated Ah1 (Abelson helper integration site 1) gene and HYDIN gene, by ChIP-seq analysis, which may connect Smyd2 signaling to the ciliopathy hypothesis in PKD.

Conclusions: Smyd2 promotes renal cyst growth in ADPKD through STAT3 and NF-κB signaling as well as p53 and ciliopathy associated signaling. Targeting Smyd2 in cystic renal epithelial cells may be a viable new therapy for ADPKD.

Funding: NIDDK Support

TH-OR050

Novel Insights into Polycystin-1 Function from the *Xenopus* Pronephric Kidney Oliver Wessely, Uyen Tran. *Cellular & Molecular Medicine, Cleveland Clinic, Cleveland, OH.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by mutations in Polycystin-1 (PKD1) or Polycystin-2 (PKD2). PKD1 is a large transmembrane, mechanoreceptor-like protein that forms multiprotein complexes at focal adhesions, cell-cell junctions and cilia. It is thought to transmit a signal to PKD2, which in turn releases calcium. Studies in mouse and other model organisms have led to the prevailing hypothesis that Polycystin-1 and Polycystin-2 regulate a range of cellular pathways, which together ensure that renal epithelial tubules establish and maintain a correct diameter. While there has been significant progress over the years, the molecular mechanism of PKD1 action is still obscure.

Methods: To address the function of PKD1 we used the *Xenopus* pronephros as a model for PKD. We knocked down *Pkd1* expression using antisense morpholino oligomers and characterized the kidney by morphology, histology, immunofluorescence and *in*

situ hybridization. To identify functional domains we subsequently re-expressed Pkd1 and fragments, thereof. Finally, we performed molecular analysis and binding assays to understand the underlying mechanism.

Results: *Xenopus* embryos lacking Pkd1 develop a PKD phenotype characterized by the formation of fluid-filled edema, dilated tubules, randomization of the mitotic spindle angle and increased DNA instability. This phenotype could be restored by re-expression of the intracellular domain of Pkd1. Moreover, structure-function analysis demonstrate that the G-protein binding domain is critically important for this activity. Based on this result, we performed binding studies with all the G-protein alpha subunits and demonstrated that Pkd1 recruits a very select subset of G-protein alpha subunits. The importance of this interaction was then subsequently validated by epistasis experiments in *Xenopus*.

Conclusions: Together, the data support the hypothesis that the intracellular domain of PKD1 recruits G-proteins and that this interaction is critical for its function.

Funding: NIDDK Support

TH-OR051

A Forward Genetic Screen Identifies a Calcium-Regulated Mitochondrial Metabolite Carrier as a Downstream Target of Polycystin-2 Alexis Hoffer,¹ Claudia Seger,¹ Terry J. Watnick,² Michael Kottgen.¹ ¹Dept of Medicine, Univ Medical Center Freiburg, Germany; ²Univ of Maryland.

Background: Polycystin-2 (aka TRPP2) is a cation channel that localizes to primary cilia and regulates developmental programs ranging from tubular morphogenesis to establishment of left-right (LR) asymmetry. Loss of TRPP2 results in polycystic kidney disease and randomized LR asymmetry. TRPP2-mediated calcium signals are thought to regulate morphogenesis. But the molecular events translating these calcium signals into morphogenetic programs are unknown.

Methods: To identify evolutionarily conserved core constituents of the TRPP2 signaling pathway, we conducted an unbiased forward genetic screen in *D. melanogaster* for mutants that phenocopy the TRPP2 loss of function phenotype. To test the conservation of newly identified genes in vertebrates, the function of candidate genes was investigated in zebrafish. The molecular function of genes was studied in mIMCD3 cells using TALEN-mediated gene deletion in combination with metabolomics.

Results: We identified a calcium-dependent mitochondrial metabolite carrier (MC) as a downstream target of TRPP2 in a large-scale mutagenesis screen for mutants that phenocopy loss of TRPP2 in *D. melanogaster*. Calcium regulation of this MC appears to be critical, since loss of MC in flies was rescued by wt MC, but not by MC with EF-hand mutations, which abolish calcium binding. In zebrafish, TRPP2 is essential for the establishment of LR asymmetry. We show that MC is also required for the determination of LR asymmetry in zebrafish. Rescue experiments in flies and zebrafish suggest that MC acts downstream of TRPP2, which is consistent with the calcium-dependence of this carrier. To investigate the molecular function of MC and TRPP2, we deleted the genes in mIMCD3 cells. Metabolomic analyses showed that TRPP2- and MC-deficient cells display impaired mitochondrial metabolism and concordant changes of several metabolites which may contribute to morphogenetic signaling processes.

Conclusions: We show that a calcium-dependent mitochondrial metabolite carrier acts in a conserved pathway linking TRPP2-mediated ciliary calcium signals to mitochondrial metabolism *in vivo*.

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TH-OR052

Modeling Polycystic Kidney Disease Cystogenesis with Genome-Modified Human Pluripotent Stem Cells Benjamin S. Freedman,^{1,2,3,5} Theodore I. Steinman,^{1,2,4,5} Jing Zhou,^{1,2,4,5} Joseph V. Bonventre.^{1,2,4,5} ¹Brigham and Women's Hospital; ²Harvard Medical School; ³Univ of Washington School of Medicine; ⁴Beth Israel Deaconess Medical Center; ⁵Harvard PKD Center.

Background: Human pluripotent stem cells (hPSCs) can self-renew extensively and differentiate into diverse tissues, including tubules expressing kidney markers. To date, however, no study has demonstrated a phenotype in these tubules relevant to kidney disease. Using the CRISPR/Cas9 genome editing system, we tested the ability of hPSC-derived kidney cells to model features of polycystic kidney disease (PKD) cystogenesis.

Methods: Cas9 nuclease and guide RNAs targeting *PKD1* or *PKD2* were transfected into hPSCs. Chromatogram analysis and immunoblotting indicated biallelic, frame-shift mutations at target sites and the absence of the corresponding full-length proteins. hPSCs were treated with specific growth factors to direct stepwise differentiation into kidney progenitor cells (SIX2⁺PAX2⁻) and subsequently proximal tubules (LTL⁺LRP2⁻). PKD hPSCs and derived tubules were inspected for cystogenesis phenotypes, compared to unmodified control cultures of otherwise identical genetic background.

Results: PKD hPSCs exhibited self-renewal and pluripotency characteristics comparable to isogenic controls, and differentiated into tubular organoids with similar efficiencies. Interestingly, in PKD hPSC cultures, we observed formation of large, translucent, cyst-like structures alongside tubules. Cyst-lining epithelia reacted strongly with LTL and surrounded hollow interior compartments devoid of cells. Time-lapse imaging revealed that cysts arose from a small minority of differentiating tubular structures. Importantly, isogenic control hPSCs, plated and differentiated in an identical manner to the PKD hPSCs, did not form cysts.

Conclusions: Our findings suggest that PKD-specific cyst formation from tubules can be reproducibly modeled in a minimal system *in vitro*. Cysts arise from both *PKD1*^{-/-} or *PKD2*^{-/-} hPSCs, but not from parental hPSCs of otherwise identical genetic background.

Genome-modified hPSCs represent a new, human model in which to investigate PKD pathophysiology, with potential for 'clinical trials in a dish' to evaluate candidate therapeutics.

Funding: NIDDK Support, Private Foundation Support

TH-OR053

Inactivation of Ift88 Gene Rescues the Phenotype in a Genetic Model of Autosomal Dominant Polycystic Kidney Disease Jing Zhou,¹ Wassim El-jouni,¹ Xiaogang Shen,^{1,2} Maoqing Wu,¹ Ivan Barrera,¹ Azadeh Tabari,¹ Nadeem Haque,¹ Ilyas Yambayev.¹ ¹Renal Div, Harvard Center for Polycystic Kidney Disease Research, Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; ²Nephrology Div, Zhejiang Provincial People's Hospital, Hangzhou, Zhejiang Province, China.

Background: Mutations in *PKD1* and *PKD2* genes are responsible for autosomal dominant polycystic kidney disease, the most common life threatening genetic disease in humans. The gene products polycystin-1 (PC1) and -2 (PC2) are localized to the primary cilia and function as a receptor channel complex on the primary cilia.

Methods: To create an animal model for ADPKD, we deleted an exon encoding part of the pore region of PC2 in mice using the Cre-loxP system. To test the ciliary function of polycystins, we genetically disrupted cilia in mice with a mutation in *Pkd2* by creating *Ift88* and *Pkd2* double knockout mice. Mice were induced at post-developmental stages and renal phenotypes were analyzed by histology. Western analyses and immunostaining methods were performed to evaluate protein levels and expression patterns.

Results: A protective effect in cystic lesions was observed in kidneys from *Pkd2.Ift88* double knockout mice when compared with *Pkd2* single knockouts. Disruption of PC2 was validated in both *Pkd2* single knockouts and *Pkd2.Ift88* double knockout mice. To examine if there is ciliogenesis defects due to the inactivation of PC2 and Ift88, we examine the length of cilia in kidneys from both *Pkd2* single knockout and *Pkd2* and *Ift88* double knockout mice. An increase in cilium length was detected in *Pkd2* knockout mice, compared with wild type mice. A significant reduction of the number and length of cilia were found in *Ift88* and *Pkd2* double knockout mice. *Ift88* knockout in the double knockout mice was also confirmed by western blot analyses. Comparative analyses of signaling events in both single and double knockout mice suggest the mammalian target of rapamycin (mTOR) pathway is activated in the early stage of cyst formation of *Pkd2* single knockouts and its aberrant activation is rescued in *Pkd2* knockout mice with *Ift88* inactivation.

Conclusions: Inactivation of IFT88 rescues the polycystic phenotype in a genetic mouse model of ADPKD. mTOR signal pathway, a cilium-mediated pathway, appears to be involved.

Funding: NIDDK Support

TH-OR054

Other Signaling Pathways Rapidly Compensate for Loss of mTORC1 in Driving Cystic Kidney Disease Florian Grahmmer,¹ Gerd Walz,^{1,2} Tobias B. Huber.^{1,2,3} ¹Renal Div, Univ Medical Center Freiburg, Freiburg, Germany; ²BIOSS Center for Biological Signalling Studies, Albert-Ludwigs Univ Freiburg, Freiburg, Germany; ³Center for Systems Biology (ZBSA), Albert-Ludwigs Univ Freiburg, Freiburg, Germany.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the leading monogenic cause of end-stage renal disease. In both mice and humans, cystic kidney disease is consistently linked to an activation of the mTORC1 pathway. Yet, the utility of mTORC1 inhibitors to treat patients with ADPKD remains controversial despite promising preclinical data.

Methods: To conclusively define the cell-intrinsic role of mTORC1 for cyst development, the essential mTORC1 scaffolding protein Raptor was selectively inactivated in renal tubular cells lacking cilia due to deletion of *Kif3A*.

Results: In comparison to a rapid onset of cyst formation and renal failure in mice with defective ciliogenesis alone, both renal function and overall survival were strikingly improved in mice additionally lacking *Raptor*. However, eventually these mice succumbed to cystic kidney disease despite mTORC1 inactivation. In-depth transcriptome analysis showed a rapid activation of other growth-promoting pathways, overriding the effects of mTORC1 deletion.

Conclusions: Our findings indicate that cystic kidney disease can adopt bypass mechanisms frequently observed in drug-resistant cancers. Thus future clinical trials will need to consider combinatorial or sequential therapies to improve efficacy in patients with cystic kidney disease.

Funding: Government Support - Non-U.S.

TH-OR055

ANKS3 Mutation in Nephronophthisis Patients Leads to Cilia and Cytoskeleton Defects In Vitro and In Vivo in Zebrafish Gweltas Ody,¹ Marion H. Delous,¹ Valentina Grampa,¹ Line De grande,¹ Anita Becker-heck,² Emilie Filhol,¹ Pauline Krug,³ Flora Silbermann,¹ Bertrand Knebelmann,³ Andreas W. Sailer,² Pierre Saint-mezard,² Alexandre Benmerah,¹ Sophie Saunier.¹ ¹Inserm U1163, Imagine Inst, Paris Descartes Univ, France; ²Novartis Inst for Biomedical Research, Switzerland; ³APHP Necker Hospital, France.

Background: Nephronophthisis (NPH) is a heterogeneous autosomal recessive renal ciliopathy that represents the major hereditary cause of end stage renal disease in children. Causative genes encode NPHP proteins which localize at the primary cilium and in some cases at cell-cell junctions. Among these genes, *ANKS3* is known for its implication in kidney development and mutations contribute to NPHP phenotype in humans.

Results: Using NGS, we identified a homozygous mutation (c.806 C>T, p.P269L) in *ANKS3*, in three siblings affected by late onset NPH with hepatic fibrosis. *ANKS3* encodes a SAM domain and Ankyrin repeat containing protein which interacts with ANKS6, NEK8 and NPHP3, three NPHP proteins located at the Inversin 'Invs' compartment (proximal part of the cilium) that controls essential ciliary signaling pathways during development and tissue homeostasis (Wnt/PCP). Surprisingly, ANKS3 did not localize at the Invs compartment but in apical cytoplasmic aggregates in tubular renal cells or at the basal body in fibroblasts. We provide evidence that the p.P269L mutation led to cilia length defects in patient's fibroblasts and *Anks3* knockdown IMCD3 cells, associated with disorganization of the Invs compartment. Moreover, it affects the interaction of ANKS3 with NPHP1 and led to defects in tight-junction and lumen formation in 3D culture, reminiscent of *NPHP1* knockdown. We next generated an *ANKS3* zebrafish mutant (TALEN) that exhibits laterality defects and lethality by 2-3 weeks. Analyses within the Kupffer's vesicle revealed normal number and length of cilia but motility defects likely explaining the laterality phenotype observed in mutant fish.

Conclusions: Altogether, these results indicate that ANKS3 plays a dual function, in controlling the composition of the Invs compartment and in epithelial morphogenesis, supporting the causative effect of the mutation in the NPH patients.

Funding: Pharmaceutical Company Support - Novartis

TH-OR056

SDCCAG8 Regulates Ciliogenesis by Mediating Endosomal Vesicle Docking to the Basal Body Merlin Airik,¹ Rannar Airik,¹ Jang W. Cho,¹ Markus Schueler,¹ Friedhelm Hildebrandt,^{1,2} ¹Div of Nephrology, Boston Children's Hospital, Boston, MA; ²Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Mutations in *SDCCAG8* gene cause a retinal-renal ciliopathy with BBS-like features in affected humans (1). Our previous characterization of the orthologous *Sdccag8*-mouse model recapitulated the retinal-renal degeneration phenotypes and identified impaired DNA damage response signaling as an underlying disease mechanism in the kidney (2). However, several other phenotypic features of *Sdccag8*^{mut/mut} mice remained unexplored. Here we have extended our studies of *SDCCAG8* function.

Methods: Immunofluorescence analysis was performed on mouse embryo cryosections and hTERT-RPE cell line. To identify *SDCCAG8* interacting proteins at the centrosome we employed a proteomic strategy using stable isotope labeling with amino acids in cell culture (SILAC). Co-immunoprecipitation assay was performed in HEK293 cells.

Results: *Sdccag8*^{mut/mut} mice have defective neural tube patterning and structural abnormalities of the skeleton, suggesting impaired Hedgehog (Hh) signaling. In cell culture studies we show that loss of *Sdccag8* affects ciliogenesis and interferes with Hh signaling. Using SILAC-assay combined with co-immunoprecipitation and immunofluorescence studies we demonstrate that *SDCCAG8* interacts with centriolar satellite (OFD1, AZI1), endosomal sorting complex proteins (RABEP2, ERC1) and non-muscle myosin motors (MYH9, MYH10, MYH14).

Conclusions: *SDCCAG8* function is required for ciliogenesis and Hedgehog signaling. Our study identifies several novel components of the basal body, that interact with *SDCCAG8*. Together, our analysis suggests that *SDCCAG8* function at the basal body is required for coupling endosomal vesicles and molecular motors to facilitate ciliogenesis.

Funding: NIDDK Support, Private Foundation Support

TH-OR057

Characterization of Cystic Kidneys in Mice Deficient in the Polarity Proteins DLG1 and CASK Steven Daniel Funk, Jinzhi Wang, Moe Mahjoub, Jeffrey H. Miner. *Renal Div, Washington Univ School of Medicine, St. Louis, MO.*

Background: Polycystic kidney disease involves dysregulation of tubular proliferation and cellular polarity leading to cystogenesis. Deletion of various apico-basal and planar cell polarity (PCP) proteins in mice, including members of the membrane-associated guanylate kinase (MAGUK) family, is sufficient for cystogenesis. *DLG1*-deficient mice exhibit PCP defects but only occasional unilateral renal agenesis or hypoplasia. Co-deletion or hypomorphic expression of *DLG1* and *CASK* in nephron progenitors (via *Six2Cre*) induces hypoplasia and cystogenesis, respectively. This work aimed to characterize the cystic phenotype in *DLG1*^{+/-}; *CASK*^{-/-} mice.

Methods: *DLG1*^{+/-}; *CASK*^{-/-} kidneys were analyzed histologically by immunohistochemistry, western blotting, and qRT-PCR at various ages. Additionally, for mechanistic insight we employed a model of cystogenesis in which cell-permeant cAMP (8-Br-cAMP) drives tubular dilation in cultured embryonic kidneys through luminal fluid flux.

Results: *DLG1*^{+/-}; *CASK*^{-/-} mice exhibit cysts as early as 90 days with severe but variable pathology by 9 months. Analysis of *DLG1*^{+/-}; *CASK*^{-/-} tubule segments indicates proximal tubule origin of cysts and dysregulation of matrix proteins, but with preservation of apico-basal polarity. Ciliary length was up to 2-fold longer in the majority of *DLG1*^{+/-}; *CASK*^{-/-} tubules, but was longer only in dilated *DLG1*^{-/-}; *CASK*^{-/-} tubules. Curiously, whereas 8-Br-cAMP induced dilations in wild-type embryonic renal tubules, *DLG1*^{+/-} or *-/-*; *CASK*^{-/-} embryonic kidneys did not exhibit tubular dilations.

Conclusions: Our data indicate that *DLG1* and *CASK* co-regulate renal development as well as homeostasis of renal epithelium independently of apico-basal polarity. IHC analysis revealed molecular features consistent with PKD phenotypes, with an unusual elongation of cilia. A cAMP-stimulated model of cystogenesis revealed a failure in PKA-dependent tubular dilations in *DLG1*^{+/-} or *-/-*; *CASK*^{-/-} embryonic kidneys. Coupled with cilia elongation and PKA effects on ciliary function, these results indicate a previously unrecognized regulation of PKA by MAGUK family members in the kidney.

Funding: NIDDK Support

TH-OR058

Serum Leptin, Pre-Existing Vascular Disease, and Arteriovenous Fistula Maturation Failure Jwa-kyung Kim,¹ Sun Ryoung Choi,² Mi jin Park,³ Sung gyun Kim.¹ ¹Internal Medicine, Hallym Univ Sacred Heart Hospital, Kidney Research Inst, Anyang, Republic of Korea; ²Internal Medicine, Shamyook Medical Center, Seoul, Republic of Korea; ³Clinical immunology, Hallym Univ Sacred Heart Hospital, Anyang, Republic of Korea.

Background: Pre-existing vascular diseases is one of the important causes of maturation failure of arteriovenous fistula (AVF). Recently, a growing proportion of incident dialysis patients are obese, and leptin is regarded as a pivotal mediator between obesity and cardiovascular disease. This study evaluated the association between serum leptin and pre-existing vascular disease and AVF maturation failure in patients with end-stage renal disease (ESRD).

Methods: Vein samples from 62 patients were collected at the time of AVF creation near the site of AV anastomosis. Histological (hematoxylin and eosin, and trichrome staining), immunohistochemical and morphometric (smooth muscle actin [SMA], vimentin and desmin) studies were performed. AVF maturation failure was defined as an AVF not possible to use successfully for hemodialysis by the third month after its creation despite radiological or surgical interventions.

Results: Mean age was 63.3 ± 13.7 years and the prevalence of obesity (BMI ≥25 kg/m²) was 49.1%. Mean serum leptin levels were 2.10 ± 1.41 pg/mL (log transformed), and patients in the highest leptin tertile had significantly increased BMI, higher triglyceride, interleukin-6, and hs-CRP levels (P<0.01). AVF maturation failure occurred in 21 (35.6%) patients, and the failure rate progressively increased from the lowest to the highest leptin tertile (p<0.001). On histological examinations, increased leptin tertiles were closely associated with intimal hyperplasia (13.3±4.5 vs. 18.2±5.2 vs. 30.3±14.3 mm in each tertile) as well as medial fibrosis. In addition, the majority of cells within the neointima were positive for SMA and vimentin and negative for desmin, suggesting a myofibroblast phenotype. Interestingly, a number of vascular sections in lowest leptin tertile also had desmin-positive contractile smooth muscle cells.

Conclusions: Obesity related fistula maturation failure may be mediated by higher serum leptin level - associated preexisting vascular diseases in ESRD patients.

TH-OR059

Time-Dependent Endothelial Dysfunction following Arteriovenous Fistula Creation Timmy C. Lee, Jennifer S. Pollock. *Univ of Alabama at Birmingham.*

Background: Vascular endothelial function plays a critical role in arteriovenous fistula (AVF) remodeling and neointimal hyperplasia development. The goal of our study was to characterize the natural history of endothelial dysfunction following AVF creation.

Methods: AVFs were created using an end to side anastomosis between the femoral vein and artery in 12-16 week old Sprague-Dawley rats. Contralateral vessels served as controls. Rats were sacrificed at 1, 7, 14, and 21 days after AVF creation and vein and artery collected for morphometric analysis. Segments from the arterial anastomosis were isolated at these time points and mounted on wire myographs to assess endothelial-dependent and -independent function by concentration-response curves to acetylcholine (ACh) and sodium nitroprusside (SNP), respectively.

Results: Maximal relaxation to ACh was significantly decreased at 7 days compared to the contralateral control (29±12% vs 110±15%; p=0.006) (figure 1), but endothelial-dependent function was fully restored by 21 days (94±2% vs 93±2%; p=0.598).

Time Point of Sacrifice (Days) Post AVF Creation	Percent (%) Maximal Relaxation					P-value
	AVF Relaxation to ACh (Endothelial-dependent response) (Mean% ± SEM)	Control Vessel Relaxation to ACh (Endothelial-dependent response) (Mean% ± SEM)	P-value	AVF Relaxation to SNP (Endothelial-independent response) (Mean% ± SEM)	Control Vessel Relaxation to SNP (Endothelial-independent response) (Mean% ± SEM)	
1 day (n=4)	61±22	92±3	0.205	107±5	99±1	0.162
7 day (n=4)	29±12	110±15	0.006	93±5	94±6	0.895
14 day (n=4)	43±25	90±3	0.168	98±2	101±3	0.349
21 day (n=4)	94±2	93±2	0.592	84±6	99±2	0.047

Endothelial-independent response to SNP was similar to the contralateral control artery at 1, 7, and 14 day time points, suggesting an adequate smooth muscle cell response necessary for vasodilation. However, at 21 days vascular relaxation to SNP was impaired compared to control (84±6% vs 99±2%; p=0.047), suggesting smooth muscle dysfunction. Our morphometric analysis showed that the greatest change in amount of arterial and venous intimal hyperplasia occurs in the 1st 7 days following AVF creation.

Conclusions: Creation of AVF results in a time-dependent endothelial dysfunction worse 7 days after creation. Therapies targeted at restoring endothelial function via increasing nitric oxide production shortly after AVF creation may help improve AVF remodeling and inhibit neointimal hyperplasia. Late changes in endothelial-independent vascular function following AVF creation needs further evaluation.

Funding: NIDDK Support, Private Foundation Support

TH-OR060

Is Preoperative Vein Morphology Associated to Vascular Access Outcome?

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Background: Vascular access (VA) stenosis is histologically characterized as neointimal hyperplasia (NH). Smooth muscle cells initially proliferate in media, and migrate to the intima where endothelial cell proliferation and angiogenesis occur. Venous NH has been primarily associated with hemodynamic stress, surgical injury, grafts and cannulation. According to recent data, uremia is likely to exacerbate endothelial dysfunction and predispose to NH before VA creation. Primary end point was to evaluate preoperative vein morphology and how it would affect VA outcome. Secondary end points were to found if other demographic and clinical factors could also have any impact.

Methods: Transversal observational study performed in 26 patients with end-stage-renal-disease. Venous specimens obtained during VA creation were evaluated for intimal inflammatory infiltrate/angiogenesis, media abnormalities and intima/global wall thickness. Postoperative clinical function and demographic parameters recorded.

Results: The majority of patients were male (84.6%); age 71.4±15.1y; 57.7% diabetic; 50.0% had central venous catheter at surgery time; maturation occurred in 53.8%. Intimal angiogenesis and media abnormality were both seen in 66.7% of patients in which VA didn't mature, but only in 14.3% and 21.4% of the ones that matured, respectively. Chi-square analysis showed that both previous findings were significantly associated with VA failure (p 0.006 and p 0.020). Intimal and global wall thicknesses were 0.0607±0.0715 and 0.7000±0.2228mm in matured VA; 0.2600±0.2442 and 1.0318±0.3227mm in nonmatured VA, respectively (p 0.006 and p 0.005). Gender, age, diabetic status and catheter presence didn't affect VA function.

Conclusions: Preexisting venous thickness, intimal angiogenesis and media abnormalities predispose to postoperative VA nonmaturation. It is possible that uremia and other pre-dialysis factors may contribute to preexisting venous abnormalities which, independently of the future hemodynamic stress, predispose patients to more aggressive NH after VA creation, contributing to inferior outcomes.

TH-OR061

The Effect of Far Infrared Therapy on the Maturation of Newly Created Arteriovenous Fistula and the Parameters of Inflammation, Endothelial Function and Oxidative Stress in Patients with Advanced Chronic Kidney Disease Chih-Ching Lin. Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: We had demonstrated that far infrared (FIR) therapy could improve the access flow and unassisted patency of arteriovenous fistula (AVF) in prevalent HD patients; however, the effect of FIR on the endothelial function as well as the markers of inflammation and oxidative stress of the newly created AVF is unknown.

Methods: We enrolled patients with advanced chronic kidney disease (CKD) by the definition of eGFR <20 ml/min/1.73m². Patients were randomly and equally allocated to FIR group (receiving FIR therapy for 40 minutes thrice weekly for 3 months) and control group (without FIR therapy). This study is aimed to evaluate (1) the effect of newly-created AV access on the markers of inflammation (hsCRP), endothelial function [asymmetric dimethyl arginine (ADMA) and L-arginine], and oxidative stress [serum malondialdehyde (MDA), serum advanced oxidation protein products (AOPPs), blood glutathione (GSH), erythrocyte glutathione peroxidase (GPx), and erythrocyte superoxide dismutase (SOD) activities], (2) the effect of FIR on access flow and the levels of the above-mentioned inflammatory, endothelial and oxidative stress markers in patients with advanced CKD in the first 3 months after the creation of AVF.

Results: Totally, 122 advanced CKD patients finished this study with 60 in FIR group and 62 in control group. In comparison with control patients, the patients in FIR group had lower mean values of incremental change of the plasma concentrations of hs-CRP (-0.68±0.93 vs. 0.39±0.46 mg/L, P=0.04) and ADMA (-0.10±0.05 vs. 0.02±0.05, P=0.02) but a higher incremental change of blood glutathione (2.45±2.23 vs. -0.44±0.67, P=0.031) and access flow of AVF from 1st to 3rd month.

Conclusions: In patients with advanced stages of CKD, AVF malfunction is associated with a higher level of plasma hs-CRP, ADMA and a lower level of blood glutathione at baseline, which could be improved by FIR therapy. Henceforth, FIR therapy improves blood flow and the maturation of AVF possibly through the mechanism of correcting inflammation, endothelial dysfunction and oxidative stress.

Funding: Government Support - Non-U.S.

TH-OR062

Use of Arteriovenous Fistula/Graft Access for Continuous Renal Replacement Therapy: A Single Center Experience Anas Al Rifai, Nidhi Sukul, Michael Heung. Internal Medicine-Nephrology, Univ of Michigan, Ann Arbor, MI.

Background: Use of arteriovenous fistula or graft (AVF/AVG) access is widely considered to be contraindicated for continuous renal replacement therapy (CRRT), yet insertion of hemodialysis (HD) catheters can carry high risk of complications in critically ill endstage renal disease (ESRD) patients. Here we report our single-center experience with using AVF/AVG access for CRRT.

Methods: Retrospective review of 43 consecutive hospitalized ESRD patients on maintenance HD who received CRRT in 2012. After exclusions (16 catheter-dependent at admission, 4 with AVF/AVG thrombosis before CRRT start), our cohort consisted of 23 patients. Data collection included patient and treatment characteristics, and access outcomes.

Results: Mean±SD age was 57±15 yrs, 48% were male, and median HD duration was 54 months (range 8-300); 14 (61%) patients had AVF and 9 (39%) had AVG. Most (83%) patients required vasopressor support at CRRT start. Mental status at CRRT initiation showed 35% to be oriented and following commands, 9% awake but confused, and 56% sedated. Median duration of AVF/AVG use for CRRT was 4 days (range 2-34). Complications related to use of the AVF/AVG for CRRT (with subsequent requirement of HD catheter placement) developed in 3 patients (13%): hematoma in 2 patients with AVF and thrombosis of AVG in 1 patient. All 3 patients with complications had documented pre-existing access problems; 1 had known subclavian vein stenosis and 2 required access intervention within the previous 1 year. Of these three patients, 1 was awake and confused while the other 2 were sedated. Among them, 1 required blood product transfusion for line insertion and 1 developed a catheter-associated bloodstream infection. Of the cohort, 16 (70%) patients survived to hospital discharge; among the survivors, AVF/AVG access was functional at the time of discharge in 15 (94%) patients.

Conclusions: Our experience suggests that use of AVF/AVG for CRRT is feasible with a relatively low complication rate and low risk of access failure. This approach may aid in avoiding the potential complications associated with HD catheter insertion in ESRD patients with a functioning vascular access.

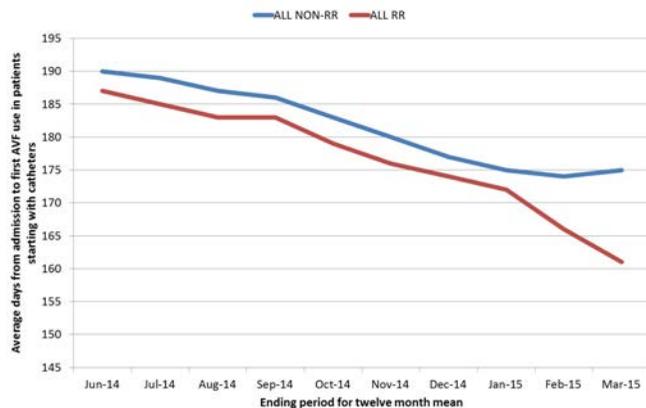
TH-OR063

Improvements in Time to Fistula Use in Incident Hemodialysis Patients in the Rapid Response Pilot Program Karen G. Butler, John W. Larkin, Deborah J. Brouwer-Maier, Sandra Bodin, Michelle L. Gilliland, Michele Inglese, Lillian A. Pryor, Len A. Usvyat, Dugan Maddux, Franklin W. Maddux. Clinical Innovation Initiatives, Fresenius Medical Care North America (FMCNA), Waltham, MA.

Background: It is known that use of a catheter hemodialysis (HD) access is associated with increased morbidity and mortality, as compared to arteriovenous fistulas (AVFs) and grafts (AVGs). FMCNA has initiated the Rapid Response (RR) pilot program in an attempt to improve time to use of AVF accesses in incident HD (iHD) patients who initiated dialysis with a catheter. The aim of this study was to determine if the RR program is associated with improvements in AVF access use in iHD patients.

Methods: In September 2014, 59 clinics initiated the RR pilot program. Clinics were selected by high census (>95 patients) and high catheter rates (>30%). The program consisted of sequential, educational modules designed to build awareness of catheter exposure, engage staff in standardized and simplified vascular access monitoring, and address lack of AVF maturation as a root cause of high catheter rates. All patients initiating dialysis with a catheter access were followed. Non-RR clinics in the same geographical location were randomly identified for controls. To determine the change in time to AVF use, the mean time to AVF use over 12 months at the end of each month from June 2014 to March 2015 was calculated.

Results: 5,248 and 4,159 iHD patients starting dialysis with a catheter at RR and non-RR clinics were included in this analysis. The mean time to AVF use was reduced in RR clinics after initiation of the program in September of 2014, as compared to control clinics (p<0.05).



Conclusions: This study demonstrates improvements associated with time to AVF use in incident patients initiating HD with a catheter access at clinics participating in the RR program.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-OR064

Impact of Poverty and Health Care Insurance on Arteriovenous Fistula Use Among Incident Hemodialysis Patients Deepti S. Moon,¹ Rahul M. Jindal,² Frank P. Hurst,² Christina M. Yuan,¹ Lawrence Agodoa,³ Kevin C. Abbott,¹ Robert Nee.¹ ¹Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; ²Uniformed Services Univ of the Health Sciences, Bethesda, MD; ³NIDDK, National Insts of Health, Bethesda, MD.

Background: We assessed the association of area and individual-level indicators of poverty and types of health care insurance on arteriovenous fistula (AVF) use among incident end stage renal disease (ESRD) patients initiated on hemodialysis (HD).

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 669,206 patients initiated on maintenance HD from January 1, 2007 through December 31, 2012. We assessed the Medicare-Medicaid dual eligibility status as an indicator of individual-level poverty and ZIP code-level median household income (MHI) data obtained from the 2010 United States Census. We conducted logistic regression of AVF use at start of dialysis as the outcome variable, as reported on the Medical Evidence Form 2728.

Results: The proportions of dual-eligible and non-dual eligible patients who initiated HD with an AVF were 12.53% and 16.17%, respectively ($p < 0.001$). Dual-eligibility was associated with significantly lower likelihood of AVF use upon initiation of HD (adjusted odds ratio [aOR] 0.91; 95% confidence interval [CI] 0.90-0.93). Patients in the lowest area-level MHI quintile had an aOR 0.97 (95% CI 0.95-0.99) compared to those in higher quintile levels. However, dual eligibility and area-level MHI were not significant in patients with Veterans Affairs (VA) coverage.

Conclusions: Individual and area level measures of poverty were independently associated with lower likelihood of AVF use at the start of HD, the only exception being patients with VA healthcare benefits. Efforts to improve incident AVF use may require focusing on pre-ESRD care to be successful. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense, or the United States government].

Funding: Other U.S. Government Support

TH-OR065

A Subset of CD64⁺ F4/80^{high} CD11b^{int} CD11c^{int} Macrophages Protects against Chronic Ischemic Kidney Injury Amrutesh Puranik,¹ Sonu Kashyap,³ Mark A. Jensen,⁴ Bruce Knudsen,³ John R. Woollard,² Tyra Witt,⁷ Stephen C. Textor,² Jeremy Stuart Duffield,⁵ Joseph P. Grande,³ Rob Simari,⁶ Lilach O. Lerman.² ¹Dept of Anesthesiology, Mayo Clinic, Rochester, MN; ²Div of Nephrology & Hypertension, Mayo Clinic, Rochester, MN; ³Laboratory Medicine & Pathology, Mayo Clinic, Rochester, MN; ⁴Dept of Rheumatology, Mayo Clinic, Rochester, MN; ⁵Biogen, Cambridge, MA; ⁶Univ of Kansas, Kansas City, KS; ⁷Cardiac Regeneration Program, Mayo Clinic, Rochester, MN.

Background: Macrophages (Mfs) have been implicated in both progression and resolution of renal injury. We tested the hypothesis that a specific Mfs subtype regulates fibrosis in chronic murine ischemic renal artery stenosis (RAS).

Methods: After 28 days of unilateral RAS in mice, stenotic kidneys were harvested and 3 Mfs populations (Figure 1), black circles) quantified using polychromatic flow cytometry by expression of the CD11b, CD11c, F4/80, MHCII, CD64, MerTK, Ly6c & CD206. Mouse macrophages were ablated using I.P injections of liposomal clodronate (2/week for 28 days), and macrophage populations were flow-sorted to study gene expression using Taqman low-density arrays.

Results: RAS induced hypertension and post-stenotic kidney atrophy, and increased the total Mfs numbers in each population. Ablation with clodronate aggravated fibrosis (figure 1 bottom graph), and increased expression of proinflammatory transcripts for Il6, Ifng, Il1b, Tnfa, and Nos2. Clodronate selectively ablated a sub-population of CD64⁺F4/80^{high}CD11b^{int}CD11c^{int} macrophages (figure 1 middle panel, right), while other populations remained intact. In healthy controls, gene expression studies on this population demonstrate significantly higher levels of genes typically expressed by tissue-resident Mfs (such as Myo7a, Nln, Slc48a, Pla2g15, Spi1, Csf1r, Pon3, Tlr4, Cebpa, Mafb, Hbp1, Mertk and Fcgr1), than monocyte-derived Mfs (figure 1, circles 1 and 2) (CD64⁺F4/80^{high}CD11b^{int}CD11c^{int}). Flow sorted CD64⁺F4/80^{high}CD11b^{int}CD11c^{int} macrophages from RAS kidneys showed increased levels of Mertk, Arg1, Agrp2, Csf1, Il10, Igf1, Angpt1 and Vegfa, factors involved in inhibiting inflammation and promoting regeneration. These factors were down-regulated upon clodronate treatment.

Conclusions: CD64⁺F4/80^{high}CD11b^{int}CD11c^{int} macrophages represent a novel population of protective kidney-resident macrophages that regulate the injury response in chronic kidney ischemia.

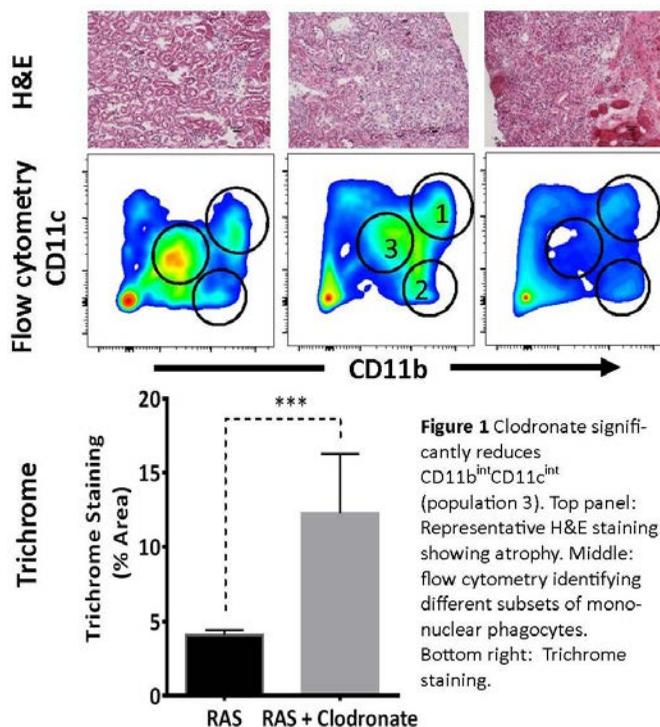


Figure 1 Clodronate significantly reduces CD11b^{int}CD11c^{int} (population 3). Top panel: Representative H&E staining showing atrophy. Middle: flow cytometry identifying different subsets of mononuclear phagocytes. Bottom right: Trichrome staining.

Funding: Private Foundation Support

TH-OR066

Spliced XBP1 Rescues Renal Interstitial Inflammation due to Loss of Sec63 in Collecting Ducts Yasunobu Ishikawa,¹ Sorin V. Fedele,¹ Rachel Gallagher,¹ Stefan Somlo.^{1,2} ¹Internal Medicine, Yale Univ School of Medicine, New Haven, CT; ²Genetics, Yale Univ School of Medicine, New Haven, CT.

Background: SEC63 is one of two genes which cause human autosomal dominant polycystic liver disease, and is located in the membrane of the endoplasmic reticulum (ER). A number of disease states alter ER function and result in ER stress, thus initiating the unfolded protein response (UPR). UPR is mediated by three major stress sensors, IRE1 α , PERK and ATF6. In particular, IRE1 α is the most conserved of the three branches and phosphorylation of IRE1 α results in spliced XBP1 (XBP1s), a transcription factor that activates transcription of chaperones and proteins involved in ER-associated degradation. We have shown that loss of Sec63 and Xbp1 in collecting ducts causes phosphorylation of IRE1 α and progressive renal interstitial inflammation leading to CKD (ASN, 2014 TH-OR162). It is known that phosphorylated IRE1 α activates Nfk β , JNK and NALP3 inflammasome. In the current work we investigated the interaction of the SEC63 and IRE1-XBP1 pathways and their role in CKD.

Methods: Animal models used in this study: WT (wild type), SKO (Sec63^{fl/fl};Pkh1-cre), DKO (Sec63^{fl/fl};Xbp1^{fl/fl};Pkh1-cre) and TKO (Sec63^{fl/fl};Xbp1^{fl/fl};Ire1a^{fl/fl};Pkh1-cre), as well as DKO;Nalp3^{-/-} and DKO expressing a cre activated ROSA-XBP1s allele. The kidneys were removed and analyzed at P70.

Results: Analysis of Nfk β and JNK phosphorylation states were no different between WT, SKO and DKO. The histology in WT and SKO kidneys appeared normal. In contrast, DKO mice showed many inflammatory cells in the renal interstitium with decline in renal function. By removing Ire1a and Nalp3^{-/-}, respectively, on the DKO background did not rescue the inflammation nor ameliorate decline in renal function. In addition, double knockout of Sec63 and Ire1a in the collecting duct also resulted in renal interstitial inflammation similar to what was observed in the DKO kidneys. Re-expression of a human XBP1 transgene that produces spliced XBP1 on the DKO background rescued the inflammatory phenotype.

Conclusions: Spliced XBP1 rescues renal interstitial inflammation due to loss of Sec63 in collecting ducts.

TH-OR067

Specific Deletion of Rictor in Macrophages Ameliorates Macrophage Activation and Obstructive Nephropathy in Mice Jiafa Ren, Chunsun Dai. Nanjing Medical Univ.

Background: Rictor/mTORC2 signaling is activated in both tubular and interstitial cells in mouse kidneys with obstructive nephropathy. Our published studies reported that Rictor/mTORC2 signaling mediates TGF β 1-induced fibroblast activation and kidney fibrosis. Regarding the critical role for macrophages infiltration in kidney fibrosis, deciphering the role and mechanisms for mTORC2 signaling in macrophage activation and its contribution to kidney fibrosis are very necessary.

Methods: In this study, a mouse model with tamoxifen-induced macrophage-specific deletion of Rictor and primary cultured macrophages from bone marrow were employed.

Results: Here, we found that Rictor/mTORC2 signaling was activated in the kidney interstitial F4/80+ macrophages in mice with UUO nephropathy. A mouse model with tamoxifen-induced macrophage-specific deletion of Rictor was generated. Compared with their control littermates, the knockout kidneys developed less kidney injury, interstitial extracellular matrix deposition and macrophage infiltration at 2 weeks after UUO surgery. In the primary cultured macrophages, compared with wild type cells, cell proliferation stimulated by M-CSF treatment was similar, whereas cell migration was markedly inhibited in Rictor-deleted macrophages. Additionally, the mRNA abundance for arginase 1, *fizzl1*, and *YM1* were largely induced in wild type macrophages treated with IL4, which were much less in Rictor-deleted macrophages.

Conclusions: Together, these results suggest that Rictor/mTORC2 signaling plays an important role for promoting macrophage activation and contributes to the development of kidney fibrosis.

Funding: Government Support - Non-U.S.

TH-OR068

Non-HLA Antibodies Targeting Angiotensin II Type 1 Receptor and Endothelin-1 Type A Receptor Induce mTOR Signaling and Endothelial Injury in Human Microvascular Endothelium *Duska Dragun, Oskar Wischnewski, Rusan Catar, Angelika Kusch. Nephrology and Intensive Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany.*

Background: Functional non-HLA antibodies (Abs) targeting G protein-coupled receptors Angiotensin II Type 1 (AT1R) and Endothelin-1 Type A receptor (ETAR) are implicated in pathogenesis of renal transplant vasculopathy. Both antibodies activate canonic G-protein related ERK 1/2. The molecular link between receptor stimulation and development of vascular obliterative lesion has not been fully established. We hypothesized the involvement of PI3K/Akt downstream signaling target mTOR and assessed functional consequences of AT1R- and ETAR-activation by non-HLA Abs.

Methods: Human microvascular endothelial cells were stimulated with AT1R-Ab and ETAR-Ab containing IgG from patients with obliterative vasculopathy. Phospho-specific antibodies against ERK and mTOR downstream targets were used to assess activation of mTORC1 and mTORC2. Scratch assay was employed to study effect of non-HLA-antibodies on wound healing. Involvement of AT1R/ETAR activation in non-HLA antibody downstream signaling was addressed by use of specific inhibitors for AT1R (Valsartan) and ETAR (Sitaxentan).

Results: Signaling activity of both, mTORC1 and mTORC2, was increased after short and long term treatment with patient IgG compared to cells treated with IgG from healthy controls. This effect could be inhibited by preincubating the cells with specific inhibitors of AT1R and ETAR. Both, activation of mTORC1 and mTORC2 were PI3K-dependent and independent from ERK-activation. mTOR inhibitor rapamycin completely abolished non-HLA Abs induced activation of mTORC1 and in addition mTORC2 after long term treatment. Impaired wound healing by non-HLA Abs could be restored by either use of specific AT1R or ETAR inhibitors.

Conclusions: We provide evidence that functional targeting AT1R and ETAR antibodies induce mTORC1 and mTORC2 signalling which is independent of canonic ERK 1/2 activation in human microvascular endothelium. Our data on impaired AT1R and ETAR-dependent wound healing induced by non-HLA Abs may provide a translational rationale for therapeutic AT1R and mTOR inhibitors in patients with non-HLA Abs.

TH-OR069

Memory Effector T Cells and OX40 Signaling Could Contribute to Chronic T-Cell Mediated Rejection *Claudia Curci,¹ Fabio Sallustio,¹ Grazia Serino,¹ Giuseppe De Palma,¹ Mirko Trpevski,¹ M. Rossini,² Loreto Gesualdo,² Marco Quaglia,³ Paolo Rigotti,⁴ Francesco Paolo Schena.¹ ¹C.A.R.S.O. Consortium, Bari, Italy; ²Univ of Bari, Bari, Italy; ³Univ of Eastern Piedmont, Novara, Italy; ⁴Univ of Padua, Padua, Italy.*

Background: Chronic T-cell Mediated Rejection (TCMR) is characterized by the reduction of vessel lumen with marked intimal thickening, fibrous hyperplasia and a large component of leukocyte infiltrate. Aim of our work was the study of gene expression profile in renal tissue, including the cellular infiltrate, in chronic TCMR.

Methods: We performed transcriptomics study using RNA extracted from archival formalin-fixed and paraffin-embedded (FFPE) renal biopsies obtained from 21 patients with chronic TCMR and 10 with acute TCMR. Controls were renal tissue samples from 52 cadaveric donors (CD). Genome-wide expression profiles were generated by Illumina platform. Real-Time PCR and immunofluorescence were used for validation of the identified transcripts.

Results: Using a FC^2 and a $FDR < 0.05$, we identified 164 genes differentially expressed in renal tissue of patients with chronic and 165 genes differentially expressed in acute TCMR, compared to CDs. Partial Least Square showed a clear difference in the gene expression of the three groups of biopsies. The study of gene pathways showed up-regulation of OX40 signaling, that is involved in the differentiation of CD8⁺ memory effector T cell, and up-regulation of KLRG1, BLIMP1 and CD25 that characterized short-lived memory effector T cells. Interestingly, we found that OX40 signaling was specific only for chronic TCMR. Next, the validation study for OX40, KLRG1, BLIMP1 demonstrated that these genes were expressed by CD8⁺ T cells in chronic but not in acute TCMR.

Conclusions: Our data suggest, for the first time, the involvement of memory committed CD8⁺ effector T cells specifically in chronic TCMR. The generation of memory effector T cells is mediated by OX40 pathway, that may be considered a potential target for specific treatment of chronic TCMR of kidney graft.

Funding: Government Support - Non-U.S.

TH-OR070

Dendritic Cell-Targeted CD40 DNA Vaccination Suppresses Th17 and Ameliorates Renal Injury in Experimental Autoimmune Glomerulonephritis *Qing Li,¹ Qi Cao,¹ Chengshi Wang,¹ Xin M. Wang,² Yuan Min Wang,³ Stephen I. Alexander,³ Yiping Wang,¹ David C. Harris.¹ ¹Centre for Transplant and Renal Research, Westmead Millennium Inst, The Univ of Sydney, Sydney, Australia; ²Flow Cytometry Facility, Westmead Millennium Inst, The Univ of Sydney, Sydney, Australia; ³Centre for Kidney Research, Children's Hospital at Westmead, Sydney, Australia.*

Background: The CD40-CD154 co-stimulatory pathway is critical for T cell activation in autoimmune disease. Our group previously found that blocking this pathway using CD40 DNA vaccine enhanced by targeting dendritic cell receptor DEC205 prevent the development of Heymann nephritis. In this study, we used DEC-CD40 DNA vaccine to treat the disease and explored its effect on Th17-mediated pathogenesis of experimental autoimmune glomerulonephritis (EAG).

Methods: The rat EAG model was established by NC1 protein injection, and DEC-CD40 vaccination was administered at week3 and week6 after NC1 injection. Renal function and histology were assessed at week12. Th subsets, key transcription factors and relevant cytokines in kidneys, spleens and lymph nodes were examined.

Results: Administration of DEC-CD40 DNA vaccine at week3 and week6 after NC1 injection reduced renal structural and functional injury in EAG. DEC-CD40 vaccination reduced the number of Th17 cells and inhibited Th17 immune responses in kidney, spleen and lymph nodes, but did not alter the number of Th1, Th2 and Treg cells. Early and late treatment showed similar effects on kidney injury and Th17 immune responses, indicating DEC-CD40 vaccination has both preventative and therapeutic roles in EAG. Serum from rats with DEC-CD40 suppressed Th17 in vitro, but not Th1 differentiation. B cell activation and M1 macrophage polarization were inhibited when co-cultured with Th17 cells induced with DEC-CD40-EAG serum but not EAG serum.

Conclusions: DNA vaccine encoding CD40 and targeting dendritic cells ameliorates renal injury in both early and late stages of experimental autoimmune glomerulonephritis. Its preventative and therapeutic effect was associated with suppression of Th17 differentiation and Th17-dependent B cell activation as well as M1 macrophage polarization.

Funding: Government Support - Non-U.S.

TH-OR071

Pharmacologic Targeting of Sirtuin-1 (Sirt1) Enhances Treg Function, Markedly Prolongs Renal Allograft Survival and Protects against Renal Allograft Dysfunction *Ulf H. Beier,¹ Zhonglin Wang,² Tricia Bhatti,¹ Wayne W. Hancock,¹ Matthew H. Levine.² ¹Children's Hospital of Philadelphia, Philadelphia, PA; ²Univ of Pennsylvania, Philadelphia, PA.*

Background: Published data show that the pharmacologic regulation of Foxp3+ T-regulatory (Treg) function provides safer, more consistent, potent and less expensive options than Treg-based cell therapy involving injection of short-lived Tregs at one or more times post-transplant (Tx). In the case of sirtuins biology, conditional deletion of the Sirt1 gene within Foxp3+ T-regulatory (Treg) cells augments Foxp3 acetylation and Treg suppressive function, and enhances heterotopic cardiac allograft survival. However, such data remain of uncertain translational significance until tested in life-supporting models using pharmacologic approaches in normal recipients. We now report such data.

Methods: To this end, C57BL/6 mice were engrafted with BALB/c kidneys (i.e. full MHC-mismatch) and underwent native nephrectomy, and blood chemistries, renal function and hematocrit were monitored weekly thereafter.

Results: Allograft recipients were divided into two groups, and treated with either a Sirt1 inhibitor, EX-527 (1 mg/kg/d for 14 days), or vehicle control. We found that allograft survival at 100 days post-Tx was 87.5% in the EX-527 group, but only 28.6% in control mice ($P=0.037$, Mantel-Cox test). Moreover, at 100 days post-Tx, the EX-527 treated group had lower BUN (71 ± 2.7 vs. 90 ± 3.6 mg/dL, $P<0.001$) and serum creatinine levels (0.33 ± 0.04 vs. 0.58 ± 0.02 mg/dL, $P<0.001$) than survivors in the control group. Histologic analysis of renal allografts retrieved after 100 days showed less allograft fibrosis ($p=0.03$) and less inflammation ($p=0.01$) in the EX-527 treated vs. control groups, respectively.

Conclusions: Pharmacologic inhibition of Sirt1 is effective at prolonging allograft survival and function. These data provide clear evidence that pharmacologic regulation of Treg function is of demonstrable value in stringent allograft models, and provide a compelling rationale for testing of Sirt1 inhibitors in pre-clinical models.

Funding: Other NIH Support - NIAID

TH-OR072

A Novel IL-2 and IL-33 Hybrid Cytokine for Lupus Glomerulonephritis (GN) Therapy Rahul Sharma, Marta Stremeska, Chao Dai, Hongyang Wang, Saleh Mohammad, Sheethal Jose, Sun-sang J. Sung, Shu man Fu. *CIIR, Univ of Virginia, Charlottesville, VA.*

Background: Autoimmune Lupus GN is caused by T-cell and immune complex (IC) mediated inflammation resulting in renal dysfunction. Low interleukin (IL)-2 levels and T-regulatory cell (Treg) deficiency is implicated in lupus GN. Based on our findings that (a) IL-2, which is critical for Tregs, also regulates the expression of ST2 (receptor for IL-33-a Th2 promoting cytokine) and (b) a major subset of Tregs express ST2; we hypothesized that both IL-2 and IL-33 will be beneficial for treating lupus GN by simultaneously promoting Tregs and Th2. Further, linking IL-2 and IL-33 in a single molecule will target Tregs more efficiently.

Methods: We made a recombinant hybrid cytokine (IL233) bearing activities of IL-2 and IL-33 and tested its efficacy to treat GN using lupus prone NZM2328 female mice, in which disease was accelerated by injection of IFN α -expressing adenovirus (Ad-IFN α). NZM2328 females were injected with saline or 66pmoles/day of IL233 or IL2/IL33 alone or in combination for 5-days before Ad-IFN α injection.

Results: IL233 and the IL-2 and IL-33 combination protected 80% and 60% mice respectively from severe proteinuria and mortality, whereas 80% of mice treated with saline or IL-2 or IL-33 alone succumbed to severe proteinuria. IL233 treatment induced robust and sustained increase in Tregs. Renal histology of mice that succumbed to proteinuria showed glomerular hypertrophy, mesangial expansion and leukocytic infiltration, which were absent in IL233 treated mice. While complement deposition was similar, IL233 treated mice showed reduced IC deposits and skewing towards IgG2b compared to predominantly IgG2a deposits in the control mice. Further, treatment with IL233 (66pmoles/day for 5days) of mice with established proteinuria (100-300mg/dL for 2 consecutive weeks) induced persistent remission in 9 out of 11 mice, which survived beyond 10 months of age, when 70% of the NZM2328 females die of severe proteinuria. IL233 treated mice had higher circulating IgG2b without any symptoms of allergic diseases.

Conclusions: IL233 hybrid cytokine can prevent and reverse lupus GN by enhancing Tregs and bears therapeutic potential.

Funding: Private Foundation Support

TH-OR073

Interleukin-27 Has Potential Predictive Role in the Onset of Post-Transplant Malignancies Paola Pontrelli,¹ F. Rascio,² Giovanni Stallone,² Matteo Accettura,¹ Margherita Gigante,¹ Giuseppe Castellano,¹ Barbara Infante,² Gianluigi Zaza,³ Loreto Gesualdo,² Giuseppe Grandaliano.² ¹Dept of Emergency and Organ Transplantation, Univ of Bari, Italy; ²Dept of Medical and Surgical Sciences, Univ of Foggia, Italy; ³Dept of Medicine, Univ of Verona, Italy.

Background: Malignancies are the third leading cause of mortality among transplant recipients and their incidence is increasing. Although the role of the immune system in the development of malignancies is known, the mechanisms of tumor escape remain unclear. Aim of the study was to evaluate the differences in transcriptomic profiles of peripheral blood mononuclear cells (PBMC) in subjects who developed post-transplant malignancies (PTM, n=8) compared to transplanted patients without malignancies (ctrl-Tx, n=8).

Methods: The two patients' groups were comparable for the main clinical/demographic features and all patients were receiving calcineurin inhibitors (CNI), mycophenolate and steroids. Transcriptomic profiles of PBMC were assessed by microarray (Agilent technologies), analyzed by statistical and functional pathway analysis and validated by qPCR in an independent set of patients (PTM n=9; ctrl-Tx n=13).

Results: The comparison between PTM and ctrl-Tx (Fold-change>1.5), revealed that 4,363 genes were differentially expressed. Among them, the most down-regulated gene was interleukin (IL)-27 (fold-change (FC): -10.88), a cytokine produced by antigen presenting cells, which regulates anti-tumor immunity promoting the cytotoxic T lymphocytes activity and the natural killer cells activation. qPCR confirmed a significant reduction of IL-27 expression level in PTM patient compared to ctrl-Tx (p<.05). Since the treatment with mTOR inhibitors (mTORi) is associated to a reduce cancer risk in transplant recipients, we investigated whether mTORi may influence IL-27 expression in vivo. Interestingly, IL-27 gene expression was significantly higher in transplant recipients receiving an mTORi (n=8) compared to those with a CNI-based therapy (p=.009).

Conclusions: Our data stress the role of the immune system in the onset of cancer and suggest that IL-27 might represent a useful marker in order to stratify patients at risk of developing post-transplant malignancies.

TH-OR074

Translation of Anti-Fibrotic MicroRNA Strategies into a Mouse Model of Chronic Allograft Dysfunction Celina Schauerer,¹ Song Rong,² Michael Mengel,³ Hermann G. Haller,² Thomas Thum,¹ Johan Lorenzen.^{1,2} ¹Inst of Molecular and Translational Therapeutic Strategies (IMTT), Hannover Medical School, Germany; ²Div of Nephrology & Hypertension, Hannover Medical School, Germany; ³Dept of Laboratory Medicine & Pathology, Univ of Alberta, Canada.

Background: Chronic allograft dysfunction (CAD) is characterized by fibrotic remodeling, renal injury and chronic inflammation. Pro-fibrotic microRNA-21 (miR-21) was shown to be upregulated in CAD. This study investigates miR-21-inhibition in an evaluated murine model of CAD.

Methods: Allogenic kidney transplantation (NTx) was performed from male C57BL/6 into female Balb/c mice. Recipient mice were treated at day -1 and day 7 either with LNA-21 (miR-21 inhibitor) or LNA-SCR (control) (20mg/kg BW, i.p.). Six weeks after NTx, kidneys were harvested and analyzed e.g. by qRT-PCR, PAS and Sirius Red staining. Potential signal mechanisms were validated *in vitro* using renal fibroblast cell line NRK49F and macrophage-like cell line RAW264.7.

Results: We determined increased expression levels of markers for fibrosis (aSMA, Col1a2, Col3, FSP-1), inflammation (IL-6, MIP-1, IL-1 β) and injury (NGAL, KIM-1) in transplanted kidneys which were rescued by miR-21 inhibition. Moreover, Sirius Red staining revealed significantly less fibrosis development due to miR-21 inhibition. Besides, BANFF chronic rejection score was decreased in allografts of LNA-21 treated mice. The miR-21 promoter region harbors a putative binding site of transcription factor STAT3, which is activated by IL-6. We identified upregulated IL-6 expression and secretion in LPS activated RAW264.7 and hypothesized, that infiltrating immune cells produce and secrete cytokines that might affect resident renal cells causing fibrosis and injury. Co-culture assays confirmed a crosstalk between RAW264.7 and NRK49F with increased expression levels of IL-6, CTGF and miR-21 in NRK49F. Similar results were observed due to IL-6 treatment of NRK49F.

Conclusions: In our murine model of CAD allograft rejection is preserved by inhibition of miR-21 due to less inflammation and fibrosis thereby suggesting a new and essentially needed anti-fibrotic treatment strategy against CAD.

TH-OR075

Regulation of the Apical Cotransporter NKCC2 by a Novel Kinase: TNIK Paulo S. Caceres,^{1,2} Pablo A. Ortiz.^{1,2} ¹Hypertension & Vascular Research, Henry Ford Hospital, Detroit, MI; ²Physiology, Wayne State Univ, Detroit, MI.

Background: The apical cotransporter NKCC2 mediates NaCl absorption by the thick ascending limb (TAL), maintaining blood pressure. Abnormally enhanced NKCC2 activity contributes to salt-sensitive hypertension. Phosphorylation of NKCC2 at amino terminal (NH₂) threonines 96,101 (Thr-96,101) increases its activity. Trafficking of NKCC2 to the apical surface also regulate TAL NaCl absorption. Only the kinases SPAK and OSR1 have been shown to target Thr-96,101. Identifying additional kinases that target NKCC2 will help understand the role of Thr-96,101 in the regulation of NKCC2. To identify additional kinases, we performed a targeted proteomics screen using a GST-NH₂-NKCC2 fusion protein as bait in pull down assays from TAL protein lysates. We found that the Traf2 and NCK interacting kinase (TNIK) binds the NH₂ terminus of NKCC2. The role of TNIK in renal function and NKCC2 regulation is unknown. We hypothesized that TNIK phosphorylates NKCC2 at Thr-96,101 and stimulates surface NKCC2 expression in TALs.

Methods: We measured NKCC2-TNIK interaction by co-immunoprecipitation in rat TAL lysates. To determine whether TNIK directly phosphorylates NKCC2, we incubated the NH₂ terminus of NKCC2 with recombinant TNIK and measured NKCC2 phosphorylation at Thr-96,101. We generated TNIK knockout mice (TNIK^{-/-}), obtained TALs and measured total NKCC2, phosphorylation at Thr-96,101 and surface NKCC2 by surface biotinylation.

Results: We observed TNIK expression in isolated perfused TALs. NKCC2 and TNIK co-immunoprecipitate in TAL lysates and TNIK directly phosphorylates NKCC2 at Thr-96,101 *in vitro*. In TALs from TNIK^{-/-} mice on a normal diet, total NKCC2 expression was decreased by 32±9% (p<0.05) and phospho/total NKCC2 was decreased by 23±6% (p<0.05). In TNIK^{-/-} mice fed a low Na diet, phospho/total NKCC2 was decreased by 51±9% (p<0.05). The surface/intracellular NKCC2 ratio was decreased by 58±4% (p<0.01) in TNIK^{-/-} mice.

Conclusions: TNIK is a new kinase that interacts with NKCC2 in TALs, it phosphorylates NKCC2 at Thr-96,101 and mediates total and surface NKCC2 expression *in vivo*. This represent a novel pathway in the field of renal ion transport.

Funding: Private Foundation Support

TH-OR076

Golgi Alpha1,2-Mannosidase IA Promotes the Efficient Degradation of NKCC2 and Its Disease Causing Mutants Kamel Laghmani, Sylvie Demaretz, Nadia Defontaine, Elie Seayfan. *Centre de Recherche des Cordeliers, INSERM/UPMC/CNRS - U1138, ERL8228, Equipe 3, Paris, France.*

Background: Mutations in the apically located Na-K-2Cl cotransporter, NKCC2, lead to type I Bartter syndrome, and inherited kidney disorder associated with salt wasting, hypokalemia, and metabolic alkalosis. We have previously shown that wild type (WT) NKCC2 protein and its mutants are subject to regulation by the endoplasmic reticulum-associated degradation (ERAD). The aim of the present study was to identify the protein partners involved in ERAD of NKCC2.

Methods: To identify novel NKCC2-interacting proteins, we screened a kidney cDNA library through yeast two-hybrid using NKCC2 C-terminus as bait. NKCC2 protein expression was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging. NKCC2 stability was assessed by cycloheximide chase assay.

Results: We identified Golgi alpha1, 2-mannosidase IA (MANIA) as a specific binding partner of NKCC2. In addition to ER mannosidases, recent reports revealed that Golgi-situated α -1, 2-mannosidases may also contribute to the ERAD of glycoproteins. Co-immunoprecipitation and co-immunolocalization experiments confirmed NKCC2-MANIA interaction in renal cells. They also showed that MANIA association involves mainly the immature form of NKCC2. MANIA co-expression decreased total cellular WT NKCC2 protein in a dose dependent manner. Cycloheximide chase assay showed that in cells over expressing MANIA, NKCC2 maturation is impaired. Importantly, MANIA co-expression had a more profound effect on the disease-associated NKCC2 folding mutants, A508T and Y998X (>90%). The MANIA induced reductions in NKCC2 expression were offset by the proteasome inhibitor MG132. Finally, kifunensine and 1-deoxymannojirimycin, two potent inhibitors of alpha1, 2-mannosidases, reproduced MG132 effect on NKCC2 regulation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Our data demonstrate the presence of a MANIA mediated ERAD pathway in renal cells promoting retention and/or degradation of misfolded NKCC2 proteins. They suggest a model whereby, Golgi MANIA contributes to ERAD of NKCC2, by promoting the retention, recycling, and ERAD of misfolded proteins that initially escape protein quality control surveillance within the ER.

Funding: Government Support - Non-U.S.

TH-OR077

Inhibition of Mitochondrial Complex-1 Prevents the Downregulation of NKCC2 and ENaCa in Obstructive Nephropathy Zhanjun Jia,^{1,2} Yue Zhang,¹ Ying Sun,¹ Guixia Ding,¹ Songming Huang,¹ Aihua Zhang,¹ ¹*Nephrology, Nanjing Children Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China;* ²*Nanjing Key Laboratory of Pediatrics.*

Background: Ureteral obstruction with subsequent hydronephrosis is a common clinical complication. Downregulation of renal sodium transporters in obstructed kidneys could contribute to impaired urine concentrating capability and salt waste following the release of a ureteral obstruction. This study was undertaken to investigate the role of mitochondrial complex-1 inhibition in modulating sodium transporters in obstructive nephropathy.

Methods: C57BL/6 mice were subjected to the sham surgery or unilateral ureteral obstruction (UUO) for 7 days. Then kidney tissues were harvested for the analyses.

Results: Following UUO, sodium transporters including NHE3, α -Na-K-ATPase, NCC, NKCC2, p-NKCC2, ENaCa, and ENaCy were remarkably reduced by 60-90% contrasting to unaltered expression of ENaCb β , as determined by qRT-PCR, Western blotting, and immunohistochemistry. This global downregulation of sodium transporters was accompanied by striking reduction of mitochondrial DNA copy number (mtDNA), mitochondrial transcription factor (mTFAM), and mitochondria-encoded NADH dehydrogenase 1 (mtN1) indicating a mitochondrial abnormality. Strikingly, specific inhibition of mitochondrial complex-1 by rotenone (500ppm in diet) completely abolished the downregulation of NKCC2, p-NKCC2, and ENaCa without affecting other sodium transporters. To study the potential mechanisms mediating the rotenone effects on sodium transporters, we examined a number of known sodium modulators, including PGE2, ET1, Ang II, natriuretic peptides (ANP, BNP, and CNP), and nitric oxide synthases (iNOS, nNOS, and eNOS) and found that all of them were strikingly elevated by 3 to 80 folds except for nNOS in obstructed kidneys. However, after rotenone administration, only BNP with a 80-fold increase and iNOS with a 4-fold increase but not others were significantly reduced by 62% and 96%, respectively.

Conclusions: These findings demonstrated a substantial role of mitochondrial dysfunction in mediating the downregulation of NKCC2 and ENaCa in obstructive nephropathy, possibly via iNOS-derived nitric oxide and BNP.

Funding: Government Support - Non-U.S.

TH-OR078

NLRP3 Inflammasome Activation Confers the Resistance to Loop Diuretics in Proteinuric Kidney Disease Aihua Zhang,^{1,2} Yibo Zhuang,¹ Guixia Ding,¹ Songming Huang,¹ Zhanjun Jia,^{1,2} ¹*Nephrology Dept, Nanjing Children Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China;* ²*Nanjing Key Laboratory of Pediatrics.*

Background: The resistance to loop diuretics is a known phenomenon in proteinuric patients, particularly in the patients with nephrotic syndrome. However, the pathogenic mechanisms remain elusive.

Methods: Kidney biopsy specimens of proteinuric patients and mouse kidney tissues from albumin overloaded mice (daily i.p injection of albumin for 12 days) were analyzed.

Results: In the present study, we analyzed Na-K-Cl cotransporter (NKCC2, target of loop diuretics) expression in proteinuric patient kidneys via immunohistochemistry (IHC) and found a significant NKCC2 downregulation which was negatively correlated with proteinuria severity. Interestingly, in NKCC2 positive tubules (thick ascending limb, TAL), NLRP3 inflammasome was strikingly elevated and showed a positive correlation with proteinuria severity. These findings suggested a possibility that proteinuria may suppress NKCC2 expression via a NLRP3 inflammasome-mediated mechanism. To validate this hypothesis, NLRP3 WT and KO mice were subjected to albumin overload. Strikingly, albumin overload in WT mice resulted in a robust reduction of NKCC2 by 80% as determined by Western blotting, qRT-PCR, and IHC in accord with a specific induction of NLRP3 in TAL. Meanwhile, the downstream components of NLRP3 inflammasome including caspase-1, IL-1 β , and IL-18 were remarkably activated. Importantly, such a reduction of NKCC2 was entirely abolished in NLRP3 KO mice. In primary cultures of renal tubular cells, albumin markedly reduced NKCC2, indicating a direct effect of albumin on NKCC2 dysregulation. In addition, WT mice with albumin overload displayed a remarkable resistance to loop diuretic furosemide (NKCC2 inhibitor), which was completely reversed by NLRP3 inactivation.

Conclusions: These novel findings demonstrated that albuminuria-stimulated NLRP3 inflammasome is highly responsible for the impaired response to loop diuretics via suppressing NKCC2 expression in proteinuric kidney diseases. This may also offer novel, effective therapeutic targets for dealing with the resistance to loop diuretics in proteinuric patients.

Funding: Government Support - Non-U.S.

TH-OR079

Targeted Knockin of Constitutively Active SPAK (CA-SPAK) in the Early Distal Convoluted Tubule (DCT) Causes Hyperkalemic Hypertension P. Richard Grimm,¹ Richard A. Coleman,¹ Eric J. Delpire,² Paul A. Welling.¹ ¹*Physiology, Univ of Maryland SOM, Baltimore, MD;* ²*Anesthesiology, Vanderbilt Univ SOM, Nashville, TN.*

Background: Familial Hyperkalemic Hypertension (FHHT) is caused by aberrant gain in WNK function, leading to hyperactivation of the thiazide-sensitive sodium chloride co-transporter, NCC, and alterations in other salt transport pathways. SPAK is thought to be the key arbiter of WNK-NCC signaling in the DCT; upon activation by WNK1/4-phosphorylation (S383 and T243), SPAK phosphorylates NCC to stimulate salt reabsorption. Here, we explore if constitutive activation of SPAK in the DCT is sufficient to produce FHHT.

Methods: Knockin-CA-SPAK lox/lox mice were created by inserting a SPAK phosphomimetic mutant (T243E and S383D) between Lox-P sites in the first exon of the SPAK gene, using homologous recombination. Upon Cre-Lox recombination, these mice express CA-SPAK under the control of the endogenous SPAK promoter. To drive DCT1-specific expression of CA-SPAK in the kidney, mice expressing Cre-recombinase under the parvalbumin promoter (Parv-Cre+) were crossed with the CA-SPAK lox/lox mice. The phenotypes of DCT-specific CA-SPAK knockin (CA-SPAK KI) were compared to matched wild-type (WT) controls.

Results: As observed by immunofluorescent-confocal microscopy, CA-SPAK was specifically targeted to parvalbumin positive tubules in CA-SPAK KI mice, consistent with DCT1-specific expression. CA-SPAK KI mice displayed significantly greater amounts of phosphorylated NCC than WT even though the abundance of CA-SPAK and WT-SPAK were comparable, verifying the constitutively active nature of the knockin. Telemetric measurements of blood-pressure (BP) revealed the CA-SPAK KI mice are hypertensive despite low renin and aldosterone levels. Elevated BP was further exacerbated by high salt diet and ameliorated by hydrochlorothiazide (HCTZ). CA-SPAK KI also displayed HCTZ-remediable metabolic acidosis, and elevated plasma potassium levels, comparable to mouse models of WNK FHHT.

Conclusions: Targeted expression of CA-SPAK in the DCT1 phenocopies FHHT, underscoring the chief role of SPAK-dependent activation of NCC in early distal tubule in the pathogenesis of the disease.

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TH-OR080

Generation and Analysis of Knock-In Mice Carrying Pseudohypoaldosteronism Type II-Causing Mutations in the Cullin 3 Gene Yuva Araki, Tatemitsu Rai, Eisei Sohara, Takayasu Mori, Yuichi Inoue, Eriko Kikuchi, Shinichi Uchida. *Dept of Nephrology, Tokyo Medical and Dental Univ, 1-5-45 Yushima, Bunkyo, Tokyo, Japan.*

Background: Pseudohypoaldosteronism type II (PHAII) is a hereditary hypertensive disease caused by mutations in four different genes: *WNK1* and *4*, *KLHL3*, and *cullin 3 (Cul3)*. *Cul3* and *KLHL3* form an E3 ligase complex that ubiquitinates and reduces *WNK4* protein. However, the molecular pathogenesis of PHAII caused by mainly intronic *Cul3* mutations is unclear. In cultured cells and human leukocytes, PHAII-causing *Cul3* mutations result in the skipping of exon 9, producing a mutant *Cul3* protein lacking 57 amino acids (A403-459). However, whether this phenomenon occurs in the kidneys and is responsible for the pathogenesis of PHAII *in vivo* is unknown.

Methods: We generated knock-in mice carrying a mutation in the C terminus of intron 8 of *Cul3*, c.1207 -1G>A, which corresponds to a PHAII-causing mutation in the human *Cul3* gene.

Results: Heterozygous *Cul3*^{G(-)A/+} knock-in mice did not exhibit PHAII phenotypes, and the skipping of exon 9 was not observed in their kidneys. However, the level of *Cul3* mRNA expression in the kidneys of heterozygous knock-in mice was approximately half that of wild-type mice. Furthermore, homozygous knock-in mice were nonviable, similar to *Cul3* knockout mice, suggesting that the mutant allele does not produce *Cul3* mRNA lacking exon 9, but behaves like a knockout allele in this mouse model. These data suggest that the production of the mutant *Cul3* may be necessary and important for the pathogenesis of PHAII.

Conclusions: Our findings highlight the pathogenic role of mutant *Cul3* protein and provide insight to explain why intronic PHAII-causing mutations in *Cul3*, which has numerous binding partners in addition to *KLHL3*, cause only kidney-specific PHAII phenotypes.

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TH-OR081

Disruption of SPAK/OSR1 Reveal Their Critical Roles in Potassium Homeostasis Mohammed Zubaerul Ferdous, Andrew Terker, James A. McCormick. *Dept of Medicine, Div of Nephrology & Hypertension, Oregon Health & Science Univ, Portland, OR.*

Background: The WNK-SPAK/OSR1 pathway has been shown to play a key role in ion homeostasis, regulation of extracellular fluid volume, and blood pressure (BP). STE20 (sterile20)/SPS1-related proline/alanine-rich kinase (SPAK) and oxidative stress-responsive kinase-1 (OSR1) activate the renal cotransporters NKCC2 and NCC by phosphorylation. SPAK knockout mice (SPAK-KO) and OSR1 knockout mice display mild renal phenotypes, and may compensate for each other. We therefore generated SPAK-KO/inducible renal OSR1-KO mice (DKO) to compare the effects of deleting both kinases with SPAK deletion alone.

Methods: To examine the effects of disrupting both SPAK and OSR1, we manipulated dietary sodium (Na) and potassium (K), and analyzed levels of phospho-NCC (pNCC) and phospho-NKCC2 (pNKCC2) and other relevant proteins. We also measured plasma and urine electrolytes, and the BP of SPAK-KO and DKO mice on different diets using telemetry.

Results: We found that DKO had lower pNCC (48% on low Na, $p=0.02$ & 40% on low K diet, $p=5 \times 10^{-7}$) and pNKCC2 (56% on low Na, $p=0.04$ & 57% on low K diet, $p=0.002$) than SPAK-KO (100%). On normal diet we found lower pNCC in DKO (40%, $p=0.01$) than in SPAK-KO but surprisingly no difference in pNKCC2. Total-NKCC2 and total-NCC levels did not differ between the strains on any diet except on low K diet where total-NCC was lower in DKO (74%, $p=0.003$) than in SPAK-KO. Surprisingly, levels of pS126-NKCC2, a non-SPAK/OSR1 target site, were lower in DKO (52%, $p=0.0003$) on normal diet. DKO displayed lower plasma potassium than SPAK-KO mice on normal (3.35 vs 3.71 mmol/L, $p=0.05$), low Na (2.83 vs 3.44 mmol/L, $p=0.00001$) and low K (2.08 vs 3.11 mmol/L, $p=6 \times 10^{-6}$) diet. Unexpectedly, urinary Na did not differ between strains, and DKO did not show lower BP than SPAK-KO.

Conclusions: Our data suggest that SPAK/OSR1 play more important roles in K homeostasis than in Na and BP homeostasis. Even after disrupting SPAK/OSR1, there was NKCC2 phosphorylation at sites reported to be SPAK/OSR1-dependent, suggesting alternative pathways for phosphorylation at these sites. Finally, disruption of SPAK/OSR1 reduced levels of pS126-NKCC2.

TH-OR082

Inducible Kidney-Specific KCNJ10 Knockout Mice Show a Salt Losing Phenotype Catherina A. Cuevas,¹ James A. McCormick,¹ Andrew Terker,¹ Chao-Ling Yang,¹ WenHui Wang,³ David H. Ellison.¹ ¹Dept of Medicine, Oregon Health & Science Univ, Portland, OR; ²Portland VA Medical Center, Oregon Health & Science Univ, Portland, OR; ³Pharmacology, New York Medical College, Valhalla, NY.

Background: Missense mutations of KCNJ10 cause EAST/SeSAME syndrome, which is characterized by epilepsy, ataxia, sensorineural deafness and a salt-wasting tubulopathy resembling Gitelman syndrome. KCNJ10 encodes the Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron. KCNJ10^{-/-} mice have a severe phenotype and die during the first two weeks of life, limiting the usefulness of this model. Results obtained in young mice show reduced basolateral K⁺ conductance, sodium chloride transporter (NCC) and SPAK (Ste20-related proline alanine rich kinase) abundances. Here, we determine the renal phenotype of kidney-specific KCNJ10^{-/-} adult mice.

Methods: Doxycycline-inducible kidney-specific KCNJ10^{-/-} mice were generated using the TetOn/CreLoxP system under the control of Pax8 promoter. Doxycycline was administered for two weeks in the drinking water (0.2 mg/ml in 5% sucrose) of 2 month old mice. Biochemical parameters were assayed in urine, blood or renal tissue in KS-KCNJ10^{-/-} mice after two weeks of the end of doxycycline treatment.

Results: Kir4.1 was absent in the KS-KCNJ10^{-/-} mice, which displayed hypokalemia, hypochloremia with metabolic alkalosis, hypocalciuria, polyuria, and renal loss of sodium and potassium ($P<0.05$). At protein level, we observed that disruption of KCNJ10 decreased the expression of NCC and pNKCC2 (Na⁺-K⁺-Cl⁻ cotransporter) without affecting the levels of WNK4 (with no lysine kinase 4) and SPAK.

Conclusions: In conclusion, disruption of KCNJ10 in adult mice induces a severe renal phenotype highlighted by hypokalemic metabolic alkalosis and renal loss of sodium with hypocalciuria. In contrast to constitutive KCNJ10^{-/-} mice in which decreased of NCC and SPAK abundance may be explained by a reduction in DCT mass, the disruption of KCNJ10 in adult mice causes a sodium wasting phenotype accompanied by decreased NCC and NKCC2 abundances, suggesting a more widespread tubulopathy involving both DCT and TAL in our model.

Funding: NIDDK Support

TH-OR083

HIV Vpr Antagonizes Mineralocorticoid Receptor Activity, Explaining Salt Wasting Koji Okamoto, Hewang Lee, Jeffrey B. Kopp, Shashi Shrivastav. *Kidney Section, NIDDK, NIH, Bethesda, MD.*

Background: Patients with HIV-associated-nephropathy (HIVAN) present with proteinuria but often lack edema, suggesting renal Na wasting. We have shown that the HIV accessory protein Vpr binds transcriptional regulators including the glucocorticoid-receptor and PPAR-g and b/d. We investigated whether Vpr regulates mineralocorticoid-receptor (MR) activity.

Methods: We have developed transgenic mice that express Vpr in proximal tubules (PEPCK/rTA-X-TetOp/Vpr). Wild type and transgenic mice were fed a high protein diet for 2 weeks to induce transgene expression. After 6 days on a Na deficient diet, urine and kidneys were obtained. A human distal cortical tubular (DCT) cell line was exposed to soluble Vpr (100 ng/mL) and aldosterone (10⁻⁸ mM).

Results: On low salt diet, Vpr transgenic mice, compared to wild-type mice, manifested renal Na wasting (28±3 vs 15±2 mmol/g body weight/d) and an increased fractional Na excretion (2.0% vs 0.7%). We examined renal RNA expression of the thiazide-sensitive cotransporter (TSC), NHE, ATP1A1, NKCC2, NaPi-2A and only TSC was decreased in Vpr mice. As TSC expression is regulated by MR, we focused the effect of Vpr on MR function. In a promoter reporter assay in CV1 cells, Vpr reduced aldosterone-stimulated MMTV and TSC promoter activity. We hypothesized that Vpr binds MR and inhibits its transcriptional activity. Using immunoprecipitation, we found that Vpr, but not Vpr with LXXLL motif mutations, bound recombinant MR. We reasoned that the interaction between Vpr and MR might interfere with the folding of the MR signal peptide, preventing nuclear entry, or might prevent MR from binding to promoter sequences. We performed WB using nuclear extracts from DCT cells and IHC, following exposure to Vpr and/or aldosterone. Vpr

inhibited nuclear entry of MR. Using genome-wide ChIP sequencing with MR antibody in distal tubules cell line with aldosterone±Vpr, we found that the peak signal of TSC promoter was disappeared after treatment with Vpr.

Conclusions: Vpr binds MR and inhibits MR transcriptional activity, providing a molecular mechanism for renal salt wasting in HIVAN.

Funding: NIDDK Support

TH-OR084

The Sodium/Proton Exchanger NHA2 Is a Novel Regulator of Sodium, Calcium and Blood Pressure Homeostasis in the Distal Convoluted Tubule of the Kidney Manuel Andreas Anderegg,^{1,2} Giuseppe Albano,^{1,2} Ganesh Pathare,^{1,2} Daniel G. Fuster.^{1,2} ¹Division of Nephrology, Hypertension and Clinical Pharmacology, Univ of Bern, Bern, Switzerland; ²Dept of Clinical Research, Univ of Bern, Bern, Switzerland; ³Dept of Anatomy, Univ of Zürich, Zürich, Switzerland.

Background: NHA2 (also known as SLC9B2) is a sodium/proton exchanger expressed in the kidney, but its function there remains unknown.

Methods: We performed in vitro and in vivo experiments to elucidate the physiological role of NHA2 in the kidney.

Results: We found NHA2 expression restricted to distal convoluted tubules in both murine and human kidney. By confocal imaging, NHA2 had an apical to subapical tubular localization. Blood pressure, measured by invasive telemetry, was significantly lower in NHA2 KO mice compared to WT mice on low, normal and high sodium diets. In addition, NHA2 KO mice exhibited normocalcemic hypocalciuria with reduced plasma PTH but unaltered 1,25-OH Vitamin D3 levels. Interestingly, immunoblotting of kidney lysates revealed reduced phosphorylation of the sodium/chloride co-transporter (NCC) in NHA2 KO mice. Similarly, phosphorylation of SPAK, as well as the abundance of WNK4, kinases regulating NCC phosphorylation, was reduced in kidney lysates of KO mice, compared with those of WT mice. In line with these findings, NHA2 KO mice exhibited a reduced natriuretic response to hydrochlorothiazide compared to WT mice. In the DCT cell line mpkDCT₄, stimulation of NCC phosphorylation was reduced upon siRNA mediated knockdown of NHA2 compared with control siRNA treated cells. In addition, knockdown of NHA2 led to a decreased WNK4 abundance and an increase of WNK4 ubiquitylation.

Conclusions: These results indicate that the renal phenotype observed in vivo upon loss of NHA2 is a result of increased degradation and therefore reduced abundance of WNK4 in the kidney.

Together, our data reveal the sodium/proton exchanger NHA2 as a novel regulator of calcium, sodium and blood pressure homeostasis in the distal convoluted tubule of the kidney.

Funding: Government Support - Non-U.S.

TH-OR085

Transgenic Mice Expressing APOL1-G0 or APOL1-G2 in Podocytes Do Not Develop Kidney Disease Leslie A. Bruggeman,¹ Zhenzhen Wu,¹ Liping Luo,¹ Sethu M. Madhavan,¹ Martha Konieczkowski,¹ Paul E. Drawz,² L. Barisoni,³ John R. Sedor,¹ John F. O'Toole.¹ ¹Medicine, MetroHealth Medical Center, Case Western Reserve Univ, Cleveland, OH; ²Medicine, Univ of Minnesota, Minneapolis, MN; ³Pathology, Univ of Miami, Miami, FL.

Background: Variants in Apolipoprotein L1 (APOL1) associate with non-diabetic kidney diseases in African Americans, however, the mechanism of renal injury associated with APOL1 risk variants remains unknown.

Methods: Since APOL1 is present only in humans and some other primates, we created transgenic mice (FVB/N strain) expressing the reference allele of APOL1 (G0) and a risk variant (G2) in podocytes using the Nephhrin promoter. Mice were phenotyped for APOL1 expression, podocyte injury, and renal disease.

Results: Numerous founders for both G0 (n=29) and G2 (n=8) were obtained and progeny transmitted the transgenes consistent with Mendelian expectations. Founders and offspring expressed variable levels of APOL1 in podocytes, but even in the highest expressing G0 and G2 mice, markers for necrosis, apoptosis, or autophagic cell death were not identified in podocytes. Aged (~300days) G0 and G2 mice did not develop spontaneous kidney pathology, proteinuria, or azotemia. An unexpected phenotype in G0 and G2 founders and their offspring was sporadic seizures and sudden death during pregnancy. Pregnant mice from both G0 and G2 models exhibited hallmarks of preeclampsia including hypertension, proteinuria, glomerular endothelial damage, and elevated sFlt-1 levels. APOL1 was expressed in placental tissues, confirming prior reports of placental expression of Nephhrin and APOL1.

Conclusions: Constitutive expression of the APOL1 G0 and G2 protein in vivo was not cytotoxic to podocytes regardless of expression level, mimicking the observations in humans that APOL1 risk genotypes are insufficient to cause kidney disease in the absence of an additional stressor. The preeclampsia phenotype was not variant-dependent and may represent placental injury related to ectopic transgene expression, however, a role for APOL1 in placental function may warrant further investigation.

Funding: NIDDK Support

TH-OR086

Kidney Disease Associated Variants of Apolipoprotein L1 Changes Conformational Dynamics of the C-Terminal Domain Sethu M. Madhavan,¹ John F. O'Toole,¹ Martha Konieczkowski,¹ Zhenzhen Wu,¹ Yaping Gu,¹ Leslie A. Bruggeman,¹ Matthias Buck,² John R. Sedor.^{1,2} ¹Medicine, MetroHealth System; ²Physiology and Biophysics, Case Western Reserve Univ, Cleveland, OH.

Background: *APOL1* risk variants associate with non-diabetic kidney diseases in African Americans; however, the mechanisms of variant *APOL1*-mediated kidney injury remain unknown. We have shown a SNARE protein VAMP8 interacts with the C-terminus of *APOL1*; *APOL1* variants change the C-terminal amino acid sequence and attenuate this interaction. Given this, we hypothesize that the structures of variant *APOL1*s are altered and disrupt protein interactions.

Methods: We modeled the 3D structure of the *APOL1* C-terminus (residues 305-398) with the threading program ITASSER. We expressed the C-terminus of *APOL1* with and without variants, (G0: reference, G1: S342G & I384M, and G2: del388-389NY) and used circular dichroism (CD) spectroscopy to experimentally verify the predicted secondary structure. Molecular Dynamics (MD) simulations assessed conformational behavior over time of G0, G1 and G2. PyMOL software modeled the *APOL1*:VAMP8 interaction.

Results: The computationally modeled structures of G0, G1, and G2 (residues 305-398) initially overlapped as three α -helices folded into a bundle, linked by short loops, and CD spectroscopy confirmed the predicted alpha helical content. *APOL1*-G0 adopted an "open" conformation in MD simulations (over 40 ns) while the G1 and G2 variants both remained in a "closed" conformation, assessed as *Ca* deviation from starting structure. Fluctuations of the Cas over the last 10 ns and principal component analysis of protein motion also demonstrated increased mobility of the G0 C-terminus compared to G1 and G2. *De novo* formation of intramolecular H-bonds mediated the structural stability of G1 and G2. The *APOL1*-G0:VAMP8 interaction is most stable with a 3:1 stoichiometry and does not involve the G1 and G2 residues.

Conclusions: *APOL1*-G0 adopts an "open" conformation but G1 and G2 both generate a "closed" C-terminal conformation, which limits protein interactions and explains attenuation of the *APOL1*:VAMP8 interaction. Kidney disease induced by G1 and G2 may result from protein conformational changes that limit interactions with SNARE proteins.

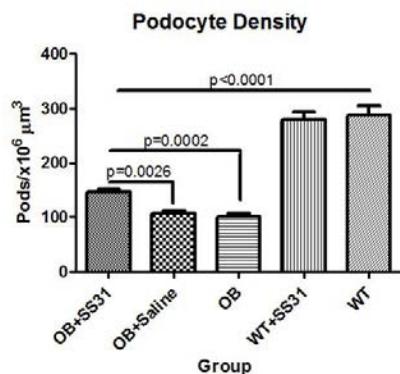
TH-OR087

SS-31, a Peptide Targeting Mitochondria, Restores Podocytes in Diabetic Nephropathy (DN) in BTBR *ob/ob* Mice Minseob Eom,¹ Anna Batorsky,¹ Hazel H. Szeto,² Dao-fu Dai,¹ Kelly L. Hudkins,¹ Charles E. Alpers.¹ ¹Pathology, Univ of Washington School of Medicine, Seattle, WA; ²Pharmacology, Weill Cornell Medical College, New York, NY.

Background: SS-31 is a novel peptide that selectively binds to cardiolipin in the inner mitochondrial membrane, where it prevents cardiolipin peroxidation and protects mitochondrial structure. We investigated the renoprotective effects of SS-31 in the BTBR *ob/ob* mice with advanced DN.

Methods: 18 week male diabetic BTBR *ob/ob* and wild type (WT) mice were randomly assigned to 5 groups: *ob/ob* with infusion of SS-31 via osmotic pump for 6 weeks, *ob/ob* with saline infusion, untreated *ob/ob*, WT, and WT with SS-31 infusion. Podocyte density, mesangial matrix (% tuft area occupied by collagen IV matrix), and glomerular macrophages were quantified by morphometry and immunohistochemistry.

Results: Podocyte density, diminished in *ob/ob* mice, was significantly restored in *ob/ob* with SS-31 infusion (147.2 ± 6.33 podocytes/ $10^6 \mu\text{m}^2$) compared with saline treated *ob/ob* mice (107.6 ± 4.78) or untreated mice (100.5 ± 6.14) ($p=0.0026$ & 0.0002).



Mesangial matrix was reduced in the *ob/ob* with SS-31 treatment (30.9 ± 0.61 %) compared to *ob/ob* with saline treated (45.2 ± 2.15) and untreated mice (46.5 ± 1.29) ($p<0.0001$). Macrophage infiltration was lower in *ob/ob* treated with SS-31 (1.3 ± 0.36 cells/glomerulus) than untreated *ob/ob* (1.9 ± 0.36) ($p=0.02$). Albumin-creatinine ratio was decreased in *ob/ob* with SS-31 (276.8 ± 60.14 mg/mg), compared with the untreated *ob/ob* (671.8 ± 250.60), but results were not statistically significant.

Conclusions: Podocyte density was restored and mesangial matrix decreased in SS-31 treated diabetic *ob/ob* mice, compared to saline treated and untreated controls. SS-31, currently in human clinical trials for other diseases, may be useful in treatment of DN and potentially other glomerular diseases in which podocytes are lost.

Funding: NIDDK Support

TH-OR088

Genetic and Pharmaceutical Targeting of GSK3 β in Podocytes Reinforces the Nrf2 Antioxidant Response and Ameliorates Podocytopathy and Proteinuria Sijie Zhou,¹ Yan Ge,¹ Zhangsuo Liu,² Rujun Gong.¹ ¹Nephrology, Brown Medical School; ²Nephrology, The First Affiliated Hospital of Zhengzhou Univ, China.

Background: Evidence suggests that the GSK3 β dictated Nrf2 nuclear exclusion and degradation is pivotal for switching off the self-protective antioxidant response following injury. This study aimed to examine the role of the GSK3 β regulated Nrf2 antioxidant response in podocyte pathobiology.

Methods: The regulatory effect of GSK3 β on Nrf2 response was examined in cultured podocytes and in a murine model of adriamycin nephropathy by genetic targeting of GSK3 β or by using SB216763, a selective small molecule inhibitor of GSK3.

Results: In cultured podocytes, adriamycin injury caused cell death, concomitant with GSK3 hyperactivity and minimal Nrf2 activation. Inhibition of GSK3 by SB216763 exerted a pro-survival effect, which was dependent on the enhanced Nrf2 antioxidant response, marked by increased expression and nuclear accumulation of Nrf2 and elevated production of the Nrf2-target hemoxygenase-1. Ectopic expression of the kinase-dead mutant of GSK3 β , the isoform of GSK3 predominantly expressed in glomerular podocytes, reinforced the Nrf2 antioxidant response upon adriamycin injury and prevented cellular death. Conversely, GSK3 β overactivity induced by a constitutively active mutant resulted in a blunted Nrf2 response and exacerbated podocyte death following adriamycin injury, which could be abolished by SB216763. In adriamycin injured mice, genetic targeting of GSK3 β by the doxycycline inducible podocyte specific knockout or pharmaceutical targeting by SB216763 attenuated albuminuria and ameliorated podocytopathic lesions, including glomerulosclerosis, loss of podocyte markers, *de novo* expression of podocyte injury marker desmin and ultrastructural changes of podocytes, like foot process effacement. This beneficial outcome was likely attributable to the enhanced Nrf2 response in podocytes, because trigonelline, a selective antagonist of Nrf2, largely abrogated the proteinuria reducing and podoprotective effect.

Conclusions: The GSK3 β regulated Nrf2 antioxidant response might represent a novel therapeutic target to protect podocytes and treat proteinuric glomerulopathies.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR089

Ablation of Podocyte-Derived Wnts Aggravates Proteinuria and Kidney Injury Dong Zhou,¹ Haiyan Fu,¹ Roderick J. Tan,² Youhua Liu.¹ ¹Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; ²Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Activation of canonical Wnt signaling has been implicated in podocyte injury and proteinuria. However, as Wnts are secreted extracellular signal proteins, whether podocyte-derived Wnts are obligatory for developing proteinuria remains elusive. Wntless (Wl), a cargo receptor protein, is required for the secretion of Wnt proteins.

Methods: We generated conditional knockout mice in which Wl was specifically deleted in podocytes by using the Cre-LoxP system. The mice were subjected to adriamycin administration, and urine and kidney were analyzed at 7 days and 21 days, respectively. We utilized another proteinuric kidney disease model by chronic infusion of angiotensin II for 4 weeks.

Results: Mice with podocyte-specific ablation of Wl (podo-Wl^{-/-}) developed normally. No albuminuria or overt pathologic lesions was observed up to 6 months of age, suggesting that Wl is dispensable for podocyte maturation, survival, and function under normal physiologic conditions. However, after adriamycin treatment for 7 days, podo-Wl^{-/-} mice developed more severe podocyte injury and albuminuria than their control littermates. Surprisingly, ablation of Wl resulted in even more profound upregulation of β -catenin, accompanied by reduction and aberrant distribution of nephrin, Wilms tumor 1 (WT1), synaptopodin, and podocalyxin. In chronic injury induced by adriamycin or Ang II infusion, increased albuminuria, aggravated podocyte lesions and extracellular matrix deposition were evident in Podo-Wl^{-/-} mice. Mechanistically, specific ablation of Wl in podocyte caused significant down-regulation of Dickkopf-3 expression. Meanwhile, NFAT1, a key downstream mediator in non-canonical Wnt signaling, was largely inhibited in Podo-Wl^{-/-} mice after ADR injection.

Conclusions: These results indicate that podocyte-derived Wnts may play an important role in protecting podocytes from injury by repressing canonical Wnt/ β -catenin signaling via promoting Dickkopf-3 expression and activating non-canonical pathway.

Funding: NIDDK Support

TH-OR090

Blockade of Wnt/ β -Catenin Signaling Exhibits Superior Therapeutic Efficacy Than RAS Inhibition in CKD Zhen Li,¹ Lili Zhou,¹ Xue Hong,¹ Youhua Liu,^{1,2} ¹Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; ²Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA.

Background: CKD has become a public health problem worldwide. Treatment options for CKD are limited and ineffective, underscoring enormous unmet medical need. The mainstay of clinical therapy for CKD is inhibition of renin-angiotensin system (RAS), using angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II type 1 receptor (AT1) blocker (ARB). However, current therapy with RAS inhibition is insufficient, partially because of compensatory upregulation of renin expression. Thus it is paramount to develop new therapeutic strategy with better outcomes.

Methods: Using two mouse models of CKD induced by adriamycin (ADR) or unilateral ischemic/reperfusion injury (UIRI), we directly compared the therapeutic efficacy of small-molecule Wnt/ β -catenin inhibitor ICG-001 with trandolapril (ACEI) alone, or the combination of trandolapril and losartan (ARB). The effect of renin on fibroblast activation was also assessed in vitro.

Results: Compared to ACEI, or ACEI plus ARB, ICG-001 displayed superior therapeutic efficacy in both models. ICG-001 almost completely abolished proteinuria, ameliorated glomerular injury and fibrotic lesions and reduced serum creatinine in ADR nephropathy, whereas trandolapril, or trandolapril plus losartan only displayed as 50% efficacy as ICG-001. Similar results were obtained in UIRI model. We found that ICG-001 completely abolished renal expression of all RAS components including angiotensinogen, renin, ACE and AT1 in both models. However, trandolapril or trandolapril plus losartan actually induced angiotensinogen and renin expression in the kidneys. In vitro, incubation of kidney interstitial fibroblasts (NRK-49F) with renin protein induced fibronectin expression, and this effect was dependent on ERK-1/2 activation. Losartan did not block renin-induced fibronectin expression, suggesting that renin elicited its effect by an angiotensin II-independent mechanism.

Conclusions: Our studies demonstrate that blockade of Wnt/ β -catenin, the master upstream regulator of all RAS genes, has superior therapeutic efficacy for the treatment of CKD than RAS inhibition.

Funding: Government Support - Non-U.S.

TH-OR091

Distinct Populations of FOXD1-Derived Renal Interstitial Cells Regulate Erythropoietin Production Hanako Kobayashi, Volker H. Haase. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: In adults, the kidney is the main physiologic production site of erythropoietin (EPO), a hypoxia-inducible factor (HIF)-2-regulated hormone that is essential for normal erythropoiesis. However, renal EPO producing cells (REPCs) are poorly characterized and their histogenetic origin is ill-defined.

Methods: To investigate the hypoxic regulation of renal EPO, we targeted the EPO/HIF-2/prolyl-4-hydroxylase domain (PHD) oxygen-sensing pathway in renal interstitial cells using *Foxd1-Cre* transgenic mice and simultaneously labeled REPCs with green fluorescent protein (GFP). FOXD1 is expressed in embryonic stromal cells that give rise to renal pericytes and peritubular interstitial fibroblasts.

Results: In order to determine to what degree FOXD1-lineage cells contribute to EPO homeostasis, *Epo* or *Hif2a* were deleted (*Foxd1-Epo*^{-/-} or *Foxd1-Hif2a*^{-/-}). As expected, *Foxd1-Epo*^{-/-} and *Foxd1-Hif2a*^{-/-} mice developed anemia. While pharmacologic PHD inhibition and hypoxia exposure (10% O₂ for 2 days) increased renal *Epo* mRNA and serum EPO (sEPO) levels in control mice, the renal EPO response was completely abrogated in both mutants, demonstrating that REPCs are exclusively derived from FOXD1-expressing stroma. To investigate the role of individual PHDs, we inactivated PHD1, PHD2 and/or PHD3 in FOXD1-lineage cells and used multi-color fluorescent *in situ* hybridization for a detailed characterization of the REPC pool. Deletion of PHD2 alone (*Foxd1-Phd2*^{-/-}), but not of PHD1 or PHD3, was sufficient to induce *Epo* in a subpopulation of GFP⁺ interstitial cells (0.8 ± 0.5% in control vs. 39.0 ± 5.5% in *Foxd1-Phd2*^{-/-} mutants). However, EPO synthesis was induced in additional GFP⁺ *Phd2*^{-/-} cells following hypoxia exposure or PHD3 deletion (73.0 ± 4.1% and 64.1 ± 8.4% respectively).

Conclusions: Our genetic studies demonstrate that REPCs consist of at least two distinct subpopulations, a) a PHD2-sensitive cell population and b) a subpopulation, in which in addition to PHD2 inactivation, hypoxia and/or PHD3 inactivation are required for EPO induction. In summary our data suggest that REPCs are entirely FOXD1 stroma-derived and are heterogeneous with regard to HIF-2-dependent oxygen sensing and their ability to synthesize EPO.

Funding: NIDDK Support, Veterans Administration Support

TH-OR092

microRNA-21 in Human Glomerular Aging Christopher Lund O'Connor, Yifan Wu, Harkamal Singh Jhaji, Jeffrey B. Hodgin, Markus Bitzer. *Internal Medicine, Univ of Michigan, Ann Arbor, MI.*

Background: Loss of podocytes is sufficient to cause progressive glomerulosclerosis (the podocyte depletion hypothesis). We have recently shown that podocytes loss and glomerular hypertrophy are critical phenotypes of normal human aging (Hodgin, Bitzer, et al. JASN 2015) and that lack of miR-21 accelerates podocyte loss in murine models of glomerular injury. We now explore the role of miR-21 in aging of human and mouse glomeruli.

Methods: Kidney tissue samples were collected from 41 patients who underwent unilateral nephrectomy at the University of Michigan. 10 computer-assisted glomerular morphometric parameters were assessed in formalin fixed paraffin embedded sections by standard chemical and immunohistochemical stains. Gene expression profiles (Affymetrix human ST 2.1) and small RNA expression (Illumina tru-seq) were generated from RNA isolated from micro-dissected glomeruli and corresponding tubulointerstitium of the same individuals. Associations between gene expression and quantitative phenotypes were then determined. In addition miR-21 deficient mice and wild type littermates (C57BL/6J and DBA/2J; n≥6 for each genotype) were aged to in excess of two years and assessed for the same morphometric parameters.

Results: In human kidneys podocyte density declined with age and was significantly associated with increases in mesangial index (p=0.003), podocyte cytoplasmic size (p<0.001) and focal global glomerulosclerosis (FGGS) (p=0.009). FGGS was significantly associated with interstitial fibrosis (p=0.006). miR-21 expression in glomeruli is positively correlated with podocyte density (p=0.041) and inversely correlated with mesangial index (p=0.02) and podocyte size (p=0.01). miR-21 expression increases with age in murine kidneys and miR-21-null mice exhibited decreased podocyte density (p<0.001) and increased mesangial index (p=0.001) compared to wildtype littermates.

Conclusions: Both humans and mice experience an age-associated loss of loss of podocytes, and a concomitant increase in podocyte size and mesangial index. In mice miR-21 ameliorates phenotypes of glomerular aging. Candidate transcripts targeted by miR-21 that may mediate the observed phenotypes are being explored.

Funding: NIDDK Support, Other NIH Support - NIA

TH-OR093

Murine Double Minute-2 Inhibition Ameliorates Established Crescentic Glomerulonephritis Dana Thomasova, Shrikant R. Mulay, Simone Romoli, Santhosh Kumar Vr, Jayasi Desai, Hans J. Anders. *Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Klinikum der Univ München, Munich, Germany.*

Background: Rapidly progressive glomerulonephritis (RPGN) is characterized by glomerular necroinflammation and crescent formation. The E3-ubiquitin ligase murine double minute (MDM)-2 is a non-redundant element of NF- κ B signalling and the negative regulator of p53-mediated cell cycle arrest. We hypothesized that the MDM2 would drive crescentic GN via NF- κ B-dependent glomerular inflammation and via p53-dependent parietal epithelial cell (PEC) hyperproliferation.

Methods: We used injection of 75 μ l of sheep anti-rat anti-GBM serum in C57BL/6 wild type and p53-deficient mice to induce crescentic GN and injection of MDM2 inhibitor nutlin-3a or vehicle every alternate day starting on day -1 for pre-emptive or day +1 for therapeutic intervention. Evaluation was performed 7 days after antiserum injection. For in vitro studies murine glomerular endothelial cells and PECs were transfected with MDM2 or p53 siRNA and analysed with qPCR or proliferation assay.

Results: The pre-emptive MDM2 blockade with nutlin-3a ameliorated all aspects of crescentic GN such as vascular necrosis, podocyte loss, glomerular crescent formation, albuminuria, as well as inflammation, preventing cytokine induction, and recruitment of glomerular leukocytes and macrophages. MDM2 inhibition with nutlin-3a had identical protective effects in p53 knockout mice, with the exception of crescent formation. In vitro experiments confirmed the MDM2 requirement for induction of NF- κ B-dependent cytokines in murine glomerular endothelial cells as well as the p53-dependency of MDM2-mediated PEC proliferation. To evaluate MDM2 blockade as a therapeutic intervention in RPGN, we treated mice with established GN with nutlin-3a. Delayed onset of nutlin-3a treatment was equally protective as the pre-emptive treatment in abrogating crescentic GN.

Conclusions: The pathogenic effects of MDM2 are mostly p53-independent, associated with NF- κ B activation and increased intraglomerular inflammation, but the p53-dependent function of MDM2 regulates the PEC proliferation and crescent formation. We therefore propose MDM2 blockade as a potential novel therapy in RPGN.

TH-OR094

The Bone Marrow Initiates and Propagates suPAR-Mediated Kidney Disease Eunsil Hahm,¹ Changli Wei,¹ Isabel Fernandez,¹ Jing Li,¹ Nicholas J. Tardi,¹ Shikha Wadhvani,¹ Vineet Gupta,¹ Sanja Sever,² Jochen Reiser.¹ ¹Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL; ²Div of Nephrology, Massachusetts General Hospital, Charlestown, MA.

Background: Proteinuria is a hallmark of glomerular kidney dysfunction, seen in both, native and post-transplant focal segmental glomerulosclerosis (FSGS). Systemic soluble urokinase plasminogen activator receptor (suPAR) is implicated in FSGS, yet the origin of suPAR in FSGS remains unclear.

Methods: Humanization techniques, adoptive transfer, cell depletion, ELISA, flow cytometry, histology, and electron microscopy were performed.

Results: Here we report that bone marrow (BM) myeloid progenitor cells (MPCs) are responsible for the production of suPAR, resulting in kidney damage and proteinuria. Using a xenograft mouse model, we found that engraftment of CD34⁺ peripheral blood mononuclear cells (PBMCs), but not CD34⁻ PBMCs, from patients with recurrent FSGS into immunocompromised mice resulted in an expansion of Gr-1⁺ murine BM myeloid cells, leading to proteinuria and FSGS-like glomerulopathy. Furthermore, adoptive transfer experiments demonstrated that Gr-1⁺ BM myeloid cells are capable of causing suPAR-mediated proteinuria and therefore transmitting disease in healthy mice. We immunophenotypically characterized uPAR⁺ Sca-1⁻ Gr-1⁺ cells as "diseased" BM myeloid progenitor cells (MPCs), which are responsible for the production of suPAR competent to investigate kidney damage and proteinuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Collectively, these results reveal a novel connection between bone marrow and kidney, and implicate myeloid progenitor cells as initiators of glomerular dysfunction with particular relevance to post-transplant FSGS.

Funding: NIDDK Support

TH-OR095

C-Reactive Protein and Myeloid Derived Suppressor Cells in Acute Kidney Injury Alexander J. Szalai, Melissa A. Pegues. *Dept of Medicine, The Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Myeloid derived suppressor cells (MDSCs) are best known for their anti-proliferative effects on immune cells. Their contribution in renal cell carcinoma and chronic kidney disease has been investigated and their association with kidney transplant survival documented, but their role in acute kidney injury (AKI) has not been studied. Renal ischemia reperfusion injury (IRI) is a frequent cause of AKI: the former triggering a systemic inflammatory response that leads to increased blood levels of C-reactive protein (CRP), a biomarker of worsened outcomes. Recently, using a CRP transgenic mouse (CRPtg) model of renal IRI, we provided direct evidence that CRP is causal in AKI, i.e. its expression exacerbates renal IRI. The purpose of the present study was to determine if this harmful effect of CRP was propelled by increased infiltration of inflammatory cells into the injured kidneys.

Methods: We compared myeloid cell populations in the kidneys of wild type (WT), human CRP transgenic (CRPtg), and CRP deficient (CRP^{-/-}) mice subjected to bilateral renal IRI.

Results: In CRP^{-/-}, which were nearly refractory to renal IRI, there was almost complete absence of MDSCs of the granulocytic subtype (g-MDSC; Gr-1^{CD11b}⁺Ly6g^{high}Ly6c^{low} cells identified by flow cytometry of kidney digest cells) in the injured kidneys. In stark contrast in CRPtg, wherein renal IRI was exaggerated, there was an abundance of g-MDSCs in the injured kidneys. Using *in vitro* T-cell proliferation assays we confirmed that these renal g-MDSCs were suppressive and *in vivo* in CRPtg, depletion of g-MDSCs prior to renal IRI (using anti-Gr-1 antibody) reduced serum/urine biomarkers of AKI. Importantly, CRPtg treated with an antisense oligonucleotide that specifically lowered human CRP levels, showed both dramatic improvement in renal biomarkers of AKI and dramatic reduction in renal infiltration of g-MDSCs after AKI.

Conclusions: To our knowledge these are the first data showing that (i) g-MDSCs contribute to the renal response to IRI and that (ii) CRP amplifies this contribution. By reducing g-MDSC infiltration into the injured kidney, CRP lowering therapy might be an effective treatment option for AKI.

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TH-OR096

C-Reactive Protein Promotes AKI by Impairing TEC Regeneration via the CD32-Smad3-p27 Dependent Inhibition of CKD2/Cyclin E Mechanism Xiao Ru Huang,¹ Weiyang Lai,² Ying Tang,³ Tan-qi Lou,² Hui Y. Lan.¹ ¹*Dept of Medicine & Therapeutics, Li Ka Shing Inst of Health Sciences, and Shenzhen Research Inst, The Chinese Univ of Hong Kong, Hong Kong, China;* ²*Dept of Nephrology, The Third affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, China;* ³*Dept of Nephrology, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen Univ, Guangzhou, China.*

Background: We have previous shown that C-reactive protein (CRP) plays a pathogenic role in acute kidney injury (AKI) by inhibiting tubular epithelial cell (TEC) regeneration. The present study tested a hypothesis that CRP may promote AKI via Smad3-p27 dependent inhibition of CKD2/cyclin E-mediated TEC regeneration *in vivo* and *in vitro*.

Methods: The hypothesis was examined in a mouse model of AKI induced in human CRP transgenic/Smad3 knockout (CRP-Tg/Smad3-KO), CRP-Tg/Smad3-WT, CRP-WT/Smad3-KO, and CRP-WT/Smad3-WT mice by clamping bilateral renal arteries for 40 minutes and in cultured HK-2 TEC line.

Results: After 24 hours of AKI, CRP-WT/Smad3-WT showed a significant increase in serum levels of creatinine and severe tubular necrosis, which was further enhanced in CRP-Tg/Smad3-WT mice but blunted in CRP-Tg/Smad3-KO and CRP-WT/Smad3-KO mice. Further studies revealed that enhanced AKI in CRP-Tg/Smad3-WT mice was associated with a marked activation of TGF- β /Smad3, upregulation of p27, and inactivation of CKD2 kinase, thereby reducing cyclin E expression and impairing TEC proliferation as determined by BrdU incorporation and PCNA. In contrast, deletion of Smad3 in CRP-Tg mice prevented the development of AKI as demonstrated by normalizing serum levels of creatinine and suppressing the Smad3-p27 pathway, thereby promoting CKD2/cyclin E-dependent TEC proliferation. *In vitro* studies confirmed these findings that CRP acted through its receptor CD32b to activate Smad3 signaling via both TGF- β -dependent and ERK/MAPK crosstalk pathway. Furthermore, we also found that activated Smad3 then bound directly to p27 to suppress CKD2/cyclin E-dependent TEC proliferation, which was inhibited by a Smad3 inhibitor (SIS3).

Conclusions: CRP promotes AKI by impairing the TEC regeneration via the CD32-Smad3-p27 mediated inhibition of CKD2/cyclin E mechanism.

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TH-OR097

Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO May M. Rabadi, Mihwa Kim, Kevin M. Brown, H. Thomas Lee. *Anesthesiology, Columbia Univ, New York, NY.*

Background: Ischemic acute kidney injury (AKI) is a devastating clinical problem without effective therapy. We recently showed that peptidylarginine deiminase-4 (PAD4) that converts peptidylarginine to peptidylcitrulline plays a critical role in ischemic AKI by promoting renal tubular inflammation. We hypothesized that PAD4 induces renal inflammation and exacerbates AKI by citrullinating IKK γ (also known as NF κ B Essential MOdulator or NEMO) and promoting renal tubular pro-inflammatory NF κ B signaling. Furthermore, we tested whether targeted NEMO inhibition attenuates renal inflammation and protects against ischemic AKI.

Methods: We first tested whether recombinant human PAD4 (1-10 mg/ml) directly citrullinates human recombinant NEMO or NEMO in human proximal tubule (HK-2) cells. We also tested whether NEMO neutralization with NEMO binding peptide (NBP, 10 μ M) attenuates rPAD4-mediated nuclear NF κ B translocation and induction of pro-inflammatory mRNAs in HK-2 cells. Finally, after Columbia IACUC approval, we tested whether NEMO neutralization (5 mg/kg) in mice attenuates rPAD4-mediated exacerbation of 20 min ischemic AKI and renal inflammation.

Results: rPAD4 directly citrullinated NEMO in a cell free system as well as in HK-2 cells. In addition, rPAD4 directly caused nuclear NF κ B-p65 subunit translocation which was attenuated by NEMO neutralization. Furthermore, NEMO neutralization significantly attenuated rPAD4-mediated induction of pro-inflammatory genes (MCP-1 by 59 \pm 11%, MIP-2 by 43 \pm 10%, TNF- α by 59 \pm 12% and IL-8 by 83 \pm 3%) in HK-2 cells (P<0.05, N=5-8). Finally, NEMO neutralization significantly attenuated rPAD4-mediated exacerbation of ischemic AKI (rPAD+veh Cr(mg/dL)=2.4 \pm 0.4 vs. rPAD+NBP Cr=1.2 \pm 0.1, N=6, P<0.01) and renal inflammation (assessed with pro-inflammatory gene expression, neutrophil infiltration) in mice.

Conclusions: Our studies show that PAD4 exacerbates ischemic AKI and inflammation by promoting renal tubular NF κ B activity via NEMO citrullination. Furthermore, we show that NEMO inhibition attenuates kidney injury and reduces the inflammatory response after renal IRI. Selective NEMO neutralization may serve as a potential therapy for this devastating clinical problem.

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TH-OR098

Severity, Frequency and Prevalence of Proximal Tubule Injury Determines Renal Prognosis Koji Takaori,¹ Jin Nakamura,¹ Tadashi Yamamoto,² Kumar Sharma,³ Motoko Yanagita.¹ ¹*Nephrology, Kyoto Univ, Kyoto, Japan;* ²*Structural Pathology, Niigata Univ, Niigata, Japan;* ³*Center for Renal Translational Medicine and Inst of Metabolomic Medicine, Univ of California San Diego, San Diego, CA.*

Background: Acute kidney injury (AKI) increases the risk to develop chronic kidney disease (CKD) and end-stage renal disease, whereas the mechanisms linking AKI to CKD remain unclear. Because proximal tubule injury is the mainstay of AKI, we postulated that proximal tubule injury triggers several features of CKD.

Methods: We generated a novel mouse model to induce selective proximal tubule-specific adjustable injury by inducing the expression of diphtheria toxin receptor (DTR) in proximal tubules with variable prevalence (*Ndr1CreERT2:iDTR* mice). For *in vitro* analysis, we utilized co-culture of renal fibroblasts and tubular epithelial cells.

Results: Administration of high-dose diphtheria toxin (DT) faithfully causes severe proximal tubule-specific injury, associated with interstitial fibrosis and reduction of erythropoietin production. Mild proximal tubule injury from a single hit triggers reversible fibrosis, whereas repeated mild injuries cause sustained interstitial fibrosis, inflammation, glomerulosclerosis and atubular glomeruli. Fibroblasts co-cultured with damaged tubular cells exhibited the induction of extracellular matrix and inflammatory genes, supporting the crosstalk between these two cell types. Proximal tubule-specific injury also triggers distal tubule injury, implying the proximal-distal tubule crosstalk.

Conclusions: Our data provide new evidence that proximal tubule injury triggers several features of CKD, and that the severity, frequency and prevalence of proximal tubule injury determine the progression to CKD. Our results indicate that fibrosis after AKI is secondary to tubular injury, and that treatment of fibrosis itself might not be enough to halt AKI-to-CKD progression. There is an urgent need to develop therapeutic strategies to protect proximal tubules from repeated injury and to restore healthy proximal tubular function.

TH-OR099

Proximal Tubule Necroptosis Is Mediated by Mixed Lineage Kinase Domain Like (MLKL) In Vivo and Ex Vivo Andreas Linkermann,¹ Nina Himmerkus,² Ina Maria Schiessl,³ Hans J. Anders,⁴ Joel M. Weinberg,⁵ Alberto Ortiz,⁶ James M. Murphy,⁷ Ulrich Kunzendorf,¹ Jan H. Braesen,⁸ Markus Bleich,² Stefan Krautwald.¹ ¹*Clinic for Nephrology and Hypertension, Univ of Kiel, Kiel, Germany;* ²*Dept of Physiology, Univ of Kiel, Kiel, Germany;* ³*Inst for Physiology, Univ of Regensburg, Regensburg, Germany;* ⁴*Medizinische Klinik und Poliklinik IV, LMU Munich, Munich, Germany;* ⁵*Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI;* ⁶*Unidad de Dialisis, Fundacion Jimenez Diaz, Madrid, Spain;* ⁷*Div of Cell Signalling and Death, Walter and Eliza Hall Institute of Medical Research, Parkville, Australia;* ⁸*Dept of Pathology, University of Hanover, Hanover, Germany.*

Background: RIPK3-dependent necroptosis is of critical relevance for many diseases including hypoxic organ damage in AKI (Linkermann and Green, NEJM 2014). However, the putative downstream mediators, such as mixed lineage kinase domain like (MLKL) have not been investigated in detail, but may trigger local tissue inflammation in a process referred to as necroinflammation (Linkermann et al, NRI 2014). Ferroptosis, an iron dependent cell death, is thought not to be affected by MLKL.

Methods: We employed video-monitoring of microperfused freshly isolated renal tubules, intravital microscopy, biochemistry, and diverse *in vivo* models of AKI and SIRS in wild type, MLKL-deficient- and RIPK3-deficient mice in the presence of newly developed necrostatins and ferrostatins.

Results: MLKL-deficient mice exhibit stronger protection against all investigated models of AKI in direct comparison to RIPK3-deficient mice. In SIRS models, RIPK3 and MLKL-ko mice are protected compared to wild type littermates, but there is no statistically significant difference between these two. In intravital microscopy, MLKL-ko, unlike RIPK3-ko, do not exhibit wider peritubular capillaries compared to wild type, but the perfusion is increased due to increased flow. In isolated renal tubules, erastin-induced synchronized renal tubular necrosis was significantly attenuated in MLKL-ko mice.

Conclusions: We identify MLKL as a master regulator of AKI and SIRS. In contrast to RIPK3, which exclusively functions in necroptosis, MLKL might affect ferroptosis.

TH-OR100

NMN, a NAD⁺ Precursor, Can Rescue the Age-Associated Susceptibility to Cisplatin Induced Acute Kidney Injury in a SIRT1-Dependent Manner Yi Guan, Chuanming Hao. *Dept of Nephrology, Huashan Hospital, Shanghai, China.*

Background: AKI is a common critical condition, the incidence of which increases with age. SIRT1, a NAD⁺-dependent deacetylase, has been shown to have beneficial effect on both life span and renal health. NMN is a NAD⁺ precursor involved in NAD⁺ recycle and SIRT1 activity. This study explores the role of SIRT1 and NMN in age-associated AKI, and mechanism by which SIRT1 deficiency aggravates AKI.

Methods: Age-associated susceptibility to AKI was investigated using 3 month-old and 20 month-old 129 mice. The role of SIRT1 in AKI was examined using SIRT1 heterozygotes. AKI was induced by cisplatin(20mg/kg). Kidney damage was assessed by BUN, kidney histology and Tunel assay. Mitochondria was examined by electronic microscope. The signaling pathway involved was explored by microarray and validated by Q-PCR, western blot and co-IP.

Results: After exposed to cisplatin, the 20-month-old mice had a more severe acute kidney injury than 3-month-old. In the aged mice, the kidney NAD⁺ level was only 30% of that in the young (5.9±2.5vs19.9±5.9 pmol/mg protein), accompanied by reduced SIRT1 expression. SIRT1 deficiency(SIRT1^{-/-}) also significantly aggravated cisplatin-induced AKI compared to SIRT1 intact littermates. Severe mitochondrial dysfunction and cell damage was observed in proximal tubules of the AKI aged mice and SIRT1 knockouts. NMN, provided from the same day as cisplatin for 4days, markedly attenuated renal damage(BUN 78.31±18.16vs148.7±9.136, P<0.001). The effect of exogenous NMN was substantially reduced in SIRT1 deficient mice, suggesting that the protective effect of NMN was dependent on SIRT1 activity. Microarray suggests that JNK pathway is a critical signaling pathway associated with SIRT1 deficiency. Activation of JNK was validated by Q-PCR and Western blot. Co-IP experiment revealed DUSP16, a JNK dephosphorylase, might be regulated by SIRT1.

Conclusions: (1)In aged kidney, NAD⁺ level and SIRT1 expression is reduced, resulting in increased age-associated susceptibility to AKI;(2)Supplementation of NMN, a NAD⁺ precursor and a metabolite of a lipid lowering drug Niacin, rescued cisplatin-induced AKI;(3)JNK activation is associated with increased renal injury in SIRT1 deficient animals.

Funding: Government Support - Non-U.S.

TH-OR101

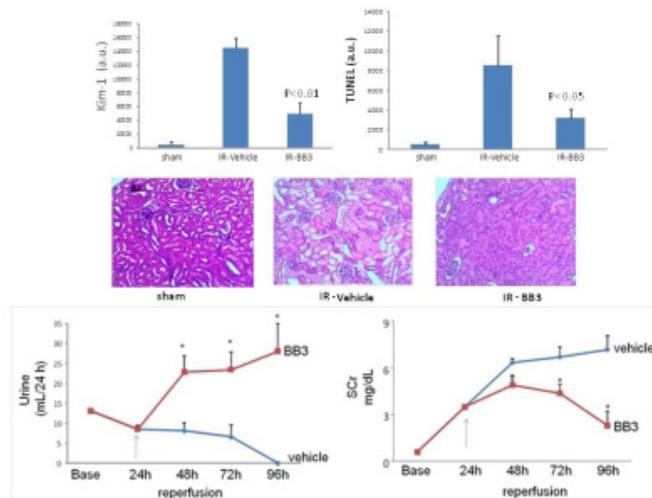
Therapeutic Effects of BB3, a Small Molecule Hepatocyte Growth Factor Mimetic, in Kidney Reperfusion Injury Prakash Narayan, Bin Duan, Xingxi Peng, Kai Jiang, Latha Paka, Michael A. Yamin, Itzhak D. Goldberg. *Angion Biomedica Corp.*

Background: Activation of the hepatocyte growth factor (HGF)/cMet pathway is therapeutic in ischemia-reperfusion (IR)-related acute kidney injury (AKI). However poor half-life makes clinical use of recombinant protein therapy in settings such as AKI or

kidney transplantation (Tx) challenging. We investigated the effects of a unique and novel small molecule with HGF-like activities, BB3, in models of AKI and Tx. BB3 selectively phosphorylates cMet and triggers the HGF/cMet pathway in multiple *in vitro* assays.

Methods: IR: Adult male rats had 60 min normothermic renal artery occlusion. At reperfusion, the contralateral kidney was excised. BB3 (2 mg/kg) was administered QD starting at 24 hour into reperfusion. Tx: Kidneys from adult male Lewis rats were cold-preserved (-4°C) for 4 hr and transplanted into syngeneic recipients whose native kidneys were excised. BB3 (2.0 mg/kg, QD) was administered until sacrifice on Day 14.

Results: IR: Treatment with BB3, starting 24 hr after reperfusion, increased tubular cMet phosphorylation *in vivo* 3.5-fold (p<0.01). BB3 decreased tubular expression of kidney injury marker-1 (KIM-1), decreased tubular apoptosis, enhanced preservation of tubular integrity, improved urine output and reduced serum creatinine (figure1) Tx: BB3 improved recipient survival (60% vs 30% for control) and mitigated renal dysfunction (e.g., Day 7 SCR: 0.84 mg/dL vs 2.72 mg/dL for control; p<0.05).



Conclusions: Starting as late as 24 hour after AKI, activation of the HGF/cMet pathway with BB3 mitigates renal injury and improves renal function. These data together with the expanded window for therapeutic intervention support the use of BB3 in Angion's Phase 2 GUARD study in AKI patients and Phase 3 GIFT study in kidney Tx recipients presenting with delayed graft function. Funded by DK-062592, -066654, -079399.

Funding: NIDDK Support

TH-OR102

CRP Exacerbates Ischemia-Reperfusion Injury in the Kidney by Down-Regulating Autophagy Ao Bian,¹ Mingjun Shi,¹ Brianna Flores,¹ Nancy Gillings,¹ Orson W. Moe,^{1,2,3} Ming Chang Hu.^{1,2} ¹*Charles and Jane Center for Mineral Metabolism and Clinical Research, UT Southwestern Medical Center;* ²*Dept of Internal Medicine, UT Southwestern Medical Center;* ³*Physiology, UT Southwestern Medical Center, Dallas, TX.*

Background: C-reactive protein (CRP), an acute biomarker, was recently reported to be closely associated with poor renal function in patients with acute kidney injury (AKI), but its pathogenic role in ischemic kidney injury remains unclear.

Methods: To examine the *in vivo* effect of CRP on autophagy in AKI induced by renal ischemia-reperfusion injury (IRI), we mated transgenic CRP overexpressing mice (CRP) with a autophagy reporter mouse (LC-3-GFP) to generate the combination mouse line (CRP;LC-3-GFP). *In vivo:* Mice were studied 2 days after IRI. *Ex vivo:* Renal tubules were isolated from LC-3-GFP mice at baseline for primary culture. *In vitro:* OK cells transfected with LC-3-GFP were used. The *ex vivo* and *in vitro* studies complement the *in vivo* study to define the direct effect of CRP on the kidney.

Results: Compared with LC-3-GFP mice, CRP;LC-3-GFP mice had higher serum creatinine (P<0.05), more tubular necrosis, and higher NGAL expression in the kidney after IRI. CRP addition exacerbated H₂O₂-increased LDH release from both primary cultured renal tubules and OK cells (P<0.01 respectively). Immunoblots showed lower LC-3 II/I ratio and higher p62, markers of autophagic flux, in the kidneys of CRP;LC-3-GFP compared to LC-3-GFP mice after IRI, and in primary culture of renal tubules and OK cells treated with CRP + H₂O₂ compared to H₂O₂ alone. Immunohistochemistry showed much fewer LC-3-GFP puncta in kidneys of CRP;LC-3-GFP compared to LC-3-GFP mice after IRI. Similarly, CRP addition reduced LC-3-GFP puncta induced by H₂O₂ in primary cultured renal tubules and in OK cells transfected with LC-3-GFP plasmid. Autophagy inducers (rapamycin and LiCl) rescued the impaired autophagy and blunted the LDH release from OK cells treated with CRP + H₂O₂ (P<0.05).

Conclusions: CRP renders the kidney more susceptible to ischemic/oxidative injury by down-regulation of autophagy flux. Autophagy inducer repairs down-regulated autophagy triggered by CRP and protects the kidney against ischemia reperfusion injury.

Funding: NIDDK Support

TH-OR103

Signal Inhibitory Regulatory Protein- α Regulates Pathologic Reactive Oxygen Species Generation in Acute Kidney Injury Natasha M. Rogers,^{1,2} Daniel N. Meijles,¹ Patrick J. Pagano,¹ Jeffrey S. Isenberg.¹ ¹*Vascular Medicine Inst, Univ of Pittsburgh, Pittsburgh, PA;* ²*Starzl Transplant Inst, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Ischemia reperfusion injury (IRI) is a major cause of acute kidney injury mediated by oxidative stress. We recently reported that signal regulatory inhibitory protein (SIRP)- α is expressed by renal tubular epithelial cells (TEC), that the protein thrombospondin-1 (TSP1) is increased following renal IRI, and TSP1 binds to SIRP α . However, it is unclear how TSP1-SIRP α signaling contributes to IRI pathophysiology.

Methods: Wild-type (WT) mice, and SIRP α mutant (SIRP α^{mut}) mice lacking cytoplasmic recruitment domains, underwent bilateral renal IRI followed by assessment of renal function and biomolecular analysis after 24 h reperfusion. Murine WT and SIRP α^{mut} TEC were studied *in vitro*. Mice were also irradiated and rescued with WT or SIRP α^{mut} bone marrow.

Results: IRI resulted in elevated serum creatinine in WT mice which was mitigated in SIRP α^{mut} animals (2.3 \pm 0.5 versus 0.98 \pm 0.4 mg/dl, p<0.01). Changes in renal function reflected improvements in renal histology, including tubular necrosis and inflammatory infiltrate. TSP1 was expressed to a similar degree in all mice post-IRI. Measurement of reactive oxygen species (ROS) in kidney demonstrated a 3-fold increase in superoxide in WT mice post-IRI (p<0.001) but no increase in SIRP α^{mut} mice when compared to sham. Expression of 3-nitrotyrosine protein modification was reduced in SIRP α^{mut} compared to WT mice, although total renal expression of NADPH oxidase 1 and 2 were unchanged. *In vitro*, WT TEC displayed upregulation of ROS in response to TSP1 (p<0.01), which was not reflected in SIRP α^{mut} cells. SIRP α is expressed by all renal cells, and chimeric mice were generated to explore differences in cell compartment contribution to IRI. SIRP α^{mut} mice, regardless of hematopoietic reconstitution, were fully protected against renal dysfunction, tubular damage and ROS generation following IRI.

Conclusions: These data provide evidence for a role for SIRP α promoting renal IRI through generation of pathologic ROS, and blockade of SIRP α may provide a therapeutic target to modify IR-mediated damage.

Funding: NIDDK Support

TH-OR104

“Urine Sediment” the Ignored Treasure Chest in the Search for Biomarkers in Acute Kidney Injury Nithin Karakala,¹ Juan Carlos Q. Velez,¹ Michael G. Janech,¹ Joseph Alge,¹ John M. Arthur.² ¹*Div of Nephrology, MUSC, Charleston, SC;* ²*Div Nephrology, UAMS, Little Rock, AR.*

Background: In the last decade novel urine biomarkers have been identified in urine supernatant. Urine sediment is extensively used in clinical practice for microscopy but has not been used for AKI biomarker discovery. We examined whether urine sediment from can be used to identify biomarkers and determine the proportion of sediment proteins that originate from brush border (BB), and mitochondria (MX).

Methods: Urine samples from patients admitted to the medical ICU at the Medical University of South Carolina were collected from 8 patients (4 without AKI and 4 with AKIN stage 3 AKI at the time of collection). The urine was centrifuged to separate sediment from supernatant. We performed liquid chromatography, tandem mass spectrometry (LC MS/MS) on each sediment and supernatant sample. We estimated the relative abundance of brush border, and mitochondrial proteins using Exponentially Modified Protein Abundance Index (empAI). Database of BB, and MX proteins were used to identify BB and MX proteins from our experiment. The molar fraction of each protein in the sample relative to the total moles of all proteins in the sample was calculated for each protein. We used this to determine the percent of moles of protein for BB, and MX proteins in the sediment.

Results: We identified 479 proteins in sediment (396 from the AKI 3 and 430 in No AKI). We identified 556 proteins from the no AKI samples, 239 proteins were present only in the sediment and 126 were identified only in the supernatant. In AKI 3 samples we identified 570 proteins, 169 proteins were unique to the sediment and 174 to the supernatant. The molar abundance percentage of BB proteins in the AKI 3 sediment and no AKI 3 sediment was 3.7 and 27.6% and MX proteins was 2.7 and 14.6% respectively.

Conclusions: We have developed an LC MS/MS technique for proteomic analysis of urine sediment. Urine sediment from no AKI and AKI 3 have proteins that are not found in supernatant. These proteins are potential biomarkers. As a percent of the molar amount of protein BB and MX is markedly less in AKI sediment. This finding has implication for the pathophysiology of shedding of renal tubular material in AKI.

TH-OR105

FGF23 Drives Progression of Chronic Kidney Disease in Mice Olena Andrukhova,¹ Svetlana Slavic,¹ Sathish Kumar Murali,¹ William G. Richards,² Reinhold Erben.¹ ¹*Dept of Biomedical Sciences, Univ of Veterinary Medicine, Vienna, Austria;* ²*Dept of Metabolic Disorders, Amgen Thousand Oaks, Thousand Oaks, CA.*

Background: Circulating fibroblast growth factor 23 (FGF23) is associated with disease progression in patients with chronic kidney disease (CKD).

Methods: Here, we elucidate the role of Fgf23 and its co-receptor Klotho in pathogenesis of CKD in mice by a dual approach, using genetic loss-of-function together with pharmacological inhibition models. CKD was induced by 5/6 nephrectomy in 3-month-old wild-type (WT) mice, vitamin D receptor (VDR) mutant mice, Fgf23^{-/-}/VDR^{ΔA}, and Klotho^{-/-}/VDR^{ΔA} compound mutant mice. All mice were kept on a rescue diet

to prevent secondary hyperparathyroidism in VDR mutant mice. Sham-operated (SHAM) mice served as controls. In addition, SHAM and CKD WT, VDR, and Klotho/VDR mice were treated with low dose anti-FGF23 antibody (anti-FGF23Ab, 50 μ g/mouse, 2 times/week) over 8 weeks.

Results: Genetic ablation of Fgf23 in Fgf23/VDR compound mutant or treatment of WT and VDR CKD mice with anti-FGF23Ab partially or completely protected against the CKD-induced weight loss, increase in mortality, reduction in glomerular filtration rate, albuminuria, volume expansion, hypernatremia, hypercalcemia, hypertension, and left ventricular functional impairment observed in untreated and vehicle-treated WT and VDR mice. Anti-FGF23Ab treatment of Klotho/VDR CKD mice, which were characterized by the highest circulating Fgf23 concentrations among all CKD groups, reduced mortality and slowed disease progression in these mice to levels found in Fgf23/VDR mutants, demonstrating that Fgf23 also has Klotho independent effects at high circulating levels. Genetic or pharmacological ablation of Fgf23 prevented hypercalcemia and volume overload in CKD mice by down-regulating renal sodium-transporting molecules, and increasing urinary excretion of sodium and calcium.

Conclusions: Collectively, our data suggest that elevated Fgf23 contributes to the pathogenesis of CKD in a vitamin D hormone- and partially Klotho-independent manner. Hence, our study may provide a mechanistic explanation for the association between circulating FGF23 and disease progression in CKD patients.

TH-OR106

In Vivo Role of Klotho in the Renal Proximal Tubules Noriko Ide,¹ Hannes Olauson,³ Tadatashi Sato,¹ Junichi Hanai,² Tobias E. Larsson,³ Beate Lanske.¹ ¹*Dept of Oral Medicine, Infection, and Immunity, Harvard School of Dental Medicine, Boston, MA;* ²*Dept of Medicine, Div of Nephrology, Interdisciplinary Medicine and Biotechnology, Medicine, Boston, MA;* ³*Div of Renal Medicine, CLINTEC, Karolinska Inst, Stockholm, Sweden.*

Background: Klotho is predominantly expressed in the distal tubules, but also in proximal tubules to regulate calcium and phosphate reabsorption, respectively. Global and total-nephron specific Klotho deletion both cause mineral disorder and premature aging. Klotho ablation from only distal tubules resulted in a mild phenotype indicating a key role for Klotho in proximal tubules.

Methods: No single Cre strain provided effective Klotho deletion in all proximal tubular segments. Therefore, three proximal tubule-specific Klotho knock-out mouse models were generated and compared by crossing PEPCK (phosphoenolpyruvate carboxykinase)-, KAP (Kidney androgen-regulated protein)-, or SLC34a1 (sodium phosphate cotransporter-2a1)-cre with Klotho^{fl/fl}(KL) mice.

Results: Klotho deletion was confirmed by qPCR, Western, and IHC. FGF23-Klotho signaling regulates phosphate homeostasis, so mineral parameters and regulatory factors were measured. In PEPCK-KL and SLC34a1-KL mice, urine phosphate excretion significantly decreased. This was not clearly detected in KAP-KL mice, despite increased renal NaPi2a mRNA and protein levels. Challenge of KL-KAP mice with high phosphate diet resulted in a significant decrease of urine phosphate excretion compared with WT. Serum phosphate level remained normal in all mouse lines. In summary, Klotho deletion in renal proximal tubules leads to a slightly decreased phosphate excretion with no changes in serum phosphate levels.

Conclusions: We demonstrate a role for Klotho in renal proximal tubules. Importantly, while global and total-nephron deletion of Klotho result in a severe phenotype, deletion in either distal or proximal renal tubules alone results in only minor changes in mineral homeostasis. This suggests a more integrated and organized cooperation between these two loci. These results are the first to show an interdependent relationship of Klotho in the distal and proximal tubules.

Funding: Other U.S. Government Support

TH-OR107

The Increased Bone Fibroblast Growth Factor 23 Expression Is Mediated by the Fibroblast Growth Factor Receptor in Experimental Uremia Ronen Levi,¹ Alia Hassan, Karina Durlacher, Justin Silver, Tally Naveh-Many, *Minerva Center for Calcium and Bone Metabolism, Nephrology, Hadassah Hebrew Univ Medical Center, Jerusalem, Israel.*

Background: Serum FGF23 is markedly elevated in CKD and has been associated with poor long-term outcomes. FGF23 expression is increased by activation of the FGF receptor 1 (FGFR1) in rats with normal renal function and *in vitro* in UMR106 osteoblast-like cells. We now demonstrate a role for FGFR in the regulation of FGF23 in a mouse model of acute kidney injury (AKI) due to high dose folic acid (FA), in rats with adenine high phosphorus induced CKD and in UMR106 osteoblast like cells.

Methods: Mice were injected with 250 mg/kg folic acid ip to induce AKI and sacrificed at 3 and 6 h. The FGFR inhibitor PD173074 was given to the mice 1 h before FA. Rats were fed an adenine high phosphorus diet for 14 d and PD173074 given for the last 2 d of the diet. Serum biochemistry, FGF23 and PTH levels were analyzed and calvaria FGF23 mRNA measured by qRT-PCR. FGF2 and PD173074 were added to UMR106 cells for 24 and 48 h and FGF23 mRNA levels measured.

Results: FA increased serum BUN and phosphate levels as expected from 3 h. Calvaria FGF23 mRNA and serum FGF23 levels were increased 2-3-fold at 6 h. PTH levels increased 6-fold from 3 h after FA. The FGFR inhibitor PD173074 prevented the FA induced increase in both FGF23 mRNA and serum levels but had no effect on serum PTH levels. A more prolonged uremia due to an adenine high phosphorus diet for 14 d resulted in high levels of serum PTH (30-fold increase) and FGF23 (3.5-fold increase). PD173074 decreased

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

serum FGF23 and mRNA levels with no effect on PTH in the adenine high phosphorus induced uremic rats. Addition of FGF2 to UMR106 cells increased FGF23 expression that was also prevented by PD173074.

Conclusions: A derangement in FGF-23 regulation starts early in the course of AKI, is in part independent of the increase in serum PTH and involves activation of FGFR. This is the first demonstration that activation of FGFR is important to the high levels of FGF23 in both acute and chronic experimental uremia. FGFR in the osteocyte may be activated by locally produced canonical FGFs such as FGF2.

TH-OR108

Acute and Chronic Inflammation Raises the Blood Levels of FGF23 in Normal Mice Shweta Bansal,^{1,2} William E. Friedrichs,¹ Chakradhar Velagapudi,¹ Sherry L. Werner,^{1,2} Paolo Fanti.^{1,2} ¹Medicine/Renal, Univ of Texas Health Sciences Center at San Antonio, San Antonio, TX; ²Renal Section, South Texas Veterans Healthcare System, San Antonio, TX.

Background: High levels of FGF23 are not fully explained by abnormal mineral metabolism in CKD. We and others found association of FGF23 with inflammation in CKD patients, but knowledge about the role of inflammation in FGF23 regulation is limited.

Methods: Inflammation was induced in FBV mice as follows (n=5 each Gr): **Gr1-acute inflammation:** single IP injection of 3.3 µg/kg of LPS (E.Coli 0111:B4) or vehicle control (Vh); **Gr2-chronic pulsatile inflammation:** daily IP injections of 3.3 µg/kg of LPS x 2 weeks; **Gr3-chronic persistent inflammation:** SQ insertion of pellets releasing 2 mg/kg/day of LPS plus Vh daily injection x 2 weeks; and **Gr4-acute on chronic inflammation:** SQ LPS pellets x 2 weeks and single IP LPS injection before sacrifice. Plasma FGF23 (c-term) and TNFα levels and spleen weight measured at sacrifice.

Results: In **Gr1**, FGF23 levels were 0.5±0.1 ng/ml 5 hours after LPS injection vs. 0.2±0.04 ng/ml in Vh (p=0.001). In **Gr2**, FGF23 was 0.2±0.02 ng/ml after 2-week daily LPS injections vs. 0.14±0.04 in Vh (p=0.02). In **Gr3**, FGF23 was 0.8±0.6 after 2-weeks LPS pellet vs. 0.14±0.04 ng/ml in Vh (p=0.04). In **Gr4**, FGF23 was the highest i.e., 1.3±0.7 after 2-week LPS pellets and single LPS injection, vs. 0.14±0.04 in Vh (p=0.006). TNFα levels rose significantly in Gr3 and Gr4 vs. Vh (respectively 11±0.8, 14±0.8, and 8.0±0.8 pg/ml). Spleen weights were significantly higher in Gr3 and Gr4 as further indication of presence of inflammation. Summary: Both acute and chronic exposure to LPS caused inflammation and stimulated the synthesis of FGF23. The effects of acute and chronic LPS exposure seemed to be synergistic.

Conclusions: Inflammation raises the FGF23 levels in FVB mice. The inflammation experienced by the Gr4 mice mimics events in CKD, where low-grade chronic inflammation is often aggravated by sporadic acute inflammation, e.g., caused by infections or translocation of inflammatory agents across the gut barrier. More studies are needed to delineate the role of inflammation in the regulation of FGF23 in the context of CKD.

Funding: NIDDK Support

TH-OR109

FGF23 Directly Targets Hepatocytes to Promote Inflammation in CKD Saurav Singh,¹ Alexander Grabner,¹ Karla J. Schramm,¹ Christopher Yanucil,¹ Alexis J. Sloan,¹ Ansel P. Amaral,^{1,2} Myles S. Wolf,² Christian Faul.¹ ¹Dept of Medicine, Univ of Miami Miller School of Medicine, Miami, FL; ²Dept of Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Chronic inflammation is a hallmark of chronic kidney disease (CKD), and biomarkers of inflammation are strong predictors of poor clinical outcome. The molecular mechanisms underlying the interrelationship between deterioration of renal function and amplification of the inflammatory state are unknown. CKD patients develop marked elevations in circulating levels of the phosphorus-regulating hormone, fibroblast growth factor (FGF) 23. Our recent data indicates that FGF23 directly induces cardiac injury by activating FGF receptor (FGFR) 4 in cardiac myocytes, independent of α-klotho. Since hepatocytes express high levels of FGFR4, we postulate that FGF23 can directly target the liver.

Methods: Using HepG2 cells, a hepatocellular carcinoma cell line, and primary mouse hepatocytes, we analyzed signal transduction and expression of inflammatory cytokines, including C-reactive protein (CRP) and interleukin-6 (IL-6) upon FGF23 treatment. FGF23 was injected intravenously into wild-type mice for 5 days, and FGFR4 knockout mice were fed a 2% phosphorus diet for 12 weeks. 5/6 nephrectomized rats were administered with an FGFR4-specific blocking antibody.

Results: FGF23 induces expression of inflammatory cytokines in hepatocytes by activating calcineurin/NFAT signaling in an FGFR4-dependent and α-klotho-independent manner. Elevation of serum FGF23 in wild-type mice via injections of recombinant FGF23 or administration of a high phosphate diet increases CRP levels in liver and blood. High phosphate diet does not elevate CRP expression in FGFR4 knockout mice. Pharmacological FGFR4 blockade reduces the expression of CRP in rats with CKD.

Conclusions: We provide a causative link between FGF23 elevations and the induction of an inflammatory response in the liver, and suggest a novel mechanism to explain the development of chronic inflammation in patients with CKD. Pharmacologic FGFR4 blockade might have anti-inflammatory effects in CKD.

TH-OR110

Differential Effects of Calcitriol on FGF23/Klotho System and LVH in Experimental Uremia Maren Leifheit-Nestler,¹ Laura Hermann,¹ Dagmar-Christiane Fischer,² Dieter Haffner.¹ ¹Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; ²Dept of Pediatrics, Univ Hospital Rostock, Rostock, Germany.

Background: Vitamin D (vitD) deficiency and excess of circulating FGF23 are significant contributors to cardiovascular (CV) mortality in CKD patients. *In vivo*, vitD metabolites downregulate genes involved in the development of left ventricular hypertrophy (LVH). However, vitD is a known stimulator of FGF23 synthesis in the bone, and thus, may have paradoxical effects on the CV phenotype in CKD. Here, we investigated the effects of vitD on the FGF23 signaling cascade mediated LVH in experimental uremia.

Methods: 5/6 nephrectomized rats (Nx) were treated with vitD for 4 and 10 weeks, and compared with controls. Heart tissue was determined for gene/protein expression of the FGF23 signaling pathway, pathological cardiac remodeling, and LVH. Cardiomyocyte cross-sectional area was quantified by immunofluorescence microscopy. Renal Klotho expression was investigated by quantitative real-time PCR.

Results: Cardiac Fgf23 levels, *Fgfr1* and *Fgfr4* mRNA, and LVH were increased significantly in 5/6Nx rats compared with controls. The calcineurin-NFAT signaling pathway was activated in uremia demonstrated by enhanced calcineurin accompanied by a strong reduction of phosphorylated NFAT protein. Pro-hypertrophic genes were increased in myocardial tissue of 5/6Nx rats. In general, vitD treatment of 5/6Nx rats resulted in reduced cardiomyocyte cross-sectional area. Although, cardiac Fgf23 levels, and *Fgfr1* and *Fgfr4* mRNA were further stimulated by vitD, vitD treated 5/6Nx rats showed reduced activation of NFAT ameliorating cardiac remodeling processes and LVH. Interestingly, renal *Klotho* expression was markedly reduced in uremic animals, and almost normalized after vitD treatment.

Conclusions: Cardiac FGF23 levels are enhanced in experimental uremia, and associated with LVH. VitD enhances NFAT phosphorylation and thereby blocks pathological remodeling processes induced by FGF23. In addition, vitD restores renal *Klotho* expression, and consequently enhances soluble Klotho, which may further be cardioprotective via binding to and neutralizing FGF23 in the heart.

TH-OR111

FGFR4 Activation Is Sufficient to Induce LVH in Mice Alexander Grabner,¹ Karla J. Schramm,¹ Saurav Singh,¹ Christopher Yanucil,¹ Alexis J. Sloan,¹ Ansel P. Amaral,^{1,2} Christian Faul.¹ ¹Medicine, Univ of Miami Miller School of Medicine, Miami, FL; ²Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Previously, we demonstrated that fibroblast growth factor (FGF) 23 is a causal factor in the pathogenesis of left ventricular hypertrophy (LVH). FGF23 directly targets cardiac myocytes via FGF receptors (FGFR) and activates calcineurin/NFAT signaling. Mammals express four FGFR isoforms (FGFR1-4). Using two loss-of-function approaches (delivery of a blocking antibody in a rat model of chronic kidney disease (CKD) and gene deletion in mice), we could show that FGFR4 is required for the development of LVH in rodents with high FGF23. To confirm this finding in a gain-of-function approach, we studied a genetic knock-in mouse model carrying a FGFR4 mutation (G385R) that causes constitutive and ligand-independent activation of FGFR4.

Methods: We studied 6 months old homozygous FGFR4-G385R knock-in mice and wild type littermates. LVH was assessed by echocardiography, H&E staining of cardiac cross sections, and cross sectional area of individual myocytes. We analyzed cardiac fibrosis by Picrosirius Red staining and qPCR. Activation of calcineurin/NFAT signaling in cardiac tissue was studied by qPCR and Western blot analysis, and serum levels of cleaved FGF23 were determined by ELISA.

Results: Compared to wild type littermates, FGFR4-G385R mice develop LVH as evident by significantly increased LV wall thickness, cross sectional myocyte area and ejection fraction. FGFR4-G385R hearts are not fibrotic, and show a significant elevation of NFAT target gene expression. Although serum FGF23 levels were increased in FGFR4-G385R mice, the elevation did not correlate with the cardiac phenotype.

Conclusions: Activation of FGFR4 per se is sufficient to induce LVH in mice independently of serum FGF23 levels. We postulate that FGFR4 is part of a novel pro-hypertrophic signaling pathway in the heart that could be activated in patients with cardiomyopathies. FGFR4 blockade might not only serve as a novel pharmacological intervention for LVH in CKD patients with elevated FGF23, but also in patients with primary cardiac disease and increased FGFR4 activity in the heart.

Funding: NIDDK Support, Private Foundation Support

TH-OR112

Downregulation of Thrombomodulin Expression in Endothelial Cells by Fibroblast Growth Factor-23 and Klotho Kenji Tanaka,¹ Yoko Oyama,² Tancharoen Salunya,³ ¹Internal Medicine, Suiyukai, Kashiwara, Nara, Japan; ²Dept of Laboratory and Vascular Medicine, Kagoshima Univ Graduate School of Medical and Dental Sciences, Kagoshima, Japan; ³Dept of Pharmacology, Faculty of Dentistry, Mahidol Univ, Bangkok, Thailand.

Background: Chronic kidney disease (CKD) is regarded as a state of excessive fibroblast growth factor-23 (FGF-23) and a Klotho (KL) deficiency. Moreover, the increased mortality risk in CKD patients associated with cardiovascular disease and endothelial dysfunction. Increasing evidence demonstrates that thrombomodulin (TM)

plays an important role in endothelial barrier. The mechanism responsible for the linkage of FGF-23 underlying endothelial damage in these patients is unclear. Here we report a downregulation of membrane TM in human umbilical vein endothelial cells (HUVEC) after FGF-23/ KL stimulation.

Methods: HUVECs were cultured in endothelial basal medium with supplement. SDS-PAGE analysis was performed to confirm the dose dependent effect of FGF-23 on TM expression in HUVECs, and to confirm the effect of KL. Next, membrane TM expression was performed by flow cytometry to confirm the effect of FGF-23 in HUVEC cell surface. Finally, immunofluorescence (IF) staining for TM expression on HUVECs was performed. Cells were visualized by double staining for TM expression and nucleus.

Results: SDS-PAGE and flow cytometry analysis shows that TM expression was markedly decreased when HUVECs were stimulated with 10 ng/ml FGF-23/ KL whereas this effect was less pronounced upon 1 ng/ml FGF-23/ KL treatment and that KL stimulation for 12 and 16 hours induced TM production significantly as compared to the controls and FGF-23 and FGF-23/ Klotho -treated cells. IF staining shows that TM is expressed on the cell surface in control cells while this number was dramatically increased after KL stimulation and that TM expression was reduced after FGF-23 and FGF-23/ KL stimulation.

Conclusions: TM is constitutively expressed in HUVEC and is suppressed by FGF-23 and FGF-23/ KL dose-dependently. Our results imply that TM response by FGF-23/ KL is a possible mechanism that leads to vascular complications in CKD patients.

Funding: Private Foundation Support

TH-OR113

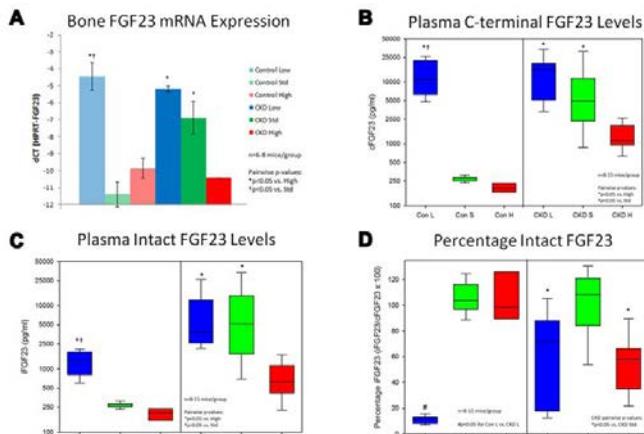
Iron Status Affects FGF23 Production and Metabolism in Mice with Chronic Kidney Disease Mark Hanudel,¹ Kristine Joy Chua,² Katherine Wesseling-Perry,¹ Elizabeth Nemeth,² Tomas Ganz,² Isidro B. Salusky.¹ ¹Pediatrics, UCLA, Los Angeles, CA; ²Center for Iron Disorders, UCLA, Los Angeles, CA.

Background: Iron deficiency anemia and elevated FGF23 levels occur early in CKD. In mice with normal renal function, iron deficiency upregulates FGF23 expression, resulting in higher circulating FGF23 levels. However, the impact of iron status on FGF23 production and metabolism in CKD is unknown.

Methods: Wild type (WT) and hepcidin knockout (HKO) C57BL/6 mice were fed diets that did or did not contain adenine (which induces CKD), with low iron (4 ppm), standard iron (335 ppm), or high iron (10,000 ppm) concentrations. The standard iron diet was sufficient to iron load the HKO mice. Mice were on the diets for 8 weeks post-weaning, then sacrificed (n=8-15 mice/group). We measured plasma C-terminal FGF23 (cFGF23) and intact FGF23 (iFGF23); BUN, phosphorus, CBC; liver iron; and bone FGF23 mRNA expression. Multiple linear regression modeling was performed to assess the independent effects of iron and phosphorus on FGF23 in CKD.

Results: In both the Control and CKD cohorts, the low iron groups had the highest FGF23 mRNA expression and highest cFGF23 levels. Among the WT CKD mice, the high iron group had the lowest serum phosphorus levels, lowest cFGF23 levels, and a lower percentage iFGF23, possibly secondary to iron sufficiency and/or normophosphatemia. The HKO CKD standard iron group had higher liver iron content, lower FGF23 mRNA expression, and lower cFGF23 levels than the WT CKD standard iron group. In the CKD mice (n=57), serum phosphorus was independently associated with higher cFGF23 levels and higher percentage iFGF23; and liver iron was independently associated with lower cFGF23 levels and higher percentage iFGF23.

Conclusions: In mice with CKD, iron status affects FGF23 production and metabolism, independent of the effects of serum phosphorus.



Association of predictor variables with log cFGF23 in CKD mice:

Predictor Variable	Coefficient (95% CI)	p-value	Adjusted R ²	n
Standardized Serum Phosphorus	0.23 (0.10, 0.36)	0.001	0.29	57
Standardized Liver Iron	-0.17 (-0.30, -0.04)	0.013		

Association of predictor variables with percentage intact FGF23 in CKD mice:

Predictor Variable	Coefficient (95% CI)	p-value	Adjusted R ²	n
Standardized Serum Phosphorus	13.7 (3.9, 23.3)	0.008	0.13	57
Standardized Liver Iron	11.4 (1.7, 21.1)	0.025		

Funding: Other NIH Support - UCLA K12 Child Health Research Career Development Award (NIH 5K12HD034610-18)

TH-OR114

Tenapanor, an NHE3 Inhibitor, Reduces Serum Phosphate in Patients with CKD Stage 5D and Hyperphosphatemia Geoffrey A. Block,¹ David P. Rosenbaum,² Maria Leonsson Zachrisson,³ Magnus Åstrand,³ Susanne Johansson,³ Mikael Knutsson,³ Anna Maria Langkilde,³ ¹Denver Nephrology, Denver, CO; ²Ardelyx Inc., Fremont, CA; ³AstraZeneca R&D, Mölndal, Sweden.

Background: Tenapanor (AZD1722), a first-in-class small molecule with minimal systemic availability, is an inhibitor of the Na⁺/H⁺ exchanger NHE3. Healthy volunteer studies show that tenapanor treatment increases stool sodium and phosphate and concomitantly reduces urinary sodium and phosphate. This double-blind, dose-finding study (NCT02081534) examined the effect of tenapanor on serum phosphate in patients with CKD stage 5D (hemodialysis).

Methods: After a 1–3-week washout of phosphate binders, 162 patients with baseline serum phosphate 6.0–10.0 mg/dL and ²⁵OH vitamin D increase from pre-washout levels were randomized to placebo or one of six tenapanor groups (1, 3, 10 or 30 mg bid, or 3 or 30 mg qd) for 4 weeks. Blood samples were collected weekly. The primary endpoint was change in serum phosphate from baseline. Dose–response analysis was a secondary endpoint.

Results: Tenapanor treatment resulted in dose-dependent reductions in serum phosphate (Table), with a significant difference between the treatment groups (p=0.012, ANCOVA). Gastrointestinal AEs were more common with tenapanor than with placebo, with higher doses associated with higher rates of diarrhea.

	N ^a	Serum phosphate, mg/dL		
		Baseline	End of treatment	Change from baseline
Tenapanor				
1 mg bid	23	7.55 (1.00)	7.02 (1.90)	-0.43 (1.55)
3 mg bid	21	7.32 (1.01)	6.19 (1.51)	-1.09 (1.39)
10 mg bid	23	7.92 (1.06)	6.14 (1.90)	-1.76 (2.02)
30 mg bid	26 ^b	7.76 (1.18)	5.80 (2.04)	-2.00 (2.01)
3 mg qd	22	7.73 (1.28)	7.14 (2.21)	-0.57 (1.76)
30 mg qd	21	7.61 (0.85)	6.32 (1.77)	-1.09 (1.47)
Placebo	26	7.87 (1.49)	7.28 (1.71)	-0.58 (1.80)

^aRandomized patients; ^bn=25 for data in table.
Data are mean (SD).

Conclusions: Tenapanor provided clinically and statistically significant reductions in serum phosphate. Higher doses of tenapanor were associated with higher rates of diarrhea, as expected based on its additional pharmacodynamic effect on stool sodium. Once- or twice-daily administration of tenapanor may offer a new treatment mechanism to reduce serum phosphate in patients with CKD.

Funding: Pharmaceutical Company Support - AstraZeneca

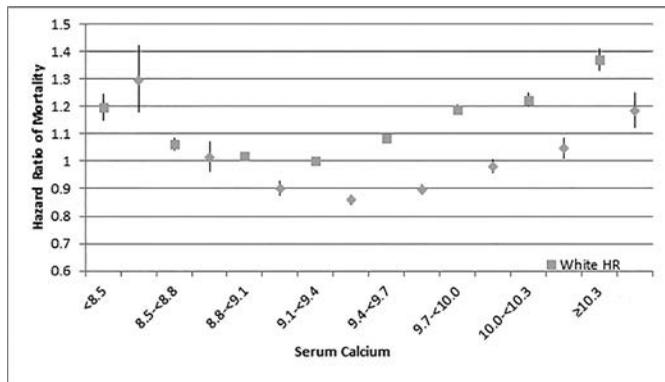
TH-OR115

Racial Differences in Association of Serum Calcium with Mortality and Incident Cardio- and Cerebrovascular Events Jun Ling Lu,¹ Miklos Zsolt Molnar,¹ Jennie Z. Ma,² Lekha K. George,¹ Kamyar Kalantar-Zadeh,³ Csaba P. Kovcsy,^{1,4} ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of Virginia, Charlottesville, VA; ³Univ of California, Irvine, CA; ⁴VA Medical Center, Memphis, TN.

Background: In CKD patients, both high and low serum calcium (CA) is associated with higher mortality. Calcium metabolism is different in African American (AA) vs. white individuals. It is unclear if CA is associated with mortality and vascular events in patients with normal kidney function and if such association differs by race.

Methods: We examined racial differences in associations between corrected CA and mortality or incident coronary disease (CHD) and stroke in a national cohort of 1,967,685 US veterans with eGFR >60ml/min/1.73m². We used multivariable Cox proportional hazards models with interaction terms for CA and race, adjusted for age, BMI, social-economics, eGFR, BP, comorbidities, and medications.

Results: The mean age (SD) was 60.6(13.5), and the mean eGFR (SD) was 83.3 (15.4) ml/min/1.73m². 15.5% of patients were AA, with a mean baseline CA of 9.5±0.4 mg/dL. Over a median follow-up of 8.2-years, there were 47,790 (15.7%) deaths, 8,129 (2.7%) strokes, and 6,175 (2.0%) CHD events in AA, compared to 299,137 (21.1%), 30,300(2.1%) and 34,304(2.4%) events in whites. A U-shaped association between CA and mortality was present in both races, but AA patients experienced lower risk relative to white patients with CA >8.8mg/dl (Figure, p<0.01 for interaction). No associations were found between CA and CHD/stroke in either race.



Conclusions: Both higher and lower CA are associated with higher mortality in patients with normal kidney function. AA patients appear to experience relatively lower risk of death compared to white patients when CCA \geq 8.8 mg/dl, but this could not be attributed to differences in incident occlusive vascular events.

Funding: NIDDK Support, Veterans Administration Support

TH-OR116

Relevance of LDL Cholesterol and C-Reactive Protein to Cardiovascular Risk Among Patients with Chronic Kidney Disease – Results from the Study of Heart and Renal Protection Ben Storey. *On behalf of the SHARP Collaboration Group, Univ of Oxford.*

Background: Previous observational studies have found J-shaped relationships between LDL-C and cardiovascular risk among patients with CKD and suggested this association may be modified by inflammation: that it is positive in the absence of inflammation but negative in its presence. Conversely, other studies suggest that statins may be most effective in people with inflammation.

Methods: SHARP was a randomised controlled trial of LDL-C lowering with ezetimibe/simvastatin (E/S) in 9270 patients with CKD. Hazard ratios (HR) for all atherosclerotic vascular events (AVE) over 4.9 years were estimated with Cox regression. The effect of E/S on major atherosclerotic events (MAE) was estimated in the presence and absence of inflammation; defined as CRP \geq 3mg/L (the study median) or in a sensitivity analysis as CRP \geq 10 mg/L and/or albumin $<$ 36 g/L (90th & 10th centiles in 3rd NHANES respectively).

Results: Among all patients, usual LDL-C was positively, and approximately log-linearly, associated with risk of AVE (HR per 1 mmol/L [39 mg/dL] higher LDL-C 1.38 [95% CI 1.22-1.56]). Compared to patients with low CRP, patients with high CRP were at higher risk, but the relationship between LDL-C and AVE risk was similar in both groups (HR per mmol/L 1.29 [1.07-1.54] and 1.43 [1.21-1.69] respectively, p for interaction=0.58). E/S was similarly effective at reducing MAE in patients with low and high CRP. (Rate Ratio 0.84 and 0.83 respectively, p for heterogeneity=0.96). Sensitivity analyses gave similar results.

Figure: Effect of allocation to E/S on major atherosclerotic events, by level of CRP

	Ezetimibe/simvastatin (n=4650)	Placebo (n=4620)	Risk ratio (95% CI)	p value
C-reactive protein ($\chi^2=0.00, p=0.96$)				
<3.0	209/2178 (9.6%)	243/2120 (11.5%)	0.84 (0.70-1.01)	
\geq 3.0	280/2142 (13.1%)	334/2163 (15.4%)	0.83 (0.71-0.97)	
All patients	526/4650 (11.3%)	619/4620 (13.4%)	0.83 (0.74-0.94)	0.0021

Conclusions: LDL-C was positively associated with risk of AVE irrespective of baseline inflammation. Furthermore, lowering LDL-C with E/S was similarly effective in the presence or absence of inflammation. While CRP is associated with vascular risk, it does not modify the association between LDL-C and risk nor the efficacy of lowering LDL-C.

Funding: Pharmaceutical Company Support - Study of Heart and Renal Protection (SHARP) was initiated, conducted and interpreted independently of the principal study funder (Merck & Co. and by Schering Plough Corporation, who merged in 2009)

TH-OR117

Utilization of Statin Medications in Non-Dialysis Dependent Chronic Kidney Disease (CKD) Patients Holly J. Kramer,¹ Talar Markossian,¹ Nicholas Burge,² Benjamin Ling,¹ Julia Koval,¹ David J. Leehey,² Kevin Stroupe.² ¹Loyola Univ Chicago; ²Hines VA Medical Center.

Background: KDIGO and KDOQI guidelines recommend statin medications for adults age \geq 50 years with non-dialysis dependent chronic kidney disease (CKD) due to demonstrated benefits of statins in reducing the risk for cardiovascular events and mortality for these patients. Results from few empirical studies suggest that statins are underused for CKD patients.

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in patients with non-dialysis

dependent CKD. Patients with non-dialysis dependent CKD stages 3-5 with no history of kidney transplantation were included in the analysis. Statin use was ascertained from pharmacy dispensing records in 2012 and 2013.

Results: Approximately sixty percent of patients with non-dialysis dependent CKD were prescribed statins. Among patients prescribed statins in 2012, 11.0% lacked statin prescriptions during 2013. Statin use varied by age (33.9% \leq 50, 53.0% 50-59, 64.6% 60-74, 58.0% \geq 75 years). Table 1 shows the frequency of statin use by CKD stage and by presence of comorbidities.

Characteristics (%)	CKD Stage undetermined (n=147, 508)	CKD Stage 3A (n=457, 528)	CKD Stage 3B (n=194, 470)	CKD Stage 4 (n=51, 299)	CKD Stage 5 (n=13, 999)
% Using statin	62.6	57.8	61.6	61.3	53.6
Comorbidities	% using statin by comorbidity	% using statin by comorbidity	% using statin by comorbidity	% using statin by comorbidity	% using statin by comorbidity
Coronary artery disease	80.6	82.9	83.2	82.5	76.5
Diabetes	75.1	70.5	71.2	70.4	61.8
Heart Failure	75.5	71.7	71.2	71.4	65.6
Myocardial infarction	82.8	77.6	77.5	77.2	73.0
Peripheral artery disease	77.5	72.9	73.1	72.5	66.3
Stroke	74.9	71.2	71.4	71.2	64.9

Conclusions: Despite KDIGO and KDOQI guidelines recommending statins for adults with non-dialysis dependent CKD, statin use is suboptimal in adults with CKD receiving care in the VA health system. Interventions are needed to increase knowledge regarding the clinical importance of statin use in adults with non-dialysis dependent CKD.

Funding: Veterans Administration Support

TH-OR118

Associations of Conventional Echocardiographic Measures with Incident Heart Failure and Mortality: The Chronic Renal Insufficiency Cohort Study Ruth E. Dubin,¹ Amanda Hyre Anderson,² Wei Yang,² Alan S. Go,³ Martin Keane,⁴ Rajat Deo,² Nisha Bansal,⁵ Raymond R. Townsend,² Michaela Shlipak.¹ ¹Univ of California, San Francisco/SF VAMC; ²Univ of Pennsylvania School of Medicine; ³Kaiser Permanente, California; ⁴Temple Univ School of Medicine; ⁵Univ of Washington.

Background: Heart failure (HF) is the most common cardiac complication for patients with chronic kidney disease (CKD). Left ventricular hypertrophy (LVH) develops early in CKD, but studies have not adequately evaluated the association of left ventricular mass index (LVMI) with HF incidence among men and women with CKD.

Methods: We evaluated two-dimensional echocardiograms among 2964 participants of the Chronic Renal Insufficiency (CRIC) Study without cardiovascular disease (CVD). LVMI was calculated using the linear method, indexed to height and analyzed using gender-specific quartiles. The primary outcomes of incident HF and all-cause mortality were adjudicated; HF analyses were censored for death.

Results: Among 2964 participants, 45% were women, 54% were non-white race, mean(SD) age was 59 \pm 11 years, mean(SD) eGFR was 44 \pm 17 ml/min/1.73m² at baseline. Over a median [IQR] follow up of 6.6 [5.7-7.6] years, 262 participants developed incident HF, and 470 participants died. In both men and women, LVMI was a strong, independent predictor of incident HF and mortality, even after adjustment for BNP and troponin T.

	Hazard Ratio (95% CI)*			
	Q1*	Q2	Q3	Q4
Heart Failure				
Men	Ref	1.9(0.68-5.4)	3.1(1.2-8.3)	3.5(1.3-9.5)
Women	Ref	1.2(0.43-3.4)	2.5 (0.9-6.7)	5.1(1.8-14)
Death				
Men	Ref	1.3(0.8-2.2)	1.7(1.0-2.9)	1.7(1.0-3.0)
Women	Ref	1.3(0.7-2.5)	2.2(1.1-4.4)	3.1(1.5-6.4)

* Model adjusted for: age, race, site, comorbidities, medications, proteinuria, eGFR, hemoglobin, PTH, FGF-23, BNP, Troponin T

There was no significant interaction for gender in this association, but the LVMI-HF association was stronger in persons without diabetes: per SD LVMI, HR[95%CI] 1.3[1.1-1.6] with diabetes and 2.2[1.6-2.8] without diabetes (p for interaction:0.01).

Conclusions: Among persons with CKD and without history of CVD, LVMI is a strong predictor of incident HF and death, even after adjustment for major cardiovascular biomarkers.

Funding: NIDDK Support

TH-OR119

Prevalence and Prognostic Significance of Apparent Treatment Resistant Hypertension in Chronic Kidney Disease: A Report from the CRIC Study George Thomas,¹ Dawei Xie,² Hsiang-Yu Chen,² Amanda Hyre Anderson,² Lawrence J. Appel,² Carolyn S. Brecklin,² Paul E. Drawz,² John M. Flack,² Edgar R. Miller,² Susan P. Steigerwalt,² Raymond R. Townsend,² Matthew R. Weir,² Jackson T. Wright,² Mahboob Rahman.² ¹Cleveland Clinic, Cleveland, OH; ²CRIC Investigators.

Background: While hypertension is common in patients with chronic kidney disease (CKD), the association between apparent treatment resistant hypertension (ATRH) and clinical outcomes is not well studied in this population.

Methods: We analyzed data on 3367 hypertensive participants in the Chronic Renal Insufficiency Cohort (CRIC) to determine prevalence, associations, and clinical outcomes of ATRH in non-dialysis CKD patients. ATRH was defined as blood pressure $\geq 140/90$ mm Hg on ≥ 3 antihypertensives, or use of ≥ 4 antihypertensives with BP at goal at baseline.

Results: The prevalence of ATRH was 40.4%. Older age, male gender, black race, diabetes, and higher BMI were independently associated with significantly higher odds of having ATRH. Compared to participants without ATRH, after adjustment for common covariates, participants with ATRH had a higher risk of clinical events (composite of myocardial infarction (MI), stroke, peripheral arterial disease (PAD), congestive heart failure (CHF), and all-cause mortality) (HR [95% CI]: (1.38 [1.22, 1.56])); renal events (ESRD or 50% decline in GFR) (1.28 [1.11, 1.46]); CHF (1.77 [1.44, 2.16]); and all-cause mortality (1.24 [1.06, 1.45]). The subset of participants with ATRH and BP at goal on ≥ 4 medications also had significantly higher risk of composite of MI, stroke, PAD, CHF, and all-cause mortality (HR [95% CI]) (1.30 [1.12, 1.51]) and CHF (1.68 [1.32, 2.12]) compared to those without ATRH. The association between ATRH and CHF and renal outcomes differed depending on baseline GFR (interaction ($p < 0.05$)); ATRH was associated with significantly higher risk for CHF and renal events only among those with GFR ≥ 30 ml/min/1.73 m².

Conclusions: Our findings show that ATRH is common, and associated with high risk of adverse outcomes in a cohort of patients with CKD.

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TH-OR120

Aryl Hydrocarbon Receptor Is Activated during Chronic Kidney Disease and Is Associated with Mortality Stephane Burty,^{1,2} Laetitia Dou,¹ Marion Sallée,^{1,2} Claire Cerini,¹ Noemie Jourde-chiche,^{1,2} Bertrand Gondouin,^{1,2} Michael S. Denison,³ Philippe Brunet.^{1,2} ¹Aix-Marseille Univ; ²AP-HM; ³UC Davis.

Background: Aryl hydrocarbon receptor (AhR) is a transcription factor activated by numerous pollutants, like dioxin. Its activation is associated with cardiovascular risk. Indoxyl sulfate (IS) and indole-3 acetic acid (IAA) are uremic toxins associated with mortality in chronic kidney disease (CKD). They are agonists of AhR. Our goal was to study the activation of AhR in patients with CKD and its association with mortality.

Methods: We included 96 non-diabetic patients with CKD (50 patients with stage 3-5 CKD and 46 patients with stage 5D) and 32 controls without CKD matched for age and gender. The median follow up was 966 days. Activation of AhR by serum was evaluated by a Chemical Activated Luciferase gene eXpression assay (CALUX) and was expressed in arbitrary units (AU). In a subset of 20 patients with CKD stage 5D and 17 controls we performed RT-qPCR to study whole blood expression of AhR target genes (*CYP1A1*, *CYP1B1* and *AHR*).

Results: The sera of patients with CKD stage 5D and CKD stage 3-5 activated AhR (means: 53.6 and 45.6 AU; 95% CI [45.6-61.6] and [32.6-58.7] respectively) compared to sera from controls (mean: 2.1 AU; 95% CI [0.5-3.8]). The activating effect of CKD serum was reduced by the addition of an AhR antagonist (CH-223191) in the CALUX assay. The expression of AhR target genes was increased in patients with CKD stage 5D compared to controls. In stage 3-5 CKD patients, AhR serum activity was inversely correlated with eGFR ($r = -0.59$, $p < 0.0001$). All-cause mortality (log-Rank $p = 0.01$) and cardiovascular mortality (log-Rank $p = 0.047$) were increased in patients with an AhR serum activity above the median (44 AU) compared to patients with value below.

Conclusions: Serum from patients with CKD activates AhR, this ability is associated with mortality. Furthermore, AhR is activated in vivo in patients with CKD. Serum AhR activation is a new biomarker to predict the cardiovascular risk of patient with CKD. It is also an attractive target to develop new therapy.

Funding: Government Support - Non-U.S.

TH-OR121

Associations of Urine Kidney Injury Biomarkers and All-Cause Mortality in the CRIC Study Meyeon Park,¹ Chi-yuan Hsu,¹ Alan S. Go,² Dawei Xie,³ Xiaoming Zhang,³ Sushrut S. Waikar,⁴ Joseph V. Bonventre,⁴ Josef Coresh,⁵ Robert G. Nelson,⁶ Harold I. Feldman,³ Paul L. Kimmel,⁶ Vasan S. Ramachandran,⁷ Kathleen D. Liu.¹ ¹UCSF; ²Kaiser Permanente of Northern California; ³U. of Pennsylvania; ⁴Harvard; ⁵Welch Center for Prevention; ⁶NIH; ⁷Boston Univ.

Background: Among individuals with CKD, we hypothesized that ongoing kidney injury would associate with an increased risk of death. We tested this hypothesis in the Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: Urine kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), and liver fatty acid-binding protein (LFABP) were measured in 2466 CRIC subjects. Cox proportional hazards models were used to examine the association between biomarker concentrations indexed to urinary creatinine and death.

Results: Mean age of study participants was 59.5 (± 10.8) years; 46% were women, 43% were white, 38% were black. 50% had diabetes mellitus and 34% had cardiovascular (CV) disease. After adjustment for baseline eGFR, albuminuria, age, sex, race, CV comorbidities, and medications, those in the highest quintile (Q5, > 2290.3 pg/g) of KIM-1/Cr levels and in the highest two quintiles of NGAL/Cr (Q5, > 64 ng/g, Q4, > 20.2 ng/g) relative to the lowest (Q1 KIM-1/Cr < 661.3 pg/g, Q1 NGAL/Cr < 2.6 ng/g) had an increased risk of death [KIM-1/Cr Q5 v. Q1, hazard ratio (HR) 1.6 (1.1-2.3); NGAL/Cr Q5 v. Q1 HR 1.8 (1.2-2.8); Q4 v. Q1 HR 1.5 (1.2-2.2)]. Both analytes were also associated with death when levels were expressed as a continuous variable [HR per log SD increase of KIM-1/Cr = 1.21 (1.06-1.39); HR per log SD increase of NGAL/Cr = 1.22 (1.07, 1.39)]. NAG/Cr was associated with death in the continuous analysis only [HR per log SD increase of NAG/Cr = 1.2 (1.04-1.37)]. LFABP/Cr was not associated with death.

Conclusions: Urine KIM-1/Cr, NGAL/Cr, and NAG/Cr are independently associated with increased risk of death in individuals with CKD. Kidney tubular injury may mark processes related to mortality risk in individuals with CKD.

Funding: NIDDK Support

TH-OR122

Endogenous Klotho Is Expressed in Human Heart and May Associated with Fibrosis Qinghua Liu,^{1,2} Tzongshi Lu,¹ Qiying Dai,¹ David M. Charytan,¹ Daniel Zehnder,³ Li-Li Hsiao.¹ ¹Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; ²Dept of Nephrology, The First Affiliated Hospital, Sun Yat-sen Univ, Guangzhou, China; ³Univ Hospital Coventry and Warwickshire NHS Trust, Coventry, UK.

Background: Cardiovascular disease is the major risk factor for patients with CKD. Emerging evidence suggests that fibroblast growth factor 23 (FGF23) is associated with left ventricular hypertrophy and cardiovascular events in ESRD patients. Klotho and fibroblast growth factor receptor (FGFR) serve as co-receptors for FGF23. We previously showed that endogenous Klotho is expressed in human arteries, and that CKD is a state of Klotho deficiency, but whether human heart expresses Klotho and whether Klotho levels is correlated with kidney function or cardiac fibrosis in CKD patients is unknown.

Methods: Human atrial appendage specimens were collected during cardiac surgery from individuals with and without CKD. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. CKD was defined as eGFR < 60 ml/min/1.73 m². Fibrosis was quantified digitally using trichrome stained sections. Paraffin embedded cardiac tissue was obtained commercially. Western blot and immunohistochemical assay were used to detect protein expressions of Klotho, FGF23 and FGFR3. Klotho mRNA expression was assessed with RT-PCR.

Results: We confirmed that FGF23 is expressed in human heart. Our results show that endogenous Klotho and its co-receptor FGFR3 are expressed in human atrial appendage and left ventricle both in protein and mRNA levels. Our results also showed that cardiac fibrosis is negatively correlated with eGFR. And the endogenous Klotho levels in the heart is significantly suppressed with decreasing eGFR and increasing cardiac fibrosis.

Conclusions: We show for the first time that endogenous Klotho expressed in human heart and that Klotho suppression is associated with the degree of cardiac fibrosis and kidney function, suggesting the endogenous Klotho may have an association with cardiac fibrosis with possible involvement of FGF23.

TH-OR123

Circulating TNF Receptors Predicts Cardiovascular Disease in CKD Patients Eunjin Bae,¹ Jung Nam An,² Jin Ho Hwang,³ Dong Ki Kim,¹ Chun Soo Lim,² Jung Tak Park,⁴ Shin-Wook Kang,⁴ Yon Su Kim,¹ Jung Pyo Lee.² ¹Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea; ²Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea; ³Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; ⁴Internal Medicine, Yonsei Univ College of Medicine, Seoul, Republic of Korea.

Background: Cardiovascular disease (CVD) is the main public health problem in patients with CKD. However, there is no definite biomarker for predicting CVD morbidity and mortality in CKD. The aim of this study is to evaluate the role of circulating tumor necrosis factor receptors (ctNFRs) as a predictor of CVD risk in CKD patients.

Methods: We recruited 1,078 patients with CKD from 11 centers prospectively between 2006 and 2012. The levels of cTNFR1 and cTNFR2 were determined by performing enzyme-linked immunosorbent assay (ELISA). The correlation coefficient between cTNFRs and various values was measured using a Pearson's correlation test. Cox regression analysis was used to calculate the hazard ratio (HR) of CVD.

Results: Among a total of 1,078 patients, 57.2% was men and mean age was 50.4±15.7 years. 261 participants (24.2%) had DM. The mean serum creatinine was 1.9±1.0 mg/dL, UPCr was 2.2±2.7 g/g creatinine, hs-CRP was 0.6±2.4 mg/dL, cTNFR1 was 271±917 and cTNFR2 was 5687±3878 pg/ml. Serum cTNFR2 was correlated with the cTNFR1 (r=0.827), each other. In addition, age, BMI, UPCr, and eGFR were significantly correlated with cTNFR1 (r=0.43 for age, r=0.15 for BMI, r=0.20 for UPCr, r=-0.63 for eGFR; p<0.001 for all). Similar correlations were observed with the cTNFR1. For the mean follow-up duration of 4 years, 51 patients experienced CVD event. Participants with CVD were older and had lower eGFR level, higher SBP, higher cTNFRs level than those without CVD. In Cox proportional hazard analyses, cTNFR1 (HR 1.907, 95% CI 1.025-3.550, p=0.0042) and cTNFR2 (HR 2.271, 95% CI 1.269-4.065, p value=0.006) predicted risk for CVD even after adjustment for clinical covariates, such as UPCr, eGFR, hs-CRP.

Conclusions: cTNFR1 and 2 associate with CVD and other risk factors in CKD, independent of eGFR and UPCr. Furthermore, cTNFRs could be relevant predictors for CVD in CKD patients.

TH-OR124

Fibroblast Growth Factor 23 and Risk of Atrial Fibrillation in Chronic Kidney Disease: The CRIC Study Rupal Mehta,¹ Xuan Cai,¹ Jungwha Lee,¹ Nisha Bansal,² Julia J. Scialla,² James H. Sondheimer,² Rajat Deo,² Jing Chen,² L. Lee Hamm,² Ana C. Ricardo,² Mahboob Rahman,² Sankar D. Navaneethan,² Alan S. Go,² Harold I. Feldman,² Tamara Isakova,¹ Myles S. Wolf.¹ ¹Northwestern Univ; ²CRIC Study.

Background: Levels of fibroblast growth factor 23 (FGF23) are elevated in chronic kidney disease (CKD) and are strongly associated with cardiovascular disease and mortality. Atrial fibrillation (AF) is a common complication in CKD that is associated with poor outcomes, but whether FGF23 is an independent risk factor for AF in CKD is unknown.

Methods: We tested the associations of FGF23 with AF in cross-sectional and longitudinal analyses of 3879 participants in the Chronic Renal Insufficiency Cohort Study who had baseline FGF23 measurements. For longitudinal time-to-incident AF analyses, we excluded the 660 individuals with AF at baseline. Incident AF was adjudicated based on review of hospital records and yearly electrocardiograms.

Results: Mean estimated glomerular filtration rate (eGFR) was 44.3 ± 15.0 ml/min/1.73m² and median C-terminal FGF23 was 146 RU/ml (interquartile range 96, 239 RU/ml). In multivariable logistic regression models, higher FGF23 expressed continuously and in quartiles was associated with greater prevalence of AF (Table 1). Over a median follow up of 7 years, 248 incident AF events occurred. In multivariable-adjusted Cox proportional hazards models, elevated baseline FGF23 was a risk factor for incident AF (Table 2). These associations remained significant across strata of sex, race, prior heart failure, and eGFR. When FGF23 was expressed in quartiles or in models that censored individuals at end-stage renal disease onset (loss of 55 incident AF events), FGF23 was no longer associated with incident AF.

Table 1: Hierarchical Unadjusted and Adjusted Associations of Fibroblast Growth Factor 23 and Prevalent Atrial Fibrillation by Natural Log-Transformed Fibroblast Growth Factor 23 and Ascending Quartiles

	Unadjusted	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
Total Population					
Per 1 SD lnFGF23	1.51 (1.36-1.68)	1.51 (1.36-1.69)	1.58 (1.40-1.78)	1.47 (1.30-1.67)	1.51 (1.32-1.73)
FGF23 Quartiles					
1	Reference	Reference	Reference	Reference	Reference
2	1.07 (0.82-1.40)	1.00 (0.78-1.31)	1.05 (0.80-1.38)	1.01 (0.76-1.34)	1.03 (0.76-1.38)
3	1.72 (1.34-2.21)	1.61 (1.25-2.08)	1.78 (1.36-2.33)	1.66 (1.26-2.20)	1.70 (1.27-2.29)
4	2.32 (1.82-2.96)	2.22 (1.73-2.84)	2.56 (1.94-3.38)	2.26 (1.68-3.03)	2.45 (1.79-3.35)

Table 2: Hierarchical Unadjusted and Adjusted Associations of Fibroblast Growth Factor 23 and Incident Atrial Fibrillation by Natural Log-Transformed Fibroblast Growth Factor 23 and Ascending Quartiles

	Unadjusted	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
Total Population					
Per 1 SD lnFGF23	1.49 (1.27-1.74)	1.62 (1.38-1.91)	1.48 (1.22-1.78)	1.38 (1.14-1.68)	1.30 (1.05-1.60)
FGF23 Quartiles					
1	Reference	Reference	Reference	Reference	Reference
2	1.31 (0.89-1.93)	1.24 (0.84-1.82)	1.14 (0.77-1.69)	1.05 (0.70-1.56)	0.95 (0.62-1.44)
3	1.78 (1.23-2.57)	1.73 (1.19-2.51)	1.46 (0.98-2.16)	1.27 (0.85-1.90)	1.17 (0.77-1.78)
4	2.10 (1.45-3.03)	2.29 (1.58-3.34)	1.78 (1.17-2.72)	1.50 (0.97-2.32)	1.35 (0.86-2.14)

Abbreviations: SD, standard deviation; ln, natural log; FGF23, fibroblast growth factor 23

^a Model 1 adjusts for age, sex, Black race

^b Model 2 adjusts per Model 1 and additionally for eGFR (estimated glomerular filtration rate) by CKD-EPI equation

^c Model 3 adjusts per Model 2 and additionally for cardiovascular disease, hypertension, diabetes, and smoking

^d Model 4 adjusts per Model 3 and additionally for calcium, urinary albumin-to-creatinine ratio, total cholesterol, parathyroid hormone and serum phosphate

Conclusions: Among individuals with moderate to severe CKD, an elevated FGF23 level was independently associated with prevalent AF and may be associated with incident AF.

Funding: NIDDK Support

FR-OR001

Effects of Cyclosporine on Renal Handling of Divalent Cations in Claudin 16-Deficient Mice Hoora Drewell,¹ Tilman Breiderhoff,² Dominik Müller,³ Michael Föhling,⁴ Sebastian Bachmann,¹ Kerim Mutig.¹ ¹Anatomy, Charité-Universitätsmedizin, Berlin, Germany; ²Physiology, Charité-Universitätsmedizin, Berlin, Germany; ³Pediatric Nephrology, Charité-Universitätsmedizin, Berlin, Germany; ⁴Vegetative Physiology, Charité-Universitätsmedizin, Berlin, Germany.

Background: Calcineurin inhibitors tacrolimus and cyclosporine are instrumental for immunosuppression after organ transplantation but cause substantial renal side effects including hypomagnesemia and hypercalciuria. The tight junctions protein Claudin 16 (Cldn16) mediates paracellular reabsorption of divalent cations along the cortical thick ascending limb and has been implicated in the adverse effects of cyclosporine. We have compared effects of cyclosporine in wild-type (WT) and Cldn16-deficient (Cldn16^{-/-}) mice.

Methods: Mice received cyclosporine (25 mg/kg) for 7 days and their kidney performance was analysed in metabolic cages. Expression of distal transport proteins has been studied by quantitative PCR and immunoblotting.

Results: Physiological analysis revealed baseline hypomagnesemia and hypercalciuria in Cldn16^{-/-} mice. Administration of cyclosporine induced marked hypomagnesemia in WT mice but did not significantly alter plasma magnesium levels in Cldn16^{-/-} mice. In contrast, cyclosporine-induced increase in urinary calcium was significantly stronger in Cldn16^{-/-} mice compared to WT controls alongside more pronounced decrease of plasma calcium levels in Cldn16^{-/-} mice. Cyclosporine stimulated distal sodium transporters leading to sodium retention in both genotypes.

Conclusions: In sum, our data corroborate the pivotal role of Cldn16 in the renal magnesium and calcium handling and suggest that Cldn16 may be involved in the cyclosporine-induced renal magnesium loss and hypomagnesemia, since genetic deletion of Cldn16 prevented these effects. In contrast, the strong manifestation of cyclosporine-induced hypercalciuria in Cldn16^{-/-} mice suggests that cyclosporine may affect transcellular calcium reabsorption pathways rather than the Cldn16-mediated paracellular transport.

FR-OR002

Ogr1 and Acid-Induced Hypercalciuria Pedro Henrique Imenez Silva,¹ Kessara Chan,¹ Marie-Gabrielle Ludwig,² Jürg Andreas Gasser,² Timothy R. Arnett,³ Olivier Bonny,⁴ Klaus Seuwen,² Carsten A. Wagner.¹ ¹Inst of Physiology, Univ of Zurich, Zurich, Switzerland; ²Novartis Insts for Biomedical Research, Basel, United Kingdom; ³Dept of Cell and Developmental Biology, Univ College London, London, United Kingdom; ⁴Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland.

Background: The Ovarian cancer G-protein coupled Receptor 1 OGR1 (GPR68) is an extracellular proton activated GPCR that stimulates inositol triphosphate (IP₃) production and increases intracellular Ca²⁺ levels. However, the physiological roles of OGR1 are not well established. In this work we aimed to identify the roles of OGR1 in acid-base and mineral balance.

Methods: Wild type (OGR1^{+/+}) and an OGR1 mice-deficient model (OGR1^{-/-}) were subjected to metabolic acidosis (280 mM NH₄Cl) or non-acidotic control condition for 1 and 7 days and basic physiological parameters were collected from blood and urine. Several organs were isolated such as kidneys, intestine, brain, heart, etc. in order to extract RNA and perform RT-PCR/real time PCR. Kidneys were also used for protein extraction/western blotting.

Results: OGR1 mRNA was found in many organs including kidney where mRNA was detected in all nephron segments. No acid-base modifications were observed in OGR1^{-/-} mice, except for a higher plasma pH in the 1 day metabolic acidosis group (7.20 ± 0.04 vs 7.12 ± 0.03, p<0.05). As was expected, metabolic acidosis caused an increase in calcium and magnesium excretion in OGR1^{+/+}, but this was not observed in OGR1^{-/-}. The mRNA levels of proteins involved in Ca²⁺ and Mg²⁺ reabsorption like Calbindin D28k, TRPV5/6, TRPM6/7 and Claudins 16 and 19 were not altered in OGR1^{-/-}. The protein expression of TRPV5, the main apical distal convoluted tubule route for calcium, was 2.4- fold increased (p<0.001) in OGR1^{-/-} under metabolic acidosis which may explain the diminished Ca²⁺ excretion in these mice.

Conclusions: OGR1 is involved in the hypermagnesuria and hypercalciuria developed during metabolic acidosis, by a mechanism involving the Ca²⁺ channel, TRPV5.

Funding: Government Support - Non-U.S.

FR-OR003

Conditional NFAT5 Knockout Causes Impaired Urinary Concentrating Ability with Renal Diabetes Insipidus and Hyponatremia without Renal Medullary Injury Christoph Kueper,¹ Franz Xaver Beck,¹ Zoran Popovic,² Hermann-Josef Groene,² Bernhard K. Krämer,³ Wolfgang Neuhofer.³ ¹Cellular Physiology, Univ of Munich, Munich, Germany; ²Molecular Pathology, German Cancer Research Inst, Heidelberg, Germany; ³Div of Nephrology, Univ Hospital Mannheim, Mannheim, Germany.

Background: This study addressed the effects of inducible deletion of NFAT5 in adult mice on the expression of components of urinary concentration, i.e. AQP-2, CIC-K1, barttin, and UT-A1. In parallel, NFAT5-dependent osmoprotective genes AR, HSP70, and others were determined along with renal functional, morphological, and systemic parameters.

Methods: Mice with tamoxifen-inducible deletion of NFAT5 were established. At the age of 3-4 weeks, conditional NFAT5 KO mice or control animals were fed with a diet

containing tamoxifen for further 3-4 weeks. Subsequently, the expression of NFAT5 target genes was determined by qRT-PCR, Western blot analysis, and immunohistochemistry in different kidney zones in animals with free access to water or in mice that were water deprived for 24 h. Urine and blood electrolyte and urea concentrations were determined by standard methods.

Results: Adult mice with conditional deletion of NFAT5 showed 80-90% reduced expression of NFAT5 in all tissues tested, particularly in renal medullary regions. Accordingly, the NFAT5 target genes AQP-2, CIC-K1, barttin, UT-A1, AR, and HSP70 were substantially downregulated. Consistently, these NFAT5-deficient mice had renal diabetes insipidus with reduced urinary concentrating ability, dehydration, and hypernatremia, particularly following water deprivation. In contrast to constitutive NFAT5 knockout animals, inducible deletion in adult mice was not associated with renal medullary injury or hydronephrosis.

Conclusions: Deletion of NFAT5 causes renal diabetes insipidus-like phenotype by diminished expression of genes essential for urinary concentration. Despite reduced expression of osmoprotective genes in the renal medulla, histological evidence of medullary cellular injury was not detectable. The lack of damage might be a consequence of diminished medullary interstitial sodium chloride and urea concentrations, and hence reduced osmotic stress in this kidney region.

FR-OR004

Effect of Concurrent P2Y2 Receptor Deletion and P2Y12 Receptor Blockade on Lithium-Induced Nephrogenic Diabetes Insipidus in Mice Yue Zhang, Kristina M. Heiney, Bellamkonda K. Kishore. *Internal Medicine, Univ of Utah & VA Med Ctr, Salt Lake City, UT.*

Background: Chronic lithium (Li) administration for bipolar disorder causes nephrogenic diabetes insipidus (NDI), characterized by polyuria, natriuresis and kaliuresis, resulting in a debilitating condition. Previously we reported that mice lacking ATP/UTP-activated P2Y2 receptor are significantly, but not completely resistant to Li-induced polyuria. Recently in a mouse model we observed that pharmacological blockade of ADP-activated P2Y12 receptor offers near complete amelioration of Li-induced polyuria. However, there were differences between these two approaches in terms of natriuresis, kaliuresis and blood Li levels. Hence, we tested the concurrent effect of both in mice.

Methods: Groups (n = 5 to 7) of age-matched adult wild type B6D2 (WT) and syngeneic P2Y2-R knockout (KO) mice were fed Li-added diet (40 mmol LiCl/kg food) ad libitum, with or without administration of clopidogrel bisulfate (CLPD; 80 mg/kg bw/day) in drinking water for 14 days and euthanized. Twenty-four hour urine samples were collected prior to and toward the end of the experimental period. Blood samples were collected at euthanasia.

Results: Compared to Li-fed WT mice: (i) Li-fed KO mice had ~50% less polyuria associated with significant amelioration of Li-induced natriuresis and kaliuresis; and (ii) Li-fed WT mice treated with CLPD had near complete amelioration of polyuria, but had no effect on Li-induced natriuresis and kaliuresis. Interestingly, Li-fed KO mice concurrently treated with CLPD showed significant amelioration of natriuresis and kaliuresis, in addition to almost complete suppression of polyuria. P2Y2-R deletion had no effect on blood Li levels, whereas P2Y12-R blockade caused modest, but significant increase in blood Li levels. However, the concurrent approach neutralized the effect of P2Y12-R blockade on blood Li levels.

Conclusions: Our results demonstrate that concurrent blockade of P2Y2 and P2Y12 receptors has the potential for better outcomes in amelioration of Li-induced NDI without causing a rise in blood Li levels. By proper optimization of CLPD dose, it should be possible to achieve better control of all parameters of NDI.

Funding: Veterans Administration Support

FR-OR005

The V-ATPase B1 Subunit Polymorphism p.E161K Is Associated with Impaired Urinary Acidification in Recurrent Stone Formers Daniel G. Fuster,^{1,3} Nasser Dhayat,^{1,3} Giuseppe Albano,^{1,3} Andreas Pasch,^{1,3} Bruno Vogt,^{1,3} Orson W. Moe.² ¹Nephrology, Hypertension and Clinical Pharmacology, Univ Hospital of Bern, Bern, Switzerland; ²Div of Nephrology, UT Southwestern Medical Center, Dallas, TX; ³Dept of Clinical Research, Univ of Bern, Bern, Switzerland.

Background: Mutations in the V-ATPase B1 subunit gene ATP6V1B1 cause autosomal-recessive distal renal tubular acidosis. We previously identified a single nucleotide polymorphism (SNP) in the human V-ATPase B1 subunit (c.481G>A; p.E161K) that displayed greatly diminished pump function in vitro.

Methods: To investigate the impact of this p.E161K SNP on urinary acidification in vivo, we conducted a genotype-phenotype analysis of recurrent stone formers in the Dallas and Bern kidney stone registries.

Results: 32 of 555 (5.77 %) of the patients examined were heterozygous for the p.E161K SNP, the remaining 523 patients (94.23%) carried two wild-type alleles. Adjusted for sex, age, BMI and dietary acid and alkali intake, p.E161K SNP carriers had a tendency to higher urinary pH under a random diet (6.31 versus 6.09; p=0.089). Under an instructed low calcium and sodium diet, urinary pH was higher in p.E161K SNP carriers (6.555 versus 6.005; p<0.005). Kidney stones of p.E161K carriers were significantly more likely to contain calcium phosphate than stones of wild-type patients. In acute ammonium chloride loading, p.E161K carriers displayed a higher trough urinary pH (5.34 vs 4.89; p=0.01) than wild-type patients. 14.58 % of wild-type patients and 52.38% of p.E161K carriers were unable to acidify their urine below 5.3 and thus had incomplete distal renal tubular acidosis.

Conclusions: In summary, our data indicate that recurrent stone formers with the V-ATPase B1 subunit p.E161K SNP exhibit a urinary acidification deficit with an increased prevalence of calcium phosphate containing kidney stones. The burden of E161K heterozygosity may be a forme fruste of distal RTA.

Funding: Government Support - Non-U.S.

FR-OR006

Proximal Tubule-Specific Glutamine Synthetase Deletion Alters Basal and Acidosis-Stimulated Renal Ammonia Excretion Hyun-Wook Lee,¹ Gunars Osis,¹ Mary E. Handlogten,¹ Jill W. Verlander,¹ I. David Weiner.^{1,2} ¹Renal Div, Univ of Florida, Gainesville, FL; ²Nephrology and Hypertension, NF/SGVHS, Gainesville, FL.

Background: Glutamine synthetase (GS) mediates the recycling of NH₄⁺ and glutamate back to glutamine. In the kidney, the majority of GS is expressed in the proximal tubule where it may decrease net ammoniogenesis and limit ammonia available for net acid excretion. This study's purpose was to determine the role of proximal tubule (PT) GS in normal acid-base homeostasis and in the renal response to metabolic acidosis.

Methods: We generated mice with proximal tubule-specific glutamine synthetase deletion (PT-GS-KO) by using Cre-loxP techniques. PT-GS-KO mice had loxP sites flanking exons 1 and 7 (GS^{fl/fl}) and expressed Cre-recombinase under control of the phosphoenolpyruvate carboxykinase (PEPCK) promoter (PEPCK-Cre). Control (C) mice were GS^{fl/fl} but PEPCK-Cre negative.

Results: Immunoblot analysis showed PT-GS-KO decreased GS protein expression by 47 ± 4% in the cortex and 89 ± 1% in the outer stripe of the outer medulla; immunohistochemistry showed efficient and specific PT GS deletion with occasional residual GS-positive cells. Under basal conditions, proximal tubule GS deletion increased urinary ammonia excretion: 102 ± 10 vs 75 ± 8 mmol/day in PT-GS-KO and C mice, respectively, consistent with our hypothesis that GS deletion increases net ammoniogenesis and thereby increases ammonia excretion. However, ammonia excretion after acid loading for 7 days increased similarly in PT-GS-KO and C mice during the first 4 days of acid loading but on days 5-7 was significantly less, by ~33%, in PT-GS-KO as compared to C mice. In acid-loaded mice, adaptive responses to PT-GS-KO included increased expression of cortical phosphate-dependent glutaminase (PDG), PEPCK, and the glutamine transporter, SN1, compared to C.

Conclusions: We conclude: 1) proximal tubule GS expression contributes to both basal and acidosis-stimulated renal ammonia excretion; and, 2) elimination of the contribution of proximal tubule GS downregulation to enhance ammoniogenesis during acid-loading is partially compensated for by adaptive increases in PDG, PEPCK and SN1 expression.

Funding: NIDDK Support, Veterans Administration Support

FR-OR007

The B1 H⁺-ATPase (Atp6v1b1) Subunit Is Required for Non-Type A Intercalated Cell Function and Defense against Alkalosis Soline Bourgeois, Jana Kovacicova, Carsten A. Wagner. *Inst of Physiology, Univ of Zurich, Zurich, Switzerland.*

Background: The final urine pH is fine-tuned by type A and non-type A intercalated cells (IC) along the connecting tubule (CNT) and collecting duct (CCD) involving the action of vacuolar H-ATPases. Mutations in the B1 subunit of H-ATPase (ATP6V1B1) in man cause distal renal tubular acidosis due to its importance in acid secretion by type A-ICs. Non-type A-IC also express the vacuolar H⁺-ATPases containing the B1 subunit isoform at their luminal and/or basolateral plasma membrane together with the luminal Cl⁻/HCO₃⁻ exchanger pendrin. The main function of non-type A-ICs is the excretion of bicarbonate during metabolic alkalosis. However, the function of the B1 isoform in non-type A-ICs has remained elusive.

Methods: We studied the metabolic behaviour of B1 deficient mice during an alkali load induced by a 4-day desoxycorticosterone (DOCA, 2 mg/mouse s.c) and 0.28M NaHCO₃ treatment in the drinking water.

Results: Induction of metabolic alkalosis resulted in a more pronounced alkalosis in B1 deficient mice associated with increased blood bicarbonate, hypokalemia, and hypochloremia. Furthermore, while, pendrin localization was preserved, total pendrin expression was reduced and pendrin activity was altered in B1 deficient mice whereas the relative abundance of pendrin expressing cells was increased. In parallel, H⁺-ATPase activity in non-type A-IC from ex vivo microperfused cortical collecting duct was strongly reduced. Finally, the E and A subunits of H-ATPase did not associate with the basolateral domain of B1 deficient non-type A-ICs leading to the non-association of V₁ domain while basolateral expression of a4 subunit, part of the V0 domain, was not disrupted.

Conclusions: Thus, the B1 subunit is required for the formation of a complete and functional basolateral H⁺-ATPases complexes and is critical for normal non-type A-IC function cells during alkalosis.

Funding: Government Support - Non-U.S.

FR-OR008

Comparing the Effect of Combination of Acetazolamide and Hydrochlorothiazide Followed by Furosemide versus Combination of Hydrochlorothiazide and Furosemide Followed by Furosemide in Treating Refractory Edema Associated with Nephrotic Syndrome: A Randomized, Double-Blind Trial Mohammad Kazem Fallahzadeh,¹ Mohammad Amin Fallahzadeh,² Banafshe Dormaneh,³ Jamshid Roozbeh,² Mohammad Hossein Fallahzadeh,² Mohammad Mahdi Sagheb.² ¹Baylor Univ Medical Center, Dallas, TX; ²Shiraz Univ of Medical Sciences, Shiraz, Islamic Republic of Iran; ³AJA Univ of Medical Sciences, Tehran, Islamic Republic of Iran.

Background: The Cl/HCO₃ exchanger pendrin and Na/Cl cotransporter (NCC) play important role in distal tubule salt reabsorption. A recent animal study has shown simultaneous inhibition of pendrin and NCC by acetazolamide and hydrochlorothiazide, respectively results in significant diuresis. The aim of this study was to evaluate the efficacy of combination of acetazolamide and hydrochlorothiazide followed by furosemide in treatment of refractory edema associated with nephrotic syndrome.

Methods: In this randomized, double-blind trial we enrolled 20 patients with nephrotic syndrome who had refractory edema despite receiving maximum furosemide dose. All patients had GFR>60 ml/min/1.73m². After a 2-week washout period when patients received no diuretics, they were randomly assigned to 2 equal groups. Group 1 received 250-mg oral acetazolamide and 50-mg oral hydrochlorothiazide daily for 1 week. Group 2 received 40 mg oral furosemide and 50-mg oral hydrochlorothiazide daily for 1 week. Then patients in both groups received 40-mg oral furosemide daily for 2 weeks. The primary outcome was the amount of change in weight from baseline to the end of the treatment phase.

Results: Although weight reduction occurred in both groups, it was significantly higher in group 1 as compared to group 2 at the end of first week (-1.4±0.52 vs. -0.65±0.41 kg, p=0.004) and of third week of treatment phase (-3±0.94 vs. -1.15±0.47 kg, p=0.001). Increase in 24-hour urine volume was also significantly higher in group 1 at the end of treatment phase. Serum Na and K levels were in reference range in all the patients during the treatment phase.

Conclusions: Combination of acetazolamide and hydrochlorothiazide followed by furosemide may be a novel and safe diuretic therapy in refractory edema associated with nephrotic syndrome.

FR-OR009

Tissue Na⁺ in Chronic Kidney Disease and Effect of Renal Transplantation on Na⁺ Stores Christoph Kopp,¹ Jonathan Jantsch,⁵ Anke Dahlmann,¹ Peter Linz,² Daniela Amslinger,² Matthias Hammon,³ Kai-Uwe Eckardt,¹ Friedrich C. Luft,⁶ Jens Titze.^{2,4} ¹Nephrology and Hypertension, Univ Hospital Erlangen, Germany; ²Junior Research Group II, Interdisciplinary Center for Clinical Research, Erlangen, Germany; ³Radiology, Univ Hospital Erlangen, Germany; ⁴Clinical Pharmacology, Vanderbilt Univ, Nashville; ⁵Clinical Microbiology and Hygiene, Univ Hospital Regensburg, Germany; ⁶Experimental and Clinical Research Center, Max-Delbrück Center, Berlin, Germany.

Background: Diminished kidney function as occurs in Chronic Kidney Disease (CKD) causes salt sensitive hypertension. By using ²³Na-Magnetic Resonance Imaging (²³Na-MRI) technology we recently could detect Na⁺ storage in humans, which was associated with hypertension. Whether impaired Na⁺ excretion in CKD results in tissue Na⁺ accumulation and if kidney transplantation affects tissue Na⁺ stores is not known.

Methods: We recruited 32 patients with CKD Stage 4 and 5 prior to preemptive living donor transplantation or dialysis treatment and 30 age- and gender-matched control subjects. ²³Na-MRI at 3Tesla was used to quantify muscle and skin Na⁺ of the lower leg before kidney transplantation/dialysis as well as 3 and 6 months after living donor transplantation. Additionally, clinical parameters including blood pressure as well as blood and urine samples were assessed.

Results: Compared to healthy control subjects, CKD-patients showed increased muscle and skin Na⁺ content (skin 15.8 ± 3.6 vs. 23.1 ± 8.2, p<0.001; muscle 15.8 ± 1.8 vs. 21.0 ± 3.9, p<0.001). Despite these differences in tissue Na⁺, serum Na⁺ concentration did not vary between both groups. Restoration of kidney function by successful renal transplantation in 15 CKD patients was accompanied by reduced blood pressure (mean arterial pressure 104 ± 12 vs. 94 ± 11, p<0.01) and mobilization of tissue Na⁺ from muscle (21.4 ± 3.1 vs. 18.4 ± 2.9, p<0.01) and skin (24.4 ± 6.2 vs. 19.2 ± 4.5, p<0.01) 6 months post-transplantation.

Conclusions: Accelerated sodium storage occurs in pre-dialysis patients with CKD that could be reversed by successful kidney transplantation. Reduction of tissue Na⁺ after kidney transplantation was associated with better blood pressure control.

FR-OR010

Small-Molecule Inhibitors of Pendrin (SLC26a4) Augment the Diuretic Action of Furosemide Onur Cil, Cristina Esteva-Font, Joseph-Anthony Tapia Tan, Puay Wah Phuan, Peter Michael Haggie, Alan S. Verkman. *Depts of Medicine and Physiology, Univ of California San Francisco, San Francisco, CA.*

Background: Pendrin (Slc26a4) is a chloride/bicarbonate exchanger expressed in type-B and non-A, non-B intercalated cells of connecting tubule and cortical collecting duct, where it mediates Cl⁻ absorption and modulates ENaC function by changing luminal HCO₃⁻ concentration. Under normal conditions, pendrin has a minimal role in renal salt metabolism; pendrin knock-out mice and patients with Pendred Syndrome (caused by loss-of-function *Slc26a4* mutations) do not manifest salt wasting. Previous studies demonstrated

that double knock-out of pendrin with other renal salt transporters causes increased urine output, volume depletion and salt wasting. It has been hypothesized that pendrin may attenuate diuretic-induced salt loss.

Methods: A cell-based high-throughput screen was established to identify pendrin inhibitors involving fluorescence plate reader measurement of chloride influx in epithelial cells stably coexpressing human pendrin and a chloride-sensing fluorescent protein. Screening of ~30,000 drug-like small molecules produced three chemical classes of pendrin inhibitors with IC₅₀ down to 1 μM. The pendrin inhibitors were administered to mice intraperitoneally (10 mg/kg) either alone or with low (5 mg/kg), intermediate (10 mg/kg) or high (20 mg/kg) dose furosemide. Urine was collected in metabolic cages for 3 hours after injection, and blood was collected afterwards.

Results: In furosemide-treated mice pendrin inhibitors of two chemically different classes produced an approximate 40% increase in urine output and osmolar clearance, without changing urine osmolality. The compounds had no effect in mice when administered alone. LC/MS analysis showed predicted therapeutic inhibitor concentrations in blood and urine.

Conclusions: Our findings suggest pendrin inhibition as a novel approach to amplify the diuretic action of loop diuretics. Such combination therapy might enhance diuresis and salt excretion for treatment of hypertension and edema, including diuretic-resistant edema.

Funding: NIDDK Support

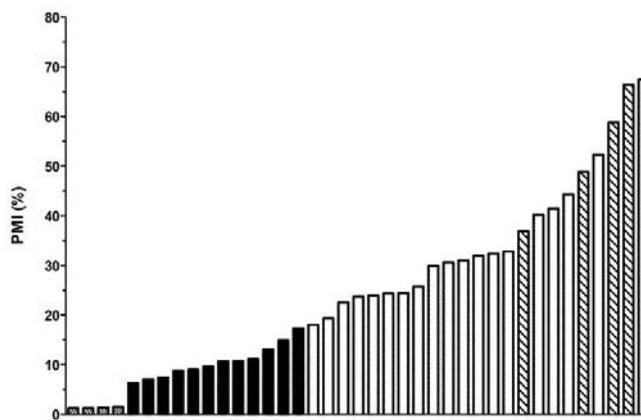
FR-OR011

Increased Synthesis of Liver Erythropoietin in Patients with Chronic Kidney Disease Sophie M. De Seigneux,¹ Stine Lundby,² Patrick Saudan,¹ Pierre-Yves F. Martin,¹ Carsten Lundby.² ¹Service of Nephrology, Univ of Geneva; ²Inst of Physiology, Univ of Zurich.

Background: Anemia of chronic kidney disease (CKD) is thought to be related to impaired renal erythropoietin (Epo) production. Epo may be synthesized by the kidney but also by the liver in humans. Epo glycosylation pattern is dependent on its synthesizing cell, thereby indicating its origin. Here we tested the hypothesis that synthesis of Epo from non-kidney cells increases to compensate for insufficient renal Epo production in patients with moderate CKD.

Methods: We determined plasma [Epo] levels and Epo glycosylation patterns in 19 moderate non-dialyzed CKD patients (stage III-IV) and compared these to values obtained in healthy volunteers, rhEPO and umbilical cord plasma (liver derived Epo mainly).

Results: Despite higher Epo levels (15.75 (11.3 - 24.2) IU/L) compared to healthy controls (8.4 (7.56 - 8.98) IU/L, p<0.01), CKD patients were moderately anemic ([Hb]: 113 ± 11 g/dl). Half of the patients presented higher Epo levels than expected from the calculated values corrected for anemia. Glycosylation was increased in CKD patients (34 ± 12 %; measured as percent migrated isoform, PMI_{open bars}) when compared to healthy controls (8.6 ± 1 %; p<0.01, black bars) and rhEpo samples (1.4 ± 1.4 p<0.01, hatched bars), whereas the pattern did not differ from umbilical cord plasma (55 ± 10 %, p>0.05, lined filled bars) which is known to contain mainly liver derived Epo.



Renal function correlated strongly to glycosylation pattern assessed by PMI (R=-0.8, p<0.01), with patients having lowest eGFR displaying higher Epo PMI values, indicating a larger part of liver derived Epo.

Conclusions: These results suggest that 1) moderate CKD patients exhibit preserved Epo levels despite declining renal function 2) this may be achieved by increasing liver Epo synthesis and 3) Epo originating from liver seems less erythropoietic.

Funding: Government Support - Non-U.S.

FR-OR012

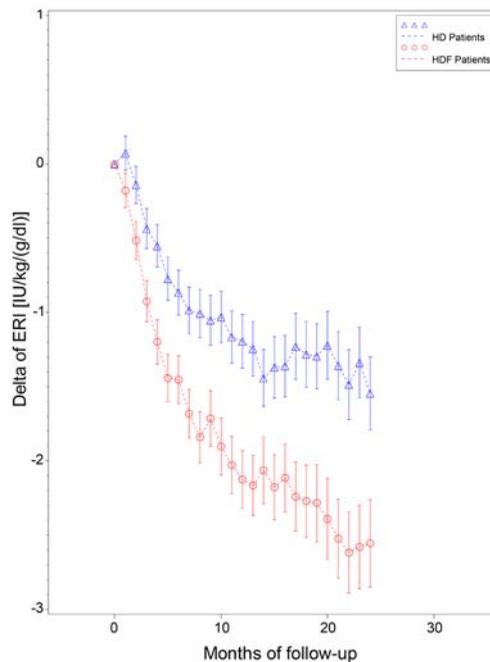
Associations Among Erythroferone and Biomarkers of Erythropoiesis and Iron Metabolism, and Treatment of Long-Term Erythropoiesis-Stimulating Agents in Patients on Hemodialysis Hirokazu Honda,¹ Yasuna Kobayashi,² Shoko Onuma,³ Keigo Shibagaki,⁴ Toshitaka Yuza,⁴ Keiichi Hirao,⁵ Toshinori Yamamoto,² Naohisa Tomosugi,⁶ Takanori Shibata.³ ¹Div of Nephrology, Dept of Medicine, Showa Univ Koto Toyusu Hospital, Tokyo, Japan; ²Div of Clinical Pharmacy, Dept of Pharmacotherapeutics, Showa Univ, School of Pharmacy, Tokyo, Japan; ³Dept of Preventive Medicine, Showa Univ, School of Medicine; ⁴Shibagaki Dialysis Clinic Jiyugaoka, Tokyo, Japan; ⁵Shibagaki Dialysis Clinic Togoshi, Tokyo, Japan; ⁶Kanazawa Medical Univ, Kanazawa, Japan.

Background: The present study aimed to identify associations between erythroferone (ERFE), a regulator of hepcidin 25, and biomarkers of erythropoiesis and iron metabolism. We also investigated the effects of the erythropoiesis-stimulating agents (ESA), continuous erythropoietin receptor activator (CERA) and darbepoetin- α (DA), on ERFE production in patients on hemodialysis (HD).

Methods: Blood samples were obtained from 59 patients before HD sessions on day 0 (baseline) for baseline cross-sectional analysis. Twenty patients who were injected with either CERA (N = 10) or DA (N = 10) at the end of the dialysis week (day 0), who were not iron-deficient (ferritin < 100 ng/mL and transferrin saturation < 20%) and had hemoglobin levels > 9 g/dL were selected from among the 59 patients. Blood was sampled serially before HD sessions on days 3, 5, 7 from patients on DA and on the same days and day 14 from those on CERA to assess impact of ESA on iron metabolism including ERFE.

Results: Levels of ERFE correlated inversely with those of hepcidin 25 and ferritin, and positively with soluble transferrin receptor. The hepcidin 25: ERFE ratio and hepcidin 25 levels positively correlated with ferritin levels. Levels of ERFE significantly increased from day 3 of treatment with DA and CERA and decreased by days 7 and 14, respectively. Levels of hepcidin 25 were decreased by ESA in accordance as those of ERFE increased.

Conclusions: Erythroferone might be associated with iron metabolism in patients on HD. Both DA and CERA increased levels of ERFE that regulated hepcidin 25 and led to iron mobilization from body stores during erythropoiesis.



Conclusions: ERI progressively decreased during the first 24 months on dialysis, but more sharply and to a great extent in the HDF group compared to the HD group. The dynamics of ERI change over the first year on dialysis may explain why previous studies encountered difficulties in recognizing ERI trends when various dialysis vintages are grouped together.

FR-OR013

Dynamics of ESA Resistance Index in Incident Hemodiafiltration and High-Flux Hemodialysis Patients Daniele Marcelli, Inga Bayh, Aileen Grassmann, Laura Scatizzi, Katharina Brand, Bernard J. Canaud. Fresenius Medical Care, Bad Homburg, Germany.

Background: Hemodiafiltration (HDF), combining diffusion and convection, provides efficient blood detoxification over a wide molecular weight range that may include erythropoiesis inhibiting agents. Study aim: to compare ESA resistance index (ERI) in incident HDF and high-flux hemodialysis (HD) patients. ERI is the weekly weight-adjusted ESA dose (U/kg/week) divided by hemoglobin level (g/dl).

Methods: 20,694 incident patients (7,674 HDF; 13,020 HD,) from 436 NephroCare clinics in 20 countries with ≥ 6 mths follow-up were studied between January 1 2007 and December 31 2013. Baseline (BL) was 6 mths after dialysis initiation; follow-up was 1.35 \pm 0.69 yrs. Exclusion criteria: BL presence of metastatic tumors, malnourishment (BMI < 18.5 kg/m²), treatment via catheter, age < 18 years, less/more than thrice weekly dialysis, modality switch in month before BL, and missing ESA dose after BL. After propensity score matching to reduce bias by indication, a total of 6,568 patients (3,284 in each arm) remained.

Results: At BL, HDF patients had a non-significant higher ERI than HD patients (7.79 vs 7.48 IU/kg/(g/dl)) (p=0.06). ERI decreased by 0.087 IU/kg/(g/dl) per mth in HDF patients and significantly less in HD patients (0.050 IU/kg/(g/dl) per mth). The difference between both groups increased by 0.036 IU/kg/(g/dl) per mth. At 8.4 mths of follow-up, ERI was lower in HDF patients compared to HD patients. The delta ERI for each time interval versus BL also reveals ERI change dynamics (Figure).

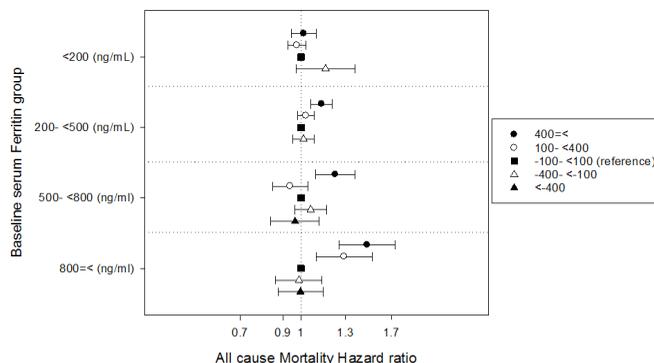
FR-OR014

Serum Ferritin Variations and Mortality in Incident Hemodialysis Patients Tae Hee Kim,¹ Joline L.T. Chen,^{1,2} Elani Streja,¹ Connie Rhee,¹ Yoshitsugu Obi,¹ Csaba P. Kovessy,³ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²VA Long Beach; ³UTHSC.

Background: Previous studies on maintenance hemodialysis (MHD) patients have shown that higher serum ferritin may be associated with inflammation and higher mortality. Additional studies have shown that serum ferritin increase sharply in the first year of MHD and gradually increase over time. However, associations between changes in serum ferritin levels over the first 6 months of dialysis and mortality are unknown. We hypothesized that a rapid rise in serum ferritin is associated with higher risk of mortality.

Methods: In a cohort of 93,996 incident MHD patients receiving treatment from a large dialysis organization during 2007-2011, we examined mortality associations of change in serum ferritin from baseline patient quarter (first 91 days from dialysis start) to subsequent quarters using Cox proportional hazard models. Models were adjusted for demographics, comorbidities, markers of the malnutrition and inflammation complex (MICS) and intravenous iron dose. Serum ferritin change was divided into five strata: (<-400, -400 to <-100, -100 to <100, 100 to <400, and ≥ 400 ng/ml over 3 months). Associations were examined across strata of baseline serum ferritin (<200, 200 to <500, 500 to <800 and ≥ 800 ng/ml).

Results: Patients were 63 \pm 15 years old, 44% female, 32% African-American, and 60% diabetic. In patients with baseline serum ferritin ≥ 200 ng/ml, a rise in serum ferritin ≥ 400 ng/ml/quarter was associated with higher all-cause mortality during the 5-year follow-up compared with no change in serum ferritin (-100 to <100 ng/ml).



Conclusions: Rapid rise in serum ferritin levels >400 ng/ml/quarter during the first 6-months after MHD initiation is associated with higher 5-year mortality in patients with elevated baseline serum ferritin. Studies evaluating the conditions influencing these serum ferritin changes and their associations with mortality are needed.

Funding: NIDDK Support

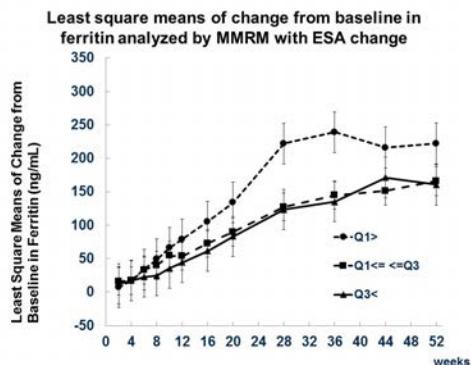
FR-OR015

Decreasing ESA Dosage Can Be a Factor of the Increase in Ferritin Under the Administration of Ferric Citrate with Improving ESA Resistance Index Keitaro Yokoyama,¹ Takashi Akiba,² Masafumi Fukagawa,³ Masaaki Nakayama,⁴ Hideki N. Hirakata.⁵ ¹Div of Nephrology and Hypertension, Jikei Univ School of Medicine, Tokyo, Japan; ²Dept of Blood Purification, Kidney Center, Tokyo Women's Medical Univ, Tokyo, Japan; ³Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; ⁴Dept of Nephrology, Hypertension, Diabetology, Endocrinology, and Metabolism, Fukushima Medical Univ School of Medicine, Fukushima, Japan; ⁵Japanese Red Cross, Fukuoka Hospital, Fukuoka, Japan.

Background: Ferric citrate (an iron based phosphate binder) controlled serum phosphorus with lower concentrations and reduced the doses for ESA and intravenous iron in HD patients. Also, serum ferritin concentrations had a tendency to increase (Phase 3 trial).

Methods: To explore potential factors associated with an increase in ferritin values, data from the 52-week phase3 clinical study in Japanese HD patients were analyzed by a mixed model for repeated measurement (MMRM) including variables that were selected based on the results of correlation, simple linear regression, and multiple regression analyses. In addition, ESA resistance index (ERI) was analyzed to determine factors which contribute to it based on the result from the MMRM.

Results: The factor of the increase in ferritin was associated with not only the dosage of ferric citrate but also the degree of decrease in ESA dosage (Q1>: dosage was decreased in the course of study. Q1≤ to ≤Q3: dosage was not changed. Q3<: dosage was increased).



In subjects whose ESA dosage was decreased in the course of the study, the ERI went lower by the administration of ferric citrate in spite of that initial dosage of ESA and ERI were higher than other subjects group.

Conclusions: Decreasing ESA dosage might increase serum ferritin level under the administration of ferric citrate with improving ERI.

Funding: Pharmaceutical Company Support - TORII PHARMACEUTICAL CO.

FR-OR016

Triferic Maintains Hemoglobin and Iron Balance Long Term: Open-Label Phase III Extension Studies Carrie D. Guss, Raymond D. Pratt, Ajay Gupta, Vivian H. Lin. R&D, Rockwell Medical Inc., Wixom, MI.

Background: The objective of the Phase 3 extension studies was to confirm the safety of Triferic administered via dialysate for up to 18 months of treatment and to assess hemoglobin and iron status.

Methods: Patients who completed the Phase 3 randomized controlled treatment studies (RCT) could continue in the open-label (OL) extension studies for up to 18 months of combined participation. In the OL extensions, patients received ESA according to their site protocol and IV iron could be administered for presumed development of iron deficiency.

Results: Approximately 70% of patients completed the pivotal RCT and enrolled in the OL extension, providing a total of 412 patient-years of exposure to Triferic. Triferic reliably administered iron with each hemodialysis treatment. The average pre-HD to post-HD increment in serum total iron concentration was 96.2 ± 44.20 mg/dL. Chronic administration of Triferic maintained Hgb levels within the target range of 9.5 to 11.5 g/dL during the study. ESA requirements and ChR also remained stable from study baseline throughout the study. Pre-dialysis serum iron values were maintained at baseline levels. Serum ferritin concentrations declined from 372.8 ± 236.78 mg/L at OL study entry to 305.2 ± 219.36 mg/L at End of Treatment (EoT). Fewer patients who had received Triferic in the RCT studies required supplemental IV iron (48%) than patients who had received placebo (58%). OL long term safety was similar to the RCT results. The most frequent AE was procedural hypotension, occurring in 34.8% of patients. When adjusted for exposure, the rates of adverse events in the OL study were similar to those observed in the RCT.

Conclusions: Triferic administered long term (up to 18 months) reliably delivered iron with every treatment. Triferic administered via dialysate maintained Hgb while not

increasing iron stores or increasing ESA doses. The safety profile was similar to that observed in the pivotal Phase 3 RCT studies. No anaphylaxis was observed in over 45,000 individual doses administered in this program.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

FR-OR017

Longer Sustained Reduction of Serum Hepcidin Level (Hep) During the Treatment of Anemia with Epoetin Beta Pegol (CERA) as Compared to Epoetin Beta (rEPO) in Predialysis Stage-5 CKD Patients Yusuke Kuroki,¹ Koji Mitsuiki,¹ Yuko Yoshida,¹ Hokuto Arase,¹ Kaneyasu Nakagawa,¹ Hideki Yotsueda,¹ Hideki N. Hirakata,¹ Naohisa Tomosugi.² ¹Nephrology & Dialysis Center, Fukuoka Red Cross Hospital, Fukuoka, Japan; ²Kanazawa Medical Univ.

Background: Efficient iron utilization is required in ESA-induced erythropoiesis in CKD patients, Hep being a key factor to modulate iron turn-over in this situation. In the present study, changes in Hep and the related iron markers were examined before and after CERA administration in comparison with rEPO in pre-dialysis ESA-naïve stage 5 CKD patients.

Methods: Twenty-three patients were subjected to the study; age 70±13 [SD] y/o, m/f=15/8, DM/nonDM=10/13, eGFR 14±5 ml/min/1.73m², Hb 9.7±1.1 g/dl. They were assigned randomly to 2 groups, being treated with either rEPO (n=13) or CERA (n=10). Their baseline data were as follows; Hb 9.8 ± 0.9 (rEPO) vs. 9.6 ± 1.3 (CERA) g/dl, serum iron (SFe) 75 ± 25 vs. 77 ± 17 mg/dl, TSAT 28 ± 8 vs. 31 ± 9 %, ferritin 129 ± 117 vs. 173 ± 91 ng/ml, albumin 3.7 ± 0.5 vs. 3.6 ± 0.6 g/dl, IL-6 3.2 ± 2.8 vs. 3.8 ± 2.3 pg/ml, hs CRP 1038 ± 2539 vs. 1730 ± 419 ng/ml, and Hep 34 ± 19 vs. 52 ± 29 ng/ml, respectively. ESA was given in the morning, SFe and Hep were measured before and on the 2nd, 4th, 7th, 14th and 28th day. On the first day, circadian variation of SFe and Hep was evaluated. Hematological parameters, TSAT and ferritin were measured before and on the 28th day.

Results: Hep level was highest at 3 pm on the first day. Hb rose significantly in both group in association with steep decrease in Hep in rEPO, being 34±19 to 7.7±8.5, and was returned to the baseline in 14 days. In CERA, Hep reduction was also observed but the trend was mild from 52±29 to 27±17 ng/ml on the 14th days. The decrease in Hep correlated significantly with the increase in reticulocyte production index, a marker of erythropoietic output, in all patients (r=0.66, p<0.01). These changes were associated with the significant decrease in SFe.

Conclusions: CERA has a sustained suppressive effect on Hep, which might contribute to its longer erythropoietic activity via enhancing iron utilization.

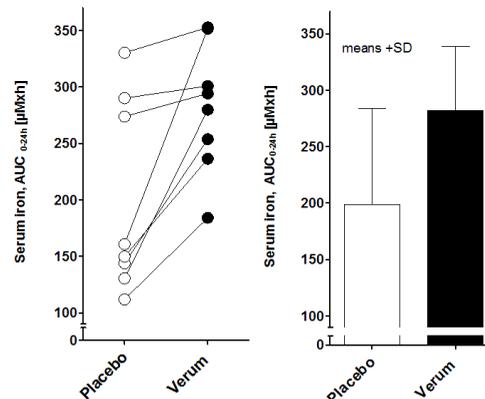
FR-OR018

Clinical Pharmacology, Efficacy, and Safety of the Anti-Hepcidin Spiegelmer Lixatepid Pegol Iain C. Macdougall,¹ Enric Vilar,² Helmut Reichel,³ Joachim H. Beige,⁴ Leela Goldstein,¹ Frank Schwöbel,⁵ Luciana Summo,⁵ Kai Riecke.⁵ ¹Dpt. of Renal Medicine, King's College Hospital, London, United Kingdom; ²Lister Hospital, Stevenage, United Kingdom; ³Nephrological Center Villingen Schwanningen, Germany; ⁴Hospital St. Georg, Leipzig, Germany; ⁵NOXXON Pharma AG, Berlin, Germany.

Background: Elevated hepcidin is frequent in hemodialysis patients and contributes to ESA-resistant anemia. Inhibiting hepcidin may therefore reduce resistance to ESA therapy and improve anemia. The anti-hepcidin L-RNA-Aptamer (Spiegelmer®) lixatepid pegol binds and inactivates hepcidin and is in development for treatment of anemia.

Methods: We studied the pharmacological effects on iron metabolism, on anemia, and the safety of lixatepid in 109 healthy subjects and patients with myeloma/lymphoma or on hemodialysis. A trial in dialysis patients with functional iron deficiency is ongoing.

Results: Lixatepid increased iron concentrations and prevented the serum iron decrease after endotoxin challenge in healthy subjects. In patients with myeloma / lymphoma and functional iron deficiency, 2 doses/week of lixatepid over 1 month increased hemoglobin by ³1 g/dL in patients with low reticulocyte Hb and high soluble transferrin receptor. In ESA-hyporesponsive dialysis patients, cross-over comparison with placebo showed increases in serum iron concentrations following lixatepid administration, consistent with its anti-hepcidin action.



The recruitment of hemodialysis patients for twice weekly treatment with lexaptetid for one month is ongoing in a randomized controlled trial. Lexaptetid was well tolerated by healthy subjects and patients.

Conclusions: Lexaptetid was safe and well tolerated and showed pharmacodynamic activity in healthy subjects and ESA-hyporesponsive dialysis patients as well as signs of efficacy in anemic cancer patients with functional iron deficiency.

FR-OR019

Neutrophil Gelatinase-Associated Lipocalin (NGAL) Is Associated with Iron Status in Anemic Patients with Chronic Kidney Disease Min Jung Kim,¹ Il Young Kim,¹ Soo Bong Lee,¹ Joo Hui Kim,¹ Dong Won Lee,¹ Su Min Park,² Jong Man Park,² Woo Jin Jung,² Sang Heon Song,² Eun Young Seong,² Harin Rhee,² Ihm Soo Kwak.² ¹Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea; ²Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea.

Background: Iron deficiency anemia is common in patients with chronic kidney disease (CKD). Neutrophil gelatinase-associated lipocalin (NGAL) is known as a biomarker of acute kidney injury and predictor of the progression of CKD. In addition, recent studies have shown that NGAL is associated with iron metabolism by binding siderophores, small molecules containing iron. We investigated whether serum NGAL levels is associated with iron status in CKD patients with anemia.

Methods: This study included 257 CKD patients [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m²] who had anemia at the time of study enroll (hemoglobin levels < 13.0 g/dl in males and < 12.0 g/dl in females). The associations between serum NGAL and iron status [iron, total iron binding capacity, ferritin, transferrin saturation (TSAT)], eGFR, albumin, uric acid, lipid profile, calcium, phosphate, and C-reactive protein (CRP) were assessed.

Results: The CKD patients with TSAT ≤ 30% had lower serum NGAL values than those with TSAT > 30% (274.9 ± 228.3 vs. 394.7 ± 232.2 ng/ml). In univariate analysis, serum NGAL correlated with eGFR (r = -0.367, P < 0.001), CRP (r = 0.253, P < 0.001), TSAT (r = 0.296, P < 0.001), and ferritin (r = 0.259, P < 0.001). In multivariate regression analysis, TSAT (β = 0.370, P < 0.001) was independently associated with serum NGAL in addition to CRP (β = 0.268, P < 0.001) and eGFR (β = -0.365, P < 0.001). However, ferritin lost its association with serum NGAL (β = 0.093, P = 0.132).

Conclusions: This study suggests serum NGAL is associated with iron status in anemic patients with CKD. Further studies are needed to demonstrate the role of NGAL in the assessment of iron deficiency and in the management of iron therapy for CKD patients.

FR-OR020

Safety and Hemoglobin Effect of Sotatercept, Administered Intravenously and Subcutaneously, for Maintenance of Hemoglobin in Hemodialysis Subjects: Interim Analysis of a Phase 2 Study Frank Dellanna,¹ Francisco Maduell,² Joan Fort,³ Xavier Warling,⁴ Hem N. Singh,⁵ William T. Smith.⁵ ¹DaVita Nephrology, Duesseldorf, Germany; ²Hospital Clinic of Barcelona, Barcelona, Spain; ³Vall d'Hebron Univ Hospital, Barcelona, Spain; ⁴Citadelle Regional Hospital Center, Liege, Belgium; ⁵Celgene Corporation, Warren, NJ.

Background: An ongoing randomized study is evaluating intravenous (IV) and subcutaneous (SC) sotatercept, an ActRIIA-IgG1 fusion protein ligand trap, for maintenance of hemoglobin (Hb) after switching from a prior erythropoietin-stimulating agent (ESA) in end-stage kidney disease (ESKD) subjects on hemodialysis (HD).

Methods: In part 1 of a 2-part phase 2 study, ESA-responsive ESKD/HD subjects with Hb between 10 and 12 g/dL were switched from ESA and randomized to open-label sotatercept (IV: 0.1 and 0.2 mg/kg; SC: 0.13 and 0.26 mg/kg) given every 14 days for up to 8 doses; a third dose group level of IV and SC is enrolling. Pharmacokinetic, safety, tolerability, and Hb effect were assessed. Intrastudy dose escalation was not permitted. Treatment failures (Hb < 9 g/dL) were rescued with ESA or transfusion.

Results: Among subjects receiving sotatercept (N=30; IV: 0.1 mg/kg [n=7], 0.2 mg/kg [n=8]; SC: 0.13 mg/kg [n=7], 0.26 mg/kg [n=8]), ³¹ adverse event (AE) occurred in 100%, 67%, 57%, and 57%, respectively. Serious AEs occurred only in the IV 0.1 mg/kg group (29%). AEs were mostly mild/moderate, unrelated to study drug, relatively similar between groups, and generally consistent with subject medical histories. No dose- or route-dependent changes were seen in home blood pressure (BP); no injection site or hypersensitivity reactions were observed. At the end of the 99-day treatment phase, mean change from baseline Hb was -0.5 g/dL (IV 0.1 mg/kg), 0.3 g/dL (IV 0.2 mg/kg), -0.3 g/dL (SC 0.13 mg/kg), and -0.3 g/dL (SC 0.26 mg/kg); 57%, 13%, 43%, and 13% experienced treatment failure requiring rescue, respectively. In the IV 0.2 mg/kg group, 3 subjects discontinued after the first dose.

Conclusions: IV and SC sotatercept demonstrated acceptable safety in ESKD/HD, with no dose- or route-dependent effects on home BP. Enrollment in the highest dose group is ongoing.

Funding: Pharmaceutical Company Support - Study was sponsored by Celgene Corporation.

FR-OR021

The Role of Activin in the CKD-MBD Keith A. Hruska,¹ Toshifumi Sugatani,¹ Olga A. Agapova,¹ Yifu Fang,¹ Hartmut H. Malluche,² ¹Pediatrics, Nephrology, Washington Univ School of Medicine, Saint Louis, MO; ²Medicine, Nephrology, Univ of Kentucky, Lexington, KY.

Background: At its inception, the CKD-MBD consists of vascular calcification, an osteodystrophy, decreased aklotho and stimulation of skeletal osteocyte FGF23 secretion. We have shown that inhibition of activin signaling through the activin type 2A receptor (ActRIIA), induced by CKD inhibits vascular calcification. Here, the other components of the CKD-MBD are analyzed.

Methods: CKD with hyperphosphatemia and 60% reduction in GFR (CKD-3) was induced at 14 weeks of age in our *ldlr*^{-/-} high fat fed model of vascular calcification. Some CKD mice were treated with RAP-011 (a type 2 activin receptor, ActRIIA, ligand trap). Skeletal histomorphometry and microCT imaging, renal klotho levels, serum chemistries and FGF23 and PTH levels were measured. Activin klotho and ActRIIA levels were measured by elisa, RT-PCR, westerns and IHC.

Results: Activin levels in the circulation were 10 fold elevated. The *ldlr*^{-/-} high fat fed model harbors a low turnover osteopenic osteodystrophy that was converted by CKD-3 to a high turnover state characterized by PTH levels of 430pg/ml (7 fold elevated), hyperphosphatemia, increased osteoblast numbers, and surfaces, increased osteoclast numbers and eroded surfaces, increased bone formation rates (BFR) but a significant decrease in BFR/osteoblast. CKD-3 decreased renal tubular klotho levels and produced marked (10 fold) elevations in FGF23 levels. Inhibiting activin by an ActRIIA ligand trap surprisingly reduced osteoblast number and surfaces, decreased BFR but increased BFR/osteoblast thereby preserving MAR. RAP-011 decreased osteoclast numbers and eroded surfaces. MicroCT imaging showed that RAP-011 increased cortical bone thickness and cortical bone area compared to CKD-3. RAP-011 treatment did not affect hyperphosphatemia, PTH levels or FGF23 levels. Inhibiting activin signaling increased renal tubular klotho levels.

Conclusions: Activin is a critical factor in the pathogenesis of the CKD-MBD causing aklotho deficiency, vascular and skeletal disease, and surprisingly playing a key role in the osteoblast dysfunction of CKD heretofore attributed solely to PTH and FGF23.

Funding: NIDDK Support, Pharmaceutical Company Support - Celgene

FR-OR022

Increase in Trabecular Bone Volume by Inhibition of GSK-3β in Uremic Mice Narihito Tatsumoto,^{1,2} Masaki Arioka,² Shunsuke Yamada,¹ Masanori Tokumoto,⁴ Kazuhiko Tsuruya,^{1,3} Takamari Kitazono,¹ Toshiyuki Sasaguri,² ¹Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ²Dept of Clinical Pharmacology, Faculty of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ³Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ⁴Dept of Medicine, Fukuoka Dental College, Fukuoka, Japan.

Background: Bone fracture increases the risk of hospitalization and mortality in patients with chronic kidney disease (CKD). Bone volume is closely related to the risk of fracture in CKD. Studies have shown that inhibition of glycogen synthase kinase (GSK)-3β, a critical component of Wnt/β-catenin signaling pathway, increases bone volume through accumulation of β-catenin. However, it remains unknown whether inhibition of GSK-3β increases bone volume in uremia.

Methods: The present *in vivo* study was performed to determine whether inhibition of GSK-3β could increase bone volume in adenine-induced CKD mice. Wild type mice were divided into three groups. One group was fed a control diet (CNT) and the other two groups were fed a diet containing 0.2% adenine with or without lithium chloride (LiCl), a GSK-3 inhibitor; CKD and CKD-LiCl group. GSK-3β heterozygous knockout mice were also fed a diet containing 0.2% adenine (CKD-GSK-3β^{+/+}). Bone and blood samples were collected after 6 weeks and trabecular (Tb) and cortical (Ct) bone were analyzed by micro-computed tomography.

Results: CKD mice developed azotemia, hyperphosphatemia, and secondary hyperparathyroidism, followed by a decrease in Ct bone thickness and no change in Tb bone volume after 6 weeks. Treatment with LiCl increased Tb bone volume, accompanied by polyuria and polydipsia. Tb bone volume increased in CKD-GSK-3β^{+/+} mice compared with CNT and CKD mice. There were no significant differences in kidney function, hyperphosphatemia, hyperparathyroidism, and Ct bone thickness among three CKD groups.

Conclusions: Inhibition of GSK-3β increased Tb bone volume in adenine-induced uremic mice.

FR-OR023

Sclerostin Knock-Out Protects from Uremia-Induced Cortical Bone Loss in a Murine Model of Chronic Renal Failure Daniel Cejka,¹ Diego Michael Parada Rodriguez,¹ Stefanie Pichler,¹ Rodrig Marculescu,⁵ Ina Kramer,² Michaela Kneissel,² Thomas Gross,³ Andreas G. Reisinger,³ Dieter Pahr,³ Marie-Claude M. Faugere,⁴ Martin Haas,¹ Hartmut H. Malluche.⁴ ¹Div of Nephrology & Dialysis, Dept of Medicine III, Medical Univ Vienna, Vienna, Austria; ²Musculoskeletal Disease Area, Novartis Insts for BioMedical Research, Basel, Switzerland; ³Inst of Lightweight Design and Structural Biomechanics, Vienna Univ of Technology, Vienna, Austria; ⁴Div of Nephrology, Bone and Mineral Metabolism, Dept of Internal Medicine, Univ of Kentucky, Lexington, KY; ⁵Dept of Laboratory Medicine, Medical Univ Vienna, Vienna, Austria.

Background: Renal osteodystrophy (ROD) affects the majority of patients with advanced chronic kidney disease (CKD) and is characterized by progressive bone loss. This study evaluates the effects of sclerostin-knock-out on bone in a murine model of CKD.

Methods: Severe CKD was surgically induced in sclerostin-knock-out-mice (SOST-KO-CKD) and wild-type (WT-CKD). Mice with normal kidney function serve as controls (SOST-KO-CTRL, WT-CTRL). After 3 months of CKD, blood was drawn and vertebrae and tibia were collected for histomorphometric and μ CT analyses.

Results: Cortical thickness (Ct.Th) of the tibia was significantly higher in sost-ko-CKD mice compared to wt-CKD mice ($p<0.001$). WT-CKD mice had lower Ct.Th compared to WT-CTRL ($p<0.05$), whereas no significant differences in Ct.Th were found between SOST-KO-CKD and SOST-KO-CTRL groups. Compared to WT-CKD mice, SOST-KO-CKD animals had higher trabecular number ($p<0.001$) and trabecular thickness ($p<0.001$) and lower trabecular separation ($p<0.001$). Mineral density of trabecular bone was higher ($p<0.001$) in SOST-KO-CKD mice compared to WT-CKD animals. In the lumbar vertebrae, bone volume/tissue volume was higher in SOST-KO-CKD mice compared to the WT-CKD group ($p<0.001$). Osteoid maturation time and mineralization lag time were not influenced by SOST-KO.

Conclusions: Sclerostin knock-out leads to increased bone mass and improved microarchitecture but does not alter osteoid mineralization in a murine model of CKD. Inhibition of sclerostin may be a promising approach to prevent bone loss in CKD.

Funding: Clinical Revenue Support

FR-OR024

Bone Health in Incident Renal Transplant Recipients: A Prospective Bone Biopsy Study Pieter Evenepoel,¹ Geert J. Behets,² Liesbeth Vaene,¹ Patrick C. D'Haese.² ¹Immunology and Microbiology, Catholic Univ Leuven, Leuven, Belgium; ²Pathophysiology, Univ of Antwerp, Antwerp, Belgium.

Background: Renal transplant recipients are at increased risk of fracture especially in the early post-transplant period. A better knowledge of the pathophysiology of post-transplant bone disease may open perspectives for targeted therapy. More specifically the role of immunosuppressive drugs, persistent hyperparathyroidism and inflammation needs to be elucidated. Bone histomorphometry is the gold standard to assess bone health.

Methods: Patients with paired bone biopsies at time of transplantation and 1 year, enrolled in an ongoing study that aims to unravel the natural history of CKD-MBD after transplantation (NCT01886950), were included in the present interim analysis ($n=36$, 29 males, age 54 ± 13 yrs). Maintenance immunosuppression consisted of steroids, a calcineurin inhibitor and mycophenolate mofetil. Mean cumulative methylprednisolone dose was 1.7 ± 0.7 g/d. None of the subjects had current or prior exposure to anti-resorptive agents.

Results: Histomorphometric parameters determined at baseline did not (or at best poorly) correlate with parameters determined at 1 year. Static parameters of bone formation (Ob.Pm/T.Pm (%): $0.6 [0.0 - 3.7]$ vs $1.9 [0.0 - 4.0]$) and resorption (Epm/B.Pm (%): $2.1 [0.1 - 4.3]$ vs $4.7 [3.3 - 8.1]$; Oc.Pm/T.Pm (%): $0.0 [0.0 - 0.6]$ vs $0.9 [0.0 - 1.4]$) decreased after transplantation. Inter-individual variation, however, was substantial, and significance was reached for bone resorption and osteoclast perimeter only. Circulating levels of TRAP5b, a biomarker of osteoclast activity, changed accordingly ($3.0 [2.0 - 4.8]$ vs $4.7 [3.0 - 7.1]$ U/L, $p=0.003$). Correlation statistics showed a significant correlation between change of Epm/B.Pm and TRAP5b over time. Trabecular bone loss during the study period was minimal. Cumulative steroid dose, but not PTH level was identified as a significant correlate.

Conclusions: Our data confirm a reduction of bone activity early after transplantation. Additional studies are required to further define underlying pathophysiological mechanisms. Trabecular bone loss in contemporaneous transplantation is minimal, most probably as a consequence of steroid minimization.

FR-OR025

Chronic Kidney Disease Is Associated with Progressive Increase in Arterial Stiffness and Bone Loss Over 1 Year Rathika Krishnasamy,^{1,2,3} Nicole M. Isabel,^{1,2} David W. Johnson,^{1,2} Tony Stanton,⁴ David Mudge,^{1,2} Scott B. Campbell,^{1,2} Sven-Jean Tan,⁵ Nigel David Toussaint,⁵ Carmel M. Hawley.^{1,2} ¹School of Medicine, The Univ of Queensland, Brisbane, Australia; ²Dept of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; ³Dept of Nephrology, Nambour General Hospital, Brisbane, Australia; ⁴Cardiovascular Imaging Research Group, The Univ of Queensland, Brisbane, Australia; ⁵Dept of Nephrology, The Royal Melbourne Hospital, Melbourne, Australia.

Background: To assess changes in arterial stiffness, bone structure and markers in stage 4/5 chronic kidney disease (CKD) compared with healthy controls.

Methods: In this prospective, single-centre, observational study, **bone indices** using peripheral quantitative computed tomography (pQCT) [cortical bone mineral density (cBMD), trabecular bone mineral density (tBMD), strength-strain index (SSI), bone mineral content (BMC) and cortical cross-sectional area (cCSA)], **arterial stiffness** [pulse wave velocity (PWV)] and **bone markers** including plasma intact fibroblast growth factor-23 (FGF23) and soluble α -klotho (sKl) were compared between CKD stage 4/5 and controls at baseline and 12 months (12m).

Results: Forty CKD [mean estimated glomerular filtration rate (eGFR): 19.5 ± 6.7 mL/min/1.73m²] and 42 controls (eGFR: 88.6 ± 12.9 mL/min/1.73m²) completed follow-up. At baseline, CKD subjects had lower cBMD ($p=0.04$), higher aortic PWV ($p=0.047$) and FGF23 ($p=0.001$) compared to controls. Lower baseline cBMD independently correlated with higher PWV ($\beta=-0.51$, $p<0.001$) in the CKD group. At 12m, CKD subjects had a significant decline in cBMD (-0.87% , $p=0.01$), tBMD (-1.70% , $p=0.03$), BMC (-2.60% , $p<0.001$), cCSA (-1.62% , $p=0.01$) and SSI (-3.79% , $p=0.02$) and an increase in PWV by 1.3 m/s (16.7% , $p<0.001$). Serum phosphate, calcium, parathyroid hormone and sKl did not significantly change over 12m. FGF23 levels increased [$240.6 (141.9 - 1129.8)$ to $396.8 (160.3 - 997.7)$, $p=0.001$] and was independently associated with changes in cBMD and PWV. Bone and vascular parameters remained unchanged in controls.

Conclusions: CKD was associated with significant losses of bone structure and greater increases in arterial stiffness and FGF23 levels over 12 months.

Funding: Pharmaceutical Company Support - Shire Australia, Private Foundation Support, Clinical Revenue Support

FR-OR026

Vascular Calcification Is Mediated by ERK-Dependent Upregulation of Pit1 via Rac1/NADPH/MR Activity Victor Manuel Barrientos,¹ Néstor Abarzúa,¹ Diego Varela,¹ Rodrigo Alzamora, Luis F. Michea.^{1,2} ¹ICBM, Univ de Chile, Chile; ²Millennium Inst on Immunology and Immunotherapy, Chile.

Background: Vascular calcification (VC) is a mayor mortality risk factor in patients with chronic kidney disease. During VC, vascular smooth muscle cells (VSMC) of the tunica media transdifferentiate into osteoblast-like cells. High extracellular phosphate (HP) promotes VC through the induction of the sodium-dependent phosphate cotransporter (Pit1) activity, increased NADPH oxidase activity (Nox1) and the expression of osteochondrogenic factors (OCF). Recent studies indicate that antagonists of the mineralocorticoid receptor (MR) ameliorate/prevent experimental VC and arteriosclerosis in mice. The small GTPase Rac1 modulates MR and Nox activity in VSMC. However, the role of Rac1 on vascular calcification remains unknown. We hypothesize that in VSMC, HP activates MR via Rac1 leading to induction of Nox and ERK1/2 activity, promoting VC.

Methods: Effects of HP on VC (Alizarin red staining) and OCF gene induction (RT-qPCR) were evaluated in rat aortic VSMC (A7r5). Inhibitors of Rac1 (NSC23766), MR (spironolactone) and Nox1 (apocynin) were used to determine signaling pathways involved in the activation of ERK caused by HP. Nox activity was determined using the Hyper H₂O₂ Biosensor. A7r5 cells were stimulated with HP, HP+NCS23766 or HP+apocynin to determine the role of Rac1 and MR on HP-induced H₂O₂ production. $n=4-5$ per group.

Results: HP increased Pit1 mRNA, OCF mRNA (cbfa1 and Sox9) and Nox1 mRNA ($p<0.05$ vs. normal phosphate (NP)) and caused mineralization. Aldosterone (100nM) potentiated the effect of HP on mineralization and gene expression ($p<0.05$). Incubation in the presence of spironolactone (10uM) prevented all the effects of aldosterone. Inhibition of Rac1 and NADPH oxidase activity prevented HP-induced H₂O₂ production (2.6% NP; 25% HP; 1.8 % HP+NCS at 20 min of stimuli; $p<0.05$ vs. HP). The presence of Rac1 or MR antagonists in culture medium suppressed HP-induced activation of ERK (2.7 times at 10 min; $p<0.05$ vs. 0 min).

Conclusions: We conclude that high phosphate-dependent calcification is mediated by ERK-dependent upregulation of Pit1 via Rac1/NADPH/MR activity. Funding: FONDECYT 1130550, IMI P09-016-F.

Funding: Government Support - Non-U.S.

FR-OR027

Inhibition of Wnt Signaling and Matrix Metalloproteinases Attenuates Calcium and Phosphate Induced Calcifications in Vascular Smooth Muscle Cells Uwe Querfeld,^{1,2} Veronika Bobb,² Christian Freise.² ¹Pediatric Nephrology, Charité, Berlin, Germany; ²Center for Cardiovascular Research, Charité, Berlin, Germany.

Background: The trans-differentiation of vascular smooth muscle cells (VSMC) into an osteoblast-like phenotype and matrix remodeling are essential in the pathogenesis of vascular calcifications in patients with chronic kidney disease (CKD). We have previously shown that the matrix metalloproteinases (MMP)-2 and -9 facilitate VSMC calcifications and, vice versa, their inhibition attenuates this process [1]. We studied the effects of calcifying conditions, recombinant MMPs and MMP-inhibitors on signal transduction in VSMC.

Methods: Mimicking the disturbed mineral balance during CKD, the trans-differentiation/calcification of murine VSMC was induced by a calcification medium (CM) containing elevated concentrations of calcium and phosphorus (Ca/P). MMP activities were modulated by recombinant MMP-2 or -9 and selective MMP inhibitors. Wnt activation was induced by a recombinant Wnt agonist and assessed in reporter plasmid (pGL4.49[luc2P/TCF-LEF RE/Hygro]) transfected VSMC. MMP-secretions and mRNA expressions were determined by substrate assays and qPCR, respectively.

Results: CM-induced calcifications in VSMC were accompanied by enhanced Wnt-signaling. Even under normal culture conditions, Wnt activation with a Wnt agonist induced VSMC calcifications associated with enhanced mRNA expression and secretion of MMP-2/-9. These Wnt-mediated effects were inhibited by MMP-2/-9 inhibitors. Treatment of VSMC with recombinant MMP-2/-9 induced a time-delayed Wnt-activation after 72h.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Enhanced levels of Ca/P induce Wnt-activation in VSMC, resulting in enhanced production of MMP-2/-9 which further promotes VSMC calcification. These results confirm clinical studies showing upregulations of MMP-2/-9 in experimental uremia [1] and in arteries of patients with CKD [2]. The therapeutic potential of MMP- or Wnt-inhibitors in the prevention of vascular calcification should be further explored in animal models of CKD-associated arteriosclerosis. [1] JASN 25: 2014 (SA-OR062, p.95A; TH-PO555, p.233A; FR-PO833, p.562A) [2] Chung A. et al, Circulation 120, 792-801 (2009).

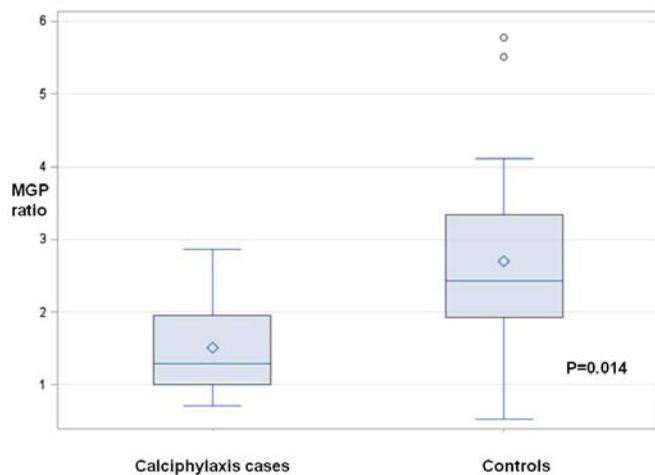
FR-OR028

Calciphylaxis Is Characterized by Vitamin K Deficiency and Impaired Matrix Gla Protein Carboxylation Sagar U. Nigwekar,¹ Rajeev Malhotra,¹ Julia Beth Wenger,¹ Sarah Booth,² Ravi I. Thadhani.¹ ¹Massachusetts General Hospital; ²Tufts Univ.

Background: Calciphylaxis, a dermal arteriolar calcification disorder linked with high mortality, has unclear pathogenesis. We investigated vitamin K metabolism and its effects on vitamin K dependent carboxylation of calcification inhibitor, Matrix Gla Protein (MGP), in calciphylaxis patients.

Methods: We prospectively recruited 20 ESRD patients with biopsy-confirmed calciphylaxis and obtained plasma samples and clinical information at the time of calciphylaxis diagnosis. Plasma samples and clinical information were also obtained from 20 controls (ESRD patients without calciphylaxis) matched to cases by age, sex, race, and warfarin status. Plasma levels of Proteins Induced by Vitamin K Absence (PIVKA-II) a sensitive measure of vitamin K deficiency, carboxylated MGP (c-MGP), and uncarboxylated MGP (uc-MGP) were measured using ELISA assays. MGP carboxylation status was derived by calculating c-MGP/uc-MGP ratio (MGP ratio). Prevalence of vitamin K deficiency (defined by PIVKA-II level ≥ 2 ng/mL) was compared between cases and controls using Chi-square analysis. MGP ratios were compared between cases and controls using a Mann Whitney U test and multivariable linear regression.

Results: Prevalence of vitamin K deficiency was higher in cases compared to controls (90% vs. 50%, P=0.006) including in patients not on warfarin/vitamin K antagonist therapy (83% vs. 35%, P=0.014). Median MGP ratio was lower in cases compared to controls (1.29 vs. 2.42, p=0.001) including in patients not on warfarin (1.64 vs. 2.98, p <0.001).



In multivariable analyses adjusted for clinical characteristics, vitamin K deficiency was associated with a 48% reduced MGP ratio (P=0.004).

Conclusions: High prevalence of vitamin K deficiency and its potential impact on MGP carboxylation in calciphylaxis call for a therapeutic trial of vitamin K supplementation in calciphylaxis.

Funding: Private Foundation Support

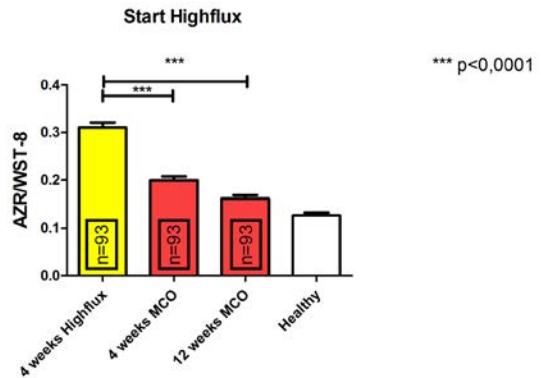
FR-OR029

Dialysis with Medium Cut-Off (MCO) Filters Reduces In Vitro Calcification of Human VSMC: Lessons from a Randomized Clinical Trial Daniel Zickler,¹ Markus Storr,³ Matthias Girndt,² Roman Fiedler,² Kevin Willy,¹ Ralf Schindler.¹ ¹Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin; ²Dept of Internal Medicine II, Martin-Luther-Univ, Halle; ³Research & Development, Gambro Dialysatoren GmbH, Hechingen.

Background: Vascular calcification is increased in CKD patients, partly caused by insufficient removal of inflammatory proteins with conventional dialysis filters. We assessed whether dialysis with MCO filters, which allow elimination of middle-sized inflammatory proteins with only limited permeability for albumine, influences vascular calcification in vitro.

Methods: 50 patients were dialysed in a randomized controlled clinical "first-in-man" trial with a MCO and a Highfluxfilter for four weeks in a randomized order. To test for longterm effects the patients were continued on their filter for eight more weeks. After each phase serum samples were drawn. In human VSMC calcification was induced and serum samples were added. After 7-12 days in vitro calcification was assessed via Alizarin red and Alkaline phosphatase assays and normalized to WST-8.

Results: Calcification in VSMC incubated with serum drawn after MCO dialysis was reduced compared to Highflux serum. Serum from patients, who started on a Highflux membrane showed a 35 % reduction (p<0,0001) of alizarin red staining after 4 weeks and a 49% (p<0,0001) reduction after 12 weeks of MCO dialysis. Alkaline phosphatase showed a 23% reduction after 4 weeks and a 32% reduction after 12 weeks MCO. Accordingly, serum from patients, who started on MCO showed an increase of calcification after switch to highflux dialysis.



Conclusions: Dialysis with MCO filter reduces in vitro vascular calcification. Our results encourage further investigation of the use of MCO filters in chronic dialysis patients with assessment of radiologic signs of vascular calcification and hard clinical end points.

Funding: Pharmaceutical Company Support - Gambro GmbH, Government Support-Non-U.S.

FR-OR030

First Experience with a Novel Inhibitor of Vascular Calcification (SNF472) in Healthy Volunteers and ESRD Patients on Hemodialysis Joan Perelló, Carolina Salcedo, Pieter H. Joubert, Ana-Zeralda Canals, Miquel D. Ferrer. Sanifit, Palma, Spain.

Background: SNF472, an intravenous (i.v.) formulation of myo-inositol hexaphosphate, is being developed for treating calciphylaxis and for preventing vascular calcification progression in patients with end-stage renal disease on hemodialysis. It selectively inhibits the final common pathway in the etiology of vascular calcification, the formation and growth of hydroxyapatite (HAP) crystals. Non-clinical investigations showed adequate evidence of efficacy and safety to warrant a first study in humans.

Methods: A double-blind, randomized, phase 1 clinical trial was performed in two cohorts of 8 male healthy volunteers (HV) and one cohort of 8 hemodialysis (HD) patients. Single ascending doses of 0.5, 5, 9 and 12.5 mg/kg of SNF472 were administered through 4-hour i.v. infusion to HV into a forearm vein. HD patients received a single i.v. dose of 9 mg/kg through the dialysis tubing before the filter during the 4 hours of dialysis. Safety parameters, including extensive ECG monitoring, were recorded. Blood samples were obtained up to 24h for safety and pharmacokinetics. A PD (pharmacodynamics) assay was used to assess the potential of ex vivo formation of HAP crystals.

Results: SNF472 was well tolerated and no systemic adverse events were observed. Several HV reported irritation at the infusion site. This effect was concentration-dependent (not dose-dependent). In HD patients SNF 472 is diluted >500-fold in the dialysis system before reaching the patient and no local irritation occurred. No effects were seen in safety parameters, including ECG. Ionized calcium was slightly below the lower limit of normal in HV at 12.5 mg/kg. The 5, 9 and 12.5 mg/kg doses produced measurable plasma concentrations above the anticipated EC50 (5µM) and showed a 70-80% reduction in the ex vivo HAP crystal formation PD assay. HD patients had similar SNF472 plasma concentrations (suggesting low SNF472 clearance through the dialysis membrane) and PD effects to HV. Plasma ionized calcium levels were stable.

Conclusions: The data available suggests a favourable benefit/risk ratio of SNF472 and supports further studies in the target population. Supported by RETOS COLABORACIÓN RTC-2014-2460-1.

Funding: Pharmaceutical Company Support - Laboratoris Sanifit, Government Support - Non-U.S.

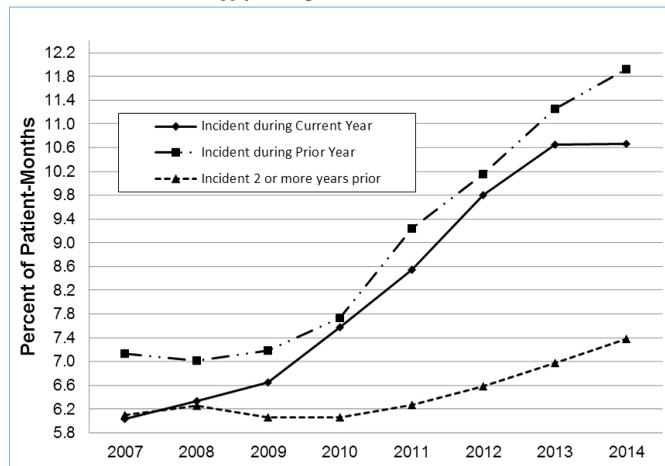
FR-OR031

Use of Peritoneal Dialysis (PD) Before and After the Bundled Prospective Payment System (PPS) Richard Hirth,¹ Tammie A. Nagra,¹ Adam S. Wilk,¹ Marc Turenne,² Jonathan H. Segal,¹ John Wheeler,¹ Kathryn Sleeman,¹ Wei Zhang.¹ ¹UM-KECC, Univ of Michigan, Ann Arbor, MI; ²Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: PD rates steadily eroded prior to the PPS. Because the PPS bundles injectable drugs, which are used less in PD relative to hemodialysis (HD) while paying the same rate for PD and HD, the PPS increases the incentive to provide PD. PD rates began to rise in anticipation of the PPS and continued to rise after its implementation. This study extends these early observations to include 4 years under the PPS and examines whether the PD supply shortages of 2014 impacted the growth of PD.

Methods: We used Medicare claims to examine trends in % of patient-months with PD during 2007-2014, for patients incident during the current year, prior year and ≥2 years prior. The study period includes 3 pre-PPS years (2007-09), a transition year when the PPS was anticipated but not yet implemented (2010) and the first 4 years of the PPS (2011-14).

Results: PD continued to increase as a % of patient-months through the transition and post-bundle period. Initial increases occurred in the current and prior year cohorts with a trailing increase in the ≥2 year cohort, reaching 10.7%, 11.9% and 7.4%, respectively by 2014 (vs. 6.0%, 7.1% and 6.1% in 2007). Growth stalled in the current year cohort during 2014, coincident with PD supply shortages.



Conclusions: PD use continued to increase under the PPS and is now reflected in increases among patients incident ≥2 years prior, suggesting that the initial increases among newer patients are translating into longer-term modality tenure. PD fluid shortages are coincident with a stalling of growth among patients incident in 2014. Monitoring modality trends among the 2014 incident cohort will help determine whether those patients eventually started PD after shortages eased or if their rates never catch up.

Funding: Other U.S. Government Support

FR-OR032

The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS): Preliminary Findings from the First Year Jeffrey Perl,¹ Junhui Zhao,² Brian Bieber,² Yun Li,³ Simon J. Davies,⁴ David W. Johnson,⁵ James A. Sloand,⁶ Hideki Kawanishi,⁷ Bruce M. Robinson,² Francesca Tentori.^{2,8} ¹St. Michael's Hospital, Univ of Toronto, Toronto, ON, Canada; ²Arbor Research Collaborative for Health, Ann Arbor, MI; ³Univ of Michigan, Ann Arbor, MI; ⁴Univ Hospital of North Midlands, Stoke-on-Trent, United Kingdom; ⁵Princess Alexandra Hospital, Brisbane, Queensland, Australia; ⁶Baxter Healthcare Corporation, Deerfield, IL; ⁷Tsuchiya General Hospital, Hiroshima, Japan; ⁸Vanderbilt Univ, Nashville, TN.

Background: The PDOPPS is a prospective cohort study underway in the United States (US), Australia, Canada, Japan, and the United Kingdom, in collaboration with the International Society for Peritoneal Dialysis. PDOPPS aims to understand the impact of clinical practices on patient outcomes, including patient and technique survival. Here, we present results from the first year of data collection.

Methods: 170 randomly selected facilities and 6000 patients will participate in the initial study. A stratified random selection of facilities has yielded national samples of facilities and patients, with 20-45 patients per site. Clinical, demographic, biochemical, and treatment data are collected at 4-month intervals. Follow up is 3-years or until death, kidney transplantation, or 120-days after a change in permanent dialysis modality. Early descriptive data are presented for the three countries.

Results: To date, 99 facilities and 2211 patients have been recruited. Selected patient and treatment characteristics vary widely across countries (Table 1).

Table 1: Selected patient and treatment characteristics in the three initial PDOPPS countries

	US	Canada	Japan
Patient characteristics			
Age, years	57.2	61.6	65.0
Female	45%	39%	35%
Time on PD, years	1.9	2.1	2.1
Diabetes*	29%	35%	31%
Glomerulonephritis*	14%	15%	32%
Coronary heart disease	27%	22%	12%
PD therapy			
# of PD patients per facility	39	75	33
APD	73%	41%	26%
# of overnight exchanges	4.6	5.3	3.6
> 1 daytime exchange	36%	49%	20%
CAPD	27%	59%	74%
# of daytime exchanges	3.9	3.5	3.4
Residual kidney function, peritoneal membrane function, and dialysis adequacy			
Urine volume, L/24hr	0.71	0.92	0.77
D/P creatinine	0.67	0.75	0.66
Total Kt/V	2.32	2.1(1.53)	1.82

As of May 2015; results are shown as mean or %

US: facility N=56, patient N=507; Canada: facility N=20, patient N=449, Japan: facility N=18, patient N=254

Data collection from Australia and the United Kingdom is just underway.

* As primary cause of ESRD

Conclusions: PDOPPS is the largest international study of PD patients and outcomes. Early findings demonstrate variability in PD practices (e.g. schedule, adequacy) across countries. PDOPPS will be a valuable resource to identify optimal practices and improve outcomes for patients on PD.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGI, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

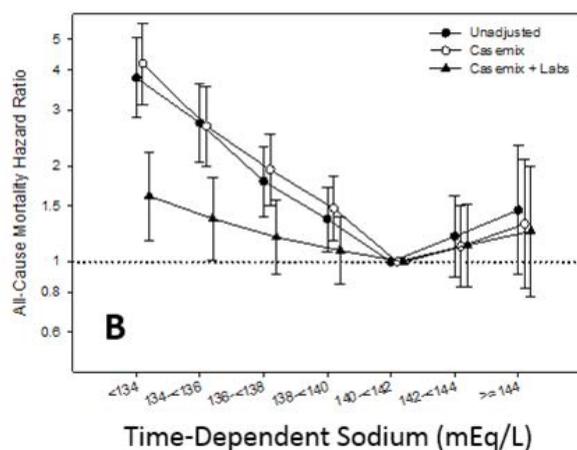
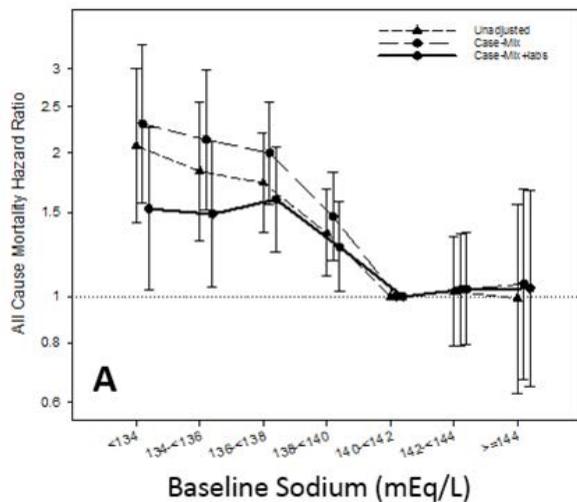
FR-OR033

Risk Factors and Sequelae of Hyponatremia in a National Peritoneal Dialysis Cohort Vanessa A. Ravel,¹ Rajnish Mehrotra,² John J. Sim,³ Kevin T. Harley,¹ Alpesh Amin,¹ Juan Carlos Ayus,⁴ Steven M. Brunelli,⁵ Elani Streja,¹ Csaba P. Kovacs,⁶ Kamyar Kalantar-Zadeh,¹ Connie Rhee.¹ ¹UC Irvine; ²UWashington; ³Kaiser Perm SC; ⁴Renal Consultants Houston; ⁵DaVita Clin Research; ⁶UTHSC.

Background: Hyponatremia is common in hemodialysis patients and has been linked with higher mortality risk. In peritoneal dialysis (PD) patients, few studies have examined the association of hyponatremia with mortality which have shown mixed findings. We sought to examine predictors of hyponatremia in a national PD cohort, and hypothesized that lower serum sodium (Na) is associated with higher death risk.

Methods: We examined a 5-year (1/2007-5/2011) cohort of 4687 incident PD patients from a large US dialysis organization with one or more serum Na measures within the 1st 91-days of dialysis. We examined predictors of baseline hyponatremia (Na<140mEq/L) using case-mix+laboratory adjusted logistic regression models. We then examined the association of Na with all-cause mortality. Baseline and time-dependent Na as a proxy of long- and short-term exposure—mortality associations, respectively, were estimated using Cox models with 3 adjustment levels: Unadjusted, case-mix, and case-mix+laboratory adjusted.

Results: Having diabetes; lower residual kidney function, albumin, PTH; and higher glucose, calcium, and ferritin were associated with higher risk of hyponatremia. Baseline Na levels <140mEq/L were associated with higher mortality across all 3 models (ref: Na 140-<142mEq/L). In time-dependent analyses, Na levels <140mEq/L were also associated with incrementally higher death risk in case-mix models. After further adjustment for laboratory covariates, Na—mortality associations persisted for levels <134mEq/L.



Conclusions: In PD patients, lower serum Na levels are associated with higher mortality. Further studies are needed to determine if correction of hyponatremia improves outcomes in this population.

Funding: NIDDK Support, Private Foundation Support

FR-OR034

Center-Specific Factors Associated with Peritonitis Risk - A Multi-Center Registry Analysis Annie-Claire Nadeau-Fredette,^{1,2,3} David W. Johnson,^{1,2} Carmel M. Hawley,^{1,2} Elaine M. Pascoe,¹ Yeoung Jee Cho,¹ Philip A. Clayton,² Sunil V. Badve,¹ Kamal Sud,¹ Monique Renee Borlace,^{1,2} Neil Boudville,² Stephen P. McDonald,² ¹Princess Alexandra Hospital, Australia; ²Australia and New Zealand Dialysis and Transplant Registry; ³Maisonneuve-Rosemont Hospital, Canada.

Background: Previous studies have reported significant variation in peritonitis rates across dialysis centers. Limited evidence is available to explain this variability. This study aimed to assess the center-level predictors of peritonitis and their relationship with peritonitis rate variation.

Methods: This registry study included all incident peritoneal dialysis (PD) patients treated in Australia between October 2003 and December 2013. The primary outcome was peritonitis rate, evaluated in a mixed effects negative binomial regression model including patient and center-level characteristics. Peritonitis-free survival was assessed as a secondary outcome in a Cox proportional hazards model.

Results: Overall, 8711 incident PD patients from 51 dialysis centers were included. Center-level predictors of lower peritonitis rates included small center size (HR 0.78, 95% CI 0.69-0.90), high proportion of PD (HR 0.87, 95% CI 0.77-0.99), low performance of peritoneal equilibration test at dialysis start (HR 0.78, 95% CI 0.66-0.93), and low proportion of hospitalisation for peritonitis (HR 0.88, 95% CI 0.75-0.96). In contrast, low proportion of automated PD exposure (HR 1.24, 95% CI 1.10-1.39), large icodextrin exposure (1.26, 95% CI 1.10-1.44) and low (HR 1.25, 95% CI 1.11-1.41) or high (HR 1.14, 95% CI 1.01-1.30) use of antifungal prophylaxis at the time of peritonitis were associated with a higher peritonitis rate. Similar results were obtained for peritonitis-free survival. Accounting for center-level characteristics appreciably decreased peritonitis variability among dialysis centers (p=0.02).

Conclusions: This study identified specific center-level characteristics associated with variation in peritonitis risk. Whether or not these factors are directly related to peritonitis risk or surrogate markers of other characteristics is uncertain and should be validated in further studies.

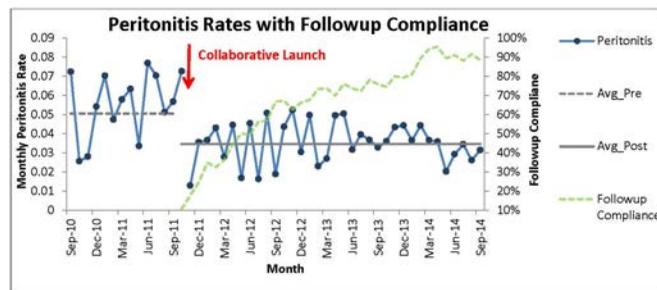
FR-OR035

Successful Reduction in Peritonitis Rates in U.S. Pediatric Dialysis Units: Results of the SCOPE Collaborative Alicia Neu,¹ Troy Richardson,² John P. Lawlor,² Jayne Stuart,² Nancy McAfee,³ Jason Newland,⁴ Bradley Warady.⁴ ¹JHMI; ²CHA; ³Seattle Children's; ⁴Children's Mercy.

Background: The Children's Hospital Association's Standardizing Care to Improve Outcomes in Pediatric ESRD (SCOPE) Collaborative seeks to minimize peritonitis in children on chronic peritoneal dialysis (PD) by increasing compliance with standardized PD catheter care practices.

Methods: Peritonitis rates and compliance with care bundles focused on PD catheter insertion, pt/caregiver training and follow-up care were collected monthly. Center-specific monthly peritonitis rates were calculated as (#infections/#pt-mos). Changes in peritonitis rates and compliance were modeled using Generalized Linear Mixed Model techniques assuming a negative binomial distribution with a natural log link function and a binomial distribution with a logit link function, respectively. Models included random effects to accommodate PD center-specific variability.

Results: Data from 24 SCOPE sites that provided peritonitis rates for the 12 mos prior to Collaborative launch were included in the analysis. In the first 36 mos, 751 catheter insertions in 644 pts, 644 training sessions and 7,977 follow up encounters were captured. Compliance with the follow up bundle increased from 11% to 88% (p<0.001) over the 36 mos, but neither insertion (22% to 36%, p=0.064) nor training compliance (75% to 71%, p=0.105) increased significantly. The peritonitis rate decreased significantly (p=0.026) from an average monthly rate of 0.052 (95% CI 0.036, 0.076) pre-launch to 0.035 (95% CI 0.026, 0.047) at 36 mos, figure 1.



Conclusions: Using quality improvement methodology pediatric dialysis units participating in SCOPE significantly increased implementation of standardized follow up care practices and significantly reduced peritonitis rates. Efforts to increase compliance with insertion and training bundles and further reduce infection rates are ongoing.

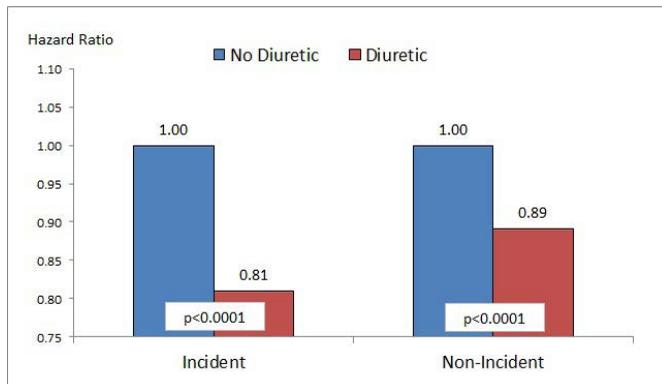
FR-OR036

Diuretic Prescription and Outcomes Among Peritoneal Dialysis Patients in the BRAZPD Study Jennifer L. Bragg-Gresham,¹ Ludimila Guedim de Campos,² Thyago Proença de Moraes,² Ana Elizabeth Figueiredo,³ Pasqual Barretti,⁴ Rajiv Saran,¹ Roberto Pecoito-Filho,² ¹KECC, Univ of Michigan, Ann Arbor, MI; ²Pontifícia Univ Católica do Paraná, Curitiba, Brazil; ³Pontifícia Univ Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil; ⁴Univ Estadual do Estado de São Paulo - UNESP, Botucatu, Brazil.

Background: Diuretics are prescribed to individuals with reduced renal function (RRF), but can continue to play a role in dialysis patients, to manage extracellular fluid volume and hypertension. We assess the prescription (Rx) of diuretics and their association with survival in a representative sample of PD patients.

Methods: We examined diuretic Rx among 9,905 patients from the BRAZPD study, a prospective cohort study launched in Dec 2004. Cox regression was used to estimate associations between baseline diuretic use and mortality, adjusting for age, sex, hypertension, diabetes, Davies score, pre-dialysis care, prior HD, and prior kidney Tx; interaction used to assess Rx by 90-day incident status.

Results: At baseline, 33.9% of patients had diuretic Rx. Patients with Rx were older, had higher BMI, more comorbidities, but longer pre-dialysis care (p<0.0001). A higher proportion of patients with Rx were incident to PD, male, diabetic, hypertensive, taking other anti-hypertensive medications and had received pre-dialysis care; while a smaller proportion of patients with Rx had received a prior Tx or HD (p<0.01). Accounting for these differences, patients with Rx had a lower risk of mortality (HR=0.87, p=0.005). The association was seen among both incident and non-incident patients.



Conclusions: Despite being older and sicker, patients with diuretic Rx had lower mortality. While more striking in incident patients, association was also seen in non-incident patients. If diuretic Rx is a marker of RRF or independently associated with better outcomes remains to be elucidated.

FR-OR037

In-Hospital Mortality Outcome of Cirrhotic Patients with End Stage Renal Disease on Hemodialysis versus Peritoneal Dialysis Mark Abi Nader,¹ Fernando Rodrigo Aguilar,¹ Michael S. Lipkowitz,¹ Parasuram Krishnamoorthy,² Ping Li,¹ Serban A. Dragoi,¹ Alex Montero,¹ Wen Shen,¹ Chanigan Nilubol,¹ Judit Gordon,¹ ¹Nephrology and Hypertension, Georgetown Univ Hospital, Washington, DC; ²Internal Medicine, Mount Sinai School of Medicine.

Background: Renal disease is a common complication in cirrhotic patients related to electrolyte and acid-base alterations, inadequate response to diuretic drugs, and hemodynamic instability, often leading to end stage renal disease (ESRD) with need for dialysis. Little is known about the preferred dialysis modality in these patients. We aimed to compare the mortality outcomes between cirrhotic patients on either Hemodialysis (HD) or peritoneal dialysis (PD).

Methods: Nationwide Inpatient Sample database between 2005 and 2012 was queried. Patients with ESRD (ICD9 585.6) and liver cirrhosis (ICD9 571.2; 571.5; 571.6; 572.3; 572.4) were included in the study. Patients having hepatocellular carcinoma were excluded (ICD9 155.0). Both groups were matched, undergoing propensity matching score, for chronic conditions including anemia, diabetes mellitus, hypertension, hepatic encephalopathy, esophageal variceal bleeding, gastrointestinal bleeding (GIB), paracentesis, hepatitis C as well as sex, race, Charlson Comorbidity Index and age. Logistic regression was used for multivariable analysis.

Results: 28,622 cirrhotic patients with incident ESRD were identified. 1.7% of them were on PD. After propensity score matching and multivariable regression analysis, cirrhotic on HD had higher mortality compared to PD patients [4.79% vs 2.70% P = 0.024]. Age > 65 and female gender were significant predictors of mortality in both HD and PD groups. Anemia was associated with less mortality rate.

Conclusions: Cirrhotic patients admitted to the hospital for dialysis have higher mortality when started on HD compared to PD.

FR-OR038

AQP1 in Peritoneal Dialysate as Predictive Biomarker of Integrity of the Peritoneal Barrier and Ultrafiltration Efficiency Simone Corciulo,¹ Maria Celeste Nicoletti,² Roberto Corciulo,³ Roberto Russo,³ Giuseppe Grandaliano,¹ Maria Svelto,² Giuseppe Procino,² Loreto Gesualdo,³ ¹Dept of Emergency and Organ Transplantation, Univ of Foggia, Foggia, Italy; ²Dept of Biosciences, Biotechnologies and Biopharmaceutics, Univ of Bari, Bari, Italy; ³Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, Italy.

Background: The water channel Aquaporin 1 (AQP1) plays a pivotal role in the mechanism of free water ultrafiltration during peritoneal dialysis (PD). Whether or not is AQP1 exclusively expressed in peritoneal capillaries or also in the mesothelial cells (MC) is still debated. It has been hypothesized that decreased expression or function of AQP1 may be responsible for some cases of ultrafiltration failure (UFF). Plasma membrane proteins are released in biological fluids through the exosome pathway to an extent proportional to their abundance at the plasma membrane.

Methods: In this work we investigated the localization of AQP1 in human peritoneum and its presence in exosomes isolated from PD effluent.

Results: Proteomic analysis of peritoneal-derived exosomes showed a significant expression of AQP1. Interestingly, the same samples were devoid of the endothelial marker CD31 but were positive for the mesothelial marker mesothelin, thus suggesting a mesothelial, rather than endothelial origin for these vesicles.

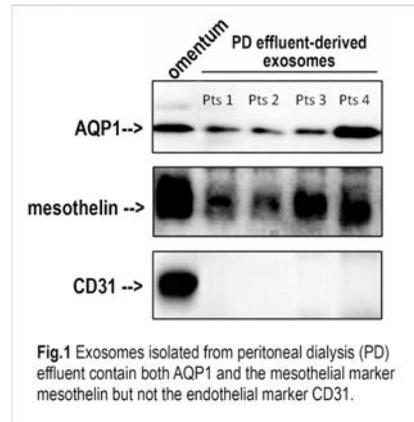


Fig.1 Exosomes isolated from peritoneal dialysis (PD) effluent contain both AQP1 and the mesothelial marker mesothelin but not the endothelial marker CD31.

In human omental biopsies, AQP1 was localized in peritoneal capillaries and at the plasma membrane of MC, where it co-localized with mesothelin.

Conclusions: Our results suggest that AQP1 is expressed in MC and released in the peritoneal cavity through the exosome pathway. This evidence opens the debate on the role of MC in regulating the efficiency of PD and suggests that AQP1 released in the PD effluent may represent a potential non-invasive biomarker of integrity of the peritoneal barrier.

FR-OR039

Vascular Endothelial Cell Damage Is an Important Factor in the Development of Encapsulating Peritoneal Sclerosis Mitsuhiro Tawada,¹ Yasuhiko Ito,¹ Chieko Hamada,² Kazuho Honda,³ Masashi Mizuno,¹ Yasuhiro Suzuki,¹ Fumiko Sakata,¹ Shoichi Maruyama,¹ Yoshifumi Takei,⁴ Seiichi Matsuo,¹ ¹Nephrology, Nagoya Univ, Nagoya, Japan; ²Nephrology, Juntendo Univ, Tokyo, Japan; ³Pathology, Tokyo Women's Medical Univ, Tokyo, Japan; ⁴Biochemistry, Nagoya Univ, Nagoya, Japan.

Background: Encapsulating peritoneal sclerosis (EPS) is a rare, but serious and life-threatening complication of peritoneal dialysis (PD); however, the precise pathogenesis remains unclear and predictors have not yet been established. The present study aimed to determine predictors of EPS in peritoneal membrane tissues obtained at catheter removal.

Methods: Eighty-three biopsy samples (10 EPS, 73 non-EPS) were assessed by pathological and immunopathological techniques to identify predictors of EPS. Tissue samples obtained at the time of catheter removal for reasons of peritonitis and a peritonitis episode within the past one month were not included. Furthermore, based on these analyses, the effects of PD solution on human umbilical vein endothelial cells (HUVEC) were studied.

Results: Univariate analysis of the pathological findings associated a thickened peritoneal membrane (P = 0.045), new membrane formation scores (P = 0.006), decreased ratio of lumen diameter to vessel diameter (L/V ratio, P < 0.001), CD31-negative vessels (P = 0.021) and fibrin deposition (P < 0.001) with the development of EPS. Stepwise Firth's multivariate logistic regression analysis identified glucose exposure scores (odds ratio 2.03, P = 0.011) among clinical factors, the L/V ratio (AUC, 0.899; OR, 0.50; P = 0.002) and fibrin deposition (OR, 8.50; P = 0.023) among the pathological factors as independent predictors of EPS. Multivariate logistic regression analysis of the 10 patients with EPS and 20 controls matched for PD treatment period, diabetes and PD solution (acidic or neutral pH) identified decreased L/V ratio as an independent predictor. In cultured HUVEC, acidic condition and high glucose concentration of PD solution induced necrosis and apoptosis, respectively.

Conclusions: Vascular endothelial cells that become damaged mainly by bioincompatible PD solution might induce vascular leakage leading to EPS, and could serve as a predictor of EPS.

Funding: Government Support - Non-U.S.

FR-OR040

Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry Accelerates Pathogen Identification and May Confer Outcome Benefit in Peritoneal Dialysis-Related Peritonitis Ming-cheng Wang,¹ Wei-hung Lin,² Te-hui Kuo,¹ ¹Div of Nephrology, Dept of Internal Medicine, National Cheng Kung Univ Hospital, Tainan, Taiwan; ²Dept of Internal Medicine, National Cheng Kung Univ Hospital, Tainan, Taiwan.

Background: Peritonitis is one of the major complications of peritoneal dialysis (PD) and contributes to technique failure and mortality in PD patients. The aim of this study was to evaluate the effects of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) on pathogen identification and clinical outcomes in PD-related peritonitis.

Methods: Ninety-eight causative microorganisms of monomicrobial PD-related peritonitis were identified using conventional standard methods, and 57 were identified using MALDI-TOF MS method. The time to pathogen identification using different identification methods was evaluated and compared. The outcome characteristics were time to dialysate effluent white blood cell < 100/mm³, length of hospital stay, catheter removal/transfer to hemodialysis, and in-hospital mortality.

Results: MALDI-TOF MS allowed the direct pathogen identification from positive blood cultures accounting for 94.9% of all cases. MALDI-TOF MS method could identify

the causative microorganisms of PD-related peritonitis earlier than the conventional standard method. The average time saved is 64 hours for all pathogens, 52 hours for Gram-positive bacteria, 65 hours for Gram-negative bacteria, 37 hours for Staphylococcus species, 68 hours for Streptococcus species, and 67 hours for E. coli and Klebsiella species. MALDI-TOF MS method group had a shorter length of hospital stay than the conventional standard group (5.2 ± 4.8 days versus 8.2 ± 4.5 days, $P = 0.001$).

Conclusions: We demonstrate the clinical effects of pathogen identification using MALDI-TOF MS in PD-related peritonitis. Integration of MALDI-TOF MS with blood culture system can promote early pathogen identification and timely pathogen-directed antibiotic therapy, and may confer outcome benefit. We propose that it is time to speed up the pathogen identification in PD-related peritonitis.

Funding: Government Support - Non-U.S.

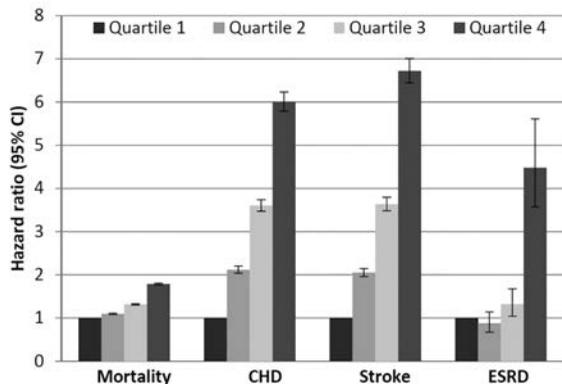
FR-OR041

Higher Systolic Blood Pressure Variability Is Associated with Increased Mortality, Coronary Heart Disease, Stroke, and End Stage Renal Disease
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Background: Blood pressure does not remain constant, but instead fluctuates dynamically. The implications of this variability in blood pressure are not yet fully understood.

Methods: From among 3,285,684 US veterans with normal eGFR during 2005-2006, we identified 2,865,157 patients who had more than 7 outpatient blood pressure measurements. Systolic blood pressure variability (SBPV) was measured using the standard deviation (SD) of all SBP values (normally distributed) in one individual. Associations of SD quartiles (<10.28, 10.28-12.68, 12.69-15.60, 15.61 mmHg) with all-cause mortality, coronary heart disease (CHD), stroke, and end stage renal disease (ESRD) was examined using Cox models adjusted for age, gender, race, and baseline eGFR, comorbidities, BMI, SBP, DBP, and antihypertensive medication use.

Results: Higher SBPV was associated with significantly higher risk of all-cause mortality, CHD, stroke, and ESRD. In fully adjusted models SD quartiles 2 through 4 (compared to the first quartile) were associated with mortality hazard ratios of 1.10, 1.32, and 1.79; CHD hazard ratios (95%CI) of 2.12, 3.60, and 6.01; stroke hazard ratios of 2.05, 3.64, and 6.72; and ESRD hazard ratios of 0.88, 1.32, and 4.48.



Conclusions: Higher SBPV is associated with increased risk for mortality, CHD, and stroke independent of confounders. The highest SD quartile was associated with increased risk for ESRD. The effect of interventions that lower SBPV on mortality will need to be examined in clinical trials.

Funding: NIDDK Support, Veterans Administration Support

FR-OR042

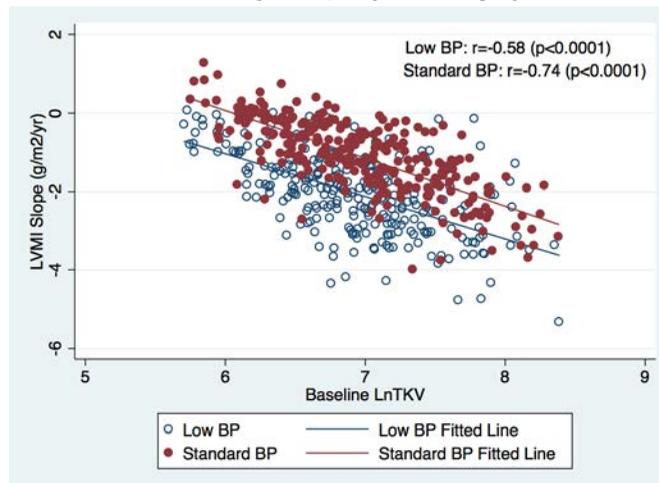
Left Ventricular Mass in Early Autosomal Dominant Polycystic Kidney Disease
 Vicente E. Torres,⁶ Ronald D. Perrone,¹ Kaleab Z. Abebe,² Kyongtae Ty Bae,² Peter G. Czarnecki,³ Robert W. Schrier,⁴ Theodore I. Steinman,⁵ Susan Spillane,² Charity G. Moore.² ¹Tufts; ²U of Pittsburgh; ³Brigham and Womens; ⁴U of Colorado; ⁵BIDMC; ⁶Mayo Clinic, for the HALT PKD Investigators.

Background: Autosomal dominant PKD (ADPKD) associates with hypertension and left ventricular hypertrophy (LVH). HALT PKD study A was designed to assess the effect of intensive BP control and dual renin angiotensin blockade on progression of total kidney volume (TKV) and left ventricular mass (LVM).

Methods: 543 subjects with eGFR >60 ml/min aged 15-50 were randomized to lisinopril (L) and placebo (P) vs L and telmisartan (T) with two levels of BP control: standard (SBP) (120-130/70-80 mmHg) vs low (LBP) (95-110/65-75 mm Hg). Cardiac magnetic resonance measurement of LVM was done at baseline, 24, 48, and 60 months. LVM adjusted for body surface area was expressed as LVM index (LVMI; g/m²).

Results: The prevalence of LVH at baseline was <1%. LBP reduced LVMI compared to SBP ($p < 0.001$) but there was no effect of dual blockade ($p = NS$). There was no impact of baseline parameters (eGFR, age, systolic BP, TKV, serum K, urine Na or K, albuminuria, urine aldosterone, sex) on the BP effect on LVMI. Higher baseline TKV and systolic BP

had significant associations with more rapid LVMI decline ($p < 0.0001$); a trend of lower baseline eGFR also associated with LVMI decline ($p = 0.07$); females had significantly reduced LVMI decline vs males ($p < 0.0001$) irrespective of BP group.



Conclusions: LVMI decreased significantly after intensive vs standard BP control. Larger TKV, higher systolic BP, male sex, and possibly decreased eGFR were associated with a greater reduction in LVMI, irrespective of the level of BP control. Patient factors associated with a worse kidney outcome predicted improvement in LVMI after a long period of carefully controlled BP. BP reduction in ADPKD shows cardiac benefit and should be a focus of treatment.

Funding: NIDDK Support, Private Foundation Support

FR-OR043

Asymmetric and Symmetric Dimethylarginine and Sympathetic Nerve Traffic After Renal Denervation in Patients with Resistant Hypertension: A Longitudinal Study
 Carmine Zoccali,¹ Gino Seravalle,² Fosca Quarti Trevano,³ Domenico Spaziani,⁴ Filippo Scalise,⁵ Carla Auguadro,⁵ Patrizia Pizzini,¹ Giovanni Tripepi,¹ Graziella D'arrigo,¹ Giuseppe Mancia,² Guido Grassi,^{3,6} Francesca Mallamaci.¹ ¹Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, CNR-IFC, Reggio Calabria, Italy; ²Istituto Auxologico Italiano, Milano, Italy; ³Clinica Medica, Dipartimento di Scienze della Salute, Univ Milano-Bicocca, Milano, Italy; ⁴Unità Operativa di Cardiologia, Ospedale Magenta, Milano, Italy; ⁵Cardiologia Interventistica, Policlinico di Monza, Monza, Italy; ⁶IRCCS Multimedica, Sesto San Giovanni-Milano, Italy.

Background: The plasma concentration of the endogenous inhibitor of nitric oxide synthase asymmetric dimethyl arginine (ADMA) associates with sympathetic activity in patients (pts) with chronic kidney disease but the driver of this association is unknown.

Methods: In this longitudinal study (follow-up: 2 weeks-6 months) we performed repeated measurements over time of muscle sympathetic nerve activity (MSNAC), plasma levels of ADMA and symmetric dimethyl arginine (SDMA) and blood pressure (BP) and heart rate (HR) in 14 pts with drug-resistant hypertension who underwent bilateral renal denervation. Stability of ADMA, SDMA, BPs and MSNAC over time (6 months) was assessed in 2 historical control groups of patients maintained on stable anti-hypertensive treatment.

Results: Time integrated changes in MSNAC following renal denervation ranged from -40.6% to +10% (average -15.1%) and these changes were strongly associated with the corresponding changes in plasma ADMA ($r = 0.62$, $P = 0.02$) and SDMA ($r = 0.72$, $P = 0.004$). Changes in MSNAC went along with simultaneous changes in standardized systolic ($r = 0.65$, $P = 0.01$) and diastolic BP ($r = 0.61$, $P = 0.02$). In the historical control groups, no change in ADMA, SDMA, BPs and MSNAC levels was recorded during a 6-months follow up.

Conclusions: In pts with resistant hypertension changes in sympathetic activity after renal denervation associate with simultaneous changes in plasma levels of ADMA and SDMA. These observations are compatible with the hypothesis that the sympathetic nervous system exerts an important role in modulating circulating levels of ADMA and SDMA in this condition.

Funding: Government Support - Non-U.S.

FR-OR044

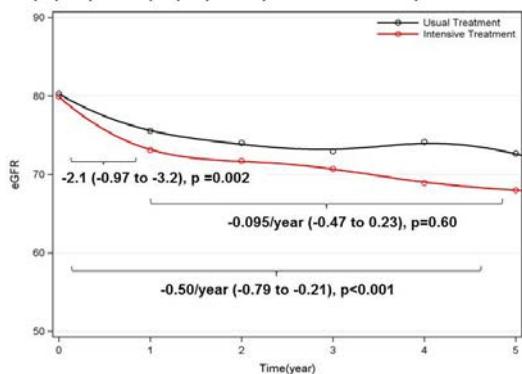
Intensive Blood Pressure Lowering and Kidney Function Decline Among Persons with prior Lacunar Stroke: The SPS3 Randomized Trial
 Carmen A. Peralta,¹ Leslie McClure,² Rebecca Scherzer,¹ Michael Shlipak,¹ Carole White,³ Oscar Benavente,⁵ Pablo E. Pergola.³ ¹UCSF; ²UAB; ³UTHSC; ⁴UCSF; ⁵UBC.

Background: The effect of intensive blood pressure (BP) lowering on kidney function among persons with vascular disease and preserved glomerular filtration rate (eGFR) is not known.

Methods: SPS3 was a multi-center trial to test effectiveness of two BP targets on secondary prevention of stroke. In a post-hoc analysis of 2611 participants randomized to lower SBP (<130 mmHg) vs. higher (130-149 mmHg) with yearly creatinine measures, we evaluated differences in annualized eGFR decline and rapid decline (>30% ml/min/1.73m²) using linear mixed models and logistic regression, respectively.

Results: Mean age was 63±11; 949(36%) were diabetic, mean eGFR was 80±19, and 410(16%) had eGFR <60 ml/min/1.73m² at randomization. At 9 months, achieved SBP was 137±15 mmHg in higher vs. 127±14 mmHg in the lower BP group, and differences persisted throughout follow-up (mean 3.2 years). Relative to higher BP arm, use of ACE/ARB, diuretic and calcium channel blocker were all increased by 20% among persons in the lower BP arm. Compared with higher, lower BP target had faster eGFR decline. Differences were most pronounced during the first year, whereas rates of eGFR decline did not differ between assigned BP groups after year 1.

The Effect of Usual vs. Intensive BP Lowering on Kidney Function Change (ml/min/1.73m² per year) over 5 years in the SPS3 Study



Splines show eGFR decline (in ml/min/1.73m² per year) by study arm over 5 years. The estimates represent differences in eGFR decline among persons in higher vs. lower BP arm.

A total of 313(24%) persons in the lower BP group had rapid kidney function decline, compared with 247(19%) in higher (OR 1.4 (95%CI 1.1 to 1.6)). Differences were apparent in the first year (OR 1.4, 1.1-1.8), but were not statistically significant after year 1 (OR 1.0, 0.73-1.4).

Conclusions: In persons with prior lacunar stroke and relatively preserved kidney function, intensive BP lowering was associated with faster renal function decline. Differences were primarily observed during the first year of anti-hypertensive treatment with no evidence of renal protection during follow up.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA

FR-OR045

Hypertension Does Not Accelerate Age-Related GFR Decline in the General Middle-Aged Population Bjorn Odvar Eriksen,¹ Vidar T. N. Stefansson,¹ Trond G. Jenssen,¹ Ulla Dorte Mathisen,¹ Jørgen Schei,¹ Marit D. Solbu,¹ Tom Wilsgaard,² Toralf Melsom.¹ ¹Metabolic and Renal Research Group, UiT the Arctic Univ of Norway, Tromsø, Norway; ²Dept of Community Medicine, UiT the Arctic Univ of Norway, Tromsø, Norway.

Background: Although hypertension is a risk-factor for ESRD, this complication only develops in a minority of hypertensive patients. Evidence is lacking to support non-malignant hypertension as a sufficient cause of reduced kidney function. This is partly due to the difficulty of assessing normal-range GFR accurately with estimated GFR. In epidemiological studies, estimated GFR has been used almost exclusively because actual measurements of GFR are costly and complicated. We aimed to investigate whether hypertension accelerates GFR decline in the general population using measured rather than estimated GFR.

Methods: We included a representative sample of the general population (age 50 to 62 years) without kidney disease, cardiovascular disease or diabetes at baseline. Baseline GFR was measured by iothexol-clearance in 1594 subjects, and 1299 (81%) had a second measurement in the RENIS Follow-Up Study (RENIS-FU) after a median observation period of 5.6 years. The effect of office blood pressure on the GFR change rate was analyzed.

Results: The mean GFR change rate was -0.95 mL/min/year. The negative sign signifies a decline. In multivariable adjusted linear mixed regression models with random intercept and slope, the increases in the change rate in mL/min/year/10 mmHg (95% confidence intervals) were 0.08 (0.03 to 0.14), 0.18 (0.07 to 0.28), 0.05 (-0.03 to 0.13) and 0.15 (0.07 to 0.24) for increasing systolic, diastolic, pulse pressure and mean arterial blood pressure respectively, indicating that GFR declined more slowly with higher blood pressure within the study time-frame. The regression analyses used time-varying measurements of blood pressure, individual classes of antihypertensive medication and all adjustment variables.

Conclusions: Hypertension is not a direct sufficient cause of accelerated GFR decline in the general middle-aged population. Additional genetic and environmental causal factors are probably necessary for primary hypertension to cause clinically manifest chronic kidney disease.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.

FR-OR046

Effect of Uric Acid Lowering on Ambulatory Blood Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Ciaran Joseph McMullan,¹ Lea Borgi,¹ Gary C. Curhan,¹ Naomi D.L. Fisher,² John P. Forman.¹ ¹Renal Div, Brigham and Women's Hospital, Boston, MA; ²Endocrine Div, Brigham and Women's Hospital, Boston, MA.

Background: Higher levels of uric acid are associated with higher blood pressure (BP) an increased risk of hypertension in many cohort studies, suggesting that uric acid may be a target for prevention of hypertension. However, the effect of lowering serum uric acid on BP is unclear.

Methods: We performed a randomized, double-blind, placebo-controlled trial of normotensive individuals with body mass index (BMI) ≥25 and uric acid level ≥ 5.0 mg/dL; subjects were randomized to receive either allopurinol 300/600mg, probenecid 500/1000mg or placebo daily for 8 weeks. Mean 24 hour systolic BP(24hSBP) was measured using 24 hour ambulatory blood pressure monitoring at baseline and 8 weeks.

Results: By the end of the trial, 22, 24 and 26 participants assigned to receive probenecid, allopurinol and placebo, respectively, had adequate 24 hour BP measurements at baseline and 8 weeks. Uric acid levels changed over 8 weeks from means of 5.9, 5.6 and 5.6 mg/dL to 3.5, 2.9 and 5.8 mg/dL in the probenecid, allopurinol and placebo groups, respectively. 24hSBP was not reduced after 8 weeks of uric acid lowering: from 127±10 mmHg to 124±8 mmHg (p-value=0.25) in the probenecid group; 125±9 to 124±10 mmHg (p-value= 0.71) in the allopurinol group; and 121±9 to 122±10 mmHg (p-value=0.61) in the placebo group. Similarly, treatment had no effect on 24 hour diastolic BP.

Conclusions: In contrast to observational studies, this randomized, double-blind, placebo-controlled trial found that uric acid lowering does not improve mean 24 hour BP in normotensive individuals with high uric acid levels, suggesting that uric acid may not be a modifiable target for prevention of hypertension.

Funding: NIDDK Support

FR-OR047

Central Role for Altered Arginine Methylation in Salt-Sensitive Hypertension in CKD: A Metabolomic Profiling Study Anna V. Mathew,¹ Adil Jadoo,¹ Jaeman Byun,¹ Robin L. Padilla,¹ Peter Kotanko,² Scott L. Hummel,¹ Brenda W. Gillespie,¹ Rajiv Saran,¹ Subramanian Pennathur.¹ ¹Univ of Michigan, Ann Arbor; ²RRI, New York.

Background: As the nitrogen donor in nitric oxide (NO) synthesis by NO synthase (NOS), arginine and its metabolic products are integrally linked to blood pressure (BP) regulation, however their role in chronic kidney disease (CKD), salt sensitivity and BP response has not been systematically studied. We explored if arginine metabolites alter with sodium restriction and predict favorable blood pressure in response to dietary sodium restriction (DSR).

Methods: Samples from 34 subjects enrolled in the LoSalt trial, a randomized crossover trial of CKD 3-4 patients who underwent DSR (<2g/day) were utilized. Targeted metabolomic analysis of arginine metabolome in pre and post DSR plasma and urine was performed by isotope dilution liquid chromatography mass spectrometry including N⁶ dimethylarginine (ADMA), N⁶ dimethylarginine (SDMA), N⁶ monomethyl-L-arginine (NMMA), arginine and citrulline. Salt sensitivity was determined by salutary changes to volume status and BP as measured by bioelectrical impedance spectroscopy (whole-body, segmental and calf) and 24-hour ambulatory blood pressure monitoring (ABPM). Pearson correlation assessed the associations between the metabolites and clinical parameters.

Results: After 4 weeks of DSR, mean urine sodium decreased by 73 ± 71 mmol/24hr and 24-hour systolic BP reduced by 10.8 ± 13.8 mmHg. Higher urine ADMA/ creatinine ratio correlated with lower total body water at baseline (r=-0.57; p<0.01). Changes in urine ADMA/ creatinine ratio (r=-0.46) and urine NOS inhibition index (NII, ADMA+NMMA/SDMA, r=-0.46) negatively correlated with changes in mean arterial ABPM (p<0.05). Urine Total Arginine Methylation Index (TAMI, (ADMA+SDMA+NMMA)/arginine, r=-0.47, p<0.05) negatively correlated with change in extracellular volume.

Conclusions: Our results strongly implicate altered arginine methylation and NOS inhibition with BP response following DSR. Further research should examine whether urinary markers of altered arginine methylation (ADMA, NII and TAMI) can consistently serve as markers of salt sensitivity in both CKD and non-CKD subjects following DSR.

Funding: Private Foundation Support

FR-OR048

Mutations in *TBX18* Cause Dominant Urinary Tract Malformations via Transcriptional Dysregulation of Ureter Development Asaf Vivante,¹ Marc-Jens Kleppa,² Julian Jakob Schulz,¹ Stefan Kohl,¹ Amita Sharma,³ Jing Chen,¹ Shirlee Shril,¹ Daw-yang Hwang,¹ Anna-Carina Weiss,² Elijah O. Kehinde,⁴ Erika J. Mancini,⁵ Richard P. Lifton,^{6,7} Velibor Tasic,⁸ Soeren S. Lienkamp,⁹ Harald Jüppner,³ Andreas Kispert,² Friedhelm Hildebrandt.^{1,7} ¹Dept of Medicine, Boston Children's Hospital, HMS, Boston, MA, USA; ²Inst für Molekularbiologie, Med Hochschule Hannover, Germany; ³Ped Nephrology, MGH, Boston, MA, USA; ⁴Div of Urology, Kuwait Univ, Safat, Kuwait; ⁵Div of Structural Bio, Univ of Oxford, UK; ⁶Dept of Human Genetics, Yale Univ, New Haven, CT, USA; ⁷Howard Hughes Medical Inst, Chevy Chase, MD; ⁸Univ Children's Hospital, Skopje, Macedonia; ⁹Dept of Med, Renal Div Freiburg Med Center, Germany.

Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the leading cause of CKD in children. Identification of monogenic causes of CAKUT permits the first insights into disease mechanisms.

Methods: We performed whole exome sequencing in a large kindred followed by high-throughput sequencing in individuals with CAKUT. Furthermore, we performed a transcriptional reporter assay, protein-protein and protein-DNA interaction studies, as well as *in vivo* studies in *Xenopus laevis*.

Results: We identified a heterozygous truncating mutation (p.G337Vfs*19) of the *T-Box transcription factor 18* gene (*TBX18*) in all 7 affected members of a large kindred. We also detected 2 mutations (p.H524Y and p.K163E) in 3 of 1,295 unrelated families with CAKUT. *TBX18* is essential for development of the ureteric mesenchyme and ureteric smooth muscle cells. We found that all 3 *TBX18* mutant proteins still dimerize with the wild type protein, but had prolonged half-life, and exhibited reduced transcriptional repression. The mutation p.K163E altered a residue critical for *TBX18*-DNA interaction, resulting in impaired *TBX18*-DNA binding. *In vivo* overexpression in *Xenopus laevis* revealed decreased biological activity on pronephric kidney development for p.G337Vfs*19 and p.K163E.

Conclusions: We discovered dominant negative *TBX18* mutations as a novel cause of human CAKUT that act *via* lack of repression of *TBX18* transcriptional activity. Our studies implicate ureter smooth muscle cell development in the pathogenesis of human CAKUT.

FR-OR049

ACTN4 Mutations Lead to Increased Contractility of Human Podocytes in Response to Injurious Stimuli and Matrix Stiffening Di Feng,¹ Ramaswamy Krishnan,² Gabriel Birrane,⁴ Julia M. Steinke,³ Jiayue Zhang,¹ Martin R. Pollak.¹ ¹Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; ²Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA; ³Pediatric Kidney Transplant Program, Helen DeVos Children's Hospital, Grand Rapids, MI; ⁴Experimental Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Alpha-actinin-4 gene (*ACTN4*) mutations cause a rare form of familial focal segmental glomerulosclerosis (FSGS) in humans. Individuals with kidney disease-causing *ACTN4* mutations tend to have mild to moderate proteinuria, with many developing a progressive decline in kidney function, and eventual end stage kidney disease. All of the disease-causing *ACTN4* mutations identified to date are located within the actin-binding domain (ABD) of the encoded protein, increasing its binding affinity to F-actin and leading to abnormal cellular aggregates. The mechanism by which the mutations give rise to FSGS is not well understood.

Methods: We used traction force microscopy to quantify contractile forces exerted by immortalized human podocytes on their underlying substrate. Immunofluorescence staining was used to examine the localization of *ACTN4* and actin.

Results: We found that human podocytes transfected with mutant *ACTN4* are more contractile in response to the injurious stimulus TGF-beta compared to podocytes transfected with WT *ACTN4*. We also found that podocytes seeded on a stiff substrate (26 kilopascal) and transfected with mutant *ACTN4* are more contractile than podocytes transfected with WT *ACTN4*. This difference in contractile force between WT and mutant was blunted when podocytes are seeded on a softer substrate (1 kilopascal). Additionally, mutant *ACTN4* transfected podocytes show much more prominent actin stress fibers, which are largely absent from WT *ACTN4* transfected podocyte.

Conclusions: We demonstrated that mutations in the *ACTN4* ABD resulted in increased podocyte contractility in response to injurious circulating stimuli and increased matrix stiffness. These observations raise the hypothesis that reducing the contractility of podocytes by pharmaceutical agents *in vivo* might mitigate podocyte disease due to *ACTN4* mutation.

Funding: NIDDK Support

FR-OR050

Assessing Two Novel Steroid-Resistant Nephrotic Syndrome Candidate Genes Using the Drosophila Model Sara Gonçalves,^{1,2} Noëlle Lachaussee,¹ Christelle Arrondel,¹ Martin Helmstaedter,³ Oliver Kretz,³ Olivia Boyer,^{1,4} Olivier Gribouval,¹ Christine Bole-feysot,¹ Patrick Nitschke,¹ Marie-Claire Gubler,¹ Tobias B. Huber,^{3,5} Geraldine Mollet,¹ Matias Simons,^{1,3,6} Corinne Antignac.^{1,7} ¹Inserm U1163 Inst Imagine, Paris Descartes Univ, Paris, France; ²Renal Div, St. Maria Univ Hosp, Lisbon, Portugal; ³Renal Div, Univ Hosp Freiburg, Germany; ⁴Ped Nephrol, Hosp Necker, Paris, France; ⁵BIOSS Albert-Ludwigs Univ, Freiburg, Germany; ⁶ZBSA, Freiburg, Germany; ⁷Genetics, Hosp Necker, Paris, France.

Background: Steroid-resistant nephrotic syndrome (SRNS) is a genetically heterogeneous disease. Using exome sequencing we previously identified two homozygous, potentially damaging, missense variants in *ADD3* and *KAT2B* in the affected members of a consanguineous family presenting syndromic SRNS. The first gene encodes adducin, an important regulator of the actin cytoskeleton, and the second the lysine acetyltransferase *KAT2B* responsible for histone acetylation.

Methods: To address the importance of *ADD3* and *KAT2B* on podocyte function and the impact of the mutations we used the *Drosophila* model. KD and rescue experiments with the WT and mutated genes were performed using the GAL4:UAS system in *Drosophila* nephrocytes, the fly counterparts of podocytes. Defects at a molecular and ultrastructural level were assessed using immunostaining and electron microscopy and functional assays were used to assess the filtration/endocytic functions of nephrocytes.

Results: In 3rd instar nephrocytes, adducin KD, but not *KAT2B* KD, disrupted the actin cytoskeleton, delocalized the slit diaphragm protein Kirre and led to decreased filtration/endocytosis. At the ultrastructural level *ADD3* KD led to decreased number of slit diaphragms and foot process effacement. At the adult stage, both adducin and *KAT2B* KD induced a reduction of nephrocytes. While *KAT2B* rescue experiments are still pending, the WT but not the mutated form of *ADD3* rescued the *ADD3* KD phenotypes, namely the actin cytoskeleton defects and Kirre mislocalization.

Conclusions: These findings suggest that *ADD3* plays a major role on podocyte morphology and function and that *ADD3* mutations maybe causative to some forms of SRNS. However the impact of the *KAT2B* mutation in the patient phenotype cannot be excluded.

Funding: Government Support - Non-U.S.

FR-OR051

A Novel Mutation in *CLCN5* Gene Associated with Silent Clinical Manifestations of Dent Disease and the Histologic Picture of FSGS Milos N. Budisavljevic, Michael G. Janech, Peifeng Deng, Robert Wilson, Thomas Morinelli, John M. Arthur. *Nephrology, MUSC, Charleston, SC.*

Background: It is increasingly recognized that focal segmental (FSGS) and focal glomerulosclerosis (FGGS) may be seen as a dominant feature in some patients with Dent disease and lead to an erroneous diagnosis of primary FSGS.

Methods: We identified two brothers, 37 and 32 years old, who presented with low grade proteinuria and renal failure. Kidney biopsies of both revealed FSGS and no nephrocalcinosis. Four additional male family members had kidney disease without an established diagnosis.

Results: Pedigree analysis suggested an X-linked mode of inheritance. Extensive evaluation of the medical history from affected individuals revealed no rickets, nephrocalcinosis or nephrolithiasis. We performed whole exome DNA sequencing on 7 family members and identified a variant of the intracellular chloride channel 5 (*CLCN5*) gene which had not previously been described. The mutation resulted in a substitution of leucine for phenylalanine at position 521 (L521F). We constructed expression vectors (pCMV6-AC-GFP) that encode for wild-type and mutant L521F *CLCN5*, respectively, and transfected HK2 cells. Transfection of HK2 cells with wild-type *CLCN5* revealed protein localization to both on the cell surface and throughout the cytoplasm. Cells transfected with the mutant construct displayed only intracellular perinuclear localization. *CLCN5* encodes the chloride hydrogen exchanger and is important for endocytosis in the proximal tubule. Recent evidence suggested that *CLCN5* also resides in the podocytes and may play an important role in proper function of the slit diaphragm. Thus, *CLCN5* mutations may affect podocyte integrity and lead to FSGS or FGGS. We have identified a novel variant of *CLCN5* associated with histologic FSGS. Whether glomerular or tubular expression of the variant is responsible for the kidney disease is not yet clear.

Conclusions: We identified a new mutation in the *CLCN5* gene in adult patients who presented with a histologic diagnosis of FSGS but without clinical manifestations of Dent disease. In cell culture, the mutation results in aberrant localization that may underlie pathogenic significance.

Funding: Private Foundation Support

FR-OR052

Defects of the Nuclear Pore Proteins NUP93, NUP205, or Exportin-5 Link Nephrotic Syndrome to Disrupted SMAD Signaling Daniela A. Braun,¹ Carolin Sadowski,¹ Stefan Kohl,¹ Svtjelana Lovric,¹ Susanne Astrinidis,² Shazia Ashraf,¹ Werner Lukas Pabst,¹ Weizhen Tan,¹ Jennifer A. Lawson,¹ Merlin Airik,¹ Richard P. Lifton,^{3,4} Heon Yung Gee,¹ Wolfram Antonin,² Friedhelm Hildebrandt.^{1,4} ¹Nephrology, Boston Children's Hospital, Boston, MA; ²Friedrich Miescher Laboratory, Max Planck Society, Tübingen, Germany; ³Dep. of Genetics, Yale Univ School of Medicine, New Haven, CT; ⁴Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid resistant nephrotic syndrome (SRNS) is a frequent cause of end-stage renal disease in the first decades of life. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain unknown.

Methods: We combined homozygosity mapping with whole exome sequencing (WES) in 100 individuals with SRNS. To identify additional mutations, we screened our cohort of ~800 individuals with SRNS by microfluidic multiplex PCR (Fluidigm Access Array™) and next generation sequencing. We examined nuclear translocation of SMAD4, utilized a luciferase reporter construct under the control of a SMAD responsive element, and performed co-immunoprecipitation to test the pathogenicity of the identified human disease alleles.

Results: By WES and multiplex PCR, we identified mutations in the genes *NUP93*, *NUP205*, and *XPO5* (encoding for nucleoporin 93, 205 and exportin-5) in 8 unrelated families with SRNS. All individuals had early onset SRNS with rapid disease progression. We show that all three proteins localize to WT1 positive podocyte precursor cells in developing rat kidney. Human mutations in *NUP93* disrupt the assembly and integrity of the nuclear pore complex (NPC). A human mutation in *NUP205* abrogates the interaction with NUP93 within the NPC. We demonstrate that NUP93 and exportin-5 interact with the transcription factor SMAD4, and that human mutations of *NUP93* abrogate this interaction. Furthermore, human mutations of *NUP93* interfere with SMAD dependent transcription downstream of BMP7.

Conclusions: We identify mutations of *NUP93*, *NUP205*, or *XPO5* as novel monogenic causes of steroid-resistant nephrotic syndrome in humans, and implicate disrupted SMAD signaling in its pathogenesis.

Funding: Other NIH Support - DK076683

FR-OR053

A Heterozygous Rare Variant in IL-XR Contributes to Autosomal Dominant FSGS in an African American Kindred Gentzon Hall,^{1,3,4} Jose A. Gomez,¹ Peter J. Lavin,⁵ Eugene C. Kovalik,^{1,3} Peter J. Conlon,⁶ Rasheed A. Gbadegesin.^{2,3,4} ¹Internal Medicine, Duke Univ; ²Pediatrics, Duke Univ; ³Nephrology, Duke Univ; ⁴Duke Molecular Physiology Inst, Duke Univ; ⁵Trinity College, Ireland; ⁶Beaumont Hospital, Ireland.

Background: FSGS is a disorder characterized by podocyte injury, focal glomerular scarring, nephrotic syndrome and rapid progression to ESKD. Although FSGS disproportionately affects African Americans (AA), there is no report of a causal FSGS gene identified in an AA index kindred. Here we report the discovery of a rare heterozygous missense variant in the interleukin-X receptor (*IL-XR*) as contributory to autosomal dominant (AD) FSGS in an AA kindred from the US.

Methods: We identified an AA kindred with six affected individuals spread over three generations. We performed whole-exome sequencing on three affected members of the family. We confirmed all pathogenic variants by direct sequencing and performed segregation analysis on the family. Complementary molecular genetic analyses were performed in conditionally immortalized human podocytes to evaluate the effects of the segregating variant on JAK/STAT signaling and cell proliferation.

Results: We identified a segregating heterozygous rare variant (K47R) within the ligand binding domain of *IL-XR* in the kindred. The variant was absent from 8,600 Caucasian chromosomes and has a minor allele frequency of 0.003 in the AA population in EVS. The change is conserved in evolution and is considered damaging by *in silico* prediction. We confirmed the expression of *IL-XR* in kidney and podocytes by RT-PCR, immunohistochemistry, and immunoblot analyses. Because *IL-XR* is known to signal through the JAK/STAT pathway, we examined the effect of *IL-XR*_{K47R} expression on STAT3 activation and proliferation in podocytes. We determined that *IL-XR*_{K47R} expression enhanced basal STAT3 activation and induced hyperproliferation.

Conclusions: We report the identification of a heterozygous rare variant in *IL-XR* as a contributor to AD FSGS in an AA kindred. *IL-XR* is expressed in the kidney and podocytes and overexpression of *IL-XR*_{K47R} significantly enhanced basal STAT3 activation and podocyte proliferation *in vitro*.

Funding: NIDDK Support

FR-OR054

Genetic Investigation and Phenotypic Characterization of Uromodulin Associated Kidney Disease Christine Gast,^{1,2} Monica Arenas Hernandez,³ Anthony Marinaki,³ Gopalakrishnan Venkat-Raman.^{1,2} ¹Wessex Kidney Centre, Portsmouth Hospitals Trust, Portsmouth, United Kingdom; ²Genetic and Genomic Medicine, Univ of Southampton, Southampton, United Kingdom; ³Purine Research Laboratory, St. Thomas' Hospital, London, United Kingdom.

Background: Uromodulin associated kidney disease (UAKD) is a difficult to diagnose, rare autosomal dominant genetic disorder caused by mutations in the *UMOD* gene. We aimed to determine the frequency and distribution of pathogenic *UMOD* mutations in a familial kidney disease cohort and to investigate any distinguishing clinical features.

Methods: CKD patients with a family history (FHx) of renal disease were ascertained from a large tertiary renal center through a questionnaire study and database search. Patients with a FHx suggesting an unknown genetic diagnosis or UAKD were recruited. DNA was extracted from blood or saliva and sequenced for *UMOD* exons 3-5. Phenotypic characteristics were compared between patients with and without *UMOD* mutations, with significance testing in SPSS.

Results: Of 3,760 patients in CKD stages 3-5, 131 patients with a compatible FHx were identified and recruited. Of these, 30 patients (23%) from 17 families had 11 distinct pathogenic *UMOD* mutations. In 12 patients (9%) from 7 families this was previously unsuspected. UAKD patients had significantly lower protein creatinine ratios (median 28, versus median 222, Mann-Whitney-U p=0.001), less hematuria (c2 p=0.0003), more electrolyte abnormalities (c2 p=0.02) and less severe anaemia (c2 p=0.049) pre renal replacement therapy (RRT). There were no statistically significant differences in uric acid, gout, allopurinol use, hypertension, renal cysts, renal size, and age at presentation or RRT.

Conclusions: UAKD is common amongst familial nephropathy patients, and is poorly predicted by clinical features. Hyperuricaemia or gout, both typical of early UAKD, did not distinguish from prevalent familial nephropathies, but less proteinuria and haematuria did. More electrolyte abnormalities in UAKD could be due to an alteration in tubular water permeability; the reason for less anaemia is unclear. Having demonstrated a high prevalence of UAKD, we advise *UMOD* testing guided by family history regardless of typical phenotype.

Funding: Private Foundation Support

FR-OR055

Chaperone Therapy in Stem Cells Derived from Fibroblasts with Missense Mutations in X-Linked Alport Syndrome Dongmao Wang,¹ Sharon D. Ricardo,² Judith A. Savage.¹ ¹Medicine, The Univ of Melbourne (Melbourne Health), Melbourne, VIC, Australia; ²Anatomy and Developmental Cell Biology, Monash Univ, Clayton, VIC, Australia.

Background: Forty % of mutations in X-linked Alport syndrome are caused by missense changes, often where Gly is substituted with another amino acid. Chaperone treatment has been useful in other diseases due to missense mutations. The aim of this study was to produce iPS from fibroblasts from a male with X-linked Alport syndrome and determine the effects of the chemical chaperone, 4 phenyl butyric acid.

Methods: Stem cells were made by the Ricardo laboratory from skin fibroblasts from a male with X-linked Alport syndrome due to p.G624D. He had developed renal failure at the age of 54, and had hearing loss, but no lenticonus or central retinopathy. Stem cells were induced to become podocytes, and examined for collagen IV a1 – a6 expression, and for markers of ER stress (ATF6, HSPA5, DDIT3), autophagy (ATG5, BECN1, ATG7) and apoptosis (CASP3, BAD, BCL2) using qRT-PCR (Applied Biosystems 7500). Levels of collagen IV a5 chain were quantitated in an in-house inhibition ELISA. These measurements were repeated after incubation with the chemical chaperone, 10 mM 4-phenyl butyric acid.

Results: The iPS expressed collagen IV a3 and a4 mRNA consistent with a podocyte phenotype. Levels of collagen IV a5 mRNA and protein were not different from those in normal male fibroblasts. However levels of both intra and extracellular collagen IV a5 were reduced suggesting degradation. The Alport iPS had increased transcripts for HSPA5, and apoptosis (CASP3 and BCL2) compared with normal. Incubation with 4 phenyl butyric acid, resulted in a reduction in all markers of autophagy and of CASP3.

Conclusions: iPS derived from Alport fibroblasts represent a model system in which to examine novel treatments. Chemical chaperone therapy has beneficial effects on cells derived from individuals with Alport syndrome due to missense mutations.

Funding: Private Foundation Support

FR-OR056

Massively Parallel Sequencing (MPS) in Diagnostically Refractory Genetic Renal Disease (GRD) Andrew John Mallett,^{1,2,4} Chirag Patel,^{2,3,4} Joanna Crawford,⁴ Bruce Bennetts,⁵ Melissa H. Little,^{4,7,8} Helen G. Healy,^{1,2} Stephen I. Alexander,⁵ Valentine Hyland,⁶ Cas Simons.⁴ ¹Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane and Women's Hospital, Australia; ²School of Medicine, The Univ of Queensland, Australia; ³Genetic Health Queensland, RBWH, Australia; ⁴Inst for Molecular Bioscience, UQ, Australia; ⁵Depts of Molecular Genetics and Nephrology, Children's Hospital at Westmead, NSW, Australia; ⁶Molecular Genetics Laboratory, Pathology Queensland, Australia; ⁷Murdoch Children's Research Inst, Melbourne, VIC, Australia.

Background: GRD accounts for 10% of adults and 50% of children with end stage kidney disease. An unknown proportion of cases remain refractory to current clinical genetic tests. Advances in MPS enable attempts to address this in a research setting. We aimed to utilize MPS with pedigree analysis in unresolved cases of GRD.

Methods: Families with clinically diagnosed GRD were recruited in whom clinical genetic testing was either negative or not available. Whole exome sequencing was undertaken and analyzed with custom in house bioinformatics assessment tools accounting for all inheritance patterns. Identified variants of interest were confirmed using Sanger sequencing in clinical laboratories.

Results: 14 families (62 participants) were recruited with a variety of GRD diagnoses and modes of inheritance. A molecular genetic diagnosis has been resolved in 5 families. These include mutations in *RMND1* (compound heterozygous), *IFT140* (compound heterozygous), *HNF4A* (heterozygous), *COL4A5* (hemizygous) and *tRNA(Phe)* (mtDNA) genes. All have been confirmed in a clinical diagnostic laboratory and reported back to the participants with further genetic counseling. Research continues in the remaining 9 families, including application of whole genome sequencing. No reportable incidental genetic findings were identified.

Conclusions: MPS confirmed and clarified a clinical genetic diagnosis in 5/14 families with previously and diagnostically refractory GRD. These results were integrated into clinical practice and demonstrate an emerging role for MPS in the delivery of clinical care. Further studies are required to resolve the remaining families.

Funding: Private Foundation Support

FR-OR057

Development and Validation of Targeted Genomic Enrichment and Massively Parallel Sequencing as a Diagnostic Test for Genetic Renal Diseases Christie P. Thomas,^{1,3} M. Adela Mansilla,² Ramakrishna Sompallaa,² Sara Mason,² Anne E. Kwitek,² Colleen Ann Campbell,² Richard J. Smith.^{1,2} ¹Internal Medicine, Univ of Iowa, Iowa City, IA; ²Inst of Human Genetics, Univ of Iowa, Iowa City, IA; ³Veterans Affairs Medical Center, Iowa City, IA.

Background: Many renal diseases have a genetic basis, although definite genetic confirmation of precise etiology is rarely sought, in spite of the value of genetic screening in patients with ESRD both to confirm a diagnosis and to guide the evaluation of living related kidney donors, who may be at increased risk of ESRD.

Methods: To enable comprehensive screening for genetic diseases, we developed a panel that combines targeted genomic enrichment with massively parallel sequencing to simultaneously interrogate 120 genes implicated in 75 renal diseases. To validate this panel, we studied 20 controls and 20 patients with presumed genetic renal disease, four of whom were transplant candidates. We also evaluated six siblings or children who were considering living donation. Samples were sequenced on the Illumina MiSeq®.

Results: On average, we identified 500 variants per sample at a mean depth-of-coverage of 390x. After filtering to remove low quality/common variants, rare/novel variants were annotated using the Human Gene Mutation Database (HGMD®). Pathogenicity of novel variants was predicted in silico using algorithms to score variants based on conservation and function. As a measure of specificity and sensitivity, we Sanger validated 876 variants, confirming all. To optimize relevance of generated data, variants were discussed in the context of clinical data and observed genetic results. We identified causal variants in six of 20 patients (30%) with presumed genetic disease, thus enabling us to counsel these patients and alter their care. We were able to confirm a genetic renal diagnosis in 3 of 4 transplant candidates and offer asymptomatic family members mutation-specific screening to determine if they carried the disease genotype.

Conclusions: This genetic renal disease panel provides a rapid, efficient, unbiased and cost-effective way to diagnose monogenic renal diseases and evaluate living donors at risk for genetic renal disease.

FR-OR058

The B Cell Survival Cytokine BAFF Promotes Murine Lupus Nephritis via Activation of TAC1, Not BAFF Receptor Shaun W. Jackson,^{1,2} Holly Jacobs,¹ Christopher Thouvenel,¹ Tanvi Arkatkar,¹ Genita Metzler,¹ Nicole Scharping,¹ David Rawlings.^{1,2} ¹Seattle Children's Research Inst, Seattle, WA; ²Dept of Pediatrics, Univ of Washington, Seattle, WA.

Background: Transgenic (Tg) over-expression of the B cell survival cytokine BAFF (also known as BLyS) promotes immune-complex glomerulonephritis in mice. Consistent with this, lupus nephritis patients have increased serum BAFF levels and the BAFF-targeted monoclonal Belimumab is an approved SLE therapy. BAFF binds two B cell receptors,

BAFF-R and TAC1. Since BAFF-R is required for mature B cell survival, this receptor is predicted to explain BAFF-Tg autoimmunity. However, potential important roles for TAC1 have not been addressed.

Methods: To test the impact of TAC1 on BAFF-driven autoimmunity, we crossed BAFF-Tg and *Taci*^{-/-} mice. Autoantibodies and urine albumin were measured by ELISA, and B cell phenotyping was performed by FACS.

Results: Despite marked splenic B cell hyperplasia, deletion of TAC1 abrogated serum anti-nuclear autoantibodies (ANA) in BAFF-Tg mice. In addition, lack of TAC1 prevented autoantibodies targeting RNA- and DNA-associated self-antigens, including Sm/RNP and dsDNA, across all immunoglobulin isotypes and subtypes, including IgM, IgG, IgA, IgG2b, IgG2c, IgG3. Aged BAFF-Tg mice develop prominent immune-complex glomerulonephritis, characterized by mesangial expansion, glomerular basement membrane thickening and capillary occlusion. Consistent with the lack of serum autoantibodies, *Taci*^{-/-}.BAFF-Tg were completely protected from murine lupus nephritis, as evidenced by lack of albuminuria and restoration of renal histology.

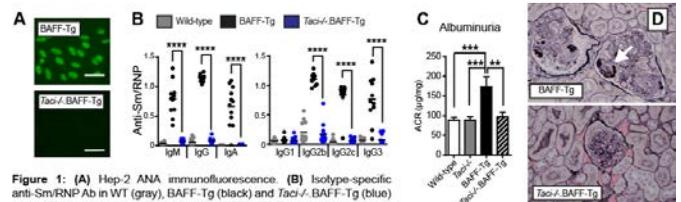


Figure 1: (A) Hep-2 ANA immunofluorescence (B) Isotype-specific anti-Sm/RNP Ab in WT (gray), BAFF-Tg (black) and *Taci*^{-/-}.BAFF-Tg (blue) mice (C) Urine albumin creatinine ratio (ACR). (D) Representative kidney histology showing prominent glomerular inflammation, mesangiolysis and capillary occlusion (arrow) in BAFF-Tg, but not *Taci*^{-/-}.BAFF-Tg mice. ***P*<0.01, ****P*<0.001, *****P*<0.0001.

Conclusions: We report the novel observation that TAC1, not BAFF-R, is the predominant B cell receptor promoting BAFF-mediated murine lupus nephritis. These findings suggest that TAC1 may be an important therapeutic target in SLE, particularly in patients with high serum BAFF levels.

Funding: Other NIH Support - K08 Career Development Award (NIAID), Private Foundation Support

FR-OR059

B Cell-Intrinsic Interferon Gamma (IFN γ) Signals Promote B Cell Activation and the Development of Lupus Nephritis Shaun W. Jackson,^{1,2} Nicole Scharping,¹ Holly Jacobs,¹ Tanvi Arkatkar,¹ David Rawlings.^{1,2} ¹Seattle Children's Research Inst, Seattle, WA; ²Dept of Pediatrics, Univ of Washington, Seattle, WA.

Background: The TH1 cytokine interferon gamma (IFN γ) has been implicated in lupus pathogenesis via direct activation of autoreactive T cells. Whether IFN γ also exerts cell-intrinsic impacts on autoantibody-producing B cells has not been studied. We developed a chimeric lupus model in which Wiskott-Aldrich syndrome protein (WAS)-deficient B cells promote spontaneous humoral autoimmunity (Jackson, et al. *J Immunol* 2014). An important advantage of the WAS chimera model is that dysregulated immune responses are limited to the B cell compartment, allowing genetic manipulation in a B cell-intrinsic fashion. In the current study, we contrast the impact of global, T cell- and B cell-intrinsic deletion of the IFN γ receptor (IFN γ R) on development of lupus nephritis.

Methods: We established lupus-prone WAS chimeras in which IFN γ R was deleted on all immune cells (global IFN γ R-null) or specifically on B or T cells. Chimeras were analyzed for autoantibodies, immune activation and immune-complex glomerulonephritis (IC GN) by ELISA, flow cytometry and immunohistochemistry.

Results: Global IFN γ R deletion prevented autoantibody (Ab) production and systemic inflammation in WAS chimeras. Strikingly, cell-intrinsic deletion of IFN γ R on either T cells or B cells recapitulated the phenotype of global IFN γ R deficiency. Mechanistically, deletion of IFN γ R on B cells prevented the formation of spontaneous germinal centers (GCs), required for class-switched Ab formation. Consistent with lack of serum autoantibodies, IC GN was abrogated in B cell IFN γ R-null chimeras. Interestingly, B cell-intrinsic deletion of the TH1 transcription factor T-bet prevented pathogenic IgG2c subclass Ab, but did not impact spontaneous GCs or systemic inflammation.

Conclusions: We report a novel T-bet-independent mechanism whereby IFN γ promotes lupus nephritis via direct actions on B cells. This study is the first to directly address the impact of B cell IFN γ activation in murine lupus, of relevance to both the understanding of disease pathogenesis and to efforts to target IFN γ therapeutically in SLE.

Funding: Other NIH Support - K08 Career Development Award (NIAID), Private Foundation Support

FR-OR060

Mechanisms of Anti-CD20 B Cell Treatment of Experimental Autoimmune MPO-ANCA Glomerulonephritis Poh-Yi Gan,¹ Joshua D. Ooi,¹ A. Richard Kitching,^{1,2} Stephen R. Holdsworth.^{1,2} ¹Dept of Medicine, Monash Univ, Clayton, Victoria, Australia; ²Dept of Nephrology, Monash Health, Clayton, Victoria, Australia.

Background: Depletion of B cells with anti-CD20 monoclonal antibody (mAb), rituximab, is an effective therapeutic for human MPO-ANCA GN. Its capacity to attenuate established disease suggests that CD20⁺ B cells are important in maintaining anti-MPO autoimmunity. Whilst B cells are clearly important in maintaining ANCA production, their role in maintaining established nephritogenic anti-MPO CD4 T cell driven autoimmunity is unknown. This study assesses this role and its importance in this disease model.

Methods: Experimental anti-MPO autoimmunity was induced by immunizing C57BL/6 (WT) mice with MPO in Freund's adjuvant and GN triggered using a subnephritogenic dose of anti-GBM globulin. Mouse anti-CD20 mAb (or control mouse anti-IgG2a mAb) was administered to mice with established anti-MPO autoimmunity (day 14) and continued through the development of GN (terminated on day 32).

Results: Administration of anti-CD20 mAb induced profound and continued B cell depletion and protected mice from the development of renal injury, compared to controls (segmental glomerular necrosis: 16±4 vs 44±4%, albuminuria: 221.0±81.6 vs 898.8±330.3mg/24hrs and glomerular CD4⁺ T cell influx: 0.4±0.07 vs 0.9±0.1, all P<0.05). Systemic anti-MPO autoimmunity was also reduced; serum anti-MPO IgG (ANCA) titres (0.21±0.02 vs 0.34±0.07 OD450nm, P<0.05) and dermal MPO induced DTH swelling (0.07±0.02 vs 0.2±0.03 Dmm, P<0.01). Anti-CD20 mAb treatment decreased MPO specific recall proliferation in draining lymph node cells (104.5±12.7 vs 217.7±55.3 counts per minute, P<0.05) with reduced frequency of IFN- γ and IL-17A producing cells (ELISPOT: 22±6 vs 115±27 cells, P<0.01 and 6±3 vs 40±18 cells, P<0.05, respectively). Furthermore anti-CD20 treatment increased the proportion of proliferating Foxp3⁺ T regulatory cells (2.9±0.1 vs 1.7±0.1 %, P<0.001; 15% of proliferating Foxp3⁺ T cells in both groups produced IL-10).

Conclusions: In addition to its known capacity to reduce humoral autoimmunity, this study shows that anti-CD20 mAb induced B cell depletion significantly reduces anti-MPO CD4 T cell effectors and enhances T regulatory cells.

Funding: Government Support - Non-U.S.

FR-OR061

Novel Anti-Peroxidase Antibodies Are Part of the Autoimmune Milieu in Preclinical and Clinical Goodpasture's Disease [Abraham Scott McCall](#),¹ Gautam B. Bhavé,¹ Vadim Pedchenko,¹ Agnes B. Fogo,³ Dustin J. Little,² Thomas P. Baker,² Stephen W. Olson,² Billy G. Hudson.¹ ¹*Nephrology and Hypertension, Vanderbilt Univ Medical Center, Nashville, TN;* ²*Nephrology, Walter Reed Army Medical Center, Bethesda, MD;* ³*Pathology, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Goodpasture's disease (GP) is an autoimmune disorder characterized by autoantibodies directed against the NC1 domains of the $\alpha3/\alpha5$ chains of collagen IV in the glomerular and alveolar basement membranes. Epidemiologically, anti-MPO positivity often occurs with GP diagnosis. The normally cross-linked collagen IV scaffold forms through the action of the heme peroxidase, peroxidase, via its HOBr production to form a sulfilimine (S=N) crosslink in the NC1 domain, however loss of the S=N crosslink changes recognition of the NC1 domain by GP antibodies.

Methods: A Vanderbilt GP patient cohort and a retrospective case-control Department of Defense Serum Repository (DoDSR) cohort were tested for recognition of peroxidase, MPO, $\alpha3$ and $\alpha5$ (IV) NC1 domains by ELISA with 3:1 age, sex, race, and age of serum matched controls from the DoDSR. Competition binding ELISA was performed to determine antigen specificity and immunofluorescence was performed on GP biopsies for peroxidase levels. Peroxidase HOBr production *in vitro* was fluorometrically tested in the presence of purified antibodies.

Results: Anti-peroxidase autoantibodies are present in GP patient sera 33%(8/24) at diagnosis, and in 66%(4/6) of pre-diagnosis GP patients. Unexpectedly, the anti-peroxidase specific antibodies cross-react with coated, but not native MPO, accounting for a subset of the currently defined dual-positive patients. We also found significantly elevated focal peroxidase staining in crescentic glomeruli of GP patients. Importantly, patient IgG containing anti-peroxidase antibodies significantly inhibited of peroxidase's HOBr production rate.

Conclusions: Peroxidase is a novel autoantigen in a subset of GP patients validated in two independent cohorts. Anti-peroxidase antibodies potentially contribute to disease pathogenesis in GP with possible implications to be explored in other anti-MPO associated disease.

Funding: NIDDK Support, Other U.S. Government Support

FR-OR062

Autoantibodies against Thrombospondin Type-1 Domain-Containing 7A Induce Membranous Nephropathy in Mice [Nicola M. Tomas](#),¹ Elion Hoxha,¹ Lars Fester,¹ Udo Martin Helmchen,¹ Gerth H. Jens,³ Friederike Bachmann,² Klemens Budde,² Friedrich Koch-nolte,¹ Gunther Zahner,¹ Gabriele M. Rune,¹ Gerard J. Lambeau,⁴ Catherine Meyer-Schwesinger,¹ Rolf A. Stahl.¹ ¹*Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany;* ²*Charité- Universitätsmedizin Berlin, Berlin, Germany;* ³*Heinrich Braun Klinikum, Zwickau, Germany;* ⁴*Inst de Pharmacologie Moléculaire et Cellulaire, Valbonne, France.*

Background: Membranous nephropathy (MN) is an autoimmune disease and a frequent cause of nephrotic syndrome in adults. Autoantibodies against the podocyte proteins phospholipase A₂ receptor 1 and thrombospondin type-1 domain-containing 7A (THSD7A) have been identified in about 75% of patients with MN. However, it is unclear whether these autoantibodies are causative for the development of MN.

Methods: Sera from two patients with anti-THSD7A autoantibody positive MN and control serum were injected into male BALB/c mice. We then analyzed the morphological and clinical development of MN in these mice.

Results: Mice that received anti-THSD7A positive serum developed subepithelial immune deposits containing human IgG (hulG), which colocalized with THSD7A, suggesting antigen specificity of bound hulG. Supporting, IgG eluted from frozen kidney sections of these mice was specific for THSD7A in Western blot analysis. All mice that

were exposed to human serum were found to have circulating mouse anti-hulG, but only mice that received anti-THSD7A positive serum had subepithelial deposits containing mouse IgG. Moreover, histological analyses revealed granular subepithelial staining for complement C3, suggesting local activation of the complement system. Electron microscopy demonstrated electron-dense deposits in a strictly subepithelial localization and focal podocyte foot process effacement. Mice injected with anti-THSD7A positive serum developed albuminuria starting day 3, while urinary albumin excretion of mice injected with control serum remained unchanged.

Conclusions: We conclude that anti-THSD7A autoantibodies are pathogenic and can induce MN in mice.

FR-OR063

Epitope Spreading in PLA2R1 Is Associated with Bad Prognosis in Membranous Nephropathy [Barbara Seitz-Polski](#),^{1,2,3} Guillaume Dolla,² Christine Payre,² Sylvia Benzaken,¹ Ghislaine Bernard,¹ Vincent L.M. Esnault,³ Gerard J. Lambeau.² ¹*Immunology, Nice Univ Hospital, Nice, France;* ²*Inst de Pharmacologie Moléculaire et Cellulaire, CNRS and Univ of Nice, Valbonne, France;* ³*Nephrology, Nice Univ Hospital, Nice, France.*

Background: The phospholipase A2 receptor (PLA2R1) is the major autoantigen in idiopathic membranous nephropathy, with two recently identified epitopes of unknown clinical significance.

Methods: Fifty PLA2R1-positive patients' sera were screened by western blot on a series of PLA2R1 deletion mutants covering the ten extracellular domains. We identified epitopes in the CysR, CTLD1 and CTLD7 domains and confirmed the reactivity against these three domains with soluble forms of each domain using a new ELISA in 69 PLA2R1-positive patients.

Results: Domain-specific ELISAs allowed stratifying 69 PLA2R1-positive patients into three subgroups: 23 CysR, 14 CTLD1 + CysR and 32 CysR + CTLD1 + CTLD7. Median ELISA titers measured using the full-length PLA2R1 antigen were not statistically different between patients' subgroups. The 23 patients with anti-CysR restricted activity were younger (p=0.008), had less nephrotic range proteinuria (p=0.018) and exhibited more spontaneous remission (p=0.03), lower rate of renal failure progression (p=0.0025) and less end-stage kidney disease (p=0.01) during follow-up. Indeed, 31/69 patients had poor renal prognosis according to KDIGO (urinary protein/creatinine ratio over 4 g/g or eGFR<45 ml/min/1.73m² at end of follow-up). High anti-PLA2R1 activity and epitope spreading beyond CysR epitope were independent risk factors of poor renal prognosis in multivariable cox regression analysis. Epitope spreading during follow-up was associated with disease worsening (n=3), whereas reverse spreading from CTLD7 profile back to CysR was associated with favorable outcome (n=1).

Conclusions: We conclude that analysis of the PLA2R1 epitope profile and spreading during follow-up is a powerful tool to monitor disease severity and stratify patients into subgroups with different renal prognosis.

Funding: Government Support - Non-U.S.

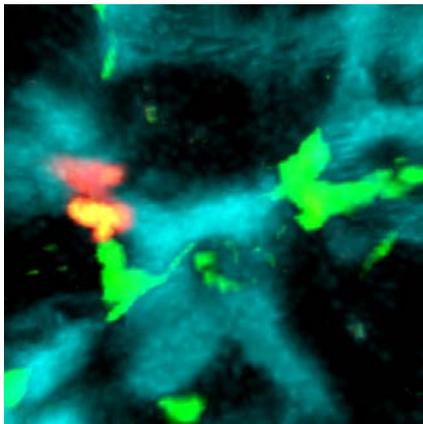
FR-OR064

Intravascular Extensions Allow Renal DC to Capture Bloodborne Antigens and Mediate T Cell Migration into the Kidney [Karim Yatim](#), Martin H. Oberbarnscheidt, *Thomas E. Starzl Transplantation Inst, Univ of Pittsburgh, Pittsburgh, PA.*

Background: We have previously shown that the kidney, a non-barrier, highly vascularized organ possesses an extensive monocyte-derived DC network with around 25% of DC sampling intravascular antigen (Ag) by extending projections into the lumina of cortical postcapillary venules. Here, we hypothesized that renal DC have an active role in immune surveillance via (1) capturing intravascular antigens such as bacteria and immune complexes (IC) and (2) mediate Ag-specific T cell migration into the kidney.

Methods: 2-Photon Intravital Microscopy (2PIM) and flow cytometry was performed on CX3CR1 GFP/+ (DC express GFP) mouse kidneys. Ovalbumin immune complexes (OVA-IC) conjugated to PE-TxRed or E.coli expressing Ovalbumin (OVA) and CFP were i.v. injected. For migration experiments, CD8⁺DsRed⁺ OT-I effector T cells were injected i.v.

Results: After systemic administration of fluorescent E. coli we observed (1) DC uptake of bacteria from the intravascular space immediately after injection (2PIM and flow cytometry) and (2) a 41% increase of DCs with intravascular processes after E.coli injection (2PIM). DC also took up i.v. OVA-IC, (2PIM). Furthermore, in the setting of a systemic CFP-OVA E.coli infection, OT-I T cells migrated into the kidney (2PIM and flow) with 2PIM showing stable DC-T cell interactions and DC (green)-mediated T cell (red) migration into the kidney (figure 1) (blood=cyan).



OT-I migration was significantly higher (2-fold) when CFP-OVA E.coli was used as opposed to non-OVA expressing WT E.coli.

Conclusions: We have shown in two different models that renal DC are actively surveilling the blood for Ag. In the case of infection, we demonstrated that DC mediate Ag-specific T cell migration into the kidney. These findings may shed light on the role of DC in infection and the pathogenesis of immune-complex mediated renal diseases.

Funding: Private Foundation Support

FR-OR065

The C5a Receptor Mediates Anti-Myeloperoxidase Auto-Immunity and Glomerulonephritis Jonathan Dick, Poh-Yi Gan, Sharon Lee Ford, Maliha A. Alikhan, A. Richard Kitching, Stephen R. Holdsworth. *Centre For Inflammatory Diseases, Monash Univ, Melbourne, Australia.*

Background: C5aR inhibition is currently the subject of a clinical trial for treatment of ANCA associated vasculitis. C5a is known to play an important role in neutrophil behaviour, however whether complement acting through the C5aR influences anti-myeloperoxidase (MPO) autoimmunity itself is unknown.

Methods: MPO autoimmunity was induced by injecting C57BL/6 (WT) or C5aR^{-/-} mice with MPO in Freund's adjuvant. In separate experiments WT mice were injected with 1×10^6 WT or C5aR^{-/-} MPO-pulsed bone marrow derived dendritic cells (DCs). Anti-MPO glomerulonephritis was triggered by a sub-nephritogenic dose of anti-GBM globulin.

Results: Autoimmunity at 10 days measured by anti-MPO IgG ELISA was significantly reduced in C5aR^{-/-} mice (0.64 ± 0.05 vs 0.20 ± 0.02 OD_{450nm}, $p < 0.001$). This was associated with a lower proportion of splenocytes that were B220⁺ B cells (58 ± 2 vs $32 \pm 2\%$, $p < 0.001$) and a higher serum BAFF (11.4 ± 0.5 vs 16.6 ± 1.4 ng/ml $p = 0.01$) compared to WT. T cell immunity to MPO was significantly attenuated in C5aR^{-/-} mice measured by proliferation of recombinant MPO stimulated lymph node culture ($[^3H]$ -Thymidine 1302 ± 253 vs 574 ± 123 counts per minute, $p = 0.01$). Th1 response was reduced measured by IFN- γ ELISPOT (55 ± 11 vs 26 ± 6 cells $p = 0.03$) and footpad DTH (0.16 ± 0.02 vs 0.04 ± 0.01 Dmm $p = 0.001$). There was no difference in Th17 response: IL17A ELISPOT (32 ± 7 vs 31 ± 8 cells). The proportion of CD4⁺CD25⁺Foxp3⁺ T regulatory cells was significantly increased in C5aR^{-/-} mice (11.8 ± 0.2 vs $13.5 \pm 0.4\%$, $p < 0.001$). To determine whether C5aR expression on DCs promotes T cell mediated anti-MPO glomerulonephritis, autoimmunity was induced by injection of MPO-pulsed C5aR^{-/-} or WT bone marrow derived DCs into WT mice. Anti-MPO glomerulonephritis was induced 10 days after DC transfer resulting in reduced renal injury (segmental glomerular necrosis $30.9 \pm 5\%$ vs $9.9 \pm 2\%$, $p = 0.005$) in the group receiving C5aR^{-/-} DCs.

Conclusions: Complement acting through the C5aR plays an important role in modulating both humoral and cellular anti-MPO autoimmunity in mice. This suggests an additional mechanism by which C5aR inhibition in ANCA associated vasculitis may be an effective treatment strategy.

Funding: Government Support - Non-U.S.

FR-OR066

Intestinal T_H17 Cells Drive Renal Tissue Injury in Crescentic Glomerulonephritis Christian F. Krebs,¹ Jan-Eric Turner,¹ Hans-Joachim Paust,¹ Tobias Koyro,¹ Jan-Hendrik Riedel,¹ Sonja Krohn,¹ Anna Kaffke,¹ Rolf A. Stahl,¹ Samuel Huber,² Ulf Panzer.¹ ¹III. Medizinische Klinik, Univ Hospital Hamburg-Eppendorf, Hamburg, Germany; ²I. Medizinische Klinik, Univ Hospital Hamburg-Eppendorf, Hamburg, Germany.

Background: T_H17 immune responses play a critical role in inflammatory disorders and autoimmune diseases. Recent studies indicate that development of T_H17 cell depends on microbial colonization of the gut. However, the impact of gut microbiota induced T_H17 cells for pathogenic T_H17 response in autoimmune diseases, such as crescentic glomerulonephritis (GN), remains unclear.

Methods: To characterize the CD4⁺ T cell response in the kidney of patients with ANCA-associated GN we established flow cytometry of human renal biopsies. In addition we traced lymphocytes in mice expressing the photoconvertible Kaede protein after induction of experimental glomerulonephritis by using the model of nephrotic nephritis (NTN).

Results: Using flow cytometry of renal biopsies we were able to demonstrate the presence of CD4⁺Ror γ ⁺ T_H17 cells in the inflamed kidney of patients with ANCA-GN. Interestingly, T_H17 cells in the kidney displayed a gut homing phenotype (CCR6⁺, CCR9⁺, ICOS⁺, IL-7R α ⁺ CD103⁻), indicating that renal T_H17 cells have been primed in the intestine. Tracing intestinal cells by photoconversion in Kaede mice, we could demonstrate that a significant proportion of the T_H17 cell in the nephritic kidney originated from the small intestine. In line, using germ free mice, we were able to show that renal T_H17 response and consecutive tissue injury in crescentic GN depends on intestinal T_H17 cells. Finally, we demonstrated that treatment of nephritic mice with intestinal microbiota depleting broad-spectrum antibiotics reduced renal T_H17 response and attenuated kidney damage.

Conclusions: These data indicate that pathogenic T_H17 cells in glomerulonephritis, originate from the intestine, migrate into the kidney and induce injury of the renal tissue. This finding might have significant implications for the treatment of renal autoimmune disorders.

Funding: Government Support - Non-U.S.

FR-OR067

T-Bet Activation in Regulatory T Cells Is Required for General Fitness, Antibody Production and Control of Th1 Responses in Crescentic Glomerulonephritis Anna Nosko,¹ Malte A. Kluger,¹ Paul Diefenhardt,¹ Simon Melderis,¹ Claudia Wegscheid,² Gisa Tiegs,² Rolf A. Stahl,¹ Ulf Panzer,¹ Oliver M. Steinmetz.¹ ¹Nephrology, Hamburg Univ Medical Center; ²Experimental Immunology, Hamburg Univ Medical Center.

Background: Mechanisms responsible for down regulation of pathogenic Th1 immunity remain widely unknown. Recently, it was proposed that activation of the Th1 characteristic transcription factor T-bet optimizes Foxp3⁺ regulatory T cell (Treg) function to counteract Th1 responses.

Methods: Nothing is known about the role of T-bet⁺ Treg1 cells in inflammatory disease. We studied their function in the NTN model of acute crescentic glomerulonephritis (GN).

Results: Kidneys of nephritic wild type mice showed increasing percentages of Treg1 cells during the course of NTN, indicating their functional importance. Naïve Foxp3⁺T-bet^{hi} mice (Treg1^{-/-}), lacking Treg1 cells, showed spontaneous skewing towards Th1 immunity. In the absence of Treg1 cells, NTN was aggravated in terms of renal function, histology and inflammatory cell infiltration with selectively elevated renal and systemic Th1 responses. Analyses of Tregs from Treg1^{-/-} mice revealed unaltered systemic numbers, activation, cytokine production and *in vitro* suppressive function. However, expression of the Th1 characteristic trafficking receptor CXCR3 was absent on T-bet deficient Tregs, resulting in significantly reduced renal Treg infiltration. In addition to diminished renal trafficking, overall fitness of Tregs from Treg1^{-/-} mice was greatly impaired. In competitive co-transfer experiments into lymphopenic hosts, T-bet deficient Tregs were outcompeted by wildtype Tregs in terms of proliferation and expression levels of Foxp3. Furthermore, T cell dependent humoral immunity was impaired in Treg1^{-/-} mice, indicating that T-bet activation in Tregs plays a hitherto unrecognized role for antibody production.

Conclusions: Our data indicate the presence of a new subtype of regulatory T cells in crescentic GN. These Treg1 cells are characterized by activation of the transcription factor T-bet, which enhances their overall fitness, directs antibody responses and optimizes their capacity to down-regulate Th1 responses by inducing CXCR3 expression.

FR-OR068

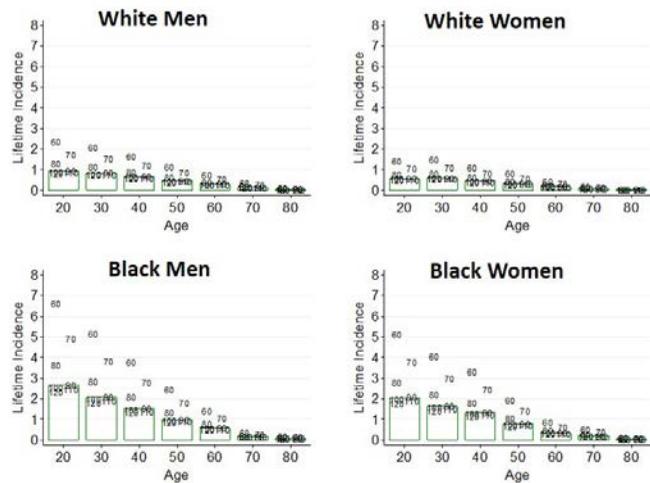
Predicting the Lifetime Risk of End-Stage Renal Disease in Kidney Donor Candidates Morgan Grams, Yingying Sang, Andrew S. Levey, Kunihiro Matsushita, Shoshana Ballew, Alex R. Chang, Bertram L. Kasiske, Csaba P. Kovcsy, Girish N. Nadkarni, Varda Shalev, Dorry L. Segev, Josef Coresh, Krista L. Lentine, Amit X. Garg. *CKD Prognosis Consortium.*

Background: A tool to comprehensively evaluate the lifetime risk of ESRD in potential living kidney donors could help standardize transplant center acceptance criteria.

Methods: We developed statistical equations to predict the lifetime incidence of ESRD according to a person's baseline demographic and health characteristics before kidney donation. Data sources included prevalence estimates from NHANES, ESRD incidence from USRDS, and ESRD risk associations in low-risk subgroups of 7 general population cohorts (N=4,580,454). Developed equations were applied to the general population (using NHANES) and the recent US donor population (using the OPTN registry) and made available in an online risk calculator (www.transplantmodels.com/lifetime).

Results: For the "base-case" potential donor (eGFR 90 ml/min/1.73 m², urine ACR 10 mg/g, systolic blood pressure 120 mmHg, and no adverse health characteristics), the predicted pre-donation lifetime incidence of ESRD varied by age, race, and sex: 2.7%, 1.1%, 0.9%, and 0.6% in 20-year-old black men, black women, white men, and white women, respectively, and 0.6%, 0.3%, 0.3%, and 0.2% in the corresponding 60-year-old candidates. The lifetime incidence of ESRD was higher with additional risk factors, particularly low eGFR or high ACR in young persons (Figure). The predicted lifetime incidence of ESRD before donation was <1% in 88% of recent US donors.

Conclusions: We suggest consideration of pre-donation lifetime ESRD risk in the evaluation and counseling of potential living kidney donors. Our equations estimate a person's lifetime incidence of ESRD in the absence of donation according to multiple demographic and clinical characteristics.



Numbers represent eGFR level before kidney donation; green bars represent lifetime ESRD risk before kidney donation for "base-case" scenario

Funding: NIDDK Support

FR-OR069

Post Donation Hypertension and Risk of Death and ESRD Hassan N. Ibrahim, Robert N. Foley, Scott Reule, Danielle M. Berglund, Arthur J. Matas, Aleksandra Kukla, Naim S. Issa, Richard S. Spong. *Univ of Minnesota, Mpls, MN.*

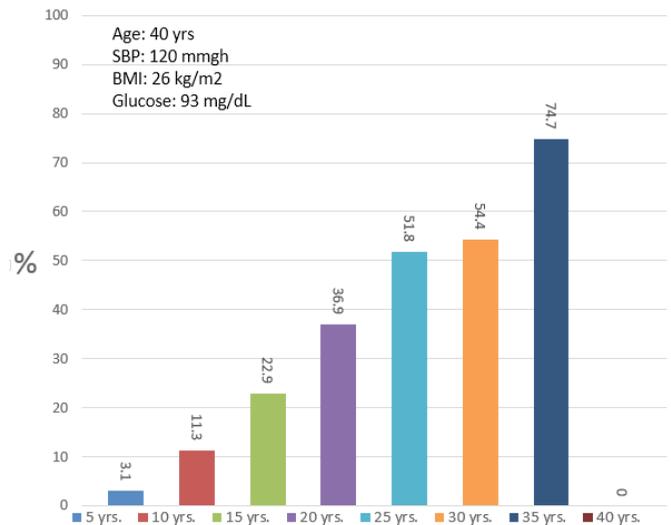
Background: Prevalence of de novo hypertension after kidney donation appears to be similar to that in the general population. Factors associated with its development, however, have not been studied. Goals: 1) ascertain donors' risk of developing HTN, 2) describe the impact of its development on death and renal function and 3) develop a HTN risk prediction model using pre-donation parameters.

Methods: Our donors are followed indefinitely through surveys inquiring about HTN, renal disease and also serial laboratory testing. Risk factors for post donation new onset hypertension were determined using stepwise proportional hazards regression.

Results: HTN status was ascertained in 3638 donors with a mean follow-up of 13±11 years. In total, 972 (27%) developed new onset hypertension. Pre-donation risk factors for development included older age, higher BMI, SBP, and serum glucose at donation (Table 1a). White donors were 40% less likely to develop hypertension, p<0.001 for all. HTN following donation was associated with a nearly 4 fold increased risk of death, proteinuria, and eGFR < 30 ml/min or ESRD (Table 1b). Coefficients from the regression model were then used to create a HTN risk calculator (C-statistic 0.65). A sample output for a 40 year old donor is shown in figure 1.

Variable	Hazard Ratio	p-value
1a) Pre-donation risk factors for HTN		
Age	1.03 (1.03-1.04)	< 0.001
BMI	1.06 (1.04-1.07)	< 0.001
SBP	1.03 (1.02-1.04)	< 0.001
Serum glucose	1.01 (1-1.01)	< 0.001
White race	0.6 (0.45-0.79)	< 0.001
1b) Post donation HTN and hard outcomes		
Death	3.69 (2.88-4.73)	<0.0001
Proteinuria	3.99 (2.62-6.07)	<0.0001
eGFR <30 or RRT	2.48 (1.38-4.46)	0.002

Figure 1. Cumulative risk of HTN for a typical White donor



Conclusions: Hypertension can be reasonably predicted in kidney donors using baseline data. Hypertension is a significant contributor to reduced GFR, ESRD and also death.

Funding: Other NIH Support - NIH(SPO1 DK013083)

FR-OR070

Effect of Changing African American Race to Apolipoprotein L1 Genotype on Kidney Donor Risk Index Bruce A. Julian,¹ Robert S. Gaston,¹ Barry I. Freedman,² William Mark Brown,² Amber M. Reeves-Daniel,² Ajay K. Israni,^{3,4} David P. Schladt,³ Stephen O. Pastan,⁵ Sumit Mohan,⁶ Jasmin Divers.² ¹Univ of Alabama at Birmingham; ²Wake Forest Univ School of Medicine; ³Minneapolis Medical Research Foundation; ⁴Hennepin County Medical Center; ⁵Univ of Minnesota; ⁶Emory Univ School of Medicine; ⁶Columbia Univ.

Background: Renal allografts from deceased African Americans (AAs) with 2 renal-risk variants in apolipoprotein L1 gene (*APOLI*) are lost sooner than kidneys from AAs with 0 or 1 variant. For the latter, allograft survival is similar to that for kidneys from European Americans. Kidney Donor Risk Index (KDRI) was developed recently, before *APOLI* effect was described, to quantitatively estimate quality of deceased-donor kidneys; it assigns higher risk for all AA donors. We postulated that replacing AA race with *APOLI* genotype in KDRI improves risk prediction for kidneys from deceased AA donors.

Methods: Using the effect size in retrospective studies, we calculated KDRI wherein only AAs with 2 *APOLI* renal-risk variants received higher KDRI scoring. Weight of *APOLI* risk variants was defined by 10-fold cross validation: 9/10 of available data was used to estimate parameter associated with *APOLI* in Cox proportional hazard regression with other 9 KDRI variables as covariates. Revised KDRI scores were computed and tested on the last subset; predictive ability was measured by c-index. Cross-validation was done 100x for comparison with original KDRI.

Results: Retrospective analyses of 1,149 kidney transplantations from deceased AA donors (979 *APOLI*=0/1; 170 *APOLI*=2 renal-risk variants) showed mean donor age, serum creatinine, and KDRI of 35.4 yr, 1.25 mg/dL, and 1.45. Observed c-index with original KDRI tested with full data was 0.89; distribution of observed *APOLI*-revised KDRI c-indices had minimum 0.55 and maximum 0.98, median 0.87. *APOLI*-revised KDRI c-index was higher than observed KDRI c-index in 44% of cases.

Conclusions: For the 13% of general AA population with 2 *APOLI* risk variants, KDRI did not change. However, for the other 87% of AAs, the revised KDRI improved by deleting AA race as a risk factor and better reflects the quality of these kidneys relative to current system.

Funding: NIDDK Support

FR-OR071

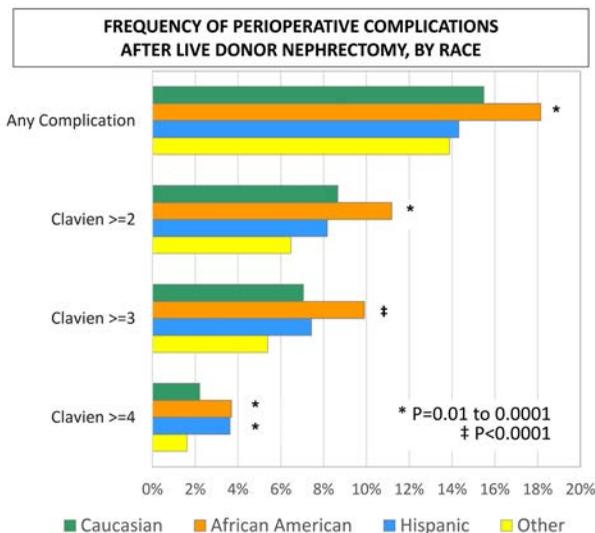
Racial Disparities in Perioperative Complications After Live Kidney Donation Krista L. Lentine,¹ Ngan Lam,² David A. Axelrod,³ Mark Schnitzler,¹ Amit X. Garg,³ Jesse D. Schold,⁴ Daniel C. Brennan,⁵ Dorry L. Segev.⁶ ¹Saint Louis Univ; ²Western Univ; ³Dartmouth; ⁴Cleveland Clinic; ⁵Washington Univ; ⁶Johns Hopkins.

Background: The frequency and severity of perioperative complications after contemporary live kidney donation are not well-described.

Methods: We integrated national U.S. donor registry data with administrative records from an academic hospital consortium (98 centers, 2008-2012) to identify predonation comorbidity and perioperative complications captured in diagnostic, procedure and registry sources. Complication severity was graded by Clavien scoring. Correlates (adjusted odds ratio, aOR) of complications were examined with multivariate logistic regression.

Results: Among 14,964 donors, 11.6% were African American (AA) and 72.6% Caucasian; 93.8% of nephrectomies began as laparoscopic, 2.4% as robotic, and 3.7%

as open procedures. Compared with Caucasians, AA donors experienced higher rates of any complication (18.2% vs 15.5%, P=0.005), and those exceeding progressive severity thresholds including Clavien >=4 (3.7% vs 2.2%, P=0.0002) (Figure).



After adjustment for demographic, clinical (including comorbidity diagnoses), procedure and center factors, AA race was associated with increased risk of any complication (aOR 1.26, P=0.001), and Clavien >=2 (aOR 1.39, P=0.0002), Clavien >=3 (aOR 1.56, P<0.0001), and Clavien >=4 (aOR 1.56, P=0.004) events. Other significant correlates of Clavien >=4 events included obesity (aOR 1.55), predonation hematologic (aOR 2.78) and psychiatric (aOR 1.45) conditions, and robotic nephrectomy (aOR 2.07), while annual center volume >50 (aOR 0.45) predicted lower risk.

Conclusions: AA race is independently associated with increased frequency and severity of perioperative complications after live donor nephrectomy. Future work should seek to identify underlying mechanisms and approaches to reducing outcome disparities.

Funding: NIDDK Support

FR-OR072

Risk Prediction of End-Stage Renal Disease in Living Kidney Donors
Allan Massie, Dorry L. Segev, Eric Chow. *Johns Hopkins.*

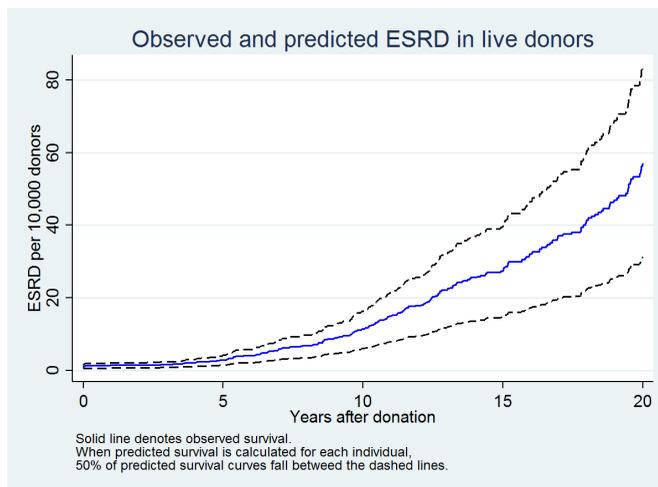
Background: Recent studies have shown increased risk of end-stage renal disease (ESRD) in living kidney donors compared with healthy nondonors. Accurate risk prediction is paramount for informed consent for donation, but individual ESRD risk is unknown.

Methods: Using national donor registry data, we modeled ESRD in 122,773 donors via Cox regression, censoring for mortality. We performed multiple imputation with 50 repetitions to impute body mass index (BMI), unavailable prior to 1999. We used baseline hazard and hazard ratios to calculate individual risk of ESRD at 5, 10, 15, and 20 years post-donation.

Results: Male sex, African-American (AA) race, and higher BMI were associated with greater ESRD risk (all p<0.01, Table 1). Older age was associated with increased risk in non-AA donors (HR per 10y = 1.22 1.40 1.60, p<0.001), but decreased risk in AA donors (HR = 0.60 0.76 0.95, p=0.02).

Risk factor	HR (*p<0.05; **p<0.01; ***p<0.001)
Male gender	1.51 1.95 2.51***
AA race (at age 40)	2.23 3.06 4.21***
Age per 10y (non-AA donors)	1.22 1.40 1.60***
Age per 10y (AA donors)	0.60 0.76 0.95*
BMI per 5 units	1.16 1.48 1.80**

Overall cumulative incidence of ESRD at 5, 10, 15, and 20 years was 3.0, 11.6, 27.7, and 56.9 events per 10,000 donors, respectively (Figure 1). Predicted individual 20-year risk ranged from 6.9 per 10,000 (0.07% chance) to 1240.4 per 10,000 (12.4% chance) of ESRD. Median (IQR) individual 20-year risk of ESRD was 49.8 (31.2-83.8) per 10,000 (Figure 1).



A web calculator of individual risk can be found at transplantmodels.com/donesrd

Conclusions: Male gender and higher BMI are associated with greater ESRD risk in kidney donors. Old age is associated with greater ESRD risk among non-AA donors, but younger age is associated with greater risk among AA donors, likely due to donor selection. Greater permissiveness may be warranted for older AA donor candidates; younger AA candidates should be evaluated carefully and counseled about long-term ESRD risk.

Funding: NIDDK Support

FR-OR073

Factors Influencing Decision About Kidney Transplant: A Survey of Dialysis Patients
Fareeha Khalil, Ming Wang, Naman Trivedi, Eric Chang, Nasrollah Ghahramani. *Pennsylvania State Univ College of Medicine, Hershey, PA.*

Background: Kidney transplant (KT) is the treatment of choice for end stage renal disease (ESRD). The decision to pursue KT involves a complex interplay of disease-related, socioeconomic and ethnic factors. We explored factors influencing patients' decision about KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants who fulfilled inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent variables were demographic factors, distance to dialysis unit, and modes of education about options. In multivariate analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of pursuing KT.

Results: Of 673 participants, 401 had been referred and 201 were listed for KT. Positive predictors of pursuing KT (n=268) included: 'received 3 or more modes of education about KT (OR:3.08;CI:1.62 to 5.87)'; 'nephrologist discussed the option of KT at least twice in previous year' (OR:2.49;CI:1.43 to 4.32). The 2 most common reasons for not pursuing KT included satisfaction with current treatment (18%) and inadequate finances (14%). Urban residence (OR: 2.64;CI: 1.33 to 5.23) and > 5 years on dialysis (OR: 1.75;CI: 1.09 to 2.81) were associated with likelihood of indicating satisfaction with current treatment as a reason not to pursue KT. Age >60 (OR: 2.18;CI: 1.21 to 3.94) and proximity to dialysis unit (OR: 2.30;CI: 1.27 to 4.17) were associated with higher likelihood of indicating inadequate finances as reason not to pursue KT. Of those pursuing KT, 36% would not consider LDKT, most commonly citing unavailability of potential donor (28%). Positive predictors of pursuing LDKT were: 'nephrologist discussed the option of transplant at least twice in last year'; and married status. Negative predictors of considering LDKT were regular attendance at religious service, age >60, being on dialysis >5 years.

Conclusions: Nephrologist-related factors (delivering diverse education) and patient characteristics (age, gender, race, health status perception, marital/socioeconomic status, duration/comfort with dialysis) are important drivers of the decision making process for choice of KT.

Funding: NIDDK Support

FR-OR074

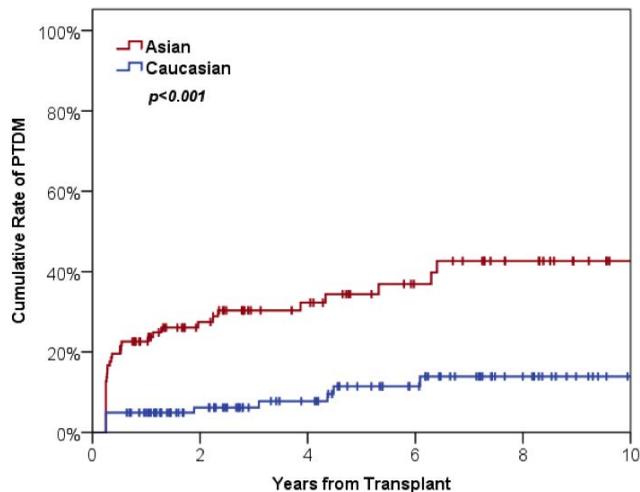
A Propensity-Matched Analysis Comparing Rates of Post-Transplant Diabetes Mellitus (PTDM) in South Asian and Caucasian Renal Transplant Recipients
Javeria Peracha, Krishan Parekh, Charles Ferro, Richard Borrows, Adnan Sharif. *Queen Elizabeth Hospital, Birmingham, United Kingdom.*

Background: South Asians have increased risk for type 2 diabetes but the risk of post-transplantation diabetes mellitus (PTDM) is unknown. The aim of this study was to compare PTDM risk in South Asian versus Caucasian kidney allograft recipients in a propensity matched analysis.

Methods: In this retrospective analysis, data was extracted from electronic patient records at a single-centre (2004-2014). 354 Caucasian and 121 South Asians met the inclusion/exclusion criteria for this study. Caucasians were more likely to be older, male and have higher BMI compared to South Asians. Propensity score matching was therefore undertaken to remove their bias effect.

Results: Propensity matching resulted in 102 pairs of kidney allograft recipients. Median follow up was 51 months (range 3-130 months). Both groups had similar baseline

characteristics, although South Asians compared to Caucasians received more deceased-donor kidneys (74% vs. 43% respectively, $p < 0.001$) and were more likely to be CMV positive (77% vs. 43% respectively, $p < 0.001$). Five-year PTDM was higher in South Asians versus Caucasians (34% vs. 11% respectively, hazard ratio 4.3 [95% CI: 2.0–9.4, $p < 0.001$]).



Donor type had significant interaction with ethnicity. While no difference in PTDM was observed in recipients of live kidneys, 5-year PTDM risk was 42% versus 5% for South Asian versus Caucasian deceased kidney recipients respectively ($p < 0.001$). No difference was observed in allograft function, rejection episodes, adverse cardiovascular events or patient/graft survival.

Conclusions: South Asian kidney allograft recipients have increased risk of PTDM, especially in the context of deceased kidney donation. It is important to recognize South Asians as high risk for PTDM to allow targeted screening and management strategies.

FR-OR075

Increased Circulating T-Lymphocytes Expressing HLA-DR in Kidney Transplant Recipients with Microcirculation Inflammation Hee-Yeon Jung,¹ Chan-Duck Kim,¹ Suhyung Lee,¹ Ji-Young Choi,¹ Se-Hee Yoon,² Jang-Hee Cho,¹ Sun-Hee Park,¹ Yong-Lim Kim.¹ ¹Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; ²Internal Medicine, Konyang Univ, Republic of Korea.

Background: Despite the clinical impact of microcirculation inflammation (MI) and T-lymphocyte on antibody-mediated rejection in kidney transplant recipients (KTRs), the association between MI in allograft biopsy and activity of T-lymphocyte in the peripheral blood is not known. This study aimed to compare the histologic grading of renal allograft according to the Banff score with activity of serum T-lymphocyte subsets and HLA-DR positive monocytes in KTRs.

Methods: A total of 137 indication biopsies from renal allografts were performed from 117 KTRs. Among them, 24 biopsy specimens from KTRs who have data of serum T-lymphocyte subsets and HLA-DR positive monocytes at the time of biopsy were included in this study. The frequencies of serum HLA-DR⁺, CD4⁺, CD8⁺, and CD25⁺ T cells, and HLA-DR positive monocytes were determined by flow cytometry. The histologic grading of renal allograft was classified according to the sum score of g+ptc (MI), i+t, ci+ct, and cv+ah based on Banff 2013 classification.

Results: The frequencies of CD4⁺HLA-DR⁺/T cells, CD8⁺HLA-DR⁺/T cells, CD4⁺HLA-DR⁺/CD4⁺ T cells, and CD8⁺HLA-DR⁺/CD8⁺ T cells were significantly increased in KTRs with MI sum score ³1 (n=13) compared to KTRs with MI sum score=0 (n=11) (all $P < 0.05$). Among four subsets, CD4⁺HLA-DR⁺/CD4⁺ T cells were positively correlated with MI sum score ($P = 0.013$). However, no significant differences were observed between two groups categorized based on the sum score of i+t, ci+ct, and cv+ah. Analysis using the receiver-operating-characteristic curve showed that antibody-mediated rejection could be predicted with a sensitivity of 83.3% and a specificity of 58.3% using a cutoff value of 12.25% frequency of CD4⁺HLA-DR⁺/CD4⁺ T cells.

Conclusions: MI was significantly associated with increased frequency of activated T-lymphocyte expressing HLA-DR in KTRs. Further large-scale studies are needed to confirm circulating CD4⁺HLA-DR⁺/CD4⁺ T cells as a useful noninvasive immunologic monitoring tool for prediction of antibody-mediated rejection.

FR-OR076

Monitoring of Calcineurin Inhibitors by NFAT-Regulated Gene Expression in De Novo Renal Allograft Recipients Claudia Sommerer,¹ Martin G. Zeier,¹ Stefan Meuer,² Thomas Giese.² ¹Nephrology, Univ Hospital, Heidelberg, Germany; ²Immunology, Univ Hospital, Heidelberg, Germany.

Background: Calcineurin inhibitors are critical-dose drugs with a narrow therapeutic range and the optimal monitoring strategies are discussed in terms of safety and efficacy. A new pharmacodynamic monitoring tool – assessing the expression of nuclear factor of

activated T cells (NFAT)-regulated genes – has been established to measure directly the functional effect of cyclosporin A (CsA) in an individual patient. Until now, only sparse data on NFAT-regulated gene expression within the early post-transplant period are available.

Methods: Altogether 80 de novo renal transplant patients were enrolled in this prospective observational trial. The immunosuppression consisted of IL-2 receptor antagonist induction, CsA, mycophenolic acid and steroids. The expression of the NFAT-regulated genes (interleukin 2, granulocyte-macrophage colony stimulating-factor, Interferon γ) was determined by qRT-PCR at CsA C0 and C2 at regular follow-up visits within 6 months after transplantation.

Results: The median age of all patients was 47.9±13.7 years (54 male). Residual NFAT-regulated gene expression showed a high interindividual variability. Inversely to reduction of CsA doses expression of NFAT-regulated genes increased from 1.78±1.33% to 8.04±7.36% in month 1 to month 6. Despite of comparable CsA C0 levels NFAT-regulated gene expression was significantly less inhibited in patients with treated biopsy-proven acute rejections (2.9±2.2% vs. 2.0±1.7%, $p = 0.047$). Patients with very low residual expression on NFAT-regulated genes were on increased risk of early infectious episodes. Residual expression of IFN γ and GM-CSF genes correlated most significantly with clinical outcome.

Conclusions: NFAT-regulated gene expression is highly inhibited in the early post-transplant period in renal allograft recipients on CsA treatment. High residual NFAT-regulated gene expression was related to acute rejection episodes but low residual expression with infectious complications. Thus, NFAT monitoring has the potential to support pharmacokinetic monitoring in the early post-transplant period.

Funding: Pharmaceutical Company Support - Novartis Germany

FR-OR077

Proteomics of Urinary Exosomes to Identify Biomarkers of BK Virus Infection and Acute Rejection Luuk Hilbrands, Mathijs van de Vrie, Jeroen Deegens, Johan Van der vlag. *Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: Acute cellular rejection (ACR) and BK virus associated nephropathy (BKVAN) are frequent causes of graft dysfunction after renal transplantation with similar symptoms but requiring different treatments. We investigated whether patients with an ACR episode or BKVAN could be distinguished based on proteins present in urinary exosomes.

Methods: Urine samples (50 mL) were collected from renal transplant patients with ACR, BKVAN or stable graft function. Urinary exosomes were isolated by ultracentrifugation (110³ at 200.000×g). For each group (ACR, BKVAN, controls) we pooled equivalent amounts of exosome proteins of 4 patients (first set) and repeated this with 4 different patients in each group (second set). Subsequently, exosomes were lysed and 40 microgram of protein was resolved by a 4-12% SDS-PAGE. After electrophoresis, gel lanes were cut into 5 pieces according to molecular mass. Proteins were in-gel digested with trypsin, and peptide mixtures were analysed using LC-MS/MS. Proteins were identified using the NCBI database. Partial least squares enhanced discriminant analysis was used to classify the patient groups based on exosomal protein content.

Results: A total of 340 individual proteins was detected in the first set of samples and 385 proteins in the second set, with 204 proteins overlapping between both sets. Our preliminary findings show a number of proteins for which the exosome content differed between ACR and BKVAN. Specific candidate proteins that can serve as urinary biomarkers include acid ceramidase, low density lipoprotein-related protein 2, copine VIII, alpha-1-acid glycoprotein 1 syndeac 4, and lactate dehydrogenase.

Conclusions: In this study we show that profiling of urinary exosomes is a promising tool to identify urinary proteins which allow differentiation between ACR and BKVAN in renal transplant patients.

FR-OR078

Identification of Signature Long Non-Coding RNAs in the Development of Diabetic Nephropathy Jianyin Long, Shawn S. Badal, Zengchun Ye, Bernard A. Ayanga, Farhad R. Danesh. *Dept of Emergency Medicine, The Univ of Texas MD Anderson Cancer Center, Houston, TX.*

Background: Long noncoding RNA (lncRNAs) have emerged as potent regulators of multiple cellular processes relevant to cellular homeostasis and differentiation. More recently, lncRNAs have also been implicated in the pathogenesis of a myriad of diseases, including cancer and heart diseases. However, the role of lncRNAs in diabetic nephropathy (DN) is unknown.

Methods: Total RNA-Seq analysis was performed on glomeruli from Type 2 diabetic, db/db mice to explore differentially expressed lncRNAs. Following identification of a candidate lncRNA, Tug1 (Taurine-upregulated gene-1) we employed CRISPR/Cas9 genome editing to deplete Tug1 in cultured podocytes. Tug1 overexpression in podocytes was used for gain of function analysis. To understand the functional role of Tug1 in vivo and because Tug1 is reduced in diabetic podocytes, we generated podocyte-specific, Tug1 transgenic, db/db mice.

Results: RNA-Seq analysis revealed that expression of Tug1, a predicted antioxidant-responsive gene, is significantly reduced in the podocytes of db/db mice. Analysis of in vivo isolated podocytes from db/db mice demonstrated that downregulation of Tug1 over time is correlated with the progression of DN. To interrogate the functional relevance of Tug1, we performed transcriptome analysis on RNA from CRISPR/Cas9 Tug1 depleted podocytes, and found expression of a number of nuclear encoded, mitochondrial genes, including the master mitochondrial regulator, Pgc1 α to be significantly decreased. Gain of function experiments revealed Tug1 mediated activation of Pgc1 α and associated mitochondrial phenotypes. To assess the therapeutic potential of Tug1 overexpression in vivo, we generated podocyte-specific, Tug1 transgenic mice on the db/db background. Importantly, we observed significant and sustained improvement in ACR and histology up to 24 weeks.

Conclusions: We have found a number of differentially regulated lncRNAs within DN and demonstrated that Tug1 is a mediator of the transcriptional response to high glucose. We demonstrate that Tug1 overexpression in a mouse model of DN exerts a renoprotective phenotype, in part, by rescuing expression of Pgc1 α .

Funding: NIDDK Support

FR-OR079

Epigenetic Abnormalities Underlie Increased Expression of Nuclear Receptor PXR in Diabetic Kidney Disease Atsushi Watanabe,¹ Takeshi Marumo,² Wakako Kawarazaki,² Mitsuhiro Nishimoto,² Nobuhiro Ayuzawa,² Daigoro Hirohama,² Kohei Ueda,² Hiroo Kumagai,¹ Toshiro Fujita.² ¹*Dept of Nephrology and Endocrinology, National Defense Medical College, Tokorozawa, Japan;* ²*Div of Clinical Epigenetics, RCAST, Univ of Tokyo, Tokyo, Japan.*

Background: Epigenetic abnormalities have been suggested to mediate the phenomenon of metabolic memory observed in diabetic complications. Because kidney is composed with various cell types, we investigated the epigenetic alterations in a cell type-specific manner and showed that epigenetic changes may induce persistent phenotypic changes of the proximal tubules in the diabetic kidney (JASN 2015 in press). PXR, a xenobiotic nuclear receptor, has recently been shown to play a critical role in metabolic changes in obesity and diabetes. In this study, we investigated the expression of PXR in normal and diabetic kidneys and explored the underlying epigenetic mechanisms and possible function.

Results: Immunohistochemistry and quantitative RT-PCR analysis demonstrated that PXR is selectively expressed in the proximal tubules. Combined bisulfite restriction analysis and bisulfite sequencing revealed that the promoter region of *Pxr* of normal proximal tubules is significantly demethylated as compared to that of non-proximal tubular cells. In diabetic mice, significant increase in *Pxr* mRNA, demethylation of DNA and increased H3K4me3 in the promoter were also observed. Epigenetic changes are likely to play a causative role in PXR induction because DNMT inhibitor and HDAC inhibitor increased mRNA expression of *Pxr* in cultured human proximal tubular cells. To identify specific functions of PXR in proximal tubules, we treated mice with PXR agonist (PCN 100mg/kg once i.p.), and analyzed transcriptome of the kidney by microarray analysis. Significant increase of *Rgc32*, a molecule known to exert fibrotic effects in the kidney, was observed in the PCN-treated kidney.

Conclusions: We revealed that PXR, expressed selectively in the proximal tubules, is increased in the diabetic kidney. Aberrant expression of PXR may be maintained by epigenetic mechanisms and contribute to the progression of diabetic kidney disease through the novel PXR-RGC32 pathway.

FR-OR080

Metabolic Control of Chromatin Remodeling by miR-93 in Diabetic Nephropathy Shawn S. Badal,¹ Yin Wang,¹ Jianyin Long,¹ Farhad R. Danesh,¹ ¹*Section of Nephrology, The Univ of Texas MD Anderson Cancer Center, Houston, TX;* ²*Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX.*

Background: How podocytes respond to metabolic cues in their environment remains a central question in kidney research. This is relevant in the pathogenesis of diabetic nephropathy (DN), where recent evidence suggests that metabolic events in podocytes may play important roles in regulating chromatin structure. However, the molecular connection linking metabolic states in the cytoplasm to chromatin dynamics remains poorly understood.

Methods: We employed a combined *in vivo* and *in vitro* approach to understand the impact and mechanism of miR-93 overexpression in podocytes within the diabetic milieu. We generated triple transgenic, podocyte-specific, tamoxifen-inducible miR-93 transgenic mice on the *Lepr^{fl}* background (*db/db*). We restored miR-93 expression in kidneys using systemically administered miR-93 mimics. Mechanistically, we employed RNA-Seq and DNase Hypersensitivity-Seq analysis to define novel targets of miR-93 in podocytes.

Results: Diabetic mice with forced expression of Pod-miR-93 exhibited a significant reduction in ACR and total albumin excretion when compared to non-induced, diabetic controls. Tamoxifen induced mice exhibited a significant reduction in mesangial expansion measured by PAS and podocyte injury measured by Desmin staining, compared to controls. Ultrastructure analysis revealed reduced podocyte effacement, and improved glomerular basement membrane thickness in miR-93 induced mice compared to controls. Restoring miR-93 expression *via miR-93* mimics delivery in diabetic mice rescued the DN phenotype in a similar fashion. RNA-Seq and DNase-Seq analysis revealed a previously unrecognized role for miR-93 as regulator of chromatin dynamics through a novel target in DN, *Msk2*.

Conclusions: Our data suggest that miR-93 is a critical metabolic/epigenetic switch in the diabetic environment linking the metabolic state to chromatin remodeling through its modulatory effect on *Msk2/H3S10* phosphorylation signaling pathway. We propose that low levels of miR-93, via chromatin remodeling, results in global changes to DN-related chromatin signature and transcriptome.

Funding: NIDDK Support

FR-OR081

C-Reactive Protein Promotes Renal Fibrosis in Type 2 Diabetes via CD32-Smad3-mTOR Signaling Pathway In Vivo and In Vitro Hui Y. Lan, Yong-ke You, Xiao Ru Huang. *Dept of Medicine & Therapeutics, Li Ka Shing Inst of Health Sciences, and Shenzhen Research Inst, The Chinese Univ of Hong Kong, Hong Kong, China.*

Background: Increasing evidence shows that patients with type-2 diabetic nephropathy (T2DN) is associated with elevated serum levels of C-reactive protein (CRP). In this study, we tested a hypothesis that CRP may promote T2DN by impairing the mTOR pathway via the Smad3-dependent mechanism.

Methods: Human CRPtg-db/db mice and their littermate controls including db/db, db/m and CRPtg-db/m mice were generated by crossing db/m mice with CRPtg mice that overexpress human CRP. Blood fasting glucose, intraperitoneal glucose tolerance test (IPGTT), intraperitoneal insulin tolerance test (IPITT), 24-hour urinary microalbumin levels were measured every 4 weeks in groups of 8 mice over the 36-week period. To study the signaling mechanism, intrarenal TGF- β /Smad3 and mTOR signaling were also studied *in vivo* and *in vitro* in HK-2 tubular epithelial cells.

Results: Compared with littermate db/db mice, CRPtg-db/db mice developed higher levels of blood fasting glucose and enhanced insulin resistance. These were associated with a marked increase in microalbuminuria and the development of more severe renal fibrosis including an increase in collagen I and IV within the diabetic kidney. Enhance renal fibrosis in CRPtg-db/db mice was associated with a marked activation of TGF- β /Smad3 and mTOR signaling. Further studies in cultured HK-2 TEC revealed that CRP acted through its receptor CD32b to promote high glucose-induced activation of Smad3 via both TGF- β -dependent and ERK/p38/MAP kinases-crosstalk pathways, which was confirmed by the finding that addition of a neutralizing antibody against CD32 or TGF- β 1 and an inhibitor to ERK or p38 was capable of inhibiting CRP-induced Smad3 signaling. Furthermore, we also found that activated Smad3 then bound directly to mTOR as determined by a ChIP assay and stimulated fibrosis in response to CRP and high glucose, which was blocked by a Smad3 inhibitor (SIS3) and a mTOR inhibitor (rapamycin).

Conclusions: CRP promotes renal fibrosis in T2DN via the CD32b-Smad3-mTOR signaling pathway.

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FR-OR082

NLR4 Knockout Ameliorates the Development of Diabetic Nephropathy in Mice Fang Yuan,¹ Yinghong Liu,¹ Ryan Kolb,² Fu-You Liu,¹ Weizhou Zhang,² ¹*Dept of Nephrology, the Second Xiangya Hospital, Central South Univ, Changsha, China;* ²*Dept of Pathology, Univ of Iowa, USA.*

Background: Diabetic nephropathy is a growing health concern with characteristic sterile inflammation. An association of diabetic nephropathy with inflammasome activation has recently been shown, but the pathophysiological relevance of this finding remains unknown. In the current study, we aimed to study the role of NLR4 inflammasome in the development of diabetic nephropathy in mice.

Methods: The expression of NLR4 inflammasome and macrophage infiltration in renal tissues of patients with DN were detected by immunohistochemistry. Then, we used *NLR4^{-/-}* mice to test the hypothesis that diabetic nephropathy is associated with renal NLR4 inflammasome activation. We used the STZ-induced diabetes model, and followed the mice for up to 8 weeks. The mice were randomly divided into 3 groups: the normal control group; the wild-type diabetic group; *NLR4^{-/-}* diabetic group. After 8 weeks, serum biochemistry and urine albumin were measured. The kidneys were collected to test the macrophage by flow cytometric analysis and the renal pathologic changes were observed by light microscopy. We also detected the level of IL-1 β by ELISA, and NLR4 inflammasome activation by western blot. NF- κ B, JNK signal transduction pathways and inflammatory cytokines in wild-type and *NLR4^{-/-}* mice were determined by western blot and real-time PCR.

Results: There were significantly increased NLR4 expression and macrophage infiltration in the renal tubules and interstitium of DN patients compared with that of control patients, and the expression of NLR4 was positive correlated with glomerular sclerosis. Inflammasome activation (caspase-1 and IL-1 β) were detected in wild-type diabetic mice. Conversely, *NLR4* deficient mice were protected against diabetic nephropathy. Furthermore, inhibition of NLR4 also suppressed NF- κ B, JNK signal transduction pathways and decreased TNF- α , TGF- β and CTGF expression in STZ-diabetic mice.

Conclusions: Our study suggests that inhibition of NLR4 inflammasome ameliorates the development of diabetic nephropathy in mice. Targeting the inflammasome may be a potential therapeutic approach to diabetic nephropathy.

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FR-OR083

Mitochondrial Lipid Overload in the Proximal Tubules Leads to Fibrosis Krisztian Stadler, Claudia Kruger. *Oxidative Stress and Disease Lab, Pennington Biomedical Research Center, Baton Rouge, LA.*

Background: While there is ample evidence for defective lipid metabolism in diabetes and insulin sensitive tissues, the role of lipid metabolism in renal disease is underappreciated. Mitochondrial lipid overload – overburdening β oxidation – is an important phenomenon in metabolic flexibility. This metabolic disturbance in the kidney has not been studied.

Proximal tubules almost exclusively use fat as their energy source, therefore it is important to understand what happens when they are overloaded with lipids. Tubular fibrosis seems to be a common pathway where all chronic kidney diseases culminate.

Methods: To test the relationship between mitochondrial lipid overload and tubular damage, we have developed a proximal tubule specific (Ggt CRE) mouse strain lacking carnitine-acetyl transferase - crAT (CrATGgt^{-/-}). CrAT is responsible for the removal of excess fatty acid products from mitochondria. In its absence, incompletely oxidized fatty acids accumulate, pyruvate oxidation is compromised and a reducing environment conducive to superoxide formation created. This can lead to hydroxyl radical production which then will induce lipid peroxidation. By deleting CrAT an ideal system can be created to specifically model lipid radical formation due to metabolic sources.

Results: Knockout mice developed fibrosis, protein casts and tubular injury as they aged when compared to fl/fl controls. This was accompanied with increased TGF β expression, an increase in serum creatinine levels, increased expression of vimentin, collagen IV, Bax, and caspase-3. Similarly to other mice models of kidney disease, CrATGgt^{-/-} mice displayed phenotypic variations from minor to more severe injury. Kim-1 expression in CrATGgt^{-/-} mice correlated with the severity of fibrosis. Interestingly, mice also developed glomerular injury and FSGS-like lesions, suggesting tubulo-glomerular interactions when tubular mitochondria are overloaded. Challenging mice with high fat diet or uninephrectomy accelerated this phenotype.

Conclusions: Our studies suggest that mitochondrial lipid overload (deletion of CrAT) in the proximal tubules may lead to metabolic/redox disturbances and tubular apoptosis and fibrosis.

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FR-OR084

Role of Neupilin-1 in Glomerular Function and Disease Christina S. Bartlett,¹ Monika Lucyina Wnuk,² Vera Eremina,³ Chengjin Li,³ Yashpal S. Kanwar,¹ Jeffrey H. Miner,⁴ Maria Pia Rastaldi,⁵ Susan E. Quaggin.¹ ¹Feinberg Cardiovascular Research Inst and Div of Nephrology, Northwestern Univ, Chicago, IL; ²Univ of Bern, Switzerland; ³Mount Sinai Hospital, Toronto, Canada; ⁴Washington Univ, St. Louis, MO; ⁵Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milano, Italy.

Background: Neupilin-1 (NP-1), a co-receptor for a variety of growth factors (e.g. VEGF, PDGF, and TGF- β), is critical for development and patterning of vascular and nervous systems. Mesangial cells strongly express NP-1 yet the physiological relevance of this is unclear. To date, onset of proteinuria in humans following antibody blockade of NP-1 hints at the importance of NP-1 in glomerular function.

Methods: NP-1 expression was assessed by immunofluorescence in biopsy samples from diabetic (DN) and IgA nephropathy (IgAN) patients. To further investigate the *in vivo* function of NP-1, we analyzed mice with perivascular cell specific deletion of NP-1. Intrinsic cell behaviors affected by NP-1 were examined in primary human mesangial cultures.

Results: DN and IgAN biopsies have notably elevated mesangial expression of NP-1 indicating that NP-1 may have a role in glomerular dysfunction. In mice, deletion of NP-1 in the mesangium restricts glomerular maturation and causes dramatic mesangial expansion, marked GBM thickening and tubular dilatation. NP-1-deficient mutants develop severe proteinuria and succumb to renal insufficiency. In mutant glomeruli lacking NP-1 in the mesangium, VEGFR2 phosphorylation is increased while podocyte ERK signaling is hyperactivated. *In vitro*, we showed that NP-1 mediates directed migration of mesangial cells towards PDGFB. Inducible gene targeting of NP-1 is currently underway to delineate developmental versus maintenance functions of NP-1 in the glomerulus particularly within the context of DN.

Conclusions: NP-1 expression in the mesangium is needed for glomerular development. NP-1 regulates matrix production and its absence compromises glomerular filtration. Increased expression of NP-1 in DN and IgAN further suggests that glomerular function relies on a finely tuned level of NP-1 signaling. Accordingly, NP-1 may be suitable as target to ameliorate glomerular disease.

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FR-OR085

Protein S Protects Podocyte from Injury in Early Diabetic Nephropathy Fang Zhong,^{1,2} Kim Lee,¹ John C. He.¹ ¹Dept of Medicine/Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY; ²Dept of Nephrology, Hang Zhou Hospital of Traditional Chinese Medicine, Zhejiang Chinese Medical Univ, Hang Zhou, Zhejiang, China.

Background: Elucidating mechanisms that mediate the early stage of diabetic nephropathy (DN) may help us identify novel preventive and therapeutic measures for patients with DN. Protein S (PS), a vitamin K-dependent protein, functions mainly as a cofactor for the formation of activated protein C (APC). APC is known to have podoprotective effects in DN. However, the role of PS in DN has not been studied.

Methods: Proteomic analysis was performed in glomeruli isolated from STZ and control rats. The podocytes cell-specific Prosl1 homozygous knockout mice (KO) were developed to determine the role of PS in DN. Immortalized human podocytes (HPC) were used for *in vitro* studies. The expression of TMA receptors and podocyte-specific genes were examined by western blot and RT-PCR. The Protein S expression was examined in human kidney biopsies by immunostaining.

Results: Proteomic analysis of glomeruli revealed higher expression of PS in diabetic glomeruli. Then, we confirmed an increase of PS expression in the glomeruli of diabetic rats by RT-PCR and immunostaining. Interestingly, PS expression also increased in human kidneys with early DN but decreased in those with advanced DN. As a control, plasma

concentrations of PS were not significantly different between diabetic and non-diabetic rats or humans. Since the staining of PS was more prominent in podocytes of human diabetic kidney, we determined the role of PS in cultured human podocytes. We found that Knockdown of Prosl1 enhanced high glucose-induced apoptosis while overexpression of Prosl1 inhibited TNF- α -induced pro-inflammatory gene expression in podocytes likely through activation of tyro3, one of the TMA receptors. To further determine the role of PS in DN, we developed podocyte-specific Prosl1 knockout mice (KO) and found that diabetic KO mice (KO-STZ) developed more proteinuria, mesangial expansion, and foot process effacement than diabetic wide-type mice (WT-STZ).

Conclusions: Our data support a protective role of PS against podocyte injury in early DN.

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FR-OR086

Deletion of SHP-1 in Podocytes Prevents Diabetic Nephropathy Farah Lizotte, Benoit Denhez, Andréanne Guay, Pedro Miguel Galdes. *Medecine, Univ of Sherbrooke, Sherbrooke, QC, Canada.*

Background: Both clinical and experimental data suggest that podocyte injury is involved in the onset and progression of diabetic nephropathy (DN) in the patients with type 1 diabetes. Although the mechanisms underlying the development of podocyte loss are not completely understood, insulin and nephrin actions have been shown to play a major role in the podocyte survival and function. We have reported that SHP-1, a protein tyrosine phosphatase, is increased in podocytes of diabetic mice and inhibited insulin and nephrin actions. However, the precise role of SHP-1 in the development of diabetic nephropathy remains to be investigated.

Methods: We have generated a non-diabetic (NDM) and diabetic Akita (DM; *Ins2^{+/C96Y}*) conditional podocyte specific SHP-1 knockout (podo-SHP-1KO) mice using the TetON-Cre lox system. Mice received or not doxycycline at 4 weeks of age and renal function (albuminuria and GFR) and pathology were examined at 7 months of age.

Results: Elevated albumin/creatinine ratio and GFR showed in DM mice are prevented by 86% and 100%, respectively in DM mice that lack SHP-1 gene specifically in podocytes. Mesangial cell expansion and glomerular hypertrophy is increased by 1.8 and 4.9 fold in DM mice and reduced by 78% and 72%, respectively in DM podo-SHP-1KO mice. Moreover, the expression of collagen type IV and TGF- β that is enhanced in DM mice compared to NDM was not increased in DM podo-SHP-1KO mice. Transmission electron microscopy analysis demonstrated podocyte foot process effacement in DM mice that is not observed in DM podo-SHP-1KO mice. Furthermore, inhibition of insulin-induced Akt and ERK phosphorylation showed in DM mice is completely prevented in DM podo-SHP-1KO mice. Similar to insulin, nephrin phosphorylation is restored in DM podo-SHP-1KO mice compared to DM mice.

Conclusions: Our data indicate that the deletion of SHP-1 specifically in podocytes restored insulin and nephrin actions and prevented renal pathology and dysfunction in diabetic mice.

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FR-OR087

Targeted Proximal Tubule Injury Promotes Progression of Diabetic Kidney Disease in Akita Mice Jae Hyung Chang, Takaharu Ichimura, Venkata Sabbiseti, Joseph V. Bonventre. *Renal Div, Dept of Medicine, Brigham and Women's Hospital, Boston, MA.*

Background: Increasing evidence suggests that the kidney tubulointerstitial injury plays an important primary role in the pathophysiology of diabetes.

Methods: In the present studies, a mouse containing the renal epithelial cell-specific Six2Cre allele was crossed with a mouse transgenic for a Cre-inducible simian diphtheria toxin receptor (DTR). The bigenic mouse was then bred with Akita mice as a genetic model of type 1 diabetes. Targeted tubule injury was induced in these animals (Akita DTR^{renal epithelial cell} (DTR^{rec})) with injection of diphtheria toxin (DT).

Results: Male Akita mice developed sustained hyperglycemia. A single sublethal dose of DT in Akita DTR^{rec} mice resulted in an acute two-fold rise in urinary albumin excretion and progression of albuminuria over the study period. By 19 weeks after DT injection, Akita DTR^{rec} mice developed an almost five-fold increase in albuminuria, 40% increase in serum creatinine level, almost two-fold increase in blood urea nitrogen (BUN) level, and reduced kidney size when compared with Akita controls. Moderate glomerular mesangial expansion, and increased interstitial fibrosis and tubular atrophy (IFTA) and glomerulosclerosis were observed in Akita DTR^{rec} mice 20 weeks after DT injection. These pathologic changes were accompanied by increased levels of the molecular marker of proximal tubule injury, kidney injury molecule (KIM)-1, in both kidneys and urines of Akita DTR^{rec} animals. Increased proximal tubule DNA damage response (DDR) activation, pro-inflammatory and pro-fibrotic cells infiltration, and peritubular capillary rarefaction were observed in kidneys of DT-treated Akita DTR^{rec} mice.

Conclusions: In diabetes, proximal tubule injury, perhaps from glycotoxins, can drive interstitial inflammation and fibrosis, capillary rarefaction, and secondary glomerular injury leading to progression of diabetic nephropathy. Our findings suggest novel therapeutic targets for the prevention and treatment of diabetic kidney disease.

Funding: Private Foundation Support

FR-OR088

Wnt11 Signals from the Ureteric Bud Direct Organization of the Nephron Progenitor Niche Determining Nephron Endowment Lori L. O'Brien,¹ Alexander N. Combes,³ Kieran M. Short,² Peter H. Whitney,¹ Odysse Michos,¹ Ali Ju,³ Luise A. Cullen-McEwen,² John F. Bertram,² Melissa H. Little,³ Andrew P. McMahon.¹ ¹USC, Los Angeles, CA; ²Monash Univ, Melbourne, VIC, Australia; ³Murdoch Childrens Research Inst, Melbourne, VIC, Australia.

Background: Normal nephron endowment requires a balance of nephron progenitor (NP) self-renewal and differentiation during kidney development. Wnt11, a non-canonical Wnt signal produced by ureteric tip (UT), has been shown to positively regulate the Gdnf-Ret signaling axis and branching morphogenesis. Our current data identifies a new role for Wnt11 in organization of the NP niche.

Results: Six2+ NPs are normally tightly associated with the UT, separating adjacent Foxd1+ interstitial progenitors from the UT. In Wnt11 mutants, inter-niche boundaries become less distinct and Six2+ and Foxd1+ cells intermix. RNA-seq of whole kidneys revealed minimal transcriptional changes within NPs suggesting Wnt11 primarily regulates cell behavior, as expected for a non-canonical Wnt. Single cell analysis of NPs *in vivo* and live imaging of kidney organ cultures shows that NPs normally make extensive membranous contacts with UTs. Long membrane projections extend to the UT from NPs that form layers above the UT. In contrast, NPs in Wnt11 mutants fail to exhibit elongated UT-directed membrane extensions. Wnts signal through Frizzled (Fzd) receptors: Fzd2 and Fzd7 are co-expressed within NPs. Fzd2-/-;Fzd7-/+ mutants display a similar disorganization of the NPs, suggesting these two receptors likely mediate the non-canonical Wnt11 response. Quantitative analyses of the Wnt11 phenotype revealed a 30% reduction in UTs and 20% reduction in kidney size by E15.5. At birth, UT numbers were further reduced by 40% and mutant kidneys were 38% smaller. Further, NP niches were significantly depleted and prematurely lost. As a consequence, adult nephron number was reduced by 50%.

Conclusions: Taken together, these data highlight the importance of non-canonical Wnt11 signals in maintaining NP behavior, and appropriate stratification and organization of distinct mesenchymal progenitor compartments in the UT niche, a prerequisite for generating a normal nephron complement in the developing mammalian kidney.

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FR-OR089

Bim Gene Dosage Is Critical in Modulating Nephron Progenitor Survival in the Absence of Dicer Activity During Kidney Development Deborah Malta Cerqueira, Andrew J. Bodnar, Yu Leng Phua, Kenneth A. Walker, Jacqueline Ho. *Dept of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, PA.*

Background: We have previously demonstrated that conditional depletion of the miRNA-processing enzyme, Dicer, in nephron progenitors results in increased apoptosis and premature depletion of this cell population during kidney development. This is accompanied by increased expression of the pro-apoptotic protein, Bim.

Methods: To determine the functional significance of increased Bim, we generated a mouse model with depletion of both *Dicer* and *Bim* from nephron progenitors in the developing kidney. To this end, *Six2-TGC^{flg/+}; Dicer^{flx/flx}* mice were crossed with a conditionally floxed *Bim* allele generating the following genotypes: *Six2-TGC^{flg/+}; Bim^{flx/+}*; *Dicer^{flx/+}* (control), *Six2-TGC^{flg/+}; Dicer^{flx/flx}; Bim^{flx/+}* (mutant), *Six2-TGC^{flg/+}; Dicer^{flx/flx}; Bim^{flx/flx}* (heterozygous rescue) and *Six2-TGC^{flg/+}; Dicer^{flx/flx}; Bim^{flx/flx}* (homozygous rescue).

Results: The depletion of *Bim* partially restored the number of nephron progenitors and improved nephron formation in *Dicer*-deficient kidneys. At the molecular level, the expression of the most abundant isoform of Bim (Bim_{EL}) was increased, while the levels of the pro-survival protein Bcl-2 were reduced in mutant compared to control kidneys. In contrast, the loss of *Bim* restored Bcl-2 expression and reduced Bim_{EL} levels in a dose-dependent manner in the homozygous and heterozygous rescue kidneys. Finally, we analyzed the survival and proliferation of nephron progenitors. The loss of *Bim* decreased apoptosis of nephron progenitors in kidneys that were *Dicer*-deficient in the progenitors, with no significant effect on cell proliferation.

Conclusions: Together these data provide evidence for a model in which miRNA-mediated regulation of Bim controls the balance between apoptosis and survival during nephrogenesis, as one potential means of regulating nephron number.

Funding: NIDDK Support

FR-OR090

DGCR8-Dependent MicroRNA Biogenesis Is Essential to the Function of Pax8-Positive Epithelial Organs Roman-Ulrich Mueller,¹ Malte P. Bartram,¹ Elena Amendola,² Gabriella De vita,² Bernhard Schermer,¹ Thomas Benzing.¹ ¹Dept II of Internal Medicine and Center for Molecular Medicine, Univ Hospital Cologne, Cologne, Germany; ²Dipartimento di Biologia e Patologia Cellulare e Molecolare, Univ degli Studi di Napoli 'Federico II', Naples, Italy.

Background: MiRNAs are small regulatory RNA molecules that have been shown to play an important role in physiology, development and disease of many organs. As to most organs our knowledge on the role of miRNAs depends on the use of Dicer-knockout models with this enzyme being a key component of the miRNA biogenesis machinery. However, Dicer has been shown to fulfill a number of other functions beyond the maturation of miRNAs. Furthermore a number of these small RNAs does not depend on Dicer in

its maturation. Consequently, the phenotypes observed might well be due to miRNA-independent functions of Dicer. For most organs examined - including renal disease models - we still lack confirmation that the phenotype observed is truly due to miRNA deficiency.

Methods: We examined mice harboring a conditional knockout allele of Dgcr8. Dgcr8 - together with its interaction Partner Drosha - is essential to the nuclear steps of miRNA biogenesis. This mouse line was crossed to a Pax8Cre line to examine and confirm the role of miRNAs in Pax8-positive epithelial organs.

Results: The knockout mice develop a cystic kidney disease and hydronephrosis. End-stage renal disease occurs by the age of 4-8 weeks. On the cellular level this phenotype is accompanied by a strong increase in both cellular proliferation and apoptosis. Furthermore severe hypoplasia of the thyroid gland and consecutive hypothyroidism were observed. The hypoplasia does not appear to depend on a block in differentiation but may rather be due to impaired cell polarization.

Conclusions: This study shows the importance of DGCR8-dependent miRNA biogenesis for both renal and thyroid function and can thus be the basis to future experiments addressing the role of specific miRNA sequences. Nonetheless, some aspects of the phenotype differ from the Dicer knockout model pointing towards miRNA-independent contributions of Dicer and Dgcr8 regarding the pathogenesis of these two organs in our mouse model.

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FR-OR091

Oxygenation and Von Hippel-Lindau Regulate Nephron Progenitor Differentiation Elina Mukherjee, Jacqueline Ho, Sunder Sims-Lucas. *Univ of Pittsburgh, Pittsburgh, PA.*

Background: During development, oxygenation plays a crucial role in kidney formation. Nephron progenitor (NP) differentiation is highly dependent on appropriate vascularization and subsequently oxygen concentration. Alterations in nephron differentiation lead to kidney malformations. The underfused NP are hypoxic, which activates the hypoxia inducible factors (HIFs). The HIF genes are potent factors involved in tissue differentiation. Upon oxygenation the Von Hippel-Lindau gene (VHL), degrades the HIFs and allows for tissue differentiation. We previously showed *in vitro* that oxygenation drives NP differentiation. Thus, we hypothesize that stabilization of HIFs in the NP will cause congenital kidney defects.

Methods: To determine the role of VHL in the NP we utilized VHL floxed mice bred with the *Six2EGFPcre* line, to generate *Six2creVHL^{lox/lox}* mutant mice. We performed a thorough histological assessment from early kidney development through to post natal ages. We coupled this with immunofluorescence (IF) of the various kidney compartments as well as immunohistochemistry (IHC) and western blot analysis to analyze VHL and HIF expression.

Results: Histology revealed that *Six2creVHL^{lox/lox}* mutant mice were underdeveloped from E15.5, with fewer differentiated NP derived structures. Postnatal mutant kidneys displayed significant pathology containing fewer nephrons, cystic tubules and proteinaceous casts. The mutant kidneys contained fewer proximal tubules, and remaining tubules were dilated. The mutant animals failed to thrive and were significantly smaller at weaning. IHC staining revealed a down regulation of VHL in the mutants coupled with an up regulation of HIF1a in the NP, which was confirmed via western blot analysis. IF staining of mutant embryonic kidneys showed a delay in NP differentiation with ectopic *Six2* remaining highly expressed in NCAM positive epithelialized structures of mutants.

Conclusions: In conclusion, VHL is critical in the NP to regulate the expression of HIFs. Inappropriate up regulation of HIFs causes alterations in NP differentiation, leading to kidney malformations.

FR-OR092

Interplay Between the Tbx2 Transcription Factors and Notch Signaling Directs Nephron Segmentation Bridgette Drummond, Yue Li, Amanda N. Marra, Christina N. Cheng, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: Nephron segment patterning remains an enigmatic process. The conservation of nephron segments across vertebrates enables insights through work with animal models, and among these the zebrafish provides a simple system for developmental genetic studies of nephrogenesis. Zebrafish nephrons contain proximal and distal tubule segments, and endocrine cells called the corpuscle of Stannius (CS) also arise from the intermediate mesoderm (IM) and are situated between the distal nephron segments.

Methods: Here, we show that the *T-box 2a/b* (*tbx2a/b*) orthologs are spatially restricted to the distal IM. *tbx2a* and *tbx2b* single and doubly deficient embryos, as well as *tbx2b^{hyp}* mutants, exhibited a modest expansion in the proximal segments accompanied by a reduction in the distal nephron, indicating that these genes have redundant roles in segment patterning.

Results: Abrogation of *tbx2a/b* expression was also associated with significantly expanded CS structures, coincident with increased expression of *sim1a*, a transcription factor that was recently demonstrated to be necessary and sufficient for CS formation. Further, we identified expression of the Notch pathway component *her9* in the developing CS. In exploring the link between *tbx2* genes and Notch, DAPT treatment was found to cause a moderate CS expansion in wildtypes, while DAPT induced further enlarged CS clusters in *tbx2* deficient embryos. Ectopic activation of Notch signaling in *Tg(hsp70::Gal4; UAS::NICD)* led to a reduced CS in wildtypes but not *tbx2* deficient embryos, suggesting the *tbx2* genes function downstream of Notch to inhibit the CS. In addition, ectopic Notch expanded proximal tubule segments at the expense of distal, reducing *tbx2* expression domains and therefore suggesting that Notch promotes proximal segments in part by inhibiting *tbx2* expression.

Conclusions: Taken together, these data suggest a model in which Tbx2a/b are essential for patterning of the distal IM from which the distal nephron segments and CS arise, and thus provide novel insights into the regulatory networks that influence renal ontogeny.

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FR-OR093

Dot1l Deficiency Leads to Increased Intercalated Cells and Up-Regulation of V-ATPase B1 in Mice Zhou Xiao,¹ Lihe Chen,² Qiaoling Zhou,¹ Wenzheng Zhang,³ ¹Internal Medicine, Xiangya Hospital, Central South Univ, Changsha, Hunan, China; ²Graduate School of Biological Sciences, Univ of Texas Health Science Center at Houston, Houston, TX; ³Internal Medicine, Univ of Texas Medical School at Houston, Houston, TX.

Background: The collecting duct in the mammalian kidney consists of principal cells (PCs) and intercalated cells (ICs), which regulate electrolyte/fluid and acid/base balance, respectively. The epigenetic regulators of PC and IC differentiation remain obscure. Using Aqp2 and V-ATPase B1B2 to label PCs and ICs, respectively, we previously reported that mice with histone H3 K79 methyltransferase *Dot1l* disrupted in Aqp2-expressing cells (*Dot1l^{ΔC}*) vs. *Dot1l^{fl/fl}* possessed ~20% more ICs and a similar decrease in PCs.

Methods: In this study, we performed multiple double immunofluorescence staining using various PC and IC markers to assess the relative abundance of PC and IC in *Dot1l^{ΔC}* and *Dot1l^{fl/fl}*. Real-time RT-qPCR, luciferase assay, and chromatin immunoprecipitation assays were conducted to determine if Dot1l regulates the transcription of *Atp6v1b1* in vivo in mouse kidney and in vitro in IMCD3 cells.

Results: *Dot1l^{ΔC}* vs. *Dot1l^{fl/fl}* had more IC and less PC, with expanded both a-IC and b-IC populations. These changes were associated with significantly upregulated V-ATPase B1 and B2, but not Aqp2, AE1, and Pendrin. Decreased V-ATPase B1 mRNA expression was coupled with a significant reduction of Dot1l and H3K79 di-methylation bound at the *Atp6v1b1* 5' flanking region. Overexpression of WT Dot1a, but not the methyltransferase-dead mutant Dot1a significantly downregulated a stably-transfected luciferase reporter driven by the *Atp6v1b1* promoter in IMCD3 cells.

Conclusions: Dot1l is a new epigenetic regulator of PC and IC differentiation and *Atp6v1b1* is a new transcriptional target of Dot1l.

Funding: NIDDK Support

FR-OR094

DNp63 Progenitor Cells Pattern the Ureteric Bud Stem Cell Niche and Give Rise to β-Intercalated Cells Yuwen Li, Jiao Liu, Altaf-M Khan, Zubaida R. Saifudeen, Samir S. El-Dahr. *Pediatrics, Tulane Univ School of Medicine, New Orleans, LA.*

Background: 1. Ureteric Bud (UB) tip cells constitute a stem/progenitor cell niche with bipotential properties enabling them to self-renew or differentiate, giving rise to all cell types in the collecting duct. Understanding how the UB tip cell commits to the Principal Cell (PC) or Intercalated Cell (IC) fate is essential for the design of strategies to re-build a kidney from stem cells and for hastening epithelial cell regeneration after injury. 2. The N-terminus-truncated p63 isoform, DNp63, is a master transcriptional regulator of epithelial stem cells in skin. 3. Here, we document expression of DNp63 in the UB tip and assess the progenitor cell identity, fate and regenerative potential of DNp63 cells.

Methods: 1. Ret-GFP¹⁸ mice were used to demonstrate expression of DNp63 in Ret tip cells. 2. DNp63^{GFP/+} knockin mice were used to define the spatiotemporal pattern of DNp63. 3. DNp63^{Cre};Rosa26^{mT/mG} or EYFP mice were used to trace the fate of DNp63 cells from embryonic to adult life. 4. DNp63^{GFP/GFP} mice were used to define the effect of DNp63 deletion on UB tip cell differentiation. 5. Adult DNp63^{Cre};Rosa26^{tdTomato} were subjected to unilateral ureteral obstruction (UUO) for 7 days to determine the response of fate-restricted DNp63 cells to injury. Cell proliferation was determined by BrdU incorporation.

Results: 1. DNp63 expression is restricted to cell clusters in UB tip until PN day 5 when expression is permanently silenced. 2. *In vivo* lineage analysis identified DNp63 as a marker of UB progenitor cells dedicated to generating H-ATPase/Pendrin⁺ cells in cortical nephrons. 3. A fraction of cortical H-ATPase/AE1⁺ cells are also DNp63-lineage⁺, supporting the notion that at least some cortical α-IC are derived from β-IC. 4. DNp63^{null} UB tip cells are maintained. In contrast, progeny of DNp63^{null} collecting duct cells lack H⁺-ATPase/carbonic anhydrase II. 5. In response to UUO, DNp63-lineage⁺ cells proliferate and contribute to collecting duct cells expressing PC and IC markers.

Conclusions: 1. UB tip DNp63 cells are unipotent progenitors of β-ICs. 2. In response to injury, fate-restricted DNp63 lineage cells regenerate damaged collecting ducts.

Funding: NIDDK Support

FR-OR095

Critical Role of Talin in Cell-Cell Adhesion and Kidney Development Sijo Mathew,^{1,4} Riya Jose Palamuttam,¹ Glenda Mernaugh,¹ Ambra Pozzi,^{1,2} Charles R. Sanders,^{3,4} Roy Zent.^{1,2} ¹Div of Nephrology and Hypertension, Dept of Medicine, Vanderbilt Univ Medical Center, Nashville, TN; ²Veteran Affairs Hospital Nashville, Nashville, TN; ³Dept Biochemistry, Vanderbilt Univ Medical Center, Nashville, TN; ⁴Center for Structure Biology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Interactions between cells and basement membranes are required for normal kidney development and function. These interactions are primarily mediated by the major cell surface adhesion receptor proteins integrins. Integrins are composed by α and β subunits and have two important functions: ligand binding and regulation of the

cytoskeleton. The cytoskeletal protein, talin, is a key regulator of integrin function. Talin has two isoforms talin 1 and 2. Both talins isoforms bind to the membrane proximal NPXY motif of integrin b1 cytoplasmic tail. Talin binding is proposed to promote integrin activation and link integrins to the actin cytoskeleton.

Results: In this study we investigated the role of talin in kidney development by generating mice lacking both isoforms in the developing ureteric bud. These mice die immediately after birth due to renal agenesis. Talin-null collecting ducts cells showed a severe adhesion defect on ECM proteins and were unable to undergo tubule formation in collagen matrigel matrix. In addition they had altered expression of cell-cell adhesion proteins claudin and E-cadherin. To better define the role of talin binding to the integrin b1 cytoplasmic tail in the collecting system development, we generated mice expressing a Y-to-A mutation in the membrane proximal NPXY motif of integrin b1 tail. Surprisingly, these mice only had a moderate developmental phenotype, characterized by a hypoplastic and dysplastic collecting system. Near complete abolition of talin binding with integrin b1 was observed in the mutant when *in vitro* binding was studied using NMR spectroscopy in isotropic bicelles.

Conclusions: Thus, we conclude that talin is essential for ureteric bud development and that some of its most important effects are likely mediated by integrin-independent processes.

Funding: NIDDK Support, Veterans Administration Support

FR-OR096

Loss of Frs2α in Peri-Wolffian Duct Stroma Leads to Abnormal Ureteric Bud Induction and Vesicoureteral Reflux Deepthi Narla,¹ Kenneth A. Walker,¹ Stacey B. Slagle,² Caitlin M. Schaefer,¹ Carlton M. Bates.¹ ¹Div of Nephrology, Univ of Pittsburgh; ²Div of Neonatal Medicine, Univ of Pittsburgh School of Medicine, PA.

Background: Deletion of fibroblast growth factor receptor 2 (Fgfr2) from peri-Wolffian duct stroma (ST) in mice results in aberrant ureteric bud induction, abnormal ureteral insertion into the bladder, and high rates of vesicoureteral reflux (VUR). It is unclear which receptor docking protein(s) is/are responsible for these actions of Fgfr2. Thus, we investigated whether the Fgfr docking protein, fibroblast receptor substrate 2α (Frs2α), had roles in peri-Wolffian duct stroma similar to Fgfr2.

Methods: We conditionally deleted *Frs2α* in per-Wolffian duct stroma with a *Tbx18cre* mouse line (*Frs2α^{ST/-}*). We assessed embryos for ureteric induction defects and for alterations in candidate downstream targets mediating induction defects. We assessed postnatal mice for VUR with euthanized cystograms and ureter insertions into the bladder via three dimensional (3D) reconstruction.

Results: Embryonic day (E) 11.5 *Frs2α^{ST/-}* embryos exhibit nearly random ureteric bud induction sites (several cranially or caudally displaced sites along the Wolffian duct) versus controls; moreover, apoptosis and proliferation rates were unchanged in *Frs2α^{ST/-}* Wolffian duct segments between the ureteric bud base and cloaca (common nephric ducts) versus control littermates. E11.5 *Frs2α^{ST/-}* embryos had significant decreased Bmp4 mRNA stromal expression, which is known to cause abnormal ureteric bud induction. Postnatal day 1 (P1) and P30 *Frs2α^{ST/-}* mice had significantly higher rates (worsening with age) and grades of VUR versus age-matched controls. Refluxing ureters in *Frs2α^{ST/-}* mice had improper ureteral insertion locations into the bladder and significantly shortened intravesicular tunnel lengths versus controls.

Conclusions: Deletion of *Frs2α* in peri-Wolffian duct stroma leads to aberrant ureteric induction sites resulting in improper ureteral insertion and shortened intravesicular length and lifelong VUR. Mechanistically, the induction site defects appear secondary to decreased Bmp4 expression in mutant stroma. Finally, it is likely that Frs2α mediates Fgfr2 signaling in peri-Wolffian duct stroma.

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FR-OR097

HCN3 Positive Urinary Pacemaker Cells Arise from the Neural Crest Norman D. Rosenblum,^{1,2,3} Meghan M. Feeney.^{1,2} ¹Dev and Stem Cell Biology, Hosp Sick Children; ²Dept Lab Medicine and Pathobiology, U Toronto; ³Div Nephrology, Dept Paediatrics, Hosp Sick Children, Toronto, Canada.

Background: Coordinated proximal to distal ureteric peristalsis is mediated by HCN3(+) pacemaker cells (PMCs) in the pelvis-kidney junction (PKJ). Perturbations in HCN3 expression and function are associated with congenital hydronephrosis and loss of Hedgehog signaling in mice. Yet, identification of the specific perturbations in PMC function has been precluded by lack of knowledge of how PMCs develop. The objective of this study is to determine the developmental lineage of HCN3(+) PMCs and identify a molecular signature of these cells during development.

Methods: To determine the lineage of origin of the HCN3(+) PMCs, we genetically labeled five distinct lineages of the urogenital system via Cre-mediated expression of ROSA-tdTomato (tdTom) fluorescent protein and analyzed for co-localization with HCN3, using antibodies, in mouse embryonic kidney tissue. To investigate the molecular signature of the PMCs, HCN3(+) cells were isolated using HCN3 antibodies and fluorescence activated cell sorting (FACS). RNA was prepared from sorted samples and gene expression was analyzed in isolated HCN3(+) PMCs via qRT-PCR and genome-wide RNA sequencing.

Results: TdTom expressed downstream of promoters specific for metanephric or tailbud mesenchyme, ureteric bud or renal stroma failed to co-localize with HCN3-marked PMCs. In contrast, tdTom, expressed downstream of the neural crest (NC) specific Wnt1 promoter, co-localized with HCN3 in the PKJ, demonstrating that HCN3(+) PMCs arise from the NC. HCN3(+) PMCs were FACS isolated from mouse embryonic kidneys with >94% purity and >8,000 HCN3(+) cells were collected per litter. Genetic analysis of HCN3(+) PMCs via qRT-PCR demonstrated enrichment of both Hcn3 and Sox10, a NC marker,

further outlining the NC origin of these cells. Analysis of isolated PMCs, compared to adjacent cells in the PKJ, via RNA sequencing, revealed a 3-7-fold upregulation of genes associated with neuronal function.

Conclusions: We conclude that HCN3(+) urinary PMCs arise from the NC and express genes associated with neuronal function. These results provide a basis to identify molecular mechanisms that control PMC development.

Funding: Government Support - Non-U.S.

FR-OR098

Sox9 Activation Highlights a Cellular Pathway of Renal Repair in the Acutely Injured Mammalian Kidney Sanjeev Kumar,¹ Jing Liu,¹ Paul D. Pang,¹ A. Michaela Krautzberger,¹ Antoine Reginensi,² Jill A. McMahon,¹ Andreas Schedl,² Benjamin D. Humphreys,³ Andrew P. McMahon.¹ ¹Dept of Stem Cell Biology and Regenerative Medicine, Univ of Southern California, Los Angeles, CA; ²Centre de Biochimie, Univ de Nice-Sophia Antipolis, Nice, France; ³Renal Div, Brigham and Women's Hospital, Boston.

Background: Surviving tubular epithelial cells repair the epithelium after acute kidney injury (AKI), but the molecular driver of such a reparative response is not known.

Methods: Mice and injury models: *Sox9^{ires-CreERT2/+}, R26^{R^{tdTomato}/tdTomato}, Slc34a1^{CreERT2/+}, TCF/Lef:H2B-GFP* mice, *Sox9^{9^{fl}/fl}* and *Pax2Cre:Sox8/9* double knock-out mutants mice. AKI was induced via renal ischemia reperfusion injury and unilateral ureteral obstruction. **Lineage tracing:** for induction of CreERT2 protein, mice were injected with low and high-dose tamoxifen pre- and post-ischemic AKI, and during nephrogenesis. **Immunofluorescence, histology, in situ hybridization, confocal microscopy, nephron microdissection. RNA-sequencing and Fluidigm PCR** based quantification of transcript levels in the kidney.

Results: We identify Sox9 as an acute epithelial stress response that drives epithelial regeneration after injury. Translating ribosome affinity purification of mRNAs from nephron compartment revealed *Sox9* as one of the most upregulated transcription factors early after injury. Sox9+ cells demarcated injured, proliferating proximal tubular epithelial (PTE) cells early after ischemic and obstructive AKI. Sox9-descendent cells regenerate a functional PT epithelium and PT-specific pre-injury deletion of *Sox9* impairs renal function recovery and PT repair with increased fibrosis. Four weeks after injury, persistent Sox9 expression demarcates injured PTE cells with unresolved injury-repair responses. During nephrogenesis, Sox9-descendent cells give rise to nearly the entire epithelial component of the nephron, including PT, and removal of *Sox9* activity in Sox8/9 conditional mutant mice resulted in striking deficiency of the nephron epithelia.

Conclusions: These findings provide a direct, intrinsic molecular link between regeneration of an injured tubular epithelium and its formation during development.

FR-OR099

AKI Up-Regulates the Transcriptional Activator Etv4 Specifically in Dedifferentiated Proximal Tubule Where It Drives Epithelial Cell Proliferation and Migration Susanne V. Fleig,¹ Fengfeng Xu,¹ Flavia G. Machado,¹ Chia-Chun Wu,¹ Rafael Kramann,¹ Motoko Yanagita,² Benjamin D. Humphreys.¹ ¹Brigham and Women's Hospital, Boston; ²Kyoto Univ, Japan.

Background: The transcriptional activator *etv4* is required during nephrogenesis but roles in adult kidney are undefined. Proximal tubule repair after AKI occurs by dedifferentiation, but the transcriptional circuitry regulating this process is unknown. We characterized the expression pattern and function of *Etv4* in repair after AKI.

Methods: For in vitro studies, we used lentiviral transduction of RPTEC for *ETV4* overexpression or inhibition with a dominant-negative *Etv4* (DN-*Etv4*) cDNA. We used an *Etv4*-nLacZ reporter strain to localize expression, and also generated a novel genetic mouse model for tamoxifen-dependent expression of DN-*Etv4* specifically in full proximal tubule (*NDRG1-CreERT2;R26-LoxP-DN-Etv4*). These mice and cre-negative littermate controls were subject to severe bilateral ischemia/reperfusion surgery.

Results: Cultured RPTEC express *Etv4* but DN-*Etv4* transduction strongly inhibited proliferation ($9.44 \pm 3.44\%$ KI67+ cells vs. $57.38 \pm 6.63\%$ in control, $p < 0.001$). By contrast, *Etv4* overexpression increased proliferation after starvation ($67.14 \pm 8.93\%$ vs. $34.75 \pm 18.03\%$ KI67+ cells, $p < 0.05$). In a wound healing assay, *Etv4* inhibition reduced migration and increased RPTEC apoptosis while *etv4* overexpression increased migration. *Etv4*-nLacZ reporter mice showed almost no expression in healthy kidney, but after IRI, *Etv4* was specifically expressed in dedifferentiated proximal tubule cells (Kim-1+, KI67+). In moderate or severe IRI timecourse, *Etv4* mRNA was strongly upregulated with a 72h maximum at 30- and 70-fold over baseline. Mice with PT-specific expression of DN-*Etv4* showed increased tubular damage at 72h post-IRI compared to controls (Kim1 mRNA 2x, Kim1 protein expression 4x higher, $p < 0.01$) with reduced tubular epithelial proliferation ($14.2 \pm 9\%$ vs. $32.9 \pm 2.8\%$ KI67+ tubule cells, $p < 0.05$).

Conclusions: *Etv4* is specifically induced in dedifferentiated proximal tubule epithelia after AKI. It is a novel positive regulator of epithelial cell proliferation and migration during kidney repair after AKI.

Funding: NIDDK Support

FR-OR100

Tubular Regeneration After Acute Kidney Injury Is Limited and Only Driven by Tubular Progenitors Elena Lazzari, Anna Julie Peired, Maria Lucia Angelotti, Francesca Becherucci, Duccio Lombardi, Laura Lasagni, Paola Romagnani. Excellence Centre DENOTHE, Univ of Florence, Italy.

Background: Traditionally, AKI was considered as reversible because of the high regenerative capacity of the tubule. Despite this, AKI is associated with increased risk to develop CKD, suggesting an incomplete repair of the tubules. In addition, it is debated whether regeneration is mediated by differentiated tubular cells or a population of tubular progenitors.

Methods: We developed inducible transgenic Pax8-rtTA/tetO-cre/ROSA26-Confetti (Pax8/Confetti) mice to track all tubular cells and the PAX2.rTA;tetO.cre;R26.Confetti mouse model (Pax2/Confetti) to track putative tubular progenitors. Administration of doxycycline at the 5th week of age drove the stochastic expression at single cell level of CFP, GFP, RFP, YFP, allowing to track Pax2+ or Pax8+ cells and their progeny. After 1 week of washout, mice underwent 30 min of unilateral ischemia followed by a 30 day reperfusion period. Inducible PAX8.rTA;tetO.cre;R26.Fucci2 (Pax8/Fucci2) and PAX2.rTA;tetO.cre;R26.Fucci2 (Pax2/Fucci2) mouse models were used to study cell-cycle (mCherry in G1 cells and mVenus in S/G2/M cells).

Results: Comparison of clonal analysis in confetti mice demonstrated that Pax2+ progenitors is the only population that undergoes clonal expansion after tubular injury, excluding involvement of other tubular cells. However, regeneration was limited, and the majority of lost tubular cells was not replaced. In addition, confocal microscopy and DNA content analysis by flow cytometry in Pax8 and Pax2/Fucci2 mouse models demonstrated that only Pax2+ progenitors complete mitosis, while other tubular cells that entered the cell cycle do not complete cytokinesis and undergo death or growth arrest.

Conclusions: In summary: 1. The tubule displays limited regenerative capacity; 2. Differentiated tubular cells enter the cycle but do not complete mitosis; 3. Only tubular progenitors undergo a complete cell division providing regeneration after injury. Taken together, these results provide an innovative explanation of the mechanisms of tubular repair and a suggestive hypothesis to explain the occurrence of CKD after AKI.

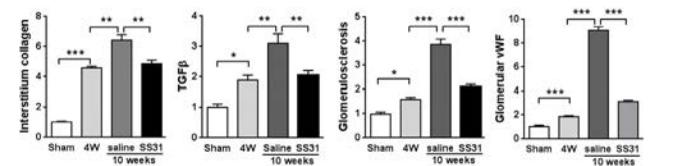
FR-OR101

Mitochondria-Targeting Peptide (SS-31, Bendavia®) Prevents Progression of Chronic Kidney Injury After Acute Ischemia Hazel H. Szeto, Shaoyi Liu, Yi Soong, Surya V. Seshan. Pharmacology and Pathology, Weill Cornell Medical College, New York, NY.

Background: It has been estimated that about 15% of patients who survive acute kidney injury (AKI) will advance to chronic kidney disease (CKD) characterized by tubulointerstitial fibrosis and glomerulosclerosis. We recently reported that mitochondria protection by SS-31 during ischemia mitigates microvascular rarefaction, inflammation and fibrosis (Am J Physiol 306:F970-F980, 2014). Here we report that delayed treatment with SS-31 can halt the progression of CKD.

Methods: Sprague-Dawley rats (n=40) were subjected to bilateral renal ischemia for 45 min followed by 4 weeks of reperfusion. Surviving animals (n=27) were then randomized to SS-31 (2 mg/kg/day) or saline by osmotic pump for 6 weeks. Kidneys were harvested for histopathology. Sham animals did not undergo ischemia.

Results: Despite recovery of renal function within 1 week after ischemia, pronounced tubular dilation, interstitial inflammation, glomerulosclerosis, and tubulointerstitial fibrosis was seen at 4 weeks. Further increase in inflammation and fibrosis, accompanied by increase in TGFβ and TNFα, were observed by 10 weeks in saline-treated rats. Pronounced changes were observed in glomeruli, with extensive fibrosis and peri-glomerular infiltration of inflammatory cells. Glomerular endothelial injury is suggested by the large increase in vWF expression. Electron microscopy revealed stressed vacuoles in podocytes and flattened foot processes. Rats that were treated with SS-31 from 4 weeks did not show any progression of glomerular or tubular injury, and prevented the upregulation of TGFβ and TNFα.



Conclusions: These results show that SS-31 can halt the progression of chronic kidney disease even when administered 4 weeks after the acute ischemic injury. SS-31 (Bendavia®) represents a novel paradigm for the treatment of CKD beyond approaches targeted at TGFβ.

Funding: Private Foundation Support

FR-OR102

Early Activation of Fibroblasts Is Required for Renal Protection and Regeneration After Acute Kidney Injury Dong Zhou,¹ Haiyan Fu,¹ Roderick J. Tan,² Youhua Liu.¹ ¹Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; ²Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Acute kidney injury (AKI) is responsible for about 2 million deaths each year worldwide, and its incidence is rising. While the role of vascular, tubular and inflammatory injury in the pathogenesis of AKI is well established, whether interstitial fibroblasts play any role in this process is poorly characterized.

Methods: To address this issue, we established moderate (20 min) and severe (30 min) renal ischemia/reperfusion injury (IRI) models. Sonic hedgehog (Shh) signaling was inhibited by cyclopamine. Conditional knockout mice in which Shh was ablated in tubular epithelial cells were generated and mice were subjected to IRI.

Results: In both moderate and severe IRI, interstitial fibroblasts became activated, as illustrated by vimentin expression, as early as 1 hour after AKI. Fibroblast proliferation as assessed by Ki67 staining was detected in renal interstitium at 4 hours and reached the peak at 12 hours. This early activation of fibroblasts was mediated by Shh signaling, as Shh protein was rapidly induced at 1 hour after IRI and Shh induced fibroblast activation and proliferation *in vivo*. To investigate the role of tubule-derived Shh in mediating fibroblast activation and injury repair, we generated tubule-specific Shh conditional knockout mice (Ksp-Shh^{-/-}) by mating Shh-floxed mice with Ksp-Cre mice. Mice with ablation of Shh in renal tubules exhibited normal phenotype under physiologic conditions, but displayed an increased level of serum creatinine and morphological injury at 1 day after IRI, compared with controls. This aggravated AKI in Ksp-Shh^{-/-} mice was associated with a decreased vimentin and desmin expression, suggesting a beneficial role of fibroblast activation in this setting. Similarly, pharmacological blockade of Shh signaling by cyclopamine also aggravated serum creatinine and histological damages through inhibiting fibroblasts proliferation.

Conclusions: These studies suggest that fibroblast activation is an early event mediated by Shh signaling and plays an essential role in conferring reno-protection and injury repair in the setting of AKI.

Funding: NIDDK Support

FR-OR103

Endothelial Sphingosine 1-Phosphate Receptor 1 (S1P1) Is Necessary for Recovery from Ischemia-Reperfusion Injury (IRI) and Prevention of Fibrosis Heather M. Perry,¹ Amandeep Bajwa,¹ Liping Huang,¹ Hong Ye,¹ Kevin Lynch,² Mark D. Okusa.² ¹Medicine, UVA, Charlottesville, VA; ²Pharmacology, UVA.

Background: Progression to fibrosis after AKI may result from maladaptive repair processes and can potentiate kidney dysfunction. The endothelium is the keystone of vascular homeostasis and vascular insufficiency after AKI may result in progressive fibrosis. S1P1, a G-protein coupled receptor, is important for endothelial function and we hypothesize that endothelial cell (EC) S1P1 is necessary for recovery from AKI and prevention of fibrosis.

Methods: Tamoxifen inducible, EC specific, S1P1 knockout mice (iTe2CreERT2S1pr^{fl/wt}; S1P1 ECKO) or control (iTe2CreERT2S1pr^{wt/wt}) mice were subject to unilateral IRI or sham operation for 24' and mice were allowed to recover for 3 days. Tamoxifen was then administered i.p. daily for 5d followed by a nephrectomy of the un-operated kidney and mice were euthanized on day 9. Plasma was collected for creatinine (PCr) measurement and kidneys were prepared for histology to assess renal injury, fibrosis by picro-sirius red, detection of aSMA+PDGFRβ+ myofibroblasts by IF, and neutrophils and macrophages by flow cytometry. Total kidney tissue mRNA was measured by RT-qPCR.

Results: S1P1 ECKO mice had higher PCr levels compared to control mice (1.24 vs. 0.38 mg/dL; p < 0.001 n = 5-6) on day 9 post IRI. S1P1 ECKO mice had increased tubular atrophy, a higher proportion of fibrotic area in the medulla and cortex (1.57 vs. 0.68 %; p < 0.05 n = 4-5), and increased density of interstitial myofibroblasts expressing COL1 and COL3 in IRI kidneys compared to controls. Leukocyte adhesion molecules Pecam-1, Icam1, E-selectin, and Vcam1 expression and the number of neutrophils and Ly6Clo macrophages were increased in IRI kidneys of S1P1 ECKO mice compared to control mice.

Conclusions: During recovery from IRI, S1P1 suppresses endothelial cell activation of leukocyte adhesion molecules and subsequent inflammation to prevent maladaptive repair and tubular atrophy in protection against fibrosis. This data suggests that pharmacological activation of EC S1P1 as a novel therapeutic strategy for preserving EC function during a critical period of recovery after AKI may prevent the progression to fibrosis.

Funding: NIDDK Support

FR-OR104

IL-4/13-Mediated Polarization and Proliferation of Renal Macrophages Are Essential for Recovery from Acute Kidney Injury Bing Yao, Yinqiu Wang, Ming-Zhi Zhang, Raymond C. Harris. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Cytokines IL-4 and IL-13 play important roles in polarization of macrophages/dendritic cells to an M2 phenotype, which is important in the recovery process following acute kidney injury (AKI). Both IL-4 and IL-13 can activate JAK3/STAT6 signaling.

Methods: Mice with selective DTR expression in proximal tubule ("DTR mice") with or without IL-4 deletion were used for diphtheria toxin-induced AKI via a single DT injection. DTR mice with or without inducible deletion of both IL-4 and IL-13 (DTR:IL-4/13^{fl/fl} mice and DTR: UBC-Cre-ERT2: IL4/IL13^{fl/fl} mice, tamoxifen treatment 2 weeks before experiment) were also used. A selective JAK3 inhibitor, CP-690550, was given via mini-pump at a dose of 15 mg/kg/day.

Results: The effectiveness of CP-690550 was confirmed by decreased p-STAT6 levels 6 days after DT injection. JAK3 inhibition led to more severe kidney injury, delayed recovery from AKI and development of more severe renal fibrosis, in association with increased levels of M1 markers (iNOS and CCL3) and decreased levels of M2 markers (arginase-1 and CD206) in macrophages/dendritic cells. In DTR mice with inducible IL-4/13, both renal IL-4 and IL-13 levels were reduced after tamoxifen injection. Similar to JAK3 inhibition, with IL-4 and IL-13 deletion, macrophages/dendritic cells expressed increased M1 markers and decreased M2 markers. Although IL-4 deletion alone only led to moderately delayed recovery from AKI, deletion of both IL-4 and IL-13 led to more severe kidney injury and

delayed recovery, persistent kidney injury (increased KIM-1 expression), and development of more severe renal fibrosis (Sirius red and Masson's trichrome staining and increased expression of α-SMA and collagen I and IV).

Conclusions: These studies demonstrate that both IL-4 and IL-13 are required to effectively polarize macrophages/dendritic cells to an M2 phenotype and to promote recovery from acute kidney injury.

Funding: NIDDK Support

FR-OR105

Select ADAM17 Substrates Released from Proximal Tubular Cells Promote Progressive Fibrotic Kidney Disease Eirini Kefalogianni, Muthu lakshmi Muthu, Venkata Sabbiseti, Benjamin D. Humphreys, Joseph V. Bonventre, Andreas Herrlich. *Renal Div, Brigham and Women's Hospital, Boston, MA.*

Background: The metalloprotease ADAM17 activates epidermal-growth-factor (EGF) ligands, tumor-necrosis-factor-alpha (TNFα) and other substrates by ectodomain cleavage of their pro-forms. Sustained EGF receptor (EGFR) activation in tubular cells is linked to injury-induced kidney fibrosis. We showed previously that ADAM17 hypomorph mice and mice with inducible proximal tubular-ADAM17 deletion are strongly protected against ischemia-reperfusion-injury (IRI)-induced fibrosis. We hypothesized that ADAM17's role extends to other fibrotic kidney injuries and that only select ADAM17 substrates mediate its effect by sustaining EGFR activation and by potentiating its pro-fibrotic downstream effects.

Methods: We used ADAM17 hypomorph mice (A17^{ex/ex}) and SLC34a1-Cre-ERT2/ADAM17^{fl/fl} mice (ADAM17 PTC-KO). Mice were subjected to severe bilateral IRI and unilateral ureteral obstruction (UUO). Human AKI and CKD urine samples were tested by ELISA. ADAM17 substrates were studied in primary tubular cells and tubular cell lines *in vitro*.

Results: ADAM17^{ex/ex} and ADAM17 PTC-KO mice are also protected against UUO-induced fibrosis. This effect can be mimicked with a specific ADAM17 inhibitor which blocks its catalytic site (A17 pro-domain). Select EGF ligands are significantly upregulated by IRI and UUO in mice, and also in urine samples of AKI and CKD patients. These specific EGF ligands have particularly pro-fibrotic and pro-inflammatory effects in primary tubular cells by sustaining EGFR and downstream pathway activation, as compared to other pro-repair EGF ligands. *In vivo* knockdown of specific pro-fibrotic ADAM17 substrates in tubular cells protects against injury-induced fibrosis. Finally, we detect evidence of activation of ADAM17-dependent pathways in human kidney biopsies of AKI and CKD patients.

Conclusions: Specific proximal tubule released ADAM17 substrates promote sustained pro-fibrotic EGFR activation and progressive kidney disease in mice and possibly humans. Mechanistic differences of molecular action explain why certain EGF ligands are pro-fibrotic and others are pro-repair.

Funding: NIDDK Support

FR-OR106

Pericyte Ablation Leads to Acute Kidney Failure Dario R. Lemos,¹ Gabriela Campanholle,² Ivan G. Gomez,¹ Jeremy Stuart Duffield.¹ ¹Molecular Discovery, Biogen; ²Pfizer.

Background: Pericytes (PCs) are tissue-resident mesenchymal progenitor cells embedded within the basement membrane of blood vessels. We recently showed that during nephrogenesis pericytes are critical in both vascular and epithelial maturation and patterning. Those data indicate that PCs are important for the maintenance of kidney homeostasis postnatally.

Methods: Diphtheria toxin was delivered *in vivo*, via intraperitoneal injection. Kidneys were collected and preserved for histology. Urine albumin was measured using Albuwell M kit (Exocell Philadelphia, PA). Urine and plasma creatinine levels were measured using creatinine Liquid reagents Assay (DIAZYME, San Diego, CA). Plasma albumin was measured using an Olympus au640 Chemistry Analyzer. Gene expression was measured by Taqman PCR, using pre-made assays (Life Technologies, Palo Alto, CA).

Results: PDGFRβ+ pericytes present in the adult kidney derive from FoxD1+ mesenchymal progenitor cells. Here we created a FoxD1-Cre; Rs26-iDTR mouse to study the effect of pericyte ablation in kidney homeostasis. We observed virtually complete depletion of PDGFRβ+ cells in the kidney, compared to the control group, after two days of daily intraperitoneal diphtheria toxin (DT) delivery without detectable variations in podocyte numbers or glomerular capillary structure. Significant decrease in vascular density, increased vascular cell proliferation and endothelial swelling was detected. This was associated with aberrant vacuolization, lipid accumulation, and injury of the proximal tubules, indicative of epithelial cell dysfunction. These observations were supported by finding elevated levels of plasma creatinine, blood urine nitrogen and albuminuria, markers of organ failure. Mice lacking pericytes progressed to rapid health deterioration and death by three days. Importantly, neither the number of macrophages nor the levels of inflammatory cytokines changed significantly during the treatment, ruling out a role for inflammation-induced damage as the cause for progressive loss of kidney integrity.

Conclusions: Our data show that by supporting homeostasis, pericytes are essential for proper kidney function.

FR-OR107

Preferential Proliferation in Response to Injury by an Interstitial-Derived Collecting Duct Subpopulation Joan Li,¹ Jinjin Guo,⁵ Jill A. McMahon,² Andrew P. McMahon,² Melissa H. Little.^{1,3,4} ¹Univ of Queensland, Brisbane, QLD, Australia; ²Keck School of Medicine of the Univ of Southern California, Los Angeles, CA; ³Murdoch Childrens Research Inst, Melbourne, VIC, Australia; ⁴Univ of Melbourne, Melbourne, VIC, Australia; ⁵Univ of Southern California Keck School of Medicine, Los Angeles, CA.

Background: We have reported the incorporation of Wnt4-expressing interstitial cells into the developing collecting duct (CD) during early postnatal development. These cells, representing a distinct CD subpopulation, may play a specific role in CD repair.

Methods: Time-mated Wnt4^{GCE/+}; R26^{tdTomato/+} females received Tamoxifen injection (25mg/kg bw) at E17.5. Male offspring (8-12 wks) were subjected to Unilateral Ureteral Obstruction (UUO) for 3 or 7 days. Mice were euthanized 3 or 7 days after UUO. Kidneys were collected and processed for immunofluorescence studies. Confocal images were analyzed and quantified using Imaris software.

Results: At 7 days after UUO the cortical CD were severely dilated. This was accompanied by down-regulation and misdistribution of Aqp2 protein as well as up-regulation of Wnt4 expression. Flattening of the CD epithelial cells and up-regulation of aSMA expression suggested epithelial-to-mesenchymal transition (EMT). Tdtomato⁺ cells within the CD represent a subpopulation derived from the interstitial Wnt4-expressing cells present at E17.5. At 7 days after UUO the percentage of Tdtomato⁺ cells within the CD increased significantly compared to control (37% vs 14%, p= 0.00001), while pHH3 positivity was significantly higher in these cells at 7 days after UUO compared to control (4.6% vs 0.2%, p=0.03). The number of Tdtomato⁺ cells within the CD and the proliferation rate were not significantly different at 3 days after UUO compared to control.

Conclusions: In response to UUO damage, CD epithelium underwent EMT accompanied by up-regulation of Wnt4 expression. An interstitial-derived, Wnt4 expressing CD subpopulation showed preferential proliferation capacity compared to ureteric bud-derived CD epithelial cells. These observations support previous work suggesting the presence of possible stem/progenitor cells within this compartment and CD plasticity and imply a distinct repair mechanism from that documented for nephron epithelial cells.

FR-OR108

Net Acid Excretion and Progression of CKD: Results from the Chronic Renal Insufficiency Cohort Study Julia J. Scialla,¹ John R. Asplin,² Mirela A. Dobres,³ Alex R. Chang,⁴ James P. Lash,⁵ Chi-yuan Hsu,⁶ Radhakrishna Reddy Kallem,⁷ L. Lee Hamm,⁸ Harold I. Feldman,⁷ Jing Chen,⁸ Lawrence J. Appel,⁹ Cheryl A. Anderson,¹⁰ Myles S. Wolf.¹¹ ¹Duke Univ; ²Litholink Corp; ³Case Western Reserve; ⁴Geisinger Health System; ⁵Univ of Illinois Chicago; ⁶Univ of California San Francisco; ⁷Univ of Pennsylvania; ⁸Tulane Univ; ⁹Johns Hopkins Univ; ¹⁰Univ of California San Diego; ¹¹Northwestern Univ.

Background: Higher diet-dependent acid load has been associated with faster CKD progression, but not using gold-standard measurements [net acid excretion (NAE)].

Methods: We measured NAE in 24h urines from 1000 CKD participants as urinary ammonia + titratable acidity (calculated from urinary phosphorus, creatinine and pH). Urinary bicarbonate (HCO₃) was negligible. 19 samples with urine pH ≥7.4 were excluded. Urinary biomarkers (UUN and K) were used to calculate net endogenous acid production (NEAP), as previously published. We modeled risk of ESRD or 50% reduction in eGFR (n=290 events) over a median of 5y using Cox models with stratification by diabetes (DM).

Results: Higher NAE associated with greater intake of meat/fish/poultry and calories by questionnaire (each p<0.01) and independently with higher eGFR (p=0.01) and lower serum HCO₃ (p<0.01). Higher NEAP associated with lower fruits and vegetables (p<0.01), but not meat/fish/poultry (p=0.7) or calories (p=0.2). Higher NEAP independently associated with lower HCO₃ (p<0.01) but not eGFR (p=0.8). Unexpectedly, higher NAE associated with lower risk of renal events after adjustment (HR 0.91 per 10mEq higher NAE; p=0.04). The HR associated with NAE differed by DM. NEAP was not associated with higher risk in either group.

Table. Adjusted hazard ratio of ESRD or 50% decline in eGFR in patients with and without diabetes

	Overall (n=918)	No Diabetes (n=461)	Diabetes (n=457)
NAE			
Quartile 1 (<20.5 mEq/d)	1.0	1.0	1.0
Quartile 2 (20.5–30.7 mEq/d)	0.91 (0.66–1.26)	1.24 (0.73, 2.10)	0.80 (0.53, 1.23)
Quartile 3 (30.8–41.9 mEq/d)	0.75 (0.54–1.05)	1.01 (0.57, 1.77)	0.65 (0.43, 0.99)
Quartile 4 (≥42.0 mEq/d)	0.73 (0.49–1.08)	0.99 (0.51, 1.92)	0.61 (0.37, 0.99)
P-trend from continuous model	0.04	0.6	0.01
P-interaction with diabetes			0.02
NEAP estimated from urine biomarkers			
Quartile 1 (<42.5 mEq/d)	1.0	1.0	1.0
Quartile 2 (42.5–57.7 mEq/d)	1.23 (0.87–1.74)	1.96 (1.04, 3.69)	0.97 (0.63, 1.49)
Quartile 3 (57.8–74.9 mEq/d)	1.09 (0.76–1.55)	1.58 (0.82, 3.05)	0.92 (0.59, 1.43)
Quartile 4 (≥75.0 mEq/d)	1.10 (0.79–1.55)	1.64 (0.87, 3.09)	0.90 (0.60, 1.35)
P-trend from continuous model	0.4	0.08	0.6
P-interaction with diabetes			0.08

*Adjusted for age, sex, race, diabetes, cardiovascular disease, eGFR, proteinuria, 24 hour urine creatinine, BMI (body mass index)

Conclusions: Higher NAE, but not NEAP, associated with lower risk of renal events in DM. This may be due to changes in renal ammoniogenesis, particularly in diabetic CKD.

Funding: NIDDK Support

FR-OR109

Meat Intake and Risk of End Stage Renal Disease in the Singapore Chinese Health Study Quan Lan J. Lew,¹ Tazeen H. Jafar,⁴ Hiromi Wai Ling Koh,² Jin Ai Zhen,³ Khuan yew Chow,³ Woon-puay Koh.⁴ ¹Singhealth Polyclinics, Singapore; ²National Univ of Singapore, Singapore; ³Health Promotion Board, Singapore; ⁴Duke NUS Graduate Medical School Singapore, Singapore.

Background: Although protein restriction is recommended as part of the management for chronic kidney disease, the evidence remains controversial. In addition, few studies have investigated the effects of different sources of protein on kidney disease.

Methods: We used data from the Singapore Chinese Health Study, a prospective cohort with 60, 198 Chinese adults aged 45-74 years at recruitment (1993-1998). Habitual diet information, including frequency and number of servings, was collected via a validated semi-quantitative 165-item food frequency questionnaire. Incident end stage renal disease (ESRD) was identified via record linkage with the nationwide Singapore Renal Registry up to 31 December 2012. Multivariable Cox proportional hazards models were used, with adjustments for total caloric intake, and other lifestyle factors and co-morbidities associated with ESRD.

Results: There were 951 participants with ESRD after a mean of 15.5 years of follow-up. Total protein intake was weakly associated with increased risk of ESRD. Compared to the lowest quartile intake, the adjusted hazard ratio (HR) for those in the upper 3 quartiles combined was 1.23 [95% confidence interval (CI): 0.99-1.53]. Among the different sources of protein, red meat intake was associated with increased risk of ESRD in a dose-dependent manner; the HR (95% CI) for the fourth quartile compared to the lowest quartile was 1.45 (1.19-1.77) (p<0.001 for trend). No statistically significant associations were found with intakes of other protein sources (poultry, fish, eggs, dairy products or legumes). Substituting one daily serving of red meat with the other protein sources significantly reduced the risk of ESRD by 51.9% to 66.3% (all P<0.01).

Conclusions: Red meat intake is associated with an increased risk of ESRD in the general population of Chinese origin. Replacing red meat intake with other sources of protein may reduce ESRD risk.

Funding: Government Support - Non-U.S.

FR-OR110

The Course of Acid Retention without Metabolic Acidosis as GFR Declines in CKD: Ten Year Follow Up Nimrit Goraya,^{1,2} Jessica Pruszynski,⁴ Jan Simoni,³ Donald E. Wesson.^{1,2} ¹Internal Medicine, Baylor Scott and White Health, Temple, TX; ²Internal Medicine, Texas A and M, Temple, TX; ³Surgery, Texas Tech Health Sciences Center, Lubbock, TX; ⁴Biostatistics, Baylor Scott and White Health, Temple, TX.

Background: Patients with CKD 2 (eGFR 60-89 ml/min/1.73 m²) compared to CKD 1 (eGFR < 90 ml/min/1.73 m²) due to macroalbuminuric hypertension-associated nephropathy have acid retention despite no metabolic acidosis but the contribution of reduced eGFR to acid retention is unknown.

Methods: We explored the role of reduced GFR in acid retention by re-assessing it after further GFR decline. Acid retention was determined by comparing observed to the expected increase in plasma [HCO₃] in response to retained HCO₃ (dose - urine excretion) eight hours after an oral NaHCO₃ bolus (0.5 meq/Kg bw), assuming 50% body weight HCO₃ space of distribution. Specifically, acid retention = [(retained HCO₃/0.5 x body weight) - observed increase in plasma [HCO₃]] x (0.5 x body weight). CKD 2 (n=40) and CKD 1 (n=26) patients had blood pressure controlled with regimens including ACE inhibition and followed ten years.

Results: Although eGFR declined in both groups, eGFR was less preserved in CKD 2 (73.5±6.1 to 51.4±4.4 ml/min/1.73 m², p < 0.01) than CKD 1 (97.4±7.7 to 84.2±9.1 ml/min/1.73 m², p < 0.01). Neither group had or developed metabolic acidosis. Potential renal acid load (PRAL), a measure of dietary acid, was not different between CKD 2 vs. CKD 1 at baseline (60.4±19.4 vs. 62.9±14.5 mmol/day, respectively, p=0.56) or ten years (64.3±17.7 vs. 61.1±12.1 mmol/day, respectively, p=0.54) and ten year vs. baseline PRAL was not different for CKD 2 (p=0.19) or CKD 1 (p=0.76). Acid retention was higher in CKD 2 vs. CKD 1 at baseline (29.8±14.9 vs. 5.3±15.1 mmol, respectively, p < 0.01) and ten years (37.6±9.6 vs. 7.1±16.9 mmol, respectively, p < 0.01). Acid retention was higher at ten years in CKD 2 (p<0.02) but not in CKD 1 (p=0.44).

Conclusions: The data show that GFR reduction exacerbates acid retention in CKD 2 patients with less well preserved eGFR but not in CKD 1 patients whose eGFR was better preserved, supporting the importance of reduced eGFR in mediating the acid retention of CKD.

FR-OR111

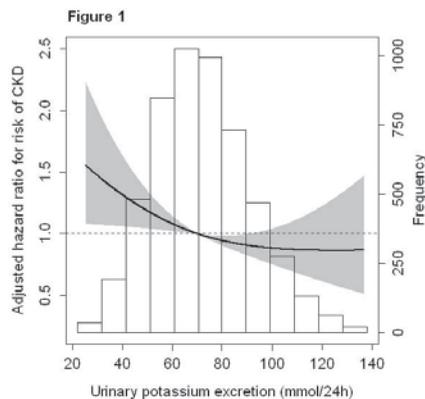
Urinary Sodium and Potassium Excretion and Risk of Developing Chronic Kidney Disease Lyanne M. Kieneker,¹ Ron T. Gansevoort,¹ Rudolf A. de Boer,² Gerjan Navis,¹ Stephan J.L. Bakker,¹ Michel M. Joosten.¹ ¹Internal Medicine, Nephrology, UMC Groningen, Netherlands; ²Cardiology, UMC Groningen, Netherlands.

Background: It is unclear whether dietary sodium and potassium intake are relevant to the development of chronic kidney disease (CKD) in the general population. Our aim was to examine the associations of urinary sodium and potassium excretion (UNaV and UKV resp.), as estimates of intake, with risk of developing CKD in the general population.

Methods: We studied 5,315 subjects free of CKD at baseline of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective, population-based cohort of Dutch men and women aged 28-75 years. UNaV and UKV were measured in two 24-hour urine specimens at baseline (1997-1998) and midway during follow-up (2001-2003). Incident CKD was defined as de novo development of creatinine+cystatin C-based estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² and/or albuminuria >30 mg/24h.

Results: Baseline UNaV and UKV were 135 mmol/24h (interquartile range [IQR]: 106-169 mmol/24h) and 70 mmol/24h (IQR: 57-85 mmol/24h), respectively. During a median follow-up of 10.3 years (IQR: 6.2-11.4 years), 872 subjects developed CKD. After multivariable adjustment for important covariables, no association was observed between UNaV and risk of CKD (hazard ratio per 50 mmol/24h decrement [1 standard deviation], 1.03; 95% confidence interval, 0.93-1.13). Each 21 mmol/24h (1 standard deviation) decrement in UKV was significantly associated with a 16% higher risk of developing CKD (multivariable adjusted hazard ratio, 1.16; 95% confidence interval, 1.05-1.29; Figure 1). Sensitivity analyses in which CKD was defined by either eGFR or albuminuria alone, rendered essentially similar results.

Conclusions: Low potassium intake and not high sodium intake was associated with an increased risk of developing CKD in the general population.



Funding: Private Foundation Support

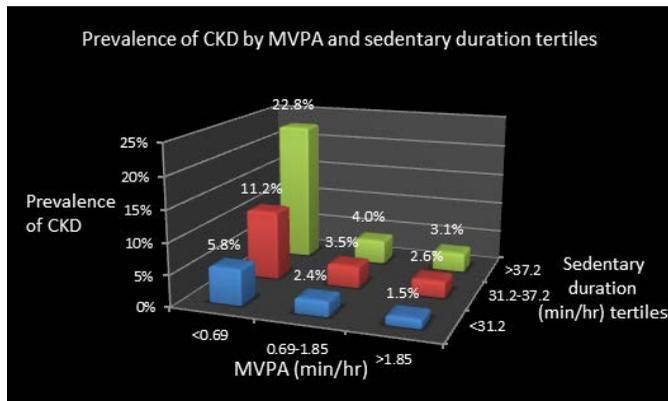
FR-OR112

Sedentary Behavior as a Risk Factor for CKD Dominique Ferranti,¹ Kate Lyden,³ Xiaorui Chen,¹ Robert E. Boucher,¹ G. Wei,¹ Srini Beddhu.^{1,2} ¹U of Utah; ²VA SLC; ³UC Denver.

Background: Sedentary behavior (engaging in activities in the seated or lying position that barely raise the energy expenditure above resting level) is commonly confused with physical inactivity (lack of moderate/ vigorous physical activity (MVPA)). Sedentary behavior is an important risk factor for DM, HTN and obesity. It is unclear whether sedentary behavior is an independent risk factor for CKD. Therefore, we examined this in 5873 participants in whom intensity and duration of physical activities were measured objectively with an Actigraph accelerometer in the 2003-2006 National Health & Nutrition Examination Survey (NHANES) data.

Methods: Based on the number of counts/min recorded, sedentary (<100/min) and moderate/vigorous (≥ 2020/min) activity durations were defined and normalized to 60 min. Logistic regression models adjusted for age, gender, race, education, smoking, alcohol use, lung disease and mobility limitations were used to examine the associations of sedentary and MVPA durations with the presence of CKD (defined as CKD-EPI eGFR < 60 ml/min/1.73 m²).

Results: The mean age was 49 ± 13 yrs. 52% were women and 9.5% were black. 7.4% had CKD. The mean sedentary duration was 34.0 ± 5.6 min/hr. MVPA duration was highly skewed with median (25th - 75th percentile) of 1.2 (0.5 - 2.3) min/hr. Prevalence of CKD by sedentary and MVPA durations are summarized in the figure.



Adjusted for MVPA duration, demographics, CAD, CHF, lung disease and mobility limitations, each 5 min/hr ↑ in sedentary duration was associated with ↑ odds of CKD (OR 1.20, 95% CI 1.09 - 1.33) in a logistic regression model. This persisted even after adjusting for DM, HTN and obesity (OR 1.18, 95% CI 1.07 - 1.31).

Conclusions: These results suggest that sedentary behavior is likely an independent risk factor for CKD and interventions that target sedentary behavior might slow the progression of CKD.

Funding: NIDDK Support

FR-OR113

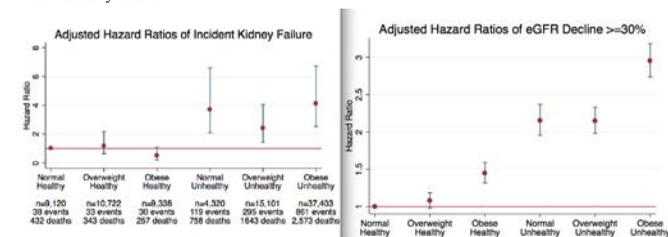
The Metabolically Healthy Obesity Phenotype and Risk of Incident Kidney Failure Alex R. Chang,¹ Morgan Grams,² Amanda Young,¹ Holly J. Kramer,³ H. Lester Kirchner.¹ ¹Geisinger Health System; ²Johns Hopkins Bloomberg School of Public Health; ³Loyola Univ Medical Center.

Background: Little data exist on the association between obesity in the absence of metabolic abnormalities (metabolically healthy obesity) and renal outcomes.

Methods: Using data from 86,004 patients in the Geisinger Health System from 2004-2014, we examined the risk of kidney failure (dialysis, transplant, or eGFR < 15 ml/min/1.73m²) and eGFR decline ≥ 30% by categories of body mass index (normal 18.5-24.9, overweight 25-29.9, obesity ≥ 30) and metabolic health (<2 of the following: triglycerides ≥ 150, HDL cholesterol <40 in men, <50 in women, blood pressure ≥ 130/85, and glucose ≥ 100). Cox regression analyses were adjusted for demographics, smoking status, history of cardiovascular disease, and baseline eGFR.

Results: Only 10.6% of patients had normal BMI with 30.0% overweight, and 54.3% obese. Proportions of metabolically healthy individuals in normal, overweight, and obesity groups were 67.9%, 30.0%, and 20.0%, respectively. Over a median follow-up time of 6.0 years, 1,376 patients developed kidney failure and 17,668 developed eGFR decline ≥ 30%. Compared to metabolically healthy persons of normal BMI, metabolically healthy overweight and obese individuals had similar or lower risk for ESRD (overweight HR 0.75, 95% CI 0.47-1.19; obese HR 0.77, 95% CI: 0.48-1.25). When examining eGFR decline ≥ 30% as the outcome, metabolically healthy overweight and obese individuals were at increased risk (overweight HR 1.08, 95% CI: 0.98-1.19; obese HR 1.45, 95% CI: 1.32-1.59). Metabolically unhealthy persons had higher risk for ESRD and eGFR decline ≥ 30%, with a similar risk regardless of BMI. (Figure) Relationships were similar using a competing risks model accounting for risk of death.

Conclusions: Metabolically healthy obesity is associated with eGFR decline ≥ 30% but not kidney failure.



Funding: Private Foundation Support

FR-OR114

The Metabolomic Signature of Diabetic Kidney Disease Predicts Diabetic Renal Disease Progression Manjula Darshi,^{1,2} Loki Natarajan,^{2,3} Minya Pu,^{2,3} Rintaro Saito,^{1,2} Kumar Sharma,^{1,2,4} ¹Center for Renal Translational Medicine, Univ of California, San Diego, La Jolla, CA; ²Inst of Metabolomic Medicine, Univ of California, San Diego, La Jolla, CA; ³Moore Cancer Center, Univ of California, San Diego, La Jolla, CA; ⁴Veterans Administration, San Diego Healthcare System, La Jolla, CA.

Background: We recently published a metabolomic signature of diabetic kidney disease (MSDKD), indicative of mitochondrial dysfunction. Presently we determined the prognostic value for chronic kidney disease progression in diabetic patients from the longitudinal FinnDiane cohort.

Methods: 60 patients with mean 55 years (SD=9.6) age and mean diabetes duration 27 years (SD = 11 years) were analyzed to predict eGFR. Predictors included baseline (BL) metabolites and clinical variables, BL eGFR, HbA1c, UACR, and diabetes duration. Principal component weights obtained from the MSDKD were designated as *PCA score1* and *PCA score2*. Linear (for continuous eGFR) and logistic (for dichotomous eGFR: > vs ≤ 3ml/min/1.73m² per year) regression models were examined to determine associations between the PCA scores and eGFR outcomes.

Results: Baseline mean eGFR levels were 86.23 (26.67) mL/min/1.73m², HbA1c were 8.3% (SD 1.1), and UACR were 11 (SD 34.1) and follow up was 6.6 (SD 3.5) yrs. eGFR levels at follow up were 81.96 (SD 24.69) mL/min/1.73m², and 25% (N=15) declined more than 3 mL/min/1.73m² per year. Statistical modeling revealed that, after adjustment for baseline eGFR and follow-up interval, the *PCA Score 2* (mean =0.4, SD=0.64) was a significant predictor of worse (i.e. lower) eGFR (coef.=12.4, p=0). For dichotomized eGFR (> vs ≤ 3 mL/min/1.73m² per year decline), the *PCA score2* was the only independent predictor that was selected (odds ratio per SD increase =7.4, 95% CI 1.78-45.73, p=0.01) by the LASSO model. A model to predict follow-up eGFR using clinical variables alone had an AUC of 0.73 (95% CI 0.58-0.88); when *score 2* was included, AUC increased to 0.88 (95% CI 0.79-0.97).

Conclusions: We demonstrate that MSDKD is a strong independent predictor for kidney disease progression in type I and type II diabetes patients, and hence may serve as prognostic biomarker for CKD.

Funding: NIDDK Support, Veterans Administration Support

SA-OR001

FMO3 Allelic Variant 158K Affects Trimethylamine Metabolism, Disease Progression, and All-Cause Mortality in Patients with CKD Catherine K. Yeung,^{1,2} Cassianne Robinson-Cohen,¹ Richard Newitt,¹ Danny D. Shen,² Allan E. Rettie,³ Bryan R. Kestenbaum,¹ Jonathan Himmelfarb,¹ ¹Kidney Research Inst, Div. of Nephrology, Univ of Washington, Seattle, WA; ²Dept of Pharmacy, School of Pharmacy, Univ of Washington, Seattle, WA; ³Dept of Medicinal Chemistry, School of Pharmacy, Univ of Washington, Seattle, WA.

Background: Elevated levels of circulating pro-atherogenic uremic toxins are implicated in the development of cardiovascular disease in chronic kidney disease (CKD) patients. Trimethylamine N-oxide (TMAO) is generated from diet and catabolized by intestinal flora to betaine and then to trimethylamine (TMA). TMA is rapidly metabolized by the hepatic enzyme flavin-containing monooxygenase 3 (FMO3) to TMAO, which accumulates in CKD. The FMO3 gene is highly polymorphic; up to 40% of individuals possess a non-synonymous variant.

Methods: We tested the association of FMO3 158K, the most common allelic variant, with plasma TMAO concentration and the TMAO/betaine ratio, CKD progression, and all-cause mortality in 339 participants from the Seattle Kidney Study (SKS), an ongoing clinic-based cohort study of CKD.

Results: Each additional minor allele at the 158K locus was associated with a 0.35 µg/mL higher serum TMAO concentration (1.42, 1.97, 2.10 µg/mL for 0, 1, 2 minor alleles, respectively; p=0.02) and a 0.20 unit higher TMAO/betaine ratio (p=0.05). A greater number of minor alleles at the 158K locus was associated with faster rates of eGFR decline. Participants who had 0, 1 and 2 minor alleles at the 158K locus experienced average eGFR losses of 8%/year, 12%/year, and 14%/year, respectively (p for trend= 0.05). Compared to participants with the homozygous dominant genotype (G/G), heterozygous (G/A) and homozygous recessive (A/A) participants had a 1.94-fold and 2.24-fold higher risk of mortality (p for trend 0.04).

Conclusions: In summary, we demonstrate that common genetic variation within the metabolizing enzyme FMO3 is associated with altered TMA substrate catabolism, CKD progression, and mortality among CKD patients. Further elucidation of these relationships could have implications for personalized recommendations for diet modification in patients with CKD.

Funding: Other NIH Support - NCATS 1KL2RR025015-01, Private Foundation Support

SA-OR002

Association Between Mitochondria DNA Copy Number and Incident Chronic Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study Adrienne Tin, Morgan Grams, A. Rosenberg, Foram N. Ashar, Josef Coresh, Dan Arking. *John Hopkins Univ, Baltimore, MD.*

Background: Mitochondria play a key role in cellular energy production. Higher mitochondrial DNA copy number (mtDNA-CN) in peripheral blood has been associated with lower risk of diabetes and lower prevalence of microalbuminuria, both risk factors of chronic kidney disease (CKD). It is unknown whether mtDNA-CN is associated with incident CKD.

Methods: We estimated mtDNA-CN from 119 mtDNA single nucleotide polymorphisms (SNPs) genotyped using the Affymetrix 6.0 microarray. Incident CKD was defined as a composite outcome of (a) baseline estimated glomerular filtration rate (eGFR) ≥ 60mL/min/1.73m² with a 25% drop to < 60mL/min/1.73m², (b) CKD-related hospitalization, or (c) end-stage renal disease (ESRD) based on linkage to the US Renal Data System (USRDS). The association between quartiles of mtDNA-CN and incident CKD was evaluated using Cox regression.

Results: Among 9060 participants, those with higher mtDNA-CN had significantly lower prevalence of coronary heart disease and diabetes, and lower levels of C-reactive protein and white blood cell count. Baseline eGFR did not differ significantly by mtDNA-CN quartiles. Over a median follow-up period of 19 years, 1459 participants developed CKD. Higher mtDNA-CN was associated with lower risk of incident CKD adjusted for age, gender, and race (quartile 4 vs. 1: hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.66-0.87, p for trend < 0.0001). This association persisted with some attenuation after further adjustment for risk factors of CKD, including prevalent diabetes, hypertension, and coronary heart disease, smoking, high sensitive C-reactive protein and white blood cell count (quartile 4 vs. 1: HR 0.89, 95% CI: 0.76-1.03, p for trend 0.03).

Conclusions: Higher mtDNA-CN is associated with lower risk of incident CKD independent of known risk factors of CKD and inflammation biomarker levels. Further research on modifiable factors influencing mtDNA-CN may lead to insight on the pathogenesis and prevention of CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR003

Urinary EGF Predicts Composite Endpoints in Three Independent Chronic Kidney Disease Cohorts Viji Nair,¹ Li Zhu,² Peter X.K. Song,³ Laura H. Mariani,^{1,4} Susan P. Steigerwalt,⁶ Jicheng Lv,² Jennifer Joyce Hawkins,¹ Hong Zhang,² Matthias Kretzler,¹ Wenjun Ju,¹ ¹Medicine, Univ of Michigan, Ann Arbor, MI; ²Medicine, Peking Univ First Hospital, PKU Inst of Nephrology, Peking, China; ³Biostatistics, Univ of Michigan, Ann Arbor, MI; ⁴Arbor Research Collaborative for Health, Ann Arbor, MI; ⁵St. John Hospital and Medical Center, Detroit, MI.

Background: The nephrology community is in need of non-invasive biomarkers that can predict CKD progression and identify patients for targeted treatment better than estimated glomerular filtration rate (eGFR) and proteinuria. Our previously identified and validated epidermal growth factor (EGF) as an intrarenal marker for eGFR. The significant correlation of urinary EGF protein (uEGF) with intrarenal EGF mRNA and eGFR suggested that it can be a non-invasive biomarker for kidney function.

Methods: We used Cox proportional hazards models to evaluate the predictive value of uEGF on CKD outcome, defined as a composite of end stage kidney disease or 40% reduction of baseline eGFR, in the Clinical Phenotyping Resource and Biobank Core (C-PROBE), the Nephrotic Syndrome Study Network (NEPTUNE), and the Peking University First Hospital IgA Nephropathy (PKU-IgAN) cohorts with average of follow-up period of 1.8-3.6 years. The goodness of fit and improved prediction ability of markers were assessed by likelihood ratio tests, C-statistics, and Akaike information criterion (AIC).

Results: Lower uEGF was associated with higher risk of reaching composite endpoints: multivariable-adjusted associations of uEGF with the hazard of progression to composite endpoints are 0.27, 0.29 and 0.53 in C-PROBE, NEPTUNE and PKU-IgAN cohort, respectively. Prediction of renal survival by eGFR and albuminuria was significantly improved by addition of uEGF to the model, with an increase of c-statistic from 0.75 to 0.87, 0.74 to 0.80 and 0.71 to 0.75, in these cohorts.

Conclusions: uEGF shows promise as an independent risk predictor of CKD progression. Inclusion of uEGF significantly improved prediction of composite end points by eGFR and proteinuria in diverse populations worldwide with a wide range of CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffmann-La Roche

SA-OR004

Normalization of Biomarkers to Urine Creatinine: Impact on CRIC Study Findings Kathleen D. Liu, Dawei Xie, Sushrut S. Waikar, Xiaoming Zhang, Venkata Sabbiseti, Joseph V. Bonventre, Theodore E. Mifflin, Josef Coresh, Robert G. Nelson, Clarissa Jonas Diamantidis, Claudia M. Lora, Francis Perry Wilson, Edgar R. Miller, Jiang He, Jeffrey R. Schelling, Mahboob Rahman, Akinlolu O. Ojo, Paul L. Kimmel, Harold I. Feldman, Vasan S. Ramachandran, Chi-yuan Hsu. *For the NIDDK CKD Biomarkers Consortium.*

Background: There is no standard approach to the reporting of urine biomarkers; some studies normalize to urine creatinine (UCr) concentration and others do not. Whether this influences findings is not well understood.

Methods: Urine kidney injury molecule-1 [KIM-1], neutrophil gelatinase associated lipocalin [NGAL], N-acetyl-beta-D-glucosaminidase [NAG], and liver fatty acid-binding protein [LFABP] were measured in 2466 Chronic Renal Insufficiency Cohort participants. Cox models were used to examine the association between biomarkers and CKD progression, defined as halving of eGFR or incident ESRD. We compared results with and without normalization of biomarkers to UCr.

Results: Baseline mean eGFR was 44±18 mL/min/1.73 m²; median albuminuria was 53 mg/g UCr (6-503). After adjustment for eGFR, albuminuria, as well as socio-demographic and clinical covariates, non-normalized KIM-1 and NAG were independently associated with CKD progression by quintile (Table) and continuous biomarker value analysis [HR per SD 1.16(1.05-1.28) and 1.14(1.04-1.25), respectively] but KIM-1/Cr and NAG/Cr were not. There were no independent associations between NGAL or LFABP and outcomes regardless of normalization.

KIM-1 quintiles (pg/mL)	Adjusted HR	NAG quintiles (mU/mL)	Adjusted HR
≤253	Referent	≤0.8	Referent
>253-522	0.93(0.66-1.31)	>0.8-1.5	1.07(0.72-1.57)
>522-918	1.39(1.01-1.92)	>1.5-2.5	0.93(0.64-1.36)
>918-1675	1.59(1.16-2.18)	>2.5-4.7	1.48(1.02-2.14)
>1675	1.39(1.01-1.93)	>4.7	1.48(1.01-2.15)

Conclusions: Normalization for UCr influences the associations of biomarkers with CKD outcomes. In theory, normalization controls for differences in urine concentration, but more studies are needed to better understand the impact on a variety of clinical outcomes. At minimum, researchers should state their approach *a priori*, measure UCr, and perform sensitivity analyses where the alternate approach is tested.

Funding: NIDDK Support

SA-OR005

Proton Pump Inhibitor Use Is Associated with Incident Chronic Kidney Disease Benjamin Lazarus,^{1,2} Yuan Chen,¹ Francis Perry Wilson,³ Josef Coresh,¹ Morgan Grams.¹ ¹Johns Hopkins Univ, Baltimore, MD; ²Royal Brisbane and Women's Hospital, Queensland, Australia; ³Yale Univ School of Medicine, New Haven, CT.

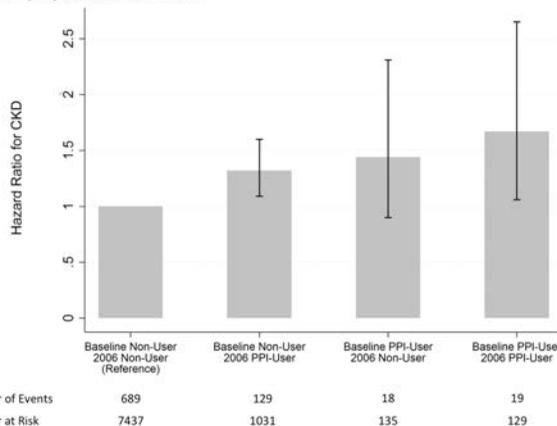
Background: Proton pump inhibitors (PPIs) are one of the most commonly used drugs worldwide, and have been linked to acute kidney injury and interstitial nephritis. We hypothesized that PPI use may also be associated with chronic kidney disease (CKD).

Methods: We followed 10,482 participants in the Atherosclerosis Risk in Communities study with an eGFR of ≥60mL/min/1.73m² from a baseline visit (1996-1999) to December 31, 2011. In primary analysis, we evaluated the association between baseline PPI use and incident CKD, using a validated definition of hospitalization and death related diagnostic codes. In sensitivity analysis, we assessed 1) PPI use as a time varying exposure, 2) an alternative outcome of reduced eGFR at follow-up (2011-2013), and 3) the risk of incident CKD in a cohort of respondents in 2006, stratified by PPI use in 2006 and at baseline. We evaluated histamine-2 receptor (H2) antagonist use as a negative control.

Results: Compared to non-users, PPI-users at baseline were more often white, obese, and taking antihypertensive medication. Baseline PPI use was associated with incident CKD in unadjusted (hazard ratio [HR], 1.45, 95% CI, 1.11, 1.90; P=0.006) and fully adjusted analyses (HR, 1.50, 95% CI, 1.14, 1.96; P=0.003). The association persisted when PPI use was modeled as a time-varying variable, and when reduced eGFR was used as the outcome. In the 2006 cohort, participants who reported PPI use at both baseline and 2006 had the highest risk, followed by those who reported use at only one time point, followed by never-users (Figure). There was no significant association between baseline H2-antagonist use and incident CKD (P=0.2).

Conclusions: PPI use is an independent risk factor for CKD. Caution against unnecessary use is warranted.

Figure. Risk of Incident Chronic Kidney Disease (CKD) in a 2006 Cohort of Proton Pump Inhibitor (PPI) Users and Non-Users



SA-OR006

Underuse of Renin Angiotensin System Inhibitors and Other Medications in U.S. Patients with Advanced Chronic Kidney Disease Receiving Nephrologist Care: Results from the International CKDopps Elodie Speyer,¹ Laura H. Mariani,¹ Charlotte Tu,¹ Lindsay Zepel,¹ Celine Lange,² Brian Bieber,¹ Christian Combe,³ Antonio Alberto Lopes,⁴ Ziad Massy,^{5,8} Roberto Pecoits-Filho,⁶ Ronald L. Pisoni,¹ Helmut Reichel,⁷ Benedicte Stengel,⁸ Bruce M. Robinson.¹ ¹Arbor Research Collaborative for Health, USA; ²Biomedicine Agency, France; ³CHU Bordeaux, Univ de Bordeaux, France; ⁴Federal Univ of Bahia, Brazil; ⁵Ambroise Pare Univ Hospital, UVSQ, France; ⁶Pontificia Univ Catolica do Parana, Brazil; ⁷Nephrological Center Villingen Schwenningen, Germany; ⁸Inserm UMR1018, France.

Background: In the US, ~86% of incident ESRD cases are attributable to hypertension or diabetes. Guideline-directed medication use may help to slow CKD progression and lower ESRD incidence. We report early findings on use of key medication classes by CKD stage in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps).

Methods: CKDopps is a prospective cohort study of patients with eGFR<60 in random national samples of nephrology clinics in Brazil, France, Germany, and the US. Early data from CKDopps (excluding Brazil and Germany for now) were used to characterize medication usage.

Results: 2,621 patients were included from 39 French, and 17 US clinics. The median number of prescriptions ranged from 7-9. Statin use was 52% and aspirin use was 31-48%. RASi (ACEI or ARB) use for CKD Stage 3 and 4 patients was 72 and 77% in France, and 51 and 35% in the US, respectively. Aldosterone blockade use was 3-6. Among diabetics, insulin use was lower in US (32%) than in France (48 and 57% for stage 3 and 4 patients, respectively), as was metformin use which was 30 and 7%, and 10 and 1%. For stage 4 patients, sulfonylurea use was higher in the US (21%) than in France (8%).

Conclusions: These early results show large international differences in medication usage for diabetes and cardiovascular disease amongst CKD patients. Patients in US were much less likely to use RASi, metformin or insulin than in France. Early data from Germany and Brazil will be available by mid 2015. Further investigation should determine the reasons for these practice variations and their impact on CKD progression, survival, and other outcomes.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Shire, WiNe Institute, Societa Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

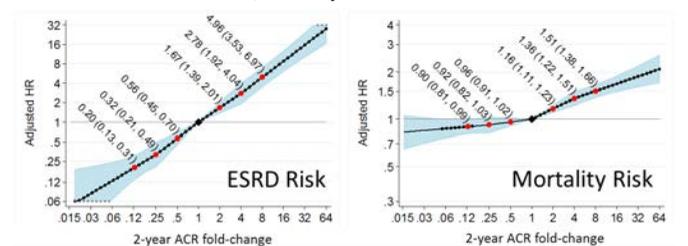
SA-OR007

Albuminuria Changes and Subsequent Risk of End-Stage Renal Disease and Mortality Juan Jesus Carrero,¹ Yingying Sang,² Alessandro Gasparini,¹ Abdul Rashid Tony Qureshi,¹ Kunihiro Matsushita,² Johan Arnlov,³ Marie Evans,¹ Peter F. Barany,² Bengt Lindholm,¹ Morgan Grams,² Shoshana Ballew,² Carl Gustaf Elinder,¹ Josef Coresh.² ¹Renal Medicine and Baxter Novum, Karolinska Inst, Sweden; ²Johns Hopkins Bloomberg School of Public Health, Baltimore; ³Medical Sciences, Uppsala Univ, Sweden.

Background: Albuminuria is used to stage chronic kidney disease (CKD). Changes in albuminuria during the course of disease may serve as early indicators of CKD progression and complications beyond eGFR, but the risk implications are not well understood in large clinical studies.

Methods: Observational study from the Stockholm CREAtinine Measurements (SCREAM) project, a laboratory data extraction of all citizens from the region of Stockholm, Sweden, with at least one serum creatinine during 2006-2011; 39802 individuals with repeated albumin to creatinine ratio (ACR) measurements were followed up until 12/31/2012. ESRD risk after baseline (908 events) was related to fold-change in ACR during a baseline window of 1, 2 or 3 years. The secondary outcome was death (3890 events). Adjustment variables included demographics, comorbid history, laboratory assessments and medication, as well as first eGFR and ACR.

Results: The association between ACR changes and ESRD risk was strong and showed a largely linear dose-response relationship (Figure for 2-y baseline period). For example, 8-fold increase in ACR (e.g., from normal of 5 mg/g to microalbuminuria of 40 mg/g) conferred ~5 fold higher risk of ESRD compared to stable ACR. The association was weaker for mortality but significant for ACR increases. The observed risk estimates were similar and consistent at 1-, 2- and 3-y time-window.



Conclusions: Increases in albuminuria were strongly and consistently associated with the risk of ESRD and mortality, suggesting their usefulness as a kidney outcome in clinical studies of CKD progression.

SA-OR008

Prevalence of Chronic Kidney Disease, Diabetes and Hypertension in Rural Tanzania Based of Different Methodologies David W. Ploth,¹ Virginia Fonner,² Bruce Horowitz,³ Philip Zager,³ Francis Fredrick,⁴ Caroline M. West,² Michael D. Sweat.² ¹Medicine, MUSC, Charleston, SC; ²Div of Family Services Research, MUSC, Charleston, SC; ³Medicine, Univ of New Mexico School of Medicine, Albuquerque, NM; ⁴Nephrology, Muhimbili Univ of Health and Allied Sciences, Dar es Salaam, Tanzania, United Republic of.

Background: Studies were conducted to explore the hypothesis that there are previously underappreciated and interrelated epidemics of chronic kidney disease (CKD), diabetes (DM), and hypertension (HTN) in rural Tanzania.

Methods: We initially assessed prevalence in a probability-based sample of 740 subjects randomly sampled from households in Kisarawe District, TZ. Prevalence of DM was obtained by measuring HbA1c. Blood pressure was measured by AHA guidelines, and kidney function by serum creatinine in blood samples obtained at home interview. Estimation of glomerular filtration rate (eGFR) was computed with the CKD-EPI equation.

Results:

NCD	Diabetes	Pre-Diabetes	CKD Stage 3-5	Pre-HTN	HTN
Criteria	HBA _{1c} >6.5%	HBA _{1c} > 5.9 to < 6.5	eGFR < 60 ml/min/1.73 M ²	BP 120-130/80-89 mmHg	BP > 140/90
Prevalence	14.7%	30.5%	12.6%	40.0%	17.5%

Following the probability based screening of households, we assessed the same NCD's in individuals who voluntarily presented for healthcare assessment in a community prevention center we established. We measured BP and assessed urine for glycosuria and proteinuria with dipsticks in 685 subjects self-selected from the community. We observed glycosuria in 3.6%, proteinuria in 8.1% and proteinuria and glycosuria in 1.8%. Hypertension was observed in 23.6 % and pre-hypertension in 34.9%. We observed a significant, direct relationship between increasing levels of BP and the prevalence of glycosuria and proteinuria (p < 0.05).

Conclusions: In summary we observed unexpectedly high and similar prevalence estimates for CKD, HTN and DM in a probability-based sample in rural Tanzania and from observations in a walk-in community clinic. The higher than expected prevalence of these NCD's will likely contribute to rapidly accelerating rates of cardiovascular morbidity and mortality in these areas. Additional studies are desperately needed to address this problem.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc, Nashville, TN

SA-OR009

Race and the Association of Blood Pressure with Clinical Outcomes in U.S. Veterans with Chronic Kidney Disease Csaba P. Kovcsdy,^{1,2} Miklos Zsolt Molnar,¹ Praveen Kumar Potukuchi,¹ Elvira Gosmanova,¹ Fridtjof Thomas,¹ Jun Ling Lu,¹ L. Ebony Boulware,³ Keith C. Norris,⁴ Kamyar Kalantar-Zadeh.⁵ ¹Univ of Tennessee Health Science Center, Memphis, TN; ²VA Medical Center, Memphis, TN; ³Duke Univ School of Medicine, Durham, NC; ⁴UCLA, CA; ⁵UC, Irvine, CA.

Background: African American (AA) patients with CKD have poorer BP control, but it is unclear if the association of BP with outcomes is different in AA vs. white patients with CKD.

Methods: We examined the association of baseline SBP with mortality, slopes of eGFR, ESRD, incident coronary heart disease (CHD) and incident stroke in 308,920 US veterans (54,852 AA and 254,068 white) with CKD over a median follow-up of 4.9 years. We used Cox models and logistic regressions with interaction terms to explore race differences in associations of SBP categories (relative to SBP 130-139 mmHg in white patients) with outcomes, adjusted for demographic and socioeconomic characteristics, comorbidities, baseline eGFR, and medications.

Results: Compared to whites, AA patients were younger, less likely to be married, had lower income, more diabetes, but less CVD. Mean baseline SBP (SD) was 133 (17) in AA and 130 (16) mmHg in whites. Elevated SBP was associated with linearly higher risk of all outcomes in both race groups. Race and elevated SBP showed no interaction for the risk of mortality, ESRD, strokes, and CHD. The association of elevated SBP with steeper eGFR slopes was, however, 1.6 fold more pronounced in AA patients.

Adjusted hazard/odds ratios (95%CI)	AA with SBP≥170 vs. white with SBP 130-139 mmHg	White with SBP≥170 vs. white with SBP 130-139 mmHg	P for interaction
All-cause mortality	1.40 (1.27-1.55)	1.44 (1.36-1.54)	0.6
Incident ESRD	10.69 (8.94-12.78)	6.09 (5.07-7.30)	0.6
Steeper slopes of eGFR (<-5 ml/min/1.73m ² /yr)	3.51 (3.13-3.93)	2.20 (2.04-2.38)	0.003
Incident ischemic stroke	1.96 (1.62-2.36)	1.86 (1.62-2.15)	0.7
Incident CHD	1.46 (1.11-1.91)	1.81 (1.48-2.20)	0.8

Conclusions: Hypertension is associated with higher incidence of mortality, vascular events and ESRD in both AA and white patients with CKD. Elevated SBP may affect the progression of CKD more in AA patients.

Funding: NIDDK Support, Veterans Administration Support

SA-OR010

Association of eGFR Decline with Post Dialysis Mortality in Late-Stage CKD Patients Who Transitioned to ESRD Keichi Sumida,¹ Miklos Zsolt Molnar,¹ Praveen Kumar Potukuchi,¹ Fridtjof Thomas,¹ Jun Ling Lu,¹ Jennie Jing,² Vanessa A. Ravel,² Melissa Soohoo,² Connie Rhee,² Elani Streja,² Lawrence Agoda,³ Kevin C. Abbott,³ Paul W. Eggers,³ Kamyar Kalantar-Zadeh,² Csaba P. Kovcsdy.^{1,4} ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³NIH, Bethesda, MD; ⁴VA Medical Center, Memphis, TN.

Background: The rate of eGFR decline is an independent risk factor for mortality in CKD. However, it is not known if pre-dialysis eGFR slopes are associated with outcomes after dialysis initiation.

Methods: We examined the association of pre-dialysis eGFR slopes with all-cause, cardiovascular (CV), and infectious mortality during two years after dialysis start in 19,254 U.S. veterans who transitioned to ESRD between October 1, 2007-September 30, 2011. eGFR slopes were categorized into four groups (<-10, -10-<-5, -5-<0, and 0+ mL/min/1.73m²/year). Associations were examined in Cox models with adjustment for age, gender, race, comorbidities, and last pre-dialysis eGFR.

Results: Patients were 68.7±11.4 years old, 98% male, 29% black, and 72% diabetic. There were 5,226 all-cause, 2,751 CV, and 613 infectious deaths. Compared to eGFR slope of -5-<0 (42% of the total cohort), the adjusted hazard ratios [95%CI] for those with eGFR slopes of <-10, -10-<-5, and 0+ were 1.26 [1.17-1.35], 1.09 [1.03-1.15], and 1.04 [0.93-1.16], respectively (Table). Similar trends were observed for the associations of eGFR slopes with CV and infectious mortality.

eGFR slopes (mL/min/1.73m ² /year)	Unadjusted HR (95% CI)	P Value	Age, sex, race-Adjusted HR (95% CI)	P Value	Fully Adjusted HR (95% CI)	P Value
<-10	0.67 (0.63-0.72)	<0.001	1.17 (1.09-1.25)	<0.001	1.26 (1.17-1.35)	<0.001
-10 - <-5	0.80 (0.76-0.85)	<0.001	1.03 (0.98-1.10)	0.24	1.09 (1.03-1.15)	0.005
-5 - <0	1.00 (reference)	N/A	1.00 (reference)	N/A	1.00 (reference)	N/A
0+	1.42 (1.29-1.57)	<0.001	1.53 (1.39-1.69)	<0.001	1.04 (0.93-1.16)	0.47

Conclusions: Patients with rapid pre-dialysis eGFR decline have higher mortality risk in the first two years after dialysis start. The rate of eGFR decline in late CKD stages can be an additional predictor of mortality in incident dialysis patients.

Funding: NIDDK Support, Veterans Administration Support

SA-OR011

A Randomized Controlled Trial of Rituximab for Severe Idiopathic Membranous Nephropathy (IMN) Pierre M. Ronco,^{1,2,8} Karine Dahan,¹ Hanna Debiec,^{2,8} Emmanuelle M. Plaisier,^{1,2,8} Marine Cachanado,³ Alexandra Rousseau,³ Laura Wakselman,³ Pierre-Antoine Michel,¹ Fabrice Mihout,¹ Bertrand Dussol,⁴ Marie Matignon,⁵ Christiane I. Mousson,⁶ Tabassome Simon.^{3,7,8} ¹Nephrology and Dialysis, AP-HP, Hôpital Tenon, Paris, France; ²UMR_S 1155, INSERM, Paris, France; ³Clinical Pharmacology and Unité de Recherche Clinique (URCEST), AP-HP, Hôpital Saint Antoine, Paris, France; ⁴Nephrology and Transplantation, AP-HM, Hôpital de la Timone, Marseille, France; ⁵Nephrology and Transplantation, AP-HP, Hôpital Henri Mondor, Créteil, France; ⁶Nephrology and Transplantation, Centre Hospitalier Univ, Dijon, France; ⁷UMR_S1148, INSERM, Paris, France; ⁸UPMC, Sorbonne Univs, UPMC Univ Paris 06, Paris, France.

Background: IMN is a common cause of nephrotic syndrome. Anti-PLA2R antibodies occur in 70% of patients. No randomized controlled trial has evaluated rituximab efficacy and safety.

Methods: Patients with biopsy proven IMN and persistent nephrotic syndrome after 6 months despite Non Immunosuppressive Antiproteinuric Treatment (NIAT) were randomly assigned to 6-month therapy with NIAT and 375 mg/m² of rituximab on days 1 and 8, or NIAT alone. At month 6, the primary end point was the rate of remission; the composite end point was defined as reduction of proteinuria > 50% and increase of serum albumin > 30%; secondary end points were proteinuria, serum albumin, serum creatinine, and PLA2R-Ab.

Results: 37 and 38 patients received NIAT with rituximab and NIAT alone. At month 3, rituximab decreased PLA2R-Ab rate and titer (P<0.001), and induced PLA2R-Ab depletion in 56 % of patients (P<0.001). At month 6, 13 (35 %) patients in the NIAT-rituximab group and 8 (21 %) in the NIAT group reached the primary end point (P=0.17); 15 (41 %) patients in the NIAT-rituximab group and 5 (13 %) in the NIAT group reached the composite end point (OR=0.22, 95% CI= [0.07; 0.70]; P=0.007). Serum albumin increased more with rituximab (P=0.029), without difference in proteinuria. Number of SAEs was comparable in both groups.

Conclusions: Rituximab induced immunological and clinical remission defined by a composite end point with a high safety profile (GEMRITUX ClinicalTrials.gov number).

Funding: Pharmaceutical Company Support - Hoffmann-La Roche, Private Foundation Support, Government Support - Non-U.S.

SA-OR012

Two-Year Outcomes of Patients with Idiopathic Membranous Nephropathy, Previously Randomized to Either Modified Ponticelli Regimen or to a Combination of Tacrolimus and Steroids *Krishan L. Gupta, Raja Ramachandran, Harbir Singh Kohli, Vivekanand Jha. Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.*

Background: The patients with idiopathic membranous nephropathy (IMN) followed for 1 year are known to relapse more often with Tacrolimus than with cyclophosphamide either given with oral steroids. The present study aimed at finding the clinical outcome in patients randomized to a combination of Tacrolimus and oral prednisolone (TAC*) or Modified Ponticelli regimen (MPR) (cyclical cyclophosphamide and steroids) at 2 years.

Methods: IMN patients (n=70) with persisting nephrotic syndrome after at least 6 months of ACEIs or ARBs or with complications of nephrotic syndrome were randomized to receive TAC* or MPR. The outcome of the study was remission at the end of 18 and 24 months of initiating therapy. Definition: Complete remission (CR): 24-hour urine protein < 500 mg/day with normal serum albumin (≥3.5 gm/dl) and serum creatinine. Partial remission (PR): 24 hour urine protein ≥500 mg/day but <2 gm/day or <50% of baseline with normal serum albumin (≥3.5 gm/dl) and serum creatinine.

Results: Of the 70 randomized patients followed for 18 months, 54 had follow-up for 24 months. Intention-to-treat analysis and remission at the end of 12 (n-70), 18 (n-70) and 24 (n-54) months are mentioned in **Table**. At the end of 18 and 24 months response rate with TAC* was lower compared to subjects treated with MPR (p<0.05). The adverse events were comparable in both the groups. PLA2R antibodies titer rose in all patients with relapse of nephrotic range proteinuria.

	12m (TAC*) (n-35)	12m (MPR) (n-35)	18m (TAC*) (n-35)	18m (MPR) (n-35)	24m (TAC*) (n-28)	24m (MPR) (n-26)
Remission	71.4	77.1	62.8	85.7	64.2	88.4
CR	54.2	51.4	54.2	65.7	42.8	69.2
PR	17.2	25.7	8.6	20	21.4	19.2
Resistant	28.6	22.8	37.2	14.3	35.7	11.6

Conclusions: Preliminary analysis suggests that at 2 years post randomization, TAC* is inferior to MPR in maintaining remission of NS (The total follow-up of 70 cases will be presented at ASN).

SA-OR013

Antibody Guided Therapy with Cyclophosphamide and Prednisone in Patients with Idiopathic Membranous Nephropathy *Anne-Els van de Logt, Julia M. Hofstra, Jack F. Wetzels. Nephrology, Radboud Univ Medical Center, Radboud Inst for Health Sciences, Nijmegen, Netherlands.*

Background: The discovery of anti-PLA2R antibodies provides options for individualized therapy in patients with idiopathic membranous nephropathy (iMN). We previously showed that the level of anti-PLA2R antibodies (aPLA2R) after 6-12 months of cyclophosphamide (CP) therapy predicted long-term outcomes (Bech, CJASN 2014). We present the first data of antibody guided therapy.

Methods: CP-therapy (combined with steroids) is started in patients with aPLA2R positive iMN and high risk of progression. aPLA2R are repeatedly monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If antibodies become negative, CP is stopped and prednisone is tapered. Otherwise, therapy is continued after 24 weeks with MMF and prednisone.

Results: We treated 22 patients (characteristics in table 1). aPLA2R were negative in respectively 15/22 (68%) after 8 weeks, 17/21 (81%) after 16 weeks and 17/20 (85%) patients after 24 weeks of treatment. A partial remission of proteinuria (PCR < 3.0 gram/10 mmol creatinine) was observed in 23 % (5/22), 44 % (8/18) and 67 % (10/15) of patients after 8, 16 and 24 weeks respectively. Thus far, 4 of the 17 patients (24%) developed an immunological relapse after 3.4 (1.6-6.7) months. All 4 patients have persistent or recurrent proteinuria. Thus far, 6 of 22 patients (27%) needed additional treatment; 1 because of

renal failure, 3 because of persisting positive aPLA2R at 24 weeks and 2 patients because of an immunological and clinical relapse. At the end of follow-up 14 of the 22 patients (64%) were in clinical remission.

Conclusions: Monitoring of aPLA2R could allow individualized therapy in patients with iMN, thus shortening overall duration of CP therapy. Longer follow-up is needed to establish that the overall relapse rate is acceptable.

Gender (male/female)	16/6
Age (years)	58 (±14)
Serum creatinine (µmol/l)	117 (96-141)
Serum albumin (g/l)	21 (16-23)
Protein-creatinine ratio (g/10 mmol/Cr)	8.7 (5.5-13.3)
Previous immunosuppressive treatment	1/22 (5%)
Follow-up duration (months)	8.0 (4.9-11.3)

Values are expressed as number (percent), means ± SD and median [interquartile ranges].

SA-OR014

Is Serum PLA₂R Monitoring Clinically Relevant in Idiopathic Membranous Nephropathy? *Harbir Singh Kohli, Raja Ramachandran, Vinod Sharma, Vivekanand Jha, Krishan L. Gupta. Nephrology, PGIMER, Chandigarh, India.*

Background: In this prospective study, we evaluated glomerular staining for PLA₂R, serum anti-PLA₂R antibodies, and its association with clinical response to therapy.

Methods: Adult IMN on immunosuppressive therapy were enrolled during Sept 2011 to Nov 2014. PLA₂R in glomerular deposits was assessed in fresh frozen tissue (Abcam ab80054) by confocal microscopy. Anti- PLA₂R was estimated in serum before, 6 and 12 months after therapy (ELISA and IIF, EUROIMMUN, Germany). The patients were treated with either alternating monthly cycles of cyclophosphamide and steroids or tacrolimus with steroids. Definitions: complete remission: 24 hr urine protein <0.5gm on 3 occasions with normal serum albumin. Partial remission: urine protein >0.5 gm to 2 gm/day or <50% of baseline with normal serum albumin.

Results: A total of 86 patient, 52 males, 34 females, mean age 42.6 yrs were studied. Sixty three (73.25%) had glomerular PLA₂R staining. Sixty (69.76%) showed elevated serum anti- PLA₂R by ELISA and 56 (65.11%) by IIF. Fifty-two (60.45%) had both serum and glomerular positivity, 11 (12.79%) had isolated glomerular positivity, 8 (9.3%) had only serum antibodies and 15 (17.44%) had no detectable PLAR in serum or glomeruli. Of 86 who completed 12 months of follow-up, 58 (67%) responded to therapy: 38 (44%) had complete and 20 (23%) partial remission. Of 60 serum PLA₂R Ab positive cases, 40(67%) had remission and 20 (33%) were resistant to therapy. Thirty-seven (92.5%) with remission had negative PLA₂R Ab at end of therapy and 18 (90%) resistant patients had elevated PLA₂R Ab titer (p<0.001). There was parallel reduction in mean PLA₂R Ab titre and 24 hr urine protein, 5 cases had clinico-serological discordance; 3 patients showed elevated 12-month anti-PLA₂R levels but were in clinical remission - all of them relapsed over the next 2 months. On the other hand, 2 cases who tested negative for anti-PLA₂R but continued to have nephrotic syndrome at 12 months, achieved remission by 14 months.

Conclusions: PLA₂R antibodies and glomerular deposits are present in over two-thirds of IMN. PLA₂R antibodies have an association with clinical response and the immunological recovery may precede clinical recovery.

SA-OR015

An Indirect Immunofluorescence Test (IFT) to Measure Thrombospondin Type-1 Domain-Containing 7A Antibodies (THSD7A-Ab) in Patients with Membranous Nephropathy (MN) *Elion Hoxha,¹ Laurence H. Beck,² Nicola M. Tomas,¹ Christian Probst,³ David J. Salant,² Rolf A. Stahl.¹ ¹III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ²Boston Univ School of Medicine, Boston Univ, Boston, MA; ³EUROIMMUN AG, Lübeck, Germany.*

Background: THSD7A is a target antigen in MN. Measurement of THSD7A-Ab might be helpful for the diagnosis of MN and when making treatment decisions in these patients.

Methods: In this study we validated an IFT to detect THSD7A-Ab in 2 cohorts of patients with biopsy-proven MN. The presence of THSD7A-Ab was correlated with clinical parameters reflective of disease activity.

Results: Using the western blot (WB) technique, we identified 35 patients positive for THSD7A-Ab, 24 in the Hamburg cohort and 11 in the Boston cohort. 34 out of the 35 cases resulted THSD7A-Ab positive in the IFT analysis. All 35 THSD7A-Ab positive patients were negative for PLA₂R-Ab in both analyses. They were 56.5±17.0years old and 14 (40%) were male. Proteinuria was 6.9±4.3g/day, serum creatinine 1.3±0.7mg/dl. In 22 patients the time between serum collection and renal biopsy was less than 6 months and 18 had no immunosuppression prior to serum collection. The control group consisted of 671 patients, 555 with MN (120 of them PLA₂R-Ab positive) and 116 with renal diseases other than MN (all of them PLA₂R-Ab negative). All these patients were negative for THSD7A-Ab when measured with the IFT. In 30 randomly selected PLA₂R-Ab positive patients sera were analyzed and resulted negative for THSD7A-Ab and positive for PLA₂R-Ab in IFT and WB analyses. For 4 THSD7A-Ab positive patients follow-up data of at least 12 months could be analyzed. In 1 patient THSD7A-Ab disappeared and he experienced

remission of proteinuria. In 3 patients THSD7A-Ab persisted, 2 of them achieved remission of proteinuria, 1 had a relapse 3 months afterwards. The third patient had no remission of proteinuria during follow-up.

Conclusions: In this cohort of patients with MN the new IFT showed 97% sensitivity and 100% specificity for the detection of THSD7A-Ab compared to WB. A larger cohort of patients and their clinical follow up will be necessary to test its usefulness in patients with MN.

Funding: Government Support - Non-U.S.

SA-OR016

Melanocortin 1 Receptor (MC1R) Is Dispensable for the Proteinuria Reducing and Glomerular Protective Effect of Melanocortin Therapy Yingjin Qiao,¹ Anna-lena Berg,² Yan Ge,¹ Zhangsuo Liu,¹ Rujun Gong,¹ ¹Brown Medical School; ²Lund Univ, Sweden.

Background: Evidence suggests that melanocortin therapy by using ACTH or non-steroidogenic melanocortin peptides attenuates proteinuria and podocyte injury in animal models of glomerular diseases and induces remission of nephrotic syndrome in patients with a variety of proteinuric glomerulopathies, even those resistant to steroids. The underlying mechanism, however, remains elusive. This study aimed to validate the role of MC1R in mediating the beneficial effects of melanocortin therapy in glomerular diseases, as suggested by recent research.

Methods: The recessive yellow MC1R-mutant (MC1R^{ec}) and wild type (WT) mice were injured by lipopolysaccharide (LPS) or adriamycin (ADR) to develop podocytopathy and the effect of NDP-MSH, a non-steroidogenic melanocortin pan agonist, was tested. In patients with steroid-resistant nephrotic syndrome and nonfunctional MC1R mutations, the effect of ACTH therapy was evaluated.

Results: Following LPS or ADR insult, NDP-MSH attenuated proteinuria in WT and MC1R^{ec} mice to the same extent and ameliorated signs of glomerular injury and podocytopathy, including loss of podocyte markers, *de novo* expression of podocyte damage markers, and podocyte foot process effacement. *In vitro* in primarily cultured podocytes, LPS or ADR elicited apoptosis and podocyte hypermotility, and impaired the filtration barrier function of podocyte monolayers. These injurious effects were mitigated by NDP-MSH to a similar degree in podocytes derived from WT and MC1R^{ec} mice. Moreover, two patients with congenital red hair and nephrotic syndrome due to idiopathic membranous nephropathy were enrolled and confirmed by gene sequencing to bear nonfunctional MC1R mutations. After failing multiple immunosuppressive regimens, including glucocorticoids, the patients were converted to synthetic ACTH monotherapy for 21 months and 8.5 months respectively (escalation and de-escalation included) and both achieved complete remission of proteinuria, denoting a steroid independent effect.

Conclusions: Melanocortin therapy confers a proteinuria reducing and podoprotective effect in proteinuric glomerulopathies *via* a mechanism independent of MC1R.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

SA-OR017

Clinical Genetic Testing for the C3 Glomerulopathies and Thrombotic Microangiopathies Using a High-Throughput Panel Fengxiao Bu, Nicolò Ghiringhelli Borsa, Michael Jones, Erika Takanami, Carla Nishimura, Jill Johanna Hauer, Hela Azaiez, Elizabeth Ann Black-Ziegelbein, Nicole Meyer, Diana Kolbe, Yingyue Li, Kathy Frees, Michael J. Schnieders, Christie P. Thomas, Carla M. Nester, Richard J. Smith. *Univ of Iowa, Iowa City, IA.*

Background: C3 glomerulonephritis (C3GN), dense deposit disease (DDD), atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) are rare diseases with phenotypic similarities and genetic commonalities. Variants in the *CFH*, *CFI*, *CFB*, *C3*, *CFHR5*, *CD46*, *DGKE*, *ADAMTS13*, *THBD* and *PLG* genes, and copy number variation of *CFHR3-CFHR1* contribute to their pathogenesis and inform diagnosis and treatment options. To improve patient care, we developed a comprehensive genetic complement panel (GCP) to screen these genes. Herein we present our one-year experience using this panel in the clinical care of these patients.

Methods: 184 patients (37 with C3G and 147 with TMA) were studied using the GCP panel.

Results: Positive genetic diagnoses were provided in 43% of C3G patients and in 41% of TMA patients.

Disease (n)	CFH	CD46	CFI	CFB	C3	CFHR5	ADAMTS13	THBD	DGKE	PLG	Total
TMA (147)	14	9	10	1	8	4	10	2	3	4	65
aHUS (118)	12(4)*	9(3)	8(2)	1	7(1)	2	6		3(2)	3	51
TTP (8)	1(1)						2	1			4
aHUS/TTP (12)	1		1				2	1		1	6
Other (11)			1		1(1)	2(1)					4
C3G (37)	6	0	2	3	5	1	1	1	3	1	23
C3GN (30)	5		1	3	3(2)	1	1	1	2	1	18
DDD (5)	1		1		2						4
C3GN/DDD (2)									1		1

17 novel and 71 rare variants (minor allele frequency <1%) were identified, which we classified as pathogenic (11), likely pathogenic (12), or of uncertain significance (65). In C3G patients, the novel/rare variant load was increased in both C3 convertase (*C3* and *CFB*) and complement regulator (*CFH*, *CFI*, *CFHR5*, and *CD46*) genes, consistent with a multifactorial genetic contribution to this disease. In TMA patients, the novel/rare variant load was increased only in complement regulator genes, consistent with an abnormality in regulation of the alternative complement pathway as a driving factor in this disease.

Conclusions: GCP panel provides a comprehensive and efficient genetic screen of complement genes. The observed differences in variant aggregation in patients with C3G and TMA refine our understanding of these diseases.

Funding: Private Foundation Support

SA-OR018

Amelioration of the Adverse Effects of Prednisolone by Rituximab Treatment in Adults with Steroid-Dependent Minimal-Change Nephrotic Syndrome Yoei Miyabe, Takashi Takei, Yuko Iwabuchi, Takahito Moriyama, Kosaku Nitta. *Tokyo Women's Medical Univ, Japan.*

Background: We previously demonstrated the efficacy of single-dose 6-monthly rituximab infusions in 25 adults with steroid-dependent minimal-change nephrotic syndrome. Herein, we assessed the safety of rituximab treatment and its effect in ameliorating the adverse effects of prednisolone (PRED) in a larger study sample.

Methods: We treated 54 adult patients with four a single-dose 6-monthly infusions of rituximab (375 mg/m² BSA per dose). We compared the adverse effects of PRED (osteoporosis, hypertension and diabetes mellitus) between the first rituximab infusion (baseline) and the end of the 24-month observation period. In addition, we examined the adverse effects of rituximab during the same period.

Results: The PRED dose was significantly lower at 24 months than at the baseline. The bone density was significantly higher at 24 months as compared to the baseline value (Z-score: -1.8 vs. -1.1; p < 0.05). Blood pressure at 24 months was significantly lower than that at the baseline (120.9/74.4 vs. 111.8/70.3 mmHg; p < 0.05). Eight patients with diabetes mellitus showed improved glycemic control at 24 months as compared to that at the baseline. There were no severe adverse effects of rituximab. However, mild infusion reactions occurred in 31 patients (57%). The frequency of the infusion reactions decreased significantly with every successive infusion.

Conclusions: Rituximab treatment was effective and safe in patients with steroid-dependent nephrotic syndrome, allowed reduction of the PRED dose, and ameliorated the adverse effects of PRED. It may be preferentially used in patients at a risk of the adverse effect of PRED.

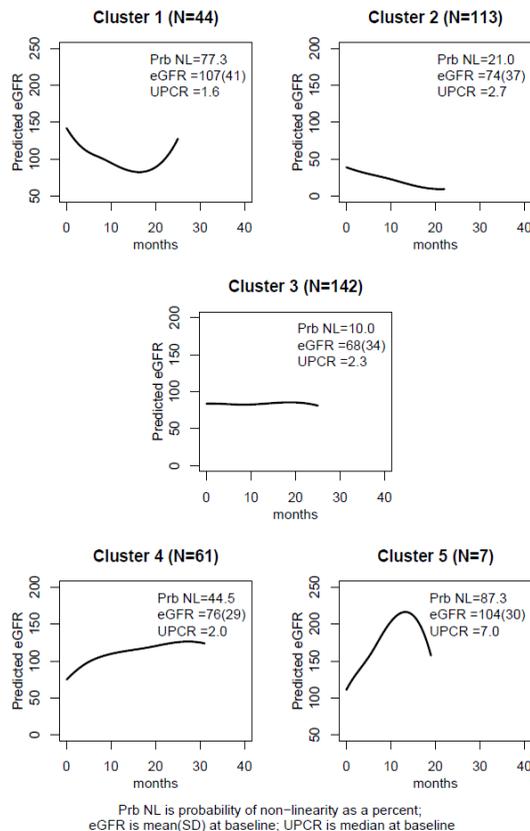
SA-OR019

Determining eGFR Trajectory Clusters in the NEPhrotic Syndrome STUdy Network (NEPTUNE) Laura H. Mariani,^{1,2} Jarcy Zee,² Tony Wang,² Viji Nair,¹ Wenjun Ju,¹ Jonathan P. Troost,¹ Debbie S. Gipson,¹ Peter X.K. Song,¹ Brenda W. Gillespie,¹ ¹Univ of Michigan; ²Arbor Research Collaborative for Health.

Background: Non-linear changes in eGFR over time are common in nephrotic syndrome. Traditional outcomes (e.g. 50% eGFR decline) may not capture these changes. We identified patient clusters via eGFR longitudinal trajectory and associated clinical characteristics with the groups.

Methods: NEPTUNE is a multi-center, prospective cohort study of children and adults with >500mg/day of proteinuria, enrolled at the time of renal biopsy. eGFR was calculated using the CKD-Epi formula for participants >18 yo and modified CKiD-Schwartz formula for those <18 yo. 367 patients with >3 eGFR measurements were included. Each patient's eGFR trajectory was estimated using Bayesian smoothing and a probability of non-linearity was calculated (Li, AJKD, 2012;59(4)). Quadratic regression coefficients from each trajectory were used in a clustering algorithm to identify distinct groups by minimizing within-cluster variance.

Results: Mean follow-up time was 26 mo. 25% (n=92) of the cohort had a trajectory with >50% probability of being non-linear and 10% (n=35) had a non-linearity probability >83%. The clustering algorithm produced five trajectory groups. Baseline mean eGFR (p<0.001) and median upcr (p<0.001) differed by cluster. Mean age was lowest in clusters 1 and 5 (28 and 25 vs. 39, 39, 31; p=0.002). Race and sex did not vary by cluster. MN composed 13-20% of each cluster whereas FSGS composed 40 and 35% of clusters 2 and 3, respectively (p=0.005).



Conclusions: This unique statistical approach identified clusters which describe individual eGFR trajectories. Non-linear trajectory groups had more young patients, higher eGFR and upcr. Further work is needed to determine whether trajectory clusters represent different underlying disease pathophysiology and to identify cluster predictors at the time of biopsy.

Funding: NIDDK Support, Other NIH Support - NCATS, ORDR

SA-OR020

The Role of Calcineurin Inhibitors in Early Treatment of Primary FSGS
 Louis-Philippe Laurin,¹ Bethany J. Foster,⁴ A. Gasim,² Caroline J. Poulton,³ J. Charles Jennette,² Ronald J. Falk,³ Patrick H. Nachman.³ ¹*Div of Nephrology, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada;* ²*Dept of Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC;* ³*Div of Nephrology and Hypertension, Univ of North Carolina at Chapel Hill, Chapel Hill, NC;* ⁴*Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada.*

Background: In primary focal segmental glomerulosclerosis (FSGS), calcineurin inhibitors (CNIs) have primarily been studied in patients deemed resistant to glucocorticoid (GC) therapy. Little data is available about their use early in the treatment of FSGS. We sought to estimate the association between choice of therapy and end-stage kidney disease (ESKD) in idiopathic FSGS.

Methods: An inception cohort of patients with biopsy-proven primary FSGS diagnosed between 1980 and 2012. Time to ESKD between different early therapies was reported with time-dependent Cox regression hazard ratio (HR) with 95% confidence interval (CI).

Results: 458 patients were studied (332 NOS, 64 Tip, 62 Collapsing): age 40.7±20.8 years; 45.6% Black; 48.7% female; follow-up time 92±94 months. 183 patients received no immunosuppression, 173 received GC alone, 90 were treated with CNIs ± GC and 12 received other immunosuppressive agents.

Multivariate determinants of ESKD	HR (95% CI)
Immunosuppression	
None	1
CNIs and/or GC	0.49 (0.28-0.86)
Age	1.00 (0.99-1.01)
Male sex	1.15 (0.76-1.73)
FSGS variant	
NOS	1
Tip	0.21 (0.09-0.48)
Collapsing	1.71 (0.99-2.95)
Baseline eGFR <30 mL/min/1.73m ²	4.28 (2.81-6.48)
Baseline proteinuria ≥3.5 g/d	1.25 (0.68-2.29)
Baseline serum albumin (per g/dL higher)	0.69 (0.53-0.90)
Baseline hypertension	1.33 (0.81-2.20)

Although not statistically significant, CNIs ± GC were associated with a lower likelihood of ESKD compared to GC alone [HR 0.42 (95% CI 0.15, 1.18)].

Conclusions: The use of CNIs as part of the early immunosuppressive regimen in primary FSGS may be associated with improved outcome, but their superiority over GC alone remains unproven.

SA-OR021

Living Donation Has a Greater Impact on Allograft Survival Than HLA Matching in Pediatric Renal Transplant Recipients
 Matko Marlais,¹ Alex J. Hudson,² Laura Anne Pankhurst,² Susan V. Fuggle,² Stephen D. Marks.³ ¹*Univ College London, United Kingdom;* ²*NHS Blood and Transplant, United Kingdom;* ³*Great Ormond Street Hospital NHS Foundation Trust, United Kingdom.*

Background: Living donor kidney transplantation accounts for around half of all paediatric (<18 years) renal transplant recipients (PRTR) and results in improved renal allograft survival, although there are no data comparing the effect of HLA-mismatching on outcomes. The UK 2006 Kidney Allocation Scheme prioritises children with good HLA mismatching (Level 1/2: 000 A,B,DR or [0 DR & £1 B]). The aim of this study was to determine the effect of HLA mismatching on deceased and living donor renal allograft outcomes in paediatric recipients.

Methods: Data were obtained from the UK Transplant Registry on all PRTR who received a donation after brain death (DBD) or living donor (LD) kidney-only transplant between 2000 and 2011. HLA A, B and DR mismatch were categorised into four levels and two groups. Data were fully anonymised and ethical principles adhered to.

Results: 1,389 paediatric renal transplant recipients were analysed; 807 (58%) received a DBD donor kidney. Using Cox proportional hazard regression modelling of renal allograft survival, the risk of graft failure is 1.55 times as likely in children who receive a well HLA-matched DBD kidney compared to those that receive a poorly HLA-mismatched LD kidney (p=0.01, 95% CI 1.11-2.18). This analysis accounts for survival improvements across transplant years. In both DBD and LD grafts, there was no difference in renal allograft survival in children who received a good or poorer HLA-mismatched transplant (p=0.16 for DBD graft, p=0.55 for LD graft).

Conclusions: In children, well HLA-matched DBD renal transplants have inferior graft outcomes when compared with poorly HLA-matched LD grafts. It is difficult to justify preferentially waiting for an improved HLA-matched DBD kidney even when a poorer HLA-mismatched LD kidney transplant is available.

Funding: Government Support - Non-U.S.

SA-OR022

UK National Registry Study of Kidney Donation After Circulatory Death for Pediatric Recipients
 Matko Marlais,¹ Laura Anne Pankhurst,² Alex J. Hudson,² Khalid Sharif,³ Stephen D. Marks.⁴ ¹*Univ College London, United Kingdom;* ²*NHS Blood and Transplant, United Kingdom;* ³*Birmingham Children's Hospital, United Kingdom;* ⁴*Great Ormond Street Hospital, United Kingdom.*

Background: Donation after circulatory death (DCD) is an important source of organs for kidney transplantation and evidence in adults suggests that similar graft outcomes are achieved to donation after brain death (DBD) kidney transplantation. There is very little evidence reporting the use of DCD kidneys in children. The aim of this study was to determine graft outcomes for children in the UK who have received a DCD kidney and compare these to outcomes for all renal transplants.

Methods: Data was collected on all kidney transplants performed for paediatric recipients (age <18 years) in the UK from the NHS Blood and Transplant registry from 2000-2014 and separated into DCD, DBD and living donor kidney transplants. Data obtained included donor and recipient characteristics with 3-year graft survival and overall patient survival. All data were fully anonymised and ethical principles adhered to.

Results: 1773 kidney transplants were performed in children in the UK from 2000-2014. 22 (1.2%) of these were from DCD donors, 955 (53.9%) were from DBD donors and 796 (44.9%) were from living donors. 3-year graft survival was 95.5% in the DCD group, 87.1% in the DBD group and 92.9% in the living donor group. Overall patient survival is 100% in the DBD group, 98.7% in the DBD group and 98.8% in the living donor group.

In the DCD group the median time to asystole was 12.5 minutes and the median standard warm ischaemia time was 13 minutes. In the DCD group there was 1 case of primary non-function and 5 cases of delayed graft function.

Conclusions: This is one of the largest studies reporting outcomes in children who receive DCD kidney transplants. In the post-2000 era children receiving a DCD kidney transplant have good graft survival at 3-year follow up, comparable to those receiving a kidney from a DBD donor or a living donor. This limited evidence encourages the use of selected DCD kidneys in paediatric transplantation as favourable graft outcomes can be achieved, and national DCD allocation algorithms may need to be amended in view of this.

Funding: Government Support - Non-U.S.

SA-OR023

Longitudinal Change in Neurocognitive Functioning in Pediatric Chronic Kidney Disease Stephen R. Hooper,¹ Matthew Matheson,² Rebecca J. Johnson,² Arlene C. Gerson,² Marc Lande,² Susan R. Mendley,² S. Shinnar,² Debbie S. Gipson,² Susan L. Furth,² Bradley Warady.² ¹UNC; ²CKiD Study Group.

Background: Few longitudinal data exist on the cognitive functioning of children with mild to moderate chronic kidney disease (CKD). We report longitudinal findings for the neurocognitive functioning of participants with mild to moderate CKD from the 48-site CKiD Study, with a particular focus on identifying CKD-related variables predictive of change in cognition over time and progression to renal replacement therapy (RRT).

Methods: The sample comprised 2,009 assessments over a span of approximately 12 years. Measures of IQ, attention, and parent ratings of executive functions were obtained. Joint longitudinal mixed models and time-to-event models with a shared random effect were used to examine the predictive value of CKD-related variables at study entry (glomerular diagnosis, age of CKD onset, iGFR, nephrotic proteinuria, elevated blood pressure, anemia) and over time (duration of disease, iGFR annual percent change) adjusting for baseline covariates (e.g., gender, maternal education), while simultaneously examining the association of neurocognitive decline with RRT.

Results: Median chronological age at study entry was 11.3 yrs; 56% Caucasian; 62% male. 33% had maternal education of a college degree. The median duration of CKD was 7.9 yrs., with 62% of children having disease onset at birth. 21% had a glomerular diagnosis; average iohexol-based GFR was 52.3 ml/min/1.73m². After adjusting, lower iGFR and elevated blood pressure at study entry were associated with declining Performance IQ. Lower iGFR and annual percent change in iGFR were associated with worse parent ratings of executive functioning. The shared parameter associating declining neurocognitive abilities with RRT showed Attention Variability to be related to progression to RRT.

Conclusions: Findings suggest that selected disease-related variables should trigger referral for neurocognitive assessment as children with lower iGFR and elevated blood pressure, and those with larger annual iGFR change may be at greatest risk for neurocognitive declines. Attention variability also was significantly associated with CKD disease progression to RRT.

Funding: NIDDK Support

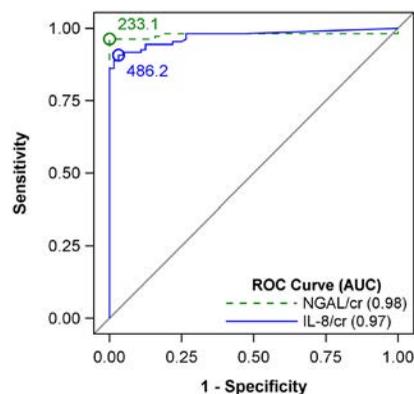
SA-OR024

Biomarkers and Urinary Tract Infection in Infants Sindri Valdimarsson, Sverker Hansson, Ulf I. Jodal. *Pediatric Urology Center, The Queen Silvia Children's Hospital, Sahlgrenska Academy, Univ of Gothenburg, Göteborg, Sweden.*

Background: Urine culture is needed to diagnose infants with urinary tract infection (UTI). Symptoms are nonspecific and urine biomarkers are a possible tool to improve the diagnostic accuracy minimizing the need for investigations and invasive procedures. The aim was to evaluate if urine biomarkers can aid in the diagnosis of UTI.

Methods: This is a prospective study of infants with first UTI. Urine biomarkers were measured in infants with UTI and in a control group of children with fever from other causes. Measured urine biomarkers were Kidney injury molecule 1, Clara cell protein, Retinol binding protein, Neutrophil gelatinase associated lipocalin, high sensitive C-reactive protein, Interleukin-1b, Interleukin-6 and Interleukin-8 (IL-8); all were adjusted for urine creatinine(cr). The area under the ROC curve (AUC) for each biomarker was compared for children with UTI versus children with fever without UTI; the optimal cutoff level for equal weight on sensitivity and specificity was determined.

Results: 108 infants with UTI, 59 boys (mean age 2.7 months) and 49 girls (mean age 4.0 months) and a control group of 64 patients with fever without UTI (23 girls and 41 boys) were included. The biomarkers NGAL/cr and IL-8/cr were superior in differentiating between children with and without UTI. AUC for NGAL/cr was 0.98 and a cutoff value of 233 had 96.3% sensitivity and 100% specificity. AUC for IL-8/cr was 0.97 and a cutoff value of 486 had 91.7% sensitivity and 95.3% specificity.



Conclusions: This prospective study shows that the urine biomarkers NGAL and IL-8 had high sensitivity and specificity for the diagnosis of UTI in infants. Infants with fever and a low NGAL/cr value were highly unlikely to have a UTI.

Funding: Government Support - Non-U.S.

SA-OR025

Phospholipase A2 Receptor Autoantibodies in Pediatric Membranous Nephropathy Rebecca Kirkwood-Wilson,¹ Maryline Fresquet,¹ Nicholas J. Webb,² Paul E. Brenchley,³ Rachel Lennon.^{1,2} ¹Wellcome Trust Centre for Cell-Matrix Research, Univ of Manchester, United Kingdom; ²Dept of Paediatric Nephrology, Royal Manchester Children's Hospital, United Kingdom; ³Manchester Inst of Nephrology and Transplantation, United Kingdom.

Background: Membranous nephropathy (MN) is the commonest cause of nephrotic syndrome in adults, with most cases being primary, or autoimmune in nature. Understanding of MN advanced with the discovery of phospholipase A2 receptor (PLA2R) as the target autoantigen and with the detection of circulating autoantibodies in the sera of adult patients. In the pediatric population, MN is rare and often presents with persistent, steroid-resistant, proteinuria and is diagnosed by typical histological features on renal biopsy. In this study, we describe the clinical phenotype, renal histological analysis, anti-PLA2R status, and autoantibody binding in 6 children with biopsy-proven PMN treated at the Royal Manchester Children's Hospital over the past 7 years.

Methods: We carried out phenotypic characterisation of patients, determination of anti-PLA2R status by ELISA, anti-PLA2R Ig subclass analysis and histological characterisation of renal biopsies. Anti-PLA2R binding was determined by comparing autoantibody reactivity to recombinant fragments of the PLA2R under denatured and native conditions.

Results: Determination of anti-PLA2R status revealed 50% of children were seropositive. Seropositivity was associated with a severe clinical phenotype with nephrotic syndrome with renal impairment and IgG4 was the predominant subclass. Seronegative patients presented with asymptomatic proteinuria. Autoantibody reactivity patterns to recombinant fragments of the PLA2R, differed with clinical phenotype at presentation.

Conclusions: Here we report, for the first time, a series of 6 children with biopsy-proven MN. We demonstrate a correlation between clinical phenotype and anti-PLA2R status and evaluate autoantibody-PLA2R binding in the paediatric MN population. Our results suggest that minor, or alternative, epitopes exist within the PLA2R which may be responsible for autoantibody binding in paediatric MN.

SA-OR026

APOLI-Associated Glomerular Disease in African-American Children in the CKiD and NEPTUNE Cohorts Derek Ng,¹ C. Robertson,² C. Gillies,² Sophie Limou,³ Robert Woroniecki,⁴ Kimberly J. Reidy,⁵ Sangeeta R. Hingorani,⁶ Keisha L. Gibson,⁷ Christine B. Sethna,⁸ Cheryll Ann Winkler,³ Jeffrey B. Kopp,⁹ Susan L. Furth,¹⁰ Bradley Warady,¹¹ John R. Sedor,¹² Frederick J. Kaskel,⁵ M. Sampson.² ¹Johns Hopkins; ²U of Michigan; ³NCI; ⁴Stony Brook Univ; ⁵Montefiore Med. Center; ⁶U of Washington; ⁷U of North Carolina; ⁸Cohen Children's Med Center; ⁹NIDDK; ¹⁰Children's Hosp of Philadelphia; ¹¹Children's Mercy Hosp; ¹²Case Western Reserve.

Background: Little is known about APOLI associated nephropathy in children. This study aimed to describe characteristics and longitudinal outcomes in African-American children with glomerular disease, stratified by APOLI risk genotype in the Chronic Kidney Disease in Children cohort (CKiD) & the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: Enrollment criteria for CKiD was age 1-16, diagnosis of CKD, & estimated glomerular filtration rate (GFR) of 30-90 mL/min. NEPTUNE subjects were enrolled with suspected primary nephrotic syndrome, proteinuria, >0.5g/day, & clinically indicated biopsy. 56 CKiD subjects with glomerular disease & 48 NEPTUNE pediatric subjects were included here (all African-American). APOLI was directly genotyped and subjects were classified as low risk (LR, 0 or 1 risk alleles) or high risk (HR, 2 risk alleles). All analyses were performed under the recessive model; LR vs HR subjects. By APOLI genotype, odds of prematurity and eGFR & proteinuria over time were modeled.

Results: All subjects were of similar age (12 to 15 yrs). HR subjects in both cohorts had a lower baseline GFR by about 20 ml/min. The combined cohort demonstrated a significantly increased odds of prematurity in HR subjects (OR: 4.57; 1.4-15.5). NEPTUNE HR subjects had 15% decline in GFR per year, comparable to that seen in all CKiD subjects, independent of genotype. LR NEPTUNE subjects had no eGFR decline (3% per year).

Conclusions: HR genotype was associated with higher odds of prematurity, suggesting an interaction between the *APOLI* HR genotype and prematurity in the development of pediatric glomerular disease and subsequent CKD. NEPTUNE children with the HR genotype had a similar decline in eGFR as CKiD subjects.

Funding: NIDDK Support

SA-OR027

Comprehensive Approach to Understand Human Renal Development Based on the Identification of Responsible Genes for CAKUT Akemi Shono, Naoya Morisada, Kandai Nozu, Kazumoto Iijima. *Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.*

Background: Although regenerative medicine using the pluripotent stem cells holds promise of the treatment for the renal failure, the complexity of the structure composed of diverse cell types makes the difficulty in the establishment of the differentiation protocol into renal nephron. Towards the comprehensive understanding of the molecular network underlying human renal development, this study aims to identify responsible genes for congenital anomalies and the kidney and urinary tract (CAKUT) and reveal the molecular mechanism of pathogenesis.

Methods: Two hundred six CAKUT cases including 115 cases from 105 families of syndromic CAKUT and 91 cases from 82 families of non-syndromic CAKUT together with some indistinguishable cases from CAKUT, were collected in agreement with participants, which was approved by the ethical committee at Kobe University. Genomic DNA samples were analyzed by the next-generation sequencing (Illumina exome and Agilent custom panels) in combination with the conventional Sanger sequencing and/or the DNA microarray subsequent to the phenotype classification based on the clinical manifestation.

Results: Responsible genes in 62 cases from 44 families were identified. The phenotype classification assisted to detect the reported responsible genes including PAX2, EYA1, HNF1B, UMOD, OFD1, SALL1 and CHD7 by Sanger sequencing, and the next-generation sequencing powerfully enabled us to identify responsible/candidate genes including PAX2, UPK3A, RET, FRAS1 and EP300 which were unpredictable from the clinical phenotype. To clarify the molecular mechanisms of candidate genes, further experiments including in vitro and in silico assays would be required.

Conclusions: These results would be significant to understand the network of disease-associated genes and the molecular mechanism underlying the human renal development, and might give us a future perspective for the regenerative medicine.

Funding: Government Support - Non-U.S.

SA-OR028

A Randomized Study of Cholecalciferol Supplementation in Incident Hemodialysis Patients – Preliminary Evaluation After 2 Years Cristina Jorge,^{1,2,5} Patricia Matias,^{1,2,5} Pedro Bravo,³ Clara Mil-homens,⁴ Cecilia Silva,⁴ Pedro M. Ponce,⁴ Carlos M.P.C. Oliveira,³ Célia Gil,^{1,2,5} Manuel A. Ferreira,^{1,2,5} ¹Nephrocare Vila Franca de Xira, Portugal; ²Dialverca, Portugal; ³Nephrocare Almada, Portugal; ⁴Nephrocare Lumiar, Portugal; ⁵NIDAN, Portugal.

Background: Studies have shown that vitamin D deficiency is associated with cardiovascular (CV) risk factors, morbidity and mortality in uremic patients (pts). Our aim is to prospectively assess the safety and efficacy of vitamin D (cholecalciferol) supplementation in incident HD pts and to compare the clinical results with a control group supplemented with placebo.

Methods: We evaluated 108 (66% M) pts in group A (GA) under VIT D 20 000 U/wk, and 95 (67% M) pts in Group B (GB) on placebo, matched in age, (mean 66 and 65 years), BMI (mean 25.7 and 26.3 kg/m²) respectively, etiology of renal disease and the presence of comorbidities such as HTN, arrhythmia, peripheral vascular disease and cancer. The prevalence of DM (42 vs 57%), ischemic heart disease (18 vs 32%) and cerebrovascular disease (16 vs 27%) was higher in GB. A follow-up of 12 and 24 months (m) was attained respectively in 67 and 18 pts in GA vs 60 and 21 pts in GB.

Results: The basal levels of 25(OH)VitD3 were similar in the two groups (median 11 ng/mL) and significantly increased at 12m in GA (30 vs 11 ng/mL in GB; p<0.001) and at 24m (38 in GA vs 15 ng/mL in GB; p<0.001). Laboratory evolution (Ca, P, PTH, bAP, Hb, CRP or albumin), was similar in both groups. There was difference in the Erythropoiesis Resistance Index (ERI) (mcg/kg/wk/g/dl) at T0 (GA=0.034 > GB=0.023, p=0.03) and at 24m (GA=0.010 < GB=0.022, p=0.01). No differences in the evolution of pulse pressure, left ventricular mass index or vascular calcifications were observed. The leading causes of hospitalization were CV and infectious, similar in both groups. There were 18 (16.7%) deaths in GA and 12 (12.6%) in GB (Log rank=0.752; p=NS, Kaplan-Meier). Treatment with antihypertensive drugs, phosphate binders, active vitamin D, or cinacalcet was similar in both groups.

Conclusions: Cholecalciferol administration at a dose of 20 000 U/week was safe and permitted a significant increase of vitamin D levels and a decrease of ERI in the supplemented group at 24m.

SA-OR029

Levodocarnitine Improves Cardiac Function in Hemodialysis Patients with Left Ventricular Hypertrophy Masanori Abe, Noriaki Maruyama, Tetsuya Furukawa, Kazuyoshi Okada. *Nephrology, Hypertension and Endocrinology, Nihon Univ School of Medicine, Tokyo, Japan.*

Background: Levodocarnitine deficiency in hemodialysis (HD) patients is common. This may contribute to clinical disorders, including cachexia, erythropoiesis stimulating agent resistant anemia, and glucose intolerance, muscle weakness, and myopathy as well as to intradialytic symptoms such as muscle cramps, hypotension, and cardiac arrhythmia. Although the effect of levodocarnitine therapy on uremic anemia has been studied in small trials, its effects on cardiac function remain unclear.

Methods: This prospective, open-label, randomized, parallel, controlled, multi-center trial examined 222 HD patients who were randomly assigned to an oral levodocarnitine therapy group (n = 110) or a control (no levodocarnitine therapy) group (n = 112). Patients were monitored for 12 months during levodocarnitine treatment (administered orally 20 mg/kg/day) or control. The primary endpoint was cardiac function measured by echocardiography. The secondary endpoints were clinical parameters and identification of factors that predict a favorable response to levodocarnitine therapy. Echocardiographic parameters were measured at baseline and after 6 and 12 months of therapy.

Results: A total of 222 patients were randomly assigned, of whom 148 patients (levodocarnitine group, n = 75; control group, n = 73) were analyzed. The ejection fraction values increased from 54.0±5.8% at baseline to 56.0±6.1% after 6 months (p<0.001) to 58.1±5.6% after 12 months (p<0.0001) in the levodocarnitine group, while no significant changes in ejection fraction were observed in the control group. Furthermore, left ventricular mass index (LVMI) and N-terminal probrain natriuretic peptide levels were significantly decreased throughout the study in the levodocarnitine group. Multivariate analysis revealed that LVMI was an independent predictor of improvement in ejection fraction following levodocarnitine therapy. Subgroup analysis revealed that responders to levodocarnitine were patients with left ventricular hypertrophy (LVH).

Conclusions: Levodocarnitine therapy is useful for hemodialysis patients with LVH; these patients may benefit from such therapy, with amelioration of cardiac function and mitigation of LVMI.

SA-OR030

Predictive Ability of Self-Rated Health and Symptom Burden for Mortality in Hemodialysis Donal J. Sexton,¹ Aoife C. Lowney,² Conall M. O'Seaghdha,³ Sinead Kinsella,⁴ Peter J. Conlon.³ ¹Medicine, HRB Clinical Research Facility, NUI Galway, Galway, Ireland; ²Palliative Medicine, Marymount Hospice, Cork, Ireland; ³Nephrology, Beaumont Hospital, Dublin, Ireland; ⁴Renal Medicine, Cork Univ Hospital, Cork, Ireland.

Background: Little is known about the ability of self-rated health to predict mortality in hemodialysis.

Methods: A prospective cohort study in hemodialysis (N=362). The Euro Quality of Life Questionnaire (EQ5D), the Palliative Care Outcome Scale Renal (POS-S Renal) and the participant self-rated health (EQ visual analogue scale: EQVAS) were used to assess HRQOL, symptom burden and self-rated health. Participants were followed from instrument completion to death or study end.

Results: Over a median (25th-75th centile) of 2.6 (1.41-3.38) years, 32% (N=116) of participants died. With competing risks survival analysis factors most notably associated with mortality adjusted hazard ratio (95%CI) included: higher symptom burden 2.4 (1.3, 4.3) P=0.004 (highest tertile), lower HRQOL 2.6 (1.3, 5.3) P=0.01 (lowest tertile), lower self-rated health 2.7 (1.4, 5.2) P=0.004 (lowest tertile). Answering 'Yes' to the questions: "problems with mobility?" 2 (1.1, 3.3) P=0.01, or "problems with usual activities?" 2.1 (1.4, 3.3), P<0.001. 55% of those aged > 60 years reporting problems with either self care, mobility or daily activities in this study died over a mean (SD) of 2.1 (1.1) years, compared to 18% over 2.5 (1) years in those reporting 'no' to these questions, P<0.001. After age adjustment area under the receiver operating curves (AUC) (95%CI) for mortality were: 0.71 (0.63, 0.80) for symptom burden, 0.76 (0.68, 0.84) for HRQOL and 0.71 (0.62, 0.79) for self-rated health.

Conclusions: Age adjusted participant-rated health and predictive models based on combinations of individual elements from the POS S Renal and EQ5D instruments could possibly aid in mortality discrimination and subsequent advance care planning in hemodialysis.

SA-OR031

Isonatric Dialysis Biofeedback in Hemodiafiltration with Online Regeneration of Ultrafiltrate in Hypertensive Hemodialysis Patients: A Randomized Controlled Study Lucile Mercadal,¹ Frederic Debelle,² Christine Fumeron,³ Lise Mandart,⁴ Isabelle Simon,⁵ Yhsou Delmas,⁶ Sophie Tezenas du montcel.⁷ ¹AP-HP, Paris; ²RHMS Baudour, Belgium; ³AURA Paris; ⁴CH Vannes; ⁵CH Erasme Bruxelles; ⁶CHU Bordeaux; ⁷Biostatistics, AP-HP, France.

Background: Biofeedback in hemodiafiltration with online regeneration of ultrafiltrate (HFR) could improve arterial hypertension by using an isonatric mode maintaining a natremia equal between start and end of the dialysis session. We evaluated the impact of Isonatric HFR (HFRiso) on hypertension compared to Conventional HFR.

Methods: 47 hemodialysis patients having an arterial pressure > 140/90 mmHg were randomized (ratio 2/1) HFR iso versus HFR during 24 dialysis sessions. The course from S1 to S24 of the predialytic systolic (SBP) and diastolic (DBP) blood pressure, the defined

daily dose (DDD) of antihypertensive treatment and of the dry weight were compared by t-test and by mixed model for repeated measurements adjusted for treatment x time interaction. The impact of age, diabetes and cardiovascular co-morbidities on response to treatment was evaluated. Tolerance was evaluated by the number of sessions complicated by symptomatic hypotension.

Results: In the Isonatric HFR group (N=32), the predialysis SBP decreased from S1 to S4 of 9 ± 20 mmHg (-0.12 ± 0.08 mmHg /day) and increased of 5 ± 24 mmHg ($+0.13 \pm 0.05$ mmHg /day) in the HFR group (N=15), variation that differed between the 2 groups (DS1-S24, $p = 0.035$; interaction treatment*time, $p=0.012$). The DBP (HFRiso -3 ± 14 mmHg vs HFR 5 ± 13 mmHg; $p=0.088$), the DDD of antihypertensive treatment (HFR iso -0.1 ± 0.9 vs HFR -0.3 ± 1.1 , $p=0.7$) and the dry weight (HFRiso 0.2 ± 1 vs HFR 0.2 ± 1.5 kg, $p=0.9$) did not vary during the study. Age influenced the PAS course independently of the treatment group (interaction age*time, $p=0.05$). The number of symptomatic hypotension was similar in the 2 groups.

Conclusions: Isonatric HFR improved blood pressure control without increasing dialysis hypotension episodes.

Funding: Pharmaceutical Company Support - Bellico

SA-OR032

Relevance of B-Lines on Lung Ultrasound in Volume Overload and Pulmonary Congestion: Clinical and Therapeutic Correlations in Hemodialysis Patients Marc M. Saad, Jeanne Kamal, Wissam Mansour, Boutros Karam, Elias Moussaly, Emad Gobran, Devjani Das, Morton J. Kleiner, Elie El-Charabaty, Suzanne E. El Sayegh. *Internal Medicine/Emergency Dept/ Nephrology, Staten Island Univ Hospital, Staten Island, NY.*

Background: Volume overload in patients on hemodialysis (HD) is an independent risk factor for death from cardiovascular events. The imminent role of B-Lines (BL) on ultrasound (US) in predicting physical performance, morbidity and mortality, raises interest in its utility for assessing volume status in patients on HD.

Methods: ESRD patients on HD at Island Rehab center older than 18 were screened. Those who have lung disease and pregnant women were excluded. Patients achieving their dry weight(DW) had a lung US in a supine position. Residents were trained to visualize BL and recorded scores in real time. Clips were reviewed by blinded certified physicians. Scores were classified as mild (0-14), moderate (15-30) and severe (>30) for pulmonary congestion, as validated by Zoccali et al.

Results: 81 patients on HD were recruited. 58 were males, mean age 59.7 years, hemoglobin 10.6 g/dL. 44 had NYHA Class 1, 24 had class 2, and 13 had class 3. In univariate analysis, NYHA class had significant correlation with BL scores and classes (<0.001), and diastolic dysfunction (0.002). In multivariate analysis, NYHA grade strongly correlates with B-Lines classification (0.01) but not with heart function (0.95). The mean difference between physicians and residents scoring was 3.77 (0.048). However this difference was not significant after classification and scores were in agreement (Kappa = 0.56).

Conclusions: At DW, NYHA grading tightly corresponded to BL classification irrespective of cardiac function. Pulmonary congestion is common among patients on HD; NYHA score is mainly driven by the extravascular water and not by heart dysfunction. These results render fluid overload estimated by BL a better predictor for ESRD patient's performance and a reliable indicator for their volume status assessment. Moreover, moderate lung congestion noted in patients with NYHA class 1 outline the importance of lung US in identifying subtle lung congestion opening a new concept for achieving DW.

SA-OR033

Combined Target Ranges for Blood Pressure and Fluid Overload Ulrich Moissl,¹ Peter Wabel,¹ Paul William Chamney,¹ Bernard J. Canaud,² Stefan Stuard.³ ¹GRD, Fresenius Medical Care, Bad Homburg, Germany; ²Medical Board, FMC, Bad Homburg, Germany; ³NephroCare Coordination, FMC, Bad Homburg, Germany.

Background: Recent research has revealed areas of increased mortality risk in the combination of systolic blood pressure (BPsys) and fluid overload (FO) (Fig 1a). It was the aim of this retrospective analysis to assess whether classifying patients according to a dedicated flow chart taking into account BP, FO and antihypertensive therapy (AHT) may indicate improved survival compared with a BP target range alone.

Methods: Pre-dialysis FO and BPsys were measured monthly in 31,349 patients from the Fresenius NephroCare Clinic Network. Patients were classified as being on/off target in January 2013 according to the flow chart in Figure 1b, which combines a BPsys target range of 130 to 160mmHg with information about AHT and FO [L] (Target1). FO was measured by bioimpedance spectroscopy. Normohydration was defined as FO normalized by extracellular volume <13% (females) and <15% (males). Target1 was compared with only a BPsys target range of 130 to 160 (Target2). All-cause mortality hazard ratios (HR) were calculated over 2 yrs follow-up time using COX analysis adjusting for 31 different co-morbidities and laboratory parameters.

Results: Unadjusted Kaplan Meier curves revealed a 2yr survival of 82% for patients on Target1, and 75% for being not on Target1 ($p<0.0001$), Fig 1c. Adjusted HR for patients being on Target1 was 0.74 [95% CI: 0.70 - 0.78]; the adjusted HR for being on Target2 was 0.84 [0.79 - 0.88]. At time of classification 66% of patients were on Target1, while 61% were on Target2.

Conclusions: Combining information on BPsys, AHT and FO indicates survival advantages compared with using only a BP target.

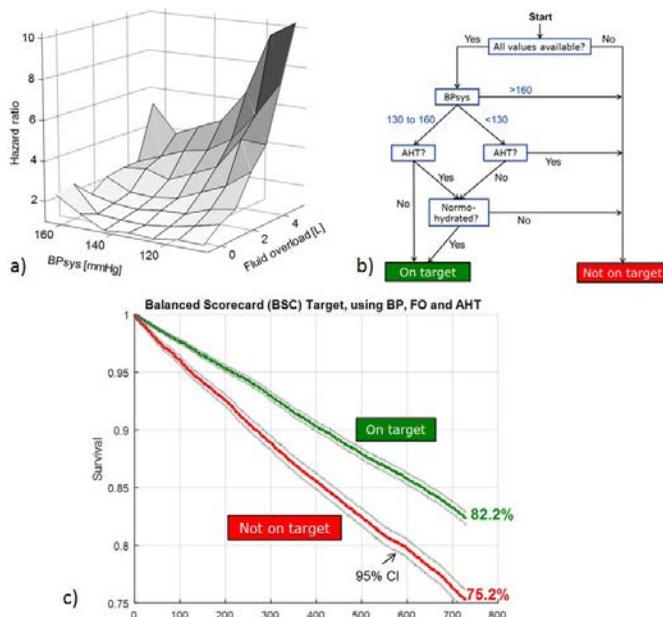


Fig 1. (a) Mortality risk of BPsys and FO. (b) Classification tree based on BPsys, AHT and FO. (c) Kaplan Meier curves for 31,349 patients being on/off target according to classification in Figure 1b.

SA-OR034

Volume Status Assessed by Bioimpedance in Hemodialysis Predicts Mortality Janice P. Lea, Laura Plantinga, Rebecca H. Zhang, Nancy G. Kutner. *Medicine, Emory Univ, Atlanta, GA.*

Background: Mortality rates average over 20% in the End-Stage Renal Disease (ESRD) US population with cardiovascular disease being the leading cause of death. Accurate intravascular volume assessment is critical in the treatment of patients who receive chronic hemodialysis (HD) therapy due to its deleterious effects on the heart and blood pressure (BP). Clinically assessed dry weight and interdialytic weight gain (IDWG) are often used as surrogates of volume status. Bioimpedance has emerged as an effective tool for volume management but is not readily available in clinical practice. Thus we examined the association of volume status determined by bioimpedance with mortality, compared to the association of IDWG and BP with mortality in ESRD patients.

Methods: ACTIVE/ADIPOSE (A Cohort Study to Investigate the Value of Exercise in ESRD/Analyses Designed to Investigate the Paradox of Obesity and Survival) was a multi-center study of prevalent HD patients coordinated by the United States Renal Data System in 2009-2011. The data collection sites were 14 outpatient dialysis clinics in Atlanta and San Francisco. Volume status by bioimpedance defined by calculation of extracellular fluid (ECF): total body water (TBW) ratio. Associations by quartiles of ECF:TBW, IDWG, and BP with 1-year mortality were estimated using Cox proportional hazards regression models.

Results: 660 patients were included in this analysis, with 36 total deaths at 1 year. After adjustments, each increase of 0.01 in ECF:TBW (range, 0.39-0.57) in quartiles was associated with a >30% increased risk of mortality, (HR- 1.32, 95% CI, 1.15-1.52) $p<0.001$. In comparison, quartiles of IDWG (HR- 0.96, 95% CI, 0.78-1.17) and BP (per 10 mmHg, systolic, HR=0.99, 95% CI, 0.82-1.19; diastolic (HR=0.90, 95% CI, 0.64-1.25), were not associated with mortality. Further, the associations of ECF:TBW with mortality were independent of BP, IDWG, and BMI.

Conclusions: Volume status by bioimpedance, but not IDWG or BP, was significantly and independently associated with greater mortality in this HD cohort. These findings question the common clinical practice of using IDWG as a surrogate of volume status in the HD population as it may not correlate with clinical outcomes.

Funding: NIDDK Support

SA-OR035

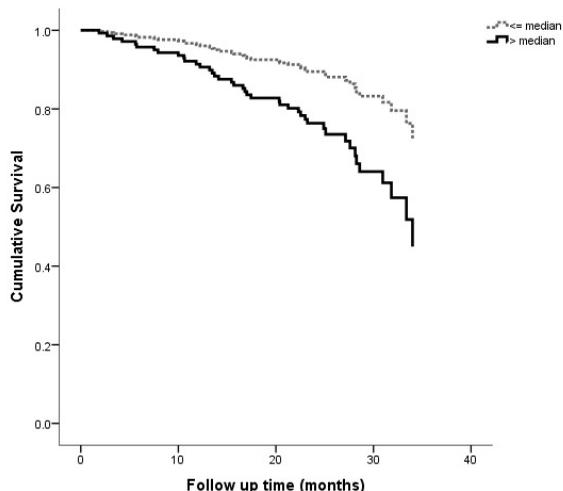
Abnormal Global Longitudinal Strain Is Associated with All-Cause Mortality in Hemodialysis Patients Diana Chiu, Darren Green, Nik Abidin, Philip A. Kalra. *Univ of Manchester, MAHSC, UK.*

Background: Cardiovascular mortality is high in hemodialysis (HD) patients. Early detection of cardiac dysfunction is important. Left ventricular global longitudinal strain (GLS) measures the maximal shortening of myocardial longitudinal length during systole compared to the resting length in diastole. Reduced GLS may reflect abnormal systolic function before loss of ejection fraction (EF) becomes apparent. We aimed to determine the prevalence, clinical correlates and prognostic value of abnormal GLS in stable HD patients.

Methods: Clinical and echocardiographic data were obtained in a prospective study of HD patients at one centre. Survival analysis for GLS was performed using Cox regression adjusted for age, co-morbidities, dialysis chronicity, laboratory data, left ventricular mass index adjusted for height (LVMIHt^{2.7}) and Teicholz EF.

Results: The mean age was 62±14years, 69% were male, 39% had diabetes, 29% heart failure, 17% coronary artery disease. The mean GLS was -13.4±3.5%, LV ejection fraction (LVEF) 63.8±12.9% and LVMIHt^{2.7} 53.6±17.2g/m^{2.7}. 98% of patients had abnormal GLS (>-20%), compared with 14% with reduced LVEF(<50%) and 55% with LV hypertrophy. Factors associated with an abnormal GLS included LVMIHt^{2.7} (OR 1.06, 95%CI 1.04-1.09, P<0.01), LVEF (OR 0.96, 95%CI 0.94-0.99, P<0.01) and diabetes (OR 2.04, 95%CI 1.08-3.9, p=0.03). Median follow-up was 24 (17-30) months, during which there were 41 deaths (21%). After adjustment for age, diabetes, coronary artery disease, LVEF, LVMIHt^{2.7}, 3 month-averaged serum potassium and albumin, a less negative GLS remained an independent predictor of all-cause mortality (HR 1.18 for each 1% worsening change in GLS, 95% CI 1.03-1.35, P=0.02).

Figure 1. Survival in <=median versus >median GLS (median = -13.7%)



Conclusions: Abnormal GLS is highly prevalent amongst HD patients, and appears to be a better marker of all-cause mortality in stable HD patients than the “standard” echocardiographic parameters LVEF and LVMIHt^{2.7}.

SA-OR036

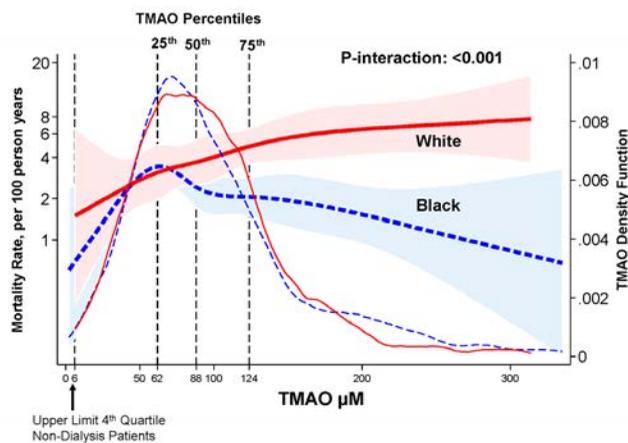
Trimethylamine-N-Oxide (TMAO) and Cardiovascular Events in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study Tariq Shafi,¹ Thomas H. Hostetter,² Timothy W. Meyer,³ Seungyoung Hwang,¹ Michal L. Melamed,⁴ Tanushree Banerjee,² Josef Coresh,¹ Neil R. Powe.⁵ ¹Johns Hopkins Univ; ²Univ of California San Francisco; ³Stanford Univ; ⁴Albert Einstein College of Medicine; ⁵Case Western Univ.

Background: Uremic toxins that contribute to cardiovascular (CV) disease and observed higher mortality in whites vs. blacks remain undefined. TMAO, a highly dialyzable metabolite, is associated with accelerated atherosclerosis and CV events in non-dialysis patients but previous studies in dialysis patients have been equivocal.

Methods: We measured TMAO in 1232 patients of the Hemodialysis (HEMO) Trial, 3-6 months after randomization and analyzed its association with CV mortality, sudden cardiac death (SCD) and first CV event, using Cox models adjusted for demographics, clinical characteristics, comorbidities, albumin and residual urea clearance.

Results: Mean age of the patients was 58 years, 34% white and 42% male. Median TMAO level was 88 μM (IQR, 62 to 124) and did not differ by race (p=0.9). The association of TMAO with outcomes differed by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with a 45% higher risk of CV mortality, 70% higher risk of SCD and 15% higher risk of CV events (Table). TMAO levels decreased in the higher Kt/V_{UREA} group but did not have an effect on outcomes (p>0.1).

Fig: Association between TMAO and CV Mortality Rate (Age and Sex Adjusted)



Adjusted HR* (95% CI) of the Association between TMAO and Outcomes

	Events	Overall	White	Black	P-interaction
CV Mortality	220	1.09 (0.96-1.24)	1.45 (1.24-1.69)	0.90 (0.77-1.06)	<0.001
Sudden Cardiac Death	126	1.18 (1.02-1.37)	1.70 (1.34-2.16)	0.92 (0.78-1.08)	<0.001
First CV Event	644	1.05 (0.97-1.13)	1.15 (1.01-1.32)	1.01 (0.92-1.10)	0.09

* Per 2-fold increase

Conclusions: The association between TMAO and CV events differs among white and black hemodialysis patients.

Funding: NIDDK Support

SA-OR037

Serum Asymmetric (ADMA) and Symmetric (SDMA) Dimethylarginine and Morbidity and Mortality in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study Tariq Shafi,¹ Neil R. Powe,² Timothy W. Meyer,³ Seungyoung Hwang,¹ Michal L. Melamed,⁴ Tanushree Banerjee,² Josef Coresh,¹ Thomas H. Hostetter.⁵ ¹Johns Hopkins Univ; ²Univ of California, San Francisco; ³Stanford Univ; ⁴Albert Einstein College of Medicine; ⁵Case Western Univ.

Background: ADMA, an endogenous nitric oxide synthase inhibitor, and SDMA, a promoter of oxidative stress, accumulate in dialysis patients and may contribute to uremic toxicity.

Methods: We measured predialysis levels of ADMA and SDMA in 1276 patients of the Hemodialysis (HEMO) Trial, 3-6 months after randomization and analyzed its association with all-cause and cardiovascular (CV) mortality, sudden cardiac death (SCD) and first CV event, using Cox model adjusted for potential confounders (demographics, clinical characteristics, comorbidities, albumin, residual urea clearance).

Results: Mean age of the patients was 58 years, 63% black and 42% male. Median (interquartile range) for ADMA was 0.9 μM (0.8, 1.0) and SDMA was 4.1 μM (3.3, 5.0). In fully adjusted models, ADMA was associated with all outcomes whereas SDMA was only associated with CV mortality (Table). Subgroup analyses did not show significant interactions with race or HEMO interventions.

Fully Adjusted Model for the Association of ADMA and SDMA with Outcomes in the HEMO Study

	Events	IR*	ADMA		SDMA	
			HR** (95% CI)	p	HR** (95% CI)	p
All-Cause Mortality	565	172	1.44 (1.13-1.83)	0.003	1.21 (1.00-1.47)	0.05
Cardiovascular Mortality	220	67	1.83 (1.29-2.58)	<0.001	1.40 (1.03-1.92)	0.03
Sudden Cardiac Death	126	38	1.79 (1.19-2.69)	0.006	1.40 (0.96-2.06)	0.08
First Cardiovascular Event	644	274	1.50 (1.20-1.87)	<0.001	0.98 (0.83-1.16)	0.83

* IR, Incidence Rate; **HR per 2-fold increase in solute

Conclusions: ADMA and SDMA are uremic solutes associated with morbidity and mortality in hemodialysis patients.

Funding: NIDDK Support

SA-OR038

Glomerulus on-a-Chip as a Model to Study the Glomerular Filtration Barrier In Vitro Stefano Da Sacco,¹ Jos Joore,² Paul Vulto,² Roger E. De Filippo,¹ Laura Perin.¹ ¹Urology, Children's Hospital Los Angeles, Los Angeles, CA; ²MIMETAS.

Background: The glomerular filtration barrier (GFB) has three major components: the podocyte with the "slit diaphragms", the glomerular basement membrane and the fenestrated glomerular endothelial cell (hGEC): each of them is essential for the correct blood filtration. Damage to any of these components often leads to a severe, irreversible GFB disruption with onset of chronic damage requiring drug treatment and eventually dialysis and transplantation. Development of alternative therapeutic approaches is limited by our poor understanding of the complex cell-matrix interactions and cellular cross-talk in vivo and the absence of in vitro GFB models. Therefore, an in vitro system that mimics the complex GFB architecture and that can be used to better study glomerular (patho)-physiology is urgently needed.

Methods: We have generated a population of renal progenitors from human amniotic fluid (hAKPC-P) that can differentiate into podocyte-like cells. Taking advantage of the peculiar characteristics of available microfluidic systems, we have developed an innovative Glomerulus-on-a-Chip system by co-culturing hAKPC-P and hGEC cells in Organoplate™ microfluidic plates. Evaluation of culture conditions, immunostainings and qPCR were performed to characterize the 3D culture.

Results: We have successfully established the conditions for in vitro co-culture of hAKPC-P/hGEC in a microfluidic plate for up to 21 days. Apoptosis and proliferation were assessed by TUNEL and PCNA. Vessel formation by hGEC was confirmed along with expression of endothelial marker VE-Cadherin while hAKPC-P-derived podocytes were positive for nephrin and podocin. De-novo deposition of collagen IV in the 3D microfluidic plates was confirmed by immunostaining.

Conclusions: Our preliminary results suggest the feasibility of Organoplates for co-culture of podocytes and hGEC in a 3D environment that more closely mimics the structure of the GFB. If successful this system might prove useful for the assessment of several aspects of cell-cell and cell-matrix interaction, thus helping to understand podocytes/endothelial crosstalk (or its perturbations) and how this might affect glomerular homeostasis.

Funding: Private Foundation Support

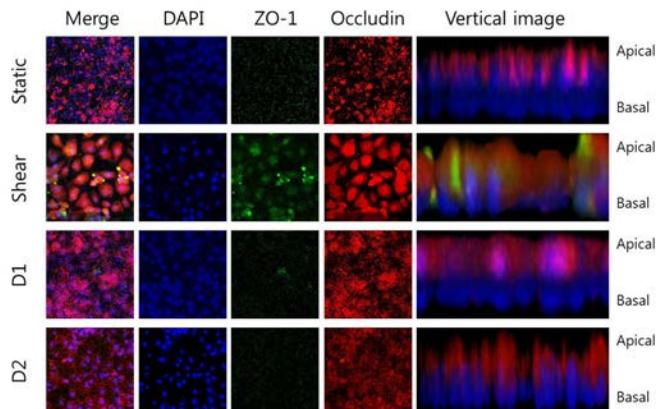
SA-OR039

Pharmacokinetic Model for Screening Nephrotoxicity Using Kidney on a Chip Sejoong Kim,^{1,2} Sasha Cai Leshner-Perez,¹ Byoung Choul C. Kim,¹ Cameron Yamanishi,¹ Joseph M. Labuz,¹ Shuichi Takayama.¹ ¹Univ of Michigan College of Engineering, Ann Arbor, MI; ²Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Korea.

Background: Animal renal clearance is usually higher than human renal clearance, which may underestimate nephrotoxicity. We developed a microfluidic device lined by kidney epithelial cells to mimic in vivo-like microenvironment. We evaluated the nephrotoxicity of two different gentamicin regimens using this kidney on-a-chip and human pharmacokinetic data.

Methods: The microfluidic device had top channels like luminal spaces and bottom channels like interstitial spaces. MDCK cells on the porous membranes between the two channels were exposed with a fluid shear stress (1.0 dyne/cm²). D1 regimen was 19.2 mM of gentamicin for initial dosage and reduction by half every 2 hours to mimic human renal clearance, and D2 regimen was continuous infusion of gentamicin (3 mM for 24 hours) in the top channels.

Results: After 6-hour shear stress, fluorescences of ZO-1 and occludin were increased and transmembrane permeability was decreased, compared to the static condition. For the next 24 hours, D1 and D2 regimens were applied under shear-stress condition. Although the junctional protein immunoreactivity was decreased in the both regimens, ZO-1 and occludin fluorescences showed higher in the D1 regimen than in the D2 regimen ($P < 0.05$).



D1 regimen sustained the permeability, while D2 led to increase in the permeability ($P < 0.05$). In addition, D1 regimen indicated less cytotoxic than D2 (Dead cell 1.43 ± 0.30 % vs. 4.9 ± 0.20 %, respectively, $P < 0.05$).

Conclusions: These data suggest that gentamicin may interrupt junctional protein complex and membrane permeability, and that single daily dose alleviate the nephrotoxicity, compared to the continuous infused regimen. Microfluidic devices can be one of novel pharmacokinetic models for evaluating nephrotoxicity.

Funding: Other NIH Support - NIH GM096040, Government Support - Non-U.S.

SA-OR040

Computational Prediction and Experimental Analyses of Proteins That Bridge Metabolite Markers of Human Diabetic Nephropathy Rintaro Saito,^{1,2,3} Anaïs Rocanin-Arjo,⁴ Minya Pu,^{1,5} Simone Nephroli,⁴ Loki Natarajan,^{1,5} Wenjun Ju,⁶ Matthias Kretzler,⁶ Robert G. Nelson,⁷ Dana Thomasova,⁴ Shrikant R. Mulay,⁴ Hans J. Anders,⁴ Kumar Sharma.^{1,2,3,8} ¹Inst Metabol Med; ²Center Renal Transl Med; ³Dept Med, UCSD, CA; ⁴Medizinische Klinik und Poliklinik IV, Klinikum der Univ München, Munich, Germany; ⁵Dept Family Med Epidem, UCSD; ⁶Dept Internal Med, Nephrology & Dept Comput Med & Bioinfo, Univ of Michigan, MI; ⁷NIDDK, AZ; ⁸VA Health Systems, SD, CA.

Background: We have previously shown that thirteen metabolites are shown to be characteristic of human diabetic kidney disease (DKD) and linked to mitochondrial dysfunction. However, novel bioinformatic tools could indicate novel connections among these metabolites to identify new relevant protein targets for human disease.

Methods: We integrated publicly available human protein-protein interaction (PPI) networks with global metabolic networks onto a software (Cytoscape) to enhance the interpretation of metabolomic data. Validation was performed with gene expression data from Nephromine and experimental studies in mice.

Results: We found that all thirteen metabolites can be connected through a single subnetwork of PPIs. We focused on bridge proteins, which were predicted to potentially connect these metabolites through their associated enzymes and found that several proteins had a significant number of connections regulating the original 13 metabolites. These included MDM2 (BH corrected $p < 0.005$, 14 connections) and PEX5 ($p < 0.005$, 9 connections). Of these, MDM2 had the strongest regulation in its gene expression in glomeruli ($p < 0.01$) and tubulointerstitium ($p < 0.01$) from two different cohorts of diabetic kidney biopsies. In vivo studies with Nutlin3a, an inhibitor of MDM2 binding site, in both healthy C57B6/JL mice and db/db type 2 diabetic mice resulted in a reduction podocytes, an increase in proteinuria and higher levels of plasma urea levels in healthy and diabetic mice.

Conclusions: Our bioinformatics approach has been demonstrated to make biologically relevant interpretation of dysregulated metabolites, highlighting the significance of MDM2 dysregulation in DKD both in experimental models and in patients with DKD.

Funding: NIDDK Support

SA-OR041

Mechanical Properties of Renal Tubules Measured Using Glass Microcantilevers Nicholas J. Ferrell. Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: The mechanical properties of tissues play an important role in maintaining tissue function, and altered biophysical properties affect disease progression. Measuring the mechanical properties of isolated biological structures, including renal tubules can be challenging, especially in tension. We have developed a new method to measure the elastic modulus of renal tubules using glass micropipettes as force measurement cantilevers.

Methods: Cortical tubules were manually dissected from normal mice. Elastic modulus was measured by clamping each tubule between a measurement microcantilever with pre-determined stiffness and a holding micropipette. The holding micropipette was translated using a micromanipulator and images were acquired at fixed displacements. Tubule strain and applied force were determined by measuring the change in the tubule length and deflection of the measurement cantilever. Tubule stress was estimated assuming the resistance to deformation was imparted primarily by the tubular basement membrane. The cross-sectional area of each tubular basement membrane was calculated based on a basement membrane thickness of 0.24 μ m. Elastic modulus was calculated from the slope of the stress-strain curve at a given strain.

Results: Stress-strain curves indicated a strain dependent increase in elastic modulus suggesting significant strain stiffening of renal tubules. At low strain (0-15%) elastic modulus was measured at 555 ± 98 kPa. At higher strain (15-30%) elastic modulus was 1113 ± 150 kPa and at even higher strain (30-50%) elastic modulus was 2161 ± 173 kPa. Strain stiffening behavior was observed throughout the range of measurable strain.

Conclusions: These results indicate that renal tubules are highly deformable structures that exhibit increased stiffness as strain increases, a response typical of extracellular matrices such as collagen gels. This method provides a relatively simple means of determining renal tubular biophysical properties and may be a useful tool for evaluating renal tubule mechanical properties in a variety of kidney diseases.

Funding: NIDDK Support

SA-OR042

Non-Invasive Measurement of Renal Blood Flow (RBF) in Rat by Magnetic Resonance Images (MRI) Cesar A. Romero,¹ Robert Knight,² Oscar A. Carretero.¹ ¹Hypertension and Vascular Research Div, Henry Ford Hospital; ²Henry Ford Hospital; ³Henry Ford Hospital; ⁴Henry Ford Hospital.

Background: Quantitative measurement of RBF provides important information on renal physiology, nephropathies and kidney viability in different animal models. Arterial Spin Labelling-MRI (ASL-MRI) is a non-invasive method to measure blood flow without exogenous contrast media, using arterial water protons labeled by radiofrequency as an endogenous tracer. However, the low signal/noise ratio and the motion artifacts pose a challenge when acquiring RBF in small animals. Our objective is to evaluate the feasibility and reproducibility of the RBF measurement by ASL-MRI under basal conditions and in a high RBF state in rats.

Methods: ASL-MRI images were obtained in seven males Sprague-dawley rats (200-300g) under the inhalatory anesthesia (isoflurane 2%). Rectal temperature probe was used to control the body temperature. After 4 days the MRI studies were repeated in 3 rats (6 kidneys) to evaluate reproducibility, using paired sample T-test and the test-retest reliability (TR) by the equation $TR = (1 - SDn/Mn) \times 100$ where M and SD are the mean and standard deviation of the RBF in "n" different sessions. RBF was also measured in a set of animals that underwent unilateral nephrectomy 24 hours before and after the surgery. MRI was acquired using a 7 Tesla Varian MRI system with a spin echo imaging sequence using respiratory triggering and navigator correction to reduce motion artifacts. The sequence was averaged 16 times and the total scan time for the entire series of ~20 minutes. In house software was used to analyze the postprocessing imaging.

Results: The mean cortical RBF was 305 ± 59 and 271.8 ± 39 ml/min/100g tissue in right and left kidney, respectively. Re-test analysis showed no differences, with the means of differences 9.4 ± 35 ml/min/100g tissue ($p=0.58$). The TR was $92.4 \pm 6\%$. The RBF before and after the nephrectomy was 270 ± 30 and 456.6 ± 34 ml/min/100g tissue ($p=0.004$), respectively, showing a relative increase of 69.1%.

Conclusions: ASL-MRI performed with navigator correction and respiratory gating is feasible and reliable non-invasive method to measure RBF in rats.

SA-OR043

Intravoxel Incoherent Motion Analysis of Diffusion Weighted Imaging to Measure Glomerular Filtration Fraction – Proof of Concept René van der Bel,¹ Oliver J. Gurney-Champion,² Wouter V. Potters,² Hein J. Verberne,³ Liffert Vogt,¹ Erik Stroes,¹ Aart J. Nederveen,² C.T.P. (Paul) Krediet.¹ ¹Internal Medicine, AMC, Univ of Amsterdam, Netherlands; ²Radiology, AMC, Univ of Amsterdam, Netherlands; ³Nuclear Medicine, AMC, Univ of Amsterdam, Netherlands.

Background: Glomerular filtration fraction (FF) can be calculated from the ¹²⁵I-thalamate clearance (glomerular filtration rate (GFR)) and ¹³¹I-hippuran clearance (effective renal plasma flow (ERPF)). This technique is costly and time consuming. Intravoxel Incoherent Motion (IVIM) analysis provides an assessment of diffusion weighted imaging (DWI) for fractions of blood and (pre-)urine within kidney tissue. This could serve as a surrogate for filtration fraction. With this study we a proof of concept for an MRI derived kidney function measurement.

Methods: After a baseline phase, 6 healthy volunteers (age 18-24 yrs) were subjected to continuous Angiotensin II (Ang-II) infusion at 3.0 ng/kg/min. Blood and (pre-)urine fractions and renal blood flow (RBF) were assessed using DWI and phase contrast MRI (Ingenia 3.0T, Philips Healthcare). Fractions were calculated via tri-exponential IVIM model fit to the DWI data (TE 45ms; TR 1344 ms; matrix: 112x68, FOV 336x204 mm²; voxel size 3.0x3.0x3.0 mm, b-values: 0, 2, 4, 8, 12, 18, 24, 32, 40, 50, 70, 110, 200, 300, 450, 600 s/mm²; gradient directions: 15). RBF was calculated in the proximal renal artery after manual vessel segmentation. During a second visit, gold standard GFR, ERPF and FF were measured during a similar infusion protocol.

Results: Ang-II decreased both GFR and ERPF ($10 \pm 7.1\%$, $p=0.016$; $24 \pm 4.5\%$, $p<0.001$), resulting in an increase in FF of $19 \pm 3.1\%$ ($p<0.001$). RBF decreased from 11.1 ± 2.07 to 8.05 ± 1.02 ml/s (by 27%, $p=0.001$). Renal IVIM imaging showed an increase in the urine fraction of $24.6 \pm 14\%$ ($p=0.002$) and a decrease of the perfusion fraction by $12 \pm 21.8\%$ ($p=0.096$). Renal IVIM measures (pre-)urine fractions and FF were correlated ($R=0.44$, $p=0.033$). RBF correlated to the gold standard ERPF ($R=0.75$, $p<0.001$).

Conclusions: These data suggest that a combination of IVIM and phase contrast kidney imaging could provide reliable and fast noninvasive FF and ERPF measurement.

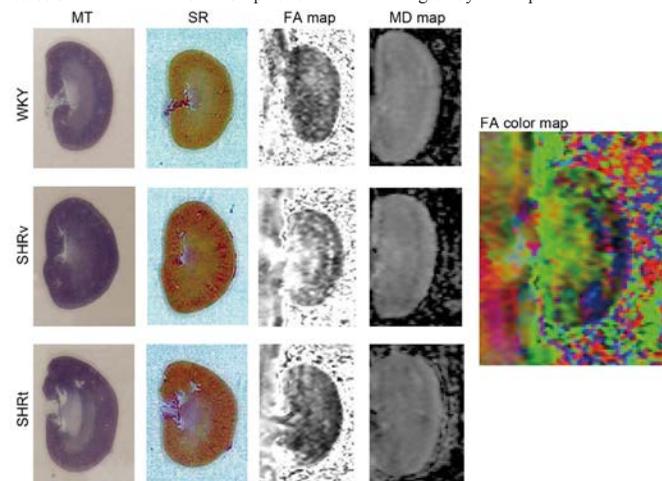
SA-OR044

Visualization of Kidney Fibrosis in Diabetic Nephropathy by DTI MRI Jun-Ya Kaimori,¹ Yoshitaka Isaka,² Masaki Hatanaka,² Satoko Yamamoto,² Hiroshi Shibata,⁴ Akira Fujimori,⁴ Akihiko Fujikawa,⁴ Sosuke Miyoshi,⁴ Naotsugu Ichimaru,¹ Toshiki Moriyama,³ Hiromi Rakugi,² Shiro Takahara.¹ ¹Dept of Advanced Technology of Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; ²Dept of Geriatrics & Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; ³Osaka Univ Health Care Center, Osaka Univ, Toyonaka, Osaka, Japan; ⁴Drug Discovery Research Inst, Astellas Pharma Inc, Tsukuba, Ibaraki, Japan.

Background: Renal fibrosis (RF) is a well-known marker for chronic kidney disease (CKD) progression. However, an available examination for evaluation of RF is invasive biopsy. Diffusion MRI was once recognized as a promising option for RF. But now it is controversial and it could not be applied to diabetic nephropathy (DN).

Methods: To seek an optimal imaging method applicable even for fibrosis in DN, we tried series of MR imaging methods, including proton density weighted imaging (PDWI), T1 weighted imaging (T1WI), T2 weighted imaging (T2WI), T2* weighted imaging (T2*WI), diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI).

Results: We identified DTI MRI by spin echo sequence plus a special kidney attachment as the best option for evaluation of UO fibrosis, compared with normal kidney in the opposite side. To confirm these results, we applied this technique to rat UO therapeutic model with anti-fibrotic reagent, Fasudil. FA values calculated from DTI MRI showed statistically significant linear correlation with RF area measured by Sirius Red or Masson trichrome staining positive area. Next, by using SHR/NDmcr-cp(cp) rat with or without telmisartan as a RF model of DN, we finally succeeded in visualization and evaluation of fibrosis accumulated in outer stripe of outer medulla region by FA map.



Conclusions: By DTI MRI with spin echo sequence, it may be possible to accurately evaluate RF in CKD including even DN.

Funding: Pharmaceutical Company Support - Astellas.Co.LTD, Government Support- Non-U.S.

SA-OR045

Super-Resolution Microscopy Reveals the Formation of a Mat of Contractile Fibers as Part of the Podocyte Foot Process Effacement Phenomenon Hani Suleiman,¹ Jeffrey H. Miner,² Andrey S. Shaw.² ¹Pathology and Immunology, Washington Univ in Saint Louis, Saint Louis, MO; ²Pathology and Immunology, Washington Univ in Saint Louis, Saint Louis, MO; ³Renal Devison, Washington Univ in Saint Louis, Saint Louis, MO.

Background: The ~200 nm resolution of traditional microscopes is limited by the wavelength of light. Imaging structures smaller than 200 nm, such as podocyte foot processes and slit diaphragms, has required electron microscopy (EM). New super-resolution imaging techniques can break the diffraction barrier of light, thus allowing us to easily image and resolve the molecular composition of structures in a nanometer range.

Methods: We used an array of antibodies for Stochastic Optical Resolution Microscopy (STORM) to study the spatial distribution of key molecules of the podocyte cytoskeleton and slit diaphragm in healthy and injured glomeruli. We also developed a novel technique that allows us to image podocyte actin cables by EM.

Results: In healthy glomeruli, synaptopodin is localized to the center of each foot process, while nephrin is at the slit diaphragm. As foot processes efface, nephrin redistributes apically away from the base of foot processes. We confirmed this in 3 different injury models. After podocyte injury the positions of synaptopodin and α -actinin-4 clusters did not change, but there was robust recruitment of myosin IIa, normally only in primary processes, to the bases of foot processes. The pattern of myosin IIa staining, in alternating stripes with synaptopodin and α -actinin-4, indicates the formation of contractile actin fibers during effacement. Using our new EM method, we observed a dramatic change in the morphology of actin fibers during effacement.

Conclusions: We demonstrate the utility of super-resolution microscopy to visualize podocyte foot processes. Our data show that in the normal podocyte, contractile actin cables are in primary processes, while only non-contractile actin filaments are in foot processes. After foot process effacement, the contractile cables fall to the bottom of the podocyte and form a sarcomere-like contractile network adjacent to the GBM.

Funding: NIDDK Support, Private Foundation Support

SA-OR046

Intravital and Organ Slice Imaging of Podocyte Membrane Dynamics Sebastian Braehler,¹ Haiyang Yu,¹ Gokul Murali Krishnan,¹ Hani Suleiman,¹ Jeffrey H. Miner,² Bernd H. Zinselmeyer,¹ Andrey S. Shaw.¹ ¹*Dept of Pathology and Immunology, Washington Univ School of Medicine, St. Louis, MO;* ²*Renal Div, Washington Univ School of Medicine, St. Louis, MO.*

Background: The elaborate network of podocyte foot processes, which is stabilized by the actin cytoskeleton, is one of the key components of the glomerular filtration barrier. The question of whether podocytes change their shape under physiological conditions or in response to injury has been vigorously debated. The Rho-family of small GTPases is at the center of this debate, as these molecular switches control assembly and disassembly of the actin cytoskeleton. Evidence as to whether and how small-GTPases change podocyte shape and dynamics is largely circumstantial, as all studies to date have been conducted *in vitro*.

Methods: Here we use intravital two-photon imaging of fluorescently labeled podocytes to answer these questions. Rosa26-confetti/Podo-Cre mice were used as reference and compared with mice expressing eGFP-labeled, constitutively active Rac1 (eGFP.CA-Rac1) in podocytes. To achieve a higher resolution we also imaged freshly isolated kidney slices in an organ bath.

Results: Podocytes in Rosa26-confetti/Podo-Cre mice showed a stable network of foot processes, with no significant membrane movement. eGFP.CA-Rac1 podocytes lost their characteristic shape and showed increased membrane dynamics and podocyte shedding. Shed podocytes seemed viable, as they were observed migrating in the tubular system. Organ slice imaging resembled the intravital results but yielded a higher temporal-spatial resolution, which validates this approach as a suitable technique to complement intravital imaging. With this approach, we were also able to show that increased membrane dynamics is a feature of injured podocytes in a glomerular disease model.

Conclusions: We show *in vivo* for the first time that Rac1 converts podocytes from a state of immobility to one with greatly increased membrane dynamics and blunted foot processes, which also occurs in a model of glomerular injury. This suggests that foot process effacement is the end result of a highly dynamic state, and that foot process instability could contribute to proteinuria itself.

Funding: NIDDK Support, Government Support - Non-U.S.

SA-OR047

Intravital Multiphoton Imaging of Podocyte Ca²⁺ Confirms the Important Role and Mechanism of TRPC6 in Glomerular Pathology Kengo Kidokoro, Anne Riquier-brison, Janos Peti-Peterdi. *Physiology and Biophysics, and Medicine, Univ of Southern, Los Angeles, CA.*

Background: TRPC6 channels in podocytes are important Ca²⁺ influx pathways involved in the modulation of the actin cytoskeleton and in the actions of angiotensin II (ANG II). TRPC6 overactivity by gain-of-function mutations and high ANGII leads to albuminuria and chronic kidney disease (CKD). However, the regulation of podocyte Ca²⁺ dynamics by TRPC6 and the mechanism of the resulting glomerular dysfunction *in vivo* and in response to injury have been elusive. We aimed to directly and quantitatively visualize and study the dynamic effects of TRPC6 on podocyte and glomerular function during the development of glomerular injury.

Methods: Serial multiphoton microscopy of the intact living kidney of the same wild type (WT), TRPC6 transgenic (TG), and TRPC6 knockout (KO) mice was performed over two weeks of high ANGII treatment (1000 ng/kg/min). All mice expressed the intensely green and calcium sensitive fluorescent protein GCaMP3 only in podocytes. Changes in single cell GCaMP3 fluorescence intensity were measured and served as readout for podocyte [Ca²⁺]_i changes.

Results: Systolic blood pressure increased from baseline 106±4 to 145±5 mmHg after ANGII treatment for two weeks in weeks in WT mice, and similarly in TRPC6 TG and KO mice. In WT mice, normalized GCaMP3 fluorescence intensity in podocytes ([Ca²⁺]_i) increased >2.5-fold, glomerular diameter increased from 64±2 to 76±2 μm, and single nephron glomerular filtration rate reduced from 9±1 to 3±1 nl/min, in response to ANGII. Podocyte GCaMP3 fluorescence intensity was increased >2-fold, but reduced by 20%, at baseline in TRPC6 TG and KO mice, respectively. Glomerular functional parameters after ANGII treatment were exacerbated in TRPC6 TG mice, while improved in TRPC6 KO mice. Podocytes with high GCaMP3 fluorescence appeared migrating to the parietal Bowman's capsule after ANGII in WT and TRPC6 TG, but not in TRPC6KO mice.

Conclusions: This study demonstrated *in vivo* direct visual evidence of the critically important pathogenic role of TRPC6 in the development and progression of glomerular disease. Podocyte TRPC6 is a promising therapeutic target for the prevention of CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Amgen

SA-OR048

Mesangial Filopodial Invasion of Glomerular Capillaries in Alport Syndrome Dominic E. Cosgrove, Daniel T. Meehan, Brianna M. Dufek, Duane C. Delimont. *Genetics, Boys Town National Research Hospital, Omaha, NE.*

Background: Recent work shows mesangial cell filopodia invade the glomerular capillaries in Alport mice and humans. Filopodia progressively deposit laminin 211 and likely other mesangial matrix proteins in the GBM. Laminin 211 activates focal adhesion kinase in podocytes, which results in up-regulation of metalloproteinases and pro-inflammatory cytokines. These novel observations, which are key to glomerular disease initiation, have been met with some skepticism, which incentivized the current study.

Methods: Three color structured illumination microscopy (SIM, an ultra-high resolution methodology) was used to label mesangial processes, glomerular endothelial cells, and the GBM. A mesangial cell culture bioassay was developed that allows induction of mesangial filopodia. RNAseq analysis of preproteomic glomeruli identified novel candidates likely involved CDC42 activation in mesangial cells. These candidates were tested in the bioassay.

Results: SIM analysis showed that integrin α8-immunopositive mesangial processes extend, contiguous with the mesangial angles, into the sub-endothelial spaces of the GBM. These processes are exclusive of CD31 immunopositive glomerular endothelium and the laminin α5 immunopositive GBM. Endothelin-1 (ET-1) activates CDC42 in mesangial cells and results in the formation of drebrin-immunopositive actin microspikes (filopodia). Of the six candidate proteins identified that may regulate endothelin A receptor (ET_AR) mediated activation of CDC42, two have been tested by siRNA knockdown. MAL2 knockdown blocked ET-1 activation of filopodia, while BMP-7 knockdown had no effect. ET_AR knockdown (a positive control) also prevented formation of actin microspikes.

Conclusions: SIM analysis unequivocally proves mesangial filopodial invasion of the glomerular capillaries in Alport mice. The bioassay shows ET-1 mediated activation of CDC42 promotes filopodia formation. RNAseq identified one novel regulator of CDC42 activation, MAL2 which is critical mediator of CDC42 activation. This bioassay can thus be exploited to identify new therapeutic targets with the potential to prevent mesangial filopodial invasion of the glomerular capillaries.

Funding: NIDDK Support

SA-OR049

The DREADD Concept: A Novel In Vivo Tool for Kidney Research Questioning the Role of Ca²⁺ on Actin Dynamics in Podocytes Sybille Köhler,^{1,2} Sebastian Braehler,⁴ Julia Binz,^{1,2} Matthias Hackl,^{1,2} Frank Schweda,³ Thomas Benzing,^{1,2} Bernhard Schermer,^{1,2} Paul T. Brinkkoetter.^{1,2} ¹*Dept II of Internal Medicine and Center for Molecular Medicine, Univ Hospital Cologne, Germany;* ²*Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Germany;* ³*Dept of Physiology, Univ of Regensburg, Germany;* ⁴*Dept of Pathology and Immunology, Washington Univ School of Medicine.*

Background: The close homology between the slit diaphragm of the kidney glomerulus and the mechanosensor in *C. elegans* led to the hypothesis that the slit diaphragm is part of a conserved mechanosensor that is closely linked to an actin-based, contractile cytoskeleton regulated by Ca²⁺.

Methods: We generated a transgenic mouse line with specific expression of a mutated (Y149C/A239G) G protein-coupled human muscarinic type 3 receptor transgene (hM₃D) in the ROSA26 locus. This receptor is exclusively activated by the synthetic compound clozapine-N-oxide (CNO) and not by the endogenous M₃-ligand acetylcholine. We mated the hM₃D-STOP^{flx/flx}-mouse with the podocin:cre mouse to achieve podocyte specific expression. We validated receptor expression and function both, *in vitro* and *in vivo* using immunofluorescence stainings, western blotting and live Ca²⁺-imaging using 2-photon microscopy.

Results: Here, we applied the DREADD (designer receptor exclusively activated by a designer drug, Conklin et al. 1998) concept to further test this hypothesis and to investigate the effects of an intracellular Ca²⁺ increase on the podocyte actin cytoskeleton. Even though we observed a strong Ca²⁺ increase in podocytes after CNO-administration no effects on the actin based cytoskeleton, glomerular perfusion or filtration were observed. Even administration of CNO over a prolonged period (4 wks) did not induce glomerular disease.

Conclusions: In conclusion, increasing Ca²⁺ levels in podocytes alone are not sufficient to induce cytoskeletal rearrangements and to affect glomerular perfusion and filtration. Hence, these results challenge our current view on actin dynamics in podocytes and their role in glomerular perfusion and filtration.

Funding: Government Support - Non-U.S.

SA-OR050

Loss of Epithelial Membrane Protein 2 Aggravates Podocyte Injury via Upregulation of Caveolin-1 Weibin Zhou,¹ Xiaoyang Wan,¹ Zhao-hong Chen,^{1,2} Won-Il Choi,³ Heon Yung Gee,³ Friedhelm Hildebrandt.^{3,4} ¹*Pediatrics and Communicable Diseases, Univ of Michigan, Ann Arbor, MI;* ²*Research Inst of Nephrology, Jinling Hospital, Nanjing, China;* ³*Boston Children's Hospital, Boston, MA;* ⁴*Howard Hughes Medical Inst.*

Background: Nephrotic syndrome is a chronic kidney disease defined by proteinuria with subsequent hypoalbuminemia, hyperlipidemia and edema, due to impaired renal glomerular filtration barrier function. Glomerular podocytes have been proposed to play a critical role in the maintenance of glomerular filtration barrier and the pathogenesis of

nephrotic syndrome. We have previously identified mutations in EMP2 (epithelial membrane protein 2) as a novel monogenic cause of this disease. Detrimental mutations in EMP2 have been found in patients with steroid-sensitive and steroid-resistant nephrotic syndrome.

Methods: To understand the pathogenic mechanism underlying EMP2 mutations, we have generated a zebrafish knockout model of emp2 using TALEN and transgenic zebrafish overexpressing caveolin-1 in podocytes. We have also characterized cultured human podocytes with shRNA-mediated EMP2 knockdown.

Results: We found that loss of emp2 in zebrafish up-regulated caveolin-1 (cav1), a major component of caveolae, in embryos and mesonephric glomeruli, and exacerbated podocyte injury. This phenotype could be partially rescued by glucocorticoids. We showed that overexpression of cav1 in zebrafish podocytes was sufficient to induce the same phenotypes seen in emp2 homozygous mutants, which were treatable by glucocorticoids. Consistently, knockdown of EMP2 in cultured human podocytes resulted in an increase of CAV1 and a decrease of podocyte survival in the presence of puromycin aminonucleoside, while glucocorticoid treatment ameliorated these phenotypes.

Conclusions: Taken together, we have established excessive CAV1 as a mediator of the predisposition to podocyte injury due to loss of EMP2, suggesting CAV1 could serve a novel therapeutic target of nephrotic syndrome and podocyte injury.

Funding: NIDDK Support, Private Foundation Support

SA-OR051

GLEPPI Deficiency Defines a Novel Glomerular Disease Eva Koenigshausen,¹ Christian Weigel,¹ Philip Schüppler,¹ Laura Lennartz,¹ Thorsten Wiech,² Catherine Meyer-Schwesinger,² Roger G. Wiggins,³ Sophie C. Collinson,⁴ Rachel Lennon,⁴ Magdalena Woznowski,¹ Ivo Quack,¹ Lars C. Rump,¹ Lorenz Sellin.¹ ¹Univ Hospital Duesseldorf, Germany; ²Univ Hospital Hamburg Eppendorf, Germany; ³Univ of Michigan; ⁴Royal Manchester Children's Hospital, United Kingdom.

Background: Albuminuria is the early clinical marker for glomerular disease. Mutations in GLEPPI were linked with podocytic diseases in children (MCD/FSGS). GLEPPI is a receptor tyrosine phosphatase present in the podocyte foot processes. Its precise function is not fully understood.

Methods: GLEPPI KO and WT mice were examined at 4 and 10 months. Mouse plasma and urine were analyzed for cystatin C, albumin and creatinine. qPCR was performed for collagen IV (col IV) a1-5, laminin (lam) a1, 5 and b1, 2. Western blot (WB) was stained for col IV a1 and lam a1. PAS staining was performed. Cryosections of kidneys were stained for col IV a1 and a2. In EM sections GLEPPI was labeled with immunogold. GBM defects were imaged by serial block-face scanning EM to generate 3-D models.

Results: GLEPPI KO mice display a significantly higher urinary ACR and cystatin C compared to WT mice at 10 months. This correlated significantly with focal thickening of the GBM in KO mice, resembling GBM humps in light microscopy and TEM. At the sights of humps, beginning foot process effacement was observed. qPCR revealed significant upregulation of col IV a1, a2 and lam a1, b1 expression while a3 expression was significantly down regulated. WB confirmed qPCR results. Immunofluorescence microscopy of KO glomeruli revealed enhanced expression of col IV a1, a2 in the GBM. The EM 3D models of the GBM confirmed the cone shaped humps and a significant podocyte foot process effacement in KO mice. Two albuminuric patients with similar GBM phenotype and without signs of MCD or FSGS were identified.

Conclusions: GLEPPI deficiency mediates the formation of GBM humps in mice and potentially in humans. GLEPPI deficiency mediates GBM composition from a mature to an immature state. This switch can only be seen in aging mice and results functionally in albuminuria and renal disease. GLEPPI deficiency defines a novel glomerular disease.

SA-OR052

The Role of Podocyte Associated Angiotensin II Type 1a Receptor in Nephrosis Kazunori Inoue, Xuefei Tian, Shuta Ishibe. *Internal Medicine, Yale Univ School of Medicine, New Haven, CT.*

Background: Inhibition of the renin-angiotensin system has demonstrated to reduce both proteinuria and the decline in GFR. This beneficial effect has been postulated to go beyond blood pressure control. Controversies remain on the direct effect of angiotensin II (Ang II) on podocytes. Dynamin plays an important role in angiotensin II receptor type 1a (AT1aR) internalization and we have previously demonstrated that podocyte specific Dynamin 1 and 2 knockout (Dnm KO) mice display severe proteinuria and glomerular sclerosis. Our objective is to determine whether podocyte specific persistent AT1aR signaling in Dnm KO mice results in podocyte injury in-vivo.

Methods: Live cell imaging of fluorescently tagged clathrin and AT1aR in primary podocytes from Wild type (WT) and Dnm KO was performed. WT, Dnm KO, Pod-Cre Agtr1a fl/fl Dnm1 fl/fl Dnm2 fl/fl (Pod Agtr1a KO Dnm KO), and Agtr1a -/- Pod-Cre Dnm1 fl/fl Dnm2 fl/fl (Agtr1a KO Dnm KO) mice were generated and characterized to unearth the role of AT1aR in podocytes.

Results: Clathrin mediated AT1aR internalization was observed after Ang II treatment in WT podocytes, but was arrested at the plasma membrane in Dnm KO podocytes. ERK, a downstream target of AT1aR, was continuously activated in Dnm KO podocytes after Ang II stimulation. Compared with Dnm KO mice, both Pod Agtr1a KO Dnm KO, and Agtr1a KO Dnm KO mice showed a decrease in proteinuria (urine albumin creatinine ratio were 3708.7 (ug/mg) (Dnm KO) vs 3089.7 (Pod Agtr1a KO Dnm KO) vs 2166.2 (Agtr1a KO Dnm KO) at 6 weeks old age respectively) and an advantage in survival. Histological examination demonstrated that Pod Agtr1a KO Dnm KO mice showed modest reduction in the progression of glomerulosclerosis, proteinaceous casts compared with Dnm KO mice. Agtr1a KO Dnm KO mice showed lower mean arterial blood pressure than Dnm KO mice, but there was no difference between the Dnm KO and Pod Agtr1a KO Dnm KO mice.

Conclusions: Our results demonstrate that deletion of Dynamin 1, 2 in podocytes results in sustained AT1aR signaling. Inhibition of AT1aR signaling in podocytes plays a fundamental role in retarding the progression of podocyte injury when compared to total deletion of Agtr1a in Dnm 1, 2 KO podocytes.

SA-OR053

The Spectrum of Nephrotic Syndrome from Minimal Change Disease to FSGS Correlates with Rac1 Activation Richard Robins, Cindy Baldwin, Lamine Aoudjit, Indra R. Gupta, Tomoko Takano. *Nephrology, McGill Univ, Montreal, QC, Canada.*

Background: Within podocytes, cytoskeletal organization is regulated by Rho-family GTPases including Rac1. Clinical and animal studies suggest that Rac1 activation within podocytes contributes to the pathogenesis of nephrotic syndrome (NS). We hypothesize that Rac1 activity is increased in clinical NS and podocyte-specific activation of Rac1 will result in NS in mice.

Methods: Kidney biopsies from patients with minimal change disease (MCD) and idiopathic focal segmental glomerulosclerosis (FSGS) were immunostained for active Rac1. Sera from FSGS patients were used for Rac1 activity assays in cultured podocytes. Mice carrying the tetracycline-inducible constitutively active Rac1 mutant (L61, CA-Rac1, Flag-tagged) were bred with mice with the podocin-driven reverse tetracycline trans-activator to generate double transgenic mice (DTG). Proteinuria was assessed by the albumin/creatinine ratio (ACR). Renal histology was evaluated by light, immunofluorescence (IF) and electron microscopy.

Results: By IF, active Rac1 staining was increased in glomeruli (co-localized with nephrin) in patients with NS. FSGS patient sera activated Rac1 in cultured podocytes. DTG mice had 1 or 2 copies of the CA-Rac1 transgene; mice with 2 copies had significantly higher proteinuria upon 5 days Dox treatment (high responders), compared with those with 1 copy (low responders). Foot process effacement was more diffuse and pronounced in high responders compared to low responders. When Dox was withdrawn after 5 days, low responders returned to baseline proteinuria after 2 weeks while high responders returned to near baseline levels after 4 weeks. When Dox was withdrawn after 2 weeks in high responders, proteinuria did not resolve. After 1 month, high responders displayed severe glomerulosclerosis.

Conclusions: Active Rac1 staining is increased in patients with NS. FSGS sera promote Rac1 activation in cultured podocytes. In mice, the amount of Rac1 activation within podocytes determines severity of foot process effacement, proteinuria, and degree of reversibility upon Dox withdrawal. The amount of Rac1 activation may be a critical factor determining whether MCD or FSGS arises within the NS spectrum.

Funding: Government Support - Non-U.S.

SA-OR054

Glomerular TNF α Expression Causes Free Cholesterol Mediated Podocyte Apoptosis in DKD and FSGS Christopher E. Pedigo,¹ Farah Leclercq,¹ Mayrin Correa-Medina,¹ Gloria Michelle Ducasa,¹ Judith T. Molina David,¹ Matthias Kretzler,² Sebastian Martini,² Robert G. Nelson,³ Alla Mitrofanova,^{1,4} Armando Mendez,⁵ George William Burke,⁴ Sandra M. Merscher,¹ Alessia Fornoni.¹ ¹Katz Drug Discovery Center, Nephrology, U of Miami; ²U of Michigan; ³NIDDK; ⁴Surgery, U of Miami; ⁵Diabetes Research Inst, U of Miami.

Background: Tumor Necrosis Factor alpha (TNF α) levels predict the development of Diabetic Kidney Disease (DKD). TNF α inhibition may be efficacious in some patients with Focal Segmental Glomerulosclerosis (FSGS). Podocyte injury is observed in both diseases and glomerular cholesterol accumulation was associated with albuminuria and reduced ATP-Binding Cassette A1 (ABCA1) expression in experimental DKD. We hypothesized that TNF α causes lipid dependent podocyte injury in FSGS and DKD.

Methods: Caspase 3 activity and cholesterol efflux was determined in human podocytes treated with TNF α . Cyclodextrin (CD) was used for cholesterol depletion.

Results: DKD and FSGS sera treated podocytes showed increased TNF α expression. Glomerular TNF α expression correlated with reduced ABCA1 expression in FSGS. Podocytes treated with sera from patients with progressive DKD showed reduced ABCA1 expression compared to non progressive DKD. TNF α treatment increased apoptosis and cholesterol content, reduced ABCA1 mediated cholesterol efflux, esterified cholesterol and Sterol-O-Acyltransferase (SOAT1) activity. ABCA1 overexpression or CD prevented TNF α induced apoptosis. ABCA1 knockdown increased esterified cholesterol content. Treatment of ABCA1 knockdown cells with SOAT inhibitors caused apoptosis that was prevented by CD. TNF α treated mice showed albuminuria and kidney cholesterol accumulation, the former was prevented by CD.

Conclusions: Podocytes treated with FSGS or DKD sera show increased TNF α expression. Increased glomerular TNF α expression correlates with reduced ABCA1 expression in patients with FSGS and reduced ABCA1 expression correlates with DKD progression. TNF α attenuates ABCA1 mediated efflux and reduces cholesterol esterification leading to free cholesterol mediated apoptosis. Our data suggest that targeting the TNF α -ABCA1-cholesterol axis may represent a new strategy to treat DKD or FSGS.

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffman La Roche

SA-OR055

Novel Score to Predict Post-Transplant Outcomes Miklos Zsolt Molnar,¹ Danh V. Nguyen,² Vanessa A. Ravel,² Elani Streja,² Mahesh Krishnan,³ Yanjun Chen,² Csaba P. Kovacs,¹ Kamyar Kalantar-Zadeh.² ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³DaVita Healthcare Partners, VA.

Background: Several previous studies have developed scoring tools to predict the allograft and patients' survival in kidney transplant patients using information, which was not available at the time of transplantation. We developed a score to predict post-transplant outcomes using pre-transplant information including routine laboratory data available at the time of transplantation.

Methods: Linking the 5-year patient data of a large dialysis organization to the SRTR, we identified 15,125 hemodialysis patients who underwent first kidney transplantation. Prediction models were developed using Cox models for (a)mortality, (b)transplant failure(death censored) and (c)combined death or transplant failure. The cohort was divided into a two-thirds development set and a one-third validation set. We used backward-selection based on Akaike's information criterion to avoid arbitrary and ineffective selection rules based on p-values. We used the bootstrap method to assess model overfitting and calibration using the development dataset. Model predictive discrimination was assessed using the index of concordance, or C statistic, which accounts for censoring in time-to-event(a-c).

Results: Patients were 50±13 years old and included 39% women, 15% African-American and 36% diabetics. For prediction of post-transplant mortality and graft loss 10-10 predictors were used (recipients' age, cause and length of ESRD, hgb, albumin, comorbidities, race and type of insurance as well as donor characteristics such as donor age, diabetes, number of HLA mismatches). The new model showed the overall best C-statistics comparing to the currently used EPTS score.

	Current model	Model based on EPTS predictors
	Discrimination C (95%CI)	Discrimination C (95%CI)
Combined	0.63 (0.62-0.65)	0.57 (0.56-0.58)
Mortality	0.70 (0.69-0.71)	0.66 (0.65-0.67)
Allograft failure	0.63 (0.62-0.65)	0.59 (0.58-0.61)

Conclusions: The new prediction tool, using exclusively data available prior to the time of transplantation, performs better to predict outcomes than currently used tool such as EPTS.

Funding: Other NIH Support - R21AG047306 and R01DK95668

SA-OR056

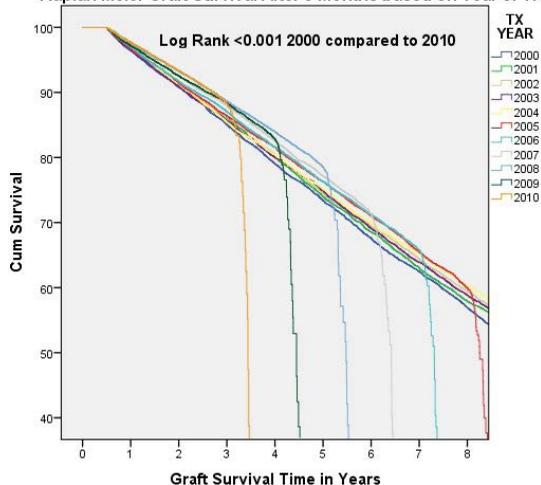
Long-Term Deceased Donor Kidney Graft Survival Has Improved in the Last Decade Douglas Scott Keith, Gayle M. Vranic, Angie G. Nishio-Lucar. Medicine, UVA, Charlottesville, VA.

Background: Long-term graft survival did not improve significantly in the 1990s. We sought to determine if long-term graft survival is improving in the last decade.

Methods: All adults deceased donor renal transplant recipients in the SRTR database between 2000 and 2010 were included in the study. K-M survival analysis was carried out based on year of transplantation in all recipients who had at least 6 months of graft survival. Graft survival, death censored graft survival and death with graft function were analyzed. Cox modeling was carried out to determine if the year of transplant affected the outcomes.

Results: 92,616 deceased donor kidney transplants survived at least six months. The rate of graft failure has improved over the last decade.

Kaplan Meier Graft Survival After 6 Months based on Year of Transplant



This occurred in spite of the decreasing quality of kidneys based on KDPI. The improvement in graft survival was exclusively due to improved death censored graft survival. The rate of death with graft function did not change. This steady improvement in graft survival occurred during a transition in maintenance immunosuppression from cyclosporine based regimens to tacrolimus. Cox analysis confirmed the improvement in graft survival and death censored graft survival but also showed that the rate of death with graft function was decreasing when adjusted for the covariates.

Transplant Year Reference: 2000	H.R. of Graft Failure (C.I.)
2001	0.97 (0.93-1.03)
2002	0.94 (0.89-0.98)
2003	0.91 (0.87-0.96)
2004	0.88 (0.84-0.93)
2005	0.85 (0.81-0.89)
2006	0.82 (0.78-0.87)
2007	0.79 (0.75-0.83)
2008	0.71 (0.67-0.75)
2009	0.73 (0.68-0.78)
2010	0.70 (0.65-0.75)

Covariates: Age, Race, Gender, Acute Rejection, DGF, KDPI, HLA mismatch, Dialysis Duration, PRA, and Retransplant

Conclusions: Long-term graft survival has improved in the last decade in spite of declining donor quality. This improvement was associated with a shift in maintenance immunosuppression to tacrolimus.

SA-OR057

Characteristics Associated with Greater Than 5 Year Kidney Graft Survival Among HIV+ Recipients Laura Panarey, Alden Michael Doyle, Karthik M. Ranganna. Nephrology and Hypertension, Drexel Univ Hahnemann Hospital, Philadelphia, PA.

Background: We have previously reported that donor factors have direct influence on the incidence of peri-operative delayed graft function (DGF), decreased time to acute cell-mediated rejection (ACR), and affect graft outcomes.

Methods: Our aim was to identify donor and recipient risk factors associated with > 5 year kidney allograft survival among HIV+ recipients by conducting a retrospective chart analysis of all HIV + transplants performed at our center with at least 5 years of follow up (N=94).

Results: In our HIV + kidney transplant cohort, greater than 5 year allograft survival was significantly associated with modifiable risk factors including: living donor allografts (LRT), minimizing cold ischemia time, and pre-transplant diagnosis of HCV. Non-modifiable demographics not associated with at least 5 year survival included: Age, Sex, BMI, and the history of CAD or DM. Implicated elsewhere; neither ethnicity nor gender mismatch of allograft appeared to significantly affect our HIV + transplant outcomes at 5years. While cellular and humoral rejection are known to affect the HIV + transplant cohort; time to ACR was significantly different, inferior graft survival experienced an earlier first ACR (188 ± 258 days vs. 458 ± 444 days, p = 0.02). Reflected in graft outcomes; inferior graft survival best GFR 50.58 mL/min ± 25 vs. 65.49 mL/min ± 23, p = 0.02.

Conclusions: Our data suggest that optimization of HIV+ kidney transplant outcomes is associated with modifiable factors such as HCV (encouraging data for new treatment); addendum of donor quality (LRT preferable) and avoidance of DGF.

Recipient Factors	p-Value	< 5 year allograft survival	> 5 year allograft survival	
Diabetes Mellitus (DM)	P = 0.126	11/73	6/14	
Cardiovascular (CAD/PVD/CVA)	P = 0.298	14/73	6/14	
Hepatitis C Virus (HCV)	P = 0.025	35/73	4/20	
Protease Inhibitors (HIV treatment)	P > 0.05	44/56	12/56	
Non-Protease Inhibitor (HIV treatment)	p > 0.05	28/38	10/38	
Donor Factors		p-Value	< 5 year allograft survival	> 5 year allograft survival
KDRI (kidney donor risk index)	P = 0.044	1.44 ± 0.5	1.18 ± 0.4	
Cold Ischemia Time (CIT)	P = 0.07	15/72	12/20	
Non-Cadaveric Transplant (LRT)	P = 0.006	3/73	4/20	
DGF	P = 0.013	48/73	11/20	

Figure 1: Risk Factors High Risk (HIV+) Kidney Transplant Cohort

SA-OR058

Identifying the Two Specific Types of Antibody-Mediated Rejection and Their Outcomes in Kidney Recipients Olivier Aubert,¹ Alexandre Loupy,¹ Luis G. Hidalgo,² Jeff Reeve,² Denis Glotz,¹ Christophe M. Legendre,¹ Carmen Lefaucheur,¹ Philip F. Halloran.² *¹INSERM; ²ATAGC.*

Background: Antibody-mediated rejection (ABMR) can be related to preformed/recurrent anti-HLA DSA or de novo anti-HLA DSA.

Methods: We included 965 kidney biopsies taken from two North American and five European centers and assessed patients with ABMR. We compared patients with preformed/recurrent DSA (Type-1 ABMR) to patients with de novo DSA (Type-2 ABMR). Microarray-based gene expression was assessed in biopsies. Patients with type-1 were managed in two centers with aggressive standardized treatment protocols; type-2 ABMR was managed as standard-of-care.

Results: We identified 278 patients with ABMR: 153 (55%) type-1 and 125 (45%) type-2. The mean time from transplantation to rejection was 10.1±18.8 vs 84.9±71.1 months for the type-1 and 2 ABMR. The mean eGFR at the time of biopsy was lower in type-1 ABMR (38±18) vs type-2 (46±20 mL/min/1.73m²) (p=0.0012). Kidney biopsies with type-1 ABMR presented with higher microcirculation injury (g+ptc score: 3.3±1.4 vs 2.4±1.5) and less transplant glomerulopathy score (0.5±0.9 vs. 1.6±1.1) (p<0.0001). C4d PTC deposition was similar (32% vs 34%). Using the gene expression assessment, type-1 ABMR exhibited a higher expression of global disturbance transcripts, injury-repair response associated transcripts (IRRATS), endothelial cell associated transcripts (ENDAT), injury-induced transcripts (IRIT3) (p<0.0001) but a lower expression of NK cell transcript burden (NKB) (p=0.0147). Type-1 and Type-2 ABMR exhibited similar high expression of transcripts reflecting γ -IFN response (GRIT1), T cell transcript burden (TCB) and macrophage-associated transcripts (QCMAT). Kidney allograft survival at 4 and 8 years after rejection was superior in type-1 ABMR (72% and 58%) compared to type-2 (51% and 35%) (p<0.0001).

Conclusions: Type-1 and type-2 ABMR present with distinct phenotypes and outcomes. The fact that type-1 ABMR is treated with aggressive defined protocols and has superior outcomes despite lower GFRs and more molecular injury at the time of biopsy suggests that trials of structured aggressive therapy protocols in type 2 ABMR deserve study.

SA-OR059

Serum Dickkopf-1, Renal Allograft Fibrosis and the Risk of Graft Failure After Kidney Transplantation Martin H. De Borst,¹ Charlotte A. Keyzer,¹ Jelmer K. Humalda,¹ Thomas Vanhove,² Gerjan Navis,¹ Dirk R. Kuypers,² Stephan J.L. Bakker.¹ *¹Dept of Nephrology, Univ Medical Center Groningen, Netherlands; ²Dept of Nephrology and Renal Transplantation, Univ Hospitals Leuven, Belgium.*

Background: Renal fibrosis is a final common pathway contributing to graft failure after kidney transplantation (KTx). Aberrant Wnt/ β -catenin signaling contributes to progressive renal fibrosis. Dickkopf-related protein 1 (Dkk-1) is a soluble endogenous inhibitor of the Wnt signaling pathway, and is induced in response to tissue injury in animal studies. We investigated whether serum Dkk-1 is associated with renal interstitial fibrosis and graft failure in renal transplant recipients (RTR).

Methods: Serum Dkk-1 was measured by ELISA (R&D) in two cohorts of outpatient RTR. In a cross-sectional cohort we analyzed the relationship between Dkk-1 and prevalent renal fibrosis using logistic regression. In a longitudinal cohort we studied the association with graft failure using Cox regression.

Results: In the cross-sectional cohort (n=225, 60% male, age 54±13 years) serum Dkk-1 was associated with renal fibrosis at two years post-KTx independent of age, sex, proteinuria and eGFR (odds ratio 2.10 [95% CI 1.11-3.95], P=0.02). In the longitudinal cohort (n=700, 57% male, age 53±13 years, 5.4 [1.9-12.0] years after KTx) 45 (6%) patients developed graft failure during 3.1 [2.6-3.8] years of follow-up. Serum Dkk-1 was inversely associated with graft failure (HR 0.45 [95% CI 0.27-0.76], P=0.003 per doubling of Dkk-1), independent of known risk factors for graft failure or Dkk-1 correlates. The association persisted in sensitivity analyses restricted to patients with interstitial fibrosis/tubular atrophy.

Conclusions: We present the first human data connecting serum Dkk-1, an endogenous inhibitor of the pro-fibrotic Wnt/ β -catenin signaling, with prevalent renal allograft fibrosis, and with long-term protection against graft failure in RTR. These findings are in line with preclinical studies suggesting that Dkk-1 is induced upon tissue injury and serves as an endogenous anti-fibrotic factor, and position Dkk-1 as a potential target for anti-fibrotic therapy after KTx.

Funding: Pharmaceutical Company Support - The generation of the cohort was made possible by a grant from the Dutch Top Institute Food and Nutrition. M.H.d.B. and C.A.K. are supported by a consortium grant from the Dutch Kidney Foundation (NIGRAM consortium, grant no. CP10.11). This study was funded by a grant from De Cock-Hadders Foundation (grant no. 2015-44).

SA-OR060

Longitudinal Assessment of Cardiac Morphology and Function following Kidney Transplantation Clark David Kensinger,¹ Antonio Hernandez,² Meagan Fairchild,⁴ Guanhua Chen,³ Loren Lipworth,⁴ Talat Alp Ikizler,⁴ Kelly A. Birdwell.⁴ *¹Dept of Surgery, Vanderbilt Univ Medical Center; ²Dept of Anesthesiology, Vanderbilt Univ Medical Center; ³Dept of Biostatistics, Vanderbilt Univ Medical Center; ⁴Dept of Medicine, Vanderbilt Univ Medical Center.*

Background: Despite improvement in traditional cardiovascular (CV) risk factors following renal transplantation, the death rate from CV disease remains high. Our aim was to evaluate the longitudinal change of cardiac morphology and function in a cohort of patients following renal transplantation, as well as to evaluate the association between Fibroblast Growth Factor 23 (FGF-23) concentrations and the evolution of cardiac morphology following transplant.

Methods: We performed a longitudinal prospective cohort study of 145 kidney transplant recipients, measuring left ventricular mass index (LVMI), left atrial volume index (LAVI) and ejection fraction (EF) by echocardiography at months 1 (baseline), 12, and 24 post-transplant. FGF-23 levels were measured at months 1 and 24 post-transplant. A linear mixed effects model was used to assess each outcome adjusting for age, race, gender, time on dialysis, CV disease, mean arterial pressure, glomerular filtration rate, diabetes, and body mass index.

Results: The cohort (mean age 49±13 years) was 74% male and 75% white. LVMI (P=<0.001), LAVI (P=<0.001), and EF (P=0.009) decreased significantly over time following transplant. Results from the multivariate models can be reviewed in Table 1. A one-unit decrease in FGF-23 was significantly associated with a 5.83 grams/meter² decrease in LVMI (P=0.04).

Conclusions: LVMI, LAVI and EF improved significantly over 12 and 24 months post-transplant. There was also a significant association between FGF-23 and LVMI following transplant.

Outcome	12 month effect	95% CI	P Value	24 month effect	95% CI	P Value
LVMI	-10.95	-16.34, -5.56	<0.001	-14.77	-22.02, -7.52	<0.001
LAVI	-3.31	-5.13, -1.49	<0.001	-4.95	-7.38, -2.52	<0.001
Ejection fraction	1.5	0.09, 2.91	0.04	2.75	0.87, 4.63	0.005

Table 1: Adjusted change in echocardiogram morphology and function following renal transplantation

Funding: NIDDK Support, Other NIH Support - UL1TR000445 from the National Center for Advancing Translational Sciences
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K23 GM100183 (Birdwell) from the National Institute of General Medical

SA-OR061

Tolerance Induction versus Conventional Immunosuppression in HLA-Matched Kidney Transplantation: Comparison at Two Years Post-Transplant John D. Scandling, Stephan Busque, Judith A. Shizuru, Asha Shori, Robert Lowsky, Kent Phillip Jensen, Richard T. Hoppe, Samuel Strober. *Stanford Univ.*

Background: Over 10 years we have studied the safety and efficacy of tolerance induction using hematopoietic cell transplantation in combination with kidney transplantation.

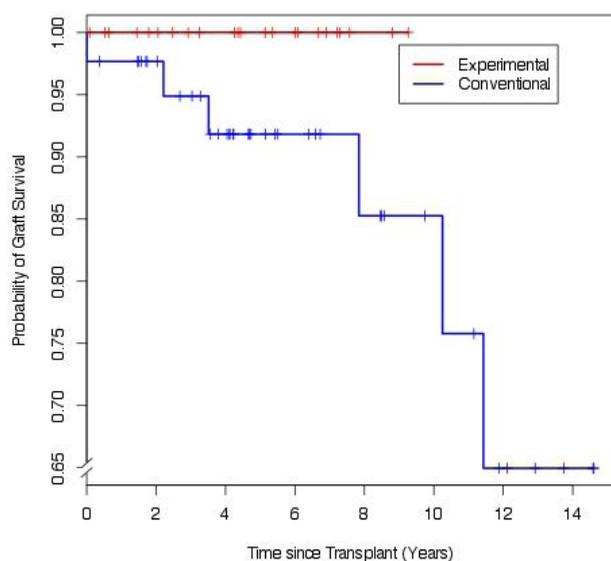
Methods: Twenty-two patients underwent HLA-matched living donor kidney transplantation followed by a conditioning regimen of 10 fractions of total lymphoid irradiation (12 Gy total) and 5 doses of ATG. Infusion of purified donor CD34+ hematopoietic progenitor cells and T cells was on day 11 post-kidney transplant. Fifty-three patients contemporaneously underwent HLA-matched living donor kidney transplantation under conventional immunosuppression.

Results: Seventeen patients developed mixed chimerism of 6 months duration or longer and have now been off immunosuppression from 1 to 7 years. Their outcomes at two years post-transplant are compared to those of the 52 (one graft was lost to thrombosis on day 1) conventionally treated patients.

	Conventionally Treated, 2000-13	Tolerance Induction, 2005-13
Number	52	17
ImmunoRx (mono/dual/triple)	2 / 34 / 16	Off drug 4 to 18 mo (of 24 mo)
Age at transplant (years)	38 +/- 11.2	40 +/- 10.5
Sex (M/F)	26/26	9/8
Cause of ESRD (DM/GN/other)	4 / 17 / 31	1 / 6 / 10
Infection (N of episodes)	8 (1 CMV, 2 v. zoster)	6 (1 CMV, 4 v. zoster)
Cancer	0	1 (breast, at 23 mo)
Acute rejection (N of patients)	3 (5.9%)	0
Creatinine (mg/dL)	1.2 +/- 0.35	1.2 +/- 0.26
Weight gain (kg)	5.2 +/- 7.36	7.4 +/- 8.39
Hypertension	27 (52%)	9 (53%)
Antihypertensive drugs (1/2/3)	15 / 9 / 36	6 / 3 / 0
Hyperlipidemia	20 (39%)	3 (18%)
Post-transplant diabetes mellitus	4 (7.8%)	0

Death-censored graft survival is shown (p=0.10).

Kaplan-Meier Curves for Graft Loss (Total)



Conclusions: Transplantation under this protocol is safe, achieves tolerance eliminating risk of acute rejection, and offers a better metabolic profile and better graft survival with time.
Funding: Other NIH Support - NHLBI, Private Foundation Support

SA-OR062

Better Renal Function Preservation with Early Conversion to Everolimus in De Novo Renal Transplant Recipients: 24-Month Results from the ELEVATE Study Johan W. De Fijter,¹ Hallvard Holdaas,¹ Patricia M. Lopez,² Cesar Escrig,² Zailong Wang,³ Josep M. Cruzado,¹ Markus van der Giet,¹ ¹For the ELEVATE Study; ²Novartis, Basel, Switzerland; ³Novartis Corporation, East Hanover, NJ, USA.

Background: Long-term exposure to calcineurin inhibitors (CNIs) is one of the key factors contributing to progressive deterioration of renal function and graft loss. We present the 24 month (M) renal outcomes from the ELEVATE study which determined whether early CNI to everolimus (EVR) conversion in renal transplant recipients (RTxRs) provides better preserved renal function compared to continuation of standard CNIs.

Methods: ELEVATE (NCT01114529) was a 24M, multicenter, open-label study, in which de novo RTxRs were randomized (RND) at 10–14 weeks post-transplant to convert from CNI to EVR (n=360; C₀ 6–10 ng/mL) or continue standard CNI (n=357; C₀ tacrolimus: 5–10 ng/mL, cyclosporine: 100–250 ng/mL); all received enteric-coated mycophenolate sodium + steroids. The primary end point was change in estimated glomerular filtration rate (eGFR; MDRD-4) from RND to M12.

Results: A total of 717 patients were RND; 229 (65%) and 283 (79%) patients completed on study drug in EVR and CNI groups, respectively. The least squares (LS) mean change in eGFR for EVR vs CNI from RND to M12 was 0.25 vs -1.45 (diff: 1.70, p=0.134) and 0.74 vs -1.07 (diff: 1.80, p=0.117) mL/min/1.73 m² for intent-to-treat (ITT)

and on-treatment (OT) analysis, respectively. Up to M24, mean eGFR was significantly higher at all time-points after RND in EVR vs CNI group for OT analysis. At M24, mean eGFR in EVR vs CNI groups was 62.5 vs 57.4 mL/min/1.73 m² (ITT: p=0.006) and 66.1 vs 59 mL/min/1.73 m² (OT: p=0.001), respectively. The difference in eGFR at M24 between EVR and CNI groups was 5.1 (ITT) and 7.1 mL/min/1.73 m² (OT), respectively, in favor of EVR. Proteinuria (³g/day) was reported in three patients in the EVR group and two in the CNI group.

Conclusions: Early conversion to EVR therapy 3M post-transplant vs continued CNI resulted in better preserved renal function up to 2-years of follow-up.

Funding: Pharmaceutical Company Support - Novartis

SA-OR063

Month 48 Follow-Up Results of the HERAKLES Study: Superior Renal Function After Early Conversion to an Everolimus-Based Calcineurin Inhibitor Free Regimen Klemens Budde,¹ Oliver Witzke,¹ Thomas Rath,¹ Peter Weithofer,¹ Johannes Jacobi,¹ Bruno Vogt,² Ingeborg A. Hauser,¹ Rolf A. Stahl,¹ Petra Reinke,¹ Martina Porstner,³ Martin G. Zeier,¹ Frank Lehner,¹ Wolfgang Arns,¹ Claudia Sommerer,¹ ¹HERAKLES Study Group, Germany; ²HERAKLES Study Group, Switzerland; ³Novartis Pharma, Germany.

Background: To follow up on renal function (GFR) at month (mo) 48 after kidney transplantation (Tx) in patients (pts) on immunosuppressive regimen with different calcineurin inhibitor (CNI) exposures.

Methods: 802 pts were included in this prospective, open-label, randomized multicenter study. After induction with basiliximab all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 mo post Tx 499 pts were randomized 1:1:1 to either a) continue standard (STD) CsA (100-180ng/ml) with EC-MPS (n=166), b) convert to a CNI-free regimen with everolimus (EVR; 5-10ng/ml) + EC-MPS (n=171) or c) convert to CNI-reduced regimen CsA (50-75ng/ml) with EVR (3-8ng/ml) (n=162).

Results: GFR (Nankivell, ITT) was similar at randomization 3 mo post Tx and had significantly improved at mo 12 by +5.6mL/min (95%CI:[+2.9;+8.3]; p<0.001) and remained significantly improved by +6.8mL/min in favor of CNI-free regimen at mo 48(p=0.02). 54% of CNI-free, 36% of CNI-reduced and 44% of STD pts had an improvement in GFR at mo 48 (p=0.09 CNI-free vs STD). All 3 groups had similar rejection rate since randomization (13% STD, 16% CNI-free, 16% CNI-reduced) and overall comparable safety profile. Mean trough levels at mo 48 were for CsA 111ng/ml in STD and 86ng/ml in CNI-reduced pts and for EVR 5.5ng/ml in CNI-free and 5.5ng/ml in CNI-reduced pts.

Conclusions: CNI-free as well as reduced CNI in combination with EVR represent both efficacious and safe regimen. CNI-reduced group had higher CsA levels than anticipated. The fact that CNI reduction was not fully accomplished might have prevented GFR differences compared to STD in this randomized treatment group. However, CNI-free regimen was associated with better GFR maintained for 4 years post Tx. The results of this large trial confirm previous reports of improved GFR after CsA withdrawal with EVR in combination with EC-MPS.

Funding: Pharmaceutical Company Support - Novartis Pharma

SA-OR064

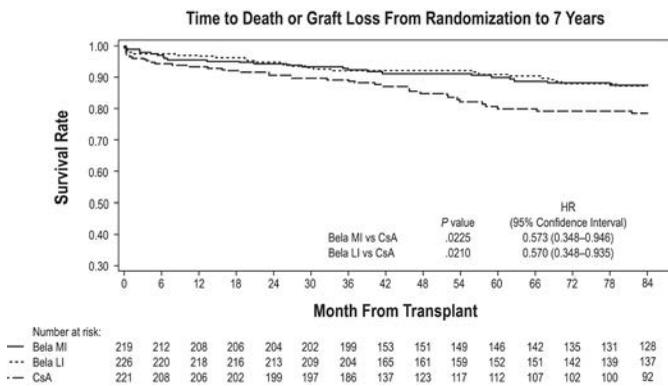
Belatacept pts Had Superior Graft Survival versus CsA pts: Final Results from BENEFIT Flavio Vincenti,¹ J. Grinyo,² R. Bray,³ L. Rostaing,⁴ B. Bresnahan,⁵ K. Rice,⁶ S.M. Steinberg,⁷ H. Gebel,³ M. Polinsky,⁸ U. Meier-Kriesche,⁸ S. Munier,⁸ R. Townsend,⁸ C.P. Larsen,³ ¹Univ of California, San Francisco; ²Univ Hospital Bellvitge, Barcelona, Spain; ³Emory Univ, Atlanta; ⁴Univ Hospital and INSERM U563, IFR-BMT, Toulouse, France; ⁵Medical College of Wisconsin, Milwaukee; ⁶Baylor Univ Medical Center, Dallas; ⁷Sharp Memorial Hospital, San Diego; ⁸BMS, Lawrenceville.

Background: At 3 and 5 yrs post-transplant in BENEFIT, renal function was improved in kidney transplant recipients administered belatacept (bela) vs CsA. We report final 7-yr results.

Methods: Pts were randomized to more (MI) or less intensive (LI) bela or CsA regimens. Outcomes were assessed for all randomized, transplanted pts at yr 7. In a prospective analysis, time to death or death-censored graft loss was compared using Cox regression. Presence of DSAs was established centrally (FlowPRA®). Kaplan-Meier estimates for the cumulative rate of de novo (DN) DSAs were derived. Mean calculated GFR (cGFR) was estimated from mos 1–84 using a repeated measures model with an unstructured covariance matrix. Differences in cGFR at each time point were also estimated.

Results: In total, 153/219 of bela MI, 163/226 of bela LI, and 131/221 of CsA pts were evaluable. HRs comparing time to death/graft loss were 0.573 for bela MI vs CsA (P=.02) and 0.570 for bela LI vs CsA (P=.02)—a 43% risk reduction in death/graft loss for bela (MI or LI) vs CsA. Cumulative event rates of DN DSAs at yr 7 for bela MI, bela LI, and CsA were 1.86, 4.64, and 17.81, respectively. Serious AE rate was similar (71%, bela MI; 69%, bela LI; 76%, CsA). Mean cGFR increased slightly over 7 yrs for both bela regimens but declined for CsA. Differences in mean cGFR at yr 7 were 25.6 mL/min/1.73 m² for bela MI vs CsA and 27.3 mL/min/1.73 m² for bela LI vs CsA differences favored each bela regimen vs CsA at all time points (P<.0001).

Conclusions: In this 7-yr analysis, bela conferred statistically better graft survival and renal function vs CsA, with a reduced incidence of DN DSAs. The bela safety profile was consistent with previous reports.



Funding: Pharmaceutical Company Support - Bristol-Myers Squibb

SA-OR065

Differential Expression of MicroRNA in Urinary Exosomes of Preeclampsia Patients Belinda Bun Jim,¹ Alison P. Sanders,³ Daniel Flores,² Rajeev Rohatgi,² ¹Medicine/Nephrology, Jacobi Medical Center, Bronx, NY; ²Medicine/Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY; ³Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Urinary exosomes are low density membrane vesicles originating from the multivesicular bodies of upstream renal epithelial cells. The exosomes contain molecules, such as microRNA (miRNA), which may serve as potential biomarkers for kidney disease, and, in particular, preeclampsia, a systemic disease with renal manifestations that affects 5-8% of pregnant women in the world.

Methods: We recruited 10 preeclamptic pregnant women and 9 healthy pregnant controls; each submitted a 50 mL spot urine sample for exosome isolation. Exosomes were isolated by sequential centrifugation and ultracentrifugation, and the exosomal miRNAs purified using miRNeasy kit (Qiagen). After isolation of miRNA from urinary exosomes, we used the Nanostring nCounter system to assess miRNA expression. Analysis of Variance (ANOVA) was performed to test for differences in exosomal miRNA expression (log2) between cases (n=10) and controls (n=9). Statistical significance was defined at p<0.05 and Storey's false discovery rate q-values were calculated.

Results: After adjusting for maternal age and experimental batch, two miRNAs remained statistically significant. miR-544a was upregulated among cases compared to controls, whereas miR-495 was downregulated. Enrichment analysis of the 624 and 913 highly predicted downstream mRNA targets showed that miR-544a targets were enriched for cardiovascular system diseases including arterial pressure (p<4.6x10⁻⁴) and vasculogenesis (p<1.2x10⁻³); whereas the targets of miR-495 were associated with renal and urological system development (p<2.8x10⁻⁶).

Conclusions: We believe that these pilot results demonstrate the potential to identify a biomarker for preeclampsia that may be mechanistically plausible. Larger studies are presently being conducted.

SA-OR066

Functional Testing of Human Epithelial Na⁺ Channel Missense Variants Identified in the GenSalt Study Evan C. Ray,¹ Jingxin Chen,¹ Tanika Kelly,² Jiang He,³ D.C. Rao,³ James E. Hixson,⁴ Dongfeng Gu,⁵ Shaohu Sheng,¹ Thomas R. Kleyman,¹ ¹Univ of Pittsburgh; ²Tulane Univ; ³Washington Univ; ⁴Univ of Texas; ⁵Peking Union Medical College.

Background: In Liddle syndrome, epithelial Na⁺ channel (ENaC) mutations that result in increased cell-surface expression are associated with early on-set hypertension, underscoring the importance of this channel in modulating blood pressure. Whether genetic variants that result in subtler increases in channel function contribute to salt-sensitive hypertension remains unclear.

Methods: A number of human ENaC variants were identified in 300 Genetic Epidemiology Network of Salt Sensitivity (GenSalt) participants with salt-sensitive hypertension and 300 with salt-independent hypertension. We used the *Xenopus* oocyte expression system to examine the functional properties of missense ENaC variants identified in the GenSalt study.

Results: Among 6 SCNN1A (encoding the ENaC α subunit) variants, 3 (aS115N, aR476W and aV481M) showed significantly greater, and one (aA334T) showed significantly lower ENaC currents than wild type. Among 3 SCNN1B (ENaC β subunit) variants, β D31N showed a significant reduction in ENaC currents; bS635N showed a significant increase in ENaC currents. Both β subunit variants substitute amino acids in intracellular domains. Among 5 SCNN1G (ENaC γ subunit) variants, one (γ L438Q) had significantly greater ENaC currents than wild type. Each of the variants located in ENaC's extracellular domain that altered channel activity also altered Na⁺ self-inhibition, a process wherein extracellular Na⁺ suppresses channel open-probability.

Conclusions: Some missense ENaC variants identified in the GenSalt study alter ENaC function and may influence salt-sensitivity of blood pressure.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR067

Nephron Specific Deletion of the Prorenin Receptor Modulates Blood Pressure and Urinary Na Excretion Nirupama Ramkumar,¹ Deborah Stuart,¹ Elena V. Mironova,² Vladislav V. Bugay,² Mykola Mamenko,³ Shuping No Wang,¹ Oleh Pochynyuk,³ James D. Stockand,² Donald E. Kohan.¹ ¹Medicine, Univ of Utah; ²Medicine, Univ of Texas Health Sciences Center - San Antonio; ³Medicine, Univ of Texas Health Sciences Center - Houston.

Background: The nephron prorenin receptor (PRR) may modulate blood pressure (BP) and Na balance.

Methods: Since previous models of PRR knockout (KO) mice had early lethality and/or structural defects, we developed an *inducible* nephron-wide PRR KO using the Pax8/LC1 transgenes.

Results: Disruption of nephron PRR at 1 month of age caused no renal histological abnormalities. On a normal Na diet, wild-type (WT) and PRR KO mice had similar BP and Na excretion. However, PRR KO mice had elevated PRC (KO- 377 \pm 77 vs WT- 127 \pm 19 ng Ang-1/ml/hr) and a 50% decrease in renal ENaC- α protein. Protein levels of NHE3, NKCC2, NCC and ENaC- β/γ were similar between the two groups. Treatment with mouse prorenin (10 nM for 30 min) increased ENaC channel number by 2-fold, but not open probability, in isolated split-open cortical collecting ducts (CCD) from WT mice; this was prevented by PRR inhibition (PRO20) and Akt inhibition (A6730) but unaffected by blockade of AT-1 (losartan), ERK1/2 (U0126) or p38 MAPK (SB203580). Addition of prorenin (10 nM) did not change isolated CCD [Ca²⁺]_i as assessed by Fura-2 loading (10 min exposure). On a low Na diet, PRR KO mice had increased Na excretion (Day 2: KO - 66 \pm 11 vs WT- 42 \pm 6 mmol/day; Day 6: KO - 39 \pm 4 vs WT - 23 \pm 4 mmol/day) however, no differences in BP were observed. PRC remained elevated in PRR KO mice on a low Na diet. PRR KO mice had an attenuated hypertensive response to Angiotensin-II (Ang-II) infusion at 600 ng/Kg/min for 2 weeks (MAP: KO - 117 \pm 4 vs WT - 133 \pm 4 mm Hg over 2 weeks). Urinary Na excretion was elevated in Ang-II treated PRR KO mice as compared to WT mice (KO-344 \pm 14 vs WT-268 \pm 30 mmol/day).

Conclusions: Taken together, these data indicate that nephron PRR, likely via direct prorenin/renin stimulation of an Akt-dependent pathway, stimulates CCD ENaC activity. Absence of nephron PRR promotes Na wasting and reduces the hypertensive response to Ang-II.

SA-OR068

Pendrin Localizes to the Adrenal Medulla and Modulates Catecholamine Release Annie Y. Park,¹ Truyen D Pham,¹ William H. Beierwaltes,³ Roy L. Sutliff,¹ Jill W. Verlander,² Carla L. Ellis,¹ Brandi M. Wynne,¹ Robert S. Hoover,¹ Susan M. Wall,¹ Yoskaly Lazo-Fernandez.¹ ¹Medicine and Pathology, Emory Univ, Atlanta, GA; ²Medicine, Univ of Florida, Gainesville, FL; ³Hypertension and Vascular Research, Henry Ford Hospital, Detroit, MI.

Background: Pendrin (Slc26a4) is a Cl⁻/HCO₃⁻ exchanger expressed in renal intercalated cells that mediates renal Cl⁻ absorption. Pendrin gene ablation reduces blood pressure and vascular volume. While pendrin gene ablation increases plasma renin concentration, serum aldosterone is not increased, suggesting that pendrin regulates aldosterone production in the adrenal cortex. The purpose of this study was to determine if pendrin is expressed in the rodent adrenal gland and if it modulates adrenal function.

Methods: Pendrin mRNA and protein abundance were explored by PCR, immunoblots and immunohistochemistry. Mean arterial pressure (MAP) was measured by telemetry. Catecholamines were measured by HPLC in plasma samples from mice bearing chronic indwelling jugular catheters.

Results: Pendrin localizes to the rodent adrenal gland in epinephrine- and norepinephrine-producing chromaffin cells of the adrenal medulla rather than in adrenal cortical cells. We examined the effect the pendrin gene ablation on adrenal medullary function by measuring stress-induced catecholamine release. While basal levels of epinephrine (E) and norepinephrine (NE) were similar, E and NE levels were ~25-50% higher pendrin null than in wild type mice after 20 min of immobilization stress. 30 min following relief of stress, NE levels were 50% higher in pendrin null than in wild type mice. MAP rose in both wild type and pendrin null mice following immobilization stress, but MAP in pendrin null mice was 16 mm Hg lower than in wild type mice under basal conditions and 12 mm Hg lower following 20 min of immobilization stress (P<0.05). However, 30 min after relief of stress, MAP was the same in both groups (Wild type 121 \pm 1.33 versus 117 \pm 3.5 mm Hg, pendrin null mice).

Conclusions: Pendrin is expressed in mouse adrenal medulla where it plays a role in restraining catecholamine release during stress, which probably modulates pendrin-dependent changes in blood pressure.

Funding: NIDDK Support, Other NIH Support - DK46493, DK085097, T32 DK07656

SA-OR069

Renal-Selective Silencing of Adrenomedullin Gene Causes Hypertension in Mice Xiaoyan Wang, Donghai Zhou, Laureano D. Asico, Hai Lin, John Edward Jones, Pedro A. Jose. *Medicine, Univ of Maryland Medical School, Baltimore, MD.*

Background: Adrenomedullin (ADM) is a potent hypotensive and natriuretic peptide whose gene variants are associated with human essential hypertension. Although the kidney is one of the ADM producing organs, the mechanism by which ADM induces a natriuresis is not clear.

Methods: To determine the role of renal ADM on blood pressure in C57BL/6J mice (3.5 months old, male) fed a 0.6% NaCl diet, we silenced the ADM gene by the renal subcapsular infusion of Adm siRNA (3 mg/day), via osmotic minipump, into the remnant kidney one week after unilateral nephrectomy. Mock siRNA (3 mg/day) was used as control. The mice were placed in metabolic cages for 24 hr urine collection before blood pressure was measured under anesthesia, via the femoral artery on day 7.

Results: Body weight, water/food intake, and serum Na⁺, K⁺, & Cl⁻ were similar in the two groups. Systolic blood pressure was elevated in Adm siRNA group (129.3±5.1, mm Hg) relative to Mock group (96.2±1.4n=5/group). The two groups of mice excreted similar amounts of sodium and water but the sodium excretion and blood pressure plot in Adm mice was shifted to the right of Mock mice. Immunofluorescence confocal microscopy in normal mice revealed that ADM was mainly located in the cortex, especially in the apical membrane of renal proximal convoluted tubules (RPCT). ADM colocalized with NHE3 but not with NKCC2 and NCC. ADM also coimmunoprecipitated with NHE3 in whole kidney homogenates. In mouse RPCT cells, Adm siRNA decreased ADM protein to 48 ±4% of Mock group (n=4/group) and doubled the protein abundance of NHE3 (192±21) but did not alter aNKA. In polarized human PPCT cells, human ADM (1 hr, n=5-6/group) inhibited apical sodium transport at 10 nM (84±4 % of vehicle) and 100 nM (81±3%), similar to that achieved with the NHE3 inhibitor EIPA (81±6%, 100 nM).

Conclusions: Our data suggest that a renal-selective silencing of ADM gene increases blood pressure and impairs sodium excretion that is related, in part, to an increase in NHE3 abundance and function in the RPCT.

Funding: NIDDK Support

SA-OR070

Vascular AT1 Angiotensin Receptors Regulate Sodium Transporter Abundance in Kidney Epithelium Matthew A. Sparks,¹ Susan B. Gurley,¹ Alicia A. McDonough,² Thomas M. Coffman,¹ ¹Duke, ²USC.

Background: Vasoconstriction is a signature physiological action of angiotensin II (AngII) acting via AT1 receptors (AT1R).

Methods: In order to define the contribution of AT1R in vascular smooth muscle cells (VSMCs) to BP control, we generated mice with cell-specific deletion of AT1AR from VSMCs (SMKOs) using Cre-loxp technology.

Results: Baseline BP was reduced by ~7 mmHg and responses to AngII-induced hypertension were blunted by in SMKO mice compared to controls (16 vs. 30 mm Hg Δ BP from baseline after 4 wks AngII, P<0.02). Baseline renal blood flow (RBF) was higher, and renal vasoconstriction to AngII was impaired in SMKOs. Moreover, SMKO mice displayed Na⁺ sensitivity and exaggerated natriuresis during chronic AngII. To investigate the mechanism of the lower baseline BP and the enhanced natriuresis during AngII infusion (1000ng/kg/min for 5 days), we measured a panel of key Na⁺ transporters in the kidney by immunoblot. Baseline measurements in SMKO vs. controls detected reductions in NKCC2 in both cortex (0.8±0.03 vs. 1±0.03; P=0.0002) and medulla (0.6±0.02 vs. 1±0.05; P<0.0001); medullary NHE3 was similarly reduced (0.6±0.07 vs. 1±0.07; P=0.002). In controls, AngII infusion was associated with reduced cortical and medullary NHE3 and medullary NKCC, consistent with the pressure-natriuresis response, whereas cortical NKCC, NCC and ENaC were all significantly activated. By contrast, in SMKOs, there was no AngII infusion dependent depression in cortical or medullary NHE3, nor medullary NKCC. However, the extent of increase in activated (cleaved) αENaC was significantly less than controls (cortex: 1.46±0.16 vs. 2.58±0.17, P=0.002; medulla: 1.49±0.09 vs. 2.22±0.31, P=0.01). Yet, 24 hr urinary aldosterone excretion was not different between the groups (18.6±2.7 vs. 15.8±4.5 ng/24hrs).

Conclusions: Our studies indicate that the lower baseline BP in SMKO mice is associated with reduced Na⁺ transporter abundance along the loop of Henle, and that attenuated hypertension and improved natriuresis during AngII infusion are associated with diminished ENaC activation. We suggest that vascular-epithelial cross-talk modulates renal Na⁺ handling and thereby contributes to BP control at baseline and during hypertension.

Funding: NIDDK Support, Veterans Administration Support

SA-OR071

Chronic Inhibition of Renal Outer Medullary Potassium Channel Not Only Prevented but also Reversed Hypertension Development and End Organ Damage in Dahl Salt Sensitive Rats Xiaoyan Zhou,¹ Wanda Sharif-Rodriguez,² Gail M. Forrest,¹ Daphne Szeto,¹ Olga Price,¹ Yonghua Zhu,¹ Andra S. Stevenson,¹ Yuchen Zhou,¹ Sloan Stribling,¹ Maya Dajee,¹ Shawn P. Walsh,¹ Alexander Pasternak,¹ Kathleen A. Sullivan.¹ ¹Merck & Co., NJ; ²Regeneron Pharmaceuticals, NY.

Background: The renal outer medullary potassium (ROMK) channel mediates potassium recycling and facilitates sodium reabsorption through the Na⁺/K⁺/2Cl⁻ cotransporter in the loop of Henle and potassium secretion at the cortical collecting duct. Evidence from the phenotype of humans and rodents with functional ROMK deficiency supports the contention that selective ROMK inhibitors (ROMKi) will represent a novel diuretic with potential of therapeutic benefit for hypertension. ROMKi have been recently synthesized by Merck & Co. The present studies were designed to examine effects of ROMKi A on systemic hemodynamic, renal function and structure, and vascular function in Dahl salt-sensitive (SS) rats.

Methods: Four experimental groups: control, high salt diet alone; ROMKi A 3 mg·kg⁻¹·d⁻¹; ROMKi A 10 mg·kg⁻¹·d⁻¹; and hydrochlorothiazide (HCTZ) 25 mg·kg⁻¹·d⁻¹ were included in the prophylactic (from week 1 to week 9 on high salt diet) and therapeutic study (from week 5 to week 9 on high salt diet), respectively. The compounds were administered in feed. Blood pressure was measured by radiotelemetry. Renal function was assessed in metabolic cage studies. Vascular function was assessed by vascular relaxation assay.

Results: ROMKi A produced sustained blood pressure reduction and improved renal and vascular function and histological alterations induced by a high salt diet. ROMKi A was superior to HCTZ at reducing blood pressure. Furthermore, ROMKi A provided beneficial effects on both lipid profile and bone mineral density.

Conclusions: Chronic ROMK inhibition not only prevented but also reversed hypertension development and end organ damage in Dahl SS rats. Our findings may suggest a great potential of ROMKi as novel antihypertensive agents, particularly in treating salt sensitive hypertension patient population.

Funding: Pharmaceutical Company Support - Merck & Co.

SA-OR072

Analysis of Children with Hypercalciuria and Kidney Stones Identified a Mutation in a 5' Upstream Regulatory Element of Claudin-14 That Increases Gene Expression R. Todd Alexander, Megan E. Ure, Wanling Pan, Emmanuelle Cordat. *Univ of Alberta, Edmonton, AL, Canada.*

Background: Kidney stones are prevalent and painful. The greatest risk factor for kidney stones is hypercalciuria for which the etiology is largely unknown. A recent GWAS study linked hypercalciuria to claudin-14, however it failed to identify the molecular mechanism mediating disease. We recently determined a role for claudin-14 in inducing calcium excretion when plasma calcium levels are elevated. We postulated therefore that children with kidney stones may have a mutation in CLDN14 increasing its expression.

Methods: To assess this hypothesis, we collected DNA from 16 children with idiopathic hypercalciuria and sequenced the target gene, including introns. To assess for a functional effect of the identified SNP we performed dual luciferase assays. We also engineered the identified mutant region in front of the SV40 promoter and the CLDN14 coding sequence and created stable cell lines. *In silico* studies were used to identify potential novel transcription factor binding sites introduced by identified SNPs and gel electrophoretic mobility shift assays to assess the binding of a transcription factor to the sequences.

Results: We found an intronic SNP in CLDN14 that occurred with greater frequency in children with hypercalciuria and kidney stones relative to ethnically matched controls (from the 1000 genome project). Dual luciferase assays found the mutant sequence doubled expression while the wild type had no effect (relative to empty vector). Despite similar numbers of the engineered constructs being incorporated into genomic DNA of the stable cell lines, the mutant sequence doubled mRNA and protein expression. *In silico* studies predicted the SNP introduced a novel INSM1 transcription factor binding site. To assess this, we expressed the WT and mutant luciferase constructs in the presence and absence of INSM1 and found a further increase in expression. Finally, gel electrophoretic mobility shift assays confirmed preferential binding of INSM1 to the mutant sequence.

Conclusions: Some children with hypercalciuria and kidney stones have a intronic mutation in CLDN14 that introduces a novel INSM1 binding site.

Funding: Government Support - Non-U.S.

SA-OR073

Oxalobacter-Derived Bioactive Factors Reduce Urinary Oxalate Excretion in a Mouse Model of Primary Hyperoxaluria Hatim A. Hassan,¹ Donna L. Arvans,¹ Yong-chul Jung,¹ Dionysios A. Antonopoulos,^{1,3} John R. Asplin,² Ignacio Granja,² Jason C. Koval,³ Mark W. Musch,¹ Eugene B. Chang.¹ ¹Univ of Chicago; ²Litholink Corporation; ³Argonne National Laboratory.

Background: Hyperoxaluria is a major risk factor for calcium oxalate kidney stones (COKS) and has no therapy. The probiotic bacterium *Oxalobacter formigenes* (*Of*) plays a critical role in preventing recurrent COKS by metabolizing its host dietary oxalate, leading to reduced intestinal absorption and urinary excretion. *Of* also interacts with colonic epithelium by inducing colonic oxalate secretion, leading to reduced urinary excretion, via an unknown secretagogue. Sustaining *Of* colonization in animals and humans in the absence of high exogenous oxalate remains problematic, underscoring the need for identifying *Of*-derived factors exerting effects similar to live *Of*.

Methods: We previously found that small molecular weight protein(s) and/or peptide(s) in *Of* culture conditioned medium (CM) significantly stimulate oxalate transport (>2-fold) by human intestinal Caco2-BBE cells. To evaluate the CM *in vivo* effects, CM or OM (control medium) was given rectally as enemas (100 μl twice daily x 23 days) to PH1 mice (a mouse model of primary hyperoxaluria type 1).

Results: The CM significantly reduced urinary oxalate excretion by 32.5% while OM has no effect (μM/mg creatinine: OM = 51.50±3.33; 46.08±2.04; CM = 47.27±3.43; 31.91±4.81; before and after treatment, respectively). To test our hypothesis that the observed reduction in urinary oxalate is due to CM-induced enhanced colonic oxalate secretion, colonic tissues were isolated and mounted in Ussing chambers. While a small net oxalate secretory flux (-1.54) is observed in distal colonic tissues from OM-treated mice, a >10-fold higher net oxalate secretory flux (-16.34) is seen in distal colonic tissues from CM-treated mice (pmol/cm²/h: OM: J_{MS} (absorptive flux) = 39.99±5.29, J_{SM} (secretory flux) = 41.53±4.59; CM: J_{MS} = 42.62±3.67, J_{SM} = 58.96±3.02), which is due to significantly increased J_{SM}.

Conclusions: We conclude that *Of*-derived bioactive factor(s) retain(s) its/their biological activity *in vivo* and significantly reduce(s) urinary oxalate excretion in PH1 mice by stimulating distal colonic oxalate secretion.

Funding: NIDDK Support, Other NIH Support - Digestive Disease Research Center of the University of Chicago(NIDDK P30 DK42086), Private Foundation Support

SA-OR074

Hyperoxaluria Requires TNF Receptors to Initiate Crystal Adhesion and Kidney Stone Disease Jonathan Nicodemos Eberhard, Shrikant R. Mulay, Jyaysi Desai, Julian A. Marschner, Santhosh Kumar Vr, Hans J. Anders. *Ludwig Maximilians Univ, Germany.*

Background: Nephro- or urolithiasis involves intratubular mineral supersaturation as well as lack of crystallization inhibitors to form crystal plugs obstructing renal tubules. Recently, NLRP3 inflammasome-related renal inflammation was added as a pathomechanism of acute oxalosis (Mulay et al, JCI 2013) as well as nephro-/urolithiasis (Knauf et al, KI 2013). As TNF receptor (TNF-R) signaling is a major mediator of inflammation in several chronic kidney diseases (CKD), we speculated that TNF-Rs would also drive the progression of nephrolithiasis-related CKD.

Methods: All *in vivo* experiments were approved by the local government authorities. Immunohistochemistry, WB, RT-PCR and atomic force microscopy (AFM) were used for data analysis.

Results: We observed that kidney immunostaining of humans and mice with hyperoxaluria-related CKD displayed strong tubular positivity for TNF- α , TNF-R1 and TNF-R2, which was absent in healthy kidneys. WB and mRNA expression analyses were consistent in mice kidneys. To test our hypothesis we fed an oxalate-rich diet to wild type (WT) mice or mice deficient for Tnfr1, Tnfr2 or Tnfr1/2. Oxalate feeding induced CaOx nephrolithiasis and progressive CKD in WT mice. Surprisingly, KO mice showed absolutely no intrarenal CaOx crystal deposits, as revealed by computed tomography as well as kidney immunostainings for CaOx, despite comparable hyperoxaluria and urinary calcium concentrations to WT mice. Further, we measured the adhesion forces between tubular epithelial cells and CaOx crystals by atomic force microscopy. We observed that lack of TNFR1/2 impairs CaOx crystal adhesion to the tubular epithelial cell surface. However, in an independent experiment we did not see any direct binding of CaOx crystals to the soluble TNF-R1-IgG fusion protein. Instead, we observed that TNF-R signaling is indeed required for inducing the expression of known crystal adhesion molecules viz. osteopontin, CD44, annexin II on tubular epithelial cells *in vitro* and *in vivo*.

Conclusions: We conclude that TNF-Rs are essential mediators of CaOx crystal adhesion at the luminal membrane of renal tubules as a fundamental mechanism of oxalate nephropathy.

SA-OR075

Critical Role of Toll-Like Receptor 4 in Crystal-Induced Inflammation and Renal Failure Venkata Surya Narayana Murty Darisipudi,¹ Christoph Daniel,² John R. Asplin,³ Ignacio Granja,³ Kerstin U. Amann,² Kai-Uwe Eckardt,¹ Peter S. Aronson,⁴ Felix Knauf.^{1,4} ¹Dept of Nephrology and Hypertension, Universitätsklinikum Erlangen, Erlangen, Bavaria, Germany; ²Dept of Nephropathology, Univ Erlangen, Erlangen, Bavaria, Germany; ³Litholink Corporation, Chicago, IL; ⁴Dept of Internal Medicine, Yale Univ School of Medicine, New Haven, CT.

Background: Crystal-induced inflammation is a serious condition associated with chronic kidney disease. We have recently demonstrated that progressive renal failure in oxalate crystal nephropathy results from NLRP3-mediated inflammation. Since interactions between NLRP3 and Toll-like receptors (TLRs) have been described, we examined the role of TLRs to identify early molecular mechanisms initiating crystal-induced renal failure.

Methods: We evaluated the expression of TLRs in renal sections of mice and humans with crystal-induced renal failure. Age- and gender-matched wild-type and Tlr4-null mice were placed on a high soluble oxalate diet and monitored for progression of renal failure longitudinally by measuring plasma creatinine via retroorbital blood collections, and animals were monitored for mortality. Urine oxalate levels were measured and renal histology examined for crystal deposition, tubular damage and macrophage infiltration using F4/80 staining.

Results: Crystal-induced renal damage was observed to upregulate TLR4 expression in renal tubule epithelial cells and interstitium in mice and humans with oxalate nephropathy. Tlr4-null mice demonstrated reduced crystal deposition, tubular damage and inflammation on renal histology despite identical urinary oxalate excretion as compared to wild-type mice. Moreover, Tlr4-null mice were completely protected from the progressive renal failure that was associated with 100% mortality in wild-type mice.

Conclusions: Taken together, these findings highlight the importance of TLR4 as a critical mediator of crystal-induced inflammation and progressive renal failure. Blocking TLR4 with neutralizing antibodies/inhibitors may represent a therapeutic approach to treat patients suffering from crystal-induced inflammatory kidney disease.

SA-OR076

ALLN-177 Oral Enzyme Therapy Reduces Urinary Oxalate in Patients with Secondary Hyperoxaluria (2^o HO) and Recurrent Kidney Stones: Results of a Phase 2 Study Gyan Pareek,¹ James E. Lingeman,² Zeph Okeke,³ Linda H. Easter,⁴ Danica Grujic,⁵ Craig B. Langman,⁶ Jennifer Nezzar,⁷ Lee Brettman.⁵ ¹Miriam Hospital, Brown Univ; ²IU Health Methodist; ³North Shore LLJ; ⁴Allena Constl; ⁵Allena; ⁶NWU; ⁷PRG.

Background: (2^oHO) can lead to kidney stones (KS) and oxalate nephropathy which can result from excess absorption of dietary oxalate of an unknown cause idiopathic hyperoxaluria (IH), or in patients with enteric hyperoxaluria (EH). Presently there are no pharmacological therapies (Rx) to reduce 2^oHO. ALLN-177 is an orally-administered,

oxalate-degrading enzyme Rx that significantly reduced oxalate excretion shown in a previous Phase 1 study. **Objective:** To test the efficacy and safety of ALLN-177 in patients with 2^oHO and a history of recurrent calcium oxalate KS.

Methods: 16 male and female patients with KS within the last 2y (5 EH and 11 IH), were enrolled in a multi-center, open-label, single arm study. Patients continued their regular diets and medical Rx (8/16 subjects had thiazides, K-citrate, or calcium supplements). The study had a 35d screening period, a 3d baseline, a 4d ALLN-177 Rx (7,500 u/meal TID) and a 4d follow up. 8x24h urines were collected. Safety assessments and 24h dietary recalls (DR) were performed. The 1^o endpoint was the per subject change in mean 24h urinary oxalate (Uox) from baseline to ALLN-177 Rx.

Results: Mean baseline Uox (SD) for all subjects was 77.7 (55.9) mg/d and during 4 days of ALLN-177 Rx, it was reduced 14mg to 63.7 (40.2) mg/d, p=0.0084. Mean daily dietary oxalate, calcium and fluid intakes based on DR were 200, 199, 840 mg and 3.4 L, respectively and did not differ by study period. Mean baseline Uox for EH and IH were 110.5(82.9) vs. 62.7(33.8) mg/d, while the reduction on ALLN-177 Rx was 22.0 (26.6) vs 10.2 (13.3) mg/d, respectively. The CaOx relative urinary supersaturation index was reduced from 11.6 to 8.8, with 95% CI of [-4.9, -0.78]. This difference was driven by oxalate reduction, but not any other urinary parameters. ALLN-177 was well tolerated, and no safety issues were noted.

Conclusions: In this Phase 2 study, ALLN-177 significantly reduced urinary oxalate excretion and supersaturation index.

Funding: Pharmaceutical Company Support - Allena

SA-OR077

Diet-Dependent Net Acid Load, Protein Intake, and Risk of Incident Kidney Stones Pietro Manuel Ferraro,^{1,2} Ernest I. Mandel,² Gary C. Curhan,² Giovanni Gambaro,¹ Eric N. Taylor.² ¹Div of Nephrology, Catholic Univ of the Sacred Heart, Rome, Italy; ²Channing Div of Network Medicine, Harvard Medical School, Boston.

Background: Higher dietary acid load and protein intake may increase risk of kidney stones (KS). However, associations between net acid load and stone risk have not been explored in population-based studies, and it is not known whether stone risk varies according to protein type.

Methods: We prospectively examined the association between estimated net endogenous acid production (NEAP), protein intake (vegetable [VP], dairy [DP] and animal non-dairy [AP]) and risk of incident KS in three large ongoing cohorts, the Health Professionals Follow-up Study (n=42,919 men), Nurses' Health Study I (n=60,128 older women), and Nurses' Health Study II (n=90,629 younger women). We used Cox hazards regression models to generate hazard ratios (HRs) adjusted for age, BMI, dietary, lifestyle, and medical factors. We also analyzed multivariable associations between NEAP and 24-h urine composition in >6,000 study participants.

Results: During 3,133,014 person-years of follow-up, there were 6,347 incident KS. There was a significant association between NEAP and KS risk in all cohorts (pooled HR for highest vs lowest quintile 1.41, 95% CI 1.16, 1.72; p-value for trend < 0.001). There was no association between VP intake and risk of KS. There was a significant association between AP intake and risk of KS in HPFS (HR 1.14, 95% CI 0.97, 1.35; p-value for trend = 0.04) and NHS I (HR 1.23, 95% CI 1.01, 1.49; p-value trend = 0.05) but not in NHS II. There was no association between DP and risk except in NHS II, where the HR was 0.83, 95% CI 0.72, 0.95; p-value trend = 0.003. After multivariable adjustment, participants in the highest compared with lowest quintile of NEAP had 85 mg/d less urine citrate, 0.18 lower urine pH, 177 mL/d less urine volume, and higher urine supersaturations with respect to calcium oxalate and uric acid (all p-values \leq 0.001).

Conclusions: In 3 large cohorts, higher NEAP is associated with higher risk of KS, as well as lower urine citrate and pH. In contrast with AP, VP and DP are not associated with higher risk of KS.

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SA-OR078

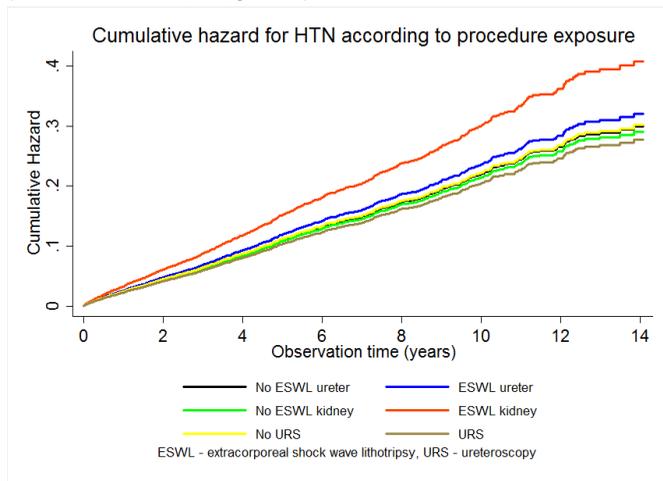
Urologic Interventions for Urolithiasis and Risk of Incident Hypertension and Chronic Kidney Disease: A Population-Based Cohort Study Michelle Denburg,^{1,2} Thomas Jemielita,² Gregory Edward Tasian,^{1,2} Kevin Haynes,² Phillip Mucksavage,² Justine Shults,^{1,2} Lawrence A. Copelovitch.^{1,2} ¹The Children's Hospital of Philadelphia; ²Perelman School of Medicine, Univ of Pennsylvania.

Background: We sought to determine if among individuals with urolithiasis, extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) are associated with a higher risk of incident hypertension (HTN) and/or chronic kidney disease (CKD).

Methods: A population-based retrospective cohort study using The Health Improvement Network comprised 11,570 participants (pts) with incident urolithiasis and 127,464 pts without urolithiasis; pre-existing HTN and CKD were excluded. 1319 and 919 of urolithiasis pts had ³1 ESWL or URS procedure, respectively. Median year for the start of follow-up was 2006. Cox regression, adjusted for age, gender, diabetes, gout, and calendar time, was used to estimate the hazard ratio (HR) for incident HTN and CKD stage 3-5 in separate analyses.

Results: Over a median of 3.7 and 4.1 years, 1423 (12.3%) and 595 (5.1%) of urolithiasis pts developed HTN and CKD, respectively. Urolithiasis was associated with a HR for HTN of 1.42 (95% CI: 1.35, 1.51; p<0.001) and for CKD of 1.82 (95% CI: 1.67, 1.98; p<0.001). ESWL was associated with an increased risk of HTN with a HR of 1.34

(95% CI: 1.15, 1.57; $p < 0.001$), while URS was not. When further stratified as ESWL to the kidney or ureter, only ESWL to the kidney was independently associated with HTN (HR 1.40, 95% CI: 1.19, 1.66; $p < 0.001$).



Neither ESWL nor URS was associated with incident CKD.

Conclusions: Given that urolithiasis itself was associated with a HR of 1.42 for HTN, an individual who undergoes ESWL to the kidney can be expected to have a HR of 1.96 (95% CI: 1.67, 2.29; $p < 0.001$) compared to an individual without urolithiasis. We recommend judicious use of ESWL if a calculus is asymptomatic or URS is a viable option.

Funding: NIDDK Support

SA-OR079

Anti-MicroRNA-21 Oligonucleotides Prevent Renal Fibrosis Progression by Blocking the Auto-Regulatory Loop of miR-21/PDCD4/AP-1 During Myofibroblasts Activation Qi Sun, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Renal fibrosis is a final common pathway of chronic kidney injury. During the injury, the resident fibroblasts are stimulated and trans-differentiated into myofibroblasts, which produce a large amount of extracellular matrix (ECM) components and ultimately lead to the loss of kidney function. Sustained activation of myofibroblasts is considered to play a key role in perpetuating renal fibrosis, but the driving force of myofibroblasts activation is only partially understood. Aberrant expression of miRNAs is associated with numerous pathologic processes including renal injury. To date, some investigations have identified specific overexpression of miR-21 in the progression of kidney fibrosis. Nevertheless, the precise role of miR-21 in myofibroblasts activation remains largely unknown.

Methods: To understand the role of miR-21 in the progression of kidney fibrosis, microarray and quantitative real-time PCR analysis were performed to examine the expression level of miR-21 in unilateral ureteral obstruction (UO)-injured mice. Then, mice were administered with control or antagomir-21 before or during surgery by tail vein injection, to determine whether blocking miR-21 in kidneys affects UO-induced renal fibrosis.

Results: In this study, we identified miR-21 was instantly up-regulated after TGF- β 1 stimulation, and maintained itself at constant high levels by employing a microRNA-21/programmed cell death protein 4/activation protein-1 (miR-21/PDCD4/AP-1) auto-regulatory loop during myofibroblasts activation. The persistent up-regulated miR-21 depressed Smad7 and PTEN expression and eventually enhanced TGF- β 1/Smad pathway to promote fibrosis progression. More importantly, we found miR-21 sequestration in mouse kidneys attenuated UO-induced renal fibrosis.

Conclusions: Altogether, these data suggest that miR-21 is a main driving force of myofibroblasts activation and keeps its high expression level by an auto-regulatory loop of miR-21/PDCD4/AP-1. Targeting this aberrantly activated feedback loop may provide new therapeutic strategy in treating fibrotic kidneys.

Funding: Government Support - Non-U.S.

SA-OR080

Silencing of MicroRNA-132 Reduces Renal Fibrosis by Selectively Inhibiting Myofibroblast Proliferation Roel Bijkerk,^{1,2} Ruben de Bruin,¹ Coen van Solingen,¹ Janine van Gils,¹ Jacques Duijs,¹ Eric P. van der Veer,¹ Ton J. Rabelink,¹ Benjamin D. Humphreys,² Anton Jan Van Zonneveld.¹ *¹Dept of Nephrology and Einthoven Laboratory for Experimental Vascular Medicine, Leiden Univ Medical Center, Leiden, Netherlands; ²Renal Div, Brigham & Women's Hospital and Harvard Medical School, Boston.*

Background: Chronic kidney disease is associated with progressive renal fibrosis. Lineage analysis has shown that FoxD1-derivative perivascular cells give rise to the majority of α -SMA positive myofibroblasts during renal fibrosis. We sought to identify pericytic microRNAs that could serve as a target to decrease myofibroblast formation.

Methods: To that end, we induced kidney fibrosis in FoxD1-GC;Z/Red-mice by unilateral ureteral obstruction (UO) followed by FACS sorting of dsRed-positive FoxD1-derivative cells and profiled for differentially expressed miRNAs.

Results: miR-132 expression selectively increased 21-fold during pericyte-to-myofibroblast formation whereas miR-132 was only 2.5-fold upregulated in total kidney lysates (both in UO and ischemia-reperfusion injury). Antagomir-induced miR-132 silencing in the UO model resulted in 35% decreased collagen deposition and decreased tubular apoptosis. Immunohistochemistry, Western blot and qRT-PCR analyses confirmed a similar decrease in α -SMA positive cells. Pathway analysis of differential gene expression in myofibroblasts identified a rate-limiting role for miR-132 in myofibroblast proliferation that was confirmed by *in vitro* studies with cultured fibroblasts. Indeed, UO kidneys of antagomir-132 treated mice displayed a significant reduction in proliferating, ki67⁺ myofibroblasts. Interestingly, this reduction in proliferation was selective for the interstitial compartment and did not impair the reparative proliferation of tubular epithelial cells, as evidenced by increased numbers of ki67⁺ epithelial cells, as well as increased (p)-RB1 and Cyclin-A and decreased RASA1 and p21 levels in total kidney lysates.

Conclusions: Taken together, silencing miR-132 counteracts the progression of renal fibrosis by selectively decreasing myofibroblast proliferation and could potentially serve as a novel antifibrotic therapy.

SA-OR081

Characterizing the Molecular Identity of Pathogenic Fibroblasts Using Single Cell RNAseq Yongen Chang,¹ Kai-Hui Sun,¹ Ian Driver,² Andrew J. King,³ Meagan Fricano,³ Jason Rock,² Nilgun Reed,¹ Dean Sheppard.¹ *¹Dept of Medicine, Univ of California San Francisco, San Francisco, CA; ²Dept of Anatomy, Univ of California San Francisco, San Francisco, CA; ³Abvie Inc., Chicago, IL.*

Background: Fibroblasts are the main effectors of organ fibrosis but their molecular identity is poorly understood. Using Col1a1-GFP mice, we isolated pathogenic fibroblasts from 3 fibrotic organs and performed single cell RNAseq analysis.

Methods: We induced fibrosis in the kidney (unilateral ureteral obstruction), lung (intratracheal bleomycin) and liver (carbon tetrachloride injections). With fluorescence-activated cell sorting, we isolated collagen-expressing GFP positive cells from each organ. Single cell cDNA was obtained via a fluidic system and libraries generated and sequenced. We performed hierarchical clustering (HC) analysis, principal component analysis (PCA) and targeted correlation assays on RNAseq data.

Results: We analyzed 130 kidney cells, 160 lung cells and 177 liver cells. HC and PCA analysis revealed 3 distinct groups of fibroblasts in fibrotic kidney and lung. Group 1 express high levels of collagen 1 and a set of fibroblast-related genes. Group 2 express low levels of collagen 1 and leukocyte markers. Group 3 express intermediate levels of collagen 1 as well as fibroblast-related genes and leukocyte markers. This group may represent circulated fibrocytes. In contrast, collagen-expressing cells in the liver are a mostly homogeneous population that differs substantially in gene expression from those of the lung and kidney. By correlation assays, we found 63 genes that highly correlate with col1a1 in renal, lung and liver fibroblasts. Some of these are known fibroblast-related genes but many are novel.

Conclusions: We characterized the molecular diversity of fibroblasts in 3 fibrotic organs. While pathogenic fibroblasts from the kidney, lung and, less so, liver share a core identity, they also each express a unique set of genes. This study may yield new biomarkers and therapeutic targets for treating fibrosis.

Funding: Pharmaceutical Company Support - Abvie Inc., Private Foundation Support

SA-OR082

Persistent Activation of Autophagy in Kidney Tubular Cells Promotes Renal Interstitial Fibrosis During Unilateral Ureteral Obstruction Man J. Livingston,^{1,2} Zheng Dong.^{1,2} *¹Georgia Regents Univ; ²Charlie Norwood VA Medical Center, Augusta, GA.*

Background: Renal fibrosis is the final, common pathway of end stage renal disease. Whether and how autophagy contributes to renal fibrosis remains largely unknown.

Methods: Using pharmacological and genetic inhibitory approaches, our study has determined the regulation of renal interstitial fibrosis by autophagy in a mouse model of unilateral ureteral obstruction (UO) and in TGF- β 1-treated proximal tubular cells.

Results: UO led to renal interstitial fibrosis, which was associated with persistent autophagy in kidney proximal tubules, as indicated by punctuate LC3 staining, LC3-II accumulation, P62 degradation as well as autophagosome formation and maturation. Pharmacological inhibitors of autophagy (chloroquine and 3-methyladenine) partially suppressed interstitial fibrosis during UO. The inhibitors also suppressed apoptosis in renal tubules. Moreover, knockout of Atg7 specifically from kidney proximal tubules (PT-Atg7 KO) not only blocked autophagy but also attenuated renal fibrosis. Proliferation and activation of fibroblasts, as indicated by the expression of α -SMA and vimentin, was inhibited in these mice, so was the accumulation of extracellular matrix components including fibronectin and collagen fibrils. UO induced 8.4% interstitial fibrosis in wild-type kidneys after 4 days of obstruction, which was further increased to 13.5% by 1 week and 25% after 2 weeks. The fibrotic lesions were significantly reduced in PT-Atg7 KO kidneys at all three time points, with 4.5% for 4-day, 7.9% for 1-week and 15.2% for 2-week respectively. UO led to FGF2 expression in wild-type kidneys, which was markedly reduced in PT-Atg7 KO mice. PT-Atg7 KO mice also showed significantly less interstitial macrophage infiltration and tubular apoptosis. In cultured proximal tubular cells, TGF- β 1 induced autophagy and the accumulation of fibronectin and, inhibition of autophagy suppressed fibronectin accumulation.

Conclusions: Together, the results suggest that persistent activation of autophagy in kidney proximal tubules promotes renal interstitial fibrosis by regulating tubular cell death, interstitial inflammation, and the production of profibrotic cytokines.

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SA-OR083

Macrophage Migration Inhibitory Factor Promotes Kidney Fibrosis in ADPKD Xia Zhou,^{1,2} Li Chen,^{1,2} Dorien J.M. Peters,³ Mihaela Gadjeva,⁴ Xiaogang Li.^{1,2} ¹Internal Medicine; ²Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; ³Leiden Univ Medical Center, Leiden, Netherlands; ⁴Harvard Medical School, Boston, MA.

Background: Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that functions to induce cell proliferation, inhibit apoptosis and regulate the inflammation. We found that MIF promoted renal cyst growth in different ADPKD mouse models (Chen et al., *JCI*, 2015). Renal cyst progression is accompanied by tubulointerstitial fibrosis which is associated with the renal function decline. However, whether MIF regulates fibrosis in ADPKD remains unknown.

Methods: To understand the role of MIF in regulating renal fibrosis *in vivo*, we generated *Pkd1^{tm1.1};MIF^{fl/fl}* mice. To explore the pathways mediated by MIF in regulating this process, we treated renal epithelial cells and fibroblasts with MIF or MIF inhibitor, ISO-1.

Results: We found that knockout of *MIF* or inhibition of MIF with ISO-1 not only delayed cyst growth but also decreased renal interstitial fibrosis as examined by Trichrome Masson staining, and decreased the expression of TGF β , Col1A1 and Col3A1 mRNA as analyzed by qRT-PCR in postnatal day 28 *Pkd1^{tm1.1}* mice compared with age matched control mice. We further found that knockout of MIF or inhibition of MIF with ISO-1 decreased the phosphorylation and activation of ERK, Akt, S6 and Rb, which were associated with the fibroblast activation and fibrosis development in human diseases, in kidneys of *Pkd1* mutant mice whereas fibroblasts treated with MIF induced the phosphorylation of ERK, Akt, S6 and Rb. In addition, MIF treatment induced the expression of 1) TGF β in mouse IMCD3 cells, 2) COL1A1 and COL3A1 in mouse fibroblasts (NIH3T3), and 3) TGF β , COL3A1 and fibronectin in rat kidney interstitial fibroblasts (NRF-49F). The expression of TGF β , COL1A1, COL3A1 and fibronectin induced with or without MIF in the above cells could be inhibited or decreased by the treatment with ISO-1.

Conclusions: MIF activates the renal fibroblasts and promotes renal interstitial fibrosis in ADPKD, which may be mediated by TGF β , ERK, mTOR and Rb signaling pathways. Targeting MIF may be a viable new therapy for ADPKD.

Funding: NIDDK Support

SA-OR084

HGF/c-met Signaling in Macrophages Attenuates Kidney Fibrosis by Regulating Matrix Remodeling and Turnover Haiyan Fu,¹ Dong Zhou,¹ Liangxiang Xiao,¹ Roderick J. Tan,² Youhua Liu.¹ ¹Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; ²Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Kidney fibrosis results from an excessive accumulation and deposition of extracellular matrix (ECM). This is mainly due to an imbalance between matrix synthesis and degradation. While significant progress has been made recently on identifying the matrix-producing cells and elucidating how they are regulated, relatively little is known about the mechanism controlling matrix degradation and turnover.

Methods: We generated hepatocyte growth factor (HGF) receptor c-met conditional knockout mice in which c-met was deleted specifically in myeloid cells including macrophages (Mac-c-met^{-/-}). Mice were then subjected to renal unilateral ischemia/reperfusion injury (UIRI) or unilateral ureteral obstruction (UUO), respectively. Cultured bone-marrow-derived macrophages were also used.

Results: Mice with macrophage-specific ablation of c-met were phenotypically normal. We found that at different time points (3, 7 and 14 days) after UUO, there was no difference in the mRNA levels of major fibrosis-related genes such as α -SMA, collagen I, collagen III and fibronectin in the kidneys between Mac-c-met^{-/-} and control mice, suggesting that HGF signaling in macrophages does not affect matrix synthesis. However, kidney fibrotic lesions as assessed by Masson's-Trichrome staining were more profound in Mac-c-met^{-/-} mice than controls. Comparable results were obtained after analysis of matrix proteins by Western blot. Similarly, in UIRI model, loss of c-met in macrophage significantly aggravated renal lesions at 10 days, with elevated serum creatinine and increased deposition of matrix proteins, whereas renal mRNA expression of major matrix genes was not changed. *In vivo*, increased deposition of ECM was closely associated with the down-regulation of tissue-type plasminogen activator (tPA) in Mac-c-met^{-/-} kidneys. *In vitro*, HGF induced tPA, uPA and MMP-12 expression in cultured bone marrow-derived macrophages.

Conclusions: These results suggested that HGF/c-met signaling in macrophages plays a critical role in reducing kidney fibrosis by promoting matrix degradation and turnover.

Funding: NIDDK Support

SA-OR085

The Hippo-Salvador Signaling Pathway Regulates Renal Tubulointerstitial Fibrosis Yong kyun Kim,¹ Sun-ah Nam,² Wan-Young Kim,² Arum Choi,² Yumi Kim,² Jin Kim.² ¹Dept of Internal Medicine, Medical College, The Catholic Univ of Korea, Seoul, Korea; ²Dept of Anatomy and Cell Death Disease Research Center, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Renal tubulointerstitial fibrosis (TIF) is the final common pathway of various renal injuries. The mammalian Hippo-Salvador signaling pathway is a highly conserved kinase cascade that regulates contact inhibition, cell proliferation, organ size control, tissue regeneration and tumorigenesis. The expression pattern and the role of Hippo-Salvador signaling pathway on development of renal TIF remain unknown. Here, we reported that activation of Hippo-Salvador pathway in tubular epithelial cell (TEC) in patients and in mouse model of TIF plays a role in TIF development.

Methods: The expression of Hippo-Salvador pathway including WW45, Mst1/2, Lats1/2, YAP/TAZ were examined. TEC-specific WW45 knockout mice (WW45^{fllox}/Ksp-Cre⁺) were generated for *in vivo* experiments and Hippo-Salvador pathway were knock-downed or overexpressed in HK2 cells. Unilateral ureteral obstruction (UUO) was used for *in vivo* model and TGF- β treatment was used for *in vitro* model of renal fibrosis.

Results: Expression of WW45 (a homolog of Drosophila Salvador and adaptor for the Hippo kinase) and TAZ (transcriptional coactivator with PDZ binding motif, a WW-domain transcriptional regulator) were increased after UUO in mice and in TEC in patients with CKD. *In vivo*, TEC-specific WW45 deletion enhanced renal TIF after UUO. TEC-specific WW45 deletion enhanced apoptosis and proliferation of TECs after UUO. The expression of TAZ was increased in the kidneys of WW45-deficient mice after UUO. *In Vitro*, WW45 deletion induced EMT by TGF- β treatment. WW45 deficiency enhances TGF- β signaling by the interaction of TAZ with Smads. WW45 deficiency also increases activated β -catenin dependent on TAZ.

Conclusions: Our data showed that Hippo-Salvador pathway regulate renal TIF and EMT through TGF- β /Smad and Wnt/ β -catenin signaling. Our experiments suggest that Hippo-Salvador pathway is a new mechanism in the pathogenesis of TIF development and indicate that regulation of Hippo signaling pathway may be a therapeutic target to reduce TIF.

SA-OR086

Cytosine Methylation Levels Determine Regeneration versus Fibrosis After Injury Kriti Gaur, Ae Seo Deok Park, Frank S. Chinga, Katalin Susztak. *Renal Electrolyte and Hypertension Div, Univ of Pennsylvania.*

Background: Cytosine methylation is an epigenetic mark that regulates gene expression, whereby increased methylation of promoter regions inhibits gene transcription by interfering with transcription factor binding. We previously showed that human CKD and DKD samples have differences in cytosine methylation levels. We hypothesize that these cytosine methylation differences are functionally important in the pathophysiology of CKD. The ten-eleven translocation (TET) family of proteins, regulate DNA methylation status by oxidizing 5-methylcytosine (mC) to 5-hydroxymethylcytosine (5hmC). In the absence of TET2, there is increased cytosine methylation and decreased hydroxymethylation. Here we examined the functional role of tubular epithelial cell (TEC) methylation levels *in vivo* by deleting TET2 in TECs.

Methods: TET2^{lox/lox} and C adherin 16 Cre mice were crossed to generate animals with renal tubular epithelial cell deletion of TET2. Kidney injury was induced by administering folic acid intraperitoneally at 6 weeks of age, at a dose of 250mg/kg of body weight and sacrificed 1 or 12 weeks later. Mouse kidneys and primary epithelial cells were analyzed by quantitative RT-PCR, and immunohistochemistry to examine fibrotic changes.

Results: Mice with TEC specific deletion of TET2 appeared histologically normal. We hypothesize that this may be due to the low turnover rate of tubule cells in the kidney. Acute kidney injury and regeneration was induced through administration of folic acid. Twelve weeks after folate administration control animals almost recovered, while fibrosis appeared more even severe in mice with TEC specific deletion of TET2. These TET2 null mice also had increased expression of collagen, activated myofibroblast and inflammatory markers. We believe that fibrosis developed as a secondary consequence of impaired epithelial cell differentiation, as TET2-deficient TECs remained undifferentiated and yet continued to proliferate.

Conclusions: TET2 is an epigenetic director of renal epithelial repair following injury. Increased TEC cytosine methylation levels interfere with epithelial cell differentiation and directs cells into a profibrotic phenotype.

Funding: NIDDK Support

SA-OR087

Roles of CCN2 and Caspase Activities in Tubular Epithelial Cells Involved in AKI Transition to CKD Takeru Kusano, Sutomou Inoue, Hirokazu Okada. *Saitama Medical Univ, Iruma-gun, Saitama, Japan.*

Background: In AKI, severely injured tubular epithelial cells (TEC) are destined to be removed by apoptosis while a small part of them survive and transform, which then facilitate interstitial fibrosis (IF). (Nat Med 16:535, 2010) We previously reported that CCN2 and caspase activities in TEC are important for IF in CKD models. (JASN 16:133, 2005, Clin Exp Nephrol (in press)) In this study, we investigate possible linkages between AKI and CKD, focusing especially on roles of CCN2 and caspase activities in TEC.

Methods: CCN2-haploinsufficiency mice (CCN2^{h/c}), mice transgenic for baculovirus pan-caspase inhibitor p35 gene in a nonexpression state (p35), and mice carrying Cre recombinase under the control of proximal tubule-specific g-glutamyltransferase promoter (g-GT.Cre) are used for generation of following mice; g-GT.Cre:p35, p35 is expressed in

TEC; g-GT.Cre:CCN2^{lox}. CCN2 expression is detected in TEC; g-GT.Cre:p35:CCN2^{lox}, defective CCN2 with p35 expression in TEC; and CCN2^{lox} as the control. We performed 1 hour ischemia and reperfusion injury (IRI) on these 4 groups of mice and evaluated renal fibrosis on day 14.

Results: The mRNA levels of collagen I (ColI), fibronectin EIIIA (FN) and TGF-β1 were significantly lower in g-GT.Cre:CCN2^{lox} mice than the control mice (ColI: 7.26±0.62 vs. 63.5±16.7, FN: 1.29±0.18 vs. 9.96±2.83, TGF-β1: 0.83±0.12 vs. 4.35±0.98)(p<0.05). The fibrosis area% in Masson trichrome stain was significantly narrower in g-GT.Cre:CCN2^{lox} mice than the control mice (7.46±1.36% vs. 34.8±3.16%)(p<0.05). In the comparison between g-GT.Cre:p35CCN2^{lox} and g-GT.Cre:CCN2^{lox} mice, the fibrosis area% was significantly wider in g-GT.Cre:p35CCN2^{lox} mice (16.4±2.12 vs. 7.26±0.62) (p<0.05). We also revealed that the number of phosphorylated histone H3-positive TEC were significantly higher in g-GT.Cre:p35CCN2^{lox} mice.

Conclusions: In conclusion, CCN2 expressed in TEC promotes IF, a typical feature of CKD, following IRI in the post-AKI kidney. Furthermore, it appears that TEC escaped from caspase activities after IRI exacerbate IF irrespectively of CCN2. Thus, caspase activities and CCN2 in TEC are likely involved in AKI transition to CKD in the opposite direction, at least after IRI.

SA-OR088

Repeated Minor AKI Accelerates Renal Fibrosis and Dysfunction in Klotho Deficit Mice Ken Tsuchiya, Hidekazu Sugiura, Miki Nishida, Kenichi Akiyama, Kosaku Nitta. *Dept of Medicine IV, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan.*

Background: It has been recognized that AKI and CKD are not independent disease but integrated syndrome in which there is bidirectional nature of the relationship between them. Especially, frequent occurrence of minor AKI induces acceleration to advancing to the CKD. On the other hand, Klotho protein is one of the key modulator in the preceding the CKD, during which expression of Klotho is markedly suppressed in CKD. Acceleration of renal fibrosis is a basic pathophysiology for progression of CKD, and previously, we showed that the renal interstitial fibrosis was severer in the *kl* (+/-) mice than those in the wild-type mice by ureteral obstruction procedure. So, we hypothesized that kidney with reduced Klotho expression was more vulnerable to minor or repeated stress during the progression of CKD pathophysiology.

Methods: We explored the effects of repeated minor AKI on the kidney in the rodent model of reduce Klotho expression. Minor AKI was induced by short time clamping of renal artery, once a week for 3 weeks in *kl* (-/+) and wild type mice. Serum creatinine level was measured and the expression levels of fibrosis related marker, such alpha SMA, MCP-1 etc., by immunostaining and RT-PCR was assessed. Internal expression of Klotho was modified by gene delivery.

Results: Frequent AKI reduced the renal function much more (70% higher in Cr) in *kl* (-/+) mice than wild type mice. Klotho expression quickly diminished after each ischemic maneuver. The expression of fibrotic markers increased (2.2 folds) in the kidney comparing with wild type kidney. The reduction of renal function and tissue damage was attenuated by Klotho gene delivery. Preliminary, gene screening suggested more down regulation of heat shock protein and ATF by AKI accumulation in *kl* (-/+) mouse kidney.

Conclusions: It is likely that reduction of Klotho levels in the kidney, such as in aging or CKD, is a risk factor for accelerating the progression of CKD, resulting in sensitive status to various kinds and frequency of renal damage, and upregulation of the Klotho may attenuate advancing the kidney dysfunction, which is one possible strategies for preventing the final pathway to the ESRD.

Funding: Government Support - Non-U.S.

SA-OR089

Global Prevalence of Protein-Energy Wasting (PEW) in Kidney Disease: Systematic Review and Meta-Analysis of Contemporary Cohort Studies by the International Society of Renal Nutrition and Metabolism (ISRNM) Juan Jesus Carrero,¹ Csaba P. Kovcsdy,² Miklos Zsolt Molnar.² ¹Karolinska Inst, Stockholm, Sweden; ²Univ of Tennessee Health Science Center, Memphis, TN.

Background: PEW is a common complication in kidney disease, but its prevalence is poorly defined. To increase awareness on the commonness of PEW, we performed a meta-analysis of its global prevalence throughout the kidney disease spectrum.

Methods: We performed a systematic review and meta-analysis of contemporary cohort studies including >50 patients with kidney disease and reporting on PEW prevalence by either subjective global assessment (SGA) or malnutrition-inflammation score (MIS). Searches were restricted to Jan 2000-Nov 2014. Data was reviewed throughout different kidney disease strata (acute kidney injury [AKI], pediatric chronic kidney disease [CKD], non-dialyzed CKD 3-5, dialysis and renal transplant [Tx]). Because PEW may reflect underlying country-specific malnutrition, studies including dialysis patients were analyzed after clustering by their countries' Gross National Income (GNI).

Results: No studies including pediatric patients fulfilled the inclusion criteria for meta-analysis. The PEW meta-prevalence of the rest of kidney disease strata is summarized in the table, along with number of patients and studies. In studies including dialysis patients, PEW prevalence increased considerably across worsening GNI clusters, being consistently higher in peritoneal dialysis (PD) as compared to hemodialysis (HD) patients.

Stratum	Nº of studies	Nº of patients	PEW Prevalence (95% CI)
AKI	4	387	63% (58-67)
non-dialyzed CKD 3-5	12	2682	21% (19-22)
Tx patients	2	1067	30% (28-33)
Dialysis, high-income countries	64	5920 3339 in HD 2581 in PD	35% (34-46) 41% (40-43)
Dialysis, upper middle-income countries	53	8923 5844 in HD 3079 in PD	42% (41-44) 50% (49-52)
Dialysis, low-income countries	8	887 588 in HD 299 in PD	62% (58-66) 74% (69-78)

Conclusions: PEW is common across the entire spectrum of kidney diseases, but it exhibits the highest prevalence among dialysis and AKI patients. Its commonness, together with its well-documented impact on patient outcomes, deserves increased medical attention.

SA-OR090

A Novel Deleterious Role for Dietary Salt-Sugar Interplay in Metabolic Syndrome and Elevated Blood Pressure in Mice Miguel A. Lanasa, Christina Cicerchi, Ana Andres-hernando, Carlos Alberto Roncal-jimenez, Takuji Ishimoto, Richard J. Johnson. *Univ of Colorado Denver, Aurora, CO.*

Background: High amounts and chronic salt intake are important risk factors for the development and progression of hypertension. Our group has described that also sugars, and in particular fructose, contribute to the pathogenesis of elevated blood pressure thus suggesting a potential interplay between both dietary components in hypertension and metabolic syndrome. Consistently, increased sodium excretion is observed in obese people. Here, we aim to determine whether dietary salt can play a deleterious role in the pathogenesis of other features of metabolic syndrome besides hypertension and if it is related to sugar metabolism.

Methods: Wild type and fructokinase deficient mice –that cannot metabolize sugar and fructose- were exposed to 1% salt in drinking water for 30 weeks and features of metabolic syndrome including elevated blood pressure, fatty liver, insulin resistance, leptin resistance and weight gain were determined.

Results: Exposure of mice to salt induced the hypertonic activation of aldose reductase and the endogenous production of fructose in liver, pancreas and fat. Consistent with increased fructose production and metabolism in these tissues, wild type but not fructokinase deficient mice demonstrated significantly higher fat deposition, fatty liver and blood pressure compared to controls. Furthermore, salt intake in wild type mice induced a significant increase in insulin resistance as determined by oral glucose and insulin tolerance test, hyperleptinemia, hypothalamic leptin resistance, increased food intake and body weight gain compared to fructokinase deficient mice.

Conclusions: Our study indicates that dietary salt can induce multiple features of metabolic syndrome besides high blood pressure. It also suggests interplay between salt and sugar in which salt will induce the endogenous production of fructose. The metabolism of endogenous fructose by fructokinase would be the underlying factor for salt-induced metabolic syndrome in mice. Thus, blockade of fructokinase could be a novel therapeutic approach for the prevention and treatment of hypertension and metabolic syndrome.

Funding: NIDDK Support

SA-OR091

Sodium Chloride Promotes Tissue Inflammation via Osmotic Stimuli in Subtotal Nephrectomized Mice Fumiko Sakata,¹ Yasuhiko Ito,¹ Masashi Mizuno,¹ Yasuhiro Suzuki,¹ Takeshi Terabayashi,¹ Takako Tomita,¹ Mitsuhiro Tawada,¹ Shoichi Maruyama,¹ Enyu Imai,² Yoshifumi Takei,¹ Seichi Matsuo.¹ ¹Nephrology and Biochemistry, Nagoya Univ, Nagoya, Japan; ²Nephrology, Nakayamadera Imai Clinic, Takarazuka, Japan.

Background: Chronic inflammation is prevalent in patients with end-stage renal disease, but the precise mechanisms remain unclear. Sodium that is reportedly stored in tissues after high salt intake induces lymphangiogenesis and autoimmune diseases via osmotic stimuli. We studied the effects and mechanisms of high salt loading on tissues and systemic inflammation (with a focus on macrophage infiltration) in sub-total nephrectomized (5/6Nx) mice and in cultured cells.

Methods: Mice underwent 5/6Nx or sham surgery (Sham), and were provided with either tap water (Water) or 1% NaCl (NaCl) for four weeks. Inflammatory changes in peritoneal wall, heart and paraaortic tissues were evaluated by immunohistochemistry, Western blot, ELISA and quantitative PCR. Inhibition studies were performed in vivo and in vitro.

Results: Significantly more macrophages infiltrated the peritoneal wall (p < 0.001), heart (p < 0.05) and paraaortic tissues (p < 0.001) of sub-total nephrectomized mice with salt loading (5/6Nx/NaCl) compared with 5/6Nx/Water. Tissue levels of IL-6, monocyte chemoattractant protein-1 (MCP-1) and tonicity-responsive enhancer binding protein (TonEBP) were significantly increased in the peritoneal wall and heart of 5/6Nx/NaCl compared with 5/6Nx/Water. The administration of furosemide or tap water after NaCl for four weeks, indicating reverse NaCl loading, reduced local macrophage infiltration associated with the suppression of MCP-1 (p < 0.05) and TonEBP mRNA (p < 0.01). A high NaCl concentration

in the culture media of mesothelial cells and cardiomyocytes induced MCP-1 protein, MCP-1 mRNA, serum- and glucocorticoid-inducible kinase 1 (Sgk1), and TonEBP mRNA, all of which were suppressed by TonEBP siRNA and upregulated in 5/6Nx/NaCl. The induction of MCP-1 by high salt did not involve Rac1.

Conclusions: High salt intake enhances macrophage infiltration via the TonEBP-MCP-1 pathway in association with inflammation, oxidative stress and Sgk1 activation during renal failure.

Funding: Government Support - Non-U.S.

SA-OR092

The Relationship of Chronic Kidney Disease Severity with Urine Sodium Excretion Cheryl A. Anderson,¹ Amanda K. Leonberg-Yoo,² Joachim H. Ix,¹ Mark J. Sarnak,² Lawrence J. Appel.³ ¹Univ of California San Diego; ²Tufts Medical Center; ³Johns Hopkins Medical Insts.

Background: In healthy individuals, the gold standard measurement for sodium intake is 24-hour urine excretion. It is unknown whether chronic kidney disease (CKD) severity affects this measurement. We aimed to evaluate whether sodium excretion differs by level of glomerular filtration rate (GFR). We hypothesized that with increased CKD severity, 24-hr urine excretion is reduced, possibly as a result of a greater fraction of sodium being excreted by non-renal pathways (e.g. sweat or lower intestinal absorption) as kidney function declines.

Methods: Baseline data from the African American Study of Kidney Disease and Hypertension (AASK) and the Modification of Diet in Renal Disease (MDRD) Study were used to separately examine the relationship between GFR measured by iothalamate clearance and 24-hour urine sodium excretion. Both studies recruited individuals with reduced GFR. Urine sodium excretion was measured using a single 24-hour urine collection. Linear regression models were adjusted for age, race, sex, and BMI.

Results: In AASK (n=1093) and MDRD (n=814), baseline mean(SD) age was 54.5(10.7) and 51.4 (12.4) years; mean(SD) for GFR (mL/min/1.73m²) was 46.8(14.1) and 33.5(12); and mean(SD) for sodium (g/day) was 3.7(2.0) and 3.5 (1.5); respectively. After adjustment, each SD reduction in GFR was associated with a 0.24 g/day (p=0.002) lower sodium excretion in AASK; and a 0.15 g/day (p=0.001) lower sodium excretion in MDRD.

Conclusions: Our findings challenge the existing paradigm that the amount of sodium excreted in a 24-hour urine collection is roughly equivalent to intake in all persons. Further, the association of reduced urine sodium excretion with advanced CKD may help explain paradoxical risk relationships in studies that did not take into account concurrent kidney function. Controlled balance studies in CKD patients are needed to confirm our findings.

Funding: NIDDK Support

SA-OR093

Lower Risk of ESRD Associated with DASH Diet in Adults with Moderate CKD and Hypertension Tanushree Banerjee,¹ Deidra C. Crews,² Meda E. Pavkov,³ Nilka Rios Burrows,³ Jennifer L. Bragg-Gresham,⁴ Rajiv Saran,⁴ Neil R. Powe.¹ ¹UCSF; ²JHU; ³CDC; ⁴U Michigan, Ann Arbor.

Background: Although the Dietary Approaches to Stop Hypertension (DASH) diet, rich in fruits, vegetables, and plant derived protein, has been shown to reduce blood pressure in individuals with normal and mildly impaired kidney function, it is not known whether the DASH diet impacts CKD progression among patients with moderate CKD.

Methods: We determined a baseline diet adherence score (higher score=great adherence), consistent with DASH diet recommendations, using a 24-hour dietary recall questionnaire in a cohort of 1,110 adults with moderate CKD (eGFR 30-59ml/min/1.73m²) and hypertension from the National Health and Nutrition Examination Survey III (1988-1994). We related this score to the development of ESRD ascertained over a median of 14.2 years of follow-up via linkage with the Medicare ESRD Registry. We examined the association of baseline level of DASH diet adherence with ESRD after adjusting for demographics, diabetes, eGFR, and albuminuria, while accounting for intervening mortality events using the Fine-Gray competing risks method.

Results: A total of 267 (24.1%) participants developed ESRD. Baseline level of adherence to the DASH diet was greater among older vs younger adults (57.9% vs 42.1%), females vs males (60.4% vs 39.6%), and whites vs blacks (61.4% vs 18.3%); ν p<0.05. Compared to quintile 5 (greatest DASH diet adherence score) there was a greater risk of ESRD with lower adherence scores --for quintile 4: Relative Hazard [95% CI] = 1.1[0.8-1.6], for quintile 3: 1.5[0.9-2.8], for quintile 2: 2.7[1.8-3.3] and for quintile 1 (lowest adherence): 1.9[1.4-2.7] (p for trend=0.001). There was effect modification by the DASH score quintiles and diabetes (p-interaction=0.03). The higher risk of ESRD with lower adherence was present among participants with diabetes (2.5[1.4-4.6]) but not among participants with no diabetes (0.7[0.4-1.4]).

Conclusions: Adherence to the DASH diet may lower the risk of progression to ESRD in adults with moderate CKD and hypertension, particularly among persons with diabetes. Our results provide evidence that the DASH diet may be beneficial for adults with moderate CKD.

Funding: Other U.S. Government Support

SA-OR094

Normal Weight with Central Obesity Is Associated with the Highest Risk of Coronary Artery Calcification in Chronic Kidney Disease Patients Mi Jung Lee,¹ Shin-Wook Kang,¹ Curie Ahn,² Tae-Hyun Yoo.¹ ¹Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; ²Dept of Internal Medicine, Seoul National Univ, Seoul, Korea.

Background: In chronic kidney disease (CKD), body mass index (BMI) showed a U-shaped association with cardiovascular (CV) risk. In contrast, central obesity was directly associated with increased CV risk. This bi-directional relationship prompted us to evaluate the CV risk assessed by coronary artery calcification (CAC) based on a combination of BMI and waist-to-hip ratio (WHR) in CKD patients.

Methods: We included 1,217 CKD stage 1 to 5 patients who enrolled in the KoreanN cohort study for Outcome in patients With Chronic Kidney Disease. Patients were divided into 3 groups by BMI (normal, 18.5≤ to <23.0; overweight, 23.0 to <27.5; obese, ≥27.5 kg/m²) and were dichotomized by sex-specific median of WHR (0.92 in male; 0.88 in female). CAC was defined as >10 Agatston using a multi-slice computed tomography. Logistic regression analysis was used to assess the independent association of CAC with BMI, WHR, and cross-categorization of BMI and WHR, respectively.

Results: CAC was observed in 500 patients (41.4%). Multivariate logistic regression analysis indicated that BMI was not independently associated with CAC (per 1 kg/m² increase, odds ratio [OR]=1.03, 95% confidence interval [CI]=0.98-1.08, P=0.24). However, WHR showed an independent linear association with CAC (per 0.01 increase, OR=1.04, 95% CI=1.02-1.07, P<0.001). Furthermore, when patients were categorized into 6 groups according to combination of BMI and WHR, normal BMI but increased WHR (OR=1.91, 95% CI=1.05-3.48, P=0.03) had the highest risk of CAC compared to others (normal BMI with lower WHR, as reference; overweight with lower WHR, OR=1.46, 95% CI=0.93-2.30, P=0.10; obese with lower WHR, OR=1.51, 95% CI=0.68-3.40, P=0.31; overweight with increased WHR, OR=1.45, 95% CI=0.95-2.22, P=0.06; obese with increased WHR, OR=1.49, 95% CI=0.88-2.53, P=0.14).

Conclusions: In CKD patients, normal weight with central obesity was associated with the highest risk of CAC, suggesting that combining BMI and WHR could be more helpful to stratify CV risk than BMI alone.

Funding: Government Support - Non-U.S.

SA-OR095

MicroRNA-27a Is Decreased in Skeletal Muscle During Atrophy and Is Regulated by Calcineurin/NFAT Signaling: A Regulatory Mechanism for Myostatin Expression Xiaonan H. Wang,¹ Russ Price,^{1,2} Jill A. Rahnert,¹ Matthew B. Hudson.¹ ¹Medicine/Nephrology, Emory Univ, Atlanta, GA; ²Atlanta VAMC, Atlanta, GA.

Background: Muscle atrophy occurs in chronic conditions like chronic kidney disease and diabetes. Production of myostatin by muscle plays a central role in the pathogenesis of atrophy during these conditions and research has recently focused on understanding how myostatin (MSTN) is controlled in muscle. MicroRNA-27a (miR-27a) can target MSTN mRNA and decrease MSTN protein in muscle; however, the mechanism(s) that control the level of miR-27a under atrophy-inducing conditions are unknown. The objective of our study was to investigate how miR-27a is regulated during muscle atrophy.

Methods: Diabetes was induced in rats by a single IV injection of 125/mg streptozotocin (STZ). Muscles were harvested 3 days later. Since glucocorticoids mediate many atrophy-inducing effects of diabetes and CKD, some studies were conducted with C2C12 muscle cells incubated with dexamethasone (DEX; 100 nM, 48 h). miR-27a was measured by quantitative RT-PCR using U6 as a control miR.

Results: In hindlimb muscles of STZ rats, miR-27a was decreased 40±3% (mean±SEM), a finding consistent with the reported elevation in MSTN during diabetes. Similarly, treatment of C2C12 myotubes with DEX reduced miR-27a 68±3% within 0.5 h and this suppression was sustained at >51% for at least 48 h. The miR-23a/miR-24-2/miR-27a cluster has been reported to be regulated by Calcineurin(CnA)/NFAT signaling and earlier, we found that CnA activity is reduced in skeletal muscle during CKD and STZ and in muscle cells following DEX treatment. Therefore, we investigated the relationship between CnA and miR-27a by measuring miR-27a following alteration in CnA activity. Infection of muscle cells with an adenovirus to overexpress constitutively active CnA increased miR-27a by 35±3%.

Conclusions: These results are consistent with a model in which atrophy-inducing conditions regulate MSTN production in skeletal muscle in part by reducing the level of miR-27a via a mechanism that involves decreased CnA/NFAT signaling. The resulting increase in MSTN will exacerbate muscle loss by accelerating proteolysis.

Funding: NIDDK Support, Veterans Administration Support

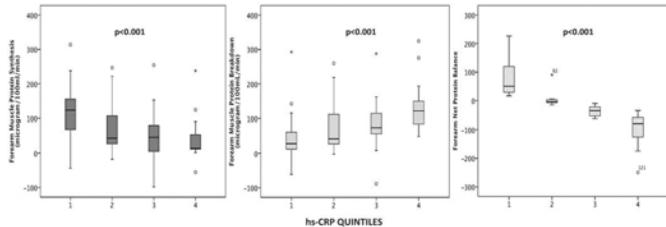
SA-OR096

Systemic Inflammation Affects Skeletal Muscle Protein Homeostasis in Maintenance Hemodialysis (MHD) Patients Serpil Muge Deger,^{1,2} Adriana Hung,^{1,2} Edward D. Siew,^{1,2} Cindy Booker,^{1,2} Talat Alp Ikizler.^{1,2} ¹Vanderbilt Univ, TN; ²VA, Nashville, TN.

Background: Systemic inflammation is closely associated with protein energy wasting (PEW) in MHD. In order to understand its metabolic effects on skeletal muscle metabolism, we examined whole body and skeletal muscle protein turnover in MHD patients with varying degrees of inflammation.

Methods: 129 MHD patients participating in metabolic studies between 1998 and 2011 were included in this analysis. Whole body and forearm skeletal muscle protein turnover was examined using primed infusions of L- (1-13) C leucine and L-(ring-2) H(5) phenylalanine.

Results: Mean age was 45 ±13 years, 73% were male, 26% were white and 22% had DM. BMI was 28.8 ±7.5 kg/m², median (IQR) hs-CRP was 13(0.8, 33.8) mg/dL and HOMA-IR 1.53 (0.74, 2.87). Forearm muscle protein synthesis (FAPS), breakdown (FAPB) and net balance (FANB) were [median (IQR)] 57 (14, 94), 69 (32, 118) and -21 (-58, 22) ug/100ml/min, respectively. Whole body PS, PB and NB were 4.7 (3.8, 5.4), 3.75 (3.2, 4.3) and 0.43 (-0.36, 0.77) mg/kgffm/min, respectively. There was a strong positive correlation between hs-CRP and FAPB (r=0.544 p<0.001) and strong inverse correlation with FAPS (r=-0.525; p<0.001) and FANB (r= -0.957, p<0.001). The FAPB was significantly higher and FAPS and FANB were lower in subjects in the highest quartile of hs-CRP versus all other quartiles (p<0.01 for all).



After adjustment for age, sex, HOMA-IR, and serum HCO₃, hs-CRP remained statistically significant predictor of all components of FA protein homeostasis. There were no significant associations between whole-body protein turnover and hs-CRP levels.

Conclusions: Hs-CRP levels independently predict skeletal muscle protein homeostasis in MHD patients. These data suggest that systemic inflammation is an appropriate target for treatment of PEW in MHD patients.

Funding: NIDDK Support, Veterans Administration Support, Private Foundation Support

SA-OR097

IL-1 Blockade Improves Adiponectin (ADPN) Levels in Patients with CKD Stages 3 and 4 Adriana Hung,^{1,2} Kristen L. Nowak,³ Talat Alp Ikizler,^{1,2} Natjalie Salas,² Heather Farmer,³ Rafia I. Chaudhry,² Michel Chonchol.³ ¹Nashville VA, TN; ²Vanderbilt Univ, TN; ³Univ of Colorado Denver, CO.

Background: Adiponectin (ADPN), an adipose tissue-derived hormone, is known to have insulin sensitizing, anti-inflammatory, and anti-atherogenic properties in the general population. ADPN secretion is suppressed by systemic inflammation, a highly prevalent condition in chronic kidney disease (CKD), and may have cardiovascular health implications in this population. In this study, we evaluated whether short-term administration of an interleukin-1 (IL-1) blocker, improves ADPN levels and insulin sensitivity in patients with CKD stages 3&4.

Methods: This study was a pilot randomized placebo-controlled double-blind trial of administration of IL-1 blockade in patients with CKD stages 3&4. Forty-two patients were randomly assigned (1:1) to receive 160 mg of an IL-1 blocker (riloncept) or placebo for 12 weeks; 37 completed the trial. The primary outcomes for this analysis were the effect of the intervention on the serum levels of ADPN, leptin, leptin adiponectin ratio (LAR) and HOMA IR. Mixed effect models were used for all analysis.

Results: Mean age was 63±11 years, the median eGFR 37.9 (IQR 29.1, 46.7) ml/min, 76% were males and 24% were African Americans. The values for ADPN, leptin, LAR and HOMA IR at baseline were 17.8±17.42 µg/mL, 27.7±22.8 ng/mL, 2.63±2.76 and 5.6±5.35, respectively. IL-1 blockade resulted in an increase in serum ADPN in the intervention group compared to placebo (p=0.03). Leptin, LAR or HOMA IR levels did not change significantly [table 1].

	IL-1 blockade	Placebo	P-value*
Adiponectin, µ/mL			
baseline	21.1 ± 21.7	13.9 ± 8.1	0.03
Week 12	23.6 ± 24.5	12.7 ± 7.1	
Leptin, ng/mL			
baseline	28.4 ± 23.7	28.3 ± 23.8	0.8
Week 12	27.2 ± 19.2	26.7 ± 25.6	
LAR			
baseline	2.86 ± 3.2	2.6 ± 2.3	0.3
Week 12	2.02 ± 2.4	3.0 ± 3.1	
HOMA-IR			
baseline	4.73 ± 4.7	6.1 ± 6.5	0.3
Week 12	4.38 ± 3.5	6.9 ± 6.1	

* P-value for test of the difference in change at week 12 between groups

Conclusions: Short-term administration of an IL-1 blocker significantly increased ADPN levels among patients with CKD stages 3&4. The intervention did not impact other insulin sensitivity parameters, including HOMA-IR, leptin and LAR. Results are consistent with those observed in dialysis patients.

Funding: Veterans Administration Support, Private Foundation Support

SA-OR098

Effects of Chronic Intradialytic Resistance Physical Exercises in Nrf2 and NF-κB Expression and Antioxidant Enzymes in Hemodialysis Patients Denise Mafra, Cinthia Da costa Abreu, Milena Barcza Stockler-Pinto, Ludmila Fmf Cardozo. *Post-Graduate Program in Cardiovascular Sciences, Fluminense Federal Univ (UFF), Niterói, Rio de Janeiro, Brazil.*

Background: Oxidative stress and inflammation are cardiovascular risk factors in patients with chronic kidney disease (CKD) on hemodialysis (HD). Nuclear factor Kappa B (NF-κB) play roles in the coordinated expression of inflammatory genes and Nuclear factor erythroid 2-related factor 2 (Nrf2) increases the transcription of genes encoding enzymes of phase II detoxifying and antioxidant enzymes. Several studies have shown that Nrf2 expression can be modulated by some factors, such physical exercise. The aim of this study was to evaluate the effects of resistance exercise program on the Nrf2 and NF-κB expression and antioxidant enzymes HD in patients.

Methods: This study included 44 patients on regular HD program, 25 patients (14 men, 46.1 ± 16.3 years and 71.2 ± 42.2 months HD) composed the exercise group and 19 patients (7 men, 46.8 ± 12.5 years and 67.4 ± 51.7 months HD) the control group. Strength exercise program was performed during HD sessions, 3 times a week (36 exercises sessions). The Nrf2 and NF-κB expressions were analysed by quantitative real time PCR. Superoxide dismutase (SOD) activity and glutathione peroxidase (GPX) levels were measured using ELISA commercial kits.

Results: The Nrf2 mRNA expression increased significantly after intervention in exercises group (0.8 ± 0.4 to 1.7 ± 0.8, p<0.01). In both groups there were no changes in NF-κB mRNA expression after intervention. The SOD levels reduced in exercise group (from 44.5±3.5U/mL to 28.4±3.3U/mL, p<0.05) and in control group (from 45.1±6.1U/mL to 31.9±4.6U/mL, p<0.05). However, GPX levels increased in exercise group (from 24.7±12.4nmol/mL/min to 53.4±20.04nmol/mL/min, p<0.0001) and in the control group there was tendency to decrease (from 26.0±5.314nmol/mL/min to 20.6±7.74nmol/mL/min, p=0.06). A negative correlation was found between the differences of NF-κB and GPX plasma levels (before and after 3 months) (R=-0.76, p=0.007).

Conclusions: Chronic intradialytic resistance exercises during 3 months seem to be able to modulate the Nrf2 activation and increase the antioxidant protection in HD patients.

SA-OR099

Evaluation of Novel Urine Biomarkers for Diagnosis of Subclinical Acute Tubular Necrosis Dennis G. Moledina, Isaac E. Hall, Mona D. Doshi, Peter P. Reese, Francis L. Weng, Bernd Schroppel, Heather Thiessen Philbrook, Joseph Ficek, Chirag R. Parikh. *TRIBE-AKI.*

Background: Rise in serum creatinine (SCR) is currently accepted as the “gold-standard” for clinical diagnosis of acute kidney injury (AKI). However, acute tubular necrosis (ATN) may occur without evidence of AKI, a condition known as “sub-clinical AKI.” We evaluated the performance of SCR and urinary biomarkers of kidney injury for diagnosis of ATN on kidney biopsy.

Methods: This is a substudy of a multicenter prospective cohort of deceased donors and associated kidney transplants. A diagnosis of ATN was assigned if the kidney biopsy report (read at organ procurement) indicated acute injury in ≥25% of tubules. AKI was defined by AKIN criteria based on admission and terminal SCR. Urine biomarkers were measured from stored samples collected at procurement.

Results: Of 581 donors with at least one kidney biopsied, 220(38%) had AKI (Stage I or higher). Of the 57 donors with ATN on biopsy, 28 (49%) did not have AKI. SCR had an area under the ROC curve (AUC) for diagnosing ATN of 0.58(95% CI 0.49, 0.67). Sensitivity and specificity for ATN were 51% and 64% using the AKIN stage 1 SCR cut-off; 26% and 83%, respectively, using the AKIN stage 2 cut-off. In the 361(62%) donors without AKI, median NGAL was higher if ATN was noted [79.5(IQR: 22.7-209.5) vs. 30.1(10.2-87.6) ng/mL for those without ATN, P=0.03]. Median L-FABP and YKL-40 were higher (though not significantly) in ATN compared to no ATN [L-FABP 25.6(6.4, 64.0) vs. 10.4(3.4, 41.0) ng/mL, P=0.08; YKL-40 4.3(0.6, 13.6) vs. 1.6(0.5, 5.2) ng/mL, P=0.11]. IL-18, KIM-1 and MCP-1 concentrations were similar regardless of ATN. Adding NGAL to SCR correctly reclassified 26% of donors for ATN events. We noted a trend for lower 6-month recipient estimated glomerular filtration rate (eGFR) [-2.6(95CI -5.4, 0.2) ml/min] for worsening degrees of ATN, but 6-month eGFR was paradoxically better [+3.6(95CI 1.7, 5.4) ml/min] for each higher stage of SCR-defined donor AKI.

Conclusions: SCR lacks sensitivity and specificity for diagnosing ATN. Urinary biomarkers like NGAL, L-FABP and YKL-40 may help distinguish “subclinical AKI,” if not improve clinical prediction of biopsy-proven ATN over that of SCR alone.

Funding: NIDDK Support, Private Foundation Support

SA-OR100

The Epidemiology and Outcome of Worldwide Acute Kidney Injury in Critically Ill Children: A Prospective Multinational Study Ahmad Kaddourah,² Rajit K. Basu,² Stuart Goldstein.² *On behalf of the “Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Critically ill Children (AWARE)” investigators; ²Cincinnati Children’s Hospital Medical Center.*

Background: Epidemiologic data for pediatric acute kidney injury (AKI) is limited to retrospective single-center studies. We conducted a prospective observational study of critically ill children to provide an international epidemiological description of pediatric AKI and associated outcomes.

Methods: 32 centers from 5 continents collected data for 3 consecutive months in 2014 from children (aged 3 months to 25 years) admitted to a pediatric intensive care

unit. AKI was defined and classified by serum creatinine and urine output KDIGO criteria within the first 7 days of admission (Stage 2-3 = severe). Outcomes were assessed at 28 days. Children with end-stage kidney disease (ESKD) or kidney transplant in the last 90 days were excluded.

Results: 5,237 children (55% males) were studied. Median age was 64.6 months (IQR 19,149). Day to day ranges of severe AKI prevalence and incidence during the first 7 days were 6.5-10.3% and 1.1-7.0%, respectively. Severe AKI incidence peaked at 7% on day 3 (127/1816). On multivariate analysis, shock on admission (OR 2.4, p=0.007), history of transplantation (OR 4.0, p<0.001) and urinary system comorbidity (OR 2.0, p<0.001) were independent predictors of Day 3 severe AKI. Table 1 depicts the univariate outcome associations with AKI.

	No/ stage 1 AKI n=4142	Severe AKI n=541	p
Mortality (%)	2.6	11.3	<0.001 (all)
Length of stay, mean (SD)	3.9 (6.1)	6.6 (6.9)	
ECMO use (%)	0.39	1.85	
Dialysis (%)	0.31	11.1	
Duration of mechanical ventilation, mean (SD)	5.2 (6.3)	7.7 (7.3)	

Severe AKI independently predicted mortality after adjustment for illness severity (OR 5.1, p<0.001). In a multivariate regression model, a 1-unit change in stage of AKI was associated with 1.28 days increase in illness-severity-adjusted length of stay (p<0.001).

Conclusions: AWARE represents the largest epidemiologic assessment of AKI in critically ill children. We demonstrate AKI is independently associated with multiple deleterious outcomes. Our data will help guide future research to develop accurate and early diagnostic models of AKI.

SA-OR101

Derivation and Validation of Risk Models for Chronic Kidney Disease following Hospitalization with Acute Kidney Injury Matthew T. James,¹ Neesh I. Pannu,² Amit X. Garg,³ Marcello Tonelli,¹ Braden J. Manns,¹ Zhi Tan,¹ Eric Mcarthur,³ Ron Wald,⁴ Pietro Ravani,¹ Robert R. Quinn,¹ Brenda Hemmelgarn.¹ ¹Univ of Calgary, AB, Canada; ²Univ of Alberta, AB, Canada; ³Western Univ, ON, Canada; ⁴Univ of Toronto, ON, Canada.

Background: Some, but not all patients, will develop chronic kidney disease (CKD) after a hospitalization with acute kidney injury (AKI). We developed and validated predictive models for progression of AKI to CKD.

Methods: We studied patients with baseline eGFR>45 mL/min/1.73m² who survived >3 months following a hospitalization with AKI. We identified those with a sustained reduction in eGFR<30 mL/min/1.73m² for >3 months. Data from 11,437 patients hospitalized with AKI in Alberta, Canada were used to develop the risk models. External validation was performed in a cohort of 9,387 similar patients from Ontario, Canada. Models were derived using logistic regression and evaluated based on discrimination, calibration, integrated discrimination improvement (IDI), and net reclassification improvement (NRI).

Results: Seven variables were associated with a higher risk of progression to CKD: older age, female sex, higher baseline serum creatinine, higher urine albumin, greater AKI severity (KDIGO Stage), lesser recovery of kidney function by the time of discharge, and heart failure. The full model showed good discrimination in the derivation and validation cohorts (c-statistics of 0.85 and 0.82, respectively). A reduced model that included age, sex, baseline serum creatinine, AKI severity, and recovery of kidney function at discharge performed similarly to the full model, but better than a base model that included age, sex, and AKI severity alone (IDI 3.3%; 95%CI 2.3-4.4%, NRI 26.4%;95%CI 18.8-33.9%).

Conclusions: These prediction models can stratify patients for risk of CKD following hospitalization with AKI. The impact of these models for guiding CKD follow-up in the community should be prospectively evaluated.

Funding: Government Support - Non-U.S.

SA-OR102

Long-Term Outcomes After Rhabdomyolysis Ian J. Stewart,¹ Tarra Ischele Faulk,¹ Jonathan Sosnov,² Kevin Chung,³ ¹David Grant Medical Center, Travis AFB, CA; ²San Antonio Military Medical Center, JBSA Fort Sam Houston, TX; ³US Army Inst of Surgical Research, JBSA Fort Sam Houston, TX.

Background: There are few data regarding long term outcomes after rhabdomyolysis. We examined the relation of rhabdomyolysis with mortality, renal function and the development of hypertension (HTN) in a US military population injured in combat.

Methods: We queried military databases for US military personnel critically injured in combat between 1 Feb 2002 and 1 Feb 2011. Patients that died within 90 days of injury, had pre-existing HTN or chronic kidney disease, or had missing data were excluded. Demographic variables, creatinine, creatine kinase (CK), mean arterial pressure (MAP), Injury Severity Score (ISS), and burn injury were extracted. Acute kidney injury (AKI) was determined by KDIGO criteria, rhabdomyolysis was defined as a CK>5000 unit/L and MAP was categorized into high (>106mmHg), normal (65-106mmHg) and low (<65mmHg). Outcomes were mortality, eGFR (by CKD-EPI) and a new diagnosis of HTN. Cox proportional hazard regression models were used to test associations.

Results: The analysis included 1962 patients. Patients with rhabdomyolysis (30.3%) were more severely injured as evidenced by higher ISS (median 24 vs 18, p<0.01), more AKI (23.8% vs 12.3% p<0.01), and more patients in the low MAP category (24.0% vs 8.9%, p<0.01). Despite a longer median follow up time for patients with rhabdomyolysis compared to those without (1.3 years vs 1.0 years, respectively), eGFR was higher in rhabdomyolysis patients (118 ± 21 vs 111 ± 20, p<0.001). The follow up period for assessing death and HTN was longer and not significantly different for those with and without rhabdomyolysis (3.7 vs 4.0 years, respectively). While rhabdomyolysis was not associated with long-term mortality, it was associated with HTN (HR 1.32, 95% confidence interval 1.05-1.66, p=0.02) after adjustment.

Conclusions: Rhabdomyolysis was not associated with a decline in eGFR or mortality after a median follow up of approximately 1 and 4 years, respectively. Rhabdomyolysis was independently associated with a new diagnosis of HTN. Long term follow-up of patients with rhabdomyolysis may be needed to understand their true risk.

Funding: Other U.S. Government Support

SA-OR103

Podocyte Injury Is a Potential Contributor to Kidney Damage and Its Irreversibility During Acute Decompensated Heart Failure with Cardiorenal Syndrome Parta Hatamizadeh, Todd Koelling, Mahboob A. Chowdhury, Su Qing Wang, Judith Grossi, Roger C. Wiggins. *Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.*

Background: Deterioration of kidney function in association with acute decompensate heart failure (ADHF) is common and may or may not be reversible. Podocytes are vital for glomerular integrity and their injury can lead to glomerular sclerosis and permanent kidney damage. Hemodynamic dysregulations and activation of inflammatory and oxidative pathways are elements of cardiorenal syndrome while both can damage podocytes. We hypothesized that podocyte injury can occur in the context of ADHF.

Methods: We examined urine pellet podocin and nephrin mRNA in 39 ADHF patients during hospitalization and post-discharge as well as 172 adult healthy controls by reverse transcription-polymerase chain reaction. Urine podocin mRNA:creatinine ratio (uPODCr) and urine nephrin mRNA:creatinine ratio (uNephCr) were considered as indices of podocyte stress and podocyte injury, respectively.

Results: Mean age of the patients was 58.9±10.9 years and 31 were male. uPODCr and uNephCr were 5 (P<0.001) and 1.9 (P=0.009) times greater in ADHF patients compared to healthy controls respectively. Post-hospital discharge uPODCr was not different from that of ADHF phase, whether it was measured within a month of discharge or after 3 months of hospital discharge. However, post-hospital discharge uNephCr was not different from ADHF phase when it was measured within a month of discharge, but it was 14 times smaller when it was measured after 3 months of hospital discharge (P=0.03).

Conclusions: In ADHF, podocytes might be under greater stress compared to healthy individuals and may become injured. Podocyte stress level remains markedly elevated several weeks after clinical stabilization of ADHF; but then drops remarkably. Podocyte injury, however, continues to progress even after 3 months of clinical stabilization. Measurement of uPODCr and uNephCr during ADHF may help with risk stratification for permanent kidney damage. Potential interventions to prevent advancement of podocyte stress to podocyte injury in the setting of ADHF, may help prevent permanent kidney injury.

SA-OR104

Micronutrient Loss in Renal Replacement Therapy for Acute Kidney Injury Weng Oh,¹ David S. Gardner,² Mark A.J. Devonald.¹ ¹Renal and Transplant Unit, NUH NHS Trust, Nottingham, United Kingdom; ²Faculty of Medicine and Science, Univ of Nottingham, Nottingham, United Kingdom.

Background: Malnutrition is common in acute kidney injury (AKI) patients receiving renal replacement therapy (RRT). No clinical study has quantified and contrasted micronutrient losses between types of RRT that use differing methods to remove solutes (e.g. IHD, by diffusion; SLED-F, by convection; CVVH, by a combination of both).

Methods: Using a prospective, observational design patients (n=24/modality) were consented to the study before their first treatment session. Blood and RRT effluent (dialysate or filtrate) were sampled at baseline (pre-RRT), mid and end-RRT. Amino acids were measured by HPLC, trace elements by ICP-MS and B-vitamins (B1, B3, B6, B9, B12) by LC-MS. Plasma concentrations and dialysate losses (gms) were corrected for dose of RRT (urea reduction ratio or solute removal index, as appropriate). Data were analysed by mixed effect models (Genstat v16).

Results: Patients receiving CVVH had significantly higher plasma amino acids, but not trace elements, at baseline (amino acids: CVVH, 3762 ± 357; IHD, 2039 ± 337; SLED-f, 2505 ± 423 µmol/L; trace elements: IHD, 4156 ± 465; SLED-f 3732 ± 521; CVVH 3982 ± 465 µg/L). At RRT end, plasma amino acids and trace elements had significantly reduced (by 429 ± 223 µmol/L; 600 ± 400 µg/L, respectively). Loss of all trace elements was similar between types of RRT, but SLED-F cleared many (>10) individual amino acids to a greater extent (e.g. lysine loss, -64 ± 23 µmol/L vs. HD) than other types of RRT. Micronutrient loss was largely through effluent but also dialyser adsorption, the latter contributing <1g amino acids. Additional effluent losses were upto 25g with CVVH, 5-6g for IHD and 8-10g for SLED-F (P<.001). Effluent losses of individual trace elements varied significantly, but in all cases were greater for CVVH (e.g. loss of copper, +850 ± 475 µg vs. HD or SLED-F).

Conclusions: RRT results in significant loss of all water-soluble micronutrients. This loss is not equal between type of RRT; SLED-F clears certain amino acids, whereas CVVH clears certain trace elements, highly effectively. This has implications for nutritional management of RRT patients.

Funding: Government Support - Non-U.S.

SA-OR105

Renal Replacement Therapy Intensity for Acute Kidney Injury and Recovery to Dialysis Independence Ying Wang,¹ Serigne N. Lo,¹ Martin P. Gallagher,¹ Qiang Li,¹ Alan Cass,¹ John A. Myburgh,¹ Robert Faulhaber-Walter,² John A. Kellum,³ Paul M. Palevsky,³ Claudio Ronco,⁴ Patrick Saudan,⁵ Ashita J. Tolwani,⁶ Rinaldo Bellomo.¹ ¹George Inst for Global Health; ²Hanover Medical School; ³Univ of Pittsburgh School; ⁴Bortolo Hospital; ⁵Univ Hospital; ⁶The Univ of Alabama.

Background: In acute kidney injury, randomized controlled trials (RCTs) have not found differences in survival with higher intensities of renal replacement therapy (RRT), but trials have not been powered for renal outcomes such as recovery of renal function.

Methods: Through an individual patient data meta-analysis we merged individual patient data from RCTs comparing high with standard intensity RRT. We assessed mortality at 28, 60 & 90 days and renal recovery at 7, 14, 28, 60 & 90 days post randomisation. Renal recovery was assessed two ways; by the proportion of patients RRT dependent and by time to RRT independence at these time points.

Results: Of the eight prospective RCTs assessing different RRT intensities, seven contributed individual patient data (n=3688) to the analysis. Mortality was not different between the high and standard intensity groups across these 7 studies at 28 days (775/1890 and 744/1798 respectively, 41% vs 41.4%, p = 0.24) after randomization, nor at any of the other time points. The proportion of patients RRT dependent at the 14 day point was greater in patients receiving high compared to standard intensity RRT (RR 1.36, 95%CI 1.12-1.65, p = 0.0016), but not at any other time point. Analysis by time to RRT independence suggested that patients receiving higher intensity therapy had less time independent of RRT (Day 28: HR 0.87, 95% CI 0.78 to 0.97, p=0.014, Day 60: HR 0.87, 95%CI 0.78 to 0.97, p=0.012, Day 90: HR 0.84, 95%CI 0.76 to 0.94, P=0.0022). This effect was more pronounced in trials that allowed the use of intermittent hemodialysis (IHD) to deliver higher intensity RRT. The robustness of these effects was confirmed in multiple sensitivity analyses.

Conclusions: Higher intensity RRT does not affect mortality but does appear to delay recipient's recovery to RRT independence. This effect appears to relate to the use of IHD to delivery higher intensity RRT.

Funding: Government Support - Non-U.S.

SA-OR106

Outcomes of In-Hospital Cardiopulmonary Resuscitation (CPR) in Patients with Acute Kidney Injury Fahad Saeed,¹ Jean L. Holley,² Sevag Demirjian.¹ ¹Cleveland Clinic; ²Univ of Illinois at Urbana-Champaign.

Background: There is paucity of data on the CPR-related outcomes in patients with AKI. Herein, we have analyzed the impact of AKI on the outcomes of in-hospital CPR.

Methods: We extracted data from the Nationwide Inpatient Sample (NIS, 2005- 2011) including patients with and without AKI who had undergone in-hospital CPR. Baseline characteristics, in-hospital complications and discharge outcomes were compared between the two groups. We determined the effect of AKI on length of hospital stay, discharge destination, and hospital mortality in patients who underwent in-hospital CPR.

Results: 180,970 patients with primary or secondary diagnosis of AKI underwent in-hospital CPR compared to 323,620 patients without AKI. Unadjusted in-hospital mortality rates were higher in the AKI group (78.2 % vs. 71.8% , p<.0001). After adjusting for age, sex, and potential confounders, patients in the AKI group had higher odds of mortality with odds ratio 1.3, 95 % confidence interval 1.2-1.4, p<.0001. Survivors in the AKI group were more likely to be discharged to nursing homes; odds ratio 1.4, 95 % confidence interval 1.3-1.5, p<.0001. Mean length of stay was significantly higher in patients with AKI; 11 ±34 days versus 7 ±26 days, p<.0001.

Conclusions: AKI independently increases the odds of in-hospital mortality and nursing home placement after in-hospital CPR. These data may facilitate CPR discussions and decision-making.

SA-OR107

Acute Kidney Injury After Surgical Aortic Valve Replacement and Long-Term Risk of Death and End-Stage Renal Disease Linda C. Ryden,¹ Ulrik Sartipy,² Martin Holzmann.¹ ¹Dept of Internal Medicine, Solna, Karolinska Inst, Stockholm, Sweden; ²Dept of Molecular Medicine and Surgery, Karolinska Inst, Stockholm, Sweden.

Background: Acute kidney injury (AKI) is a common complication after cardiac surgery that is associated with adverse outcomes. The incidence of AKI after surgical aortic valve replacement (SAVR) and its association with long-term mortality and end-stage renal disease (ESRD) is not known. The aim of this study was to determine the incidence of AKI and its relationship to mortality and long-term renal outcomes in a large cohort of patients who underwent a first isolated SAVR from 1999 to 2013 in Sweden.

Methods: We included all 9,047 patients from the SWEDEHEART register who underwent primary isolated SAVR between 1999 and 2013 in Sweden. AKI was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria: stage 1: serum Creatinine (sCr) concentration ≥ 0.3 mg/dL (26.5 mmol/L) or 1.5- to 1.9-fold increase in sCr; stage 2: 2.0- to 2.9-fold increase in sCr; Stage 3: 3.0-fold increase in postoperative sCr compared to baseline value, or initiation of renal replacement therapy.

Results: In total, 17% of patients developed AKI postoperatively, of whom 13% were AKI stage 1 and 3.7% AKI stages 2-3. During a mean follow-up of 5.6 (standard deviation [SD] 3.7) years, 2,109 patients (23%) died and 29 (0.3%) developed ESRD. After multivariable adjustment, the hazard ratio (HR) with 95% confidence interval (CI)

for death in AKI stage 1 was 1.27 (1.12-1.44) and in AKI stages 2-3 was 2.47 (2.03-3.00). The redistribution HR for ESRD in AKI stage 1 was 4.4 (1.7-12), and in stage 2 to 3 was 5.3 (1.6-18).

Conclusions: AKI is common after a first isolated SAVR and is associated with an increased long-term risk of both death and ESRD, independent of preoperative renal function.

SA-OR108

Incidence and Predictors of Acute Kidney Injury After Total Hip Replacement Kamel A. Gharaibeh, Abdurrahman M. Hamadah, Nelson Leung, Ziad El-Zoghby. *Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Total hip replacement (THR) is a common procedure that has increased in number with the improvement in life expectancy. Nonsteroidal antiinflammatory drugs (NSAID) are commonly used pre and post THR but their risk of causing acute kidney injury (AKI) in this setting is not well quantified.

Methods: Between 2004 and 2014, 10,327 patients underwent THR. We retrospectively collected demographic and co-morbidities data on those who developed AKI (defined by AKIN criteria) after THR. A control group without AKI was matched by age, gender and year of surgery. Variables associated with AKI were determined by univariate and multivariate logistic regressions.

Results: Mean age was 64.6 ± 13.8 years, 48.6% were male and 114 patients (1.1%) developed AKI (79% stage 1, 18.4% stage 2, 2.6% stage 3). Older age (RR 1.8, per decade, p<0.001) and male gender (RR 1.8, p=0.0016) were associated with AKI. Characteristics of those with and without AKI are shown in table-1. Several variables were associated with AKI (table-1) on univariate analysis but on multivariate analysis only CHF (OR 27.7, p<0.001); HTN (OR 2.8, p<0.001); CKD (OR 2.9, p<0.001) and transfusion (OR 3.5, p<0.001) remained significant. Diabetes (OR 2, p = 0.064); NSAID (OR 0.9, p=0.9); ACEi/ARB (OR 1.5, p=0.23) and diuretics exposure (OR 0.8, p=0.6) were not associated with AKI.

Table-1

Variables	AKI(n=114)	Control(n=114)	P-value
Age±SD	73.4±11.3	73.4±11.5	
Gender (male)	63.2%	63.2 %	
BMI	34.2±11	31.3±7.6	0.02
CKD	49%	21%	<0.001
eGFR(CKD-EPI)	64±1.7	77±1.7	<0.001
CHF	28.1%	0.9%	<0.001
Diabetes	34.2%	16.7%	0.002
HTN	87.7%	64%	<0.001
ACEi/ARB use	67.5%	44.7%	<0.001
Diuretics use	64%	42.1%	<0.001
NSAID use	51.8%	67.5%	0.015
NSAID+ACEi/ARB+Diuretics	36.8%	28.1%	0.16
Hemoglobin (pre-op)	12.8±1.7 (8.7-17.1)	13.5±1.4 (8.4-16.4)	0.0016
Hemoglobin (post-op)	9.9±1.3 (6.5-14.5)	10.6±1.3 (7-13.5)	<0.001
transfusion	61(53.5%)	23(20.2%)	<0.001

Conclusions: The incidence of AKI after THR is low. Several known risk factors were independently associated with AKI after THR; however, ACEi/ARB, diuretics and NSAID exposure were not. A prospective study is needed to confirm these results.

SA-OR109

Discovery and Testing in Rat Models of UT-A1 Urea Transporter Inhibitors Cristina Esteve-Font,¹ Onur Cil,¹ Tao Su,¹ Sujin Lee,¹ Marc O. Anderson,² Alan S. Verkman,¹ Puay Wah Phuan.¹ ¹Medicine and Physiology, Univ of California, San Francisco, San Francisco, CA; ²Chemistry and Biochemistry, San Francisco State Univ, San Francisco, CA.

Background: Inhibitors of urea transport function have potential clinical applications as first-in-class salt-sparing diuretics for treatment of edema and hyponatremia (Nat Rev Nephrol 11, 113-123, 2015). Our goal is to develop small-molecule, UT-A1-selective inhibitors and demonstrate their diuretic efficacy in clinically relevant animal models.

Methods: Screening of >250,000 drugs and synthetic small molecules was done using a cell-based fluorescence assay involving osmotic volume response to an urea gradient (Chem Biol 20, 1235-1244, 2013). Pharmacokinetics (PK) was measured in rats by liquid chromatography and mass spectrometry; diuretic efficacy was studied using metabolic cages and in a model of SIADH produced by chronic minipump infusion of dDAVP (5 ng/h) with liquid diet administration.

Results: 22 distinct chemical classes of UT-A1 inhibitors were identified and optimized by structure-activity studies on > 3,000 analogs. Compounds with high UT-A1 vs. UT-B selectivity were identified, some with nanomolar inhibition potency. In addition, analog and natural-product screening identified dimethylthiourea (DMTU) as a non-selective UT

inhibitor. Several classes of compounds gave good PK in rats with predicted therapeutic concentrations in blood and urine. Salt-sparing diuretic action was demonstrated in control, hydrated rats and rats administered dDAVP acutely. Up to a 2.5-fold increase in hourly urine volume and 2-fold reduction in urine osmolality was found. Compounds also prevented hyponatremia in rats chronically treated with dDAVP.

Conclusions: UT-A1 inhibitors show salt-sparing diuretic action in rats, and efficacy in a clinically relevant model of hyponatremia. In contrast to existing diuretics that target renal tubule salt transporters, UT-A1 inhibitors have a novel diuretic mechanism of action involving disruption of urinary concentration by renal countercurrent multiplication.

Funding: NIDDK Support

SA-OR110

Pathways for Urea Transport Across the Rat Inner Medullary Thin Limbs of Henle's Loops Kristen K. Evans,¹ William H. Dantzer,¹ Alan S.L. Yu,² Thomas L. Pannabecker.¹ ¹Physiology, The Univ of Arizona, Tucson, AZ; ²The Kidney Inst, Univ of Kansas, Kansas City, KS.

Background: Transepithelial solute flows in thin limbs of Henle's loops play critical roles in countercurrent exchange and the urinary concentrating mechanism; our goal is to identify the urea transport pathways in these segments. The rat inner medullary long-loop descending thin limbs (DTLs) consist of water permeable upper and water impermeable lower segments, positioned in the upper and lower 50% of the inner medulla, respectively. Mean transepithelial urea permeabilities of upper DTL are approximately 60 E-5 cm/sec and permeabilities of lower DTL and ascending thin limb (ATL) are approximately 350 to 450 E-5 cm/sec. A urea transporter, UT-A2, has been identified by immunohistochemistry only in a very limited region of the upper DTL, near the outer medullary-inner medullary border and only in the presence of vasopressin.

Methods: Tubules were isolated without enzyme digestion and perfused with concentric glass micropipettes by the method of Burg. The lumen-to-bath transepithelial urea flux was determined and permeabilities were calculated.

Results: Urea transport in isolated perfused upper and lower DTL is not inhibited by peritubular 0.25 mM phloretin and urea transport in lower DTL is not inhibited by 10 mM ouabain and is unaffected by a 125 mM lumen Na⁺ and 0 mM bath Na⁺ concentration gradient. The urea flux in upper and lower DTLs is almost completely and reversibly inhibited by peritubular 5 mM lanthanum. Activation energy for transepithelial urea permeability measured at 37° and 16° C in isolated perfused lower DTLs and ATLs is approximately 13 kJ/mol, a value that is consistent with channel-like activity.

Conclusions: The data suggest that a substantial fraction of the transepithelial urea flux occurs independently of known facilitated urea transporters such as UT-A1-3, is unlikely to be coupled to Na⁺ flux and occurs, in large part, by way of a plasma membrane or paracellular channel-like pathway.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR111

Comparative Analysis of Vasopressin V1a and V2 Receptors Distribution in the Mammalian Kidney Torsten Giesecke,¹ Taka-aki Koshimizu,² Katsumasa Kawahara,³ Sebastian Bachmann,¹ Kerim Mutig,¹ ¹Dept of Anatomy, Charité Universitätsmedizin Berlin, Berlin, Germany; ²Dept of Molecular Pharmacology, Jichi Medical Univ, Shimotsuke-shi, Tochigi-ken, Japan; ³Dept of Physiology, Kitasato Univ School of Medicine, Kitasato, Japan.

Background: Vasopressin (AVP) promotes urinary concentration by activating the vasopressin V2 receptor (V2R). Parallel activation of the vasopressin V1a receptor (V1aR) may affect renal acid-base balance and stimulate the renin-angiotensin-aldosterone axis. Analysis of the renal distribution of these receptor subtypes has been difficult owing to the lack of suitable, specific antisera. Here we have extended available data on their distribution and function using subtype-specific antibodies. Subtype-selective agonists were used for functional analysis.

Methods: Antibodies to V1aR- and V2R-specific peptides were generated. Segmental and cellular distribution of the subtypes along mouse and rat nephron were characterized by immunofluorescence and high-resolution immunocytochemistry. Functional studies were performed in AVP-deficient Brattleboro rats using subtype-specific agonists; AO-4-67 was used for V1aR, and desmopressin for V2R activation at short term.

Results: The V2R was localized basolaterally in mouse and rat kidney thick ascending limb (TAL), distal convoluted tubule (DCT), connecting tubule (CNT) and collecting duct (CD) epithelia; macula densa (MD) and intercalated cells were negative. Conversely, application of the anti-V1aR antibody produced basolateral signal exclusively in MD cells and intercalated CNT/CD cells. Staining was controlled using V2R- and V1aR-deficient mouse kidneys, respectively. In line with the localization data, administration of desmopressin in Brattleboro rats induced the activation and trafficking of distal tubular NaCl transporters and of aquaporin 2 in the CNT/CD principal cells, whereas application of AO-4-67 resulted in luminal trafficking of V-ATPase in intercalated cells of CNT/CD.

Conclusions: These data provide morphological support for the distinct epithelial effects of AVP mediated by V2R or V1aR and may improve our understanding of the pathophysiology of nephrogenic diabetes insipidus.

SA-OR112

Role of Nedd4-2 Underlying V2R Activation of ENaC Alan C. Pao,^{1,2} Yu Chen,¹ Sheela V. Thomas,¹ Mollie E. Jacobs,¹ Sindhu Chandran,¹ Mariana Labarca,¹ Vivek Bhalla.¹ ¹Div of Nephrology, Stanford Univ School of Medicine, Stanford, CA; ²Veterans Affairs Palo Alto Health Care System, Palo Alto, CA.

Background: Arginine vasopressin (AVP) can increase renal sodium (Na⁺) reabsorption in the cortical collecting duct (CCD) by stimulating the epithelial Na⁺ channel (ENaC). One presumed mechanism by which AVP stimulates ENaC is through activation of vasopressin-2 receptor (V2R) and inhibition of the E3 ubiquitin ligase Nedd4-2. Snyder and colleagues first demonstrated that cAMP/PKA signaling reverses Nedd4-2 inhibition of ENaC. However, how V2R signals through Nedd4-2 to regulate ENaC is not fully understood.

Methods: We therefore tested mechanisms by which V2R inhibits Nedd4-2 and increases ENaC cell surface expression in transfected HEK293T kidney cells, an established model for the study of Nedd4-2 function.

Results: We found that V2R, similar to cAMP, relieved Nedd4-2 inhibition of ENaC cell surface expression, but surprisingly V2R did not decrease the interaction between Nedd4-2 and ENaC. Instead, V2R increased expression of Nedd4-2, which in turn increased the pool of Nedd4-2 that interacted with ENaC. The V2R-dependent increase in Nedd4-2 expression was blocked with introduction of mutations that eliminate phosphorylation of Ser-444 of Nedd4-2. While V2R increased Nedd4-2 expression, V2R still relieved Nedd4-2 inhibition of ENaC cell surface expression if Ser-338, Thr-363, and Ser-444 remained intact. If all three residues were disrupted, V2R-mediated stimulation of ENaC was attenuated but not fully prevented, suggesting that V2R signals through additional residues on Nedd4-2 or independent of Nedd4-2.

Conclusions: Our findings provide a molecular basis for how AVP signals through Nedd4-2 to increase ENaC activity and demonstrate how the level of Nedd4-2 expression or interaction with ENaC is not necessarily an accurate surrogate for Nedd4-2 function.

Funding: NIDDK Support

SA-OR113

Vasopressin Lowers Renal Epoxyeicosatrienoic Acid Levels by Activating Soluble Epoxide Hydrolase Alexander Paliege,¹ Allein Plain,² Markus Bleich,² Sebastian Bachmann,¹ Nina Himmerkus.² ¹Anatomy, Charité, Berlin, Germany; ²Physiology, CAU, Kiel, Germany.

Background: Activation of the thick ascending limb (TAL) Na⁽⁺⁾-K⁽⁺⁾-2Cl⁽⁻⁾ cotransporter (NKCC2) by vasopressin (AVP) is an essential mechanism of volume homeostasis and may also contribute to the development of arterial hypertension and chronic kidney disease. AVP effects in the kidney are counteracted by locally produced eicosanoids including epoxyeicosatrienoic acids (EETs). The effects of AVP on the renal expression of EETs and their metabolizing enzymes have not been determined.

Methods: Adult AVP-deficient Brattleboro rats were treated with the AVP receptor agonist desmopressin (dDAVP, 5ng/h; 3d) via osmotic minipump. Renal EET-levels were measured by mass spectrometry. Regulation of EET-metabolizing enzymes was determined by Affymetrix microarray analysis. Microarray results were confirmed by real-time PCR, immunohistochemistry and Western blot. EET effects on TAL transport activity were studied using the isolated perfused tubule setup.

Results: dDAVP treatment significantly lowered renal EET levels (-56±3% for 5,6-EET, -50±3.4% for 11,12-EET and -60±3.7% for 14,15-EET relative to controls; p<.05). Microarray analysis revealed elevated mRNA levels for the principal EET-degrading enzyme soluble epoxide hydrolase (sEH) and unchanged mRNA-levels for the EET-synthesizing epoxigenases. Regulation of sEH was confirmed by real time PCR (+160±37%, p<.05) and Western blot (+120±26%; p<.05). Immunohistochemistry in control animals demonstrated abundant expression in the macula densa, connecting tubule (CNT), and in the cortical (CCD), outer (OMCD) and inner (IMCD) medullary collecting duct. dDAVP treatment increased protein levels in CNT, CCD, and OMCD with close proximity to TAL profiles. Preincubation of TAL segments with 5,6-EET (1µM; 30 min) significantly reduced furosemide inhibitable short circuit current (-45±5%; p<.05) thus confirming inhibitory effects of EETs on NKCC2 transport activity.

Conclusions: We have shown that activation of AVP signaling causes upregulation of renal sEH biosynthesis and enzyme activity. The resulting reduction of EET tissue levels may be instrumental for increased NKCC2 transport activity during AVP-induced antidiuresis.

Funding: Government Support - Non-U.S.

SA-OR114

MicroRNA-132 Regulates Diuresis by Mediating Vasopressin Production Roel Bijkerk,^{1,2} Ruben de Bruin,¹ Coen van Solingen,¹ Ton J. Rabelink,¹ Benjamin D. Humphreys,² Peter M.T. Deen,³ Anton Jan Van Zonneveld.¹ ¹Dept of Nephrology and the Einthoven Laboratory for Experimental Vascular Medicine, Leiden Univ Medical Center, Netherlands; ²Renal Division, Brigham & Women's Hospital and Harvard Medical School, Boston; ³Dept of Physiology, Radboud Univ Nijmegen Medical Centre, Netherlands.

Background: The collecting duct (CD) principal cells of our kidneys are critical in the maintenance of blood water levels, as binding of vasopressin (AVP) to its V2-receptor and the subsequent translocation of aquaporin-2 (AQP2) water channels to the apical membrane fine-tunes water balance. AVP dependent regulation of water homeostasis can be modulated

by renal prostaglandin E₂ (PGE₂), a metabolite of the cyclooxygenase (Cox) pathway, by inducing the internalization and lysosomal degradation of AQP2. A role for microRNAs (miRNAs) in the regulation of water and electrolyte balance remains virtually unexplored.

Methods: We generated antagonists to silence miR-132 function. Synthetic AVP (ddAVP) was administered with osmotic minipumps. Mice were housed in metabolic cages and sacrificed 1 day after i.v. or i.c.v. injection of the antagonists or scrambled controls.

Results: Silencing of miR-132 caused severe weight loss as a result of acute diuresis characterized by increased plasma osmolality and decreased urine osmolality. In addition, urinary PGE₂ levels were elevated and hypothalamic AVP mRNA expression and blood AVP levels were decreased, resulting in less translocation of AQP2 in CD cells. We identified Cox2 as a direct target of miR-132, but administration of Cox2-inhibitor Celecoxib did not affect antagonist-induced diuresis, suggesting a PGE₂ independent pathway. In contrast, infusion of synthetic AVP (ddAVP) reversed antagonist-induced diuresis, suggesting an effect on hypothalamic AVP production. Confirming this hypothesis, i.c.v. injection of antagonist miR-132 similarly resulted in acute diuresis and decreased AVP production and we found miR-132 to target and increase hypothalamic MeCP2, which is known to block AVP transcription.

Conclusions: Taken together, silencing of miR-132 causes acute diuresis. Our data indicate that this is the result of a MeCP2 mediated decrease in hypothalamic AVP synthesis.

SA-OR115

Dephosphorylation at Ser-261 Is a Determinant for the Regulated AQP2 Apical Accumulation Naofumi Yui, Sei Sasaki, Shinichi Uchida. *Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.*

Background: AQP2 apical plasma membrane accumulation is crucial for vasopressin (VP)-regulated urine concentration. It is well known that VP induces post-translational modification on AQP2 phosphorylation at several serine (S) sites in its C-terminus, however, how these complicated phosphorylation and dephosphorylation regulate AQP2 apical accumulation is unknown. Recently, we identified that 1) pS261-AQP2 is continuously targeting to the apical plasma membrane, then internalized into the cytoplasm without any stimulations, 2) pS269-AQP2 is observed intracellularly at 1 min in the initial phase of forskolin (FK) stimulation, 3) S269 phosphorylation preceded S261 dephosphorylation in polarized MDCK cells. Therefore, we hypothesized that dephosphorylation at S261 is crucial for regulated AQP2 apical accumulation at the downstream step during the stimulation.

Methods: To test this hypothesis, we expressed mutated AQP2 and analyzed them in MDCK cells focusing on phosphorylation status at S261 and S269.

Results: In P262L-AQP2, a recessive NDI causing mutant, pS269 was greatly increased with continuous S269 phosphorylation after forskolin (FK) stimulation (20 μM, 10 min) as well as wild-type AQP2 (WT-AQP2), whereas, pS261 was increased after FK treatment contrary to WT-AQP2 (20 μM, 10 min). Surprisingly, pS269-AQP2 was accumulated in the basolateral membrane after FK treatment (20 μM, 10 min). S269A-AQP2, a S269-dephosphorylation mimic, accumulates in the apical membrane after FK treatment (20 μM, 30 min) with a striking reduction of phosphorylation at S261. Interestingly, it took longer time (20 min) to dephosphorylate S261 in S269A-AQP2 compared to WT-AQP2 (within 5 min).

Conclusions: These results demonstrated that FK-mediated subcellular translocation of pS269-AQP2 is greatly affected by phosphorylation status at S261 and that FK-mediated AQP2 apical accumulation might be determined by S261 dephosphorylation, which is likely to be facilitated by precedent phosphorylation at S269. Further investigation how VP-mediated S269 phosphorylation catalyzes dephosphorylation at Ser-261 would be important to draw a complete picture of AQP2 translocation mechanism.

Funding: Other U.S. Government Support

SA-OR116

ILK Is Important for Recycling of AQP2 and Its Subsequent Entry into the Exocytotic Pathway Fahmy Mamuya,¹ Jose Luis Cano-Peñalver,² Dennis Brown,¹ Hua Ann Jenny Lu.¹ ¹Dept of Medicine, Massachusetts General Hospital, Boston, MA; ²Inst Reina Sofia de Investigación Renal and Red de Investigación Renal (REDinREN), Inst de Salud Carlos III, Madrid, Spain.

Background: Within the past decade tremendous efforts have been made to understand the mechanism behind aquaporin-2 (AQP2) water channel trafficking and recycling, in order to open a path towards effective diabetes insipidus therapeutics. A recent study has shown that Integrin Linked Kinase (ILK) conditional-knockdown (cKD-ILK) mice developed polyuria along with decreased expression of AQP2.

Methods: To better understand the role of ILK in this process, we performed *in vitro* analysis using LLCPK1 cells stably expressing rat AQP2 (W2 cells).

Results: Upon treatment of W2 cells with ILK-SiRNA and the ILK inhibitor, Calbiochem-cpd22, we observed an accumulation of AQP2 in the perinuclear region, without accumulation of AQP2 in the plasma membrane. We next examined the effect of ILK inhibition on endocytosis using a fluid phase marker, FITC-dextran (10 KDa). There was no significant difference in endocytosis of FITC-dextran in W2 cells after ILK inhibition. When we examined the clathrin mediated endocytotic pathway using rhodamine conjugated transferrin, a perinuclear accumulation of rhodamine transferrin was detected in the presence of ILK inhibition, which colocalized with AQP2. To further test whether we could "rescue" AQP2 accumulated in the perinuclear patch, lysine vasopressin (LVP) was added in conjunction with ILK-SiRNA or ILK inhibitor. Interestingly, the canonical LVP induced AQP2 membrane accumulation was prevented. To examine whether these effects were due to an alteration of AQP2 phosphorylation, we performed western blotting of AQP2 phosphorylation, targeting the S256, 261, 269 and 264 sites. Our data did not reveal any significant effects on AQP2 phosphorylation patterns after ILK inhibition.

Conclusions: Therefore, while our data suggest that the ILK signaling pathway modulates AQP2 trafficking, this is not through affecting endocytosis of AQP2 nor modulating the phosphorylation of AQP2. Because ILK inhibition results in the formation of a perinuclear patch in which cellular AQP2 is concentrated we hypothesize that ILK is important for recycling of AQP2 and its subsequent entry into the exocytotic pathway.

SA-OR117

GI Regulation of Vesicle Osmotic Swelling Is Required for Nonsecretory Vesicle Fusion: Aquaporin 2 Water Channel as a Paradigm Giovanna Valenti,¹ Maria De santo,² Mariangela Centrone,¹ Maria Grazia Mola,¹ Marianna Ranieri,¹ Vincenzo Formoso,² Grazia Tamma.¹ ¹Dept of Biosciences, Biotechnologies and Biopharmaceutics, Univ of Bari, Italy; ²Dept of Physics, Univ of Calabria, Italy.

Background: We have previously shown that the heterotrimeric G protein Gai3, associated with AQP2 vesicles, is required for the water channel fusion to the plasma membrane. On the other hand, swelling of secretory vesicles has been implicated in exocytosis. Here we address the question of whether vesicle swelling is also a prerequisite for fusion of nonsecretory vesicles. The role of Gai3 in this process is investigated. AQP2 vesicles are chosen as paradigm of nonsecretory vesicles.

Methods: AQP2 vesicles isolated from rat kidney were analyzed by high resolution dynamic imaging using the atomic force microscope (AFM), allowing analysis of unfixed vesicles in a hydrated environment at nanoscale resolution. In parallel, a rapid fluorescence-based assay of vesicle or cell volume changes in a multiwell format was applied to analyze real time fluorescence kinetic data.

Results: α subunits of PTX-sensitive G proteins, Gai3, was found associated to isolated AQP2 vesicles. Treatment of renal AQP2-transfected MCD4 cells with pertussis toxin (PTX), which inhibits G proteins of the Gi family, inhibited cAMP-triggered increase in osmotic water permeability implicating a critical role of Gai3. Dynamic imaging of isolated AQP2 vesicles by AFM revealed that mastoparan, known to stimulate Gi proteins, caused a significant increase in vesicle swelling. This effect was confirmed by fluorescence-based assay of vesicle volume changes. Of note, mastoparan-induced vesicle swelling was abolished by anti-Gai3 antibodies or by anti-AQP2 antibodies.

Conclusions: Our results demonstrate that Gai3 localized in AQP2 vesicles mediates vesicle swelling regulating rapid water entry through AQP2, a potentially important prerequisite for vesicle fusion to the plasma membrane. We conclude that vesicle swelling is required also for nonsecretory vesicle fusion committed to insert a channel into the plasma membrane and depicts a general mechanism for vesicle fusion.

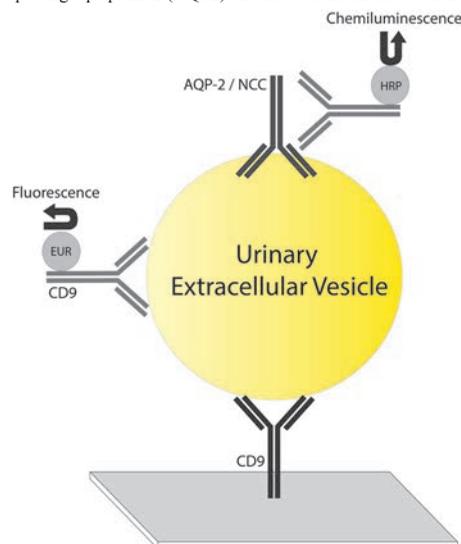
Funding: Government Support - Non-U.S.

SA-OR118

An Enzyme Immunoassay for Urinary Extracellular Vesicles Mahdi Salih,¹ Robert A. Fenton,² Robert Zietse,¹ Ewout J. Hoorn.¹ ¹Internal Medicine, Erasmus MC, Rotterdam, Netherlands; ²Biomedicine, Aarhus Univ, Denmark.

Background: Urinary extracellular vesicles (uEVs) are derived from epithelial cells of the kidney and urinary tract. uEVs (also called exosomes) contain disease-related proteins and also transfer information to target cells. As such uEVs offer exciting opportunities for nephrology, but current isolation techniques rely on time-consuming ultracentrifugation hindering high-throughput clinical application.

Methods: To navigate this problem, we designed an enzyme-linked immunosorbent assay (ELISA) that isolates uEVs using a biotinylated CD9 antibody. uEVs are then lysed with a detergent and treated with an antibody targeting the protein of interest. The use of two conjugated antibodies allows quantification of the protein of interest and CD9. We tested the set-up using aquaporin-2 (AQP2) and the sodium chloride cotransporter (NCC).



Results: CD9 but not CD63 coated immunobeads isolated AQP2+ and NCC+ uEVs. Urinary creatinine and CD9 correlated strongly (n=20, r=0.9, P<0.001); thus CD9 can also be used for normalization in spot urines. Our uEV-ELISA sensitively detected AQP2

and NCC (coefficients of variance 5.6 and 3.3%). To verify whether expected effects of vasopressin on AQP2 and NCC were captured by our uEV-ELISA, we performed overnight thirsting followed by water loading in 4 volunteers. After water loading, similar 2-3 fold decreases in AQP2 and NCC were observed using either uEV-ELISA or immunoblotting after isolating uEVs with ultracentrifugation. The results by uEV-ELISA showed good correlations with immunoblot ($r=0.8$ for AQP2, $r=0.6$ for NCC, both $P<0.001$).

Conclusions: We successfully developed an ELISA to capture and quantify uEV-proteins and validated this technique for AQP2 and NCC. Our uEV-ELISA set-up does not require ultracentrifugation or measurement of urinary creatinine and may be used as a platform to examine other uEV proteins of interest in nephrology.

TH-PO001

The Long Non-Coding RNA Landscape in Hypoxic and Inflammatory Renal Epithelial Injury Jennie Lin, Xuan Zhang, Chenyi Xue, Sager Jayesh Gosai, Hanrui Zhang, Michael G. Shashaty, Nuala J. Meyer, Alison Grazioli, Katalin Susztak, Mingyao Li, Muredach Reilly. *Medicine, Univ of Pennsylvania, Philadelphia, PA.*

Background: Long non-coding RNAs (lncRNAs) are emerging as key regulators of disease processes. To identify lncRNAs involved in acute renal epithelial injury, we performed whole transcriptome profiling of human proximal tubular epithelial cells (PTECs) in hypoxic and inflammatory conditions.

Methods: Strand-specific RNA-seq (50 million paired-end reads per library) was performed on poly-adenylated RNA fraction of control PTECs and PTECs subjected to 12 hours of hypoxia or cytokine (IL6, TNF- α , and IFN- γ cocktail) stimulation. A transcript was considered differentially expressed (DE) between control and stimulation at > 1.5 fold change with FDR-adjusted $p < 0.05$.

Results: 3,728 mRNAs and 69 lncRNAs were DE between cytokine-stimulated and control PTECs, while 2730 mRNAs and 70 lncRNAs were DE between hypoxic and control cells. Three lncRNAs were prioritized for further study based on abundance. Linc-ATP13A4-8 was specifically upregulated (8.1-fold at 12 hours, FDR $p < 0.001$) in PTEC hypoxia, peaked its expression 15-fold at 24 hours, is located in the nucleus and cytoplasm, and has both synteny and 80.6% conservation of a 206 bp sequence with the mouse genome. Linc-KIAA1737-2 was specifically upregulated after cytokine treatment (4.6-fold at 12 hours, FDR $p < 0.001$), was over 50-fold upregulated at 48 hours, is located primarily in the nucleus with an enhancer region (high H3K4me1/H3K4me3 overlying H3K27ac mark for adult kidney on NIH Epigenomics Roadmap), and is syntenic with mouse with no sequence conservation. Linc-POU5F1-1 increased in expression (2 to 4 fold, FDR $p < 0.001$) in both stimulations, declined in expression after 12 hours, is located in the nucleus with a canonical promoter region shared with protein-coding POU5F1, and is human-specific. All three lncRNAs are expressed in human PTECs from healthy donor nephrectomy kidneys previously micro-dissected and sequenced.

Conclusions: Transcriptome profiling of stimulated renal epithelial cells reveals different lncRNAs that may regulate the cellular response to distinct stressors relevant to acute kidney injury.

Funding: NIDDK Support, Other NIH Support - NHLBI

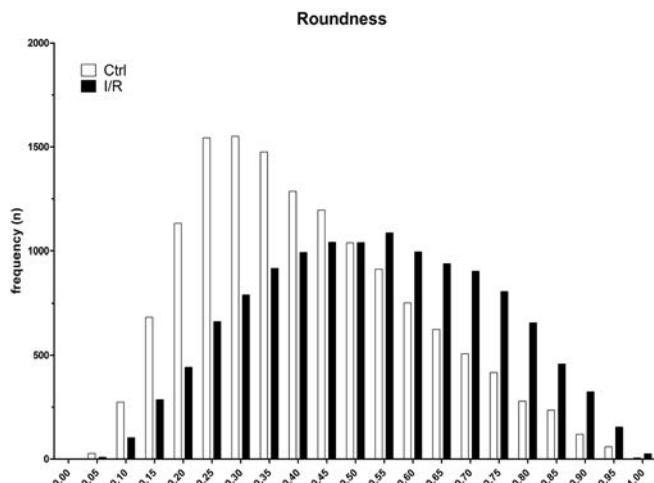
TH-PO002

Cortical Consequences of Ischemia-Reperfusion Injury: Computational Studies of the Renal Microvasculature Gunnar Schley,¹ Bernd Klanke,¹ Kai-Uwe Eckardt,¹ Seymour Rosen,² Carsten Willam.¹ ¹Nephrology and Hypertension, Univ of Erlangen-Nuremberg, Erlangen, Germany; ²Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: The acute injury of the ischemia-reperfusion (I/R) kidney model affects mainly the outer stripe (OS) of the outer medulla, but its long-term consequence is extensive cortical involvement. We were therefore interested in the long-term effects of such ischemic injury on the cortical capillary network.

Methods: Male C57BL/6 mice (n=11) were subjected to bilateral renal I/R for 25 min and sacrificed 2 weeks later. Untreated mice (n=5) served as controls. Kidney sections were stained for MECA-32 to visualize the renal microvasculature. Vessel geometry was selectively quantified in damaged tissue regions by computer-assisted morphometric analysis.

Results: In the normal subcapsular cortex peritubular capillaries appeared elongated and formed an organized network. Although I/R initially affects the OS, 2 weeks after I/R, marked chronic tubular atrophy occurred in the cortex. Adjacent microvessels' shape remarkably changed: capillaries were significantly smaller (perimeter, diameter decreased) and rounder (circularity and roundness increased, see Figure, aspect ratio decreased) compared to control vessels.



Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
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These alterations resulted in an abnormal structural organization. We validated our technique by comparing geometric parameters of vasa recta and the capillary plexus in the inner stripe of the outer medulla in controls kidneys.

Conclusions: Long-term effects of renal I/R involved cortical tubules and microvessels. Semiautomated morphometric analysis of cortical capillaries showed a remarkable shift from organized and elongated towards disorganized, smaller and rounder forms. Thus the late consequences of I/R, a primary medullary insult, are those of profound changes in the cortical microvasculature.

TH-PO003

Glomerular Injury Induces a Calcium Signal in Proximal Tubular Cells – A Multiphoton *In Vivo* Study Julia Binz, Matthias Hackl, Bernhard Schermer, Thomas Benzing. *Dept II of Internal Medicine and Cologne Center for Molecular Medicine, Univ of Cologne, Cologne, Germany.*

Background: Recently it has been demonstrated that renal tubular cells undergo synchronized necrosis after ischemic injury, implying that the death of a single cell can induce a disastrous chain reaction. An early event in damage signaling is a massive increase in intracellular calcium levels. Therefore we investigated if a localized damage to glomerular cells can influence tubular calcium levels downstream of the damage site.

Methods: 4 weeks old mice expressing the calcium indicator GCaMP3 in proximal tubular cells (Pax8:cre) were anaesthetized, an arterial catheter was placed into the right carotid artery and the left kidney was exteriorized for *in vivo* multiphoton microscopy. Blood vessels were labelled by injection of 70 kDa Texas Red dextrane. Acute glomerular injury was induced by focusing the laser beam on a podocyte to cause a localized injury. The resulting calcium response in tubular cells was recorded with in a time series of the glomerulus and the originating proximal tubulus.

Results: Upon laser induced injury of a podocyte, a strong calcium signal can be observed within seconds in the continuous stretch of proximal tubular cells downstream of the glomerulus. The signal lasts for a few seconds and then the calcium signal returns to baseline. The calcium response in proximal tubular cells is faster than the known calcium wave in podocytes after injury.

Conclusions: Glomerular injury induces a calcium signal in proximal tubular cells *in vivo*, linking glomerular injury to tubular damage signaling. The almost instantaneous calcium increase in tubular cells suggest that the release of podocyte cell content and most probably damage-associated molecular pattern molecules (DAMPs) affects tubular cells, uninjured by the initial damage.

TH-PO004

Inhibition of Oxygen-Sensing Prolylhydroxylases 1 (PHD1) Protects from Acute Kidney Injury Almut Grenz,¹ Raechel Peralta,² Uladzimir Shabeka,¹ Sue Murray,² Shuling Guo,² Gene Hung.² ¹Dept of Anesthesiology, UC Denver, Denver, CO; ²ISIS Pharmaceuticals, ISIS Pharmaceuticals, Carlsbad, CA.

Background: Acute kidney injury (AKI) due to ischemia is associated with dramatic increases of morbidity and mortality. Conditions of ischemia with limited oxygen availability inhibit oxygen-sensing prolyl hydroxylases (PHD1-3) with subsequent stabilization of hypoxia-inducible factors (HIFs) resulting in a transcriptionally regulated response towards hypoxia adaptation. *Thus, we hypothesize that a new pharmacological approach to inhibit PHDs on a transcript level via specific antisense treatment before the onset of ischemic injury mediates protection.*

Methods: Mice were studied in two ischemic models of AKI. With a hanging weight system we only compress the renal artery whereby we clamp the whole pedicle by using micro vessel clamps. Renal function was determined by inulin clearance, serum creatinine, BUN, renal NGAL and KIM-1.

Results: Our previous studies in gene-target mice (PHD1-3 KO mice) has shown that renal protection from ischemia was associated with PHD1. To pursue our hypothesis, we first treated wild type mice with PHD1 specific antisense inhibitors (ASO1 and ASO2). We tested the compounds over 2 to 6 week treatment periods in different doses. The optimal treatment length was 2 weeks before renal ischemia (30min ischemia and 24 hours reperfusion by utilizing the hanging weight system) in a dose of 100mg/kg per week. Treatment reduces renal PHD1 RNA by 90% and 60%, respectively and improved the glomerular filtration rate (GFR) by almost 300% in both treatment groups compared to untreated mice following 30min of renal ischemia. In a next step we used the clamp model to induce kidney ischemia. PHD1 specific antisense inhibitor treatment showed comparable kidney protection as in the hanging weight model demonstrated in GFR improvement, serum creatinine and renal tubular injury markers (NGAL, KIM1).

Conclusions: In conclusion, PHD1 oligo treatment before renal ischemia in two different ischemia models shows a tremendous attenuation from renal injury due to ischemia. If translatable from mice to human, these data have important therapeutic implications.

Funding: Pharmaceutical Company Support - ISIS Pharmaceuticals, Private Foundation Support

TH-PO005

Role of Thioredoxin-Interacting Protein (TXNIP) in Mitochondrial Function of Renal Tubular Cells in Ischemia Reperfusion Injury AKI Model

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Background: Thioredoxin-interacting protein (TXNIP) has been found to regulate the cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin in a redox-dependent fashion. However, little is known about the role of TXNIP in acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of TXNIP in renal function in bilateral renal ischemia/reperfusion injury (IRI) model using TXNIP knock-out (KO) and wild type (WT) mice. cultured renal tubular cells (NRK-52E cells) as an in vitro model. To elucidate the functional roles of TXNIP, we evaluated mitochondrial enzymes, morphology, and apoptotic change by transfection of siRNA for TXNIP in cultured renal tubular cells.

Results: TXNIP KO mice had significantly higher SCr (0.78±0.28 versus 0.45 ± 0.20 mg/dl) and significantly higher BUN (152.5±32.5 versus 75.3±18.2 mg/dl) at 24h post ischemia compared to WT mice. Immunohistological examination showed severer tubular injury in cortex and outer medulla in TXNIP KO mice compared to WT mice. The number of TUNEL positive tubular cells was increased in TXNIP KO mice compared to WT mice. The protein expressions of mitochondrial enzymes (ATP5a, UCP2 and complex IV) were decreased in TXNIP KO mice at 24h post ischemia. In vitro experiments, protein and mRNA levels of ATP5a, complex IV, UCP2, PGC-1α were significantly decreased by H₂O₂, and siRNA for TXNIP amplify the reduction of these enzymes in NRK-52E cells.

Conclusions: These data demonstrate that TXNIP protects from IRI induced AKI. TXNIP changes mitochondrial function in oxidative conditions. These results indicate that TXNIP plays a key role in the pathophysiology of AKI.

TH-PO006

TWEAK Decreases PGC-1α Expression in Renal Injury and Promotes Mitochondrial Dysfunction in Tubular Cells

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Background: There is currently no satisfactory therapy for acute kidney injury (AKI). Successful testing of mitochondria-targeted nephroprotective agents suggests a key role of mitochondrial injury in AKI. We hypothesized that an improved understanding of the regulation of factors responsible for mitochondrial biogenesis may provide clues to novel therapeutic approaches to AKI. Thus, we explored the interaction between inflammation and mitochondrial biogenesis regulators.

Methods: Transcriptomics databases from cultured murine tubular epithelial cells and folic acid-induced AKI in mice identified downregulation of PGC-1α and target genes regulated by the inflammatory cytokine TWEAK. Functional studies in vivo ad cell culture studies characterized the TWEAK- PGC-1α relationship.

Results: Transcriptomics identified decreased expression of PGC-1α mRNA and PGC-1α-dependent genes encoding mitochondrial proteins (Ndufs1, Sdha and Tfam) as a shared feature between AKI and TWEAK-stimulated cultured tubular cells. Neutralizing anti-TWEAK antibodies prevented the decrease in kidney PGC-1α and its targets during AKI. TWEAK stimulation decreased kidney PGC-1α expression in healthy mice. TWEAK also decreased the expression of PGC-1α and its targets as well as mitochondrial membrane potential in cultured tubular cells. Adenoviral-mediated PGC-1α overexpression prevented TWEAK-induced downregulation of PGC-1α-dependent genes and the decrease in mitochondrial membrane potential. TWEAK promoted histone H3 deacetylation at the murine PGC-1α promoter. TWEAK-induced downregulation of PGC-1α was prevented by histone deacetylase (HDAC) or NfκB inhibitors.

Conclusions: TWEAK decreases PGC-1α and target gene expression in tubular cells through NfκB activation and histone deacetylation. This information may be used to design therapeutic approaches that preserve mitochondrial function during kidney injury.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO007

miR-21 Targets Prolyl Hydroxylase Domain Protein 2 in Renal Ischemia/reperfusion

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Background: We previously reported that up-regulation of miR-21 attenuated renal ischemia-reperfusion injury, which was associated with increased hypoxia inducible factor (HIF)-1α expression. HIF-1α is mediated by prolyl hydroxylase domain protein 2 (PHD2). We hypothesized that miR-21 regulated HIF-1α by targeting PHD2 in the renal ischemic preconditioning (IPC).

Methods: Luciferase reporter assay was performed to examine if miR-21 could target the 3'-untranslated region of PHD2. *In vitro*, hypoxia (1% O₂) for 6h was followed by reoxygenation for 0.5h in HK-2 cell. *In vivo*, bilateral kidneys of mice were clamped for

15min to induce IPC, followed by 35min ischemia 4 days later in the IPC/IR group. The mice for Sham/IR group were subjected to 35min ischemia without IPC. Locked nucleic acid (LNA) modified anti-miR-21 or scrambled anti-miR was transfected into cells or delivered into the mice via tail vein injection less than 1 hour prior to IPC.

Results: miR-21 targeting of PHD2 was confirmed by 3'-untranslated region reporter assay. miR-21 was significantly up-regulated by hypoxia/reoxygenation in HK-2 cell, while PHD2 protein decreased significantly. LNA anti-miR-21 significantly decreased miR-21 levels and increased the abundance of PHD2. *In vivo*, IPC up-regulated miR-21 expression 24h after the second ischemia. PHD2 expression decreased significantly with up-regulation of HIF-1α protein and VEGF mRNA in the IPC/IR group. miR-21 induced by delayed IPC was effectively inhibited by the LNA anti-miR-21. With down-regulation of miR-21, the protection of delayed IPC was attenuated and PHD2 protein was increased. Furthermore, up-regulation of HIF-1α and VEGF were abolished in the IPC/IR mice after the LNA anti-miR-21 treatment.

Conclusions: miR-21 could protect kidney against IRI via HIF-1α by inhibiting PHD2. The study suggested a new mechanism mediating the effect of miR-21 on HIF-1α and renal IRI.

Funding: Government Support - Non-U.S.

TH-PO008

Mir-668 Is Induced via HIF-1 to Prevent Mitochondrial Fragmentation and Protect Kidneys from Ischemia-Reperfusion Injury

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Background: MicroRNAs are important regulators in various pathophysiological condition including ischemic acute kidney injury (AKI). We identified mir-668 that was significantly up-regulated in ischemic AKI. mir-668 induction was attenuated in kidney proximal tubule-HIF-1-knockout mice, suggesting a role of HIF-1 in the inductive response.

Methods: Analysis of the sequence of the potential promoter region of mir-668 predicted two HIF-1 binding sites. The binding of HIF-1 to one of the sites was verified by Chromatin immunoprecipitation (CHIP) assay, suggesting that HIF-1 may directly regulate mir-668 transcription.

Results: Functionally, inhibition of mir-668 exacerbated kidney injury, supporting a protective role of this microRNA. Consistently, inhibition of mir-668 led to apoptosis in cultured rat proximal tubular cells (RPTC) and overexpress mir-668 reduced ATP-depletion mediated RPTC apoptosis. Interestingly, mir-668 inhibition also induced significant mitochondrial fragmentation, a pathogenic event in renal tubular cell death in ischemic AKI. To further examine the regulation mechanism of mitochondrial morphology by mir-668, we identified a list of potential mir-668 targets by Ago2 immunoprecipitation and RNA deep sequencing.

Conclusions: In summary, mir-668 is up-regulated via HIF-1 during ischemic AKI. Following the induction, mir-668 may play a role in the preservation of mitochondrial dynamics and morphology for the protection of kidney cells and tissues. n also induced significant mitochondrial fragmentation, a pathogenic event in renal tubular cell death in ischemic AKI. To further examine the regulation mechanism of mitochondrial morphology by mir-668, we identified a list of potential mir-668 targets by Ago2 immunoprecipitation and RNA deep sequencing.

Funding: NIDDK Support, Veterans Administration Support, Private Foundation Support

TH-PO009

Implication of AMPK Activation in Experimental Aristolochic Acid Nephropathy: Use of a Targeted Metabolomic Analysis

Anne-Emilie Declèves,¹ Inès Jadot,³ Vanessa Colombaro,³ Kefeng Li,² Nathalie Caron,³ Joelle L. Nortier,¹ Robert K. Naviaux,² ¹Free Univ of Brussels; ²Univ of California, San Diego; ³Univ of Namur.

Background: Experimental aristolochic acid nephropathy (AAN) is a progressive tubulointerstitial injury, characterized by early and transient acute tubular necrosis. In order to better explore the pathogenesis of AAN, a targeted metabolomic analysis was performed in plasma of AA-intoxicated mice. In addition, the effect of AMP-activated Protein Kinase (AMPK) activation with AICAR was also investigated.

Methods: C57BL/6J male mice were randomly subjected to i.p. injection of either sterile saline solution, AA, AA+AICAR, the specific AMPK activator for 4 days. Mice were then euthanized at day 5. Targeted metabolites were detected in plasma using an AB SCIEX QTRAP 5500 triple quadrupole mass spectrometer equipped with a Turbo V electrospray ionization (ESI) source, and Shimadzu LC-20A UHPLC system.

Results: Thirty metabolites were dysregulated in this acute phase of the experimental AAN model. Among them, 23 metabolites were significantly increased in AA-treated mice and 7 were significantly decreased. AICAR treatment ameliorated the change of 15 of these metabolites. Among the observed changes, several metabolic pathways were affected, in particular gut microbiome metabolism, liver and bile acid metabolism, tryptophan metabolism, purine and pyrimidine metabolism and mitochondrial metabolism. Tryptophan-derived metabolites considered as uremic toxin such as xanthurenic acid, kynurenic acid were increased in AA-treated mice and reduced with AICAR.

Conclusions: These metabolomic approach provided novel findings regarding early perturbations occurring in metabolic pathways in AAN. Moreover, our results suggest 1)

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a crosstalk between gut microbiome and kidney, especially in relation with tryptophan metabolism and accumulation of uremic toxins; 2) a beneficial role of AMPK in reducing the level of uremic toxins.

Funding: Private Foundation Support

TH-PO010

Suppressed Renal Mitochondrial Biogenesis After Liver Transplantation in Rats *Zhi Zhong*,¹ Qinlong Liu,^{1,2} Yasodha Krishnasamy,¹ Hasibur Rehman,¹ Peifeng Deng,¹ John J. Lemasters,¹ Rick G. Schnellmann.^{1,3} ¹*Medical Univ of South Carolina, Charleston, SC;* ²*Darlian Medical Univ, 2nd Affiliated Hospital, Dalian, China;* ³*Ralph H. Johnson VA Medical Center, Charleston, SC.*

Background: Suppressed mitochondrial biogenesis (MB) contributes to acute kidney injury (AKI) after renal ischemia-reperfusion and sepsis. AKI occurs frequently after liver transplantation (LT), which substantially increases mortality. This study investigated whether suppressed MB plays a role in AKI after LT.

Methods: Livers were explanted from Lewis rats and implanted after 18 h cold storage. Liver, kidney and blood were collected 18 h after LT or survival was determined at 7 days.

Results: Seven-day survival after LT decreased to 25%. Focal necrosis, apoptosis and leukocyte infiltration occurred in liver grafts, and serum ALT and total bilirubin increased markedly after LT. In the kidney, nuclear DNA-encoded oxidative phosphorylation (OXPHOS) protein ATP synthase- β and mitochondrial DNA (mtDNA)-encoded OXPHOS protein NADH oxidase-3 decreased 44% and 81%, respectively, and their associated mRNAs decreased 72% and 46%, respectively, indicating suppressed OXPHOS protein synthesis. Renal PGC-1 α , the master regulator of MB, decreased 57% after LT and mitochondrial transcription factor-A (TFAM), which controls mtDNA replication and transcription, decreased 66%. PGC-1 α and TFAM mRNAs also decreased. mtDNA was reduced by 60%. Together, these data indicate marked MB suppression in the kidney after LT. Inhibited MB was associated with 17- and 13-fold increases in NGAL and cleaved caspase-3 in the renal tissue. Mild to moderate histological changes were observed in the kidney, including loss of brush border, vacuolization of tubular cells in the cortex, cast formation and necrosis in some proximal tubular cells. Myeloperoxidase and ED-1 also increased in the kidney after LT, indicating inflammation. Serum creatinine increased >2 fold.

Conclusions: MB is disrupted in the kidneys of recipients of liver grafts after long cold storage, which may contribute to the occurrence of AKI and increased mortality after LT.

Funding: NIDDK Support

TH-PO011

TXNIP Is Involved in the Mitochondrial ROS Mediated NLRP3 Inflammasome Activation in Ischemia/Reperfusion Induced AKI *Liu Yiran*, Wen Yi, Tang Taotao, Bi-Cheng Liu. *Inst of Nephrology, Southeast Univ, Nanjing, Jiangsu Province, China.*

Background: Renal ischemia reperfusion is a leading cause of acute kidney injury (AKI). Previous studies suggest that mitochondrial dysfunction and NLRP3 inflammasome activation are important events of AKI. TXNIP, an endogenous inhibitor of the antioxidant thioredoxin and ROS sensor, may have a role in NLRP3 inflammasome activation. In this study, we explored the relationship between TXNIP on NLRP3 inflammasome activation in ischemia/reperfusion induced AKI.

Methods: Ischemic mice models were built as previously reported. MitoTEMPO, a mitochondria-targeted antioxidant, was used to attenuate ROS production. Also, HK-2 cells were cultured for 8h with hypoxia-hypoglycemic plus 2 h normoxia/normal glucose incubation. siRNA of NLRP3 and TXNIP were applied to interrupt the signaling.

Results: In this study, we established an ischemia reperfusion induced-AKI model characterized by tubular necrosis and excessive mROS production. The renal expression of NLRP3 inflammasome, IL-1 β and IL-18 were significantly increased in this animal model. However, kidney dysfunction and mitochondrial damage were attenuated obviously in NLRP3^{-/-} mice compared with WT mice with ischemia AKI. In vitro study, oxygen-glucose deprivation injury time dependently increased the expression levels of NLRP3 inflammasome axis and TXNIP. The mitochondrial injury in damaged HK2 cells was suppressed by silence of NLRP3. Furthermore, MitoTEMPO could restore mitochondrial function and dissociate TXNIP from NLRP3 to inhibit NLRP3 inflammasome activation. TXNIP siRNA significantly abrogated the mROS and NLRP3 inflammasome activation.

Conclusions: NLRP3 inflammasome activation induced by excessive ROS production in ischemic AKI is mediated by TXNIP. And the mROS-TXNIP-NLRP3 inflammasome pathway can be a potential target for AKI therapy.

Funding: Other NIH Support - National Natural Science Foundation of China

TH-PO012

PPAR Activation in Regulatory T Cells Enhances Protection from Kidney Ischemia Reperfusion Injury *Gilbert R. Kinsey*, Didier Portilla, Liping Huang, Mana Yang, Michael N. Pham, Brian K. Stevens. *Medicine, Univ of Virginia, Charlottesville, VA.*

Background: Regulatory T cells (Tregs) are anti-inflammatory lymphocytes that protect the kidney from multiple types of injury. Our recent studies suggest that Tregs must express the surface receptor programmed death 1 (PD-1) to mediate protection. A metabolic program favoring mitochondrial oxidative phosphorylation (OxPhos) over glycolysis in Tregs is critical for Treg development and function in other models. PD-1 and peroxisome proliferator-activated receptors (PPARs) promote OxPhos in several cell types, but their role in Treg-mediated renal protection is not known.

Methods: Mitochondrial membrane potential (TMRE) and mass (Mitotracker) were assessed using flow cytometry. Tregs isolated from WT or PD-1 KO mice were adoptively transferred to naive WT recipients 1 hr prior to ischemia reperfusion injury (IRI). WT and PD-1 KO Tregs were exposed to the pan PPAR activator bezafibrate (BEZA) or vehicle (DMSO) overnight, then washed, prior to adoptive transfer in the IRI model.

Results: PD-1 KO Tregs had significantly lower mitochondrial mass and mitochondrial membrane potential (TMRE mean fluorescence intensity: $45 \pm 10\%$ of WT Tregs, $p < 0.05$). In contrast to WT Tregs, untreated PD-1 KO Tregs offered no protection from kidney IRI in terms of plasma creatinine levels, ATN scores and kidney neutrophil accumulation at 24 hr of reperfusion. Treatment of WT Tregs with bezafibrate overnight significantly enhanced the ability of a sub-optimal number of Tregs to protect the kidney from IRI (24 hr plasma creatinine (mg/dl): Sham 0.4 ± 0.1 ; IRI + saline 1.8 ± 0.1 ; IRI+ WT Tregs (DMSO) 1.1 ± 0.3 ; IRI + WT Tregs (BEZA) $0.6 \pm 0.1^*$, $N=7$ per group, $*P < 0.01$ vs. DMSO). Bezafibrate treatment endowed PD-1 KO Tregs with modest, but statistically significant, protective ability in the kidney IRI model.

Conclusions: These results demonstrate that PD-1 must be expressed on Tregs in order for them suppress kidney IRI and that PPAR activation *ex vivo* enhances subsequent Treg activity in this model. Our findings suggest that enhanced OxPhos in Tregs promotes their ability to protect the kidney.

Funding: NIDDK Support

TH-PO013

Effects of Short Chain Fatty Acids on Inflammatory Process in Acute Kidney Injury *Sung Yoon Lim*,¹ Young Ju Na,¹ Myung-gyu Kim,¹ So-young Lee,² Sang-Kyung Jo,¹ Won-Yong Cho.¹ ¹*Dept of Nephrology, Korea Univ Hospital, Seoul, Korea;* ²*Dept of Nephrology, Eulji Univ Hospital, Korea.*

Background: Short chain fatty acids (SCFAs) are the metabolic end products of normal bacterial fermentation of fibers in the large intestine. Emerging evidence suggest the role of gut-kidney crosstalk in regulating inflammatory processes. Purpose of the present study was to elucidate the role of SCFAs in an acute kidney injury (AKI) in which the inflammatory process has a major role.

Methods: Bilateral ischemia reperfusion injury (IRI) was induced in C57BL/6 mice. Sodium acetate were given to mice 30 minutes before ischemia and at the moment of reperfusion. Biochemical values, histological kidney damage and tissue inflammation were assessed. In vitro analysis, immune cells harvested from mice spleen were stimulated with LPS and the effect of sodium acetate on cytokine production was measured. Effects of SCFAs on T cell proliferation was also determined.

Results: Treatment with SCFAs attenuated IRI and reduced inflammation. Tubular cell apoptosis, determined by TUNEL stain also was decreased by SCFAs. The anti-inflammatory effects of SCFAs persisted until IRI day 14, thereby attenuating renal fibrosis after injury. Significantly lower level of pro-inflammatory cytokines was observed in the supernatant of cells from spleen co-treated with LPS and SCFAs, compared with those treated with LPS alone. Especially, IL-12p70, major inflammatory cytokine of dendritic cells was also reduced, suggesting that SCFAs might modulate the function of dendritic subset. In addition, administration of SCFAs can dose dependently inhibit normal T cell proliferation induced by anti-CD3 Ab stimulation.

Conclusions: Thus, our findings provide evidence that the SCFAs have renoprotective effect in AKI and also that this might be partially mediated by its immune modulatory effect.

TH-PO014

The Renoprotective Effect of Abatacept in Ischemia/Reperfusion Injury in Mice *Masaki Saito*, Shinya Kaname, Hideki Shimizu, Yoshinori Komagata, Yoshihiro Arimura. *Kyorin Univ School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo, Japan.*

Background: Although AKI is still an important complication in hospitalized patients, its prognosis remains poor, thus elucidation of the pathogenic mechanism and its effective treatment is urgently needed. Recently, a role for T cells in the renal ischemia/reperfusion injury (IRI) and also the renoprotective effect of abatacept, an inhibitor for CD28-CD80 T cell costimulatory signals, in the IRI have been reported, while its precise mechanisms are not fully understood. The purpose of this study is to determine the effect and mechanism of abatacept in the IRI model in mice.

Methods: Heminephrectomized mice were divided into three groups; the mice treated with ischemia/reperfusion (22 min) with normal saline or abatacept, and those treated with sham operation without renal ischemia as a control. Renal function (serum urea nitrogen and Cr, urine albumin excretion), pathology including T cell infiltration, expression of mRNA and protein for various parameters in the kidney were evaluated at 1 day after ischemia/reperfusion procedures.

Results: Compared with normal saline-treated mice, renal injury in the abatacept-treated mice were markedly attenuated both functionally and pathologically, with serum parameters improved to almost control levels. In addition, in abatacept-treated mice, apoptosis and expression of KIM-1 and PAI-1 were significantly suppressed as compared with normal saline-treated mice. Although the number of inflammatory cells and expressions of MCP-1 reduced by abatacept, the number of CD3-positive T cells, which was increased after ischemia/reperfusion, was not altered by abatacept.

Conclusions: We here showed that abatacept dramatically ameliorate IRI in mice, suggesting that it might be a new therapeutic option. It may be that abatacept, by blocking CD80-mediated signal in some cells responsible for the pathogenesis, exhibit anti-inflammatory effects, resulting in improvement of IRI, independently of T-cell-mediated acquired immune mechanisms.

TH-PO015

Autophagy Is Activated to Protect against Kidney Injury following in Lipopolysaccharide Treatment Shuqin Mei,^{1,2} Man J. Livingston,² Changlin Mei,¹ Zheng Dong,² ¹Nephrology, Shanghai Changzheng Hospital, Shanghai, China; ²Cellular Biology and Anatomy, Georgia Regents Univ, Augusta, GA.

Background: Sepsis, characterized by systemic inflammation, is a major cause of acute kidney injury (AKI) in hospitalized patients, especially in intensive care unit. The pathogenesis of septic AKI is poorly understood. Autophagy is a conserved, cellular catabolic pathway that plays crucial roles in cellular homeostasis including the maintenance of cellular function and viability. The regulation and role of autophagy in septic AKI remains unclear.

Methods: Lipopolysaccharide (LPS), an endotoxin, was injected in C57BL/6 mice to induce endotoxic/septic AKI. Autophagy reporter (*CAG-RFP-EGFP-LC3*) mice were used to monitor the dynamic changes of autophagy following LPS treatment. To determine the pathological role of autophagy, autophagy was inhibited pharmacologically with chloroquine or genetically by using proximal tubule-specific *Atg7* (Autophagy gene-7) ablated mice. Blood urea nitrogen (BUN) and serum creatinine were measured to evaluate renal function. HE staining and TUNEL staining were used to detect kidney injury. For *in vitro* study, cultured proximal tubular cells were treated with LPS in the absence or presence of chloroquine.

Results: LPS induced AKI in mice as indicated by increased BUN and serum creatinine, and tubular injury, which was accompanied by an increase in LC3II expression. In *CAG-RFP-EGFP-LC3* mice, LPS induced mRFP and EGFP-labeled autophagic puncta in renal tubular cells, further verifying the activation of autophagy. Chloroquine enhanced kidney injury during LPS treatment. For *in vitro* study, we detected LC3II expression accumulation and P62 degradation after LPS treatment for 12 hours, which was consistent with the mRFP, EGFP-labeled autophagic puncta results showed in proximal tubular cells.

Conclusions: Autophagy is activated in LPS-induced AKI and plays a renoprotective role.

Funding: NIDDK Support, Veterans Administration Support, Government Support - Non-U.S.

TH-PO016

Vascular Endothelial Growth Factor (VEGF) Contributes to Sepsis-Induced Acute Kidney Injury Arnaldo F. Lopez-Ruiz, Andrea P. Soljancic, Kiran B. Chandrashekar, Luis A. Juncos. Nephrology, Univ of Mississippi Medical Center, Jackson, MS.

Background: Sepsis is the most common cause of acute kidney injury (AKI) in the ICU. However, we still have an incomplete understanding of the mechanisms that cause it, and consequently our therapies provide only suboptimal protection at best. Previous studies have shown that VEGF is upregulated in sepsis and plays a role in its associated morbidity and mortality. We recently found that sFlt-1, an endogenous VEGF inhibitor is upregulated in both sepsis and AKI; however not sufficiently to normalize VEGF levels or neutralize its deleterious effects. We tested whether administering additional sFlt-1 protects against AKI and improves the balance between deleterious and protective cytokines and factors.

Methods: We used the cecal ligation and puncture technique (CLP) to induce sepsis. Male Sprague-Dawley rats were randomized into 4 groups: 1) Sham. 2) Sham + sFlt-1, 3) CLP, 4) CLP + sFlt-1. We administered sFlt-1 (12 µg/kg SQ) 6 hrs after the CLP or sham procedure. At 24hrs the rats were euthanized after collecting blood and kidneys for determination renal function and injury.

Results:

	VEGF pg/ml	sFlt-1 pg/ml	Creat mg/dl	uKIM-1 pg/ml	TNF pg/ml	i-NOS pg/ml	HO-1 ng/ml
SHAM	370± 10	30± 5	0.5± 0.07	135± 5	20± 0.8	1.8± 0.3	0.53± 0.01
CLP	780± 15 *	330± 10 *	2.2± 0.09 *	1900± 50 *	265± 10 *	13± 0.5 *	3.0± 0.1 *
CLP+sFlt-1	530± 10 * #	500± 15 * #	1.4± 0.1 * #	1100± 45 * #	130± 6 * #	6± 0.4 * #	7.5± 0.2 * #

Data: Mean ± SEM * p<0.05 vs Sham #p<0.05 vs CLP

Conclusions: CLP causes AKI within 24hrs and is associated with increased intra-renal expression of VEGF, i-NOS, TNF and only a modest increase in renal HO-1. Administering sFlt-1 during sepsis attenuated the severity of AKI and blunted the increase in i-NOS, VEGF and TNFα, while paradoxically causing a large increase in HO-1. Our data demonstrate a protective effect of sFlt-1 in sepsis-induced AKI, suggesting that excessive VEGF is deleterious in this condition, and that sFlt-1 associated induction of HO-1 may play a role in its beneficial actions.

Funding: NIDDK Support, Private Foundation Support

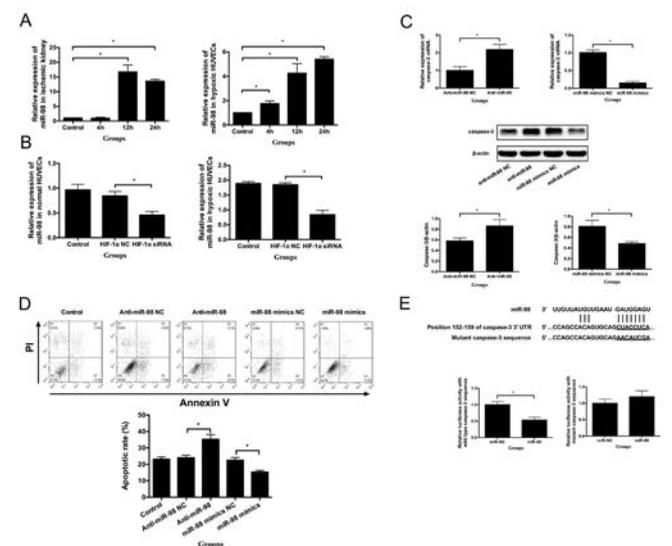
TH-PO017

Up-Regulation of miR-98 in the Kidney with Ischemia Reperfusion Injury Protects Endothelial Cells against Apoptosis by Targeting Caspase-3 Guang Yu, Xueli Lai. Dept of Nephrology, Changhai Hospital, the Second Military Medical Univ, Shanghai, China.

Background: Endothelial dysfunction is one of the main pathophysiological processes involved in renal ischemia reperfusion injury. In our previous study, we screened the aberrantly expressed miRNAs in the kidney with ischemia reperfusion injury (IRI) by microarray assay, among which miR-98 was predicted to target caspase-3. The present study was performed to whether miR-98 was involved in the regulation of endothelial apoptosis under hypoxia and re-oxygenation (HR) conditions.

Methods: The level of miR-98 in IRI kidney and HR HUVECs was determined by real-time PCR. HUVECs were treated with HIF-1α siRNA to investigate the role of HIF-1α on miR-98 regulation. HUVECs were transfected with miR-98 mimics or antisense oligonucleotides against miR-98 to identify the effect of miR-98 on the expression of caspase-3, as well as the hypoxia-induced apoptosis. Finally, the relationship between miR-98 and caspase-3 was confirmed by dual-luciferase reporter assay.

Results: Both of IRI and HR induced significantly up-regulation of miR-98 in the ischemic kidney and hypoxic HUVECs, respectively (Figure 1A). HIF-1α siRNA remarkably down-regulated the expression of miR-98 in both normal and hypoxic HUVECs (Figure 1B). MiR-98 mimics significantly inhibit caspase-3 expression in HUVECs, while anti-miR-98 significantly up-regulated it (Figure 1C). Furthermore, miR-98 protected HUVECs against apoptosis induced by hypoxia, while anti-miR-98 had the reverse effect (Figure 1D). The dual-luciferase reporter assay showed that miR-98 decreased the luciferase activity when transfected with wild-type caspase-3 sequence, but not mutant sequence at the predicted binding site (Figure 1E).



Conclusions: Renal IRI induces up-regulation of miR-98 potentially dependent on HIF-1α, which protects endothelial cells against apoptosis by targeting caspase-3.

Funding: Government Support - Non-U.S.

TH-PO018

Endothelial Caspase-8 Is a Key Mediator of Sepsis-induced Acute Kidney Injury Bradley K. Hack, Lihua Bao, Chang Xu, Patrick Cunningham. Section of Nephrology, Univ of Chicago, Chicago, IL.

Background: Acute kidney injury (AKI) is a frequent complication of gram negative sepsis. Prior work has demonstrated the importance of tumor necrosis factor (TNF) in endotoxin (LPS)-induced AKI. Caspase-8 is a key downstream effector of TNF, leading to apoptosis, and possibly facilitating inflammation. Mice genetically deficient in caspase-8 die *in utero* due to abnormal cardiovascular development.

Methods: To define the importance of caspase-8 activation in the endothelium in sepsis, we generated mice deficient in endothelial cell caspase-8 (EC-Casp8^{-/-}), using Cre expressed in the endothelium under inducible control of the VE-cadherin promoter, activated after tamoxifen administration. After one week of tamoxifen followed by a washout period, mice were injected with 0.25 mg/g E. coli LPS i.p. At baseline, EC-Casp8^{-/-} mice showed an absence of caspase-8 staining in endothelium after tamoxifen. Mice were sacrificed at 24 h and blood collected for cytokines, BUN, and creatinine. Kidney tissue was analyzed for light microscopic and immunohistochemistry. A subset of mice underwent renal cortical blood flow measurement by laser Doppler.

Results: As expected, wildtype mice developed significant AKI with elevation of BUN and subtle pathologic injury. In contrast, EC-Casp8^{-/-} mice had significantly less AKI (24 h BUN of 45.3 ± 11.2 v. 114.9 ± 9.9 mg/dl, p < 0.01). LPS induced a decrease in renal cortical blood flow that was restored in EC-Casp8^{-/-} mice (24 h renal blood flow of 1472 ± 61 perfusion units (BPU) in saline injected controls, 614 ± 89 BPU in LPS injected wildtype mice, and 1320 ± 159 BPU in LPS injected EC-Casp8^{-/-} mice, p < 0.01). EC-Casp8^{-/-} mice

also had reduced evidence of pathologic injury on light microscopy (cortical injury score 0.9 ± 0.20 in LPS injected EC-Casp8^{-/-} mice v. 1.7 ± 0.15 in wildtype, $p < 0.05$), and evidence of less vascular and tubular apoptosis on TUNEL staining.

Conclusions: These findings point to a key role of endothelial caspase-8 in sepsis-induced AKI. Further work will determine the relative role of caspase-8 in affecting renal microvascular perfusion, inflammation, and apoptosis in sepsis-induced AKI.

Funding: NIDDK Support

TH-PO019

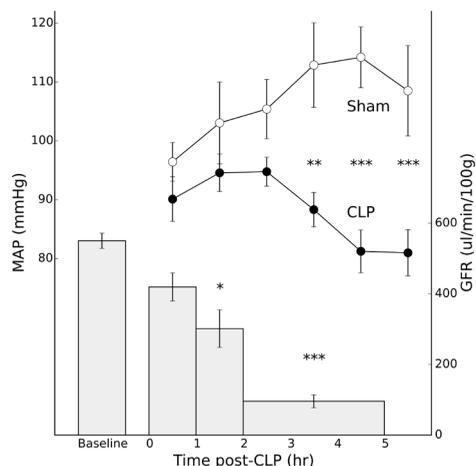
Sepsis Reduces Kidney Function in Mice Before Hemodynamic Alterations or Clinical Symptoms Become Apparent Jonathan Street, Yuning George Huang, Peter S.T. Yuen, Robert A. Star. *NIDDK, Bethesda, MD.*

Background: Acute kidney injury (AKI) increases the mortality and morbidity of sepsis. A rise in serum creatinine is used to detect AKI clinically and experimentally, but the slow kinetics prevents early detection of injury. To expand our understanding of the onset of AKI following sepsis we used a novel transcutaneous measurement of the plasma clearance of a fluorescent marker to directly measure GFR in near real-time.

Methods: Sepsis was induced in male CD-1 mice by cecal ligation and puncture (CLP). Blood pressure, heart rate, and activity/locomotion were simultaneously monitored by an implanted telemetry device. FITC-Sinistrin was injected at 0 and 90 min after surgery enabling GFR to be monitored for 5 hours via transcutaneous fluorescence, measured by a miniaturized fluorimeter attached to the mouse back.

Results: Log transformation of FITC-Sinistrin fluorescence decay allowed easy identification of when single pool kinetics applied, permitting calculation of GFR. GFR following CLP was similar to baseline during the first hour. During the second hour GFR fell by 30%, and dropped to 20% of baseline by 5 hours ($p < 0.01$). In contrast, mean arterial pressure, and heart rate were stable immediately following CLP, but then began to decrease, and were statistically significantly different from sham 3, and 4 hours later, respectively ($p < 0.01$). Activity/locomotion began to decline in the second hour, and was significantly different from sham 4 hours after CLP ($p < 0.01$).

Conclusions: Transcutaneous fluorescence measurement of plasma clearance longitudinally enables greater temporal resolution in measured GFR than prior approaches, revealing novel pathophysiology during early AKI. GFR was initially stable after sepsis surgery, then fell rapidly 2 hours later. The fall in GFR preceded hemodynamic alterations and the appearance of clinical symptoms such as reduced activity.



Funding: NIDDK Support

TH-PO020

Urinary AIM/CD5 Interacts with Kidney Injury Molecule-1 (KIM-1) and Promotes Recovery from Acute Kidney Injury via Enhancing Intraluminal Debris Clearance Toru Miyazaki, Kento Kitada, Satoko Arai. *Molecular Biomedicine for Pathogenesis, Faculty of Medicine, The Univ of Tokyo, Tokyo, Japan.*

Background: Acute kidney injury (AKI) is associated with prolonged hospitalization and high mortality, and may predispose patients to chronic kidney disease. To date, no effective treatments have been established for AKI. The apoptosis inhibitor of macrophage (AIM; also called CD5L) protein is a circulating protein that associates with IgM pentamers in blood, which protects AIM from renal excretion and maintains high levels of AIM (approximately 5 mg/mL in humans and mice) in blood.

Methods: By *in vivo* studies using AKI mouse models on a wild-type and AIM-deficient background, as well as *in vitro* experiments including phagocytosis assay focusing on the functional relationship between AIM and kidney injury molecule-1 (KIM-1), we here present that AIM is a ligand of KIM-1 and promotes potent clearance of pathogenic dead cell debris by tubular epithelial cells, which is crucial for overall recovery from AKI.

Results: The blood AIM dissociates from IgM upon AKI attack and excreted in urine in AKI patients and mice. The urinary AIM accumulates on intratubular dead cell debris. The accumulated AIM binds to KIM-1 on injured tubular epithelial cells and induces the phagocytic removal of the debris by epithelial cells, facilitating kidney tissue repair. When

subjected to ischemia/reperfusion-induced AKI, AIM-deficient mice exhibit abrogated debris clearance and markedly higher mortality due to progressive renal dysfunction than wild-type mice. AIM administration promotes the rapid removal of the debris, thereby ameliorating AKI in both AIM-deficient and wild-type mice.

Conclusions: Our study demonstrates that the AIM/KIM-1 cooperation efficiently promotes recovery from acute kidney injury through rapid clearance of intraluminal debris. These findings could be the basis for novel AKI therapies.

Funding: Government Support - Non-U.S.

TH-PO021

Renal Handling of Circulating and Renal Synthesized Hephcidin and Its Protective Effects against Hemoglobin-Mediated Kidney Injury Rachel Van Swelm, Jack F. Wetzels, Vivienne G.M Verweij, Coby M.M. Laarakkers, Jeanne C.L.M. Pertijs, Rosalinde Masereeuw, Dorine W. Swinkels. *Radboudumc, Nijmegen, Netherlands.*

Background: In multiple clinical observational studies it has been demonstrated that increased urinary hepcidin levels are associated with reduced risk of developing acute kidney injury (AKI) due to hemolysis in cardiac surgery patients. This study aimed to get more insight in renal hepcidin handling and its potential protective effects against heme-mediated AKI.

Methods: C57Bl/6 mice were treated with i) a single i.p. dose of 10 µg human hepcidin-25 (hhep25) to study renal handling of systemic hepcidin, ii) a single i.v. dose of 5 mg hemoglobin (Hb) to induce AKI, and iii) Hb combined with hhep25 to evaluate the protective effects of hhep25 on Hb-mediated kidney injury.

Results: Systemic hhep25 was rapidly cleared from plasma and excreted to urine. In addition to hhep25, we also detected the smaller isoforms hhep22 and hhep20 in urine, but not in plasma, showing that hhep25 is degraded in the tubular lumen. Urine hhep25 was 20-fold increased in megalin deficient mice compared to control ($p < 0.05$) and immunofluorescence staining showed that hepcidin was present in tubules expressing megalin, but NOT in megalin-deficient tubules, demonstrating that megalin is responsible for hhep25 uptake in the proximal tubules. Administration of hhep25 simultaneously or 4h after Hb injection in wildtype mice significantly attenuated the Hb-induced rise in urinary NGAL and KIM1 levels, and renal IL6 and NGAL mRNA expression. Interestingly, simultaneous administration of Hb and hhep25, but not Hb or hhep25 alone, resulted in an increase in renal Hamp1 mRNA expression (15 fold, $p < 0.05$). Administration of hhep25 to Hb-treated mice reduced renal mRNA expression of HO-1, DMT1, H-ferritin and L-ferritin (all $p < 0.05$), possibly reflecting the mechanisms by which hepcidin exerts its protective effects.

Conclusions: Systemic hepcidin is filtered to the urine, partly reabsorbed via megalin in the proximal tubules and degraded in the tubular lumen. Moreover, our data suggest that both systemically delivered hepcidin and locally produced hepcidin are involved in renal protection against heme-induced AKI.

TH-PO022

The Lungs in Mice with Acute Kidney Injury Have an Exuberant Inflammatory Response to Endotoxin Hyo-Wook Gil, Chris Altmann, Ana Andres-heraldo, Danielle Soranno, Sarah Faubel. *Internal Medicine Renal, Univ of Colorado, Denver, CO.*

Background: Sepsis occurs in 40% of patients after the diagnosis of acute kidney injury (AKI) that may be related to impaired immune function. We sought to determine immune function specifically in the lungs in mice with AKI.

Methods: AKI was induced by bilateral renal pedicle clamping. Lung immune function was assessed by intratracheal instillation of either endotoxin (LPS) or Pseudomonas bacteria to induce pneumonia.

Results: Intratracheal LPS was administered 4 hours or 7 days after Sham or AKI. 4 hours after intratracheal LPS, lung inflammation as judged by bronchoalveolar fluid TNF, lung myeloperoxidase (MPO) activity (a marker of lung neutrophils), and lung CXCL1 (a neutrophil chemokine) was greater after AKI+IT LPS versus Sham+IT LPS in both the 4 hour and 7 day group ($P < 0.05$ for all endpoints $n=4$). To determine the role of alveolar macrophages, alveolar macrophages were recovered by bronchoalveolar lavage 4 hours after Sham or AKI, placed in culture, and exposed to endotoxin. Media TNF- α was significantly higher in alveolar macrophages from AKI. Since the response to endotoxin was excessive, we tested the response to pneumonia. AKI or Sham was performed and pneumonia was induced at 2 different time points post procedure: 1) 5 minutes and 2) 7 days. 24 hours after induction of pneumonia, blood cultures were 0 colony forming units (CFU) in Sham and 61 CFU in AKI ($n=10$); notably, 0% of Sham were bacteremic ($n=0$ of 10) and 60% of AKI were bacteremic ($n=6$ of 10) in the 5 minute group; in the 7 day group, blood cultures were higher in AKI and were 31% positive in sham (4 out of 13), and 70% positive in AKI (7 out of 10). Inflammation (as judged by lung MPO activity) was greater in AKI + pneumonia versus Sham + pneumonia in both 5 min and 7 d groups. Lung cultures were similar in Sham and AKI in both time groups indicating similar infection fighting ability between Sham and AKI.

Conclusions: In mice with AKI, the lung immune response to bacteria or gram negative bacteria is characterized by an exuberant inflammatory response which leads to bacteremia during pneumonia.

Funding: Other NIH Support - NHLBI

TH-PO023

Inhibition of MEK/ERK by Trametinib Attenuates Sepsis-Induced Systemic Inflammation and Multi-Organ Injury in Mice Joshua Andrew Smith,¹ Philip R. Mayeux,² Rick G. Schnellmann.¹ ¹*Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC;* ²*Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Background: MEK/ERK signaling is an essential component of the innate immune response in sepsis. We previously demonstrated that a potent and specific inhibitor of MEK1/2, trametinib, prevents endotoxin-induced renal injury in mice. Our goal was to further assess the efficacy of trametinib in a more clinically relevant model of sepsis induced by cecal ligation and puncture (CLP) in mice.

Methods: Male C57BL/6 mice (40 weeks of age) were subjected to CLP, and trametinib (1 mg/kg, i.p.) was administered at 6 h post-CLP. Serum cytokine levels were determined using a Luminex-based multiplex assay. Standard assays were used to measure clinical markers of organ/cellular injury including serum creatinine (SCR), blood urea nitrogen (BUN), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LDH) in the serum. Renal microvascular perfusion was evaluated by intravital microscopy. Transcript levels of tubular injury markers and pro-inflammatory cytokines in the renal cortex were determined by qPCR.

Results: Delayed trametinib administration partially attenuated increases in circulating pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, GM-CSF) and development of hypothermia at 18 h post-CLP. In addition, MEK/ERK inhibition restored SCR to baseline levels and reduced other markers of organ/cellular injury (serum ALT, CK, LDH) in CLP animals. In the kidney, trametinib completely reversed the early deficits in peritubular capillary perfusion and decreased mRNA expression of tubular injury markers including KIM-1, NGAL, and HO-1. MEK/ERK blockade also attenuated CLP-mediated up-regulation of cytokines (TNF- α , IL-1 β , IL-6) in the renal cortex.

Conclusions: These data reveal that the MEK/ERK inhibitor trametinib attenuates systemic inflammation, AKI, and other organ injury in a clinically relevant model of sepsis, even with delayed administration. Since trametinib is FDA approved, this drug may represent a readily translatable approach to limit organ injury in sepsis.

Funding: Other NIH Support - NIGMS Support, Veterans Administration Support

TH-PO024

Chemokine Receptor 5 Blockade Modulates Inflammation and Immunity in Renal Ischemic Reperfusion Injury Kyung Don Yoo,¹ Hajeong Lee,¹ Ran-hui Cha,² Jung Pyo Lee,¹ Yon Su Kim,¹ Seung Hee Yang.³ ¹*Seoul National Univ College of Medicine;* ²*National Medical Center;* ³*Seoul National Univ Kidney Research Inst.*

Background: The CC chemokine receptor (CCR5) is an important regulator of macrophage trafficking in the kidney in response to inflammation and immunity. Therefore, we investigated a role of CCR5 in the pathogenesis of experimental ischemic reperfusion injury (IRI).

Methods: Bilateral renal artery pedicles clamping for 30 min followed by reperfusion was performed on B6 wild type and CCR5 KO mice. We performed adoptive transfer of LPS treated RAW cells following depletion of macrophage by liposome clodronate (LC) in mice.

Results: CCR5 KO mice showed less aggravated IRI in terms of the apoptosis of tubular epithelial cells and creatinine compare to B6 wild type. CCR5 deficiency decreased mRNA expressions of proinflammatory cytokines but increased mRNA expressions of Th2 cytokines. CXCR3 positivity in CD11b+ cells and iNOS were attenuated in CCR5 KO mice compared to that in B6 wild type mice. On the contrary, the CCR5 KO mice showed increased numbers of Arg1- or CD206-expressing macrophages. LC-treated wild type mice showed severe injury compared to CCR5 KO mice after transfer of M1 macrophage. Adoptive transfer of LPS-treated RAW cells, which constitutively express iNOS, reverses the functional protection against IRI only in wild-type, not CCR5 KO mice. When CCR5 was knocked out in macrophages, bone marrow-derived macrophages showed M2 macrophage activation. The migration of Bone marrow-derived macrophage from wild type mice toward primary tubular epithelial cell with rCCR5 was increased. Moreover, blockade of CCR5 inhibited migration of macrophages. Renal tissue of patients with delayed graft function frequently contained CCR5 cells, and the number of these cells tended to positively correlate with acute tubular necrosis severity.

Conclusions: These findings show that CCR5 deficiency favors M2 macrophages activation and provide a potential strategy for treating acute kidney injury through blocking CCR5.

TH-PO025

Early Activation of Inflammasome in Acute Kidney Injury After Renal Sympathetic Denervation in Pig Il Young Kim,¹ Min Jung Kim,¹ Joo Hui Kim,¹ Dong Won Lee,¹ Soo Bong Lee,¹ Su Min Park,² Jong Man Park,² Woo Jin Jung,² Harin Rhee,² Sang Heon Song,² Eun Young Seong,² Ihm Soo Kwak.² ¹*Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea;* ²*Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea.*

Background: Renal sympathetic denervation (RDN) is available and implemented as a strategy for the treatment of resistant hypertension. In the aspect of chronic safety, renal function, as assessed by serum creatinine, eGFR(MDRD), and cystatin C was reported to be unchanged from baseline at 6 months. We investigated whether RDN might cause subtle inflammation and subclinical damage in the early phase of acute kidney injury (AKI).

Methods: Female pigs were divided into 6 groups; normal control (group A), Sham-operated control (group B), contrast media control (group C), and renal sympathetic denervation groups subdivided into 3 groups according to the time of sacrifice; immediately (group D), 1 week later (group E), and 2 weeks later (group F) after RDN. We checked IL-1 α , 1 β , 18, 6, 10, TNF- α , cystatin C, caspase-1, ASC, and NLRP3 as early biomarkers of inflammation and AKI.

Results: There were no significant changes in group B and C compared to group A. Hb, BUN, serum Na, K, Cl, CRP, urine protein/creatinine ratio, and urine albumin/creatinine ratio showed no significant changes between groups. Serum creatinine and cystatin C were increased from 1st week after RDN. Serum LDH was increased immediately after RDN, and then decreased at 2nd week. IL-1 α , -1 β and -18 were increased immediately after RDN, and showed a tendency to be decreased at 2nd week after RDN. IL-6 was increased immediately after RDN, and also increased in contrast media control group. TNF- α was increased from 1st week after RDN. IL-10 was increased immediately after RDN, and decreased at 2nd week. Caspase-1 and ASC expression were increased from 1st week, and decreased at 2nd week after RDN. However NLRP3 expression showed no significant changes between groups.

Conclusions: RDN did not cause clinically significant damages on kidneys. However, RDN can induce the activation of pro-inflammatory cytokines, caspase-1 and then cause transient and self-limited acute kidney injury.

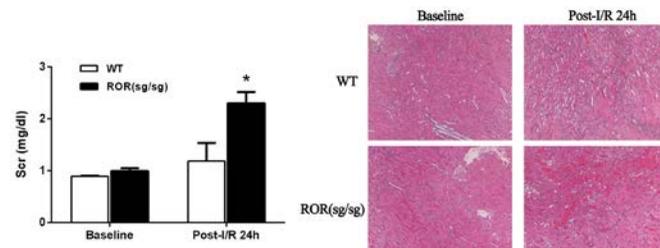
TH-PO026

The Orphan Nuclear Receptor ROR Alpha Exerts a Protective Potential in Acute Kidney Injury via Transcriptional Activation of HIF-1 Jieru Cai,¹ Rende Xu,² Xiaofang Yu,¹ Xiaoqiang Ding.¹ ¹*Dept of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China;* ²*Dept of Cardiology, Zhongshan Hospital, Fudan Univ, Shanghai, China.*

Background: Emerging evidence indicates that retinoid-related orphan receptor alpha (ROR α), a member of the ROR subfamily of nuclear receptors, mediates key cellular adaptations to hypoxia and contribute to pathophysiology of many disease states. However, the potential renal functions of ROR α in response to ischemia/reperfusion (I/R) injury remain unclear. Here, we investigated the renal expression and biological function of ROR α in acute kidney injury (AKI).

Methods: I/R injury was induced by 35min bilateral clamping of the renal pedicle and 24h reperfusion in wild-type and staggerer (ROR α (sg/sg)) mice, a natural mutant strain lacking ROR α expression. Renal injury and ROR α abundance were analyzed. In addition, human proximal tubular cell line (HK-2) was used to investigate the expression of ROR α under hypoxia.

Results: ROR α was detected in both mouse renal endothelial and tubular epithelial cells. Significant up-regulation of ROR α was found after renal I/R injury. Compared with wild-type, ROR α (sg/sg) mice displayed significantly increased levels of serum creatinine (2.30 \pm 0.21 vs. 1.18 \pm 0.35mg/dl, p<0.01), renal tissue damage, and pro-inflammatory cytokine production after ischemic kidney injury.



Further mechanistic studies indicated that ROR α agonists enhanced transcriptional activity of hypoxia-inducible factor 1 α (HIF-1 α) in HK-2 cells, which was abolished by siRNA-mediated silencing of endogenous ROR α .

Conclusions: These results suggest that ROR α protects kidney from I/R damage through transcriptional activation of HIF-1 and represents a potential therapeutic target for AKI.

Funding: Government Support - Non-U.S.

TH-PO027

Immunosuppressive Double Negative $\alpha\beta$ T Cells Protect Mice from Ischemic Acute Kidney Injury Maria Noel Martina,¹ Sanjeev Noel,² Ankit Saxena,¹ Richa S. Majithia,¹ Samatha Bandapalle,² Abdel Hamad,¹ Hamid Rabb.² ¹*Dept of Pathology;* ²*Dept of Medicine, Johns Hopkins Univ, Baltimore, MD.*

Background: TCR $\alpha\beta$ +CD4-CD8- double negative (DN) T cells are one of the least understood T cells, partly due to their rarity. We recently found them at high frequency in both murine and human kidney and demonstrated that they secrete large amounts of the anti-inflammatory cytokine IL-10. We tested the hypothesis that DNT cells are immunosuppressive in a mouse model of ischemic AKI and *in vitro*.

Methods: Immunosuppressive functions of kidney DNT cell were assessed by their ability to inhibit CD4 T cell proliferation using a standard T cell suppression assay. DNT cells isolated from the periphery of FasL-deficient *gld* mice (which accumulate large numbers of DN T cells in lymph nodes) were adoptively transferred in to wild type (WT) mice in the presence or absence of anti-IL-10 antibody and assessed their ability to

modulated ischemic AKI. Serum creatinine (SCr) was measured to assess kidney function and histology was studied. DNT cells from human peripheral blood was studied to lay the foundation for translational studies.

Results: Murine kidney DNT cell significantly ($p < 0.001$) inhibited proliferation of CD4 T cells *in vitro*, using CD4⁺CD25⁻ T cells as controls. Transfer of DNT cells significantly ($p < 0.01$) improved kidney function in WT mice ($SCr = 0.5 \pm 0.1$) following IR-induced AKI compared to WT mice that either received no cells ($SCr = 1.3 \pm 0.4$) or conventional T cells ($SCr = 1.4 \pm 0.4$). Histological evaluation showed significantly reduced tubular necrosis ($p = 0.03$) in mice that received DNT cells. This protection was lost in mice that received DNT cells with anti-IL-10 Ab ($p < 0.01$). DNT cells were found in normal subjects ($n = 3$) ($n = 3, 1.6 \pm 0.4\%$) and higher in renal cell carcinoma patients ($n = 3, 3.5 \pm 0.1\%$, $p < 0.001$).

Conclusions: Kidney resident DNT cells suppress CD4 T cell proliferation *in vitro* and protect WT mice from IR-induced AKI via IL-10. Furthermore, DNT cells are found in human peripheral blood and increase with kidney cancer. Future studies are warranted to better understand immunosuppressive properties of DNT cells and their clinical significance in AKI and other kidney diseases.

Funding: NIDDK Support

TH-PO028

Interleukin-37 Diminishes the Inflammatory Response of Ischemia/Reperfusion-Susceptible Renal Tubular Epithelial Cells Luuk Hilbrands,¹ Wilco P. Pulskens,¹ Sandrine Florquin,² Leo Ab Joosten,³ Janin A. Blubitz,¹ Johan Van der Vlag.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Pathology, Academic Medical Center, Amsterdam, Netherlands; ³Internal Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Renal ischemia and subsequent reperfusion (IR) induces excessive local inflammation that results in tubular injury and renal dysfunction. Therapeutic strategies aiming to dampen inflammation might therefore provide new opportunities to diminish renal IR injury. The human cytokine Interleukin (IL)-37 inhibits inflammation via nuclear as well as cell-surface receptors. IL37 is expressed by different cell types, including renal epithelium and circulating monocytes. Cell type-specific effects of IL37 in renal IR remain however unknown.

Methods: Primary tubular epithelial cells (PTECs) and bone marrow-derived macrophages (BMDMs) were isolated from WT and transgenic mice expressing human IL37 (hIL37tg) and cultured. *In vitro*, cells were pretreated with different concentrations of recombinant human IL37 protein (rhIL37) or vehicle and subsequently stimulated with LPS for 4 or 24hrs. Cytokine release (ELISA) and mRNA expression (quantitative RT-PCR) were determined.

Results: After 24hrs of LPS stimulation, the release of both CXCL1 and IL6 was reduced in hIL37tg PTECs as compared to WT PTECs. This was preceded by diminished CXCL1 and IL6 mRNA levels after 4hrs of LPS stimulation. rhIL37 pretreatment of WT PTECs reduced CXCL1 mRNA, but not IL6 mRNA expression after 4hrs. In hIL37tg BMDMs CXCL1 mRNA levels and protein release were both reduced after 4 and 24hrs of LPS stimulation, as compared to WT BMDMs. IL6 release was only diminished after 24hrs, whereas IL6 mRNA levels did not significantly differ. In contrast, rhIL37 pretreatment of WT BMDMs reduced IL6 mRNA expression after 24hrs of LPS stimulation, but neither affected CXCL1 nor IL6 release.

Conclusions: Our data indicate that both endogenous and exogenous IL37 diminishes inflammatory responses of renal epithelial cells and macrophages, both central players in the pathophysiology of renal IR injury.

TH-PO029

Compensatory Induction of IL-17 Producing NKT Cells in Post Ischemic T Cell Deficient Rats Fed High Salt Diet Purvi Mehrotra, Carlie M. Ivancic, Jason Andrieu Collett, Seth D. McKinney, David P. Basile. *Dept of Cellular and Integrative Physiology, Indiana Univ of Medicine, Indianapolis, IN.*

Background: Surviving AKI patients have a higher risk for developing chronic kidney disease (CKD) but the mechanism of AKI to CKD transition is unclear. Previous studies have shown inhibition of T-cell activity by mycophenolate blocked the proteinuria, fibrosis and hypertension in post ischemic rats fed a high dietary salt and that Th17 helper cells are dramatically increased in post ischemic rats on high salt diet. Therefore, we hypothesized that T-cell deficient athymic rats would manifest an attenuated salt sensitive progression of CKD following AKI.

Methods: Athymic rats (Foxn1^{tm-1m}) or heterozygote control euthymic rats (Foxn1^{tm+/+}) were subjected to a model of AKI-to-CKD in which rats are allowed to recover from unilateral I/R (40 min ischemia) for 5 weeks on standard salt diet (0.4% NaCl) and then subjected to contralateral UNX and 4% NaCl diet for 4 additional weeks.

Results: As expected we observed that MMF treatment in control-euthymic rats (day 35-63) lead to significant reduction in renal CD4⁺ infiltration (35%±4.8, $p < 0.05$). Th-17 cells (78%±5.2, $p < 0.05$) and reduced fibrosis by 50% vs vehicle. T cell deficient athymic rats showed an unexpected and similar level of renal fibrosis as compared to euthymic rats and MMF treatment did not have any effect. The increased fibrosis could not be explained by enhanced initial injury in athymic vs euthymic rats, which was similar 24 hours following bilateral I/R, indicating that athymic rats may operate an alternative pro-inflammatory pathway in the absence of T cells. Interestingly, athymic rats showed an increase population of IL-17⁺ Natural Killer T cells (NKT) (126018±7507) as compared to euthymic rats (63892±12656), which was not sensitive to MMF treatment.

Conclusions: Taken together these data suggest that in the absence of T cells, compensatory NKT cell activity may mediate cytokine production and participate in salt diet induced fibrosis post AKI.

Funding: NIDDK Support

TH-PO030

Chronic Kidney Disease and the Chromogranin A Pathway: From Pathogenic Molecule to Disease Sucheta M. Vaingankar, Saiful A. Mir, Wai W. Cheung, Kuixing Zhang. *Medicine, Univ of California at San Diego.*

Background: The human chromogranin A gene (*CHGA*) variants are associated with autonomic blood pressure regulation and hypertension in the majority population, as well as hypertensive renal disease in African Americans. CHGA proprotein is the master switch for nucleation of catecholamine granules in neuroendocrine tissue. In this study we address the effect of CHGA in acute kidney injury.

Methods: Experimental chronic kidney disease (5/6th nephrectomized) mouse models were used to study susceptibility of mouse strains (wild type and *Chga*^{-/-}) to kidney injury. Kidney tissues of sham and nephrectomized mice were examined by histology and also profiled for genome-wide expression using NimbleGen microarray. The murine glomerular function was measured by LC-mass spectrometry based assay for creatinine. Array data was analyzed for differentially expressed genes using Bioconductor. The differentially regulated genes were analyzed by GO enrichment analysis using DAVID Bioinformatics Resources. The molecular function and biological process terminologies in the PANTHER database were considered during the GO analysis; the P-value cutoff was set at 0.01. The human study involved twin data set of European ancestry 129 monozygotic and 58 dizygotic twin pairs.

Results: A significantly greater loss of eGFR function was observed in nephrectomized mice expressing CHGA as compared to *Chga* knock out mice. Kidney injury resulted in far greater response of increased plasma CHGA, azotemia, catecholamine and systolic blood pressure in *Chga*^{+/+} mice. Kidney biopsy also showed greater pathology and interstitial fibrosis associated with nephrectomized *Chga*^{+/+} mice. In nephrectomized mice, the differentially up regulated genes in the *Chga*^{+/+} strain include panoply of mitochondrial genes, oxidoreductases and extracellular matrix proteins, wound healing genes and transcription factors. In humans the plasma CHGA concentration has an inverse relationship to plasma creatinine levels.

Conclusions: CHGA expression is inversely correlated to glomerular function and is detrimental to kidney injury outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO031

Inhibition of $\alpha v \beta 5$ Integrin Protects against Renal Ischemia-Reperfusion Injury Amy T. Mccurley,¹ Robert W. Dunstan,¹ Taylor L. Reynolds,¹ Silvia B. Campos-bilderback,² Ruben M. Sandoval,² Bruce A. Molitoris,² Shelia Violette,¹ Michael Crackower.¹ ¹Biogen, Cambridge, MA; ²Div of Nephrology, Indiana Univ School of Medicine, Indianapolis, IN.

Background: Ischemia-reperfusion injury is a leading cause of acute kidney injury (AKI), which is a common clinical complication that lacks effective therapies and can lead to the development and progression of chronic kidney disease. The $\alpha v \beta 5$ integrin, a receptor for RGD-containing extracellular matrix proteins, has been suggested to be important in acute injury settings including septic shock and acute lung injury. To examine the *in vivo* function of this receptor in AKI we tested the impact of inhibiting $\alpha v \beta 5$ in a rat model of renal ischemia reperfusion injury (IRI).

Methods: IRI was induced by removing the right kidney and clamping the renal artery of the left kidney for 30 minutes. Rats were administered $\alpha v \beta 5$ -blocking antibody or an isotype control antibody subcutaneously at various doses and times prior to ischemia.

Results: $\alpha v \beta 5$ antibody-treatment significantly reduced serum creatinine levels with a single administration 6 hours prior to ischemia. $\alpha v \beta 5$ inhibition led to significantly reduced renal damage by 3 days after ischemia as assessed by histopathological scoring of fixed kidneys. Antibody blockade of $\alpha v \beta 5$ also resulted in significantly fewer apoptotic tubular cells, and significant reductions in urinary KIM-1 and serum MCP-1 levels in IRI rats. Global gene expression profiling of kidneys identified several established injury markers that were impacted by $\alpha v \beta 5$ inhibition including reduced levels of *haver1* (KIM-1), *lcn2* (NGAL), and *adamts1* transcripts after ischemia. Finally, a single dose of $\alpha v \beta 5$ antibody 8 hours post-ischemia was shown to significantly reduce serum creatinine levels at 24 hours, suggesting protection from injury with therapeutic dosing is possible.

Conclusions: This study identifies a novel role for $\alpha v \beta 5$ integrin biology in the pathogenesis of renal ischemia-reperfusion injury. Inhibition of $\alpha v \beta 5$ integrin with antibody administration may hold therapeutic promise for the treatment of acute kidney injury.

Funding: Pharmaceutical Company Support - Biogen

TH-PO032

Blocking $\alpha v \beta 6$ Integrin Provides Protection in Renal Ischemia-Reperfusion Injury Shelia Violette,¹ Amy T. Mccurley,¹ Paul H. Weinreb,¹ Silvia B. Campos-bilderback,² Ruben M. Sandoval,² Bradley J. Maroni,¹ Michael Crackower,¹ Bruce A. Molitoris.² ¹Biogen, Cambridge, MA; ²Indiana Univ School of Medicine, Indianapolis, IN.

Background: The $\alpha v \beta 6$ integrin is a key mediator of TGF- β activation and plays an important role in promoting tissue injury and fibrosis. $\alpha v \beta 6$ is expressed at low levels in normal tissue and upregulated on epithelial cells in disease, providing a target for localized suppression of TGF- β . Function-blocking $\alpha v \beta 6$ antibodies are protective in models of kidney, lung, and liver fibrosis and a humanized $\alpha v \beta 6$ antibody (BG00011) is in clinical development in patients with idiopathic pulmonary fibrosis. We evaluated the role of $\alpha v \beta 6$ in renal ischemia reperfusion injury (IRI), a model in which $\alpha v \beta 6$ is upregulated in tubular epithelium.

Methods: IRI was induced in rats by removing the right kidney and clamping the renal artery of the left kidney for 30 minutes. A single 3 mg/kg dose of $\alpha v \beta 6$ antibody (3G9)

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Underline represents presenting author.

or an isotype control was administered 6, 12 or 18 hours pre-ischemia or 4, 8 or 12 hours post-ischemia. Serum creatinine (Scr) was evaluated 24, 48 and 72 hours post-injury and gene expression and histology in kidneys evaluated at 72 hours.

Results: 3G9 treatment significantly reduced Scr levels at all time points evaluated whether administered pre- or post-induction of ischemia. Equivalent effects were detected when 3G9 was administered 6, 12 or 18 hours pre-ischemia and maximal effects observed when administered 4 to 8 hours post-ischemia. 3G9 reduced kidney damage as assessed by histopathological scoring of tubular necrosis, dilation and casts. Gene expression profiling of kidneys identified transcripts impacted by α v β 6 inhibition suggesting promotion of repair. This included reduced levels of cell death and necrosis markers such as GADD45, ATF3, and RIPK3, and an upregulated cell growth signature including cyclins, cyclin-dependent kinases, and epidermal growth factor.

Conclusions: The combined role of α v β 6 in regulating IRI and fibrosis highlight the potential for therapeutic intervention with BG00011 in acute kidney injury, a common clinical complication that lacks effective therapies and can lead to the development and progression of chronic kidney disease.

Funding: Pharmaceutical Company Support - Biogen Idec

TH-PO033

Suramin Protects from Cisplatin-Induced Acute Kidney Injury Tess Dupre,¹ Mark A. Doll,¹ Parag P. Shah,¹ Michael T. Scherzer,¹ Cierra Sharp,¹ Judit Megyesi,⁴ Lavona Casson,¹ Levi J. Beverly,¹ Rick G. Schnellmann,³ Leah J. Siskind.¹ ¹Pharmacology/Toxicology, Univ of Louisville, Louisville, KY; ²Univ of Arkansas for Medical Sciences; ³Medical Univ of South Carolina.

Background: Acute kidney injury (AKI) resulting from cisplatin administration remains an obstacle in chemotherapeutic treatments. Suramin, an FDA approved drug for the treatment of trypanosomiasis, has been previously shown to speed recovery from multiple models of AKI and chronic kidney disease and is currently in clinical trials for combination therapy with cisplatin for the treatment of lung cancer.

Methods: In this study we examined the efficacy of the prophylactic use of suramin in a murine model of cisplatin-induced AKI. Nine-week old C57Bl/6 male mice were pre-treated with 10mg/kg suramin via tail vein injection 72h prior to cisplatin administration (20mg/kg, i.p) and sacrificed 72h after cisplatin treatment.

Results: Our data indicate that pre-treatment with suramin protects the kidney from cisplatin injury according to markers of kidney function (BUN, Serum Creatinine), kidney injury (urinary Kim-1, and NGAL). Assessment of renal histology also indicated that suramin pre-treatment significantly protects mice from cisplatin-induced injury. The expression of many pro-inflammatory chemokines and cytokines (TNF- α , IL-1 β , IL-6, MCP-1, and CXCL-1) involved in the response of cisplatin-induced AKI were examined via qRT-PCR. Mice pretreated with suramin had significantly reduced expression of all the above inflammatory markers. Western blot analysis indicated that mice pre-treated with suramin were protected from death receptor-mediated apoptosis. We also utilized the same experimental design using 10-month old FVB mice expressing mutant KRAS driven lung tumors. The assessment of both renal and pulmonary histology and markers of kidney function (BUN and Serum Creatinine) indicate that suramin protects mice from cisplatin-induced kidney injury and more importantly does not inhibit cisplatin's anti-tumor efficacy.

Conclusions: Thus, data presented suggest that suramin shows great potential as a renoprotective agent for the treatment and prevention of cisplatin-induced AKI.

Funding: NIDDK Support

TH-PO034

ATIII Attenuates Acute Kidney Injury following Acute Severe Pancreatitis Feng Wang,¹ Zeyuan Lu,¹ Guangyuan Zhang,¹ Jianyong Yin,¹ Niansong Wang,¹ Mingyu Liang.² ¹Nephrology, Shanghai Jiao Tong Univ Affiliated People's Hospital, Shanghai, China; ²Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: Antithrombin III (ATIII) is the major anti-coagulation molecule in vivo and has anti-inflammatory effects. Acute kidney injury (AKI) is the most common organ failure following acute severe pancreatitis (ASP), which often results in death. Herein, we hypothesized that ATIII could protect against AKI following ASP.

Methods: Acute severe pancreatitis was induced in rats by retrograde pancreatic duct infusion of 3.5% sodium taurocholate. Intravenous injection of ATIII (500mg/kg) was carried out 30 min before induction of ASP. Animals were sacrificed 24 hours later. Renal tubular injury and renal function were assessed. Serum amylase, glutamic-pyruvic transaminase (ALT), and serum Ca²⁺ were also measured.

Results: Renal tubular injury scores were increased from 0.5 \pm 0.2 in control rats to 4.2 \pm 0.5 in the ASP group and to 2.7 \pm 0.3 in the ASP+ATIII group 24 hours after ASP induction (P<0.05, one-way ANOVA, n=6). Serum creatinine was increased from 23.2 \pm 1.6 mmol/L to 92.3 \pm 8.6 mmol/L in the ASP group and to 34.8 \pm 3.2 mmol/L in the ASP+ATIII group (P<0.05, n=6). Blood urea nitrogen was increased from 5.2 \pm 0.3 mmol/L to 47.0 \pm 1.3 mmol/L in the ASP group and to 30.0 \pm 1.9 mmol/L in the ASP+ATIII group (P<0.05, n=6). There were no significant differences between ASP group and ASP+ATIII group in serum amylase, ALT, serum Ca²⁺ and pancreatic injury.

Conclusions: ATIII attenuates AKI following ASP.

Funding: Government Support - Non-U.S.

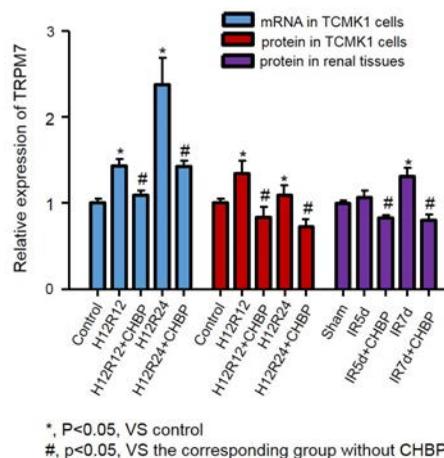
TH-PO035

TRPM7 in Renal Ischemia Reperfusion Injury and Renoprotection of Erythropoietin Derived Cyclic Helix B Peptide Aifen Liu,¹ Jing Wu,² Cheng Yang,³ Yuanyuan Wu,⁴ Yufang Zhang,¹ Yaqiu Long,⁵ Tongyu Zhu,³ Yaping Fan,² Bin Yang.^{1,2,6} ¹Basic Medical Research Centre, Medical School of Nantong Univ; ²Nephrology, Affiliated Hospital of Nantong Univ; ³Urology, Zhongshan Hospital, Fudan Univ; ⁴Pathology, Medical School of Nantong Univ; ⁵CAS Key Laboratory of Receptor Research, Shanghai Inst of Materia Medica, Chinese Academy of Sciences; ⁶Infection, Immunity and Inflammation, Univ of Leicester, Univ Hospitals of Leicester.

Background: Transient receptor potential melastatin 7 (TRPM7) is multi-function ion channel and kinase. The novel cyclic helix B peptide (CHBP), erythropoietin derivative, improves renal ischemia reperfusion injury (IRI). Here, the role and mechanism of TRPM7 in IRI and CHBP renoprotection were investigated.

Methods: TRPM7 mRNA and protein, apoptosis, inflammation, renal function and structure were measured in TCMK1 cells and mouse kidneys subjected to 12-h hypoxia (H)/30-min ischemia followed by reoxygenation (R) at different time points. 2-APB (TRPM7 inhibitor) and CHBP were also applied in HR cells and/or IRI kidneys. The correlations between TRPM7 and other injury parameters were analysed.

Results: TRPM7 mRNA and protein were increased in the TCMK1 cells exposed to 12 and 24-h IR, while TRPM7 protein was also increased by 42%, 35% and 30% in IRI kidneys at 12 and 24 h, and 7 d. Increased apoptotic cells were reduced 65% by 2-APB in TCMK1 cells post HR, while LDH in supernatant and HMGB1 in TCMK1 cells were also increased. Further more, CHBP reduced TRPM7 in HR TCMK1 cells, as well as IRI kidneys.



TRPM7 was significantly correlated with LDH and HMGB1; and serum creatinine, blood urea nitrogen, inflammation, apoptosis and tubulointerstitial damage in these *in vitro* and/or *in vivo* models.

Conclusions: TRPM7 is involved in renal IR-related injuries and CHBP renoprotection, which might be a biomarker for diagnosis and intervention.

Funding: Government Support - Non-U.S.

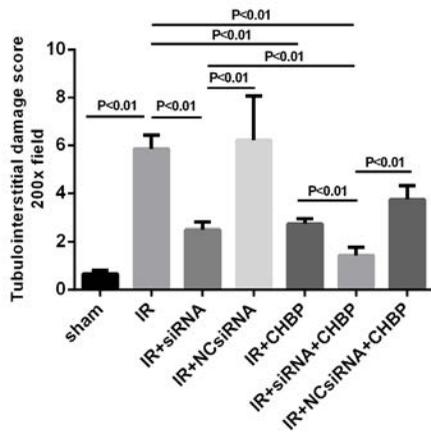
TH-PO036

Caspase-3 siRNA and CHBP Ameliorate Renal Ischemia Reperfusion Injury in Mice Weiwei Chen,¹ Cheng Yang,⁴ Yuanyuan Wu,³ Yufang Zhang,² Aifen Liu,² Jing Wu,¹ Yaqiu Long,⁵ Tongyu Zhu,⁴ Yaping Fan,¹ Bin Yang.^{1,2,6} ¹Nephrology, Affiliated Hospital of Nantong Univ; ²Basic Medical Research Centre, Medical School of Nantong Univ; ³Pathology, Medical School of Nantong Univ; ⁴Urology, Zhongshan Hospital of Fudan Univ; ⁵CAS Key Lab of Receptor Research, Shanghai Inst of Materia Medica, Chinese Academy of Sciences; ⁶Infection, Immunity and Inflammation, Univ of Leicester, Univ Hospitals of Leicester.

Background: Ischemia/reperfusion (IR) is a main cause of acute kidney injury (AKI). Up-regulated caspase-3, a key enzyme involved in inflammation and apoptosis, was revealed in renal IR injury and reversed by a novel cyclic helix B peptide (CHBP), derived from erythropoietin. Here, caspase-3 small interfering RNA (C3siRNA) and/or CHBP were applied in a mouse model to further explore underlying mechanisms.

Methods: Bilateral renal occlusion for 30 min was performed in male C57BL/6 mice and followed by 48 h reperfusion. 0.03 mg/kg C3siRNA or its negative control (NC) was injected intravenously 2 h before ischemia. 24 nmol/kg CHBP was injected intraperitoneally post reperfusion. Serum and kidney samples were collected for renal function, histology and molecular biology analyses.

Results: Serum creatinine and tubulointerstitial damage (TID) score were increased by IR injury, but decreased by C3siRNA and/or CHBP (all P<0.01). In addition, the expression of 17 kD active caspase-3, active caspase-3+ cells and apoptotic cells were raised by IR injury, but reduced by C3siRNA and/or CHBP (P<0.01). More interestingly, there was a significant reduction in TID in the kidneys treated with both C3siRNA and CHBP compared with its sole treatment.



Conclusions: C3siRNA and CHBP ameliorated IR injury, both of which might have certain synergetic effects. CHBP might reduce active caspase-3, subsequently affect apoptosis, and improve renal function and structure.

Funding: Government Support - Non-U.S.

TH-PO037

Resveratrol Ameliorates Contrast-Induced Nephropathy Through Activation of SIRT1-PGC-1 α -FoxO1 Signaling in Murine Model Gang Jee Ko,¹ Yu ah Hong,² So yeon Bae,¹ Heui-jung Pyo,¹ Young-Joo Kwon.¹ ¹Div of Nephrology, Dept of Internal Medicine, Korea Univ School of Medicine, Seoul, Republic of Korea; ²Div of Nephrology, Dept of Internal Medicine, Catholic Univ College of Medicine, Daejeon St. Mary's Hospital, Daejeon, Republic of Korea.

Background: Contrast-induced nephropathy (CIN) is a common cause of acute kidney injury among impatient, but the pathogenesis has not been clearly defined. We aimed to investigate whether upregulation of situin 1 (SIRT1)-dependent signaling by resveratrol could attenuate CIN through modulation of renal oxidative stress and tubular apoptosis.

Methods: CIN were established in vivo and vitro model by administration of iohexol in male C57BL/6J mice and rat tubular cells (NRK-52E). Resveratrol (30mg/kg in vivo/10 and 50 μ M in vitro) was treated with iohexol or saline as an activator of SIRT1. SIRT1 expression was reduced by siRNA treatment in vitro study. Tubular cell injury caused by iohexol was examined.

Results: Increase of serum creatinine and tubular injury measured by histologic examinations after iohexol administration was significantly attenuated by resveratrol treatment (creatinine 1.79 \pm 0.48 vs 0.72 \pm 0.59 mg/dL, p<0.001). It resulted in reduction of oxidative stress which were demonstrated by reduced malondialdehyde (MDA) levels and increased Mn superoxide dismutase (SOD). Increased apoptosis in CIN was also reduced by resveratrol treatment examined with caspase 3 expression and TUNEL staining. Attenuation of CIN with resveratrol treatment was accompanied with the increase of SIRT1 expression, activation of PPAR γ co-activator 1 α (PGC-1 α) and dephosphorylation of forkhead box O (FoxO1). Resveratrol treatment also reduced inflammatory cell infiltration induced by iohexol into kidney. On the other hand, SIRT1 inhibition by siRNA treatment accentuated cytotoxicity by iohexol.

Conclusions: Our results suggest that resveratrol attenuates CIN by modulation of renal oxidative stress and apoptosis through the activation of SIRT1-PGC-1 α -FoxO1 signaling, and SIRT1 provides a potential therapeutic target to minimize CIN.

TH-PO038

Loss of Alpha(E)-Catenin-Fscn2 Signaling Increases Cisplatin-Induced Apoptosis in Aged Kidney Xinhui Wang, LaNita A. Nichols, Elizabeth A. Borgmann, Alan R. Parrish. Medical Pharmacology and Physiology, Univ of Missouri School of Medicine, Columbia, MO.

Background: Aging patients are highly susceptible to acute kidney injury. Previous studies in our laboratory demonstrated a dramatic decrease of α (E)-catenin expression in proximal tubular epithelium in the aged kidney.

Methods: We created stable α (E)-catenin knock-down NRK-52E (C2) cells (NT3 is the non-targeted control) and observed a significant loss of viability in C2 cells as compared with NT3 cells after cisplatin challenge. In this study, we aimed to delineate the pathway by which loss of α (E)-catenin increases cisplatin injury.

Results: Increased caspase-8 and -9 activation, BID cleavage and cytochrome C release were observed in C2 cells after cisplatin treatment. Blocking apoptosis, using caspase-8 or -9 inhibitors, completely abolishes the increased susceptibility of C2 cells. Interestingly, the expression of fascin actin bundling protein 2 (Fscn2) is decreased in α (E)-catenin knock-down cells. Re-expression of Fscn2 in C2 cells attenuates the increased apoptosis following cisplatin challenge. Furthermore, our *in vivo* study showed a significant increase in serum creatinine, KIM-1 and in situ apoptosis levels at 72 hr after a single dose of cisplatin in 24-month-old rats, but not in 4-month-old rats. The expression of Fscn2 was also decreased in aged kidney.

Conclusions: Taken together, these results suggest that loss of α (E)-catenin-Fscn2 signaling increases cisplatin-induced apoptosis in aged kidney.

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TH-PO039

Adenosine A1 Receptors Alleviate Cisplatin-Mediated Acute Kidney Injury Yuan Liu, Dongli Tian, Xuemei Li, Limeng Chen. Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China.

Background: We have observed the incidence of acute kidney injury (AKI) in 479 lung cancer patients using platinum is 10.39% and AKI is the independent risk factor of in-hospital mortality. The results of previous studies about adenosine A1 receptors (A1ARs) in cisplatin-mediated AKI are controversial. In this study, we aimed to investigate the role of A1ARs in AKI induced by cisplatin and the involvement of mitochondria-mediated cell apoptosis.

Methods: 8- to 10-week-old male C57BL/6J wild type (WT) and A1AR^{-/-} mice were given a single intraperitoneal injection of either vehicle (saline) or cisplatin (25mg/kg, 1mg/ml). Weight, blood pressure and heart rate were monitored. Mice were euthanized 24h/72h after cisplatin. Blood samples were collected to measure serum creatinine and urea. Acute tubular necrosis assessments were done through PAS staining. Western Blot and RT-PCR were used to study the expression change of CD73, A1AR and mitochondria-mediated apoptosis markers.

Results: 1) 72h after cisplatin injection, serum creatinine and urea were substantially elevated (85.9 \pm 65.59 vs 8.5 \pm 1.16mmol/L, 63.3 \pm 33.84 vs 6.7 \pm 1.24mmol/L, p<0.05) in WT mice which suggested AKI happened. The systolic blood pressure, heart rate and body weight remarkably declined (64 \pm 4 mmHg vs 105 \pm 2 mmHg, 412 \pm 16 bpm vs 721 \pm 48 bpm, p<0.05) compared with control mice. 2) 24h after cisplatin, the expression of A1AR in WT mice was significantly higher than control mice. Cisplatin also induced the expression of A2bAR and Bax, targets of mitochondria-mediated apoptosis. 3) Compared with WT mice, serum creatinine elevation and tubular injury were more obvious in A1AR^{-/-} mice (25.8 \pm 19.28 vs 11.4 \pm 0.43mmol/L, p<0.05). But contrast to WT mice, A2bAR and Bax expression were not elevated in A1AR^{-/-} mice. The expression of CD73 was up-regulated significantly.

Conclusions: A1AR may be involved in cisplatin-mediated AKI and could alleviate the cisplatin nephrotoxicity. But it doesn't work through mitochondria-mediated apoptosis pathway. A1AR agonists are potential to protect the kidney in cisplatin-mediated AKI.

Funding: Government Support - Non-U.S.

TH-PO040

Testosterone Upregulates Heme-Oxygenase-1 – A Potential Mechanism to Protect against Acute Kidney Injury Andrea P. Soljancic, Arnaldo F. Lopez-Ruiz, Kiran B. Chandrashekar, Luis A. Juncos. Medicine-Nephrology, Univ of Mississippi Medical Center, Jackson, MS.

Background: Sex hormones modulate renal injury during ischemia-reperfusion-induced acute kidney injury (I/R-AKI). We reported that testosterone is reduced during I/R-AKI and that supplementing this hormone ameliorates the renal injury. This protective effect is dependent on the chronicity of therapy and dose (chronic exposure and high doses may exacerbate injury). In this study, we investigated a possible mechanism by which acute administration of low-dose testosterone propionate (A-LD-TP) can protect against I/R-AKI. Because we found that A-LD-TP increased hypoxia inducible factor-1 α (HIF-1 α), which in turn induces heme oxygenase-1 (HO-1), we hypothesized that the protective effect of A-LD-TP during I/R-AKI is mediated by HIF-1 α dependent upregulation of HO-1.

Methods: SD rats were randomized into 4 groups; 1) Sham, 2) I/R-AKI, 3) I/R-AKI+TP, 4) I/R-AKI+A-LD-TP+2-ME. I/R-AKI was induced by 40 min bilateral renal pedicle clamping. A-LD-TP was given 3 h after releasing the clamps, and a HIF-1 α antagonist, 2-Methoxyestradiol [2-ME] was given 1 day before inducing AKI. Rats were followed for 48hs. Blood, urine and tissue were collected to evaluate renal function, injury, and expression of pro-inflammatory cytokines and the HIF-1 α - HO-1 cascade.

Results:

	Creat(mg/dl)	KIM-1(pg/ml)	TNF α (pg/ml)	HIF-1 α (pg/ml)	HO-1 (ug/ml)
Sham	0.51 \pm 0.06	450 \pm 120	30 \pm 8	0.45 \pm 0.05	0.55 \pm 0.1
I/R-AKI	2.4 \pm 0.07*	4500 \pm 190*	190 \pm 15*	5.6 \pm 0.3*	5.8 \pm 0.3*
I/R-AKI+TP	1.4 \pm 0.08#	1700 \pm 200#	115 \pm 6#	10.6 \pm 0.8#	11.7 \pm 0.6#
I/R-AKI+TP+2-ME	2.2 \pm 0.1	4400 \pm 350	175 \pm 12	3.95 \pm 0.4	6.2 \pm 0.4

Conclusions: A-LD-TP supplementation ameliorated I/R-AKI-induced renal dysfunction, inflammation and tubular injury. These beneficial changes were associated with further upregulation of HO-1. Blocking HIF-1 α attenuates the cytoprotective effects conferred by A-LD-TP. This data supports the hypothesis that A-LD-TP supplementation activates the renal HIF-1 α pathway and its downstream cytoprotective factor (HO-1), which protects against I/R-AKI, thus providing a potential therapeutic target.

Funding: Private Foundation Support

TH-PO041

Endotoxin Preconditioning Induces an Effective Immune Response That Avoids Collateral Tissue Damage Takashi Hato, Pierre C. Dagher. *Medicine, Indiana Univ, Indianapolis, IN.*

Background: Endotoxin preconditioning is a powerful model of renoprotection against a variety of insults. Harnessing these protective pathways has important therapeutic potential in sepsis. However, the protective molecular pathways remain unknown. Here we examined the metabolic profiles of endotoxin preconditioning.

Methods: Mice were divided into 3 groups: control, endotoxin injury (LPS 5 mg/kg ip) and preconditioning (0.25 mg/kg followed by 5 mg/kg LPS). Renal injury was assessed by serum creatinine and tissue KIM1. Cecal ligation and puncture (CLP) was used to evaluate mortality and bacterial load. Tissues and sera were examined using cytokine assays, 2DIGE proteomics and metabolomics.

Results: Preconditioning improved survival after CLP (75% vs. 25% in non-preconditioned mice). This protection was accompanied by reduced bacterial load in solid organs including kidneys (320 vs. 1,200 cfu/gram tissue). Macrophages harvested from preconditioned mice exhibited robust phagocytic activity. Preconditioning also resulted in renal protection after toxic dose LPS (mean serum creatinine 0.08 mg/dL vs. 0.40 mg/dL in non-preconditioned mice; tissue KIM1 mRNA fold changes 110 vs. 2,960). 2DIGE proteomics analyses revealed upregulation of molecules required for the activation and maintenance of phagocytosis in the preconditioned group. These molecules include clusterin, serum amyloid P-component, neutrophil gelatinase-associated lipocalin, and complement factor B. Despite the activation of these efficient bacterial clearing pathways, serum and tissue proinflammatory cytokine levels were broadly downregulated in preconditioned animals. Tissue metabolomic analysis revealed that preconditioning increased metabolites involved in tissue repair (proline and spermidine), antimicrobial activity (itaconate) and antioxidant pathways (ergothioneine), while uremic toxin levels were reduced (p-cresol sulfate, 3-indoxil sulfate, pseudouridine).

Conclusions: Preconditioning confers tissue protection and increases survival through an organized upregulation of a modified innate immune response characterized by enhanced bacterial clearing and yet lacking the proinflammatory tissue damage frequently observed with ordinary innate immunity.

Funding: NIDDK Support

TH-PO042

Myeloid Cell Specific Nrf2 Activation Protects Elderly Mice from Acute Kidney Injury Sanjeev Noel,¹ Samatha Bandapalle,¹ Sekhar P. Reddy,² Hamid Rabb.¹ ¹Dept of Medicine, Johns Hopkins Univ, Baltimore, MD; ²Dept of Pediatrics, Univ of Illinois, Chicago, IL.

Background: Transcription factor Nrf2 confers protection against ischemia-reperfusion (IR)-induced acute kidney injury (AKI) in mice by upregulating antioxidant and cytoprotective genes, but the specific cell types where Nrf2 is working is unknown. We recently demonstrated that T cell Nrf2 activity is a major modulator of IR-induced AKI in mice with increased T cell Nrf2 (*J Am Soc Nephrol*, in press). In this study we tested the hypothesis that Nrf2 activation in myeloid cells (neutrophils, macrophages) is protective against IR-induced AKI. We tested our hypothesis in young and elderly mice with genetic deletion of Nrf2 inhibitor, keap1 in myeloid cells (Lysm keap1^{-/-}).

Methods: Young (7-8wks) and old (32-48wks) male Lysm keap1^{-/-} and keap1^{fl/fl} (control) mice underwent 30 minute bilateral kidney ischemia. Serum creatinine (Scr) was measured at 0, 24, 48 and 72h post ischemia. Histological and inflammatory changes in kidney were examined at 72h.

Results: We observed significantly reduced Scr levels in young (0.6±0.1 vs 1.3±0.2, p<0.02, 24h) and elderly (0.4±0.2 vs 1.3±0.3, p<0.02, 48h and 0.2±0.03 vs 0.9±0.2, p<0.02, 72h) Lysm keap1^{-/-} mice as compared to age matched keap1^{fl/fl} mice. Histological examination of corticomedullary region of kidney tissue revealed a significantly lower necrotic debris (24±8.7 vs 54±3.8, p<0.01), regeneration (22.1±7.0 vs 41.1±4.0, p=0.04) and higher percent of normal tissue (53.8±15.7 vs 5.0±0.6, p<0.01) in elderly Lysm keap1^{-/-} mice. Young Lysm keap1^{-/-} mice did not show any significant difference in kidney histology post AKI compared to young keap1^{fl/fl} mice. Cytokine analysis showed significantly (p<0.04) higher levels of TGF-β, IL-1β, IL-2, IL-6, IL-10, IL-13, IL-17 and TNF-α in elderly Lysm keap1^{-/-} kidneys. These cytokines were comparable in young Lysm keap1^{-/-} and keap1^{fl/fl} kidneys post AKI.

Conclusions: These data demonstrate that enhancing Nrf2 activity in myeloid cells can provide protection against IR-induced AKI, which is markedly enhanced in elderly mice. These findings reveal that myeloid cell oxidative stress responses are a mechanism by which elderly are more susceptible to AKI.

Funding: NIDDK Support

TH-PO043

Sphingosine-1-Phosphate-3 Deficient Dendritic Cells Modulate Splenic Responses to Ischemia-Reperfusion Injury Amandeep Bajwa,¹ Elvira Kurmaeva,¹ Liping Huang,¹ Joseph C. Gigliotti,¹ Hong Ye,¹ Diane L. Rosin,² Peter I. Lobo,¹ Mark D. Okusa.¹ ¹Medicine-CIIR, UVA, Charlottesville, VA; ²Pharmacology, UVA, Charlottesville, VA.

Background: The plasticity of dendritic cells (DCs) permits phenotypic modulation *ex-vivo* by gene expression or pharmacological agents, and these DCs can exert therapeutic immunosuppressive effects *in-vivo* through direct interactions with T-cells by either inducing T regulatory (Treg) cells or causing anergy. Sphingosine 1-phosphate (S1P), a sphingolipid that is the natural ligand for five G-protein coupled receptors (S1P1-5Rs), and S1PR agonists

reduced kidney ischemia-reperfusion injury (IRI) in mice. *S1pr3^{-/-}* mice are protected from kidney IRI due to the inability of dendritic cells to mature. We tested the therapeutic advantage of *S1pr3*-deficient bone marrow-derived DC (BMDC) transfers in kidney IRI.

Methods: Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old C57BL/6 WT and *S1pr3^{-/-}* male mice were used for generating highly pure BMDCs from whole BM precursors.

Results: IRI produced a rise in plasma creatinine (PCr) in naïve mice, no cell (NC) and in mice pretreated with WT BMDCs. However, *S1pr3^{-/-}* BMDC-pretreated mice were significantly protected from kidney IRI. *S1pr3^{-/-}* BMDC-pretreated mice had significantly higher numbers of splenic Tregs compared to NC and WT BMDC-pretreated mice. *S1pr3^{-/-}* BMDC-induced protection of the recipient kidney required an intact spleen, B/T cells, and CD11c⁺ DCs, as *S1pr3^{-/-}* BMDCs were ineffective in attenuating IRI in splenectomized, *Rag-1^{-/-}* or CD11c⁺ DC-depleted mice. Additionally, *S1pr3^{-/-}* BMDC dependent protection requires CD169⁺-marginal zone (MZ) macrophage dependent CCL22/macrophage-derived-chemokine (MDC) signaling to increase Treg.

Conclusions: We conclude that genetically induced deficiency or pharmacological blockade of *S1pr3* on allogenic BMDCs could serve as a useful therapeutic approach to prevent IRI-induced acute kidney injury or delayed graft function associated with transplant.

Funding: NIDDK Support

TH-PO044

Spleen Plays a Critical Role in Hepcidin-Mediated Protection against Renal Ischemia-Reperfusion Injury Sundararaman Swaminathan,¹ Yogesh M. Scindia,¹ Mark D. Okusa,¹ Diane L. Rosin,^{1,2} Liping Huang,¹ Paromita Dey.¹ ¹Medicine, Univ of Virginia, Charlottesville, VA; ²Pharmacology, Univ of Virginia, Charlottesville, VA.

Background: We showed previously that pretreatment with hepcidin mitigates kidney IRI by acting on hepato-splenic iron compartments. In these studies we observed that changes in the splenic iron content and ferroportin expression far exceeded that in the kidney and liver. We therefore hypothesized that hepcidin-mediated protection is through its iron-retaining effect on the spleen, and that splenocytes are necessary in preventing renal injury following kidney IRI.

Methods: Mice (C57Bl/6, n=6-8) were splenectomized 1 week prior to treatment with saline or 50 mg of hepcidin and 24 hours later were subjected to bilateral renal IRI (26 min). In some experiments, splenocytes (1e6-1e7) from 24 hour saline or hepcidin treated animals were adoptively transferred and the recipient mice were subjected to similar IRI regimen. Outcomes (renal function, injury markers, histopathology and inflammation) were examined after 24 hours of reperfusion.

Results: Splenectomy worsened IR-induced kidney injury (P_{cr}: IRI; 1.9 Vs Splenectomy+IRI; 2.4, p < 0.005). Importantly, hepcidin was not able to rescue splenectomized mice from renal IRI (P_{cr}: Hepcidin+Splenectomy+IRI; 2.1). Acute tubular necrosis and immune cell infiltration in splenectomized mice treated with or without hepcidin were comparable to untreated mice subjected to IRI. Adoptive transfer of 1e7 splenocytes from hepcidin-treated (but not PBS) mice to naïve mice was sufficient to completely protect kidneys of recipient mice from IRI (P_{cr}: PBS treated splenocytes; 2.3 Vs Hepcidin-treated splenocytes; 0.25, p < 0.001).

Conclusions: Our results demonstrate that protection afforded by hepcidin during episode of renal IRI, is dominantly mediated through its action on the spleen. Moreover, splenocytes of hepcidin-treated mice by themselves are capable of mitigating IRI *in vivo*, supporting our ongoing hypothesis that manipulation of splenic iron metabolism has therapeutic potential for AKI.

TH-PO045

Endothelial Krüppel-Like Factor 4 Mediates the Protective Effect of Statins against Ischemic Acute Kidney Injury Tadashi Yoshida, Maho Yamashita, Matsuhiko Hayashi. *Apheresis and Dialysis Center, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.*

Background: Endothelial cells participate in the pathophysiology of ischemic acute kidney injury (AKI) by increasing the expression of cell adhesion molecules and by recruiting inflammatory cells. Results of our previous studies showed that endothelial Krüppel-like factor 4 (Klf4) regulated Vcam1 expression and neointimal formation following carotid injury. The aim of the present study was to determine if endothelial Klf4 is involved in ischemic AKI.

Methods: Endothelial *Klf4* conditional knockout (*Klf4* cKO) mice were generated by breeding *Tek-Cre* mice and *Klf4* floxed mice, and their phenotype was analyzed after bilateral renal ischemia.

Results: *Klf4* cKO mice were phenotypically normal before the surgery. However, endothelial *Klf4* deletion exacerbated renal ischemia-reperfusion injury, as indicated by elevated serum levels of urea nitrogen and creatinine and aggravated renal histology. Moreover, *Klf4* cKO mice exhibited the enhanced accumulation of neutrophils and the elevated expression of cell adhesion molecules including Vcam1 and Icam1 in injured kidneys. Interestingly, statins ameliorated renal ischemia-reperfusion injury in control mice, but not in *Klf4* cKO mice, suggesting that the protective effect of statins against ischemic AKI is mediated by endothelial Klf4. Mechanistic analyses in cultured endothelial cells revealed that statins increased *Klf4* expression, and that Klf4 mediated the suppressive effect of statins on tumor necrosis factor-α-induced *Vcam1* expression through reducing the binding of NF-κB to the *Vcam1* promoter.

Conclusions: These results provide evidence that endothelial Klf4 is a mediator of statins and plays a protective role in ischemic AKI by regulating the expression of cell adhesion molecules with concomitant recruitment of neutrophils.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO046

Kidney Endothelial Progenitors Play a Critical Role in Susceptibility to Acute Kidney Injury

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Background: Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function leading to renal failure, and contributing to high percentages of morbidity and mortality. Kidney formation involves the production of nephrons each with a rich vascular supply surrounding it. This complex and high vascularization makes the kidney especially susceptible to ischemic injury. We hypothesize that malformations of the vascular system during kidney development compromise its ability to cope and recover from AKI.

Methods: We generated mice with a conditional deletion of Vegfr2 (floxed) in the Foxd1 cre positive renal stroma (Vegfr2^{ST-/-}), and evaluated the formation of the vasculature via histology, immunohistochemistry and fluorescent microangiography. Furthermore we performed ischemia reperfusion injury (IRI) on control and mutant mice and determined their ability to recover 1 (injury phase) and 7 days (repair phase) post injury. Lastly, we performed a lineage tracing study where Foxd1 cre mice were bred with a TdTomato reporter (permanently labeling all Foxd1 derived cells) and performed IRI and interrogated the percentage of Foxd1 derived endothelial cells that were present in the IRI and contralateral control kidneys.

Results: We determined that the Vegfr2^{ST-/-} mice had dilated microvasculature embryonically and post-natally. Furthermore, when we stressed the Vegfr2^{ST-/-} animals with IRI they had an increased injury compared to controls (both histologically and inflammatory markers). This increased susceptibility in the mutants continued to be observed 7 days following the injury. Lineage tracing experiments showed the Foxd1 derived endothelial cells are highly plastic during the repair phase of IRI and their deletion in the Vegfr2^{ST-/-} is likely the reason for the increased susceptibility to injury.

Conclusions: From this we determined that Foxd1 derived endothelial cells are highly pertinent to normal formation of the renal vasculature and their risk of AKI. Patients that have an underlying perturbation of the renal microvasculature are likely at higher risk of suffering long term renal damage following AKI.

TH-PO047

Diadenosine Pentaphosphate Reduces Glomerular Filtration Rate

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Background: Mechanisms and participating substances responsible for the reduction of glomerular filtration (GFR) rate in contrast induced acute kidney injury (CI-AKI) are still matter of debate. Here we hypothesize that diadenosine polyphosphates are released by the action of contrast media and may act on glomerular arterioles thereby reducing GFR.

Methods: Rat tubules were freshly isolated using a modified iron oxide sieve technique and treated with iodoxanol (47 mg iodine/ml) at 37°C for 20 min. The supernatant was analyzed regarding the content of Ap_nA (n=3-5) by using reversed phase chromatography, affinity chromatography and MALDI-MS. Concentration response curves for Ap_nA (n=3-5, 10⁻¹²-10⁻⁵ mol/l) were measured in isolated perfused glomerular arterioles. The GFR was obtained in conscious mice by inulin clearance.

Results: Treatment of tubules with iodoxanol increased the concentration of Ap_nA (n=3-5) significantly in the supernatant. Ap_nA (n=3-5) reduced afferent arteriolar diameters dose dependent, but did not influence efferent arterioles. Ap₅A acted strongest; its effect weakened with time. Suramin blocked the Ap₅A effect. Further, application of Ap₅A in conscious mice significantly reduced the GFR.

Conclusions: The data indicate that contrast media induced release of Ap₅A act differentially on glomerular arterioles resulting in the reduction of the GFR. This mechanism may add to the reduced GFR in CI-AKI.

TH-PO048

Effect of Anakinra on Inflammation Markers in Hepatorenal Syndrome Type 1

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Background: Hepatorenal syndrome (HRS) type 1 is a life threatening complication of cirrhosis with limited therapeutic options. We hypothesize that Inflammation plays a major role in HRS type 1 and we investigated this in a mouse model by blocking IL-1 β , an end product of inflammation pathway by Anakinra, so that it could serve as a potential therapeutic agent in patients at risk for HRS type 1.

Methods: C57BL/6 mice received 1mL/kg of carbon tetrachloride (CCl4) biweekly for 12 weeks induce liver cirrhosis. A 6 mg/Kg of Lipopolysaccharide (LPS) was given intraperitoneally to mice to induce acute kidney injury by simulating the inflammatory stressor caused by acute infection. A 30 mg/kg of Anakinra was given intraperitoneally 3 hours before and 1 hour after LPS to CCl4 and LPS treated mice. Four mouse populations were studied. (1) control mice (2) CCl4 treated mice (3) CCl4 treated mice with LPS (4) CCl4 treated mice with LPS and Anakinra (N=6 per group). Renal function was monitored by measuring urine output, urinary sodium, and serum creatinine measured 10 hrs after administration of Anakinra. The mouse kidneys were then harvested and analyzed by western blot for the presence of inflammation markers: IL-1 β , caspase 1, and apoptosis-associated speck like protein (ASC) and the therapeutic effect of Anakinra on these inflammatory markers.

Results: Control and CCl4 treated mice showed no change in renal function. The CCl4+LPS treated mice had a significant decrease in urine volume (p<0.05) and urinary

Na (p<0.05) and marked increase in serum creatinine (p<0.05) compared to the other 3 mice groups. In CCl4+LPS+Anakinra treated mice IL-1 β , caspase 1, and ASC expression significantly decreased (p<0.05) compared with CCl4+LPS treated mice.

Conclusions: In the CCl4-induced cirrhotic mouse model, simulating HRS type 1 by administration of LPS, accompanied by an increase in the expression of IL-1 β , caspase-1, and ASC in mouse kidney. Anakinra resulted in down regulation of these markers and improvement in renal function. This suggests that agents like Anakinra could be a potential therapeutic option for patients at risk of HRS type 1.

TH-PO049

Matrix Metalloproteinase-7 Protects against Acute Kidney Injury in Mice

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Background: Matrix metalloproteinase-7 (MMP-7), a secreted and zinc-dependent endopeptidase that proteolytically degrades a broad range of extracellular matrix and other substrates, is a direct downstream target of the canonical Wnt/beta-catenin signaling. MMP-7 is specifically induced in the tubular epithelium of the kidneys in a variety of chronic kidney diseases. However, whether MMP-7 plays a role in acute kidney injury (AKI) is still ambiguous.

Methods: MMP-7 expression in the kidneys after AKI was assessed. MMP-7 knockout and wild-type control mice were subjected to renal ischemia/reperfusion injury (IRI) and cisplatin administration, respectively. Cultured proximal tubular epithelial cells (HKC-8) were used in an *in vitro* model.

Results: MMP-7 was markedly induced in renal tubular epithelial cells at 12 hours after IRI. To investigate the role of MMP-7 in AKI, we utilized MMP-7 knockout mice (MMP-7^{-/-}). Mice with global ablation of MMP-7 were phenotypically normal with no appreciable defects in kidney morphology and function. In AKI induced by either IRI or cisplatin, loss of MMP-7 substantially aggravated renal lesions, compared with wild-type controls. MMP-7^{-/-} mice displayed higher mortality rate, elevated serum creatinine, and more severe morphologic injury, which was accompanied by an increased expression of FasL, Caspase 7 and FADD, while little change with Bax. In MMP-7^{-/-} kidneys, more prevalent apoptotic cells were detected in renal tubular epithelial cells after injuries. Moreover, deficiency of MMP-7 also promoted the expression of pro-inflammatory cytokines and chemokines, such as TNF- α , MCP-1 and RANTES, and caused an increased inflammatory cell infiltration as illustrated by immunostaining for CD3⁺, CD45⁺ and F4/80⁺ antigens. *In vitro*, recombinant MMP-7 protein protected human kidney proximal tubular cells (HKC-8) against apoptosis through inhibiting FasL/Caspase-7/FADD axis.

Conclusions: MMP-7 plays a protective role in the setting of AKI through inhibiting FasL-mediated apoptotic pathway and reducing renal inflammation.

Funding: NIDDK Support

TH-PO050

Metformin Protects against Cisplatin-Induced Acute Kidney Injury via an AMPK-Dependent Manner

Jianzhong Li, Chunsun Dai. *Nanjing Medical Univ.*

Background: Metformin, one of the most common prescriptions for the therapy of type 2 diabetes, is beneficial for early diabetic nephropathy. However, the role and mechanisms for metformin in treating acute kidney injury remain to be established.

Methods: Adult male CD1 mice were injected with cisplatin intraperitoneally to induce AKI. Rat Kidney tubular epithelial cells (NRK-52E) were incubated with cisplatin to induce cell death.

Results: Here, we found that mice exhibited severe kidney injury at day 2 after cisplatin injection. Metformin treatment could markedly ameliorate kidney dysfunction and kidney morphologic abnormality. Cell apoptosis in kidney tissue presented as TUNEL and anti-cleaved caspase 3 staining was much less in metformin-treated mice compared with the diseased control. Anti-Ly6b and anti-F4/80 staining demonstrated that the inflammatory cells infiltration in the kidneys was also diminished in metformin-treated mice. In addition, LC3-II, an autophagy biomarker, was induced at 1h and peaked at 12h in the kidneys after cisplatin injection, whereas autophagy induction as well as p-Ampk abundance were largely enhanced in metformin-treated mice. In cultured NRK-52E cells, cell apoptosis was markedly induced at 12h after cisplatin treatment and metformin could largely attenuate it. Furthermore, cells pretreated with metformin dramatically increased the abundance of phosphorylated Ampk. LC3-II protein level was also significantly induced after metformin treatment. Knocking down Ampk expression with small interfering RNA or using 3-methyladenine to block metformin-induced autophagy could largely diminish the protective effect of metformin on cell apoptosis.

Conclusions: In summary, metformin may protect against cisplatin-induced AKI through promoting tubular cell survival by inducing AMPK activation and tubular cell autophagy.

Funding: Government Support - Non-U.S.

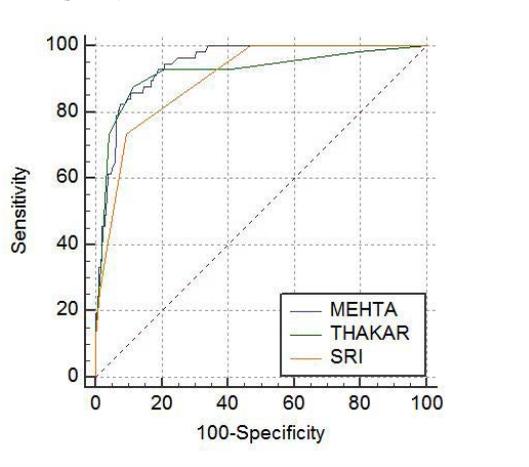
TH-PO051

A Comparison of Three Prediction Models for Acute Kidney Injury Requiring Renal Replacement Therapy After Coronary Artery Bypass Graft Surgery *Ailene Ramos Buelva-Martin, Aina Bautista-Duque, Oscar D. Naidas. Dept of Medicine, Section of Nephrology, St. Luke's Medical Center, Quezon City, Metro Manila, Philippines.*

Background: Acute kidney injury (AKI) following cardiac surgery is associated with increased post-operative morbidity and mortality. Scoring systems to predict acute kidney injury requiring renal replacement therapy (RRT) among patients undergoing cardiac surgery have been developed to assess risk pre-operatively and give necessary prophylactic agents and also assist clinicians on the management post-operatively.

Methods: Cross sectional analytic study of 427 patients who underwent coronary artery bypass graft from January 2009-October 2014. The following were excluded: a) on hemodialysis b) with missing data. Primary outcome: acute kidney injury requiring RRT after CABG. Risks were calculated using the three models: Cleveland scoring by Thakar, Simplified Renal Index by Wijeyesundera, and the Bedside Tool for Predicting Risk of Postoperative Dialysis by Mehta. The area under the receiver operating curve (AUROC) was determined for each model.

Results: AKI was documented in 25.5% (n=109), 13.3% (n=57) underwent post-operative RRT. Discrimination for the prediction of RRT was good for the three scoring models using AUROCs: Mehta: 0.94 (95% CI, 0.916 to 0.963); Thakar: 0.92 (95% CI, 0.890 to 0.944), and SRI: 0.90 (95% CI, 0.867 to 0.926). Mehta showed the highest predictive value, with significant difference with SRI (P = 0.0053). However, it was not significantly different with Thakar (p=0.23).



Conclusions: The Bedside Tool for Predicting Risk of Postoperative Dialysis by Mehta showed the highest predictive value but with no significant difference with the predictive value of the Cleveland scoring system. The advantages of the Cleveland scoring over Mehta are the applicability in cardiac surgeries other than CABG and the less number of variables.

TH-PO052

Effect of Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery on Acute Kidney Injury *Ailene Ramos Buelva-Martin, Oscar D. Naidas. Dept of Medicine, Section of Nephrology, St. Luke's Medical Center, Quezon City, Metro Manila, Philippines.*

Background: Acute Kidney Injury (AKI) is one of the serious complications of cardiac surgery. AKI is associated with increased mortality and morbidity. Coronary artery bypass graft (CABG) surgery can be done with a beating-heart (off-pump) or with a cardiopulmonary bypass machine (on-pump). There are conflicting studies regarding reduction of acute kidney injury with the use of the Off-pump CABG vs. On-Pump CABG.

Methods: Adult patients who underwent CABG using Off-pump and the On-pump technique from January 2005 to October 2014 were included in this retrospective cohort study. The following patients were excluded: a)chronic hemodialysis b)baseline eGFR <15ml/min/1.73m² c)missing data. The outcomes were: AKI defined as absolute increase in the serum creatinine concentration of ≥0.3 mg/dL from baseline within 48 hours after CABG and AKI requiring renal replacement therapy. Odds ratio were calculated between the use of Off-pump and On-pump CABG with the respective outcomes.

Results: Postoperative Acute Kidney Injury The incidence of acute kidney injury with off-pump group was lower (4/28 [14.3%]) vs on-pump group (109/427 [25.5%]) with OR 2.05 [95% CI, 0.69 to 6.59]); however, it was not significantly different at p-value 0.19. **Postoperative Acute Kidney Injury with Renal Replacement Therapy** Out of the 109 patients who had acute kidney injury after On-pump CABG, 53 (48.6%) patients underwent hemodialysis. While in the Off-pump CABG group, no one underwent hemodialysis out of the 4 patients who had acute kidney injury postoperatively (OR 8.8 [95% CI 0.5327 to 146.9], P=0.1283). [table1]

Conclusions: There was a lower incidence of AKI and AKI requiring renal replacement therapy in the Off-pump CABG group, however, it was not statistically significant with the On-pump CABG group. There is still insufficient evidence to say that the use of Off-pump CABG technique reduces incidence of AKI. Limitations of this study are: small sample

size, confounding variables since this study is a retrospective study, off-pump CABG population may not have been represented accurately. A multi-center study to increase sample size is recommended.

TH-PO053

Renal Dysfunction Detected by an Automatic Alert System: DETECT-H Project *Pedro J. Labrador, Silvia Gonzalez S, Santiago Polanco Candelario, Elena Davin carrero, Jesús P. Marin, Ines Castellano, Juan R. Gomez-Martino. Nephrology, San Pedro de Alcantara Hospital, Caceres, Spain.*

Background: The aim was to analyse the prevalence of chronic kidney disease (CKD) and acute kidney injury (AKI), length of stay (LOS) and in-hospital mortality.

Methods: To evaluate renal dysfunction in admissions we developed a fully automated electronic alert system which identifies all adult patients with reduced glomerular filtration rate according to CKD-EPI. Two alert levels were established, <60 and <30 mL/min/1.73m² in patients over 80. Patients admitted to nephrology unit and on dialysis were excluded. Detected patients were retrospectively analysed. CKD and AKI was defined according to KDIGO guidelines. Baseline serum creatinine was the lowest between 0.5-6 months before admission. LOS and in-hospital mortality was recorded.

Results: Between January and June 2014, issued alerts were 1.241 from 11.022 adult admissions (11.3%), from 1.079 patients (13.1% multiple admissions). Median age 77 years (interquartile range (IQR) 70-81), and 53.9% were men. Previous renal function was present in 1.042 patients (84%). Stage 1 9.6%, stage 2 37.7%, stage 3a 25%, stage 3b 17.7%, and stages 4-5 10%. Previous CKD was only registered in 31.9%. AKI was present in 846 admission episodes (69.9% of alerts and 7.7% of overall admissions). AKI stage 1, 2 and 3, respectively was 421 (49.7%), 207 (24.5%) and 218 (25.8%). AKI episode was specified to be suffered in 33.2% patients at discharge. In patients with CKD not AKI 7.5%, in overall AKI patients 45.3%, in AKI 1 30.4%, in AKI 2 47.8% and in AKI 3 71.6%; p<0.001. LOS in overall admissions in the same period was 5.31 days, for overall detected patients median LOS was 8 days (IQR 4-13 days). Median LOS for CKD not AKI, or AKI stage 1, 2 and 3 was 6 (3-10), 8 (5-13), 8 (6-14) and 10 (5-19) days; p<0.001. Mortality for all detected patients was 14.9% (185 patients). In-hospital mortality for CKD not AKI, or AKI stage 1, 2 and 3 was 4.3%, 10.9%, 22.7% and 33.9%. Mortality in patients with AKI stage 3 requiring dialysis was 57.1%, p<0.001.

Conclusions: Electronic alerts could be a useful tool to detect in-hospital renal dysfunction patients to improve CDK and AKI hospital outcomes.

Funding: Private Foundation Support

TH-PO054

Identification of a Pediatric Inpatient Cohort at Risk for Developing Acute Kidney Injury Using Machine Learning Methods *Michael G. Semanik, Sangeeta R. Hingorani. Pediatric Nephrology, Seattle Children's Hospital, Seattle, WA.*

Background: Acute kidney injury (AKI) is prevalent amongst pediatric inpatients, and its prevention requires rapid detection of those at risk. A rise in creatinine often comes too late for prevention to be effective. Therefore, this study seeks to apply machine learning methods to routine clinical data in order to identify patients at risk for AKI before creatinine levels rise.

Methods: A cohort of pediatric inpatients with at least one creatinine value was created, then split into AKI and non-AKI groups. AKI was defined using KDIGO creatinine-based criteria. Information on demographics, vital signs, lab values, procedures, and medications were collected for each patient. For the AKI group, only data collected 24 hours before each patient's peak creatinine value were used. Simple logistic regression was used to identify features that predicted the development of AKI, and these features were used to produce two algorithms: a logistic regression-based algorithm and a Bayes Net probability-based algorithm. Both algorithms used 10-fold cross validation to create a training and test set.

Results: 4064 patients were included in the cohort, of whom 370 (9.1%) developed AKI. Sixty features were significantly associated with AKI. The logistic regression algorithm created from these features identified 144/370 AKI patients and 3653/3694 non-AKI patients (giving it a sensitivity of 39% and specificity of 99%). The Bayes Net algorithm's sensitivity was 48% (identifying 176/370 AKI patients) and its specificity was 91% (identifying 3347/3694 non-AKI patients). The ROC areas for the algorithms were 0.84 and 0.81, respectively.

Conclusions: Machine learning methods can be used to identify a cohort of pediatric inpatients that are at increased risk of developing AKI before serum creatinine rises. Identification of this population allows for both additional testing (such as urinary biomarkers) and preventative treatment (such as removal of nephrotoxic drugs). Acute kidney injury predictive algorithms have the potential to improve patient care, and, if correctly implemented, will become more accurate as more data is collected.

Funding: Other NIH Support - NIH T32 Training Grant

TH-PO055

The Jelliffe Method for GFR Estimation with Non Steady State Creatinine Performs Better for Subjects with Higher Weight and Baseline Chronic Kidney Disease *Reejis Stephen, Sevag Demirjian, Steve Campbell. Nephrology, Cleveland Clinic, Cleveland, OH.*

Background: The Jelliffe method is used to estimate the glomerular filtration rate(GFR) when creatinine is in a non-steady state, such as in patients with acute kidney injury (AKI). We explored the agreement between iohalamate-measured renal function (iGFR) and estimated GFR by the Jelliffe method (eGFR) in subjects with AKI after undergoing partial nephrectomy.

Methods: iGFR was measured within a week of partial nephrectomy in subjects who sustained AKI (>0.3 mg/dl rise in serum creatinine from baseline) after partial nephrectomy. iGFR and eGFR based on creatinine drawn at the time of iGFR measurement, were compared using Pearson's correlation (r) in subjects grouped by weight (above and below median weight; 86 Kg) and baseline chronic kidney disease status (CKD; GFR<60ml/min/1.73m²).

Results: 69 of 90 subjects undergoing partial nephrectomy sustained AKI. Mean age was 61±11 years, and 55 were male. eGFR had a high correlation with iGFR (r=0.75, p<0.001). Correlation of eGFR with iGFR is shown and was significant except in the group with both CKD and lower weight (Table). Subgroup analysis showed that subjects with lower body weight and no CKD had lower correlation (r=0.54) than those with both CKD and the higher weight (r=0.96). The group with no CKD but higher weight had a strength of correlation in between these extremes.

Group; Mean±SD (Kg)	No CKD	CKD
Low Weight; 74 ± 9	0.54 (p 0.003)	0.40 (ns)
High Weight; 105 ± 15	0.79 (p < 0.001)	0.96 (p < 0.001)

Conclusions: GFR estimated by the Jelliffe equation correlates well with measured GFR in the AKI setting. Higher body weight and CKD at baseline are associated with higher creatinine levels, which may account for the better performance of the Jelliffe method in these states.

TH-PO056

Development of a Multicenter Ward-Based Acute Kidney Injury (AKI) Prediction Model *Jay L. Koyner, Richa Adhikari, Dana P. Edelson, Matthew M. Churpek. Dept of Medicine, Univ of Chicago.*

Background: Early identification of those at risk for the development of AKI on the general wards prior to increases in serum creatinine (SCR) would enable preemptive evaluation and intervention to minimize the risk and severity of AKI. We aimed to develop an AKI risk prediction algorithm using electronic health record (EHR) data in non-ICU patients.

Methods: All hospitalized ward patients who had SCR measured in 5 hospitals were included. Patients with a first measured SCR>3.0mg/dl or who developed inpatient AKI outside the general ward were excluded. Using a discrete-time survival model, demographics (age, sex), continuous variables (respiratory rate, pulse, temperature, pulse pressure index, oxygen saturation, systolic and diastolic blood pressure, complete blood count, hepatic panel and blood chemistries) were modeled as restricted cubic splines with 4 knots. The algorithm was derived in 60% of the data and prospectively validated in the remaining 40%. Area under the curve (AUC) was calculated for the prediction of SCR-based KDIGO AKI within 12 or 24 hours. Subgroup analyses were conducted across baseline glomerular filtration rate (eGFR) groups and severity of AKI stage.

Results: Among the 206,192 included patients, 17,522 (8.5%) developed KDIGO AKI on the wards, with 792 progressing to stage 2 and 257 to stage 3 during their hospital stay. The AUC(95%CI) of the model was 0.74(0.74-0.74) for predicting AKI within 24 hours and 0.76(0.76-0.76) for within 12 hours. Accuracy was highest for predicting AKI stage 3 in the next 12 hours (AUC 0.90(0.89-0.92)).

Subgroup	AUC(95%CI)	
	12hr outcome	24hr outcome
Baseline GFR		
GFR ≥90	0.71(0.69-0.70)	0.69(0.68-0.70)
GFR 60-89	0.76(0.75-0.76)	0.74(0.73-0.74)
GFR 30-59	0.75(0.74-0.76)	0.73(0.72-0.73)
AKI Stage		
Stage 1	0.76(0.76-0.76)	0.74(0.74-0.74)
Stage 2	0.77(0.76-0.78)	0.73(0.73-0.74)
Stage 3	0.90(0.89-0.92)	0.87(0.86-0.89)

Conclusions: Readily available EHR data can be used to predict impending AKI on the general wards with good to excellent accuracy across different patient subgroups. Real-time use of this model, prior to changes in SCR, would allow early diagnostic and therapeutic interventions for those at high risk of AKI and may improve cost and outcomes.

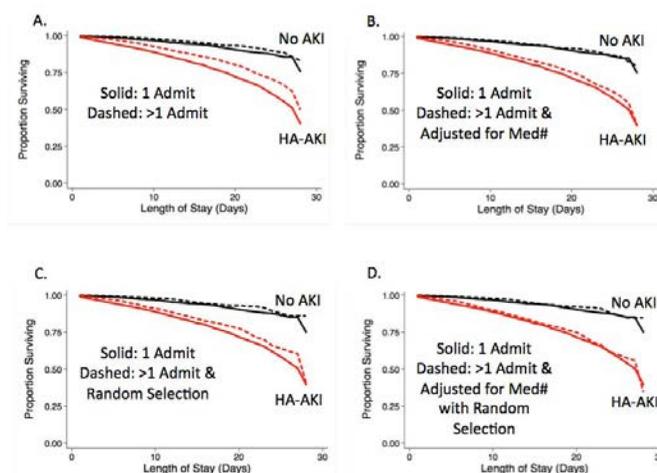
TH-PO057

Survivor Bias: Utilization of Multiple Admissions for Evaluation Risk of Inpatient Mortality Associated with Hospital-Acquired (HA) Acute Kidney Injury (AKI) *David G. Warnock, T. Clark Powell, John P. Donnelly. Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Inpatient deaths censored the cohort at risk, introducing survivor bias favoring those with >1 admission. Analysis of first admissions avoids this bias, but also loses information about those who survive multiple admissions. We evaluated inpatient mortality associated with AKI for adult admissions to UAB Hospital for FY2010-FY2013.

Methods: We used ICD9 codes and all inpatient serum creatinine (sCr) values for 109,456 adult patients with 5,452 inpatient deaths. We excluded patients with patients with <2 sCr values, ESRD, post-renal transplant, eGFR (<5 or >500 ml/min.1.73 m²), length of stay <1 and >28 days, and patients with community-acquired AKI. Minimum sCr for each admission was used as baseline, and HA-AKI was defined by peak sCr > (0.3 mg/dL + minimal sCr) and date-time for minimal sCr < date_time peak sCr. No-AKI was defined as (peak Scr - minimal sCr) <0.3 mg/dL. Survivor functions included HA-AKI, median age, black race, male gender, Deyo_Charlson comorbidity score, and median admissions for each patient (Med#).

Results: For 40,471 patients with 1 admission, there were 7,594 cases of HA-AKI (19%) with 1,290 deaths (17%), For 14,860 patients with 23,633 admission, there were 6,633 cases of HA-AKI (22%) with 732 deaths (11%). Figure shows survival curves for 1 versus >1 admissions (A); 1 versus >1 admissions adjusted for Med# (B), 1 versus selected >1 random selected admission (C), and 1 versus >1 random selected admission adjusted for Med# (D).



Conclusions: Survivor curves for multiple admissions (dashed lines) fell above the curve for single admissions, demonstrating survivor bias. Combining random selection and adjustment for Med# resolved the survivor bias, permitting inclusion of patients with multiple admissions in risk models for inpatient mortality.

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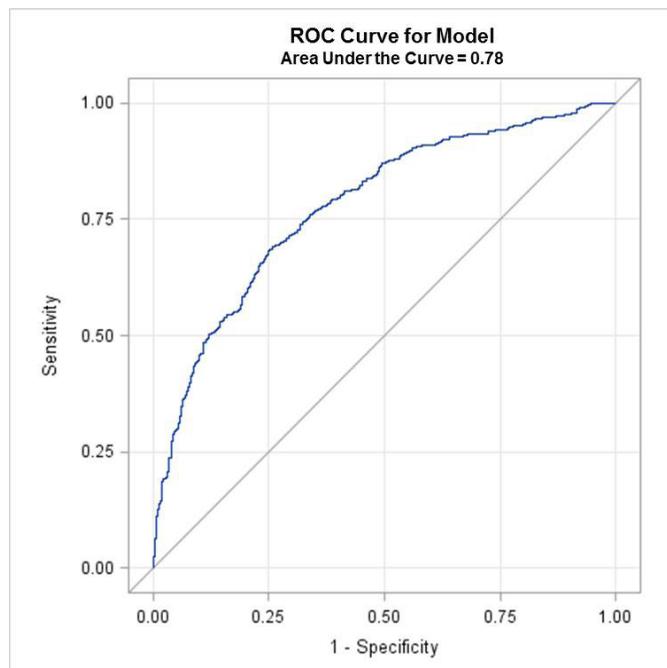
TH-PO058

Validation of the Acute Renal Failure Trial Network (ATN) Study Risk Model for Predicting Mortality in Critically Ill Adults with Acute Kidney Injury *Ridhmi P. Rajapakse,¹ Christopher M. Keener,² Paul M. Palevsky,^{1,3} John A. Kellum,² Emily Foldes.² ¹Medicine, Univ of Pittsburgh, Pittsburgh, PA; ²Critical Care Medicine, Univ of Pittsburgh, Pittsburgh, PA; ³Renal Section, VA Pittsburgh HCS, Pittsburgh, PA.*

Background: Disease specific severity of illness scoring systems have been developed to predict survival of patients with acute kidney injury. Performance of these scoring systems outside of the population in which they have been generated has been poor. We therefore evaluated the performance of the recently developed ATN Study risk model predicting 60 day all-cause mortality in intensive care unit (ICU) patients at initiation of dialysis for acute kidney injury (AKI).

Methods: We evaluated the performance of the ATN Study risk model using the High Density Intensive Care (HiDenIC) Database which contains data on all adult patients admitted to any of the eight ICUs at UPMC between July 2000 and October 2008. Clinical data and physiologic variables were closely matched with the original study model; missing data were imputed by either assuming clinical normality or viewing these data elements following similar rules used to build the original model. Model discrimination was assessed via area under the receiver operating characteristic curve (AUROC). Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Results: 1747 patients were initiated on renal replacement therapy (RRT) for AKI during this interval; full data for model testing were available for 1300 patients (74%). The AUROC for the model was 0.78 (95% CI: 0.75-0.80) with a Hosmer-Lemeshow goodness-of-fit test p-value of 0.59 (Figure).



Conclusions: The ATN score demonstrated good discrimination and calibration for predicting 60-day all-cause mortality in in ICU patients initiating RRT for AKI in a population separate for the population in which it was developed.

TH-PO059

A Multifaceted Quality Improvement Programme for Tackling Acute Kidney Injury in a Large Teaching Hospital Leonard Ebah, Prasanna Hanumapura subbegowda, Deryn Jennifer Waring, Rachael Challiner, Robert Henney, Alastair J. Hutchison. *Manchester Acute Kidney Injury Strategy; Dept of Renal Medicine, Central Manchester Univ Hospitals, Manchester; United Kingdom.*

Background: Acute kidney injury (AKI) is now widely recognised as a serious health care issue. Up to 25% of hospital patients have been reported to develop it, often with worse outcomes compared to those without AKI. AKI care in hospitals has been shown to be substandard. This study aimed to use quality improvement methodology to improve AKI care and outcomes in a large teaching hospital.

Methods: Several areas of documented poor AKI care were identified and specific improvement activities implemented through sequential Plan-Do-Study-Act (PDSA) cycles. An electronic alert system for AKI was developed, a ten point Priority Care Checklist (AKI PCC) was tested with the aid of specialist nurses and pharmacists whilst targeted education activities were carried out. Impact on key AKI care processes and patient outcomes was studied.

Results: The electronic alert had a sensitivity of 99% for the detection of new cases of AKI. Nine aspects of the PCC saw significant improvements in their attainment: Baseline creatinine 66% to 84%, identification of a cause for AKI 62% to 77%, fluid balance assessment 77% to 92%, appropriate investigations 61% to 77% catheterisation 92% to 99% ultrasound scans 79% to 95% renal or intensive care referrals 80% to 100%, fluid charts 64% to 71% after, and appropriate drugs review 57% to 87%. The intervention led to a significant reduction in variability of delivered AKI care. AKI incidence showed a trend towards reduction; 9.9% of all hospitalisations before any intervention to 7.8% towards the end of the intervention period. AKI related length of stay dropped from 20.2% to 15.5% and AKI deaths also showed a trend towards reduction, from 44 deaths averagely per month to 31 deaths. The number of cases of hospital acquired AKI were down from 107 to 90 per month.

Conclusions: This study demonstrates the success of an AKI care checklist implemented with the aid of a nurse/pharmacist in improving key processes of care and showing an early improvement in key patient outcomes.

TH-PO060

The Quality of Hospital Discharge Communications About AKI Raquel C. Greer,¹ Yang Liu,¹ Deidra C. Crews,¹ Bernard G. Jaar,¹ Hamid Rabb,¹ L. Ebony Boulware.² ¹Johns Hopkins Univ; ²Duke Univ.

Background: Post-hospital discharge (DC) care for patients hospitalized with AKI could influence patients' subsequent risks of CKD and related morbidity. High-quality written hospital DC communications (DC summaries to outpatient providers and patient DC instructions) about AKI may help facilitate adequate follow-up and patient self-care.

Methods: We reviewed electronic health records of patients hospitalized with community and hospital-acquired AKI in 2012 at a single hospital in Baltimore MD to characterize the quality of written hospital DC communications about AKI. We assessed

patient and system characteristics independently associated with higher quality DC communications (greater number of quality elements out of 10 possible) in a multivariable model.

Results: Among 75 randomly selected hospitalized patients with AKI stratified by KDIGO stage 1 to 3 (n=25 per stage), mean age was 56 years, 48% were African American, 15% had known CKD, median length of stay was 9 days and 65% were discharged from medical (vs. surgical) services. Less than half of DC communications included key elements about AKI.

Presence of 10 Quality Elements about AKI in Discharge Communications (n=75)			
Type of Quality Element	Quality Elements Possible	Presence of Quality Element N (%)	
		Physician Discharge Summary	Patient Discharge Instructions
Mention of AKI occurrence	2	33 (44)	10 (14)
Mention of AKI cause	2	32 (43)	1 (1)
Description of AKI course	1	23 (31)	NA
Recommended/scheduled follow-up appointments	2	60 (80)	67 (94)
Recommendations for care specific to AKI	2	11 (15)	6 (8)
Named outpatient provider to receive the discharge summary	1	58 (77)	NA

NA:Not applicable

Communications featured a median of 4 quality elements. Quality elements were greater in communications for patients with more severe AKI (number of additional quality elements (β) [95% CI]: 2.0 [0.6-3.4] for Stage 3 vs. Stage 1) and those discharged from medical (vs. surgical) services (β [95% CI]: 1.2 [0.1-2.3]).

Conclusions: Few hospital DC communications provided information or recommendations for AKI care in sufficient detail to facilitate adequate follow-up. Improvements in this important aspect of care for patients with AKI are urgently needed.

Funding: NIDDK Support, Other NIH Support - National Center for Research Resources, a component of the NIH and the NIH Roadmap for Medical Research

TH-PO061

Prognosis of Contrast Induced Nephropathy After Outpatient Computed Tomography in Chronic Kidney Disease Patients Sehoon Park, Seokwoo Park, Eunjeong Kang, Hajeong Lee, Jung Pyo Lee, Kwon Wook Joo, Yon Su Kim, Dong Ki Kim. *Dept of Internal Medicine, Seoul National Univ Hospital.*

Background: Most studies regarding contrast induced nephropathy (CIN) were done in angiography era but computed tomography (CT) is more common cause of contrast exposure in general population. There were few prognosis data concerning CIN after outpatient CT.

Methods: Patients with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² underwent outpatient CIN prophylaxis program for contrast CT from 2008 to 2014 in Seoul National University Hospital. Patients received intravenous isotonic saline and oral N-acetylcysteine. Baseline blood sample was done within 2 weeks before CT. Basic data was collected retrospectively by medical chart review. Prognosis was surveyed from death registry of National Statics Korea and dialysis registry of The Korean Society of Nephrology. CIN was defined by ≥0.5mg/dl or ≥25% increase of serum creatinine (sCr) from baseline within 48-96 hours after CT. Primary outcome was event of renal replacement therapy (RRT), duration from CT to RRT and survival period after CT. **Results:** 12179 cases of CT were performed with CIN prophylaxis protocol and 2816 cases of CT had baseline eGFR<60 without RRT history and follow up sCr 48-96 hours after CT. 84 (3%) cases of CIN were found and 99 (3.5%) cases went RRT, 551 death reported after CT. Prognosis was analyzed after adjustment with age, sex, baseline eGFR, history of diabetes and hypertension. No relationship between death, RRT incidence, doubling of sCr and CIN was shown. However, we found shorter period from CT to RRT in CIN cases. So we performed analysis with RRT within 6 months as outcome with subgroup divided by eGFR. CIN was risk factor for RRT within 6 months in cases with baseline eGFR<30 (aRR 4.70, 95% CI 1.39-15.90, P=0.013). However, in cases with eGFR≥30, start of RRT in acute period was not increased by CIN.

Conclusions: CIN due to CT contrast after appropriate prophylaxis was not related to long term renal prognosis. CIN was a risk factor for start of RRT within 6 months after CT in cases with baseline eGFR<30, but even this relationship was not seen in patients with relatively preserved renal function.

TH-PO062

Outcomes following Intra Arterial Contrast in Chronic Kidney Disease Louise Goodall,² Thomas Hugh Douglas Patterson,² Jane Elizabeth Cross,¹ William E. James,¹ Venkataraman Manickavasagam.¹ ¹Nephrology, Lismore Base Hospital, Lismore, NSW, Australia; ²Medicine, Univ of Western Sydney, Sydney, NSW, Australia.

Background: Contrast Induced Nephropathy (CIN) is a recognised complication of angiography. Risk factors include chronic kidney disease (CKD), advanced age, diabetes and cardiac insufficiency. Although incidence in the general population is 2-5%, reported

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

incidence of CIN in CKD is 15-27%. The risk of CIN may have been over-estimated in CKD. We hypothesise that pre-procedure optimisation decreases incidence and improves outcome of CIN. The aim of this study is to determine the incidence and outcome of CIN in CKD patients in our centre.

Methods: Consecutive patients with stage III-V CKD, undergoing peripheral (group 1) or cardiac (group 2) angiography, at a regional Australian hospital between 2005-2015 were included. Pre procedure optimisation included oral N-AcetylCysteine, intravenous hydration with Normal Saline and withholding Metformin and Frusemide. Low osmolality contrast diluted to 1/3 strength (group 1) or half strength (group 2) was used. CIN was defined as serum creatinine rise of >25% from baseline within 72 hours. Primary outcome was incidence of CIN. Secondary outcomes were mortality at 6 months, progression to dialysis and progression of CKD. follow up ranged from 2-73 months.

Results: 537 patients with CKD stage III-V underwent angiography. 222 patients concurrently dialysing were excluded. Median ages were similar in both groups (75 years in group 1, 76 years in group 2, P=0.25); diabetes was more prevalent in group 1 (70.5% versus 48.4%, P=0.001) and ischaemic heart disease more prevalent in group 2 (60.0% versus 44.3%, P=0.02). Median volume of contrast used was significantly lower for group 1 (35mls, range 2.5-350mls) than group 2 (75mls, range 20-357mls) (P<0.001). The incidence of CIN was 3.7%. Incidence of CIN did not differ between groups (group 1 = 4.1%, group 2 = 3.2%, P=0.74). No patient with CIN died within 6 months or progressed to higher CKD stage or dialysis.

Conclusions: Pre procedure optimisation of CKD patients may reduce incidence of CIN. In our study, incidence of CIN in CKD patients was low and did not lead to death or progression of chronic kidney disease.

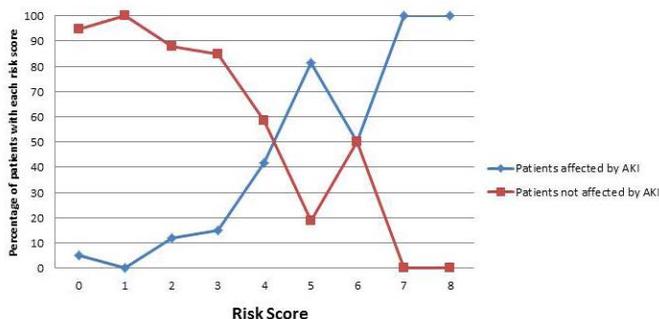
TH-PO063

AKI Risk Scores in Acute Admissions: Selecting the High-Risk or Missing the Vulnerable? Amy Jeanne Riddell, Christopher J. Mulgrew. *Renal Unit, Royal Devon and Exeter Hospital, Exeter, Devon, United Kingdom.*

Background: AKI commonly complicates acute illness. 2014 UK NICE AKI guidelines stress early identification of those at high risk. In patients with many co-morbidities, while risk scores in select groups have been studied, there remains debate as to the effective use of AKI risk scoring in 1st and 2nd care populations (currently being investigated by the UK National AKI Programme). If correctly identified, steps could be taken to minimise risk and manage AKI earlier. Alternatively, should we not treat all acutely ill patients as 'at risk'?

Methods: Review of acute admissions to the AMU on 4 weekdays between Mar'14&Mar'15. 158 cases were reviewed and risk scored based on NICE/KDIGO published risk factors. Any AKI, demographic data, specialist nephrology input, length of stay and overall outcomes were recorded.

Results: Of 158 patients, 35 (22%) had AKI during their hospital stay. Most had AKI1 (24/35), vs AKI2 (7/35) and AKI3 (4/35). 28 had AKI on admission vs 7 after admission. Patients with AKI (at any time) had higher median scores (4, (0-9)) than non-AKI (2, (0-7)).



The 7 post-admission AKI cases had a median score of 4 (2-5). Length of stay (LoS) was greater in AKI group (9.2d vs 5.8d). AKI was due to sepsis/volume depletion in 68%, alongside other risk factors. There was one death in the AKI group (AKI3).

Conclusions: 2nd care AKI risk scoring aims to identify those at high risk to prevent deterioration, but a greater challenge seems to be in 1st care than acute settings. Our data would suggest that while patients developing AKI post-admission may have a range of risk scores on arrival, with high scores correlating with AKI and LoS, the majority with AKI arrive from primary care with high scores. A validated risk score for use in 1st care, aiming to prevent admission, may be more useful than stratifying all acute hospital admissions - are they not all 'high risk' anyway?

TH-PO064

Acute Kidney Injury Care Bundle Compliance in a Large District General Hospital in UK Preetham Boddana, Shiva Sreenivasan, Israr Baig, Nerys Conway. *Renal Unit, Gloucestershire NHS Foundation Hospitals, Gloucester, Gloucestershire, United Kingdom.*

Background: AKI is a common and harmful condition, which is often treatable and avoidable. The incidence of AKI in patients admitted to a hospital is approximately 3 – 7%. Gloucestershire Hospitals NHS Foundation Trust sees about 500 cases of acute kidney injury (AKI) monthly from a catchment population of 612,000.

Methods: An audit of patients with AKI showed deficiencies in care. We created an AKI care bundle (senior review, medication review, fluid balance, and repeat creatinine within 24 hours) for those patients with AKI, prompted by an AKI sticker for the case notes.

Results: For patients receiving an AKI flag, case notes were audited for appropriate use of the care bundle. We reviewed audit results over a 2-year period to see if the AKI bundles were being used appropriately and if patient care had improved. There has been improvement in AKI care bundle compliance. Figures up to August 2014 show that compliance for AKI care bundle use is 87%.



The compliance since its launch has generally exceeded the Commissioning for Quality and Innovation (CQUIN) targets set in place by the project.

Conclusions: We have shown an improved care in patients with acute kidney injury by using an electronic alert system prompting early management. AKI can easily be identified and managed early and appropriately by frontline staff by frontline staff using an ALERT system. On going study is being taken place in our department to assess if this has reduced patient mortality, morbidity and length of stay in hospital.

TH-PO065

Reducing Post-CABG Acute Kidney Injury by Multipronged Preventive Interventions Wisit Cheungpasitporn, Michael A. Mao, Charat Thongprayoon, Qi Qian. *Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Acute kidney injury (AKI) post cardiac surgery is frequently a multifactorial event, associated with an increased morbidity and mortality. As AKI has no specific treatment, prevention is critical. This study aims to apply multipronged preventive measures to reduce AKI after coronary artery bypass grafting (CABG).

Methods: Prospective randomized interventional study. Non-dialysis and non-kidney transplant adults (>18 years old) undergoing elective CABG in March 2014-February 2015 were randomized (1:1 ratio) to control and intervention groups. The intervention group was intervened to minimize potential nephrotoxic conditions perioperatively (48 hours prior to the operation to 5 days postoperation). Outcome measures included the incidence and severity of post-CABG AKI using the AKIN criteria, length of hospital stay, discharge disposition and hospital mortality. Data from a similar cohort in March 2013-February 2014 were extracted and compared with the results from the control group to assess the spillover effects.

Results: Post-CABG AKI occurred in 19% (n=33) of the 174 patients in the intervention group; 30% (n=51) of the 172 in the control group, p=0.02, consistent with a 36% AKI risk reduction with the interventions [RR = 0.64 (95% CI: 0.44-0.94)]. Number needed to prevent one AKI was 10. The AKI severity was mostly mild and similar between the two groups; 98% and 94% were in stage 1 AKI in the control and intervention groups, respectively. Compared to non-AKI, AKI patients in both groups had a longer length of hospital stay and higher risk of being discharged to a care facility. No hospital mortality was noted in both groups. The AKI occurrence in the year prior to the study was similar to that in the control group.

Conclusions: Multipronged preventive measures can significantly reduce post-CABG AKI. The implementation of the preventive measures is uncomplicated. This approach can potentially be adopted in most hospital settings. These results should encourage initiatives towards developing AKI prevention protocols.

TH-PO066

Outcomes of Early Initiation of Continuous Renal Replacement Therapy in Elderly Patients with Acute Kidney Injury: A Multicenter Prospective Cohort Study Jae Yoon Park,¹ Dong Ki Kim,¹ Hyung Jung Oh,² Kwon Wook Joo,¹ Yun Kyu Oh,¹ Chun Soo Lim,¹ Shin-Wook Kang,² Yon Su Kim,¹ Jung Tak Park,² Jung Pyo Lee.¹ ¹Seoul National Univ College of Medicine, Seoul, Korea; ²Yonsei Univ College of Medicine, Seoul, Korea.

Background: Continuous renal replacement therapy (CRRT) is essential in the management of critically ill patients with acute kidney injury (AKI). However the optimal timing for initiating CRRT remains controversial, especially in elderly patients. Therefore we investigated outcomes of early initiation of CRRT in elderly patients with AKI.

Methods: A total of 616 patients aged equal or over 65 years who started CRRT due to AKI from August 2009 to December 2013 were enrolled prospectively at three centers. They were divided into 2 groups based on the median 6-hours urine output immediately before CRRT was applied.

Results: The mean age of both group was 74.3 years. The median 6-hours urine output was 80 mL. 186 patients (60.0%) were male in early initiation group and 179 patients (60.3%) in late initiation group. The most common cause of AKI was sepsis (45.9% versus 46.0%). Mean arterial pressure was higher in early initiation group (79.8 mmHg versus 76.8 mmHg). Prothrombin time-international normalized ratio, total bilirubin, aspartate aminotransferase and alanine aminotransferase were lower in early initiation group (P<0.05).

Overall cumulative survival and 28-days survival rates were higher in early initiation group (Log-rank $P < 0.001$ for both). Furthermore, early CRRT treatment was associated with lower mortality rate after adjustment for age, sex, mean arterial pressure, Charlson comorbidity index, Sequential Organ Failure Assessment score, hemoglobin, serum C-reactive protein, serum albumin level and prothrombin time (hazard ratio, 0.752; 95% confidence interval 0.595-0.951, $P = 0.008$).

Conclusions: Early initiation of CRRT was associated with a better prognosis in critically ill elderly patients with AKI.

TH-PO067

Outcomes in Patients with Persistent Dialysis-Dependent AKI Aedan Olaso, Daniel Tseytin, Hope Kincaid, Sharon E. Maynard. Lehigh Valley Health Network, Allentown, PA.

Background: We sought to describe clinical characteristics & outcomes in patients with persistent dialysis-dependent AKI at the time of hospital discharge.

Methods: We performed a retrospective descriptive study of patients requiring dialysis for AKI at the time of hospital discharge in Lehigh Valley Health Network Subacute Dialysis Program between October 2012 & July 2014.

Results: Of 55 patients enrolled in the program, 26(47.3%) recovered renal function & 29(52.7%) developed ESRD. Clinical characteristics of these patients are shown below. The median duration of dialysis in the renal recovery group was 3.5 weeks. Although 75% of patients who recovered renal function did so by 5.1 weeks, 2/26(7.7%) recovered >3 months after dialysis initiation.

Clinical Characteristics	Renal Recovery (n=26)	No renal recovery (n=29)
Age	64	74
Comorbidities - n(%)		
HTN	18 (69.2)	25 (86.2)
CHF	5(19.2)	10 (34.5)
CAD	6(23.1)	10 (34.5)
DM	16 (61)	10 (34.5)
Cerebrovascular ds	3 (11.5)	1 (3.4)
PVD	4 (15.4)	3 (10.3)
Baseline creatinine (mg/dl)	1.3	2.0
Creatinine on hospital admission (mg/dl)	2.5	3.9
Creatinine on dialysis initiation (mg/dl)	5.2	5.5
Change in creatinine between week 3 & 4 after dialysis initiation	-0.86*	+0.13
Etiology - n (%)		
ATN	15 (57)	7 (24.1)
Multiple myeloma	0 (0)	5 (17.2)
CIN	2 (7.7)	2 (6.9)
AIN	1 (3.8)	1 (3.4)
ANCA	1 (3.8)	1 (3.4)
CRS	3 (11.5)	3 (10.3)
Acute renal allograft rejection	1 (3.8)	2 (6.9)
Other	2(7.7)	5 (17.2)

* Among those who recovered renal function but were still dialysis dependent at 4 weeks.

Conclusions: This study indicates that patients who did not recover renal function were older & had higher creatinine levels at each time point than those who recovered renal function. While there was a decrease in serum creatinine from week 3 to week 4 in patients with renal recovery, there was an increase for those who did not recover. More patients who did not recover renal function had HTN, HF & CAD. Additionally, more patients who had ATN recovered renal function, while all patients with multiple myeloma did not. Hypothesis-testing studies are needed to explore whether or not these clinical characteristics may be used to predict which patients are likely to recover renal function and which are not.

TH-PO068

Acute Kidney Injury Episodes Accelerates Rate of Loss of Renal Function in Diabetes Mellitus Charuhas V. Thakar,^{1,2} Anthony C. Leonard,^{1,3} Karthikeyan Meganathan,^{1,3} V. Shane Pankratz.⁴ ¹Internal Medicine, Univ of Cincinnati, Cincinnati, OH; ²Medicine, Cincinnati VAMC, Cincinnati, OH; ³Family Medicine, Univ of Cincinnati, Cincinnati, OH; ⁴Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: Although acute kidney injury (AKI) is a risk factor for chronic kidney disease (CKD), whether it accelerates the rate of loss of estimated glomerular filtration rate (eGFR) is not known.

Methods: In a de-identified cohort of 3,678 type 2 diabetes patients we studied the impact of AKI on the rate of decline in eGFR. Patients with an entry eGFR of > 30 ml/min and at least two creatinine (Cr) values at least one month apart were followed until their eGFR was < 15 ml/min, death, or the end of the study. Cr measurements spanned over an average of 65 months. Estimated rates of linear eGFR decline were compared between those with and without AKI. We assessed the effect of AKI on the outcome of a rapid decline in eGFR (defined as > 5 ml/min/year) adjusting for demographics, proteinuria, and baseline CKD status (initial eGFR greater or less than 60) in a multivariable logistic model, and expressed this as odds ratios (OR) and 95% confidence limits (95% CI).

Results: Patients' mean (standard deviation) age was 62 (11) years at study entry with an average eGFR of 79.7 (22.5). In 3,055 non-AKI patients the mean eGFR decline was 2.7 vs 4.2 ml/min/yr in the 623 AKI patients ($p < .0001$). For 499 AKI patients with both pre and post-AKI eGFR slopes, the mean decline pre-AKI was 2.7 ml/min/yr versus 6.3 ml/min/yr post-AKI ($p = .03$; paired t-test). In the non-AKI group 23.4% met the rapid decline outcome, compared with 36.0% in AKI group ($p < .0001$); within AKI patients, rapid decline occurred in 37% of patients pre-AKI and 46% post-AKI (paired OR = 1.4; 95% CI, 1.1-1.8, McNemar $p = .008$). AKI was associated with rapid decline (OR 1.8; 95% CI, 1.5-2.2; $p < .0001$), adjusted for age, gender, race, proteinuria, and CKD status.

Conclusions: Compared to no-AKI, diabetic patients with AKI experience an accelerated rate of decline in eGFR; and it occurs at twice the pace in the post- vs pre-AKI periods. Biological and process of care factors may be responsible for this effect.

Funding: Veterans Administration Support, Clinical Revenue Support

TH-PO069

Impact of Transient or Persistent Acute Kidney Injury on Chronic Kidney Disease Progression and Mortality After Gastric Surgery for Gastric Cancer Chang Seong Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Dept of Internal Medicine, Chonnam National Univ Hospital, Gwangju, Republic of Korea.

Background: Acute kidney injury (AKI) was common after gastric surgery for gastric cancer and associated with adverse outcomes. However, impact of transient or persistent AKI on clinical outcomes after gastric surgery for gastric cancer has not been described. The objective of this study was to determine the incidence, factors, and clinical outcomes associated with transient or persistent AKI after gastric surgery.

Methods: We performed a retrospective study of 4,886 patients with normal renal function who underwent partial or total gastrectomy for gastric cancer between June 2002 and December 2012. Transient AKI was defined as return of serum creatinine to the no-AKI range at discharge after gastric surgery. Our outcomes included occurrence of new-onset chronic kidney disease (CKD), and long-term kidney function and mortality.

Results: AKI occurred in 638 (13.1%) after gastric surgery. Of these, transient AKI was documented in 556 (87.1%). Length of intensive care unit (ICU) and hospital stay, and ICU admission rate (5.8% versus 1.0%) were higher in patients with transient AKI than in those without AKI. Male, use of diuretics and postoperative vasopressor, and lower baseline creatinine were common risk factors for persistent and transient AKI after gastric surgery. After adjusting for confounding factors, patient with transient and persistent AKI had a significantly higher new-onset CKD (odds ratio [OR], 1.62; 95% CI, 1.16-2.26, $P = 0.005$; OR, 3.60; 95% CI, 1.77-7.34, $P < 0.001$, respectively) and 1-year mortality (OR, 1.75; 95% CI, 1.15-2.66, $P = 0.009$; OR, 12.70; 95% CI, 7.57-21.31, $P < 0.001$, respectively) compared with no-AKI.

Conclusions: Not only persistent AKI but Transient AKI is associated with increased of hospital complications and a significantly higher risk of CKD progression and long-term mortality than patients without AKI after gastric surgery.

TH-PO070

Use of Non-Tunneled Versus Tunneled Catheters for Renal Replacement Therapy in Acute Kidney Injury Mallika L. Mendu, Sushrut S. Waikar. Div of Renal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: Treatment of severe acute kidney injury requiring renal replacement therapy (AKI-RRT) requires vascular access, with either temporary, non-tunneled dialysis catheters (NTDC), or tunneled dialysis catheters (TDC). The relative risks and benefits of these two vascular access options have not been well studied.

Methods: We conducted a 1-year prospective cohort study in an academic medical center to compare outcomes between TDC and NTDC for AKI-RRT. We collected information about catheter placement including reasons for type of catheter used, number of insertion attempts, duration of use, and infectious and mechanical complications.

Results: Over one year we collected information on 140 NTDC and 80 TDC placement procedures on 154 patients with AKI-RRT. Compared to NTDCs, TDCs required fewer insertion attempts (1.0 vs. 1.5), had longer median duration of use (58.5 vs. 6.5 days), and had fewer infectious and mechanical complications (6% vs. 25%) (all $p < 0.001$). The most common reasons for NTDC over TDC placement were immediate need for use (74%) and suspicion of systemic infection (21%). Tunneled line conversion (22%), infection (11%) and catheter not working (7%) were the most common reasons for NTDC removal. Infection (4%) was the most common reason for TDC removal.

AKI Causes	NTDC (N=140, N (%))	TDC (N=80, N (%))
Acute Tubular Necrosis	42 (30)	36 (45)
Hypotension	15 (11)	5 (6)
Ischemia	12 (9)	5 (6)
Prerenal	12 (9)	5 (6)
Hospital location		
Intensive care unit	133 (95)	39 (49)
Floor	7 (5)	41 (51)
Mean Insertion Attempts		p-value
	1.5	1.0
		<0.001
Total Number of Complications (mechanical and infectious)		
	35 (25)	5 (6)
		<0.001
Median Days Duration of Use (IQR)		
	6.5 (4,10)	58.5 (12, 267)
		<0.001

Catheter Placement Characteristics

Conclusions: Compared to NTDCs, the placement of TDCs was associated with fewer complications and longer duration of use in patients with AKI-RRT. In appropriate patients, TDCs should be the first choice for vascular access in AKI-RRT.

TH-PO071

Nonapnea Sleep Disorders and the Risk of Acute Kidney Injury: A Population-Based Retrospective Cohort Study Hugo You-Hsien Lin,^{1,2,3} Yu-Han Chang,¹ Chi-chih Hung,¹ Shang-Jyh Hwang,¹ Hung-Chun Chen.¹ ¹Dept of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan; ²Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; ³Graduate Inst of Medicine, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Nonapnea sleep disorders (NASD) and sleep-related problems, which are high prevalent in patients with kidney diseases, are associated with cardiovascular disease, type 2 diabetes mellitus (DM) and chronic kidney disease (CKD). However, whether NASD is associated with acute kidney injury (AKI) development and prognosis have not been thoroughly investigated. The aim of this study is to determine whether NASD is an independent risk factor of AKI by using the database of National Health Insurance Research Database (NHIRD), which is one of the largest medical databases of the world.

Methods: The retrospective study used an 11-year nationwide database, which randomly sampled of 1,000,000 individuals covered by the National Health Insurance in Taiwan, to analyze the incidence. The patients with NASD were identified through diagnostic and medication codes. Kaplan-Meier and Cox regression analyses were performed.

Results: From 2000 to 2010, 9,316 newly diagnosed NASD cases compared with 27,948 control participants without sleep disorders randomly selected, frequency matched by age, sex, index year from the general population. We demonstrated that the NASD cohort had an adjusted hazard ratio (HR; 95% confidence interval [CI] = 1.16-1.71) of subsequent AKI 1.44-fold higher than that of the cohort without sleep disorders. Elder age, lower monthly income, hypertension, DM, cerebrovascular disease, CKD status, depression and higher Charlson comorbidity index were significant factors associated with the increased risk of AKI (p<0.05). Male and younger (age< 65 year-old) female increased significant risk of AKI development with NASD (HR=2.23; 95% CI = 1.57-3.16, p<0.001).

Conclusions: This nationwide population-based cohort study provides evidence that patients with NASD are at higher risk of developing AKI than people without NASD.

Funding: Clinical Revenue Support

TH-PO072

Subarachnoid Hemorrhage Induces Transient Renal Dysfunction Naoki Ikegaya,¹ Kiyoshi Mori,⁵ Yasuhiro Yamamura,⁴ Mamoru Tomida,⁴ Seiya Takehara,⁴ Takuya Yoshida,⁶ Hiromichi Kumagai,⁶ George Seki,² Akira Hishida.² ¹Dept of Medicine, Yaizu City Hospital, Yaizu, Japan; ²Dept of Nephrology, Yaizu City Hospital, Yaizu, Japan; ³Dept of Neurology, Yaizu City Hospital, Yaizu, Japan; ⁴Dept of Neurosurgery, Yaizu City Hospital, Yaizu, Japan; ⁵Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ⁶Dept of Clinical Nutrition, Univ of Shizuoka, Shizuoka, Japan.

Background: Subarachnoid hemorrhage (SAH) is known to induce acute cardiovascular stress as reflected by ECG changes, and renal dysfunction is associated with poor prognosis in SAH. However, the precise effect of SAH on renal function and the possible mechanisms of renal dysfunction in SAH have not been fully understood.

Methods: First, we retrospectively analyzed renal function by serum creatinine (Scr) on day 1, 2, 3, 7, 14, and 28 in 317 patients with stroke including SAH, cerebral infarction (CI) and cerebral hemorrhage (CH). The relationship between renal dysfunction and ECG

abnormalities including ST elevation, depression, negative T-wave was evaluated. Next, we prospectively analyzed urinary albumin, NGAL, and L-FABP and serum Cr and NT-proBNP in 22 SAH patients on day 1, 2, and 14.

Results: The retrospective study showed that there was a significant transient increase (+40.7%) in Scr in patients with SAH in the first three days of the acute phase. However, no significant changes in Scr were observed during the course in patients with CI and CH. ECG abnormalities were observed in 57% of patients with SAH. In the prospective study, SAH patients showed increased levels of albuminuria and NT-proBNP on day 0, 1 and 14 and NGAL on day 1 and 14. Eleven SAH patients with increased levels of NT-proBNP (more than 400 pg/ml) on day 2 showed significantly higher albuminuria (108 ±147 vs. 21±11.8 mg/gCr, p< 0.005) and urinary NGAL (67.5±101.7 vs. 17.5±15.0 ng/ml, p< 0.05) than eleven patients with lower NT-proBNP (less than 400 pg/ml).

Conclusions: Significant renal dysfunction was induced in the acute phase of SAH but not in CI and CH. Renal dysfunction was associated with NT-proBNP elevation, suggesting some interactions between heart, brain and kidneys.

TH-PO073

Acute Kidney Injury Post Nephrectomy in Living Donors? Marilina Antonelou, Andrew Davenport. *Royal Free London NHS Foundation Trust.*

Background: In 2014, the NHS UK introduced an AKI screening algorithm that was integrated into all UK biochemistry laboratories to report cases with AKI with 50% increase in serum creatinine. We aimed to measure the incidence of AKI in healthy living kidney donors post laparoscopic nephrectomy and determine whether this leads to reduction in renal function in the short term.

Methods: Retrospective data collection from 71 living kidney donors presenting between 2006-2011. We calculated serum creatinine (sCr) changes defined as stage 1 AKI as per the KDIGO guidelines (sCr increase by 26.5 umol/L within 48 hours or 1.5-1.9 times baseline increase) and stage 2 AKI (2.0-2.9 times baseline increase).

Results: 54.9% of patients developed AKI: 52.1% AKI stage 1 and 2.8% AKI stage 2. The median age was 53 years (IQR 21-66 years) in the group of patients that developed AKI and 52 years (IQR 27-71 years) in the non-AKI group. 39.7% were males (26.8% with AKI) and 60.6% females (28.2% with AKI) (p 0.07). The AKI group had a lower mean sCr at baseline: 71±22.3 umol/L vs 84±18.0 umol/L (p=0.01). However, there was no difference in the CKD_e at baseline (91.6±18.6 ml/min in the AKI group vs 89±17.3 ml/min, p=0.14) as well as the raw and adjusted for surface area isotopic EDTA-GFR at baseline (101±38.2 ml/min in the AKI group vs 96±22.9 ml/min (p= 0.31) and 89±20.2 ml/min in the AKI group vs 86±16.2 ml/min (p=0.41) respectively). Post nephrectomy there was no difference in absolute renal function (CKD_e in the AKI group 62.8±15.4 ml/min vs 60.2±10.7 ml/min, p=0.06) or change in renal function (33.4±16.5% decrease in CKD_e in the AKI group vs 35.4±14.0%, p=0.25) at 6 months.

Conclusions: Although 54.9% of patients fulfilled the diagnostic criteria for AKI as reported by the laboratory AKI screening algorithm this might not reflect actual kidney injury, and there were no differences in renal function measured after 6 months.

TH-PO074

Fluid Overload and Mortality in Neonatal Intensive Care Unit Patients Requiring Continuous Renal Replacement Therapy Heeyeon Cho,¹ Sang Taek Lee,¹ Hye Won Park.² ¹Dept of Pediatrics, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea; ²Dept of Pediatrics, Seoul National Univ Bundang Hospital, Sungnam, Korea.

Background: Continuous renal replacement therapy (CRRT) has emerged as a favored modality in the management of the high risk neonates with acute kidney injury (AKI) and with inborn errors of metabolism. Recently, there are some reports that lesser degrees of fluid overload (FO) at CRRT initiation was associated with improved outcomes in children in pediatric intensive care unit (PICU). However, there has been little data that have analyzed the fluid status, risk factors, and outcome of neonates who receiving CRRT. The aim of this study is to evaluate the factors including FO associated with the outcome of neonates with CRRT.

Methods: A retrospective medical record review was performed 34 hemodynamic unstable neonates with AKI who underwent at least 48 hours of CRRT in neonatal intensive care unit (NICU) at Samsung Medical Center between January 2007 and December 2014. We divided into two groups with survivor (N=15) and non-survivor (N=19). Data were collected regarding demographic characteristics, fluid overload, CRRT parameters, and mean circuit time. Fluid overload from NICU admission to CRRT initiation, defined as a percentage equal to {(CRRT initiation weight [kg]-NICU admission weight [kg])/NICU admission weight [kg]} x 100%. CRRT was initiated without anticoagulation, and decided to use the anticoagulation if the initial circuit lifespan was less than 12 hours.

Results: Survivors were more likely to have longer gestational age, fewer days in NICU prior to CRRT, lower percent FO at CRRT initiation, and higher urine output at the end of CRRT. There was no significant difference in mean daily effluent volume between survivors and non-survivors. Adjusted regression analysis revealed that FO at CRRT initiation was associated with mortality, duration of CRRT, and hospitalization period.

Conclusions: Fluid overload might cause mortality, prolonged hospitalization period, and duration of CRRT in neonates. Early initiation of CRRT before severe fluid overload might improve the outcome of neonates requiring CRRT.

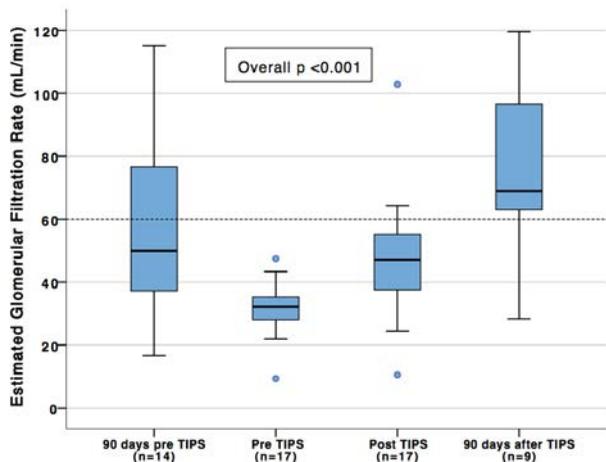
TH-PO075

Survival and Renal Outcomes following Transjugular Intrahepatic Portosystemic Shunt Placement in Hepatorenal Syndrome: A Case Series Guillermo Ortiz,¹ Andrew S. Allegretti,¹ Jie Cui,¹ Julia Beth Wenger,¹ Ishir Bhan,¹ Raymond T. Chung,² Ravi I. Thadhani,¹ Zubin Irani. ¹*Nephrology Div, MGH, Boston, MA;* ²*Gastrointestinal, MGH, Boston, MA;* ³*Radiology, MGH, Boston, MA.*

Background: Few effective treatment options are available for hepatorenal syndrome (HRS). There may be a role for the placement of a transjugular intrahepatic portosystemic shunt (TIPS) in reversing the pathophysiologic changes in HRS.

Methods: We performed a multicenter, retrospective review of patients who underwent TIPS placement concurrent to having HRS from 1995 to 2014 using a centralized clinical data warehouse. Two clinicians adjudicated HRS diagnosis and classified cases as Type 1 (T1-HRS) or Type 2 (T2-HRS) based on review of medical records. Estimated glomerular filtration rate (eGFR), survival, and other parameters were assessed immediately before and after TIPS, and 90 days pre- and post-procedure.

Results: We identified 17 cases. Mean age was 54±12 years, 12 (71%) were male, 7 (41%) had T1-HRS and 10 (59%) had T2-HRS. Median MELD score at time of procedure was 21 (quartile 1, quartile 3: 14, 33). TIPS significantly reduced portal pressure gradient from 16 (14, 20) to 7 (5, 8) mmHg (p<0.001). Median eGFR 90 days pre TIPS was 50 (37-77) mL/min; TIPS significantly improved eGFR from 32 (28, 35) pre-TIPS to 47 (38, 55) mL/min post-TIPS (p=0.003) and 69 (63,97) mL/min at 90-days post TIPS (p=0.006).



Ninety-day survival was 53%; 1 subject (6%) received a liver transplant during follow-up.

Conclusions: TIPS improves eGFR in HRS post-procedure and at 90 days follow-up. Further study is needed to identify those who would benefit from the procedure.

TH-PO076

Evolution of the Management of Multiple Myeloma and Impact on Survival and Dialysis Independence Manon Laforet, Noemie Jourde-chiche, Stephane Burtey, Bertrand Gondouin. *Centre de Nephrologie et Transplantation Rénale, Assistance Publique Hopitaux de Marseille, Marseille, France.*

Background: During the past decade, the management of myeloma has evolved. Several studies found an improved disease-free survival since the late 2000s with the advent of new molecules in first line chemotherapy (Bortezomib and / or IMiDs (Revlimid, Thalidomide). Nevertheless, this benefit is mostly seen in patients of less than 65 years old and survival and renal outcomes are not well studied in elder patients. Our study aimed to compare two cohorts of patients according to the period of treatment: before or after 2008 focussing on global and renal outcomes.

Methods: We retrospectively collected clinical and biological data of 135 patients admitted to the University Hospital of Marseille from 1999 to 2014 with a diagnosis of multiple myeloma and acute renal injury (as defined by an increase in serum creatinine above 120 mcmol/L). We separated this cohort based on the year of admission (<08> to 2008, respectively group 1 and group 2). The parameters studied were: overall survival and dialysis independence 2 years after initial chemotherapy.

Results: 88 patients were included in group 1 and 47 in group 2. No differences were seen in terms of baseline characteristics between groups: median age (67.1 vs 70.2), sex ratio, conventional biological parameters. A higher proportion of relapsing patients was found in group 2 (10/47 (22%) in group 2 versus 9/88 (10%) in group 1). A higher proportion of dialysis dependent patients at diagnosis was found in group 2 (26/47, (55.3%) in group 2 versus 36/88 (40%) in group 1). **No difference was seen in terms of overall survival or dialysis independence 2 years after diagnosis of AKI when group 2 was compared to group 1** (OR 1.9 (0.8-4.1) and HR 0.7 (0.4-1.2) respectively).

Conclusions: In our cohort, we did not observe any benefit on overall survival or dialysis independence at 2 years according to the treatment period. Our results are not in accordance with previous papers. Our patients were older with a high proportion of dialysis dependence at diagnosis. More studies are needed to clarify the benefit of the use of novel agents in older patients with severe AKI.

TH-PO077

Effect of Genes Involved in Endogenous Ouabain Synthesis on the Development of AKI After Cardiac Surgery Marco Simonini, Simona Pozzoli, Elena Frati, Elena Bignami, Lorena Citterio, Chiara Lanzani, Nunzia Casamassima, Guido Gatti, Paolo Manunta. *San Raffaele Scientific Inst, Italy.*

Background: Acute kidney Injury (AKI) is an important complication of cardiac surgery. Elevated levels of Endogenous Ouabain (EO), an adrenal stress hormone with haemodynamic and renal effects, have been associated with worse renal outcome after surgery. Polymorphisms in candidate genes related to EO synthesis, as LSS (lanosterol synthase) and HSD3B1 (steroid dehydrogenase), have been described to be involved in determination of EO activity. Aim of this work is to investigate the relationship between these genes and the development of AKI.

Methods: 700 consecutive patients, undergoing cardiac surgery at our Hospital, were genotyped. The primary outcome was AKI according to Acute Kidney Injury Network. Secondary outcomes were length of ICU stay and total in-hospital mortality. Total AKI incidence was 25.1%.

Results: No difference in basal EO plasmatic levels was observed according to LSS or HSD3B1. Patients carrying the derived alleles of the LSS studied polymorphism had a more severe clinical presentation (EuroSCORE: 5.17±4.81 vs 4.88±5.74 vs 3.54±3.49; p=0.05). Likewise, AKI incidence according to LSS polymorphism was greater (34.9% vs 27.5% vs 21%; p=0.029). Even after adjustment for the main covariates (sex, age, eGFR, EF, hypertension, DM, type of surgery and EuroSCORE) results remain significant (AKI logistic regression: Exp(B) 1.97, IC95% 1.05-3.70; p=0.038). Finally, in a higher percentage of the same patients (25.5% vs 17.0% vs 12.6%) i.v. furosemide was used in the immediate post-operative time to maintain adequate diuresis. No other effects of LSS or HSD3B1 were observed.

Conclusions: Patients with at least one derived allele of LSS polymorphism investigation have a greater chance of developing AKI after cardiac surgery, despite on clinical presentation. Moreover, in a higher percent of the same patients, i.v. furosemide was needed to maintain adequate diuresis. These effects appear to be independent on EO plasmatic levels. We believe that these preliminary findings could be interesting for the identification of new cellular mechanisms undergoing the development of post-surgical AKI.

TH-PO078

Obstructive Nephropathy in Ovarian Hyperstimulation Syndrome and Successful Delivery Katherine M. Wang, Syed S. Haqqie, Arif Asif. *Albany Medical Center, Albany, NY.*

Background: Ovarian hyperstimulation syndrome (OHSS) is a well-described iatrogenic complication of exogenous gonadotropin administration preceding *in vitro* fertilization (IVF). Underlying pathophysiology stems from influx of reproductive hormones and inflammatory vasoactive mediators that increase capillary permeability and cause intravascular volume depletion due to large fluid shifts into the interstitial space. Most cases are mild and can be managed on an outpatient basis with close monitoring. We present an intriguing and rare case of severe OHSS with acute renal failure secondary to obstructive nephropathy. Our patient is a nulliparous 38 year old black female stimulated with beta-human chorionic gonadotropin (β-hCG) prior to transfer of fresh embryos resulting in a diamniotic dichorionic twin gestation. She presented to the OB-GYN service with progressive ascites, gaining 17 kg in 1 week, and also acute renal failure due to mechanical obstruction of both ureters from bilaterally enlarged fluid-filled ovaries. Initial ultrasonography estimated the dimension of the left ovary at 22 cm, containing 1.7 L of fluid volume. Her baseline creatinine of 0.8 mg/dL peaked at 5.8 mg/dL prior to placement of bilateral nephrostomy tubes, which led to rapid and effective relief of obstruction and normalization of kidney function within days. At follow-up, patient had spontaneous intrauterine demise of one fetus at 9 weeks; however, she successfully delivered the other fetus preterm at 35 weeks gestational age via C-section. The nephrostomy tubes remained in place for the duration of her pregnancy. This case highlights a rare presentation of a well-known, but potentially life-threatening complication of ovarian induction, which has become an increasingly popular treatment for infertility.

Methods: Cinical course of the patient during the entire pregnancy and the outcome.

Results: Successful fetal outcome.

Conclusions: Patient presented with severe obstructive uropathy from very large kidneys from hyperstimulation resulting in acute renal failure and bilateral nephrostomy tube placements. This resulted in release of obstruction, normalization of renal function, and a successful delivery.

TH-PO079

Analysis of the VA/NIH Acute Renal Failure Trial Network Data: Comparison of Outcomes in Nutrition Delivery in Acutely Dialyzed Patients Youngho Kim, V. Shane Pankratz, Eduardo A. Alas, Christos Argyropoulos, Mark L. Unruh. *Div of Nephrology, Univ of New Mexico School of Medicine, Albuquerque, NM.*

Background: The optimal nutrition management for acute kidney injury (AKI) is not well defined and recommendations for nutritional support in acutely ill patients who undergo renal replacement therapy (RRT) are largely based on expert opinion.

Methods: In order to better understand associations between nutrition and outcomes of critically ill patients with AKI requiring RRT, we analyzed data available from the ATN study. Patients were classified by nutritional support provided at the time of enrollment

into the following groups: NPO, Tube feed (TF), Total parenteral nutrition (TPN), and Oral (PO). Two competing outcomes were considered: mortality and continued dialysis dependency among survivors.

Results: Characteristics among groups were similar. ICU predictive scoring systems and disease etiology were strongly associated with mode of nutrition delivery. High ICU predictive score and a surgical primary treating service were associated with a higher percentage of patients treated with TPN. There were significant differences in 60-day outcomes among nutrition groups (p=0.011) [Figure 1]. Notably, PO group had better survival and RRT independency. After adjustment for patient characteristics, the strength of association between mode of nutrition delivery and outcomes weakened and was not statistically significant (p=0.106), although the patterns of association were similar to the unadjusted analyses with TPN having the highest and PO the lowest adjusted risks of death and continued dialysis dependency.

Figure 1: Dialysis dependency and mortality at 60 days

Baseline Nutrition	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
	Dialysis Dependency	Death	Dialysis Dependency	Death
NPO	1.72 (0.86–3.45)	1.89 (1.24–2.88)	1.43 (0.69–2.97)	1.46 (0.90–2.38)
Tube Feed	1.89 (0.89–4.03)	2.11 (1.33–3.36)	1.47 (0.66–3.30)	1.54 (0.90–2.63)
TPN	2.87 (1.11–7.46)	3.15 (1.68–5.92)	2.18 (0.77–3.80)	3.14 (1.54–6.41)
PO	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)

Conclusions: There was no significant global association between baseline nutrition modalities and 60-day mortality or 60-day dialysis dependency. Further investigation could be performed to prospectively elucidate the benefit of enteral vs. TPN feeding in AKI.

TH-PO080

Pilot Trial of Dietary Restriction for Protection from Acute Kidney Injury in Cardiac Surgery Franziska Grundmann, Torsten Kubacki, Roman-Ulrich Mueller, Maximilian Scherner, Michael Faust, Ingrid Becker, Martin Späth, Marc Johnsen, Thomas Benzing, Volker Rolf Burst. *Univ of Cologne, Cologne, Germany.*

Background: Even small acute changes in kidney function as a result of acute kidney injury (AKI) can result in short-term and long-term complications including chronic kidney disease, end-stage renal disease and death. However, despite an increasing incidence of AKI few preventive and therapeutic options exist. Short-term reduction of calorie intake has been shown to provide effective protection from ischemic AKI in mice.

Methods: In this single-center randomized controlled trial (ClinicalTrials.gov Identifier: NCT01534364) 82 patients with at least one risk factor for postsurgical AKI scheduled for cardiac surgery (CABG, valve replacement) were randomly assigned in a 1:1 ratio into a diet group (DG: 60% of calculated energy expenditure for 7 days prior to surgery) or an ad libitum food intake control group (CG). The intention-to-treat population encompassed 76 patients. The primary endpoint was defined as the change in serum creatinine from baseline to 24 hours after surgery, secondary endpoints included incidence of AKI (KDIGO criteria).

Results: Demographic and surgery associated characteristics were similar in both groups (DG 80% male vs. CG 77.5% male; age: DG 72y[63-76] vs. CG 75y[70-77], body weight: DG 84.6kg[72-91.7] vs. CG 79.1kg[75.0- 72.7], crossclamp time: DG 59min[52-82] vs. CG 59min[44-82]). Average calorie intake in the DG was 1323 kcal and a 3 kg[-4.0 to -2.2] weight loss was observed (no weight change in the CG). With respect to the primary outcome measure there was no difference between the groups. Overall incidence of AKI was similar in both groups with considerably less patients with stage 1 AKI in the DG (n.s.). Length of stay, need for renal replacement therapy and mortality did not differ.

	Diet Group	Control Group
no AKI	21(58.3%)	21(52.5%)
KDIGO 1	7(19.4%)	13(32.5%)
KDIGO 2	6(16.7%)	5(12.5%)
KDIGO 3	2(5.6%)	1(2.5%)

Conclusions: Dietary restriction is safe and feasible in patients awaiting cardiac surgery. Despite its beneficial effect in animal studies restriction of calorie intake did not alter serum creatinine dynamics or AKI incidence after cardiac surgery.

Funding: Pharmaceutical Company Support - Fresenius Kabi

TH-PO081

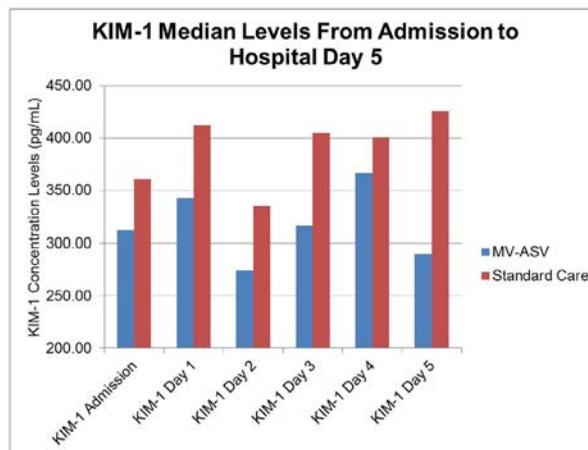
Minute Ventilation-Targeted Adaptive Servo Ventilation Reduces Kidney Injury in Patients with Acute Decompensated Heart Failure Matt Kawahara,³ Boris Arbit,¹ Elizabeth Lee,³ Trenton Gluck,³ Kathleen Sarmiento,² Atul Malhotra,² Alan S. Maisel.¹ ¹Div of Cardiovascular Medicine, Univ of California, San Diego, La Jolla, CA; ²Div of Pulmonary and Critical Care Medicine, Univ of California, San Diego, La Jolla, CA; ³Cardiac Research, VA San Diego Healthcare System, La Jolla, CA.

Background: Acute kidney injury (AKI) is a frequent comorbidity in patients admitted for acute decompensated heart failure (ADHF). Minute ventilation targeted adaptive servo ventilation (MV-ASV) relieves apneas, pulmonary congestion, and renal hypoxia. Kidney

injury molecule (KIM-1) is a marker of AKI and could be used to detect early injury and the improvement of kidney function. MV-ASV may mitigate AKI in patients admitted of ADHF compared to standard care.

Methods: This is a pilot study in which twenty-one consecutive patients with ADHF were randomized to receive either MV-ASV therapy (S9 VPAPAdapt, ResMed Corp.) with standard care, or standard care alone. MV-ASV therapy was administered for a minimum of six hours per day for up to 5 days, or until discharge. Daily measurements of plasma KIM-1 were obtained with SMCTM technology (Singulex). Daily serum creatinine levels were measured and used to calculate eGFR.

Results: Median baseline KIM-1 levels in the MV-ASV and standard groups were 312pg/mL and 361pg/mL, respectively. In the control group KIM-1 increased 18 % to 426pg/mL while the group with MV-ASV demonstrated a mitigation of kidney injury with a 7% decrease to 290pg/mL. These changes correlated with subsequent changes in serum creatinine and eGFR.



Conclusions: The use of MV-ASV therapy resulted in mitigation of kidney injury typically seen in patients with ADHF during hospitalization.

Funding: Pharmaceutical Company Support - Resmed

TH-PO082

Early Volume Expansion Improves the Outcome of Shigatoxin-Associated Hemolytic Uremic Syndrome – Data from the North Italian HUS Network Gianluigi Ardissino,¹ Francesca Tel,¹ Ilaria Possenti,¹ Sara Testa,¹ Dario Consonni,² Stefania Salardi,¹ Rosaria Colombo,³ Erminio Torresani.³ ¹Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy; ²Unit of Epidemiology, Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy; ³Unit of Microbiology, Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy.

Background: Shigatoxin-associated hemolytic uremic syndrome (STEC-HUS) is a severe disease which has no specific treatment and among supportive care, fluid management is concentrated on preventing fluid overload because of oligo/anuric AKI. Hemoconcentration is associated with more severe disease, but it is unknown whether volume expansion (VE) can improve disease outcome. A network of pediatric hospitals has been operating in Northern Italy with the aim of early diagnosis and referral of STEC infections and to investigate the efficacy of VE to minimize disease severity.

Methods: All children with STEC-HUS referred to our centre in 2012-2014 received intravenous saline targeted at inducing a moderate VE (+10% of working weight) on the basis of the hypothesis that prompt restoration of circulating volume can limit thrombi formation and ischemic tissue damage. Their short- and long-term outcomes were compared with those of 38 patients (pts) referred to our centre during the years immediately before the network was established, when their fluid intake was routinely restricted.

Results: The pts undergoing VE showed a mean increase in body weight of 12.5%vs0% in their predecessors and had significantly better short-term outcomes with a reduced rate neurological involvement (7.9%vs23.7%,p 0.059), less need for dialysis (26.3%vs57.9%,p 0.005) or intensive care support (median 8.5,IR 3.5-15.5vs2.0,IR 1-4.5 days,p 0.022), and required fewer days of hospitalisation (median 12.0, IR 7.0-18.0vs9.0,IR 7.0-12.0 days,p 0.025). Long-term outcomes were also significantly better in terms of renal and extra-renal sequels (13.2%vs39.5%,p 0.009).

Conclusions: Pts with STEC-HUS benefit greatly from VE. Early and generous fluid infusions can reduce thrombi formation and ischemic organ damage, and thus have positive effects on both short- and long-term disease outcomes.

TH-PO083

Role of Statins on Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention Ricardo M. Heguilen, Amelia R. Heguilen, Martin J. Ortemberg, Amador A. Liste. *Nephrology, Hospital Juan A Fernandez, Buenos Aires, Argentina.*

Background: The occurrence of contrast-induced kidney injury (CIAKI) increased and is responsible for ~10% episodes of hospital-acquired AKI. The mechanism of renal dysfunction is incompletely understood; vasoconstriction, hyperosmolality, free radicals and direct toxicity may play additive roles. Statins reduce O₂ stress, increase renal NO and may prevent AKI. The aim of this retrospective study was to analyse the association between statin and the development of RCIN, defined by an increase in SCr >25 % 48–72 h after the administration of low osmolar contrast agents, in high risk patients (Ps) undergoing percutaneous coronary intervention (PCI).

Methods: Data from 165 consecutive adults with SCr >1.25 mg/dl, undergoing non-emergent PCI during a 24- mo period were assessed. All had received prophylaxis for RCIN (volume expansion + NAC). 31 Pts were removed due to absence of follow up SCr data or lacked information on statin use. Continuous variables are expressed as mean (sd) and categorical variables as frequency. Unpaired t-test, chi2 or Fischer’s exact test were used as appropriate. Those variables resulting significantly related to RCIN on univariate analysis, were included in a multivariate logistic regression model. P-values <0.05 were considered significant.

Results: 134 Pts met the admission criteria; 67 were on statins prior PCI. Both groups had similar clinical, and laboratory baseline conditions. 18 Pts (13.4%) developed RCIN. There was a lower incidence of RCIN among Pts on statins (4.47%) vs. those not on statins (22.4%) (OR: 0.16; 95% CI: 0.04–0.59; P=0.004). Multivariate logistic regression revealed that, after adjusting for covariates with significant association with RCIN in the univariate analysis (diabetes, hiponatremia, etc), statins demonstrated to be an independent predictor of decreased risk for RCIN.

	OR	95% CI	p value
Statin	0.14	0.037- 0.5653	0.005
DBT	3.67	1.168- 11.540	0.026
HypoNa	2.45	0.728- 8.262	0.148

Conclusions: Our data suggest that statin use before PCI reduces the risk of RCIN. Further prospective, well designed, randomized clinical trials in a larger number of individuals are necessary to confirm these findings.

TH-PO084

Statin Use and Survival After Acute Kidney Injury Sandeep Brar, Neesh I. Pannu. *Dept of Medicine, Univ of Alberta, Edmonton, AB, Canada.*

Background: The incidence of acute kidney injury (AKI) in hospitalized patients is rising, and there is a lack of effective therapies for treatment. Recent studies suggest that nephrology follow-up may reduce long term mortality after AKI; however, the processes of care that underlie this finding remain unknown. The objective of this study was to determine if statins which are of known benefit in chronic kidney disease (CKD) are also associated with improved mortality in survivors of AKI with CKD.

Methods: Retrospective cohort study of adults 65 years of age or older, residing in Alberta, who were admitted to hospital between 2002 and 2011, developed AKI during the index hospitalization and progressed to CKD (n= 27,470 mean age 78.7 years, mean post-discharge eGFR 49.6 mL/min/1.73m²).

Results: Within two years of discharge, only 39.1% of the participants received a statin. Over a subsequent two-year follow up period, the adjusted hazard ratio (HR) (95% confidence interval [95% CI]) for mortality associated with use of a statin was 0.64 (0.59, 0.69). Patients who received a statin also had a lower risk of cardiovascular events (adjusted HR, 0.87; 95% CI, 0.80, 0.94) and all cause re-hospitalization (adjusted HR, 0.81; 95% CI, 0.77, 0.84).

Conclusions: Among AKI survivors with CKD, statin use was associated with decreased mortality, cardiovascular events and re-hospitalization rates.

TH-PO085

Effect of Rosuvastatin on Acute Kidney Injury (AKI) in Sepsis-Associated Acute Respiratory Distress Syndrome (ARDS) Raymond K. Hsu,¹ Jonathon Truwit,² Michael Matthay,¹ Joseph Levitt,³ Boyd Taylor Thompson,⁴ Kathleen D. Liu.¹ ¹UCSF; ²Medical College of Wisconsin; ³Stanford; ⁴MGH-Harvard.

Background: While statins may be protective in animal models of sepsis-induced AKI, few human studies have addressed this question.

Methods: We analyzed data from the NHLBI ARDS Network Statins for Acutely Injured Lungs in Sepsis (SAILS), a multicenter randomized controlled trial. 745 patients with sepsis-associated ARDS were randomized to receive rosuvastatin or placebo. Subjects who had AKI at enrollment and subjects with new or worsening AKI were defined by KDIGO creatinine-based AKI criteria. In a secondary analysis, we corrected serum creatinine (SCr) for cumulative fluid balance. The association between statin and AKI was modeled using logistic regression.

Results: 644 subjects did not have ESRD and had available SCr data. Age, sex, race, baseline SCr, and severity of illness were similar in the 2 treatment arms. Among the 511 without AKI at enrollment, AKI incidence was similar in the two groups (38% statin vs

40%, P=0.66). The association remained non-significant after adjustment for demographics and severity of illness, and after correcting SCr for fluid balance. Among 93 subjects with stage 1 AKI at enrollment, the statin arm had a higher incidence of worsening AKI (61% vs 41% placebo, P=0.06). The association was strengthened after adjustment (OR 3.06, P=0.03). However, in the secondary analysis using fluid-corrected SCr, rosuvastatin was not associated with worsening AKI.

Risk of new AKI in patients without AKI at enrollment (n=511)	OR (Rosuvastatin vs Placebo)	p
Crude	0.92 (0.65-1.32)	0.66
Adjusted	0.99 (0.67-1.44)	0.94
Crude + SCr corrected for fluid balance	0.84 (0.59-1.21)	0.35
Adjusted + SCr corrected for fluid balance	0.91 (0.63-1.34)	0.64
Risk of worsening AKI in patients with stage 1 AKI at enrollment (n=93)		
Crude	2.26 (0.97-5.24)	0.06
Adjusted	3.06 (1.14-8.22)	0.03
Crude + SCr corrected for fluid balance	1.41 (0.61-3.27)	0.42
Adjusted + SCr corrected for fluid balance	1.85 (0.70-4.84)	0.21

Conclusions: Rosuvastatin did not prevent de novo AKI, and may have led to worsening of pre-existing AKI in patients with sepsis-associated ARDS.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO086

Potential Nephroprotective Effects of Carnitine and Phosphodiesterase-5 Inhibitor Therapy in Contrast-Induced Nephropathy Zaher Anis Armalay,¹ Suheil Artul,² Adel Rafik Jabbour,³ Raymond Farah,⁴ Amir Abd Elkadir,¹ Bishara Bisharat.¹ ¹Dept of Nephrology, E.M.M.S. Hospital, Bar Ilan Univ, Nazareth, Israel; ²Dept of Radiology, E.M.M.S. Hospital, Nazareth, Israel; ³Dept of Biochemical Laboratory, E.M.M.S. Hospital, Nazareth, Israel; ⁴Internal Medicine “B”, Ziv Medical Center, Faculty of Medicine, Bar Ilan Univ, Safed, Israel.

Background: Contrast induced nephropathy (CIN) is connected with , prolonged hospitalization, need for dialysis and increased morbidity and mortality. The current available prophylactic measures are not sufficient to protect against CIN. Therefore, there is unmet need for novel therapeutic agents to prevent the development of CIN. This study examines whether phosphodiesterase type 5 (PDE-5) inhibitor or carnitine exert nephroprotective effects in individuals undergoing imaging that involves radioccontrast media (CM) administration as compared with N- acetyl Cysteine.

Methods: The study included 3 arms of patients with CKD (stage 3-4) as follows:1- Control group (n=14) , who were treated with Acetylcysteine of 600 mg twice daily, day before and on the day of CM administration; 2- Carnitine group (n=10), where the patients were infused with 20 mg/kg carnitine over 10 minutes 2 h prior to the CM administration and 24 hours post CT; 3- Phosphodiesterase type 5 inhibitor group (n= 12), where patients were given orally 20 mg tablets of PDE5 inhibitor-Tadalafil 2 h prior to the administration of the CM and in the subsequent day. Urine and blood samples were collected before and at the following time sequence: 2, 6, 12, 24, 48, 120 hours after the contrast administration, for creatinine and NGAL determination.

Results: Administration of CM to CKD patients who were pretreated with Acetyl cysteine caused a significant increase in urinary NGAL, but not of plasma NGAL and SCr. In contrast, pretreatment with carnitine prior to CM prevented the increase in urinary NGAL throughout the follow up period and reduced SCr below basal levels. Similarly, tadalafil administration attenuated the elevation in CM-induced urinary NGAL, but did not affect neither plasma NGAL nor SCr.

Conclusions: These results suggest that carnitine and PDE-5 inhibition may comprise novel nephroprotective approaches aganist CIN.

TH-PO087

Acute Interstitial Nephritis: Case Series, 1998-2015 Xuemei Li. *Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: Acute interstitial nephritis (AIN) is an important cause of acute kidney injury. The time and effectiveness of steroids for treatment of AIN is debated.

Methods: Study Design: Case series. **Study population:** 40 cases with acute interstitial nephritis(secondary AIN was excluded) conformed by renal biopsy in PUMC hospital between 1998 and 2015 years were analysed. **Outcomes:** The complete recovery was defined as improvement in serum creatinine level to 124umol/L; partial recovery as a 50% decrease in serum creatinine level from its peak value, but not reaching to 124umol/L; and no recovery as failure to meet criteria for complete or partial recovery or remaining on renal replacement therapy.

Results: The causes were not available in most cases (63%), 15% were identified due to drugs. Infectious causes were 13%. Idiopathic AIN were 10%. 68% patients had no records of baseline serum creatinine levels, which were available for 13 patients only (106±14.7umol/l), and 5(38%) patients had CKD as defined by baseline eGFR <60 mL/min/1.73 m². 30% patients had hematuria. 33% patients had glycosuria. Some degree of proteinuria (less than 1g/L) was present in 75% of patients. 60% patient had anaemia

(105±14.8). Most of the patients had normal urine output. 5 patients (12.5%) had larger kidney in ultrasound. 33 patients (83%) used steroids treatment. The periods of steroid treatment were 12±4.7 months. The time which began to use steroids was 33±15.2 days from SCr increased. The doses of steroid were 49±10.1 mg/d. The SCr level was 210±83.8 μmol/l when started steroid treatment. Only 5 patients (13%) added immune inhibitors. Of the 40 patients, 48%, 38%, and 10% had complete, partial, and no recovery respectively in discharge. 65% had normal renal function and 30% had CKD by 15±9.7 months. Of the 6 patients who required dialysis or CRRT, no patients were still on dialysis therapy in discharge, all of whom had drug-induced AIN. No patients had ESRD, with no difference by cause of AIN.

Conclusions: The cause of AIN may be different. Steroid treatment may be effective in recovery of kidney function of AIN.

TH-PO088

Causality Assessment in Determining Drug-Induced Renal Injury
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Background: Drug induced renal injury (DIRI) accounts for 18-27% of cases of acute kidney injury (AKI) and is usually recognized based on the timing and duration of drug exposure. The Naranjo (NJ) and Liverpool (LP) causality assessment tools (CAT) are validated for identifying adverse drug reactions and serious skin reactions, respectively. We hypothesized that inter-rater and inter-tool agreement using the two CAT would not be specific to identify DIRI.

Methods: The drug induced renal injury (DIRECT) study is an ongoing prospective multicenter study evaluating genetic determinants of DIRI. Each enrolled case was adjudicated for causality by two independent nephrologists. We analyzed the first consecutive 86 adult (n=69) and pediatric (n=17) AKI cases. Two nephrologists adjudicated each case and used both CAT to determine likelihood of AKI due to a particular medication(s). We determined inter-rater and inter-tool agreement using percent agreement and kappa scores.

Results: Adjudicators agreed 87.2% (n=75) had DIRI. A single drug was involved in 54.7% (n=47), 2 drugs in 37.2% (n=32), and 3 drugs in 8.1% (n=7) of cases. The inter-rater agreement was better with the NJ vs LP tool (61.6% vs 48.8%) and was significant for adults (p<0.038) however the inter-tool kappa score was slight (0.181) and was fair (kappa 0.325) for pediatric patients (p=0.006).

Categories	Inter-rater		Inter-tool
	Naranjo	Liverpool	
All Cases	61.6 0.251 (p=0.01)*	48.8 0.140 (p=0.04)*	50 0.181 (p=0.001)*
DIRI	58.7 0.206 (p=0.052)	52 0.049 (p=0.557)	49.3 0.109 (p=0.074)
No DIRI	81.8 0 (p=1)	27.3 0.064 (p=0.489)	54.5 0.16 (p=0.147)
1 Drug	57.4 0.199 (p=0.126)	57.5 0.250 (p=0.011)*	58.5 0.312 (p<0.001)*
Adult	59.4 0.224 (p=0.038)*	49.3 0.154 (p=0.026)*	47.8 0.142 (p=0.017)*
Pediatric	70.6 0.351 (p=0.116)	47.1 0.131 (p=0.441)	58.8 0.325 (p=0.006)*

*, denotes significant p-value <0.05

Conclusions: For most categories, inter-rater percent agreement and kappa scores were superior using the NJ tool. Neither tool had better than moderate inter-rater agreement. Agreement between the tools was at best fair in determining likelihood of DIRI. Better causality assessment tools need to be developed for DIRI.

Funding: Private Foundation Support

TH-PO089

Gadolinium Nephrotoxicity Kamlesh Reddy Kurre, Ashraf El-Meanawy, Sameer Gupta. *Nephrology, Zablocki VA Medical Center, Milwaukee, WI.*

Background: Gadolinium-based contrast (GBC) agents are widely used as contrast agents for magnetic resonance imaging (MRI) and have generally been considered to be safe. Early on, phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity. In the US, approximately 34.9 million MRI scans were performed in 2014 and in 45% of these cases a gadolinium chelate was administered. As with iodinated radiocontrast agents, concern for contrast-induced nephropathy existed with gadolinium-contrast as it possessed many similar qualities (hyperosmolar, renal excretion via glomerular filtration). Gadolinium-based contrast agents have recently been reported to induce a usually reversible decrease of glomerular filtration rate in a high-risk population group, especially in patients with altered baseline renal function. The lethal dose of gadolinium in animals is increased by 100 folds when gadolinium is in the form of a chelate. This raises a concern that the leaching of free metal from the chelate can pose health risk.

Methods: We present a prospective study involving 122 patients (48 male and 74 female) who had an elective MRI performed. Subjects have been fasting for at least 8 hrs prior to the imaging. We collected a blood sample 1 hr prior to the imaging and followed up with a repeat blood sample collection 48 hrs after completion of the imaging procedure.

Results: These samples were analyzed for serum creatinine and BUN levels. Preliminary data shows that 46.43% (52 out of 112) of the study subjects exhibited worsening of renal function while 53.57% (60 out of 112) had normal or slightly improved renal function.

Conclusions: Preliminary data analysis suggests gadolinium induces nephrotoxicity in general population including patients with normal kidney function and with chronic kidney disease. We appreciate the limitation of the study which are mainly the number of subjects and the fasting status of subjects. Since there was no exclusions, patient who are on diuretics and ACEI inhibitors could display a higher base line creatinine which might explain the improvement of renal function post study in some subjects.

TH-PO090

Risk of Pediatric Acute Kidney Injury Is Increased with Vancomycin and Piperacillin-Tazobactam Combination Therapy Joseph Michael Rusnak,¹ Cristin Kaspar,¹ Timothy E. Bunchman,¹ Nianzhou Xiao,¹ Megan M. Lo,¹ Jeremy S. Stultz,² *¹Pediatric Nephrology, Children's Hospital of Richmond at Virginia Commonwealth Univ, Richmond, VA; ²Pharmacotherapy and Outcomes Science, Virginia Commonwealth Univ, Richmond, VA.*

Background: Hospitalized pediatric patients at risk for infection are often treated with vancomycin (vanc) and piperacillin-tazobactam (PT). Risk of nephrotoxicity from vanc and other antimicrobials (e.g. aminoglycosides, beta-lactams) is well-described. Recently, an increased risk of acute kidney injury (AKI) resulting from combination therapy of vanc with PT has been reported in the adult literature, but not in the pediatric literature.

Methods: Retrospective single center study of hospitalized pediatric patients £20 years who received vanc, PT, or the combination for 48 hours or more. Data collection included creatinine levels, medication and demographic characteristics. Patients on ECMO or dialysis were excluded.

Results: 164 patients identified, 30 (18.3%) developed AKI (definition: ≥ 50% above baseline creatinine) after beginning treatment with the antimicrobials. Eight patients in the vanc alone and PT alone groups (8%) versus 22 patients in the combination group (34.4%) developed AKI (p<0.0001). The median percent creatinine change from baseline was significant (p=0.03) between the combination and single therapy groups of 104% and 52.3%, respectively.

	AKI	Non-AKI
Total Number (%)	30 (18.3%)	134 (81.7%)
Median Age, years (range)	9.5 (3 months - 20 years)	9 (1 month - 19 years)
Vanc Only	4 (8.2%)	45 (91.2%)
PT Only	4 (7.8%)	47 (92.2%)
Combination Vanc & PT	22 (34.4%)	42 (65.6%)

Conclusions: Results of this study suggest a higher risk of AKI in pediatric patients receiving the combination therapy of vanc and PT compared to single drug therapy with either. Further studies are needed to determine if other confounding factors (e.g. dehydration, medical diagnosis, or additional nephrotoxins) contribute to the risk of AKI with this particular combination, or if there is a safer alternative for broad-spectrum antimicrobial coverage in the pediatric population.

TH-PO091

Associations Between Vancomycin, Other Antibiotics, Acute Kidney Injury and Mortality in Hospitalized Patients Victoria Gutgarts,^{1,2} Christian Suarez,^{1,2} Ladan Golestaneh,^{1,2} Michal L. Melamed.^{1,2} *¹Nephrology, Montefiore Medical Center, Bronx, NY; ²Nephrology, Albert Einstein College of Medicine, Bronx, NY.*

Background: Vancomycin is a commonly prescribed antibiotic. Animal and human studies suggest that vancomycin can cause acute kidney injury (AKI). We hypothesized that exposure to vancomycin with other nephrotoxic antibiotics (aminoglycosides) will be associated with AKI compared to vancomycin use with non-nephrotoxic antibiotics in hospitalized patients.

Methods: We performed a retrospective observational study, including patients 18 years or older admitted from 2008 and 2010 at Montefiore Medical Center. All patients had at least two serum creatinine values during their admission and a baseline creatinine within 6 months prior to admission. AKI was defined as a 50% increase in baseline serum creatinine. One year mortality data was from the Social Security Death Index.

Results: Of 46,580 admissions, 2,104 developed AKI (4.7%). 7,889 patients (17%) had exposure to vancomycin, 1,172 patients (2.5%) had exposure to aminoglycosides and vancomycin, 3,700 patients (7.9%) had exposure to fluoroquinolones and vancomycin and 3,994 patients (8.6%) had exposure to cephalosporins and vancomycin. Those developing AKI were more likely female (70% vs 63% p<0.001), had GFR < 60 (37% vs 22% p<0.001) and vancomycin exposure (31% vs 16% p<0.001). The AKI risk associated with vancomycin alone was 1.55 (1.37, 1.76), combining vancomycin and gentamicin the risk was 1.95 (1.56, 2.45) while vancomycin with fluoroquinolones was 1.38 (1.17, 1.63) and vancomycin with cephalosporins was 1.37 (1.16, 1.62). The risk of mortality associated

with vancomycin alone was 2.27 (2.06, 2.49), combining vancomycin and gentamicin the risk was 3.87 (3.26, 4.58), combining vancomycin with fluoroquinolones the risk was 3.42 (3.05, 3.84), and combining vancomycin with cephalosporins the risk was 2.62 (2.34, 2.95).

Conclusions: Our data suggests that vancomycin exposure is associated with a high risk of AKI and mortality, especially in combination with aminoglycosides. Further studies should be conducted to evaluate whether aminoglycosides should not be used in combination with vancomycin in order to prevent AKI.

TH-PO092

Adverse Renal Effects of Targeted Anti-Cancer Therapies: A Systematic Review of Data from the FDA Adverse Event Reporting System Kenar D. Jhaveri, Rimda Wanchoo, Daniel W. Ross, Vipulbhai Sakhiya, Steven Fishbane. *Nephrology, Hofstra NSLLJ, NY.*

Background: Novel molecular targeted anti-cancer therapies have shown improvement in patient survival compared to standard chemotherapy. Renal toxicities of novel targeted therapies are limited to case reports.

Methods: We reviewed the FDA Adverse Event Reporting System's (FAERS) quarterly legacy data file (2011-2014). We queried the database for medications listed below. The adverse events queried were: hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, proteinuria, renal failure acute. To compare what has been published, we searched PubMed for each medication plus each adverse event.

Results: Total number of adverse events reported were 1,657. Ipilimumab had the highest number of events (341) and these were mostly acute renal failure (126) and hyponatremia (112). In PubMed review all case reports were diagnosis of renal failure. The second highest number of events occurred in cetuximab and most of the events were impaired renal function (128). For all targeted therapies listed below in figure, the most common adverse event was acute renal failure (549). The most common electrolyte abnormality was hypokalemia (367). More males developed renal failure at mean age of 65y as opposed to females with mean age of 61y (<0.01). More females got electrolyte disorders at mean age of 59y compared to males at 61y (<0.01). For all medications, renal adverse events were more common in males mean age 63y compared to females mean age 59y (<0.01). Hypokalemia was more common in females (<0.01) and hyponatremia more common in males (<0.01). Figure below compares all agents searched.

Drug name	Established Toxicity by Literature Review	First, Second Most Common Adverse Event in FAERS
AFATINIB	No reported adverse renal toxicity	Kidney Injury, Hyponatremia
CETUXIMAB	Hypokalemia, Hypomagnesemia	Kidney Injury, Hypokalemia
CRIZOTINIB	Hypophosphatemia, Kidney Injury	Kidney Injury, Hyponatremia
DABRAFENIB	No reported adverse renal toxicity	Kidney Injury, Hyponatremia
ERLOTINIB	Small number of Hypokalemia, Hypophosphatemia	Kidney Injury, Hyponatremia
GEFITINIB	Case report of nephritis, Case report of Proteinuria	Hypokalemia, Hyponatremia
IMATINIB	Hypophosphatemia, Case reports of kidney injury	Kidney Injury, Hyponatremia
IPILIMUMAB	Case reports of nephritis, Case reports of Hyponatremia	Kidney Injury, Hyponatremia
LAPATINIB	Hyponatremia, Hypophosphatemia	Hypokalemia, Kidney Injury
PANITUMUMAB	Hypokalemia, Hypomagnesemia	Hypomagnesemia, Hypokalemia
Pertuzumab	No reported adverse renal toxicity	Kidney Injury, Hypokalemia
REGORAFENIB	Proteinuria, Hypophosphatemia, Renal Failure	Kidney Injury, Hyponatremia
TRAMETINIB	Hypokalemia	Kidney Injury, Hyponatremia
TRASTUZUMAB	Kidney Injury, Hyponatremia	Hypokalemia, Kidney Injury
Trastuzumab Emtramsine	No reported adverse renal toxicity	Hyponatremia, Renal Failure
VANDETANIB	Hypophosphatemia	Kidney Injury, Hyponatremia, Hypomagnesemia
VEMURAFENIB	Kidney Injury, Proteinuria	Kidney Injury, Hyponatremia

Conclusions: Our data elucidate previously unknown adverse renal events in targeted therapies. Older males are at higher risk for renal failure and females are at higher risk for electrolyte disorders from certain targeted anti-cancer therapies.

TH-PO093

Vemurafenib and Dabrafenib Related Renal Toxicities Kenar D. Jhaveri, Rimda Wanchoo, Vipulbhai Sakhiya, Steven Fishbane. *Nephrology, Hofstra NSLLJ School of Medicine, NY.*

Background: Vemurafenib and dabrafenib, selective BRAF inhibitors has shown significant improvement in patient survival compared to standard therapy in V600 mutant metastatic melanoma. No cases of AKI have been reported with dabrafenib use. AKI has been recently reported in few case series with vemurafenib use. One case series included a patient who had a kidney biopsy demonstrating acute tubular necrosis as a potential mechanism of renal injury.

Methods: We reviewed the FDA Adverse Event Reporting System's (FAERS) quarterly legacy data file from 3rd quarter of 2011 to 2nd quarter of 2014 for vemurafenib and 2nd quarter of 2013 to 2nd quarter of 2014 for dabrafenib. Vemurafenib and dabrafenib related renal adverse event data were extracted through formation of a query using FAERS assigned unique case identifiers. Search terms utilized were "renal insufficiency, elevated creatinine, renal failure, renal injury, proteinuria, renal impairment, blood creatinine increase, renal failure acute, low phosphorus, hypophosphatemia, hypercreatinemia, hyponatremia, hypokalemia, renal damage".

Results: 132 cases of AKI were reported secondary to vemurafenib to the FAERS in the time frame reviewed. Eighty five patients were men and 47 women (p=0.01). Average age of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from around the world with France, USA and Germany having most of the cases. Fourteen cases of electrolyte disorders were reported (hypokalemia-6 cases and hyponatremia-8 cases). A total of 13 cases were reported of AKI from dabrafenib to the FAERS in the time frame stated above. Twelve patients were men. Average age of the men were 55 and 75 years for women (p=0.0022). Eight cases of electrolyte disorders were reported (hypokalemia-2 cases and hyponatremia-6 cases).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: While the FAERS reporting system is a crude database with scant demographic information, the number of cases reported of AKI is still alarming with the BRAF inhibitors. Vemurafenib appears to be more nephrotoxic than dabrafenib. This renal toxicity seems to be more prominent among male patients with melanoma. Dermatologists, oncologist and nephrologists need to be made aware of this important toxicity.

TH-PO094

Protective Effects of Oral L-Arginine Supplement in Patients with Chronic Kidney Disease After Intravenous Contrast Media Injection: A Randomized Controlled Trial Theerasak Tangwonglerit. *Medicine, Phramongkutkiao Hospital.*

Background: Contrast-induced acute kidney injury (CI-AKI) is a common complication in hospitalized patients. Nitric oxide-signal transduction plays an important role in prevention of CI-AKI. L-Arginine is an amino acid involved in ammonia detoxification, and is well known as a precursor to nitric oxide, a key component of endothelial-derived relaxing factor.

Methods: A randomized, double blind, placebo controlled trial was done in CKD stage 3-4 patients undergoing computer tomography. Eligible patients were randomly assigned into two groups: arginine 3 g in 6 gelatin capsules orally per day, and placebo 6 capsules as the same manner for 3 days before contrast media injection. Serum cystatin C, creatinine, electrolyte, estimated GFR and urinary nitric oxide were measured at baseline and 48 hours after procedure.

Results: A total of 84 patients were screened. Sixty percent were male with mean age of 74 years. 27 patients in arginine group and 34 patients in placebo group were analyzed. There were no significant differences between the arginine and placebo groups regarding baseline demographic and biochemical characteristics, including baseline GFR (48.8 ± 8.8 mL/min/1.73 m2 versus 48.8 ± 7.5 mL/min/1.73 m2). The incidence of CI-AKI was 3.7% (1 patient) in the arginine group and 23.53% (8 patients) in the placebo (p = 0.036). No serious adverse event was detected in the both groups. There is a trend toward an increase in urinary nitric oxide difference in patients with CI-AKI.

Conclusions: This study indicated that oral L-arginine supplement before intravenous contrast media injection plus the standard hydration regimen can prevent CI-AKI in hospitalized patients with CKD stage 3-4.

TH-PO095

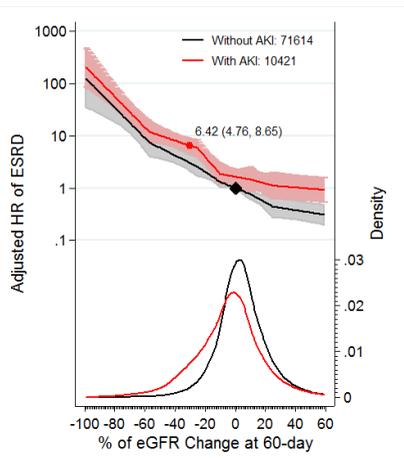
Decline in Estimated Glomerular Filtration Rate After Acute Kidney Injury: A Surrogate Endpoint? Morgan Grams,¹ Yingying Sang,¹ Josef Coresh,¹ Shoshana Ballew,¹ Kunihiro Matsushita,¹ Tom Greene,² Andrew S. Levey,³ Miklos Zsolt Molnar,⁴ Zoltan Szabo,⁵ Kamyar Kalantar-Zadeh,⁶ Csaba P. Kovesdy,^{4,7} ¹JHU; ²Utah; ³Tufts; ⁴UTHSC; ⁵Linköping Univ; ⁶UC Irvine; ⁷Memphis VA Medical Center.

Background: Often a transient condition, acute kidney injury (AKI) is not currently accepted as an endpoint for drug registration trials by the US FDA. We sought to determine whether an intermediate-term change in eGFR after AKI has a sufficiently strong relationship with subsequent ESRD to serve as an alternative endpoint in clinical trials of AKI prevention and/or treatment.

Methods: We evaluated 161,185 US veterans who underwent major surgery between 2004-2011. Post-surgical AKI was defined by the KDIGO creatinine criteria; decline in eGFR was calculated from pre-hospitalization value to two time-points post-discharge (60-days, 90-days) and related to ESRD and mortality using Cox proportional hazards regression.

Results: In-hospital mortality varied by AKI status, ranging from 1% for patients without AKI to 35% for those with dialysis-requiring AKI. An eGFR decline of ≥30% at 60-days was relatively frequent: 2.5%, 9.7%, 17.2%, and 28.6% in those with no AKI, Stage 1 AKI, Stage 2 AKI, and Stage 3 AKI, respectively. There was a graded relationship between eGFR decline at 60-days and risk of ESRD in persons both with and without AKI (Figure). Compared to stable eGFR/no in-hospital AKI, the adjusted hazard ratio (HR) of ESRD associated with a 30% decline at 60-days after AKI was 6.42 (95% CI: 4.8-8.7). Risks for mortality associated with eGFR decline were smaller: the HR for 30% decline 60-days after in-hospital AKI was 1.59 (95% CI: 1.46-1.73). Risk relationships were similar at 90-days.

Conclusions: A 30% decline in eGFR from pre-hospitalization baseline to 60-days or 90-days after an episode of AKI may be an acceptable surrogate endpoint in trials of AKI prevention and/or treatment.



Funding: NIDDK Support, Private Foundation Support

TH-PO096

Creatinine Changes After Contrast: Chloride Poor versus Chloride Rich Solutions *Asish Thakkar, Rima Kang, Salem Almaani, Udayan Y. Bhatt. Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH.*

Background: There has been recent emphasis on utilization of chloride poor solutions for the prevention of acute kidney injury (AKI). The purported mechanism is the potential for chloride rich fluids to possibly impair renal blood flow. Similarly, exposure to intravenous radiographic contrast is known to induce renal vasoconstriction. Given these findings, the objective of this project was to examine the effect of chloride rich versus chloride poor intravenous (IV) fluids on the change in serum creatinine occurring after IV contrast administration.

Methods: This project was performed under an IRB-approved Honest Broker Protocol. Retrospective data was obtained from patients receiving IV contrast over a 4 week period. Variables collected included: age, race, gender, type of contrast procedure, baseline creatinine, creatinine at days 1 and 2, and all intravenous medications. Chloride rich solutions (normal saline) and chloride poor solutions (sodium bicarbonate, Plasmalyte, and Lactated Ringers) were identified. Multivariate linear modelling was used to examine the primary endpoint of change in creatinine at day 2 relative to baseline (delta creatinine).

Results:

	Cl Poor(N=22)	Saline(N=220)	p-value
Age	62.4±11.6	58.7±16.8	NS
Male	6(27.3%)	120(54.5%)	0.021
Caucasian	18(81.8%)	172(78.2%)	NS
Heart Catheterization	2(9.1%)	10(4.5%)	NS
Baseline Creatinine	1.38±0.88	0.94±0.49	0.003
Delta Creatinine	0.09±1.00	-0.06±0.37	NS
Multivariate analysis			
	Delta Creatinine Chloride rich verse Cl poor		p-value
Saline	-0.370		0.000

The change in creatinine after IV contrast in the chloride rich group, after adjusting for all variables including baseline creatinine, was 0.37±0.09 lower than in the chloride poor group (p=0.000).

Conclusions: Patients receiving chloride rich IV solutions appeared to have a significantly lower change in serum creatinine after administration of IV contrast compared to patients receiving chloride poor solutions. On this basis, more investigation is needed on chloride poor solutions to fully define the most appropriate utilization.

TH-PO097

Clinical Characteristics in Patients with Alcoholic Ketoacidosis and Acute Kidney Injury *Hyeon-Cheol Park, Shinhan Song, Jae seok Kim, Jae Won Yang, Byoung Geun Han, Seung-Ok Choi. Internal Medicine, Yonsei Wonju College of Medicine, Korea.*

Background: Alcoholic ketoacidosis (AKA) is a serious disorder that has a high mortality. Acute kidney injury (AKI) is a typical complication of AKA, which is known to be associated with increased mortality. This study aimed to investigate clinical characteristics and risk factors for AKI in patients with AKA.

Methods: We retrospectively reviewed records of 357 patients who had been diagnosed with AKA in Wonju Severance Christian Hospital from January 2004 to March 2014. We investigated clinical history and characteristics, laboratory data, progress and mortality.

In addition, we estimated Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score for assessing severity of patients. Lastly, we investigated the risk factors for AKI.

Results: A total of 357 patients were included in the study. Among them, 293 patients (82.1%) were diagnosed with AKI by AKIN (Acute Kidney Injury Network) criteria; stage I (n=80, 22.4%), stage II (n=70, 19.6%), stage III (n=143, 40.1%). Mortality was reported in 84 patients (23.6%), and mean interval from initial visit to mortality was 6.0 ± 10.7 days. As the AKI stage advanced (non-AKI vs. stage I vs. stage II vs. stage III), the mortality rate increased (3.1 vs. 7.5 vs. 25.7 vs. 40.6%), and APACHE II / SOFA scores were elevated as well (11.1 vs. 13.2 vs. 19.4 vs. 22.5 / 3.6 vs. 4.5 vs. 7.3 vs. 9.5). In addition, clinical history of liver cirrhosis, complications of rhabdomyolysis, pancreatitis, infection, and in hospital cardiac-arrest showed the more occurrence frequencies in the advanced AKI stages. However, alcohol histories including duration of total alcohol intake, last drinking day before the visit, and alcohol amounts to intake were not associated with AKI stages. Lastly, our study demonstrated that independent risk factors for AKI in the patients with AKA included rhabdomyolysis (odds ratio, 7.1, 95% confidence interval, 2.3-22.2) and pancreatitis (3.7, 1.1-11.8).

Conclusions: This study indicates that AKI in the patients with AKA is associated with higher mortality, and the major risk factors for AKI include complications of rhabdomyolysis and pancreatitis.

TH-PO098

Renal Cortical Necrosis following Postpartum Hemorrhage: A Case Series *Marie Frimat,¹ Mélanie Decambrat,¹ Celine Lebas,² Viviane Gnemmi,³ Benedicte Sautenet,⁴ Francois Glowacki,¹ Eric Rondeau,⁵ Christian Noel,¹ Francois Provot,¹ Alexandre Hertig.⁵ ¹Nephrology, CHRU Lille, Lille, France; ²Nephrology, CH Valenciennes, Valenciennes, France; ³Anatomopathology, CHRU Lille, Lille, France; ⁴Nephrology, CHRU Tours, Tours, France; ⁵Nephrology, APHP, Tenon Hospital, Paris.*

Background: Pregnancy-related renal cortical necrosis induces severe kidney damage and may thus result in end stage renal disease. Although this obstetrical complication had virtually disappeared in high-income countries, we noted new cases in France during the past few years, all in the aftermath of a postpartum hemorrhage.

Methods: We retrospectively identified 18 patients from 5 French departments of Nephrology who developed renal cortical necrosis following postpartum hemorrhage between 2009 and 2013. Obstetrical and renal features, therapeutic measures, and renal outcome were studied. In order to identify prognostic factors for renal outcome, we stratified the analysis according to the estimated glomerular filtration rate at 6 months postpartum: $\leq 15\text{ml/min}$ or dialysis-dependent (Gp1) versus $> 15\text{ml/min}$ (Gp2).

Results: All patients had a severe postpartum hemorrhage (mean blood loss: $2.6 \pm 1.1\text{L}$). Hemodynamic instability and disseminated intravascular coagulation were reported in 5 and 11 patients, respectively. All had a rapid onset of acute kidney injury and required hemodialysis. Diagnosis of renal cortical necrosis was performed 4 to 33 days following delivery. At 6 months post-partum, 8 patients remained dialysis-dependent and none recovered normal renal function. Retrospectively, the severity of the initial presentation was comparable between the Gp1 (n=9) and Gp2 (n=9) groups. Only the maintenance dose of tranexamic acid treatment was significantly more prolonged in the Gp1 patients (7.1 ± 4.8 hours versus 2.9 ± 2.4 hours, $p=0.031$).

Conclusions: The pejorative outcome of pregnancy-related renal cortical necrosis seems darkened by a prolonged use of tranexamic acid. In a setting of gravid endothelium, disseminated intravascular coagulation and concomitant use of fibrinogen, we speculate that the accumulation of this antifibrinolytic drug due to acute kidney injury might facilitate the uncontrolled clotting in renal cortex.

TH-PO099

Intermittent Hemodialysis (IHD) versus Sustained Low Efficiency Dialysis (SLED) for Lithium Toxicity: A Case Series *Justine Bunka, Alejandro Quiroga. Dept of Pediatric Nephrology, Dialysis, and Kidney Transplant, Helen DeVos Children's Hospital, Grand Rapids, MI.*

Background: Severe lithium toxicity is a medical emergency requiring hemodialysis when patients present with toxic levels (above 2.5mmol/L) and/or are symptomatic. This case series describes two pediatric patients who presented with severe lithium toxicity, one who was treated with intermittent hemodialysis (IHD) and the other who was treated with sustained low efficiency hemodialysis (SLED). We report a successful single use of SLED in a pediatric patient with lithium toxicity without the need for further dialysis.

Methods: A 16 year old female with history of depression was admitted to the Pediatric ICU after ingestion of multiple medications as a suicide attempt including lithium carbonate extended release 300 mg tabs. The patient was started on continuous CVVHDF due to hemodynamic instability requiring multiple vasopressor agents. CVVHDF was initiated when the patient's lithium level was 0.62mmol/L and it was continued for 12 hours. Eighteen hours after cessation of CVVHDF, the lithium level rebounded to 2.5mmol/L and conventional intermittent hemodialysis (IHD) was required for 2 consecutive days. After IHD, lithium level decreased to below 1mmol/L when dialysis was discontinued. A 12 year old male with history of bipolar depression on chronic lithium therapy presented to the Pediatric ICU with altered mental status and tremors with a lithium level of 4.0. Sustained low efficiency dialysis (SLED) was done for 8 hours until lithium level was below 1.0. After SLED was discontinued the rebound lithium level peaked at 1.4 and the neurologic symptoms resolved, indicating no further dialysis was needed.

Conclusions: SLED is an effective modality for lithium clearance and may reduce the total duration needed for IHD due to less rebound of lithium level.

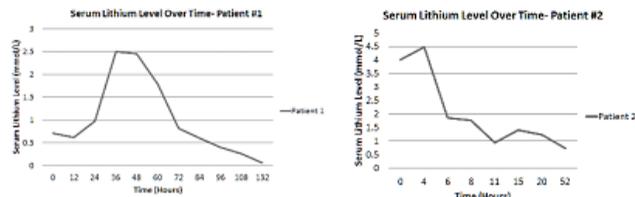


Figure 1. serum lithium levels for Patient #1 and Patient #2 Patient #1 (left) lithium level peaked at 2.5mmol/L which occurred 18 hours after CVVHDF was completed. The remaining levels were taken over the next two days during which the patient received 2 rounds of hemodialysis. Patient #2 (right) had a Lithium level at presentation of 4.02mmol/L. After 8 hours of SLED the lithium level was 1.0mmol/L. The peak level of the rebound effect was 1.4mmol/L and then the level continued to decrease without any further dialysis.

TH-PO100

Demographic Characteristics of Acute Kidney Injury and Utilization of Continuous Renal Replacement Therapy with Extracorporeal Life Support in Adult Patients Christopher Hebert, Brain Lima, Britton Blough, Avery Smith, Omar Hernandez. Dept of Internal Medicine, Div of Nephrology, Baylor Scott and White Health Care System, Dallas, TX.

Background: Extracorporeal life support (ECLS), also known as extracorporeal membrane oxygenation (ECMO) has been used over the last 40 years to help manage patients with severe cardiovascular or respiratory illnesses. Acute kidney injury is a very common complication in this particular patient population as is the need for renal replacement therapy. Much of the success and experience related to extracorporeal therapies has been limited to neonatal and pediatric populations. More recent data suggests that centers who perform a higher volume of ECMO cases have better outcomes. This study presents a demographic assessment of the first 199 cases of ECMO utilization over the last 36 months along with outcomes, specifically related to acute kidney injury.

Methods: We collected data for review of the first 199 cases of patients treated with ECLS at Baylor Scott and White Health Care System since July of 2012. We examined the patient demographics, type of ECLS, indication, location, comorbidities, incidence of acute kidney injury by RIFLE criteria and need for renal replacement therapy. Specific outcome measurements we looked at were overall survival, ability to wean from ECLS or bridge to transplant, withdraw of care, need for long term dialysis, and death.

Results: In our ECMO program, 144 patients were male (72%) and 56 were female (28%). Regarding the types of ECLS, 136 were VA ECMO, 61 were VV ECMO and there were 2 RVADs. The main indications for ECLS were Cardiac in 129 cases, pulmonary in 63 cases, and 8 were ECPR. There were 61 patients who required CRRT. The majority of these were VA ECMO (41 patients) and the rest were VV ECMO (20 patients). A total of 129 patients were weaned from ECLS, 92 of which survived to discharge. Survival was worse in patients with AKI, overall survival on ECMO was 64.5% versus 36% for those on CRRT with AKI.

Conclusions: Our data set is fairly consistent with ELSO registry numbers. AKI appears to impact mortality in similar fashion. We hope to gain insight into more prospective research regarding this unique patient population.

TH-PO101

Performance of Renal Replacement Therapy for Acute Kidney Injury in Adult Patients on Extracorporeal Life Support Christopher Hebert. Dept of Internal Medicine, Div of Nephrology, Baylor Scott and White Health Care System, Dallas, TX.

Background: Extracorporeal life support is being used more commonly in adult patients with severe cardiovascular and respiratory illnesses. Acute kidney injury requiring renal replacement therapy is a very common complication in this patient population. Much of the data regarding the technical aspect of these concurrent procedures has been limited to neonatal and pediatric patient populations. We sought to examine the most efficient and effective ways to deliver renal replacement therapy in conjunction with extra corporeal life support.

Methods: Between July 2012 and March 2015, our institution performed 200 cases of extracorporeal life support. Of these cases, 61 required renal replacement therapy. Individual decisions regarding timing of initiation of renal replacement therapy and specific modality were based on physician discretion regarding other patient comorbidities, type of ECMO, and overall goals of care. Data was then collected on isolated cases that faced specific complications with respect to the technical aspect of performing renal replacement therapy. Our institution utilized the NXStage System One dialysis machine, and the Macquet Rotaflow or Cardiohelp ECMO machine.

Results: The most common and effective way to perform continuous renal replacement therapy was to place the arterial line after the pump in the circuit, and return the blood before the oxygenator in the circuit. This minimized the risk of potential thrombosis to the patient and circuit clotting. Machine alarms would have to be interpreted in light of circuit position, and often had to be overridden. These included positive arterial pressures, high venous pressures, arterial blood flow during ECMO “chattering”, and high chamber pressures.

Conclusions: Continuous renal replacement therapy can easily be safely and effectively implemented into almost any extracorporeal life support system circuit. There are technical

challenges with each type of machine, that can be circumvented through a thorough understanding of each circuit. A good understanding of ECLS and CRRT allows teams to troubleshoot a different set of challenges than traditional CRRT. We hope to evaluate this patient population in a more standardized fashion with respect to interventions and outcomes in future studies.

TH-PO102

Prescribed versus Delivered Dose of Continuous Veno-Venous Hemodialysis in a Non-Study Population Aqsa F. Rahman, Majid A. Khan, Akshar N. Patel, Krystal Hunter, Lawrence S. Weisberg, William D. Sirover, Christopher B. McFadden. Nephrology, Cooper Univ Hospital, Camden, NJ.

Background: Critically ill patients requiring continuous renal replacement therapy (CRRT) experience high mortality rates. In randomized studies, intensification of CRRT by increasing effluent volumes from 20 to 35 ml/kg/hr did not improve survival. These studies ensured achievement of prescribed dose. We evaluated how often a subject achieves the prescribed dose in a non-study population.

Methods: We conducted a retrospective, observational cross sectional study and examined the electronic medical records (EMR) of subjects receiving CRRT. An automated, real time wireless link from the dialysis machines to EMR, contained data on the CRRT settings and hourly effluent volumes. With this data we calculated percentages of prescribed dosages achieved and compared subjects who did or did not achieve the prescribed dose. Access problems, procedures, electrolyte disturbance or no clear reason documented were investigated as variables in subjects not achieving prescribed doses. Pearson Chi Square or Fisher exact tests were used to compare dichotomous, and Independent T test or Mann Whitney U tests were used to compare continuous variables.

Results: This study represents an analysis of 73 of a planned 90 subjects. We found that 14% subjects achieved 100% of prescribed dose, 53% achieved 80-99% and 33% achieved < 80%. Mean prescribed dose was 25 ml/kg/hr and achieved dose was 20 ml/kg/hr. Access/Filter problems were present in 63.4%, imaging/procedure 12% , electrolyte imbalance 2% and no clear reason documented in 19.2% when goal dose was not achieved. Subjects in whom CVVHD was not interrupted achieved > 96% of prescribed dose which was statistically significant (P<0.001) compared to 76.5% achieved in subjects that had interruptions.

Conclusions: In a non-study population the proportion of patients who do not achieve prescribed CRRT dose is very large. In order to achieve a dose of 20 ml/kg/hr effluent volume the prescribed dose may need to be significantly higher in a non-study population. Timely correction of access/filter problems is another area of focus which may need attention for better dose achievement.

TH-PO103

A Predictive Model for Successful Conversion of Continuous Renal Replacement Therapy to Intermittent Hemodialysis for Acute Kidney Injury in Critical Ill Patients Ji Hyeon Park, Jee Eun Park, Subin Hwang, Hye Ryoung Jang, Woosong Huh, Dae Joong Kim, Yoon-Goo Kim, Ha Young Oh, Jung eun Lee. Nephrology, Samsung Medical Center, Seoul, Korea.

Background: Continuous renal replacement therapy (CRRT) is preferred modality of renal replacement therapy (RRT) in critical ill patients with acute kidney injury (AKI). However, it has several disadvantage such as high cost and risk of continuous anticoagulation. Therefore, initial application of CRRT and subsequent conversion to intermittent hemodialysis (IHD) could be practical. However, there has been no standard criteria for optimal timing of conversion to IHD in patients receiving CRRT. The aim of this study was to develop a predictive model for successful conversion of CRRT to IHD.

Methods: This case-control study was conducted by retrospective chart review. We identified 513 adult patients who received CRRT at least 24 hours and then IHD subsequently in ICU between April 2009 and February 2014. Failure in conversion to IHD was defined when CRRT was re-applied within 72 hours after CRRT stop, and 83 out of 513 patients corresponded failure criteria: failure group. Equal number of patients were selected randomly from remaining 430 patients: success group.

Results: Cardiovascular (CV) SOFA score and neurologic (NR) SOFA score at CRRT stop day were only two independent predictors of conversion failure. The risk of failure was discriminated between score 0,1 and score 2-4 for both CV and NR SOFA. CV SOFA score 2-4 was associated with 13 fold increased Odds ratio for failure (95% C.I. 4.6 - 38.3, Ref 0-1) and NR SOFA score 2-4 was associated with 5.4 fold increased Odds ratio for failure (95% C.I. 2.6 - 11.4, Ref 0-1). Final prediction model included CV SOFA and NR SOFA weighting CV SOFA (≥ 2) as 2 points and NR SOFA (≥ 2) as 1 point. Risk score ranged from 0 to 3 points (0; 47%, 1; 29%, 2; 13%, 3; 11%). The performance of this model was acceptable with area under the receiver operating characteristic curve of 0.79 (95% C.I. 0.77-0.86).

Conclusions: The prediction model might provide an objective criteria for conversion to IHD in patients receiving CRRT and contribute to establish cost-effective protocol of RRT for AKI in critical ill patients.

TH-PO104

Mortality Factors in Septic Shock Patients Requiring Continuous Renal Replacement Therapy and Timing Effect Based in Urine Output
 Xose Luis L. Perez-Fernandez,¹ Florentina E. Sileanu,² Joan Sabater Riera,¹ Kathleen D. Liu,³ John A. Kellum.² ¹Servei de Medicina Intensiva, Hospital Univ de Bellvitge, L' Hospitalet de Llobregat, Barcelona, Spain; ²Critical Care, Univ Pittsburgh Medical Center, Pittsburgh, PA; ³Nephrology & Critical Care, Univ California San Francisco Parnassus MC, San Francisco, CA.

Background: Our primary objective was to identify factors associated with mortality in patients with septic shock and severe acute kidney injury (AKI) in order to design future interventional trials.

Methods: Observational retrospective study conducted in two tertiary care hospitals with more than 100 intensive care unit (ICU) beds each. Data were from 2000-2008 at UPMC (Pittsburgh, USA) and 2006-2012 at HUB (Barcelona, Spain). The final cohort included 938 patients who received CRRT and presented with septic shock. Cox models were used to identify variables associated with 90 day mortality. Timing analyses were performed in patients with severe AKI at ICU admission who were started on RRT within the first 5 days of ICU stay.

Results: Overall 90day mortality was 62.9%. Independent risk factors for death included: age, SOFA score at ICU admission, days from hospital admission to ICU admission, days from ICU admission to CRRT initiation, and medical (vs surgical) admission. Both lower creatinine at CRRT start and lower urine output in the 24 hours before start of CRRT were associated with lower survival. ROC curve analysis identified urine output less than 500 ml in the 24 hours prior to CRRT initiation as the best variable to discriminate between survivors and non-survivors.

Conclusions: In patients with septic shock and advanced AKI (KDIGO stage 3), survival is lower when CRRT is started in the setting of low urine output. However, whether this finding represents differences in severity of illness between study subjects or is a useful tool to time CRRT initiation needs to be evaluated in a future randomized controlled trial.

Funding: Government Support - Non-U.S.

TH-PO105

Outcomes in Acute Kidney Injury Patients Undergoing Continuous Venovenous Hemodiafiltration and Regional Citrate-Based Anticoagulation: A Comparison Between Individuals with and without Liver Dysfunction
 Thais O.C. Santos,¹ Marisa S. Oliveira,¹ Henrique Pinheiro Konigsfeld,¹ Virgilio Gonçalves Pereira,² Marcelo Costa Batista,^{1,2} Oscar Santos,^{1,2} Bento C. Santos,^{1,2} Julio M. Monte,^{1,2} Marcelino Souza Durao.^{1,2} ¹Univ Federal de São Paulo, Brazil; ²Hospital Israelita Albert Einstein, Brazil.

Background: Regional citrate-based anticoagulation (RCA) has been widely used in intensive care unit (ICU) to treat subjects with acute kidney injury (AKI). Patients with liver failure (LF) have citrate metabolism impairment and are likely to experience citrate toxicity.

Methods: A prospective observational study was performed in a private hospital ICU, comparing clinical and laboratory data including citrate (Ci) plasma concentration from patients with and without LF. LF was defined as an International Normalized Ratio (INR) ≥ 2.5 . Trisodium-citrate 4% was infused in the dialysis system to keep post-filter ionized calcium between 0.25-0.35mmol/L. Patients with LF had a Ci fixed-set infusion of 17mmol/h (120 ml/h) regardless of the post-filter ionized calcium value.

Results: Two hundred patients were evaluated. LF group patients showed a higher mortality rate (70.5% vs 51.8%, $p=0.014$). Ci was significantly higher in the LF group (median 3.497vs2.786mg/dL, $p<0.03$) in all evaluated days. LF group showed higher INR (median 2.68vs1.42, $p<0.001$), lactate levels (median 34vs16mEq/L, $p<0.001$) and lower serum bicarbonate (median 15.8vs19.4mEq/L, $p<0.001$) at baseline, as well as throughout the study period. There was no significant difference regarding systemic ionized calcium levels. LF group patients also underwent more red blood cell transfusions (median 3 vs 1, $p<0.001$). There were no differences in relation to delivered dose (33ml/kg/h), number of filters used and total dialysis time. Analyzing the relationship between serum levels of citrate and total calcium/ionized calcium ratio (CaT/Cai), we found a weak positive correlation, with the highest correlation coefficient of 0.354.

Conclusions: LF group showed higher mortality. Despite the LF group have presented higher citrate levels, there were no signs of toxicity, especially ionic hypocalcemia. There was a poor correlation between CaT/Cai ratio, a predictor of citrate toxicity, and Ci levels.

Funding: Government Support - Non-U.S.

TH-PO106

Outcomes in a Cohort of Patients with Acute Kidney Injury Submitted to Continuous Venovenous Hemodiafiltration: The Role of Negative Fluid Balance and Early Dialysis
 Thais O.C. Santos,¹ Marisa S. Oliveira,¹ Henrique Pinheiro Konigsfeld,¹ Marcelo Costa Batista,^{1,2} Oscar Santos,^{1,2} Bento C. Santos,^{1,2} Virgilio Gonçalves Pereira,² Julio M. Monte,^{1,2} Marcelino Souza Durao.^{1,2} ¹Univ Federal de São Paulo, Sao Paulo, Brazil; ²Hospital Israelita Albert Einstein, Sao Paulo, Brazil.

Background: Several factors are associated with adverse outcomes in acute kidney injury (AKI). These include some comorbidities, sepsis, high prognosis scores, positive fluid balance, and delay in beginning dialysis.

Methods: In a prospective and observational study, we evaluated risk factors for death in 183 patients with AKI requiring continuous venovenous hemodiafiltration (CVVHDF).

Results: Sepsis was the main cause of AKI (57%). Overall mortality was 58%. The median cumulative fluid balance (FB) during dialysis was -4127mL among non-survivors and +646mL among the survivors. There were 114 oliguric individuals. Independent risk factors for death in multivariate analysis were chronic obstructive pulmonary disease (COPD) (OR 3.07, 95% CI 1.01 to 9.32, $p=0.047$), liver cirrhosis (OR 4.47, 95% CI 1, 77 to 11.3, $p=0.002$), hematologic malignancy (OR 6.19, 95% CI 1.83 to 20.93, $p=0.003$), oliguria (OR 3.01, 95% CI 1.43 -6.32, $p=0.004$), positive cumulative FB during dialysis (OR 1.13, 95% CI 1.06 to 1.20, $p<0.001$) and time between ICU admission and beginning of CVVHDF (OR 1.13, 95% CI 1.01 to 1.25, $p=0.039$). Among survivors, nearly 30% were discharged dependent on dialysis and, among those who were discharged out of dialysis, there was a statistically significant reduction in glomerular filtration rate in relation to admission (81 vs 50mL/min/1.73m², $p<0.001$). The SAPS 3 score at ICU admission showed unsatisfactory performance as a predictor of death in patients with AKI (AUC=0.637, 95%CI, 0.557 to 0.717).

Conclusions: We found an association between positive FB during dialysis, oliguria, late starting dialysis and death in patients with AKI submitted to CVVHDF. Others factors related to death were COPD, hematologic malignancy and liver cirrhosis.

Funding: Government Support - Non-U.S.

TH-PO107

The Impact of Dialysis-Dependent Acute Kidney Injury on Mortality in Myeloma: Findings from England Hospital Episode Statistics Data
 Punit Yadav,^{1,2} Felicity K. Evison,¹ Jason Sangha,³ Daniel Ian Ray,^{1,2} Adnan Sharif,¹ Jennifer H. Pinney,¹ Mark Trehane Drayson,^{1,2} Mark Cook,^{1,2} Paul Cockwell.^{1,2} ¹Univ Hospital Birmingham, UK; ²Univ of Birmingham, UK; ³St. James Univ Hospital, UK.

Background: In patients with myeloma, severe acute kidney injury requiring in-hospital dialysis treatment is a life-threatening complication. However the current incidence and mortality risk associated with dialysis is unknown. We aimed to examine the incidence and impact of dialysis on the survival of patients with first diagnosis of myeloma.

Methods: We utilised hospital episode statistics to analyse data from 36,348 patients with a first diagnosis of myeloma in England from April 2006 to March 2014. We examined the incidence and impact of in-hospital dialysis on overall survival, by year of presentation. Cox proportional outcome models were used to adjust for age, gender, area socio-economic deprivation, ethnicity and comorbidity.

Results: We identified 1240 (3.4%) patients who received dialysis treatment within 28 days of a diagnosis of myeloma. In Kaplan-Meier analysis patients who did not receive dialysis had better median overall survival (3.0 years; interquartile range [IQR] 0.7-8.1) than patients who received dialysis [1.4 years; IQR 0.2-4.6]. From 2006/7 to 2010/11 survival improved from 2.6 years [IQR 0.6-7.7] to 3.3 years [IQR 1.0-not reached] for patients who did not receive dialysis and 0.6 [IQR 0.1-2.7] to 1.2 years [IQR 0.4-4.0] for those who received dialysis respectively. Compared to patients who did not receive dialysis, those who received dialysis were more likely to be older, male, and less socio-economically deprived.

Conclusions: Dialysis is a major independent risk factor for increased mortality in patients with myeloma; the overall survival of patients with myeloma requiring dialysis is improving.

TH-PO108

Predictors of Survival in the ICU Patient on Continuous Venovenous Hemofiltration (CVVH)
 Amina Saqib, Jwalant R. Modi, Gautam Kishore Valecha, Abdul H. Siddiqui, Suzanne E. El Sayegh. *Medicine, Staten Island Univ Hospital.*

Background: In the ICU setting, Acute Renal Failure is a part of multiple organ dysfunction syndrome with mortality in these patients ranging from 28%-90%. Continuous Venovenous hemofiltration (CVVH) is most commonly used for renal replacement therapy in ICU's. The objective of this study is to describe demographic characteristics and to establish an association between these characteristics and variables that define the severity of illness and in-hospital mortality outcomes of patients undergoing CVVH.

Methods: Medical records of patients who underwent CVVH from January 2007 to December 2013 in the intensive care at our institution were analyzed. Chi Square test was done for categorical variables. Descriptive analysis was used to identify demographic data.

Results: 233 patients underwent CVVH from January 2007 to December 2013. The overall mortality was 75.22%. 49.3% of patients required ventilatory support. Acute respiratory failure requiring mechanical ventilation was associated with significantly increased mortality, 76.74% vs 40.0% ($p=0.04$) in patients who did not require mechanical ventilation. Septic Shock was the most common reason for ICU admission, 71.2% followed by post-operative admissions at 18.8%. The most common indication for CVVH was ATN (63.9%) followed by hyperkalemia (57.0%). However, CVVH for metabolic acidosis was associated with highest mortality at 81.06% vs. 67.02% in patients who underwent CVVH for other indications. Poor APACHE II scores were associated with higher mortality. Scores ranging from 0-24 were associated with an overall mortality of 69.9% whereas scores between 25-50 were associated with an overall mortality of 80.53%.

Conclusions: This observational study in patients undergoing CVVH in an ICU setting revealed that patients presenting with worse baseline APACHE II scores had poor in-hospital outcomes. CVVH initiation for metabolic acidosis and use of mechanical ventilation was associated with higher mortality. There are no established guidelines for use of CVVH. This study may aid in delineating the group of patients who may benefit the most from use of CVVH and help us in more judicious use of health care resources. .

TH-PO109

Clinical Effectiveness of Diuretics following Continuous Renal Replacement Therapy Do Hee Kim, Subin Hwang, Jin Hae Kim, Jee Eun Park, Ji Hyeon Park, Jung Eun Lee, Woosong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh, Hye Ryoung Jang. *Div of Nephrology, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea.*

Background: There is no consensus regarding diuretics administration in acute kidney injury (AKI) in patients weaning from continuous renal replacement therapy (CRRT). The effect of diuretics on the clinical course of critically ill patients with AKI was analyzed focusing on urine output and renal recovery following CRRT. In addition, we tried to identify the most optimal administration method of diuretics.

Methods: A total of 1213 adult patients who survived more than 3 days after discontinuing CRRT between September 2009 and December 2014 were included. Changes in renal function and urine output as well as the prescription of diuretics during the 3 days after discontinuation of CRRT were retrospectively analyzed. Patients were categorized depending on re-initiation of RRT within 3 days.

Results: There was no difference in baseline characteristics among all groups. CRRT cessation group had greater urine output after discontinuation of CRRT compared with other groups. Overall, patients who were treated with diuretics (diuretics subgroup) showed greater urine output than patients without diuretics (control subgroup) after cessation of CRRT and there was no difference in the degrees of serum creatinine elevation between control and diuretics subgroups. In CRRT cessation group, continuous infusion of furosemide showed greater urine output compared to other administration methods. However, serum creatinine increased significantly compared to other methods when the infusion was continued for more than 1 day.

Conclusions: Diuretic therapy following CRRT increases urine output significantly without causing significant deterioration of renal function. Compared with other methods using diuretics, continuous infusion of furosemide increases urine output significantly, but also increases serum creatinine further when continued for more than 1 day. Our study suggests that diuretics in patients who had received CRRT may be clinically useful.

TH-PO110

The Prognostic Value of Volume Status Assessment by Bioelectrical Impedance Analysis and Lung Ultrasound on Mortality in Septic Acute Kidney Injury Patients Undergoing Continuous Renal Replacement Therapy Sul A Lee, Shin-Wook Kang, Tae-Hyun Yoo. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Volume overload affects clinical outcome in patients with acute kidney injury (AKI). However, the significance of various methods to evaluate volume status has not been fully evaluated. Therefore, the prognostic value of volume status assessment measured by bioelectrical impedance analysis (BIA) and lung ultrasound (US) on mortality was investigated in septic AKI patients requiring continuous renal replacement therapy (CRRT).

Methods: Septic AKI patients requiring CRRT between April 2014 and February 2015 at Yonsei University Health System were included. Surrogates of volume status were 1) percent of body weight change between CRRT initiation and admission day, 2) over-hydration (OH)/extracellular water (ECW) measured by BIA, and 3) B-lines measured by lung US. Prognostic values of surrogates of volume status for 28-day mortality were evaluated.

Results: Among the 36 enrolled patients, 19 (52.8%) patients died during the follow-up duration. The mean percentage of weight change and OH/ECW measured by BIA was $5.3 \pm 20.7\%$ and 0.3 ± 0.1 L/L. The median number of B-lines counted by lung US was 6 (interquartile range, 4-10). OH/ECW was significantly correlated ($r=0.39$, $P=0.02$) with 48-hour fluid balance before CRRT initiation, while the number of B-lines was not. Kaplan-Meier analysis showed that 28-day mortality was higher in patients with the highest OH/ECW tertile compared to patients with lower OH/ECW values ($P=0.02$). Percent of weight change and the number of B-lines were not significantly associated with 28-day mortality ($P=0.44$ and $P=0.45$, respectively). Multivariate Cox proportional hazard regression analysis showed that higher OH/ECW was an independent risk factor for 28-day mortality after adjustment of confounding factors (HR=3.83, 95% CI=1.04-14.03, $P=0.04$).

Conclusions: Higher OH/ECW measured by BIA was an independent risk factor for 28-day mortality in septic AKI patients undergoing CRRT. Determining fluid status by BIA could be a useful method to stratify mortality risk in this patient group.

TH-PO111

Effect of Fluid Overload on the Outcome Among Acute Kidney Injury Patients Receiving Renal Replacement Therapy After Cardiac Surgery Zhouping Zou,^{1,2} Jiarui Xu,^{1,2} Wenlv Lv,^{1,2} Bo Shen,^{1,2} Yi Fang,^{1,2} Jianzhou Zou,^{1,2} Jie Teng,^{1,2} Xiaoqiang Ding.^{1,2} *¹Dept of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China; ²Shanghai Inst for Kidney and Dialysis, Zhongshan Hospital, Fudan Univ, Shanghai, China.*

Background: We explored the effect of fluid overload in different periods on the outcome among acute kidney injury (AKI) patients receiving renal replacement therapy (RRT) after cardiac surgery in order to guide the fluid management strategy.

Methods: Clinical data of patients who developed AKI requiring RRT after cardiac surgery from January 2009 to April 2014 in our hospital were prospectively analyzed.

Demographic characteristics were recorded. The absolute fluid overload (FO) = fluid in (L) - fluid out (L). Percent fluid overload (%FO) = [(fluid in - fluid out) / admission weight] × 100. %FO³10% baseline weight was defined as fluid overload.

Results: A total of 297 patients were enrolled, the hospital mortality was 64.7% (n=192). The %FO at RRT initiation and at the end of RRT in death group was significantly higher than in survival group [5.0 (2.4, 9.3) vs. 2.5 (0.2, 5.8)%; 8.4 (3.6, 14.2) vs. 3.9 (0.4, 9.2)%; $P<0.05$]. Even though the fluid overload before RRT was corrected at the end of RRT, the overall mortality and rate of renal completely recovery was not improved ($P>0.05$). Compared with patients without fluid overload during the whole ICU stay, patients without fluid overload before RRT but had fluid overload at the end of RRT had significantly higher mortality ($P<0.05$) and lower renal complete recovery ($P<0.05$). Among AKI-RRT patients, the incidence of low cardiac output syndrome (LCOS) in death group was significantly higher than in survival group ($P<0.001$). The hospital mortality in LCOS group was significantly higher than non-LCOS ($P<0.001$). The %FO at RRT initiation and at the end of RRT in LCOS group was higher than in non-LCOS group [4.7 (1.7, 7.9) vs. 3.1 (1.1, 5.2), $P<0.05$; 8.9 (4.4, 15.3) vs. 4.8 (1.4, 11.3), $P<0.05$].

Conclusions: Among patients with AKI-RRT after cardiac surgery, absolute FO and %FO in death group were higher than in survivor group. Fluid overload and LCOS increased the risk of mortality in AKI-RRT patients after cardiac surgery.

Funding: Government Support - Non-U.S.

TH-PO112

Carnitine Deficiency in Children Receiving Continuous Renal Replacement Therapy Kristen Sgambat, Asha Moudgil. *Children's National, Washington DC.*

Background: Carnitine deficiency is known to occur in chronic hemodialysis, however the effect of continuous renal replacement therapy (CRRT) on carnitine homeostasis has not been studied. The purpose of this study was to investigate carnitine deficiency in critically ill patients with acute kidney injury undergoing CRRT in the pediatric intensive care unit. We hypothesized that patients receiving CRRT are at risk for deficiency due to continuous removal, absent intake, and comorbidities related to critical illness.

Methods: Records of patients with acute kidney injury receiving CRRT at Children's National between 2011 and 2015 were reviewed for total carnitine (TC), free carnitine (FC), Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score indicators, and survival outcome. PELOD-2 score was calculated to measure of severity of illness on a scale from 0 to 33 (maximum severity of illness). The proportion of carnitine deficient patients at baseline, 1, 2, and ≥ 3 weeks on CRRT were compared by Chi square, and relationships with other variables assessed by Pearson's correlation and linear regression.

Results: The study group included 44 CRRT patients, age 8.1 ± 1.1 years. Severity of illness of the population determined by PELOD-2 score ranged from 2 to 19 (mean 11.2 ± 0.43). Of 44 patients, only 14 (31.8%) survived. The prevalence of total and free carnitine deficiency, according to age-and-sex-specific reference values, significantly increased with time on CRRT. At baseline, 26.6% and 40% of patients were TC and FC deficient. Within 1 week, 65.6% ($p=0.01$) and 71% ($p=0.04$) were TC and FC deficient, and prevalence of deficiency increased to 80% ($p=0.008$) and 90% ($p=0.01$) by 2 weeks; 100% of patients were deficient ≥ 3 weeks ($p=0.002$ and $p=0.01$, respectively, vs. baseline). TC and FC negatively correlated with days on CRRT ($r=-0.4$, $p=0.001$ and $r=-0.37$, $p=0.003$). Lower TC and FC levels significantly associated with higher mortality ($\beta=10.1$, $p=0.03$ and $\beta=8.1$, $p=0.02$ respectively).

Conclusions: Carnitine is significantly and rapidly depleted with longer time on CRRT, and carnitine deficiency is associated with increased mortality. Consequences of deficiency and benefits of supplementation in the pediatric CRRT population should be investigated.

TH-PO113

The Relationship Between Hypophosphatemia and Outcomes During Two Different Intensities of Continuous Renal Replacement Therapy Soo Young Kim,¹ Joung Wook Yang,¹ Ye Na Kim,¹ Ho Sik Shin,¹ Ji-hwan Kim,² Yeon Soon Jung,¹ Hark Rim,¹ Bong Geon Chun,³ Hyun Yul Rhew.⁴ *¹Internal Medicine, Kosin Univ College of Medicine; ²Internal Medicine, Good GangAn Hospital; ³Pathology, Kosin Univ College of Medicine; ⁴Urology, Kosin Univ College of Medicine.*

Background: To identify risk factors for development of hypophosphatemia in patients treated with two different intensities of continuous renal replacement therapy (CRRT) and to assess the independent association of hypophosphatemia with major clinical outcomes.

Methods: We performed retrospective analysis of data collected from 620 patients. We allocated patients to two different intensities of CRRT (more than or less than 40 mL/kg/hour of effluent generation) and obtained daily measurement of serum phosphate levels.

Results: We obtained total 1800 phosphate measurements in day 0, 1 and 2 and identified 49 patients (8%), 93 patients (15%) and 142 patients (23%) with hypophosphatemia. With lower intensity CRRT, there were 23 episodes of hypophosphatemia/1000 patient days, compared with 83 episodes/1000 patient days with higher intensity CRRT ($P < 0.01$).

Table 2. Baseline characteristics and outcomes of patients with at least one episode of hypophosphatemia

No. of patients	Serum phosphorus ≥ 2.5 mg/dL (n=432)	Serum phosphorus < 2.5 mg/dL (n=188)	P value
Male:Female	277:155	107:81	0.001
Age, year (range)	62.3 \pm 14.3	63.6 \pm 15.9	0.478
CKD (%)	154 (35.6)	40 (21.3)	0.011
Death (%)	231 (53.4)	90 (47.8%)	0.152
APACHE III score	81.2 \pm 32.8	77.3 \pm 35.3	0.356
Oliguria (%)	162 (37.6)	61 (32.6)	
Mechanical ventilation (%)	179 (41.5)	76 (40.4)	0.901
Vasoactive drug (%)	330 (76.3)	145 (77.2)	1.000
Conventional HD (%)	80 (18.5)	31 (16.5)	0.876
Sepsis (%)	220 (50.9)	96 (51.0)	0.902
Underlying disease (%)			0.784
No	99 (22.9)	57 (29.7)	
DM	137 (31.9)	55 (28.6)	
AMI	62 (14.3)	16 (8.8)	
CHF	35 (8.1)	16 (8.8)	
Chronic liver disease	9 (1.9)	4 (2.2)	
Malignancy	78 (18.1)	38 (19.8)	
Cerebrovascular disease	12 (2.9)	2 (0.7)	
No. of organ failure (range)	2.5 \pm 1.1	2.5 \pm 1.3	0.598
Renal function at initial dialysis			
Urine output, mL/24 hrs	1074 \pm 1293	1175 \pm 1108	0.515
BUN, mg/dL	43.8 \pm 31.7	32.0 \pm 26.2	0.003
Serum creatinine, mg/dL	2.9 \pm 2.6	2.2 \pm 1.9	0.019
Phosphorus level, mg/dL			
Day 1	4.2 \pm 2.4	2.8 \pm 1.6	0.001
Day 2	5.2 \pm 2.0	3.7 \pm 1.9	0.001
Day 3	4.3 \pm 1.7	1.7 \pm 0.5	0.001

On multivariable logistic regression analysis, higher intensity CRRT and hypokalemia were independently associated with an increased odds ratio (OR) for hypophosphatemia. On multivariable models, when analysis was confined to patients alive at 48 hours, hypophosphatemia was not independently associated with clinical outcomes.

Conclusions: Hypophosphatemia is common during CRRT and its incidence increases with greater CRRT intensity. Hypophosphatemia may be not an independent predictor of mortality.

TH-PO114

Determinants of Filter Clotting in Acute Kidney Injury (AKI) Cancer Patients in the Intensive Care Unit (ICU) Submitted to Regional Citrate Anticoagulation (RCA) for Continuous Venovenous Hemodialysis (CVVHD)
 Veronica T. Costa E Silva, Renato Antunes Caires, Juliana Silva Bezerra, Elerson Costalonga, Ludhmila Abrahão Hajjar, Ana paula Leandro Oliveira, Luciane Oikawa, Cilene Muniz Soares, Luis Yu, Emmanuel A. Burdmann. *Sao Paulo State Cancer Inst, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Determinants of filter clotting in AKI cancer ICU patients submitted to RCA have not been studied.

Methods: We prospectively analyzed all CVVHD performed in AKI adult cancer pts in the Sao Paulo State Cancer Institute ICU from January 2010 to December 2011. RCA for CVVHD was utilized according to an adapted protocol published by Mehta et al. CVVHD was performed with a Diapact machine (BBraun) with polysulphone hemofilter.

Results: A total of 7,198 hours of CVVHD therapy (250 filters) were performed in 122 AKI pts. They were 61 \pm 16 years-old, 61.5% male, 75.4% on vasopressors and 41.8% on mechanical ventilation. Most (78%) patients had solid cancer, 37.7% with metastatic disease (MD) and 48.4% with previous chemotherapy (CT). Sepsis was the most important AKI etiology factor (71.1%). Hospital mortality was 78.7%. Venous access was temporary triple lumen catheter (11 Fr) in 97% (70% femoral and 27% internal jugular veins). Blood flow was 150 (120 – 150) ml/min and citrate dose was 20.4 (16.3 – 24.5) mmol/hr. Dialysis dose was 28.2 (22.3 – 30.2) ml/Kg/hr and achieved ultrafiltration was 1042 (573 – 1712) ml/24hrs. Median filter patency was 24.8 (11 – 43) hrs and post-filter ionized calcium level was 1.60 (1.40 – 1.80) mg/dL. The independent factors related with clotting on logistic regression model are depicted.

Logistic regression model for clotting during CVVHD

Variable	P	OR (95% CI)
Cancer status: no tumor evidence	0.050	0.44 (0.18 - 0.99)
Genitourinary cancer	0.006	1.83 (1.18 - 2.81)
Platelet count (each 10,000/mm ³)	0.005	1.02 (1.00 - 1.04)
INR	0.005	0.59 (0.41 - 0.85)
Citrate flow (each 10mL/hour)	0.002	0.88 (0.82 - 0.95)

Conclusions: Filter clotting in AKI ICU cancer patients submitted to RCA is related to lower citrate dose, higher INR (international normalized ratio), higher platelet level, genitourinary cancer and uncontrolled cancer disease.

TH-PO115

Pre-Dilution Haemodiafiltration Improves Outcomes in Acute Haemodialysis
 Caburn Chamberlain, Preetham Boddana. *Renal Dept, Gloucestershire NHS Foundation Hospitals, Gloucester, Gloucestershire, United Kingdom.*

Background: Haemodialysis is an extracorporeal blood treatment for Renal Failure that requires effective anti-coagulation in order to prevent loss of the blood circuit due to clotting. A haemodialysis blood circuit contains approximately 250ml of blood, equivalent to 1 unit of packed cells. In routine Haemodialysis, this is achieved by the administration of Heparin, or its equivalent, during the treatment, which may be up to four hours duration.

In the Acute setting, the administration of Heparin may be contra-indicated for a number of reasons – pre or post surgery, post-stroke, Gastro intestinal bleeds, deranged clotting factors, and so on. Care must then be taken to avoid loss of blood in the dialysis circuit.

Methods: Observational study looking at the effectiveness of traditional anti coagulation strategies such as saline flushes in acute haemodialysis had shown increased frequency of blood circuits lost on dialysis. Over a period of 4 weeks, we used pre-dilution haemodiafiltration instead of conventional post dilution haemodiafiltration. This modality dilutes the blood just before it passes through the dialysis filter. As the majority of the clotting starts as the blood passes along the filter membranes, diluting the blood at this point would theoretically reduce the amount of clotting occurring.

Results: By using this technique, we were able to reduce the number of clotted circuits from 100% down to just 30%, with only 10% leading to loss of the entire blood circuit. There was no significant change in the effectiveness of the treatment, and no significant increase in the cost of the treatment provided.

Conclusions: Over the next few months, we were able to improve on these outcomes still further, by optimizing the variables, and in some cases, adding saline flushes in addition to the pre-dilution HDF. Having used this technique now for some hundreds of treatments, we have reduced the number of blood circuits lost to all but zero. Hence this has become a highly effective technique which has drastically improved patient outcomes, reduced the need for blood transfusions, and saved money without cost implications.

TH-PO116

Nationwide Use of Hemodialysis and Other Extracorporeal Therapies in Poisoned Patients, 2006-2013
 Joshua D. King,^{1,2} Priyanka Vakkalanka,¹ Diana M. Robinson,³ Christopher Holstege.¹ ¹Div of Medical Toxicology, Univ of Virginia, Charlottesville, VA; ²Div of Nephrology, Univ of Virginia, Charlottesville, VA; ³Dept of Psychiatry, Univ of Virginia, Charlottesville, VA.

Background: Nationwide use of extracorporeal therapies (ECT) in poisoned patients has not been characterized since 2005. The purpose of this study was to review the use of hemodialysis (HD), hemoperfusion (HP), and other ECT in poisoned patients throughout the United States from 2006 until 2013.

Methods: The National Poison Data System (NPDS) was queried for all poisoning cases reported to U.S. poison centers between 2006 and 2013 where HD, HP, or other ECT was performed. Data analyzed included demographics and geography, clinical characteristics, exposure chronicity, and reported substances used by patients. The annual prevalence of each therapy per 1,000,000 human exposures was evaluated. The top 30 substances reported among all deaths were characterized among patients receiving HD.

Results: There were 18,252 patients who received ECT, of which 17,900 (98.0%) received HD, 257 received HP, and 214 received some other ECT. The patient population was predominantly 40-59 years of age (45.0%). Poisonings were acute in 56.7% of patients. The prevalence of ECT (per million human exposures) was 865 in 2006 versus 1,140 in 2013. The substances most frequently identified among patients receiving HD included ethylene glycol (n=3,828), lithium (n=3,385), sedatives (n=2,711), salicylates (n=2,352), and opioids (n=1,783). Overall, 9.4% of patients receiving ECT for poisoning died. The three leading substances reported among all deaths included acetaminophen (22.1%), opioids (18.3%), and sedatives (15.3%).

Conclusions: The use of HD in the management of poisoning has continued to increase. While ethylene glycol, lithium, and salicylates remain frequent indications for dialysis, HD seems to be used more often in a supportive role as well given the number of patients treated for opioid and sedative poisoning. We were not able to distinguish the use of intermittent HD versus continuous renal replacement due to database limitations. Hemoperfusion has continued to be rarely used.

TH-PO117

Dialysis Treatment Options for Acute Kidney Injury in the Canadian Intensive Care Unit: A Systematic Review and Cost-Utility Analysis
 Danielle Marie Nash,^{1,2} Ron Wald,⁴ Michel Louis Grignon,¹ Sebastian Przech,³ Daria O'Reilly.¹ ¹Clinical Epidemiology and Biostatistics, McMaster Univ, Hamilton, ON, Canada; ²Kidney, Dialysis and Transplantation Program, Inst for Clinical Evaluative Sciences, ON, Canada; ³Epidemiology and Biostatistics, Univ of Western Ontario, London, ON, Canada; ⁴Medicine, Univ of Toronto, Toronto, ON, Canada.

Background: Up to 67% of all patients admitted to the intensive care unit (ICU) will develop acute kidney injury (AKI). Treatment for these patients is very expensive. For example, in the United States, the incremental health care costs attributed to AKI are upwards of \$10 billion USD per year. In this health economic analysis, we simulate the cost per quality-adjusted life year (QALY) gained comparing three dialysis treatments for patients with AKI in a Canadian ICU setting: continuous renal replacement therapy (CRRT), intermittent hemodialysis (IHD), and sustained low efficiency dialysis (SLED).

Methods: A decision analytic model, with a 1-year time horizon, was developed to compare the incremental cost per QALY gained for the three dialysis modalities. The model used a public payer perspective, with Canadian costs and relevant utility values obtained from targeted searches of the literature. A systematic review of randomized controlled trials was performed to determine the clinical parameters for the model, including the probability of in-hospital death, dialysis dependence and death at one year post-discharge. One-way sensitivity analyses were performed by varying all parameters by +/- 10%.

Results: The incremental cost per QALY gained for SLED compared to IHD was \$68,501. Compared to IHD and SLED, CRRT was extendedly dominated (i.e. it is more

cost-effective to provide SLED to some of the eligible patients and IHD to the remaining patients than to provide CRRT). The sensitivity analyses showed that the results are generally robust across a wide-range of parameter values.

Conclusions: Similar to previous economic evaluations, these results suggest that CRRT is not cost-effective compared to IHD. A novel finding is that SLED may be cost-effective depending on the willingness-to-pay threshold.

TH-PO118

Efficacy of Acute Peritoneal Dialysis (PD) Over Sustained Low Efficiency Dialysis (SLED) in Critically Ill ICU Patients with Acute Kidney Injury – A Comparative Study *Mitul Bora. Nephrology, Ayur Sundra Super Speciality Hospital, Guwahati, Assam, India.*

Background: Acute peritoneal dialysis (PD) has largely been replaced by continuous renal replacement therapies (CRRT) and sustained low efficiency dialysis (SLED) in critically ill ICU patient.

Methods: Patient admitted in the ICU with acute kidney injury and multiple organ dysfunction were included in the study irrespective of the etiology of renal failure. Patients were randomly divided in to two group. Group A patients received acute PD and group B patients received SLED. Primary outcomes were correction of uremia, metabolic acidosis, fluid overload, dyselectrolytemia, and mortality. Secondary outcomes were improvement in sensorium, hemodynamic stability, ICU length of stay, cost of treatment and duration of mechanical ventilation.

Results: 116 were enrolled in this study. The mean age was 41.23±11.56 years in group A where it was 45.87± 13.45 years in group B. Average duration of dialysis was 72.80± 67.90 and 19.07 ± 11.08 hours in PD and SLED group respectively. Correction of uremia [Urea 24.78± 10.31 ml/min vs 26.23 ± 9.34 ml/min, creatinine 8.89 ± 3.78 ml/min vs 9.98± 7.09 ml/min, p value <0.001] were similar. Significant acidosis was present in 36 patients in Group A (92%) and in 23 patients (28%) in Group B. SLED had a better correction of acidosis in comparison to PD. Correction of fluid overload was faster in SLED and net ultrafiltration was significantly higher in group B (22.21±21.67 L vs 4.87±5.09 L in group A, P<0.001). No significant differences were seen in correction of hyperkalemia, altered sensorium. PD group had a better hemodynamic stability. Mortality was almost similar in both the groups (81% v 76%). Renal function recovery (21% vs 24%) were also similar. Acute Physiology and Chronic Health Evaluation II score was similar (25.8±5.4 versus 23.9±7.9) and also the duration of ventilatory support (11.9 ±7.3 vs 13.5± 8.7 days). Cost of treatment was much cheaper in the PD group.

Conclusions: Acute PD still remains as a viable alternative to SLED in critically ill patients in low cost setting. Advantages are its low cost, ease of administration, needs less expertisation and its metabolic and clinical outcomes are not inferior to SLED.

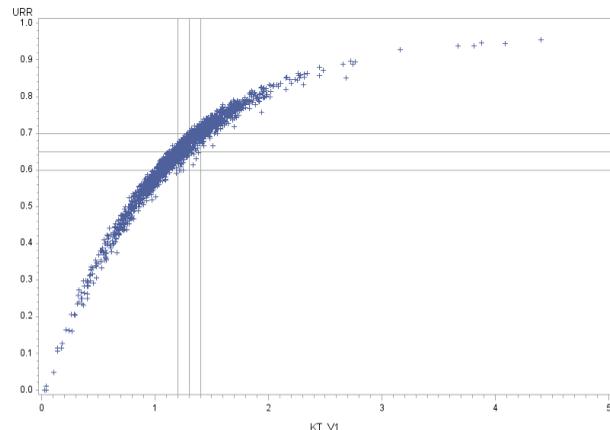
TH-PO119

Measurement of Adequacy of Intermittent Hemodialysis in Acute Kidney Injury: Is There a Simpler Approach? *Kelly V. Liang,¹ Jane Hongyuan Zhang,² Paul M. Palevsky,³ ¹Renal-Electrolyte Div, Univ of Pittsburgh, Pittsburgh, PA; ²Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT; ³Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, PA.*

Background: The KDIGO Guideline for Acute Kidney Injury (AKI) recommends a minimum single pool Kt/V_{urea} of 1.3 when intermittent hemodialysis (IHD) is delivered thrice weekly. However, Kt/V in AKI is complicated by uncertainty regarding volume of distribution of urea and non-steady state rates of urea generation. In the Acute Renal Failure Trial Network (ATN) Study, adequacy of IHD was assessed using Kt/V. Using data from the ATN Study, we assessed whether the simpler urea reduction ratio (URR), which does not require assessment of volume status, would provide sufficient correlation with Kt/V to provide a reliable assessment of adequacy of hemodialysis in AKI.

Methods: Using data from IHD in the ATN Study, values of URR were plotted against Kt/V. We determined URR thresholds corresponding to Kt/V values ≥ 1.2, 1.3, and 1.4 and generated receiver operating characteristic (ROC) curves at each level of Kt/V to identify optimal URR thresholds.

Results: There was tight correlation between URR and Kt/V (figure).



Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

The area under the ROC curves were 0.99 for all three Kt/V thresholds. The sensitivity and specificity of URR³0.67 for corresponding values of Kt/V³1.2 were 0.769 (95% CI 0.745 to 0.793) and 0.999 (95% CI 0.997 to 1.000), and for corresponding values of Kt/V³1.4 were 0.998 (95% CI 0.995 to 1.000) and 0.791 (95% CI 0.771 to 0.811), respectively.

Conclusions: A URR ³0.67 provides a specificity of 0.999 that the corresponding value for Kt/V is ³1.2 and a sensitivity of 0.998 that the corresponding value of Kt/V is ³1.4. Therefore, this URR threshold provides a simplified means of assessing adequacy of IHD provided for management of AKI in the acute care setting.

Funding: NIDDK Support, Veterans Administration Support

TH-PO120

A Novel Treatment for Edema and Fluid Overload: Transdermal Removal of Interstitial Fluid *Leonard Ebah,^{1,2,3} Paul E. Brenchley,^{1,2,3} Sandip Mitra,^{1,2,3} Idalia Dawidowska,³ ¹Renal Medicine and Research, Manchester Royal Infirmary, Manchester, United Kingdom; ²Inst of Cardiovascular Sciences, Univ of Manchester, Manchester, United Kingdom; ³Renephra Limited, Manchester, United Kingdom.*

Background: Fluid overload is highly prevalent in kidney and heart failure, contributing to worse outcomes. Diuretics are the mainstay of treatment; they sometimes become ineffective requiring intravenous treatment and/or invasive approaches to fluid removal such as dialysis. Transdermal fluid removal from interstitial fluid (ISF), the main fluid reservoir in these overloaded patients presents a potentially attractive elegant solution to fluid removal in these patients.

Methods: Plastic solid microneedle arrays and standard hypodermic needles were tested as methods of accessing epidermal ISF whilst vacuum pressure and superabsorbent wound dressings were investigated as fluid flow enhancers.

Results: 144 interventions were performed, with 71 (49%) resulting in the extraction of at least 1ml of ISF and 36 (25%) at least 5ml. Microneedle access was superior with spontaneous significant flow of ISF in 56% of cases compared to 10% for hypodermic needles (p<0.0001). Vacuum pressure correlated with extracted ISF volume; r=0.42, p=0.03. ISF volume also increased linearly with time (r=0.24, p=0.008) by the equation volume(ml)=5.7t(hr)-4.5. Of the patient characteristics, edema grade (r=0.46, p=0.003), edema refill time (r=0.28, p=0.01) and serum albumin (r=-0.33, p=0.004) were significantly related to ISF volume extracted. ECFV/TBW was the strongest correlate of ISF volume extraction (r=0.40, p=0.0001). With a Bio-ratio of 0.50 or higher, the OR for extracting 5ml of more was 10.4 [3.4-31]. Microneedle access with suction and a high Bioratio could achieve ISF extraction rates of 2ml/cm²/hr which equates to 800ml over 4 hours using a 10by 10cm skin surface. The microneedle interventions were safe, painless and bloodless.

Conclusions: Microneedle access with vacuum pressure seems promising as a potential safe, minimally invasive transdermal treatment of significant fluid overload. Further evaluation to refine device characteristics and clarify patient stratification may lead to a potential clinical utility of such a device.

TH-PO121

Comprehensive Program to Treat Acute Kidney Injury (AKI) Using Peritoneal Dialysis (PD) in Developing Countries *John Callegari,^{1,2} Grzegorz Wystrychowski,³ Nathan W. Levin,^{1,2} Ewa Zukowska-szczechowska,³ Mary Carter,^{1,2} ¹Renal Research Inst, New York, NY; ²Sustainable Kidney Care Foundation, New York, NY; ³Dept of Internal Medicine, Diabetology and Nephrology, Medical Univ of Silesia, Zabrze, Poland.*

Background: HD as a therapy for acute kidney injury (AKI) is unavailable in most developing countries due to lack of trained staff, equipment, electricity, water treatment, and funding. However, peritoneal dialysis (PD) can be established in almost any setting as a cheaper modality that requires few resources. A team of pediatric & adult nephrologists with nurses, a functional laboratory, and delivery of PD catheters and supplies. Nephrologists should be trained to place single cuff Tenckhoff catheters.

Methods: In compliance with these prerequisites, AKI PD programs have been started in Benin, Ghana, Tanzania, Cameroon, Ivory Coast, Ethiopia, Uganda and Cambodia with support provided by the Sustainable Kidney Care Foundation (SKCF) and the Saving Young Lives consortium comprised additionally by the International Society of Nephrology (ISN), International Society for Peritoneal Dialysis (ISPD), International Pediatric Nephrology Association (IPNA).

Results: So far, 129 AKI patients were treated with PD in these countries. Approximately 55% recovered kidney function and were discharged with no need of further dialysis; nearly 20% were diagnosed with end-stage renal disease and referred to hemodialysis where available or given palliative care; 1 in 4 patients died during hospitalization (table 1). Peritonitis rates were 12.3% and were not a factor in outcomes (logistic regression analyses).

Location	Total Patients	Died		Restored Kidney Function		ESRD		Peritonitis	
	N	N	%	N	%	N	%	N	%
Abidjan, Ivory Coast	11	3	27.3%	5	45.5%	3	27.3%	2	18.2%
Cotonou, Benin	24	5	20.8%	16	66.7%	3	12.5%	3	12.5%
Accra, Ghana	8	2	25.0%	5	62.5%	1	12.5%	1	12.5%
Kumasi, Ghana	61	20	32.8%	30	49.2%	11	18.0%	3	4.9%
Morshi, Tanzania	23	4	17.4%	14	60.9%	5	21.7%	7	30.4%
Bahmenda, Cameroon	11	1	9.1%	6	54.5%	4	36.4%	1	9.1%
Totals	138	35	25.4%	76	55.1%	27	19.6%	17	12.3%

Conclusions: PD is a viable treatment modality in low-resource settings and decreases mortality rates in the course of AKI to the levels seen in developed countries. The frequency of PD-related peritonitis is low and does not affect treatment outcomes.

Funding: Private Foundation Support

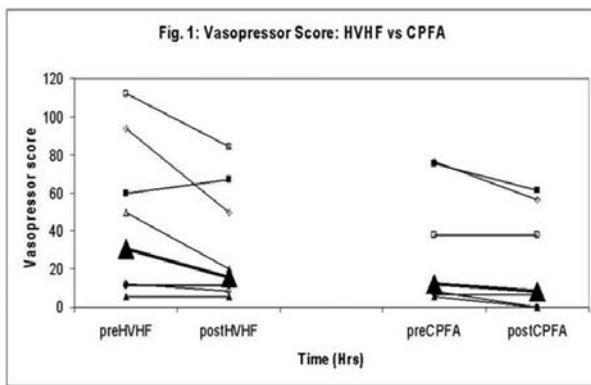
TH-PO122

Pulse High Volume Hemofiltration versus Coupled Plasma Filtration Adsorption in Septic Shock – A Pilot Randomized Study Paolo Lentini,¹ Luca Zanoli,² Massimo de Cal,¹ Stefania Rastelli,² Andrea Contestabile,¹ Antonio Granata,³ Roberto Dell'Aquila.¹ ¹Nephrology, St. Bassiano Hospital, Bassano Del Grappa, Italy; ²Univ of Catania, Italy; ³St. Giovanni di Dio, Italy.

Background: Acute kidney Injury(AKI), a frequent complication in critically ill septic patients is an independent risk factor for increased mortality, particularly when patients require renal replacement therapy(RRT). High Volume Hemofiltration (HVHF) and Coupled Plasma Filtration Adsorption(CPFA) have shown potential improvement in hemodynamics; however, no studies have compared these two methods. Our aim was to compare the hemodynamic effects of HVHF and CPFA in septic shock patients undergoing Continuous Renal Replacement Therapy (CRRT).

Methods: A cross-over study enrolling pts with septic shock undergoing CRRT. Pts were treated with pHVHF+CVVH on Day 1 and CPFA+CVVH on Day 2. HVHF was performed for 8-10 hrs with a replacement fluid rate (Qr) of 85 ml/kg/hr. CPFA was performed for 8-10 hrs using Mediasorb (Bellico®Italy) with a maximum plasma flow rate of 15%. CVVH was performed for the rest of the day with a Qr of 35 ml/kg/hr. Both HVHF and CVVH used polysulfone filters. The primary endpoints were changes in vasopressor requirement (expressed as vasopressor score, VS), in noradrenaline (NA) dose (mg/kg/min), and in mean arterial pressure (MAP) before and after pHVHF and CPFA. These values were compared using nonparametric paired tests.

Results: 8 pts (5M/3F, 70.5 yr, SOFA 12.5, SAPS II 69.5). VS and NA dose were significantly decreased after CPFA (p=0.04). These endpoints were not significantly different after pHVHF (p=0.13). When CPFA and pHVHF are compared between each other, the change in VS and NA dose becomes NS (p=0.22). There was no significant change in MAP with either pHVHF or CPFA.



Conclusions: The data provide no evidence for a difference in hemodynamic effects between pHVHF and CPFA in patients with septic shock undergoing CRRT.

TH-PO123

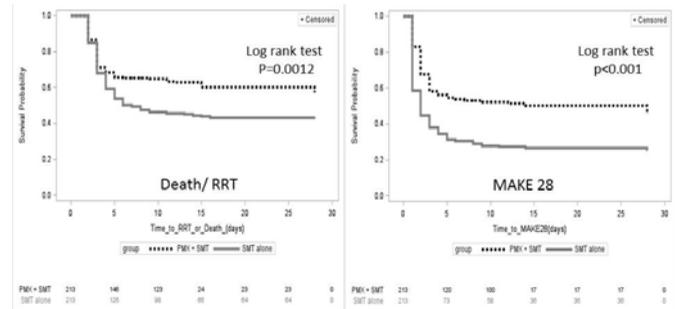
Polymyxin B Hemoperfusion and Renal Outcomes in Septic Shock: A Propensity-Matched Analysis Dinna Cruz,¹ Jing Zhang,¹ Tsukasa Nakamura.² ¹Univ of California San Diego; ²Shinmatsudo Hospital, Japan.

Background: Septic acute kidney injury (AKI) is a common ICU complication with high mortality. Only supportive management is available at this time. Hemoperfusion with Polymyxin B fiber column (PMX) reduces blood endotoxin levels & vasopressor requirement, & increases blood pressure. These may improve renal perfusion & decrease renal tubular cell apoptosis. We hypothesized that PMX may improve renal outcomes in sepsis.

Methods: Single center retrospective study of 697 septic shock patients. Patients were treated with PMX (n=337) if they met all criteria: SIRS, documented/suspected infection, vasopressors despite adequate fluid resuscitation, ¹ organ failure, Gram(-) organism &/or elevated endotoxin levels; 360 pts were treated with standard medical therapy (SMT) alone. PMX patients were matched 1:1 with SMT patients, based on a propensity score for the likelihood of receiving PMX. Groups were compared using survival curve analysis & Cox regression for: 1) death or need for RRT at 28-days, and 2) Major Adverse Kidney Events (MAKE28): death, need for RRT, or ¹ point increase in renal SOFA score.

Results: Propensity score matching created a matched cohort of 426 patients. The PMX & SMT groups were well-matched in terms of baseline characteristics, including initial ICU Cr, endotoxin levels, type of organism, & APACHE score. The risk of death/RRT and MAKE28 was significantly lower among PMX patients (Figure). On multivariable analysis, PMX was associated with lower risk for death/RRT (adj HR 0.48, 95%CI 0.36,0.65) and MAKE28 (adj HR 0.48, 95%CI 0.37,0.61). Peak & nadir Cr, ICU & hospital length of stay were also lower in PMX group.

Conclusions: In this retrospective study, PMX, when added to SMT, was associated with better renal outcomes in septic shock. These results warrant further exploration with prospective trials.



Outcomes	PMX+SMT	SMT alone	p
Peak Cr (mg/dl)	2.2 (1.8,3.3)	3.0 (1.2,1.8)	<0.001
Nadir Cr (mg/dl)	1.1 (0.8,1.4)	1.5 (1.2,1.8)	<0.001
Peak minus baseline Cr	0.1 (0,0.4)	0.8 (0.3,1.6)	<0.001
Peak minus nadir Cr	1.0 (0.8,1.6)	1.6 (1.0,2.3)	<0.001
ICU days	6 (4,8)	11 (7,14)	<0.001
Hospital days	21 (14,31)	28 (14,44)	<0.001

TH-PO124

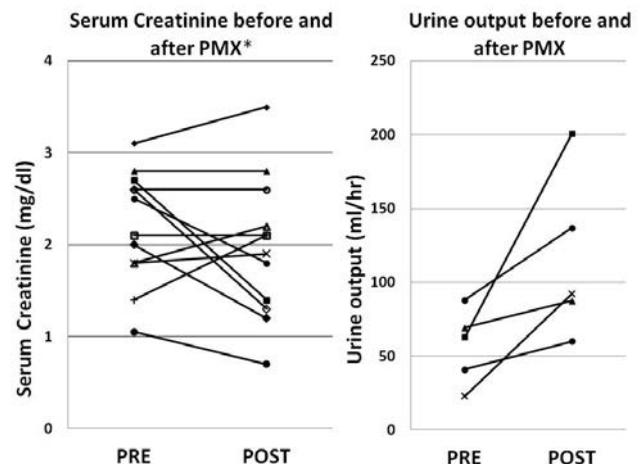
Effect of Polymyxin B Hemoperfusion on Septic AKI: A Systematic Review Dinna Cruz, Deepti Mundkur, Ravindra L. Mehta. UCSD, San Diego.

Background: Septic acute kidney injury (AKI) is common in the ICU, and associated with high mortality. Polymyxin B fiber column (PMX) is a medical device that reduces blood endotoxin levels in sepsis. In a prior metaanalysis, PMX hemoperfusion was shown to improve blood pressure and reduce vasopressor requirement, which could help renal perfusion. PMX possibly reduces proapoptotic activity of septic plasma on renal tubular cells. A systematic review was performed to assess renal outcomes when PMX is used in sepsis.

Methods: We searched MEDLINE, PubMed to identify studies on PMX hemoperfusion in sepsis. Full-text articles were screened for renal-related outcomes. The primary endpoint was need for acute RRT after enrollment. Secondary endpoints included development of AKI, change in Cr, BUN, urine output, urine protein and biomarkers after PMX.

Results: A total of 18 studies (n=591 pts) with renal outcomes were identified. In 6 RCTs & 1 non-RCT, patients were treated with either PMX+standard medical therapy (SMT) (n=188) or SMT alone (n=136). In 10 cohort studies 267 pts were treated with PMX+SMT. The following renal outcomes were reported: need for RRT (n=4 studies), serum Cr &/or CrCl (n=10), BUN (n=4), urine output (n=5), urine protein/biomarkers (n=6). One study reported severe AKI (Failure) in 0/8 PMX and 1/8 SMT patients at 72h. Pooled analysis showed a non-significant trend for reduced need for RRT with PMX (OR 0.44, 95%CI 0.19,1.04). Figure 1 shows Cr and urine output before and after PMX. Weighted mean difference for Cr after PMX was not significant but there was an increase in urine output by 45 ml/hr (95%CI 15,74) after PMX.

Conclusions: Based on published studies, PMX has no significant effect on RRT need or Cr in patients with septic shock when added to SMT, although urine output appeared to improve post-PMX. These data provide evidence for scientific equipoise for a randomized clinical trial to address this question.



*2 studies reported summary Cr values separately for survivors and non-survivors

TH-PO125

Four Hour Infusion Piperacillin-Tazobactam in CRRT Patients Is Associated with Improved Target Attainment Compared to 30 Minute Infusion Matthew S. Shotwell,¹ Ed Gould,² Phillip Madonia,³ Ross Marshall Nesbit,² Charbel A. Salem,³ Milen Amde,³ Olufemi Aduroja,³ Seth R. Bauer,⁴ Michael J. Connor,³ Joseph J. Groszek,² Maria E. Taylor,⁵ Peilin Wei,⁵ Ashita J. Tolwani,⁵ William Henry Fissell.² ¹BioStatistics, Vanderbilt Univ, Nashville, TN; ²Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; ³Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; ⁴Pharmacy, Cleveland Clinic, Cleveland, OH; ⁵Nephrology, Univ of Alabama, Birmingham, Birmingham, AL.

Background: Sepsis is the leading cause of death in acute kidney injury. Dose adjustments to account for kidney failure and continuous renal replacement therapy (CRRT) may result in poor target attainment. Four hour infusion (EI) of beta lactams may result in improved target attainment compared to 30 minute infusion (SI). We conducted a multicenter observational study of piperacillin pharmacokinetics in patients receiving CRRT and compared predicted target attainment in a typical patient receiving EI or SI.

Methods: Piperacillin concentrations were measured in subjects at Cleveland Clinic (3 gm q6h, q8h, or q12h SI; n=29) University of Alabama Birmingham (2 gm q6h or q8h, 3g q6h SI, n=25) and Vanderbilt University (3 gm q8h or q12h, EI; n=14). A two-compartment pharmacokinetic model was fitted simultaneously to all data using nonlinear mixed effects regression in R. Target attainment was quantified as the fraction of the dosing cycle wherein piperacillin concentration was greater than 64 µg/mL. Target attainment for a typical patient was estimated using the population mean (fixed-effect) for each pharmacokinetic parameter.

Results: For EI versus SI in the two most common dosing patterns, 2g q6h and 3g q8h, target attainment was improved by 27% (95% CI: 19, 35) and 23% (95% CI: 18, 28), respectively.

Conclusions: Limits of the study include that it is solely observational, and that subjects in Cleveland and Birmingham were enrolled earlier than subjects in Nashville. These results characterize the typical patient in this population. Additional analysis is warranted to examine the sensitivity of our findings to population pharmacokinetic heterogeneity.

Funding: NIDDK Support, Pharmaceutical Company Support - Gambro Renal Systems

TH-PO126

Effects of Complement Factor H and Factor I Deficiency on Anti-MPO Induced Crescentic Glomerulonephritis in Mice Hong Xiao,¹ Peiqi Hu,¹ Cheng Wan,¹ Matthew C. Pickering,² Ronald J. Falk,¹ J. Charles Jennette,¹ ¹Pathology and Laboratory Medicine, Univ of North Carolina, Chapel Hill, NC; ²Molecular Genetics, Imperial College, London, United Kingdom.

Background: Complement alternative pathway (AP) activation plays a critical role in the pathogenesis of anti-neutrophil cytoplasmic autoantibodies (ANCA) crescentic glomerulonephritis (CGN). AP is negatively regulated by complement factor H (CFH) and factor I (CFI). Deficiency of either of these regulators results in uncontrolled C3 activation with secondary depletion of C3, factor B and properdin. In this study, we investigate the effects of CFH and CFI deficiency in anti-MPO induced CGN in mice.

Methods: 9-11 wk-old CFH and CFI KO and WT B6 mice were injected with anti-MPO IgG and were sacrificed at day 6 and kidney tissue was obtained for pathologic examination and IF staining with anti-C3 antibodies. Circulating C3 levels were determined by ELISA. In vitro neutrophil function was assayed.

Results: At day 6 of anti-MPO treatment, all CFH^{-/-} mice (n=5) developed much more severe CGN (mean 85% glomeruli with crescents) compared to the WT control mice (n=8, 11% crescents). In contrast, no CGN developed in CHI^{-/-} mice (n=8). Glomerular C3 staining shown strong (score 4+) linear capillary wall staining in CFH^{-/-} mice, whereas CHI^{-/-} mice had weak (1.5+) mesangial staining. On day 0 and day 6 after anti-MPO treatment, the circulating C3 level had no significant differences in WT and CFI^{-/-} mice (p>0.05) and substantially reduced in CFH^{-/-} mice (p<0.001). *In vitro* neutrophil function assay showed that anti-MPO IgG caused similar activation of neutrophils from CFH^{-/-}, CHI^{-/-} and WT mice.

Conclusions: 1) Absence of the CFH causes more severe anti-MPO induced CGN. This is probably because they have uncontrolled alternative pathway activation and sufficient glomerular capillary wall deposition of complement activation fragments to synergistically attract and amplify anti-MPO activated neutrophils. 2) CHI deficiency protects from anti-MPO CGN. This might be because of no glomerular capillary wall C3 deposits and consumption of circulating AP components, such as factor B and properdin, as a consequence of uncontrolled AP activation.

Funding: NIDDK Support

TH-PO127

Can a Bacterial Protein Rescue Disease-Linked Mutations in Complement Factor H? Heather Kerr,¹ Edwin K.S. Wong,³ Andrew P. Herbert,² Anna Richards,¹ David Kavanagh,³ Paul N. Barlow.² ¹Centre for Inflammation Research, Univ of Edinburgh, Edinburgh, United Kingdom; ²School of Chemistry, Univ of Edinburgh, Edinburgh, United Kingdom; ³Inst of Genetic Medicine, Newcastle Univ, Newcastle, United Kingdom.

Background: Factor H (FH) regulates the complement system. Mutations and polymorphisms in FH are implicated in atypical haemolytic uraemic syndrome and C3 glomerulopathies. Studies using short FH fragments suggested detrimental functional consequences of many disease-linked amino acid substitutions. The protein PspC from

Streptococcus pneumoniae hijacks host-derived FH in a complement-evasion strategy. Binding of PspCN (N-terminal region of PspC) to wild-type (WT) FH was shown to enhance complement regulation implying that PspCN might restore useful levels of regulatory activity to disease-related variants of FH.

Methods: Overcoming technical hurdles to recombinant full-length FH production, two mutant versions, R53H and S1191A V1197L, were prepared in *Pichia pastoris*. Using surface plasmon resonance (SPR), binding of mutants to C3b, and their C3bBb decay-accelerating activities (DAA), were compared with WT FH. Mutants were also compared to WT FH in erythrocyte DAA and co-factor lysis assays. Measurements were repeated in the presence of PspCN.

Results: R53H decreased FH affinity for C3b and impacted negatively on both assays used to measure DAA as well as the haemolysis-based assay of co-factor activity. The double mutant had WT-like abilities to bind C3b and decay C3b convertase on an SPR chip, but was deficient in cell-based assays, and especially in co-factor activity. PspCN enhanced both C3b binding and DAA on the SPR chip by both mutants and WT. The effects of PspCN on cell-based assays were less clear.

Conclusions: These studies with full-length FH imply that disease-linked substitutions in its C-terminal surface-recognition region (unlike those in the functionally critical N-terminal region) have little effect on SPR-based assays performed on a non-native and hence, in effect, foreign surface. Whether the enhancing effects of PspCN in SPR-based assays can be replicated on host-cell surfaces has therapeutic implications and will be discussed in the light of ongoing measurements.

TH-PO128

Recombinant Complement Factor H in a Model of C3 Glomerulopathy Heather Kerr,¹ Andrew P. Herbert,² Talat H. Malik,³ Anna Richards,¹ Paul N. Barlow,² Matthew C. Pickering.³ ¹Centre for Inflammation Research, Univ of Edinburgh, Edinburgh, United Kingdom; ²School of Chemistry, Univ of Edinburgh, Edinburgh, United Kingdom; ³Centre for Complement and Inflammation Research, Imperial College, London, United Kingdom.

Background: C3 glomerulopathy (C3G) is an inflammatory renal disorder that is associated with abnormal complement alternative pathway activation. This includes deficiency of complement factor H (FH), the negative regulator of the alternative pathway. FH gene-targeted (FH^{-/-}) mice are a model of C3G and spontaneously develop reduced plasma C3 levels and abnormal deposition of C3 within the glomerulus. We tested the efficacy of recombinant murine FH (mrFH) to restore C3 regulation in FH^{-/-} mice.

Methods: mrFH was produced in *Pichia pastoris*. Plasma-purified mFH or hrFH (human) was used as a control. In experiment 1, mice received an injection of mrFH or mFH and were culled at 24 hours. In experiment 2, mice received a daily injection of mrFH or hrFH for 10 days and were culled at 11 days.

Results: A single injection of mrFH resulted in increased plasma FH and C3 levels peaking at 6 hours. In mice receiving mFH, plasma FH and C3 levels remain elevated at 24 hours. Glomerular histology at 24 hours showed a decrease in glomerular C3 staining both for mice receiving mFH and mrFH. In experiment 2, mice receiving daily injections of either mrFH or hrFH exhibited elevated levels of both plasma FH and C3 at 24 hours, but these decreased to baseline within five days. All mice showed reduced C3 glomerular staining at 11 days. Mice receiving hrFH showed strong glomerular IgG staining at 11 days.

Conclusions: Restoration of complement regulation is the goal of treatment for C3G. In our experiments mrFH increased plasma C3 and FH levels and reduced glomerular C3 deposition. The rapid reduction in FH and C3 levels (relative to a slower decline in mice treated with plasma-purified FH) may be due to glycosylation differences between plasma-purified and recombinant protein. Administration of recombinant FH is a rational treatment choice for patients with C3G associated with deficiency or dysfunction of FH. However, the challenges of this approach include plasma half-life, immunogenicity and large scale production.

TH-PO129

Reduced Renal Infiltration of Inflammatory Cells following Selective Endothelial Injury in Mice Deficient for C3, C3aR or C5aR Jan Sradnick, Anika Luedemann, Vladimir T. Todorov, Christian Hugo, Bernd Hohenstein. *Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany.*

Background: Complement dysregulation leads to kidney specific diseases such as C3 glomerulopathy and thrombotic microangiopathy. However, data on the specific role of the complement system for local inflammation after endothelial cell injury (ECI) is limited. We here investigated the inflammatory response following site selective renal ECI in mice deficient (-/-) for C3, C3aR or C5aR.

Methods: Renal ECI was induced by intra-arterial injection of Concanavalin(ConA)/anti-ConA in C3^{-/-} (day 2: n=5; d4: n=4), C3aR^{-/-} (d2: n=5; d4: n=4), C5aR^{-/-} (d2: n=4; d4: n=3) deficient and C57Bl/6 wildtype (wt) mice (n=5; n=4). Six wt mice served as sham control (ctrl). Kidneys were harvested on day 2 or day 4. Multicolor FACS analysis was used to count macrophages (M), neutrophils (N) and T-cells (T). Cells were stained with the following antibodies: CD11b+ F4/80+ GR1- CD11c- (M), GR1+ CD11b+ (N) and CD4+ CD8+ (T). Histology was used to analyze macrophages (MAC2, F4/80) and the ECI (CD31).

Results: Inflammatory cells were increased in C57Bl/6 mice 2 days after ECI (C57Bl/6: M=1.3%±0.4; N=2.9%±1.0; T=0.8±0.3 vs. sham: M=0.1%±0.04; N=0.15%±0.09; T=0.2%±0.2; p<0.01). Compared to C57Bl/6 wt mice a reduced influx of macrophages (C3^{-/-}: 0.3%±0.05; C3aR^{-/-}: 0.4%±0.2; C5aR^{-/-}: 0.5%±0.3) and neutrophils (C3^{-/-}: 0.9%±0.74; C3aR^{-/-}: 0.9%±0.9; C5aR^{-/-}: 0.7%±0.5; ctrl: 0.15%±0.09) was observed in C3, C3aR and C5aR deficient mice (p<0.01). CD8+ cells were reduced in C3^{-/-} mice (C3^{-/-}: 0.3%±0.03

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

d2: wt:0.8%±0.33). Histological analysis using MAC2 and F4/80 support these findings. While histology demonstrated enhanced ECI, no differences in ECI were detected between C3, C3ar and C5ar and wt mice.

Conclusions: The recruitment of inflammatory cells into the kidney after selective ECI depends on the presence and function of C3, C3ar and C5ar. However, C3, C3ar and C5ar deficiency did not modulate the extent of ECI in this disease model.

TH-PO130

Investigating a Pathogenic Role of C5a-C5aR1 Signaling in Diabetic Nephropathy Sih Min Tan,^{1,2} Vicki Thallas,¹ Alison Skene,³ Richard J. MacIsaac,^{4,5} David A. Power,^{3,4} Mark E. Cooper,^{1,2} Elif Ekinici,^{3,4} Trent M. Woodruff,⁶ Melinda T. Coughlan,^{1,2} ¹*Diabetic Complication, Baker IDI Heart & Diabetes Inst, Melbourne, VIC, Australia;* ²*Central Clinical School, Monash Univ, Melbourne, VIC, Australia;* ³*Endocrine Centre, Austin Health, Melbourne, VIC, Australia;* ⁴*Dept of Medicine, The Univ of Melbourne, VIC, Australia;* ⁵*Dept of Endocrinology & Diabetes, St. Vincent's Hospital, Melbourne, VIC, Australia;* ⁶*School of Biomedical Sciences, Univ of Queensland, Brisbane, Australia.*

Background: Complement 5a is a potent pro-inflammatory effector molecule. Although previous studies indicate a link between activation of the complement pathway and diabetic nephropathy (DN), the role of C5a and its receptor C5aR1 in DN has yet to be determined.

Methods: Complement signaling was characterized in type 1 diabetic (T1D) human, rat and mouse kidneys. C5a-C5aR1 signaling axis was inhibited by using the highly selective and potent C5aR1 antagonist, AcF-[OPdChaWR] (PMX53), in streptozotocin (STZ)-induced diabetic mice (2mg/kg/day, drinking water, 24 weeks, n=6-15 mice/group). C5 and C5aR1 were measured by qRT-PCR and immunohistochemistry. Urinary C5a and albumin were measured by ELISA.

Results: The expression of C5aR1 was increased in renal biopsies from patients with DN compared to healthy donor kidneys (4.2±1.3 vs 15.7±1.8%; p<0.001, n=9-23). C5aR1 expression was upregulated in the renal cortex of STZ-induced diabetic rats (1.0±0.1 vs 1.5±0.2 fold change; p<0.05) and spontaneously diabetic Ins2-Akita mice (1.0±0.1 vs 1.4±0.1 fold change; p=0.05) compared to controls. Urinary C5a was increased in the diabetic rats (181±56 vs 1153±297 ng/24hr; p<0.05) and Ins2-Akita mice (50±9 vs 151±32pg/24hr, p<0.01) after 16 and 26 weeks of diabetes, respectively and was associated with albuminuria (p<0.05). Blockade of C5aR1 signaling with PMX53 attenuated albuminuria in STZ-induced diabetic mice when compared to vehicle-treated diabetic controls (247±30 vs 74±28 µg/24hr; p<0.001).

Conclusions: The C5a-C5aR1 signaling is activated in human and experimental DN. A pilot study using PMX53 indicates that pharmacological blockade of C5aR1 is renoprotective in DN. Further studies are required to validate C5aR as a therapeutic target in DN.

Funding: Private Foundation Support

TH-PO131

Identification of Glycosaminoglycans That Inhibit Specific Complement Pathways Ditmer Talsma,¹ Romain Vives,² Marc Maj Seelen,¹ Coen A. Stegeman,¹ Jacob van den Born,¹ ¹*Nephrology, UMCG, Groningen, Netherlands;* ²*Inst. for Struct. Biol., Univ of Grenoble, Grenoble, France.*

Background: Complement has been shown to play a role in renal diseases, such as hemolytic uremic syndrome, C3 glomerulopathy and renal transplantation. It is well known that heparin and other glycosaminoglycans (GAGs) reduce complement activation. However, no studies have yet compared the complement pathway specific inhibitory properties of a library of GAGs. We have tested over 70 different GAGs for their complement inhibiting potential and their specificity for either of the complement pathways.

Methods: 72 GAG-based polysaccharides were tested for their complement inhibiting potential in the Wieslab complement screening assay. To pinpoint the inhibitory effect of GAGs on the lectin pathway (LP), the interference of GAGs on the binding of MBL to mannan and further C4 activation was tested. GAGs were also tested in the Wieslab ficolin 3 screening kit to evaluate their effect on ficolin based LP activation. Direct binding of LP components to heparin was assessed by detecting MBL and MASP 1 & 2 after serum incubation to immobilized heparin-albumin.

Results: Unfractionated regular and partially desulfated heparin exhibit dose-dependent inhibitory potential of all three complement pathways, while small heparin and heparan sulfate (HS)-derived oligosaccharides show specific LP inhibition. These small heparin/HS derivatives do not interfere with the binding of MBL to mannan, but do inhibit the MASP-based activation of C4 and ficolin-3 mediated LP activation. We also find a dose-dependent binding of the MBL/MASP 1&2 complex to immobilized heparin-albumin, but not to albumin.

Conclusions: A large number of heparin(oids)block all three pathways of complement, however small heparin/HS oligosaccharides inhibit the LP of complement specifically, according to our data via the inhibition of the MASP enzymes. Our data also suggest that HS on cell surfaces and in basement membranes might act as a docking platform for the MBL-MASP complex. We speculate that GAG-derived polysaccharides may be useful as MASP specific LP inhibitors.

TH-PO132

Anti-GBM Antibody-Mediated Glomerular Injury Depends on Neutrophil Degranulation Dawn J. Caster,^{1,2} Erik Korte,¹ Liliane Hobeika,¹ David W. Powell,¹ Kenneth R. McLeish,^{1,2} ¹*Medicine, Univ of Louisville, Louisville, KY;* ²*Dept of Veterans Affairs, Louisville, KY.*

Background: Acute proliferative glomerulonephritis (GN) induced by ANCA or by anti-GBM antibodies is neutrophil (PMN) dependent. In vitro studies suggested that endothelial injury induced by ANCA was dependent on PMN granule enzymes, not release of reactive oxygen species. To test the hypothesis that PMN degranulation is responsible for acute GN, degranulation was inhibited in an in vivo model of heterologous anti-GBM disease in mice.

Methods: After collection of urine for baseline protein excretion, two groups of 10 C57BL/6 mice received an intravenous injection of sheep anti-rat GBM (1.5 mg/25 g body weight) at time 0. One group also received an intravenous injection of a TAT-fusion protein, TAT-SNAP-23 (0.5 mg/kg body weight) at time 0 and 6 hr later. We showed previously that TAT-SNAP-23 inhibited PMN degranulation in vitro and in vivo. At 24 hr urine was collected for protein excretion, and then mice were sacrificed and kidney tissue prepared for histology. Urine protein was measured as the protein:creatinine (ug/mg). Glomerular proliferation and mesangial expansion were graded on a 0 to 4+ scale.

Results: Baseline urine protein:creatinine did not differ between groups (18 + 3.3 vs 22 + 3.5, untreated vs TAT-SNAP-23 treated). Anti-GBM induced a significant increase in proteinuria, and that increase was significantly inhibited by TAT-SNAP-23 treatment (376 + 108 vs 73 + 15, untreated vs TAT-SNAP-23 treated). By light microscopy there was no difference in proliferation (2.2 + 0.2 vs 2.0 + 0.2) or mesangial expansion (1.2 + 0.3 vs 1.2 + 0.2) between the two groups. By electron microscopy the degree of podocyte foot process effacement was reduced by TAT-SNAP-23 treatment.

Conclusions: We conclude that PMN degranulation plays a critical role in acute glomerular injury induced by anti-GBM antibody deposition. We postulate that proteinuria may result from direct podocyte damage by PMN granule enzymes.

Funding: Other NIH Support - NIAID, Veterans Administration Support

TH-PO133

Shared and End Organ Specific Transcriptional Networks in Skin versus Kidney Biopsies in Systemic Lupus Celine C. Berthier, Jasmine N. Stannard, Emily M. Myers, Lori Lowe, Tamra J. Reed, Sean Eddy, Matthias Kretzler, J. Michelle Kahlenberg. *Univ of Michigan.*

Background: Patients with subacute cutaneous (sCLE) lesions have higher risk of lupus nephritis (LN) compared to those with discoid (DLE) lesions. We hypothesized that renal flares may be triggered via a crosstalk between skin and kidneys. To determine the potential factors contributing to this increased risk, we used systems biology approaches to integrate the regulatory events occurring specifically in sCLE and DLE and compared with those in LN.

Methods: Formalin-fixed paraffin-embedded tissue from 8 normal, 22 DLE and 24 sCLE rash biopsies were analyzed via microarrays. Gene expression profiles from 22 class III + IV LN and 14 healthy microdissected human renal biopsies (ERCB) were compared.

Results: Analyses using Genomatrix and Ingenuity softwares highlighted a strong upregulation of IFNγ associated pathways unique to DLE, and IL-4 a likely prominent DLE-specific regulator. Type I IFN signaling predominated in sCLE, with unique CD14, CCL-2,-20 chemokine expression. Respectively 415 and 435 genes were regulated in the same direction in the glomeruli of LN patients vs controls and in DLE and sCLE vs normal (q-value <0.01). The 85 genes regulated only in the LN glomeruli and DLE rashes represented a mainly down-regulated network highlighting MEP1B, CDH1 and CD8a as main nodes. Top pathways were epithelial adherens junction signaling. The 105 genes specific to LN glomeruli and sCLE showed a mainly up-regulated network with ITGB2, CD40, SYK, TIMP1 as major nodes. Ingenuity top pathway was crosstalk between dendritic cells and natural killer cells, both of which may play a role in cutaneous and renal lupus pathogenesis.

Conclusions: DLE and sCLE have overlapping and unique transcriptional expression signatures which may guide therapeutic decisions and predict renal involvement. Further analysis of these specific profiles may identify the molecular crosstalk mechanism between skin and kidneys, as well as targets for novel therapy of cutaneous lupus lesions which could help to prevent or delay the renal disease. Our data suggest an inflammatory cell crosstalk between skin and kidneys in sCLE, which may not happen in DLE.

Funding: Other NIH Support - NIAMS R03-AR-066373

TH-PO134

Molecular Determinants of Myeloperoxidase-ANCA Glomerulonephritis: Transcriptomic Analysis Across Three Species Maja Lindenmeyer,¹ Hamad Al nuaimi,² Peter W. Hewett,² Viji Nair,³ Caroline O.S. Savage,² Matthias Kretzler,³ Mark Alan Little,⁵ ¹*Klinikum Harlaching, Germany;* ²*Univ of Birmingham, United Kingdom;* ³*Univ of Michigan;* ⁴*UMC Groningen, Netherlands;* ⁵*TCD, Ireland.*

Background: Human myeloperoxidase (MPO)-ANCA vasculitis causes crescentic GN that results in glomerular destruction. This has been modelled in rats (EAV) and mice (MEV), although it tends to resolve spontaneously in these models with little glomerular scarring. To investigate conserved and divergent molecular pathways involved in glomerular injury we analysed the glomerular transcriptome in EAV, MEV and humans with MPO-ANCA vasculitis.

Methods: Glomeruli were microdissected from WKY rats immunised with MPO (EAV) or human albumin (control), from mice receiving anti-MPO (MEV) or BSA (control) antibodies raised in MPO-/- mice (n=5/group), and from patients with MPO-ANCA GN (n=7) and healthy controls (n=18). RNA expression was analysed on Affymetrix arrays. Differential regulation was assessed by ChipInspector and rodent/human orthologs identified using HomoloGene. After restriction of gene lists using co-citation at sentence level, the human network was used to overlap with mouse and rat networks using TALE. In 74 selected genes, regulation was confirmed by rtPCR.

Results: 3512, 1725 and 783 glomerular genes were significantly associated with GN in humans, mice and rats respectively. We observed overlap between human and mouse in 675 (12.9%), human and rat in 134 (3.1%) and across all 3 species in 179 (2.9%) genes. Of these 179 genes, 135 (75.4%) were differentially regulated in the same direction and 44 (24.6%) in opposite directions. We identified 12 canonical pathways (p value <0.001) conserved between human and mouse, and 5 between human and rat.

Conclusions: The transcriptomic profile in MEV was more similar to human disease than EAV. 2.9% of differentially regulated genes were conserved across all 3 species, with a quarter of these regulated in opposite directions between rodent and human. These data provide insights into both shared pathophysiology and mechanisms underpinning the divergent clinical phenotype between rodent and human MPO-ANCA GN.

Funding: Government Support - Non-U.S.

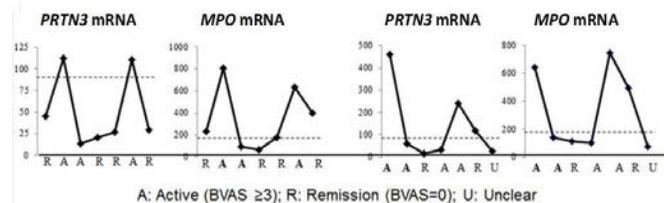
TH-PO135

PRTN3 and MPO Expression Correlates with Disease Activity in a Large Inception Cohort with Longitudinal and Serial Measurements Among Patients with ANCA Disease Jia Jin Yang,¹ JulieAnne G. McGregor,¹ Elizabeth J. Brant,¹ Caroline J. Poulton,¹ Candace Henderson,¹ Britta E. Jones,² J. Charles Jennette,^{2,1} Dominic J. Ciavatta,³ Ronald J. Falk,^{1,2} William Franklin Pendergraft.¹ ¹Medicine, UNC-CH; ²Pathology, UNC-CH; ³Genetics, UNC-CH, Chapel Hill, NC.

Background: We demonstrated aberrant up-regulation of autoantigen genes, *PRTN3* and *MPO*, in mature neutrophils and monocytes from patients with ANCA disease (J Am Soc Nephrol 2004, 15:2103-14). Here, we performed a longitudinal and serial analysis of *PRTN3* and *MPO* expression following their disease course.

Methods: A total of 1063 leukocyte samples were collected from 152 ANCA-patients during various stages of disease activity and compared to 152 healthy controls. These patients were followed serially every 3 months over the past 5 years. Q-PCR was used to measure mRNA levels.

Results: *PRTN3* (155±506, p<0.0001) and *MPO* (384±940, p<0.0001) mRNA levels were significantly up-regulated in leukocytes from patients with ANCA disease compared to healthy controls (*PRTN3*:16±34; *MPO*:56±54). *PRTN3* and *MPO* gene transcription correlated closely with disease activity. In the majority of patients with systemic vasculitis, their disease course was characterized by elevated expression in active disease and reduced expression in remission. The duration of increased *PRTN3* and *MPO* expression was variable from several days to several months. Increased *PRTN3* and *MPO* mRNA levels returned to normal in all patients with stable remission.



However, low *PRTN3* and *MPO* mRNA levels were also observed in some active patients, particularly in those with limited organ involvement.

Conclusions: Our longitudinal and serial analysis of *PRTN3* and *MPO* expression in patients with ANCA disease indicates that regulation of *PRTN3* and *MPO* genes strongly tracks with disease activity suggesting that expression of these ANCA autoantigens is involved in disease pathogenesis.

Funding: NIDDK Support

TH-PO136

Galactose-Deficient IgA1-Containing Immune Complexes Induce Proliferation of Human Mesangial Cells and Activate PDGF/PDGFR Signaling Pathway Zhi qiang Huang,¹ Xianwen Zhang,^{1,2} Qi Bian,^{1,3} Joshua Charles Anderson,¹ Stacy D. Hall,¹ Christopher D. Willey,¹ Bruce A. Julian,¹ Jan Novak.¹ ¹Univ of Alabama at Birmingham, Birmingham, AL; ²Medicine, Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; ³Medicine, Changhai Hospital, Second Military Medical Univ, Shanghai, China.

Background: Our prior kinomic profiling showed that circulating immune complexes (CIC) and engineered immune complexes (EIC) consisting of galactose-deficient IgA1 (Gd-IgA1) bound by anti-Gd-IgA1 autoantibodies activated multiple tyrosine kinases in cultured human mesangial cells (hMCs) and induced cellular proliferation. Activation of PDGF signaling and an anti-apoptotic processes were two major processes detected. In this study, we assessed the mechanisms involving PDGF/PDGFR and ERK1/2 signaling in hMC stimulated with CIC from sera of patients with IgAN and EIC.

Methods: CIC were isolated from sera of IgAN patients using size-exclusion chromatography. EIC were prepared using Gd-IgA1, anti-Gd-IgA1 recombinant IgG1, and human serum and then isolated using size-exclusion chromatography. hMC proliferation was determined using bromodeoxyuridine (BrdU) uptake. Gene expression of PDGF A, PDGF B, PDGF receptor- α (PDGFR- α) and PDGFR- β was determined using RealTime RT-PCR. Signaling induced by CIC or EIC was assessed by analyzing cell lysates using SDS-PAGE and Western blotting.

Results: Twenty-four hour incubation of hMC with CIC increased cellular proliferation by 30-50%; incubation with EIC increased cellular proliferation by 30-40%. Incubation with CIC and EIC for 15 min and 24 h enhanced phosphorylation of PDGFR- β and ERK1/2. Incubation of hMC with CIC for 24 h enhanced expression of mRNA of PDGF A, PDGF B, and PDGFR- α . Incubation with EIC for 24 h enhanced expression of PDGFR- α and PDGFR- β .

Conclusions: CIC and EIC stimulated proliferation of hMC and activated PDGFR and ERK1/2 signaling. Understanding how CIC and EIC mediate signaling in hMC may lead to future therapeutic approaches for IgAN.

Funding: NIDDK Support, Private Foundation Support

TH-PO137

The Pathogenic Role of NLRP3 Inflammasome in IgA Nephropathy and Establishment of a Therapeutic Strategy Shuk-Man Ka,¹ Yu-Juei Hsu.² ¹School of Medicine, Graduate Inst of Aerospace and Undersea Medicine, National Defense Medical Center, Taipei, Taiwan; ²Div of Nephrology, Dept of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: IgA nephropathy (IgAN) is the most common cause of primary glomerular disorders induced by IgA immune complex. Inflammatory responses have been shown to correlate with the progression of IgAN. NLRP3 inflammasome, a multiprotein complex, positively regulates caspase-1 activity and the maturation and release of IL-1 β . NLRP3 inflammasome plays an important role in inflammatory response and controls the pathogenesis of various inflammatory diseases. However, the potential pathogenic role of NLRP3 inflammasome on IgAN is unclear.

Methods: The pathogenic role of NLRP3 inflammasome and molecular mechanisms on IgAN pathogenesis using NLRP3 deficient mice and NLRP3 in kidney were specific knockdown by an ultrasound-mediated microbubble shRNA gene transfer method.

Results: NLRP3 deficient and blockage resulted in attenuation of albuminuria, improved renal function, and blocking of renal progressive lesions, including glomerular proliferation, and periglomerular mononuclear leukocyte infiltration. These findings were associated with (1) inhibiting ROS production and NF- κ B activation in the kidney, (2) reducing NLRP3 inflammasome activation in the kidney, (3) inhibiting effect/memory T-cell activation and IL-17 expression, and (4) inhibiting maturation and activation of dendritic cells.

Conclusions: These results indicate that activation NLRP3 inflammasome is involved in the development of IgAN, and a kidney-specific knockdown of NLRP3 may have therapeutic potential for IgAN.

Funding: Government Support - Non-U.S.

TH-PO138

Effects of DPPIV Inhibitor on Renal Function in Mice Model of Adriamycin Induced Nephropathy Hye Sook Min,¹ Jin Joo Cha,¹ Kitae Kim,¹ Jungyeon Ghee,¹ Jung Eun Kim,¹ Ji Eun Lee,² Hyunwook Kim,² Jee Young Han,³ Dae R. Cha,¹ Young Sun Kang.¹ ¹Internal Medicine, Korea Univ Medical College Ansan Hospital, Republic of Korea; ²Internal Medicine, Wonkwang Univ Sanbon Hospital, Republic of Korea; ³Pathology, Inha Univ College of Medicine, Republic of Korea.

Background: The murine model of adriamycin(ADR) induced nephropathy is characterized by severe proteinuria, development of podocyte injury and glomerulosclerosis. The aim of our study was to investigate the mechanism and preventive effect of fibrosis in glomerular, tubular and interstitial tissue associated with DA1229 treatment in ADR-induced nephropathy.

Methods: 6-week-old balb/c mice were divided into 4 groups as follows: 1) untreated after injection of ADR(control of group 2), 2) immediately treated with DA1229 for 3 weeks after injection of ADR(preventive protocol), 3) untreated after injection of ADR(control of group 4), 4) treated with DA1229 for 2 weeks after 3 weeks from injection of ADR(therapeutic protocol).

Results: Treatment with DA1229 showed preventive effect on weight gain and renal hypertrophy after 5 weeks of injection of ADR. Plasma DPPIV activity was significantly decreased in treatment with DA1229. DPPIV activity in kidney was significantly increased after injection of ADR and was decreased with DA1229. Notably, both preventive and therapeutic protocol significantly decreased proteinuria and albuminuria induced by ADR injection. Urinary excretion of nephrin was significantly decreased and inflammatory and fibrotic molecules in kidney tissue were significantly inhibited with DA1229 treatment. Additionally, infiltration of macrophages and fibrosis in the kidney were attenuated with DA1229 treatment in ADR groups.

Conclusions: Our data suggest that DA1229 might protect renal injury from podocyte injury in ADR-induced nephropathy, via antiinflammatory and antifibrotic effects. DA 1229 might be a potential therapeutic agent in a variety of glomerular disease inducing proteinuria.

TH-PO139

Effects of Highly Selective Adenosine 3 Receptor Antagonist on Renal Function in Mice Model of Adriamycin Induced Nephropathy Hye Sook Min,¹ Jin Joo Cha,¹ Kitae Kim,¹ Jung Eun Kim,¹ Jungyeon Ghee,¹ Ji Eun Lee,² Hyunwook Kim,² Jee young Han,³ Sung Jin Kim,⁴ Young Sun Kang,¹ Dae R. Cha.¹ ¹Internal Medicine, Korea Univ Medical College Ansan Hospital, Republic of Korea; ²Internal Medicine, Wonkwang Univ Medical College Sanbon Hospital, Republic of Korea; ³Pathology, Inha Univ College of Medicine, Republic of Korea; ⁴Internal Medicine, Anyang Sam Hospital.

Background: Concentration of adenosine in normal kidney increases markedly during renal hypoxia and ischemia. Previous studies have reported that mice lacking renal A3 adenosine receptor(A3AR) show significant protection against acute kidney injury, such as ischemia-reperfusion injury and myoglobinuria-induced injury. Moreover, A3AR antagonist blocked the development and attenuated the progression of renal fibrosis. The aim of this study was to investigate the effects of highly selective adenosine 3 receptor antagonist(LJ1888) treatment in ADR-induced nephropathy.

Methods: We designed three animal groups as following: 1) 6-week-old balb/c mice(control), 2) untreated with LJ1888 after injection of ADR(11mg/kg), 3) treated with LJ1888(10mg/kg) for 2 weeks after 5 weeks of injection of ADR.

Results: Body weight was significantly decreased in both ADR injection groups. ADR injection significantly induced proteinuria and albuminuria, which were notably reduced after treatment of LJ1888. Urine 8-isoprostane and kidney lipid peroxidase level were also decreased with LJ1888. Urinary excretion of nephrin was significantly reduced and kidney nephrin stain showed increased nephrin expressions in the glomeruli of LJ1888 group. Less glomerular injury and macrophage infiltration were observed in LJ1888 treated kidney. Immunoreactions with profibrotic molecule were significantly decreased with LJ1888. Additionally, protein expressions of Nox4, TGF- β 1, NF- κ B were attenuated with LJ 1888.

Conclusions: These renoprotective effects of LJ1888 on ADR-induced nephropathy may be associated with protective effect on podocyte injury. LJ1888 might be a potential therapeutic agent for glomerulonephropathy inducing proteinuria.

TH-PO140

Innate Immunity Is Activated Early in Adriamycin Nephropathy and Is Strongly Associated with Lymphocyte Infiltration Viviane D. Faustino, Simone CA Arias, Flavia P. Albuquerque, Camilla Fanelli, Victor F. Avila, Lisienny CT Rempel, Orestes Foresto-Neto, Gizely CS Moreira, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels OS Camara, Roberto Zatz, Clarice K. Fujihara. *Univ of Sao Paulo, Brazil.*

Background: Protein overload promotes interstitial injury by unclear mechanisms that may involve innate immunity (INIM). Here we investigated the time course of INIM activation in adriamycin nephropathy (AN), and the participation of lymphocytes (LY) in this process.

Methods: AN (5 mg/kg iv) was induced in 30 Munich-Wistar rats. Control rats (C, N=10) received saline only. At 2 (AN_{2wk}), 4 (AN_{4wk}) and 20 (AN_{20wk}) wks, albuminuria (ALB, mg/day), interstitial macrophages (M Φ) and LY (cells/mm²), α -SMA and collagen (COL). Renal INIM was assessed by gene expression (NLRP3 and IL-6, 2^{- $\Delta\Delta$ CT}) and protein content (IL-1 β , Casp1, TLR4). Four additional AN rats received mycophenolate mofetil (MMF, 10 mg/Kg/day, vo), and their ALB, LY, α -SMA, COL and renal content of IL-1 β , Casp1 and TLR4 were assessed at 30 days.

Results:

	C	AN _{2wk}	AN _{4wk}	AN _{20wk}
ALB	4 \pm 2	336 \pm 34 ^a	356 \pm 49 ^a	505 \pm 34 ^{abc}
M Φ	10 \pm 2	213 \pm 50 ^a	188 \pm 29 ^a	272 \pm 49 ^{abc}
LY	19 \pm 5	149 \pm 23 ^a	188 \pm 18 ^a	234 \pm 22 ^{abc}
% α -SMA	2 \pm 1	9 \pm 2 ^a	12 \pm 2 ^a	19 \pm 3 ^{abc}
%COL	3 \pm 1	10 \pm 3 ^a	13 \pm 2 ^a	27 \pm 2 ^{abc}
IL-1 β	0.5 \pm 0.1	1.3 \pm 0.4	1.8 \pm 0.4 ^a	4.4 \pm 0.9 ^{abc}
NLRP3	1.0 \pm 0.1	1.8 \pm 0.3 ^a	2.4 \pm 0.3 ^a	2.1 \pm 0.2 ^a
Casp1	1.0 \pm 0.2	1.6 \pm 0.3	1.5 \pm 0.5	4.0 \pm 0.6 ^{abc}
TLR4	1.0 \pm 0.2	3.4 \pm 0.9 ^a	3.4 \pm 1.0 ^a	8.5 \pm 1.4 ^{abc}
IL-6	1.0 \pm 0.1	8.1 \pm 2.7 ^a	8.5 \pm 2.3 ^a	12.0 \pm 1.9 ^a

Mean \pm SE, ^ap<0.05 vs C, ^bp<0.05 vs. AD2wk, ^cp<0.05 vs. AD4wk

Massive ALB promoted early and intense M Φ /LY infiltration and % α -SMA/COL, and activated renal INIM. Ly correlated strongly with INIM parameters. All parameters increased with time. MMF treatment significantly reduced LY (81 \pm 12), α -SMA (4 \pm 1) and COL (6 \pm 1), without changing ALB.

Conclusions: In AN, INIM is activated in concomitance with the early development of renal injury, and relates strongly with lymphocyte infiltration. Both inflammation and INIM activation parallel the progression of renal injury in tis model. FAPESP/CNPq.

TH-PO141

Inhibition of NF- κ B Signaling in Podocytes Ameliorates Albuminuria in Adriamycin-induced Nephropathy Tadashi Yoshida, Maho Yamashita, Matsuhiko Hayashi. *Apheresis and Dialysis Center, Keio Univ School of Medicine, Shinjuku, Tokyo, Japan.*

Background: Inflammation involving the activation of the NF- κ B signaling has been shown to contribute to proteinuria in chronic kidney disease. NF- κ B is expressed not only in inflammatory cells, such as lymphocytes and macrophages, but also in podocytes. We herein examined the role of NF- κ B in podocytes in adriamycin-induced nephropathy.

Methods: Podocyte-specific truncated I κ B expressing (Pod-I κ BDN) mice, in which the NF- κ B signaling was inhibited selectively in podocytes, were generated and analyzed their phenotype following the intravenous injection of adriamycin. Expression of nephrin and podocin was examined by immunostaining.

Results: Pod-I κ BDN mice did not exhibit any abnormalities in body weight, blood pressure, and the heart rate before the treatment. Following the administration of adriamycin, albuminuria was observed in both Pod-I κ BDN mice and control mice. However, of importance, the amount of albuminuria in Pod-I κ BDN mice (373 \pm 122 mg/g creatinine) was significantly lower than control mice (992 \pm 305 mg/g creatinine) 14 days after adriamycin injection. Serum concentrations of urea nitrogen were not different between these mice. Expression of nephrin and podocin in the glomeruli was decreased in adriamycin-treated control mice, but not in Pod-I κ BDN mice.

Conclusions: Results suggest that NF- κ B in podocytes plays an important role in proteinuric renal disease by regulating the expression of podocyte-specific proteins.

Funding: Government Support - Non-U.S.

TH-PO142

Apoptosis Signal Regulating Kinase 1/p38 Signalling Promotes Renal Inflammation in a Rat Model of Crescentic Glomerulonephritis Liv A. Amos,^{1,2} Yingjie Han,^{1,2} John T. Liles,³ David J. Nikolic-Paterson.^{1,2} ¹Dept of Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; ²Dept of Medicine, Southern Clinical School, Monash Univ, Clayton, Victoria, Australia; ³Gilead Sciences Inc, Foster City, CA.

Background: Apoptosis signal-regulating kinase 1 (ASK1) is required for p38 mitogen-activated protein kinase (MAPK) signalling in tubular cells in response to angiotensin II and oxidative stress, but not to IL-1 or LPS. However, it is not known whether ASK1 is required for p38-dependent glomerular injury. The aim of the study was to determine whether blockade of apoptosis signal-regulating kinase 1 (ASK1) can suppress renal injury in rapidly progressive glomerulonephritis.

Methods: Accelerated anti-glomerular basement membrane (GBM) disease was induced in groups of 6-8 rats. Treatment with ASK1 inhibitor GS-444217 (30mg/kg/po/bid) or vehicle began 1hr before anti-GBM serum injection and continued until animals were killed on day 1 or 14.

Results: Compared to normal controls, anti-GBM disease showed a 3-fold increase in phosphorylated (activated) p38 in glomeruli on day 1 which was prevented by ASK1 inhibition. In addition, the 20-fold increase in urine protein/creatinine ratio at day 1 was prevented by ASK1 inhibitor treatment. In a separate study, vehicle treated anti-GBM disease exhibited 30 \pm 3% (mean \pm SD) crescents on day 14, which was reduced to 10 \pm 2% by ASK1 inhibitor (P<0.001). ASK1 inhibitor treatment reduced proteinuria by 50% compared to the vehicle group (P<0.01), and prevented an increase in serum creatinine (40 \pm 9umol/L vs. 27 \pm 9umol/L; P<0.05). Glomerular macrophage and T cell infiltration was also reduced by the ASK1 inhibitor (P<0.05), with an associated reduction in macrophage M1/M2 markers (iNOS, CD206). Finally, immunostaining and PCR analysis showed a reduction in renal fibrosis with ASK1 inhibitor treatment.

Conclusions: This study suggests that ASK1 is involved in activating p38 MAPK signalling in glomerular inflammation. In addition, treatment with GS-444217 decreased glomerular inflammation and crescent development. Further studies are required to investigate potential effects of therapeutic intervention in established anti-GBM disease.

Funding: Government Support - Non-U.S.

TH-PO143

Transforming Growth Factor β -Activated Kinase 1(TAK1) Attenuates Experimental Glomerulonephritis Liv A. Amos,^{1,2} Elyce Ozols,^{1,2} Yingjie Han,^{1,2} David J. Nikolic-Paterson.^{1,2} ¹Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; ²Medicine, Southern Clinical School, Monash Univ, Clayton, Victoria, Australia.

Background: Activation of p38/JNK signalling promotes glomerular inflammation. TAK1 is an upstream kinase in the p38/JNK pathway. TAK1 regulates the response to a range of stimuli which promote glomerular inflammation (TNF- α , IL-1 and TLR ligands). Therefore, we investigated whether TAK1 activates p38/JNK signalling in acute glomerular inflammation.

Methods: Global Tak1 gene deletion was induced in Tak1^{fl/fl}ER^{Cre} mice via tamoxifen, while Tak1^{fl/fl}Pod^{Cre} mice have conditional Tak1 deletion in podocytes. Accelerated anti-glomerular basement membrane (GBM) disease was induced in Tak1^{fl/fl}ER^{Cre} and Tak1^{fl/fl}Pod^{Cre} littermate controls (n=8-11) and killed after 3hr or 24hr. Disease was also induced in Tak1^{fl/fl}Pod^{Cre} and Tak1^{fl/fl} littermate controls (n=5) and killed at 24hr.

Results: Compared to controls, global deletion of TAK1 had no effect upon the initial inflammatory response at 3hr in terms of neutrophil and macrophage infiltration and platelet deposition. However, at 24hr TAK1 deletion caused exacerbation of glomerular

injury compared to littermate controls in terms of: proteinuria (11.9±5 vs 5.4±0.5 mg/mmol; P=0.03); thrombosis (59±11% vs 8±3% glomeruli; P=0.001); renal function (1.4-fold increase in serum cystatin c; P<0.01); p38 and JNK activation (p-p38+ cells/gcs 20.81±0.45 vs 9.8±0.611; P<0.001; p-c-Jun+ cells/gcs 14.62±1.35 vs 8.171±1.12; P<0.05). The neutrophil infiltrate had largely subsided in control mice at 24hr; however, prominent neutrophil infiltration and platelet deposition was evident in mice with global TAK1 deletion at 24hr (neutrophils/gcs 3.27±0.29 vs 0.42±0.06; P<0.05; platelet clumps/gcs 29.88±3.37 vs 16.69±1.75; P<0.05). This exacerbation of glomerular damage was not due to a direct effect upon podocytes since Tak1^{fl/fl}Pod^{Cre} mice showed no difference compared to controls in proteinuria, p38/JNK activation or thrombosis at 24hr.

Conclusions: TAK1 is a negative regulator of glomerular p38/JNK signalling and acute renal inflammation, which may operate via limiting neutrophil-mediated glomerular injury.

Funding: Government Support - Non-U.S.

TH-PO144

Absence of Osteopontin Accelerates Oxidative Stress-Induced Fibrosis in Glomerulonephritis Gabriela E. Garcia,¹ Jessica Helen Trostel,¹ Luan D. Truong,^{2,3} Richard J. Johnson.¹ ¹Medicine, Univ of Colorado Denver, Aurora, CO; ²Pathology, Baylor College of Medicine, Houston, TX; ³Pathology, The Methodist Hospital, Houston, TX.

Background: Osteopontin (OPN) is a pro-and anti-inflammatory and profibrotic molecule that simultaneously attenuates oxidative stress in the inflammatory milieu. Evidence suggests that oxidative stress plays a significant role in the progressive fibrosis by upregulating fibrosis related genes. Moreover, elevation of biomarkers of increased oxidative stress has been demonstrated in patients with chronic kidney disease. OPN is highly induced in nephritic kidney and inactivation of macrophages (MΦ) by an A_{2A}R agonist, attenuated OPN expression and protected from progressive kidney injury.

Methods: To further characterize the role of OPN in kidney injury we use OPN^{-/-} mice in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), an inflammatory and progressive model of kidney disease.

Results: Wild type and OPN^{-/-} mice did not show histological differences in the glomeruli and the tubulointerstitium. However, nephritic kidneys from OPN^{-/-} mice showed severe kidney damage compared with those in WT mice. Fibrinoid necrosis, crescent formation, and tubulointerstitial injury were significantly higher in OPN^{-/-} mice compared to WT mice. In addition, collagen (Col) I, Col III, and Col IV deposition were increased in nephritic kidneys from OPN^{-/-} mice compared with WT mice. MΦ and T cell infiltration in nephritic kidneys was not different between WT mice and OPN^{-/-} mice. Elevated expression of the reactive oxygen species (ROS)-generating enzyme Nox 4 was observed in nephritic kidneys from OPN^{-/-} mice. In contrast, MΦ isolated from WT mice and OPN^{-/-} mice did not show difference in the expression of Nox4. Importantly, the antigen-specific humoral immune response and the glomerular immunoglobulin G deposition were not affected in OPN^{-/-} mice.

Conclusions: These findings suggest that in global OPN^{-/-} mice elevated Nox4 creates a redox imbalance with increased oxidative stress induced-fibrosis. Targeting MΦ OPN could be protective to attenuate inflammation and inflammation-associated fibrosis without affecting the anti-oxidative stress of OPN.

Funding: NIDDK Support

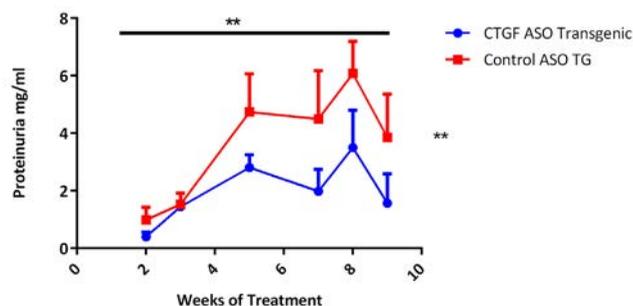
TH-PO145

Investigating Connective Tissue Growth Factor as a Critical Mediator of Cryoglobulinaemia Gayathri K. Rajakaruna,¹ Charles E. Alpers,² Alan D. Salama.¹ ¹UCL Centre for Nephrology, Univ College London, Royal Free Campus, London, United Kingdom; ²Dept of Pathology, Univ of Washington, Seattle.

Background: Cryoglobulins are immunoglobulins that precipitate at temperatures below 37°C. Cryoglobulinaemic vasculitis (CV) is commonly associated with hepatitis C (HCV) infection and causes a membrano proliferative glomerulonephritis (MPGN) in the kidney. Through a serendipitous finding we have previously established the development of CV in Connective tissue growth factor (CTGF) over expressing transgenic mice. CTGF, a matricellular protein involved in cell proliferation and key regulatory pathways, is elevated in patients with HCV-induced CV. Thymic stromal lymphopoietin (TSLP) transgenic mice also develop CV and have high serum CTGF levels. Higher TSLP levels have been shown in patients with HCV-induced CV. We hypothesized that CTGF overexpression is the key driver for cryoglobulin formation, and represents and potential therapeutic target.

Methods: TSLP Tg animals were used for this pilot study. We investigated whether CTGF anti sense oligonucleotides (ASO) attenuated CV, in comparison to control ASO. 14 TG and 12 WT animals were studied over a 10 week period.

Results: There were no deaths amongst CTGF ASO group whilst one control animal died. The incidence of ulcerative ear and neck lesions was 50% lower in the CTGF ASO group compared to the controls.(p=0.0549). The CTGF ASO cohort had lower proteinuria compared to the controls; this was significant between treatment arms and the duration of treatment (p=0.0092 and p=0.0034 respectively).



There was less severe histological injury in the CTGF ASO cohort (mean mesangial expansion score 1.485±SD 0.2824 vs. 2.247± SD 1.116, p=0.0458).

Conclusions: This preliminary pilot study suggests that antagonism of CTGF ASOs may attenuate CV in TSLP Tg animals. Larger studies are required to confirm this observation.

TH-PO146

The Toll-Like Receptor Signaling Pathway Is Activated Before the Development of Renal Injury in the 5/6 Nephrectomy Model Camilla Fanelli, Jessica K. Okuma, Simone CA Arias, Flavia G. Machado, Victor F. Avila, Viviane D. Faustino, Gizely CS Moreira, Orestes Foresto-Neto, Lisienny CT Rempel, Claudia R. Sena, Vivian L. Viana, Hatylas Azevedo, Denise M. Malheiros, Niels OS Camara, Clarice K. Fujihara, Roberto Zatz. *Univ of Sao Paulo.*

Background: Mechanisms of activation of inflammation in Chronic Kidney Disease (CKD) are unclear. We examined the participation of innate immunity in the 5/6 nephrectomy model (Nx) from its beginning to advanced phases.

Methods: Munich-Wistar rats underwent Nx (N=40) or Sham (S, N=10) operation. Tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h) glomerulosclerosis index (GSI) and cortical interstitium (%INT) were assessed 7, 15, 60 and 120 days after Nx. Gene and protein content of Tlr4, Casp1, Il1b and Nlrp3 were also evaluated. PCR-Array and gene enrichment analysis (GEA) by z-score evaluated gene expression of innate and adaptive immunity components.

Results:

	S	Nx7	Nx15	Nx60	Nx120
TCP	142±1	168±5a	188±5ab	209±3abc	216±4abc
ALB	8±2	44±11a	108±15ab	112±18ab	177±11abcd
GSI	0±0	0±0	0±0	29±8abc	105±17abcd
%INT	0±0	1±0	1±0	4±1abc	5±1abc
Cytokine Cytokine-Receptor Interaction		-2.1a	-2.0a	-2.0a	-2.1a
Hematopoietic Cell Lineage		-1.8a	-0.2a	-1.7a	-1.8a
Type I Diabetes Mellitus				-1.6a	-1.8a
Jak Stat Signaling Pathway					-0.2a
Toll Like Receptor Signaling Pathway		-1.8a	-1.8a	-1.9a	-1.7a
Natural Killer Cell Mediated Cytotoxicity					-1.7a
Fc Epsilon Ri Signaling Pathway					-1.7a
Cell Adhesion Molecules		-1.6a	-1.7a	-1.7a	-1.4

Mean±SE: *p<0.05 vs S, *p<0.05 vs Nx7, *p<0.05 vs Nx15, *p<0.05 vs Nx60

In addition, Tlr4, Tlr9, Nlrp3, Lbp2 and Irf7 genes were twice as high in Nx7 vs S. The same was seen for Casp1, Il1b, Tlr2 and Tlr5 after 15d. Tlr4, Casp1 and Il1b protein content increased following gene expression. GEA showed heightening of the Tlr Signaling Pathway (TlrSP) at all times in Nx.

Conclusions: The TlrSP, among other immune-related signaling pathways, is activated in the Nx model since its earliest stages until advanced phases, suggesting that they may contribute to initiate and maintain renal injury in this model.

TH-PO147

TLR2/TLR4-MyD88-NF- κ B Pathway Is Involved in Tubulointerstitial Inflammation Caused by Proteinuria Lihong Ding, Dan Liu, Hong Liu, Kunling Ma, Bi-Cheng Liu. *Inst of Nephrology, Zhong Da Hospital, Southeast Univ, Nanjing, Jiangsu, China.*

Background: Proteinuria, an independent risk factor for progression of chronic kidney diseases (CKD), has been suggested to initiate or aggravate tubulointerstitial inflammation (TI). While the potential mechanism is still to be clarified. In this study, we hypothesized that activation of the TLR2/TLR4-MyD88-NF- κ B pathway might be involved in proteinuria induced TI.

Methods: We established an albumin-overload nephropathy rat model, and the expression of TLR2, TLR4, MyD88, NF- κ B as well as TNF- α and IL-6 were detected by immunohistochemistry, real-time PCR and Western blot. *In vitro*, we investigated the impact of albumin stimulation on these parameters in HK-2 cells. Furthermore, siRNA for TLR2, TLR4 and BAY 11-7082, the inhibitor of NF- κ B, was applied to study their influence on the expression of TNF- α and IL-6 caused by albumin stimulation.

Results: Rats treated with albumin-overload induced a significant increase of proteinuria, proteinaceous casts and tubulointerstitial inflammation. The expression of TLR2, TLR4, MyD88 and NF- κ B in the proximal tubular cells were significantly increased as well as TNF- α and IL-6 expression. In addition, the expression of TNF- α and IL-6 was significantly correlated with proteinuria. Albumin-overload induced TNF- α and IL-6 expression by TLR2/TLR4-MyD88-NF- κ B pathway activation, which could be attenuated by the siRNA for TLR2, TLR4 or NF- κ B inhibitor BAY 11-7082 in HK-2 cells.

Conclusions: This study demonstrated that proteinuria might play as an endogenous danger-associated molecular pattern (DAMP) that induced renal TI via the TLR2/TLR4-MyD88-NF- κ B pathway.

Funding: Government Support - Non-U.S.

TH-PO148

Targeting Integrin CD11b/CD18 Reduces Inflammation and TLR-Mediated IFN Responses Implicated in Lupus Nephritis Samia Khan,¹ Shehryar J. Khaliqina,¹ Mohd Hafeez Faridi,¹ David J. Cimbaluk,¹ Mariana Klapam,² Vineet Gupta.¹ ¹Internal Medicine, Rush Univ Medical Center, Chicago, IL; ²Systemic Autoimmunity Branch, National Insts of Health (NIH), Bethesda, MD.

Background: GWAS studies show strong associations between SNPs in the ITGAM locus, which encodes for the α -subunit (CD11b) of the β 2 integrin CD11b/CD18 and susceptibility to lupus nephritis. CD11b/CD18 is a leukocytic adhesion receptor that modulates their biological functions and negatively regulates TLR-mediated pro-inflammatory signaling. Insufficient activity of CD11b/CD18 drives disease pathogenesis, hence making it a promising therapeutic target.

Methods: We tested whether activation of CD11b/CD18 with small molecule agonist, leukadherin-1 (LA1), suppresses pro-inflammatory TLR and IFN signaling pathways *in vitro* and *in vivo*. Since stimulation of TLR-induced overproduction of inflammatory cytokines drives lupus nephritis, we also tested whether dampening of these pathways with LA1 treatment reduces kidney injury in lupus prone MRL/lpr mice.

Results: Treatment of macrophages or neutrophils with LA1 and TLR4 agonist LPS or TLR7/8 agonist R848 induced a significant decrease in IL-6, TNF α and MCP-1, as well as type I IFN pathways, as compared to controls. In a murine model of severe sepsis, LA1 treatment significantly prolonged survival and reduced serum IL-6 and IL-1 β levels as compared to controls. In a murine model of lupus nephritis (MRL/lpr), renal pathology of kidneys from LA1 treated mice revealed significantly reduced kidney damage as compared to controls. LA1 treatment also reduced proteinuria and IgG levels in the kidney, while protecting glomerular expression of WTI, SYNPO and activated b1 indicating enhanced kidney function. Renal tissue from LA1 treated mice displayed normal foot process width as compared to controls.

Conclusions: LA1-mediated CD11b/CD18 activation suppresses TLR-induced production of pro-inflammatory cytokines and IFN pathways. LA1 treatment also dampens TLR-stimulated overproduction of cytokines *in vivo*, which drives lupus nephritis. These findings indicate a crucial role for CD11b/CD18 in suppressing inflammation and identify LA1 as a promising therapeutic agent for human autoimmune diseases.

Funding: NIDDK Support

TH-PO149

Allopurinol Attenuates Innate Immunity Activation and Renal Injury in the Nx Model, Despite Low Uric Acid Levels Orestes Foresto-Neto, Victor F. Avila, Simone CA Arias, Camilla Fanelli, Lisienny CT Rempel, Denise M. Malheiros, Hugo Abensur, Niels OS Camara, Roberto Zatz, Clarice K. Fujihara. *Univ of Sao Paulo, Brazil.*

Background: Allopurinol (Allo) attenuates renal damage in experimental CKD. It is unknown whether this protection is due to inhibition of uric acid (UA) synthesis or to a direct action on oxidative stress and innate immunity (NIM). We studied the effect of Allo in the 5/6 nephrectomy model (Nx) in rats, in which UA degradation by uricase allows its effect on renal injury and NIM to be studied without its confounding action on UA levels.

Methods: Munich-Wistar rats (N=33) underwent Nx or sham operation (S, N=16). Nx rats were divided in: Nx, untreated; and Nx+Allo, given Allo 36 mg/kg/day *vo*. Tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h), glomerulosclerosis (GS), urinary NGAL (uNGAL, mg/24h), interstitial collagen 1 (COL) and macrophages (M Φ , cells/mm²), renal xanthine oxidase activity (rXO, mU/mg), plasma UA (pUA, mg/dL) and renal content of IL-1 β (pg/g) and TLR4 (fold increase vs C) were assessed on Day 60.

Results:

	S	Nx	Nx+Allo
TCP	134 \pm 2	212 \pm 8*	191 \pm 6 ^{ab}
ALB	3 \pm 1	111 \pm 15*	89 \pm 10*
% GS	0 \pm 0	15 \pm 4*	10 \pm 3*
% COL	2 \pm 1	9 \pm 1*	5 \pm 1 ^{ab}
uNGAL	29 \pm 4	48 \pm 5*	32 \pm 3 ^b
M Φ	22 \pm 2	187 \pm 26*	130 \pm 20 ^{ab}
rXO	70 \pm 5	116 \pm 7*	69 \pm 5 ^b
pUA	1.3 \pm 0.2	2.1 \pm 0.2*	0.8 \pm 0.2 ^b
IL-1 β	1.5 \pm 0.2	4.7 \pm 0.6*	2.4 \pm 0.3 ^b
TLR4	1.0 \pm 0.1	3.3 \pm 0.4*	2.3 \pm 0.2 ^{ab}

Mean \pm SE, *p < 0.05 vs S; ^bp < 0.05 vs Nx

As expected, pUA was only slightly (though significantly) elevated in Nx, remaining far lower than previously seen with uricase inhibition. Allo normalized rXO activity and cancelled the slight increase of pUA observed in Nx. Despite the low pUA, Allo attenuated hypertension and promoted selective tubulointerstitial protection, reducing uNGAL, COL and M Φ . In addition, Allo lowered the renal content of TLR4 and IL-1 β , which correlated positively with both TCP and ALB.

Conclusions: In the Nx model, Allo exerts a renoprotective effect even in the context of low UA levels, which is associated, at least in part, with inhibition of innate immunity. FAPESP/CNPq.

TH-PO150

Megalin/Cubulin-Lysosome-Mediated Albumin Reabsorption Is Involved in the Tubular Cell Activation of NLRP3 Inflammasome and Tubulointerstitial Inflammation Dan Liu, Bi-Cheng Liu. *Inst of Nephrology, Zhong Da Hospital, Southeast Univ School of Medicine, Nanjing, Jiangsu, China.*

Background: Albuminuria contributes to the development and progression of chronic kidney disease (CKD) by inducing tubulointerstitial inflammation (TI) and fibrosis. However, the exact mechanisms of TI in response to albuminuria are unresolved. We previously demonstrated that NLRP3 and inflammasomes mediate albumin-induced lesions in tubular cells. Here, we further investigated the role of endocytic receptors and lysosome rupture in NLRP3 inflammasome activation.

Methods: We established an albumin-overload induced rat nephropathy model. The adult male Wistar rats that were uninephrectomized or sham operated under anesthesia 5 days before starting BSA injection. *In vitro*, tubular epithelial cell line (HK-2) was cultured with or without megalin/cubulin gene siRNA transfection and then stimulated with BSA for different time durations (6h, 12h, 24h, 48h) and concentrations (5, 10, 20, 40 mg/ml). Cell lysates and supernatants were collected and determined by western blotting and ELISA. Cathepsin B and Cathepsin D with or without their inhibitors were detected by western blotting and immunofluorescence staining.

Results: The priming and activation signals for inflammasome complex formation were evoked simultaneously by albumin excess in tubular epithelial cells. The former signal was dependent on albumin-triggered NF- κ B pathway activation. This process is mediated by the endocytic receptor, megalin and cubilin. However, the silencing of megalin or cubilin inhibited the albumin-induced NLRP3 signal. Notably, subsequent lysosome rupture and the corresponding release of lysosomal hydrolases, especially Cathepsin B, were observed in TECs exposed to albumin. Cathepsin B release and distribution is essential for NLRP3 signal activation, and inhibitors of Cathepsin B suppressed the NLRP3 signal in TECs.

Conclusions: Taken together, our findings suggest that megalin/cubilin and lysosome rupture are involved in albumin-triggered tubular injury and TI.

TH-PO151

Targeted Inhibition of Protein Kinase C- α Ameliorates Nephrotic Nephritis Nino Kvirkvelia,¹ Maggie McMenamin,¹ Vanessa Iris Gutierrez,¹ Istvan Czikora,² Rudolf Lucas,² Michael P. Madaio.¹ ¹Medicine, Georgia Regents Univ, Augusta, GA; ²Pharmacology and Toxicology, Georgia Regents Univ, Augusta, GA.

Background: Protein kinase C (PKC) is a ubiquitous phospholipid-dependent enzyme, with multiple isoforms that differ in their structure, biochemical properties, tissue distribution, subcellular localization, and substrate specificity. Since PKC- α expression was shown to be increased in patients with chronic kidney disease and in podocytes in renal biopsies of patients with diabetic nephropathy, we investigated the effect of specific PKC- α inhibition on renal injury in a murine model of acute kidney inflammation.

Methods: Mice were divided into four groups: 1) controls, 2) NTN, 3) NTN + PKC- α inhibitor Ro-32-0432 given *i.p.* after induction of nephritis on day 2, and 4) NTN group + PKC- α inhibitor conjugated to glomerular specific antibodies (*i.e.* a well-defined, human mAb (F1.1) directed against α 3(IV) collagen) on day 2 to achieve kidney targeted drug delivery.

Results: On day 7, all NTN mice had severe nephritis, as evidenced by increased BUN, proteinuria and histology, whereas mice that received PKC- α inhibitors in either form had minimal evidence of kidney injury. BUN levels were reduced from 99.84 \pm 0.33mg/

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

dL in NTN mice to 32.29 ± 1.70 mg/dL in mice receiving free PKC- α inhibitor and to 36.07 ± 4.51 mg/dL in mice injected with F1.1 conjugated-PKC- α inhibitor. Serum levels of cytokines, assessed in multiplex analysis (MagPix) further confirmed reduction of inflammation.

Conclusions: These results suggest that PKC- α is an important mediator of antibody-mediated glomerulonephritis, and that glomerular targeted inhibition of this enzyme is feasible. This methodology, has the advantage of diminishing systemic side effects while limiting and/or reversing ongoing damage associated with severe inflammation. This approach has potential therapeutic implications for the treatment of human kidney diseases.

Funding: NIDDK Support

TH-PO152

Renal Sympathetic Nerve Activity Controlled by Renal Afferent Sympathoexcitatory or Inhibitory Nerves? Tilmann Ditting,¹ Kristina Rodionova,¹ Sonja Heinlein,¹ Karl F. Hilgers,¹ Christian Ott,¹ Roland E. Schmieder,¹ Martin Hindermann,¹ Kerstin U. Amann,² Roland Veelken.¹ ¹*Nephrology & Hypertension, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany;* ²*Pathology, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany.*

Background: Renal sympathetic nerve activity (RSNA) is important in hypertension, volume disorders or renal disease. It is unclear if increases of RSNA in disease are due to sympathoexcitatory or impaired sympathoinhibitory renal afferent nerves. We present data from nephritic rats suggesting the latter.

Methods: Nephritis due to OX7-antibodies in male Sprague-Dawley-rats. Methohexital anesthetized nephritic rats & controls were instrumented to stimulate renal afferent nerve activity (ARNA) in order to influence RSNA: ipsilateral renal arterial catheter for intrarenal administration (IRA) of the TRPV1 agonist capsaicin to stimulate ARNA (CAP 6.6×10^{-7} M) and induce the release of the tachykinin receptor agonist SP from renal afferents; contralateral stainless steel electrode for RSNA recording; before and after IRA CAP the tachykinin-receptor blocker RP67580 was given. Baseline RSNA & ARNA were assessed. Some nephritic rats were pretreated with tachykinin receptor antagonists to prove increased SP effects.

Results: IRA CAP decreased RSNA from 67.5 ± 12.0 mV*sec to 14.8 ± 4.2 mV*sec ($p < 0.05$) over 60 minutes while in nephritis RSNA suppression was abolished. Suppressed RSNA in controls was transiently reversed by the tachykinin inhibitor. Under resting conditions RSNA was higher, ARNA lower in nephritis as compared to controls. Tachykininreceptor antagonism ameliorated damage in renal nephritis suggesting increased SP release from renal afferent nerves despite lack of the tachykinin dependant sympathoinhibition seen in controls.

Conclusions: Our data suggest that a tachykinin dependant reno-sympathetic reflex mechanism exerts sympathoinhibitory effects being impaired under pathophysiological circumstances.

Funding: Government Support - Non-U.S.

TH-PO153

Fan1^{-/-} Mice Develop Karyomegalic Interstitial Nephritis Rannar Airik,¹ Markus Schueler,¹ Merlin Airik,¹ Jonathan Porath,¹ Friedhelm Hildebrandt.^{1,2} ¹*Division of Nephrology, Dept of Medicine, Boston Children's Hospital, Boston, MA;* ²*Howard Hughes Medical Inst, Chevy Chase, MD.*

Background: Karyomegalic interstitial nephritis (KIN) is a chronic interstitial nephropathy, characterized by tubulointerstitial nephritis and formation of enlarged nuclei in kidneys and other tissues (1). We recently reported that recessive mutations in the gene encoding FANCD2/FANCI-Associated Nuclease 1 (FAN1) cause KIN in humans (2). In order to study the function of Fan1 in kidneys we generated a Fan1 knock-out mouse model.

Methods: Targeted *Fan1*^{tm1aiv} ES cells were obtained from EUCOMM and injected into blastocysts to generate *Fan1*^{-/-} mice. Abrogation of Fan1 expression in the mutant mice was confirmed by qRT-PCR. Renal histology was studied using hematoxylin/eosin, PAS and Masson's trichrome staining. Tubular damage was induced with intraperitoneal cisplatin injection. Cell culture experiments were performed using mouse embryonic fibroblasts or mesenchymal stem cells isolated from *Fan1*^{-/-} and wild type animals.

Results: *Fan1*^{-/-} mice were born at Mendelian ratio and appeared healthy with no gross abnormality in kidney. Treatment of *Fan1*^{-/-} and wild type mice with 10 or 20 mg/kg cisplatin caused severe tubular injury with cast formation and tubular dilation in *Fan1*^{-/-} animals ($n=5$), accompanied with dramatic weight loss and lethality. Chronic injection of cisplatin at 2 mg/kg induced karyomegalic interstitial nephritis that lead to renal failure within 5 weeks in *Fan1*^{-/-} animals, but not in wild type mice. Cell culture studies demonstrated decreased survival and reduced colony formation of *Fan1*^{-/-} cells in response to treatment with genotoxic agents.

Conclusions: *Fan1*^{-/-} mice provide a new model to study the pathomechanisms of chronic kidney disease. We demonstrate that *Fan1*^{-/-} mice are highly sensitive to genotoxic insults that lead to kidney failure. Our data indicate that Fan1 is involved in the physiological response of the kidney cells to DNA damage, which has been recently acknowledged to contribute to the pathophysiology of the chronic kidney disease (2, 3).

Funding: NIDDK Support, Private Foundation Support

TH-PO154

Down Regulation of Vitamin D Receptor (VDR) Expression Determines Initiation and Progression of HIV-Associated Nephropathy (HIVAN) with Variable Angiotensinogen (Agt) Copies Xiqian Lan, Hongxiu Wen, Anjali Maheshwari, Gauri P. Patil, Ramachandra prasanna Bongu, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: Agt transgenic mice have accelerated renin angiotensin system (RAS). On that account, we hypothesized that mice with enhanced expression of Agt would display accelerated progression of HIVAN. We evaluated the effect of different copies of Agt in the initiation and progression of HIVAN in genetically engineered HIVAN mice (Tg26).

Methods: Control and Tg26 mice with 2 (Tg26/Agt-2) and 4 (Tg26/Agt-4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and hypertension at 8 weeks and 16 weeks. Renal cortical sections were stained with sirius red and PAS. RNA was extracted from renal tissues and probed for AT1, AT2, VDR and molecules involved in profibrotic and epithelial mesenchymal transition (EMT) pathways.

Results: Tg26/Agt-4/8wks showed lower blood pressure ($P < 0.01$) vs. Tg26/Agt-2/8 wks, while Tg26/Agt-4/16wks displayed higher blood pressure vs. Tg26/Agt-2/16wks. Tg26/Agt-4/8wks displayed attenuated expression of PAI-1 vs. Tg26/Agt-2/8wks; however, Tg26/Agt-4/16wks showed 3-fold greater PAI-1 expression than to Tg26/Agt-2/16wks. Tg26/Agt-2/8wks displayed attenuated expression VDR and enhanced production of Ang II vs. Tg26/Agt-4/8wks, however this pattern reversed at 16 wks. Tg26/Agt-4/8wks displayed attenuated expression of AT1 and AT2 and down regulation of Tert, TGF- β , Snail, and vimentin when compared to Tg26/Agt-2/8wks. However, all these markers were comparable between these groups at 16 wks of age. Tg26/Agt-2/8wks developed renal lesions which were more advanced than Tg26/Agt-4/8wks. Conversely, Tg26/Agt-4/16wks displayed more advanced renal lesions vs. Tg26/Agt-2/16wks.

Conclusions: Tg26/Agt-4 displayed slower progression of HIVAN initially at 8 weeks associated with enhanced renal tissue VDR expression and attenuated expression of AT1, TGF- β , PAI-1, Tert and EMT markers. However, Tg26/Agt-4 at 16 wks displayed accelerated growth due to attenuated VDR expression leading to high blood pressure, upregulation of EMT and profibrotic molecules.

TH-PO155

Egr1 Deficiency Abolishes Inflammatory and Fibrotic Responses of Renal Tubular Cells Li-chun Ho,¹ Junne-Ming Sung,² Yau-Sheng Tsai.¹ ¹*Inst of Clinical Medicine, National Cheng Kung Univ, Tainan, Taiwan;* ²*Internal Medicine, National Cheng Kung Univ Hospital, Tainan, Taiwan.*

Background: Early growth response-1 (Egr-1) is a transcription factor that has been found to regulate inflammation and fibrosis in non-kidney tissues, but its role in renal failure has not been well established.

Methods: Wild type and Egr1^{-/-} mice were fed with adenine-enriched diet to induce tubulointerstitial nephritis (TIN), and primary tubular epithelial cells (PTECs) were treated with pro-inflammatory and pro-fibrotic cytokines. In addition, human kidney tissues were obtained from diabetic patients with renal failure and from non-diabetic patients without renal failure. The cell-type in which Egr-1 was activated was assessed using immunofluorescence and immunohistochemical stain. The levels of inflammatory and fibrotic markers were analyzed using RT-PCR and Western blotting. Kidney sections were also stained with H&E and Masson's trichrome to assess immune cell infiltration and fibrotic area.

Results: In mouse kidneys with TIN as well as in human kidneys with renal failure, tubular epithelial cell is the primary site for Egr-1 activation and undergoing nuclear translocation. Egr1^{-/-} mice were protected from renal failure, reflected by lower levels of serum urea and creatinine. This is consistent with Egr-1 deficiency-related reductions of immune cell infiltration, NF- κ B activity, and expression of cytokines and chemokines in the kidneys. In addition, Egr1^{-/-} mice with TIN had less fibrotic area and attenuated TGF β signaling than wild-type mice with TIN. Egr-1 deficiency also abolished the ordinary responses of PTECs to TNF α and TGF β .

Conclusions: Egr-1 activation in the renal tubular cell plays an integrative role for renal inflammation, fibrosis and the subsequent renal failure. Thus, Egr-1 may serve as a therapeutic target for human kidney diseases.

TH-PO156

Angiopietin-1 Overexpression Attenuates Renal Fibrosis Through Decreasing Inflammation Fan-Chi Chang,^{1,2} Ming-Hsuan Tsai,² Yu-hsiang Chou,² Shuei-Liong Lin.^{2,3} ¹*Internal Medicine, Taipei Medical Univ Hospital, Taipei, Taiwan;* ²*Graduate Inst of Physiology, College of Medicine, National Taiwan Univ, Taipei, Taiwan;* ³*Renal Div, Dept of Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.*

Background: Our previous studies have found dysregulated angiogenic growth factors in fibrotic kidney. We thus hypothesized that dysregulated angiopoietin-Tie system is related to microvascular destabilization and inflammation in the injured kidney.

Methods: We use unilateral ureteral obstruction (UUO) and 5 to 6 subtotal nephrectomy (5/6Nx) as animal models of progressive renal fibrosis. Specific overexpression of angiopoietin-1 (Angpt1) is induced with cross-breed between Pax8-rTA (with C57BL/6 background) and pTRE-hAngpt1 (with ICR genetic background). Under the control of mouse Pax8 promoter, doxycycline administration directs high levels of expression of the reverse tetracycline-dependent transactivator (rtTA) to all proximal, distal tubules and

the entire collecting duct system of both embryonic and adult kidneys. Double transgenic mice inherit both Pax8/rtTA and pTRE-hAngpt1 responder. Littermates that inherited one or no transgenes serve as experimental controls.

Results: In animal model of UUO and 5/6Nx, Angpt1 decreases whereas Angpt2 and Angpt2/Angpt1 ratio increase as renal fibrosis progresses. Cross-breed of pTRE-hAngpt1 (with ICR genetic background) and Pax8-rtTA (with C57BL/6 background) lines is conducted for conditional overexpression. Overexpression of Angpt1 by tubule cells, include all proximal, distal tubules and the entire collecting duct system is induced after doxycycline administration in offspring with two transgenes. Compared to littermate control, transgenic mice with Angpt1 overexpression attenuate interstitial fibrosis in UUO kidney demonstrated by picrosirius red staining. Further analyses demonstrate decrease of inflammatory cell infiltration in UUO kidney of mice with Angpt1 overexpression.

Conclusions: These studies indicate that Angpt1 supplement may provide a novel therapy to attenuate renal fibrosis through reduction of inflammatory cell infiltration in UUO kidney.

Funding: Government Support - Non-U.S.

TH-PO157

Benidipine Targets Leukocyte Kv1.3-Channels and Slows the Progression of Renal Fibrosis in Rats with Advanced Chronic Renal Failure Ituro Kazama, *Physiology I, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.*

Background: Leukocytes, such as lymphocytes and macrophages, predominantly express delayed rectifier K⁺-channels (Kv1.3) in their plasma membranes. In our previous study, the overexpression of these channels in leukocytes was strongly associated with their proliferation in kidneys and the progression of renal fibrosis in the advanced stage chronic renal failure (CRF). Since benidipine, a long-acting 1,4-dihydropyridine Ca²⁺ channel blocker, is also highly potent as a Kv1.3-channel inhibitor, it could exert therapeutic efficacy in advanced CRF.

Methods: Male Sprague-Dawley rats that underwent 5/6 nephrectomy followed by a 14-week recovery period were used as the model of advanced CRF. Benidipine hydrochloride (5mg/kg) was started at 8 weeks after nephrectomy and orally administered daily for 6 weeks. The histopathological features of the kidneys were examined in vehicle-treated and benidipine-treated CRF rat kidneys. Cellular proliferation of leukocytes and the cortical expression of pro-inflammatory cytokines were also examined.

Results: In CRF rat kidneys, Kv1.3-channels began to be overexpressed in leukocytes as early as 8 weeks after nephrectomy. In the cortical interstitium of benidipine-treated CRF rat kidneys, both immunohistochemistry and real-time PCR demonstrated decreased expression of fibrotic markers. Benidipine treatment significantly reduced the number of proliferating leukocytes within the cortical interstitium and decreased the expression of cell cycle markers and pro-inflammatory cytokines.

Conclusions: This study demonstrated for the first time that benidipine slowed the progression of renal fibrosis in rat kidneys with advanced CRF. Kv1.3-channels overexpressed in leukocytes were thought to be the most likely therapeutic targets of benidipine in decreasing the number of proliferating leukocytes and repressing the production of inflammatory cytokines.

Funding: Government Support - Non-U.S.

TH-PO158

Renoprotection by Treatment with CXA10, an Endogenous Nitro-Fatty Acid Cynthia M. Arbeen,¹ Hong Ling,¹ Mandy M. Smith,¹ Stephen O'Brien,¹ Stefan Wawersik,¹ Steven R. Ledbetter,¹ Diane K. Jorkasky,² ¹Genzyme, a Sanofi Company, Framingham, MA; ²Complexa, Inc., Pittsburgh, PA.

Background: CXA10 is an electrophilic nitro-fatty acid that modulates anti-oxidant and anti-inflammatory pathways through activation of NRF2 and reduction of NFkB activity. Here, we examine the potential therapeutic benefit of CXA10 in a mouse model of hypertension-induced chronic renal injury that mimics human Focal Segmental Glomerular Sclerosis (FSGS).

Methods: Uninephrectomized male mice (129/sv) were implanted with a DOCA salt pellet (or placebo) at 2 and 5 weeks post-surgery, maintained on 1% NaCl (drinking water), and supplemented with 24% fat diet. Animals (n=8-10/group) were treated for 4 weeks with CXA10 (2.5mg/kg, p.o.); or with enalapril (20mg/kg; in drinking water) as the positive control.

Results: Body weight was slightly decreased and blood pressure was increased with DOCA treatment, and neither parameter was significantly altered by intervention. Kidney- and heart-to-body weight ratios were increased with DOCA and were significantly reduced in the CXA10 but not in the enalapril group, whereas plasma cholesterol levels were reduced in both groups. CXA10 and enalapril significantly reduced albuminuria and nephrinuria but did not significantly improve the reduction in GFR following DOCA. Histologic evaluation revealed that both treatments improved interstitial lesions and fibrosis, whereas only CXA10 reduced glomerular sclerosis and hypertrophy. Molecular markers of glomerular injury and podocyte number were unchanged in all groups, suggesting that structural glomerular injury was modest. Even so, markers of inflammation and fibrosis were elevated in tissue and urine samples in this model. CXA10 reduced urinary MCP-1 as well as mRNA levels encoding MCP-1, osteopontin, collagen III, fibronectin, and PAI-1. Enalapril treatment did not significantly alter this expression profile.

Conclusions: These results provide in vivo evidence that CXA10 is renoprotective in a kidney disease model by affecting anti-inflammatory, anti-oxidant and anti-fibrotic pathways and that the beneficial effects of CXA10 were differentiated from enalapril in this model.

TH-PO159

Selective Knock-Out of Glycogen Synthase Kinase 3-β in Proximal Renal Tubular Epithelial Cells (RTE) Attenuates Inflammation and Tubular Injury After Unilateral Ureteral Obstruction (UUO) Josef Bautista, Eman Mohammad Shaban, Evelyn Tolbert, Rujun Gong, Lance D. Dworkin. *Medicine, Brown Univ, Providence, RI.*

Background: Glycogen synthase kinase 3-beta (GSK-3β) is a ubiquitous serine/threonine protein kinase that regulates a large number of processes in diverse cell types including RTE. Systemic administration of small molecule inhibitors of GSK-3B reduces inflammation and fibrosis and lessens acute and chronic kidney injury. However, the extent to which the beneficial effects of GSK-3β inhibition depend on blocking the enzyme specifically in kidney cells is unknown. We investigated whether gene deletion of GSK3β in RTEs alone would reduce inflammation and progression of CKD.

Methods: The GSK-3β gene was selectively deleted in the renal tubular cells by crossing mice in which exon 2 of the GSK3b gene was "floxed" with mice expressing CRE recombinase under a YGT promoter expressed only in adult proximal RTE (KO). Injury was induced by UUO in wild type (WT), KO, and WT mice given low-dose (1 mg/kg) thiazolidinone (TDZD), a specific GSK3β inhibitor. After 7 days, kidneys were weighed and examined for tubular and glomerular injury, interstitial edema, and macrophage infiltration. Groups were compared by ANOVA.

Results:

Group	Kidney Wt (gm/100g body wt)	Injured Tubules (%)	Glomerular Injury Score	Interstitial edema score
KO (n=7)	0.74 ± 0.09	35% ± 0.15 *	2.14 ± 0.94	1.47 ± 0.32
WT (n=11)	0.79 ± 0.16	57% ± 0.09	1.54 ± 0.66	1.59 ± 0.35
TDZD (n=11)	0.69 ± 0.12	46% ± 0.12	1.52 ± 0.82	1.77 ± 0.28

*P<0.01 KO vs. WT

Macrophage infiltration assessed by immunohistochemistry also declined by about 40% in KO mice

Conclusions: Selective deletion of GSK-3β in RTE attenuated macrophage infiltration and reduced tubulo-interstitial, but not glomerular injury after UUO. Elimination of GSK-3β signaling in RTE was more effective than systemic, low dose GSK-3β inhibition. Our data suggest that GSK-3β dependent pathways in RTEs play a critical role in promoting interstitial inflammation and tubular injury in CKD.

Funding: NIDDK Support, Clinical Revenue Support

TH-PO160

TIMP-1 Up-Regulates the Expression of MCP-1 Through NF-κB Pathway in Rat Mesangial Cells Xiang-Mei Chen, Xizhao Chen, Qing-gang Li, Guangyan Cai. *Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases.*

Background: In mesangial proliferative glomerulonephritis (MesPGN), tissue inhibitors of metalloproteinases (TIMPs) can regulate transcription factors and cytokines and participate in immune and inflammation reactions in an MMP-independent way. We found that in the anti-Thy-1 nephritis model, TIMP-1 and monocyte chemoattractant protein 1 (MCP-1) were significantly increased at the mesangial dissolved phase and peaked at the mesangial proliferative phase, finally backed to normal at the recovery phase. Our hypothesis is that TIMP-1 can regulate MCP-1 expression through NF-κB in mesangial cells.

Methods: (1) We established the anti-Thy-1 nephritis model. Animals were sacrificed at day 0, 1, 2, 3, 5 and 7, mRNA levels of TIMP-1 and MCP-1 were detected at separate time points by Taqman probe technique. (2) TIMP-1 over-/low-expression rat mesangial cell model were established by GFP-TIMP-1 lentivirus transfection and siRNA interference. (3) The cells of TIMP-1 over-expression were harvested at day 5, 6, 7, and low-expression cells at 48h. Then we detected the mRNA and protein levels of TIMP-1, MMP2, MMP9, NF-κB and MCP-1 by Taqman probe technique and Western blot. (4) TIMP-1 over-expression cells were treated with NF-κB inhibitor BAY 11-7082 (5mmol/L) at 4th day. After 48h-culture, mRNA level were detected.

Results: (1) In rat anti-Thy-1 nephritis, the expression levels of TIMP-1 and MCP-1 was increased gradually and peaked at day 5, then began to decrease. MCP-1 followed the same trend but peaked at day 2. (2) We established the TIMP-1 over-/low-expression model successfully. (3) When TIMP-1 presented over-expression, MMP9, NF-κB and MCP-1 were up-regulated (P<0.05); When TIMP-1 presented low-expression, these were down-regulated. (P<0.001) The change in expression of MMP2 was not obvious. (4) At 48h after inhibition with NF-κB inhibitor, the expression level of MCP-1 in the TIMP-1 over-expression cells was down-regulated (P<0.01).

Conclusions: TIMP-1 could participate in the immune and inflammation reactions of MesPGN by up-regulating the expression of MCP-1 through NF-κB in rat mesangial cells.

Funding: Government Support - Non-U.S.

TH-PO161

Calcitriol Protects against Renal Tubular Cell Apoptosis by Promoting M2 Macrophage Polarization in Diabetic Nephropathy Rats

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Background: Renal tubular apoptosis is a key event in initiating kidney damage in DN. Heterogeneity of macrophage phenotype and function ultimately determines the outcome of DN. Therefore, we sought to investigate whether calcitriol, known as an important renal-protective drug, is sufficient to protect against tubular cell apoptosis by promoting M2 macrophage in DN rats.

Methods: DN model rats were established by intraperitoneal injection with streptozocin (STZ). The rats were subsequently receiving either calcitriol (0.1mg/kg/d) or vehicle by gavage. Rats were sacrificed at 18w for histological and molecular analysis. In addition, we performed in vitro study using Raw264.7 cells cultured with either high glucose or high glucose followed by 1,25-dihydroxyvitamin D3 medium to assess macrophage phenotype.

Results: Calcitriol significantly improved renal function and ameliorated renal histology in DN rats. The increased tubular cell apoptosis in DN rats was alleviated by calcitriol. Calcitriol up-regulated the expression of anti-apoptotic protein Bcl-2, down-regulated the expression of pro-apoptotic protein such as Bax and caspase-3. Interestingly, calcitriol significantly enhanced M2 macrophage polarization in interstitium with elevated expressions of M2 markers, including CD163, Arg-1 and MR. Moreover, the ratio of CD163/CD68 considered as the proportion of M2 macrophage was about 2.9 fold highly after calcitriol treatment. In vitro, 1,25-dihydroxyvitamin D3 also promote high glucose-induced pro-inflammatory M1 macrophage toward anti-inflammatory M2 polarization.

Conclusions: Calcitriol protects against renal tubular cell apoptosis by promoting M2 macrophage polarization in STZ-induced DN rats.

Funding: Government Support - Non-U.S.

TH-PO162

APOL1 Risk Variants Induce Aberrant THP-1 Monocyte Differentiation and Increased Eicosanoid Production

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Background: Apolipoprotein L1 (APOL1) is an innate immune protein and its risk variants are strongly associated with kidney disease. We investigated the effects of APOL1 variants on monocyte differentiation and eicosanoid production in macrophages, as activated tissue macrophages in kidney might contribute to injury.

Methods: THP-1 cells, a human monocytic cell line, were transiently transfected with APOL1-A isoform G0 (ancestral allele) or the renal risk variants G1 and G2 and cultured for 36 hr before RNA was obtained for gene expression studies.

Results: APOL1-transfected THP-1 cells manifested a 6-8 fold increase in CD14 and CD68 gene expression, similar for all three variants, and similar to that seen with phorbol-12-myristate acetate treatment. Furthermore, APOL1 risk variants induced activated monocytes into atypical M1 macrophages with increased RNA encoding M1 markers CD80, TNF, IL1 β , and IL6 (all vs EV p <0.05, G1 vs G2 p >0.05), modest increase in M2 markers CD163, CD206, and TGF β 1 with G1 transfection (all RNAs vs EV p <0.05) and CD204 and TGF β 1 with G2 transfection (both RNAs vs EV p <0.05). Gene expression for eicosanoid generating enzymes was increased as well: cyclo-oxygenase-2, G0, 1.3 \pm 0.9 fold over empty vector (EV), G1, 4.1 \pm 0.5 and G2, 4.5 \pm 0.5 (both G1 and G2 vs G0 p <0.01) and thromboxane synthase, G0, 2.1 \pm 0.8 fold over EV, G1, 5.2 \pm 0.9 and G2, 4.5 \pm 0.5 (both G1 and G2 vs G0 p <0.05). Thromboxane A2 receptor (TXA2R) gene expression was unchanged with G0, 1.8 \pm 0.4 fold over EV (p >0.05), and increased with G1, 6.1 \pm 1.0, and G2, 4.1 \pm 0.5 (G1 vs G0 p <0.001, G2 vs G0 p <0.01). Higher levels of thromboxane B2, a stable metabolite of thromboxane A2, were present in the supernatant of cultured THP-1 cells transfected with G1 (10.0 \pm 1.3 pg/mL/10⁶ cells, p <0.05 vs G0) and G2 (15.1 \pm 3.0 pg/mL/10⁶ cells, p <0.01 vs G0) compared to G0 (6.0 \pm 1.0 pg/mL/10⁶ cells), which was similar to EV (6.7 \pm 1.0 pg/mL/10⁶ cells, p >0.05 vs EV).

Conclusions: These results demonstrate a novel role of APOL1 variants in the regulation of monocyte differentiation and eicosanoid metabolism, which could modify the immune response and promote inflammatory signaling within the kidney and elsewhere.

Funding: NIDDK Support

TH-PO163

Purification and Analysis of Exosomes Derived from Primary Human Proximal Epithelial Cells (PTEC)

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Background: Exosomes are extracellular vesicles secreted by multiple cell types in the body which contain a tissue-type signature courtesy of their incorporated RNA and protein cargo. Exosomes have crucial roles in extracellular communication and are implicated in kidney inflammation and disease progression. Human PTEC play a central role in renal disease yet their exosome expression remains virtually unknown. Here we characterize exosomes from primary human PTEC cultured under normal, hypoxic and inflammatory conditions.

Methods: Exosomes were purified from normal, hypoxic (1% O₂) and inflammatory (IFN- γ /TNF- α treated) PTEC cultures using ultracentrifugation and density gradients

and analyzed for morphology (electron microscopy), size/concentration (qNano) and CD9/63/81 expression (Western blot). Protein and microRNA content were analyzed by mass spectroscopy (MS) and sequencing respectively.

Results: Exosomes from all three culture conditions displayed the same size range (50-120nm) and morphology (spherical doughnut shape) with a similar expression of CD9 (high), CD63 (medium) and CD81 (low). However, concentrations of exosomes from both hypoxic and inflammatory conditions increased by more than two fold compared to normal culture conditions. MS analysis demonstrated exosomes from hypoxic cultures contained 134 proteins not expressed in those from normal cultures, whilst inflammatory exosomes contained 152 unique proteins. A number of these proteins have been implicated in development of chronic kidney disease.

Conclusions: Collectively, our data indicate that exosome secretion is increased under "diseased" conditions, and importantly, there is condition specific differential protein expression. Further investigation of exosome protein/microRNA cargo will identify novel targets whose utility in therapies and disease biomarkers warrant analysis.

Funding: Government Support - Non-U.S.

TH-PO164

HIF-2 α in Dendritic Cells in Renal Injury

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Background: Hypoxia-inducible transcription factors, HIF-1 α and -2 α play key roles in cellular adaptation to hypoxia and have been linked to innate immune responses. In macrophages they are non-redundant and are expressed depending on polarization. However, in other innate immune cells, such as dendritic cells (DCs), the differential role of HIF α isoforms is less clear. DCs are abundant in the kidney and have been implicated in renal (patho)physiology. As shown previously, HIF-1 α in DCs affects maturation and T cell stimulation, but whether HIF-2 α plays a specific role is elusive. The aim of our study was therefore to elucidate the functional properties of HIF-2 α in DCs in vitro and in vivo during renal injury.

Methods: Murine primary DCs (BMDC) were generated from bone marrow of tissue specific conditional knock-out mice (CD11c Cre-HIF-2 α ^{lox/lox}). BMDCs were then stimulated with hypoxia and LPS followed by mRNA, FACS and protein analysis. Bilateral renal ischemia and reperfusion injury (IRI) was used as a model of acute renal injury. To induce chronic kidney injury, mice were subjected to either a 3 week adenine rich diet or to unilateral ureteral obstruction (UUO), followed by the above mentioned analyses.

Results: HIF-2 α protein is detected in BMDC after LPS treatment and with hypoxic stimulation. Loss of HIF-2 α does not affect expression of maturation markers such as CD86 or MHCII after LPS and the ability of T cell activation. In vivo during acute or chronic renal injury, loss of dendritic HIF-2 α does not affect renal function, inflammatory cell responses or the expression of fibrotic or inflammatory markers.

Conclusions: Taken together, our data indicates that loss of HIF-2 α in DCs does not affect maturation in vitro and leukocyte infiltration or renal function in models of acute and chronic renal injury in vivo. Thus, in contrast to macrophages, HIF α isoforms in DCs do not seem to play functional opposing roles. This might have important implications for the development of pharmacologic agents targeting HIF α in DCs to modulate immune responses during renal injury.

Funding: Government Support - Non-U.S.

TH-PO165

Fecal Transplantation from Uremic Mice Aggravates Kidney Fibrosis

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Background: Emerging evidence showed the important role of kidney-gut crosstalk in diverse pathological processes. Alterations in intestinal barrier or microbiota has been demonstrated in chronic kidney disease (CKD) and thought to be associated with increased cardiovascular risks or progression of CKD. The purpose of this study was to investigate the effect of gut microbiota in the animal model of kidney fibrosis with using fecal transplantation.

Methods: Unilateral ischemia/reperfusion injury (IRI) for 45min was performed in C57/BL6 mice for fibrosis model. Supernatants of centrifuged feces from 5/6 nephrectomized mice (8wks) or age matched control mice were administered 3 times per wk for 3 wks after gut decontamination and degree of fibrosis was compared (CKD feces vs control feces).

Results: Compared to mice with fecal transplantation from control mice, mice who were transplanted with CKD feces showed aggravated fibrosis at 2 wks after unilateral ischemia in the analysis of the Masson's trichrome staining and Western blot for type 4 collagen. Ex vivo analysis of immune cells showed increased number of mature CD80+ CD11c+ cells in mesenteric lymph node whereas percentage of splenic Tregs increased in mice transplanted from uremic mice. Immune cells from these mice showed significantly suppressed cytokine release upon LPS stimulation compared mice with WT feces.

Conclusions: This study showed the possible effect of kidney-gut crosstalk on the progression of CKD and this effect is thought to be partially mediated by immune modulatory effect.

TH-PO166

A Novel Mineralocorticoid Receptor Blocker Protects the Remnant Kidney Better Than Eplerenone as an Add-On to Late Losartan Clarice K. Fujihara,¹ Mark Kowala,² Matthew D. Breyer,² Claudia R. Sena,¹ Mariliza V. Rodrigues,¹ Simone CA Arias,¹ Camilla Fanelli,¹ Denise M. Malheiros,¹ Jose E. Krieger,¹ Roberto Zatz.¹ ¹Univ of São Paulo, Brazil; ²Eli Lilly.

Background: Aldosterone (Ald) worsens, whereas MR blockers, e.g. eplerenone (E), slow CKD, but cause hyperkalemia, especially with RAS inhibitors, e.g. Losartan (L). LY2180176 (LY) is a novel, nonsteroidal, high-affinity MR blocker (Ki 1.6 nM vs 124 for E). We tested LY as an add-on to L in 5/6 ablation (Nx) rats.

Methods: Male Munich-Wistar rats underwent Nx (N=89) or sham (S, N=24) surgery, being divided in (all drugs in mg/kg/d, from Day 60 to 150 post Nx): Nx, untreated; Nx+L, given L, 50; Nx+L+E, L 50 + E 150; Nx+L+LY, L 50 + Ly 20. ALB, albuminuria, mg/d; TCP, tail-cuff pressure, mmHg; PR, plasma renin, ng/mL/h; plasma Ald, pg/mL; Serum K⁺, mmol/L; GS, Glomerulosclerosis; COL, cortical collagen; interstitial AngII+, cells/mm². Genes (italic): RT-PCR (x increase).

Results:

	S	Nx	Nx+L	Nx+L+E	Nx+L+LY
ALB	5±1	162±12 ^a	79±18 ^{ab}	35±5 ^{abc}	5±1 ^{bcd}
TCP	125±2	216±5 ^a	168±5 ^{ab}	155±4 ^{abc}	124±3 ^{bcd}
PR	3±1	1±1 ^a	16±12 ^a	112±78 ^{abc}	147±48 ^{abcd}
Ald	175±23	394±83 ^a	132±30 ^b	775±117 ^{abc}	2478±290 ^{abcd}
K ⁺	4.3±0.2	5.2±0.2 ^a	5.5±0.2 ^a	5.8±0.2 ^a	5.3±0.2 ^a
%GS	0.1±0.1	30.2±4.0 ^a	19.2±4.0 ^{ab}	10.5±2.1 ^{abc}	6.7±1.4 ^{abc}
%COL	4±1	29±3 ^a	20±3 ^a	18±4 ^a	12±2 ^{abc}
AngII+	0.8±0.2	6.9±1.0 ^a	6.3±1.7 ^a	4.8±0.8 ^a	2.9±0.6 ^{ab}
Renin	1.0±0.1	0.6±0.1 ^a	1.4±0.4 ^b	2.7±0.6 ^{abc}	11.7±1.3 ^{abcd}
SGK1	1.2±0.3	1.3±0.2	0.8±0.2	0.5±0.1 ^{ab}	0.7±0.1
NHE3	1.1±0.1	0.6±0.1 ^a	0.6±0.1 ^a	0.7±0.1	0.8±0.1 ^{bcd}
NKCC2	1.0±0.1	0.6±0.1 ^a	0.6±0.1 ^a	0.9±0.1	1.2±0.1 ^{bc}
WNK1	1.0±0.1	0.7±0.1	0.9±0.1	0.9±0.1	1.1±0.1 ^b
SGLT1	1.0±0.1	0.7±0.1 ^a	0.7±0.1 ^a	0.8±0.1	1.1±0.1 ^{bcd}

LY normalized TCP and ALB and slowed CKD better than E. LY strongly raised PR and Ald, and restored transporter expression, suggesting volume loss. Despite strong MR blockade, LY did not raise K⁺.

Conclusions: LY may become a new asset in the therapy of CKD.

TH-PO167

Role of Innate Immunity in a Model of CKD following Brief Dietary Adenine Overload Gizely CS Moreira, Ricardo P. Mazzonetto, Lisienny CT Rempel, Orestes Foresto-Neto, Camilla Fanelli, Simone CA Arias, Viviane D. Faustino, Claudia R. Sena, Victor F. Avila, Vivian L. Viana, Denise M. Malheiros, Niels OS Camara, Clarice K. Fujihara, Roberto Zatz. Univ of São Paulo, Brazil.

Background: Adenine (ADE) excess leads to accumulation of crystals (Crys) at the renal interstitium (INT) through NF-κB activation (AJPRenal:F155,2013). After ADE cessation, INT nephritis progresses even as Crys disappear. Here we verified whether AngII and innate immunity (INIM) are activated in the acute and/or chronic phases of this model.

Methods: Adult male Munich-Wistar rats (n=76) received no treatment (C) or 0.5% ADE in chow for 1 wk, after which Crys/mm², tail-cuff pressure (TCP, mmHg), glomerulosclerosis (GS, %), INT collagen (COL, %), INT macrophage (Mφ) and AngII+ (cells/mm²), renal IL1β (pg/mg), and renal IL6, NLRP3 (2^{-ΔΔCt}) and TLR4 (WB, fold) were assessed. Measurements were repeated 4 and 24 wk after ADE cessation.

Results:

	1 wk ADE+		4 wk ADE-		24 wk ADE-	
	C	ADE	C	ADE	C	ADE
Crys	-	1.3±0.2 ^a	-	0.6±0.2 ^a	-	0.2±0.1 ^{ab}
TCP	130±2	157±4 ^a	134±2	141±3 ^b	137±3	150±4 ^a
GS	0±0	0±0	0±0	0±0	0.4±0.2	2.1±1.0 ^{ab}
COL	5±1	5±1	4±1	9±2	4±1	12±2 ^{ab}
Mφ	16±2	90±8 ^a	24±6	65±6 ^{ab}	20±1	64±7 ^{ab}
AngII+	1±0.3	4±0.6 ^a	1±0.4	4±0.6 ^a	1±1	7±2 ^{ab}
IL1β	0.9±0.1	6.7±1.1 ^a	1.1±0.3	3.0±0.6 ^a	1.6±0.6	1.4±0.4 ^b
IL6	1.2±0.3	4.9±0.9 ^a	1.2±0.3	1.8±0.3 ^a	1.2±0.3	1.1±0.2 ^b
NLRP3	1.0±0.1	2.0±0.1 ^a	1.0±0.1	1.5±0.1 ^{ab}	1.0±0.1	1.2±0.1 ^b
TLR4	1.0±0.4	3.6±0.8 ^a	1.0±0.4	1.0±0.1 ^b	1.0±0.2	1.2±0.2 ^b

(Mean ± SE, ^ap <0.05 vs C, ^bp <0.05 vs 1 wk)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Innate immunity activation was seen at 1 week. However, only Mφ and AngII+ remained elevated as chronic renal injury settled in, despite disappearance of Crys.

Conclusions: INIM may participate, along with renal AngII production and Mφ infiltration, in the acute phase of this model. However, INIM seems not to influence the late progression to chronic glomerular and interstitial injury, which may depend on as yet unidentified mechanisms. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

TH-PO168

Assessing the Role of B7.1 in Diabetic Nephropathy Marcela Herrera,¹ Magnus Soderberg,² Johan C. Molne,³ Beatriz Santamaria Pérez,⁴ Angela M. Valverde,^{4,5} Stephanie C. Heasman,¹ Lutz Jermutus,¹ David J. Baker,¹ Carol Patricia Moreno Quinn.¹ ¹Cardiovascular & Metabolic Diseases, MedImmune, Cambridge, United Kingdom; ²AstraZeneca, Molndal, Sweden; ³Pathology, Sahlgrenska Univ, Gothenburg, Sweden; ⁴Inst for Biom Res Alberto Sols, CSIC, UAM, Madrid, Spain; ⁵Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (ISCIII), Madrid, Spain.

Background: Upregulation of podocyte B7.1 has been reported in kidney biopsies of Diabetic Nephropathy (DN) patients and in stressed cultured human podocytes. Blocking B7.1 with a CTLA4-Fc fusion (Abatacept) protects the injured podocyte in vitro and improves DN pre-clinically. B7.1 is found in antigen presenting cells and binding of CTLA4-Fc to B7.1 prevents T-cell activation. Since inflammation is an important feature of diabetes, we hypothesized that Abatacept protects the kidneys during DN primarily by blocking T-cell activation.

Results: We investigated B7.1 expression in 42 DN kidney biopsies using immunohistochemistry. B7.1 expression was not detected in podocytes but predominantly localized in a limited number of macrophages, with no differences found between control and DN patients (0.15±0.23 vs. 0.19±0.22cells/mm²). In situ hybridization confirmed these results. In cultured human podocytes, B7.1 was found at relatively low levels when assessed by qPCR, and treatment with high-glucose (30mM for 3, 5, 10 and 14 days) or LPS (20 and 50ug/uL for 24 hrs) did not enhance B7.1 expression. Western blotting analysis confirmed these results. LPS-induced F-actin re-organization was not prevented by Abatacept (10-100ng/mL). We then tested Abatacept in the STZ-induced DN model (high fat-diet-C57Bl6). After 3 weeks of diabetes induction, Abatacept was dosed s.c. at 50mg/kg every 2 days for 12 weeks. At 3 weeks of dosing, urinary albumin:creatinine ratio increased from 3.6±0.8 to 8.3±0.9ug/umoles in the diabetic animals (p<0.05) while in the Abatacept group UAC was 4.0±0.6ug/umol (p<0.05 vs. DN group). Glucose or HbA1c were unaffected across groups and throughout the study.

Conclusions: B7.1 is a valid target for DN where the mechanism of action is more likely inhibition of T-cell activation rather than podocyte protection.

Funding: Pharmaceutical Company Support - MedImmune AstraZeneca

TH-PO169

Systemic Overexpression of Endogenous Secretory RAGE Attenuates Diabetic Kidney Injury Through TLR4 Not TLR2 Signaling Xiaochen Chen,¹ Jin Ma,¹ Elisabeth G.D. Stribos,¹ A. Lianne Messchendorp,¹ Moumita Paul,¹ Eithne Cunningham,¹ Alexandra Sharland,¹ Steven J. Chadban,^{1,2} Huiling Wu.^{1,2} ¹Kidney Node Laboratory, Charles Perkins Centre, Univ of Sydney, Australia; ²Royal Prince Alfred Hospital, Australia.

Background: Endogenous secretory RAGE (esRAGE) is a soluble decoy receptor that can competitively bind ligands for TLRs/RAGE, including HMGB1. Here we test whether: 1) esRAGE after the induction of diabetes can prevent the development of diabetic nephropathy (DN) in mice with streptozotocin-induced diabetes; 2) the protective effects of esRAGE are attributable to interruption of signaling via the HMGB1 receptors (TLR2, TLR4 and RAGE).

Methods: DN was induced in WT, TLR4^{-/-} and TLR2^{-/-} mice by intraperitoneal injection of streptozotocin. At 2 weeks after STZ injection, mice received an IP injection of 5x10¹¹ vector genome copies rAAV encoding either esRAGE or HSA, or saline-control. Samples were collected at week 12 post-induction of diabetes.

Results: Diabetic mice that received rAAV-esRAGE, rAAV-HSA or saline developed equivalent degrees of hyperglycaemia. Diabetic WT-mice given rAAV-HSA or saline developed significant albuminuria versus non-diabetic WT-mice (ACR309±213 & 313±215 versus 55±10, p<0.05-0.01), whilst rAAV-esRAGE treated-diabetic-mice were protected (118±42, p<0.05). WT diabetic-mice developed histological damage including glomerular hypertrophy, podocyte injury, macrophage accumulation and interstitial fibrosis. These changes were significantly attenuated in diabetic mice given rAAV-esRAGE versus rAAV-HSA (p<0.05-0.01). While both TLR2^{-/-} mice and TLR4^{-/-} mice were partially protected against DN, esRAGE treatment provided additional protection to TLR2^{-/-} mice, but not TLR4^{-/-} mice. A further study of esRAGE treatment in RAGE^{-/-} mice is underway.

Conclusions: High-level expression of serum esRAGE after the induction of diabetes provided partial protection against the development of DN in STZ-induced diabetic mice, which may operate through the TLR4 pathway.

TH-PO170

Calcitriol Inhibits Advanced Glycation End Product (AGE)-Elicited Mesangial Cell Damage by Sequestered RAGE-NF- κ B Signaling

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Background: Activated vitamin D3 (Calcitriol) can effectively slow the progression of chronic kidney disease and its mechanism is not very clear. The advanced glycation products (AGEs) accumulate in the kidney disease through RAGE receptors. The aim of this experiment was to explore the effect and mechanism of Calcitriol on the inflammatory of mesangial cells caused by AGEs, and to further expand the clinical application of activated vitamin D3.

Methods: AGE-HSA was prepared and human glomerular mesangial cells were cultured in vitro. The purpose of the present study was to investigate the efficacy of calcitriol on AGEs-induced inflammatory in human mesangial cell. Pretreatment or not with calcitriol, the human mesangial cell was treatment with various concentrations and time period of AGEs. IL-6 and MCP-1 were measured by real-time PCR and ELISA. The expression of vitamin D receptor (VDR), receptor of advanced glycation end products (RAGE), NF- κ B p65 and phosphorylated p65 was measured by Western-blot. NF- κ B p65 translation was determined by immunofluorescence. Cellular oxidative stress was measured by reactive oxygen species (ROS) production.

Results: (1) AGE-HSA induces IL-6 and MCP-1 expressing in human mesangial cells, and calcitriol inhibits this effect. (2) Not AGE-HSA but calcitriol induces Vitamin D receptor (VDR) expression in human mesangial cells. And calcitriol inhibits this effect through VDR. (3) AGE-HSA induced Receptor for advanced glycation end products (RAGE) expression, and effects was blocked by calcitriol. (4) Effect of calcitriol on ROS production induced by AGE-HSA in mesangial cells. (5) NF- κ B activation in renal mesangial cells was induced by AGE-HSA, and the effect was inhibited by calcitriol.

Conclusions: Calcitriol could attenuate the AGE-induced up-regulation of IL-6 and MCP-1 though VDR by suppressing RAGE expression and subsequent ROS generation and reducing NF- κ B activation.

Funding: Government Support - Non-U.S.

TH-PO171

GLP-1 Receptor Agonist Exendin-4 Ameliorates Renal Injury by Reducing Cholesterol Deposition and Inflammation in Glomerular Endothelial Cell via ABCA1-JAK2/STAT3 Pathway in Diabetic apoE^{-/-} Mice

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Background: Lipid accumulation in glomerular endothelial cells has been found a unique feature, which may contribute to the renal inflammation in diabetic kidney disease. The ATP-Binding Cassette Transporter (ABCA1) is an important transporter responsible for cholesterol efflux. This study was performed to examine the effect of GLP-1R agonist exendin-4 on cholesterol deposition and inflammation in diabetic kidney disease and to explore the possible mechanism.

Methods: The human renal biopsy specimens with diabetic kidney disease were examined by electron microscope to determine lipid droplets. Oil Red O staining and CD31 double staining was also performed. In vivo, the double immunofluorescent staining of CD31 with GLP-1R, ABCA1, p-JAK2 and p-STAT3 was detected in the kidney tissues of exendin-4 treatment diabetic apoE^{-/-} mice. The expression of proinflammatory cytokine (e.g. IL-6, TNF- α), CaMKK, CaMKIV, ABCA1, p-JAK2 and p-STAT3 was examined in the isolation of glomeruli from diabetic apoE^{-/-} mice and exendin-4 treatment diabetic apoE^{-/-} mice and in human renal glomerular endothelial cells (HRGECs) were cultured in high glucose and with cholesterol, exendin-4, STO-609 (CaMKK inhibitor), ABCA1 siRNA and AG 490 (JAK2 inhibitor).

Results: Extensive lipid accumulation in glomerular endothelial cells of kidney biopsies from DKD patients. Double-labeling of GLP-1R, ABCA1, p-JAK2, p-STAT3 and CD31 was detected in the glomerulus of the renal tissues. Exendin-4 treatment upregulated the expression of CaMKK, CaMKIV, ABCA1, p-JAK2 and p-STAT3 and downregulated IL-6 and TNF- α , as well as ameliorated lipid accumulation compared with diabetic mice. In vitro, exendin-4 decreased the expression of IL-6, TNF- α , whereas, STO-609 (CaMKK inhibitor), ABCA1 siRNA and AG 490 (JAK2 inhibitor) all increased IL-6 and TNF- α in HRGECs.

Conclusions: GLP-1R agonist exendin-4 reduced cholesterol deposition and regulated ABCA1 via CaMKK/CaMKIV pathway in glomerular endothelial cells, and then activated ABCA1-JAK2/STAT3 pathway, which may ameliorate renal inflammation in diabetic apoE^{-/-} mice.

Funding: Clinical Revenue Support

TH-PO172

Renal Consequences of Coxsackievirus Infection in Non-Obese Diabetic Mice

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Background: Diabetes is the leading cause of end stage renal disease in the United States, however, it is difficult to predict which diabetic patients will go on to develop diabetic nephropathy. Recently, viruses have been found to mediate many autoimmune

diseases, such as type 1 diabetes (T1D), that result in kidney damage. While research on viral induction of T1D has been brought into focus, effects of viral infection in the kidneys of T1D patients has remained undefined. Characterizing the consequences of viral infection in the kidney will allow for a better understanding of kidney disease progression in patients with virus-mediated T1D.

Methods: The non-obese diabetic (NOD) mouse is genetically predisposed to develop T1D over time. Disease onset can be accelerated by viral infection, making it a novel model to study virus-mediated kidney damage. In the current study, NOD mice were infected with coxsackievirus at 8-10 weeks of age and euthanized 3, 7, 10 and 14 days and 3, 7, 12 and 17 weeks post infection. Gene expression was measured by real-time PCR.

Results: Coxsackievirus expression in NOD mouse kidneys was upregulated acutely (3 days post infection) along with genes involved in glomerular and tubular damage and the inflammatory response (Lcn2, TLR3, MCP-1, IL-6, TNF α , etc.).

Conclusions: This study characterizes both acute and chronic virus-mediated alterations in the kidneys of NOD mice predisposed to develop T1D. Results will provide information regarding acute and chronic effects of coxsackievirus after a one-time infection, identifying functional changes occurring in the kidney and the immunological responses associated with these changes. These results will provide a better understanding of virus-mediated kidney injury in NOD mice genetically predisposed to develop T1D as a step towards understanding mechanisms of diabetic nephropathy in humans. Funding: OHF, JOW-ECDR and OU BF, SEA and GSS-OWG.

Funding: Private Foundation Support

TH-PO173

Renal Protection by Atorvastatin in Sickle Cell Nephropathy

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Background: Sickle Cell Disease (SCD) affects approximately 100,000 people in the USA. Renal involvement begins early commonly manifested as hyposthenuria with microalbuminuria occurring ~20% of SCD patients <18 years. Current treatment options for sickle cell nephropathy include ACE inhibitors or ARBs to prevent progressive proteinuria. Statins have pleiotropic effects in addition to their lipid lowering properties. Here we investigated the functional effects of Atorvastatin treatment on the development of nephropathy in a murine model of sickle cell disease.

Methods: Cohorts (n=10) of 8-12 week homozygous sickle cell mice were treated with atorvastatin (10mg/kg) or vehicle daily for 8 weeks by oral gavage. We assessed effects of atorvastatin on albuminuria, maximum urine concentrating ability and GFR at baseline and week 8. Urine was collected in metabolic cages for 24hrs and albuminuria quantified by ELISA. GFR was measured by plasma clearance of FITC-Inulin. Mice were water deprived for 12hrs and spot urine for maximum urine concentrating ability. Kidneys were prepared appropriately for light microscopic analysis and glomerular morphology.

Results: After 8 weeks of daily treatment mice receiving atorvastatin were found to have statistically significant improvement in urine concentrating abilities and improvement in GFR (p < 0.01 and p < 0.001 respectively). Urine protein excretion was unchanged by treatment with atorvastatin. Under light microscope there were no gross changes in appearance of glomeruli or glomerular vasculature. In addition we did not find significant statistical changes in glomerular tuft size.

Conclusions: We assessed the pleiotropic effects of statins in SCD. While we did not find differences in urine albumin excretion and glomerular tuft size we found that atorvastatin increased the low baseline GFR and improved urine concentrating abilities in sickle cell mice. These complications of are found both in animal and human models. Further studies will examine microscopic examination of podocyte and endothelial structures and look at biomarkers of renal injury.

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TH-PO174

Endothelin Receptor Antagonism Protects from Sickle Cell Nephropathy

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Background: Sickle-cell disease (SCD) is characterized by chronic hemolysis and recurrent episodes of vaso-occlusive events that affect the microcirculation and lead to ischemic tissue injury with multi-organ dysfunction. Sickle cell nephropathy (SCN), a major mortality risk factor in SCD, is characterized by an early increase in glomerular filtration rate with subsequent progressive decline of renal function. Focal and segmental glomerulosclerosis (FSGS) and hypertrophied glomeruli with distended capillaries are the major hallmarks of glomerular lesions. We investigated the effects of chronic mixed ET receptor antagonism in a model of SCD-mediated FSGS.

Methods: We used SAD Hbbsingle/single hemizygous mice on the C57BL/6J background. At 3 months of age SAD mice displayed little evidence of chronic renal damage but significant glomerulomegaly compared to controls. Glomerulomegaly persisted, and was worse, at 6 months of age (average glomerular section area: 2372±207 vs. 1519±180 μ m², p<0.001). In addition, SAD mice had significant glomerulosclerosis. Based on these data we treated SAD mice and controls aged 3 months with the dual ET receptor antagonist bosentan for 9 months in a preventative study, and 6 months old SAD mice for 6 months in a therapeutic study. We assessed blood pressure, kidney structure and function after 6 and 9 months of continuous treatment.

Results: In the preventative study, 6 months of bosentan therapy was associated with ~4-fold less glomerulosclerosis compared to untreated SAD mice (22±8 vs. 86±4%, p<0.001). Additionally, there was an 80% reduction in mean glomerular surface area (p<0.05). In the therapeutic study, there was a significant reduction in glomerulosclerosis (p<0.01) and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

glomerulomegaly ($p < 0.01$) compared to untreated mice but this was less effective than in the preventative study ($p < 0.05$). Furthermore, chronic ET-1 receptor antagonism alleviated the development of tubulointerstitial fibrosis in both groups and limited the rise of blood urea nitrogen levels that characterized untreated aged SAD mice.

Conclusions: ET receptor antagonism is a potentially useful preventative or therapeutic approach in SCN. Based on these data clinical trials are warranted.

TH-PO175

Erythropoietin and Its Carboxylated Derivative Protected against Chronic Cyclosporine Nephropathy Wenhan Peng, Jianghua Chen. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Erythropoietin (EPO) is known to raise hemoglobin and protect tissues and its carboxylated derivative (CEPO) has no effect on hemoglobin but could induce tissue protection. The aim of this study is to determine the effect of EPO and CEPO on the animal model of chronic cyclosporine nephropathy.

Methods: We evaluated therapeutic effects of EPO and CEPO using a rat model of chronic cyclosporine nephropathy. Rats were randomly divided into five groups: (1) the saline treatment group (control group, $n=12$); (2) EPO treatment group at low dose (low EPO group, 100U/kg, $n=12$); (3) CEPO treatment group at low dose (low CEPO group, 100U/kg, $n=12$); (4) EPO treatment group at high dose (high EPO group, 500U/kg, $n=12$); (5) CEPO treatment group at high dose (high CEPO group, 500U/kg, $n=12$).

Results: In control group, the levels of sodium, protein and NAG enzyme of urine, the values of serum creatinine and urea nitrogen, the concentration of MDA and GSH-PX of kidney tissue were significantly increased. Those of EPO and CEPO treatment groups were significantly lower than those of control group. EPO and CEPO could promote to produce new endothelial cells and promote microvascular formation by analysis of CD31 + / CD 34+ cell number of blood and kidney tissue. EPO and CEPO decreased collagen fibers, tubular apoptosis and expression of TGF- β 1, Caspase-3 and α -SMA in kidney tissue. The higher doses of EPO and CEPO showed more protection effects. But EPO treatment increased hemoglobin concentration and induced infarction.

Conclusions: EPO and CEPO could effectively antagonize cyclosporine nephrotoxicity through anti-fibrosis, anti-inflammatory cell infiltration, anti-apoptotic, anti-oxidant, promotion new growth of renal tubular epithelial and endothelial cells, and the promotion of release and proliferation of endothelial progenitor cells.

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TH-PO176

Glucose Promotes Secretion-Dependent Renal Cyst Growth Andre Kraus,¹ Gunnar Schley,¹ Karl Kunzelmann,² Rainer Schreiber,² Kai-Uwe Eckardt,¹ Bjoern Buchholz.¹ *¹Dept of Nephrology, Univ Erlangen-Nuernberg, Erlangen, Germany; ²Dept of Physiology, Univ Regensburg, Regensburg, Germany.*

Background: ADPKD is characterized by continuous cyst growth which is highly based on transepithelial Cl⁻ secretion into the cyst lumen. Since ADPKD is a long-lasting, chronic disease, there is a significant number of patients suffering from both, ADPKD and type 2 diabetes mellitus. Recently, ADPKD patients with type 2 diabetes mellitus were shown to have kidneys with almost double the volume compared to non-diabetic ADPKD patients. Therefore, we wanted to test for the impact of glucose on renal cyst growth.

Methods: We examined the effect of different glucose concentrations ranging from 5.6 mmol/l up to a maximum of 25.0 mmol/l on cyst growth of MDCK cells within a collagen matrix as well as in ex vivo cultured embryonic mouse kidneys treated with forskolin. In addition, we analysed changes in expression of potentially relevant ion channels and transporters at different glucose levels. Furthermore, we performed Ussing chamber experiments with MDCK cells in order to detect alterations of transepithelial Cl⁻ secretion upon changes in glucose concentration.

Results: Cyst expansion highly correlated with the levels of glucose in both cyst models, revealing already significant increase of cyst growth by elevating glucose concentration from 5.6 mmol/l to 11.1 mmol/l. These effects were neither referable to changes in pH or lactate, nor due to osmotic changes demonstrated by the use of equivalent doses of mannitol. However, elevated levels of glucose resulted in significantly increased transcription of the Ca²⁺-activated Cl⁻ channel Anoctamin (ANO) 1 which we have previously shown is involved in renal cyst growth. In line with these data, CaCCInh-AO1, a specific inhibitor of ANO1, inhibited glucose-dependent cyst expansion in both models. In addition, Ussing chamber experiments revealed a significant increase of Ca²⁺-dependent Cl⁻ secretion at elevated glucose levels which could be inhibited by the use of CaCCInh-AO1.

Conclusions: Increased glucose levels could augment secretion-dependent cyst growth in ADPKD. Therefore, tight glucose control might be beneficial in ADPKD to reduce cyst growth and preserve renal function.

Funding: Government Support - Non-U.S.

TH-PO177

Kidney Stones Provide a “Third Hit in Autosomal Dominant Polycystic Kidney Disease” Jacob A. Torres,¹ Mina Rezaei,¹ Saeed R. Khan,² Thomas Weimbs.¹ *¹Molecular Cellular and Developmental Biology, Univ California Santa Barbara, Santa Barbara, CA; ²Dept of Pathology, Univ of Florida, Gainesville, FL.*

Background: The progression of autosomal-dominant polycystic kidney disease (ADPKD) exhibits high inter- and intrafamilial variability suggesting the possibility that unknown environmental factors may play an important role. Work on mouse models has led to the idea that renal injury is required as a so-called “third-hit trigger” for the initiation of renal cysts. We hypothesized that a much more frequent and prevalent form of renal insult may determine the speed of progression in ADPKD. We report here that chronic or acute hyperoxaluria leads to very rapid dilation of renal tubule diameters in response to CaOx crystal deposition.

Methods: Mice and rats were challenged with intraperitoneally administered oxalate to rapidly produce calcium oxalate crystals or were fed oxalate producing compounds to form oxalate stones inside the kidney. To test the effect of the mTOR pathway, mTOR was inhibited with the administration of rapamycin prior to oxalate administration.

Results: The mTOR and STAT3 signaling pathways are rapidly activated in dilated tubule cells. Fast tubule dilation can be prevented by mTOR inhibition. Once crystals are cleared, mTOR and STAT3 signaling is inhibited and tubule diameters return back to normal. Our results suggest that tubule diameter dilation is an active mechanism employed by the kidney to clear lodged crystals. Both, mTOR and STAT3 have previously been shown to be aberrantly activated in cyst-lining cells in ADPKD and drive cyst growth. We find that challenging pre-conditioned mice lacking primary cilia with oxalate leads to persistent tubule dilation.

Conclusions: These results suggest that cilia are required for reestablishing normal tubule diameters after crystal clearing. Furthermore, these results suggest that renal crystal deposition may be a clinically relevant, environmentally controlled “third-hit trigger” that affects disease progression in ADPKD. This suggests that dietary changes or treatments to reduce renal crystal burden may be effective in slowing ADPKD progression.

Funding: Private Foundation Support

TH-PO178

Soluble RAGE Alleviates Disease Progression in Autosomal Dominant Polycystic Kidney Disease by Down-Regulation of Cell Proliferation Jong Hoon Park, Eunji Lee, Hyowon Mun, Je Yeong Ko, Do Yeon Kim. *Dept of Biological Science, Sookmyung Women's Univ, Seoul, Republic of Korea.*

Background: Autosomal polycystic kidney disease (ADPKD) is a one of the common genetic renal diseases in which epithelial-lined fluid-filled cysts appear in kidneys. It is accompanied by hyper-activation of cell proliferation, interstitial inflammation and fibrosis around the cyst lining cells, finally reaching end-stage renal disease (ESRD). Previously, we found high expression of ligands stimulating the receptor for advanced glycation endproducts (RAGE) in ADPKD mice. Furthermore, gene silencing of RAGE was revealed to reduce cystogenesis via down-regulation of cell proliferation in vitro, while intravenous administration of anti-RAGE adenovirus in vivo also displayed alleviation of the disease.

Methods: Using either mice primary cells or human ADPKD cell line WT9-12, both sRAGE treatment and over-expression of sRAGE with cloned construct we established herein were tested in vitro. In addition, in vivo test via intraperitoneal injection using ADPKD mice model jck, and confirmed the in vitro results in in vivo systems.

Results: Here, we attempted to identify the role of soluble RAGE (sRAGE) in inhibiting the progression of ADPKD, in vivo. sRAGE is an endogenously expressed form of RAGE which has no membrane-anchoring domain, thereby being able to neutralize the ligands that stimulate RAGE signals. Both over-expression of sRAGE and sRAGE treatment blocked RAGE-mediated cell proliferation in vitro. In addition, sRAGE-injected ADPKD mice showed reduced cysts accompanied by enhanced renal function, inhibition of cell proliferation, inflammation and fibrosis.

Conclusions: These positive therapeutic effects of sRAGE displayed little liver toxicity, suggesting it as a new potential therapeutic target of ADPKD with low side effects.

Funding: Government Support - Non-U.S.

TH-PO179

Metformin Inhibits Cyst Formation in a Zebrafish Model of Polycystic Kidney Disease Ming-Yang Chang. *Kidney Research Center and Dept of Nephrology, Chang Gung Memorial Hospital, Chang Gung Univ College of Medicine, Kueishan, Taoyuan, Taiwan.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by enhanced fluid secretion and abnormal cell proliferation in renal tubular epithelial cells. Recent research has proposed that activation of AMP-activated kinase (AMPK) is a novel treatment strategy for ADPKD. We examined the effects of metformin on the initiation of pronephric cysts in a PKD2 zebrafish model.

Methods: Morpholino-mediated knockdown of *pkd2* was performed in wt-1b pronephric-specific GFP-expressing zebrafish embryos to induce visible pronephric cysts for observation. *Pkd2* morphants were incubated with metformin (2.5 to 10 mM) in the embryo medium until 48 hours post fertilization.

Results: Metformin significantly reduces the frequency of cyst formation and pronephric tubular cell proliferation in *pkd2* morphant embryos. Whole mount in situ hybridization for L-plastin mRNA showed significantly reduced macrophage infiltration

in metformin-treated pkd2 morphants. RT-PCR showed that P2X7, IL-1 β and IL-10 mRNA expression were significantly inhibited by metformin. Simultaneously morpholino knockdown of AMPK α 1 prevents the rescue effects of metformin on cystogenesis.

Conclusions: We showed that metformin decreases cyst formation through inhibiting cell proliferation and macrophage accumulation in a pkd2 zebrafish model. These results indicate that metformin reduces the earliest cyst formation in polycystic kidney disease, although its effect on progression of disease remained to be investigated.

Funding: Government Support - Non-U.S.

TH-PO180

Cardiac Hypertrophy and Cardiac mTORC1/2 Signaling in Rodent Models of PKD

Kameswaran Ravichandran, Qian Wang, Charles L. Edelstein. *Univ Colorado Denver.*

Background: Cardiac disease is the commonest cause of death in ADPKD patients. Young normotensive ADPKD adults and children have higher LVMI compared to controls. Aim of study was to determine in rodent PKD models: 1) whether there is cardiac hypertrophy and increased mTORC1/2 signaling in the heart 2) the effect of mTOR kinase inhibition on cardiac hypertrophy.

Methods: Heart weight was determined in Pkd1 $-/-$ mice, Pkd2WS25/ $-/-$ (Pkd2 $-/-$ mice) and Han:SPRD (Cy/+) rats. pS6 and p4E-BP1, markers of mTORC1 and pAktSer473, marker of mTORC2, were determined by immunoblot analysis of 3 separate experiments. Pkd2 $-/-$ mice were treated with an mTOR antisense oligonucleotide (ASO) that inhibits mTORC1/2 and PKD from 4-16 wks of age. Cy/+ rats were treated with the mTOR kinase inhibitor, PP242, that inhibits mTORC1/2 and PKD from 3-8 wks of age.

Results: There was increased heart weight in 150 d old Pkd1 $-/-$ mice, 16 wk old Pkd2 $-/-$ mice, 8 wk old normotensive Cy/+ rats and Pkd2 $+/-$ mice that are haplo-insufficient for Pkd2 and do not have hypertension. There was increased pS6, p4E-BP1 and pAkt in Pkd1 $-/-$ hearts and increased p4E-BP1 and pAkt in Pkd2 $-/-$ and Pkd2 $+/-$ hearts. mTOR ASO resulted in less p4E-BP1 and pAkt and less cardiac hypertrophy in Pkd2 $-/-$ mice. mTOR kinase inhibitor, PP242, resulted in less cardiac hypertrophy in normotensive Cy/+ rats HW/TBW(%) was 0.4 in +/+, 0.52 in Cy/+ (P<0.05 vs +/+) and 0.44 in Cy/+PP242 (P<0.05 vs. Cy/+).

	++	Pkd1 $-/-$	++	Pkd2 $-/-$	Pkd2 $-/-$ ASO	+/+	Pkd2 $+/-$
HW/TBW (%)	0.46	0.61*	0.52	0.66*	0.56**	0.52	0.69*
p/tS6	+	+++	+	+	+	+	+
p/t 4E-BP1	+	+++	+	++	+	+	++
p/t 4E-BP1	+	++	+	++	+	+	++
*P<0.05 vs +/+		**P<0.05 vs Pkd2 $-/-$	HW=heart weight	p/t=phospho/total			

Conclusions: There was increased heart weight in normotensive Cy/+ rats and Pkd2 $+/-$ mice. There was increased mTORC1 and 2 signaling in Pkd1 $-/-$, Pkd2 $+/-$ (without PKD) and Pkd2 $-/-$ hearts. mTOR kinase inhibition, that blocks both mTORC1 and 2, resulted in less cardiac hypertrophy. Discovery of an agent e.g. mTOR kinase or 4E-BP1 inhibitor that decreases early cardiac hypertrophy in PKD in addition to decreasing PKD would be a significant finding and would increase the enthusiasm to use these agents in ADPKD patients.

Funding: Veterans Administration Support

TH-PO181

Polycystic Kidney Disease – A Case of Suppressed Autophagy?

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Background: Autophagy is a normal physiological process that involves the degradation of damaged cellular components. Autophagy in general promotes cell survival while apoptosis that promotes cell death. We have reported (Edelstein et al, *AJP*, 2011) that there are features of autophagy like autophagosomes, mitophagy and autolysosomes in normal tubules and tubular cells lining cysts in Cy/+ rats with PKD and that there is suppression of autophagic flux in cpk mice with PKD.

Methods: 150 day old mice with PKD due to a kidney specific Pkd1 knockout were studied. MDCK cells with a stable knockdown of PC1 was achieved by lentiviral-mediated delivery of a specific siRNA for PKD1 were studied. MDCK cells that form tubules were used as controls. LC3-II, a marker of autophagic flux and cleaved caspase-3, a marker of apoptosis, were measured by immunoblot analysis of at least 3 separate experiments. Pkd1 $-/-$ mice were treated with bafilomycin-A1 (5 mg/kg/d IP), a lysosomal inhibitor, for 3 days. MDCK cells were treated with bafilomycin 100 nm.

Results: In Pkd1 $-/-$ mouse kidneys there was an increase in LC3-II compared to wild type. The increase in LC3-II in Pkd1 $-/-$ versus wild type kidneys suggests increased autophagosome synthesis or decreased degradation in the lysosome. To investigate these possibilities, Pkd1 $-/-$ mice were treated with bafilomycin-A1. Bafilomycin-A1 had no effect on LC3-II in PKD kidneys of Pkd1 $-/-$ mice. To determine the direct effect of PC-1 knockout on autophagy, PC-1 $-/-$ MDCK cells were studied. In PC-1 $-/-$ cells, there was a decrease in LC3-II compared to control MDCK. In PC1 $-/-$ cells treated with bafilomycin,

there was a further suppression of LC3-II, indicating decreased autophagic flux. Increased apoptosis is a feature of PKD kidneys. In the PC-1 $-/-$ cells there was a 2-fold increase in cleaved caspase-3, a marker of apoptosis, associated with the decrease in autophagic flux.

Conclusions: The lack of effect of the lysosomal inhibitor bafilomycin-A1 to increase LC3-II in Pkd1 $-/-$ kidneys and in PC-1 $-/-$ cells suggests a defect in autophagy resulting from a block of autophagosome-lysosome fusion and degradation. There was an association between suppressed autophagy and increased apoptosis in PC-1 $-/-$ cells.

Funding: Veterans Administration Support

TH-PO182

Retinoid X Receptor Pathway: A Novel Signaling Cascade Responsible for Cystogenesis in Three Rodent Models of Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is the most common inherited renal disorder and is characterized by innumerable cysts and tubular epithelial cell proliferation. We previously speculated that retinoid X receptor (RXR) may be related to cystogenesis in the Han:SPRD-Cy (Cy/+) rat, since VDR/RXR activation, LPS/IL-1-mediated inhibition of RXR function, and LXR/RXR activation were altered in diseased kidneys. RXR is known to induce cellular proliferation and is normally degraded by ubiquitin after binding to its cognate ligand. In human hepatocellular carcinoma, the degradation rate of RXR is abnormally reduced, and treatment with a RXR agonist suppressed its proliferative activity (Adachi, *Hepatology* 2002). We therefore determined the expression and distribution of renal RXR, and the effect of a RXR agonist in polycystic kidneys.

Methods: Kidneys were obtained from three rodent models: Cy/+ rats, jck and pcy mice. Expression of RXR was confirmed by western blot analyses. Co-localization of RXR with PCNA, an index for cell proliferation, was detected by standard procedures. In addition, Cy/+ rats were orally treated with 30mg/kg bexarotene (BEX), a RXR agonist, from 4 to 10 weeks of age.

Results: In all three models, renal RXR levels were increased compared with age-matched rats/mice with normal kidneys. Total RXR was detected in the nuclear extract of cystic kidneys, and increased RXR was co-localized with PCNA in cystic epithelia nuclei. In Cy/+ rats, BEX treatment significantly decreased RXR expression and kidney weight adjusted to body weight.

Conclusions: RXR was related to aberrant cell proliferation in PKD progression in three different animal models, and a RXR agonist suppressed disease progression in Cy/+ rats. These findings suggest that RXR signaling may have an important role in cystogenesis and that RXR ligands may have therapeutic potential.

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TH-PO183

Integrin Linked Kinase Promotes Cyst Growth and Fibrosis in ADPKD

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Background: Aberrant expression of extracellular matrix (ECM) molecules and secreted factors contribute to renal cyst growth and fibrosis in ADPKD. Periostin, a matricellular protein involved in tissue development and repair, is overexpressed in kidneys of ADPKD patients and murine models of PKD. Gene knockout of periostin reduced renal cyst growth and interstitial fibrosis, and prolonged the survival of PKD mice. Periostin binds to α_v -integrins ($\alpha_v\beta_3$, $\alpha_v\beta_5$) and induces cell proliferation via integrin linked kinase (ILK) activation of Akt/ mTOR, a key signaling pathway involved in PKD. We have determined if knockdown/knockout of ILK prevents periostin-induced proliferation of human ADPKD cells and reduces cyst growth and fibrosis in an ADPKD mouse.

Methods: We knocked down ILK expression in ADPKD cells using lentiviral shRNA. Activation of the Akt/ mTOR pathway was determined by measuring phosphorylation of Akt and S6 kinase (S6K), a downstream target of mTOR. To determine if ILK may be a potential therapeutic target, we knocked out ILK in collecting ducts of Pkd1^{flax/flax}; Pkhd1-Cre mice, an orthologous model of ADPKD, by breeding these mice with ILK^{flax/flax} mice. At postnatal day 25, mice were euthanized and kidney weight/body weight (%KW/BW), cystic index, interstitial fibrosis and cell proliferation were measured.

Results: We found that ILK knockdown blocked periostin-induced phosphorylation of Akt and S6K and proliferation of human ADPKD cells. CPD-22, an ILK inhibitor, also blocked the effect of periostin on the Akt/ mTOR pathway and ADPKD cell proliferation. Gene knockout of one ILK allele (Pkd1^{flax/flax}; ILK^{flax/+}; Pkhd1-Cre) or both alleles (Pkd1^{flax/flax}; ILK^{flax/flax}; Pkhd1-Cre) significantly decreased %KW/BW, renal cystic index and cell proliferation. Furthermore, ILK knockdown reduced renal interstitial edema and fibrosis in PKD mice, suggesting that blockade of the ILK signaling pathway may reduce both cyst growth and fibrosis in ADPKD.

Conclusions: Aberrant expression of periostin stimulates ILK activation of signaling pathways that contribute to renal cyst growth and fibrosis, suggesting that ILK may be a therapeutic target for ADPKD.

Funding: NIDDK Support

TH-PO184

Periostin Regulates Polycystic Kidney Cell Proliferation and Cyst Formation via CFTR and JAK2/STAT3 Signaling Pathway Sun Ae Han,¹ Hayne C. Park,² Hyunsuk Kim,³ Hyunjin Ryu,³ Kook-Hwan Oh,³ Young-Hwan Hwang,⁴ Curie Ahn.³ ¹Transplantation Research Institute, Seoul National Univ Medical Research Center, Seoul, Korea; ²Dept of Internal Medicine, Armed Forces Capital Hospital, Sungnam-si, Gyunggi-do, Korea; ³Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; ⁴Dept of Internal Medicine, Eulji General Hospital, Seoul, Korea.

Background: Renal cyst formation and fibrosis are the hallmark of autosomal dominant polycystic kidney disease (ADPKD). ADPKD cyst-lining cells have an increased proliferation rate and are surrounded by an abnormal extracellular matrix (ECM). The matricellular protein periostin was shown to be activated in cyst-lining cells in ADPKD and PKD mouse models and may drive renal cyst growth, but the mechanism of periostin-induced cyst formation is still unclear. We examined the effect of periostin expression on cystic fibrosis transmembrane conductance regulator (CFTR) and phosphorylated levels of Janus kinase 2 (JAK2) /signal transducers and activators of transcription 3 (STAT3) signaling pathway.

Methods: Periostin expression was analyzed using immunohistochemistry and western blot analysis in ADPKD cells and normal human kidney (NHK) cells. Cell growth and western blot analysis for related molecular levels were assayed after suppression of periostin by small interfering RNA (siRNA). Finally, a three-dimensional culture was performed to understand how periostin affected cyst formation, in vitro.

Results: The periostin expression was highly increased in ADPKD cells compared to NHK cells. Transfection of ADPKD cells with periostin siRNA decreased cell growth and reduced the expression of CFTR and phosphorylated levels of JAK2/STAT3. In three-dimensional culture, addition of recombinant periostin enhanced cyst formation, whereas periostin depleted cells showed lower level of cystogenesis.

Conclusions: Periostin stimulated cyst formation via CFTR and JAK2/STAT3 signaling pathway in ADPKD.

TH-PO185

The Possible Role of mTORC1 and TCA Cycle in Renal Cyst Formation and Transformation Luca Drusian,^{1,2} Monika Pema,¹ Valeria Mannella,¹ Isaline Rowe,¹ Marco Chiaravalli,¹ Musco Giovanna,¹ Alessandra Boletta.¹ ¹Div Genetics and Cell Biology, San Raffaele Scientific Inst, Milan, MI, Italy; ²Univ Vita-Salute San Raffaele, San Raffaele Scientific Inst, Milan, MI, Italy.

Background: We have recently shown that PKD is characterized by an increased use of glycolysis in a process resembling the Warburg effect. This feature of PKD is in part dependent on mTORC1. However, mTORC1 upregulation, increased proliferation and the Warburg effect are hallmarks of cancer. In contrast, ADPKD patients do not have a propensity to increased rates of cancer as compared to the normal population. We aimed at investigating this conundrum.

Methods: We generated a mouse model carrying kidney-specific inactivation of the *Tsc1* gene (*Tsc1*KO), which survives for up to three months and displays cyst formation, followed by cystadenomas and transformation into carcinomas.

Results: This phenotype is fully penetrant and the lesions manifest progressively within a reproducible window of time (P20 to P80). We performed metabolomic profiling both by NMR spectroscopy and by mass spectrometry on these kidneys collected at different time points (P20, P50 and P80). The analysis revealed the presence of major changes at the level of the TCA cycle and a strong accumulation of fumarate, which is completely non-detectable in normal kidneys at any stage. We are currently investigating if these metabolic changes can account for the progressive transformation of cysts into carcinomas. Notably, a preliminary study of metabolomic profiling in kidneys derived from mice carrying a kidney-specific inactivation of the *Pkd1* gene, revealed that fumarate does not accumulate in these mutants. We hypothesize that ADPKD kidneys display a mild metabolic change affecting glycolysis, but not the TCA cycle, while cancerous lesions have a more profound metabolic alteration.

Conclusions: These studies will hopefully help identifying metabolic changes specific for PKD and likely good targets for therapy.

TH-PO186

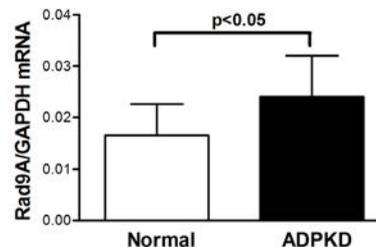
Aberrant Expression of Rad9 in ADPKD Wei Wang, Michel Chonchol, Berenice Y. Gitomer. Dept of Medicine, Univ of Colorado, Aurora, CO.

Background: The pathogenesis of ADPKD is still not fully understood, however, increased proliferation of renal tubular epithelial cells is a key factor in cyst growth. There are similarities between cyst growth in ADPKD and the characteristics of benign tumor. Dysregulated expression of genes involved in cell cycle gene regulation as a result of epigenetic modification by DNA methylation has been associated with oncogenesis. We thus hypothesized that aberrant methylation of cell cycle related genes might be an underlying mechanism in ADPKD.

Methods: Genomic DNA was extracted from normal (HK-2) and ADPKD (WT9-12) tubular epithelial cells using a DNeasy blood and tissue kit (Qiagen). A cell-cycle DNA methylation PCR array (Qiagen) was used to examine gene methylation. RNA was extracted from normal and ADPKD kidneys using RNeasy RNeasy-4-PCR kit (Ambion). mRNA levels were examined using real-time RT-PCR.

Results: Among the 22 cell cycle genes examined, Rad9 was significantly different between the control HK-2 and cystic WT 9-12 cells. 62.2% of the gene was methylated

in HK-2 cells as compared to only 1.4% in WT 9-12 cells. Rad9 mRNA levels were significantly higher in human ADPKD (0.024±0.008; n=7) kidneys than in normal kidney tissues (0.0166±0.006; n=4).



Conclusions: Aberrant expression of Rad9 occurs in ADPKD kidneys. This is at least partly due to the decreased methylation of the gene. Expression of Rad9 part of the 9-1-1 (Rad9-Hus1-Rad1) complex is increased and has been associated with DNA damage and with tumor growth. Increased susceptibility for genomic DNA damage has been demonstrated in ADPKD which may affect cyst development or growth. While the role of Rad9 in ADPKD merits further study it is intriguing to postulate that Rad9 may play a role in cyst growth.

Funding: NIDDK Support

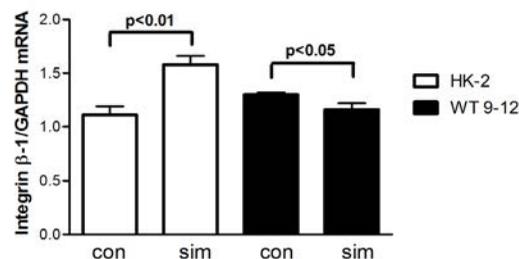
TH-PO187

Effect of Simvastatin on Cell Adhesion in ADPKD Wei Wang, Michel Chonchol, Melissa A. Cadnapaphornchai, Berenice Y. Gitomer. Dept of Medicine, Univ of Colorado, aurora, CO.

Background: We have previously shown that statin treatment reduced the rate of cyst growth in children and young adults with autosomal dominant polycystic kidney disease (ADPKD) suggesting that this may be an effective intervention to slow progression of renal disease in ADPKD, however the mechanisms are unclear. Treatment of cultured cystic renal tubular cells with simvastatin significantly reduces cell viability in cystic epithelial cells (WT 9-12) in a time and dose dependent manner but had minimal effect on normal tubular epithelial cultures (HK-2). We hypothesized that loss of viability was associated with reduced cell adhesion due to reduced expression of cell adhesion proteins.

Methods: Cystic tubular epithelial cells and normal renal tubular epithelial cells were treated with 1μM simvastatin for 24 hours and mRNA expression of integrin β-1 and E-cadherin assessed by quantitative PCR.

Results: In normal tubular cells simvastatin significantly increased integrin β-1 expression while a significant decrease in expression was observed in the cystic tubular cells.



In untreated cystic tubular epithelial cells E-cadherin expression was significantly lower compared to normal control cells. Expression of E-cadherin was slightly reduced in the cystic cells after treatment with simvastatin. This cytotoxic effect on cystic cells was increased with simvastatin compared to pravastatin.

Conclusions: Simvastatin may have pleiotropic effects on cystic epithelial cells including an effect on cell adhesion. The lack of effect on normal tubular epithelial cells indicates that simvastatin may have specific therapeutic benefits in human ADPKD. Future clinical trials will be necessary to test the benefits of simvastatin on slowing cyst growth.

Funding: NIDDK Support

TH-PO188

Identification of a Renal Pkd1/Pcl Self-Amplification Mechanism via c-Myc in Polycystic Kidney Disease Marie Trudel, Almira Kurbegovic, Delphine Cotteverte, Jennifer Lake. Molecular Genetics and Development, Inst de Recherches Cliniques de Montréal, Montréal, QC, Canada.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic disorder associated mainly with *Pkd1* mutations. One of the most extensively studied dominant polycystic kidney disease (PKD) mouse model is the transgenic SBM mice produced by specific targeting of c-Myc expression in the kidneys. All mice reproducibly developed tubular and glomerular cysts leading to renal insufficiency with high similarities to the orthologous *Pkd1* dosage-increased and -reduced mouse models.

Methods: The cystogenic mechanisms of SBM and *Pkd1* orthologous models were investigated concomitantly by molecular and cellular analyses.

Results: We first determined that Pkd1 dosage-increased and -reduced mouse models lead to stimulation of renal c-Myc expression (5-10-fold) as in ADPKD renal tissues, identifying a key downstream effector and the high relevance of SBM mice. This prompted analysis of SBM mice that showed enhanced protein expression of c-Myc full length and nick-Myc in tubular epithelial cells. C-Myc immunostaining determined intense nuclear sub-localization mainly in cell clusters of cystic tubules. Renal SBM proliferation index was increased 10-fold over non-transgenic controls. Analysis of c-Myc downstream target, the cystogenic hypoxia inducible factor 1 alpha (Hif1 α) in SBM kidneys showed intense stimulation as observed in ADPKD, particularly in epithelial cells of cystic tubules and glomeruli. SBM kidneys also displayed a marked activation of β -catenin in renal epithelium that was stimulated as well in both Pc1 dosage-increased and reduced mouse models. Importantly, SBM caused striking upregulation of polycystin-1/Pc1 and Pkd1 ~6-17-fold over endogenous levels in kidneys. SBM and Pkd1 mouse models uncovered a reciprocal cystogenic targeting and an inter-regulatory network of c-Myc and Pc1 in PKD.

Conclusions: Together our data support a regulatory positive Pkd1/Pc1 self-amplification loop via c-Myc that governs ADPKD.

Funding: Government Support - Non-U.S.

TH-PO189

DNMT1 Promotes Renal Cyst Growth in Autosomal Dominant Polycystic Kidney Disease Xia Zhou,^{1,2} Xiaoyan Li,^{1,2} Yijian Chen,^{1,2} Senta K. Georgia,³ Xiaogang Li,^{1,2} ¹Internal Medicine; ²Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; ³Children's Hospital Los Angeles, Los Angeles, CA.

Background: DNA methylation was the first epigenetic modification to be identified. Aberrant expression of DNA methyltransferases (DNMTs) and disruption of DNA methylation patterns are closely associated with human disease. However, the roles and underlying mechanisms of DNMTs in polycystic kidney disease remain unknown. In this study, we investigated the direct involvement of DNMT1 in regulating cystogenesis.

Methods: To understand the role of DNMT1 in cyst growth *in vivo*, we generated *Pkd1* and DNMT1 double conditional knockout *Pkd1^{flx/flx};DNMT1^{flx/flx};Pkh1-Cre* mice. To identify the novel DNMT1 target genes involving in cystogenesis, we performed ChIP-seq, MBD-seq and RNA-seq analysis.

Results: We found that knockout of DNMT1 delayed cyst growth characterized by decrease of 1) cyst index; 2) the kidney weight (KW)/body weight (BW) ratios; and 3) the blood urea nitrogen (BUN) levels ($p < 0.01$); as well as the 1) the phosphorylation of ERK, Rb, S6 and STAT3; and 2) the expression of cyclin D1, which were upregulated and contributed to cyst growth in ADPKD. Further, we identified 8 novel DNMT1 target genes which were found within the intersection of the DNMT1 binding genes identified by ChIP-seq and the CpG islands hypermethylated genes identified by MBD-seq, and were downregulated in cystic renal epithelial cells as analyzed by RNA-seq. The downregulation of these candidate genes were validated by qRT-PCR. One of these genes named Ptpm (protein tyrosine phosphatase receptor type M) is a tumor suppressor gene which regulates the tyrosine phosphorylation of proteins and is hypermethylated in cancers. Inhibition of DNMT1 with 5-azacytidine increased the expression of Ptpm mRNA but decreased the phosphorylation of ERK, Rb, S6 and STAT3 as well as the expression of cyclin D1 as that in *Pkd1* and DNMT1 knockout kidneys.

Conclusions: DNMT1 promotes renal cyst growth in ADPKD through methylation of Ptpm gene to inhibit its expression, leading to increase the phosphorylation and activation of PKD associated pathways.

Funding: NIDDK Support

TH-PO190

Triptolide Retarded Disease Progression in Polycystic Kidney Disease Through Reducing Polycystin-2 Over-Expression and Suppressing JAK2/STAT3 Pathway Ming Wu, Changlin Mei. *Kidney Inst, Dept of Nephrology, Shanghai Changzheng Hospital, Shanghai, China.*

Background: The beneficial effect of triptolide in polycystic kidney disease (PKD) has been shown in several animal models and also in a clinical trial. It is suggested that triptolide inhibits cell proliferation in PKD by activating endoplasmic reticulum bounded calcium channel polycystin-2 (PC2) and thereby enhancing intracellular calcium level. The aim of current study was to prove a new working mechanism of triptolide in PKD that triptolide directly inhibit PC2 mediated mitogenic signaling pathways which is independent of calcium.

Results: Triptolide inhibited ADPKD cell proliferation which was correlated with decreased PC2 protein level and reduced JAK2/STAT3 activation. Over-expression of PC2 restored triptolide suppressed cell proliferation and JAK2/STAT3 activity. Blockage of PC2 by siRNA abolished triptolide mediated inhibition on cell proliferation and JAK2/STAT3 activity. Twelve weeks triptolide treatment reduced BUN and creatinine level by 22% and 25% respectively in cystic Cy/+ Han:SPRD rats. Administration of triptolide decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 18.6% and 12.7% respectively. Western blot analysis showed that triptolide decreased polycystin-2 protein level and reduced JAK2/STAT3 activation *in vivo*.

Conclusions: Our study revealed a novel triptolide's mechanism of action in PKD. Reducing PC2 over-expressed could be a new strategy for PKD treatment in the future.

Funding: Government Support - Non-U.S.

TH-PO191

Resveratrol Delayed Disease Progression in Polycystic Kidney Disease Through Attenuating P50/p65 Induced Inflammation Ming Wu, Changlin Mei. *Kidney Inst, Dept of Nephrology, Shanghai Changzheng Hospital, Shanghai, China.*

Background: The natural anti-inflammatory compound resveratrol displayed beneficial effects in a variety of diseases. The current study aimed to study the efficacy of resveratrol in polycystic kidney disease (PKD) and reveal its underline mechanism.

Results: Five weeks resveratrol treatment reduced BUN and creatinine level by 20% and 24% respectively in cystic Cy/+ Han:SPRD rats. Administration of resveratrol decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 15% and 24% respectively. The proliferation index and the macrophage infiltration index were reduced by 40% and 43% respectively in resveratrol treated cystic kidneys in comparison to vehicle treated cystic kidneys. Resveratrol reduced protein levels of pro-inflammatory factors such as MCP-1, TNF- α and CFB in Cy/+ kidneys, which was correlated with decreased activity of NF- κ B (p50/p65). Resveratrol and NF- κ B specific inhibitor QNZ inhibited the expression of MCP-1, TNF- α and CFB and reduced NF- κ B activity in ADPKD cells. Moreover NF- κ B blockage minimized the reduction but not completely abolish the inhibition of inflammatory factor production by resveratrol treatment.

Conclusions: NF- κ B signaling pathway is activated in PKD and partly responsible for PKD inflammation. Targeting inflammation through resveratrol could be a new strategy for PKD treatment in the future.

Funding: Government Support - Non-U.S.

TH-PO192

Increased Hedgehog Signaling in *jck* Mice and in Human ADPKD Luciane M. Silva, Bailey A. Allard, Damon T. Jacobs, Gail Reif, Archana Raman, Darren P. Wallace, Pamela Vivian Tran. *Anatomy and Cell Biology, Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by disruption of Polycystin-1 and Polycystin-2, which localize to primary cilia of renal epithelial cells. Activation of the Hedgehog (Hh) pathway relies on primary cilia. Previously, we showed that renal cystic disease in mice caused by deletion of *Thm1*, a ciliary gene and negative regulator of Hh signaling, was attenuated by genetically downregulating the Hh pathway, suggesting a role for enhanced Hh activity in renal cystogenesis. We aim to determine whether a role for dysregulated Hh signaling extends to cystic disease in *jck* mice and in human ADPKD.

Methods: We determined whether Hh activity correlated with disease progression in *jck* mutants. Hh signaling was downregulated in *jck* mice by deleting *Gli2*, the primary transcriptional activator of the Hh pathway, using a ubiquitous, tamoxifen-inducible Cre recombinase. To examine Hh status in human ADPKD, we compared Hh levels in normal human kidney (NHK) and ADPKD tissue and primary cells using Q-PCR, immunohistochemistry and immunofluorescence.

Results: In *jck* mice, expression of Hh target genes, *Gli1*, *Gli3* and *Ptch2*, were elevated at seven weeks of age and increased further at 18 weeks of age. Immunohistochemistry for GLI1 revealed increased expression in renal epithelial and interstitial cells, suggesting both paracrine and autocrine signaling mechanisms. Further, *jck*, *Gli2* double mutants showed decreased renal cystogenesis compared to single mutant littermates, suggesting a causative role for increased Hh signaling in *jck* cystic disease. In human ADPKD cells and tissues, Hh target gene expression was elevated and GLI1 protein expression was increased in both cystic epithelial cells and interstitial cells. Additionally, even in the absence of a Hh agonist, ADPKD cells showed localization of the Smoothed signal transducer to primary cilia, reflecting increased basal pathway activity.

Conclusions: Increased Hh signaling appears to play a role in renal cystogenesis and could represent a novel therapeutic target for ADPKD.

Funding: Other NIH Support - NIGMS

TH-PO193

The Development of a Clinically Relevant Mouse Model for Autosomal Dominant Polycystic Kidney Disease Wouter N. Leonhard,¹ Hester Happé,¹ Emile De Heer,² Dorien J.M. Peters.¹ ¹Human Genetics; ²Pathology, Leiden Univ Medical Center, Netherlands.

Background: To perform pre-clinical studies for Autosomal Dominant Polycystic Kidney Disease (ADPKD), it is desirable that the models have an adult onset of PKD with cysts derived from all tubular segments, but within a time-window that is suitable for therapeutic testing. As described previously, *Pkd1* deletion in neonatal mice leads to rapid PKD and *Pkd1* deletion in adult mice leads to slow PKD. The differences in rate of PKD progression are largely explained by a rather sharp developmental switch that occurs around P13 (Piontek *et al.* 2007). This suggests that there is limited flexibility in generating models with intermediate phenotypes. Surprisingly, in this study, *Pkd1* inactivation at different ages in tamoxifen inducible *Pkd1* knockout mice led to multiple models for PKD with different characteristics.

Methods: To inactivate *Pkd1*, tamoxifen administration was done on three consecutive days at P10, P16, P18 or P40. Disease progression was monitored by measuring Blood Urea concentration. The cystic burden and segmental origin of the cysts was studied using PAS staining and IHC for segment specific markers.

Results: P10 mice developed PKD within 3 to 4 weeks, with large distal and collecting duct cysts and few proximal tubular cysts. The progression rate in P16 mice was highly variable. By contrast, P18 mice developed end-stage PKD at an age of 14-17 weeks, with

cysts derived from all tubular segments that contributed equally to the phenotype. P40 mice developed end-stage PKD at an age of approximately 22 weeks with predominantly proximal cysts.

Conclusions: Despite a sharp developmental switch at P13 that has been proposed previously (Pontek *et al.* 2007) it is possible to generate multiple models with different progression rates and different origins of cyst. Notably, *Pkd1* deletion at P18 reproducibly led to adult onset PKD within a time-window that is highly suitable for therapeutic testing. In addition, since cysts were derived from all tubular segments, this model will contribute to finding a clinically relevant therapy for ADPKD patients.

TH-PO194

Identification of New Signaling Pathways Related to Polycystic Kidney Disease: From Animal Models to Treatment Olaya Lamas-Gonzalez,¹ Susana Bravo,¹ Ana Belen Sanz,² Ana Barcia de la Iglesia,¹ Alberto Ortiz,² Terry J. Watnick,³ Gregory G. Germino,⁴ Candido Diaz Rodriguez,¹ Miguel A. Garcia-Gonzalez.¹ ¹Health Research Inst of Santiago de Compostela, Spain; ²Fundación Jiménez Díaz, Spain; ³Univ of Maryland School of Medicine; ⁴National Inst of Diabetes and Digestive and Kidney Disease National Inst of Health.

Background: Pathogenesis of Polycystic Kidney Disease (PKD) has been related to a number of different mechanisms that make it very complex and there is no therapy for complete inhibition of cystogenesis, although there are advances in controlling cyst volume and cyst progression.

Methods: Taking advantage of the identified developmental window in PKD using the *Pkd1* conditional KO mouse, we have identified the differential proteome of the cystic and non-cystic *Pkd1* mutant kidneys. We identify TWEAK as a window dependent modulator of cystogenesis, inhibiting cystic progression in the cystic window, and promoting cystogenesis in the non-cystic window. We perform an exhaustive proteomics analysis of each cyst developmental stage by MALDI-TOF/TOF analysis of peptides and proteins separated either by LC or 2D-PAGE.

Results: We establish the proteomics fingerprint of each physiopathologic condition and refine new therapeutic targets to a very short list of 12 candidate targets. During cystogenesis, cytoskeleton interactions with the extracellular matrix (focal adhesions) seemed to be altered and, thus their downstream signaling and regulatory pathways. Cell polarity, endocytosis and trafficking of proteins to nucleus are altered as well. Processes such as acyl-CoA, free fatty acid metabolism and their transport are downregulated. Fructose metabolism is also downregulated. We have targeted the identify pathways both inhibiting complete cystogenesis deriving from distal nephron segment, as well as, reducing/delaying global cystic progression.

Conclusions: Here, we first describe the proteome related to the developmental cystic window as well those pathways associated to the cystic progression under inflammatory respond, triggering new possible targeting pathways for both controlling origin and progression of cystogenesis.

TH-PO195

Cytokine Tweak as an Intermediary in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Olaya Lamas-Gonzalez,¹ Ana Belen Sanz,² Maria D. Sanchez-Niño,² Ana Barcia de la Iglesia,¹ Adrian Cordido-Eijo,¹ Alberto Ortiz,² Miguel A. Garcia-Gonzalez.¹ ¹Health Research Inst of Santiago de Compostela, Spain; ²Fundación Jiménez Díaz, Spain.

Background: The pathogenesis of Polycystic Kidney Disease (PKD) remains unclear, but appears to involve altered tubular cell proliferation, cell death, differentiation and polarity as well as inflammatory and pro-fibrotic factors. It has been reported that acute kidney injury (AKI) and inflammation accelerate cystogenesis. TWEAK is a TNF-like cytokine that has a key role in AKI since anti-TWEAK antibodies prevented experimental loss of kidney function and renal inflammation, cell death and proliferation.

Methods: We hypothesize that response to treatment and cyst progression depend on a particular developmental window, so the correct dose and timing of a drug may prevent cystogenesis and make chronic treatment unnecessary. Here, we use a mouse model in which conditional inactivation of the *PKD1* gene by Cre-mediated recombination results in cystogenesis at different ages depending on when *PKD1* is inactivated.

Results: *PKD1* inactivation at day 12 resulted in massive cyst growth by day 30. Under these conditions systemic TWEAK administration for 10 days significantly decreased kidney cystogenesis. By contrast, *PKD1* inactivation at day 14 did not result in cyst growth by day 30. Under these conditions systemic TWEAK administration for 10 days significantly promoted kidney cystogenesis. Inflammation background, tissue remodeling and immune response to kidney injury could be playing a key role in the development and progression of ADPKD. Interestingly, liver appeared to present a different developmental pattern than kidney since TWEAK had mild effects in its cystogenesis.

Conclusions: These results demonstrate a developmental impact of *PKD1* inactivation and TWEAK in cystogenesis and are pointing out the antagonistic effects of the same molecule in different cyst developmental stages. Under the conditions of early *PKD1* inactivation of the human condition, TWEAK may protect from cystogenesis if administered early in the disease course. However, detailed time course are needed before human extrapolation given that TWEAK induce cystogenesis in some settings.

TH-PO196

Defects in Epithelial Morphogenesis of Fibrocystin-Deficient Cells Are Associated with Disturbed Cell Adhesion Wolfgang H. Ziegler, Birga Soetje, Lisa P. Marten, Dieter Haffner. *Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.*

Background: Mutations of the *Pkhd1* gene cause autosomal recessive polycystic kidney disease (ARPKD). *Pkhd1* encodes fibrocystin (FPC), a type I transmembrane protein of largely unknown function, which has been suggested to affect adhesion signaling of cells. Contributions of epithelial cell adhesion and contractility to the disease process of ARPKD remain to be defined. Having established a link between loss of FPC function and epithelial morphogenesis in 3D cell culture, we now aim to determine FPC-mediated parameters of (i) cell contact formation and (ii) the function / orientation of the actin cytoskeletal and microtubular networks.

Methods: We analyze FPC function in Madin-Darby canine renal collecting duct epithelial cells (MDCK) based on *Pkhd1* silencing. Cells are being studied on micro-patterned chips in 3D cell culture conditions, which induce formation of epithelial spheroids. To determine critical differences in cell adhesion parameters, MDCK cells are analyzed in their one and 2(4)-cell stages after seeding on chips using fluorescence microscopy.

Results: Based on defined adhesion conditions, we quantified the impact of FPC-deficiency on size / density of adhesion sites, cell shape characteristics and initiation of an apical surface. In cells deficient for FPC, cell culture conditions supporting correct epithelial morphogenesis induced significantly reduced cell area and number of cell adhesion sites per cell, with differences originating from defects in cytoskeletal organization rather than reduced cell size. Further insight is expected from ongoing analysis of centrosome positioning. Analysis of quantitative parameters in FPC-deficient cells provides a set of cell characteristics that correlate with and are expected to reveal causes of defective epithelial morphogenesis.

Conclusions: FPC silencing in MDCK cells disturbs adhesion signaling and cell-cell interaction resulting in impaired epithelial morphogenesis. Using a cell-based model system, we can address molecular consequences of and analyze rescue strategies for FPC deficiency in collecting duct epithelia.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO197

Identification of FUBP1 as a PKD2 mRNA 3'UTR Binding Protein That Suppresses Its Translation Wang Zheng, Xing-Zhen Chen. *Dept of Physiology, Univ of Alberta, Edmonton, AB, Canada.*

Background: PKD2, also called polycystin-2, a Ca²⁺-permeable non-selective cation channel that is mutated in around 15% autosomal dominant polycystic kidney disease (ADPKD). Increasing evidence indicates that the PKD2 protein level is important for embryo development, cell response to ischemic renal injuries, and cyst formation, but there are limited studies so far about how PKD2 protein level is regulated.

Methods: Here, with dual luciferase assays, western blotting, biotin-RNA pull down, gene knockdown in zebrafish, co-immunoprecipitation and GST-pull down, we studied how PKD2 mRNA translation is regulated by its 3' untranslated region (3'UTR).

Results: First, by dual luciferase assays, we identified a fragment in PKD2 3'UTR, named 3F1 (3' fragment inhibitory), that negatively regulates luciferase activity. Western blotting with a luciferase antibody confirmed the data obtained from the luciferase assays. By biotin-RNA pull down and mass spectrometry, we identified a 3F1-binding protein, called far upstream element binding protein 1 (FUBP1) that was originally found to promote transcription of oncogene c-Myc. Over-expression and knockdown of FUBP1 decreased and increased the PKD2 protein level, respectively, without altering the mRNA level. More interestingly, tail curvature induced by PKD2 morpholino (MO) knockdown in larval zebrafish was rescued by FUBP1 MO co-injection. Further, by co-IP and GST pull-down, we showed that FUBP1 directly binds with 4EBP1, a translational repressor that binds with eIF4E. Interestingly, 3F1 RNA was shown to strengthen this binding.

Conclusions: Therefore, our data indicate that FUBP1 inhibits PKD2 translation through anchoring to PKD2 mRNA 3F1 and interacting with 4EBP1.

Funding: Government Support - Non-U.S.

TH-PO198

Towards Understanding the Structure-Function Relationships of Polycystin-1 Robin L. Maser,¹ Brenda S. Magenheimer,¹ Aaron Matthew Smalter Hall.² ¹Univ of Kansas Med Ctr, Kansas City, KS; ²Univ of Kansas, Lawrence, KS.

Background: Appropriate levels of functional polycystin-1 (PC1), product of the *PKD1* gene, are the key determinant preventing the development of renal cysts in ADPKD. Recent work revealed the existence of hypomorphic missense mutations of *PKD1* and the importance of the proper biogenesis and trafficking of PC1, and suggested that mutation-specific therapies could potentially be designed to correct the biogenesis of mutant PC1. These advances underscore our lack of knowledge regarding PC1 structure and emphasize the importance of understanding PC-1 structure-function relationships. As such, we seek to generate a plausible tertiary structure model of human PC1.

Methods: A combination of comparative protein structure modeling along with validation by biochemical analyses is being used to predict and refine a human PC1 structure model. Our initial goal is to generate a 3D model of the arrangement of the 11 transmembrane (TM) segments and their connecting intra- and extracellular loops. Methodology involves secondary structure prediction and homology modeling between PC1 and known TM domains (using overlapping partitions of PC1 sequence), biophysical parameter-based

prediction of transmembrane domain bundling, and experimental biochemical analyses to validate predicted models. Use of the predicted secondary structure or template-modeled tertiary structure of loops is used to constrain and refine TM segment arrangement.

Results: Initial work has focused on TM segments connected by shorter loops. Thus far, N-linked glycosylation scanning experiments have confirmed the de novo modeling results for TM segments 9 and 11. Glycosylation analyses for TM segment 10 are not entirely consistent with the predicted model, due to an extension of the length of the domain. Such discrepancy may result from the inherent membrane-associating property of this loop region of PC1, as described in earlier published work.

Conclusions: Preliminary, proof-of-concept work has resulted in a coarse model of the last 3 TM segments of PC1. These analyses will provide important knowledge for understanding structure-function relationships of PC1 and for the development of new ADPKD treatments.

Funding: Other NIH Support - KU-NIH Center of Biomedical Research Excellence in Protein Structure and Function

TH-PO199

A Sorting Nexin 3 Retromer Complex Regulates the Surface Localisation and Activity of Wnt-Activated Polycystin-1 Regulated Polycystin-2 Channels Andrew J. Streets,¹ Shuang Feng,¹ Vasyli Nesin,² Leonidas Tsiokas,² Albert C. Ong.¹ ¹Kidney Genetics Group, Academic Nephrology Unit, Univ of Sheffield Medical School, Sheffield, United Kingdom; ²Dept of Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background: Autosomal dominant polycystic kidney disease (ADPKD), is caused by inactivating mutations in *PKD1* (85%) or *PKD2* (15%). The ADPKD proteins, polycystin-1 (PC1) and polycystin-2 (PC2) form a plasma membrane receptor-ion channel complex. PC2 is a member of the transient receptor potential (TRP) superfamily and functions as a non-selective calcium channel. PC2 has been localised to multiple cell compartments in renal epithelial cells including the endoplasmic reticulum, plasma membrane and primary cilia. However the mechanisms controlling the subcellular localization of PC2 are complex and not well understood.

Methods: Y2H, Co-immunoprecipitation and GST pulldown assays were used to identify protein interactions. IF, siRNA knockdown and surface biotinylation was used to monitor protein trafficking and siRNA knockdown and electrophysiology used to monitor PC2 dependent Ca²⁺ channels.

Results: Here, we identify a new isoform of sorting nexin 3 (SNX3-102, isoform 5) as a novel interacting partner of PC2. Compared to the classical SNX3 isoform (SNX3-162, isoform 1), SNX3-102 cannot bind PtdIns(3)P but instead binds directly to the C-terminus of PC2. SNX3-162 binds indirectly to the N-terminus of PC2 via the retromer cargo-specific adaptor protein VPS35. SNX3-102 is expressed mainly in clathrin-coated vesicles whereas SNX3-162 is expressed in early endosomes. Knockdown of SNX3 or VPS35 in LLCPK-1 cells results in increased expression of PC2 and PC1 in the plasma membrane and upregulated Wnt-activated PC2 dependent Ca²⁺ channel activity.

Conclusions: Our results support a sequential model where SNX3-102 regulates PC2 endocytosis by directly binding PC2 and clathrin to cluster PC2 in clathrin-coated vesicles before relaying it to early endosomes where SNX3-162 and VPS35 regulate its sorting and fate. Molecular targeting of endosomal sorting of PC1 and PC2 could lead to new therapeutic approaches in this major human disease.

TH-PO200

Leucine Stimulates the Proliferation of Pkd1-Null Renal Epithelial Cells via ERK/MAPK and Mtor Pathway Junya Yamamoto, Saori Nishio, Tasuku Nakagaki, Tatsuya Atsumi. Dept of Medicine II, Hokkaido Univ Graduate School of Medicine, Sapporo, Japan.

Background: Mammalian target of rapamycin (mTOR) cascade is one of the important pathways regulating cyst growth in ADPKD and branched-chain amino acids (BCAA) modulate various physiological effects through activating mTOR cascade. We have recently reported that BCAA supplementation accelerates cyst development and disease progression in *Pkd1* conditional knockout mice (*Pkd1^{fllox/lox}; Mx1-Cre* mice).

Methods: To elucidate the effects of BCAA in ADPKD, *Pkd1^{-/-}*(PN) and *Pkd1^{+/+}*(PH) renal epithelial cell lines were utilized and cultured in a medium with or without leucine. We evaluated cell proliferation by cell count. 3x10⁵ cells were plated on a 10-cm dish, 3 days later the total number of cells was counted. We also performed Ki-67 stains and western blotting of signaling pathway of proliferation.

Results: PN cells treated with leucine significantly increased the rate of proliferation compared to without leucine, but not in PH cells. Ki-67 positive ratio increased only in PN cells treated with leucine. In western blotting analysis, leucine promoted phosphorylation of p70S6 kinase in dose-related manner both in PN cells and PH cells, but leucine activated phosphorylation of ERK only in PN cells. PD98059 (MEK1 inhibitor), U0126 (MEK1 and MEK2 inhibitor) and rapamycin (mTOR inhibitor) attenuated leucine-induced cell proliferation by inhibiting ERK/MAPK pathway and mTOR pathway respectively.

Conclusions: Our findings suggest that leucine accelerates cyst development in ADPKD by promoting cystic epithelial cell proliferation via ERK/MAPK and mTOR pathways.

TH-PO201

Activation of the Polycystin Complex by WNT Ligands Seokho Kim,¹ Hongguang Nie,¹ Vasyli Nesin,¹ Uyen Tran,² Patricia Outeda,³ Chang-Xi Bai,¹ Jacob Keeling,¹ Dipak Maskey,¹ Terry J. Watnick,³ Oliver Wessely,² Leonidas Tsiokas.¹ ¹Cell Biology, Univ of Oklahoma HSC, Oklahoma City, OK; ²Cellular and Molecular Medicine, Cleveland Clinic, Cleveland, OH; ³Medicine/Nephrology, Univ of Maryland School of Medicine, Baltimore, MD.

Background: PKD1 (Polycystin 1) is considered an orphan, atypical G protein coupled receptor complexed with TRPP2 (Polycystin 2 or PKD2), a Ca²⁺-permeable ion channel. Inactivating mutations in their genes cause autosomal dominant polycystic kidney disease (ADPKD), one of the most common genetic diseases. However, the molecular identity of the extracellular ligands activating the Polycystin complex is unknown. WNT ligands induce Ca²⁺ signaling on target cells. Here, we tested whether WNTs can bind and activate the Polycystin complex.

Methods: Experimental approaches include electrophysiology, protein-protein-interactions using co-immunoprecipitations, directed cell migration assays, and embryological experiments in *Xenopus laevis*.

Results: Our data show that secreted WNTs bind to the extracellular domain of PKD1 and induce large whole cell currents and Ca²⁺ influx dependent on TRPP2, but independent of Frizzled (FZD) receptors. Pathogenic *PKD1* or *PKD2* mutations that abrogate complex formation, compromise cell surface expression of PKD1, or diminish TRPP2 channel activity suppress activation by a WNT protein. *Pkd2^{-/-}* fibroblasts lack WNT-induced Ca²⁺ currents and are unable to polarize during directed cell migration. In *Xenopus* embryos, PKD1 acts independently of FZD8, but within the same pathway with Disheveled 2 to preserve normal kidney tubulogenesis.

Conclusions: These data define PKD1 as a new class of WNT (co)receptors and implicate defective WNT/Ca²⁺ signaling as one of the causes of ADPKD.

Funding: NIDDK Support

TH-PO202

Caffeine Consumption Contributes to Cyst/Kidney Enlargement and Progression of Polycystic Kidney Disease in a Pkd1-Deficient Mouse Model Renata Meca,¹ Bruno E. Balbo,² Milene Subtil Ormanji,¹ Luiz F. Onuchic,² Ita Pfefferman Heilberg.¹ ¹Nephrology Div, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; ²Nephrology Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disease, characterized by progressive cyst formation and growth, leading to kidney failure. In cultured cells from ADPKD patients, caffeine increased the levels of cyclic AMP and induced apoptosis and proliferation. We aimed to examine the *in vivo* effects of Caffeine on cyst growth and progression of renal disease using a murine model orthologous to human ADPKD1.

Methods: Male and female *Pkd1^{cond/cond}; Nestin^{cre}* (cystic - CysCaf) and *Pkd1^{cond/cond}* (NonCystic - NonCysCaf) mice consumed caffeine (3mg/day, in drinking water), from conception to 12 weeks of life. Caffeine was orally administered to the mother until puppy weaning (5 weeks) and thereafter directly supplemented in drinking water. Cystic control animals consumed water (CysCtrl) for the same period.

Results:

	CysCaf	CysCtrl	NonCysCaf
Global Renal Cystic Index(%)	38.5 (15.3-54.3)* n=21	9.4 (2.1-15.2) n=16	NA
Total kidney volume/Body Weight(mm³/g)	25.5 (22.1-34.4)* n=21	17.4 (15.6-19.5) n=16	NA
sCystatin(pg/ml)	5.95± 1.14* n=13	2.07 0.57 n=4	3.36 0.71 n=4
sUrea(mg/dl)	83.7 21.5** n=22	48.1 16.6 n=17	64.5 11.4 n=11
Renal Fibrosis Index(%)	0.84 (0.38-1.18)** n=18	0.37 (0.06-0.47) n=6	0.30 (0.19-0.63) n=13
Cell Proliferation Index - Ki67(%)	5.34 1.66* n=8	2.52 1.34 n=5	0.57 0.23 n=6
* p<0,01 vs CysCtrl, † p<0,05 vs NonCysCaf			
Data are mean±SD or median(interquartile range);NA-not applicable			

Ultrasonographic analysis showed higher global renal cyst index and total kidney volume in the CysCaf group versus CysCtrl. CysCaf group presented higher serum Urea (sUrea) and Cystatin C (sCystatin) and lower maximum urine osmolality (data not shown) when compared to the NonCysCaf and CysCtrl groups. Renal fibrosis was higher in CysCaf than in the other groups and cell proliferation was higher in CysCaf than NonCysCaf kidneys.

Conclusions: Present findings demonstrate that caffeine induced an increase in renal volume and accelerated the progression of polycystic kidney disease in *Pkd1*-deficient mice.
Funding: Government Support - Non-U.S.

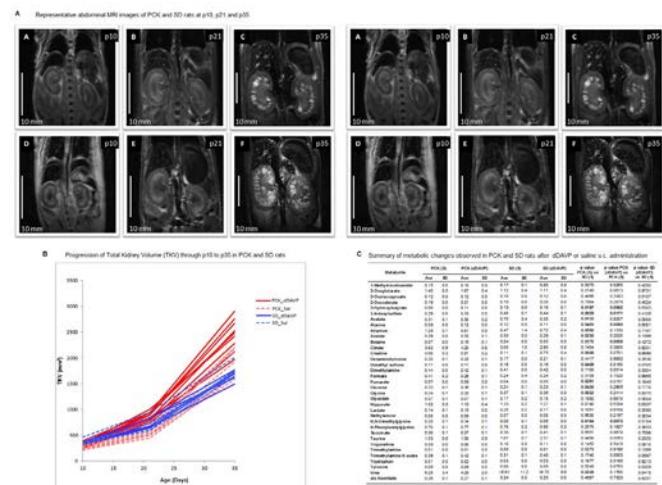
TH-PO203

Changes in Urine Metabolites in PCK Rat Induced by dDAVP Administration Maria V. Irazabal, Ivan Vuckovic, Song Zhang, Fouad T. Chebib, Xiaofang Wang, Hong Ye, Petras P. Dzeja, Slobodan Macura, Vicente E. Torres. *Mayo Clinic.*

Background: V2 receptor agonist 1-deamino-8-D-arginine vasopressin (dDAVP) aggravates the cystic disease of PCK rats by increasing renal cAMP without inducing cystic changes in wild-type rats (WT). We aimed to investigate the urinary metabolic changes in 1) PCK vs WT, and 2) response to dDAVP in PCK and WT rats.

Methods: PCK and WT rats were treated with 20 ng sc of dDAVP b.i.d. from p7 to p21, increasing to 40 ng sc b.i.d. from p22 to p35 inclusive or sc injections of isotonic (0.15 M) saline (S) at identical intervals. Abdominal MRI was performed at p10, p21 and p35 for kidney volume (KV). ¹H-NMR-based metabolomics analysis was performed from 24h urine collections at p30. The urine spectra were normalized to creatinine.

Results: Administration of dDAVP significantly aggravated the disease in PCK rats as evidenced by KV at p10, p21 and p35 (p=0.04, <0.001 and <0.001), but did not increase significantly KV or generate a cystic phenotype in WT rats (Fig1A-B). BUN levels were not different between groups at p35. Thirty seven urinary metabolites were identified. Thirteen metabolites were significantly different between PCK (S) and WT (S) (Fig1C). dDAVP induced significant changes in 5 metabolites in PCK but only 1 in WT rats. For example, urinary concentration of betaine, an important osmoregulatory compound, was significantly increased in PCK (S) compared to WT (S) and increased even further with dDAVP only in PCK rats.



Conclusions: ¹H-NMR-based metabolomics analysis identified 13 significantly different metabolites between PCK(S) and WT(S) rats. dDAVP aggravated the cystic disease and induced significant changes of urinary metabolites in PCK rats. Measurements of kidney tissue and plasma metabolites, in progress, will assist in the interpretation of these findings.
Funding: NIDDK Support

TH-PO204

Localized Changes in MicroRNAs Are Critical to the Development of Fibrosis in PKD Ameja P. Patil, William E. Sweeney, Ellis D. Avner. *Pediatric Nephrology, Dept of Pediatrics, Medical College of Wisconsin, Wauwatosa, WI.*

Background: ADPKD is characterized by proliferation and growth of tubular cysts and development of progressive interstitial fibrosis. These phases are consistently reproduced in the *Pkd1*^(nl/mcw) mouse, an orthologous model of *Pkd1*. In this mouse model, as in human ADPKD, the progression of fibrosis, rather than cyst size, leads to ESRD. MicroRNA's (miRNA's) are small noncoding RNA's that act as potent regulators of gene expression. In ADPKD, the progression of interstitial fibrosis in distinct patterns suggests that crosstalk between cystic epithelia and interstitial cells create a "pro-fibrotic" microenvironment. We hypothesize that changes in miRNA expression are critical to development of fibrosis in ADPKD.

Methods: Laser capture micro-dissection (LCM) of trichrome positive interstitium and, adjacent cystic tubular epithelia were profiled separately for local miRNA expression with Qiagen miScript 384 HC miRNA PCR arrays at four distinct time points during which fibrosis is initiated and progresses. The miRNA profile was compared to age-matched whole kidney miRNA profiles, correlated with fibrosis pathway arrays, and immunohistochemical analysis.

Results: From PN21 to 28, interstitium and adjacent cystic epithelia demonstrated significant changes in miRNA expression (20 upregulated, 15 downregulated). These changes correlated with: a shift in the site of proliferation; a change in macrophage subtypes

and number; significant increase in Tgf-B1,2,& 3, p-Smad2 and col3a1 and significantly decreased BMP7 expression. 9 miRNA's exhibited a variable expression with initiation and then progression of the disease.

Conclusions: 1. Compartmental changes in miRNA expression seen with LCM were not seen in the whole kidney analysis, demonstrating the value of the approach. 2. Pro-fibrotic and ADPKD specific miRNA's(predicted to regulate TGFβ1, 2 and 3, collagen 3a1, 4a1, 4a4 and 4a5 and most interestingly EGFR, and STAT3) are significantly altered in peri-cystic interstitium. 3. We speculate that such compartment specific changes in miRNA expression are critical to development of fibrosis in ADPKD and may provide future therapeutic targets to halt the progression of ADPKD.

Funding: Pharmaceutical Company Support - Taisho pharmaceutical ltd., Private Foundation Support

TH-PO205

miR-21 Promotes Cyst Growth in Polycystic Kidney Disease Ronak Lakhia,¹ Sachin S. Hajarnis,¹ Darren Williams,¹ Karam S. Aboudehen,² Matanel Yheskel,¹ Vishal Patel.¹ ¹Internal Medicine, UT Southwestern, Dallas, TX; ²Internal Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the presence of numerous fluid-filled cysts in the kidney. MicroRNAs (miRNAs), short noncoding RNAs that regulate gene expression, have emerged as promising new therapeutic targets for many common diseases. The goal of this study was to identify miRNAs that represent new drug targets for ADPKD.

Methods: Microarrays, Q-PCR, and ISH were performed to determine miR-21 expression in PKD. ChIP and promoter luciferase reporter assays were performed to understand the mechanisms that underlie miR-21 regulation in cystic kidneys. To study the role of miR-21 in ADPKD, miR-21 was inactivated in *Pkhd1*/Cre; *Pkd2*^{fl/fl} (*Pkd2*-KO) mice, an orthologous mouse model of ADPKD. RNA-Seq was performed to elucidate the differential gene expression pattern between *Pkd2*-KO and *Pkd2*-miR-21^{-/-} KO mouse kidneys.

Results: miR-21 expression was increased in multiple mouse models of PKD, including two orthologous models of PKD. Upregulation of miR-21 was primarily localized to mouse kidney cyst epithelial cells. Increased miR-21 expression was also seen in cysts of human ADPKD tissue samples. cAMP-CREB signaling transactivated the miR-21 promoter in kidney cells. Inactivation of miR-21 in *Pkd2*-KO mice reduced kidney size, cyst number, and prolonged survival. RNA-Seq and subsequent pathway analysis identified cell death as the main biological effect of miR-21 deletion. Accordingly, compared to *Pkd2*-KO mice, *Pkd2*-miR-21^{-/-} KO mice exhibited increased apoptosis of cyst epithelial cells without any change in proliferation. Expression of *Pdcd4*, a pro-apoptotic miR-21 target, was increased in cysts of *Pkd2*-miR-21^{-/-} double knockout mice, indicating that miR-21 inhibits *Pdcd4* in cystic kidneys.

Conclusions: Upregulation of miR-21 is a common feature of mouse and human forms of PKD. Deletion of miR-21 attenuates cyst burden and prolongs survival. miR-21 may promote cyst growth in ADPKD by preventing apoptosis of cyst epithelial cells through direct suppression of *Pdcd4*. Our studies suggest that inhibiting miR-21 may be a useful therapeutic strategy for ADPKD.

Funding: NIDDK Support, Other NIH Support - NIH institutional T32 grant, Private Foundation Support

TH-PO206

Macrophages Programmed by Polycystic Kidney Disease Cyst Cells Produce Soluble CXCR2 Ligands That Promote Cyst Cell Proliferation Sally M. Salah, Darren P. Wallace, Timothy A. Fields, Katherine Swenson-Fields. *The Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: The presence of renal macrophages in animal models of PKD has been shown to promote disease progression. The mechanisms underlying this phenomenon are incompletely understood but are likely due to reciprocal interactions between infiltrating macrophages and cyst epithelial cells: cyst cells stimulate macrophage differentiation to an M2-like, pro-proliferative phenotype and, in turn, these now "programmed" macrophages secrete unknown factors that promote cyst cell proliferation.

Methods: To identify macrophage-secreted factors that promote disease progression, macrophages were incubated for 48 h with conditioned media from primary human ADPKD cyst cells. These programmed macrophages were either collected and analyzed by RNAseq or were washed extensively and incubated for a further 24 h to allow production of secreted pro-proliferative factors, which were subjected to protein/proteome analysis and antibody array. Similar analyses of resting macrophages were carried out in parallel for comparison.

Results: Co-culture of ADPKD cyst cell conditioned media with macrophages enhances macrophage production of protease-sensitive, pro-proliferative activity. RNAseq and cytokine array analysis revealed up-regulation of multiple candidate pro-proliferative factors in programmed macrophages, including several ligands of the CXCR2 receptor. The addition of a CXCR2 receptor antagonist (SB225002) to ADPKD cells significantly reduced proliferation stimulated by programmed macrophage conditioned media.

Conclusions: Efforts are underway to identify the specific CXCR2 ligands produced by programmed macrophages that are responsible for this pro-proliferative effect. These factors and their signaling pathways could provide new targets for the development of therapies to slow PKD progression.

Funding: Other NIH Support - NCATS and NIGMS

TH-PO207

PKD2-Related Autosomal-Dominant Polycystic Kidney Disease (ADPKD): Mutation Spectrum, Clinical Presentation, and Prognosis Emilie Cornec-Le Gall,^{1,2} Marie-Pierre Audrezet,^{1,2} Christophe Charasse,⁵ Cecile M. Vigneau,⁶ Lise Mandart,⁷ Claude Ferec,^{1,2} Yannick Le Meur.¹ ¹CHRU Brest, France; ²INSERM 1078; ³CH Saint Malo; ⁴CHRU Nantes; ⁵CH Saint Brieu; ⁶CHRU Rennes; ⁷CH Vannes.

Background: The milder severity of PKD2 related ADPKD (~15% of the pedigrees) as compared to PKD1 is well acknowledged, but population-based studies, enabling to depict the exact burden of the disease, are currently lacking. In this study, we aimed to describe the clinical presentation and the mutation spectrum in a large cohort of PKD2 patients.

Methods: Genkyst is a cross-sectional cohort which aims to include all consenting ADPKD patients followed in 23 Nephrology centers from the western part of France. Clinical data were collected and a comprehensive molecular analysis of PKD1 and PKD2 genes was undertaken.

Results: A total of 70 different PKD2 mutations were identified in 248 patients from 172 pedigrees (i.e. 20.2% of the mutation-positive pedigrees from Genkyst). A recurrent 28-kb deletion involving exons 10-15 was identified in 45 patients from 23 pedigrees confined in an area of ~3500 km², which represents to our knowledge the first case of founder mutation in ADPKD. Median age at diagnosis in the total cohort was 41.5 yrs. At age 70, cumulative probability of ESRD obtained by Kaplan Meier analysis was 37.4%, whereas probabilities for hypertension, pains related to cysts and gross hematuria were respectively of 93.3%, 46.6% and 23.3%. Although there was no gender influence on renal survival, multiple linear regression demonstrated that men had significantly lower kidney function than women. Disease variability was observed in some patients harbouring the same mutation, suggesting that additional genetic or environmental factors may modulate the disease severity in PKD2 patients. In line with this hypothesis, familial study led to the identification of PKD1 hypomorphic alleles possibly acting as disease modifiers in 2 PKD2 pedigrees with marked intra-familial variability.

Conclusions: This large cohort confirms that PKD2 patients typically present with a mild disease and therefore a vast majority of them may not require emerging targeted therapies.

Funding: Government Support - Non-U.S.

TH-PO208

Transcriptome Analysis Identifies A Novel Candidate Therapy for Polycystic Kidney Disease Robert L. Bacallao,^{1,2} Sherry G. Clendenon,³ James A. Glazier,³ Rita M.c. De almeida.⁴ ¹Medicine, Indiana Univ School of Medicine, Indianapolis, IN; ²Medicine, Richard Roudebush VAMC, Indianapolis, IN; ³Physics, Biocomplexity Inst, Indiana Univ, Bloomington, IN; ⁴Physics, Instituto Nacional de Ciencia e Technologic, Univ Federal do Rio Grande do Sul, Porto Alegre, R.S., Brazil.

Background: ADPKD is a genetic disorder characterized by accumulation of renal cysts culminating in renal failure. A critical need exists ameliorate ADPKD. Transcriptogram analysis is a new method for whole genome gene expression data analysis that more sensitively identifies affected molecular networks and pathways.

Methods: Genes are ordered into a list using a Monte Carlo simulation that minimized distance between associated gene products, such that proximity on the list correlates with co-participation in biological processes. Transcriptogram profiles are then produced by calculating the average transcription level for genes within a moving window. The resulting transcriptogram reveals which pathways are differentially expressed.

Results: Using this approach, gene chip analysis revealed cystic epithelial have significant over expression of cGMP phosphodiesterases, components of inflammasome pathway (IL6, IL1B, NFKB1A, CCL2, BIRC3, TNFAIP3, IL18, PYCARD, MAPK13), and potassium ion transport (KCNJ12, KCNK3, KCNC4, KCNMB4, KCNQ1, KCNS1). Conversely many genes participating in oxidative phosphorylation are expressed at significantly lower levels in cystic epithelia. To test the significance of cGMP phosphodiesterases; human cystic epithelial cells were grown in 3D collagen culture with forskolin plus or minus sildenafil. Strikingly the cGMP phosphodiesterase inhibitor inhibited cyst growth at all doses (4 ug/ml, 2 ug/ml and 1 ug/ml). Average cyst size was decreased compared to controls (p<1 E-6 for 4 ug/ml dose, p<0.01 for 2 ug/ml dose, and p<0.01 for the 1 ug/ml dose). Also frequency analysis of cyst sizes we found that large cysts were absent from sildenafil treated cultures.

Conclusions: Transcriptogram analysis of gene chip data provides a powerful new way to analyze changes in the gene expression profile in ADPKD. Secondly, sildenafil blocks kidney epithelial cyst growth in 3D culture.

Funding: Private Foundation Support

TH-PO209

Gene Discovery for Autosomal Dominant Polycystic Liver Disease (ADPLD) Whitney E. Besse,¹ Yiqiang Cai,¹ Ali G. Gharavi,² Simone Sanna-Cherchi,² Terry J. Watnick,³ York P. Pei,⁴ Vicente E. Torres,⁵ Stefan Somlo.¹ ¹Internal Medicine, Section of Nephrology/Genetics, Yale School of Medicine, New Haven, CT; ²Div of Nephrology, Columbia Univ Dept of Medicine, NY; ³Div of Nephrology, Univ of Maryland School of Medicine, Baltimore, MD; ⁴Div of Nephrology, Univ Health Network, Toronto, ON, Canada; ⁵Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: ADPLD involves identical polycystic liver disease to that seen in ADPKD, but without clinically relevant kidney cysts. While mutations in PKD1 lead to ADPKD, mutations in genes that indirectly affect Polycystin 1 (PC1) expression or function cause ADPLD. Study of two identified ADPLD genes, SEC63 and PRKCSH, has shown the importance of co/post-translational modifications in the ER for PC1 function, and demonstrated the critical role of PC1 dosage in cyst pathogenesis. We hypothesize that discovery of additional ADPLD genes in patients will identify other functional modulators of PC1.

Methods: We have established a cohort of 161 unrelated individuals and families with ADPLD. Those without known mutations (Discovery Cohort) underwent whole exome sequencing together with linkage analysis where sufficient family material existed. Initial evaluation focused on candidate genes with rare heterozygous loss of function mutations. We established an in vitro bioassay to test a subset of candidates by evaluating PC1 expression and cilia trafficking following knockout of the candidate gene by CRISPR in cell culture.

Results: We found that 65/161 (40%) of ADPLD probands have mutations in SEC63 (18%) or PRKCSH (22%). Initial analysis of exome sequencing of our Discovery Cohort identified three candidate genes that function in ER biogenesis pathways related to the known genes and explain a total of 10 unrelated cases. We have generated cell knockout of one of these new candidate genes and shown a decrease in PC1 expression and as well activation of XBP1s, similar to our earlier findings in Sec63 knockouts.

Conclusions: ADPLD gene discovery using whole exome sequencing coupled with in vitro assays of PC1 function is an unbiased and achievable approach to identify necessary proteins and pathways for PC1 function, and thus help to better define cyst pathogenesis in ADPLD and ADPKD.

Funding: NIDDK Support

TH-PO210

Morpholino and Mutant Studies of Pde3A and Pde1a in Renal Cystogenesis Using Zebrafish Caroline R. Sussman, Raad B. Chowdhury, Matthew Durant, Peter C. Harris, Vicente E. Torres. *Nephrology & Hypertension, Mayo Clinic, Rochester, MN.*

Background: Numerous studies demonstrate the role of cAMP in cyst development and Polycystic Kidney Disease (PKD) progression. Studies in zebrafish using morpholinos show that Phosphodiesterase (Pde) 1A modulates renal cyst development and associated phenotypes, consistent with its hydrolysis of cAMP.

Methods: MOs were used to assess effects of Pde3A on renal cyst development and associated phenotypes, hydrocephalus and otolith defects. Additionally, we have generated 3 *Pde1a* mutant zebrafish lines using TALENs. Phenotypes were evaluated blinded, and data were analyzed using chi-square on embryos summed within treatments from 3-4 experiments.

Results: Depletion of Pde3A using two splice-blocking MOs increased the incidence of renal cysts at 2 days post-fertilization (dpf). Both MOs targeted exon 12 of *pde3a*, the first exon of the hydrolytic domain, encoding the conserved HD required for hydrolysis. Splice acceptor MO induced cysts with dose dependence at 5 ng (13%) and 10 ng (33%) vs. control MO (p<0.002, n>57 embryos / treatment). Splice donor MO induced cysts with dose dependence at 1 ng (13%), 2.5 ng (22%), and 5 ng (59%) vs. 5 ng of control MO (0%) (p<0.003, n≥40 embryos/treatment). The splice-donor MO also induced hydrocephalus at 2.5 ng (25%) and 5 ng (60%), and otolith defects at 2.5 ng (38%) and 5 ng (79%) vs. 5 ng of control MO (0%) (p<0.001, n≥60 embryos/treatment). Injection of 1 ng caused a non-significant trend toward induction of hydrocephalus (3%, p=0.3) and otolith defects (8%, p=0.06) (n≥40 embryos / treatment). Sequencing of cystic embryos showed altered splicing at the targeted exon. Similar to MOs, *Pde1a* TALENs were generated targeting the exon encoding the conserved HD. We have obtained 3 unique mutant lines which disrupt the HD. In initial studies, *Pde1a*^{-/-} fish are found at expected frequencies in adult populations, indicating survival equivalent to that of *Pde1a*^{+/+} fish.

Conclusions: MO studies of Pde3A suggest its involvement in renal cystogenesis and associated phenotypes, similar to previous studies using Pde1A MOs. TALENs effectively induced function-blocking mutations in *Pde1a*, which will allow studies of *Pde1a*^{-/-} fish.

Funding: NIDDK Support, Private Foundation Support

TH-PO211

Transcriptional Repression of PKD1 by Gene-Body Hypermethylation Induces Renal Cyst Development in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common human genetic disease characterized by the formation of multiple fluid-filled cysts in bilateral kidneys. Although mutations in *polycystic kidney disease 1 (PKD1)* are predominantly responsible for ADPKD, the focal and sporadic property of individual cystogenesis suggests another molecular mechanism such as epigenetic alterations.

Methods: To determine the epigenomic alterations in ADPKD and their functional relevance, ADPKD and non-ADPKD individuals were analyzed by unbiased methylation profiling genome-wide and compared with their expression data.

Results: Intriguingly, *PKD1* was hypermethylated in gene-body regions, and its expression was downregulated in ADPKD. Hypermethylation of *PKD1* gene-body was associated with recruitment of methyl-CpG-binding domain 2 (MBD2) proteins. Moreover, treatment with DNA methylation inhibitors retarded *in vitro* cyst formation, accompanied with the upregulation of *Pkd1* expression.

Conclusions: These results are consistent with previous studies that knock-down of *PKD1* was sufficient for cystogenesis. Therefore, our results reveal a critical role for hypermethylation of *PKD1* and cystogenesis-related regulatory genes in cyst development, suggesting epigenetic therapy as a potential treatment for ADPKD.

Funding: Government Support - Non-U.S.

TH-PO212

Age- and Sex-Dependent Salt Sensitivity in *Pkhd1*^{pk} Rats

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Background: Most forms of hypertension are influenced by gender and salt sensitivity. However, interplay of these two factors and their functional consequences in PKD-associated hypertension are incompletely understood. Thus, we tested the hypothesis that age and male sex would pre-dispose animals with PKD to hypertension and risk of renal injury.

Methods: We used *Pkhd1*^{pk} rat model of autosomal recessive PKD to study sex difference in blood pressure in response to high salt (HS) diet. Two month- and eight month-old male and female *Pkhd1*^{pk} rats were surgically implanted with telemetry transmitters and allowed to recover for at least one week before obtaining baseline mean arterial pressure (MAP). Rats were then fed a high salt (HS; 4% NaCl) diet for 3 weeks. At the end of the study, rats were placed in metabolic cages and a 24 hr urine sample was collected before taking a terminal blood sample and kidneys removed.

Results: In the 2-month old *Pkhd1*^{pk} rats, blood pressures were in a normal range and there were no differences between male and female animals. Furthermore, 3 weeks on a high salt diet had no effect on 24 hr MAP. In 8-month old rats, again there were no sex differences between animals on normal rat chow. MAP was progressively increased in both male and female rats after 3 weeks of HS diet treatment. MAP increased from 127±6 to 171±6 mmHg in male and from 112±3 to 127±3 mmHg in female rats, both p<0.05. However, the MAP increase was significantly greater in male (Δ44±6 mmHg) versus female (Δ15±5 mmHg, p<0.05) rats. The blood pressure increase in male rats was associated with higher urinary protein excretion compared to female rats (1015±134 vs. 478±45 mg/day, p<0.05). These male rats had also higher kidney weight to body weight (bwt) ratio compared to female rats (1.0±0.2 vs. 0.5±0.1 g/100 g bwt, p<0.05).

Conclusions: Our studies demonstrate that male *Pkhd1*^{pk} rats with advanced cystic kidney disease are more vulnerable to salt sensitive hypertension and renal injury than age-matched females.

Funding: Other NIH Support - NHLBI

TH-PO213

Sodium Intake versus Disease Progression in Experimental Polycystic Kidney Disease

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Background: Vasopressin, a known determinant of disease severity and progression in ADPKD, increases in response to an increase in plasma osmolarity, of which sodium is the most important osmol. We hypothesized that lowering sodium intake reduces vasopressin concentration and thereby may improve disease progression in ADPKD.

Methods: We used a tamoxifen-inducible kidney epithelium-specific *Pkd1*-deletion mouse model. All mice were treated for 3 weeks with either a low sodium (LS: 0.39 g/kg) or high sodium (HS: 15.2 g/kg) diet, after which physiological effects were studied and mice were sacrificed.

Results: The attached table summarizes the results after the dietary intervention. A higher water intake was seen in *Pkd1*-mice in comparison with healthy controls (HC), in line with the impaired urine concentrating capacity occurring in PKD. For both HC and *Pkd1*-mice water intake was higher in HS groups, in line with the physiological effects of sodium intake. In contrast to our hypothesis, a LS diet did not result in improved disease progression as total kidney weight (TKW), TKW per body weight (TKW/BW), cyst ratio and renal function (creatinine) were similar in all *Pkd1*-mice, regardless of the diet.

	HC LS	HC HS	<i>Pkd1</i> LS	<i>Pkd1</i> HS
N	15	15	23	25
Weight (g)	16.6 (16.4-18.2)	15.8 (14.2-17.3)	17.2 (14.8-18.0)××	14.6 (13.6-16.0)
TKW (mg)	235 (204-247)**	227 (206-271)**	415 (361-448)×	356 (320-399)
TKW/BW (%)	1.3 (1.3-1.4)***×	1.5 (1.4-1.6)**	2.5 (2.0-2.8)	2.5 (2.1-2.9)
Cyst ratio (%)	5.0 (2.6-7.3)**	6.4 (4.3-9.4)**	27.4 (17.3-30.3)	29.6 (20.8-34.5)
P _{creatinine} (μmol/L)	7.0 (7.0-9.0)**	6.0 (6.0-8.0)**	11.0 (9.0-13.0)	9.0 (7.0-12.0)
P _{Na+} (mmol/L)	147 (146-148)	146 (145-148)	147 (143-150)	147 (145-149)
Water intake (g)	2.8 (2.6-2.9)*×	3.2 (3.0-3.8)**	3.7 (2.9-4.1)×	4.1 (3.8-5.3)
Na ⁺ excr (μmol/24h)	161 (89-169)×	556 (372-1210)	45 (39-57)×	488 (276-676)

Variables are given as median (IQR). *p<0.05, **p<0.01; HC vs *Pkd1* ×p<0.05, ××p<0.01; LS vs HS, same group.

Conclusions: A low sodium diet results in less water intake, but does not improve disease progression in *Pkd1*-mice.

TH-PO214

Tuba, a CDC42-Specific Guanine Nucleotide Exchange Factor (GEF), Is Necessary for Ciliogenesis and Kidney Development

Jeong-in Baek,¹ Soo Young Choi,¹ Xiaofeng Zuo,¹ Joshua H. Lipschutz.^{1,2} ¹*Div of Nephrology, Medical Univ of South Carolina, Charleston, SC;* ²*Renal Section, Ralph H. Johnson VAMC, Charleston, SC.*

Background: Polycystic kidney disease (PKD) is associated with perturbations in renal primary cilia structure and/or function. The exocyst, a highly conserved eight-protein membrane trafficking complex, is essential for ciliogenesis, and is regulated by Cdc42. Our previous studies showed that Cdc42 deficiency disrupts renal ciliogenesis and causes PKD in zebrafish and mice, and that Tuba is also necessary for ciliogenesis in cultured MDCK cells.

Methods: Tuba knockdown MDCK cells were grown on Transwell filters and in three dimensional (3D) collagen gels, and zebrafish embryos were generated in which *tuba* was knocked down using antisense morpholinos. Ciliary and kidney defects caused by *tuba* deficiency were analyzed at molecular, histological and phenotypic levels.

Results: *Tuba* depletion resulted in an absence of cilia with impaired apical polarization of MDCK cell cysts. In hepatocyte growth factor-induced tubulogenesis, we found that *Tuba* knockdown significantly inhibited tubule formation. In zebrafish, *tuba* was expressed in ciliated organs, including the brain, eye, neurostem cells, and kidney. *Tuba* morphants phenocopied *cdc42* morphants, with ciliary mutant phenotypes that included: a curly tail, hydrocephalus, and abdominal fluid accumulation. In *tuba* morphant kidneys, pronephric cilia were short and disordered, and glomeruli were disorganized. Moreover, *tuba* morphants showed defects in cardiac laterality, consistent with ciliary dysfunction. Following co-injection of small amounts of *tuba* and *cdc42* morpholinos, that alone had no effect, a severe phenotype was observed, suggesting that *tuba* and *cdc42* act in the same pathway.

Conclusions: Our study showed that *Tuba* plays a critical role in ciliogenesis and kidney development in MDCK cells and zebrafish. We are generating *tuba* knockout zebrafish and *Tuba* kidney-specific knockout mice, using CRISPR and the Cre-lox binary mouse system, respectively. These animal models will allow us to better understand the pathogenic mechanisms of PKD, and could lead to novel treatments.

Funding: Veterans Administration Support

TH-PO215

Kidney-Specific Inactivation of the Exocyst Gene Sec10 in Mice Leads to Primary Cilia Defects and a Cystic Kidney Phenotype

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Background: The primary cilium is a sensory organelle that projects from the apical surface of renal epithelial cells, and has been implicated in the pathogenesis of polycystic kidney disease. The exocyst complex is responsible for guiding the polarized exocytosis of subsets of secretory vesicles. Previous studies in cultured epithelial cells implicated exocyst activity, and particularly its Sec10 subunit, in primary cilia assembly. Our previous inhibition of Sec10 in a zebrafish model resulted in defective ciliary signaling, but no measurable defects in cilia structure.

Methods: To allow *in vivo* studies of the exocyst complex in mammalian kidney development and disease, we have generated a novel transgenic mouse to conditionally knockout the Sec10 gene using the Cre-loxP system. Here, we used the Ksp-Cre mice to specifically delete Sec10 in ureteric bud-derived epithelial tissues, which include distal renal tubules. We analyzed the renal phenotype and primary cilia in the Sec10-mutant kidneys.

Results: Conditional deletion of Sec10 showed a surprising neonatal lethal phenotype of prenatal ureter obstructions, although a small percentage of mice were non-obstructed and survived until at least 3 weeks of age. Histological analysis revealed the 20-day old Sec10^{FL/FL};Ksp-Cre mice had a polycystic kidney phenotype not seen in control littermates. Using immunostaining and confocal microscopy, we visualized primary cilia in renal

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

tubules of Sec10 mutant and control mice. Sec10-knockout tubules showed a 38.5% average ciliation ratio compared to 84.5% in control kidneys ($p < 0.0001$). The primary cilia that were detected in Sec10-knockout tubules were much shorter than those in the control littermates ($p < 0.0001$). Furthermore, significantly elevated blood urea nitrogen levels in knockout animals compared to controls suggested impaired kidney function.

Conclusions: Findings from our mouse model provide the first *in vivo* evidence of the exocyst's involvement in mammalian primary cilia assembly and links Sec10 and the exocyst to the pathogenesis of polycystic kidney disease.

Funding: NIDDK Support, Other NIH Support - NIGMS, Private Foundation Support

TH-PO216

Whole Exome Sequencing (WES) Resolves ARPKD-Like and Meckel Syndrome (MKS)-Like Pedigrees Unresolved by Sanger/Ciliopathy Panel Screening Katharina Hopp, Sarah J. Koon, Christina M. Heyer, Vicente E. Torres, Peter C. Harris. *Mayo Clinic*.

Background: ARPKD and MKS have phenotypic and genetic overlap with other ciliopathies, with many unresolved pedigrees after Sanger sequencing of commonly mutated genes (ARPKD: ~10% of severe and ~50% of mild cases; MKS: ~45% of cases).

Methods: We performed WES (Agilent SureSelect, Illumina HiSeq 2000) of 18 Sanger screened, unresolved pedigrees, of which 13 were also assessed by targeted next-generation sequencing (NGS, 258 ciliopathy/cilia genes). Identified variants were filtered/scored based on quality, population frequency, segregation and substitution/gene significance.

Results: Screening for homozygous, compound heterozygous, and *de novo* variants identified disease-alleles in 4 pedigrees. Ped 1, ARPKD diagnosis at 4y, was homozygous for a novel *BBS9* mutation (c.437_438insA), although the proband lacked key Bardet-Biedel Syndrome (BBS) features (retinal dystrophy, obesity, polydactyly, learning disability). The variant was missed by the targeted NGS panel due to preferential WT allele enrichment. Ped 2, two MKS diagnosed fetuses with PKD, polydactyly, hepatic fibrosis, but no CNS abnormalities, inherited two novel *BBS7* variants (c.1405_1406delCA and p.V266E [scored as pathogenic]). Of note, BBS rarely causes embryonic lethality. Ped 3, a 15w MKS-like fetus with occipital encephalocele, sloping forehead and bifid tongue, inherited two *C2CD3* mutations (p.C1114=, caused ex18 skipping, and p.V899M [scored as pathogenic]). This verified findings of the targeted NGS panel and excluded additional genetic disease causes. *C2CD3* is linked to oral-facial-digital syndrome 14 but the fetus lacked key associated features (polydactyly, microcephaly). Ped 4, a 16w MKS fetus with PKD, was initially diagnosed with a single *CC2D2A* variant (c.2182-2A>G). WES identified a second variant (c.3289-1delG) missed by Sanger sequencing.

Conclusions: We show here the value of WES for resolving Sanger/NGS panel unresolved ciliopathy pedigrees, although with low detection rates. In addition, we show BBS genes associated with a broad ciliopathy disease spectrum, reporting for the first time *BBS9* mutations in an ARPKD-like case and *BBS7* mutations in a MKS-like pedigree.

Funding: NIDDK Support, Private Foundation Support

TH-PO217

IFT81, Encoding an Intraflagellar Transport Protein, as a Rare Cause of a Ciliopathy Phenotype Jan Halbritter,¹ Isabelle Perrault,² Jonathan Porath,¹ Xavier Gerard,² Daniela A. Braun,¹ Heon Yung Gee,¹ Hanan Fathy,³ Richard P. Lifton,⁴ Jean-michel Rozet,² Friedhelm Hildebrandt.¹ ¹Medicine, Boston Children's Hospital, Boston, MA; ²Imagine Inst, Paris Descartes, Paris, France; ³Pediatric Nephrology, Univ of Alexandria, Alexandria, Egypt; ⁴Genetics, Yale Univ, New Haven, CT.

Background: Bidirectional intraflagellar transport (IFT) consists of two major protein complexes, IFT-A and IFT-B. In contrast to the IFT-B complex, all components of IFT-A have recently been linked to human ciliopathies when defective. We therefore hypothesized that mutations in additional IFT-B encoding genes can be found in patients with multisystemic ciliopathies.

Methods: We screened 1,628 individuals with reno-ocular ciliopathies by targeted next-generation sequencing, including all IFT-B encoding genes.

Results: Consequently, we identified a homozygous mutation in *IFT81* affecting an obligatory donor splice site in an individual with nephronophthisis and polydactyly. Further, we detected a loss-of-stop mutation with extension of the deduced protein by 120 amino acids in an individual with neuronal ceroid lipofuscinosis-1 (CLN1). This proband presented with retinal dystrophy and brain lesions including cerebellar atrophy, a phenotype to which the *IFT81* variant might contribute. Cultured fibroblasts of this latter affected individual showed a significant decrease in ciliated cell abundance compared to controls and increased expression of the transcription factor GLI2 suggesting deranged sonic hedgehog signaling.

Conclusions: This work describes identification of mutations of *IFT81* in individuals with symptoms consistent with the clinical spectrum of ciliopathies. It might represent the rare case of a core IFT-B complex protein found associated with human disease. Our data further suggest that defects in the IFT-B core are an exceedingly rare finding, probably due to its indispensable role for ciliary assembly in development.

TH-PO218

Loss of Aatf in Murine Tubular Cells Leads to a Nephronophthisis-Like Phenotype Manaswita Jain,¹ Heide Irene Heinen,¹ Heike Goebel,² Bernhard Schermer,¹ Thomas Benzing,¹ Katja Hoepker.¹ ¹Internal Medicine II, Univ Hospital Cologne, Cologne, Germany; ²Dept of Pathology, Univ Hospital Cologne, Cologne, Germany.

Background: Genomic integrity is continuously being challenged by DNA damage of endogenous or exogenous sources. Aatf is a key regulator of the tumor suppressor p53 in the DNA-damage response signaling cascade. Aatf inhibits the ability of p53 to transactivate pro-apoptotic target genes. The conventional knockout of Aatf in mice is pre-implantation lethal. A central role of DNA-damage signaling in tubular cells and cystic kidney diseases has been suggested. Here we show that deletion of Aatf in developing distal tubular and collecting duct cells leads to a degenerative, cystic phenotype, much alike juvenile nephronophthisis.

Methods: Conditional knockout mice, histology, phenotypic analysis.

Results: Aatf was knocked out using the Ksp:Cre mouse line in a floxed Aatf genetic background. The homozygous Aatf deletion results in weight loss and kidney failure at the age of 6-10 weeks. The mice show polyuria, polydipsia and have a reduced urine osmolality. Their kidneys are small, pale and show small cysts predominantly at the cortico-medullary border. Histological examination shows tubular and glomerular cysts and interstitial fibrosis as well as an increased rate of apoptotic cell death.

Conclusions: Altering the outcome of the p53-driven DNA-damage response in the Ksp:Cre:Aatf knockout leads to clinical and histological signs of juvenile nephronophthisis that links DNA damage response signaling close to cystic kidney disease.

Funding: Government Support - Non-U.S.

TH-PO219

Proliferation and Polarization in Regulation Interstitial Macrophage Proliferation and Polarization During Kidney Maturation and Injury Cheng 'Jack' Song,¹ Kurt Zimmerman,¹ Michal Mrug,² Bradley K. Yoder.¹ ¹Dept of Cell Developmental and Integrative Biology, Univ of Alabama at Birmingham, Birmingham, AL; ²Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Induction of cilia loss in juvenile mice results in rapid cyst development while induction of cilia loss in adult mice causes a much slower rate of cyst progression. Rapid cyst formation can be initiated in the adult-induced IFT mutants by ischemic reperfusion (IR) injury suggesting a possible role for inflammation in cyst development. This was recently confirmed by liposome clodronate (LC) mediated depletion of phagocytic macrophages that reduced cyst severity and improved renal function. However, the crosstalk between primary cilia located on epithelial cells and the interstitial macrophages during cyst progression is unknown. Here, we investigate potential connections between primary cilia associated cystogenesis and changes in macrophage populations.

Results: Our preliminary data suggest the presence of a kidney resident macrophage population, likely derived from the yolk sac, which are present in juvenile mice and re-emerge in adult-induced cilia mutants following IR injury. Renal resident macrophage demonstrates rapid proliferation following IR injury in adult-induced IFT88 mutant mice as early as 3 days following injury and persists for at least day 21. In contrast, resident macrophages from control mice show peak proliferation 3 days following IR injury that then abates at days 7-21.

Conclusions: This work suggests communication between the cilia on epithelial cells and the resident macrophages is important for kidney maturation and repair after injury. Our prediction is that defects in this communication will result in persistent resident macrophage proliferation that contributes to the rate of cyst formation. This work will provide possible targets for therapeutic intervention.

Funding: NIDDK Support

TH-PO220

Ciliary Trafficking of Polycystin-1 and Polycystin-2 Is Interdependent Chong Luo, Maoqing Wu, Wassim El-jouni, Jing Zhou. *Harvard Center for Polycystic Kidney Disease Research and Renal Div, Dept of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: Mutations in *PKD1* account for over 85% cases of autosomal dominant polycystic kidney disease (ADPKD). About 30% of the *PKD1* mutations are missense mutations which likely produce full-length proteins that are defective in trafficking to the primary cilia. We have recently shown that multiple sequences including a coiled-coil (CC) motif in the C-terminal tail of PC1 regulate full-length PC1 trafficking to primary cilia. PC1 remains to traffic to the primary cilia in cells depleted of PC2. The proteolytic cleavage at the GPS site of PC1 is not required for its ciliary trafficking.

Methods: A set of deletion/mutation constructs in mouse PC1 including those corresponding to ADPKD patient-derived mutations, as well as chimeric constructs with different mPC1 C-terminal motifs were developed. Transient transfection and immunostaining methods were used.

Results: We found that all pathogenic mutations we tested are defective in ciliary trafficking. Ciliary localization of full-length PC1 or its mutants is completely abolished in PC2 knockout cells. However, this defect can be rescued by co-expression of PC2 in a dose dependent manner. Overexpression of PC2 even drives the C-tail-less PC1 mutant to the primary cilia in IMCD-3 cells. This promotion doesn't rely on the previously identified ciliary targeting VxPx motif at the N-terminus of PC2. The ciliary targeting of PC2 is also

regulated by the dose of PC1. Analyses of the C-tail of PC1 also led to the identification of a potential ciliary targeting sequence within the C-terminal tail of PC1 in addition to the previously identified VxPx motif. This sequence is sufficient to drive a chimeric construct to the cilia in IMCD-3 cells and is independent of the presence of PC2.

Conclusions: Ineffective ciliary trafficking of PC1 may represent a pathogenic mechanism of ADPKD. The mechanisms of polycystins trafficking to the primary cilia are complex involving multiple motifs and factors. Ciliary trafficking of full-length PC1 and PC2 are interdependent, they mutually promote each other to traffic to the primary cilia.

Funding: NIDDK Support

TH-PO221

Anoctamin 6 Is Localized in the Primary Cilium of Renal Tubular Cells and Is Involved in Apoptosis-Dependent Cyst Lumen Formation Bjoern Buchholz,¹ Victoria Forschbach,¹ Margarete Goppelt-struebe,¹ Karl Kunzelmann,² Rainer Schreiber,² Andre Kraus,¹ Kai-Uwe Eckardt.¹ ¹Dept of Nephrology, Univ Erlangen-Nuernberg, Erlangen, Germany; ²Dept of Physiology, Univ Regensburg, Regensburg, Germany.

Background: Anoctamin (ANO) 6 is a member of a novel family of Ca²⁺-activated Cl⁻ channels. Although ANO6 is the most widely expressed paralogue, only little is known about its subcellular localization. Recently, we could show that ANO6 together with ANO1 is expressed in renal cyst-lining cells. Unlike ANO1, which was involved in cyst expansion, the role of ANO6 remained elusive. Therefore, we analyzed the localization of ANO6 in renal tubular cells and tested for a role in cyst formation.

Methods: We stained polarized MDCK cells for ANO6 in comparison to stably ANO6-deficient cells. In addition, we analyzed human collecting duct (HCD) cells and primary human tubular cells to test for species- and segment-specific expression. We also examined the effect of ANO6 deficiency on MDCK cyst formation and performed Ussing chamber experiments to test for changes in transepithelial Cl⁻ secretion. Additionally, we stained kidney sections comprising healthy and cystic tissues from ADPKD patients for ANO6.

Results: ANO6 was localized in the primary cilium of all tubular cells irrespective of species or tubular origin. In addition, ciliary localization of ANO6 could be detected in human kidneys. ANO6 knockdown resulted in loss of ciliary ANO6 signals but had no effect on ciliogenesis or MDCK cyst growth. In line with these data, ANO6-deficient MDCK cells revealed no alteration in Ca²⁺-dependent Cl⁻ secretion. However, lumen formation was markedly disturbed in ANO6-deficient cysts which could be referred to an increased number of cells situated within the cyst lumen which normally would get removed by apoptosis. However, ANO6-deficient cells showed a strong reduction of Ca²⁺-dependent phospholipid scrambling as well as TUNEL- and Caspase3 signals. In addition, apoptotic cyst cells in human ADPKD were characterized by strong co-expression of ANO6.

Conclusions: ANO6 is a ciliary protein and involved in apoptosis-dependent cyst lumen formation.

Funding: Government Support - Non-U.S.

TH-PO222

Regulation of Cilia Function by Protein Palmitoylation Kasturi Roy, Levente Jozsef, Ethan P. Marin. *Internal Medicine / Nephrology, Yale School of Medicine, New Haven, CT.*

Background: Cilia are microtubule based protrusions of the plasma membrane which serve sensory and signaling functions. Abnormalities in cilia cause diseases known as ciliopathies, which include autosomal dominant polycystic kidney disease and nephronophthisis. Many ciliopathies involve abnormal trafficking of proteins to cilia. Trafficking of proteins may be affected by cysteine palmitoylation, the reversible post-translational attachment of the lipid palmitate to proteins. Since numerous cilia proteins are palmitoylated, here we have explored the role of palmitoylation in cilia function and protein trafficking. As a model, we have used Arl13b, a palmitoylated monomeric G protein that localizes to cilia and that causes a ciliopathy in humans when mutated.

Methods: Mouse inner medullary collecting duct cells (IMCD3) were used as a model system to study cilia structure and function. A combination of genetic engineering, biochemical, and microscopic approaches were used to determine Arl13b palmitoylation status, localization, and effects on cilia formation.

Results: IMCD3 cells engineered using CRISPR/Cas9 to have mutations disrupting the Arl13b gene did not form cilia unlike the WT parent cells. Preventing palmitoylation of Arl13b by mutagenesis or by chemical inhibitors blocked trafficking to the cilia. Introduction of a myristoylation site restored proper localization of palmitoylation-deficient Arl13b. In order to identify enzymes involved in Arl13b palmitoylation, we characterized localization and activity of all 24 ZDHHC family protein acyl transferases. Five were found to increase Arl13b palmitoylation at least 3-fold. Further, several were found to be expressed in a compartment proximal to the cilia.

Conclusions: These data collectively show that Arl13b is necessary for cilia formation in IMCD3 cells, and that palmitoylation is as a key regulator of Arl13b localization. Further, these studies identify acyl transferase enzymes that may be novel regulators of Arl13b and thus cilia function. Given the large number of palmitoylproteins in cilia, palmitoylation may be a general mechanism regulating localization of cilia proteins and thus controlling cilia function.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

TH-PO223

Cell Cycle-Dependent Ubiquitylation and Destruction of NDE1 by CDK5-FBW7 Regulates Cilium Biogenesis Dipak Maskey, Leonidas Tsiokas. *Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: The primary cilium is an antenna-like organelle housing numerous signaling pathways. Loss of primary cilia can have opposing effects on cystogenesis: in general, it induces cystogenesis, but it suppresses cyst formation in mouse models of autosomal dominant polycystic kidney disease (ADPKD). Therefore, inhibiting ciliogenic pathways can be beneficial in treating ADPKD. Cilia are formed when cells exit the cell cycle and disassemble when cells re-enter the cell cycle. We have previously identified NDE1 as a suppressor of ciliogenesis and showed that its expression is markedly reduced when cells exit the cell cycle. However, the mechanisms controlling its downregulation upon cell cycle exit are unknown.

Methods: Methods used in the study included Western blotting and co-immunoprecipitations, sire-directed mutagenesis, ubiquitylation assays, and indirect immunofluorescence.

Results: Focusing on the mechanisms mediating its downregulation, we have now discovered a pathway involving the CDK5 kinase and the FBW7 E3 ubiquitin ligase that controls ciliary formation. Specifically, CDK5, which is active only in quiescent cells, phosphorylates NDE1 at a specific site, which is in turn recognized by the FBW7 E3 ligase and targets NDE1 for degradation through the Skp1, Cullin 1, FBW7 (SCF^{FBW7}) ubiquitin ligase. The destruction of NDE1 by SCF^{FBW7} allows ciliogenesis to proceed normally, cilia to reach their appropriate length and function properly. However, when this pathway is inhibited by depletion of FBW7, CDK5, or chemical inhibition of CDK5, NDE1 levels rise causing a reduction in ciliary length and function.

Conclusions: Our study furthers our knowledge on the mechanisms of ciliary formation and function and helps develop new approaches to treat cystic diseases.

Funding: NIDDK Support, Other NIH Support - Oklahoma Center for the Advancement of Science and Technology

TH-PO224

Platelet-Derived PAI-1 Accelerates Podocyte Detachment in FSGS Namiko Kobayashi,^{1,2} Yukina Takahashi,¹ Taiji Matsusaka,³ Michio Nagata.¹ ¹Renal Pathology, Univ of Tsukuba, Tsukuba, Japan; ²Nephrology, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan; ³Depts of Molecular Life Science and Inst of Medical Science, Tokai Univ School of Medicine, Isehara, Japan.

Background: Platelet activation has been shown to be involved in glomerular diseases by releasing cytokines and pro-coagulant factors. In FSGS mice, we have previously shown that PAI-1 is upregulated within the glomerular capillary, which accelerates detachment of remnant podocytes through uPAR-mediated b1 integrin endocytosis. Endothelial cells and platelets are the possible producers of intracapillary PAI-1. Although endothelial cells were involved in the early stage in our study, the role of platelet-derived PAI-1 in FSGS is unknown. Here we tested whether platelet-derived PAI-1 is involved in podocyte loss in FSGS mice.

Methods: We used an immunotoxin inducible FSGS model, NEP25 mice. NEP25 mice were injected with immunotoxin (LMB2, 4 ng/g body weight) on day 0 and treated with 2 mg of anti-mouse platelet antibody (Ab group, n=10) or PBS (C group, n=10) on day-1,4,9. Proteinuria, histology, and PAI-1 localization were examined on day 1 and 12. The WT-1-positive cell number was counted on day -1 and 12.

Results: Platelet depletion decreased proteinuria (P < 0.05) with the protection of podocyte number on day 12 (3.15 ± 0.21 in Ab group vs. 1.55 ± 0.27 in C group, P < 0.05). Glomerular PAI-1 mRNA expression was increased on day 1 in both groups, but it was decreased on day 12 in Ab group (0.14 ± 0.02 in Ab group vs. 1.0 ± 0.23 in C group, P < 0.05). Immunostaining showed glomerular PAI-1 was colocalized with CD31 (endothelial cell marker), but not with CD41 (platelets marker) on day 1 in both groups. PAI-1 was colocalized with CD41, and occasionally with synaptotodin, but not with CD31, on day 12 in C group.

Conclusions: In podocyte injury, PAI-1 was initially induced in the endothelial cells and shifted to the platelets later. Since intracapillary PAI-1 has been shown to promote additional podocyte detachment via integrin endocytosis, inhibition of platelets is a plausible strategy to slow progression of FSGS.

TH-PO225

Podocyte Knockdown of Plasminogen Activator Inhibitor-1 (PAI-1) Is Insufficient to Replicate Protective Effect of Systemic PAI-1^{-/-} in Chronic Kidney Disease Tareq M. Altuhafi,¹ Jae Won Yang,¹ Taiji Matsusaka,² Haichun Yang,¹ Agnes B. Fogo.¹ ¹Dept of Pathology, Microbiology, and Immunology, Vanderbilt Univ, Nashville, TN; ²Dept of Molecular Life Science, Tokai Univ School of Medicine, Isehara-shi, Kanagawa, Japan.

Background: Podocyte injury is a major trigger for glomerulosclerosis. PAI-1 is upregulated in injured podocytes and sclerosing glomeruli. We assessed the role of podocyte vs. systemic PAI-1 in a primary podocyte injury model.

Methods: We generated a podocyte injury model with intact (PAI-1^{+/+}/Nep25, n=8) or systemic PAI-1 deficiency (PAI-1^{-/-}/Nep25, n=8) by crossing wild type or PAI-1^{-/-} with Nep25 mice, which express human CD25 receptor on podocyte and develop sclerosis after immunotoxin (LMB2) injection. We also generated podocyte PAI-1 knock down mice (PAI-1^{loxexel}/Podocin Cre/Nep25, n=7) and its control (PAI-1^{loxexel}/Nep25, n=7) by mating PAI-1^{loxexel/loxop}/teTO-Cre⁺/Podocin-rTA⁺ with PAI-1^{loxexel/loxop}/Nep25 mice. Doxycycline was given from day -7 till day 10. All mice received LMB2 at day 0, and were sacrificed at day 10.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Results: Nep25 mice with systemic PAI-1 deficiency had less body weight increase, an index of edema, but similar proteinuria, when compared to those with intact PAI-1, and also had more preserved podocytes, as shown by higher synaptopodin expression and glomerular WT-1⁺ density (PAI-1^{-/-}/Nep25 5.07±0.17 vs. PAI-1^{+/+}/Nep25 2.59±0.22x10³/μm², p<0.05). Total glomerular CD44 positivity, a marker for activated parietal epithelial cells (PEC), was increased in PAI-1^{-/-}/Nep25 vs PAI-1^{+/+}/Nep25 (5.06±0.35 vs 3.84±0.36/glom, p<0.05). In contrast, Nep25 mice with podocyte specific PAI-1 knockdown had similar edema and proteinuria as its control, and WT1⁺ density and glomerular CD44 positivity were not different between PAI-1^{flloxid}/Podocin Cre/Nep25 and PAI-1^{flloxid}/Nep25. However, synaptopodin was higher in mice with podocyte PIA-1 knockdown vs its control (3.82±0.87 vs 1.98±0.23%, p<0.05).

Conclusions: We conclude that podocyte PAI-1 knockdown was insufficient to produce a similar protective effect as seen in systemic PAI-1 knockout in a podocyte-specific kidney injury model. We speculate that this may partially relate to PEC to podocyte transition.

Funding: NIDDK Support

TH-PO226

Reversal of Podocyte Loss in Mice with Membranoproliferative Glomerulonephritis (MPGN) by Imatinib Noppanit Pattanachaiwit, Masayuki Iyoda, Tomasz A. Wietecha, Kelly L. Hudkins, Charles E. Alpers. *Univ of Washington, Seattle, WA.*

Background: Mice transgenic for thymic stromal lymphopoietin (TSLP-Tg) develop cryoglobulinemia and MPGN. Platelet-derived growth factor (PDGF)-D, expressed by podocytes in humans, with its receptor (PDGFR-β) are likely mediators of mesangial expansion in MPGN. Inhibition of PDGFR-β by imatinib, a tyrosine kinase inhibitor, reduces mesangial proliferation in TSLP-Tg mice. The importance of podocyte loss and PDGF-D expression in MPGN are currently unknown. This study sought to identify possible podocyte loss and investigate the effect of imatinib on podocyte density in mice with MPGN.

Methods: Three-week old female mice were assigned to three groups: TSLP-Tg mice treated with imatinib (50 mg/kg) daily by intraperitoneal injection for eight weeks; control TSLP-Tg mice treated with sterile water; and wild type (WT) control mice. Podocytes were identified by immunohistochemical stain (IHC) for p57, and their density morphometrically quantitated. Expression of PDGF-D and PDGFR-β was detected by IHC. Albuminuria was measured from timed urine samples.

Results: Podocyte density in TSLP-Tg mice was significantly less than WT controls (182.67 ± 21.15 vs 278 ± 6.19 podocytes/10⁶ μm², p = 0.005), and was markedly increased by imatinib (249.17 ± 14.49, p = 0.029). TSLP-Tg mice had significantly increased mesangial (but not podocyte) expression of PDGF-D (248.23 ± 40.75 μm²) and slightly increased PDGFR-β expression (192.91 ± 17.31) compared to WT controls (124.17 ± 10.46, p = 0.028 and 175.55 ± 6.61, p = 0.388 respectively). The overexpression of PDGF-D was significantly reduced (129.02 ± 10.95, p = 0.025) whereas the expression of PDGFR-β was increased after imatinib treatment (260.51 ± 18.62, p = 0.024). Albuminuria in TSLP-Tg mice was higher than WT controls (16.6 ± 4.66 vs 4.23 ± 0.76 μg/24 h, p = 0.036), and was decreased by imatinib (4.97 ± 1.64, p = 0.049).

Conclusions: This study demonstrates podocyte loss in MPGN. Restoring podocyte number may be a key to reversal of MPGN. Imatinib largely reversed podocyte loss and reduced mesangial injury, PDGF-D overexpression and albuminuria in TSLP-Tg mice. Unlike humans, mesangial cells rather than podocytes express PDGF-D in mice.

Funding: NIDDK Support

TH-PO227

Role of Epithelial Membrane Protein 2 in Nephrotic Syndrome Michael D. Donnan, Rizaldy P. Scott, Tuncer Onay, Anna Woo, Susan E. Quaggin. *Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.*

Background: Mutations in the human gene EMP2 (Epithelial Membrane Protein 2) have recently been linked to childhood-onset nephrotic syndrome. Its gene product, a tetraspan integral membrane protein, affects various cell behaviors including regulation of cell adhesion, migration, proliferation, apoptosis and tumorigenesis. EMP2 protein modulates the expression of GPI-anchored proteins, caveolin-1, integrin, and the growth factor VEGFA. EMP2 is also necessary for embryo implantation and chlamydial infectivity. We studied the renal expression pattern of EMP2 and generated a conditional EMP2 knockout (KO) mouse as first steps towards understanding its role in glomerular disease.

Methods: We created a floxed *Emp2* (*Emp2*^{2lox/lox}) mouse containing a LacZ reporter gene controlled by the endogenous *Emp2* promoter. We assessed *Emp2* expression in kidneys using whole-mount β-galactosidase (β-gal) histochemistry. To complement this analysis, we used an antibody against EMP2 to assess its localization by immunofluorescence (IF). Podocyte-specific KO mice (*Emp2*^{2lox/lox}) were generated by breeding *Emp2*^{2lox/lox} mice to the *Nphs1-Cre* driver strain and were assessed for proteinuria.

Results: β-gal staining reveals that *Emp2* is prominently expressed within major vascular bundles and a distinct band of cells within the cortex and renal papillae. Double-label IF using an EMP2 antibody and Lotus lectin suggests that the *Emp2* expression within the renal cortex is in proximal tubules. The EMP2 antibody did not stain the renal papilla or renal vasculature. Whether this disparity is due to cell-specific post-translational modification (e.g. glycosylation) remains to be addressed. However, in both β-gal and IF assays *Emp2* within the glomerulus was not seen. By 3 months of age, *Emp2*^{2lox/lox} do not have proteinuria.

Conclusions: In contrast to a previous report, we did not observe *Emp2* expression in podocytes while *Emp2*^{2lox/lox} mice do not develop overt kidney disease. Genetic deletion of *Emp2* in tubular and endothelial compartments will provide additional insights regarding the etiology of renal dysfunction in patients with EMP2 mutations.

TH-PO228

Discovery of Mesencephalic Astrocyte-Derived Neurotrophic Factor as a Urine Biomarker for Endoplasmic Reticulum Stress-Related Kidney Diseases Yeawon Kim,¹ Heedoo Lee,¹ Scott R. Manson,² Jeffrey H. Miner,¹ Fumihiko Urano,³ Ying Maggie Chen.¹ ¹Renal Div, Washington Univ, St. Louis, MO; ²Div of Urology, Washington Univ, St. Louis, MO; ³Div of Endocrinology, Metabolism and Lipid Research, Washington Univ, St. Louis, MO.

Background: Accumulating evidence has highlighted the important role of endoplasmic reticulum (ER) stress in the pathogenesis of a variety of kidney diseases. Thus, it is imperative to develop non-invasive biomarkers for detecting ER stress in podocytes or tubular cells in the incipient stage of disease, when clinically a kidney biopsy is not yet indicated. Moreover, restoration of ER homeostasis before irreversible kidney cell injury may hold significant promise as an attractive therapeutic strategy. Here for the first time we discovered mesencephalic astrocyte-derived neurotrophic factor (MANF) as a potential urine biomarker for detecting ER stress in associated kidney diseases.

Methods: We used mouse models of human nephrotic syndrome (NS) caused by podocyte ER stress and of acute kidney injury (AKI) triggered by the ER stressor tunicamycin or ischemia/reperfusion (I/R)-induced tubular ER stress.

Results: In our NS mouse model carrying the C321R laminin β2 (LAMB2) mutation in podocytes, podocyte ER stress was induced. The mutants exhibited MANF induction in podocytes at P24, when proteinuria was minimal, compared with controls. *In vitro*, secretion of MANF by mutant primary podocytes was increased as compared to that by control podocytes. Most importantly, MANF was easily detected in the crude urines of C321R mutants in the incipient stage of disease as compared to the controls. Meanwhile, in tunicamycin or I/R-induced AKI mouse models, urinary MANF excretion concurrent with tubular cell ER stress preceded clinical or histological manifestations of acute tubular injury.

Conclusions: MANF can potentially serve as a urine biomarker to help stratify disease risk and predict disease progression in the ER stress-related kidney diseases. In addition, MANF can help identify subgroups of patients who can be treated with ER stress modulators and monitor treatment response in a highly-targeted manner.

Funding: NIDDK Support, Other NIH Support - UL1TR000448, Private Foundation Support

TH-PO229

Identification of Differentially Expressed Genes in Rat Puromycin Aminonucleoside (PAN) Nephropathy, a Mimic of MCNS with Next-Generation Sequencing Yoshiyasu Fukusumi, Hiroshi Kawachi. *Dept of Cell Biology, Inst of Nephrology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: To explore the novel therapeutic targets of nephrotic syndrome resulted from podocyte dysfunction, we intend to identify the molecules of which gene expression is changed in rat nephrotic models by the Next-Generation Sequencing analysis.

Methods: The profile of gene expression of PAN nephropathy was analyzed by next generation high-throughput RNA sequencing (RNA-Seq) with Solid system 5500. 581 molecules, whose mRNA was clearly altered (more than 5 times increase or less than 20% decreased to normal level), were identified. 20 molecules, which were expected to play a role in maintaining podocyte function, were selected, and the kinetic of the mRNA expression of these molecules were precisely analyzed in several nephrotic models including anti-nephrin antibody (ANA)-induced nephropathy, a proteinuric model caused by the disarrangement of the SD molecules, and in ADR nephropathy, a mimic of FSGS, as well as PAN nephropathy.

Results: In PAN nephropathy, mRNA expression of 153 genes were increased (> 5 times) at 1 h when abnormal proteinuria was not detected yet. mRNA expressions of 121 genes were increased on day 10 when proteinuria peaked. mRNA expressions of 37 genes were increased both time points. 297 genes, whose mRNA expression was lowered to less than 20%, were identified. mRNA expressions of 186 genes were decreased similarly on day 10, and those of 121 genes were decreased at both 1h and day 10. For further analyses Phospholipase A2, group IID (Pla2g2d) and proto cadherin alpha 5 (Pcdha5) were focused. mRNA expression of Pla2g2d was decreased to 11% at 1h and 13 % on day 10 of PAN nephropathy. mRNA expression of Pcdha5 was decreased to 2.7% at 1h and 1.5% on day 10 of PAN nephropathy and 15% on day 5 of ANA nephropathy, whereas the mRNA expression was clearly increased on day 5 of ADR nephropathy.

Conclusions: RNA-Seq is a powerful tool for profiling gene expression and the detection of differentially expressed gene in proteinuric state. It is assumed that the decrease in the mRNA expression of Pla2g2d and Pcdha5 is involved in the development of proteinuria.

Funding: Government Support - Non-U.S.

TH-PO230

Comprehensive Polysome Analysis in Injured Podocytes Masahiro Okabe,^{1,2} Yoichi Miyazaki,² Takashi Yokoo,² Masafumi Fukagawa,¹ Taiji Matsusaka.¹ ¹Tokai Univ School of Medicine, Isehara, Japan; ²Jikei Univ School of Medicine, Tokyo, Japan.

Background: Podocyte injury is the key event for progressive renal failure. It is difficult to isolate the RNA of podocytes from the kidney, which is made up with multiple-type cells.

Methods: To solve this problem, we used Ribotag transgenic mouse line (established by Dr. Amieux PS), in which HA-tag is inserted into the C-terminus of Rpl22, a component of the ribosomal protein, in the presence of Cre recombinase. Ribotag line was mated with nephrin-Cre and NRP25, an immunotoxin-inducible podocyte-selective injury model.

Glomeruli were isolated before or after induction of podocyte injury. Podocyte-specific polysome was yielded by immunoprecipitation with anti-HA antibody and analyzed by Agilent's 8X66K microarray (n=12) and qRT-PCR (n=8).

Results: In a basal condition, microarray analysis revealed 5070 (9.1%) probes were significantly and more than 2-fold enriched in podocytes within the glomerulus, which include most known podocyte genes. qRT-PCR confirmed that Nphs1 and Nphs2 RNAs were concentrated in podocytes (15 and 8.6-fold), while mesangial and endothelial RNAs were diluted. Seven days after immunotoxin injection, 3130 (5.6%)/1938 (3.5%) probes were significantly and more than 2-fold up/down-regulated in podocytes from the basal condition. Nphs1, Podxl, Synpo and Wt1 were decreased (0.37, 0.39, 0.28 and 0.49-fold), and Des, Relb, Gadd45b and Cxcl1 were markedly upregulated (8.1, 6.9, 20 and 160-fold), which were confirmed by qRT-PCR. These changes were significantly correlated with those in Actn4 KO podocytes reported in TRAP study (R=0.520, p<0.001), suggesting that these represent common pathogenic responses. Separately, reviewing 84 published CKD candidate genes identified by GWAS, thirteen, including Vegfa, were found concentrated in normal podocytes whereas Dach1 and Af3 decreased after podocyte injury (0.42, 0.64-fold) similarly to Vegfa (0.28-fold), suggesting their important functional role in podocytes.

Conclusions: Thus, these comprehensive data provide potentially important insights for understanding podocyte pathophysiology.

Funding: Government Support - Non-U.S.

TH-PO231

Expression of Mouse uPAR Alternative Isoform 2 Produces a Dimeric Protein and Severe Renal Disease Changli Wei,¹ Brian D. Adair,² Jing Li,¹ Liu Shuangxin,¹ Nicholas J. Tardi,¹ Jochen Reiser.¹ ¹Rush Univ Medical Center; ²Massachusetts General Hospital, Harvard Medical School.

Background: Soluble urokinase receptor (suPAR) has been proposed as a circulating factor in focal segmental glomerulosclerosis (FSGS) by direct activation of podocyte aVb3 integrin. Mouse secretive uPAR isoform 2 (msuPAR) is an alternatively spliced uPAR variant. This study was aimed to evaluate the ability of this isoform to function as a circulating factor.

Methods: For structural study, msuPAR was cloned from podocytes, and expressed in HEK cells with a Flag tag. The recombinant msuPAR protein was purified with Flag beads and analyzed by electron microscopy (EM). For functional study, a transgenic mouse model was created that drives msuPAR expression from adipocytes with consequent release into circulation.

Results: Negative-stain EM and single particle image analysis reveal that msuPAR protein forms a compact, well-defined structure in solution, which is formed by a dimer of two globular domains. The three-dimensional reconstruction shows one of the domains, which provides a good fit for domain 1, connected to the other globular domain in an open conformation, in contrast with the tight closed conformation seen in crystal structures of the intact protein (isoform 1). msuPAR transgenic mice are fertile and they start to develop proteinuria 1 month after birth. With rising serum msuPAR level, progressive proteinuria develops in most animals. By 7 to 8 months old, about 20% of msuPAR transgenic mice developed FSGS-type lesions, while 80% of mice showed mild glomerular damages. Transmission EM analysis showed variant degree of podocyte foot process effacement that correlated to the proteinuria and the light microscopy changes. Analysis of serum level of the inflammatory marker, CRP or IL-6 did not distinguish msuPAR transgenic mice from littermate control. Glomerular b3 integrin activity however was significantly increased in msuPAR transgenic mice.

Conclusions: The mouse secretive isoform uPAR 2 forms a dimeric protein with globular domains. Its expression in transgenic mice results in increased podocyte integrin activation and progressive renal disease with a spectrum from minimal change to FSGS type kidney lesion.

Funding: NIDDK Support, Pharmaceutical Company Support - Therumo BCT

TH-PO232

Sildenafil-Dependent Reduction of TRPC6 Expression, Podocyte Injury and Proteinuria Is Mediated via PPAR γ Ramon Sonneveld,¹ Joost Hoenderop,² Carole Hénique,³ Jo H.M. Berden,¹ Pierre-Louis Tharoux,³ Johan Van der Vlag,¹ Tom Nijenhuis.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; ³Cardiovascular Research Centre, INSERM, Paris, France.

Background: Increased transient receptor potential channel C6 (TRPC6) activity in the podocyte leads to glomerular injury and proteinuria. Sildenafil (Viagra®) is used to treat erectile dysfunction and pulmonary arterial hypertension where it reduces TRPC6 activity and expression. The nuclear receptor PPAR γ is a downstream target of sildenafil via the cGMP-activated protein kinase G (PKG) axis. PPAR γ agonists like Pioglitazone (Pio) may be antiproteinuric. We hypothesized that sildenafil has renoprotective effects, with PPAR γ as central mediator modulating TRPC6 expression and activity in podocytes.

Methods: Using pharmacological compounds in cultured podocytes, rat and mouse models, the role of the PPAR γ -PKG in mediating TRPC6 expression/activity was tested.

Results: TRPC6 expression was upregulated in adriamycin-injured podocytes, which was dose-dependently downregulated by sildenafil, the cGMP derivative 8-Br-cGMP or the PPAR γ agonist Pio. The PKG blocker KT5823 or the PPAR γ antagonist GW9662 enhanced TRPC6 expression. The effects of sildenafil and 8-Br-cGMP were counteracted by inhibition of PKG by KT5823 and PPAR γ by GW9662. The effect of Pio was negated only by GW9662. Similar results were shown for TRPC6 promoter activity and calcium influx. Chromatin immunoprecipitation showed binding of PPAR γ to the TRPC6 promoter. Healthy rats treated with GW9662 showed proteinuria and upregulation of TRPC6 expression in the

podocytes, which was also observed in podocyte-specific PPAR γ knock-out mice. Renal injury and increased TRPC6 expression in adriamycin induced nephropathy rats could be prevented by sildenafil and Pio treatment.

Conclusions: Amelioration of podocyte injury by sildenafil involves cGMP- and PKG-dependent binding of PPAR γ to the TRPC6 promoter, thereby inhibiting TRPC6 promoter activity, expression and activity. Our data identify sildenafil as a novel antiproteinuric agent, which acts by inhibiting deleterious TRPC6-mediated intracellular podocyte signaling.

TH-PO233

APOL1 Risk Variants Enhance Initiation but Retard the Terminal Part of Autophagy in Podocytes Xiqian Lan,¹ Hongxiu Wen,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,² Pravin C. Singhal.¹ ¹Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; ²Medicine, Rambam Health Care Campus, Haifa, Israel.

Background: Patients with APOL1 Variants carry 10 fold higher chance for the development of HIVAN if not on antiviral therapy. HIV is known to hijack autophagy in the host cells-enhancement of autophagosome formation (the site of viral replication) but inhibits the delivery of autophagosomal cargo (AC) to the lysosomes and thus, prevents viral degradation. Since podocytes are terminally differentiated cells their protein homeostasis is tightly regulated by autophagy. We hypothesized that APOL1 risk variants would also have potential for augmenting the initial phase but would inhibit the terminal phase of autophagy.

Methods: We used human podocytes (HPs) stably expressing APOL1G0, G1, or G2 (Vec/HPs, G0/HPs, G1/HPs, and G2/HPs). Pseudo type HIV or empty vector (control) virus was transduced into Vec/HPs, G0/HPs, G1/HPs and G2/HPs. After 48 h, cells were harvested and assayed for vacuolar density (number of autophagosomes) by staining with acridine orange or monodansylcadaverine (MDC). Protein blots of HPs (Vec, G0, G1, and G2) were probed for mTOR (pathway modulating autophagy), beclin-1 and LC3-II (markers of early steps of autophagy), p62 (marker of degradation of AC) and reprob for actin. HPs were co-labeled for APOL1 and endosomal/lysosomal markers to delineate route of APOL1.

Results: G0/HPs, G1/HPs and G2/HPs displayed greater number of autophagosomes when compared to Vec/HPs. Protein blots of G1/HPs and G2/HPs demonstrated enhanced expression of LC3II and beclin-1 and thus indicating enhancement of initiation of autophagy. Protein blots of G1 and G2/HPs also displayed enhanced expression of p62, which indicated that AC did not reach to lysosomes. Additionally, G1/HPs and G2/HPs showed attenuated mTOR expression. HIV expression by G1/HPs and G2/HPs further enhanced early markers of autophagy but displayed further attenuation of lack AC at lysosomal compartment. Co-labeling studies of APOL1 revealed decreased presence of APOL1 in lysosomal compartment.

Conclusions: APOL1 risk variants enhance initiation but inhibit terminal phase of autophagy both in control and HIV stimulated states.

TH-PO234

Disparate APOL1 Expression in HIV-Associated Nephropathy Reflects Podocyte Injury Xiqian Lan,¹ Hongxiu Wen,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,² Pravin C. Singhal.¹ ¹Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; ²Medicine, Rambam Health Care Campus, Haifa, Israel.

Background: ApolipoproteinL1 (APOL1) variants G1 and G2 contribute to the higher percent of kidney diseases in African Americans. Renal biopsy specimens in patients of focal segmental glomerulosclerosis (FSGS) and HIV-associated Nephropathy (HIVAN) revealed lower expression of APOL1 by podocytes but higher expression by vascular smooth muscle cells (VSMC). The involved mechanisms for disparate expression of APOL1 by two different cell types in the affected population is not clear. We hypothesized that modulation of APOL1 expression is a marker of ongoing podocyte injury.

Methods: Human podocytes (HPs) and VSMCs were transduced with equal amounts of lentivirus (vector, G0, G1, and G2) and cultured for 48 hours. Subsequently, cells were evaluated for reactive oxygen species (ROS) generation (DCFDA loading and co-labeling with mitotracker green and Red CC1), viability (MTT/Trypan blue assays), apoptosis, and necrosis (morphologic assay by staining with H33342 and propidium iodide). VSMC proliferation was determined by cell counting and labeling for PCNA. In parallel sets of experiments, APOL1 expression in these cells was quantified by Western blotting analysis.

Results: Compared to Vector and G0, HPs expressing G1 and G2 displayed higher rates of ROS generation, enhanced loss of cell viability, greater number of apoptosed and necrosed cells. HPs transduced with G1 and G2 displayed lower expression of APOL1 when compared to G0. VSMCs transduced with G0, G1, and G2 displayed comparable expression of APOL1 expression. VSMCs transduced with either G0 or G1/G2 displayed minimal loss of viability, number of apoptosed or necrosed cells, but they displayed greater number of proliferating cells when compared to Vector transduced HPs.

Conclusions: APOL1 variants expressing podocytes experience higher degree of oxidative stress but display lower APOL1 expression. On the other hand, VSMCs expressing G1 and G2 experience lesser degree of injury when compared to vector transduced VSMCs. These findings suggest that APOL1 expression by podocytes may be a marker of ongoing stress.

TH-PO235

A Soluble Guanylate Cyclase Activator Is Superior to a Phosphodiesterase Type 5 Inhibitor and a Soluble Guanylate Cyclase Stimulator in Protecting from Diabetic Nephropathy in the ZSF1 Rat *Kathleen A. Lincoln*, Paul Harrison, Hongxing Chen, Hong Wang, Holly Clifford, Hu Sheng Qian, Diane Wong, Christopher Sarko, Ryan M. Fryer, Jeremy G. Richman, Glenn A. Reinhart, Steven S. Pullen, Carine Boustany. *Cardiometabolic Disease Research, Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT.*

Background: Therapies which restore cyclic GMP (cGMP) levels within the kidney are hypothesized to slow disease progression. We evaluated the effects of BI703704, a soluble guanylate cyclase (sGC) activator, EX76637; a sGC stimulator, and EX77619; a phosphodiesterase type 5 (PDE5) inhibitor, on the progression of diabetic nephropathy in obese ZSF1 rats.

Methods: Male ZSF1 rats, implanted with telemetry devices, were treated with either BI703704 at 2 mg/kg, EX76637 at 1 or 3 mg/kg, EX77619 at 5 or 15 mg/kg for 10 weeks, during which mean arterial pressure (MAP) and urinary protein excretion (UPE) were determined. At study end, glomerular and renal interstitial lesions were assessed. Alpha smooth muscle actin (α -SMA, a marker of myofibroblast activation) and p-57 (a marker of podocyte health) were determined by immunohistochemistry. Renal cGMP levels were quantified as a measure of target engagement.

Results: By Week 10, similar reductions in MAP were achieved (~8mmHg) across treatment groups vs. vehicle. In parallel, sGC activation resulted in significant reductions in UPE (-31% vs veh), while there was no significant effect of EX76637 (+4% at 1 mg/kg; -16% at 3 mg/kg vs veh), or EX77619 (-15% at 5 mg/kg; -9% at 15 mg/kg vs veh). Importantly, BI703704's effects on UPE were accompanied by reductions in the incidence of glomerulosclerosis (-21% vs veh), while neither EX76637 nor EX77619 were effective. In addition, interstitial lesions were modestly reduced by BI703704 (-13% vs veh) and EX77619 (-18% vs veh). α -SMA was reduced by BI703704 (-27% vs veh) and EX76637 (-8% vs veh), while P57 was significantly increased by BI703704 (+11% vs veh) but not by EX76637 or EX77619. Importantly, target engagement was confirmed for EX77619.

Conclusions: Despite similar effects on MAP, BI703704 was superior to EX76637 or EX77619 in reducing proteinuria and preventing renal damage in kidneys of ZSF1 rats.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim Pharmaceuticals

TH-PO236

Localization of Phosphodiesterase 4 Isoforms in the Renal Cortex *Xianzhong Lau*, Yuan Zhang, Darren J. Kelly, Robyn G. Langham. *Dept of Medicine (St Vincent's), Univ of Melbourne, Melbourne, Victoria, Australia.*

Background: There are limited therapeutic options for the treatment of chronic kidney disease (CKD). Our recent studies have found that Phosphodiesterase 4 (PDE4) inhibitor rolumilast (RFL) was effective in attenuating renal decline in subtotal nephrectomized (STNx) rats, a model of CKD, indicating that PDE4 inhibition is may be effective in treating CKD. There have been studies on the contribution of cAMP hydrolysis by PDE4 in nephron segments and the mRNA expression distribution of PDE4 isoforms in several cultured renal cells. However, the localization of PDE4 isoforms in the kidney has yet to be explored. Hence, we sought to investigate the distribution of PDE4 isoforms in the renal cortex, as it may also elucidate the renal cell types that RFL targets.

Methods: Sprague-Dawley rats underwent either STNx or sham surgery, further randomized after 2 weeks to receive an oral dose of either RFL (1 mg/kg/day) or vehicle, and sacrificed at 12 weeks. PDE4 isoforms (PDE4A, PDE4B, PDE4C) were localized with immunohistochemistry. Immunofluorescence was used to co-localize PDE4 isoforms with podocytes.

Results: The distribution pattern for each PDE4 isoform was distinct. However, positive staining was mainly localized on the podocytes in the glomerulus (for PDE4A, PDE4B and PDE4C) and distal tubules and in tubulointerstitium (for PDE4A and PDE4C). In the STNx group, positive staining on the podocytes was significantly more intense than the sham group. RFL treatment significantly reduced the elevated expression of PDE4 isoforms in the podocytes.

PDE4 Isoform	Sham	Sham+RFL	STNx	STNx+RFL
PDE4A	3.22±0.49	2.84±0.64	11.38±0.88****	8.44±1.30****
PDE4B	0.38±0.18	0.50±0.17	8.75±1.50****	5.49±1.21**†
PDE4C	2.17±0.31	2.63±0.25	12.44±1.86****	8.01±0.87**†

Conclusions: PDE4 isoforms are distributed throughout the renal cortex, especially in the podocytes and distal tubules. During CKD, the expression of PDE4 isoforms in the podocytes increases. As the reduction in PDE4 expression with RFL treatment was associated with the attenuation of renal decline, PDE4 inhibition may be especially relevant in preserving podocyte health.

Funding: Government Support - Non-U.S.

TH-PO237

The Glomerular Parietal Epithelial Cell Phenotype Depends on SPARC Levels *Shokichi Naito*. *Nephrology, Kitasato Univ School of Medical Sciences, Sagamihara, Kanagawa, Japan.*

Background: Parietal epithelial cell (PECs) might play a critical role in a glomerular repair through their progenitor function. Conversely, PECs might paradoxically contribute to the deterioration of glomerular function by augmentation of scarring and crescent formation under certain conditions. The factors governing these PEC functions are not well understood. We have previously shown that SPARC (secreted protein acidic and rich in cysteine) plays a causal role in mediating podocyte detachment and accelerating glomerulosclerosis in experimental crescentic glomerulonephritis. However, the effect of SPARC levels on PECs is unknown.

Methods: Experimental glomerular disease was induced in aged-matched SPARC^{+/+} and SPARC^{-/-} mice by intraperitoneal injection of a sheep anti-rabbit glomerular antibody. Immunostaining methods were then employed on days 0 and 7 of disease.

Results: The number of PEC transition cells, defined as cells co-expressing a PEC marker (PAX2), and podocyte marker (Synaptopodin) was higher in diseased SPARC^{-/-} mice compared with SPARC^{+/+} mice (1.35 ± 0.18 vs. 0.46 ± 0.14, P < 0.01 vs. SPARC^{+/+} mice). WT1 staining along Bowman's capsule was higher in diseased SPARC^{-/-} mice (2.57 ± 0.30 vs. 1.37 ± 0.30, P < 0.01 vs. SPARC^{+/+} mice). This observation was accompanied by increased PEC proliferation (measured by Ki-67 staining, (4.56 ± 0.46 vs. 2.66 ± 4.99; P < 0.01) and an increase in immunostaining for a progenitor marker, neural cell adhesion molecule (1.35 ± 0.05 vs. 1.21 ± 0.05, P < 0.05 vs. SPARC^{+/+} mice), in a subpopulation of PECs in diseased SPARC^{-/-} mice.

Conclusions: PECs have the potential to become glomerular epithelial transition cells. SPARC expression in PECs favors a decrease in the number of PEC transition cells.

TH-PO238

Low Dose Hydralazine Augments Losartan Mediated Reversal of Epigenetic Alterations in Diabetic Nephropathy (DN) *Himanshu Vashistha*,¹ Nirupama Chandel,² Xi-qian Lan,² Anjali Maheshwari,² Nairuti H. Shah,² Ashwani Malhotra,² Leonard G. Meggs,¹ Pravin C. Singhal.² ¹Medicine, Ochsner Health System, New Orleans, LA; ²Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: Epigenetics has been demonstrated to play a role in the development and progression of DN. Recently, we observed that losartan reverses high glucose-induced podocyte epigenetic alterations. We now hypothesized that low (non-hypertensive) dose hydralazine (HYDZ) will further augment losartan-induced reversal of epigenetic alterations in DN.

Methods: Protein blots of renal tissues/renal cortical sections of 2, 4, and 6 month old control and Akita mice (n=3) were probed for methylation at histone (H3) lysine (K)4 residue, acetylation at H3 lysine (K)9 residue, SNAIL, vitamin D receptor (VDR), and nephrin. *In vitro* studies, protein blots of control and high glucose (30 mM, HG) treated human podocytes (HPs) were probed for SNAIL, VDR, nephrin, H3K4me3, H3K9ac and actin. Podocyte VDR and nephrin gene methylation status (pyrosequencing) and SNAIL binding at VDR and nephrin promoter (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

Results: Protein blots of renal tissues of Akita mice displayed enhanced expression of SNAIL and H3K4me3 but down regulation of VDR and nephrin. Podocytes in renal cortical sections also displayed similar profile; losartan not only decreased proteinuria but also partially reversed epigenetic alterations and associated SNAIL, VDR and nephrin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further augmented these effects when combined with losartan. HG/HPs displayed enhanced expression of SNAIL and H3K4me3 and attenuated expression of VDR, nephrin, and H3K9ac. Both nephrin and VDR displayed more than 70% cytosine methylation. HG/HP displayed deacetylation of nephrin and degradation via ubiquitination. ChIP assay revealed binding of SNAIL at VDR and nephrin promoter.

Conclusions: Optimal reversal of epigenetic alterations can be used as a therapeutic strategy in DN.

TH-PO239

Klotho Ameliorates Proteinuria by Targeting TRPC6 Channels in Podocytes *Jian Xie*,² Ji-Hee Kim,¹ Kyu-Hee Hwang,¹ Yueh-lin Wu,² Noelynn Oliver,³ Chou-Long Huang,² Seung-Kuy Cha.¹ ¹Wonju College of Medicine, Yonsei Univ, Wonju, Korea; ²Dept of Medicine, UT Southwestern Medical Center, Dallas, TX; ³Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT.

Background: Klotho is a type-1 membrane protein mainly produced in the kidney tubules. The extracellular domain of klotho is secreted into extracellular space. Whether klotho is expressed in podocytes and whether and how it may protect the glomerular filter are unknown.

Methods: TRPC6-mediated Ca²⁺ influx, cytoskeletal remodeling, and transepithelial albumin flux were studied in cultured mouse podocytes. Klotho expression in cultured podocytes and the kidney was examined by immunostaining, in situ hybridization, and RNA sequencing. Effects of klotho on albuminuria were studied using mouse models with genetically altered expression of TRPC6 and klotho.

Results: Recombinant secreted soluble klotho suppressed ATP-stimulated, TRPC6-mediated Ca²⁺ influx in cultured mouse podocytes. Cytoprotection by klotho on cultured podocytes is supported by the reduction in ATP-stimulated actin cytoskeletal remodeling

and transepithelial albumin leakage. Overexpression of TRPC6 by gene delivery in mice induced albuminuria, and exogenous administration of soluble klotho ameliorated the albuminuria. Heterozygous klotho-deficient sham-operated mice had no basal albuminuria vs WT sham mice, but het-klotho chronic kidney disease (CKD) mice had aggravated albuminuria compared to that in WT CKD mice with a similar degree of hypertension and reduced clearance function. Klotho is expressed in podocytes of mouse and human kidney. Disrupting the integrity of glomerular filter increased urinary excretion of soluble klotho.

Conclusions: Klotho protects podocytes from injury by suppressing TRPC6-mediated Ca²⁺ entry. Cytoprotection of podocytes in the native state may be through membranous klotho present on podocyte cell surface or soluble klotho present in Bowman's space. Soluble klotho may be a treatment for proteinuria.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO240

Aminopeptidase A Is Up-Regulated in the Intact Areas of Segmentally Sclerotic Glomeruli in Advanced Focal Segmental Glomerulosclerosis Juan Carlos Q. Velez, Michael G. Janech, Wayne R. Fitzgibbon. *Div of Nephrology, Medical Univ of South Carolina, Charleston, SC.*

Background: Angiotensin (Ang) II is involved in the pathogenesis of focal segmental glomerulosclerosis (FSGS). We hypothesized that FSGS may be associated with adaptive changes in glomerular expression of Ang-metabolizing peptidases.

Methods: Using fawn-hooded hypertensive (FHH) rats as a model of FSGS, we examined the pattern of glomerular expression of Ang converting enzyme (ACE) and the robust Ang II-cleaving enzyme aminopeptidase A (APA) by Western blot (WB) and immunohistochemistry (IHC).

Results: ACE was absent in glomeruli by both WB and IHC. Overall expression of APA in glomerular extracts was found to gradually decrease over time, with 87% reduction at 60 weeks compared to 6 weeks of age (p<0.0001). Glomerular extracts from 30 week-old FHH rats had lower APA expression and lower APA activity compared to age-matched Wistar rats (p<0.05). By IHC, 60-week kidneys showed loss of glomerular APA in globally sclerotic glomeruli as well as on the sclerosed area of the segmentally sclerotic glomeruli. On the other hand, the "surviving" intact areas within the segmentally sclerotic glomeruli as well as some normal-appearing glomeruli exhibited a markedly accentuated APA expression. In contrast, the podocyte marker GLEPP1 was not only absent in all sclerotic areas but also attenuated in the intact areas within the segmentally sclerotic glomeruli and in normal-appearing glomeruli, suggesting that APA increases during the late response phase to podocyte injury. To determine whether the APA augmentation corresponded to a feedback response to Ang II, cultured mouse podocytes were incubated with Ang II (100 nM) for 24-72 hours. No change in APA abundance was observed, nor could APA abundance be induced by infusing Ang II in 8-week FHH rats for 4 weeks.

Conclusions: In conclusion, podocyte-localized APA is up-regulated in the "surviving" non-sclerosed segmental areas in glomeruli of FHH rats. However, the mechanism of up-regulation does not appear to be directly mediated by Ang II. Understanding the mechanism of APA up-regulation may provide tools to enhance the actions of a potentially renoprotective peptidase.

Funding: Private Foundation Support

TH-PO241

Anti-VEGF Treatment by Transfection of the Natural Inhibitor sFlt-1 Increases Albuminuria in Type 1 Diabetic Mice Pascal Bus, Jan A. Bruijn, Hans J. Baelde. *Dept of Pathology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands.*

Background: It has been shown that VEGF-A is involved in diabetic nephropathy (DN). In diabetic mice, treatment with anti-VEGF antibodies reduced glomerular hypertrophy. On the other hand, women with pre-eclampsia develop proteinuria due to increased levels of soluble Flt-1 (sFlt-1) – a natural inhibitor of VEGF-A. In this study we investigated the effects of systemic VEGF-A inhibition by sFlt-1 transfection in type 1 diabetic mice.

Methods: Diabetic mice were transfected with an sFlt-1 construct at the onset of diabetes. After five weeks of treatment mice were sacrificed. Collection of urine and blood was performed at baseline, and week 1, 3, and 5. Albuminuria was measured using Rocket Electrophoresis. Kidneys were sectioned and stained for PAS, FA-11 (macrophages) and WT1 (podocytes). Glomerular hypertrophy was measured using Philips Digital Pathology Solutions. One-way ANOVA was performed to measure differences between the groups. Differences with a probability level (P) < 0.05 were considered statistically significant.

Results: Diabetic mice transfected with sFlt-1 had higher albuminuria levels than mice with diabetes alone (p<0.05). However, glomerular hypertrophy as well as the number of glomerular macrophages were reduced in the treated group (p<0.05). No effect on podocyte numbers was observed.

Conclusions: In contrast to other studies investigating VEGF-A, we reduced VEGF levels with the use of a natural inhibitor. In line with previous findings we showed that sFlt-1 treatment reduced glomerular hypertrophy in diabetic mice. In addition, sFlt-1 treatment resulted in higher albumin levels in diabetic mice. These results show that treatment for reducing VEGF-A levels has to be performed with care since treatment has both beneficial and detrimental effects.

TH-PO242

Apolipoprotein C1 Transgenic Mice Develop Gomerulosclerosis: A Potential Role for Macrophages Pascal Bus,¹ Rosalie Bor,¹ Jimmy F. P. Berbee,² Jan A. Bruijn,¹ Emile De Heer,¹ Hans J. Baelde.¹ ¹Dept of Pathology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands; ²Dept of Medicine, Div of Endocrinology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands.

Background: Associations between an APOC1 polymorphism and the development of diabetic nephropathy (DN) have been identified and confirmed in several meta-analyses. In addition, patients with type 1 and type 2 diabetes have higher serum levels of APOC1 compared to healthy control subjects. APOC1 transgenic (APOC1tg) mice develop albuminuria and glomerulosclerosis at 15 months of age. In this study we investigated the role of macrophages in APOC1 induced glomerulosclerosis in APOC1tg mice.

Methods: APOC1tg and wild-type (WT) mice were sacrificed at various ages. Kidneys were sectioned and stained for APOC1, F4/80 (macrophages), CD11b (M1 macrophages), CD163 (M2 Macrophages) and TNF-alpha. RT-PCR was performed to measure APOC1 mRNA levels. To confirm data from APOC1tg mice, human autopsied kidneys with DN and healthy controls were included, sectioned and stained for APOC1. Correlations were assessed using the Pearson's correlation test.

Results: In APOC1tg mice, the number of glomerular macrophages were already increased at 15 weeks of age, long before the development of glomerular damage, and increased even further in time. A strong linear correlation was found between the number of glomerular macrophages and glomerular damage (p<0.001). These macrophages were found to be of the M1 type and expressed high amounts of APOC1 and TNF-alpha. In patients with DN, glomerular APOC1 expression was significantly increased compared to healthy control subjects.

Conclusions: Both our mice and our human autopsied data indicate that APOC1 could play a crucial role in the development of glomerular damage. We hypothesize that APOC1-expression by macrophages causes glomerular damage, potentially by increasing the inflammatory state of these macrophages.

TH-PO243

Decreased Renal α -Klotho Expression Is Associated with Urinary Calcium Excretion in Early Diabetic Nephropathy in db/db Mice Kyung don Ju, Tsogbadrakh Bodokhsuren Bodokhsuren, Hyo Jin Kim, Seungmi Lee, Miseon Park, Curie Ahn, Kook-Hwan Oh. *Div of Nephrology, Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.*

Background: Hypercalciuria is one of the early manifestations of diabetic nephropathy (DN). We surveyed the role of α -Klotho, a protein expressed predominantly in the distal tubules (DTs). α -Klotho is known to up-regulate transient receptor potential vanilloid type 5 (TRPV5) expression, involved in tubular calcium reabsorption.

Methods: We used db/db mice, a type II diabetes mellitus (DM) model. We employed puromycin aminonucleoside (PAN)-induced nephrotic mice and db/m mice for control. PAN mice was induced by injecting 150 mg/kg PAN intraperitoneally for every 2 weeks.

Results: Animals were sacrificed at the age of 15th week. At 15th week, db/db mice and PAN mice developed albuminuria (218 ± 33 mg/day and 68 ± 9 mg/day, respectively), while db/m mice were normoalbuminuric (14 ± 3 mg/day). Urinary calcium excretion (UCa/UCr) significantly increased in db/db mice (0.91 ± 0.09 mg/mg Cr), compared to PAN (0.30 ± 0.02 mg/mg Cr) or db/m mice (0.29 ± 0.03 mg/mg Cr). mRNA and protein expression levels of α -Klotho in the distal tubule were markedly ameliorated. Urinary klotho concentration (UKL/UCr) was significantly decreased in db/db mice (1.45 ± 0.02 fM/mg Cr) compared to PAN (10.77 ± 3.01 fM/mg Cr) or db/m mice (6.39 ± 0.40 fM/mg Cr). By immunohistochemistry and immunofluorescence staining, we also confirmed reductions of renal α -Klotho, FGF receptor type 1 (FGFR1) and TRPV5 expressions in db/db mice.

Conclusions: Thus, renal loss of α -Klotho may affect urinary calcium excretion via inhibition of TRPV5 expression in DTs in early diabetic nephropathy.

TH-PO244

NF- κ B System Inhibition Attenuates Renal Injury in Diabetic Nephropathy Orestes Foresto-Neto, Amanda H. Albino, Simone CA Arias, Lisienny CT Rempel, Gizely CS Moreira, Victor F. Avila, Viviane D. Faustino, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels OS Camara, Clarice K. Fujihara, Roberto Zatz. *Univ of Sao Paulo, Brazil.*

Background: The NF- κ B system may be involved in the pathogenesis of diabetic nephropathy (DN). We investigated whether NF- κ B inhibition with pyrrolidinedithiocarbamate (PDTTC) exerts renoprotection in experimental DN.

Methods: Diabetes was induced in 27 adult male Munich-Wistar rats through streptozotocin injection (65 mg/kg, iv) and maintained moderately hyperglycemic with daily insulin. Rats were divided in untreated (DM) and PDTTC-treated, 60 mg/kg/day (DM+PDTTC). Untreated nondiabetic rats (C, n=12) were also followed. Body weight (BW, g), blood glucose (BG, mg/dL), tail-cuff pressure (TCP, mmHg), urinary albumin/creatinine ratio (Ualb/Ucr), kidney/body weight ratio (KW/BW), % glomerular sclerosis (%GS), interstitial and glomerular macrophage infiltration (intMØ and glomMØ, cells/mm²) and % glomerular zonula occludens (ZO-1, %) were assessed after 12 months of follow-up.

Results:

	C	DM+V	DM+PDTC
BW	408±9	335±5 ^a	335±3 ^a
BG	98±2	378±24 ^a	386±7 ^a
TCP	135±3	134±2	131±2
Ualb/Ucr	1.5±0.2	5.1±1.2 ^a	1.3±0.3 ^b
KW/BW	0.49±0.01	0.72±0.01 ^a	0.64±0.02 ^{ab}
%GS	2.6±0.4	7.9±1.9 ^a	2.1±0.7 ^b
intMØ	57±6	85±8 ^a	45±5 ^b
glomMØ	16±3	54±15 ^a	33±10 ^b
ZO-1	77±1	61±2 ^a	75±2 ^b

Mean±SE. ^ap<0.05 vs C; ^bp<0.05 vs DM+V.

After 12 mo, untreated DM rats exhibited high Ualb/Ucr, renal hypertrophy, high %GS, intMØ and glomMØ, and loss of %ZO-1, without changes in TCP. Treatment with PDTC attenuated renal hypertrophy and prevented the increase in Ualb/Ucr, %GS, intMØ and glomMØ, and the loss of ZO-1, without interfering with BG or TCP.

Conclusions: PDTC exerts a renoprotective effect on the progress of DN in diabetic rats, suggesting the involvement of the NF-κB system in the pathogenesis of the disease and the possibility that this system becomes a therapeutic target. The beneficial effects of PDTC may also be the result of an antioxidant effect of the drug. FAPESP/CNPq.

TH-PO245

Renin Accelerates Progression of HIVAN-Associated Nephropathy (HIVAN) Through Kidney Cell HIV Gene Expression Partab Raj, Rivka Lederman, Shabirul Haque, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: The activation of renin-angiotensin system has been demonstrated to play an important role for the development and the progression of HIVAN. However, the progression of HIVAN attributed predominantly to Ang II generation by kidney cells. Recently, HIV has been demonstrated to stimulate renin generation by kidney cells *in vitro* studies. We hypothesized that HIV-induced kidney cell renin production might also be enhancing kidney cell HIV gene expression, which may accelerate progression of renal lesions, independent of the effects of Ang II.

Methods: Human podocytes (HPs) were transduced with either empty vector (EV/HP) or HIV (NL4-3, HIV/HP). To increase endogenous renin production, EV/HPs and HIV/HPs were transfected with siRNA vitamin D receptor (siRNA-VDR/HIV/HPs) or scrambled (Scr-siRNA/HIV/HP) siRNA; protein blots were probed for renin and actin. To evaluate the effect of renin *in vivo*, mRNA expressions of HIV genes from renal tissues of HIVAN (Tg26) mice with high endogenous renin (Tg26 mice either with 2, 3 and 4 copies of angiotensinogen [Agt] or lacking VDR) were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and then renal tissues were evaluated for HIV gene expression. Additionally, gene expression and progression of renal lesions were compared in Tg26 mice and Tg26 mice lacking renin.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vif. On the other hand, treatment of HIV/HPs with VDA downregulated HIV gene expression. Renal tissues of Tg26-Agt-4 displayed 2-4 fold increase in mRNA expression of gp120, Vpr, Tat, Nef and Vpu vs. Tg26-Agt-2. Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared with Tg26 mice with intact VDR. VDA treatment of Tg26 also down regulated renal tissue expressions of renin as well of HIV genes. Tg26 mice lacking renin, displayed attenuated renal tissue HIV gene expression and slowed progression of renal lesions.

Conclusions: Renin enhances progression of HIVAN through HIV gene expression.

TH-PO246

Podocyte and Tubule Injury Have Different Effects on Renal Handling of Apolipoprotein A-I (ApoA-I) and Its Receptors Jianyong Zhong,^{1,2} Haichun Yang,² Yohei Tsuchida,¹ Taiji Matsusaka,³ Agnes B. Fogo,² Valentina Kon.¹ ¹*Pediatric Nephrology, Vanderbilt;* ²*Pathology, Microbiology and Immunology, Vanderbilt Univ, Nashville, TN;* ³*Dept of Molecular Life Science, Tokai Univ School, Isehara-shi, Kanagawa, Japan.*

Background: CKD disrupts HDL composition and function. ApoA-I, the major lipoprotein of HDL, modulates many of its beneficial effects. To determine how injury affects renal handling of ApoA-I, we studied tubule- and podocyte-specific injury models.

Methods: Diphtheria toxin transgenic mice (DT) express human DT receptor in proximal tubular epithelial cells and DT injection causes acute tubule necrosis. Folic acid injury induces crystal formation in distal nephron and distal tubule necrosis. Nphs1-hCD25 transgenic mice (NEP25) express human CD25 in podocytes which can be injured by injection of immunotoxin, LMB2.

Results: Compared to baseline (W0), DT increased urinary KIM-1 and doubled ApoA-I at week 2 (W2 18580±1543 vs. W0 10319±2641 ng/mg, p<0.05). Folic acid caused greater increase in Ngal than KIM-1, consistent with distal but not proximal injury with no change in urinary apoA-I or albuminuria. Low dose LMB2 induced edema and albuminuria.

Urinary apoA-I increased >10-fold at W2 and remained elevated at W6 (>7-fold) although albuminuria normalized. High dose LMB2 reduced GFR, caused glomerulosclerosis, and increased apoA-I excretion 1400-fold.

In DT, proximal tubule expression of cubilin was reduced and ApoA-I localized to the apical side. By contrast, low-dose LMB2 stimulated cubilin expression without changing ApoA-I localization. Neither injury affected abundance or localization of ApoA-I transporters. High dose LMB2 not only increased cubilin expression but translocated ApoA-I to the cytoplasm of tubular cells and to peritubular capillaries. ABCA1, but not G1 or SRBI, translocated from the apical membrane to cytoplasm of parietal and proximal tubule epithelial cells.

Conclusions: Renal handling of ApoA-I is determined by the glomerular filtration barrier and proximal, but not distal, tubules through mechanisms that involve cubilin and ABCA1. Podocyte injury increases ApoA-I in glomerular filtrate and may be a sensitive marker of injury to the glomerular filtration barrier.

Funding: Other NIH Support - NHLBI

TH-PO247

Increased Toxicity of APOL1 Kidney Risk Variants Is Not due to Decreased VAMP8 Binding Patrick D. Dummer,¹ Alison Hickman,¹ Jurgen Heymann,¹ Michael Kruhlak,² Katalin Susztak,³ Cheryl Ann Winkler,² Jeffrey B. Kopp.¹ ¹*NIDDK, Bethesda, MD;* ²*NCI, Bethesda, MD;* ³*Univ of Pennsylvania, Philadelphia, PA.*

Background: Developing effective therapies for APOL1 nephropathies will require insights into the mechanisms of APOL1-associated cell damage. Disease-associated G1 and G2 mutations in the C-terminus of APOL1 increase toxicity through lysosomal membrane permeability (LMP). Vesicle-associated membrane protein (VAMP) 8, a lysosomal soluble NSF attachment protein receptor (SNARE), has been proposed to inhibit APOL1 function by binding the C terminus, with the G1 and G2 mutations decreasing affinity compared to the ancestral G0 variant.

Methods: GFP-LC3 (autophagosome marker), GFP-SNAREs (to monitor vesicle trafficking), and His6-, GFP-, and mCherry-tagged APOL1-A isoform were expressed by transient co-transfection of HeLa and HEK293 cells. Autophagy was assessed by microscopy using GFP-LC3. Endoplasmic reticulum (ER) stress was measured by Western blot for BiP and phospho-PERK. Toxicity was measured by SyTox Blue staining.

Results: APOL1-A G1 and G2 variants increased ER stress and autophagy compared to the ancestral G0 variant. All APOL1 variants traffic to Rab7-, LBPA-, and VAMP8-positive late endosomes and lysosomes. Deletion of the APOL1 C terminus abolished APOL1-induced autophagy and toxicity, but not trafficking to lysosomes. APOL1 bound all R-SNAREs, with greatest affinity for lysosomal VAMP7 and VAMP8. There were no differences in affinity to VAMP8 among the APOL1 variants, and truncation of the APOL1 C terminus did not abolish the interaction. Co-expression of VAMP8 increased APOL1 toxicity. A non-toxic APOL1-A protein lacking the N-terminal signal peptide exhibited the greatest affinity to VAMP8.

Conclusions: APOL1 G1 and G2 toxicity may not be due to decreased VAMP8 affinity, as previously proposed. The APOL1 C terminus is required for toxicity but not for lysosomal trafficking, suggesting the increased toxicity of APOL1 risk variants is not due to altered APOL1 trafficking to lysosomes. Cellular stress pathways beyond LMP, such as autophagy and ER stress, may contribute to the increased toxicity of APOL1 risk variants.

Funding: NIDDK Support, Other NIH Support - NCI

TH-PO248

N-Acetylmannosamine Mitigates Neuraminidase-Induced Podocyte Injury in Mice Marjan Huizing,¹ Obiageri Okafor,¹ Patricia M. Zerfas,² Steven Bodine,¹ Matthew F. Starost,² A. Rosenberg,³ William A. Gahl,¹ Jeffrey B. Kopp,¹ May christine V. Malicdan.¹ ¹*Medical Genetics Branch, NHGRI, NIH;* ²*Office of Research Services, OD, NIH;* ³*Kidney Disease Section, NIDDK, NIH, Bethesda, MD.*

Background: Podocyte injury is present in many glomerular diseases. Current therapies do not achieve sustained remissions and often have adverse events. Recent findings suggest that a subset of patients with glomerular disease may have ongoing desialylation or impaired resialylation of certain renal glycans (glycoproteins and glycolipids), as detected by lectin histochemistry.

Methods: We induced podocyte injury in mice by a single intraperitoneal injection of *Vibrio cholerae* neuraminidase (NA), an enzyme that removes α2,6 linked sialic acid end-groups from glycans. The sialic acid precursor N-acetylmannosamine (ManNAc) was administered in drinking water at a ~1 g/kg/d dose, either prophylactic (starting 10 days prior to NA and continued for 5 days), or therapeutic (starting 12 hours after NA and continued for 4.5 days).

Results: NA-injected wild type mice developed proteinuria and renal insufficiency in a dose-dependent manner. Podocalyxin and other glomerular glycans were hyposialylated. Histopathology showed acute renal injury predominantly in the cortical region, swollen podocytes, and glomerular mesangial cell hyperplasia and hypertrophy. Ultrastructural studies showed podocyte foot process effacement. Importantly, both prophylactic and therapeutic ManNAc treatments increased renal glycan sialylation and markedly reduced urine albumin/creatinine ratio (ACR) and podocyte injury at Day 5 (N=14 per group).

Neuraminidase	Treatment	ACR Day 0.5	ACR Day 5
-	None	41 ± 26	72 ± 36
+	None	1860 ± 840	485 ± 90
+	Prophylactic ManNAc	2087 ± 1840	85 ± 66*
+	Therapeutic ManNAc	3078 ± 2510	150 ± 72*

* P<0.05 compared to NA with no treatment

Conclusions: ManNAc holds promise to mitigate hyposialylation-related disease mechanisms of glomerular diseases; ManNAc has minimal toxicity and is orally administered. ManNAc is currently tested in a Phase 2 clinical trial for the rare hyposialylation disorder GNE myopathy. We plan a Phase 1 clinical trial of ManNAc in patients with glomerular diseases.

Funding: NIDDK Support, Other NIH Support - NHGRI

TH-PO249

A Mismatch Between Glomerular Volume and Podocyte Mass Is Associated with Albuminuria and Accelerated Podocyte Hypertrophic Injury in Leptin-Deficient Zucker Rats Akihiro Fukuda,¹ Yuji Sato,¹ Takashi Iwakiri,¹ Kazuo Kitamura,¹ Roger C. Wiggins,² Shouichi Fujimoto.¹ ¹First Dept of Internal Medicine, Univ of Miyazaki, Miyazaki, Japan; ²Nephrology Div, Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Background: Glomerular hypertrophy is a well-established component of diabetic nephropathy. We previously reported that failure of podocytes to match glomerular tuft enlargement (in response to growth signaling through the mTORC1 pathway) can trigger proteinuria, glomerulosclerosis and progression to end stage renal disease in dominant negative AA-4E-BP1 Tg rat model. We therefore tested the hypothesis that a mismatch between glomerular volume and podocyte mass causes progression of diabetic nephropathy.

Methods: We used the leptin-deficient Zucker Diabetic Fatty (ZDF-fatty) rat model of type 2 diabetes compared with heterozygous ZDF rats as a control. Glomerular volume and podocyte number per tuft, density (podocyte number per glomerular tuft volume), mass (Glepp1 positive volume) and the urine podocin:aquaporin2 mRNA ratio were measured. Rats were evaluated over a 45 week time-course.

Results: ZDF-fatty rats gained weight much faster than control rats over the first 15 weeks, but did not become hypertensive over the study period. ZDF-fatty rats became diabetic with increased blood glucose and glycosuria by 10 weeks. Albuminuria and urine podocin:aquaporin2 mRNA ratio were also significantly increased by 10 weeks. Sequential kidney biopsies at 15, 30, and 45 weeks revealed that by 15 weeks glomerular volume was already significantly increased above control (1.5-fold, P<0.01) and podocyte density was significantly reduced (P<0.01), although podocyte number per tuft was not detectably decreased. By 45 weeks glomerulosclerosis was present and the Glepp1 peroxidase positive podocyte tuft area was significantly reduced in the ZDF-fatty rats but not in controls.

Conclusions: These data indicate that a mismatch between glomerular volume and podocyte mass (reduced podocyte density) is associated with development of albuminuria and accelerated podocyte hypertrophic stress in this model of type 2 diabetes, compatible with data previously reported in Pima Indians.

TH-PO250

An ER Stress-Regulated Transcript Hosting a MicroRNA Megacluster as Therapeutic Target in the Early Stage of Diabetic Nephropathy Mitsuo Kato, Mei Wang, Zhuo Chen, Supriya Deshpande, Kirti Bhatt, Hyung Jung Oh, Linda L. Lanting, Rama Natarajan. *Beckman Research Inst, City of Hope, Duarte, CA.*

Background: microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have important roles in the pathogenesis of diabetic nephropathy (DN). We observed that the miR-379 megacluster (MGC, ~40 miRNAs) and its host transcript lncRNA (lncMGC) were upregulated in glomeruli of streptozotocin (STZ)-injected diabetic mice through the ER-stress induced transcription factor, CHOP. Targets of the MGC miRNAs had functions related to DN. We hypothesized that lncMGC may be a therapeutic target in early DN to prevent progression.

Methods: The expression of cluster miRNAs, lncMGC, miRNA targets and profibrotic genes, and early features of DN [glomerular hypertrophy, extracellular matrix (ECM) accumulation] were examined in STZ-injected diabetic CHOP knockout (KO) mice, and also in diabetic mice injected with GapmeRs (LNA-modified antisense oligonucleotides) targeting lncMGC. These parameters were also examined in human mesangial cells (HMC) transfected with GapmeR targeting human lncMGC.

Results: Key miR-379 cluster miRNAs, lncMGC and profibrotic genes were decreased, whereas targets of miR-379 cluster miRNAs were increased in glomeruli of diabetic CHOP KO mice compared to wild type. Glomerular hypertrophy and ECM accumulation were ameliorated in diabetic CHOP KO mice. GapmeR targeting lncMGC decreased lncMGC, cluster miRNAs and profibrotic genes, and also attenuated glomerular hypertrophy and ECM accumulation, but reciprocally upregulated targets of the cluster miRNAs in diabetic mice. GapmeR targeting human lncMGC inhibited lncMGC, miR-379 cluster miRNAs and profibrotic genes, but upregulated cluster miRNA targets in HMC.

Conclusions: These results demonstrate that a unique ER stress-regulated lncRNA and component cluster of miRNAs co-ordinately regulate the expression of several genes involved in glomerular hypertrophy and ECM accumulation associated with early DN.

Furthermore, a single oligonucleotide targeting the host lncRNA was effective in preventing these early features of DN, highlighting the GapmeR approach for targeting lncRNAs as a novel therapy for DN.

Funding: NIDDK Support

TH-PO251

No Difference in Cytotoxicity of APOL1-G0 or Risk Variants G1 and G2 John F. O'Toole,¹ Sethu M. Madhavan,¹ Martha Konieczkowski,¹ Yaping Gu,¹ Liping Luo,¹ Zhenzhen Wu,¹ William P. Schilling,² Leslie A. Bruggeman,¹ John R. Sedor.^{1,2} ¹Medicine, MetroHealth Medical Center, Cleveland, OH; ²Physiology and Biophysics, Case Western Reserve Univ, Cleveland, OH.

Background: The genetic evidence linking variation in the APOL1 gene to kidney disease in ancestral African populations is strong; however, the biological mechanisms that underlie the association remain uncertain. Autophagy and cell death has been observed after the expression of APOL1 and variant dependent cell death has been reported with the transient expression of APOL1. Therefore we sought to examine autophagy and cell death for variant dependent effects in stable expression systems.

Methods: Stable tetracycline inducible HEK293 cells were generated for the expression of APOL1-G0 (reference), the -G1, and -G2 risk variants. Murine podocytes were isolated from transgenic animals expressing human APOL1-G0 or APOL1-G2 under the Nephin promoter and control animals. Autophagy was monitored with biochemical methods and three assays of cell death were used; a fluorescent assay, an MTT assay and a clonogenic assay.

Results: Three stable HEK293 clones of each genotype were assayed for autophagy and cell death after induction of APOL1 with tetracycline. We noted significant variability in the kinetics of APOL1 induction between clones, which was not dependent upon APOL1 genotype. Stable expression of APOL1-G0, -G1, and -G2, all increased autophagic flux to a similar degree. The stable expression of all APOL1 genotypes (G0, G1 and G2) resulted in cell death in all three assays, without variant dependent differences. Inhibitors of autophagy or autophagy did not reduce APOL1-G0, -G1, or -G2 induced cell death and none of the APOL1s activated the apoptosis effector caspase 3. The expression of APOL1 in differentiated mouse podocytes did not induce autophagy or cell death.

Conclusions: Stable expression of APOL1 in cell culture leads to cell death and autophagy induction in a variant independent manner, but the regulated expression of APOL1 in differentiated podocytes does not. The absence of variant dependence of autophagy induction or cell death suggest that alternative mechanisms underlie the genetic association of APOL1 with kidney disease.

Funding: NIDDK Support, Other NIH Support - NCATS UL1TR000439

TH-PO252

NGAL Regulates TH17 Immunity in ANCA Vasculitis Adrian Schreiber,¹ Erik M. Disteldorf,² Ulf Panzer,² Ralph Kettritz.¹ ¹Dept of Nephrology and Intensive Care Medicine, CVK Charité, Berlin, Germany; ²III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: ANCA activate neutrophils and thereby participate in necrotizing crescentic glomerulonephritis (NCGN). NGAL is a marker of intrinsic kidney injury and is expressed by neutrophils and renal tubular cells. Whether or not NGAL is merely a diagnostic marker or participates mechanistically in renal damage is not known. We hypothesized that neutrophil NGAL plays a pathogenic role in ANCA NCGN.

Results: Patients with active ANCA disease demonstrated increased NGAL serum levels by western blot analysis (47.3±13.1OD) compared to patients in remission (19.4±8.1) and healthy controls (2.1±0.4). We then assessed ANCA-activated neutrophils as a potential source for upregulated serum NGAL. By ELISA, both PR3-ANCA and MPO-ANCA stimulated NGAL release from human neutrophils (887±72 and 961±70ng/ml), whereas control IgG induced much lower levels (105±21ng/ml). Mice with anti-MPO-induced NCGN demonstrated upregulated NGAL serum levels by ELISA (data not shown). To assess the role of neutrophil NGAL in vivo, we used a murine model of anti-MPO induced NCGN, where MPO-KO mice were immunized with mMPO and subsequently transplanted with either WT- or NGAL-KO bone marrow (BM). NCGN was significantly aggravated in mice that received NGAL-KO BM (34.8±6.1% crescents in NGAL-KO versus 13.4±2.8% in WT mice). With respect to intrinsic neutrophil function, migration, ROS generation, degranulation and apoptosis were similar in NGAL-KO and WT neutrophils. In addition, humoral immunity did not differ. In contrast, FACS demonstrated increased T cell immunity in NGAL-KO mice: CD4 cells were 28.7±6.1% of renal CD45 cells in NGAL-KO versus 13.9±0.6% in WT mice, TH17 cells were 21.7±7.6% of renal CD4 cells versus 5.7±1.0%, whereas TH1 cells did not differ (14.4±3.8% versus 14.9±1.2% CD4 cells). Furthermore, splenocytes from NGAL-KO BM transplanted mice showed increased IL-17 production. When WT and NGAL-KO mice were immunized with mMPO, we observed an increased percentage of TH1 and TH17 cells in the latter.

Conclusions: Our findings indicate that neutrophil NGAL down-regulates inflammation in ANCA-induced NCGN by inhibiting TH17 immunity.

TH-PO253

Streptococcus mutans Strains with Collagen-Binding Protein May Cause IgA-Like Glomerulonephritis in Rats Taro Misaki,¹ Shuhei Naka,² Ryota Nomura,² Taisuke Isozaki,¹ Kazuhiko Nakano.² ¹Div of Nephrology, Seirei Hamamatsu General Hospital, Hamamatsu, Shizuoka, Japan; ²Dept of Pediatric Dentistry, Osaka Univ Graduate School of Dentistry, Suita, Osaka, Japan.

Background: The precise pathological mechanisms of IgA nephropathy (IgAN) remain unclear. It is known that 10-20% of healthy subjects harbor strains of *Streptococcus mutans*, a known pathogen of dental caries, that possess Cnm, a cell surface collagen-binding protein encoded by the *cnm* gene. Furthermore, it is widely accepted that an association between *S. mutans* with Cnm protein and systemic diseases exists. We previously found that the rate of *cnm*-positive *S. mutans* organisms isolated in saliva specimens was significantly higher in an IgAN group as compared to the controls, and reported those findings at ASN Kidney Week 2014 and in *Clinical and Experimental Nephrology* in 2014. The aim of this study was to investigate whether nephritis is induced by Cnm-positive *S. mutans* strains inoculated into the oral cavity of a rat model of dental caries.

Methods: Cnm-positive *S. mutans* strains (JD-17R, JD-52R, JD-74R) were isolated from the oral cavities of 3 IgAN patients. Those along with MT8148, a standard oral isolate, were inoculated into the oral cavities of 2-week-old Sprague-Dawley rats fed a 56% sucrose-containing diet and then we confirmed that the strains were harbored in the oral cavity of each rat 1 week later. From 10 weeks of age, findings of severe dental caries were confirmed in all rats. They were euthanized at 24 weeks of age, then kidney tissues were extirpated and stained with PAS, and immunohistochemistry with the IgA antibody was performed for histopathological analysis.

Results: Dental caries in nearly all of the rats were found extending to the pulp space, which contains nerves and blood vessels. In rats harboring Cnm-positive strains in the oral cavity, mesangial cell proliferation was observed and immunohistochemical staining of the IgA antibody was seen in the para-mesangial area. However, no abnormal findings were observed in extirpated kidney tissues from rats harboring MT8148 in the oral cavity.

Conclusions: Our results indicate that Cnm-positive *S. mutans* strains harbored in the oral cavity may cause IgA-like glomerulonephritis.

TH-PO254

Prevention of Lupus Nephritis in the BXSB-Yaa Mouse by Metabolic Inhibitors Byron P. Croker,^{1,2} Derry C. Roopenian,³ Laurence Morel.¹ ¹Pathology, Immunology and Laboratory Medicine, Univ of Florida, Gainesville, FL; ²Pathology and Laboratory Medicine Service, NF/SG VHS, Gainesville, FL; ³The Jackson Laboratory, Bar Harbor, ME.

Background: In a heavily Type II gamma interferon activated model of lupus nephritis (LN) we showed metabolic inhibition by chronic oral combination of 2 deoxyglucose (2DG) and metformin (Met) reversed LN. We now show 2DG + Met prevents LN in the heavily Type I alpha interferon driven BXSB-Yaa LN.

Methods: Mice were treated chronically with test medications in drinking water. At sacrifice blood and tissues were taken for analysis and correlation of renal histopathology with a LN classification modeled on the ISN-RPS classification of LN. For clarity of presentation, % animals with global proliferative glomerulonephritis (Pg) will be given for each treatment group in results. Other animals were classified as normal to mesangiopathic LN (data not shown).

Results: 2DG (Pg 0.0%), 2DG + Met (Pg 0.0%) and rapamycin (Pg 0.0%) all showed marked reduction in LN. Dichloroacetic acid (Pg 20.0%) and Met (single agent, Pg 40.0%) showed moderate but significant reduction of LN compared to disease controls (Pg 76.5%). Untreated C57Bl/6 mice were used as a normal (disease free) control (Pg 0.0%). Target organ preservation is supported by in vivo and in vitro determination of immunologic and metabolic parameters.

Conclusions: This study presents a second model of LN that responds favorably to metabolic inhibition and normalization by existing drugs utilized for other clinical indications.

Funding: Private Foundation Support

TH-PO255

Successful Treatment of a Mesangial Proliferative Glomerulonephritis by Foxd1⁺ Metanephric Mesenchymal Cells Li Zhang,¹ Meiling Jin,^{1,2} Qing-gang Li,¹ Guangyan Cai,¹ Xiang-Mei Chen.¹ ¹Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases; ²Medical College, NanKai Univ.

Background: This study is aiming to observe the effect of Foxd1⁺ metanephric mesenchymal cells on MsPGN.

Methods: 1. We use Foxd1^{cre}/GFP transgenic mice and Rosa-DTR^{lox} transgenic mice to screen target embryonic kidney cells, and isolate Foxd1⁺ metanephric mesenchymal cells by adding diphtheria toxin; 2. We detect Foxd1⁺ cell proliferation, cell surface markers, and osteogenic adipogenic differentiation potential. 3. 24h after establishment of anti-Thy1 mesangial proliferative glomerulonephritis, Foxd1⁺ cells were injected via intravenous, and this group was set as group of treatment. We detect renal pathology and renal function at different time points on control, model and treatment group. 4. Mesangial cells were stimulated by PDGF-BB, we detect the influence of Foxd1⁺ cells on the proliferation and migration of activated mesangial cells.

Results: 1. The results showed that CD90 positive rate was 0.9605, CD 44 91.11%, CD106 96.69, CD34 0.53, CD34 0.53%, CD45 0.35%. After the induction, we found that Foxd1⁺ cells had good osteogenic and adipogenic differentiation capacity. 2. After intravenous injection of Foxd1⁺ cells could improve the pathological changes in the kidney and could reduce urinary protein significantly. 3. CCK-8 results showed that Foxd1⁺ cells condition medium could antagonize proliferation of mesangial cells activated by PDGF-BB from 48 hours. Transwell migration assay results showed that Foxd1⁺ cells could significantly inhibit activated mesangial cell migration.

Conclusions: 1. Foxd1⁺ metanephric mesenchymal cells could be isolated using transgenic mice, and also are proved that they have the characteristics of stem cells. 2. Foxd1⁺ metanephric mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

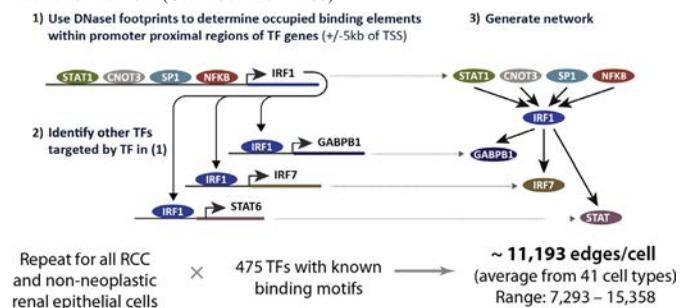
Funding: Government Support - Non-U.S.

TH-PO256

Beyond HIF1 α - Regulatory Genomic Insights into Renal Cell Carcinoma Revealed by DNaseI-seq Shreeram Akilesh. Pathology, Univ of Washington, Seattle, WA.

Background: Clear cell renal cell carcinoma (RCC) is the most common sporadic malignancy affecting the kidney. Inactivation of the *VHL* tumor suppressor gene and subsequent stabilization of the HIF1 α transcription factor (TF) is very common in RCC. However, it is unclear how HIF1 α and the closely related HIF2 α (EPAS1) interact with each other and other TFs to produce and maintain the RCC phenotype. Here, we delineate the regulatory genomic landscape of RCC using DNaseI-seq and define the transcriptional regulatory network of RCC.

Methods: Fresh normal human kidney tissue and RCC were disaggregated and cultured to generate primary tubular and renal cell carcinoma cultures. These were subjected to DNaseI-seq and RNASeq according to established protocols. DNaseI hypersensitivity profiling (DNaseI-seq) allows for comprehensive mapping of regulatory DNA at a genomic scale and with single nucleotide resolution. Examination of footprinting depth DNaseI-seq data identifies DNaseI-protected transcription factor (TF) motifs within the promoter of other TFs. Mapping these TF footprints across all TFs with known motifs results in a TF interaction network (*Cell*. 150: 1274-1286).



Results: Even though HIF1 α plays an important role in RCC biogenesis, it does not prominently feature in the TF interaction network of RCC. Instead, several other TFs (e.g. FOX, CEBP, SMADs nuclear receptors, etc.) interact to control the regulatory network of RCC with a relatively minor contribution from HIF2 α (EPAS1).

Conclusions: While the HIF transcription factors play an important role in RCC oncogenesis, DNaseI-seq reveals that other TFs are responsible for maintaining the RCC phenotype. Systematically testing this regulatory circuitry promises to identify novel pathways to intervene in the growth of this deadly cancer. These techniques/approaches are also being applied to other primary kidney cells such as endothelial cells and podocytes.

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TH-PO257

Uneven Reinnervation After Unilateral Renal Denervation: Afferents Dominate Efferents Kristina Rodionova,¹ Franziska Günther,² Eric Grouzmann,⁵ Michael J.m. Fischer,² Sonja Heinlein,¹ Winfried Neuhuber,³ Christian Ott,¹ Roland E. Schmieder,¹ Kerstin U. Amann,⁴ Roland Veelken,¹ Tilmann Ditting.¹ ¹Nephrology & Hypertension, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany; ²Physiology 1, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany; ³Anatomy 1, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany; ⁴Pathology, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany; ⁵Pharmacologie et Toxicologie, CHUV Lausanne, Lausanne, Switzerland.

Background: Renal nerve ablation is a beneficial, but controversial treatment for resistant hypertension. We found morphological evidence that intrarenal perivascular afferents reinnervate more thoroughly than efferent sympathetic nerves. We now measured the tissue content of the afferent and efferent neurotransmitters, calcitonine gene related peptide (CGRP) and norepinephrine (NE) within 12 weeks after denervation.

Methods: Tissue levels of CGRP and NE from 24 male SD rats (ELISA-test, mass-spectrometry) were measured in denervated left (L) and non-denervated right kidneys (R) 1, 4 and 12 weeks after renal denervation=phenol.

Results: CGRP decreased by 72% in denervated (L) kidneys compared to (R) kidneys in week 1 [W1_R: 3.20±0.33 vs. W1_L: 0.97±0.25; p<0.05 (ng/g kidney)]. In week 12 CGRP content in (L) kidneys did not differ from (R) kidneys. We observed a 78% decrease of NA tissue levels [pmol/mg kidney] in week 1 due to surgical denervation [W1_R: 1.09±0.16 vs. W1_L: 0.24±0.06; p<0.05]. In contrast to the CGRP tissue levels there was no complete recovery of NA in week 12. The commonly used addition phenol to the surgical denervation procedure did not influence these results significantly. All data are given as mean±SEM.

Conclusions: We could show that there is a complete reinnervation of CGRP positive perivascular nerves within 12 weeks after renal denervation. However, NA tissue content did not recover completely in spite of complete morphological regrowth of sympathetic nerve fibers. This might potentially result in a net surplus of afferent sympatho-inhibitory influence, adding to the beneficial effect of renal denervation in some cases of resistant hypertension.

Funding: Government Support - Non-U.S.

TH-PO258

An Aristolochic Acid-Induced Nephropathy (AAN) Model for Stable CKD in Mice Hiroshi Kojima, Xuzhen Hu, Yuning George Huang, Ana C. Souza, Jonathan Street, Peter S.T. Yuen, Robert A. Star. *Renal Diagnostics and Therapeutics Unit, NIDDK, NIH, Bethesda, MD.*

Background: ACEi/ARB are standard therapy for progressive CKD but do not slow progression in ~50% of patients. To obtain novel therapies of CKD in humans, better preclinical models are needed. A few mouse models for CKD have been developed, each with strengths and weaknesses. In humans, Aristolochic Acid (AA) causes Balkan nephropathy, with chronic interstitial fibrosis and slow progression to ESRD. However, published AAN mouse models have poorly characterized CKD outcomes.

Methods: CD-1 or C57BL/6 mice were injected i.p. with AA dissolved in DMSO using two regimens: R1: AA i.p. (3 mg/kg) every 3 d for 6 wk, then 6 wk of disease development; R2: AA i.p. (2.5 mg/kg) every 7 d for 3 wk, then 1 wk of disease development. Spot urine samples and non-invasive GFR by plasma disappearance of FITC-Sinistrin were obtained weekly: serum and kidney were collected at euthanasia. Using aged animals, or addition of salt-loading, uninephrectomy (UNx), or an adenine-rich diet were tested to increase the severity of the model.

Results: CD-1 mice (R1) had severe body weight (BW) loss at 3 wk and was discontinued. Both CD-1 and C57BL/6 (R2) showed moderate loss of BW. All R2 mice survived. Both CD-1 and C57BL/6 mice had elevated BUN, and developed severe tubulointerstitial injury. CD-1 mice showed higher injury score and fibrosis (%) than C57BL/6 mice. There was no elevation of blood pressure in CD-1 (R2). Neither regimen nor strain developed progressive CKD model as urinary albumin transiently peaked then fell, and GFR dropped by 60%, but plateaued within two weeks. Aging, salt-loading, UNx, or an adenine-rich diet did not increase injury or lead to progressive CKD.

Conclusions: AA caused a strain- and regimen-dependent severity of tubulointerstitial injury, with moderate but stable decreases in kidney function (~ human CKD stage 3). AAN may still be a foundation of a progressive CKD model, but additional renal insults might be needed to achieve a progressive CKD model.

Funding: NIDDK Support

TH-PO259

The Polymeric Immunoglobulin Receptor Is Expressed in Scattered Cells of Human Kidney and Increase in Expression following Kidney Injury Krzysztof Krawczyk,¹ Helén Nilsson,¹ Jenny C. Nystrom,² Martin E. Johansson.¹ ¹Dept of Translational Medicine, Lund Univ, Malmö, Sweden; ²Dept of Physiology, Inst of Neuroscience and Physiology, Univ of Gothenburg, Gothenburg, Sweden.

Background: We have previously shown that the proximal tubules of human kidney contain a scattered cell (SC) population of importance for kidney regeneration, where the markers for SC are identical to those of the parietal epithelium of Bowman's capsule. Using gene expression analysis of the SC we found that these may express the Polymeric immunoglobulin receptor (PIGR), a transporter classically attributed to export of secretory IgA and IgM to the mucosal side of the respiratory and gastrointestinal tracts.

Methods: Biopsy material was procured from normal and diseased kidneys. Nephrotic and nephritic diseases were included along with cases of diabetes nephropathy. Immunofluorescence was used for colocalization of PIGR to the SC and immunohistochemistry was performed to assess the distribution of PIGR in the various disease states. Sandwich ELISA was used to measure secretory IgA levels in urine and blood samples from the same disease categories. Primary culture of renal tubular epithelium on permeable supports was used to establish an in-vitro system for functional studies of IgA transcytosis.

Results: Colocalization studies showed that PIGR indeed localizes to the SC of human kidney. Furthermore, the tubular PIGR expression increases as an early response to both acute and chronic renal injury. ELISA measurements of secretory IgA levels in serum and urine samples from patients suffering from various kidney diseases show and increased urinary content of secretory IgA. In vitro, we show that primary renal epithelial cells perform vectorial transport of secretory IgA towards the apical compartment.

Conclusions: The human kidney uses PIGR to export secretory IgA into the tubular luminal contents, a function similar to the established secretion of dimeric IgA onto the mucosal surfaces of the respiratory and gastrointestinal tracts. The levels of urinary secretory IgA increase prominently in response to renal injury.

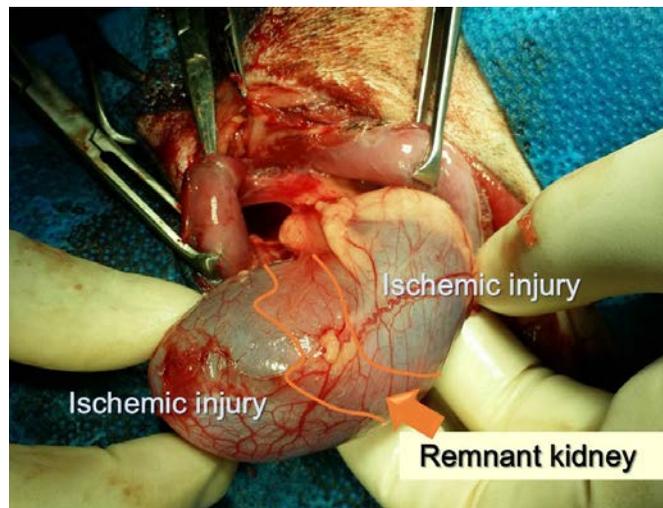
Funding: Government Support - Non-U.S.

TH-PO260

Establishment of Canine Remnant Kidney Model in Beagle Dogs Hajeong Lee,¹ Jun gu Kang,² Seung Hee Yang,² Dong Ki Kim,^{1,2} Kwon Wook Joo,^{1,2} Yon Su Kim.^{1,2} ¹Internal Medicine, Seoul National Univ Hospital; ²Kidney Research Inst, Seoul National Univ College of Medicine.

Background: The remnant kidney model has been well established in the rodents, whereas it has not been fully understood in higher and bigger animals. Canine remnant kidney model is important for better medical applications. We aimed to establish 1/16 canine remnant kidney model.

Methods: Remnant kidney model was induced in beagle dogs by a two-step subtotal nephrectomy. First, left kidney was exposed by flank incision. Among a total of eight branches of left renal arteries, seven-eighths of left renal arteries were ligated. Ischemia induction was confirmed by visual identification of topical cyanosis.



After 1 week, right kidney was removed and consequently 1/16 remnant kidney model was completed. A total of 20-weeks of subtotal nephrectomy, we sacrificed the animals and their renal histopathologic changes were examined.

Results: During 20 weeks, CKD dogs (n=12) and sham-operated dogs (n=2) were monitored. Blood pressure of CKD dogs had been maintained highly at 2 weeks. In spite of anti-hypertensive medication, 3 CKD dogs died from uremia and hypertension. After surgery, body weights were declined in both CKD and sham-operated dogs in first 2 weeks. Sham-operated dogs had recovered their body weight within 3 weeks, however, CKD dogs had recovered slowly until 3-months after surgery. Blood urea nitrogen, serum creatinine and proteinuria amount were significantly higher than those of sham-operated dogs during overall period. Renal function decline were accentuated during first 3 weeks after subtotal nephrectomy and last 2 weeks before sacrifice. Intra-renal infiltration of inflammatory cells, apoptosis of renal tubular cells, and renal fibrosis were prominent in CKD dog than in sham.

Conclusions: We successfully established 1/16 remnant kidney model by renal artery ligation in beagle dogs.

TH-PO261

Molecular Score of Acute Kidney Injury Identifies Discarded Kidneys That Are Potentially Transplantable Konrad S. Famulski,¹ Silke V. Niederhaus,² Jeff Reeve,¹ Jonathan Bromberg,² Philip F. Halloran.¹ ¹Univ of Alberta, Edmonton, AB, Canada; ²Univ of Maryland, Baltimore, MD.

Background: Many kidneys from older deceased donors are discarded due to uncertainty based on conventional features (clinical or histology). We previously showed that the molecular AKI score in implantation biopsies (Bx) predicts future graft function better than histology. Now we hypothesize that AKI scores in kidneys accepted for transplantation will be similar to some discarded kidneys when decision to transplant is based on conventional features.

Methods: Pre-implantation Bx from accepted and discarded kidneys were obtained from brain dead >50 years donors. Decision to discard was based on MAPI scores of wedge Bx in 20/28 discards. Molecular AKI scores and global gene expression were analyzed by microarrays.

Results: The molecular AKI scores in all kidneys were compared by principal component analysis (PCA).

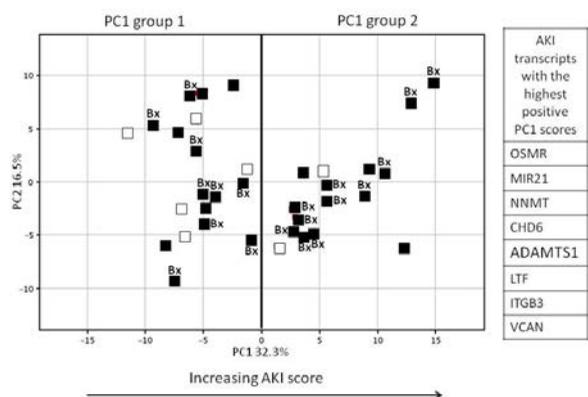


Figure 1. PCA analysis of pre-implantation biopsies from transplanted and discarded kidneys based on the molecular AKI score. □ Accepted kidneys, ■ Discarded kidneys, Bx – decision to discard was based on the biopsy findings.

PCA defined two sets of kidneys. Group 1 had low AKI scores and included 14 discarded kidneys and 5 accepted kidneys. Thus many discarded kidneys had low AKI scores similarly to accepted kidneys and were potentially transplantable. Group 2 contained 14 discarded kidneys and 2 transplanted kidney, all with high AKI scores. 1852 transcripts associated with PC1 of the AKI scores. Pathway analysis demonstrated that Group 2 kidneys had decreased expression of genes related to oxidative phosphorylation suggestive of activation of MTORC2 pathway, and had increased expression of genes related to antigen presentation driven by IFNG and to response to wounding. Thus Group 2 kidneys with high AKI scores were more stressed than other potentially acceptable kidneys.

Conclusions: Addition of molecular features to the evaluation of biopsies may lead to improved kidney utilization from older donors and offers mechanistic insights into why such kidneys have impaired performance.

TH-PO262

Characterization of Injury in Renal Proximal Tubules During Cold Incubation and Rewarming Anja H. Bienholz,¹ Gesine Pless-Petig,² Andreas Kribben,¹ Ursula Rauen.² ¹Nephrology, Univ Duisburg-Essen, Essen, Germany; ²Physiological Chemistry, Univ Duisburg-Essen, Essen, Germany.

Background: Cold incubation and rewarming induce an essential component of preservation injury which is iron-dependent in many cell types. In rat hepatocytes a chloride-dependent component of injury has been described, while chloride-poor solutions accentuated damage in endothelial cells. This work examines the injury induced by cold incubation and rewarming in isolated renal proximal tubules.

Methods: Rat renal proximal tubules were isolated by collagenase digestion and Percoll gradient centrifugation. The vascular storage solution TiProtect® and a chloride-poor modification +/- iron chelators (IC; deferoxamine 0.5mM, LK614 20µM) were used for cold incubation. Incubation of 5ml tubular suspension respectively was performed in closed flasks at 4°C, followed by rewarming in an extracellular buffer (3h at 37°C). LDH release, ATP content and resazurin reduction were measured as indicators of cellular integrity, energy content and metabolic activity.

Results: No differences in LDH release were detected after 24h of cold incubation. After rewarming LDH release was less in solutions with IC (23+6% vs 39+10%; p<0.05 chloride-rich and 25+6% vs 50+7%; p<0.001 chloride-poor; n=3). After 48, 120 and 168h of cold incubation LDH release was less in solutions with IC. Without IC LDH release showed a tendency to be higher in chloride-poor solutions (53+4% vs 30+7% after 48h of cold incubation; p<0.001; n=8). Following rewarming metabolic activity was tendentially better conserved in tubules stored with IC (109+35% vs 47+17%; ns; n=4, chloride-rich). After 48h of cold incubation ATP content was better conserved in chloride-rich than in chloride-poor solutions (51+20% (chloride-rich, without IC) and 67+12% (with IC) vs 18+6% (chloride-poor, without IC) and 27+6% (with IC); p min. <0.05; n=8). These results were confirmed after 120h of cold incubation.

Conclusions: The results confirm an iron-dependent component of injury in proximal tubules during prolonged cold incubation and rewarming. This data for the first time shows a benefit of chloride-rich solutions for preservation of energy content in renal proximal tubules during cold incubation.

Funding: Private Foundation Support

TH-PO263

Apoptosis During Extreme Cold Ischemia and Rewarming Involves a Caspase Independent Pathway Swati Jain, Charles L. Edelstein, Alkesh Jani. Renal, Univ of Colorado, Aurora, CO.

Background: Cold ischemia (CS) followed by warm reperfusion (REW) during hibernation is a natural model we have used to understand Delayed graft function (DGF). We have shown that hibernating ground squirrel kidneys and tubular cells (RTEC) survive CS for several days in torpor followed by REW in Arousal without RTEC apoptosis. In contrast mouse & human kidneys demonstrate significant tubular apoptosis after CS/REW. We have previously shown that apoptosis during CS/REW in mouse RTECs is mediated in part by a caspase dependent pathway. Here we explore whether a caspase independent pathway

of apoptosis is activated during CS/REW. We hypothesized that increased mitochondrial injury during CS/REW in mouse RTECs would result in release of mitochondrial AIF, thus activating caspase independent apoptosis. Furthermore, we hypothesized that squirrel RTECs would be protected from apoptosis and not release AIF during CS/REW.

Methods: Squirrel and mouse RTECs were subjected to cold storage (CS) in UW solution followed by rewarming (REW) in normal media as previously described (Jain, S. Transpl Int, 2015). Apoptosis was quantified by TUNEL assay. AIF was examined in mitochondrial and cytosolic fractions.

Results: Mouse RTECs exposed to CS/REW had significantly increased apoptosis vs. squirrel RTECs. Furthermore, mouse RTECs subjected to CS/REW had significantly increased mitochondrial AIF translocation to the cytosolic fraction vs. squirrel RTECs.

	Squirrel RTECs		Mouse RTECs	
	Cont	CS/REW	Cont	CS/REW
TUNEL +ve cells	0.25±0.2	2.0±0.4	2.7±0.4	26±2.2*
AIF	-	-	-	++++

n = 3; * p <0.05 vs squirrel RTECs

Conclusions: The data provide evidence of mitochondrial disruption in mouse RTECs during CS/REW, resulting in caspase independent apoptosis mediated by AIF. One potential reason for the remarkable ability of hibernators to survive prolonged CS/REW far in excess tolerable by nonhibernators is mitochondrial preservation that prevents release of AIF. Understanding caspase independent pathways during CS/REW may lead to improved organ preservation, and novel therapies for DGF.

Funding: Other NIH Support - R03 DK96151-01 to Alkesh Jani

TH-PO264

Phenotype of Renal Tubular Cell Death During Delayed Graft Function Swati Jain, Robert J. Plenter, Danica Galesic Ljubanovic, Chelsea M. Ruller, Trevor L. Nydam, Alkesh Jani. Renal, Univ of Colorado, Aurora, CO.

Background: Delayed graft function (DGF) independently predicts reduced 5 yr kidney transplant survival. Treatments of DGF are lacking. Cold ischemia (CI) is a significant risk factor for DGF but the mechanism by which CI leads to DGF is unknown. The aim of this study was to determine the effects of CI on donor kidneys alone versus CI followed by warm reperfusion after kidney transplant (CI+Txp). We hypothesized that CI alone would produce a different injury phenotype to CI+Txp.

Methods: Male C57BL6 mice aged 8-12 weeks, were subjected to mouse kidney transplant. Donor kidneys were subjected to 3 hours CI in UW solution, and processed immediately or subjected to syngeneic mouse kidney transplant. Renal function was assessed by serum creatinine (Scr). Renal tubular cell (RTC) apoptosis and necrosis were quantified by an independent nephropathologist. TLR4, RIP3, cleaved BID, Bax, cleaved caspase-8 (CC8) and cleaved caspase-3 (CC3) were examined by immunoblot.

Results: CI+Txp resulted in a significantly increased Scr (1.9±0.15) vs. transplant without CI (0.3±0.05). CI alone results in increased RTC apoptosis and CC3 but did not result in necrosis. In contrast, CI +Txp led to; (1) increased CC8, cleaved BID, Bax and CC3, and thus increased RTC apoptosis and also increased programmed necrosis; (2) increased RTC necrosis that was associated with increased RIP3 and TLR4.

	Control	Donor Kidney (CI)	Transplant Kidney (CI+Txp)
Apoptosis/10hpf	0.6±0.3	10.33±0.8*	13.33±0.3*
ATN Score	0.06±0.03	0.1±0.05	4.83±0.1*
CC3	0.04±0.02	0.37±0.02*	0.21±0.04†
CC8	ND	ND	0.13±0.06†
BID	0.1±0.04	0.2±0.03	0.53±0.01†
Bax	ND	0.03±0.01	0.33±0.04†
TLR4	0.5±0.3	ND	0.34±0.01†
RIP3	ND	ND	0.65±0.2†

n=3; *p<0.05 vs. control, †p<0.05 vs. CI; ND=not detected

Conclusions: CI results in RTC apoptosis alone without necrosis. In contrast CI+Txp results in a distinct injury phenotype of RTC apoptosis, and also programmed necrosis that is associated with: (1) increased RIP3 and TLR4; (2) CC8 activation of BID, which may further promote bax activation and thus programmed necrosis. Understanding the phenotype of injury following prolonged CI and kidney transplant may lead to novel therapies for DGF.

Funding: Other NIH Support - R03 DK96151-01 to Alkesh Jani

TH-PO265

Abstract Withdrawn

TH-PO266

Swine Leukocyte Antigens and Orthotopic Kidney Transplantation in Yorkshire Piglets and Yucatan Miniature Swine Todd D. Merchen,¹ Victor Monterroso,² Daniel Moralejo,² Andrea Saucedo,² Daniel Kleven,³ Chak-Sum Ho,⁴ N. Stanley Nahman,⁵ ¹Surgery, Georgia Regents Univ; ²Laboratory Animal Sciences, Georgia Regents Univ; ³Pathology, Georgia Regents Univ; ⁴Gift of Life Michigan, Ann Arbor, MI; ⁵Medicine, Georgia Regents Univ.

Background: PCR with sequence-specific primers (PCR-SSP) is a rapid and inexpensive approach to low-resolution (Lr) swine leukocyte antigen (SLA) genotyping. PCR-SSP may be used in Yorkshire pigs (Yorks), cheaper than expensive Yucatan miniature swine (YMS), for kidney transplantation (KT). We performed dual exchange allogeneic KT (DEAK) in both Yorks and YMS, and correlated outcome with SLAs.

Methods: Orthotopic DEAK (30 kg sows) was performed in 2 YMS (Pig #9, SLA haplotype Lr-4.5/6.7, blood type A; and Pig #10, SLA Lr-4.5/4.5, A) and 2 Yorks (Pig #7, SLA Lr-6.12/22.15b, non-A; and Pig #8, SLA Lr-4.4/40.12, A). Species couples were operated simultaneously. For YMS Pig #9, the left kidney (LK9) was resected, ex vivo perfused on ice, and stored in an ice bath. LK10 was then removed, perfused and stored while LK9 was transplanted into #10. Then LK10 was transplanted into #9. Both R kidneys were removed. The same procedure was performed in Yorks. No immunosuppression was used; animals were sacrificed (sac) on POD 2-10.

Results: Mean pre-op creatinine (Cr) was 1.05 mg/dl. For YMS, Pig #10 rejected LK9 and died on POD-6 (Cr 19.6). Pig #9 accepted LK10 with Cr 2.4 at sac on POD-9. For Yorks, Pig #7 showed hyperacute rejection (RFX) of LK8 (POD-2, Cr 12.1) and Pig #8 had vascular RFX of LK7 (POD-2, Cr 4.4). All KT organs were well perfused at sac. For YMS, one SLA haplotype mismatch (Lr-6.7) led to RFX of LK9 by Pig #10, whereas complete SLA match in the other direction allowed graft acceptance of LK10 by Pig #9; both animals were blood type A. For Yorks, hyperacute RFX occurred in Pig #7 due to blood type incompatibility. Vascular RFX in Pig #8 resulted from a two class I haplotype-one class II haplotype mismatch.

Conclusions: Orthotopic DEAK and SLA typing with PCR-SSP are equally effective in Yorks and YMS, allowing for predictable patterns of RFX/acceptance. Yorks may offer a reasonable alternative to YMS for the study of experimental KT.

Funding: Private Foundation Support

TH-PO267

Development of Experimental Model of Renal Thrombotic Microangiopathy in Rat Allogeneic Bone Marrow Transplantation Takafumi Kanemitsu, Go Kanzaki, Yusuke Okabayashi, Michiko Aoki, Kiyotaka Nagahama, Akira Shimizu. *Dept of Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.*

Background: Renal thrombotic microangiopathy (TMA) after clinical hematopoietic stem cell transplantation (HSCT) is a well-recognized complication that carries a high risk of death. In TMA after HSCT, total body irradiation, use of immunosuppressants for prophylaxis against graft versus host disease (GVHD), viral infection, and GVHD have been proposed as risk factors. However, so far, experimental model of renal TMA after HSCT or bone marrow transplantation (BMT) has not been reported.

Methods: In order to develop the experimental rat model of renal TMA after allogeneic BMT, we performed BMT from Lewis (RT11) bone marrow cells (6.0×10^7 cells) to DA (RT1a) rats after 10G irradiation without immunosuppression. We examined the clinical and pathological characteristics of several organs, including the skin, liver, gut and kidney during 9 months after BMT.

Results: In syngeneic BMT and non-BMT control DA rats, acute or chronic GVHD and renal TMA did not develop by 9 months. In DA rats after Lewis BM cell transplantation without immunosuppression, renal TMA in the kidney developed in 3 out of 6 rats 9 months after BMT with GVHD in the skin, gut, and liver. Renal dysfunction including the increased levels of the serum creatinine (0.33 ± 0.1 mg/dL) and urinary protein (0.4 ± 0.1 g/day) developed at 9 months with skin rash, alopecia, decreased body weight, and liver dysfunction (AST: 231 mg/dl; ALT: 112 mg/dl; LDH: 987 mg/dl). Renal pathology showed collapsed and sclerotic glomeruli with endothelial cell injuries in all animals. Renal TMA findings were characterized by the glomeruli with mesangiolysis, duplication of the GBM, and fibrin thrombi formation. Exudative lesions in small arteries were also seen. These renal findings were quite similar findings as renal TMA after HSCT in humans.

Conclusions: In 50% of animals, renal TMA associated with GVHD developed with renal dysfunction after Lewis to DA rat allogeneic BMT. Further studies are needed to assess the mechanism of renal TMA after BMT.

TH-PO268

Beneficial Effect of Exendin-4 on Autophagy Dysfunction During Tacrolimus-Induced Pancreatic Islet Injury Sun Woo Lim, Long Jin, Jian Jin, Chul Woo Yang. *Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: Autophagy is a cellular degradation-recycling system for aggregated proteins and damaged organelles. Previously, we reported that chronic calcineurin inhibitors (CNIs)-induced nephropathy is characterized by excessive autophagosome formation and decreased autophagic degradation rate. We suggested that lysosomal dysfunction may associate in the process of autophagic degradation. In this study, we evaluated the autophagic function in CNI-induced pancreatic beta cell injury, and combined treatment of exendin-4 (Exd), anti-diabetic agent has therapeutic effect by improving CNI-induced lysosomal dysfunction.

Methods: Rats were treated with tacrolimus (TAC, 1.5 mg/kg, s.c.) and Exd, (1 ug/kg, i.p.) for 4 weeks. The effects of Exd on TAC-induced pancreatic beta cell dysfunction were evaluated by IPGTT, serum insulin level, HOMA-IR index, and islet size. Using an INS-1 cells, we examined the effect of Exd on TAC-induced lysosomal dysfunctions such as pH increase, reduced cathepsin B activity and LAMP-2A. Autophagosome formation and autophagic protein aggregates were confirmed by the expression of LC3-II and p62, respectively. Oxidative stress was measured by the concentration of 8-OHdG, MnSOD, catalase, and H₂DCF-DA. The influence on apoptosis was examined by TUNEL assay, Annexin V, and active caspase-3.

Results: Four weeks of TAC treatment increased blood glucose levels and HOMA-IR index, and decreased serum insulin level and islet size. But co treatment with Exd-4 attenuated TAC-induced pancreatic beta cell dysfunction and islet size. Exd treatment improved TAC-induced pH increase, cathepsin B activity, and LAMP-2A expression in INS-1 cells. These were accompanied by restored expression of LC3-II and p62 which is markers for autophagic degradation rate. The markers for oxidative stress and apoptosis were also recovered by cotreatment of Exd.

Conclusions: The results of our in vivo and in vitro studies demonstrate that Exd has an effective antidiabetic agent that exerted antioxidative and antiapoptotic effects via restoring TAC-induced autophagic dysfunction.

Funding: Government Support - Non-U.S.

TH-PO269

Klotho Deficiency Is Associated with Chronic Tacrolimus-Induced Oxidative Injury Sun Woo Lim, Jian Jin, Long Jin, Byung ha Chung, Chul Woo Yang. *Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: We previously demonstrated that experimental animal model of chronic calcineurin inhibitors (CNIs)-induced nephropathy showed down regulated Klotho in renal tissues. We suggested that Klotho deficiency is highly associated with prolonged treatment of CNI-induced oxidative injury and resultant apoptosis and renal dysfunction. To determine whether Klotho deficiency is closely associated with CNI-induced renal injury via oxidative stress, Klotho heterozygote mice were compared with wild type control.

Methods: Mice of wild type (+/+) and Klotho heterozygote (Kl/+) were daily treated TAC (0.25, 0.5, 1 mg/kg, s.c.) for 4 weeks under the 0.01% sodium diet. The effects of various dose of TAC and Klotho deficiency on renal function, fibrosis, and apoptosis. The expression of Klotho was measured in renal tissue and serum. Oxidative stress was evaluated with measuring 8-OHdG and MnSOD. Using a HK-2 cells, we examined the protective effect of recombinant Klotho under TAC treatment by measuring oxygen consumption rate (OCR), ATP production, amount of ROS, mitochondrial membrane potential (MMP), and apoptosis.

Results: Four weeks of TAC treatment induced renal dysfunction, renal fibrosis, and apoptosis in a dose-dependently in +/+ mice. These changes were aggravated in Kl/+ mice receiving TAC. Reduced Klotho level in urine, serum, and renal tissue was accompanied increased renal injury by TAC treatment. Moreover, 8-OHdG was increased in +/+ mice treated with TAC, and Kl/+ mice showed further increased 8-OHdG. The expression of MnSOD was reversely responded. Based on the in vivo results, in vitro test using HK-2 cells also performed by treatment of recombinant Klotho and/or TAC. Klotho treatment reversed the mitochondrial function such as OCR, ATP production, MMP as well as ROS production and apoptosis.

Conclusions: The results of our in vivo and in vitro studies demonstrate that Klotho has a renoprotective role against TAC-induced renal dysfunction and cellular injury by reducing oxidative stress. These results suggest that Klotho has therapeutic potential in CNI-induced nephrotoxicity.

Funding: Government Support - Non-U.S.

TH-PO270

Discrepant Effect of Metformin on Hyperglycemia in Rats with Tacrolimus- or Sirolimus-Induced Diabetes Mellitus Jian Jin, Long Jin, Ji Hyun Yu, Sun Woo Lim, Byung ha Chung, Chul Woo Yang. *Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: Metformin is the first choice used drug in the treatment of diabetes mellitus. However, the effect of metformin on immunosuppressant-induced hyperglycemia is still controversy. In this study, we aimed to investigate the effects of metformin in tacrolimus- or sirolimus-induced diabetes mellitus.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: Six groups of Sprague-Dawley rats were studied: animals received tacrolimus (1.5 mg/kg) or sirolimus (0.3 mg/kg) and metformin (200 mg/kg) or vehicle for 4 weeks. Body weight, water intake, and urine volume were measured before sacrifice. The effect of metformin on tacrolimus or sirolimus-induced hyperglycemia was evaluated by assessing intraperitoneal glucose tolerance test (IPGTT), islet size, and insulin level. For further analysis, isolated rat islets from normal rats were treated with tacrolimus (30 ng/ml) or sirolimus (90 ng/ml) and metformin (165 ng/ml) for 12hr, then glucose stimulated insulin secretion (GSIS) were performed.

Results: After four weeks, tacrolimus or sirolimus-treated animals showed decreased body weight and increased water intake and urine volume compared with vehicle group. Treatment with tacrolimus or sirolimus caused elevated blood glucose level and reduced serum insulin level. Islet size by measuring insulin-positive area was significantly decreased in tacrolimus or sirolimus-treated group. Combined treatment of metformin did not improve tacrolimus-induced blood glucose level. On the other hand, metformin recovered these value compared with the sirolimus alone. In vitro study of GSIS, combined treatment with metformin and tacrolimus showed a reduction in insulin secretion ability compared with tacrolimus alone. But, sirolimus and metformin-treated group showed higher level of insulin secretion than sirolimus alone.

Conclusions: In this study, we found that metformin confers to the insulin secretion capacity during sirolimus treatment, but not in tacrolimus. Therefore, use of metformin should be considered in transplant recipients receiving tacrolimus.

Funding: Government Support - Non-U.S.

TH-PO271

Effect of Vitamin D on Th17 Related Immune Responses in Tacrolimus-Based Immune Suppression *Byung Ha Chung, Hyunseon Kim, Chul Woo Yang. Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea.*

Background: The aim of this study is to investigate the effect of vitamin D on Th17 allo-immune responses in tacrolimus (Tac)-based immune suppression.

Methods: First, we investigated the clinical significance of 25-hydroxyvitamin D (25(OH)D) level on the development of acute rejection or serum Th17 associated cytokine levels in kidney transplant recipients (KTRs). Second, we determined the suppressive effect of 1 α ,25-dihydroxyvitamin D3 (1,25(OH)₂D3) on T cell proliferation upon T-cell specific stimulation or on inflammation of human primary tubular epithelial cells (HPREpiC) induced by interleukin-17 (IL-17) or TNF- α . Third, we investigated the pathway of the protective action of 1,25(OH)₂D3 on T cell or HPREpiC.

Results: In renal transplant recipients under Tac based immunosuppression, 25(OH)D level at KT was significantly associated with the development of acute rejection and the level was inversely correlated with Th17 related cytokines such as IL-17, IL-22, IL-23 and IL-1 β in another KTR patients group. In T cell experiment, Tac suppressed Th1, Th2 and regulatory T cells in a concentration-dependent manner, but did not suppress Th17 cells even at high concentration. In contrast, addition of 1,25(OH)₂D3 significantly suppressed Th17 proliferation. Next, IL-17 and TNF- α significantly induced the secretion of IL-6 and IL-8 from HPREpiC, however, addition of 1,25(OH)₂D3 significantly reduces the secretion of those cytokines.

Conclusions: This study suggests that addition of 1,25(OH)₂D3 to Tac is beneficial by suppression of Th17 alloimmune responses and hence it could be proposed as therapeutic strategy to improve allograft outcome.

TH-PO272

Use of D-Lactate for Therapeutic Immunosuppression *Ulf H. Beier,¹ Zhonglin Wang,² Wayne W. Hancock,¹ Matthew H. Levine.² ¹Children's Hospital of Philadelphia, Philadelphia, PA; ²Univ of Pennsylvania, Philadelphia, PA.*

Background: Current immunosuppressive therapies are limited by non-specificity and toxicity. Lactic acid is a carboxylic acid present as L- and D- optical isomers. In mammals including humans, lactate is present almost entirely as L-lactate. L-lactate can accumulate in the contexts of ischemia and/or Warburg metabolism, and suppress T cell function.

Methods: We hypothesized that since D-lactate is more slowly eliminated than L-lactate, it may have immune modulatory effects similar to L-lactate that maybe exploited for therapeutic immunosuppression, and tested both optical isomers in vitro and in vivo.

Results: We observed that while both D- and L-lactate (5-40 mM) markedly impaired murine and human CD4 and CD8 T cell proliferation in vitro, D-lactate had stronger effects than L-lactate. Neither D- nor L-lactate affected cell viability and apoptosis (7AAD, annexin V), and IL-2 and IFN- γ cytokine production by CD4 and CD8 T cells were unaffected. However, adding 20 mM D-lactate to CD⁴CD25-Foxp3⁻ T-effector cells (Teff) under polarizing conditions increased Foxp3⁺ Treg formation by 46.2 \pm 31.5% (P<0.03, n=4), whereas the effects of L-lactate were not statistically significant (22.8 \pm 22.7%, p=0.09). To test effects of D-lactate in vivo, we adoptively transferred 1 \times 10⁶ Teff with or without 1.25 \times 10⁵ Tregs into Rag1^{-/-} mice, and treated each group with 90 mmol/kg D-lactate or control NaCl for 5 days, and assessed T cell proliferation. D-lactate reduced Teff cell proliferation (P<0.001, n=5), and de-novo Foxp3⁺ Treg formation was increased in D-lactate (21.2 \pm 7.4%) vs. NaCl (11.9 \pm 3.4%) treated animals (P<0.01, n=5).

Conclusions: Together, these results show that sodium D-lactate can impair T cell proliferation and promote Foxp3⁺ Treg induction. Our data suggest that use of specific, defined metabolites may have important therapeutic value as novel immunosuppressive agents.

Funding: Other NIH Support - NIAID

TH-PO273

Environment and Graft Interaction Impact on Endothelium After Experimental Kidney Transplantation *Diana A. Papazova, Nynke R. Oosterhuis, Jaap A. Joles, Marianne C. Verhaar. Nephrology & Hypertension, Univ Medical Center Utrecht, Netherlands.*

Background: At transplantation (TX) into a CKD recipient, the donor's endothelium is exposed to uremic and oxidative stress that may negatively influence graft function and structure. We hypothesized that in CKD milieu, graft endothelial damage is determined by both donor quality and exposition to uremic and oxidative stress. We also investigated whether healthy environment halts progressive endothelial loss in expanded criteria donor (ECD) graft.

Methods: Male inbred Lewis rats were used as donors and recipients. CKD developed in 24 rats after bilateral ablation of 2/3 of kidney mass. Control rats (n=24) were age-matched. Orthotopic TX was performed: healthy kidney to healthy rat (HD-HR); CKD kidney to healthy rat (CD-HR); healthy kidney to CKD rat (HD-CR); CKD kidney to CKD rat (CD-CR). Right donor kidney served as reference for left kidney (graft) injury at TX. Contralateral kidney of recipient was removed 10-14 days after TX. At wk 6, we evaluated graft function and morphology, and systemic oxidative (TBARS) and vascular damage (aorta calcification).

Results: Graft function (inulin & PAH clearance) at wk 6 after TX confirmed marked impairment after ablation and was not affected by environment (CD-HR vs. CD-CR and HD-CR vs. HD-HR, all NS). TX of healthy vs. CKD graft did not influence oxidative and vascular damage at wk 6 post-TX (CD-HR vs. HD-HR and HD-CR vs. CD-CR, both NS). Grafts from healthy donors developed more glomerulosclerosis (GS) and tubulointerstitial injury (TI) and a reduction in glomerular and interstitial endothelium (JG12 stain) compared to reference kidneys after TX in a CKD donor (all P<0.05). However, despite similar ischemia-reperfusion, TI and GS did not worsen in ECD grafts and TX of ECD grafts in healthy recipients did preserve glomerular and interstitial endothelium.

Conclusions: TX to CKD environment was less detrimental for ECD graft as shown by preserved endothelium compared to healthy graft, possibly due to preconditioning. In the reverse model, healthy environment halted progression of endothelial damage in ECD grafts. Thus, depending on environment, ECD grafts appear to maintain their structure.

TH-PO274

Heparan Sulfate in the Glycocalyx of Donor Renal Allografts Modulates Transplant Rejection *William L. Clapp, Sriram Ambadapadi, Dara N. Wakefield. Univ of Florida; Univ of Florida; Univ of Florida.*

Background: The molecular mechanisms underlying transplant allograft vasculopathy and chronic rejection are not fully elucidated. Glycosaminoglycans (GAGs) modulate inflammatory cell responses and Heparan sulfate (HS) is the predominant GAG in the endothelial glycocalyx. Binding to GAGs plays an important role in the function of chemokines. The role of donor allograft GAGs in renal transplant rejection is not well defined. In these studies, we investigated the effects of selective HS deficiency and interference with HS-chemokine interaction on renal allograft rejection in the mouse.

Methods: Donor renal allografts from mice with conditional deletion of the N-deacetylase-N-sulfotransferase-1 gene (Ndst1) in endothelial and myeloid/lymphoid precursors leading to HS deficiency were examined. M-T7, a viral-derived secreted glycoprotein was used to block HS-chemokine interaction. Donor renal allografts from C57B1/6 (WT) or Ndst1^{-/-} mice were transplanted into Balb/C mice and then treated with either saline (control) or M-T7.

Results: Compared to the WT, the Ndst1^{-/-} donor renal allografts had significantly reduced scores for lesions induced by rejection including infiltrates, tubulitis, peritubular capillaritis, glomerulitis, vasculitis and mesangial matrix. M-T7 treatment of WT donor renal allografts significantly reduced the histologic markers of rejection. However, the M-T7 mediated decrease in rejection was not observed in the Ndst1^{-/-} donor allografts.

Conclusions: Donor renal allografts, deficient in endothelial glycocalyx HS, reduces renal rejection. Although M-T7 reduces rejection in WT donor renal allografts, M-T7 treatment in Ndst1^{-/-} donor renal allografts is inactive, and negates the reduction of rejection mediated by the Ndst1^{-/-} donors. Donor kidney HS and HS/chemokine interactions may have a major role in reducing allograft rejection.

TH-PO275

Identification of Key Meta-Signatures Associated with Acute Rejection Post Kidney Transplant *Weijia Zhang,¹ Zhengzi Yi,¹ Karen Lok yee Keung,¹ Li Li,² Madhav C. Menon,¹ Barbara T. Murphy.¹ ¹Renal Div, Medicine, Icahn School of Medicine at Mount Sinai; ²Dept of Genetics and Genomics, Icahn School of Medicine at Mount Sinai.*

Background: Acute rejection (AR) is a major contributor to chronic allograft dysfunction and graft failure in kidney transplantation. Molecular expression profiling of kidney biopsies has been performed by several independent studies in recent years, but the AR-associated signatures identified from these studies vary.

Methods: Meta-analysis and Bayesian network analysis were performed on 6 kidney biopsy expression datasets to identify key meta-signatures associated with acute rejection and the key drivers were validated in independent expression datasets of kidney transplant and kidney diseases.

Results: Using 733 biopsy samples (239 AR episodes) from 6 expression datasets as discovery cohort, we identified 982 meta genes with differential expression in AR vs noAR patients at FDR<0.05. Gene Ontology enrichment analysis indicated that genes involved in immune response, T/B cell activation and proliferation, antigen processing and presentation,

protein kinase cascade and NFkB signaling pathways were upregulated, while genes involved in metabolism were downregulated. The expression data of metagenes was used to build a meta-coexpression network from which functional submodules were identified. 14 key driver genes were subsequently derived from these network submodules that had differential connectivity in AR compared to noAR patients. The differential modules and key drivers also themselves significantly correlated with HLA antibody and graft survival. Finally, the differential expression of key drivers was validated in independent expression datasets from kidney transplants (N=839) as well as other kidney diseases (IgA and Diabetic nephropathy and Lupusnephritis).

Conclusions: We identified a set of AR-associated key drivers that may play a common and pivotal role for driving the inflammatory responses in acute rejection in kidney transplantation as well as other kidney diseases, which will help the better understanding of molecular mechanism of acute rejection post transplant and therefore improve the early diagnosis/treatment of acute rejection to prevent renal failure.

Funding: NIDDK Support

TH-PO276

SNPs of Solute Carrier Family Genes Associated with Acute Renal Allograft Rejection in Korean Population Byeongwoo Kim,¹ Yeong Hoon Kim,¹ Sang ho Lee,² Sunwoo Kang.¹ ¹*Dept of Nephrology, Inje Univ, Busan Paik Hospital, Busan, Korea;* ²*Dept of Nephrology, College of Medicine, Kyung Hee Univ, Seoul, Korea.*

Background: Solute carrier family has been reported to be associated with various kinds of renal diseases. Thus, we hypothesized that single nucleotide polymorphisms (SNPs) of the solute carrier family genes might have association with acute rejection of kidney transplantation (KT) in Korean population. This study sought to investigate whether polymorphisms of solute carrier family genes are involved in the development of acute renal allograft rejection.

Methods: We firstly selected 349 solute carrier family genes in NCBI gene database and searched the nonsynonymous SNPs on coding region in each genes. Finally we selected 4200 exonic SNPs. The genotypes of these SNPs were performed using AxiomTM genome-wide human assay. SNPStats and SPSS 18.0 were used for the analysis of genetic data. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value.

Results: A total of 90 renal allograft recipients transplanted in Pusan Paik hospital. Acute rejection developed in 49 patients among them. Among 4200 SNPs of 349 solute carrier family genes, three SNPs (rs5036 in SLC4A1, rs11643718 in SLC12A3, and rs1047099 in SLC04A1) only showed significant association with acute rejection (p<0.05).

Conclusions: These results suggest that these significant SNPs (rs5036 in SLC4A1, rs11643718 in SLC12A3, and rs1047099 in SLC04A1) may be associated with the susceptibility to the acute rejection in the KT patients of Korean population.

Funding: Clinical Revenue Support

TH-PO277

The Expression and Role of Human Cytomegalovirus-Induced Viral Chemokine Receptor US28 in Smooth Muscle Cells of Renal Allografts Wouter Lollinga,¹ Raymond H. De Wit,² Gwenda F. Vasse,¹ Afsar Rahbar,³ Annelies Riezebos-brilman,⁴ Cecilia Söderberg-naucner,³ Willem Van Son,¹ Johannes S. Sanders,¹ Martine J. Smit,² Jacob van den Born.¹ ¹*Nephrology, UMC Groningen, Groningen, Netherlands;* ²*Medicinal Chemistry, VU, Amsterdam, Netherlands;* ³*Medicine, Karolinska Inst, Stockholm, Sweden;* ⁴*Medical Microbiology, UMC Groningen, Groningen, Netherlands.*

Background: Renal transplantation is the preferred treatment for end-stage renal disease. Human cytomegalovirus (HCMV) infection is associated with decreased renal graft function and survival. HCMV expresses US28, a chemokine receptor that enables HCMV to escape immune surveillance and affect microenvironment in the graft. Our aim was to localize the expression of US28 in renal biopsies and determine its effect on viral dissemination in vitro.

Methods: US28 and immediate early antigen (IEA) expression was semi-quantitatively scored in recipient renal transplant biopsies (n=49) from HCMV-seropositive donors using immunohistochemistry. Expression in glomeruli, endothelium, smooth muscle cells, epithelium and inflammatory infiltrates was analyzed. Primary vascular smooth muscle cells were infected (MOI 0.01) with HCMV WT and US28-deficient HCMV (dUS28) carrying a GFP-tag, to follow viral dissemination in vitro.

Results: IEA was uniformly distributed over the renal compartments. US28 was expressed during active infection and latency. It was expressed in all compartments, but prevalent (Kruskal-Wallis; P<0.001) in vascular smooth muscle (42% cells positive) and tubular epithelial cells (30%). It was also expressed in the neointima. Smooth muscle cells were permissive to HCMV and underwent lytic infection in vitro, but dissemination was delayed for US28-deficient HCMV.

Conclusions: In short, HCMV-induced US28 is expressed in smooth muscle cells of renal allografts. US28 expression here suggests a role in vascular disease following viral infection, especially given its presence in the neointima. Absence of US28 decreased HCMV dissemination in smooth muscle cells in vitro, yielding it an interesting target for intervention. The observation that HCMV may interfere with vascular function through the expression of chemokine receptor US28 is an intriguing finding worth further exploring.

TH-PO278

Multiple Domains of CTGF Amplify Pericyte Activation to Become Pathological Matrix Producing Cells Shuyu Ren, Bryce Gordon Johnson, Gamze Karaca, Ivan G. Gomez, Jeremy Stuart Duffield. *Research & Development, Biogen, Cambridge, MA.*

Background: Connective tissue growth factor (CTGF), a member of the CCN gene family, is an extracellular matrix (ECM)-associated heparin-binding protein involved in matrix production. CTGF has been shown to contribute to progression of fibro-proliferative diseases and scarring by modifying of proliferation, migration, and adhesion of fibroblasts. CTGF has also been shown to play a role in ECM remodeling in normal physiological processes including embryogenesis, implantation, and wound healing. However recent new insights into the pathogenesis of fibrosing kidney diseases lead us to re-evaluate CTGF in this context at a cellular level. We therefore generated a mouse model which facilitates tissue specific, conditional over-expression of CTGF using homologous recombination.

Methods: We generated mice conditionally over expressing CTGF in pericytes only. We cloned domains of CTGF and the WNT inhibitor DKK1 and tested their function on primary pericyte cultures.

Results: Overexpression of CTGF in pericytes has no impact on nephrogenesis or adult homeostasis but amplifies fibrogenic and inflammatory responses to kidney disease. CTGF domain IV activates WNT/b-catenin signaling in pericytes, which is inhibited by recombinant DKK-1. CTGF Dom-IV rapidly phosphorylates the co-receptor of WNT/b-catenin signaling - LRP6. DKK-1 blocks CTGF domain IV mediated fibrotic responses in culture including fibrotic gene activation, pericyte morphology changes and migration in JNK MAP kinase dependent, WNT partially dependent pathway. CTGF Dom-I also activates pericyte migration which is also inhibited by DKK-1, JNK inhibition or Wnt ligand secretion.

Conclusions: CTGF over expression restricted to kidney stroma *in vivo* is sufficient to amplify cell activation and myofibroblast transition. Multiple domains of CTGF drive fibrogenic responses in pericytes through WNT and JNK signaling pathways.

Funding: Pharmaceutical Company Support - Biogen

TH-PO279

Sphingosine Kinase 2 Mediates Kidney Fibrosis Through Epigenetic Change Tsuyoshi Inoue,¹ Amandeep Bajwa,¹ Heather M. Perry,¹ Liping Huang,¹ Hong Ye,¹ Youichiro Wada,² Diane L. Rosin,¹ Mark D. Okusa.¹ ¹*Univ of Virginia;* ²*The Univ of Tokyo.*

Background: In numerous forms of organ injury, interstitial fibrosis is a final common pathway. Despite recent epidemiological studies, therapies to focus on fibrosis and to delay progressive renal failure are limited. We recently found that sphingosine kinase 2 deficient-mice (SphK2KO) develop less fibrosis after folic acid (FA)- or ischemia-reperfusion-induced kidney injury. Sphingosine 1-phosphate (S1P) is produced by two sphingosine kinase isoforms (SphK1 and SphK2). S1P is involved in diverse functions, but the role of S1P produced by SphK2 is gathering attention as treatments focused on epigenetics have been developed. SphK2 is primarily located in the nucleus, SphK1 is cytoplasmic. S1P produced by SphK2 inhibits histone deacetylase (HDAC) and change in histone acetylation status, which can lead to an altered target gene expression. The aim of this study is to elucidate new mechanisms of kidney fibrosis through epigenetic changes.

Methods: Transcriptome analysis and ChIP-seq of H3K9ac and H3K27ac using primary renal fibroblasts from WT, SphK1KO and SphK2KO mice were applied to find new target genes that regulate fibrosis through histone acetylation.

Results: Microarray analysis identified 135 down-regulated (<1/4) genes and 245 up-regulated (>4) genes in SphK2 KO compared to SphK1KO mice. ChIP-seq (QuEST) revealed that 258 genes have H3K27ac and 589 genes have H3K9ac only in SphK1KO and not in SphK2KO. The combination of microarray and ChIP-seq analysis yielded 21 candidate genes. To determine the *in vivo* relevance of gene expression was evaluated using an *in vivo* fibrosis model (FA model and unilateral IRI). We further applied SphK2 knock down to WT fibroblasts and overexpression to fibroblasts from SphK2KO to determine if the selected genes are regulated by SphK2. Based on these strategies, candidate genes were identified that are regulated by SphK2 through the change of histone acetylation.

Conclusions: The combination of microarray and ChIP-seq of H3K9ac and H3K27ac identified 21 candidate genes. A more detailed investigation is needed, but some genes regulated by SphK2 appear to modulate kidney fibrosis through epigenetic changes.

TH-PO280

MCP-1 Directly Induces Renal Tubulointerstitial Fibrosis Independently of Monocytes/Macrophages Infiltration Meiyan Wu, Hye-Young Kang, Mi Jung Lee, Shin-Wook Kang. *Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Previous studies have demonstrated the importance of monocyte chemoattractant protein-1 (MCP-1) and its receptor, C-C chemokine receptor 2 (CCR2), in the pathogenesis of tubulointerstitial fibrosis via the recruitment and activation of monocytes/macrophages. However, recent *in vitro* evidence has suggested that MCP-1 per se may act directly on renal cells via CCR2. Therefore, the results of a number of former studies showing the impacts of MCP-1/CCR2 blockade on renal injury may be partly attributed to a direct inhibitory effect of MCP-1 on renal cells, but this has not been clarified *in vivo* to date.

Methods: Monocyte/macrophage-deficient mice were induced by either liposome-clodronate or diphtheria toxin. These mice were treated with MCP-1-expressing lentivirus (LV) and/or RS102895, a specific inhibitor of CCR2. NRK-52E cells were treated with

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

recombinant MCP-1 with or without RS102895, or CCR2 siRNA. The mRNA and protein expression of fibronectin and type I collagen in cultured NRK-52E cells and the whole kidney were evaluated by Western blot and real-time PCR.

Results: Fibronectin and type I collagen expressions were increased in NRK-52E cells exposed to MCP-1, which was then significantly abrogated by co-administration with RS102895 or CCR2 siRNA. LV-MCP-1 transfection in mice (n=6) resulted in significant increases in infiltrated macrophages, fibronectin, and type I collagen mRNA and protein expression in the kidney. However, LV-MCP-1 transfection in monocyte/macrophage-deficient mice (n=6) resulted in increases in fibronectin and type I collagen in spite of an absence of increased macrophage infiltration. This up-regulation of fibronectin and type I collagen protein and mRNA expression in monocyte/macrophage-depleted mice were significantly ameliorated by RS102895 treatment (n=8).

Conclusions: The MCP-1/CCR2 system is directly involved in MCP-1-induced renal fibrosis and blockade of the MCP-1/CCR2 system can be a promising approach to treat various kidney diseases such as diabetic nephropathy, of which MCP-1-induced renal fibrosis is involved in the pathogenesis.

TH-PO281

T-Type Calcium Channel Blocker Attenuates Unilateral Ureteral Obstruction-Induced Renal Interstitial Fibrosis via Activation of the Nrf2 Antioxidant Pathway Soojeong Kim, Eun Sil Koh, Cheol Whee Park, Seok Joon Shin, Sungjin Chung. *Internal Medicine of Nephrology, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Besides the effect on high blood pressure, T-type calcium channel blocker has been reported to exert a renoprotective effect in experimental models with renal fibrosis. However, the exact mechanism of T-type calcium channel blocker on tubulointerstitial fibrosis has not been elucidated. In the present study, we investigated whether the renoprotective effect of T-type calcium channel blocker is associated with modulation of the signaling of oxidative stress-induced renal fibrosis.

Methods: Treatment with a nonhypotensive dose of efonidipine, a T-type calcium channel blocker, or nifedipine, an L-type channel blocker, was initiated one day before unilateral ureteral obstruction (UO) in C57BL/6 mice, and was continued until 3 and 7 days after UO. Markers of renal fibrosis, inflammation, apoptosis and oxidative stress were evaluated.

Results: In the obstructed kidneys of UO mice, treatment with efonidipine significantly attenuated interstitial fibrosis, collagen deposition and inflammation increased by UO creation compared with treatment with nifedipine. Efonidipine significantly increased the expression of antioxidant enzymes such as HO-1, NQO1, catalase and SOD1. Increased apoptotic cell death and decreased Bcl-2 expression in the obstructed kidneys were also significantly ameliorated by treatment with efonidipine. The expression of the histone acetyltransferase p300/CBP-associated factor, which is known as a regulator of inflammatory molecules, was significantly inhibited by efonidipine. These beneficial effects of efonidipine were attributed to the increased nuclear expression of Nrf2 on UO day 3 and the increased expressions of both total and nuclear Nrf2 with elevated Keap1 on UO day 7, suggesting that efonidipine would promote activation of Nrf2 differently depending time course after UO. Nifedipine had little effect on antioxidant enzymes, anti-apoptosis and Nrf2 signaling.

Conclusions: These results suggest that T-type calcium channel blocker exerts beneficial effects in renal interstitial fibrosis by activating Nrf2 and subsequent antioxidant enzymes.

TH-PO282

Fimasartan, the Novel Angiotensin Receptor Antagonist, Protects against Renal Inflammation and Fibrosis in Mice with Unilateral Ureteral Obstruction: A Possible Role of Nrf2 Soojeong Kim, Sungjin Chung, Hye Eun Yoon, Ji hee Lim, Bum soon Choi, Cheol Whee Park, Seok Joon Shin. *Internal Medicine of Nephrology, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: A newly developed angiotensin II receptor blocker, fimasartan, has effective blood pressure lowering effect via blocking renin-angiotensin system. Renal interstitial fibrosis is a final pathological process in the progression of chronic kidney disease, which is believed to be due to oxidative injury. Transcription factor nuclear-erythroid 2-related factor 2 (Nrf2) is known to regulate cellular oxidative stress and induce antioxidant genes. This study investigated the role of Nrf2 in fimasartan-mediated antioxidant effects in mice with renal fibrosis induced by unilateral ureteral obstruction (UO).

Methods: Fimasartan was administered intraperitoneally (3mg/kg/day) from the day of UO surgery in C57BL/6 mice and was continued for 7 days after operation.

Results: UO-operated mice revealed renal inflammation and fibrosis as evidenced by the degree of fibrosis and inflammatory cell infiltration in histopathological findings, total collagen content in kidney tissues and the expression of fibrotic markers in immunoblot analysis, which were reversed in the obstructed kidneys of fimasartan-treated mice. Fimasartan treatment upregulated renal expression of Nrf2 and its downstream signaling molecules, such as NQO1, HO-1, Nox 1, 2 and 4, GSTm2 and GSTm3 in both protein and mRNA levels. Furthermore, fimasartan increased the expression of antioxidant enzymes including CuSOD, MnSOD and catalase. Significantly less apoptosis in TUNEL staining, decreased pro-apoptotic protein, along with increased anti-apoptotic protein were observed in fimasartan-treated mice.

Conclusions: In conclusion, these results demonstrate that fimasartan has beneficial effects on renal oxidative stress, inflammation and fibrosis, which may be via upregulating of Nrf2 signaling, subsequently the induction of antioxidant pathways.

TH-PO283

The Na/K-ATPase Signaling and Oxidative Stress Contribute to PNx-Mediated Cardiac and Renal Fibrosis in Mice Muhammad A. Chaudhry,¹ Kyle D. Maxwell,¹ Xiaoliang Wang,² Yanling Yan,¹ Preeya Tushar Shah,¹ Zi-jian Xie,² Jiang Liu,¹ Joseph I. Shapiro.¹ ¹Pharmacology, Physiology and Toxicology, Marshall Univ JCE School of Medicine, Huntington, WV; ²Marshall Inst for Interdisciplinary Research, MIIR at Marshall Univ, Huntington, WV.

Background: We have shown that the Na/K-ATPase signaling regulates cardiac and renal fibrosis both *in vivo* and *in vitro*. We have also demonstrated that increases in oxidative stress activate Na/K-ATPase signaling. Here we report that administration of CoPP (an inducer of heme oxygenase-1, HO-1) and pNaKtide (a Na/K-ATPase signaling antagonist) attenuate 5/6 renal partial nephrectomy (PNx) mediated fibrosis in heart and kidney in C57BL/6 mice.

Methods: The C57BL/6 mice were randomly divided into six experimental groups. (1) Sham surgery (Sham), (2) PNx surgery (PNx), (3) Sham+CoPP, (4) PNx+CoPP, (5) Sham + pNaKtide, and (6) PNx+pNaKtide. CoPP (5mg/KG BW, ip) was given 5 day and one day before surgery as well as every 5 day after PNx surgery. pNaKtide (25mg/KG BW, ip) was given weekly 7days after surgery. All experimental mice were sacrificed 4 weeks after PNx surgery. Expression of collagen-1, HO-1, and protein carbonylation of heart and kidney was determined by western blot.

Results: Comparing with sham, PNx surgery significantly stimulates type I collagen expression both in heart and kidney assayed by western blot and histology analyses. Induction of HO-1 by CoPP significantly attenuates PNx-mediated collagen production and protein carbonylation. Administration of pNaKtide, which blocks Na/K-ATPase-mediated c-Src activation, also attenuates PNx-mediated collagen production. Transthoracic Echocardiography analysis demonstrates that treatment with CoPP and pNaKtide restores PNx-induced changes in relatively wall thickness (RWT) and myocardial performance index (MPI).

Conclusions: Attenuating oxidative stress and blocking Na/K-ATPase signaling is capable of restoring PNx-mediated cardiac and renal fibrosis as well as cardiac function.

TH-PO284

Wnt4 Induces Renal Fibrosis by Activating p38 Mitogen-Activated Protein Kinase Pathway Jae Eun Um, Seonghun Kim, Bo Young Nam, Hye-Young Kang, Meiyan Wu, Jimin Park, Tae-Hyun Yoo, Shin-Wook Kang. *Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Previous studies demonstrated that Wnt signaling pathway plays a key role in the pathogenesis of renal fibrosis and is related to various kidney diseases. However, although Wnt4 is abundantly expressed in renal tubule cells, the roles of these specific Wnt subfamilies in the pathogenesis of renal fibrosis have not been fully explored. Therefore, the effect of Wnt4 on renal tubulointerstitial fibrosis via p38 mitogen-activated protein kinase (MAPK) pathway was examined in unilateral ureteral obstruction (UO) animals and tumor growth factor- β 1 (TGF- β 1)-stimulated renal tubular cells.

Methods: *In vivo*, UO was performed in C57BL/6 mice (n=12). The kidneys were harvested after 6 days of UO. Immunohistochemistry was conducted with renal tissues. *In vitro*, renal proximal tubular cells (NRK-52E) and inner medullary collecting duct cells (IMCD) were each treated with recombinant TGF- β 1 with or without Wnt4 siRNA transfection. The effect of recombinant Wnt4 protein treatment was also examined in NRK-52E and IMCD cells. Real-time PCR and Western blot analysis were performed to evaluate Wnt4, fibronectin (FN), collagen type 1 (Col I), α -SMA, phospho-p38 and p38.

Results: Immunohistochemistry revealed a significant up-regulation in kidney Wnt4 expression in UO mice compared to control mice. The mRNA and protein expression of Wnt4 were significantly higher in recombinant TGF- β 1-stimulated NRK-52E and IMCD cells compared to control cells. Protein expression of fibrosis-related proteins such as FN, Col I and α -SMA as well as phospho-p38 MAPK were significantly increased in cells treated with recombinant TGF- β 1. Increased fibrosis-related proteins and phosphorylation of p38 MAPK were significantly ameliorated by Wnt4 siRNA transfection in TGF- β 1 treated cells. Furthermore, recombinant Wnt4 treatment also led to increase in protein expression of fibrosis-related proteins and phospho-p38 in NRK-52E and IMCD cells.

Conclusions: These findings suggest that Wnt4 may play a role in renal tubulointerstitial fibrosis by activating the p38 MAPK pathway.

TH-PO285

Peroxiredoxin 5 Protects TGF- β Induced Renal Fibrosis by Modulating Stat3 Activation Hoon In Choi,¹ Jung Sun Park,¹ Seong Kwon Ma,² Eun Hui Bae,² Jong un Lee,¹ Soo Wan Kim.² ¹Dept of Physiology, Chonnam National Univ Medical School, Gwangju, Korea; ²Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: Renal fibrosis is common final pathway of end-stage kidney diseases which is induced by aberrant accumulation of myofibroblasts. This process is triggered by reactive oxygen species (ROS) and proinflammatory cytokines generated by various source of injured kidney cells. Peroxiredoxin 5 (Prdx5) is a thiol-dependent peroxidase that reduces oxidative stress by catalyzing intramolecular disulfide bonds. Along with its antioxidant effects, expression level of Prdx5 also was involved in inflammatory regulation by immune stimuli. However, the physiological effects of Prdx5 in renal fibrosis have not been fully characterized and the underlying mechanisms remain poorly understood.

Methods: As *in vivo* and *in vitro* model of renal fibrosis, Sprague-Dawley rats were subjected to unilateral ureteral obstruction (UO) for 1 or 7 days. Fibroblast-like rat proximal tubule cells (NRK49F) were treated with transforming growth factor β (TGF- β) for 0, 1, 3, or 5 days. To access the involvement of its peroxidase activity in TGF- β induced renal fibrosis, wild type Prdx5 (WT) and double mutant Prdx5 (DM), converted two active site cysteines at Cys 48 and Cys 152 residue to serine, were transiently expressed in NRK49F cells.

Results: The protein expression of Prdx5 was reduced in UO kidneys. Upregulation of fibrotic markers, such as fibronectin, vimentin, and alpha-smooth muscle actin (α -SMA), were declined at 5 days in time point of higher Prdx5 expression in TGF- β treated NRK49F cells. The overexpression of wild type Prdx5 by transient transfection in NRK49F cells attenuated the TGF- β induced upregulation of fibronectin and α -SMA. On the other hand, the transient transfection of double mutant Prdx5 did not prevent the activation of fibrotic markers. Overexpression of Prdx5 also suppressed the TGF- β induced upregulation of Stat3 phosphorylation, while phosphorylation of Smad2/3 was unchanged.

Conclusions: Prdx5 protects TGF- β induced renal fibrosis in NRK49F cells by modulating Stat3 activation in a peroxidase activity dependent manner.

TH-PO286

Fucoidan reduces Pressure-Induced Fibrotic Responses in Renal Tubular Cells Through Down-Regulating β -Catenin Tso Hsiao Chen, Cheng-hsien Chen. *Div of Nephrology, Wan Fang Hospital, Taipei Medical Univ, Taipei, Taiwan.*

Background: Fucoidan is a kind of natural fucose-enriched sulfated polysaccharides found mainly in various species of brown algae and brown seaweed. In recent years, many studies show fucoidan reduces hypoxia nephropathy, and also inhibits liver fibrosis. However, the influence of fucoidan on renal fibrosis is not clear yet.

Methods: Rat renal tubular cells (NRK-52E) are applied in this study. We study the influence of low-molecular-weight fucoidan (500 Da) on renal fibrosis in a pressure-stressed cell model. Sixty mmHg of pressure will be applied on NRK-52E cells for different periods to induce EMT. The expression of EMT markers and β -catenin will be monitored by Western blotting.

Results: NRK-52E cells were subjected to 60 mmHg of pressure for the indicated periods. Cellular E-cadherin, TGF- β , CTGF, fibronectin, α -SMA and Snail were detected by Western blotting. We found sixty mmHg of pressure induces EMT markers expression in NRK-52E cells. Fucoidan (0.1 – 1 mg/ml) reduced pressure-induced α -SMA and fibronectin in NRK-52E cells. Fucoidan reduced pressure-induced CD44 and β -catenin, which may be a critical mechanism of anti-fibrosis effect of fucoidan. NRK-52E cells were pretreated with fucoidan for 30 min and then treated with TGF- β for 24 h. We found fucoidan could reduced TGF β -induced α -SMA and fibronectin in NRK-52E cells.

Conclusions: In summary, fucoidan at adequate doses inhibits pressure-induced fibrotic responses in rat renal tubular cells. The investigation of the protective effect of fucoidan against renal fibrosis may provide a new therapeutic agent for CKD patients.

Funding: Government Support - Non-U.S.

TH-PO287

Indoxyl Sulfate Exacerbates Oxidative Stress and Impairs NF- κ B/Nrf2 Levels in RAW Macrophages Denise Mafra,¹ Milena Barca Stockler-Pinto,¹ Juliana Saldanha,² Christophe O. Soulage,³ Denis Fouque.⁴ *¹Post-Graduate Program in Cardiovascular Sciences, Fluminense Federal Univ (UFF), Niterói, Rio de Janeiro, Brazil; ²Post-Graduate Program in Medical Sciences, Fluminense Federal Univ (UFF), Niterói, Rio de Janeiro, Brazil; ³INSA de Lyon, CarMeN, INSERM U1060, Univ de Lyon, Villeurbanne, France; ⁴Dept of Nephrology, Centre Hospitalier Lyon Sud, INSERM 1060, CENS, Univ de Lyon, Pierre Bénite, France.*

Background: Indoxyl sulfate (IS), a uremic toxin produced by intestinal bacterias, is accumulated in Chronic Kidney Disease (CKD) patients and exhibits potent inflammatory effects. However, no informed scientific evidence has evaluated the effects of this toxin on nuclear E2-related factor 2 (Nrf2) and nuclear factor- κ B (NF κ B) expression, which regulate the expression of many detoxifying enzymes and the transcription of pro-inflammatory cytokines genes, respectively, in CKD. Thus the aim of the study was to evaluate the influence of IS in Nrf2, NF- κ B and malondialdehyde (MDA) levels in RAW macrophage cells.

Methods: Mouse RAW 264.7 macrophage cells were incubated overnight with IS (250, 500, 1000 or 4000mM) according to the recommendations of the European Uremic Toxin Work Group. Nucleus and cytoplasm were separated using a specific Kit. Quantitative Real-Time PCR analysis and Western Blotting were performed to evaluate the Nrf2 and NF- κ B levels. MDA levels were measured by High Performance Liquid Chromatography with visible detection.

Results: In macrophages culture Nrf2 nuclear translocation and NF- κ B protein were not activated by IS, however, NF- κ B mRNA expression was stimulated by IS at the concentration of 1000 mM, 4 fold higher than detected in CKD patients i.e.

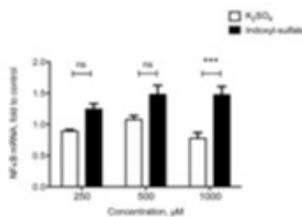


Figure 1. IS up-regulates NF- κ B mRNA expression in RAW macrophages

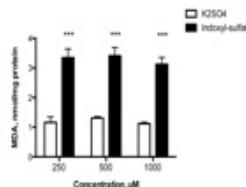


Figure 2. IS exacerbates lipid peroxidation in RAW macrophage

MDA levels were increased by IS in the cells (Figure 2).

Conclusions: IS exacerbates oxidative stress and could activate NF- κ B mRNA expression especially for the highest concentrations in RAW macrophages culture.

TH-PO288

Association of Intraglomerular Cytokine Environment with Distinctive Infiltrating Myeloid Cell Populations in Lupus Nephritis Sun-sang J. Sung,^{1,4} Yan Ge,¹ Chao Dai,^{1,4} Hongyang Wang,^{1,4} Shu Man Fu,¹ Thu H. Le,^{1,4} Jing Yu,^{2,4} Rahul Sharma,^{1,4} Mark D. Okusa,^{1,4} Kline Bolton,^{1,4} Young Hahn,³ Jessica R. Lawler.^{1,4} *¹Medicine, U. of Virginia, Charlottesville, VA; ²Cell Biology, U. of Virginia, Charlottesville, VA; ³Microbiology, U. of Virginia, Charlottesville, VA; ⁴Center for Immunity, Inflammation, and Regenerative Medicine, U. of Virginia, Charlottesville, VA.*

Background: Glomerular infiltrating myeloid cells are important in mediating intraglomerular tissue damage, cellular dysfunction, and functional obliteration in lupus nephritis.

Methods: A spontaneous chronic lupus model using NZM2328 mice and an anti-GBM-induced GN model were used to assess glomerular cytokine environment and myeloid cell infiltration in SLE by confocal microscopy. Glomeruli were isolated by magnetic bead trapping and single cell suspensions were analyzed by flow cytometry.

Results: In NZM2328 mice with severe proteinuria, increased CD11b+ dendritic cells (DC), CD103+ DC, and MHCII+ and MHCII- macrophages were found infiltrating the kidney interstitium. However, glomerular infiltrating cells in these sick mice consisted mostly of MHC-CD11b+ M2-like macrophages but not MHCII+ cells. Microarray analysis of FACS-purified mesangial cells followed by confocal microscopy analysis of cytokine staining showed that mesangial cells mainly produced IL-6, M-CSF, stem cell factor, KC, and MIP2. Immunofluorescence also showed that endothelial cells produced IP-10 whereas podocytes produced IL-1 β . These cytokines likely determine the differences in cellular distribution between the interstitium and glomerulus and mediate GN. Anti-GBM-induced GN showed disproportionately high glomerular infiltration of PMN and Ly6C+ macrophages compared to NZM2328 mice with chronic GN, which suggest significant differences in pathogenesis between the 2 SLE models.

Conclusions: The secretion of selected cytokine and chemokines by glomerular parenchymal cells support a pathway for mediating the infiltration of Ly6C+ monocytes and PMN by CXCR2 and CXCR4 chemokines and the development of monocytes into CD11b+MHC-low macrophages. These infiltrating cells are likely to interact with other cells to cause the pathological conditions in GN.

Funding: Other NIH Support - NIAID

TH-PO289

Mono-Sodium Urate (MSU) Activates PKR and NLRP3 Inflammasome in Human Renal Proximal Tubular Cells (HRPTCs) Shabirul Haque, Nairuti H. Shah, Rabani Bharara, Ramachandra prasanna Bongu, Gauri P. Patil, Amrita Kaur Chawla, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: Protein kinase R (PKR) is triggered by double stranded RNA (ds-RNA) which directly interacts with NLRP3 and activates NLRP3 inflammasomes. Inflammasome is a multiprotein complex consists of caspase-1, ASC, and NLRPs proteins. Inflammasome activation and maturation augments secretion of proinflammatory cytokines interleukin (IL)-1 β and IL-18. High serum uric acid levels have also been reported to promote both acute and chronic tubulointerstitial disease. However, the role of

PKR in MSU mediated tubular cell inflammasome complex has not been investigated. We hypothesized that MSU triggers PKR pathway to activate NLRP3 inflammasomes in tubulointerstitial fibrosis.

Methods: Human renal proximal tubular cells (HRPTCs) were incubated with MSU (100 µg/ml) for either 24 or 48 hours and assayed for pyroptosis by a morphologic assay (through staining with H33342 and propidium iodide). To determine the involved mechanism, protein blots of HRPTCs treated with MSU (100 mg/ml) for 48 hrs were probed for PKR and actin. Total RNA was extracted from HRPTCs treated under similar conditions and cDNAs were amplified with specific primers. To establish causal relationship between caspase-1 activation and pyroptosis, HRPTCs were pulsed with MSU in the presence or absence of caspase-1 inhibitor and then assayed for pyroptosis. To establish a causal relationship between NLRP3 mediated induction of K-efflux and inflammasome formation, HRPTCs were treated with MSU with/without glyburide.

Results: MSU exposure enhanced tubular cell pyroptosis. MSU promoted transcription of NLRP3, caspase-1, and IL-1β. MSU exposure augmented protein expression of PKR, NLRP3, IL-1β and caspase-1. MSU-induced pyroptosis was attenuated by caspase-1 inhibitor. Glyburide treatment showed downregulation of NLRP3, caspase-1 and IL-1β expressions in MSU treated HRPTCs.

Conclusions: MSU activates PKR which leads to NLRP3 inflammasome activation and pyroptosis in HRPTCs.

TH-PO290

Hyperglycemia-Induced NLRP3 Inflammasome Formation Contributes to Podocyte Dedifferentiation via IL-1β and p53 Shabirul Haque, Gauri P. Patil, Amrita Kaur Chawla, Anjali Maheshwari, Ramachandra prasanna Bongu, Rabani Bharara, Rivka Lederman, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: NLRP3 inflammasomes have been reported to play a role in hyperglycemia associated morbidities including diabetic nephropathy. Functionally active inflammasome pathway promotes the maturation of proinflammatory cytokines such as IL-1β and IL-18. We hypothesize that hyperglycemia-induced NLRP3 inflammasome complexes would down regulate p53 pathway through the generation of IL-1β. These interactions would lead to dedifferentiation of podocytes in high glucose milieu.

Methods: Human podocytes (HPs) were incubated in media containing either buffer (C/HP) or high glucose (35 mM, HG/HP) for variable time periods. High glucose (HG) and normal glucose (NG) conditioned media (CM) were collected. Total RNA was extracted from cellular lysates and cDNAs were amplified with specific primers for inflammasome molecular markers (IMMs, NLRP3, ASC, caspase-1, IL-1β, and IL-18). Protein blots of C/HPs and HG/HPs were probed for NLRP3 and reprobated for protein expression of IMMs and actin. To establish a causal relationship between HG and IMMs, HPs were incubated in media with/without HG in the presence or absence of caspase-1 inhibitor/glyburide (K-efflux inhibitor) for 48 hours followed by mRNA and protein analysis for IMMs. Effects of IL-1 β alone and HG-CM were evaluated on podocyte dedifferentiation (loss of podocyte markers- nephrin and synaptopodin by Western blot analysis and immunolabeling).

Results: HG upregulated mRNA and protein expressions of NLRP3, caspase-1, ASC, IL-1β in HPs. Both caspase-1 inhibitor and glyburide inhibited mRNA and protein expression of IMMs in HG/HPs. HG-CM not only downregulated p53 mRNA transcription but also induced dedifferentiation in HPs in the form of attenuated expression of nephrin and synaptopodin. IL-1β down regulated p53, nephrin and synaptopodin expressions in HPs.

Conclusions: Hyperglycemia induces dedifferentiation of HPs through inflammasome formation and down regulation of p53.

Funding: NIDDK Support

TH-PO291

Human Renal Proximal Tubular Epithelial Cells: Effects of Primary Cilia Loss on Epithelial Phenotype and Function Michael Higgins, Tara McMorrow. *School of Biomolecular and Biomedical Science, Conway Inst, Univ College Dublin, Dublin, Ireland.*

Background: The primary cilium is a hair-like microtubule based structure, protruding from nearly all mammalian cells. Originally thought to be a vestigial organelle, it is now well established as a crucial signalling hub. The importance of the primary cilium in cell signalling has become clear with a range of diseases associated with its loss (ciliopathies). Recently there has been increased interest in the link between the primary cilium and the development and progression of cancer, with several cilia associated genes dysregulated in numerous cancers. The primary cilium has been found to be absent in renal cell carcinomas, breast and pancreatic cancers. The aim of this study was to investigate the functional and mechanistic link between cilia and important epithelial characteristics including epithelial marker expression and barrier function. This involved assessing the effects of cilia loss in a human renal proximal tubular epithelial cell line (RPTEC/TERT1).

Methods: Deciliating agents were used to induce loss of the primary cilium. Immunofluorescent labelling of the ciliary marker acetylated α-tubulin was used to detect the primary cilium in the RPTEC/TERT1 cells. Western blotting was used to assess epithelial marker expression and tight junction protein expression. Trans-epithelial electrical resistance (TEER) was measured to assess epithelial barrier function following cilia loss.

Results: Removal of cilia from RPTEC/TERT1 cells by deciliating agents was confirmed by acetylated α-tubulin staining. Deciliation was found to cause alteration of tight junction protein expression, in particular claudin family members. Cilia loss caused an increase in TEER, suggesting a decrease in tight junction permeability and a change in epithelial barrier function following deciliation.

Conclusions: Results suggest an altering of epithelial cell junctions and barrier function following deciliation. Further analysis is being carried out to understand the relationship between the primary cilium and the maintenance of an epithelial phenotype and function.

TH-PO292

Development of a Novel Human Renal Proximal Tubule Epithelial Cell Culture Model That Retains Robust Mitochondrial Respiratory Capacity, and Critical *In Vivo* Renal Functional Attributes Diana Zepeda-Orozco,¹ Kathryn S. Brown,¹ Arpit Sharma,² Ian M. Thornell,³ Eric Taylor.² ¹*Pediatrics, Univ of Iowa, Iowa City, IA;* ²*Biochemistry, Univ of Iowa, Iowa City, IA;* ³*Internal Medicine, Univ of Iowa, Iowa City, IA.*

Background: Renal mitochondrial dysfunction and oxidative stress are implicated in diabetic kidney disease, acute kidney injury, and the progression of chronic kidney disease. The renal proximal tubule is a mitochondria-rich nephron segment that relies on oxidative phosphorylation to carry out its multiple, metabolically demanding absorptive and buffering functions. However, mechanistic investigation of proximal tubule mitochondrial biology with cell culture systems *in vitro* is challenging because available immortal proximal tubule epithelial cells exhibit a transformed, glycolytic metabolism concomitant with loss of key functional parameters.

Methods: In this study, primary human renal proximal tubule epithelial cells (PTECs) were immortalized (iPTEC) by retroviral transduction with hTERT and papilloma virus. To test their utility as a cell culture model of *in vivo* kidney function, we evaluated iPTECs for retention of mitochondrial respiratory capacity and key proximal tubule cell functional attributes.

Results: iPTECs maintained capacity for mitochondrial respiration and oxidative phosphorylation utilizing several substrates including pyruvate and glutamine. Furthermore, iPTECs retained critical proximal tubule functional characteristics, including monolayer formation with expression of E-cadherin, expression of proximal tubule cell transporters, and the ability to perform gluconeogenesis and ammoniogenesis. iPTECs plated on millicell cell culture inserts developed transepithelial potential that was maximal on day 20 and mediated in part by polarized Na/K-ATPase expression in the basolateral membrane.

Conclusions: The development of an immortalized PTEC line with broad retention of *in vivo* functional attributes, including robust oxidative phosphorylation, will enable the study of mitochondria biology in kidney health and disease.

TH-PO293

Pangenomic Analyses of Hypoxia Inducible Factor (HIF) Pathway Activation in Human Primary Renal Tubular Cells Steffen Grampp,¹ Franziska Bertelshofer,² Margarete Goppelt-Strube,¹ Kai-Uwe Eckardt,¹ Johannes Schödel.¹ ¹*Dept of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany;* ²*Computer Graphics Group, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.*

Background: In the kidney, epithelial integrity is crucial for organ function. Ischemic or toxic damage of tubular cells can cause acute kidney injury. Preconditional stabilization of hypoxia inducible factor 1 alpha (HIF-1α) in tubular cells is beneficial in animal models of acute kidney injury. The precise protective mechanisms and the relevance of the HIF system in human kidneys remain unknown. Therefore, the aim of this study was to characterize the hypoxic response and to investigate direct HIF effects in primary human tubular cells.

Methods: Healthy human kidney tissue from patients undergoing tumour nephrectomy was used for tissue studies and isolation of primary tubular cells. HIFs were stabilized using hypoxia (1%) or the hypoxia-mimetic dimethyl oxallylglycine. We used genome-wide analyses of open chromatin (FAIRE-seq) and HIF DNA-binding (ChIP-seq) in freshly isolated primary human tubular cells from several individuals to define conserved regulatory DNA elements and HIF-binding sites.

Results: Immunohistochemistry experiments using human kidney tissue revealed the presence of HIF-1α protein in tubular cells. Co-staining with 11β-hydroxy steroid dehydrogenase localized HIF-1α signals predominantly in the distal convoluted tubule and the collecting duct. Using ChIP-seq we identified over 500 high-stringency HIF-1 binding sites. HIF DNA-binding was strongly enriched in regions of open chromatin and regulatory regions. Patterns of HIF-DNA interactions were conserved across several individuals. Functional clustering of HIF-binding genes showed strong enrichment for protective pathways and included novel binding sites at renoprotective genes such as HO-1 and MUC1.

Conclusions: The importance of the HIF system for cell survival and integrity is well documented for rodent kidneys. We expand analyses of the renal HIF response to human kidneys and identify important mechanisms to potentially preserve tubular function in human kidney disease.

Funding: Government Support - Non-U.S.

TH-PO294

The Na-H Exchanger Regulatory Factor Isoform 1 Is a Critical Determinant of Renal Proximal Tubule Brush Border Composition Rebecca Murray,^{1,2} Corey James Ketchem,¹ Amanda R. Sherwood,¹ Michael Merchant,¹ Lauren D. Grant,¹ Barbara Clark,^{1,3} Syed J. Khundmiri,^{1,2,4} Eleanor D. Lederer.^{1,2,4} ¹Medicine, Univ of Louisville, Louisville, KY; ²Medical Services, Robley Rex VA Medical Center, Louisville, KY; ³Biochemistry and Molecular Biology, Univ of Louisville, Louisville, KY; ⁴Physiology, Univ of Louisville, Louisville, KY.

Background: The Na-H Exchanger Regulatory Factor Isoform 1 (NHERF1), a multifunctional scaffolding protein, is required for regulated forward trafficking and brush border membrane (BBM) anchoring of the type IIa sodium phosphate cotransporter, Npt2a. We have shown that OK cells, a model of proximal tubule, lacking NHERF1 (OKH) have decreased BBM expression of Npt2a, SGLT1, ezrin, GGTase and Munc18. OKH cells also show a 50% decrease in total RNA levels and a near absence of Npt2a mRNA. We hypothesize that NHERF1 plays a defining role in BBM protein expression.

Methods: To test this hypothesis, we performed proteomic analysis of BBM proteins from WT and NHERF1 deficient (KO) mice and measured mRNA expression of selected transport proteins from WT and OKH cells.

Results: We identified 148 proteins whose expression was downregulated at least two fold and 78 proteins whose expression was upregulated at least three fold in KO mouse BBM. 14 proteins were absent in KO. Integrity Pathway Analysis demonstrated that 113 of the downregulated proteins were involved in cellular organization, assembly, function, or maintenance, specifically, microvilli and actin cytoskeleton structure (Shroom4, Fascin), protein trafficking (CLIC1 and 4), signaling (taperin, FGFR2), and repair. Immunohistochemistry of KO kidneys and scanning electron microscopy of OKH cells show no obvious defects in cell structure/polarity. The mRNA levels of Npt2a, SGLT1, and NHE3 in OKH were less than 50% of WT but promoter activity of SGLT1 was similar.

Conclusions: We conclude that the presence of NHERF1 defines renal BBM protein expression through post-transcriptional, trafficking, and anchoring mechanisms.

Funding: Other NIH Support - NIA, Veterans Administration Support, Clinical Revenue Support

TH-PO295

Tamm-Horsfall Protein (Uromodulin) Regulates IL-23 Expression in S3 Segments by Inhibiting the Rac-1-NOX2 Signaling Pathway of Oxidative Stress Radmila Micanovic, Shehnaz Khan, Frank Witzmann, Tarek M. El-Achkar. *Indiana Univ School of medicine.*

Background: We recently showed that Tamm-Horsfall protein regulates granulopoiesis by inhibiting the expression of IL-23 in S3 segments and the resultant activation of the IL-23/IL-17 axis. The molecular mechanism of this observation is unclear.

Methods: We performed laser micro-dissection (LMD) of S3 segments from THP-/- and THP+/+ kidney sections followed by 2 Dimensional -Differential Gel Electrophoresis (2D-DIGE) to identify pathways that are modulated by THP in vivo. We also used an unbiased, label free proteomics approach to understand the signaling of THP on human proximal HK-2 cells. Additional experimental methodology is described in Results.

Results: Bioinformatics analysis of differentially expressed proteins in S3 segments dissected from THP-/- compared to THP+/+ kidneys revealed that the free radical scavenging network had the highest score of clustering, suggesting that THP regulates redox balance in S3 segments. Using in vivo reporter dyes and by measuring enzymatic markers of oxidative stress (OS), we found increased OS in S3 segments from THP-/- compared to THP+/+ kidneys. Label-free proteomic analysis of HK-2 cells revealed that incubation of these cells with THP inhibited multiple pathways that converge on Rac-1 signaling. Since Rac-1 signaling is essential to the activation of NADPH oxidase (NOX), a major source of reactive oxygen species in cells, we verified that THP-/- mice had increased expression of Rac-1 and Nox-2 but not Nox-4. Treatment of HK-2 cells with THP directly decreased IL-23 expression. In addition, oxidative insult using H2O2, but not LPS, stimulated IL-23 mRNA expression in these cells, suggesting that oxidative stress but not classical endotoxin signaling, is needed for IL-23 induction in epithelial cells.

Conclusions: Taken together, our data support that THP inhibits Rac-1/NOX-2 oxidative stress in S3 segments, which in turn regulates the production of IL-23 and activation of the IL-23/IL-17 axis. These findings significantly enhance our understanding of how THP shapes the function and reactivity of S3 segments, which could have both renal and systemic implications, through the regulation of granulopoiesis.

Funding: Veterans Administration Support

TH-PO296

Abstract Withdrawn

TH-PO297

Hydrophobic Motif Site Phosphorylation of Protein Kinase CbetaII by mTORC2 Regulates High Glucose (HG)-Induced Mesangial Cell Hypertrophy Falguni Das, Nandini Ghosh-choudhury, Meenalakshmi M. Mariappan, Balakuntalam S. Kasinath, Goutam Ghosh-Choudhury. *Univ of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Protein kinase C beta II (PKCβII) has been implicated in diabetic nephropathy (DN). Mesangial cell (MC) hypertrophy is a pathologic feature of DN. PKCβII undergoes phosphorylation at the hydrophobic motif site Ser-660 for its activity. We have shown that mTOR complex 1 (C1) regulates MC hypertrophy. How activation of PKCβII by Ser-660 phosphorylation fits into mTOR signaling to control MC hypertrophy is not known.

Methods: Human MCs, immunoblotting, siRNA and shRNA transfections, protein synthesis assays were used.

Results: HG significantly increased phosphorylation of PKCβII at Ser-660 in a PI 3 kinase-dependent manner. siRNAs against PKCβII, dominant negative PKCβII and nonphosphorylatable mutant of PKCβII, PKCβII S660A, blocked mTORC1 activity due to lack of PRAS40 phosphorylation, resulting in significant inhibition of HG-induced MC protein synthesis and hypertrophy. Also, PKCβII S660A attenuated phosphorylation of Akt at Ser-473, a putative mTOR complex 2 (C2) site. Specific inhibition of mTORC2 by shRNAs against rictor or Sin1, two exclusive and required components for its activity, suppressed HG-induced phosphorylation of PKCβII Ser-660, PRAS40 and Akt Ser-473, resulting in attenuation of mTORC1 activity leading to inhibition of MC hypertrophy. Constitutively active (CA) Akt or CA mTORC1 reversed shRictor- or shSin1-mediated inhibition of HG-induced MC hypertrophy. Furthermore, CA PKCβII reversed the shRictor- or shSin1-induced inhibition of HG-stimulated Akt Ser-473 phosphorylation and MC hypertrophy. Finally, we show increased phosphorylation of PKCβII Ser660, PRAS40 and Akt Ser-473 in association with activation of mTORC1 in renal cortices of OVE26 mice with type 1 diabetes.

Conclusions: These results provide the first evidence that HG-induced activation of mTORC2 phosphorylates and activates PKCβII to increase the phosphorylation of Akt at Ser-473 to finally activate mTORC1 to induce MC hypertrophy. Thus, we uncover a specific role of mTORC2 for Akt/mTORC1 activation via PKCβII Ser-660 phosphorylation.

Funding: NIDDK Support, Veterans Administration Support

TH-PO298

Hyaluronan Mediated Motility Receptor Regulates Cell Motility in Glomerular Endothelial Cells in Response to Shear Stress Hesham e Hussien Elhegny, Gavin Iain Welsh, Simon C. Satchell. *Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.*

Background: Laminar shear stress (LSS) is an important determinant of vascular health. The glycocalyx is a carbohydrate-rich layer that covers the endothelial cell surface. Glycocalyx translates shear forces into intracellular signals. Hyaluronan (HA) motility mediated receptor (HMMR) promotes cell motility and invasion through interactions with HA on the cell surface in non-renal cells.

Methods: Human conditionally immortalized glomerular endothelial cells (GEnC) were exposed to LSS (10 dyn/cm²) using an orbital rotator for 0, 24, 48 and 72h. Effects on expression of glycocalyx-related genes were analysed using a custom designed focused Taqman qPCR array. HMMR and CD44 (another hyaluronan receptor) and production of HA itself by radiolabelling were also assessed. Motility assays (scratch assay, 2D chemotaxis and Electric Cell-Substrate Impedance Sensing) were performed on GEnC and siRNA HMMR knockdown GEnC with and without HA fragments. HMMR expression was assessed on freshly isolated and cultured glomeruli.

Results: There was a significant increase in versican expression, peaking at 24h. Thrombomodulin expression significantly increased and reached a plateau within 24h. CD44 expression peaked at 72h of LSS. There was a dramatic decline in HMMR expression by 24h of LSS (10-fold decrease p<0.0001) and levels remained suppressed over 72h. Furthermore, HMMR recovered to nearly pre-LSS level after a period without LSS for 24h. LSS increased release of HA into culture medium. What is more, HA fragments increased cell motility where LSS for 24h reduced it. HA fragments did not increase cell motility on siRNA HMMR knockdown GEnC. HMMR expression was increased in isolated glomeruli after 24h in culture.

Conclusions: HMMR is exquisitely shear-sensitive in vivo and ex vivo and acts as a marker for LSS exposure in endothelial cells. Chronic LSS reduces cell motility. Our data suggest this is due to HMMR expression changes and that HMMR is likely to play important roles in glomerular physiology and disease.

Funding: Government Support - Non-U.S.

TH-PO299

Cell Surface Expression of TRPC6 in Podocytes Depends on Synaptopodin Stability Hao Yu,¹ Andreas D. Kistler,² James Otto Meyer,³ Jochen Reiser.¹ ¹Internal Medicine, Rush Univ, Chicago, IL; ²Internal Medicine, Cantonal Hospital Frauenfeld, Frauenfeld, Switzerland; ³Neuroscience, Univ College London, London, United Kingdom.

Background: TRPC6 gain-of-function mutations and increased TRPC6 expression in podocytes were found in familial FSGS and acquired glomerular diseases. TRPC6 is expressed in synaptopodin (synpo) rich podocyte yet only a fraction is located on plasma membrane. Modulation of localization and function of TRPC6 harbors potential for treatments.

Methods: Immunogold and co-IP were performed to examine co-localization and interaction of TRPC6 and synpo. Cell surface biotinylation and high throughput analysis were used for quantitative analysis of cell surface levels of TRPC6. Calcium imaging was performed to measure calcium influx mediated by TRPC6. Glomerular isolation, biotinylation and podocyte enrichment were performed to determine podocyte membrane TRPC6 levels in vivo.

Results: Co-localization of TRPC6 and synpo was observed in podocyte foot processes by immunogold double labeling in mouse kidney. Interaction of the two proteins was observed by co-IP in cultured podocytes and mouse glomeruli. TRPC6 levels on cell surface increased in synpo knockdown podocytes and decreased in synpo overexpressing podocytes. Consistent with the changes in expression levels, calcium influx mediated by TRPC6 was enhanced in synpo knockdown podocytes and reduced in synpo overexpressing podocytes. Mechanistically, we found both actin and microtubule cytoskeletons were involved in regulating membrane TRPC6 expression affected by synpo. Membrane TRPC6 expression in podocytes was elevated upon LPS treatment and was restored by cyclosporine A (CsA) in WT mice. Functionally, CsA treatment significantly reduced LPS proteinuria in WT mice (71%) and to a lesser extent in TRPC6^{-/-} mice (45%).

Conclusions: Synaptopodin limits expression of TRPC6 on podocyte plasma membrane. CsA, a drug that stabilizes synpo, is shown to lower podocyte surface TRPC6 levels upon LPS treatment. The partial benefit of CsA in reducing LPS proteinuria in TRPC6^{-/-} mice suggests that CsA protects podocytes partially by lowering cell surface expression of TRPC6 through stabilization of synpo.

Funding: NIDDK Support

TH-PO300

APOL1 Risk Variants Enhance Podocyte Oxidative Stress Xiqian Lan, Hongxiu Wen, Ashwani Malhotra, Karl Leon Skorecki, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: APOL1 variants have been implicated for increased prevalence and acceleration in the rate of progression of kidney diseases amongst African Americans. Since oxidative stress has been demonstrated to play a role for loss of podocytes in both experimental animal and human kidney disease models, we hypothesized that APOL1 variants could be inducing podocyte injury through augmentation of oxidative stress.

Methods: Human podocytes (HPs) stably expressing Vector, APOL1G0, APOL1G1, or APOL1G2 were used. Pseudo type HIV or empty vector (control) virus was transduced into Vector/HPs, G0/HPs, G1/HPs, and G2/HPs. After 48 h, cells were loaded with DCFDA and ROS generation was assayed every 10 min for 60 min by a fluorometer. Three sets of experiments were carried out in triplicate. Protein blots of HPs expressing Vector, APOL1G0, APOL1G1 and APL1G2 were probed for molecular markers for oxidative stress and associated down stream signaling (phospho-p53, phospho-Foxo3A, p27, BAD, RIP3, MnSOD, and catalase). To evaluate the status of apoptotic pathway, protein blots of HPs expressing Vector, APOL1G0, APOL1G1, and APOL1G2 were probed for caspase-3 and then reprobed for actin. To determine the role the activation of Ang II type I (AT1R) and II (AT2R), protein blots of HPs expressing APOL1 and variants were probed for AT1R and AT2R.

Results: Both HP/G1 and HP/G2 displayed increased ROS generation when compared to Vec/HPs and G0/HPs. G1/HPs and G2/HPs displayed higher expression of pro-oxidant molecules, including RIP3, P27, BAD, phospho-FOXO3A, phospho-P53; HP/G1 and HP/G2 also enhanced expression of cleaved caspase-3 when compared with vector/HPs and G0/HPs. However, both G1/HPs and G2/HPs displayed lower expression of MnSOD and AT2R. Both G1/HPs and G2/HPs displayed greater ROS generation and enhanced expression of pro-oxidant molecules in HIV milieu when compared to vector/HPs and G0/HPs.

Conclusions: These results indicate that APOL1 risk variants have potential to augment oxidative stress in podocytes and this effect is further exacerbated in HIV milieu.

TH-PO301

The SMAD2/3 Ratio Is Controlled by PLCE1 in Podocytes Carl J. May,¹ Gavin Iain Welsh,¹ Moin Saleem.^{1,2} ¹Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom; ²Children's Renal Unit, Bristol Children's Hospital, Bristol, United Kingdom.

Background: Podocytes are thought to be the target cell in nephrotic syndrome pathogenesis. Mutations in PLCE1: which encodes a lipid signalling enzyme, have been reported in patients with early onset nephrotic syndrome. However, the effects of mutations in PLCE1 in the mature podocyte are not clear.

Methods: A conditionally immortalised human podocyte cell line was established from a patient, with a SNP at nucleotide 321 of PLCE1 that leads to a stop codon. This mutation severely truncates the protein such that no protein expression was detected. This cell line was characterised in order to investigate the deleterious effect of this mutation on podocyte phenotype and function.

Results: The PLCE1 mutant podocytes express lower levels of both epithelial and podocyte markers than wild-type cells. Morphologically they appear more mesenchymal. They demonstrate a diminished response to TGF-B1 compared to the wild-type. Interestingly the PLCE1 mutant podocytes show no SMAD2 phosphorylation but a robust SMAD3 phosphorylation. Whereas, the wild-type podocytes which show marked SMAD2 phosphorylation and only low level SMAD3 phosphorylation. It is thought that the SMAD2 pathway is anti-fibrotic while the SMAD3 pathway is pro-fibrotic. The PLCE1 mutant podocytes had equal levels of SMAD2 and SMAD3 while the wild-type podocytes had twice the amount of SMAD2 compared to SMAD3. This biases TGF-B1 signaling along the anti-fibrotic SMAD2 pathway in the wild type. Despite the 1:1 ratio between SMAD2 and SMAD3 the lack of SMAD2 phosphorylation shows that the PLCE1 mutant podocytes

are biased towards the pro-fibrotic SMAD3 signaling. Most interestingly, however, PLCE1 knockdown by siRNA in the Wild-type podocytes increased the expression of SMAD3 relative to SMAD2. This changes the SMAD bias of the podocyte.

Conclusions: This work suggests that by altering the SMAD2/3 ratio within the podocyte, the PLCE1 mutant enhances the pro-fibrotic response to TGF-B1. This provides a novel therapeutic target to modulate the podocyte's response to TGF-B1 and may prove to be protective against the development of fibrosis.

TH-PO302

Dynamin Oligomerization Plays a Catalytic and Structural Role with Regard to Actin Dynamics During Actin-Dependent Clathrin Mediated Endocytosis Changkyyu Gu, Sanja Sever. *Nephrology, Massachusetts General Hospital, Charlestown, MA.*

Background: The GTPase dynamin is essential for podocyte structure and function as it plays a role in regulating endocytosis and the actin cytoskeleton. Recently, using a combination of different dynamin mutants and Bis-T-23, we showed that it is possible to directly target actin cytoskeleton dynamics by targeting the dynamin oligomerization cycle in the whole organism. It has been shown that direct dynamin-actin interactions are required for the scission of the clathrin-coated pits in yeast. While actin is critical for endocytosis in yeast cells, data suggest that it plays a cell type specific role in endocytosis in mammalian cell. In this study, we aim to investigate the functional role for dynamin oligomerization in endocytosis.

Methods: Actin polymerization assay was performed to investigate dynamin oligomerization-driven actin polymerization using purified proteins or cytosolic extracts. Electron microscopy was used to explore the effects of dynamin on actin structures. Tfn uptake assay and **Transmission electron microscopy were used to examine endocytosis and Clathrin coated pits profiles respectively.** Total internal reflection fluorescence microscopy was used to monitor clathrin mediated endocytosis.

Results: Here we show, using a combination of diverse dynamin mutants and a small molecule that specifically promotes actin-dependent dynamin oligomerization named Bis-T-23, that dynamin provides a physiological link between gelsolin and Arp2/3 complex driven actin polymerization. Dynamin promoted Arp2/3 complex driven nucleation by providing free barbed ends via gelsolin displacement in vitro, in cell extracts and in the cell. In addition, dynamin oligomers exhibited a structural role with regard to the actin cytoskeleton by crosslinking microfilaments. This dual role of dynamin oligomerization with regard to the actin cytoskeleton (kinetic and structural) regulated actin dynamics at distinct stages of clathrin-coated vesicle formation, including coated pit formation, constriction and fission.

Conclusions: Dynamin oligomerization plays a catalytic and structural role with regard to actin dynamics during actin-dependent clathrin mediated endocytosis.

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TH-PO303

Functional Characterization of β -Catenin in Podocyte Damage Michelle Duong, Beina Teng, Hermann G. Haller, Mario Schiffer. *Nephrology, Medical School Hanover.*

Background: β -Catenin plays a crucial role in the Wnt signaling pathway as well as in cell adhesion. In the kidney β -Catenin is critically involved in the development of proteinuria and podocyte damage. Here we investigated if the injury is associated with a certain subcellular localization of β -Catenin and/or is mediated via its binding partner: α -Catenin is an essential binding partner of β -Catenin, which leads to a proper adhesion between cells while the function of β -Catenin as a gene transcription regulator is linked with TCF (T cell-lymphoid factor).

Methods: We used the zebrafish model to express human β -Catenin mutants lacking the ability to bind α -Catenin or TCF. To examine the impact of β -Catenin acting in only one of its subcellular localization, we expressed β -Catenin either in the membrane or in the nucleus. Knockdown of endogenous β -Catenin was conducted by morpholino injection and co-expression of the mutants by injection of mRNA. After that the integrity of the glomerular filtration barrier was analyzed.

Results: Our analysis revealed that β -Catenin tethered to the membrane only seems to be able to partially retain the glomerular filtration barrier, whereas nuclear β -Catenin alone cannot abrogate the impact of the β -Catenin knockdown and leads to loss of high molecular weight proteins from the circulation. Further, zebrafish with β -Catenin missing the function of binding TCF have a normal glomerular filtration function, while the expression of β -Catenin unable to bind to α -Catenin leads to proteinuria.

Conclusions: These results suggest that the cell-cell adhesion function of β -Catenin is of greater importance for the maintenance of the glomerular filtration barrier than its role as a transcription factor.

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TH-PO304

Vitamin D (VD) Upregulates Nephron in HIV-Induced Dedifferentiated Podocytes Through Down Regulation of SNAIL Nirupama Chandel, Rivka Lederman, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: HIV infection of kidney cells plays a key role in the development of HIV-associated nephropathy (HIVAN). We recently observed that HIV-induced dedifferentiations of podocytes regulated through SNAIL. We hypothesize that VD has potential to prevent

the Nephron downregulation through modulation of SNAIL expression. VD may be down regulating SNAIL either through demethylating the signature of active transcription (H3K4 trimethylation) at snail promoter or at Nephron promoter (H3 K27 trimethylation) or either through reversal of HIV-induced stabilization of SNAIL.

Methods: Renal tissues were harvested from (FVB/N) and HIV-transgenic (Tg26) mice, and VD (EB1089) receiving FVB/N and Tg26 mice for two weeks (n=3, 4 wk old). *In vitro* studies, human podocytes (HPs) were transfected with either empty vector (EV) or NL4-3(HIV). EV/HPs and HIV/HPs were treated with EB1089 for 48 hours. Protein blots of renal tissues, EV/HPs and HIV/HPs with/without VD were probed for SNAIL, p62 (marker of endosomal cargo degradation), and histone trimethylation. Immunoprecipitation (IP) studies were carried in cellular lysates of EV/HPs and HIV/HPs with SNAIL antibody. Binding of SNAIL at VDR promoter was evaluated by ChIP assay. Additionally, we evaluated the effect VD on disruption of SNAIL repressor complex at nephron promoter.

Results: Renal tissues from Tg26 mice (n=3) displayed enhanced SNAIL transcription as well as translation but downregulation of nephron. VD not only down regulated SNAIL but also upregulated nephron expression in renal tissues of Tg26 mice as well as in HIV/HPs. Chip assay revealed enhanced trimethylation at SNAIL promoter and binding of SNAIL at Nephron promoter in HIV/HPs. VD also enhanced nephron expression through disruption of SNAIL repressor complex at nephron promoter in HIV/HPs. HIV/HP displayed decreased levels of p62 which signifies increased HIV induced autophagy in *in vitro* system.

Conclusions: VD has potential to upregulate nephron expression in HIV-induced dedifferentiated podocytes through multiple ways including modulation of HIV-induced epigenetic alterations, autophagy, and disruption of SNAIL repressor complexes.

TH-PO305

Krüppel-Like Factor 15 Mediates Glucocorticoid-Induced Podocyte Differentiation Sandeep K. Mallipattu,¹ Lucia Roa,¹ Timothy W. Miller,¹ Jason Ling,¹ Victoria Ly,¹ Monica Patricia Revelo Penafiel,³ John C. He.² ¹Medicine/Nephrology, ²Stony Brook Medicine; ³Medicine/Nephrology, Mount Sinai School of Medicine; ³Pathology, Univ of Utah.

Background: Glucocorticoids (GCs) are the initial and often, the primary, treatment for primary glomerulopathies such as MCD and FSGS. The mechanism by which GCs restores podocyte differentiation and improves cell survival is unclear. We previously demonstrated that Krüppel-Like Factor 15 (KLF15), a kidney-enriched zinc-finger transcription factor, was required for podocyte differentiation. Here, we hypothesize that KLF15 mediates GC-induced podocyte differentiation.

Methods: Human podocytes (HP) and primary mouse podocytes (MP) were treated with and without dexamethasone (DEX) (1µM, 10µM) for 3, 6, 12, and 24 hours. Initially, we generated podocyte-specific knockout mice, *Podocin-Cre Klf15^{fllox/fllox} (Klf15^{-/-})*. Proteinuria was induced in *Klf15^{-/-}* and wildtype mice with LPS (10mg/g) and subsequently treated with or without DEX (1mg/kg). HP with stable overexpression of KLF15 (*LentiORF-KLF15*) were generated. Immunostaining for KLF15 was performed on kidney biopsies from patients with healthy donor nephrectomies (n=16), GC-responsive (n=20), and GC-nonresponsive (n=15) FSGS and MCD.

Results: *KLF15* expression was induced in HP and primary MP within 3 hours of DEX treatment. TRANSFAC promoter analysis revealed that KLF15 binding sites occupy genes involved in GC signaling. LPS-treated *Klf15^{-/-}* mice exhibited less podocyte recovery (albuminuria, podocyte effacement, nephrin, and synaptopodin expression) after DEX administration as compared to LPS-treated wildtype mice. The pattern of *Tnfr1*, *Il-6*, *Il-1β*, and *Infy* were unchanged in the serum and glomerular extracts between both groups of mice treated with DEX. Furthermore, actin stress fiber formation was preserved with G1/S cell cycle arrest in HP with *LentiORF-KLF15* as compared to *LentiORF-RFP* with LPS treatment. Finally, reduced expression of KLF15 in the glomeruli correlated with non-responsiveness to GCs in patients with MCD and FSGS.

Conclusions: These findings suggest that KLF15 is essential for GC-mediated restoration of differentiation markers, ultrastructure, and cell survival in the setting of podocyte injury.

Funding: NIDDK Support

TH-PO306

CXCR4 Plays a Crucial Role in Mediating Oxidative Stress-Induced Podocyte Injury Hongyan Mo,¹ Xue Hong,¹ Lili Zhou,¹ Youhua Liu.^{1,2} ¹Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; ²Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA.

Background: Oxidative stress is key mediator to podocyte damage and proteinuria. However, the underlying mechanism remains to be elucidated. In this study, we investigated the potential role of CXCR4, the chemokine receptor for SDF-1α, in mediating oxidative stress-induced podocyte injury.

Methods: In a mouse model of adriamycin nephropathy (ADR), CXCR4 mRNA and protein expression, as well as oxidative stress was examined. AOPPs, advanced oxidation protein products, were utilized to trigger oxidative stress, and their effects on podocyte dysfunction and CXCR4 expression were assessed. AMD3100, a specific inhibitor of CXCR4, was used to block CXCR4 action both *in vitro* and *in vivo*.

Results: CXCR4 expression was significantly induced in podocytes as early as 3 days after injection of adriamycin. This was accompanied by an increased upregulation of oxidative stress in podocyte, as detected by MDA assay of kidney homogenate, nitrotyrosin staining in podocyte, and induction of NOX2, a major subunit of NADPH oxidase. Similar results were obtained when we stained for CXCR4 in human kidney biopsies from patients with proteinuric kidney diseases including IgAN, crescent and FSGS. Using immortal podocyte cell line MPC5 and mouse models of podocyte injury induced by ADR or AOPPs, we found that AOPPs induced significant loss of podocyte marker WT1, nephrin

and podocalyxin, accompanied by upregulation of mesenchymal marker desmin both *in vitro* and *in vivo*. Furthermore, AOPPs worsen proteinuria, aggravated glomerulosclerosis and renal fibrotic lesions. Concomitantly, SDF-1α/CXCR4 signaling was remarkably induced in podocytes by AOPPs. Administration of AMD3100, a specific inhibitor of CXCR4, reduced proteinuria, ameliorated podocyte dysfunction and renal fibrotic lesions triggered by AOPPs.

Conclusions: These results suggest that chemokine receptor CXCR4 may play a crucial role in mediating oxidative stress-induced podocyte injury, proteinuria and renal fibrotic lesions.

Funding: Government Support - Non-U.S.

TH-PO307

PKCε Is Identified as a Novel Binding Partner of β-Catenin in Podocytes Xuejiao Yu,¹ Beina Teng,¹ Michelle Duong,¹ Mario Schiffer.¹ ¹Medical School Hannover.

Background: PKCα, one conventional isoform of PKC, is a binding partner of β-catenin. However, a link between PKCε, a novel isoform, and β-catenin remains unclear. PKCε regulates the cytoskeleton by phosphorylating IQGAP1, a protein involved in the regulation of β-Catenin in the cell-cell adhesion complex. So, we investigated the association between PKCε and β-catenin.

Methods: Staining was performed on murine kidney sections and podocytes to examine the β-catenin expression. Time courses were performed in murine wild type and PKCε^{-/-} podocytes. 7 promising phospho-motifs in β-catenin were selected and site-specific mutations were produced. The interaction between the β-catenin mutants and PKCε were verified by immunoprecipitation. The mutants were overexpressed in murine podocytes using adenovirus. Zebrafish larvae were injected with mutant β-catenin RNA.

Results: During the development of mice β-catenin showed increasing expression level in the glomeruli. However, the upregulation of β-catenin in wild type mice was much higher than those of PKCε^{-/-} mice. While in wild type podocytes, β-catenin showed a translocation from the perinuclear areas to the nuclei during differentiation, the distribution of β-catenin switched the reverse way in PKCε^{-/-} podocytes from the nuclei to the perinuclear areas. During the time course, the expression of active β-catenin was increased and total β-catenin decreased in the wild type podocytes under the stimulation of PMA. However, in the PKCε^{-/-} podocytes, both active β-catenin and total β-catenin displayed decreased expression level. 3 of 7 mutant β-catenin exhibited decreased interaction with PKCε in immunoprecipitation, indicating these phospho-motifs as important binding sites. Overexpression of these 3 mutants in wild type podocytes, showed no changes in the time course. These 3 mutant β-catenin were unable to rescue the β-catenin knockdown zebrafish.

Conclusions: It is the first time to indicate that PKCε binds β-catenin directly and they are involved in the process of glomerular disease and podocytes differentiation. 3 phospho-motifs in β-catenin are proved as binding sites for PKCε.

TH-PO308

Reactive Lipids Affect Podocyte Homeostasis Through the Redox Sensitive RhoA-Slit Diaphragm Protein-Akt Axis Krisztian Stadler, Claudia Kruger. *Oxidative Stress and Disease Lab, Pennington Biomedical Research Center, Baton Rouge, LA.*

Background: Podocyte loss is a characteristic early feature of obesity and diabetes related glomerular disease. Despite much attention on reactive lipids in diabetic kidney disease, surprisingly little is really known regarding their biological role in podocytes.

Methods: Here we developed a quantitative lipid radical generating system using the donor AAPH, and conditionally immortalized podocytes to test the effects of reactive lipids on podocyte homeostasis.

Results: Surprisingly, low levels of reactive lipids led to improved motility, dynamic rearrangements of F-actin filaments, increased basal Akt phosphorylation, and increased levels of slit diaphragm proteins nephrin and WT-1. As nephrin directly activates Akt, these observations can be interpreted as beneficial adaptation, adjusting podocyte physiology to an initial stress. Only higher levels of reactive lipids led to motility decline, F-actin aggregates and low levels of pAkt. Since motility and F-actin filaments were affected, we hypothesized that lipid radicals may be sensed through the redox active master regulator protein RhoA, modulating GTP-bound RhoA levels. RhoA has two redox sensitive cysteine residues that may serve as redox switches, resulting in GDP/GTP exchange and modulation of RhoA activity. When tested with a novel G-LISA assay, exposure of podocytes to low levels of reactive lipids indeed rapidly activated RhoA. Next, we have generated constructs to mutate Cys16, Cys20 or both residues on RhoA to ultimately test if RhoA activation is key in the redox sensing mechanism.

Conclusions: In contrast to the traditional view, our results suggest that lipid radicals may act on an adaptive to maladaptive scale to control redox sensitive mechanisms and podocyte physiology. Lipid radicals may affect important signaling elements of podocyte homeostasis in a tightly regulated fashion, through the RhoA-slit diaphragm proteins-Akt axis. Therefore, modulating their levels can be a novel basis for redox-targeted drug development in diabetic complications, such as nephropathy.

Funding: NIDDK Support

TH-PO309

The Redox Sensitive Glycogen Synthase Kinase (GSK) 3 β Suppresses the Self-Protective Antioxidant Response in Podocytes upon Oxidative Glomerular Injury Changbin Li,¹ Yan Ge,¹ Ai Peng,² Rujun Gong,¹ ¹Nephrology, Brown Medical School, Providence, RI; ²Dept of Nephrology, Tongji Univ, Shanghai, China.

Background: GSK3 has been recently implicated in the pathogenesis of kidney diseases, including proteinuric glomerulopathy. However, prior studies were less conclusive because they relied solely on chemical inhibitors of GSK3, which provide poor discrimination between the isoforms of GSK3 apart from potential off target activities. This study aimed to examine the effect of podocyte specific ablation of GSK3 β on glomerular pathophysiology.

Methods: GSK3 β was selectively knocked out (KO) in mature glomerular podocytes in adult mice by employing the tetracycline-inducible Cre-loxP site specific gene targeting system. KO mice and control littermates were subjected to intraperitoneal protein overload followed by examination of proteinuria and glomerular histology.

Results: In murine kidneys, the β rather than the α isoform of the redox sensitive GSK3 was found to be predominantly expressed in glomeruli and distributed intensely in podocytes. Podocyte specific ablation of GSK3 β resulted in a phenotype no different from control littermates with normal kidney function. Electron microscopy demonstrated more glycogen accumulation in podocytes but otherwise normal glomerular ultrastructures in KO mice. Upon oxidative glomerular injury induced by protein overload, KO mice excreted significantly less albuminuria and had much attenuated podocytopathy, characterized by glomerulosclerosis, the loss of podocyte specific marker synaptopodin and by de novo expression of podocyte injury marker desmin, as shown by fluorescent immunohistochemistry staining and by immunoblot analysis of isolated glomeruli. The antiproteinuric and glomerular protective effect observed in KO mice was concomitant with diminished accumulation of reactive oxygen species and attenuated oxidative injuries in glomeruli, which was likely secondary to a reinforced Nrf2 antioxidant response in glomerular podocytes.

Conclusions: Collectively, our data suggests that GSK3 β is dispensable for glomerular function and histology under normal circumstances but may serve as a therapeutic target for protecting from oxidative glomerular injuries.

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TH-PO310

Vitamin D Receptor (VDR) Inversely Modulates Renin Angiotensin System (RAS) Through MDM2 and p53 in Kidney Cells Hongxiu Wen, Shabirul Haque, Xiqian Lan, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: Vitamin D has been reported to be a negative regulator of renin transcription. However, this concept is not able to provide a logical explanation for activation of the RAS in VDR knockout (KO) mice. We hypothesized that VDR inversely modulates the RAS through modulation of MDM2 and p53 expression. Since MDM2 is a negative regulator of p53 (MDM2 induces transcriptional repression and proteosomal degradation), VDR would also negatively regulate p53 via MDM2. p53 is known to activate the via transcription of angiotensinogen (Agt) and AT1R. On that account we further hypothesize that vitamin D down regulates the RAS through upregulation of VDR/MDM2 and down regulation of p53.

Methods: Protein blots of control and VDRKO mice were probed for MDM2. The same blots were reprobed for p53, angiotensinogen (Agt), renin, AT1R, and actin. RNAs were extracted from renal tissues of control and VDRKO mice. cDNAs were probed with specific primers for MDM2, p53, Agt, and renin. Human podocytes (HP) and tubular cells (HPTC) were silenced for VDR. Protein blots of control and siRNA-VDR/ HP and siRNA/HPTC were probed for MDM2, p53, Agt, and AT1R. To evaluate the role p53, cells were transfected with either p53 plasmid or siRNAp53. To evaluate relationships amongst VDR, MDM2, and p53, protein blots of VDR agonist treated-p53/HP and p53/HPTCs and si-RNAP53/HP and HPTCs were evaluated for MDM2 and p53 expressions.

Results: Renal tissues of VDRKO mice displayed attenuated protein and mRNA expression of MDM2 but enhanced expression of p53, Agt, renin, and AT1R. Both podocytes and tubular cells lacking VDR also displayed attenuated expression of MDM2 but enhanced expression of p53, Agt, renin, and AT1R. HPs and HPTCs displaying enhanced expression of p53 also displayed down regulation of VDR but activation of RAS; on the other hand, HPs and HPTCs silenced for p53 displayed upregulation of VDR but down regulation of RAS. VDR agonist enhanced expression of VDR and MDM2 but down regulated expression of p53 and the RAS.

Conclusions: VDR determines the status of the RAS through modulation of MDM2 and p53 expression in kidney cells.

TH-PO311

The Role of CD133 Molecule in Renal Papillary Cells and Its Possible Involvement in Wnt Signaling and Cellular Senescence Prevention Elli Papadimitriou, Alessia Brossa, Benedetta Bussolati. *Dept of Molecular Biotechnology and Health Sciences, Univ of Turin, Turin, Italy.*

Background: The nature of cells involved in homeostasis/repair of adult human kidney is unclear. In human tissue, using the AC133 antibody, recognizing a stem cell-specific glycosylation-dependent epitope of prominin (CD133), CD133+ cells with phenotypic and functional progenitor-like properties were detected in all nephron segments as scattered distinct cells with a dedifferentiated phenotype that survive and proliferate after damage.

However, the role of the CD133 in the progenitor phenotype and its possible modulation is unknown. In the present study we aim to evaluate the role of the CD133 in the maintenance of cellular stem-like phenotype and its involvement in cellular senescence.

Methods: CD133+ progenitor cells were isolated from the inner medullary of human kidney biopsies. We generated CD133 knock-down (kd) cell lines by infecting them with lentiviruses carrying GFP-shPROM plasmids. Cytotoxicity was evaluated by BrdU uptake or MTT assay. Spheroid formation was evaluated by sphere counting and MTT assay after 48h of hypoxia. The senescence was evaluated by β -galactosidase expression and telomere length measurement by real time PCR. The activity of the Wnt pathway was investigated using a Wnt-reporter luciferase assay.

Results: Preliminary data showed CD133 kd cells downregulated the stem-related gene Oct4A and acquired the differentiation marker AQP1. The activity of Wnt pathway seemed to be reduced in CD133 silenced cells both in basal culture conditions as well as after damage, as shown by a Wnt-reporter assay. Functionally, CD133 kd cells did not modify their response to cisplatin, cyclosporine or hydrogen peroxide, suggesting that CD133 may not be involved in resistance to damage. At variance, in CD133 kd cells the sphere formation was slightly reduced, both in number and size. Interestingly CD133 kd cells showed an increased expression of β -galactosidase, a marker of senescence, compared to CD133+ cells, along with a telomere length shortening.

Conclusions: Our preliminary data suggest that CD133 may be involved in the maintenance of a stem-like phenotype in renal cells along with a delay of senescence.

Funding: Government Support - Non-U.S.

TH-PO312

The Effect of Wnt5a/Ca²⁺ Pathway on High-Glucose Induced Fibrosis of Human Peritoneal Mesothelial Cells Jin Liu, Jianfei Ma, Ye Hu, Linshan Jiao, Yichen Chen. *Nephrology, The First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning, China.*

Background: Fibrosis is the main reason of ultrafiltration failure. Human Peritoneal Mesothelial Cells (HPMC) expresses wnt5a, which induces noncanonical wnt signaling pathway. Increase cytosolic free [Ca²⁺], then dephosphorylation of nuclear factor of activated T-cells 2 (NFAT2) translocate to nuclear. The wnt5a/Ca²⁺/NFAT2 signaling pathway may be activated and necessary for the fibrosis of HPMC.

Methods: HPMC were cultured under normal glucose, high glucose (HG126mM) or BAPTA-AM (calcium chelator, BA for short) /HG for 24h, or BA for 2h, or different concentrations of HG (60 mM, 126 mM, 220 mM) for 24h, or HG126 mM for 0h, 6h, 12h, 24h. Western Blot technique detects Wnt5a expression in cells and NFAT2 expression in nucleus. Nuclear translocation was observed by immunofluorescence microscopy. The Wnt5a mRNA was detected by RT-PCR. The expression of connective tissue growth factor (CTGF) was detected by Elisa.

Results: Western blot shows the expression of Wnt5a elevated in HG groups, which depended on concentration and action time. Wnt5a mRNA elevated in HG group in early stage, and in 48h it decreased. According to the results of Western blot and immunofluorescence in HPMC after HG treatment, NFAT2 translocated from cytoplasm to nucleus, NFAT2 increased in the nuclei by the dependence of action time and concentration of HG. Interestingly, in BA/HG group the expression of NFAT2 decreased in the nucleus, and in BA group there was no statistical significance controlled with normal glucose. The stimulation of HG increased CTGF, which depends on action time and concentration, and after join BA in HPMCS the expression of CTGF reduced.

Conclusions: The noncanonical wnt5a/Ca²⁺/NFAT2 signaling pathway is activated by high glucose induced fibrosis of Human Peritoneal Mesothelial Cells, and inhibition of this pathway may contribute to the anti-fibrogenesis of HPMC, prolong the period of peritoneal dialysis.

Funding: Government Support - Non-U.S.

TH-PO313

The Serine Protease Hepsin Mediates Urinary Secretion and Polymerisation of Zona Pellucida Domain Protein Uromodulin Martina Brunati,¹ Simone Perucca,¹ Ling Han,² Celine Schaeffer,¹ Sara Santambrogio,¹ Eric Olinger,³ Romain Perrier,⁴ Marcel Bokhove,² Angela Bachi,⁵ Edith Hummler,⁴ Olivier Devuyst,³ Qingyu Wu,⁶ Luca Jovine,² Luca Rampoldi.¹ ¹San Raffaele Scientific Inst, Milan, Italy; ²Karolinska Inst, Stockholm, Sweden; ³Univ of Zurich, Zurich, Switzerland; ⁴Univ of Lausanne, Lausanne, Switzerland; ⁵FIRC Inst of Molecular Oncology, Milan, Italy; ⁶Lerner Research Inst, Cleveland.

Background: Uromodulin is the most abundant protein in the urine. Genetic and functional evidence demonstrated that this protein, exclusively produced by renal epithelial cells, plays key roles in kidney function and disease. Uromodulin mainly exerts its function as an extracellular filamentous matrix whose assembly depends on a conserved, specific proteolytic cleavage leading to conformational activation of a Zona Pellucida (ZP) polymerisation domain. In this work we aimed at understanding the nature of such cleavage.

Methods: We used a comprehensive approach, ranging from biochemistry, molecular and cell biology in cells stably expressing uromodulin and in urine and kidney samples of relevant knock-out mice.

Results: Starting from the observation that uromodulin is uniquely cleaved at the urinary site and assembled into polymeric filaments in MDCK cells we demonstrate that physiological cleavage of uromodulin depends on a serine protease, and that this enzyme is likely membrane bound. Differential expression analysis in different cell models identified two candidate enzymes, hepsin and prostatin. Both interact with uromodulin, and could induce its specific cleavage in transfected cells and in vitro. Through gene silencing in

MDCK cells and extensive analysis of urinary uromodulin processing in vivo in hepsin and prostaticin knock-out mice, we demonstrate that hepsin is the enzyme responsible for the physiological cleavage releasing urinary uromodulin.

Conclusions: Our findings define a key aspect of the biology of uromodulin that could pave the way for future studies on the regulation of its secretion. Given the similar function of the ZP domain and the high conservation of cleavage site in ZP domain proteins, our results are likely relevant for other members of this protein family.

Funding: Private Foundation Support

TH-PO314

The Favorable Effect of AdipoRon on Diabetic Nephropathy through Improvement of Endothelial Dysfunction in *db/db* Mice Yaeni Kim, Ji Hee Lim, Min Young Kim, Hyung Wook Kim, Cheol Whee Park. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Adiponectin is one of the numerous adipocyte-derived adipokines that interplays with others to exert the milieu of metabolic syndrome. It binds to adiponectin receptors (AdipoR), AdipoR1 and AdipoR2 and exhibits antidiabetic effects via activation of AMPK and PPAR- α . Orally active synthetic small-molecule AdipoR agonist, AdipoRon binds to both AdipoR and ameliorates obesity-related disease. Therefore, we investigated the possible role of AdipoRon in renal physiology in the view of prevention and development of diabetic nephropathy in diabetic mouse model.

Methods: Male *db/db* mice were fed a diet containing AdipoRon (30 mg/kg/day p.o. for 4 weeks from 17 to 20 weeks of age). Serum, urine and renal tissue were obtained to analyze for changes in metabolic parameters, molecular levels and renal structure.

Results: AdipoRon treatment showed decreased amount of albuminuria with no significant changes in the levels of serum adiponectin, glucose and creatinine and it seems to be weight neutral. Increased expressions of AdipoR1 in the renal cortex and consistent up-regulations of phosphorylated AMPK and PPAR- α level were associated with AdipoRon treatment. AdipoRon treatment showed favorable effects on diabetes-induced GBM thickening, foot process widening and slit diaphragm space narrowing and further decreased glomerular matrix expansions and inflammation.

Conclusions: Increased expressions of renal AdipoR1, not AdipoR2, indicates that renal injury may cause a compensatory up-regulation of relevant receptors in kidneys to mitigate further renal injury. AdipoRon may control oxidative stress in glomerulus through AMPK and PPAR- α activated pathways and further contribute to prevent deterioration of renal function. The protective role of AdipoRon against the development of albuminuria seems to occur through a direct action on podocytes independently of systemic effects of adiponectin. Its reduction of oxidative stress provides protection against albuminuria and podocyte damage thereby ameliorating endothelial dysfunction in diabetic nephropathy.

TH-PO315

Diabetes-Induced Impairments in Slit-Robo Signaling Augment Glomerular Angiogenesis Darren A. Yuen,¹ Stephen G. Szeto,^{1,2} Mingliang Lu,¹ Lauren Yuk-sum Chan,¹ Krystale A. De Freitas,¹ Lisa Robinson,³ Ahmad Mohammad Omar Siddiqi,^{1,2} ¹St. Michael's Hospital Keenan Research Centre for Biomedical Science, Toronto, ON, Canada; ²Faculty of Medicine, Univ of Toronto, Toronto, ON, Canada; ³The Hospital for Sick Children, Toronto, ON, Canada.

Background: Diabetic nephropathy is characterized by glomerular endothelial cell (GEC) injury. One of the earliest manifestations of this injury is glomerular angiogenesis, a process that classically is thought of as being driven by increased glomerular VEGF production. Slit2 is a regulator of endothelial function, eliciting either pro- or anti-angiogenic effects through its Robo1 and Robo4 receptors, respectively. We have shown previously that glomerular endothelial Robo4 expression is downregulated by high glucose exposure, whereas Robo1 expression is unchanged. **Objectives:** To determine whether high glucose-induced alterations in Robo1 and Robo4 expression regulate VEGF-induced angiogenesis in the diabetic kidney.

Methods: GEC responsiveness to VEGF in angiogenesis assays was examined in both normal glucose (NG) and high glucose (HG) conditions, and following Robo1 knockdown. Using Robo4 knockout (KO) mice, the effect of Robo4 deficiency on diabetic glomerular angiogenesis was also analyzed using fluorescence microangiography (FMA) and PECAM-1 immunohistochemistry.

Results: As compared to GEC grown in NG medium, GEC grown in HG medium expressed lower levels of the anti-angiogenic Robo4 receptor, but not the pro-angiogenic Robo1 receptor, and exhibited greater VEGF responsiveness. Loss of Robo1 eliminated VEGF-induced GEC network formation and migration in both normal and high glucose conditions. In contrast, Robo4 deficiency was associated with enhanced PECAM-1 density and glomerular capillary length in Robo4 KO mice (compared to their WT littermates) after 4 weeks of STZ-induced diabetes.

Conclusions: Our observations suggest that diabetic glomerular angiogenesis is driven not only by enhanced VEGF production, but also by enhanced glomerular endothelial VEGF responsiveness. Our data also suggest that this increased responsiveness is promoted by a shift in glomerular endothelial Slit2-Robo signalling, favouring more pro-angiogenic Robo1, and less anti-angiogenic Robo4 activity.

Funding: Government Support - Non-U.S.

TH-PO316

Dynamic Regulation of Endothelial Specific Molecule 1 in Diabetic Mouse Kidney Xiaoyi Zheng,¹ Fariborz Soroush,² Sanchita Bhattacharya,³ Mohammad F. Kiani,² Vivek Bhalla.¹ ¹Div of Nephrology, School of Medicine, Stanford Univ, Stanford, CA; ²Dept of Mechanical Engineering, College of Engineering, Temple Univ, Philadelphia, PA; ³Dept of Pediatrics, School of Medicine, UC San Francisco, San Francisco, CA.

Background: Performing glomerular gene expression profiling in diabetic mouse models with differential susceptibility to nephropathy (DN), we identify endothelial specific molecule 1 (Esm-1), as a novel candidate gene in the development of DN.

Methods: We studied Esm-1 function using a bioinspired microfluidic assay (bmFA) and Esm-1 expression by qPCR and ELISA in diabetic and non-diabetic mice.

Results: Esm-1 is proposed to disrupt LFA-1: ICAM-1 interactions at the leukocyte: endothelial cell interface, and leukocyte infiltration into glomeruli is a known risk factor for DN. In a bmFA, pre-treatment of leukocytes with Esm-1 inhibits rolling and transmigration in a dose-dependent manner. Consistent with the diminution of leukocyte infiltration, 4 weeks after induction of diabetes, Esm-1 mRNA is markedly attenuated in glomeruli from DN-susceptible, DBA/2J, compared to DN-resistant, C57BL/6J, mice (relative fold: 0.085 \pm 0.012, $p < 0.05$). Secretion of Esm-1 is also lower from glomeruli of DN-susceptible mice (132.6 \pm 41.6 vs 226.4 \pm 79.3 pg/mL, $p < 0.05$). These changes occurred in the background of a dynamic response of kidney Esm-1 to diabetes. Urine Esm-1 excretion increases in diabetic vs. non-diabetic mice (307.7 \pm 51.6 vs 102.3 \pm 29.7 pg/mg creatinine, $p < 0.05$), despite no increase in urine albumin and a $\sim 50\%$ decrease in circulating Esm-1 in diabetic mice. Further *in vitro* studies in cultured glomeruli show that hyperglycemia significantly increases Esm-1 mRNA and protein and suggest that urine Esm-1 reflects increased production by glomeruli.

Conclusions: These results demonstrate that diabetes induces Esm-1 in glomeruli, and this induction is attenuated in DN-susceptible mice. These data suggest that increased production of glomerular Esm-1 would be sufficient to attenuate leukocyte infiltration and consequently, DN. Furthermore, we propose urine Esm-1 as a non-invasive candidate biomarker for resistance to DN.

Funding: NIDDK Support, Private Foundation Support

TH-PO317

Activation of Rho/Rho-Kinase Pathway in Proximal Tubules as a Culprit in Obesity-Related Nephropathy Makiko Naitoh, Hirobumi Tokuyama, Koji Futatsugi, Shu Wakino, Hiroshi Itoh. *Keio Univ, Tokyo, Japan.*

Background: A small GTP-binding protein, Rho, and its effector, Rho-kinase, have several pathological functions. We previously demonstrated that in obesity adipocyte cellular hypertrophy activates Rho/Rho-kinase signaling through mechanical stretch, leading to inflammatory changes (Science signaling, 2011). We have also documented enlarged and vacuolated proximal tubules (PT) in obesity-related kidney damage (Int J Obesity, 2012). We examined whether Rho/Rho-kinase was activated in enlarged PT that were supposed to be under the mechanical stress and contributed to the pathophysiology of obesity-induced kidney damages.

Methods: We created mice that overexpressed dominant negative RhoA genes specifically in PT under the control of promoter of sodium-phosphate co-transporter (PT-DN-RhoA TG). PT-DN-RhoA TG mice (DN) and their wild-type littermates (WT) were fed a high fat (HFD) or low fat diet (LFD) for 12 weeks and compared in phenotypes.

Results: WT on HFD not only developed obesity but also manifested histological changes, including the enlargement in PT as well as in glomeruli, vacuolation of PT, the infiltration of inflammatory cells and the overexpression of stress fibers, which paralleled the increase in urinary albumin and NGAL of tubular injury markers. Enhanced Rho-kinase activity was noted particularly in PT. Inflammatory cytokines were subsequently overexpressed in WT on HFD as compared with those in WT on LFD. In DN, the activation of Rho kinase was attenuated in PT region leading to the decrease in the size, vacuolation and stress fiber formation in PT cell, the decrease in inflammatory cells infiltration and cytokine expressions, and the reduction in albuminuria and PT impairment.

Conclusions: Excess fat intake causes obesity-induced renal injury, which are mediated by an Rho/Rho-kinase activation in PT and inflammatory process. It is surmised that hypertrophic process in PT during obesity formation affects Rho-kinase activation presumably through mechanical stress. This process subsequently induces inflammation and accelerates the histological changes of PT. The intervention of Rho/Rho-kinase may constitute a novel strategy blocking the progression of obesity-induced renal damages.

TH-PO318

SUL121: A Novel Compound Preserving Endothelial Function and Inhibiting Progression of Kidney Damage in Type 2 Diabetes Mellitus in Mice Leo E. Deelman, Sebastiaan Lambooy, Arash Bidadkosh, Hendrik Buikema, Robert H. Henning. *Clinical Pharmacy and Pharmacology, Univ Medical Center Groningen, Univ of Groningen, Groningen, Netherlands.*

Background: Diabetic nephropathy is a common complication of Type 2 Diabetes mellitus (T2DM), a chronic metabolic disorder with increasing incidence worldwide. To stop the progression of diabetic kidney disease, new strategies are urgently needed. Endothelial dysfunction (ED) and reactive oxygen species (ROS) are important targets for novel therapies to stop diabetic nephropathy. To improve ED and inhibit ROS, we recently developed the compound SUL121, a putative hydrogen sulfide (H₂S) inducer and inhibitor of ROS.

Methods: To test the therapeutic effects of SUL121 in diabetic and normal mice, db/db mice and lean control mice were subcutaneously implanted with osmotic mini pumps delivering SUL121 or vehicle from age 10 to 18 weeks. Mice were placed in metabolic cages every two weeks until termination at which time endothelial mediated relaxation in aortic rings was assessed. ROS status and H₂S levels were measured in plasma, and renal expression of H₂S producing enzymes was determined.

Results: While treatment with SUL121 did not alter the glycemic state in db/db, it prevented albuminuria and diabetic kidney damage, as evidenced by an inhibition of the progression of albumin excretion rate, lower albumin creatinine ratio, decreased focal glomerular sclerosis score and normalization of kidney weight. In addition, SUL121 normalized systemic ROS formation, increased renal expression of the H₂S producing enzymes, cystathionine gamma lyase and cystathionine beta synthase (CSE and CBS), and prevented the development of endothelial dysfunction in db/db. SUL121 treatment in lean control mice demonstrated no observable side-effects, indicating that SUL121 is well tolerated.

Conclusions: Thus, SUL121 represents a novel compound inhibiting the progression of experimental diabetic kidney damage via a mechanism that inhibits both oxidative stress and preserves vasorelaxation.

Funding: Pharmaceutical Company Support - This study was partially financed by Sulfateq B.V., a company that owns patents on SUL121, and produces and markets similar compounds., Government Support - Non-U.S.

TH-PO319

Coagulation Factor Xa and Protease-Activated Receptor 2 as Novel Targets for Treating Diabetic Nephropathy Yuji Oe,¹ Emiko Sato,^{1,2} Hiroshi Sato,^{1,2} Sadayoshi Ito,¹ Nobuyuki Takahashi,^{1,2} ¹*Div of Nephrology, Endocrinology, and Vascular Medicine, Tohoku Univ Graduate School of Medicine, Sendai, Japan;* ²*Div of Clinical Pharmacology and Therapeutics, Tohoku Univ Graduate School of Pharmaceutical Sciences, Sendai, Japan.*

Background: Role of hypercoagulability in pathogenesis of diabetic nephropathy (DN) remains elusive. We have recently demonstrated that elevated coagulation factor III (tissue factor) exacerbates DN (J Thromb Haemost 2010, PNAS 2011). Tissue factor activates factor X (FXa), which in turn stimulates protease-activated receptor 2 (PAR2). PAR2 causes inflammation and fibrosis. Accordingly, we hypothesized that activation of FXa- PAR2 signaling exacerbates DN.

Methods: To test this hypothesis, we used diabetic mice with reduced expression of endothelial NO synthase (*Nos3*) as a model of DN. We first tested whether inhibiting FXa ameliorates DN by administering an oral FXa inhibitor Edoxaban (50 mg/kg/day) for 3 months to diabetic mice lacking eNOS (*Ins2^{Akim}+/+*; *Nos3^{-/-}*). We next tested whether lack of PAR2 ameliorates DN using diabetic mice lacking PAR2 (*F2r1^{-/-}*; *Ins2^{Akim}+/+*; *Nos3^{+/+}*). Finally, the effects of FXa or PAR2 agonist (SLIGKV) on human endothelial cells (EA.hy926) and conditionally immortalized murine podocytes were evaluated.

Results: Renal expression of FX and PAR2 was up-regulated in DN, together with elevation of FXa activity in the urine. Edoxaban and lack of PAR2 both reduced renal expression of inflammatory and profibrotic genes, and ameliorated diabetic glomerulosclerosis and urinary albumin excretion. FXa or a PAR2 agonist (SLIGKV) increased IL-8 secretion and gene expression of *MCP1* and *PAII* in human endothelial cells. These treatments also increased *Mcp1* mRNA level in murine podocytes.

Conclusions: We conclude that FXa - PAR2 signaling exacerbates DN possibly through up-regulating inflammatory response. FXa - PAR2 signaling is a promising target for treating or preventing DN.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO320

Herniation of the Mesangium Together with Sprouting of Blood Vessels Out of the Glomerular Entrance Is a frequent Feature of Diabetic Nephropathy Wilhelm Kriz, Jana Loewen. *Anatomy, Univ of Heidelberg, Medical Faculty Mannheim, Mannheim, Germany.*

Background: In contrast to diabetic retinopathy, where neovascularizations have a central pathogenic impact, in diabetic nephropathy (DN) angio-proliferative processes are generally not considered as a major factor underlying disease progression. The studies by Osterby and Nyberg (J Diab Compl 1987, 1:122) and Min and Yamanaka (Virchows Arch A Pathol Anat 1993, 423:201) have shown neovascularizations in DN but have found little attention.

Methods: Re-evaluation of biopsies of DN (archive: Dep. of Molecular Pathology, German Cancer Research Center, Heidelberg) has revealed that the proliferation of newly formed blood vessels out of the glomerular entrance into the surroundings of the glomerulus is a frequent feature in DN.

Results: In a total of 437 biopsies (so far evaluated) 60.2% contained aberrant vessels at the vascular pole or in periglomerular position. 13% of these cases were associated with diffuse mesangial sclerosis (DMS), 35% with transitional stages from DMS to nodular sclerosis (NS) and 52% with NS. The outgrowth is based on extensive widening of the glomerular entrance accompanied by herniation of the expanded mesangium with displacement of the extraglomerular mesangium and the macula densa. The aberrant vessels spread into glomerular surroundings, preferentially along the outer aspect of Bowman's capsule finally draining into peritubular capillaries. These vessels mostly have the structure of small arterioles. Frequently, almost regularly, accumulations of exudative material are encountered beneath the endothelium or within the layer of smooth muscle cells.

Conclusions: It is suggested that the exposure of mesangial areas to environmental stimuli accounts for the angio-proliferations. As derivatives from glomerular capillaries the aberrant vessels are likely perfused under high pressure accounting for the exudative

lesions. The periglomerular matrix and fibrotic envelopes frequently seen in DN (in 69.6% in our material) seem to emerge in response to exudations and possibly other stimuli from the aberrant vessel. The encroachment of these processes along the transition to the tubule likely contributes to the tubulo-interstitial disease.

TH-PO321

Exploiting Angiopoietin-Tie Signaling for Treatment of Diabetic Nephropathy Tomokazu Souma,¹ Isabel Anna Carota,¹ Benjamin R. Thomson,¹ Jing Jin,¹ Susan E. Quaggin.¹ ¹*Div of Nephrology/Hypertension, Feinberg Cardiovascular Research Inst, Feinberg School of Medicine, Northwestern Univ, Chicago, IL;* ²*Aerpio Therapeutics, Cincinnati, OH.*

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in the US, and is characterized by microvascular dysfunction. The Angiopoietin-Tie signaling pathway plays a key role in endothelial health and survival. The endothelial Tie2 receptor tyrosine kinase becomes activated upon binding its endogenous ligand Angiopoietin1 (ANGPT1). This activity elicits a cascade of intracellular signaling events, leading to junctional reinforcement and vasculo-protection. VE-PTP is a Tie2 selective phosphatase, which negatively modulates Tie2 signaling intensity. Here we tested whether augmentation of Tie2 signaling by VE-PTP inhibition protects against DN.

Methods: To test the therapeutic potential of Tie2 activation, we treated *Ins2^{Akim}* DBA/2J Mice with a VE-PTP inhibitor (AKB-9785, Aerpio) or vehicle control (n=8 in each group). In parallel, cell-based analyses were performed to elucidate ANGPT-Tie signaling events. The role of VE-PTP on the phosphorylation status of Tie2 expressed in HEK293 cells was determined by LC-tandem mass spectrometry (LC-MS/MS).

Results: 17-week treatment of AKB-9785 improved the general status of *Ins2^{Akim}* mice (body weight change from baseline; vehicle +15%, AKB-9785 +35%, P<0.01). Further, AKB-9785 preserved mGFR of *Ins2^{Akim}* mice (vehicle 560 ml/min, AKB-9785 945 ml/min with 6-week daily treatment, P<0.067). LC-MS/MS identified 13 phospho-tyrosine residues in Tie2; all sites were dephosphorylated by VE-PTP co-expression. Treatment with either recombinant Angpt1 or AKB-9785 rapidly induced Tie2 phosphorylation, suggesting Tie2 can be activated in a ligand-independent fashion. Administration of AKB-9785 to Angpt1 KO mice confirmed ligand-independent Tie2 activation occurs *in vivo*.

Conclusions: Our data suggest that the small molecule inhibitor, AKB-9785 is a potent activator of Tie2 phosphorylation, has positive effects in a preclinical rodent model of Type I diabetes and is an attractive therapeutic candidate for DN.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute (NHLBI)

TH-PO322

Berberine Ameliorate High Glucose and Advanced Glycation End Products Induced Glomerular Endothelial Cell Hyperpermeability Nanmei Liu. *Jimin Hospital of Shanghai.*

Background: Glomerular endothelial cells (GENC) are important part of the glomerular filtration barrier. The dysfunction of glomerular endothelial cells (GENCs) could be a characteristic of early stage diabetic nephropathy (DN). Accumulating evidence indicate that advanced glycation end products (AGEs) play a pivotal role in the progressive of glomerulosclerosis or thickening of the glomerular basement membrane in DN. Berberine, an extracts from some Chinese plant medicine such as Huanglian Letasiova S (Rhizoma coptidis); Huangbai (cortex phellodendri), Gold Seal (hydrastis canadensis), was reported lower blood sugar and attenuated diabetic nephropathy, but the mechanism still need verified. This study was to investigate the changes of monolayer permeability in GENCs caused by high concentration glucose and AGEs, and the effects of Berberine.

Methods: GENCs were cultured in growth medium causing cell proliferation, then seed in a Transwell chamber culture system to form confluent monolayer. The cell was treated with ordinary glucose (5.5mM), or high glucose (25mM), AGE 100mg / mL, berberine (3uM) inspectively. The GENC permeability was evaluated by measuring the diffusion of biotin-conjugated bovine serum albumin (biotin-BSA) across a cell monolayer. The changes of cytoskeleton was observed under Confocal laser scanning fluorescence microscopy after double staining of F-actin and G-actin.

Results: The protein leakage rate was increased slightly after treated with high glucose (25mM), but increased significantly in high glucose plus AGE 100mg/mL compared with low glucose control group. High glucose and AGE strongly affected orientation of F-actin fibers, induced rearrangement of F-actin fibers. While berberine intervention can reduce protein leakage rate (P<0.05), improved the F-actin cytoskeletal actin disorder significantly.

Conclusions: High glucose and AGE increased permeability of the GENC monolayer and leads to long-term alterations of F-actin structures. Berberine has a protective effect. The mechanism may be related to inhibit endoplasmic reticulum stress and reduce the cytoskeleton injury.

Funding: Government Support - Non-U.S.

TH-PO323

Arginase Inhibition: A New Treatment for Preventing Progression of Established Diabetic Nephropathy Hanning You,¹ Ting Gao,¹ Timothy K. Cooper,² Sidney M. Morris,³ Alaa S. Awad.¹ ¹Medicine, Penn State Univ College of Medicine, Hershey, PA; ²Comparative Medicine, Penn State Univ College of Medicine, Hershey, PA; ³Microbiology and Molecular Genetics, Univ of Pittsburgh, Pittsburgh, PA.

Background: Our previous publication showed that inhibition of arginase prevents the development of diabetic nephropathy (DN). However, identification of targets that retard the progression of established DN--which is more clinically relevant--is lacking. Therefore, we tested the hypothesis that arginase inhibition would prevent the progression of established DN. Effects of arginase inhibition were compared to treatment with the ACE inhibitor captopril, a current standard of care in DN.

Methods: Experiments were conducted in *Ins2^{AKita}* mice treated with the arginase inhibitor S-(2-boronoethyl)-L-cysteine (BEC) or captopril starting at 6 wks of age for 12 wks (early treatment) or starting at 12 wks of age for 6 wks (late treatment).

Results: Early and late treatment with BEC resulted in protection from DN as indicated by reduced albuminuria, histological changes, kidney macrophage infiltration, urinary TBARS, and restored nephrin expression, kidney nitrate/nitrite, kidney eNOS phosphorylation, and renal medullary blood flow compared with vehicle-treated *Ins2^{AKita}* mice at 18 wks of age. Interestingly, early treatment with captopril reduced albuminuria, histological changes, and kidney macrophage infiltration without affecting the other parameters, but late treatment with captopril was ineffective.

Conclusions: These findings highlight the importance of arginase inhibition as a new potential therapeutic intervention in both early and late stages of diabetic renal injury.

Funding: NIDDK Support

TH-PO324

Transgenic TGF- β 1 Receptor Type II (TbRII) Overexpression in Podocytes Promotes STZ Induced Diabetic Nephropathy in Rats Sigrid C. Hoffmann, Stamatia Matina Papagiannarou, Wilhelm Kriz, Tamara Micakovic. *Medical Faculty Mannheim, Univ Heidelberg, Mannheim, Germany.*

Background: Glomerular TGF- β 1 is increased early in the course of diabetic nephropathy. The podocytes are sources and targets of TGF- β 1. This study addresses the hypothesis that increased TGF- β 1 in diabetic rats stimulates the development of diabetic nephropathy via selective signalling in podocytes.

Methods: Transgenic rats carrying the TGRT β RII driven by the podocin promoter were generated. Transgene expression was verified by Northern blotting, in-situ hybridization and Western blotting. Glomerular expression profiling was performed by real time RT-PCR, Western blotting and immunohistochemistry. Podocyte density was determined by counting WT-1 stained podocytes per glomerular area, which was determined morphometrically in 200 glomeruli per rat. At 2 months of age rats received STZ (40mg/kg i.v.) or diluent, respectively. Body weight and kidney function were evaluated by urinary albumin excretion in the 24h-urine and by creatinine clearance at monthly intervals.

Results: TGR expressed the transgenic receptor specifically in podocytes. Glomerular TbRII protein levels were almost twice that of WT. At 5 months of age 40 % of TGR exhibited moderately increased albumin excretion up to 2.2 mg/24hr vs. 0.11 mg/24hr in WT. 3 months after STZ, albumin excretion was significantly increased in 80% of TGR with an average of 4 mg/24hr (max: 7.3) but only slightly elevated in 40% of the WT with in average 0.7mg/24hr (max: 2.2). Expression profiling in isolated glomeruli revealed that in TGR PAI-1 was significantly upregulated and the survival marker bcl-2 and podocyte differentiation marker synaptopodin, podocin and nephrin were significantly down-regulated relative to WT. Podocyte number per glomerulus was significantly decreased in diabetic TGR vs. diabetic WT.

Conclusions: Podocyte-selective TbRII-overexpression contributes to the leakage of the glomerular filter in the course of STZ induced diabetic nephropathy which might be mediated by podocyte loss due to podocyte dedifferentiation, downregulation of bcl-2 and PAI-1 upregulation.

Funding: Government Support - Non-U.S.

TH-PO325

Comparison of Glomerular and Podocyte mRNA Profiles in eNOS^{-/-} Diabetic Mice Induced by Streptozotocin Jia Fu,^{1,2} Chengguo Wei,² Kim Lee,² Weijia Zhang,² Peter Y. Chuang,² Zhihong Liu,¹ John C. He.^{2,3} ¹National Clinical Research Center of Kidney Diseases, Jinling Hospital; Nanjing Univ School of Medicine, Nan Jing, Jiangsu, China; ²Div of Nephrology, Dept of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; ³Renal Program, James J Peters VA Medical Center at Bronx, New York, NY.

Background: Gene expression profiles have never been reported in primary podocytes isolated from the diabetic kidney. Here, we compared mRNA profiles in both isolated glomeruli and sorted podocytes between diabetic and control mice.

Methods: IRG mice carrying a two-color fluorescent reporter gene were first crossed with eNOS^{-/-} mice and then with podocin-rTTA and TetON-Cre mice allowing us to permanently label podocytes. Then, mice were injected with either streptozotocin (STZ-eNOS^{-/-}) or vehicle (CL-eNOS^{-/-}). STZ-eNOS^{-/-} mice developed typical findings of diabetic nephropathy at 10 weeks after STZ injection. mRNA sequencing was performed in both isolated glomeruli and sorted podocytes from STZ-eNOS^{-/-} and CL-eNOS^{-/-} mice.

Results: Consistent with the previous reports, expression of podocyte-specific markers in the glomeruli were down-regulated in the STZ-eNOS^{-/-} mice compared to CL-eNOS^{-/-} mice. However, these differences disappeared when mRNA levels were corrected for podocyte number/glomerulus. Interestingly, expression of these markers in sorted podocytes did not differ between diabetic and non-diabetic mice. These data suggest that reduced expression of podocyte markers in isolated glomeruli is likely secondary to reduced podocyte number/glomerulus, rather than loss of differentiation markers. Analysis of the differentially expressed genes (DEGs) between diabetic and non-diabetic mice revealed distinct pathways between glomeruli and podocytes. The up-regulated DEGs in isolated glomeruli were involved mostly in the regulation of mitochondrial function and oxidative stress pathway, while the up-regulated DEGs in sorted podocytes were heavily involved in the actin organization.

Conclusions: In conclusion, our data suggest that podocyte-specific gene expression in transcriptome obtained from glomeruli may not represent those of podocytes in diabetic kidney.

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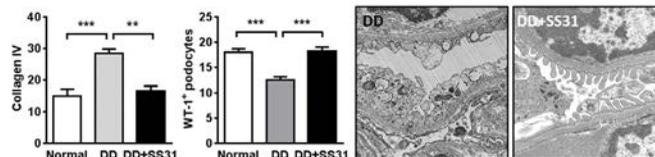
TH-PO326

SS-31, a Mitochondrial Therapeutic, Prevents High Fat Diet-Induced Podocyte Injury Hazel H. Szeto, Shaoyi Liu, Yi Soong, Nazia Alam, Glen T. Prusky, Surya V. Seshan. *Pharmacology, Physiology, Pathology, Weill Cornell Medical College, New York, NY.*

Background: High fat diet (HFD) leads to rapid onset of microalbuminuria and podocyte injury that precedes the onset of insulin resistance and hyperglycemia in mice. It was recently suggested that glomerular injury is triggered by palmitate-induced mitochondrial dysfunction in podocytes (Sun et al., *Kidney Int*, 2015). We investigated the protective effects of SS-31, a mitochondrial therapeutic, against HFD-induced podocyte injury in mice.

Methods: 4 week-old C57BL/6 mice were fed normal diet (ND) or HFD for 28 weeks. 4 weeks later, HFD mice received streptozotocin (40 mg/kg, qd x 5d). Body weight (BW), blood glucose (BG) and glucose tolerance tests (GTT) were determined after 8 and 24 weeks of HFD. SS-31 (2 mg/kg, sc) or saline was administered to HFD mice daily starting at 8 weeks. Kidneys were harvested at 28 weeks for histopathology.

Results: GTT was abnormal at 8 weeks despite no change in BW or BG. BW and BG were significantly increased at 28 weeks. Histological examination revealed mesangial expansion, thickening of the glomerular basement membrane, elevated collagen-IV, and loss of podocyte markers (podocin and synaptopodin). Electron microscopy revealed extensive vacuolization and swelling in podocytes, with swollen mitochondria, autophagic vacuoles, and loss of foot processes. TGF β , TNF α and MCP-1 were all significantly increased. Treatment with SS-31 significantly prevented these HFD-induced pathological changes in the glomeruli without affecting BW, BG or GTT.



Conclusions: These results suggest that SS-31 can protect podocytes against HFD-induced mitochondrial toxicity without changing BW, insulin resistance or hyperglycemia. SS-31 (BendaviaTM), currently in clinical trials for acute kidney injury, may be useful in the treatment of diabetic nephropathy.

Funding: Private Foundation Support

TH-PO327

Tristetraprolin Overexpression Ameliorated Inflammation in db/db Mice and Mouse Podocytes Guo Jia, Zhangsuo Liu. *The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China.*

Background: Tristetraprolin (TTP) is a well-characterized, zinc-finger-containing, RNA-binding protein, which plays a role in the regulation of inflammatory factors expression by targeting the 3' untranslated region (3'UTR). We investigated whether TTP modulates inflammation in high glucose induced-podocytes and in db/db mice kidneys.

Methods: Differentiated mouse podocytes were treated by high glucose, and TTP expression and inflammatory factors was measured by quantitative real-time PCR, western blot or ELISA. TTP siRNA or lentiviral vectors containing TTP sequences were transfected into podocytes to down-regulate or up-regulate TTP expression. Db/db mice were used as the diabetic model in the in vivo experiment. At the age of 10 weeks, db/db mice were injected via tail vein with lentiviral vectors containing TTP sequences. At the age of 14 weeks, the lentiviral injection was repeated. Inflammatory factors and podocyte makers were examined in both podocytes and mice kidneys. Urine albumin to creatinine ratio and serum creatinine was also detected.

Results: TTP was down-regulated while IL-6, IL-18, TNF- α were up-regulated in high glucose-induced mouse podocytes. Silencing TTP by siRNA induced inflammatory factors expression. Overexpression of TTP reduced the expression of inflammatory factors in high glucose-induced podocytes. TTP expression was significantly decreased in db/db mice

kidneys compared with db/m mice. Overexpression of TTP by lentivirus injection ameliorated inflammation in db/db mice. Urine albumin to creatinine ratio and urine inflammatory factors was also decreased in db/db mice overexpressing TTP.

Conclusions: TTP is involved in the regulation of inflammation in diabetic conditions. Targeting TTP might be effective in diabetic kidney disease.

Funding: Government Support - Non-U.S.

TH-PO328

CIN85 Deficiency Prevents Nephron Endocytosis in Podocytes Under Diabetic Conditions Beina Teng, Hermann G. Haller, Mario Schiffer. *Medical School Hannover, Hannover, Germany.*

Background: Podocytes are important for the maintenance of the glomerular filter in the kidney. Podocyte damage is associated with ultrastructural changes and decreased expression of components of the slit diaphragm in many glomerular diseases. Nephron, a podocyte specific protein is crucial for the intact filtration barrier. Loss of nephron has been observed in rodent models of experimental diabetes as well as in human diabetic kidney disease. CIN85, a homologue of CD2AP, was identified as a binding partner of nephron and mediates the nephron endocytosis via ubiquitination in podocytes.

Methods: Using STZ injection, we induced a type I diabetes in BLC57/N wild type and CIN85Dex2 mice to examine diabetes induced dysregulation of glomerular filtration barrier and alteration of extracellular matrix. We then generated immortalized cell lines of podocytes for the CIN85Dex2 and the CD2AP^{-/-} to examine nephron endocytosis in both cell types on the molecular level. To inquire the impact of CIN85 and CD2AP on filtration barrier integrity in zebrafish, we examined proteinuria in zebrafish injected with capped mRNAs.

Results: We can demonstrate that the loss of nephron expression and onset of the proteinuria in diabetic mice correlates with an increased accumulation of ubiquitinated proteins and expression of CIN85 in podocytes. The CIN85Dex2 deficiency leads to preserved nephron surface expression, reduced proteinuria and Collagen-IV deposition in glomeruli under diabetic conditions. High glucose levels induced an increased CIN85 expression in contrast to a significantly reduced expression of CD2AP and nephron in both murine and human podocytes. Furthermore, by high glucose stimulation, the CD2AP^{-/-} podocytes, which express more full-length CIN85, showed an increased nephron endocytosis compared to the CIN85 knockout podocytes. In addition, injection of capped CIN85 mRNA induced a severe edema and proteinuria in zebrafish embryos which could be rescued by co-injection of CD2AP mRNA.

Conclusions: Our findings suggest that CIN85 is involved in the endocytosis of nephron in podocytes under diabetic conditions promoting the development of glomerulopathy. Therefore CIN85 might be a novel treatment target to prevent diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO329

Atrasentan Ameliorates Diabetic Nephropathy and Restores Podocyte Number in BTBRob/ob Mice Kelly L. Hudkins, Tomasz A. Wietecha, Floortje Steegh, Kristina M. Sorg, Noppanit Pattanachaiwit, Minseob Eom, Julia K. Shankland, Charles E. Alpers. *Pathology, Univ of Washington, Seattle, WA.*

Background: Leptin deficient BTBRob/ob mice develop type 2 diabetes and DN that closely mimics human DN, including mesangial expansion, podocyte loss, and proteinuria. This study tested the effect of atrasentan (A), an endothelin-1 receptor antagonist, with or without concurrent RAAS inhibition by losartan (L) on DN and whether this can restore podocyte number.

Methods: Cohorts of 18 week old BTBRob/ob mice and BTBR WT littermates were treated via drinking water with A (5 mg/kg/day), A plus L (25 mg/kg/day) or normal water for 6 weeks. Mice were analyzed for body weight, blood glucose, serum creatinine, proteinuria and morphometric measures of numbers of p57 expressing podocytes, collagen IV staining mesangial matrix.

Results: Treatment with A alone had no effect on body weight or blood glucose. Combined treatment with A and L also had no effect on body weight, but significantly decreased blood glucose levels in both BTBR WT (243 + 14.8 vs 160 + 5.6, p<0.005) and BTBRob/ob (595 + 5.3 vs 382 + 51.5, p<0.01) mice. Treatment with A and combined A and L decreased proteinuria in BTBRob/ob mice, although this did not reach statistical significance due to wide variations within the groups. Serum creatinine was elevated in BTBRob/ob compared to WT mice, and was decreased by treatment with A plus L (p<0.05). Mesangial collagen IV was reduced in both the A and A plus L treated mice (p<0.05). There were decreased podocytes (p57 expressing cells) in BTBRob/ob (149.7 + 6.7) compared to WT mice (188.7 + 9, p<0.05). Podocytes increased in BTBRob/ob mice receiving A (167.0 + 7, ns, p=0.093) and were restored to WT numbers in mice receiving A plus L (190.4 + 5.7, p<0.001).

Conclusions: Treatment with A plus L significantly increased podocyte number in diabetic BTBRob/ob mice. A treatment alone increased podocyte number, but to a lesser degree. Podocyte restoration correlated with decreased blood glucose, serum creatinine, and mesangial matrix with A plus L treatment. The benefit of combined A and L treatment in patients with DN may occur in part through a previously unrecognized restoration of podocytes.

Funding: Pharmaceutical Company Support - Abbvie Pharmaceuticals

TH-PO330

Insulin Signaling in Glomeruli and Podocytes from Insulin Resistant db/db DBA/2J Mice Mette Viberg Østergaard,^{1,2} Jesper Worm,¹ Lisbeth N. Fink,¹ Richard Coward.² ¹Global Research, Novo Nordisk A/S, Maalov, Denmark; ²Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

Background: Impaired insulin signalling in the podocyte may contribute to the glomerular pathology in systemic insulin resistance and type 2 diabetes (T2D). We hypothesize that insulin signalling in the podocyte is altered early during development of insulin resistance and T2D due to altered insulin receptor (IR), IGF-1 receptor (IGF-1R) or insulin/IGF-1 hybrid receptor (HR) expression levels.

Methods: The development of insulin resistance, T2D, albuminuria, and renal pathology was characterised in db/db DBA/2J mice and wild-type (wt) littermates from 6 weeks of age. Insulin-induced phospho-Akt, phospho-ERK1/2 signalling, and IR, IGF-1R and HR expression levels were investigated in the glomeruli of insulin resistant db/db DBA/2J mice. The PodCre, ROSA^{mt/mG} reporter strain enriched in the DBA/2J background is crossed with the db/db DBA/2J strain to enable isolation of insulin resistant GFP⁺ podocytes by FACS and characterisation of podocyte IR, IGF-1R and HR expression levels.

Results: The body weight was >50% higher in db/db vs. wt mice (P<0.001) from 8 weeks. From week 9, db/db males were hyperglycaemic with non-fasting blood glucose ranging from 23.4-30.7 mM (wt range 6.3-7.7 mM; P<0.05). Insulin tolerance tests showed development of whole-body insulin resistance by 8 weeks in male and female db/db vs. wt mice (P<0.05). The urinary albumin-to-creatinine ratio was elevated in db/db vs. wt mice from 7-12 weeks of ages (range of means 2451-9597 vs. 75-479 µg/mg; P<0.01). GFP⁺ podocytes were successfully isolated from glomerular single cell suspensions from PodCre, ROSA^{mt/mG} mice and their purity validated by qPCR analysis of *Nphs2*, *Pecam1*, and *Pdgfrb*. Podocytes are currently being isolated from 9-week-old insulin resistant db/db PodCre, ROSA^{mt/mG} DBA/2J mice to characterise IR, IGF-1R and HR expression levels.

Conclusions: The db/db mouse in the DBA/2J background show early signs of systemic insulin resistance and glomerular disease. Isolating podocytes from this model will allow us to further clarify the roles of IR, IGF-1R and HR in podocytes during the development of insulin resistance and diabetic nephropathy.

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PKC-α Triggers EGFR Ubiquitination, Endocytosis and MAPK/ERK Activation in Podocytes with High Glucose Stimulation Hua Su, Yanhong Wei, Chun Zhang. *Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: PKCα and EGFR are both involved in diabetic kidney disease, however the association between these two proteins during high glucose induced podocyte injury is unclear.

Methods: Diabetes was induced in SD rats by a single intra-peritoneal injection of STZ at a dose of 55 mg/kg body weight in sodium citrate buffer. 14 days later the rats were sacrificed and the cortex of kidney was removed and subjected to plasma membrane isolation and lipid raft fraction. In vitro study human podocyte cell line was employed, and after differentiation it was treated with high glucose or osmotic control for 24 h. The membranous protein expression and endocytosis were assessed by biotinylation and MesNa treatment. Gö6976 and PYR-41 were used as an inhibitor for PKCα and ubiquitin activating E1 enzyme respectively.

Results: By plasma membrane isolation and lipid raft separation we identified that in diabetic rat the abundance of PKCα in membranous fraction and lipid raft domain was elevated, whereas EGFR level was reduced in above-mentioned compartments. Consistently, in vitro high glucose treated podocyte the membranous EGFR was downregulated accompanying with the increased membranous PKCα expression which was examined by biotinylation and plasma membrane isolation. Furthermore by immunoprecipitation, biotinylation and MesNa treatment experiments it showed that the ubiquitination and endocytosis of EGFR were enhanced in podocyte under high glucose stimulation which accompanied with MAPK/ERK signaling activation and the injury of podocyte which was proved by the reorganization of F-actin fibers and increased desmin level. However above processes could be ameliorated by either PKCα or ubiquitin activating E1 enzyme inhibitor.

Conclusions: Our observations demonstrate that in high glucose treated podocyte PKCα mediates EGFR ubiquitination, endocytosis from cell plasma membrane and eventually leads to the activation of MAPK/ERK signaling pathway which partially attributes to podocyte injury in diabetic kidney disease.

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Activation of Protein Kinase C-β in the Podocyte by Diabetes-Associated Inflammatory Mediators Brad Dieter,¹ Rick L. Meek,¹ Robert J. Anderberg,¹ Sheryl K. Cooney,¹ Katherine R. Tuttle.^{1,2} ¹Providence Health Care, Spokane, WA; ²School of Medicine, Univ of Washington, Seattle, WA.

Background: Activation of protein kinase C-beta (PKC-β) is a key signal transduction mediator strongly implicated in development and progression of diabetic kidney disease (DKD). However, the potential role of PKC-β in podocyte mechanisms of DKD has not been previously studied. The aim of this study was to determine whether advanced glycation end-products (AGE) or serum amyloid A (SAA), inflammatory mediators in DKD, activate PKC-β and downstream consequences of inflammation and apoptosis in podocytes.

Methods: Podocytes were exposed to AGE (300 mg/ml) or exogenous SAA (10 mg/ml) for 1 hour. PKC-β activity was measured as the phosphorylated form and by membrane

fraction (Western blot). Immunostaining with imaging by confocal microscopy was used for PKC- β localization. PKC- β was inhibited by LY379196 (100 nm) in podocytes exposed to SAA and AGE for 20 hours. Outcomes included mRNA (qRT-PCR) for pro-inflammatory proteins: C-X-C motif chemokine ligand 5 (CXCL5), C-C motif chemokine ligand 5 (CCL5), monocyte chemoattractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), SAA, and TUNEL assay (apoptosis).

Results: AGE and SAA exposure increased PKC- β activation in podocytes as evidenced by increased phosphorylation (1.3-fold, $p=0.007$ and 1.4-fold, $p=0.001$, respectively) and increased PKC- β in the membrane fraction (2.1-fold, $p<0.001$ and 1.6-fold, $p=0.002$, respectively). Immunostaining for PKC- β revealed greater membrane localization. AGE and SAA exposure also increased podocyte TUNEL staining (2.1-fold, $p=0.002$ and 3.4-fold, $p<0.001$, respectively). PKC- β inhibition reduced expression of CXCL5, CCL5, MCP-1, iNOS, SAA, and TUNEL staining.

Conclusions: PKC- β activity is increased in podocytes after exposure to diabetes-related inflammatory mediators. Consequent podocyte inflammatory and apoptotic responses are mediated by the PKC- β pathway.

Funding: Private Foundation Support

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Podocyte SIRT1 Deficiency Contributes to Albuminuria and Renal Fibrosis in Diabetic Kidney Damage in Mice Yi Guan, Chuanming Hao. *Dept of Nephrology, Huashan Hospital, Shanghai, China.*

Background: SIRT1 has been shown to play an important role in stress response, metabolic disorder and aging process, and is suggested to be involved in the pathogenesis of diabetic kidney damage. The study examines whether and how SIRT1 deficiency is involved in diabetic nephropathy.

Methods: High fat diet plus 5-day-low-dose STZ was used to model type 2 diabetes. The role of SIRT1 in diabetic kidney is examined using SIRT1 heterozygotes (C57BL/16). Urinary albumin excretion, kidney histology and extracellular matrix protein accumulation were used to assess diabetic kidney damage. Blood pressure was determined by tail-cuff method. Endothelium selective SIRT1 knockout was generated by crossing floxed SIRT1 mice with SCLCreER, and recombination was induced by tamoxifen. Podocyte selective SIRT1 knockout were generated by crossing floxed SIRT1 mice with PodocinCre. Deletion of SIRT1 in endothelium and podocytes was confirmed by immunohistochemistry.

Results: In diabetic kidney, SIRT1 expression was significantly reduced. Urinary albumin excretion of diabetic SIRT1 heterozygote was markedly increased by 4 fold compared with littermates. Renal histology showed mesangial expansion, Sirius red staining revealed more fibrosis and qPCR indicated higher expression of *PAI-1*, *aSMA*, *Col 18a1*, *Lox12 gene*, in diabetic SIRT1 knockout than wild type. Losing one allele of SIRT1 did not alter blood pressure in diabetic mice, suggesting that the diabetic kidney damage in the SIRT1 deficient mice is not caused by blood pressure change. To further examine the mechanism by which SIRT1 deficiency increased diabetic damage, endothelium and podocyte SIRT1 was selectively deleted respectively. Following STZ challenge, podocyte SIRT1 deficient mice showed higher albuminuria and developed diabetic kidney damage, compared with wild type. Podocyte SIRT1 deficiency did not alter blood pressure. In contrast, endothelium SIRT1 deletion did not cause significant change in albuminuria and kidney damage in diabetic mice.

Conclusions: SIRT1 deficiency, especially in podocyte is responsible for the development of albuminuria and renal fibrosis. The mechanism by which podocyte SIRT1 protects the kidney from diabetic kidney damage remains to be explored.

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β -Arrestins Promote Podocyte Injury in Diabetic Nephropathy Fan Yi. *Pharmacology, Shandong Univ School of Medicine, Jinan, Shandong, China.*

Background: Although autophagy has been implicated in the pathogenesis of diabetic nephropathy (DN), the precise roles and regulatory mechanisms of autophagy are largely unknown. β -arrestins are multifunctional proteins originally identified as negative adaptors of G protein-coupled receptors (GPCRs). Emerging evidence has also indicated that β -arrestins can activate signaling pathways independent of GPCR activation.

Methods: Ten-week-old male β -arrestin-1 and β -arrestin-2 deficient mice (β -arrestin-1^{-/-} and β -arrestin-2^{-/-}, 18-20g) were induced by tail-vein injection of streptozotocin (STZ) and were maintained for 12 weeks.

Results: We found that both β -arrestin-1 and β -arrestin-2 were up-regulated in the kidney from streptozotocin-induced diabetic mice, diabetic db/db mice and kidney biopsies from diabetic patients. We further revealed that either β -arrestin-1 or β -arrestin-2 deficiency ameliorated renal injury in diabetic mice. *In vitro*, we observed that podocytes increased both β -arrestin-1 and β -arrestin-2 expressions under hyperglycemia condition, which were associated with suppressing autophagy by negative regulation of ATG12-ATG5 conjugation and the activation of Wnt/ β -catenin signaling pathways. Finally, we evaluated the genetic therapeutic efficiency targeting to β -arrestin-1 or β -arrestin-2 in DN showing that *in vivo* gene silencing of β -arrestin-1, β -arrestin-2 or both by intrarenal lentiviral gene delivery ameliorated diabetic renal injury in mice.

Conclusions: This study for the first time demonstrate that β -arrestin-1 and β -arrestin-2 share common mechanisms to mediate podocyte autophagic process (Figure 1), indicating that β -arrestins are critical components of multiple signal transduction pathways that link renal injury to reduced autophagy in DN. Modulation of these pathways may be an innovative therapeutic strategy for treating patients with DN.

Funding: Government Support - Non-U.S.

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Myo-Inositol Oxygenase (MIOX) Contributes to Renal Tubular Injury via Endoplasmic Reticulum (ER) Stress and a Hyaluronic Acid (HA) Production Tatsuya Tominaga,² Toshio Doi,² Yashpal S. Kanwar,¹ *¹Pathology, Northwestern Univ, Chicago, IL; ²Nephrology, Tokushima Univ, Tokushima, Japan.*

Background: MIOX is a renal tubular enzyme which channels myo-inositol into xylulose-pentose pathway. We previously indicated its increased expression in diabetic nephropathy and its transcriptional regulation by high glucose, osmotic agents and oxidant stress. Both ER stress and a macrophage accumulation are contributing factors for progression of the renal tubular injury. In this study, we examined the role of MIOX for the ER stress and chemokine induction.

Methods: MIOX knockout mice were fed with high fat diet (HFD) or treated with tunicamycin (Tm). We crossbred MIOX transgenic mice with PEPCK Cre mice for generating mice with predominant tubular expression of MIOX. HK2 cells were subjected to Tm treatment and transfected with MIOX siRNA. ER stress was gauged by examining the expression of C/EBP homologous protein (CHOP), sXBP1 (transcriptional factor), GRP78 and GRP94 (ER molecular chaperons) in kidney tissues or HK2 cells.

Results: sXBP1, CHOP, GRP78 and GRP94 increased in mice receiving HFD or Tm treatment. These expressions decreased in the MIOX KO mice compared with wild type mice. While, the expressions of GRP78, GADD153 in kidneys increased in MIOX transgenic mice. Also, tubular injury observed following Tm treatment was alleviated in MIOX KO mice and but worsened in MIOX transgenic mice. MIOX expression increased with Tm treatment in a dose-dependent (0.3 - 10 mg/mL) and time-dependent (0.5 - 24 hr) manner in HK2 cells. The sXBP1 and GRP78 expressions also increased following Tm treatment in HK-2 cells. Simultaneously, Tm treatment increased HA synthesis in HK2 cells. The transfection of MIOX siRNA decreased the expression of sXBP1, MCP1, IL6 and hyaluronan synthase 2 (HAS2) under the Tm treatment. Overexpression of MIOX increased sXBP1, CHOP, GRP78 and GRP94, as well as induction of MCP1, IL6 and HAS2.

Conclusions: These findings indicate that MIOX contributes to ER stress and HA synthesis and chemokine induction possibly initiated by macrophage accumulation.

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Mitochondrial-Targeted MitoQ Attenuated Renal Tubular Damage in Diabetic Nephropathy by Regulation of Mitochondrial Quality and Modulating Mitophagy Li Xiao,¹ Dang Tang,¹ Jiahui Wang,¹ Xiaoxuan Xu,¹ Yashpal S. Kanwar,² Lin Sun,¹ Fuyou Liu.¹ *¹Dept of Nephrology, 2nd Xiangya Hospital, Central South Univ, Changsha, China; ²Depts of Pathology and Medicine, Northwestern Univ, Chicago, IL.*

Background: The protection of Mitochondria-targeted ubiquinone (mitoQ) on mitochondrial oxidative damage in various diseases including diabetic kidney disease (DKD) has been reported. However, the mechanism by which Mito Q reverses renal injury in DKD is unclear.

Methods: 15 of renal biopsy samples from patients with DKD were obtained, 20 db/db mice and HK-2 cells, a proximal tubular cells line were used for this study. Patients with MCD and db/m mice used as control. db/db mice were intravenously injection of MitoQ with 5 mg/kg twice/week for 12 weeks. The pathological change of renal tissues was observed by HE, PAS, Mass staining. Mitophagy, mitochondrial fragmentation, mitochondrial ROS production, and mitophagy-related mRNA and protein were detected by EM, mitoSOX staining, immunofluorescence, cofocal, Real-time PCR and western blot.

Results: Compared to MCD patients and db/m mice, defective mitophagy was observed in the kidney tubular of DKD patients and db/db mice, which associated with increased mitochondrial fragmentation, oxidative stress, caspase-3 activity and apoptosis. Furthermore, down-regulated expression of mitophagy-related genes and proteins, such as Pink/parkin, Atg7, NIX and Tom20 were observed, while VDAC is upregulated. These changes above were partially reversed in that of treated with mito Q, and consistent with attenuated tubular damage and urine protein excretion. *In vitro* study, high glucose (HG) reduced mitophagy with downregulated mitophagy-related proteins as well as LC3 and P62 accumulation. It also increased mitochondrial fragmentation, oxidative stress, caspase-3 activity and apoptosis. However, mito Q abolished these effects. In addition, parkin-siRNA and NIX-siRNA inhibited the beneficial effect of mitoQ.

Conclusions: These results indicating that MitoQ could improve mitochondrial quality and attenuate oxidative damage through regulation of mitophagy under DKD condition. MitoQ may be as a potential therapeutic agent for amelioration of DKD.

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Evaluation of iNOS Inhibition on Kidney Functions in High-Fat Diet-Induced Obesity Anne-Emilie Declèves,^{1,2} Blanche Martin,² Vanessa Colombaro,² Inès Jadot,² Isabelle Habsch,² Joelle L. Nortier,¹ Nathalie Caron.² *¹Laboratory of Experimental Nephrology, Faculty of Medicine, Univ Libre de Bruxelles (ULB); ²Molecular Physiology Research Unit-URPHYM, Univ of Namur (UNamur).*

Background: Central obesity is related to caloric excess promoting deleterious cellular responses in targeted organs. Nitric oxide (NO) has been determined as playing a critical role in the pathogenesis of metabolic diseases. Here, we investigated the implication of iNOS in the development of progressive renal dysfunction leading to obesity-induced kidney disease.

Methods: C57Bl/6 male mice were randomized to a low fat diet (LFD - 10% of total calories from fat) or a high-fat diet (HFD - 60% of total calories from fat) and treated with L-NIL, a specific iNOS inhibitor (0.1 % in drinking water) for 16 weeks.

Results: Mice fed a HFD exhibited a significant increase in body weight, fasting blood glucose, plasma levels of NEFA, triglyceride and insulin. iNOS inhibition with L-NIL prevented these changes in mice fed a HFD. Interestingly, the significant increase in albuminuria and mesangial matrix expansion was not ameliorated with L-NIL while there was a significant amelioration in glucosuria and proteinuria, suggesting that iNOS inhibition is more suitable for tubular function than glomerular function. Moreover, the urinary hydrogen peroxide level, a stable product of ROS production, significantly higher in mice fed a HFD, was reduced with L-NIL. In order to better determine the beneficial effect of L-NIL in the development of obesity, peri-renal white adipose tissue were also investigated. The histological analysis revealed an increasing size of adipocytes in mice fed a HFD. This change was significantly reduced with L-NIL treatment. Inflammation, as attested by macrophage infiltration and enhanced MCP-1 level, was also prevented by L-NIL in the adipose tissue.

Conclusions: These results suggest that inhibition of iNOS leads to beneficial effects in kidney and adipose tissue in mice fed a HFD. This study opens new area of investigations on the involvement of iNOS in obesity-induced organ injury.

Funding: Government Support - Non-U.S.

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The Impact of Diabetes on Total Glomerular Number and Size in Kidney Estimated by Synchrotron Radiation Micro-CT in SPring-8 Yumi Takiyama,¹ Toshihiro Sera,² Masanori Nakamura,³ Ryoichi Bessho,¹ Kentaro Uesugi,⁴ Naoto Yagi,⁴ Masakazu Haneda.¹ *¹Dept of Medicine, Asahikawa Medical Univ, Hokkaido, Japan; ²Dept of Mechanical Engineering, Kyushu Univ, Fukuoka, Japan; ³Graduate School of Science and Engineering, Saitama Univ, Saitama, Japan; ⁴Research & Utilization Div, Japan Synchrotron Radiation Research Inst, Hyogo, Japan.*

Background: To investigate the impact of diabetes on the number and volume of glomeruli in the whole kidney, we explored CT imaging of male type 2 diabetic db/db mice and of nondiabetic db/m mice at 22 week of age using synchrotron radiation.

Methods: Perfused kidneys with contrast medium were removed and visualized using the synchrotron radiation micro-CT in SPring-8. X-ray image was detected on the fluorescent screen lens coupling sCMOS camera detector with 15.5mm in the pixel size. A segmentation algorithm was conducted to identify and count all glomeruli within the whole kidney, using image analyzing Amira™ software.

Results: Db/m mice had larger kidney volume and more glomerular number in right kidney than left kidney. Intriguingly, diabetes abolished this laterality in db/m mice. Db/db mice had larger glomerular volume than db/m mice. Especially, the cortical glomerular size was remarkably increased. On the other hand, diabetes failed to affect the total glomerular number in kidneys. The mean glomerular volume was strongly correlated with fasting blood glucose, kidney volume, urinary volume and glomerular number in all mice, and urinary volume was a significant independent determinant of the mean glomerular volume, whereas the mean glomerular volume was associated with glomerular number.

Conclusions: Our study, for the first time, showed the impact of diabetes on total glomerular number and glomerular volume of the whole kidney by developing new imaging analyzing system, providing the possibility of glomerular hypertrophy in subjects before diabetes onset.

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NADPH Oxidase-Nox5 Plays a Deleterious Role in Diabetic Nephropathy Jay Chandra Jha,¹ Stephen P. Gray,¹ Claudine Banal,¹ Harald H. Schmidt,² Mark E. Cooper,¹ Rhian Touyz,³ Chris R. Kennedy,⁴ Karin Jandeleit-Dahm.¹ *¹Diabetes Complications Div, Baker IDI Heart and Diabetes Inst, Melbourne, Australia; ²Dept of Pharmacology, Maastricht Univ, Maastricht, Netherlands; ³Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom; ⁴Dept of Medicine, Ottawa Hospital Research Inst, Ottawa, Canada.*

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease. It has been indicated that recently discovered NADPH oxidase, Nox5 could play a role in DN. Nox5 is present in humans but not in mice or rats. Thus, there is a paucity of information about Nox5 in animal models of DN. We examined the role of Nox5 in a model of human inducible Nox5 transgenic mice expressing Nox5 selectively in either endothelial cells (VEcadNox5⁺) or vascular smooth muscle cells (SM22Nox5⁺) in the setting of diabetes.

Methods: VEcadNox5⁺ or SM22Nox5⁺ mice were rendered diabetic via streptozotocin injections. At week 10 urine samples were collected for the assessment of albuminuria. Animals were culled and kidneys were removed for the assessment of structural damage as well as gene and protein expression of markers of inflammation and fibrosis.

Results: Both VEcadNox5⁺ and SM22Nox5⁺ mice demonstrated a further increase in albuminuria (ug/24hrs) compared to their respective Nox5 deficient mice in the presence of diabetes (control & diabetic VEcadNox5⁺: 209±33 & 4139±714; control & diabetic VEcadNox5⁻: 184±21 & 5888±771; control & diabetic SM22Nox5⁺: 177±19 & 3036±394; control & diabetic SM22Nox5⁻: 147±14 & 4273±537). In addition, both diabetic Nox5 transgenic mouse groups appeared to have increased glomerulosclerosis and mesangial area as well as increased gene and protein expression of fibronectin and MCP-1 in the renal cortex when compared to Nox5 negative diabetic mice.

Conclusions: Our findings of an additional increase in albuminuria and glomerulosclerosis as well as increased expression of pro-fibrotic and pro-inflammatory markers in Nox5 transgenic diabetic mice suggest a deleterious effect of Nox5 in the context of diabetic nephropathy and emphasize its role as a target for new renoprotective agents.

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Resveratrol Exhibits Protective Effects on Early-Stage Diabetic Nephropathy by Restoring Mitochondrial Function of Renal Tubular Cells Hao Ding, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Diabetic nephropathy (DN) is a progressive and irreversible renal disease. Mitochondrion plays an important role in the pathogenesis of DN. Resveratrol (RSV), a naturally occurring sirtuin-1 (SIRT1) activator, has been shown to promote mitochondrial function. The aim of the present study is to investigate the renoprotective effects of RSV and delineate its underlying mechanism in early-stage DN.

Methods: Diabetes was induced by streptozotocin (STZ) injection in male CD-1 mice. Two weeks after the onset of DM, the DM mice were further divided into three subgroups concomitantly treated with placebo, RSV 50mg/kg or RSV 100mg/kg for 28 consecutive days. At the end of RSV treatment course, the mice were sacrificed. Primary kidney proximal tubular cells (PTCs) were cultured in high glucose with indicated concentrations of RSV.

Results: In diabetic mice, RSV treatment postponed the progression of DN, as demonstrated by ameliorating the increases of urine albumin excretion, mean artery pressure level, plasma blood glucose level and plasma triglyceride level. Meanwhile, the increases of plasma creatinine level, plasma BUN level, glomerular diameter, mesangial accumulation and renal fibrosis in diabetic mice were also reduced by RSV treatment. Moreover, orally administration of RSV partly restored the distribution and expression of nephrin, WT1 and podocin. We demonstrated that hyperglycemia increased mitochondrial mass and mitochondrial DNA content, upregulated mRNA and protein expression of oxidative phosphorylation enzyme complexes in early-stage DN but led to mitochondrial dysfunction both in vitro and in vivo. RSV acted as a phosphodiesterase 4B inhibitor and SIRT1 activator, attenuated high glucose-induced mitochondrial network fragmentation and impaired oxidative phosphorylation capacity both in vitro and in vivo. Furthermore, it was shown that the protective role of RSV on early-stage DN was probably through AMPK-ACC pathway.

Conclusions: These findings suggested that RSV exhibited a strong ability to inhibit high glucose-induced PTCs damage and may serve as a promising new therapeutic approach for treating early-stage DN.

Funding: Government Support - Non-U.S.

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Possible Implication of Xanthine Oxidase Activation on the Pathogenesis of Diabetic Nephropathy Seiji Itano, Minoru Satoh, Atsushi Uchida, Hiroyuki Kadoya, Hajime Nagasu, Tamaki Sasaki, Naoki Kashihara. Dept of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: Endothelial dysfunction represents a predominant early feature of diabetes and makes diabetic patients prone to renal complications. Recent evidence has indicated possible role of xanthine oxidase (XO) in the pathogenesis of vascular dysfunction associated with diabetes. However, it is not clear whether XO activity is involved in pathogenesis of diabetic nephropathy (DN). We investigated the contribution of XO activation on the progression of mouse DN by selective XO inhibitors, Topiroxostat (Top) and Febuxostat (Feb).

Methods: Male Ins2Akita heterozygote (Akita; 10 weeks old) mice were used. Wild-type (WT) mice were used for control. Akita mice were treated with Top (3mg/kg/day), Feb (1mg/kg/day) or Vehicle (Vehi) for 4 weeks. Serum uric acid and urinary albumin excretion (UAE) were measured. Glomerular pathological changes were also examined by light microscope and electron microscope. Glomerular permeability was assessed using 2 photon microscopy and fluorescent labeling albumin.

Results: Serum uric acid levels showed no significant difference between all groups. Akita+Top or Akita+Feb groups showed significant reduction of UAE in comparison with Akita+Vehi group. Mesangial expansion, glomerular collagen IV deposition, and glomerular endothelial injury (examined by lectin stain and transmission electron microscope) were ameliorated in Akita+Top or Akita+Feb group compared with Akita+Vehi group. Furthermore, glomerular permeability was deteriorated in Akita+Vehi group compared with WT group. These changes were ameliorated with addition of Top or Feb.

Conclusions: XO inhibitors preserved glomerular endothelial function and improved deteriorated glomerular permeability, indicating that XO activation is involved in pathogenesis of DN.

TH-PO342

Effect of Mitochondria-Targeted Ubiquinone Q in Tubular Oxidative Injury of Diabetic Nephropathy Modulate by Mitochondrial ROS/NLRP3/IL-1 β Biological Axis Xiaoxuan Xu,¹ Li Xiao,² Chun Hu,³ Yachun Han,⁴ Yashpal S. Kanwar,⁵ Fuyou Liu,⁶ Lin Sun.⁷ ¹The Second Xiangya Hospital of Central South Univ; ²The Second Xiangya Hospital of Central South Univ; ³The Second Xiangya Hospital of Central South Univ; ⁴The Second Xiangya Hospital of Central South Univ; ⁵Northwestern Univ, Chicago; ⁶The Second Xiangya Hospital of Central South Univ; ⁷The Second Xiangya Hospital of Central South Univ.

Background: To understand the underlying mechanism by MitoQ attenuate the progression of DN.

Methods: 18 patients with DN or primary minimal changes disease were enrolled. Renal pathological changes were observed. MitoQ was intraperitoneally injected to the db/db mice twice a week for 12 weeks (5mg/kg). The injury of kidney and expression of NLRP3, IL-1 β , Caspase-1 were tested. HK-2 cells were incubated with D-glucose treated by MitoQ and NLRP3 siRNA. The expression of NLRP3, Caspase-1, IL-1 β , FN, Collagen I, Mitochondrial membrane potential (MMP), mt ROS and the mitochondrial translocation of NLRP3 were observed.

Results: The expression of NLRP3, IL-1 β , IL-18 increased in kidney of DN patients, which were positively associated with the renal pathological change, oxidative injury in db/db mice. MitoQ ameliorated proteinuria, renal damage, mitochondrial dysfunction, oxidative stress, and apoptosis in the kidney of db/db mice, which was accompanied with decreased NLRP3/IL-1 β biological axis related protein and Caspase-1, FN, Col-I. MitoQ also decreased the expression of NLRP3, IL-1 β , Caspase-1, FN, Col-I and attenuated mtROS and apoptosis in HK-2 cells. It also recovered MMP and decreased mitochondrial translocation of NLRP3 induced by high glucose. These effects were blocking partially in transfection with lentiviral vectors expressing NLRP3 plasmid, while this effect was abolished by treated with NLRP3 siRNA.

Conclusions: This data indicated that MitoQ ameliorated injury of renal tubular of DN through mtROS/NLRP3/IL-1 β axis.

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Inhibition of Enhanced Xanthine Oxidoreductase Activity Prevents the Progression of Diabetic Nephropathy by Attenuating Oxidative Stress Goshi Nagao,¹ Takayo Murase,¹ Ryusuke Sakamoto,¹ Takashi Iwanaga,² Naoki Ashizawa,² Takashi Nakamura.¹ ¹Sanwa Kagaku Kenkyusho, Co., Ltd., Japan; ²Fuji Yakuhin, Co., Ltd., Japan.

Background: Topiroxostat, a xanthine oxidoreductase (XOR) inhibitor, has been approved as a medicine for hyperuricemia and gout in Japan, and showed a decrease of urinary albumin excretion (UAE) in hyperuricemic stage 3 chronic kidney disease patients in clinical trial. Meanwhile, the induction of oxidative stress and morphological changes known as the representative evidences of diabetic nephropathy (DN) has been reported. We aimed to test the hypothesis that XOR-induced oxidative stress was associated with progression of DN.

Methods: Nine-week-old male diabetic db/db mice were fed with diet containing topiroxostat (0.1-10 mg/kg) for 4-8 weeks. The levels of plasma uric acid, UAE concentration for 24 hours, and XOR activity of kidney were determined. PAS staining was performed in paraffin section of renal tissue, and then glomerular tuft area, diameter and cell height of proximal tubules were measured with image analysis software. In addition, immunohistochemical staining for nitrotyrosine was performed.

Results: Treatment with topiroxostat decreased the levels of plasma uric acid and UAE. XOR activity of kidney in db/db was significantly elevated compared with that in db/m, which was inhibited by treatment with topiroxostat (db/m: 47.1 \pm 12.6, db/db: 87.2 \pm 19.7, and 3 mg/kg: 16.6 \pm 4.6 pmol/min/mg protein; P<0.01, mean \pm SD). In morphometric analysis, glomerular hypertrophy in db/db control was significantly attenuated by treatment with topiroxostat 3 mg/kg (db/m: 2952 \pm 302, db/db: 4028 \pm 301, and 3 mg/kg: 3692 \pm 270 μ m²; P<0.05). The diameter and cell height of proximal tubules in topiroxostat 3 mg/kg group were significantly smaller than those in db/db control (db/m: 38.6 \pm 2.7, 15.9 \pm 1.2, db/db: 43.8 \pm 2.0, 18.5 \pm 0.9, and 3 mg/kg: 41.7 \pm 1.8, 16.8 \pm 0.7 mm; P<0.05, respectively). As compared to db/m, glomerular nitrotyrosine positive area in db/db was increased 7.4-fold, which was reduced by 46% by treatment with topiroxostat.

Conclusions: Topiroxostat decreased UAE and attenuated renal morphological changes, at least in part, by inhibition of enhanced XOR-induced oxidative stress in DN.

TH-PO344

Knockout of Matrix Metalloproteinase 2 Attenuates the Progression of Renal Disease in Streptozotocin-Induced Diabetic Dahl Salt Sensitive Rats Takashi Hirata,^{1,2} Fan Fan,¹ Naoki Kojima,² Teisuke Takahashi,² Noriyuki Miyata,³ Richard J. Roman.¹ ¹Pharmacology and Toxicology, Univ of Mississippi Medical Center, Jackson, MS; ²Pharmacology Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, Japan; ³Pharmaceutical Business Planning, Taisho Pharmaceutical Co., Ltd., Tokyo, Japan.

Background: We have found that chronic blockade of MMPs with a broad spectrum inhibitor, XL784, reduced renal injury in type 2 diabetic nephropathy rats. However, the isoforms involved in the development of diabetic nephropathy are unclear.

Methods: The present study examined the role of MMP2 in the development of diabetic nephropathy using a MMP2 knockout (KO) rat in the Dahl salt sensitive (SS) genetic

background that we created. Nine week old SS and MMP2 KO rats (n=10) were treated with intravenous injection of streptozotocin (STZ, 50 mg/kg) to induce diabetes and given an insulin implant (2 U/day) to maintain blood glucose around 400 mg/dL. Blood pressure and proteinuria were followed for 12 weeks. Age-matched SS rats (n=5) were studied to serve as a non-diabetic control for the assessment of renal hemodynamics and injury.

Results: Blood glucose and HbA1c levels increased to the same extent in STZ-treated SS (SS-STZ) and MMP2 KO (MMP2 KO-STZ) rats. Systolic blood pressure rose to 195 \pm 3 in SS-STZ rats versus 163 \pm 3 mmHg in MMP2 KO-STZ rats. Proteinuria increased to 5-fold to 557 \pm 33 in SS-STZ rats versus 94 \pm 8 mg/day in MMP2 KO-STZ rats. The urinary excretion of MMP2 increased from 45 \pm 10 to 2496 \pm 365 ng/day in SS-STZ rats but it was absent in MMP2 KO-STZ rats. The kidneys of SS-STZ rats developed more severe glomerulosclerosis, mesangial expansion, and renal fibrosis than MMP2 KO-STZ rats. Glomerular filtration rate (GFR) in SS-STZ rats fell by 33% in comparison to time control SS rats, but GFR only fell by 12% in MMP2 KO-STZ rats.

Conclusions: These data indicate that activation of MMP2 may contribute to the development of diabetes induced renal injury and suggest that a MMP2 selective inhibitor may be useful to prevent the progression of renal disease in diabetic patients.

TH-PO345

Role of DUSP4 in Diabetic Nephropathy Benoit Denhez,¹ Farah Lizotte,¹ Mannix Auger-Messier,² Pedro Miguel Geraldes.¹ ¹Dept of Medicine, Div of Endocrinology, Univ of Sherbrooke, Sherbrooke, QC, Canada; ²Dept of Medicine, Div of Cardiology, Univ of Sherbrooke, Sherbrooke, QC, Canada.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease and is characterized by dedifferentiation and apoptosis of podocytes, which are highly specialized epithelial cells involved in the glomerular filtration process. Podocyte apoptosis is a strong predictor of DN progression. It has been shown that the activation of p38 MAPK induced by hyperglycemia plays an important role in podocyte dysfunction and apoptosis. However, the precise mechanisms leading to the sustained activation of p38 MAPK remain unresolved. DUSP4, a dual specificity phosphatase, is known to bind directly to p38 MAPK and inhibits its activity. Our goal is to evaluate the role of DUSP4 in p38 MAPK activation induced by hyperglycemia, which contributes to podocyte dysfunction and apoptosis in diabetic nephropathy.

Methods: Type 1 diabetic (DM) mice with deletion of DUSP4 (DM-DUSP4KO) was generated and studied during 7 months to evaluate renal function and pathology. Glomerular filtration rate (GFR) and 24h albumin excretion levels were measured in DM mice with or without deletion of DUSP4. Activation of p38 MAPK and expression levels of DUSP4 in podocytes exposed to high glucose (HG) concentrations for 96 hours were evaluated by qPCR and immunoblot.

Results: The mRNA expression of DUSP4 is reduced by 50% in the renal cortex of DM mice. Although elevated GFR in DM mice was similar in DM-DUSP4KO (0.34 vs 0.35 ml/min), albumin excretion was further exacerbated by 3.4 fold in DM-DUSP4KO compared to DM mice. *In vitro*, immunoblot analysis showed that HG level exposure reduced the expression of DUSP4 by 40%, which correlated with an increase of p38 MAPK phosphorylation by 70% in podocytes.

Conclusions: Our results suggest that decrease of DUSP4 expression in podocytes and renal cortex of diabetic mice contributes to podocyte dysfunction in diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO346

Telomerase Deficiency-Dependent Senescence Promotes Diabetic Nephropathy (DN) Progression Huifang Cheng,¹ Xiaofeng Fan,¹ Paisit Pauksakon,² Raymond C. Harris.¹ ¹Medicine, Vanderbilt Univ Medical School, Nashville, TN; ²Pathology, Microbiology and Immunology, Vanderbilt Univ Medical School, Nashville, TN.

Background: Diabetes is a common disease in the elderly, and a link with telomere shortening has been reported, although whether it is Diabetes is a common disease in the elderly, and a link with telomere shortening has been reported, although whether it is a cause or a consequence of the disease has not been determined. Both telomerase reverse transcriptase (TerT) and telomerase RNA (TerC) are essential to maintain telomere length.

Methods: To investigate the role of telomerase in DN, we measured telomerase expression in kidneys from mice with streptozotocin (STZ)-induced (type I) and db/db (type II) diabetes. We also studied DN in wild type (Wt) and fourth generation (G4) mice with TerC or TerT deletion. *In vitro* studies were performed in primary cultured glomerular endothelial cells (GENCs).

Results: Renal telomerase expression decreased in both type I and type II diabetic mice, compared with age-matched controls. 26 weeks after STZ injection, TerC and TerT KO mice had more albuminuria than Wt, and EM indicated increased GBM thickness, although mesangial expansion was similar. β -galactosidase, a marker of cell senescence, was mildly elevated in non-diabetic TerC and TerT KO mice. Diabetes accelerated senescence, especially in TerC and TerT KO. In glomeruli, senescence was predominately detected in endothelial cells. GENCs from TerC deletion mice proliferated much slower than Wt in normal glucose medium (glucose 5.5 mM). After incubation for 96 hours in high glucose (30 mM) medium, GENCs exhibited cellular senescence, with a marked increase in cells with TerC deletion. There was minimal senescence with incubation with the mannitol osmolality control.

Conclusions: These results indicate that telomerase deficiency promotes DN progression and accelerates glomerular endothelial senescence, implicating a role for the telomere shortening of aging as a predisposing factor for development of DN.

Funding: NIDDK Support, Veterans Administration Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO347

Interaction of the EGF Receptor and the Hippo Pathway in Diabetic Nephropathy Jianchun Chen, Raymond C. Harris. *Medicine, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Activation of both EGFR and the Hippo signaling pathway can control cell proliferation, apoptosis and differentiation, and their dysregulation can contribute to tumorigenesis. Previous studies have shown that activation of EGFR signaling in renal epithelial cells can exacerbate diabetic kidney injury. YAP is a transcriptional regulator that is regulated by the Hippo signaling pathway, which is a kinase cascade in which Mst1/2 kinases and Sav1 form a complex to phosphorylate and activate LATS1/2, which phosphorylate and inhibit the downstream effector, YAP.

Methods: We induced type I diabetes in proximal tubule EGFR deletion mice (EGFR^{pkO}) and their wild type littermates (WT) by daily low dose streptozotocin injections for 5 consecutive days. A subset of wild type diabetic mice were administered the EGFR kinase inhibitor, erlotinib. Cell signaling studies were performed in a proximal tubule epithelial-like cell (LLCPKCl4).

Results: STZ injection induced similar levels of hyperglycemia in EGFR^{pkO} and WT mice. Both total and phosphorylated YAP (at Ser127) increased in diabetic WT mice, primarily in proximal tubule cells, and these increases were inhibited in EGFR^{pkO} mice or by administration of erlotinib. Further studies demonstrated that EGFR-PI3K-Akt signaling pathway activation mediated YAP gene expression, YAP nuclear translocation and interaction with the TEAD transcription complex, which led to up-regulation of expression of TEAD-dependent genes, CTGF and AREG (amphiregulin). In a renal proximal tubule cell line, either pharmacologic or genetic inhibition of EGFR or Akt blunted YAP expression in response to high glucose treatment. In addition, knocking down YAP expression by specific siRNA inhibited cell proliferation in response to high glucose or exogenous EGF.

Conclusions: This is the first study to demonstrate that the Hippo pathway downstream effector YAP activation is a mediator of EGFR-mediated renal epithelial injury in diabetes.

Funding: NIDDK Support, Veterans Administration Support

TH-PO348

Role of Histone Modification in 12-Lipoxygenase Related P21 Gene Regulation Hang Yuan,¹ Nian Liu,² Weixia Sun,¹ Fu-zhe Ma,¹ Tao Sun,¹ Mindan Sun,¹ Zhong-gao Xu.¹ *¹Nephrology, The First Hospital of Jilin Univ, Changchun, Jilin, China; ²Urology, The First Hospital of Jilin Univ, Changchun, Jilin, China.*

Background: Glomeruli hypertrophy is characteristic pathological changes of diabetic nephropathy, which is associated with p21 protein overexpression under diabetic condition. It has been demonstrated epigenetic histone modifications like acetylation (Ac) and methylation (Me) are involved in gene transcriptional regulation. We have certified 12-Lipoxygenase (12-LO) and its metabolic product 12(S)-HETE can active p21 expression, but the mechanism details are still unclear.

Methods: Mesangial cells (MC) from Rat were used for this study. Chromatin immunoprecipitation assay, QRT-PCR and Luciferase assay were used to detect transcriptional activity, enrichment of H3K Ac as well as Me in the p21 promoter (P) and transcribe (T) regions induced by 12(S)-HETE; transfection was used to overexpression of p300 to see changes of 12(S)-HETE related p21 regulation as well as epigenetic modifications.

Results: 12(S)-HETE enhanced p21 transcriptional activity and mRNA expression; in the promoter regions of P1, P2 and T1 transcribe region, 12(S)-HETE induced significant H3K9Ac as well as H3K4Me1 epigenetic modifications, but no changes were seen in T2 region; on the contrary, 12(S)-HETE treatment prevented H3K9Me3 at p21 promoter obviously, suggest complex Me involved in 12(S)-HETE associated p21 regulation; furthermore, overexpression of p300 obviously enhanced basal as well as 12(S)-HETE associated p21 transcriptional regulation in MC. At same time, 12(S)-HETE treatment also induced histone acetyltransferase p300 occupancy at p21 promoter, reduced demethylase LSD1 nuclear expression and occupancy at p21 promoter.

Conclusions: 12(S)-HETE can induce p300 occupancy at p21 promoter, reduced LSD1 nuclear expression and occupancy at p21 promoter, therefore enhanced H3K9Ac as well as H3K4Me1 at p21 promoter and transcribe regions, decreased H3K9Me3 at p21 promoter, increased p21 expression.

Funding: Government Support - Non-U.S.

TH-PO349

E-Box CpG Hypomethylation of NMN-Producing Enzyme Nampt in Proximal Tubules Enables a Constant Supply of NMN from Tubules to Glomeruli, which Is Disrupted in Diabetic Nephropathy Hirokazu Muraoka, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. *Keio Univ.*

Background: Nicotinamide mononucleotide (NMN)-producing enzyme nicotinamide phosphoribosyltransferase (Nampt) cooperates with a longevity gene, Sirt1, to exert the stress resistance. We previously reported that high expression levels of Nampt lead to NMN production in the proximal tubules (PTs), which contributes to the sufficient supply of NMN to glomeruli (Nat Med 2013). Downregulation of Nampt and NMN in PTs in diabetic nephropathy (DN) leads to glomerular damage. However, the underlying molecular mechanisms by which Nampt is regulated remain unknown. Here, we investigated how Nampt expression is consistently retained at high levels in PTs under normal conditions and decreased in DN.

Methods: Expression levels of Sirt1, TGF- β , and Nampt were measured in PTs of mice with DN. A promoter analysis was performed, and luciferase reporter and gel

electrophoresis mobility shift assays were used to examine promoter binding. Methylation levels were investigated with methylation-specific PCR and bisulfite sequencing using laser-microdissected PT regions.

Results: Sirt1 expression in mouse PTs was decreased 8 weeks after DN onset. At 24 weeks, TGF- β production increased, which directly lowered Nampt expression in PT. Human renal biopsy samples showed the same patterns seen in mice. CpG islands at -323 to -456 bp in human and at -510 to -28 bp in mice were found to contain four **enhancer (E) boxes** (E1-E4). The basal transcription of Nampt depended on AhR/ARNT binding to **E3** and **E4**, identifying this as a core promoter. We found that TGF- β activated Dnmt1, leading to the hypermethylation of CpGs in E3 and E4. This hypermethylation blocked AhR/ARNT binding and decreased Nampt expression. The methylation levels of E3 and E4 were significantly higher in DN mice than in non-DN mice.

Conclusions: Although E-boxes are generally enhancer regions, Nampt's E-box is a core promoter with low CpG methylation and is easily bound by AhR/ARNT. This binding results in the regularly high protein expression of Nampt providing sufficient NMN under normal conditions. DN-induced PT TGF- β production and its concomitant hypermethylation of the E-box disrupt this balance.

TH-PO350

MicroRNA-21 Silencing as Novel Therapeutic Strategy in Diabetic Nephropathy Malte Kölling,¹ Tamás Kaucsár,² Celina Schauerer,¹ Joon-Keun Park,¹ Martin Busch,³ Claudia Bang,¹ Peter Hamar,² Hermann G. Haller,¹ Thomas Thum,¹ Johan Lorenzen.¹ *¹Hanover Medical School, Germany; ²Semmelweis Univ, Hungary; ³Jena Univ Hospital, Germany.*

Background: Diabetic nephropathy (DN) is the main cause of end-stage renal disease. We therapeutically inhibited microRNA-21 (miR-21) in mice with DN.

Methods: We used miRNAome analysis, qPCR, in situ PCR, Western Blot, electrophoretic mobility shift assay and bioinformatic algorithms. Furthermore, we fused the 3'UTR of cell division cycle 25a (Cdc25a) and cyclin-dependent kinase 6 (Cdk6) to a Luciferase reporter gene. Luciferase activity was measured after overexpression of miR-21. 28 patients and 20 controls were included. Mesangial cells (MC) and renal fibroblasts were treated with TGF- β . F-Actin staining, Cell Cycle FACS, scratch migration and BrdU incorporation revealed functional changes. In vitro and in streptozotocin-induced diabetic mice, miR-21 was silenced by locked nucleic acid. Immuno-, PAS- and Sirius red stainings were performed.

Results: MiR-21 was among the most up-regulated miRNAs in kidneys of diabetic mice and was mainly increased in the glomerular and interstitial compartment. In kidney biopsies of patients, miR-21 correlated with the tubulointerstitial injury. Moreover, miR-21 was tightly associated with albuminuria, hypertension and inflammation. Activator Protein-1 regulated miR-21 expression. Cdc25a and Cdk6 were identified as novel targets of miR-21 in MC. MiR-21 mediated repression of Cdc25a and Cdk6 resulted in G1-phase arrest and subsequent MC hypertrophy. In renal fibroblasts, we identified dual specificity phosphatase 8 (Dusp8) as novel target of miR-21, in association with extracellular-signal-regulated kinase signaling activation, increasing renal fibroblast proliferation, migration and extracellular matrix production. MiR-21 silencing in diabetic mice ameliorated various functional parameters including mesangial expansion, tubulointerstitial fibrosis, inflammatory cell infiltration, albuminuria and podocyte loss.

Conclusions: MiR-21 antagonism might thus be a viable therapeutic option in future clinical trials involving patients with DN.

TH-PO351

The NMDA Receptor Antagonist MK-801 Reduces Progression of Nephropathy in Two Mouse Models of Type-1 Diabetes Hila Roshanravan, Eunyong Kim, Stuart E. Dryer. *Biology and Biochemistry, Univ of Houston, Houston, TX.*

Background: Podocytes express ionotropic NMDA receptors that can be activated by endogenous circulating agonists such as L-homocysteic acid and quinolinic acid. Sustained activation of NMDA receptors causes cytotoxicity and oxidative stress in podocytes. Here we examined if the prototypical antagonist MK-801 can reduce nephropathy in mouse type-1 diabetes.

Methods: We examined two mouse models: the Akita mice on a DBA/2J background (with DBA/2J mice as controls), and the low-dose streptozotocin (STZ) protocol in DBA/2J mice. MK-801 or saline were administered by surgically implanting subcutaneous Alzet osmotic minipumps (protocol approved by local IACUC). Nephropathy was monitored by periodic analysis of 24-hr urine samples, and by histology and electron microscopy at the end of the protocol. NMDA subunit expression in renal cortex was examined by immunoblot.

Results: MK-801 treatment was initiated in 7-week Akita mice. Urine albumin secretion is already slightly elevated at that age. Over the next 28 days, albumin excretion increased 3-4 fold in saline-treated mice, but did not show a significant increase in the MK-801 group. At the time of sacrifice there was less foot process effacement in MK-801-treated animals compared to controls. The STZ protocol was carried out at 10 weeks of age, and MK-801 or saline treatment was initiated 15 weeks later. With this model, albuminuria was more severe at the time that drug treatment was initiated. In saline-treated controls albuminuria continued to increase over the next 28 days but did not worsen in the MK-801 group. Foot process effacement, glomerulosclerosis, tubular atrophy and interstitial fibrosis were reduced in MK-801-treated animals. Akita and STZ-treated mice are smaller than their controls. MK-801 did not alleviate this. We observed markedly increased expression of NMDA receptor NR1 and NR2C subunits in renal cortex of Akita and STZ-treated mice compared to controls.

Conclusions: These data support the hypothesis that sustained NMDA receptor expression and/or activation contribute to the progression of diabetic nephropathy, and suggest that targeting these receptors might be a useful therapeutic strategy.

Funding: Private Foundation Support

TH-PO352

Role of the N-Type Calcium Channel in a Mouse Model of Diabetic Nephropathy Shoko Ohno,¹ Hideki Yokoi,¹ Kiyoshi Mori,² Masato Kasahara,³ Takashige Kuwabara,^{1,4} Moin Saleem,⁵ Kazuwa Nakao,² Motoko Yanagita,¹ Masashi Mukoyama,^{1,4} ¹Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ²Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ³Inst for Advancement of Clinical and Translational Science, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ⁴Dept of Nephrology, Graduate School of Medical Sciences, Kumamoto Univ, Kumamoto, Japan; ⁵Academic Renal Unit, Univ of Bristol, Bristol Children's Hospital, Bristol, United Kingdom.

Background: Recent clinical studies have shown that an L-/N-type calcium channel blocker cilnidipine reduces urinary protein in hypertensive patients with proteinuria. In the present study, to explore the functional role of N-type calcium channel (Ca_v2.2) in diabetic nephropathy, we investigated renal injury in Ca_v2.2-deficient diabetic *db/db* mice.

Methods: We employed mice lacking the N-type calcium channel $\alpha 1$ subunit gene (Ca_v2.2^{-/-}) to generate *db/db* (diabetic), Ca_v2.2^{-/-} double mutant mice. Because the genetic background plays an important role in developing diabetic nephropathy, in this study, we backcrossed Ca_v2.2 knockout mice on the C57BL/6J background to those on the C57BLKS background.

Results: Ca_v2.2 was localized in glomeruli, including podocytes, and vascular walls. Diabetic Ca_v2.2^{-/-} mice showed lower BP than diabetic WT mice by ~20 mmHg, and exhibited ~50% reduction in urinary catecholamines. Compared with diabetic WT mice, both diabetic Ca_v2.2^{-/-} and Ca_v2.2^{-/-} mice revealed a significant reduction (by ~70%) in UAE. The increase in mesangial matrix and downregulation of nephrin in diabetic WT mice were alleviated in diabetic Ca_v2.2^{-/-} mice. There was an improvement in glycemic control in diabetic Ca_v2.2^{-/-} mice but not in diabetic Ca_v2.2^{-/-} mice. Furthermore, *db/db* mice receiving cilnidipine showed a significant reduction in UAE. *In vitro*, depolarization-dependent calcium entry was abolished by ω -conotoxin, a Ca_v2.2-specific inhibitor. The reduction of nephrin expression by TGF- β was abolished with ω -conotoxin and cilnidipine in podocytes.

Conclusions: The inhibition of Ca_v2.2 exerts renoprotective effects against the progression of diabetic nephropathy.

TH-PO353

D-Carnosine Prevents Diabetic Nephropathy in *db/db* Mice Giuseppe Pugliese, Carla Iacobini, Stefano Menini. Dept of Clinical and Molecular Medicine, La Sapienza Univ, Rome, Italy.

Background: The endogenous dipeptide L-carnosine was shown to act as a quencher of reactive carbonyl precursors of advanced glycation end products (AGEs). However, in humans, it is rapidly inactivated by carnosinase. This study was aimed at evaluating the efficacy of the carnosinase-resistant compound D-carnosine (DC) in preventing diabetic nephropathy in *db/db* mice.

Methods: Adults male *db/db* mice and the corresponding *db/m* controls were treated with a DC derivative (60 mg/kg body weight in the drinking water) or vehicle for 14 weeks. Glomerular sclerosis index (GSI), mean glomerular area (mGA), fractional mesangial area (fMA), and mean glomerular volume (mGV) were assessed morphometrically. Renal expression of inflammatory and disease progression markers were assessed by immunohistochemistry and/or RT-PCR. Serum AGEs and isoprostane-8-epi-PGF₂ were measured by ELISA, pentosidine by HPLC and total carbonylated proteins (PCOs) by slot blot immunoassay.

Results: DC treatment induced a significant attenuation of renal disease in *db/db* mice, whereas it did not influence renal structure in *db/m* control mice. Proteinuria (-35%), GSI (-31%), mGA (3.22 ± 0.27 vs. 3.52 ± 0.21 mm² × 10³), mGV (137.5 ± 10.1 vs. 157.2 ± 13.7 mm³ × 10³), mMA (428.0 ± 82.5 vs. 588.5 ± 48.7 μ m²) and fMA (13.2 ± 1.8 vs. 16.8 ± 1.7%) decreased significantly (P < 0.001) in DC-treated *db/db* mice, as compared with untreated animals. Glomerular staining for HNE adducts (5.6 ± 2.7 vs. 13.5 ± 2.8 % glom area), fibronectin (11.7 ± 2.6 vs. 19.7 ± 1.8 % glom area) and collagen IV (13.2 ± 3.4 vs. 24.6 ± 3.1 % glom area) were also significantly reduced (P < 0.001) in DC-treated vs. untreated *db/db* mice. The mRNA levels of F4/80, CXCR3, MCP-1, TNF- α , CHOP, RAGE, galectin-3 and CD36 were also significantly lower in *db/db* mice treated with DC. Finally, serum AGE, pentosidine, PCOs, and isoprostane-8-epi-PGF₂ levels were lower in DC-treated vs. untreated *db/db* mice.

Conclusions: DC is effective in reducing carbonyl reactive species and preventing renal injury in *db/db* mice, thus suggesting that carbonyl stress plays a major role in diabetic nephropathy and that DC derivatives might be useful for treatment of this complication.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO354

Effect of an Oral Adsorbent AST-120 on Type 2 Diabetes Rats and Mice Rieko Aoki, Yusuke Yamashita, Sumie Goto, Hiroko Iijima, Fujio Sekine, Shigeaki Miyazaki, Yoshiharu Itoh. Pharmaceuticals Div, Kureha Corporation, Tokyo, Japan.

Background: Diabetic nephropathy is a major complication of diabetes and the leading cause of end-stage renal disease. An oral adsorbent AST-120 has been used clinically as a medicine for patients with chronic kidney disease (CKD) to slow down the progression of CKD. However, there is little evidence to support therapeutic efficacy of AST-120 for early stage overt diabetic nephropathy. Our previous study showed that the administration of AST-120 reduced the urinary protein and albumin excretion on SHR/NDmcr-cp (SHR/ND) rats, model rats of metabolic syndrome/ type 2 diabetes. In this study, we aimed to assess the effect of AST-120 on the pathological changes in renal tissues of SHR/ND rats and on other type 2 diabetic model animals, KK-A^y mice.

Methods: Male SHR/ND rats, aged 7 weeks, were administered 8% AST-120 for 12 weeks in their diets. WKY rats were used as a normal. At every 4 weeks, serum and 24-hour urine samples were collected for biomedical studies. The podocyte foot process width (FPW) was measured by Transmission Electron Microscopy as foot process effacement. Pathological changes in renal tissues stained with periodic acid-Schiff (PAS) and Hematoxylin-Eosin (HE) were investigated by light microscopy. Monocyte/macrophage infiltration in renal tissues and tubular injury was investigated by ED-1 staining and kidney injury molecule-1 (KIM-1) staining. Male KK-A^y mice, aged 7 weeks, were administered 8% AST-120 for 8 weeks in their diets. C57BL/6J mice were used as non-diabetic animals. At every 4 weeks, serum and 24-hour urine samples were collected for biomedical studies.

Results: AST-120-administered SHR/ND rats showed significantly lower levels of urinary protein excretion, urinary albumin excretion, and the FPW as compared with SHR/ND rats. The renal histological damage, the number of ED-1 positive cells and KIM-1 positive area were reduced by the administration of AST-120. AST-120-administered KK-A^y mice also showed lower levels of urinary protein and albumin excretion.

Conclusions: These results indicate that the administration of AST-120 at an early stage of diabetic nephropathy has a protective effect on the disease progression.

TH-PO355

Blockade of KCa3.1 Attenuated Diabetic Nephropathy Through Induction of Autophagy Chunling Huang, Xinming Chen, Carol A. Pollock. Renal Lab, Kolling Inst of Medical Research, Univ of Sydney, Sydney, New South Wales, Australia.

Background: Autophagy is emerging as an important pathway in many biological processes and diseases including diabetic nephropathy. It was reported that oxidative stress plays a critical role in diabetic nephropathy, and blockade of KCa3.1 ameliorates renal fibrotic responses in diabetic nephropathy through inhibition of the TGF- β 1 pathway. The aim of the study is to identify the role of KCa3.1 on dysfunctional tubular autophagy in diabetic nephropathy.

Methods: Human proximal tubular cells (HK2 cells) transfected with scramble siRNA or KCa3.1 siRNA were exposed to TGF- β 1 for 48h. The formation of autophagosomes was examined using transmission electron microscopy (TEM). The autophagy marker LC3-II was measured by western blotting and immunofluorescence staining. The activation of oxidative stress was measured by nitrotyrosine using immunofluorescence staining. The signaling pathways of PI3K, Akt and mTOR were assessed with western blotting. *In vivo*, the expression of LC3-II and nitrotyrosine were examined by immunofluorescence or immunohistochemistry staining in kidneys from diabetic KCa3.1^{+/+} and KCa3.1^{-/-} mice.

Results: TEM results demonstrated that several autophagic vacuoles appeared in HK2 cells transfected with scramble siRNA exposed to TGF- β 1 but decreased autophagic vacuoles were observed in HK2 cells transfected with KCa3.1 siRNA. Western blotting and immunofluorescence staining results showed TGF- β 1 significantly increased LC3-II in scramble siRNA-transfected HK2 cells which was reduced in KCa3.1 siRNA transfected-HK2 cells. Blockade of KCa3.1 with transfected siRNA reversed TGF- β 1 induced-activation of PI3K, Akt and mTOR signaling pathways. *In vivo*, diabetic induced upregulation of LC3-II and nitrotyrosine were dramatically attenuated in the kidneys of diabetic KCa3.1^{-/-} mice compared to diabetic KCa3.1^{+/+} mice.

Conclusions: Blockade of KCa3.1 attenuated diabetic nephropathy through induction of autophagy.

TH-PO356

PBI-4050 Protects against Renal Fibrosis and Improves Pancreatic Function in the Type II Diabetes *db/db* Mouse Model Lyne Gagnon, Kathy Hince, Lilianne Geerts, François Sarra-Bournet, Alexandra Felton, Liette Gervais, Alexandre Laverdure, William Gagnon, Martin Leduc, Mikaël Tremblay, Marie-Pier Cloutier, John Moran, Frank Cesari, Pierre Laurin, Brigitte Groulx. ProMetic BioSciences Inc., Laval, QC, Canada.

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in metabolic syndrome associated with diabetes, displays antifibrotic activities via a novel mechanism of action. In a double-blind single ascending dose (400 to 2400 mg) in healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in CKD patients with no SAEs observed at 800 mg for 10 consecutive days. In the present study, we examined whether PBI-4050 affected hyperglycemia, insulin resistance and the development of renal fibrosis as well as biomarkers in obese *db/db* mice.

Methods: db/db mice were uninephrectomized at week 6 and received vehicle (water) or PBI-4050 (100 or 200 mg/kg/day) by daily gastric gavage from 6 to 24 weeks of age.

Results: PBI-4050 treatment ameliorated the fasting hyperglycemia and abnormal glucose tolerance tests seen in vehicle-treated db/db mice. In addition, PBI-4050 led to higher serum insulin, C-peptide and GIP levels which correlates with the improvement of β -cells function observed by immunohistochemistry analysis. Kidney function was also improved by PBI-4050 treatment as shown by significant decrease in hyperfiltration, proteinuria and mesangial expansion lesions. Furthermore, expression of IL-6, Collagen I, MMP2 and Timp1 in kidney were downregulated by PBI-4050 treatment. Moreover, using a mouse cytokines multiplex panel, serum IL-6 and IL-9 levels were significantly reduced in PBI-4050-treated mice.

Conclusions: These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production and β -cells function and survival, and prevents renal fibrosis in association with regulation of pro-fibrotic and fibrotic biomarkers.

TH-PO357

Kallistatin Protects against Diabetic Nephropathy in db/db Mice by Suppressing AGE-RAGE-Induced Oxidative Stress Wai Han Yiu,¹ Dickson WL Wong,¹ Hao-Jia Wu,¹ Ruixi Li,¹ Loretta Y.Y. Chan,¹ Joseph C K Leung,¹ Hui Y. Lan,² Kar Neng Lai,¹ Sydney C.W. Tang.¹ ¹Dept of Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong; ²Dept of Medicine and Therapeutics, and Li Ka Shing Inst of Health Sciences, The Chinese Univ of Hong Kong, Hong Kong.

Background: Kallistatin is a serine protease inhibitor that exerts anti-inflammatory, anti-apoptotic and anti-oxidative effects in regulating cellular dysfunction. As oxidative stress plays a critical role in the pathogenesis of diabetic nephropathy, we aim to investigate the effect and mechanisms of kallistatin gene transfer on diabetic renal injury in the db/db mouse model of type 2 diabetes.

Methods: Plasmid with kallistatin gene was injected into the kidney of db/db mice using ultrasound-mediated microbubble-inducible gene transfer. The therapeutic potential of kallistatin in diabetic kidney was evaluated by histopathology, renal function, oxidative and fibrotic pathways.

Results: Kallistatin expression was induced in tubules of kidney after gene transfer compared with mice treated with empty plasmid. In db/db mice, kallistatin overexpression reduced serum creatinine and BUN levels, ameliorated glomerulosclerosis and tubulointerstitial injury and attenuated renal fibrosis by inhibiting TGF- β signaling and the downstream plasminogen activator inhibitor-1 and type IV collagen expression. Furthermore, kallistatin gene transfer significantly attenuated elevated oxidative stress in db/db mice as evidenced by suppressed levels of Nox4 and the oxidative marker (8-OHdG and MDA) in diabetic renal tissue. Finally, kallistatin inhibited expression of RAGE in both diabetic kidney and AGE-stimulated cultured proximal tubular epithelial cells, reflecting an anti-oxidative mechanism via AGE/RAGE axis.

Conclusions: Our results suggest a renoprotective role of kallistatin against progression of diabetic nephropathy via anti-oxidative properties. Kallistatin reduced AGE-RAGE-induced Nox4 expression, leading to suppression of oxidative stress and TGF- β -mediated renal fibrosis.

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TH-PO358

Kidney pSMAD2 in Type 1 and Type 2 Diabetic Nephropathy Patients and in Mouse Models of Diabetic Nephropathy Lise Thomsen,^{1,2} Troels Krarup Hansen,² Morten Tonnesen,¹ Emile De Heer,³ Peter Dijke,⁴ Alexander Rosendahl.¹ ¹Diabetes Complications Biology and Pharmacology, Novo Nordisk A/S, Måløv, Denmark; ²Dept of Clinical Medicine – Dept of Endocrinology and Internal Medicine, Aarhus Univ Hospital, Aarhus, Dominican Republic; ³Depts of Pathology, Leiden Univ Medical Center, Netherlands; ⁴Depts of Molecular Cell Biology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Fibrosis is a hallmark of diabetic nephropathy (DN) leading to chronic kidney disease. However, we lack good animal models resembling kidney pathology of human DN. Renal fibrogenesis has been suggested to be caused by dysregulation of SMAD signalling by members of the TGF β superfamily. The purpose of this study was to evaluate these events in kidneys from patients and compare to DN mouse models.

Methods: Human (type 1 and type 2 diabetes patient; T1D and T2D) and murine (db/db and streptozotocin (STZ) treated mice) kidneys were stained for pSMAD2. Kidney transcriptional signature of 44 genes including TGF β /BMP target-genes, BMP modulators, TGF β -superfamily ligands and EMT markers was evaluated in the mouse models.

Results: Nuclear as well as cytoplasmic pSMAD2 expression was increased in tubules of diabetes patients. T1D patients displayed elevated staining in proximal tubuli, whereas T2D patients showed elevated staining in distal tubuli. Increase in SMAD2 activation in distal tubules was also observed in STZ-treated mice, while db/db mice showed no SMAD2 activation. Genetic profiling showed increased expression of BMP antagonists and other genes (CTGF, Gremlin, KCP, USAG1) promoting increased TGF β activity in both models of DN.

Conclusions: Early experimental DN displays little fibrogenesis, but studying the nuclear pSMAD2 expression suggests that the TGF β /activin A pathway is upregulated in diabetes patients and mouse DN models. The tubular compartment showed increased pSMAD2 activity in both mouse and man but expression pattern differed between T1D

and T2D patients and translated poorly into the mouse models of DN tested in this study. Genetic profiling of murine tissue indicates local blockade of BMP pathways suggesting dampening of the renoprotective BMP7 pathway in both T1D and T2D models.

TH-PO359

Role of Liver X Receptors in Diabetic Nephropathy and Obesity Related Glomerulopathy Michal Herman-Edelstein,¹ Ana Tobar,¹ Talia R. Weinstein,¹ Uzi Gafti,¹ Avry Chagnac,¹ Vivette D. D'Agati,³ Moshe Levi,² ¹Rabin Medical Center-Felsenstein, Tel Aviv Univ, Israel; ²Univ of Colorado; ³Columbia Univ.

Background: Our recent human and rodent studies have associated ectopic lipid accumulation and abnormal lipid metabolism in the kidney with diabetic nephropathy (DN) and obesity-related glomerulopathy (ORG). Liver X receptors (LXR) α and β are nuclear receptors that are master regulators of cholesterol metabolism and also inhibit inflammation. Next-generation RNA sequencing data show downregulation of LXR pathways in DN. To obtain insight into the pathophysiology of obesity-induced renal lipotoxicity, we investigated the expression of LXRs and their target genes in human DN and ORG kidney biopsies.

Methods: Renal lipid contents, inflammation genes involved in cholesterol and fatty acid metabolism, and LXRs target genes, were studied on amplified mRNA of laser capture microdissection (LCM) isolated glomeruli and tubules from kidney biopsies of patients with established DN (n=16), ORG (N=16), and normal kidneys (n=16).

Results: LXR α and LXR β mRNA were higher in the glomerular compared to the tubular fraction. LXR α and β mRNA and protein were significantly decreased in DN and ORG kidneys. We found a significant relationship between LXRs mRNA, eGFR, glomerulosclerosis, and inflammation. Furthermore, we studied the anti-inflammatory effect of different LXR agonists including DMHCA, TO-901317 and GW3965 against oxLDL and palmitate-induced lipotoxicity in culture podocytes. Our results indicate that all LXR agonists induce cholesterol efflux while DMHCA exhibited limited effect on SREBP1c. Furthermore treatment of diabetic db-db mice with the LXR agonist resulted in significant decreases in albuminuria and expression of the proinflammatory cytokines IL-6 and TNF α in the kidney.

Conclusions: Our results suggest that decreased glomerular and tubular expression of LXRs seems to have a role in DN and ORG. Consequently, decreased activity of LXR and related downstream pathway mediators may contribute to lipotoxicity, inflammation and GFR decline. We suggest that modulation of LXR receptors in the kidney may serve as a novel therapeutic target in DN and ORG.

Funding: NIDDK Support

TH-PO360

Dual Activation of FXR and TGR5 by INT-767 Mediates Protection from Diabetic Nephropathy and Retinopathy Xiaoxin Wang,¹ Michal Herman-Edelstein,² Jonathan Levi,³ Uzi Gafti,² A. Rosenberg,³ Jeffrey B. Kopp,³ Luciano Adorini,⁴ Maria B. Grant,⁵ Moshe Levi.¹ ¹Univ of Colorado Denver; ²Rabin Medical Center; ³NIDDK; ⁴Intercept; ⁵Indiana Univ, Indianapolis, IN.

Background: Bile acids are agonists for the nuclear hormone receptor, farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5. We have found that FXR and TGR5 expression are decreased in human diabetic nephropathy.

Methods: We examined the effect of their combined activation by the dual FXR/TGR5 agonist INT-767 on diabetic nephropathy in DBA/2J mice fed a Western diet and streptozotocin (STZ) induced hyperglycemia.

Results: Diabetic mice developed marked albuminuria, increased glomerular area and mesangial expansion, decreased podocyte (WT-1) density. Diabetic mice also had increased renal triglyceride and cholesterol accumulation, increased NF- κ B activity, and increased oxidized protein accumulation. Treatment with 30 mg/kg BW/day INT-767 for 8 weeks normalized albuminuria (ACR), glomerular area and mesangial expansion, podocyte density (WT-1), kidney cholesterol (CHOL), NF- κ B transcriptional activity, oxidized proteins, and profibrotic growth factors TGF- β and CTGF and significantly decreased kidney triglycerides (TG). In addition, in the retina INT-767 also reduced the number of acellular capillaries, decreased the inflammatory infiltration into the retina, and corrected the diabetes-associated endothelial progenitor cell dysfunction, restoring cell migration to nondiabetic levels.

	Control	STZ	STZ + INT-767
ACR: mg/g	88±11	603±113*	50±18**
Podocyte Density	42±2	30±2*	38±1**
Kidney TG: μ mol/g	7.5±1.3	33.6±2.7*	20.5±2.3**
Kidney CHOL: μ g/g	6.6±0.5	9.4±0.7*	6.3±0.7**
NF- κ B Activity	1.0±0.1	1.4±0.1*	1.2±0.1**
Oxidized Proteins	0.7±0.1	1.2±0.1*	0.8±0.1**

Conclusions: Our studies therefore indicate that dual activation of FXR and TGR5 protects from diabetic nephropathy and retinopathy by decreasing inflammation, oxidative stress, lipid accumulation, and fibrosis.

Funding: NIDDK Support

TH-PO361

High Fat Diet and BCL2-Modifying Factor (Bmf) Overexpression Together Promote Tubular Apoptosis in BMF-Transgenic Mice via Reactive Oxygen Species Generation Anindya Ghosh,¹ Hasna Maachi,¹ Shaaban Abdo,¹ Yixuan Shi,¹ Chao-Sheng Lo,¹ Isabelle Chenier,¹ Janos G. Filep,² Julie R. Ingelfinger,³ Shao-Ling Zhang,¹ John S.D. Chan.¹ ¹CRCHUM, Univ de Montreal, Montreal, QC, Canada; ²Research Centre, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada; ³Pediatric Nephrology Unit, Mass Gen Hosp, Boston, MA.

Background: We previously reported that the pro-apoptotic gene Bmf is up-regulated in renal proximal tubular cells (RPTCs) of diabetic obese mice (db/db) compared to normal lean mice (db/m+). We investigated whether high-fat diet (HFD) regulates Bmf expression and RPTC apoptosis and studied its underlying molecular mechanism(s) in RPTCs.

Methods: Non-transgenic (non-Tg) mice, catalase-Tg (Cat-Tg) and Bmf-Tg mice overexpressing rat Cat and human Bmf in RPTCs, respectively, were fed normal chow or HFD from 4 to 20 weeks of age. All animals were euthanized at 20 weeks. Blood glucose (BG), systolic blood pressure (SBP) and urinary albumin creatinine ratio (ACR) were monitored bi-weekly. Renal oxidative stress and ROS generation were quantified by dihydroethidium staining and lucigenin assay, respectively. RPTC apoptosis was evaluated by TUNEL assay, immunostaining for active caspase-3 and Bax expression. Pro-apoptotic protein and gene expression were assessed by Western blotting and quantitative-PCR. Rat RPTCs stably transfected with the plasmid pGL4.20 containing rat Bmf gene promoter were also studied.

Results: Non-Tg mice fed HFD had increases in BG, ACR, acetylated p53, renal oxidative stress and pro-apoptotic genes (Bax, Bmf) expression and RPTC apoptosis. Catalase overexpression prevented HFD-induced RPTC apoptosis and pro-apoptotic gene expression in Cat-Tg mice. In contrast, overexpression of Bmf gene in RPTCs with or without HFD aggravated RPTC apoptosis, pro-apoptotic genes expression and ACR. In vitro, high glucose and palmitate attenuated SIRT1 expression, enhanced acetylated p53 expression and stimulated Bmf gene transcription.

Conclusions: We conclude that HFD and Bmf may act in concert to induce ROS-mediated tubular apoptosis, suggesting an important role for Bmf in tubular atrophy in diabetes.

Funding: Government Support - Non-U.S.

TH-PO362

Prevention of Diabetic Nephropathy and Other End Organ Damage by Stem Cell-Based Cure of Type I Diabetes Mellitus in Mice and Rats Christof Westenfelder,^{1,2,3} Anna Gooch,³ Jon D. Ahlstrom,³ Zhuma Hu,³ Evan Hurlow,^{1,3} Ping Zhang,³ ¹Medicine, U of Utah and VAMC, Salt Lake City, UT; ²Physiology, U of Utah, Salt Lake City, UT; ³SymbioCellTech, Salt Lake City, UT.

Background: Endogenous insulin replacement by pancreas or islet transplants is currently the optimal treatment to achieve insulin-independence and end organ protection in patients with T1DM. However, the limited availability of cadaveric pancreas donors, and both the need for permanent antirejection therapy and repeated islet transplants continue to prevent the wide spread use of these therapies. Auto- and allo-immune isolation of transplanted islet cells is currently tested with encapsulation technologies, several of which have failed early. Because β -Cells cannot be adequately expanded ex vivo, Embryonic or induced Pluripotent Stem Cells are evaluated instead. In our present studies, we succeeded to cure T1DM in mice and rats by achieving both adequate culture expansion of islet cells and dual immune isolation by exploiting the robust immune modulating and other trophic activities of Mesenchymal Stem Cells (MSCs).

Methods: Immune isolation of islet cells was accomplished by two methods: either by fusing islet cells and MSCs, creating heterokaryons (β -MSCs), or by generating islet-sized cell clusters (Pseudo islets) composed of islet cells and MSCs. Islet cell expansion was accomplished via reversible epithelial-mesenchymal transition.

Results: Streptozotocin (STZ) diabetic rats and mice and spontaneously diabetic female NOD mice were infused i.p. with either β -MSCs or Pseudo islets. STZ-diabetic NOD/SCID mice were identically treated with canine Pseudo islets. Long-term euglycemia and normal i.p. Glucose Tolerance Tests were obtained in all treated animals. No antibody responses were detected in allogeneic groups, no adverse events were observed and no evidence of diabetic nephropathy or other end organ damage was detected. Retrieval of administered cells resulted in prompt return of hyperglycemia.

Conclusions: We conclude that our pre-clinical data have significant translational utility for clinical T1DM. In further preparation for clinical trials, we are currently conducting a Phase I/II Trial in dogs with T1DM.

Funding: Veterans Administration Support

TH-PO363

High Glucose Modulates Hedgehog Interacting Protein (Hhip) Gene Expression in Diabetic Related Proximal Tubular Cell Damage Shiao-Ying Chang,¹ Xin-Ping Zhao,¹ Min-Chun Liao,¹ Isabelle Chenier,¹ Julie R. Ingelfinger,² John S.D. Chan,¹ Shao-Ling Zhang.¹ ¹CRCHUM, Univ of Montreal, Montreal, QC, Canada; ²Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, MA.

Background: Hedgehog Interacting Protein (Hhip) is a putative antagonist of hedgehog (Hh) signaling, since both the full length Hhip and its soluble form (sHhip) bind Hh ligands with nanomolar affinity to attenuate the Hh signaling. We previously reported that high glucose (HG) modulates Hhip gene expression and then, targets TGF β 1 signaling in

embryonic renal cells, resulting in impaired kidney formation. Given our prior findings we hypothesized that Hhip might be involved in the evolution of kidney damage in diabetic conditions, such as proximal tubular injury during the development of diabetic nephropathy.

Methods: Two diabetic animal models-- the spontaneously diabetic Akita (T1DM) and db/db (T2DM) mouse models were used for *in vivo* studies. Renal morphology, immunohistochemistry (IHC), promoter activity analysis and gene expression were assessed by standard methods. Rat immortalized renal proximal tubular cells (IRPTCs) were used *in vitro* studies.

Results: As compared to non-diabetic Akita littermates and lean db/db animal (db/m), renal Hhip expression/urinary sHhip levels were significantly increased in adult Akita and db/db mice at 20 weeks of age. There was strong Hhip-and TGF β 1-IHC expression in diabetic kidneys, mostly localized to glomerular endothelial cells and renal proximal tubular cells. *In vitro*, high glucose significantly stimulated the activity of the plasmid containing mouse Hhip gene promoter in dose-dependent manner. HG stimulated intracellular Hhip and inhibited sHhip level protein expression in time-dependent manner. Hhip siRNA attenuated the stimulatory effect of HG on intracellular Hhip and TGF β 1 gene expression in IRPTCs.

Conclusions: Our data suggest that high glucose increases both Hhip and TGF β 1 gene expression acting in a paracrine fashion to promote renal tubulointerstitial fibrosis in DN, both *in vivo* and *in vitro*.

Funding: Government Support - Non-U.S.

TH-PO364

Development of Diabetic Nephropathy in Streptozotocin-Treated Id1 Knockout Mice Matthew D. Plotkin. Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: Cell injury induces expression of Id1, a bHLH transcription factor inhibitor that regulates cell cycle and differentiation. Id1 knockout results in increased tissue fibrosis in injury models. Since Id1 may have an important role in maintaining vascular stability during hyperglycemia and oxidative stress associated with diabetes, preliminary studies were done to determine if Id1 knockout would result in kidney pathology in a diabetic nephropathy resistant strain of mice.

Methods: Id1 $-/-$ mice in a B6;129 background and WT littermates were treated with streptozotocin (STZ) 125 mg/kg I.P. for 2 doses to induce type I diabetes (DM). Mice with persistent blood glucose levels > 300 mg/dL (n = 10/genotype) were sacrificed at 3 months. Endothelial and perivascular cells from WT and KO mice were cultured in 2% FBS and used at passages 1 and 2.

Results: In WT B6;129 mice, Id1 levels were increased 15-fold at 3 months in response to STZ induced DM with increased expression detected in glomerular capillary endothelial cells compared with normal mice. WT mice had no pathological changes despite severe hyperglycemia. In contrast, Id1 $-/-$ mice developed mesangial expansion and matrix deposition, focal capillary aneurysms and glomerular arteriolar hypertrophy and increased proteinuria (albumin/cr: 0.61 \pm 0.26 mg/mg vs. 0.30 \pm 0.14 mg/mg, p = .05). KO mice showed a 5-fold increase in glomerular endothelial and tubular epithelial cell proliferation by Ki67 immunohistochemistry. These changes occurred despite no significant difference in average glucose between WT and KO mice. Comparison of primary co-cultures of WT and KO endothelial and perivascular cells demonstrated 10-fold decreased angiopoietin-1 expression by qPCR and decreased autophagy in response to TGF β 1 in KO cells. These results correlated with marked p62 accumulation in glomerular arterioles in normal and diabetic KO mice.

Conclusions: Glomerular endothelial Id1 expression is increased with type I DM. KO mice develop diabetic nephropathy suggesting a protective effect of endothelial Id1.

Funding: Veterans Administration Support

TH-PO365

Heterogeneous Nuclear Ribonucleoprotein F Stimulates Sirtuin 1 Expression and Attenuates Renal Proximal Tubular Cell Apoptosis in Mice with Type 2 Diabetes Chao-Sheng Lo,¹ Yixuan Shi,¹ Isabelle Chenier,¹ Janos G. Filep,² Julie R. Ingelfinger,³ Shao-Ling Zhang,¹ John S.D. Chan.¹ ¹CRCHUM, Univ de Montreal, Montreal, QC, Canada; ²Research Centre, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada; ³Pediatric Nephrology Unit, Mass. Gen. Hosp., Boston, MA.

Background: We hypothesized that overexpression of the transcription factor heterogeneous nuclear ribonucleoprotein F (hnRNP F) can stimulate sirtuin 1 (SIRT1, a NAD⁺-dependent deacetylase) expression and signaling in renal proximal tubular cells (RPTCs), subsequently attenuating RPTC apoptosis in type 2 diabetic db/db mice.

Methods: We made and studied db/db (BKS strain) transgenic (Tg) mice specifically overexpressing hnRNP F in their RPTCs. Blood glucose (BG), systolic blood pressure (SBP) and albuminuria were monitored bi-weekly in adult male non-diabetic db/m+ littermates, db/db and db/db hnRNP F-Tg mice from 10 to 20 weeks of age. Kidneys were processed for histology and apoptosis studies. Renal oxidative stress and reactive oxygen species (ROS) generation were quantified by dihydroethidium staining and lucigenin assay, respectively. Renal proximal tubular (RPT) gene expression was evaluated by respective real time-qPCR and Western blotting. Rat immortalized RPTCs stably transfected with hnRNP F cDNA or SIRT 1 gene promoter were also studied.

Results: Db/db mice developed higher BG, SBP, renal hypertrophy and albuminuria at week 20 as compared to db/m+ littermates; db/db hnRNP F-Tg mice did not have elevated SBP, renal hypertrophy or albuminuria. ROS generation, apoptosis, acetylated p53, Bax and active caspase-3 expression were significantly increased in RPT of db/db mice but not in db/db hnRNP F-Tg mice. In contrast, SIRT 1 and catalase expression were significantly decreased in RPT of db/db mice but not in db/db hnRNP F-Tg mice.

Finally, overexpression of hnRNP F stimulates SIRT1 protein, mRNA and gene promoter activity and reverses high glucose (35 mM D-glucose) and palmitate inhibition of SIRT1 expression in rat RPTCs in vitro.

Conclusions: Overexpression of hnRNPF attenuated RPTC apoptosis in type 2 diabetic mice via up-regulation of SIRT1 gene expression and signaling.

Funding: Government Support - Non-U.S.

TH-PO366

Lack of CD2AP Disrupts Glucose Transporter 4 Trafficking and Attenuates Glucose Uptake Sanna H. Lehtonen, Surjya Narayan Dash, Zydrune Polianskyte-prause, Vincent Dumont, Tuomas Alekski Tolvanen. *Dept of Pathology, Univ of Helsinki, Finland.*

Background: Recent data indicate that adapter protein CD2AP is downregulated in diabetic conditions via PI3K/Akt signaling in podocytes. In this study we investigated the role of CD2AP in insulin-dependent glucose transporter 4 (Glut4) trafficking and glucose uptake.

Methods: Glucose uptake was measured using tritium-labeled 2-deoxyglucose. CD2AP^{-/-} and wildtype (WT) podocytes expressing HA-Glut4-GFP were utilized to quantify the amount of Glut4 on the plasma membrane and to study the trafficking of Glut4 by live cell imaging. Protein complexes were analyzed by coimmunoprecipitation and Duolink proximity ligation assay (PLA).

Results: The level of glucose uptake was 32% lower in CD2AP^{-/-} podocytes compared to WT podocytes in the basal state. After insulin stimulation, glucose uptake in WT cells increased 19%, whereas CD2AP^{-/-} podocytes failed to respond. Knockdown of Cd2ap in L6 myoblasts with siRNA lowered glucose uptake by 20% in the basal state and blunted insulin-induced glucose uptake. In line with this, insulin stimulation increased HA-Glut4-GFP on the plasma membrane by 50% in WT podocytes, whereas no difference was observed in cells lacking CD2AP. Live cell imaging revealed dynamic trafficking of HA-Glut4-GFP in response to insulin in WT cells, whereas in CD2AP^{-/-} podocytes HA-Glut4-GFP formed insulin unresponsive clusters in the perinuclear region. Subcellular fractionation indicated that CD2AP is found in intracellular membrane fractions together with Glut4, IRAP and sortilin, constituents of Glut4 storage vesicles (GSVs). Coimmunoprecipitation and PLA assays revealed that CD2AP forms a complex with GGA2, a clathrin adaptor which sorts Glut4 to GSVs. We further found that lack of CD2AP increases the interaction between GGA2 and clathrin. Insulin stimulation further increased GGA2-clathrin interaction and led to perinuclear accumulation of the complex in CD2AP^{-/-} podocytes.

Conclusions: Our results indicate that CD2AP facilitates glucose uptake into podocytes and muscle cells. Interaction of CD2AP with GGA2 suggests a role for CD2AP in sorting of Glut4 to GSVs and insulin-responsive trafficking of Glut4 to the plasma membrane in podocytes.

Funding: Private Foundation Support

TH-PO367

Tauroursodeoxycholic Acid (TUDCA) Ameliorates Both Tubular and Glomerular Injury in Diabetic Nephropathy, Thus Providing an Added Value to ACE-Inhibition Moh'd Mohanad Ahmad Al-Dabet, Andi Marquardt,¹ Fabian Bock,^{1,2} Khurram Shahzad,^{1,3} Madhusudhan Thati,¹ Berend Heinrich Isermann.¹ *¹Inst of Clinical Chemistry and Pathobiochemistry, Otto-von-Guericke-Universität Magdeburg, Germany; ²Dept of Internal Medicine I and Clinical Chemistry, Univ of Heidelberg, Heidelberg, Germany; ³Univ of Health Sciences, Khayaban-e-Jamia Punjab, Lahore, Pakistan.*

Background: Therapeutic inhibition of the Renin-Angiotensin Aldosterone System (RAAS) is firmly established in diabetic nephropathy (dNP). Despite efficient RAAS inhibition dNP frequently progresses to end-stage renal disease, necessitating the need of additional and mechanistically distinct therapeutic approaches. We have recently demonstrated that amelioration of endoplasmic reticulum stress using TUDCA protects mice from dNP (Madhusudhan et al., Nat Commun 2015). To foster clinical evaluation of TUDCA, which is approved for other medical indications, we determined the efficacy of TUDCA in db/db mice in addition to ACE-inhibition (Enalapril).

Methods: 16 weeks old db/db mice with established albuminuria were randomly assigned to control (PBS), Enalapril (50mg/L, drinking water), TUDCA (150mg/Kg, i.p. daily), or combined Enalapril and TUDCA treatment. Mice were analyzed after 6 weeks of treatment. Albuminuria, glomerular and tubular damage (PAS-staining, electron microscopy, marker proteins), and markers of ER-stress were analyzed.

Results: Both agents (Enalapril and TUDCA) resulted in a significant reduction of UACR, glomerular hypertrophy, and FMA (fractional mesangial area). The combined treatment was more efficient with regard to UACR reduction, but similarly protective against glomerular sclerosis. Unlike Enalapril, TUDCA conveyed additional tubular protection, which was associated with reduced ER-stress (e.g. nuclear ATF6) in the tubular compartment.

Conclusions: A combined therapy of TUDCA and Enalapril is more efficient than Enalapril alone in preventing the progression of dNP in db/db mice. These results should foster translational efforts evaluating TUDCA in patients with dNP.

Funding: Government Support - Non-U.S.

TH-PO368

Fatty Acid Binding Protein 3 Might Mediate Diabetic Nephropathy in Mouse Lacking eNOS Gene Shota Ozawa,^{1,2} Shuko Ueda,¹ Kiyoshi Mori,¹ Katsuhiko Asanuma,¹ Motoko Yanagita,^{1,3} Takahiko Nakagawa.¹ *¹TMK Project, Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Japan; ²Pharmacology Research Laboratories II, Mitsubishi Tanabe Pharma Corporation, Japan; ³Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Japan.*

Background: Insulin deficiency leads to an increase in serum free fatty acid concentration. Diabetic glomerular nodules often contain lipid droplet, suggesting that abnormal fatty acid metabolism might contribute to the development of diabetic glomerular injury. However, its precise mechanism remains unclear. Fatty acid binding proteins (FABPs) are currently considered as key molecules for lipid metabolism.

Methods: Since diabetic eNOS knockout (KO) mouse is considered to be a good model for human diabetic nephropathy, we here investigated whether FABP could mediate glomerular and tubular injury in this model.

Results: First of all, oil red O staining demonstrated that lipid droplets were accumulated in the injured glomeruli in diabetic eNOSKO mice, suggesting that lipid abnormality was involved in the injured process. Microarray assay with isolated glomeruli revealed that among 10 isoforms in FABP family, FABP3 mRNA was most highly expressed in diabetic eNOSKO mice compared to non-diabetic eNOSKO mice. We found that FABP3 protein was predominantly located in the mesangial cells while glomerular injuries were associated with inflammatory processes, such as macrophage infiltration and MCP-1 induction in the diabetic eNOSKO mice. Overexpression of FABP3 resulted in a greater response to palmitate, a saturated FA, to induce MCP-1 in the rat mesangial cells. Furthermore, tubular FABP3 was likely exclusively translocated from cytoplasm to basolateral membrane in proximal tubular epithelial cells under diabetic condition. In turn, the heart, a major organ for FABP3 protein in normal condition, did not show any significant changes in its expression level under diabetic condition in either wild type or eNOSKO mice.

Conclusions: FABP3 likely mediates diabetic glomerular and tubular injury.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma

TH-PO369

Cinacalcet Ameliorates Diabetic Nephropathy Through Intracellular Ca⁺⁺-CaMKK β -LKB1-AMPK Activation Ji Hee Lim, Min Young Kim, Yaeni Kim, Eun Nim Kim, Soojeong Kim, Hyung Wook Kim, Cheol Whee Park. *College of Medicine, Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: In cardiovascular system, the Calcium-sensing receptor (CaSR) stimulates the production of NO in the endothelial cells. A decrement in NO bioavailability associated with AMPK inactivation and increased generation of reactive oxygen species are critical to the pathogenesis of diabetic vascular complications. Therefore, we evaluated the renoprotective effect of cinacalcet on glucotoxicity through AMP-protein kinase (AMPK)-eNOS-NO pathway in diabetic nephropathy in db/db mice and human glomerular endothelial cells (HGECs).

Methods: Male C57/BLKS db/db mice and db/m controls at 8 weeks of age were divided to receive either a regular diet chow or a diet containing cinacalcet (10 mg/kg; n=8, respectively). Mice were followed for 12 weeks and were evaluated for renal functions, pathologic phenotypes, and AMPK-eNOS-NO pathway.

Results: Cinacalcet ameliorated albuminuria in db/db mice without influencing the changes in blood glucose and Ca⁺⁺ concentrations. The mesangial area expansion and inflammatory cell infiltration in the glomerulus were observed in db/db mice, which were all restored by cinacalcet treatment. Cinacalcet increased expression of CaSR, phosphorylation of CaMKK β and LKB1 and subsequent AMPK activation, which in turn activated PGC-1 α and phospho-Ser1177 eNOS-NO. As a result, an increase in the ratio of Bcl-2/Bax in renal cortex and decrease in urinary 8-hydroxy-deoxyguanosin and isoprostane concentrations enhanced the expression of superoxide dismutase; SOD1 and SOD2. In cultured HGECs, cinacalcet decreased oxidative stress and apoptosis by increasing intracellular Ca⁺⁺ and by enhancing phosphorylation of CaMKK β , LKB1 and AMPK, which were associated with an increase in the phosphorylation of eNOS-NO as well.

Conclusions: In conclusion, the results suggest that cinacalcet improves glucotoxicity through an increase in intracellular Ca⁺⁺ and subsequent activation of the CaMKK β -LKB1-AMPK signaling in the kidney, especially HGECs, and may be a potential therapeutic modality for type 2 diabetic nephropathy.

TH-PO370

Ectopic Expression of TIMP-1 and LTBP-2 in Proximal Tubule-Specific Namp1 Conditional Knockout Mice Aggravates Bridging Fibrosis in Diabetic Nephropathy Kazuhiro Hasegawa, Hirokazu Muraoka, Shu Wakino, Hiroshi Itoh. *Keio Univ.*

Background: Nicotinamide phosphoribosyltransferase (Namp1), the rate-limiting enzyme for nicotinamide adenine dinucleotide (NAD) synthesis, and Sirt1, an NAD-dependent histone deacetylase, exert protective effects in various tissues, leading to enhanced stress resistance and extended longevity. We previously reported that proximal tubule (PT)-specific Sirt1 transgenic mice are protected against diabetic nephropathy (DN), and that PT-specific conditional knockout (CKO) aggravates DN (Nat Med 2013). However, the role of Namp1 in DN remains unknown. In this study, we established PT-specific conditional Namp1-deficient mice to investigate the role of Namp1 in DN initiation and progression.

Methods: We generated PT-specific, Namp1-deficient mice by crossing Namp1^{fllox} mice with γ -GT-Cre mice. Wild-type (WT) and CKO mice were injected with saline (Sal; control) or streptozotocin (STZ) to induce DN. The phenotypes of four groups of mice, WT+Sal, CKO+Sal, WT+STZ, and CKO+STZ, were analyzed at 8 and 24 weeks after treatment.

Results: At 24 weeks in WT+STZ mice, Namp1 expression was reduced in PTs in parallel to renal fibrosis progression. PAM, Masson trichrome, and EVG staining revealed thickening of the tubular basement membrane and basement membrane of Bowman's capsule. Peritubular and periglomerular fibrosis in the cortex and perivascular fibrosis surrounding interlobular arteries and veins in the medulla were clearly detected in CKO+Sal mice. These fibroses were bridging fibrosis connecting the tubule and glomerulus. DNA microarray, real-time PCR, and immunoelectron microscopic findings clearly showed that expression of tubular tissue inhibitor of metalloproteinase 1 (TIMP-1) and latent transforming growth factor beta binding protein 2 (LTBP-2) was elevated in CKO+Sal ectopically in PTs. Such expression caused basement membrane thickening and fibrosis. All changes were further enhanced in CKO+STZ mice.

Conclusions: Namp1 deficiency in PTs induces bridging fibrosis and overproduction of TIMP-1 and LTBP-2. Disruption of Namp1 in PTs causes the initiation and progression of DN-induced fibrosis through the novel mechanism of PT-periglomerular-perivascular fibrotic interplay.

TH-PO371

The Presence of the Anti-Fibrotic MicroRNA Crosstalk in the Effect of N-Acetyl-Seryl-Aspartyl-Lysyl-Proline on Kidney Fibrosis in Diabetes Keizo Kanasaki,^{1,2} Swayam Prakash Srivastava,¹ Shi Sen,¹ Daisuke Koya,^{1,2} ¹Diabetology and Endocrinology, Kanazawa Medical Univ, Kahoku, Japan; ²Div of Anticipatory Molecular Food Science and Technology, Kanazawa Medical Univ, Kahoku, Ishikawa, Japan.

Background: N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is an endogenous peptide with anti-fibrotic activity. We have shown that restoration of fibroblast growth factor receptor1 (FGFR1) and concomitant induction of microRNA (miR)-let-7s were involved in the anti-fibrotic action of AcSDKP. Endothelial-mesenchymal transition (EndMT) could be the important source of matrix producing mesenchymal cells in fibrotic kidney. Interferon (IFN) γ is potential inhibitor of FGFR1; miR-29 targets IFN γ 3'UTR.

Methods: Streptozotocin-induced diabetic CD-1 mice were used for all animal experiments. Mice were sacrificed at 6 months after the induction of diabetes; either AcSDKP or PBS was given by osmotic mini-pump for 1 month from 5 months after diabetic induction. In vitro experiments were performed using Human Dermal Microvascular Endothelial Cells (HMVEC).

Results: Diabetic CD-1 mice with fibrotic kidneys exhibited suppressed levels of AcSDKP in urine, anti-fibrotic miRs, such as miR-29s and miR-let-7s, as well as the prominent induction of IFN γ and EndMT; these alterations were all reversed by AcSDKP treatment. Transfection studies in HMVEC revealed that miR-29s and miR-let-7s demonstrated crosstalk regulation against the mesenchymal cell activation program. Antagomirs for miR-29 induced IFN γ and suppressed both FGFR1 and miR-let-7s; neutralising antibody for IFN γ restored the levels of both FGFR1 and miR-let-7s.

Conclusions: The present study provides insight into the physiologically relevant anti-fibrotic actions of AcSDKP via anti-fibrotic miRs crosstalk mechanisms. IFN γ is the significant regulator of the miR crosstalk between miR-29s and miR-let-7s. Restoring such anti-fibrotic programs (mediated by AcSDKP) could demonstrate potential utility in combating kidney fibrosis in diabetes.

TH-PO372

Novel Drug-Inducible Megalin Knockout Mice Reveal Marked Increase of Both Total Nephron Glomerular Filtration and Tubular Reabsorption of Albumin in Early Diabetic Nephropathy Keita P. Mori,¹ Hideki Yokoi,¹ Masato Kasahara,² Takahige Kuwabara,³ Hirotaka Imamaki,¹ Akira Ishii,¹ Kazuwa Nakao,⁴ Tomomi Endo,¹ Motoko Yanagita,^{1,4} Masashi Mukoyama,³ Kiyoshi Mori,⁴ ¹Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ²Inst for Advancement of Clinical and Translational Science, Kyoto Univ Hospital, Kyoto, Japan; ³Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; ⁴Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: The early phase of Diabetic nephropathy (DN) is characterized with hyperfiltration (or increased clearance) of creatinine or inulin. On the other hand, recent reports using micropuncture technique or multi-photon microscopy for superficial nephrons indicated that glomerular filtration of albumin is not increased and tubular reabsorption is decreased in rodent models of early DN.

Methods: Tamoxifen (Tam)-inducible megalin knockout mice (iMegKO) were generated by crossbreeding megalin floxed mice (from Professor T. Willnow, Max Delbrück Center) with Ndr1-CreERT2 mice (from Professor Yanagita), which enable efficient gene disruption in proximal tubules of adult mice. For analysis of DN, iMegKO mice were given low-dose Tam at 8 weeks after streptozotocin (STZ) treatment.

Results: Low or high-dose Tam-treated, non-diabetic iMegKO exhibited 15-fold increase of urinary albumin excretion (UAE), which should represent total nephron glomerular filtration of albumin in normal mice. Megalin protein elimination was almost complete by high dose Tam, but some expression remained in S3 by low dose. By comparing STZ;iMegKO and non-STZ;iMegKO mice, total filtration of albumin was estimated to be

elevated by 1.7-fold with STZ. Importantly, total reabsorption of albumin, calculated by subtraction of UAE before Tam from that after Tam, was also elevated by 1.6-fold with STZ. These changes were normalized by insulin treatment.

Conclusions: By use of iMegKO, which allows overall quantitation of albumin handling in the whole kidney including juxtamedullary nephrons, total filtration and total reabsorption of albumin was markedly increased in STZ diabetic mice.

TH-PO373

Erythropoiesis Stimulating Agents Cannot Improve Circulating Endothelial Progenitor Cell Counts in Patients with End-Stage Renal Disease on Maintenance Hemodialysis Because of Erythropoietin Resistance Hong Joo Lee,¹ Ju-Young Moon,² Sang Ho Lee,² Chun-Gyoo Ihm,² Tae Won Lee,² Kyung-hwan Jeong,² ¹Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea; ²Dept of Nephrology, Kyung Hee Univ School of Medicine, Seoul, Republic of Korea.

Background: Decreased circulating endothelial progenitor cells (EPCs) associate with occurrence of cardiovascular disease and all cause mortality in end stage renal disease (ESRD) patients on hemodialysis. It is known that erythropoiesis stimulating agents (ESA) connect to vasculoprotective effects such as enhanced nitric oxide production in endothelial cells and mobilization of EPCs. Patients with ESRD on hemodialysis have markedly decreased EPC counts although they are often treated with ESA. We investigated that ESA can improve EPC levels in hemodialysis patients. Or not, we hypothesized that erythropoietin resistance index (ERI) may associate with decreased effect of ESA on EPC.

Methods: We quantified ESA dose and EPCs in blood samples from 86 patients with ESRD on hemodialysis. The ERI was calculated by dividing the weekly erythropoietin dose per kilogram of weight (μ g/wk.kg) by the Hb level (g/dL). Participants were divided into 4 groups based on the lowest, median, highest ERI and no use of ESA group.

Results: The number of circulating EPCs at baseline ranged from 1 to 350 cells/200ml, with a mean \pm SD of 26.0 \pm 48.2 cells/200 μ L. There was no significant association with ESA dose and EPC counts. However, the EPCs counts of lowest ERI group were significantly higher than the medium, highest EPI and no use of ESA group. There was no different occurrence of cardiovascular events among the groups.

Conclusions: Administration of EPO may not always increase the number of circulating EPCs in ESRD patients on HD. The resistance to erythropoietin may associate with decreased circulation EPC counts.

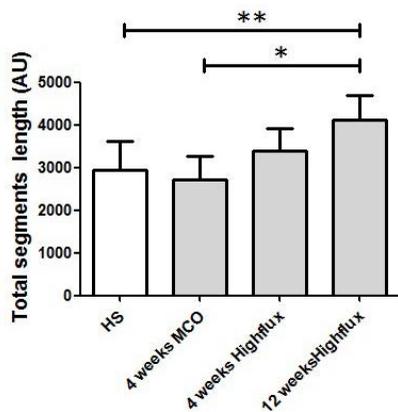
TH-PO374

Dialysis with Medium Cut-Off Membranes (MCO) Modulates Endothelial Function In Vitro: Findings from a Randomized Controlled "First in Man" – Trial Daniel Zickler,³ Kevin Willy,⁵ Ralf Schindler,⁵ Matthias Girndt,¹ Roman Fiedler,¹ Markus Storr,⁴ Christian Luecht,⁵ Duska Dragun,⁵ Rusan Catar.⁵ ¹Dept of Internal Medicine II, Martin-Luther-Univ, Halle, Germany; ²Inst for Epidemiology and Applied Biometry, Eberhard-Karls-Univ Tübingen, Tübingen, Germany; ³NMI Technology Transfer GmbH, Reutlingen, Germany; ⁴Research & Development, Gambro Dialysatoren GmbH, Hechingen, Germany; ⁵Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin, Germany; ⁶Inst for Chemistry / Food Chemistry, Martin-Luther-Univ, Halle, Germany.

Background: Cardiovascular mortality in dialysis patients is in part caused by insufficient removal of proinflammatory interleukins. We examined the influence of serum samples from an RCT on markers of EC function. MCO membranes that allow elimination of 45 kd molecules were used for the first time.

Methods: 50 patients were dialyzed with a Highflux and a MCO membrane for 4 or 12 weeks. Serum samples were drawn and tested in an endothelial cell model. Neangiogenesis was assessed by the measurement of total segments length and KLF2 mRNA, a flow-responsive endothelial transcription factor, was measured. VEGF expression and VEGF protein release was investigated.

Results: Highflux serum enhances neoangiogenesis in EC compared to healthy serum, with MCO filters a reduction was noted. This effect was enhanced after 12 weeks of dialysis (MCO 12 weeks 3206 \pm 340SEM, p < 0.05 vs. highflux). The serum drawn from the patients started on MCO showed diametrically opposite results. Antiparallel to neoangiogenesis a significant reduction of KLF2 expression in EC was noted with Highflux serum, while MCO serum showed results comparable with healthy serum. Neither VEGF mRNA nor protein release was significantly altered in EC.



Conclusions: Our findings underline that dialysis with a higher cut-off influences endothelial cell function in vitro.

Funding: Pharmaceutical Company Support - Gambro GmbH, Government Support - Non-U.S.

TH-PO375

Pharmacological Inhibition of Prolyl-4-Hydroxylase Improves the Impaired Angiogenic Response to Ischemia in Chronic Kidney Disease Karl F. Hilgers,¹ Julian Panesar,¹ Nada Cordasic,¹ Johannes Jacobi,¹ Nicolai Burzlaff,² Kai-Uwe Eckardt,¹ Carsten Willam,¹ Kerstin U. Amann.¹ ¹Univ Hospital Erlangen; ²Univ of Erlangen-Nürnberg, Germany.

Background: Ischemia-induced angiogenesis is impaired in chronic kidney disease (CKD). Activation of hypoxia-inducible factors has been shown to improve angiogenesis. Here, we investigated whether activation of hypoxia-inducible factors can improve capillary supply in rats with CKD. Inhibition of prolyl-4-hydroxylase (PHD) was started a few hours after onset of hindlimb ischemia.

Methods: CKD was induced in rats by 5/6 nephrectomy; controls were sham operated. After 8 weeks, ischemia of the right limb was induced by ligation & resection of the femoral artery. Post-conditional activation of hypoxia-inducible factors was induced by 2 intraperitoneal injections of the PHD inhibitor 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetate (ICA), 12.5 mg/kg, 2 and 6 hours after onset of ischemia. Further animals received placebo injections. Rats were sacrificed 24 h or two weeks after the onset of ischemia. Computer-assisted integration of capillary area normalized for the number of muscle fascicles was performed after double staining for CD31 and laminin of sections of the gastrocnemius muscle.

Results: In control rats, capillary area increased in the ischemic vs. non-ischemic hindlimb by 38±3 % after 2 weeks (p<0.01, N=8). In contrast, there was no significant increase in the ischemic over the opposite limb in CKD (5±4%, N=8, p>0.1). ICA increased capillary supply of ischemic limbs of CKD rats by 45±5 % compared to CKD-placebo rats (n=8, p<0.01), and by 36±4 % (p<0.05) compared to non-ischemic limbs of CKD-ICA animals. After ICA treatment, capillary supply of ischemic limbs was no longer different between CKD and control rats. RT-PCR showed that the ischemia-induced stimulation of VEGF-A was doubled after 24 h by ICA in CKD. The short treatment with ICA did not affect hematocrit levels.

Conclusions: Transient PHD inhibition restores ischemia-induced angiogenesis in CKD rat hindlimb even if applied in a therapeutic approach after onset of ischemia.

Funding: Government Support - Non-U.S.

TH-PO376

Vascular Access Choice in Elderly ESRD Patients Eunjin Bae, Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Yon Su Kim, Kwon Wook Joo. *of Internal Medicine, Seoul National Univ College of Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.*

Background: The number of elderly ESRD patients is rapidly increasing. Their high prevalence of comorbidity and short life expectancy result in substantial challenges for choice of vascular access. The aim of this study is to suggest optimal choice of vascular access in elderly ESRD patients who require hemodialysis(HD).

Methods: We included outpatients visiting vascular access clinic between January 2008 and March 2014, retrospectively. We divided these patients into 3 groups by age as follows: younger (<65yrs), elderly (65–79yrs) and very elderly (≥80yrs). Various clinical and vascular access associated characteristics were compared among these groups. Cox proportional model was used to analyze the effect of vascular access type on maturation failure, access failure and all-cause mortality.

Results: Among a total of 1,109 patients, 59.1% were men and the mean age was 61±14 years. At the time of HD initiation, 56.4% of patients used central catheters, 38.9% used AVFs and 4.7% used AVGs. Of these, 87.4% (n=973) were chosen AVFs as their permanent vascular access and the proportion of AVF was decreased with age. Compared with AVG, AVF was associated with better survival rate, require less intervention to maintain patency and have lower access failure. Very elderly patients had higher proportion of proximal vascular access and also required more preoperative surveillance and interventions. In total

patients, the rate of mortality, access failure, maturation failure was 15.7%, 7.1% and 32%. The mortality benefit with RC AVF was superior to that with both BC AVF and AVG for all age. In elderly group, BC AVF has lowest access failure and highest 1yr patency rate compared with RC AVF or AVG. However, in very elderly group, there was no significant associations between access type and access failure or 2ndary outcomes when adjusted for confounding factors.

Conclusions: We concluded that AVF is the preferred form of vascular access for long term outcome in elderly patients. Nevertheless, BC AVF could be considered by individual characteristics in elderly patients who has complicated radiocephalic site and a short life expectancy.

TH-PO377

Evaluation of Renal Perfusion in CKD Patients Using Arterial Spin Labelling (ASL) Magnetic Resonance Imaging (MRI) Tsutomu Inoue,¹ Eito Kozawa,² Masahiro Ishikawa,³ Kei Sugiyama,¹ Takeru Kusano,⁴ Naoki Kobayashi,³ Hirokazu Okada.¹ ¹Nephrology, Saitama Medical Univ, Iruma, Saitama, Japan; ²Dept of Imaging Diagnosis, Saitama Medical Univ International Medical Center, Hidaka, Saitama, Japan; ³School of Biomedical Engineering, Faculty of Health and Medical Care, Saitama Medical Univ, Hidaka, Saitama, Japan; ⁴Dept of General Internal Medicine, Saitama Medical Univ, Iruma, Saitama, Japan.

Background: The evaluation of renal blood flow in chronic kidney disease (CKD) is beneficial for the determination of drug efficacy and prognostic expectations of CKD. At present, radionuclide scanning or contrast agents are required for this purpose. In this study, we employed arterial spin labeling (ASL) MRI, which is a non-invasive method of measuring tissue perfusion using magnetized blood as an endogenous contrast agent, for the evaluation of CKD patients.

Methods: A total of consecutive 50 CKD patients (33 males and 17 females, 57.1±16.1 years old) were subjected to MRI, including T1-weighted images, ASL and blood oxygen level-dependent (BOLD)-MRI. MRI was performed using a 3.0-T Imager (Skyra; Siemens, Erlangen, Germany). MATLAB, a technical computing language for data analysis, was used for the production of a perfusion map; while OsiriX, image-processing software for digital imaging and communications in medicine (DICOM), was used for measuring the signal intensity on each map.

Results: The perfusion map showed that the signal intensity of the renal cortex is higher than that of the medulla. Similarly, T2* map obtained by BOLD MRI showed the same tendency. These findings appear to reflect the differences in the volume of blood flow and tissue oxygenation in each area. Mean cortical blood flow was 134.1±43.8 in G4-5 and 180.0±48.6 in G3a/b (ml/min/100g tissue weight, p<0.05), with significant differences observed between the two groups.

Conclusions: A reliable, non-invasive and repeatable system for monitoring renal blood flow is currently clinically unavailable. ASL MRI at 3.0 Tesla provides a method of measuring renal perfusion in CKD patients as well as healthy subjects without the need for the administration of exogenous compounds.

Funding: Government Support - Non-U.S.

TH-PO378

In-Vivo Studies of the Microcirculation in Experimental Uremia Uwe Querfeld,^{1,3} Hans-Ulrich Prommer,² Johannes Maurer,² Karoline Websky,³ Dorothea Burghardt,¹ Rudi Sampati,² Kerstin Sommer,³ Axel Pries.² ¹Pediatric Nephrology, Charité, Berlin, Germany; ²Physiology, Charité, Berlin, Germany; ³Center for Cardiovascular Research, Charité, Berlin, Germany.

Background: Endothelial dysfunction is a clinical hallmark of cardiovascular disease in patients with CKD. We analyzed morphology and function of the microcirculation in-vivo in mice with experimental uremia.

Methods: In-vivo microscopy of the musculus cremaster capillary bed was performed in BALB/c mice with moderate to severe uremia due to 5/6 nephrectomy or adenine feeding (n=18), and in healthy controls (n=5). Morphological measurements included capillary length, capillary density, and the non-vascularized area. Functional parameters included the arterio-venous difference in oxygen saturation (avΔO₂) and the change in diameter (ΔD/D) before and after application of acetylcholine, sodium-nitroprusside, papaverine and adenosine.

Results: Capillary length was inversely associated with the degree of experimental uremia, with a reduction of 15% per 100 mg/dL increase of serum urea. Overall, there was a heterogeneous pattern of capillary rarefaction, with areas of normal capillary density and capillary-free areas. The mean non-vascularized area in severely uremic animals (urea > 400 mg/dL) was 19.8x10³ mm² ± 50.5x10³ mm², and 3.1x10³ mm² ± 3.7x10³ mm² in controls. The ΔD/D after pharmacological vasodilatation was 15.4% ± 3.7% in controls, 12.4% ± 4.2% in moderately uremic animals and 7.0% ± 3.5% in severely uremic mice. The avΔO₂ was 13.1% ± 2.6% in controls, 11.8% ± 3.3% in moderately uremic and 9.8% ± 2.9% in severely uremic mice, indicating an arteriovenous shunt effect and a diminished oxygen delivery.

Conclusions: These in-vivo studies show a loss of microcirculation in the musculus cremaster of mice with experimental uremia, occurring in a heterogeneous "wipe-out" pattern. Morphological changes (capillary rarefaction) and functional changes (ΔD/D, avΔO₂) were associated with the degree of experimental uremia. These data suggest that a diseased microcirculation (uremic microangiopathy) contributes to endothelial dysfunction and precedes macrovascular disease in uremia.

TH-PO379

Arterial Biopsies of Children with CKD Show Altered Morphology, Calcium Content and Gene Expression Uwe Querfeld,^{1,2} Betti Schaefer,³ Aysun Bayazit,⁴ Ursula Schulz,² Kerstin Sommer,² Markus J. Kemper,⁵ Guido Laube,⁶ Francesca Mencarelli,⁷ Sandra Habbig,⁸ Franz S. Schaefer,³ Rainer Büscher,¹⁰ Claus Peter Schmitt,³ Christian Freise.² ¹*Pediatric Nephrology, Charité, Berlin, Germany;* ²*Center for Cardiovascular Research, Charité, Berlin, Germany;* ³*Pediatric Nephrology, Univ of Heidelberg, Heidelberg, Germany;* ⁴*Pediatric Nephrology, Cukurova Univ, Adana, Turkey;* ⁵*Pediatric Nephrology, UKE, Hamburg, Germany;* ⁶*Pediatric Nephrology, Univ of Zurich, Zurich, Switzerland;* ⁷*Pediatric Nephrology, Policlinico S. Ursula Malphigi, Bologna, Italy;* ⁸*Pediatric Nephrology, Univ of Cologne, Cologne, Germany;* ⁹*Pediatric Nephrology, AKH, Wien, Austria;* ¹⁰*Pediatric Nephrology, Univ of Essen, Essen, Germany.*

Background: The prospective 4C study investigates cardiovascular comorbidity in children with CKD. We have studied arterial biopsies of 4C-patients and age-matched controls.

Methods: Arterial biopsies were performed at the time of renal transplantation of patients aged 15.4 (8-21) years (n=21). Age-matched healthy control biopsies were obtained from a biobank (Deutsches Herzzentrum Berlin) collecting arterial biopsies from children undergoing elective cardiac surgery. Calcium concentrations were determined by the OCPC method. Intima-media thickness (IMT) was measured manually (Image J software) in H&E stained sections. Gene expressions were analyzed by a Custom RT² Profiler PCR Array. Statistical significances were determined using the Holm-Sidak method, with $\alpha=5.000\%$.

Results: IMT was correlated with the calcium content of biopsies ($r=0.41$; $P<0.05$). Marked transcriptomic alterations were detected in the arteries of the CKD patients: Amongst 34 significantly regulated genes ($P<0.05-0.0001$), SP7 (osterix; ratio 4C/control: 247.5), NOS2 (35.8), RUNX2 (24.8), IL-10 (11.3), TNF (8.3) and TRPV6 (7.7) were upregulated, whereas COL1A2 (0.07), TIMP2 (0.26) and ENPP1 (0.31) were downregulated.

Conclusions: Arterial biopsies from children with stage 5 CKD show an increased calcium content and an upregulation of osteogenic proteins (VSMC and matrix), calcium-transporting proteins, inflammatory cytokines, and downregulation of calcification inhibitors. These findings most likely reflect an early stage of a CKD-specific calcifying arteriopathy.

TH-PO380

Capillary Rarefaction in Omental Biopsies of Children with CKD Uwe Querfeld,¹ Dorothea Burghardt,¹ Betti Schaefer,² Maria Bartosova,² Hamoud Nasser,¹ Bernd Lahrmann,³ Joan Nyarangi-Dix,⁶ Anja Lingnau,⁴ Claus Peter Schmitt.² ¹*Pediatric Nephrology, Charité, Berlin, Germany;* ²*Pediatric Nephrology, Univ of Heidelberg, Heidelberg, Germany;* ³*BioQuant TIGA Center, Univ of Heidelberg, Heidelberg, Germany;* ⁴*Pediatric Urology, Charite, Berlin, Germany;* ⁵*Pediatric Surgery, Charite, Berlin, Germany;* ⁶*Pediatric Urology, Univ of Heidelberg, Heidelberg, Germany.*

Background: Endothelial dysfunction in CKD could be related to a damaged microcirculation. We studied microvascular density in omental biopsies of children with CKD (stage 5) and in healthy age-matched controls.

Methods: Omental tissue was collected from 34 healthy children (0-18 years) undergoing elective abdominal surgery. In a case-control study, we selected 24 age-matched cases with stage 5 CKD from the biobank of the International Peritoneal Dialysis Network with stored omental tissue taken at the time of PD catheter insertion. Biopsies were analyzed by immunohistochemistry for capillary density (CD-31 antibody, Ab), autophagy (LC3A/B (D3U4C) XP® Rabbit mAb), apoptosis (Caspase-3-AK), VEGF-1 (Abcam, Rabbit) and VEGF-R-II expression (VEG Fr-2 (Flk-1)). Capillary density was measured by 2 trained observers with a digital microscope (BZ-9000 and Analyzer Software®) and fully automated with Nanozoomer Digital Pathology System and NDP Viewer Software (Hamamatsu Photonics, Japan).

Results: Capillary density was significantly reduced in CKD (median surface area 0.53% vs. 0.95%, $p<0.001$ in controls). This was confirmed by automatic imaging (0.89% vs. 1.17% $p=0.01$). Capillary density was inversely associated with age in uremic ($r=-0.88$, $p<0.0001$) and healthy children ($r=-0.63$, $p<0.0001$) and there was an inverse correlation between capillary density and serum BUN ($r=-0.53$, $p<0.05$), serum creatinine ($r=-0.58$, $p<0.05$), and hemoglobin ($r=-0.59$, $p<0.05$). VEGF-1 was reduced by 50% ($p<0.05$), but VEGF-R-II was not different ($p=0.89$). There were no differences in autophagy and apoptosis between groups.

Conclusions: Capillary density was significantly reduced in omental biopsies of children with stage 5 CKD and associated with diminished VEGF signaling. Capillary rarefaction could be an essential part of the cardiovascular pathology induced by CKD.

Funding: Clinical Revenue Support

TH-PO381

CD40 Silencing Reduces NF- κ B Activation and the Progression of Atherosclerotic Lesions in the ApoE^{-/-} Murine Model Miguel Hueso,¹ Laura De ramon,³ Estanislao Navarro,² Josep M. Cruzado,¹ J. Grinyo,¹ Joan Torras.¹ ¹*Nephrology, Hospital Bellvitge IDIBELL;* ²*Laboratori d'Oncologia Molecular, IDIBELL;* ³*Laboratori de Nefrologia Experimental, IDIBELL.*

Background: Chronic kidney disease (CKD) and inflammation are risk factors for atherosclerosis. In inflammatory states NF- κ B is frequently activated and the CD40/CD40L axis may be a link between inflammation, atherosclerosis and thrombosis. The goal of this work is to study the evolution of atherosclerotic lesions, inflammation and mRNA profiling in an animal model of hypercholesterolemia after CD40 silencing.

Methods: 35 APOE^{-/-} mice of 8 weeks old were sequentially euthanased (at 8, 10, 14 and 24 weeks of age). We compared a group treated with a siRNA against CD40 with a control group treated with a scrambled siRNA. Atherosclerotic lesions (red-oil, HE), number of macrophages (F4/80) and degree of NF κ B activation, in the aorta, were quantified. Furthermore, a mRNA profiling by microarray hybridization was performed.

Results: Silencing CD40 reduced the number (Control-14w:13.7 \pm 3%, siRNA-14w:7.7 \pm 4%, Control-24w:13.7 \pm 7%, siRNA-24w:8.8 \pm 5%, $p=0.015$) and the progression of lesions (Control-10w:0.10 \pm 0.09mm², siRNA-10w:0.01 \pm 0.02mm², Control-14w:0.27 \pm 0.21mm², siRNA-10w:0.18 \pm 0.12mm², Control-24w:0.68 \pm 0.061mm², siRNA-24w:0.33 \pm 0.16mm², $p=0.002$). SiRNA group displayed lower numbers of infiltrating macrophages ($p=0.04$) and a lower NF- κ B activation than controls ($p=0.026$). mRNA profiling detected 1996 genes up-regulated and 1285 genes down-regulated associated with the progression of lesions. CD40 silencing showed 190 genes up-regulated and 403 genes down-regulated. The analysis of these genes detected the enrichment of biological processes related with tissular remodeling, macrophage differentiation and apoptosis. CD40 silencing was associated with IFN- γ production, chronic inflammation, endothelial cell migration and apoptosis.

Conclusions: CD40 and NF- κ B were associated with the progression of atherosclerotic lesions in the APOE^{-/-} model.

Funding: Government Support - Non-U.S.

TH-PO382

Diabetic Cardiomyopathy Is Associated with Loss of Endothelial Glycocalyx in Coronary Microvessels Yan Qiu,¹ Kenton P. Arkill,² Gavin Iain Welsh,¹ Andy Salmon,¹ Rebecca R. Foster,¹ Paolo Madeddu,³ Simon C. Satchell.¹ ¹*Academic Renal Unit;* ²*School of Biochemistry;* ³*Bristol Heart Inst, Univ of Bristol, United Kingdom.*

Background: Endothelial glycocalyx (Glx) contributes to the microvascular permeability barrier and its dysfunction correlates with diabetic nephropathy. Microalbuminuria represents a major risk factor for cardiovascular disease in diabetes. We hypothesised the albuminuria associated with glomerular endothelial Glx damage in diabetes would be accompanied by coronary microvascular Glx dysfunction in diabetic cardiomyopathy (DCP).

Methods: CD1 and FVB mice were rendered diabetic with low doses of streptozocin (STZ) i.p. daily for 5 days. Echocardiography was applied to assess DCP by E/A ratio. A group of diabetic CD1 mice were treated with vitamin B₁ analogue Benfotiamine (BFT, 70mg/kg/d) after DCP development.

Results: Microvessels from diabetic CD1 heart had decreased MOA lectin binding at 16 weeks after the development of DCP. Recovered MOA intensity was associated with BFT's beneficial effect on DCP (Ctrl: 17.78 \pm 3.48; DCP: 2.53 \pm 1.24; DCP+BFT: 30.85 \pm 3.80, $p<0.05$, one-way ANOVA).

FVB mice showed increased albuminuria (7 fold) at six weeks after STZ injection ($p<0.001$, two-way ANOVA); developed DCP at 7 weeks after STZ injection ($p<0.01$, two-way ANOVA). Reduced MAL I lectin binding was noted in microvessels from diabetic FVB heart (DCP: 1.64 \pm 0.27; ctrl: 2.70 \pm 0.27, $p<0.05$, t test), but not MOA or SNA lectins. Electronic microscopy (EM) of 4%PFA-fixed paraffin-embedded heart sections stained with biotinylated MAL I and streptavidin-conjugated quantum dots indicated MAL I binding molecules localised on endothelial Glx. EM of capillaries from diabetic heart perfusion fixed with alcian blue and glutaraldehyde showed reduced Glx depth (DCP: 14.54 \pm 0.79; ctrl: 27.88 \pm 5.82 nm, $p<0.05$, t test).

Conclusions: These evidence suggest Glx damage is associated with DCP development. Recovered heart function with BFT treatment parallels with reversed Glx intensity. Identification of Glx with simpler technique is possible, i.e. specific lectins staining. Thus, correction of disarranged Glx may have therapeutic potential for DCP and other diabetic vascular complications, e.g. diabetic nephropathy.

Funding: Private Foundation Support

TH-PO383

Monocyte Subpopulations of Hemodialysis Patients Exhibit Distinct Changes of Cold Shock Y-Box Protein-1 Expression Lara Ewert,¹ Florian Gunnar Scurt,¹ Christos D. Chatzikirykou,¹ Sabine Brandt,¹ Peter R. Mertens.¹ *Nephrology, Hypertension, Diabetes and Endocrinology, Otto-von-Guericke Univ Magdeburg.*

Background: The cold-shock protein YB-1 is a ubiquitously-expressed RNA/DNA binding protein involved in proliferation, signal transduction, and inflammation. In monocytes YB-1 expression is regulated as part of the cellular differentiation process.

Upon acetylation YB-1 is secreted via a non-classical pathway, influencing inflammatory processes by acting as mitogen and chemokine. In dialysis patients prone to inflammations we investigated monocyte populations and their YB-1 content and degree of acetylation.

Methods: The monocyte phenotypes Mo1/Mo2/Mo3 were differentiated by flow cytometry with the surface marker CD14 and CD16. After permeabilisation and antibody staining intracellular content of acetylated and non-acetylated YB-1 was measured.

Results: In dialysis patients (n=63; 63±17 years; m 41; f 22) leukocyte numbers varied markedly (6,500 +/- 2,000/ul) while monocyte fractions were equal among control (n=100; 43±11 years, m: 59; f: 41) and patient cohorts. An analysis of the monocyte YB-1 content revealed that non-acetylated YB-1 was significantly lower in the dialysis cohort (healthy control: MFI 18000; dialysis cohort: MFI 12000, p<0,001), whereas the amount of acetylated YB-1 was increased in all three monocyte subpopulations in comparison with healthy controls (healthy control: MFI 4850; dialysis cohort: MFI 6700; p<0,001). Amongst the CD14 positive monocytes two distinct subpopulations could be assigned according to their YB-1_{acetyl} content (CD14⁺⁺YB-1_{acetyl}⁺; CD14⁺⁺YB-1_{acetyl}⁺⁺). In dialysis patients monocytes belonging to the CD14⁺⁺YB-1_{acetyl}⁺⁺ population were significantly more abundant. Notably, challenge with LPS (5 ng/ml for 2h) resulted in a major shift with loss of the CD14⁺⁺YB-1_{acetyl}⁺⁺ population.

Conclusions: Monocyte subpopulations and their YB-1 content are highly regulated and differ significantly between healthy controls and dialysis patients. The cold shock protein YB-1 undergoes acetylation in dialysis patients, which may causally linked to the pro-inflammatory state.

TH-PO384

Epoetin Beta Pegol Improves Endothelial Function in Diabetic Nephropathy Rats Even After Onset of Endothelial Dysfunction Ken-ichi Serizawa, Kenji Yogo, Yoshihito Tashiro, Ryohei Kawasaki, Michinori Hirata, Koichi Endo, Yasushi Shimonaka. *Product Research Dept, Chugai Pharmaceutical Co., Ltd., Japan.*

Background: Endothelial dysfunction is a powerful surrogate marker of cardiovascular events in nephropathy patients, and flow-mediated dilation (FMD) is a useful indicator of endothelial function in clinical settings. Epoetin beta pegol (continuous erythropoietin receptor activator, C.E.R.A.) is a drug for the treatment of renal anemia. In this study, we examined the ameliorating effect of C.E.R.A. on vascular endothelial function as evaluated by FMD in diabetic nephropathy rats.

Methods: Male Spontaneously Diabetic Torii rats (SDT, 22 wks old) were used as type-2 diabetic rats. Male Sprague-Dawley rats (SD) were used as age-matched control. C.E.R.A. (0.6, 1.2 µg/kg) was administered subcutaneously once every 2 wks for 8 wks. At 1 wk after last administration (31 wks old), we assessed endothelial function by FMD in the femoral arteries of anesthetized rats.

Results: Blood glucose level was over 500 mg/dL in SDT rats. FMD was significantly decreased in SDT rats before the start of C.E.R.A. treatment (22 wks old; SD, 16.2 ± 1.3%; SDT, 10.0 ± 1.3%; n = 8), and persisted to 31 wks old (SD, 17.8 ± 1.7%; SDT, 10.4 ± 1.8%; n = 7-8). C.E.R.A. dose-dependently improved FMD in SDT rats (31 wks old; C.E.R.A. 0.6 µg/kg, 17.0 ± 2.0%; C.E.R.A. 1.2 µg/kg, 19.2 ± 2.1%; n = 7-10) without lowering blood glucose. Endothelium-independent vasodilation by nitroglycerin and kidney function were not changed by C.E.R.A. treatment. Because long-term treatment with C.E.R.A. increased hemoglobin (Hb), we also examined the relationship between Hb up-regulation and FMD improvement in a separate experiment. We found FMD was not significantly improved 1 wk after single administration of C.E.R.A. (SD, 15.5 ± 1.6%; SDT, 10.8 ± 0.5%; C.E.R.A. 5 µg/kg, 12.5 ± 2.1%; n = 6-8), whereas Hb levels were comparable with those in long-term C.E.R.A. treatment.

Conclusions: These results demonstrated that C.E.R.A. improved endothelial function as evaluated by FMD in type-2 diabetic rats, even after onset of endothelial dysfunction, and these effects were exerted independently of the increasing shear stress induced by hematopoiesis.

Funding: Pharmaceutical Company Support - Chugai Pharmaceutical Co., Ltd.

TH-PO385

Determinants and Progression of Intimal and Medial Arterial Changes in Children with CKD Frida Dangardt, Devina Bhowruth, Daniela Thurn-Valsassina, Alicja Rapala, Marietta Charakida, Franz S. Schaefer, John Eric-Deanfield, Rukshana Shroff. *Vascular Physiology, UCL, London, United Kingdom.*

Background: In CKD, both intimal and medial arterial disease occur, and may have different risk factors. A novel imaging technique, very high resolution ultrasound (VHRUS) enables visualization of vessel wall layers separately. We hypothesize that vascular remodeling begins pre-dialysis, progresses on dialysis, and may be reversible after kidney transplantation, and these changes are due to modifiable pathophysiology.

Methods: Intimal (IT) and medial (MT) thickness of the carotid (CA), radial (RA) and dorsal pedal (DPA) arteries were measured by VHRUS (40-50MHz) in 54 children (19 pre-dialysis CKD, 20 on dialysis and 15 post-transplant) at baseline. One year follow up measurements were performed in 24 children (11 pre-dialysis CKD and 15 post-transplant). Conventional ultrasound (CUS) for CA IMT was measured.

Results: Children on dialysis for >1 year had greater CA and DPA MT compared to those on dialysis for <1 year (p = 0.007). In the CKD and dialysis cohort (n=39), higher CA MT at baseline was associated with increased serum phosphate (p<0.001, r=0.42) and PTH levels (p=0.03, r=0.27). No vascular measures were correlated to 25(OH)D, FGF23 or BMI. Renal transplant patients had better GFR and lower serum phosphate and PTH levels, but higher BP, BMI and lipid levels compared to the CKD or dialysis cohort (p<0.01 for all). Transplanted patients had higher CA and RA IT associated with higher lipid levels (p=0.02,

r=0.31). At 1-year follow-up transplanted children had a decrease in CA MT (p = 0.01) but not IT. Increased DPA IT in transplanted patients was associated with a higher systolic BP z-score (p = 0.2, r = 0.22). CA IMT by CUS did not reveal any significant changes.

Conclusions: VHRUS assessment of arterial morphology in CKD patients identified potentially modifiable risk factors for intimal and medial vascular disease that were not detected by conventional US. Differential thickening in media and intima in dialysis vs transplant patients suggests vascular remodelling in response to a changing cardiovascular risk factor profile after renal transplantation.

Funding: Private Foundation Support, Clinical Revenue Support, Government Support - Non-U.S.

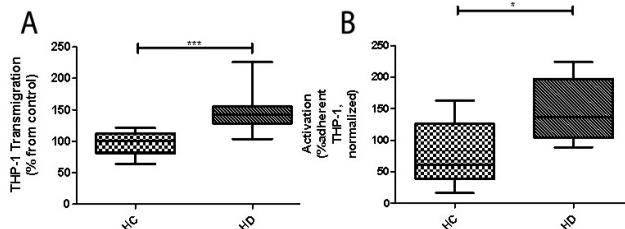
TH-PO386

Is Polymorphonuclear Leukocytes' Priming a Prerequisite for Monocyte Activation and Transmigration, Initiating the Atherosclerotic Process? Batya Kristal,² Eynav Kliger,¹ Galina Shapiro,¹ Ronit Geron,² Shifra Sela.¹ ¹Liachar Research Laboratory, Galilee Medical Center, Nahariya, Israel; ²Nephrology Dept, Galilee Medical Center, Nahariya, Israel.

Background: Endothelial dysfunction and monocytes transmigration underlie the development of atherosclerosis. Increased counts and priming of peripheral polymorphonuclear leukocytes (PMNLs) are associated with future or ongoing atherosclerosis, however, the role of PMNLs in the accelerated atherosclerotic process of hemodialysis (HD) patients is still unclear. We hypothesize that atherosclerosis is a circulatory disease, where circulating primed PMNLs activate monocytes and the endothelial layer, at the circulator. Our aims are to examine endothelial dysfunction, monocytes transmigration, post-transmigration activation and differentiation, induced ex-vivo by primed PMNLs (HD).

Methods: A unique ex-vivo co-cultivation system of 3 cells types was developed, enabling interaction among: primary endothelial cells (HUVEC), in-vivo primed PMNLs and monocytes (THP-1), mimicking the initiation of the atherosclerotic process. The interactions among these cells was examined at the cellular, protein and gene expression levels.

Results: THP-1 transmigration through pre-treated HUVEC with HD PMNLs showed a significant increase in: transmigration



A, post-transmigration activation, B compared to transmigration through HUVEC pre-treated with PMNLs from healthy subjects (HC). THP-1 transmigration correlates with the PMNLs counts and priming state. Pre-treatment with primed PMNLs induced higher MCP-1 expression (2-folds) in HUVEC.

Conclusions: The higher levels of monocytes transmigration, post-transmigration activation and endothelial MCP-1 expression mediated by primed PMNLs suggest a novel mechanism for the initiation of the atherosclerotic process, emphasizing the pivotal role of PMNLs in the initiation of the atherosclerotic process.

TH-PO387

The Effect of End-Stage Renal Disease (ESRD) on Differentiation of Circulating T Cell Subsets Eun hye Seo,¹ Chae ho Lim,¹ Seunghyun Lee,² Young-II Jo.¹ ¹Nephrology, Konkuk Univ Medical Center, Konkuk Univ School of Medicine; ²Dept of Microbiology, Konkuk Univ School of Medicine.

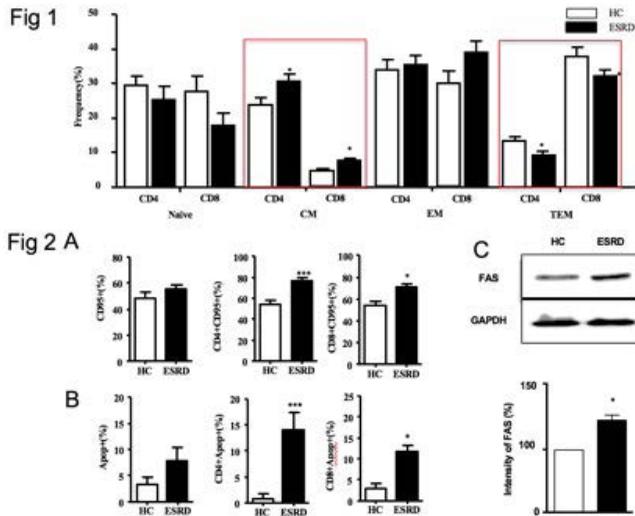
Background: Progressive loss of renal function is associated with a dysregulation of circulating T cells that may underlie their impaired T-cell immunity. However, it is not known how dysregulation of circulating T cells contribute to the ESRD-related immune deficiency. In this study, we investigated the ESRD-related changes in subsets and differentiation of circulating T cells in ESRD patients.

Methods: Adult ESRD patients on HD and healthy subjects were recruited. Peripheral blood mononuclear cells were collected and staining CD4, CD8, CD45RO, CCR7 and CD95(FAS). The frequency of apoptotic cells was calculated by scoring annexin-V binding cells after back-gating of CD4/CD8 T cells. CD95(FAS) protein levels were confirmed by Western blot analysis and Flow cytometry.

Results: A total of 20 adult ESRD patients on HD (male:female 12:8, DM 65%) and 17 healthy subjects (male:female 6:11) were enrolled. The ESRD patients revealed an increased frequency of CD4+CD25+ Treg and CD14+ cell compared with healthy subjects. However, the frequency of CD4+ and CD8+ T cells decreased in ESRD patients. (Figure. 1-A). Circulating of naive, central-memory(CM), effector-memory(EM), and terminal effector-memory(TEM) subsets of CD4+ and CD8+ T cells. The CD4+ and CD8+ TEM cell subsets showed a statistically significant decreased in ESRD patients (Figure. 1-B). In ESRD patients, the differentiation of effector memory CD8+ T cells increased (Figure 1), showing a significantly higher percentages of CD4+ TEM (8.7-12.3%, P<0.05) and CD8+ TEM cells (26.8-34.2%, P<0.05). The FAS and apoptosis level showed a statistically significant decreased in ESRD patients (Figure 2).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.



Conclusions: These results suggested that the T cell dysregulation may play a role in ESRD-related immune deficiency.

TH-PO388

CB1 Cannabinoid Receptor Antagonist Attenuates Cardiac Hypertrophy and Fibrosis in Experimental Chronic Kidney Disease *Yu-Juei Hsu, Sung-Sen Yang, Shih-Hua P. Lin. Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, Taipei, Taiwan.*

Background: Cannabinoid receptor type 1 (CB1R) has been shown to participate in the development of myocardial hypertrophy and fibrosis—two main pathological features of uremic cardiomyopathy. However, it remains unknown whether CB1R is involved in the pathogenesis of uremic cardiomyopathy. Here, we aimed to elucidate the role of CB1R in the development of uremic cardiomyopathy via modulation of Akt signalling.

Methods: The myocardial hypertrophy and fibrosis were evaluated by echocardiography and immunohistochemical staining, respectively, in 5/6 nephrectomy chronic kidney disease (CKD) mice treated with a CB1R antagonist. CB1R and fibrosis marker expression levels were determined by immunoblotting in cardiac tissue obtained from CKD mice and in H9c2 cells exposed to the uremic toxin indoxyl sulfate (IS), with an organic anion transporter 1 inhibitor or a CB1R antagonist or agonist. Akt phosphorylation was also assessed to examine the signaling pathways downstream of CB1R activation in both in vitro and in vivo models of uremic cardiomyopathy.

Results: CKD mice exhibited marked left ventricular hypertrophy and myocardial fibrosis, which were reversed by treatment with the CB1R antagonist. CB1R, collagen I, transforming growth factor (TGF)- β , and α -smooth muscle actin (SMA) expression showed time- and dose-dependent upregulation in H9c2 cells treated with IS. The inhibition of CB1R by either CB1R antagonist or small interfering RNA-mediated knockdown attenuated the expression of collagen I, TGF- β , and α -SMA in IS-treated H9c2 cells, while Akt phosphorylation was enhanced by CB1R agonist and abrogated by CB1R antagonist in these cells.

Conclusions: CB1R blockade attenuates LVH and Akt-mediated cardiac fibrosis in a CKD mouse model. Uremic toxin IS stimulates the expression of CB1R and fibrotic markers and CB1R inhibition exerts anti-fibrotic effects via modulation of Akt signalling in H9c2 myofibroblasts. Therefore, the development of drugs targeting CB1R may have therapeutic potential in the treatment of uremic cardiomyopathy.

TH-PO389

The CD4 T-Cell Response to Cytomegalovirus Targets the Endothelium and Is Linked to Increased Arterial Stiffness in ANCA Associated Vasculitis *Dimitrios Chanouzas, Matthew David Morgan, Lovesh Dyall, Jessica Anne Dale, Paul Moss, Lorraine Harper. Univ of Birmingham, United Kingdom.*

Background: Cytotoxic CD4+CD28- cells have been linked to cardiovascular disease (CVD) but their origin remains unclear. We previously showed that in ANCA associated vasculitis (AAV) these cells are only present in CMV seropositive patients and are independently linked with mortality. CVD is a leading cause of mortality in AAV. Here we have characterised CD4+CD28- cells in AAV and examined their relationship to central pulse pressure (cPP), a marker of arterial stiffness and CVD risk.

Methods: We phenotyped CD4+CD28- cells after overnight stimulation with CMV lysate via flow cytometry and measured cPP using the Vicorder device in 43 CMV+ AAV patients in remission. We stained for CX3CR1, the fractalkine receptor implicated in endothelial damage, and Tbet as Th1 cells are linked to atherogenesis. We used Mann Whitney U for between group comparisons, Spearman rank for correlations and multivariate regression to adjust for confounders.

Results: CD4+CD28- cells expressed Tbet and CX3CR1 and secreted large amounts of IFN γ after CMV lysate stimulation compared to CD4+CD28+ cells (15.7 vs. 0.5%, p<0.001).

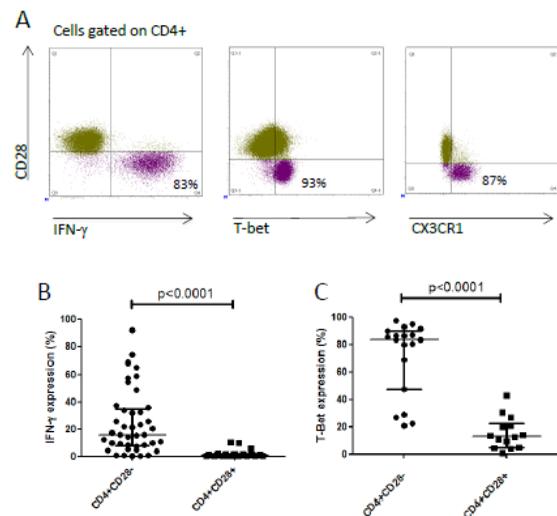


Figure 1 Peripheral blood mononuclear cells were stained after overnight stimulation with CMV lysate and analysed via flow cytometry. (A) Representative staining of IFN- γ , T-bet and CX3CR1 with CD4+CD28- cells shown in purple. (B, C) CD4+CD28- cells secrete significantly more IFN- γ and express significantly more T-bet after CMV lysate stimulation compared to their CD4+CD28+ counterparts.

The CD4+CD28- % correlated with IFN γ secretion after CMV lysate stimulation ($r=0.614, p<0.001$). The CMV specific CD4+CD28-IFN γ + percentage as well as absolute count correlated with cPP ($r=0.501, p=0.001$) and this persisted after controlling for age, gender, mean arterial pressure, urinary ACR and GFR (R square=0.58, B=0.13 (95%CI 0.05-0.21), $p=0.003$).

Conclusions: CD4+CD28- cells in AAV are proinflammatory, Th1, CMV specific cells, able to target the endothelium through expression of CX3CR1 and are independently associated with higher arterial stiffness, a risk factor for CVD. This opens therapeutic possibilities not only in AAV but also in CKD where CD4+CD28- cells are prevalent and linked to CVD.

Funding: Other NIH Support - This study was funded by the Wellcome Trust as part of a Research Training Fellowship awarded to Dimitrios Chanouzas.

TH-PO390

A Novel Interacting Molecule with AT1 Receptor, ATRAP, Inhibits Ang II-Induced Proliferative Activity and Oxidative Stress in Vascular Smooth Muscle Cells *Koichi Azuma,¹ Kouichi Tamura,² Takayasu Taira.¹ ¹Dept of Medical Science and Cardiorenal Medicine, Zenjinkai Group, Yokohama, Kanagawa, Japan; ²Dept Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.*

Background: Ang II influences the structure and function of vascular smooth muscle cells, and plays an important role in reactive oxygen species production. Superoxide anions are recognized as mediators of intracellular signaling cascades and are known to participate in cardiovascular diseases such as arteriosclerosis and hypertension. Previous studies reported that the production of superoxide is modulated by many factors including Ang II - AT1 receptor signaling. One of the major sources of superoxide in the aorta is NADPH oxidase located in the smooth muscle cells.

Methods: We cloned a novel molecule interacting with carboxy-terminal domain of AT1 receptor, which we named ATRAP (for AT1 receptor-associated protein), using the yeast two-hybrid strategy. In this study, we tested the hypothesis that vascular smooth muscle cells express ATRAP and that ATRAP attenuates Ang II-induced proliferative activity and oxidative stress in vascular smooth muscle cells. We used rat smooth muscle cells and used adenoviral gene transfer for ATRAP overexpression. We used real time PCR, ELISA of TGF- β , p22phox, Rac1, Nox1 and BrdU incorporation assay for cell proliferation.

Results: We identified that the ATRAP mRNA and protein were endogenously expressed in VSMC, and found a colocalization of ATRAP and AT1 receptor in Ang II-stimulated VSMC. The results of gain-of-function studies by adenoviral gene transfer demonstrated that overexpression of ATRAP significantly inhibited Ang II-mediated increases in c-fos gene transcription, BrdU incorporation, and mRNAs expression of NADPH oxidase complex.

Conclusions: These results indicate that ATRAP significantly attenuates Ang II-mediated proliferative activity and oxidative stress in vascular smooth muscle cells, and suggests a novel strategy to inhibit cardiovascular disease such as arteriosclerosis and hypertension.

TH-PO391

Myostatin: A Playmaker in Chronic Kidney Disease and Vascular Damage
 Daniela Verzola,¹ Giacomo Garibotto,¹ Maria bianca Bertolotto,² Samantha Milanese,¹ Barbara Villaggio,¹ Jan Lindeman,³ Giorgio Ghigliotti,⁵ Claudio Brunelli,⁵ Pietro Ameri,⁵ Domenico Palombo,⁴ Chiara Barisione.⁵ *1*Div Nephrology, Genoa Univ; *2*1st Clinic of Internal Medicine, Univ of Genoa -IRCCS A.U.O. San Martino-IST; *3*Dept Vascular Surgery, LUMC, Leiden, the Netherlands; *4*Unit of Vascular and Endovascular Surgery Univ of Genoa; *5*Research Centre of Cardiovascular Biology Univ of Genoa, Italy.

Background: Patients with abdominal aortic aneurysms (AAA) have higher prevalence of chronic kidney disease (CKD), that may contribute to arterial deterioration in a mutual detrimental feedback. Myostatin (Mstn), a TGF- β family member with cell-cycle inhibitory effects, is up regulated by CKD, but its role in vascular remodeling is unexplored. We hypothesized that Mstn may play a role in the progression of vascular damage.

Methods: In human AAA(N=8), non aneurysmatic atherosclerotic lesions (NAAL) samples(N=7) and normal abdominal aortas (N=3): RT-PCR for Mstn and Smoothelin, a protein with contractile function (Smtn), immunostaining for Mstn, Smtn, CD45 and α SMA. In vitro studies: A7R5 vascular smooth muscle cells (VSMC) and human monocytes exposed to normal sera (NS), sera from patients with AAA (AAAS) or Mstn (500 ng/ml) for 48 hours. VSMC: proliferation, rt-PCR for Mstn and Smtn. Human monocytes: rt-PCR for Mstn, α -SMA and MCP-1 dependent chemotaxis.

Results: Mstn mRNA was overexpressed (by 8 folds, $p<0.05$) in AAA. Mstn immunostaining was also higher in AAA and NAAL and associated with downregulated Smtn ($p<0.05$). Mstn colocalized with VSMC (α SMA) and leukocytes (CD45). In A7R5, AAAS upregulated Mstn and downregulated Smtn ($p<0.05$); Mstn exposure decreased Smtn and cell proliferation. In monocytes, AAAS upregulated Mstn and α -SMA and Mstn increased α SMA and chemotaxis ($p<0.01$).

Conclusions: Our data suggest that Mstn is overexpressed in atherosclerotic lesions at sites of leukocyte infiltration and de-differentiated VSMCs. Unrecognized circulating factors in AAA patients enhance Mstn expression in VSMCs and monocytes. In turn, Mstn leads to VSMCs dedifferentiation, blunting their contractile function. In addition, Mstn activates monocytes, contributing to the inflammatory milieu in the aortic wall.

TH-PO392

Carbamylation of Plasma Proteins in Children with Chronic Kidney Disease
 Christine Pietremont,¹ Anja Christine Sander,³ Stephane Jaisson,² Laetitia Gorisse,² Philippe Gillery,² Uwe Querfeld, Franz S. Schaefer.³ *1*Pediatric Dept, Nephrology Unit, Univ Hospital of Reims, Reims, France; *2*Laboratory of Pediatric Biology and Research, Univ Hospital of Reims, Reims, France; *3*Div of Paediatric Nephrology, Center for Pediatric and Adolescent Medicine, Heidelberg, Germany.

Background: In adults with ESRD, Hcitr concentration predicts increased CV risk and mortality. In adults with CKD and ESRD, CV morbidity and mortality are affected by traditional risk factors which tend to override effects of uremia such as carbamylation due to enhanced post-translational carbamylation of lysine and homocitrullin formation. Such mechanisms may be sensitively studied in children with CKD. Here, we analyzed plasma Hcitr levels in a large cohort of children with CKD followed as they progressed to RRT.

Methods: Plasma Hcitr concentrations were analysed, by mass spect, in 114 6 to 17 yo children from the 4C (Cardiovascular Comorbidity in Children with CKD) Study cohort with CKD stages 3-5 both cross-sectionally and longitudinally when treatment modality changed to dialysis (n=55) or transplantation (n=59). Factors predicting the change in Hcitr were analyzed by multivariate linear modeling.

Results: Hcitr concentrations were independent of age but correlated with eGFR ($r=-0.56$, $p<0.0001$) urea ($r=0.61$, $p<0.0001$) and albumin ($r=0.36$, $p=0.0001$) successively increasing from 277 ± 86 mmol/mol Lys in CKD3 to 634 ± 527 in CKD5. Hcitr levels declined by an average of 14.6 % after initiation of dialysis, and by 58.1% after transplantation ($p<0.0001$). When adjusting for baseline levels, Hcitr concentrations decreased significantly more markedly in patients starting peritoneal dialysis (PD) than in those starting hemodialysis (HD) (-106 ± 226 vs. -52 ± 169 mmol/mol Lys, $p<0.05$).

Conclusions: Hcitr is strongly inversely correlated to eGFR and urea. Dialysis only partially compensates for the continued carbamylation process, although continuous PD appears to lower Hcitr more efficiently than intermittent HD. After transplantation Hcitr concentrations rapidly decrease to the range observed in CKD stage 3. Further studies are underway to analyze the role of protein carbamylation for the early occurrence of intermediate CV endpoints in this pediatric population.

Funding: Government Support - Non-U.S.

TH-PO393

Effect of Far Infrared Radiation on Platelet Adhesion to Human Umbilical Vein Endothelial Cells
 Wen-Yi Chen,¹ Daw-yang Hwang,² Ke-Li Tsai,¹ Shang-Jyh Hwang.^{2,3} *1*Dept of Physiology, Kaohsiung Medical Univ, Kaohsiung, Taiwan; *2*Division of Nephrology, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; *3*Faculty of Renal Care, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Far-infrared Radiation (FIR) is an invisible electromagnetic waves with wavelength between 3-1000mm. FIR has multiple effects on the cardiovascular system, including increasing eNOS and heme oxygenase-1 (HO-1) expression in the endothelial cells. FIR improves dialysis fistulas function in hemodialysis patients with impaired endothelial function. Activation of thromboxane A2 receptor (TBXA2R) increases von

Willebrand factor (vWF) expression and release, which lead to increased platelet adhesion to endothelial cells and vascular thrombosis. We hypothesize that FIR may reduce TBXA2R expression and decrease platelet adhesion to endothelial cells.

Methods: Cultured HUVECs were treated with or without FIR radiation for 30 minutes. Cells were harvested and total RNA was extracted for RNA-Seq. Total protein expressions of TBXA2R were assessed by western blot. To examine platelet-HUVEC interactions, we labeled platelet with calcein AM and co-cultured calcein AM-labeled platelet with FIR-treated or controlled HUVECs followed by fluorescence microscopy analysis.

Results: The RNA-Seq results showed increased RNA expression in 665 genes and decreased RNA expression in 1,428 genes. There were 34 pathways of genetic expressions were significant different. Nineteen genes were involved in platelet aggregation (including GNA12, F2RL2, TBXA2R) after FIR radiation. Significant decreases in TBXA2R protein levels were observed after FIR radiation. The platelet binding to HUVEC cells was significantly less in the FIR-treated versus control.

Conclusions: These data suggest that FIR irradiation reduced TBXA2R RNA and protein expressions with decreased platelet adhesion to HUVECs. Our result may provide further mechanisms of FIR in the prevention of thrombus formation.

Funding: Clinical Revenue Support

TH-PO394

Vitamin D Analogs-Induced Ectodomain Shedding of Tumor Necrosis Factor Receptor 1 as an Anti-Inflammatory Action
 Su-Kil Park, Won Seok Yang. *Div of Nephrology, Univ of Ulsan, Asan Medical Center, Seoul, Republic of Korea.*

Background: 1,25-Dihydroxyvitamin D₃ (1,25D₃), causes a disintegrin and metalloprotease 10 (ADAM10)-mediated ectodomain shedding of tumor necrosis factor receptor 1 (TNFR1) in human aortic smooth muscle cells (HASMCs) and thereby decreases responsiveness of the cells to TNF- α . In this study, we examined the potencies of other vitamin D₃ and D₃ analogs to induce ectodomain shedding of TNFR1 in HASMCs.

Methods: TNFR1 was measured by Western blot. Intracellular Ca²⁺ was measured using Fluo-4 AM. ADAM10 was localized by immunofluorescence staining.

Results: 25-Hydroxyvitamin D₃ (25D₃) and elocalcitol (an analog of 1,25D₃) caused ectodomain shedding of TNFR1 at 30 min in a dose-dependent manner, whereas 1,25-dihydroxyvitamin D₂ (1,25D₂) and paricalcitol (a derivative of 1,25D₂) did not. Both 25D₃ and elocalcitol rapidly induced extracellular Ca²⁺ influx and caused a marked increase in intracellular Ca²⁺, which was blocked by verapamil, an L-type Ca²⁺ channel inhibitor. In contrast, 1,25D₂ and paricalcitol caused only small increases in intracellular Ca²⁺. 25D₃- and elocalcitol-induced TNFR1 ectodomain sheddings were abolished by verapamil and in Ca²⁺-free media. Both 25D₃ and elocalcitol caused the translocation of ADAM10 to the cell surface, which was inhibited by verapamil, while 1,25D₂ and paricalcitol did not cause ADAM10 translocation. Depletion of ADAM10 by ADAM10-siRNA prevented 25D₃- and elocalcitol-induced ectodomain shedding of TNFR1. 1,25D₂ and paricalcitol did not antagonize, but rather increased 1,25D₃-induced ectodomain shedding of TNFR1.

Conclusions: In summary, both 25D₃ and elocalcitol caused ADAM10-dependent ectodomain shedding of TNFR1, whereas 1,25D₂ and paricalcitol did not. This was due to the differences in the potency to induce extracellular Ca²⁺ influx. By causing TNFR1 ectodomain shedding and thereby decreasing responsiveness to TNF- α , vitamin D₃ analogs may regulate inflammatory response of vascular smooth muscle cells.

TH-PO395

Effect of Mycophenolate Mofetil on Cytokine Release and Cholesterol Transport in Different Subsets of Polarized Macrophages
 Joseph Mattana, Nobuyuki (Bill) Miyawaki, Isaac Teboul, Iryna Voloshyna, Allison B. Reiss. *Medicine, Winthrop-Univ Hospital, Mineola, NY.*

Background: Patients with systemic lupus erythematosus (SLE) have a 5-9 fold increased incidence of cardiovascular disease (CVD). Lupus nephritis is commonly treated with mycophenolate mofetil (MPA). We examined the effect of MPA on cytokine release and expression of the proteins involved in cholesterol transport in M0, M1 and M2 human macrophages (M Φ).

Methods: THP-1 human monocytes were differentiated to a non-polarized phenotype (M0) (100nM PMA) and then incubated \pm MPA (0.5, 1, 5, 10 and 20mg/ml). Supernatants were collected and level of IL-10, IFN- γ and TNF- α were analyzed. M0 were then incubated with 20 ng/ml interferon- γ +100 ng/ml LPS to obtain M1 or 20 ng/ml IL-4 to obtain M2 subsets. M0, M1 and M2 M Φ were incubated \pm MPA (0.5, 1, 5mg/ml). Total RNA and protein were isolated. Expression of the major proteins involved in cholesterol transport, ABCA1, CD36 and SRA1, were evaluated by real-time PCR and confirmed with Western blot. Foam cell formation (FCF) was assessed by incubating \pm 50 mg/ml oxLDL and Oil-red-O staining.

Results: MPA decreased release of IFN- γ and TNF- α at 1mg/ml. At 5mg/ml level of cytokines was as in untreated cells and higher concentrations (10 and 20mg/ml) increased cytokine release up to 1.5 and 1.6 fold. In M0 M Φ MPA increased expression of ABCA1 (reaching 1.83 ± 0.07 at 5mg/ml) and decreased expression of CD36 and SR-A1 to 0.75 ± 0.03 , 0.6 ± 0.08 , respectively (n=3, $P<0.05$). FCF was decreased 0.75 times at 1mg/ml but returned to the level of untreated cells at 5mg/ml. In M2 M Φ MPA displayed a significant effect only on SR-A1 decreasing its expression to 0.7 ± 0.04 at 5mg/ml. Effect of MPA on M1 M Φ was contradictory to other subtypes, reducing ABCA1 (0.71 ± 0.04) and augmenting CD36 and SR-A1 expression (2.4 ± 0.1 and 1.9 ± 0.08 at 5mg/ml, respectively). Accordingly, FCF was enhanced 1.5 times at 5mg/ml.

Conclusions: MPA has effects on MΦ cytokine release and cholesterol handling which are dependent on MΦ subtype and concentration. These effects may be important in modifying atherogenesis in patients with SLE and may have relevance in kidney transplantation as well.

Funding: Other NIH Support - 5
NCCAM R21 AT007032 02 Allison B. Reiss

TH-PO396

Mitochondria Derived Reactive Oxygen Species and Microvascular Dysfunction in Chronic Kidney Disease Danielle L. Kirkman,¹ Meghan G. Ramick,¹ Bryce J. Muth,¹ Raymond R. Townsend,² David G. Edwards.¹ ¹Kinesiology and Applied Physiology, Univ of Delaware; ²Clinical and Translational Research Center, Univ of Pennsylvania.

Background: Endothelial dysfunction in chronic kidney disease (CKD) is characterized by reduced nitric oxide bioavailability as a consequence of oxidative stress. Damaged and dysfunctional mitochondria as a result of CKD are likely a large contributor to reactive oxygen species. The aim of this study was to determine if mitochondria derived reactive oxygen species contribute to impairments in nitric oxide mediated microvascular function in CKD.

Methods: Cutaneous vasodilation in response to local heating was assessed in 8 CKD patients (age:67±7 years; eGFR:48±11 ml/kg/1.73m²) and 8 matched healthy individuals (age:60±6 years; eGFR:91±11 ml/kg/1.73m²). Participants were instrumented with 2 intradermal microdialysis fibers for the infusion of 1) Ringers solution and 2) mitochondria specific superoxide scavenger mitoTempo. Skin blood flow in response to local heating (42°C) was assessed at the microdialysis sites by laser-Doppler flowmetry. Cutaneous vascular conductance (CVC) was calculated as a percentage of the maximum CVC achieved during sodium nitroprusside infusion at 43°C.

Results: CVC was attenuated in CKD patients compared to healthy controls (86±5 vs 95±3%; *p*<0.01). MitoTempo significantly improved CVC in CKD patients (CKD Ringers vs CKD MitoTempo: 86±5 vs 93±6; *p*<0.05) to levels similar to that of healthy controls (CKD MitoTempo vs Healthy Ringers: 93±6 vs 95±3; *p*=0.67).

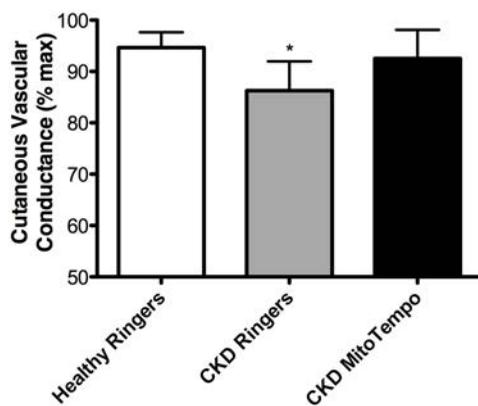


Figure 1. Cutaneous vascular conductance in response to local heating. **p*<0.05 vs Healthy Ringers and CKD MitoTempo.

Conclusions: MitoTempo improved cutaneous microvascular function in CKD patients suggesting that mitochondria derived reactive oxygen species play a role in microvascular dysfunction in CKD. Improving mitochondria health and reducing mitochondria derived oxidative stress may be a potential therapeutic target for improving endothelial function in CKD.

Funding: Other NIH Support - National Heart Lung and Blood Institute R01HL113514

TH-PO397

Indolic Uremic Solutes-Aryl Hydrocarbon Receptor-Tissue Factor: A Novel Uremic Thrombosis Axis and Aryl Hydrocarbon Receptor as an Emerging Antithrombotic Target Moshe Shashar, Laith Al-Rabadi, Mostafa Belghasem, Lawrence Prince-Wright, Jamaica Siwak, Jean M. Francis, Vipul C. Chitalia. Renal Section, Boston Medical Center, Boston, MA.

Background: Thrombosis, a highly prevalent complication in CKD patients, remains an area of high unmet clinical need with poorly defined pathogenesis. While recent work has implicated indolic uremic solutes as potent prothrombotic toxins acting through Tissue Factor (TF), a procoagulant protein, it also uncovered Aryl Hydrocarbon Receptor (AHR) as a key mediator of this regulation and a druggable target for thrombosis. Since AHR blockers (AHRBs) inhibited thrombosis in uremic milieu, we hypothesized that inhibition of AHR activity destabilizes TF through its ubiquitination.

Methods: Sera from 25 ESRD patients on hemodialysis matched with controls were used. RNA silencing oligos to carboxy terminus of *hsc70-interacting protein* (CHIP), full-length and a truncation of TF and full-length CHIP were expressed in various cell lines. Tissue factor expression and activity were examined using western blotting and a surface procoagulant activity assay, respectively.

Results: Our data showed that TF ubiquitination is inhibited in uremic milieu, a process substantially restored by AHRBs. The kinetic profile of this regulation suggested

a post-translational mechanism. AHR is known to interact with CHIP, a RING-finger E3 ubiquitin ligase, and thus we posited that CHIP regulates TF ubiquitination. Binding and immunofluorescence studies supported an interaction of CHIP and TF in the cytosol. Deletion of the intracellular domain of TF substantially abrogated the interaction with CHIP suggesting that CHIP binds at the intracytosolic tail of TF. CHIP knock-out and silenced cells showed both significantly elevated TF expression and activity and prolonged TF half-life in uremic milieu supporting CHIP's role as an E3 ligase of TF.

Conclusions: Our data suggest CHIP as a candidate E3 ligase of TF and raise a tantalizing possibility of AHRBs regulating TF ubiquitination and thrombosis through CHIP. While supporting a novel post-translational regulation of TF, this work in future will unveil a potential mechanism of action of AHRBs, an emerging class of anti-thrombotics in CKD.

Funding: Private Foundation Support

TH-PO398

APOL1-B3 G2 Risk Variant Perturbs Cholesterol Homeostasis in THP-1 Macrophages Alex Dinh,¹ Hidefumi Wakashii,¹ Jurgen Heymann,¹ Alessia Fornoni,² Jeffrey B. Kopp.¹ ¹NIDDK, NIH, Bethesda, MD; ²Dept of Medicine, Univ of Miami, Miami, FL.

Background: Apolipoprotein L1 (APOL1) circulates in human plasma bound to high-density lipoprotein (HDL). APOL1 G1 and G2 variants increase the risk of developing chronic kidney disease. We examined differences in cholesterol homeostasis in THP-1 macrophages stably expressing G0 and G2 variants of the APOL1-B3 (intracellular) isoform.

Methods: THP-1 cells were stably transfected with the G0 or G2 APOL1-B3 variants or an empty vector, and activated with phorbol myristate acetate (PMA) for 3 days. For cholesterol efflux assays, cells were incubated with 1 μCi/mL [3H]-cholesterol for 24 h. Efflux ligands were added to the media for 4 h, after which [3H]-cholesterol in media and cells was quantified. For amphotericin B lysis, cells were exposed to amphotericin B for 5 h. Cell viability was assessed using the CellTiter-Glo luminescent assay. To generate foam cells, THP-1 cells were stimulated with PMA for 2-3 d and incubated with 20 mg/ml oxidized LDL for 18 h. Cells were stained with Oil Red O.

Results: THP-1 macrophages expressing the APOL1-B3 G2 variant exhibited increased survival compared to cells expressing the APOL1-B3 G0 variant at amphotericin B concentrations of 10 mg/ml (93.2%±2.6% vs 79.4%±2.6%), 100 mg/ml (52.4%±0.3% vs 30.8%±0.5%), and 250 mg/ml (11.0%±0.8% vs 8.0%±1.1%), all *p*<0.01. Cells expressing the APOL1-B3 G2 variant had increased cholesterol efflux compared to cells expressing the APOL1-B3 G0 variant (25.2%±3.5% vs 11.6%±5.6%, *p*<0.05). Following incubation with oxidized LDL, APOL1-B3 G2 expressing cells had qualitatively less Oil Red O staining compared to APOL1-B3 G0 expressing cells, indicating a relative decrease in neutral lipid uptake.

Conclusions: Stable expression of the APOL1-B3 G2 risk variant in THP-1 macrophages increased cholesterol efflux and decreased neutral lipid content compared to APOL1 G0 cells, which could lead to cellular cholesterol depletion. This finding may explain the observed protective effect of APOL1 risk variants on cardiovascular mortality in African Americans with type 2 diabetes, a disease characterized by decreased cholesterol efflux and increased propensity to form foam cells.

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TH-PO399

Indoxyl Sulfate-Induced Endothelial Microparticles Stimulate Vascular SMC Proliferation and Neointimal Hyperplasia Formation Through TGF-β Induction Jung-hwa Ryu, Shina Lee, Dong-Ryeol Ryu, Duk-Hee Kang, Kyu Bok Choi, Seung-Jung Kim. Internal Medicine, College of Medicine, Ewha Womans Univ, Seoul, Republic of Korea.

Background: Vascular access stenosis occurs frequently and predominantly as a result of neointimal hyperplasia formation caused by vascular smooth muscle cell (SMC) proliferation. Previous reports showed that endothelial microparticle (EMP) is closely associated with vascular dysfunction and atherosclerosis. In this study, we investigated the effects of EMP on TGF-β signaling and its association with proliferation of vascular SMC and neointimal hyperplasia formation.

Methods: To produce EMPs, HUVECs were stimulated by indoxyl sulfate (IS). IS-induced EMPs were collected by ultracentrifugation of culture media and sorted by flow cytometry. Human aortic SMCs (1.0x10⁶) were treated by EMPs of 2x10⁶ particles. Western blot analysis was done for Akt, ERK1/2, p38 MAPK, and Smad3. SMC proliferation was measured by BrdU cell proliferation assay. TGF-β production was measured by PCR and ELISA. Porcine internal jugular veins were cultured *ex vivo* in the presence of EMPs for 12 days, and immunohistochemistry for TGF-β and phospho-specific TGF-β signaling was done.

Results: EMPs stimulated the proliferation of aortic SMCs in a dose-dependent manner. EMPs induced TGF-β secretion from aortic SMCs as well as the phosphorylation of its down-stream signaling molecules including Akt, ERK1/2, p38 MAPK, and Smad3. The proliferation of aortic SMCs and the phosphorylation of the signaling molecules were significantly reduced by anti-TGF-β neutralizing antibody. In *ex vivo* culture of porcine internal jugular veins, neointimal hyperplasia was significantly developed in EMP-treated venous tissues. The expression of TGF-β and the phosphorylated signaling molecules were significantly up-regulated in the area of neointimal hyperplasia.

Conclusions: IS-induced EMPs stimulated the proliferation of vascular SMCs and the production of TGF-β by vascular SMCs, and the proliferation of these cells was mediated by TGF-β. Accordingly, EMPs induced neointimal hyperplasia formation and TGF-β expression in cultured venous tissue. Further investigation is needed to demonstrate the role of EMPs on vascular access stenosis.

TH-PO400

Inflammation, Apoptosis, Fibrosis and Vascular Calcification in a Model of Balloon Injury in Rats with Chronic Kidney Disease Artur P. Mendes. *ISNI, CHLO, Lisboa, Portugal.*

Background: Cardiovascular disease (CVD) is more prevalent and has a worse prognosis in chronic kidney disease (CKD) patients than in the general population and is the leading cause of morbimortality in those patients. Not only traditional risk factors of CVD but also uremia-related ones like inflammation, fibrosis and mineral disorder may contribute to the poor CVD prognosis.

Methods: We developed a model of accelerated vasculopathy in rats with CKD to study the vascular damage in CKD: inflammation, apoptosis, fibrosis and vascular calcification. The animal model consisted of inducing a balloon injury (BI) with angioplasty in the carotid arteries (CA) of 5/6 nephrectomy rats and compare the lesion with non-CKD rats (NR). We used 24 Wistar rats.

Results: We analyzed the normal and injured CA of NR and CKD rats with histology, immunohistochemistry (IH) and RT-PCR, 1 week after the BI. With HE, we saw similar intimal hyperplasia in the CA with BI in both groups. With Masson trichrome and sirius red we observed connective tissue mainly in adventitia layer. With IH for fibronectin we saw abundant expression in hyperplasia areas of the intima of the CA submitted to BI. The expression in the media layer was higher in CKD than NR. In cellular proliferation studies with Mib1 Ab we also appreciated a higher expression of the Ab in the neointima of CKD rats. In IH for activated caspase 3 no expression was noticed in both groups. In the anti-CD68 Ab study we could see macrophages mainly in the adventitia layer of injured CA of the CKD rats than on the NR. We didn't observe tissue calcification with Von Kossa staining in any group. In the RT-PCR studies there were more type 1 collagen and fibronectin in the injured CA than in the non injured CA of the NR, as expected, but also more type 1 collagen and fibronectin in the non injured CA of the CKD rats than in the NR and much more in the injured CA of CKD rats.

Conclusions: In a model of accelerated vasculopathy we have shown a more intense activation of the inflammation and fibrosis pathways in the CKD rats than in NR.

TH-PO401

Post-Transcriptional Guidance of Monocyte to Macrophage Differentiation by the RNA-Binding Protein Quaking Jurrien Prins, Ruben de Bruin, Janine van Gils, Ton J. Rabelink, Anton Jan Van Zonneveld, Eric P. van der Veer. *Nephrology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands.*

Background: Kidney injury is associated with excessive recruitment and influx of monocytes to sites of tissue damage and their ensuing differentiation into macrophages. This differentiation is associated with a striking increase in protein expression levels of the RNA-binding protein Quaking (QKI). We therefore set out to investigate the role of QKI in monocyte and macrophage function.

Methods: Monocytes expressing an shRNA against QKI were studied for their capacity to adhere, migrate and differentiate into macrophages. RNA-seq and microarray analysis of human monocytes and macrophages, including those of a unique QKI haploinsufficient patient, was performed to identify QKI-mediated splicing events. Identified splice variants of the actin capping protein γ -Adducin were validated using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK⁻) was performed and analysed.

Results: Specific depletion of QKI protein significantly impaired monocyte adhesion, migration and differentiation into macrophages in vitro. RNA-seq and microarray analysis revealed 571 and 629 splicing events in monocytes and macrophages, respectively. One such event was the inclusion of a cassette exon in γ -Adducin, which occurred after depletion of QKI protein, and was found to reduce monocyte migration when ectopically expressed. UUO in hypomorphic QK⁻ mice revealed a two-fold reduction in macrophage markers (F4/80 and CD115) and decreased interstitial collagen deposition compared to controls.

Conclusions: We show that QKI post-transcriptionally guides monocyte and macrophage function in vitro and in vivo, partially by mediating alternative splicing of pre-mRNA targets of QKI such as γ -Adducin. The reduced infiltration of monocytes and ensuing differentiation into macrophages, and deposition of interstitial collagen observed in a UUO model in QK⁻ mice identifies QKI as a novel target for therapeutic intervention in renal and inflammatory disease.

TH-PO402

Induction of Autophagy and Its Role in Endothelial Cell Injury in Response to Carbamylated Low-Density Lipoprotein (cLDL) Chhanda Bose,^{1,2} Sudhir V. Shah,^{1,2} Oleg K. Karaduta,^{1,2} Alexei G. Basnagian,^{1,2} Gur P. Kaushal.^{1,2} *¹Dept of Internal Medicine, Div of Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR; ²Medicine Service, Renal Section, Central Arkansas Veterans Healthcare System, Little Rock, AR.*

Background: We and others have demonstrated that plasma levels of carbamylated proteins are elevated in CKD patients and that they are significant predictors of cardiovascular events and all-cause mortality. Autophagy is a highly conserved process of protein and organelle degradation and is involved in regulation of cellular injury. Its induction and role in endothelial cell injury in response to cLDL has not been examined.

Methods: A time course (for up to 24 hours) and concentration dependence of cLDL (0 μ M to 500 μ M) was performed for autophagy measurements. The effect of cLDL on autophagy was evaluated by increased formation of punctate immunofluorescence staining of GFP-LC3-II from GFP-LC3-1 following transfection with GFP-LC3 plasmid

and conversion of LC3-I to LC3-II as determined by western blot. The effect of inhibition of cLDL-induced autophagy on cell death and DNA fragmentation was determined using 5mM 3-methyladenine (3-MA) and chloroquine. DNA fragmentation will be measured by a TUNEL assay.

Results: Carbamylated LDL treatment of human coronary artery endothelial cells (HCAECs) increased LC3-II punctate dots in a dose- and time-dependent manner. Autophagy induction in response to cLDL was observed by conversion of LC3-I to LC3-II by western blot. The formation of cLDL-induced LC3-II vesicles were markedly inhibited by 3-MA. These studies provide the first evidence that cLDL increases LC3-II protein and autophagosome formation in endothelial cells. The autophagy inhibitor 3-MA suppressed cLDL-induced LDH release, EndoG activation, and DNA fragmentation, suggesting that inhibition of cLDL-induced autophagy provides a cytoprotective role against EndoG activation and cell death in HCAECs.

Conclusions: HCAECs respond to cLDL by induction of autophagy in a dose- and time- dependent manner, and inhibition of cLDL-induced autophagy is cytoprotective against cLDL-induced cell death, DNA fragmentation, and EndoG activation.

Funding: Veterans Administration Support

TH-PO403

Fractalkine Receptor CX3CR1 on Bone Marrow Derived Cells Is Required for Excess Atherosclerotic Inflammation in Renal Impairment Shuwang Ge, Johannes Nordlohne, Barbara Hertel, Hermann G. Haller, Sibylle Von Vietinghoff. *Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.*

Background: Reduced kidney function is an important risk factor of aggravated atherosclerosis. Inflammatory leukocytes are attracted to the lesion and regulate lesion growth and composition. Fractalkine receptor CX3CR1 is highly expressed on peripheral blood leukocytes, but also resident vascular cells such as smooth muscle cells. This study investigated the role of CX3CR1 in atherosclerotic inflammation a mouse model with moderate renal impairment.

Methods: Apolipoprotein E (ApoE^{-/-}) and LDL receptor (LDLR^{-/-}) deficient mice underwent unilateral nephrectomy or sham surgery and were maintained on high-fat diet. Bone marrow transplantation was conducted after lethal irradiation. Aortic lesion size was quantified macroscopically and histologically in the aortic root and leukocyte infiltration determined by microscopy and flow cytometry.

Results: ApoE^{-/-} mice without CX3CR1 were protected from increased aortic atherosclerotic lesion size and macrophage accumulation in renal impairment. LDLR^{-/-} mice were similarly protected. Renal impairment increased CX3CR1 expression on aortic macrophages. Conversely, in renal impairment, aortic macrophage numbers were significantly decreased in the absence of CX3CR1. In mixed chimeric mice, absence of CX3CR1 on bone marrow cells only sufficed to decrease atherosclerotic macrophage numbers and aortic root lesion size in renal impairment.

Conclusions: CX3CR1 was instrumental in enhanced atherosclerosis in renal impairment. This effect was beyond the CX3CR1 effect observed in normal renal function suggesting that CX3CR1 inhibition should be investigated as a targeted treatment approach in this high-risk group.

TH-PO404

Afferent Arteriolar Endothelial-Dependent Dysfunction Precedes Radiation-Induced Nephropathy and Hypertension John D. Imig,¹ Eric P. Cohen.¹ *¹Medical College of Wisconsin; ²Univ of Texas Southwestern.*

Background: Chronic kidney disease (CKD) occurs in 15% of hematopoietic stem cell transplant (HSCT) patients, and has been clearly linked to irradiation at the time of the HSCT. Radiation nephropathy is expressed in rats and in humans as azotemia and hypertension. There is a latent period of 6-8 weeks after irradiation to the development of proteinuria, azotemia, and hypertension in rats. We tested the hypothesis that afferent arteriolar responses to the endothelial-dependent dilator acetylcholine are impaired prior to the development of azotemia and hypertension in rats exposed to total body irradiation (TBI).

Methods: Male WAG/RijCmc rats were subjected to TBI (11 Gy) and afferent arteriolar responses to acetylcholine using the juxtamedullary nephron technique were determined at one, three, and six weeks.

Results: Systolic blood pressure (117 \pm 6 vs. 119 \pm 4 mmHg) and BUN (15.6 \pm 1.4 vs. 15.8 \pm 0.8 mg/dl) were not different between control and TBI groups at 6 weeks. Afferent arteriolar diameters averaged 22.5 \pm 0.8 mm (n=30) in controls and 21.7 \pm 0.7 mm (n=27) in TBI rats and were not different between control and TBI groups at 1, 3, or 6 weeks. Acetylcholine dilator responses were progressively attenuated from one to six weeks in TBI compared to control rats. During exposure to acetylcholine (0.01, 0.1, 1, and 10 mmol/L), afferent diameter increased by 8 \pm 2%, 18 \pm 3%, 27 \pm 2% and 31 \pm 3% in control rats (n=6), and 3 \pm 2%, 9 \pm 3%, 12 \pm 3%, and 16 \pm 3% in kidneys of 3 week TBI rats (n=8, p<0.05). However, TBI did not change the nitroprusside vasodilator responses at 1, 3, or 6 weeks. Renal microvessels were isolated from control and TBI groups at 3 and 6 weeks for protein expression assessment of endothelial enzymatic pathways Cyp2C, COX, and NOS. We found that epoxygenase Cyp2C protein expression was significantly lower 3 and 6 weeks following TBI compared to control rats.

Conclusions: Taken together, these results indicate that the impaired afferent arteriolar endothelial-dependent acetylcholine responses and decreased epoxygenase enzymes precede the development of proteinuria, azotemia, and hypertension in irradiated rats.

Funding: Veterans Administration Support

TH-PO405

Elevated Lp-PLA2 Plasma Activity Is an Independent Predictor of Subclinical Atherosclerosis in CKD5-D Patients – No Correlation with Lp-PLA2 mRNA Expression in Isolated Monocyte Subsets Christof Ulrich, Bogusz Trojanowicz, Roman Fiedler, Felix Kohler, Anna-Franziska Wolf, Eric Seibert, Matthias Girndt. *Internal Medicine II, Martin-Luther-Univ Halle-Wittenberg, Germany.*

Background: The continued search for biomarkers indicating future cardiovascular events among patient on renal replacement therapy is well-founded by the extraordinarily high cardiovascular mortality rate in these patients. The combination of inflammatory cells capable of expressing atherogenic molecules within the plaque makes the monocyte-/ Lp-PLA2-axis an interesting subject to study in patients on maintenance dialysis (CKD5-D).

Methods: CKD5-D were stratified upon the presence (A+) or absence (A-) of subclinical atherosclerosis by carotid artery ultrasound. Lp-PLA2 plasma activity was measured by an enzymatic kinetic test and leucocytic Lp-PLA2 mRNA expression by real time PCR. Monocyte subsets were analyzed flow-cytometrically and defined as classical CD14++CD16- (Mo1), intermediate CD14++CD16+ (Mo2) and non-classical CD14+CD16++ (Mo3). mRNA expression analysis of these subsets (N=24) was done after sorting of cells using ARIA II FACS-sorter.

Results: 60 CKD5-D (62.3±15.5 years) patients and 39 healthy control subjects (54.0±8.4 years) were enrolled in a cross-sectional study. Lp-PLA2 mRNA expression in leucocytes and plasma Lp-PLA2 activity were significantly higher in CKD5-D. CKD5-D patients diagnosed with subclinical atherosclerosis (A+) had the most prominent Lp-PLA2 activity values, which even remained significantly different compared to A- after adjustment for age and HbA1c. Among different monocyte subsets Mo1 and Mo2 had the highest Lp-PLA2 mRNA level, but it was Lp-PLA2 mRNA expression on “patrolling” Mo3 cells which was significantly elevated in A+ versus A-.

Conclusions: We conclude that Lp-PLA2 activity is an independent predictor of subclinical atherosclerosis in CKD5-D patients. Among monocyte subsets Mo3 cells appear to have an exceptional position within the setting of atherosclerosis. These vessel patrolling cells may reflect a physiological response to vascular inflammation in CKD5-D patients.

Funding: Private Foundation Support

TH-PO406

Hypoxanthine, a Uremic Small Solute, Induces Cholesterol Accumulation in Hepatocytes and Incites Atherosclerosis in APO E Deficiency Status Yong-Lim Kim,^{1,2} Hye-Myung Ryu,¹ Sukyung Lee,¹ Hee-Yeon Jung,¹ Se-Hee Yoon,³ Ji-Young Choi,¹ Chan-Duck Kim,¹ Sun-Hee Park,¹ Jang-Hee Cho.¹ *¹Div of Nephrology and Dept of Internal Medicine, Kyungpook National Univ Hospital, Daegu, Korea; ²BK21 Plus KNU Biomedical Convergence Program, Dept of Biomedical Science, Kyungpook National Univ, Daegu, Korea; ³Dept of Internal Medicine, Konyang Univ, Daejeon, Korea.*

Background: Hypoxanthine which originates from purine metabolism is a small free water-soluble uremic toxin. Its biological functions remain unknown. In this study, we investigated the role of hypoxanthine on chronic kidney disease (CKD) and cholesterol synthesis with atherosclerosis development, particularly in apolipoprotein E (APOE)-deficient mice.

Methods: The effect of hypoxanthine on the regulation of cholesterol synthesis and atherosclerosis were evaluated in cultured HepG2 cells and Apoe knockout (KO) mice.

Results: Hypoxanthine had no effect on the renal interstitial fibrosis in CKD mouse. The effect of hypoxanthine on the regulation of cholesterol synthesis and atherosclerosis were evaluated in cultured HepG2 cells and Apoe knockout (KO) mice. In HepG2 cells, hypoxanthine increased intracellular ROS production. Hypoxanthine increased cholesterol accumulation and decreased APOE and ATP-binding cassette transporter A1 (ABCA1) mRNA and protein expression in HepG2 cells. Furthermore, H₂O₂ also increased cholesterol accumulation and decreased APOE and ABCA1 expression. This effect was partially reversible by pre-treatment with the antioxidant N-acetyl cysteine. Hypoxanthine and APOE knockdown using APOE-siRNA synergistically induced cholesterol accumulation and reduced APOE and ABCA1 expression. Hypoxanthine markedly increased serum cholesterol levels and the atherosclerotic plaque area in Apoe KO mice.

Conclusions: Hypoxanthine induces cholesterol accumulation in hepatic cells through alterations in enzymes that control lipid transport and induces atherosclerosis in APOE-deficient cells and mice. These effects are partially mediated through ROS produced in response to hypoxanthine.

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TH-PO407

Atherosclerosis following Renal Injury Is Ameliorated by Pioglitazone and Losartan via Macrophage Phenotype Suguru Yamamoto,^{1,2} Jianyong Zhong,^{1,3} Haichun Yang,³ Yiqin Zuo,³ Ichie Narita,² Valentina Kon.¹ *¹Dept of Pediatrics, Vanderbilt Univ Medical Center, Nashville, TN; ²Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Science, Niigata, Japan; ³Dept of Pathology, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Chronic kidney disease (CKD) amplifies atherosclerosis which involves renin-angiotensin system (RAS) regulation of macrophages. RAS influences peroxisome proliferator-activated receptor-γ (PPARγ), a modulator of atherogenic functions of macrophages, however, little is known about its effects in CKD related vasculopathy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: Apolipoprotein E knockout mice were uninephrectomized (UNx) and treated with pioglitazone, losartan, or both (UNx+Pio/Los) for 10 weeks. Extent and characteristics of atherosclerotic lesions and macrophage phenotypes were assessed. Peritoneal macrophages and RAW264.7 cells were used to examine pioglitazone and losartan effects on macrophage phenotype and inflammatory response.

Results: UNx significantly increased atherosclerosis. Pioglitazone and losartan each significantly reduced the atherosclerotic burden by 29.6% and 33.5%, respectively; however the benefit was dramatically augmented by combination treatment (55.7%). Assessment of plaques revealed significantly greater macrophage area in UNx+Pio/Los with more apoptotic cells. The expanded macrophage-rich lesions of UNx+Pio/Los had more alternatively activated, Ym-1 and arginine 1-positive M2 phenotypes. There was no difference in plaque collagen content or calcifications. *In vitro*, pioglitazone alone and together with losartan was more effective than losartan alone in dampening lipopolysaccharide-induced cytokine production, suppressing M1 phenotypic change while enhancing M2 phenotypic change.

Conclusions: Combination of pioglitazone and losartan is more effective in reducing renal injury-induced atherosclerosis than either treatment alone. This benefit reflects mitigation in macrophage cytokine production, enhanced apoptosis, and a shift toward an anti-inflammatory phenotype.

Funding: NIDDK Support

TH-PO408

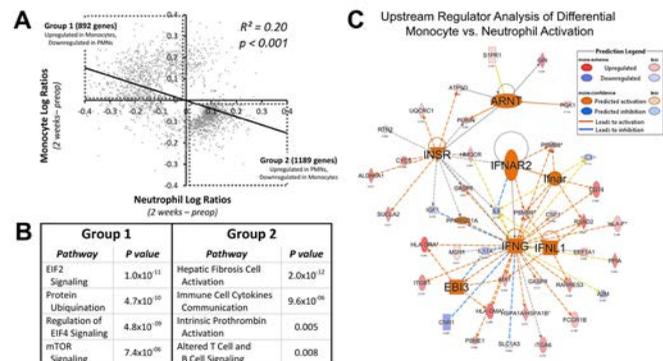
Differential Activation of Monocyte and Neutrophil Genomics following Fistula Placement Christopher S. Kuppler,^{1,2} Lyle L. Moldawer,² Scott A. Berceci,^{1,2} The HFM Study Group.³ *¹Div of Vascular Surgery and Endovascular Therapy, Univ of Florida, Gainesville, FL; ²Dept of Surgery, Univ of Florida, Gainesville, FL; ³NIDDK, NIH.*

Background: Systemic inflammation is an important regulator of flow mediated vascular adaptation. We evaluated the genomic response of circulating leukocytes after fistula (AVF) placement, hypothesizing that this severe flow environment induces unique monocyte (mono) and neutrophil (PMN) expression patterns.

Methods: Blood samples were collected pre-op, 2 weeks, and 6 weeks following AVF creation (n=74). Mono and PMN mRNA was isolated and analyzed for 44,699 genes using the HTA 2.0 microarray. BRB ArrayTools and Ingenuity Pathway Analysis was used to identify leukocyte genome changes, relevant ontologies, and upstream regulators.

Results: Compared to pre-op levels, 1,014 mono and 1,594 PMN genes were found to be differentially expressed 2 weeks after AVF placement (p<0.001), but returned to baseline by 6 weeks post-op [91 (mono) and 1 (PMN); p<0.001]. Mono and PMN showed a divergent, inversely correlated expression pattern (A, p<0.001), with 892 genes upregulated in mono/downregulated in PMN (Group 1) and 1189 genes upregulated in PMN/downregulated in mono (Group 2). Group 1 genes were mostly associated with intracellular translational control and cell survival; Group 2 genes were associated with the extrinsic stimulation of non-inflammatory systems (B). Upstream regulator analysis revealed enhanced interferon signaling in monocytes as the driver of these divergent expression patterns (C).

Conclusions: Following AVF creation and exposure to this new flow environment, there is a significant but divergent shift in the genomic profile of leukocytes. We hypothesize that this unique activation pattern has important implications in early AVF adaptation. Integration with the anatomic, physiologic and outcome data sets from the parent HFM study is ongoing.



Funding: NIDDK Support

TH-PO409

Identification of Angiotensin Peptides Modulating the Harmful Effects of Ang II Inchronic Renal Failure Joachim Jankowski, Vera Jankowski. *Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, NRW, Germany.*

Background: Angiotensin II (Ang II) is essential in the physiology and pathology of vascular regulation. Ang II is the principal vasoactive substance of the renin-angiotensin system (RAS), having a variety of physiological actions. In the past few years, the classical concept of the RAS system has experienced substantial conceptual changes. Angiotensin peptides such as Ang 1-7, Ang III and Ang IV were identified as mediators involved in vascular regulation. Progress of mass-spectrometric techniques affords the opportunity for identification of unknown angiotensin peptides. When screening the molecular mass range of Ang II for novel peptides, we observed two signals which could represent further angiotensin peptides.

Methods: In order to identify novel angiotensin peptides, we isolated these peptides from human plasma. Chromatographic purification and structural analysis by mass spectrometry revealed Ang II like octapeptides Pro-Glu-Val-Tyr-Ile-His-Pro-Phe and Ala-Arg-Val-Tyr-Ile-His-Pro-Phe. We named these peptides *Angioprotectin* and *Ala-Angiotensin (Ala-Ang)*.

Results: *Angioprotectin* antagonises the contractile actions of Ang II. These physiological antagonism of vasoconstrictor actions of Ang II by *Angioprotectin* is mediated by the Mas receptor. *Angioprotectin* has a stronger affinity to the Mas receptor than Ang-1-7. Plasma concentrations in healthy human volunteers were about 15 % and in CKD patients up to 50 % of plasma Ang II concentrations. Ang A has the same affinity to the AT₁ receptor as Ang II, but a higher affinity to the AT₂ receptor. Ang A revealed a less vasoconstrictive effect than Ang II in-vitro, which is not modified in the presence of the AT₂ receptor antagonist PD 123319, suggesting a lower intrinsic activity at the AT₁ receptor. In healthy subjects, Ang A concentrations are less than 20% of the Ang II concentrations, but the ratio Ang A / Ang II is higher in CKD.

Conclusions: In conclusion, *Angioprotectin* and Ang A are novel human, vasoconstrictive angiotensin-derived peptides. Due to stronger agonism at the MAS and AT₂ receptor, respectively, and -furthermore- their increased plasma concentration in CKD. Ang A may modulate the harmful effects of Ang II.

TH-PO410

Phosphate (Pi)-Induced Endothelial Microparticles Express Histone H2B which Supports Thrombin Generation Nima Abbasian,¹ Karl Herbert,² James O. Burton,^{1,3} Nigel J. Brunskill,^{1,3} Alan Bevington.¹ ¹*Dept of Infection, Immunity, & Inflammation, Univ of Leicester, Leicester, United Kingdom;* ²*Dept of Cardiovascular Sciences, Univ of Leicester, Leicester, United Kingdom;* ³*John Walls Renal Unit, Univ Hospitals of Leicester, Leicester, United Kingdom.*

Background: Cardiovascular disease is common in patients with chronic kidney disease. Hyperphosphatemia is a well-known cardiovascular risk factor which we have recently shown can induce the formation of pro-coagulant endothelial microparticles (EMPs) through an elevation of intracellular P_i concentration, and that EMPs express VE-cadherin and superficial phosphatidylserine (PSer) on their surface; however, a comprehensive characterization of the antigenic composition of Pi-induced EMP has been poorly defined.

Methods: EAhy926 endothelial cells were treated with control 1mM vs. high 2.5mM P_i. EMPs were separated from the cultured medium by centrifugation. EMPs were subjected to 'shotgun proteomics' using LC MS/MS analysis. The presence of H2B in EMPs was probed by immunoblotting using anti-H2B antibody. The presence of DNA and RNA in EMPs was determined by Burton DNA Assay and using an Agilent RNA 6000 Pico Kit.

Results: MS analysis demonstrated that high Pi-induced EMPs contain nucleosome components (H2B, H2A, H2A.x, H3.2, and H4), enzymes, proteins involved in vesiculation & signalling, chaperones, and cytoskeleton associated proteins. Immunoblotting using anti-H2B antibody confirmed Pi-induced EMPs are enriched in H2B. DNA and RNA measurements showed EMPs contain both DNA and RNA.

Conclusions: These data for the first time show that Pi-induced EMPs are enriched in H2B, along with DNA, and RNA. H2B promotes activation of the contact pathway and inhibition of fibrinolysis and hence supports coagulation in vivo. In conclusion, Pi-induced EMPs influence thrombosis through expressing PSer, inhibition of fibrinolysis and activation of the contact pathway by expressing H2B. Further studies are needed to confirm the exact mechanistic role of these molecules expressed on Pi-induced EMPs in the pathogenesis of thrombosis in vivo.

Funding: Private Foundation Support

TH-PO411

Identification of the "Vasoconstriction Inhibiting Factor" (VIF) – A Potent Endogenous Cofactor of Angiotensin II Acting on the AT₂ Receptor Joachim Jankowski, Vera Jankowski. *Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen.*

Background: The renin-angiotensin-system and especially the angiotensin peptides play a central role in blood pressure regulation. Here, we hypothesize that a yet unknown peptide is involved in the action of Ang-II modulating the vasoregulatory effects as a cofactor.

Methods: The peptide with vasodilatory properties was isolated from adrenal glands chromatographically. The effects of this peptide were evaluated in-vitro and, in-vivo and the receptor affinity was analysed.

Results: The plasma concentration in humans was quantified in chronic kidney disease patients, heart failure patients and healthy controls. The amino acid sequence of the peptide from bovine adrenal glands was HSSYEDELSEVLEKPNQAEPEVTEEVSSKDAAE, which is a degradation product of Chromogranin-A. The sequence of the peptide isolated from human plasma was HSGFEDELSEVLEKPNQSSQAELEAVEPESSKDVME. Both peptides diminished significantly the vasoconstrictive effect of Ang-II in-vitro. Therefore, we named the peptide "vasoconstriction inhibiting factor" (VIF). The vasoregulatory effects of VIF are mediated by the AT₂-receptor. VIF impairs Ang-II-induced phosphorylation of the p38MAPK-pathway but not of ERK1/2. The vasodilatory effects were confirmed in-vivo. The plasma concentration was significantly increased in renal and heart failure patients.

Conclusions: VIF is a vasoregulatory peptide which modulates the vasoconstrictive effects of Ang-II by acting on the AT₂-receptor. It is likely that the increase in VIF may serve as a counter-regulatory effect to defend against hypertension. The identification of this target may help us to understand the pathophysiology of renal and heart failure and may form a basis for the development of new strategies for the prevention and treatment of cardiovascular disease.

TH-PO412

A Novel Microfluidic System for Studying Human Microvascular Integrity Graham Marsh, Angela Huang, Jeremy Stuart Duffield. *Research & Development, Biogen, Cambridge, MA.*

Background: The microvasculature of the kidney plays a critical role in kidney physiology, injury, and disease. Proper hemodynamic and biochemical signals are pivotal for sustaining normal functions in kidney microvasculature, which are greatly altered during kidney injury. Traditional 2D cultures *in vitro* fail to reconstruct the microenvironment of the kidney capillary network and cannot accurately examine the microvasculature in injury conditions. To bridge the gap between *in vitro* and *in vivo* models, we developed a novel platform to study kidney microvasculature by building a 3D capillary using a Nortis microfluidic system.

Methods: We seeded primary kidney endothelial cells from a human fetal donor into a 120 mm tube in a collagen matrix. We then flowed media through the device with a controlled shear stress to mimic *in vivo* conditions. The system allows for cells to be grown in co-culture by embedding supporting cells, such as pericytes, in the collagen matrix. In this engineered microenvironment, we are able to deliver growth factors or stimulants in controlled doses to observe changes in microvessel function and morphology. This platform has allowed us to visualize the microvessel with a high resolution by confocal microscopy, to observe cell-cell interactions, study the basement membrane composition, and measure vessel integrity. We evaluated the barrier function of the capillary network by examining vascular leak under normal conditions and in an injury model with TNF α activation.

Conclusions: There was a significant increase in the permeability of the vessels when they are activated with TNF α compared to resting condition, and microvessels co-cultured with pericytes had significantly enhanced microvascular integrity and lowered vascular leak. The microfluidic platform has enormous potential to study the human kidney microvasculature *in vitro* while maintaining the structure and morphology observed *in vivo*.

Funding: Pharmaceutical Company Support - Biogen

TH-PO413

The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherogenesis by Regulating Plasminogen Activator Inhibitor-1 and Cellular Adhesion Molecules Generation Hideyuki Negoro. *Medicine, Harvard Medical School, Boston.*

Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence plasminogen activator inhibitor-1 (PAI-1) and cellular adhesion molecules, such as monocyte chemoattractant protein-1 (MCP-1) and intracellular adhesion molecule-1 (ICAM-1) which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of PAI-1, MCP-1 and ICAM-1 in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in MCP-1 and ICAM-1 expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include circulating fibrinogen and PAI-1, which are significantly elevated in Bmal1KO mice. We confirmed that PAI-1 levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating PAI-1 and cellular adhesion molecules generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Other U.S. Government Support

TH-PO414

TNF-Alpha Receptor 1 Is Associated with Mortality in Persons with Coronary Artery Disease Meyeon Park, Daniela Maristany, Eric Vittinghoff, Mary Whooley, Michael Shlipak. *UCSF.*

Background: Inflammation is a possible mechanism to explain the association between atherosclerosis and mortality. Chronic kidney disease is associated with high levels of inflammation. This study evaluated circulating tumor necrosis factor receptor type 1 (TNFR1A), a marker of inflammation, as a risk factor for mortality.

Methods: In the Heart and Soul Study, a cohort with established coronary artery disease (CAD), we measured TNFR1A from baseline serum samples and defined elevated levels of TNFR1A by the highest quartile (Q4, > 3.4 ng/ml). Our outcomes were myocardial infarction, heart failure hospitalizations (HF), and death. We evaluated the associations of high TNFR1A with outcomes using Poisson regression and adjusting for age, race, smoking, hypertension, diabetes, cholesterol, albuminuria, and baseline estimated glomerular filtration rate (eGFR).

Results: Among 981 participants who had TNFR1A measurements at baseline, median TNFR1A was 2.47 ng/ml (1.9-3.4). Median TNFR1A in individuals with eGFR < 60 was 2.9 (3.8-5) and 1.7 (2.1-2.7) in those with eGFR > 60. Median follow-up time was 8.9 years. Higher levels of TNFR1A (Q4 v. Q1-3) were associated with a higher risk of MI in

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

unadjusted analyses [incident rate ratio (IRR) 2.56 (95% CI 1.73-3.81). This was attenuated by adjustment [IRR 1.59 (0.92-2.72)]. TNFR1A was strongly associated with HF in both unadjusted and adjusted analyses [adjusted IRR 1.79 (1.12-2.86)] as well as with death [adjusted IRR 1.6 (1.22-2.1)].

Conclusions: Levels of TNFR1A are elevated in CKD. TNFR1A is independently associated with HF and mortality. These findings implicate inflammation as a potential contributor to the elevated mortality risk in persons with CAD.

Funding: NIDDK Support

TH-PO415

Blood Monocyte Profiles and P2X7 Receptor Expression in Chronic Kidney Disease and End-Stage Renal Disease Serika D. Naicker, Susan Logue, Deirdre Cotter, Matthew D. Griffin. *REMEDY, School of Medicine, National Univ of Ireland, Galway, Ireland.*

Background: Monocytes are innate immune cells with 3 subsets [Classical (CD14⁺⁺CD16⁻), Intermediate (CD14⁺⁺CD16⁺) and Non-classical (CD14⁺CD16⁺⁺)] which have distinct pathogenic roles in chronic inflammation and atherosclerosis. We quantified blood monocyte subsets in a cohort of patients with CKD and ESRD/chronic hemodialysis (cHD) and evaluated their expression of the inflammasome-activating ATP receptor P2X7.

Methods: CKD stage 1-5 was assigned based on MDRD eGFR. PBMCs from healthy adults (CTRL, n=25), patients with CKD stages 1-5 (n=100) or ESRD prior to and after HD (n=32) were analyzed by 8-colour flow cytometry to quantify monocyte subsets and their surface expression of P2X7 receptor. PBMC stimulation cultures were carried out using optimized concentrations of TLR ligands ± ATP.

Results: Total monocyte numbers progressively increased from CTRL through CKD stage 1-5 and ESRD/cHD. Among the subsets, Intermediate monocytes were most highly expanded in CKD in a stage-dependent manner. ESRD patients additionally demonstrated higher numbers of non-classical monocytes which diminished significantly following HD. Surface expression of P2X7 was readily detected on all monocyte subsets in CTRL, CKD Stages 1-5 and ESRD but was most highly expressed by Non-classical monocytes. Compared to CTRL, all stages of CKD were associated with higher monocyte expression of P2X7 but, in ESRD, this was further increased on Non-classical monocytes following HD. High-level interleukin (IL)-1 β release by monocytes from CTRL and CKD/ESRD patients was observed upon brief exposure to the P2X7 ligand ATP following priming with ligands for TLR4 (highly expressed by Classical monocytes) or TLR7/8 (highly expressed by Non-classical monocytes) indicating active inflammasome response in multiple monocyte subsets.

Conclusions: CKD is associated with a stage-dependent increase in circulating monocytes that is greatest for the Intermediate subset. Non-classical monocytes are also expanded in ESRD and modulated by HD. The P2X7 receptor, which mediates inflammasome activation via extracellular ATP, is expressed by all monocyte subsets in CKD/ESRD but most highly by Non-classicals.

Funding: Government Support - Non-U.S.

TH-PO416

Activation of CXCL16/CXCR6 Pathway by Inflammation Accelerates the Progression of Atherosclerosis in ESRD Patients Zebo Hu,¹ Kun ling Ma,¹ Yang Zhang,¹ Wu Yu,¹ Bi-Cheng Liu.¹ *¹Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China; ²Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China.*

Background: Objective Chronic inflammation plays a crucial role in the progression of atherosclerosis (AS). The current study aimed to observe the effects of inflammation on lipid accumulation in the radial arteries of end-stage renal disease (ESRD) patients with arteriovenostomy and further investigate whether inflammation accelerates the progression of AS via the dysregulation of the CXCL16/CXC chemokine ligand 16, CXCL16)/CXCR6(CXC chemokine receptor 6,CXCR6) pathway.

Methods: Forty-seven ESRD patients were divided into control group (n=20) and inflamed group (n=27) according to plasma C-reactive protein (CRP) level. Biochemical index and lipid profile of patients were measured. Surgically removed tissues from the radial arteries of patients receiving arteriovenostomy were used in the experiments for preliminary evaluation of AS. Foam cell formation was observed by Hematoxylin-eosin (HE) and Filipin staining. CXCL16/CXCR6 pathway related protein expressions and the expressions of monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor α (TNF α), and CD68 were detected by immunohistochemistry staining and immunofluorescence staining.

Results: Immunohistochemical staining demonstrated that inflammation increased both protein expressions of MCP-1 and TNF- α in radial arteries of inflamed group accompanied with macrophage infiltration. Further analysis showed that there were significantly increased foam cell formation in continuous cross-sections of radial arteries of inflamed group compared to the controls, which were closely correlated with increased protein expressions of CXCL16, CXCR6, and decreased protein expression of ADAM10.

Conclusions: Inflammation contributed to foam cell formation in the radial arteries of ESRD patients via the activation of the CXCL16/CXCR6 pathway.

TH-PO417

Ablation of Pericytes Induces Capillary Rarefaction and Proximal Tubular Injury Janewit Wongboonsin, Rafael Kramann, Susanne V. Fleig, Flavia G. Machado, Benjamin D. Humphreys. *Renal Div, Brigham and Women's Hospital, Boston.*

Background: We recently showed that Gli1⁺ cells in the pericyte niche are the predominant source of myofibroblasts in kidney fibrosis. One hypothesis for the mechanism of capillary rarefaction observed in fibrotic kidney disease is that injury induces pericyte detachment from endothelium, leading to capillary dropout and hypoxia. There is no direct evidence supporting this idea, however. In this study we measured pericyte detachment during injury, and asked whether ablation of pericytes in the absence of any other injury destabilizes capillaries and induces tubular injury.

Methods: We performed unilateral ischemia reperfusion injury (IRI) in bigenic Gli1CreER:tdTomato mice and performed fluorescence microangiography (FMA) at 2 weeks after injury to delineate the renal microvasculature and quantify detachment of Gli1⁺ cells from capillaries. In a second set of experiments we ablated Gli1⁺ in Gli1CreER, iDTR mice by diphtheria toxin injection, performed FMA and analyzed peritubular capillary changes by automated software-based quantification over a time course of 56 days.

Results: After IRI, Gli1⁺ cells proliferate and detach from the renal microvasculature. Specific genetic ablation of Gli1⁺ cells triggers peritubular capillary rarefaction and induces mild focal cortical tubular injury. While peritubular capillary number decreased, peritubular capillary perimeter and area remain unchanged. Injured tubules were characterized by focal Kim1⁺ expression in cortical areas with decreased FMA⁺ perfused capillaries. Renal Kim1 and Hif1 α mRNA expression increased early after Gli1⁺ cell ablation. Interestingly, while α SMA and Collagen1 α 1 mRNA expression decreased early after ablation, confirming the role of Gli1⁺ cells as myofibroblast progenitors, we detected increased expression of both fibrotic readouts at 56 days after ablation. Immunostaining for α SMA showed focal cortical areas with myofibroblast expansion and scar formation.

Conclusions: Ablation of Gli1⁺ pericytes in healthy kidney causes peritubular capillary rarefaction, focal tubular epithelial injury and focal fibrosis in the outer cortex most likely due to hypoxia.

Funding: NIDDK Support

TH-PO418

Activation of Tie2 by Deletion of VE-PTP Increases GFR in Mice Isabel Anna Carota,^{1,2} Chengjin Li,³ Vera Eremina,³ Tuncer Onay,¹ Susan E. Quaggin.¹ *¹Div. of Nephrology/Hypertension and Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago; ²Eli Lilly and Company; ³Samuel Lunenfeld Research Inst, Mount Sinai Hospital, Toronto, Canada.*

Background: With an increasing number of patients suffering from CKD, there is an urgent need for new therapeutic targets. The Angiotensin-Tie2 signaling pathway has been implicated in the development of kidney disease. In CKD patients elevated levels of circulating Angpt-2, the antagonist of the tyrosine kinase receptor Tie2, correlate with a decrease in glomerular filtration rate (GFR). Additionally it has been shown that loss of Angpt-1, the Tie2 agonist, leads to enhanced glomerular scarring in diabetic Angpt-1 KO mice. These findings suggest that an imbalance of Tie2 ligands is associated with progression of renal disease. Here we investigate the impact of Tie2 activation on baseline renal function by genetic deletion of its negative regulator the endothelial specific phosphatase VE-PTP in an inducible KO mouse model.

Methods: To study the effect of Tie2 activation following loss of VE-PTP, we generated inducible VE-PTP KO mice. Kidneys were examined histologically and phosphorylation level of Tie2 was quantified by IP from lung lysates followed by Western blot analysis. GFRs were measured using the FITC-Sinistrin clearance method (n=7 KO, 6 contr. at 10 weeks).

Results: Knock-out of VE-PTP enhances Tie2 phosphorylation 2-fold resulting in enhanced Tie2 activity in a ligand-independent manner. Deletion of VE-PTP before embryonic day 13.5 leads to the formation of dilated glomerular capillaries, which are not observed in kidneys of mice when VE-PTP is deleted after E18.5. In contrast, mGFRs of VE-PTP iKO mice (deletion after E18.5) were increased from 298.6±28.0 in controls to 458.1±27.9 ml/min in KO litter mates (p=0.016). Both groups showed no difference in blood pressure, albuminuria or renal histology.

Conclusions: Inhibition of VE-PTP leads to elevated Tie2 phosphorylation suggesting VE-PTP as a potential target to rescue the effects of increased Angpt-2 levels that occur in CKD patients. The increased GFR observed in VE-PTP iKO mice suggest that disrupting VE-PTP-Tie2 interactions may be a strategy to slow progression of CKD.

Funding: Other NIH Support - RC1HL124120, Pharmaceutical Company Support - Eli Lilly and Company

TH-PO419

Circulating VEGF-C Levels Are Associated with Insulin Sensitivity in End Stage Renal Disease Patients Serpil Muge Deger,^{1,2} Adriana Hung,^{1,2} Edward D. Siew,^{1,2} Feng Sha,¹ Charles D. Ellis,¹ Jens Titze,¹ Talat Alp Ikizler.^{1,2} *¹Vanderbilt Univ, Nashville, TN; ²VA, Nashville, TN.*

Background: Insulin resistance (IR) is a common metabolic derangement in advanced kidney disease. We have previously demonstrated that inflammation is a key mediator of IR in end-stage renal disease (ESRD). Vascular Endothelial Growth Factor C (VEGF-C) is a key regulator of lymphangiogenesis that may contribute to IR. Recent experimental data suggest that the VEGF-C pathway may have important effects on adipose tissue IR by promoting macrophage recruitment. The relationship between VEGF-C and IR in humans

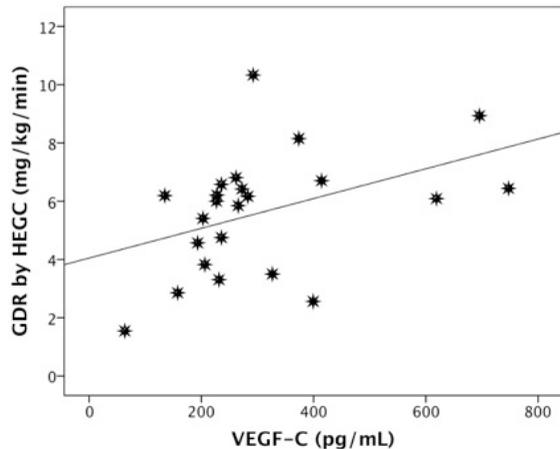
not been well characterized. We aimed to examine the relation between circulating VEGF-C and insulin sensitivity by the gold standard hyperinsulinemic euglycemic clamp (HEGC) in patients on chronic dialysis.

Methods: Fourteen HD and 10 PD patients who participated HEGC were included in this analysis. Serum VEGF-C values were measured by ELISA.

Results: Characteristics of study population are summarized in (table 1).

	HD	PD	p
Age (years)	55(38, 60)	48(35, 55)	0.21
Gender(M,%)	93	50	0.03
Race(AA, %)	79	60	0.29
BMI(kg/m ²)	29(26, 33)	30(26, 35)	0.75
Diabetes(%)	21	10	0.43
GDR by HEGC(mg/kg/min)	5.4(3.5, 6.2)	6.4(6, 8.1)	0.07
hs-CRP(mg/L)	4.8(2.5, 11.3)	2.5(1.5, 14)	0.37

Median serum VEGF-C levels were 350 (270, 638) pg/mL in PD and 230 (184, 270) pg/mL in HD patients (p=0.029). The median glucose disposal rate (GDR) derived by HEGC tend to lower in HD compared to PD patients. There was a significant positive correlation between serum VEGF-C and GDR by HEGC (r=0.495, p=0.016).



The association remained significant after adjusted by age, gender, and hs-CRP (p=0.026).

Conclusions: Our data suggest that the lymphangiogenic growth factor VEGF-C may be an important contributor to IR in the chronic uremia and a potential therapeutic target. Further studies are needed to delineate this relation.

Funding: Veterans Administration Support, Private Foundation Support

TH-PO420

Disruption of Angiopoietin-Tie2 Signaling Leads to Cystic Kidney Disease
 Yael Kenig-Kozlovsky,¹ Rizaldy P. Scott,^{1,2} Benjamin R. Thomson,^{1,2} Shinji Yamaguchi,¹ Christine Jiang Wu,¹ Stefan Heinen,² Susan E. Quaggin.^{1,2} ¹Div of Nephrology-Hypertension and Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; ²Lunenfeld-Tanenbaum Research Inst, Toronto, Canada.

Background: Angiopoietin ligands Angpt1 and Angpt2 and their cognate receptor Tie2/Tek are essential for development of the heart and systemic blood vasculature. While investigating their function in the shaping of the complex renal vasculature, we uncovered that mid-gestational inactivation of the Angpt1/Angpt2-Tie2 signaling axis remarkably causes cystic kidney disease.

Methods: Using a tetracycline-inducible gene targeting approach we deleted both Angpt1 and Angpt2 or Tie2 at embryonic stage E16.5 in the mouse.

Results: Compound deletion of Angpt1 and Angpt2, or loss of Tie2 led to kidney cyst formation detectable as early as 2 weeks after birth. By 8 weeks of age, enlarged cysts had severely distorted the renal architecture and glomerular filtration rate dropped by ~40%. Surprisingly, mutants did not manifest proteinuria, urine concentrating defects or blood pressure differences relative to control littermates. Cyst formation was predated by a distinctive pattern of renal vascular rarefaction, most notably at the corticomedullary junction. Cysts were lined by flattened mesenchymal-like cells, which expressed vimentin and a-smooth muscle actin but not classic markers for tubular epithelium, blood or lymphatic endothelium.

Conclusions: Recently, we reported that inactivation of angiopoietin-Tie2 signaling impairs the development of lymphatic vasculature and specialized “hybrid” vessels (exhibiting features of both blood and lymphatic vessels) of the eyes resulting in abnormal drainage of aqueous humor, ocular hypertension and glaucoma. Based on these findings, including the renal vascular rarefaction in the absence of Angpt1/Angpt2-Tie2 signaling, we hypothesize that renal cystogenesis may be attributed, in part, to defective vascular

and/or lymphatic drainage of interstitial fluid in the kidney. Our study highlights a hitherto unidentified role of angiopoietin-Tie2 signaling in the pathogenesis of renal cysts and suggests this pathway as a potential therapeutic target to alleviate cystic kidney disease.

Funding: Other NIH Support - Grant R01HL124120

TH-PO421

Role of Macrophage in Hyaluronic Acid-Induced Lymphangiogenesis in UO Model
 Won Kim, Jong-Hwan Jung, Yujin Jung, Kyung Pyo Kang, Sik Lee, Sung Kwang Park. Chonbuk National Univ Medical School.

Background: Hyaluronic acid (HA) is one of important component of extracellular matrix proteoglycan, has many biologic and pathologic effects such as inflammation, angiogenesis, wound healing and tissue remodeling. Renal lymphangiogenesis has been demonstrated in a rat remnant kidney model and in mouse unilateral ureteral obstruction (UO) model. However, there is few data about role of macrophage in HA-induced lymphangiogenesis in UO. We investigated the effect of macrophage in HA-induced lymphangiogenesis in UO.

Methods: RAW 264.7 cells (RAW cell, macrophage cell line) were incubated with TGF b1 and HA production was evaluated by ELISA. LYVE-1-positive lymphatics, HA, vascular endothelial growth factor (VEGF)-C were evaluated by immunofluorescence and ELISA in UO-induced fibrotic kidney treatment with or without clodronate (macrophage depleting agent).

Results: To evaluate the changes in HA expression in macrophages, RAW cell were treated with TGF-b1. We found that TGF-beta1 (1, 5, and 10 ng/mL) increased hyaluronic acid synthase (HAS)1, HAS2 and HAS3 mRNA expression in the cells. ELISA data demonstrated that treatment of RAW cells with TGF-b1 (10 ng/mL) increased HA production in a time-dependent manner. In UO model, renal HA level was higher in ureteral obstruction operated kidney than that of sham-operated kidney. Our immunofluorescence finding showed that HA is expressed on interstitial space in UO kidney. HA accumulation is correlated with the number of LYVE-1-positive lymphatic vessels after ureteral obstruction. HA expression was also co-stained with F4/80-positive renal macrophages 7 days after ureteral obstruction. Depletion of macrophage with clodronate significantly decreased UO-induced renal HA expression and UO-induced increased density of LYVE-1-positive lymphatic endothelial cells. We also found that VEGF-C expression in the kidney was significantly decreased in UO kidney after treatment with clodronate compared to that after treatment with control buffer.

Conclusions: These results suggest that macrophage has a partial role in HA production and HA-induced renal lymphangiogenesis in UO model.

TH-PO422

Nfat5/TonEBP Deficiency in B Cells Results in Reduced Antibody Formation, Hypoplastic Cutaneous Lymph Capillary Formation, and Salt-Sensitive Hypertension
 Jens Titze,^{1,2} Ljiljana Rokvic,¹ Patrick Neubert,¹ Kento Kitada,² Wolfgang Schuh,³ Hans-Martin Jack,³ Friedrich C. Luft.^{2,4} ¹Interdisciplinary Center for Clinical Research, UC Erlangen; ²Dept of Clin. Pharm., Vanderbilt Univ; ³Div. of Mol. Immun., UC Erlangen; ⁴MDC, Charite Berlin.

Background: Interstitial Na⁺ storage induces pro-inflammatory responses in macrophages (Mφ), which are mediated by the osmoprotective transcription factor *Nfat5* to promote host defense. However, Mφ also reduce salt concentration in the subcutaneous barrier by *Nfat5*/VEGF-C driven lymphatic clearance of electrolytes, protecting the organism from excess interstitial Na⁺ storage and hypertension. The role of *Nfat5* in B cells is unknown. We hypothesized that *Nfat5* in B cells boosts pro-inflammatory and homeostatic immune responses.

Methods: We fed 6 control (*mb1^{cre}Nfat5^{fllox/fllox}*) and 5 *mb1^{cre}Nfat5^{fllox/fllox}* (genetic deletion of *Nfat5* in B cells) mice a high-salt diet (4% NaCl chow/ 0.9% saline; HSD) for 8 weeks and studied their ability to produce antibody after vaccination with trinitrophenyl conjugated to keyhole limpet hemocyanin (TNP-KLH; 100µg i.p.), followed by a boost injection (50 µg) after 6 weeks. We also studied the size of cutaneous lymph capillaries and mean arterial blood pressure (MAP) in these mice fed a HSD.

Results: On HSD, *mb1^{cre}Nfat5^{fllox/fllox}* mice showed a >30% reduction in total IgM / IgG (p<0.05), and TNP-KLH-specific IgM / IgG (p<0.05) antibody production versus control, indicating reduced pro-inflammatory immune function. Additionally, these mice showed reduced lymph capillary diameters (40±9µm vs. 25±8µm, p<0.05), accompanied with increased MAP (117±8mmHg vs. 129±8mmHg, p<0.05), indicating reduced homeostatic immune function.

Conclusions: *Nfat5* in B cells is important for specific antibody formation, suggesting that Na⁺ storage and B cell osmoprotection is relevant for the T cell/Dendritic Cell (DC)-mediated adoptive immune response in secondary lymphatic organs. We currently study Mφ, DC, or T-cell driven modulation of the cutaneous lymph capillary network to better understand hypoplastic cutaneous lymph vessel formation, extrarenal lymphatic electrolyte clearance, and the salt-sensitive hypertension in *mb1^{cre}Nfat5^{fllox/fllox}* mice.

TH-PO423

Novel Mechanisms for Salt Sensitive Hypertension in Humans: Effects of Salt Loading on Skin Sodium, VEGF-C and Blood Pressure Viknesh Selvarajah,¹ Kaisa Maki-Petaja,¹ Liliana Domingues Pedro,² Sylvaine Fa Bruggeraber,² Carmel M. McEniery,¹ Ian Wilkinson.¹ ¹*Div of Experimental Medicine and Immunotherapeutics, Univ of Cambridge, Cambridge, United Kingdom;* ²*MRC Human Nutrition Research Unit, Fulbourn, Cambridge, United Kingdom.*

Background: Dietary sodium is an important trigger for hypertension. Animal studies show that the skin buffers dietary salt and salt-loading induces lymphangiogenesis mediated by VEGF C from macrophages, helping to maintain BP in response to salt load. The relevance of these mechanisms in humans is unclear.

Methods: We conducted a double-blind randomised crossover trial examining the effects of dietary salt loading on skin sodium, systemic haemodynamics, ambulatory BP and plasma VEGF-C in 48 healthy participants. Participants were placed on a low salt diet (70mmol sodium/day). Dietary compliance was checked using 24hr urine collections. Skin biopsies were taken after placebo and slow-sodium treatment (200mmol daily for 7 days). Skin Na and K concentrations (mg/g tissue) were analysed by ICPOES. Results were expressed as the ratio of Na:K to correct for variability in sample hydration. Plasma VEGF C was analysed by ELISA.

Results: Skin data was available for 47 individuals. Mean age was 29.9 ± 8.3 with mean baseline urinary sodium 98.8 ± 55.0 mmol/24 hours. 24hr urine sodium excretion increased from 71.4 ± 43.1 to 225.9 ± 89.0 mmol (p < 0.001) with salt loading. Ambulatory MAP showed a non-significant increase from 88 ± 7.0 to 89 ± 7 mmHg (p=0.10). Office MAP was unchanged. Skin Na:K increased from 2.91 ± 0.56 to 3.12 ± 0.62 (p=0.01). Percentage change in Na:K was negatively correlated with baseline Na:K (r=-0.40, p=0.007). Changes in ambulatory MAP correlated positively with baseline skin Na:K (r=0.30, p=0.048). Stroke volume correlated with skin Na:K post placebo (r = -0.42, p=0.002) and slow sodium (r = -0.53, p<0.0001) respectively. No significant change was noted in plasma VEGF C.

Conclusions: Skin sodium appears to increase with dietary salt loading and the degree of change correlates with baseline Na:K levels. Ambulatory blood pressure change with dietary salt loading correlates with baseline skin Na:K, supporting a possible role for the skin as a buffer for dietary sodium.

TH-PO424

Albuminuria Downregulates NKCC2 via Stimulation of COX-2/mPGES-1/PGE2 Cascade in Thick Ascending Limb Zhanjun Jia,^{1,2} Yibo Zhuang,¹ Guixia Ding,¹ Yue Zhang,¹ Songming Huang,¹ Aihua Zhang.^{1,2} ¹*Nephrology Dept, Nanjing Children Hospital, Nanjing Medical Univ, Nanjing, China;* ²*Nanjing Key Laboratory of Pediatrics.*

Background: Impaired response to loop diuretics is a common phenomenon in nephrotic syndrome patients. However, the pathogenic mechanisms remain elusive. Here we hypothesized that albuminuria itself may act as a key intrarenal factor leading to the dysregulation and dysfunction of NKCC2, as well as the subsequent resistance to loop diuretics.

Methods: C57BL/6 mice were subjected to albumin overload via i.p injection for 12 days. The mouse kidney tissues and renal biopsy specimens from proteinuric patients were analyzed.

Results: After albumin overload, we found an 80% downregulation of Na-K-Cl cotransporter (NKCC2) as determined by Western blotting, qRT-PCR and immunohistochemistry (IHC). Meanwhile, the COX-2 and mPGES-1 were strikingly elevated by 2.1 and 3.5 folds, respectively, as determined via Western blotting and qRT-PCR. By IHC, stimulation of COX-2 and mPGES-1 were localized in the thick ascending limb (TAL, NKCC2 positive tubules). Accordingly, the urinary PGE2 excretion was significantly enhanced by 82% following albumin overload. Interestingly, inhibition of COX-2 via a specific COX-2 inhibitor Celebrex in albumin overloaded mice entirely reversed NKCC2 downregulation in line with normalized urinary PGE2 output. In addition, mice with albumin overload exhibited a remarkable resistance to loop diuretic furosemide (NKCC2 inhibitor), which was completely reversed by COX-2 inhibition. Next, we examined NKCC2 expression in kidney biopsy specimens of proteinuric patients via IHC and found a 50% downregulation of NKCC2 which was negatively correlated with proteinuria severity. Meanwhile, mPGES-1 was strikingly elevated in TAL in parallel with a remarkable increment of urinary PGE2, and both mPGES-1 and urinary PGE2 showed a positive correlation with proteinuria severity.

Conclusions: These novel findings highly suggest that albuminuria plays an important role in mediating the downregulation and dysfunction of NKCC2 via a stimulation of COX-2/mPGES-1/PGE2 cascade in TAL, which could contribute to the impaired response to loop diuretic in proteinuric kidney disease.

Funding: Government Support - Non-U.S.

TH-PO425

The Physiological Roles of Moesin, a Cytoskeletal-Associated Protein, in Renal Salt Reabsorption Kotoku Kawaguchi, Ryo Hatano, Shinji Asano. *Molecular Physiology, College of Pharmaceutical Sciences, Ritsumeikan Univ, Kusatsu, Shiga, Japan.*

Background: Tubular reabsorption of electrolytes in the kidney is an essential function in regulating fluid balance in the body. In the thick ascending limb of the loop of Henle (TAL), 20-40% Na⁺ filtered by the glomeruli are reabsorbed by Na⁺-K⁺-2Cl⁻ cotransporter

type 2 (NKCC2). In humans, mutations in the gene coding for NKCC2 were identified in patients of Bartter syndrome type 1, which is characterized by severe salt losing tubulopathy. Despite of the physiological importance of NKCC2 in NaCl homeostasis, the molecular mechanisms for its membrane trafficking have not been fully elucidated. In 2012, Carmosino *et al.* (*Biol. Cell.* **104**(11): 658-676) reported that moesin, which is a member of ERM (Ezrin-Radixin-Moesin) family, plays an important role in the apical membrane trafficking of NKCC2 by *in vitro* experiments.

Methods: We examined the physiological impact of Moesin in the regulation of renal function *in vivo* by using male moesin-null (*Msn*^{-/-}) mice. Wild-type (*Msn*^{+/+}) and *Msn*^{-/-} mice were kept in metabolic cages and daily urinary volume and urinary contents of electrolytes were measured. Western blotting and immunostaining were performed to investigate the expressions and localizations of proteins in the medullary tubules.

Results: Fractional excretions of Na⁺, K⁺ and Cl⁻ were significantly increased in *Msn*^{-/-} mice compared to *Msn*^{+/+} mice. On the other hand, GFR and blood pressure were decreased in *Msn*^{-/-} mice possibly due to body fluid loss. Immunoblotting for apical surface membrane proteins of medullary tubules did not show a significant difference in NKCC2 expression level between *Msn*^{+/+} and *Msn*^{-/-} mice whereas the distribution of NKCC2 in the lipid raft was decreased in *Msn*^{-/-} mice.

Conclusions: Our results suggest that urinary loss of electrolytes in *Msn*^{-/-} mice would be due to the disturbed localization of NKCC2 in the apical membrane domain. Since phosphorylated moesin, which represents an active form, is concentrated in lipid raft fractions in *Msn*^{+/+} mice, moesin might play a pivotal role in the regulation of lipid raft localization of NKCC2 rather than the regulation of membrane trafficking of NKCC2 in TAL.

TH-PO426

Paracellular Cation Selectivity in the Thick Ascending Limb of Henle's Loop Increases Under the Control of Vasopressin Nina Himmerkus,¹ Allein Plain,¹ Rita D. Marques,² Jens G. Leipziger,² Markus Bleich.¹ ¹*Inst of Physiology, Christian-Albrecht-Univ, Kiel, Kiel, Germany;* ²*Dept of Biomedicine, Physiology and Biophysics, Aarhus Univ, Aarhus, Denmark.*

Background: The thick ascending limb of Henle's loop (TAL) has the highest paracellular cation selectivity along the nephron. Trans- and paracellular pathways are strongly interdependent. The transepithelial voltage as driving force for the paracellular reabsorption of cations can be generated either by transcellular transport properties or by paracellular cation diffusion. Arginine vasopressin (AVP) has been shown to stimulate active transcellular NaCl transport and we hypothesize that paracellular permeability properties are co-regulated to support the increase in NaCl reabsorption.

Methods: To measure long term regulation 8-10 week old mice were kept for 4 days on low (antidiuresis, AD, 0.26ml/gBM/d) or high (water diuresis WD, 0.78ml/gBM/d) water intake. Spot urine osmolality was determined as treatment indicator. For acute AVP experiments mice were kept at water ad libitum. mTAL were isolated perfused and transcellular electrophysiological properties (transepithelial resistance R_{es}, voltage V_{es}, equivalent short circuit current I_{sc}) were assessed as well as paracellular properties (NaCl dilution potential, ion permeabilities P_{Na} and P_{Cl}).

Results: mTAL of AD mice showed a higher active transcellular transport compared to the WD group tubules, represented by a two-fold increase in I_{sc}. Urine osmolality was positively correlated to I_{sc}. NaCl dilution potential was increased in the AD group, indicating a higher P_{Na}/P_{Cl} and a higher P_{Na} compared to WD. P_{Na}/P_{Cl} as a measure of paracellular cation selectivity was also positively correlated to urine osmolality. mTAL from untreated mice were stimulated acutely *ex vivo* for 12 minutes by basolateral application of 10 nM AVP, (n=6), in paired experiments. I_{sc} increased while it decreased in a time control group. At the same time, AVP induced an increase in P_{Na}/P_{Cl} compared to time controls.

Conclusions: Acute application of AVP as well as water restriction increase paracellular cation selectivity and permeability in mTAL in parallel to the increase of active transcellular NaCl transport.

TH-PO427

Adult Nephron-Specific MR-Deficient Mice Develop a Severe Renal Pseudohypoaldosteronism Type 1 Phenotype Jérémie Canonica,^{1,2} Chloe Sergi,¹ Marc P. Maillard,³ Petra Klusonova,⁴ Alex Odermatt,⁴ Bernard C. Rossier.^{1,2} Simona Frateschi,^{1,2} Edith Hummler.^{1,2} ¹*Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland;* ²*National Center of Competence in Research Kidney, CH, Switzerland;* ³*Service of Nephrology Dept, Univ Hospital of Lausanne (CHUV), Lausanne, Switzerland;* ⁴*Dept of Pharmaceutical Sciences, Univ of Basel, Basel, Switzerland.*

Background: Aldosterone is the main mineralocorticoid hormone controlling sodium balance, fluid homeostasis and blood pressure by regulating sodium reabsorption in the Aldosterone Sensitive Distal Nephron (ASDN). Germline loss-of-function mutations of the mineralocorticoid receptor (MR) in humans and in mice lead to the "renal" form of type 1 pseudohypoaldosteronism (PHA-1), a case of aldosterone resistance characterized by salt wasting, dehydration, failure to thrive, hyperkalemia and metabolic acidosis.

Methods: To investigate the importance of MR in adult epithelial cells, we generated nephron-specific MR knockout mice (MR^{Par&LCl}) using a doxycycline inducible system.

Results: Under standard diet, MR^{Par&LCl} mice exhibit inability to gain weight and significant weight loss compared to control mice. Interestingly, despite failure to thrive, MR^{Par&LCl} mice survive but develop a severe PHA-1 phenotype with higher urinary Na⁺ levels, decreased plasma Na⁺, hyperkalemia and higher levels of plasma aldosterone. This phenotype further worsens and becomes lethal under a sodium-deficient diet. NCC protein expression and its phosphorylated form are downregulated in the MR^{Par&LCl} knockouts, as

well as α ENaC protein level, whereas the expression of glucocorticoid receptor (GR) is increased. A diet rich in Na⁺ and low in K⁺ does not restore plasma aldosterone to control levels, but is sufficient to restore body weight, plasma and urinary electrolytes.

Conclusions: In conclusion, MR expression along the nephron and in the collecting duct system during adulthood is crucial for Na⁺ and K⁺ homeostasis, and its deletion cannot be compensated neither by sodium transporters including ENaC, nor by GR overexpression, but solely by a high Na⁺ and low K⁺ rescue diet.

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TH-PO428

The Succinate Receptor 1 Is a Physiological Regulator of the Renin-Angiotensin Aldosterone System Peter M.T. Deen,¹ Claudia Carmone,¹ Ana Carolina Ariza,¹ Steef Kurstjens,¹ Olivier Devuyst,² Joris Hubertus Robben.¹ ¹Physiology, Radboud Univ Medical Centre, Nijmegen, Netherlands; ²Physiology, Univ of Zürich, Zürich, Switzerland.

Background: It has been shown that oxidative cell stress in diabetes type I (T1DM) induces tubular release of mitochondrial succinate and that subsequent activation of the SUCNR1 in the juxta-glomerular apparatus is needed for renin release and T1DM-induced hypertension. Here, we tested whether the SUCNR1 also has a physiological role in renal water and electrolyte handling.

Methods: Wild-type (wt) and SUCNR1^{-/-} mice 10 weeks old were placed in metabolic cages and 24h clinical parameters were analyzed in order to assess physiologically relevant differences. After sacrifice, kidneys were weighed and collected for further analysis.

Results: Blood and urine analysis of wt and SUCNR1^{-/-} mice showed that loss of SUCNR1 increased sodium and urea excretion, reduced renal renin and plasma angiotensin II (AngII) and aldosterone levels. Immunoblotting revealed a downregulation of the most crucial sodium transporters (NHE3, NCC and ENaC) in SUCNR1^{-/-} mice. Fractional excretion of urea and water were increased in absence of the receptor, coinciding with reduced AQP2 abundance. With an unchanged overall morphology, wet, but not dry, weights of kidneys of SUCNR1^{-/-} mice were significantly increased than of wild-type littermates.

Conclusions: Our data reveal that the SUCNR1 is essential for the physiological maintenance of renin and AngII levels, and proper proximal tubule and collecting duct sodium reabsorption. The increased wet kidney mass is likely due to tubular dilation due to increased tubular pressure because of life-long diuresis. Our data thus indicate that the mammalian SUCNR1 is a physiological regulator of water and volume homeostasis.

Funding: Government Support - Non-U.S.

TH-PO429

Adult Nephron-Specific Beta- and Gamma-ENaC Knockout Mice Develop a Severe Pseudohypoaldosteronism Type 1 (PHA1) Emilie Boscardin,¹ Romain Perrier,² Chloe Sergi,¹ Bernard C. Rossier,¹ Edith Hummler.¹ ¹Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; ²Inst of Chemistry and Biology of Membranes and Nano-Objects, Univ of Bordeaux, Pessac, France.

Background: The epithelium sodium channel (ENaC) consists of three subunits (alpha, beta and gamma ENaC) that are expressed at the apical side in tight epithelia in the kidney, and is limiting for sodium reabsorption. Mutations in ENaC subunits is causative for the human pseudohypoaldosteronism type 1 (PHA-1), a salt-losing syndrome. Since mice with ubiquitous and constitutive gene inactivation of beta- and gamma-ENaC die soon after birth, the consequences of a kidney-specific deletion of either beta- or gamma-ENaC cannot be studied in adulthood. Therefore, we aimed to unveil the specific role of these ENaC subunits in the adult kidney using an inducible and kidney-specific CreloxP-mediated recombination system.

Methods: We used 4-weeks old doxycycline inducible nephron-specific beta- and gamma-ENaC knockout mice obtained by crossing the double transgenic mouse (PAX8/LC1), which express the reverse tetracycline transactivator under the control of a tetracycline response element (Traykova-Brauch et al., 2008) with the floxed Senn1b and Senn1g mice, respectively (Mérillat et al, 2009).

Results: Already following 3-4 days of doxycycline treatment, beta- and gamma-ENaC KO mice develop a severe and lethal PHA-1, characterized by severe body weight loss, severe hyperkalemia (beta-ENaC KO: 11mM, n=7, Ctl: 5 mM, n=21, p<0.001; gamma-ENaC KO: 11mM, n=6, Ctl: 5mM; n=7, p<0.001), and dehydration. Beta-ENaC KO additionally suffer from severe hyponatremia, while the gamma-ENaC KO present with significant decreased plasma sodium concentration.

Conclusions: Our data demonstrate that the single beta- and gamma-ENaC subunits are crucial for daily maintaining sodium and potassium balance in adulthood.

Funding: Government Support - Non-U.S.

TH-PO430

New Mechanistic Insights into the Regulation of ENaC by AMPK in Kidney Epithelial Cells Hui Li,^{1,2} Kenneth R. Hallows.^{1,2} ¹Medicine, Univ of Pittsburgh School of Medicine, Pittsburgh, PA; ²Medicine, Univ of Southern California Keck School of Medicine, Los Angeles, CA.

Background: Renal collecting duct epithelial Na⁺ channels (ENaCs) play a key role in total body volume and blood pressure control. The metabolic sensor AMP-activated protein kinase (AMPK) inhibits ENaC currents in kidney and other epithelial cells, but

the mechanisms involved are unclear. We hypothesized that AMPK regulation of ENaC could occur via modulation of ENaC degradation, ENaC subunit cleavage status, and/or ENaC protein synthesis.

Methods: Mouse polarized kidney cortical collecting duct (mpkCCD_{cl4}) cells were cultured on Transwells for immunoblot analysis and equivalent short-circuit current (I_{sc}) measurements of ENaC following AMPK activity modulation and proteasomal or lysosomal inhibitor treatments. Apical domain biotinylation assays were performed to measure changes in ENaC apical membrane expression, and cycloheximide chase assays were performed to investigate ENaC stability.

Results: AMPK activation decreased cellular ENaC stability in cycloheximide chase assays. ENaC-dependent I_{sc} was inhibited by the AMPK activators AICAR and A769662 (Abbott), and these effects were blocked by the proteasomal inhibitor MG132, but not by the lysosomal inhibitor leupeptin. Western blot analyses revealed that AMPK activation decreased both mature and immature b-ENaC expression as well as cleaved g-ENaC expression, while increasing uncleaved g-ENaC expression. Moreover, treatment of mpkCCD_{cl4} cells with AMPK activators decreased p70S6K expression, suggesting decreased signaling of the mTOR pathway involved in protein synthesis and cell proliferation. Finally, AMPK activation decreased apical cell surface expression of both mature b- and cleaved g-ENaC, the active forms of ENaC, an effect that was blocked by MG132.

Conclusions: AMPK-dependent regulation of ENaC in mpkCCD_{cl4} cells occurs by: 1) increased targeting of ENaC for proteasomal degradation, thereby decreasing cellular ENaC stability; 2) inhibition of g-ENaC cleavage and g-ENaC surface expression; and 3) inhibition of ENaC protein synthesis along with mTOR pathway inhibition.

Funding: NIDDK Support

TH-PO431

Sodium Retention in Nephrotic Syndrome Occurs Independently of Proteinuria Alexey Larionov,¹ Geraldine Mollet,² Corinne Antignac,³ Franziska Theilig.¹ ¹Medicine, Anatomy, Fribourg, Switzerland; ²Inserm U1163, Paris, France; ³Inserm U983, Paris, France.

Background: Patients with nephrotic syndrome often present symptoms of volume retention, such as edema formation or hypertension. The primary dysregulation was localized to the renal cortical collecting duct and involves an inappropriate activation of the epithelial sodium channel, ENaC. Plasma proteases passing the leaky glomerular filter were made responsible; however, clinical observation demonstrated signs of volume retention before the initiation of proteinuria.

Methods: To elucidate the relationship between sodium retention and proteinuria tamoxifen-inducible podocin^{Cre}; Nphs2^{fl/fl} were used and metabolic cage experiments for 4 weeks were performed and functional renal parameters were determined. Additionally, morphological and biochemical analysis were performed on kidneys harvested 9 days or 21 days after the beginning of the treatment. **Results:** Compared to Nphs2^{fl/fl}; podocin^{Cre}; Nphs2^{fl/fl} demonstrated reduced sodium excretion on day 7 (Na⁺/creatinine: 246±10 vs. 220±8 μmol/mg) while proteinuria occurred on day 11 (protein/creatinine: 13±1 vs. 6.85±0.8 mg/mg). Blood pressure started to increase on day 10 (BP: 120±12 vs. 74±10 mmHg) and remained high till the end of the experiment. In mice with nephrotic syndrome western blot analysis of kidneys harvested on the day 9 of the experiment demonstrated no change in the full length ENaC subunit abundance and a 3-fold increase in the 30 kDa α ENaC cleavage product. Nephrotic kidneys at the day 21 of the experiment demonstrate strongly increased abundance of full length and cleaved forms of α - and γ ENaC.

Conclusions: Our experiments demonstrate the occurrence of a possibly endogenous protease responsible for cleaving α ENaC which may lead to increased sodium retention and hypertension in the early phase of the nephrotic syndrome.

Funding: Government Support - Non-U.S.

TH-PO432

Altered Renal Electrolyte Handling in Mice with Genetic Knockout of the Insulin-Like-Growth Factor-1 Receptor (IGF1R) from the Collecting Duct Principal Cell Carolyn M. Ecelbarger, Marcus J. Byrd, Patrice Dixon, Lijun Li. Dept of Medicine, Georgetown Univ, Washington, DC.

Background: IGF1, produced predominantly in liver, can be increased in the circulation during metabolic syndrome (MetS) due to hyperinsulinemia. In addition to anabolic effects, IGF1 has been shown to activate the epithelial sodium channel (ENaC) in the renal collecting duct (CD); however, the role of the IGF1R in these effects is uncertain, since the insulin receptor can also bind IGF1.

Methods: To address the role of IGF1R in the CD, we produced CD-principal-cell-select knockout (KO) mice, by crossing mice with Cre-recombinase driven by an aquaporin-2 promoter with mice with loxP sites flanking IGF1R gene. Adult KO mice were of normal body weight and had no overt alterations in kidney structure/function. To test the impact of IGF1 infusion on urinary electrolytes, anesthetized male WT and KO mice were infused via the jugular vein with either saline vehicle (V) or a 290 μM solution of IGF1 (I) in saline at a rate of 15 μl/min for 60 minutes (n = 5/genotype/treatment). Urine was collected via a cannulated bladder.

Results: Urine volume was reduced by IGF1 and the reduction was blunted in the KO (μl/60 min): 142 ± 41 (WTV), 45 ± 9 (WTI), 86 ± 9 (KOV), 73 ± 8 (KOI), p < 0.018 for treatment. In WT, IGF1 infusion led to a significant 42, 65, and 67% reduction in the concentration of Na⁺, K⁺, and Cl⁻, respectively in urine. Total urine Na⁺ in the WTI was 20% of WTV. In contrast, the excretion of electrolytes was relatively maintained in KO, i.e., IGF1 led to a 19, 21, and 17% reduction in Na⁺, K⁺, and Cl⁻ concentrations, respectively, and means (KOV versus KOI) were not significantly different. The ratio of Na⁺ to K⁺ in the urine was also affected by genotype, i.e., increased by 76% in the WT, but reduced

by 9% in the KO ($p = 0.023$ for interaction). A benzamil test (ENaC antagonist, 1.4 mg/kg-bw, i.p.) revealed 23, 34, and 27% (all significant) reduced total Na⁺, K⁺ and Cl⁻ in KO versus WT in 4-hour urine.

Conclusions: These results support a role for IGF1 via the IGF1R to increase Na⁺ and Cl⁻ reabsorption in the CD, through activation of ENaC. Thus, IGF1 may play a role in sodium retention associated with MetS.

Funding: NIDDK Support

TH-PO433

ENaC Activity in the Cortical Collecting Duct of HKA₁ H,K-ATPase knockout Mice Is Uncoupled from Na Intake James D. Stockand,¹ Elena V. Mironova,¹ Vladislav V. Bugay,¹ I. Jeanette Lynch,^{2,3} Michelle L. Gumz,^{2,3} Charles S. Wingo,^{2,3} ¹Univ of Texas HSC, San Antonio, TX; ²NF/SG VHS, Gainesville, FL; ³Univ of Florida, Gainesville, FL.

Background: The renal H,K-ATPases are integral membrane proteins of the collecting duct (CD), a segment that mediates Na reabsorption via the mineralocorticoid regulated epithelial Na channel, ENaC. ENaC activity is inversely related to dietary Na intake, a relationship essential to blood pressure (BP) regulation, and its dysfunction contributes to salt-sensitive hypertension. Mineralocorticoids stimulate the activity and expression of renal H,K-ATPases. We hypothesized that HKA₁ H,K-ATPase knockout (KO) would affect ENaC activity.

Methods: Na reabsorption was measured by *in vitro* microperfusion in CCD from KO and control mice fed a 0.2% Na diet. Single channel analysis of ENaC activity in split open CCD by cell-attached patch clamp and measurements of urinary ATP were performed on KO and control mice fed a 0, 0.2, or 2.0% Na diet.

Results: Na reabsorption in the KO was significantly less than in controls and was not significantly inhibited by benzamil. ENaC activity in the KO is uncoupled from Na intake. When fed a 2.0% Na diet ENaC activity is higher in the KO vs. controls; and is lower on a 0% Na diet in KO vs. controls with no difference in activity in the KO on any of the Na diets. Preliminary results suggest that purinergic regulation of ENaC by a local signaling system is abnormal in the KO contributing to inappropriate channel responses to changes in dietary Na. KO mice have lower urinary ATP than controls and show no dietary Na-effect on ATP in contrast to controls where ATP is proportionally related to dietary Na intake. The defect in the KO is likely upstream of the inhibitory purinergic receptor since ENaC in the KO responds normally to exogenous ATP.

Conclusions: These results implicate the HKA₁ H,K-ATPase in the maintenance of Na homeostasis. The lack of response to Na intake implies that renal Na excretion and BP in the KO are expected to be abnormal particularly at extremes in dietary Na intake. Dysfunctional regulation of ENaC and compromised purinergic signaling in the CD are predicted to contribute to the expected BP phenotype.

Funding: Veterans Administration Support

TH-PO434

High Cholesterol Diet (HCD) Impairs K Secretion in the Rabbit Cortical Collecting Duct (CCD) Rolando Carrisoza-Gaytan, Daniel Flores, Lisa M. Satlin. *Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The apical BK channel in the CCD mediates flow-induced K secretion (FIKS). BK channels possess multiple cholesterol recognition/interaction motifs in the α subunit and, in non-renal cells, are inhibited by enhanced cholesterol content in the lipid membrane and hypercholesterolemia. Cholesterol determines membrane fluidity, and changes in membrane cholesterol are expected during postnatal development and in response to HCD. We speculated that HCD, via enhanced incorporation of cholesterol into the plasma membrane (PM), inhibits BK channel-mediated FIKS in the CCD.

Methods: NZW rabbits were randomized after weaning to receive either a standard or a cholesterol enriched diet (HCD; 0.3%) for 4-5 wks, at which time the animals were sacrificed. Kidneys were dissected for (i) isolation of renal cortical membranes for immunoblotting of BK α , ROMK and ENaC β , and (ii) microperfusion of isolated CCDs to measure net Na absorption (JNa) and net K secretion (JK).

Results: Rabbits fed HCD ($n=5$) vs. control ($n=4$) showed lower plasma [Na⁺] (130.7±0.7 vs. 137.1±0.7 mM; $P<0.001$), no difference in plasma [K⁺], and greater serum cholesterol (30,491.6±253.6 vs. 1413.2±231.1 mg/mL; $P<0.01$). Immunoblotting demonstrated a greater abundance of ROMK and ENaC in total membranes and lower abundance of BK and ENaC in cortical PMs of HCD vs. control ($n=2$ in each group). In 5 HCD CCDs, JNa increased from 14.4±7.9 to 32.3±10.0 pmol/min.mm ($P<0.02$) in response to an increase in flow rate from 1 to 5 nl/min.mm; this flow-stimulated increase in JNa was less than observed in historical controls (13.2±2.1 to 72.2±10.3; $n=13$; $P<0.01$). In HCD CCDs, JK increased from -4.8±1.6 to -12.4±2.5 pmol/min.mm ($P<0.05$) in response to a 5-fold increase in flow rate; these transport rates are half those observed in historical controls (-10.4±2.2 to -22.7±5.6; $n=13$; $P<0.04$).

Conclusions: Our results suggest that HCD blunts flow-stimulated but not basal JNa, and inhibits basal JK and FIKS, which may be due to a reduced abundance of ENaC and BK channels in the CCD. Whether enhanced incorporation of cholesterol into the PM of the CCD underlies these changes in transport is currently under investigation.

Funding: NIDDK Support

TH-PO435

Net K Secretion in Thick Ascending Limb of Mice on Low Na High K Diet Bangchen Wang, Donghai Wen, Ryan J. Cornelius, Yang Yuan, Huaqing Li, Jun Wang-France, Steven C. Sansom. *Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.*

Background: It has been long understood that thick ascending limb (TAL) reabsorbs Na⁺, Cl⁻ and K⁺, and high K diet inhibits NaCl reabsorption in TAL. In the present study, however, we found a persistent NaCl reabsorption and a net K secretion in TAL of mice on a low Na high K diet (LNaHK) that is dependent on β_4 subunit of large Ca-activated K channels (BK). We hypothesized that K secretion in the TAL was the result of K recycling via BK- α/β_4 from the medullary collecting ducts (MCD).

Methods: Wild-type (WT) and mice with a knock-out of BK β_4 (KO) were fed either a control or LNaHK diet for 7-10 days. They received intraperitoneal (IP) injections of vehicle (veh), furosemide (furo), amiloride (ami), or furosemide + amiloride (furoami) and were placed in metabolic cages for 12 hours to collect urine. Urine and plasma [Na] and [K] were measured with flame photometry. Micropuncture was used to measure [K] in the early distal tubule (EDT) of mice before and after IP injection of furo. Fluorescent immunohistochemistry (FIHC) and western blotting were used to determine BK- α and Na-K-Cl cotransporter (NKCC2) expressions.

Results: In WT on a control diet, K clearance was higher in furo-treated mice compared to veh due to increased distal flow. However, in WT on LNaHK, K clearance was significantly lower in furo-treated mice despite increased distal flow, and furoami decreased K clearance more than either drug alone. In KO on LNaHK, K clearance was not different between furo and veh groups. Micropuncture studies showed that furo decreased [K] in EDT of WT on control diet but increased [K] in EDT of WT on LNaHK. In WT on LNaHK, Na clearance was higher and urine osmolality lower in furo-treated mice compared to veh, indicating NKCC2 was still active. NKCC2 expression in medullary TAL was higher in WT on LNaHK compared to control diet. FIHC showed that BK- α was expressed in the apical membranes of MCD of WT on LNaHK, but not KO, which may mediate K recycling in MCD.

Conclusions: These results suggest that there is a furosemide-sensitive BK β_4 -dependent net K secretion in the thick ascending limb of mice on LNaHK diet.

Funding: NIDDK Support

TH-PO436

A Decrease in ENaC and ROMK Activity in the Late Distal Convoluted Tubule/Connecting Tubule May Contribute Hyperkalemia in PHAII Mutant WNK4 Knockin Mice WenHui Wang. *Pharmacology, New York Medical College, Valhalla, NY.*

Background: Pseudohypoaldosteronism type II (PHAII) is caused by mutations in with-no-lysine kinase 1 (WNK1) and WNK4. Mice harboring PHAII WNK4 mutant by genomic manipulation (TgWNK4^{PHAII}) developed typical PHAII phenotypes characterized by hypertension and hyperkalemia. While the hypertension is caused by an excessive Na absorption through NCC in the distal convoluted tubule (DCT), hyperkalemia has been attributed to a low Na delivery to the distal nephron. However, the role of ENaC and ROMK in causing hyperkalemia is not explored.

Methods: In the present study, we used the whole-cell patch-clamp technique to examine the ROMK and ENaC activity in the late DCT (DCT2) and early connecting tubule (CNT). The tubule was split open to expose the apical membrane and was bathed in a solution containing 135 K-gluconate and 10 KCl. The pipette contains a symmetrical K solution.

Results: Western blot confirmed that NCC expression is upregulated in TgWNK4^{PHAII} mice in comparison to the WT and TgWNK4^{WT} mice. The whole cell recording detected amiloride-sensitive Na currents and TPNOQ-sensitive K currents (ROMK) in DCT2/CNT. However, both Na currents (40 pA/per cell) and ROMK currents (350 pA per cell) in DCT2/CNT of TgWNK4^{PHAII} mice were significantly smaller than those in WT (Na currents, 260 pA per cell; ROMK 1190 pA per cell) and TgWNK4^{WT} mice (Na currents, 230 pA per cell; ROMK, 960 pA per cell). We also measured the whole cell K currents in the DCT1 which lacks apical ROMK and ENaC channels. In contrast to Na and ROMK currents in the DCT2/CNT, the basolateral K currents in the DCT1 were similar among WT, TgWNK4^{WT} and TgWNK4^{PHAII} mice. This suggests that the upregulation of NCC in TgWNK4^{PHAII} mice did not stimulate the basolateral Kcnj10 channels.

Conclusions: We conclude that ENaC and ROMK channel activity are inhibited in TgWNK4^{PHAII} mice and that WNK4^{PHAII}-induced inhibition of ENaC and ROMK may contribute to the suppression of K secretion in the DCT2/CNT in addition to a reduction of Na delivery.

Funding: NIDDK Support

TH-PO437

Gilz Regulates Sodium and Potassium Balance During Dietary Sodium Restriction Priyanka Rashmi, Michael Ng, David Pearce. *Univ of California San Francisco, San Francisco, CA.*

Background: The hormonal regulation of ion transport by the kidney tubules is critical for regulating sodium and potassium balance in blood, extracellular fluid volume and blood pressure. The renin-angiotensin-aldosterone (RAAS) system is the primary regulator of Na⁺ reabsorption and K⁺ secretion. RAAS regulates multiple transporters implicated in electrolyte homeostasis such as Na⁺Cl⁻ cotransporter (NCC) and epithelial sodium channel (ENaC). While both ENaC and NCC mediate Na⁺ reabsorption, they affect K⁺ differently: Electrogenic Na⁺ reabsorption via ENaC stimulates K⁺ excretion, while

electroneutral reabsorption of Na⁺ via NCC inhibits K⁺ secretion by competing with ENaC for Na⁺ reabsorption. Glucocorticoid induced leucine zipper protein (Gilz) is an aldosterone-regulated gene product reported to cause changes in ion balance but the mechanism has not been explored. In this study we use the Gilz knock out (Gilz^{-/-}) mouse generated in our laboratory to show that during sodium deprivation Gilz^{-/-} mice come into sodium balance *more quickly*, than do wild type (WT) and become significantly hyperkalemic. These observations raised the possibility that loss of Gilz results in hyperactivation of an electroneutral Na⁺ transporter, which does not stimulate K⁺ secretion. Indeed, Gilz knock out mice are more sensitive to thiazide diuretics suggesting increased NCC activity. Consistently, expression of phosphorylated NCC (pT53/58) at the plasma membrane is also higher in the kidneys of Gilz knock out mice than in the WT mice maintained on a sodium deficient diet. In HEK293T cells, overexpression of Gilz isoform 1 (Gilz1) inhibits NCC activation in response to hypotonic low-Cl conditions as assessed by its phosphorylation at T53 and T58. Gilz mediated NCC inhibition is lost in the presence of constitutively active SPAK suggesting that it is at least in part mediated by WNK1/4-SPAK pathway. Indeed, co-expression of Gilz1 inhibits SPAK phosphorylation at S373. Together, our results suggest that during sodium restriction, Gilz1 shifts sodium reabsorption from NCC to ENaC, thus favoring K⁺ excretion. This effect may be critical for the maintenance of eukalemia in the face of Na⁺ restriction.

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TH-PO438

Pharmacological Inhibition of the Circadian Regulatory Casein Kinases 1Δ/ε Prevents Aldosterone-Mediated Induction of Na-Cl Cotransporter Activity Michelle L. Gumz,^{1,2} Kristen Solocinski,^{1,2} Robert S. Hoover,^{3,4} Benjamin S. Ko.⁵ ¹Medicine/Nephrology, Univ of Florida, Gainesville, FL; ²Biochemistry and Molecular Biology, Univ of Florida, Gainesville, FL; ³Medicine/Nephrology, Emory Univ, Atlanta, GA; ⁴Research Service, Atlanta Veteran's Administration Medical Center, Atlanta, GA; ⁵Medicine, Univ of Chicago, Chicago, IL.

Background: The circadian clock protein Per1 transcriptionally regulates the Na-Cl co-transporter NCC and members of the WNK kinase cascade. Per1 must be phosphorylated by casein kinase 1Δ/ε (CK1Δ/ε) in order to enter the nucleus. Previously, we showed that inhibition of CK1Δ/ε decreased Per1 nuclear protein levels and decreased NCC activity under basal conditions in mouse distal convoluted tubule cells (mDCT15).

Methods: mDCT15 cells were treated with a CK1Δ/ε inhibitor prior to either aldosterone (100 nM for 24 hr) or Angiotensin II (AngII) (10⁻¹¹M for 30 or 120 min) treatment. NCC activity was determined by measuring thiazide-sensitive, Cl-dependent ²²Na uptake.

Results: NCC activity was significantly increased following either aldosterone or AngII treatment, consistent with previously published data. In the presence of the CK1Δ/ε inhibitor, however, the aldosterone-dependent increase in NCC activity was prevented. In contrast, the AngII-dependent increase in NCC activity was not affected by CK1Δ/ε treatment.

Conclusions: Inhibition of Per1 nuclear entry via pharmacological blockade of CK1Δ/ε appears to prevent the aldosterone-mediated but not AngII-mediated induction of NCC activity. These results suggest an important role for the circadian clock proteins Per1 and CK1Δ/ε in aldosterone-dependent regulation of NCC with possible implications for the treatment of hypertension.

Funding: NIDDK Support, Veterans Administration Support, Private Foundation Support

TH-PO439

Disruption of 14-3-3 γ Binding to NCC Altered the Aldosterone-Mediated Regulation of NCC Protein Expression Xiuyan Feng,^{1,2} Zhizhi Zhuang,¹ Courtney Marie Caroti,^{1,2} Hui Cai.^{1,2} ¹Medicine, Emory Univ School of Medicine, Atlanta, GA; ²Section of Nephrology, Atlanta Veterans Administration Medical Center, Decatur, GA.

Background: 14-3-3 γ belongs to a family of multifunctional regulatory proteins that mainly bind to phosphorylated Ser/Thr residues in the target proteins. Previous data have shown that 14-3-3 proteins regulate renal ion channel and transporter such as ENaC and UT-A1 by altering their ubiquitinations. We have previously shown that aldosterone increases both total and surface expressions of sodium chloride co-transporter (NCC) via reducing NCC ubiquitination. Thus, we investigated whether 14-3-3 γ is involved in the aldosterone-mediated regulation of NCC.

Methods: Cell culture, transfection, western blot analysis, immunostaining, confocal microscopy, co-immunoprecipitation and C57/B6 mice were used for this study.

Results: Co-immunoprecipitation (co-IP) in Cos-7 cells showed that 14-3-3 γ is the strongest one binding to NCC among all isoforms of 14-3-3. Immunostaining and confocal microscopy also showed that 14-3-3 γ is localized in distal convoluted tubule in mice. Co-IP experiments in Cos-7 cells showed that wild-type (WT) 14-3-3 γ binds to NCC, whereas 14-3-3 γ K50E mutant almost completely loses its binding to NCC. Western blot analysis showed that WT 14-3-3 γ significantly decreased total NCC expression by 63 % compared to the control group, whereas 14-3-3 γ K50E mutant did not change NCC protein expression. WT 14-3-3 γ increased NCC ubiquitination by 1.5 fold (1.5 ± 0.44 vs 1.00), whereas 14-3-3 γ K50E mutant did not alter NCC ubiquitination compared to the control group. In addition, we implanted aldosterone osmotic mini-pump to WT mice for 14 days and then harvested the kidney tissues. Western blot analysis showed that aldosterone treatment increased total NCC expression by 1.68 folds (1 ± 0.28 vs 1.68 ± 0.15) and decreased the ubiquitinated NCC by 56 %. Co-IP also showed aldosterone decreased the 14-3-3 γ binding to NCC by 57 % without changing total 14-3-3 γ expression.

Conclusions: These results suggested that aldosterone up-regulates NCC expression by disruption of 14-3-3 γ binding to NCC that leads to decreasing NCC ubiquitination.

Funding: Veterans Administration Support, Private Foundation Support

TH-PO440

Calcineurin Inhibitors Upregulate the Thiazide-Sensitive NaCl Cotransporter in Urinary Exosomes of Kidney Transplant Patients Omar Tutakhe,¹ Mathijs van de Vrie,¹ Marco Valdez Flores,¹ Ewout J. Hoorn,² Luuk Hilbrands,¹ Joost Hoenderop,¹ René J. Bindels.¹ ¹Physiology and Nephrology, Radboud Univ Medical Center, Nijmegen; ²Div of Nephrology & Transplantation, Erasmus Medical Center, Rotterdam, Netherlands.

Background: Calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (Tac), are the cornerstone of immunosuppression and superior in preventing acute allograft rejection. This benefit, however, comes at the cost of common adverse effects including hypertension. Recently several studies have shown that CNI-induced hypertension is largely mediated by activation of the thiazide-sensitive NaCl cotransporter (NCC). The aim of the present study was to further substantiate the role of NCC in CNI-induced hypertension by assessing the abundance and activity of NCC in urinary exosomes of CNI-treated patients.

Methods: Kidney transplant patients were enrolled 6 months after transplantation and treated with CsA (n=14), Tac (n=18) or a CNI-free immunosuppressive regimen (n=13). Six healthy subjects were also included. Urinary exosomes were isolated from 10 ml midstream urine samples by ultracentrifugation and normalized by urinary creatinine. The corresponding immunoblots were probed with antibodies specifically recognizing NCC and pNCC-T58. To confirm equal loading of the samples the abundance of the exosomal marker CD9 was determined.

Results: NCC was detected in urinary exosomes by immunoblots as two bands of ~260 and ~130 kDa representing the dimeric and monomeric forms, respectively. Abundance of both NCC and pNCC-T58 in urinary exosomes of CsA and Tac groups was significantly increased in comparison to patients treated with a CNI-free immunosuppressive regimen and healthy subjects. Moreover, both the NCC and pNCC-T58 abundance was 2.5-fold higher in CsA group compared to Tac group. CD9 abundance in urinary exosomes was similar between the various groups.

Conclusions: The present study demonstrates that: *i*) total and phosphorylated NCC abundance is increased in urinary exosomes of CNI-treated kidney transplant patients; *ii*) urinary exosomes can be used as a novel biomarker to assess NCC abundance and activity in CNI-treated kidney transplant patients.

Funding: Government Support - Non-U.S.

TH-PO441

Generation of Hypertension-Associated STK39 Polymorphism Knock-in Cell Lines with the CRISPR/Cas9 System Shintaro Mandai, Takayasu Mori, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Previous genome-wide association studies identified *STK39*, encoding STE20/SPS1-related proline/alanine-rich kinase (SPAK), as one of a limited number of hypertension susceptibility genes. A recent meta-analysis confirmed the association of *STK39* intronic polymorphism rs3754777 with essential hypertension, among previously reported hypertension-associated *STK39* polymorphisms. However, the physiological function of this polymorphism is yet to be clarified.

Methods: To investigate whether SPAK and the downstream targets are modulated by this polymorphism, we generated *STK39* rs3754777 G > A knock-in human embryonic kidney (HEK293T) cell lines with the clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system, using a double-nickase (Cas9-D10A), single guide RNAs targeting *STK39* intron 5 around SNP, and a 100-bp donor single-stranded DNA oligonucleotide.

Results: Homozygous (A/A) and heterozygous (G/A) knock-in cell lines were generated. Reverse transcription-polymerase chain reaction (RT-PCR) with sequencing analyses revealed the identical *STK39* transcripts among the wild-type and both knock-in cell lines. Quantitative RT-PCR showed increased *STK39* mRNA expression, and immunoblot analysis revealed increases in total and phosphorylated SPAK with increased phosphorylated Na-K-Cl cotransporter isoform 1 (NKCC1) in both knock-in cell lines. The largest increases in these molecules were observed in the homozygous cell line.

Conclusions: *STK39* intronic polymorphism rs3754777 increases *STK39* transcription, leading to activation of the SPAK-solute carrier family 12 (SLC12A) signaling cascade. Activation of the target cation-chloride cotransporters may be responsible for hypertension susceptibility in individuals with this polymorphism.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO442

The Major Contribution of WNK4 to the Pathogenesis of Pseudohypoaldosteronism Type II (PHAII) Caused by the KLHL3 Mutation R528H Koichiro Susa, Eisei Sohara, Daiei Takahashi, Tatemitsu Rai, Shinichi Uchida. *Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.*

Background: Recently, we reported that KLHL3^{R528H/+} knock-in mice, a PHAII model mouse, exhibit the activation of OSR1/SPAK-NCC signaling by the increased protein levels of both WNK1 and WNK4 due to impaired protein degradation by the mutant KLHL3. Previously we have demonstrated that the amount of phosphorylated and total NCC decreased to almost undetectable levels in the WNK4^{-/-} mice, indicating that WNK4 plays the major role in NCC regulation and that other WNKs including WNK1 and WNK3 cannot compensate for the absence of WNK4. In this study, we sought to determine the contribution of WNK4 to the activated OSR1/SPAK-NCC signaling in the KLHL3^{R528H/+} knock-in mice.

Methods: We generated WNK4^{-/-}KLHL3^{R528H/+} mice by crossing the WNK4^{-/-} mice with the KLHL3^{R528H/+} mice. In addition, we also generated WNK4^{-/-}KLHL3^{R528H/R528H} mice. Thereafter, WNK-OSR1/SPAK-NCC phosphorylation signal cascade was examined in kidneys from these mice.

Results: As previously reported, compensatory increased WNK1 was observed in the WNK4^{-/-} mouse kidney, compared to WNK4^{+/+}. Expectedly, both WNK4^{-/-}KLHL3^{R528H/+} mice and WNK4^{-/-}KLHL3^{R528H/R528H} mice showed further increases in WNK1 in the kidney, due to the KLHL3 mutation. However, although phosphorylated SPAK was increased in the whole kidney to the levels comparable with that in wild-type mouse, total NCC and NCC phosphorylated at S71 were almost completely absent even in WNK4^{-/-}KLHL3^{R528H/R528H} mice.

Conclusions: As in the wild-type mice, WNK4 plays the major positive role in the regulation of NCC in the KLHL3^{R528H/+} PHAII model mice.

TH-PO443

Mechanism of Regulation of WNK Kinases Elizabeth J. Goldsmith. *Biophysics, Univ of Texas Southwestern Med Center Dallas, Dallas, TX.*

Background: WNK1 is a protein kinase on pathway for the regulation of cation-chloride cotransporters. We demonstrated that the kinase domain of WNK1 binds chloride ion and inhibits WNK1 autophosphorylation (Piala et al. *Sci Signaling* 7 ra41 2014). New crystallography improves our understanding of the mechanism of this regulation.

Methods: New crystals of the kinase domain of WNK1 (210-483)/S* (phosphorylated) were obtained using peg-ion screening, that yielded crystals diffracting to 2.1 Å. Data were collected at the APS Beamline 19, and data were processed in HKL2000; the structures was solved by molecular replacement. In addition, the structure of a chloride sensing mutant was solved in an unphosphorylated form of the same construct on diffraction to 2.5 Å.

Results: The structure of the phosphorylated form reveals conformational changes associated with dislodging the chloride from the active site of WNK1, and how a ATP analog, AMP-PNP, binds to the unique WNK1 active site. The structure adopted however, is not in a fully active configuration based on numerous structural cues. The structure of the mutant WNK1/L299F reveals aspects of the contacts of chloride with the protein structure.

Conclusions: The new structural data confirms the chloride regulation of WNK1, and strongly suggests that activation is a multistage process.

Funding: NIDDK Support, Private Foundation Support

TH-PO444

Characterisation of the Cullin-3 Mutation That Causes a Severe Form of Familial Hypertension and Hyperkalaemia Keith Siew,¹ Frances-Rose Schumacher,² Thimo K. Kurz,² Kevin O'Shaughnessy.¹ *¹EMIT, Dept of Medicine, Univ of Cambridge, Cambridge, United Kingdom; ²MRC PPU, College of Life Sciences, Univ of Dundee, Dundee, United Kingdom.*

Background: Deletion of exon-9 from Cullin-3 (CUL3, residues 403-459: CUL3^{A403-459}) causes pseudohypoaldosteronism type IIE (PHA2E), a severe form of Familial Hyperkalaemia and Hypertension (FHHT). CUL3 bound to KLHL3 ubiquitylates WNK kinases, promoting their ubiquitin-mediated proteasomal degradation. Mutations in both KLHL3 and WNK kinases cause PHA2 by disrupting Cullin-RING-Ligase formation, and since WNKs activate Na-Cl co-transporters (NCC) to promote salt retention, CUL3 regulates blood pressure. The aim of our study was to understand the pathophysiology of CUL3^{A403-459} mutations which underlies PHA2E severity.

Methods: Blood pressure traces and *in vivo* pressor responses were obtained in CUL3^{WT/A403-459} and CUL3^{WT} mice by catheterisation of the right carotid artery and jugular vein under anaesthesia (isoflurane). After sacrifice by exsanguination, tissues were harvested for electrolyte and western blot analysis. All data are mean±SEM; student t-test statistical analysis (* P<0.01; ** P<0.001).

Results: CUL3^{WT/A403-459} compared to CUL3^{WT} have elevated blood pressure [93.9±1.2 vs 81.0±0.7** MAP mmHg], hyperkalaemia [5.1±0.2 vs 4.3±0.1** K⁺ mmol/L] and hyperchloraemia [119.4±0.4 vs 115.6±0.6** Cl⁻ mmol/L] due to renal WNK4 accumulation causing NCC hyperphosphorylation. CUL3^{WT/A403-459} mice also have stiffened arteries [50.2±1.6 vs 42.6±1.8 Augmentation Index %], increased phenylephrine maximal pressor response [183.9±2.5 vs 164.9±1.4* Systolic E_{max} mmHg] and a 1.7-fold higher phosphorylation of MYPT1 in aorta suggesting increased vasoconstriction.

Conclusions: We report here a novel knock-in mouse model of CUL3^{WT/A403-459} that fully recapitulates the human PHA2E phenotype. The PHA2E mutant, CUL3^{A403-459}, is severely compromised in its ability to ubiquitylate WNKs, probably due to altered structural

flexibility. Our discovery of a vascular phenotype suggests an explanation for the severity of PHA2E. It will be important to establish if this vascular phenotype exists in PHA2E patients and can be normalised by thiazide treatment.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO445

Paracellular Na⁺ Transport by Claudin-2 Enhances the Efficiency of Oxygen Usage by the Kidney and Protects against Ischemic Injury Lei Pei,¹ Glenn Solis,² Lynn Magenheimer,¹ Mien T.X. Nguyen,³ Nikhil Kamat,³ Min Zhuo,¹ Jiahua Li,¹ Timothy A. Fields,¹ William J. Welch,² Alicia A. McDonough,³ Alan S.L. Yu.¹ *¹Univ Kansas Medical Center; ²Georgetown Univ; ³Univ Southern California.*

Background: Claudin-2 is a tight junction protein that mediates paracellular Na reabsorption in the proximal renal tubule (PT). We previously showed that claudin-2 null mice (KO) were able to conserve Na normally by upregulating transcellular Na-K-2Cl transport in the thick ascending limb. Paracellular transport exploits pre-existing electrochemical gradients to drive passive diffusion without consumption of additional ATP. We therefore hypothesized that the shifting of Na transport to transcellular pathways would lead to increased O₂ consumption, intrarenal hypoxia, and increased susceptibility to ischemic injury.

Methods: The ratio between whole kidney Na reabsorption (T_{Na}) and O₂ consumption (QO₂ = RBF X A-VO₂) was determined in KO mice and WT littermates. Intrarenal PO₂ was measured by Clark-type O₂ microelectrode. Mice were subjected to 23 min of bilateral renal ischemia and assessed for injury 48 h after reperfusion.

Results: T_{Na}/QO₂ (mol/mol) in KO mice (16.36±1.31) was significantly lower than in WT (10.34±1.33), indicating decreased efficiency of O₂ utilization. The outer medullas of KO mice kidneys were relatively hypoxic, but after furosemide, KO exhibited a 2.7-fold greater increase in PO₂ compared to WT mice. After ischemia-reperfusion injury, BUN (246.98±12.46 mg/dl KO, 72.19±21.04 mg/dl WT) and plasma creatinine (0.33±0.16 mg/dl KO, 1.45±0.08mg/dl WT) were significantly higher in KO compared to WT mice. mRNA of the injury marker, KIM-1, was also higher in KO. KO kidneys exhibited markedly worse tubule injury by histology compared to WT.

Conclusions: Our results indicate that paracellular Na transport in the PT is required for efficient utilization of oxygen in the service of sodium transport. The cost of loss of paracellular transport is medullary hypoxia and increased susceptibility to ischemic injury. Our results suggest that paracellular permeability may have evolved as a general strategy in epithelia to maximize energy efficiency.

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TH-PO446

The Diuretic and Natriuretic Effect of the GLP-1 Receptor Agonist, Exendin-4, Is Independent of Tubular NHE3 Yiling Fu,¹ Panai Song,¹ Akira Onishi,¹ Falk Bernhard Batz,¹ Manoocher Soleimani,² Meinrad Busslinger,³ Volker Vallon.¹ *¹Div of Nephrology, UC San Diego & VA San Diego Healthcare System, La Jolla, CA; ²Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; ³Research Inst of Molecular Pathology, Vienna, Austria.*

Background: Exendin-4 (EX-4) activates the glucagon-like receptor GLP-1R and is used as an antidiabetic drug, but also induces natriuresis. The natriuretic effect of EX-4 has been associated with phosphorylation and potential inhibition of Na-H-exchanger 3 in proximal tubules, but the quantitative contribution has not been defined.

Methods: Tubule-specific NHE3 knockdown mice were generated (Pax8-Cre/NHE3fl/fl [tubNHE3^{-/-}]) and compared with littermate controls (NHE3fl/fl [WT]). a) EX-4 (10 mg/kg) or vehicle was applied i.p. in a cross-over design together with an oral NaCl load (30 ml/g bw of 0.85% saline) and the urine quantitatively collected over 3 hours in metabolic cages. b) Terminal ³H-inulin clearance studies determined effects of EX4 on GFR, blood pressure (BP), and fractional fluid excretion (FE).

Results: Western blotting revealed non-detectable renal NHE3 in tubNHE3^{-/-}. tubNHE3^{-/-} and WT showed a) similar diuresis and natriuresis during vehicle application (not shown) and EX-4-induced increase in diuresis (50±14 vs 60±17 %) and natriuresis (103±34 vs 100±28 %) (each P<0.01 vs vehicle; n=9-10/group), and b) similar basal values (not shown) as well as EX4-induced changes in GFR (14±6 vs 13±9 %) and blood pressure (-3±3 vs -7±2 %); EX-4 induced similar increase in FE in tNHE3^{-/-} (1.1±0.1 to 3.1±0.8%) and WT (1.1±0.4 to 2.5±0.5%) (each P<0.01 vs basal); n=7-8/group).

Conclusions: The acute EX-4-induced diuresis and natriuresis does not require tubular NHE3 in mice.

Funding: NIDDK Support, Pharmaceutical Company Support - Astra-Zeneca

TH-PO447

Protein Carbonylation of a Single Amino Acid Residue of Na/K-ATPase a1 Subunit Dictates Na/K-ATPase Signaling and Sodium Transport in Renal Proximal Tubular Cells Yanling Yan,¹ Anna P. Shapiro,² Jiang Tian,² Deepak K. Malhotra,² Zi-jian Xie,³ Joseph I. Shapiro,^{1,2} Jiang Liu.^{1,3} *¹Pharmacology, Marshall Univ JCE School of Medicine, Huntington, WV; ²MIR at Marshall Univ, Huntington, WV; ³Medicine, Univ of Toledo, Toledo, OH.*

Background: We have demonstrated that direct carbonylation modification of the Na/K-ATPase a1 subunit regulates Na/K-ATPase signaling and subsequent transepithelial sodium transport in renal proximal tubules.

Methods: Mutation of Pro224 of rat a1 subunit. Assays for protein carbonylation, c-Src and ERK1/2 activation, Na/K-ATPase activity, NHE3 activity, active transepithelial ²²Na⁺ transport, cellular redistribution of ion transporters, etc.

Results: Cardiotonic steroids (CTS, such as ouabain) signaling through Na/K-ATPase, regulate sodium reabsorption in renal proximal tubule (RPT). By direct carbonylation modification of the actuator (A) domain of the Na/K-ATPase a1 subunit, reactive oxygen species (ROS) are required to initiate ouabain-stimulated Na/K-ATPase/c-Src signaling and subsequent regulation of active transepithelial ²²Na⁺ transport. A single mutation of Pro224 to Ala in rat a1 subunit was established into a stable cell line, and the mutant cells were compared to the wild-type RPT cells by characterization with Na/K-ATPase a1/b1 expression, [³H] ouabain binding and ouabain-sensitive ⁸⁶Rb⁺ uptake assays. The mutation of Pro224 to Ala abolishes ouabain-stimulated Na/K-ATPase/c-Src signaling, protein tyrosine phosphorylation, protein carbonylation, redistribution of Na/K-ATPase and sodium/proton exchanger isoform 3 (NHE3), and inhibition of active transepithelial ²²Na⁺ transport. However, a mutation of Ala416 to Pro in rat a1 subunit, also characterized as aforementioned, does not affect ouabain-mediated Na/K-ATPase signaling and sodium handling. The data indicates that carbonylation modification of Pro224 in rat a1 subunit dictates ouabain-mediated RPT Na/K-ATPase signal transduction and subsequent sodium transport.

Conclusions: Direct carbonylation of a single amino acid dictates ouabain-mediated Na/K-ATPase signaling and related sodium handling in renal proximal tubules.

TH-PO448

The Mineralocorticoids Receptor Regulates the Expression of Na⁺-K⁺-ATPase b₃ Subunit in Kidney Collecting Duct Cells Pablo Diaz, Cristian Degregorio, Luis F. Michea, Magdalena Gonzalez. *Univ de Chile, Chile.*

Background: Aldosterone modulates the activity of the Na⁺-K⁺-ATPase (NKA) in principal cells (PC) of kidney collecting duct (CD) via activation of the mineralocorticoid receptor (MR). The NKA is a heterodimer with a catalytic α subunit and a regulatory β subunit. a₁, b₁, and b₃ are the only subunit isoforms expressed in the kidney. The β subunit may be determinant of subcellular localization and trafficking of the α - β heterodimers, and also may have a role in the cell-cell adhesion that may be relevant in paracellular permeability. Previous studies addressed the modulation of a₁ and b₁ expression in response to aldosterone. However the role of aldosterone in the regulation of the b₃ subunit has not been analyzed. We tested the hypothesis that the activation of the MR modulates the expression of NKA b₃ subunit in CD.

Methods: C57BL/6 mice underwent adrenalectomy (ADX) or sham surgery (SHAM). The ADX mice received high salt diet or hormone replacement therapy with deoxycorticosterone (ADX+DOCA, 10mg/mL/day). In a second set of experiment mice received spironolactone (Spi, 50 mg/Kg/day) or vehicle (Control) treatment. After 3 days we obtained the kidneys (cortex and medulla) for the analysis of NKA a₁, b₁, and b₃ subunits (mRNA and protein abundance by qRT-PCR and Western blot). Finally, we studied the effect of aldosterone (0.1-100 nM) in primary culture of inner medullary collecting ducts cells (IMCD, 24 hours).

Results: Adrenalectomy increased b₃-subunit mRNA and protein abundance in mouse renal medulla but not in kidney cortex (200% vs control, P<0.05 n=4 for mRNA and 65% vs control, P<0.001, n=9 for protein). Similarly, Spi treatment increased the abundance of b₃-subunit mRNA and protein in renal medulla only (250% vs control, P<0.01, n=8 for mRNA and 100% vs control, P<0.05, n=5 for proteins). Both the ADX mice as the Spi-treated mice showed no-significant changes in the abundance of a₁ or b₁ transcripts and proteins. The treatment with Aldosterone decreased b₃ mRNA in IMCD cells (50% vs control, P<0.01, n=5).

Conclusions: We conclude that the NKA b₃ subunit expression is downregulated by the activation of the MR.

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TH-PO449

Purified Recombinant ApoL1 Forms Anion Channels in Phospholipid Bilayers John C. Edwards. *Internal Medicine, Saint Louis Univ, Saint Louis, MO.*

Background: Variants in the protein ApoL1 confer the increased risk of certain types of chronic kidney disease that is observed in people of African ancestry. ApoL1 has been reported to function as an ion channel but reports vary on the nature of this activity. We sought to characterize ApoL1 channels with anticipation that detailed properties of the channel activity of WT and variant ApoL1 may provide insight into the pathophysiology of ApoL1-associated kidney disease.

Methods: Recombinant ApoL1 was expressed in bacteria with a N-terminal GST tag replacing the signal sequence and separated from the ApoL1 coding region by a thrombin cleavage site, and with a C-terminal V5-6Histidine tag. N-octyl glucoside-solubilized protein was bound to glutathione agarose. The bound fusion protein was cleaved with thrombin, releasing ApoL1-V5His which was further purified by Ni-affinity. Channel activity was assessed using vesicle-based voltage dependent Cl and K efflux assays employing ion selective electrodes. Single channel properties were investigated using the Tip-Dip lipid bilayer approach with ApoL1 added to the bath solution.

Results: The preparation yields highly purified soluble ApoL1. Introduction of ApoL1 into phospholipid vesicles either by reconstitution via detergent dialysis, or by direct insertion into pre-formed vesicles yields a Cl selective permeability that supports voltage-driven chloride transport. The Cl channel activity requires that the protein interacts with the lipids at low pH (5.0). We do not find potassium-selective permeability when assayed at either pH 5 or 7.5. In tip-dip bilayer, ApoL1 spontaneously inserts at low pH, generating

transitions with single channel conductance of about 5 pS, and with a non-rectifying current-voltage relationship. We do not find enhanced channel activity if the bath solution is changed to pH 7.5.

Conclusions: Purified recombinant ApoL1 can insert directly into phospholipid membranes at low pH and function as an anion selective channel. A prominent difference between our preparation and that of others reported to function as a cation channel is that our method avoids denaturation and refolding. Whether the disease associated variants show altered channel properties remains to be determined.

Funding: Other NIH Support - NHLBI

TH-PO450

Using ChlopHensor to Measure Intracellular Cl⁻ in a Transporting Renal Epithelium Aylin R. Rodan,¹ Qifei Sun,¹ Drew Stenesen,² Helmut Kramer.² ¹Internal Medicine, UT Southwestern, Dallas, TX; ²Neuroscience, UT Southwestern.

Background: *Drosophila melanogaster* eat a K⁺-rich diet and secrete a KCl-rich fluid from the main segment of the renal tubule. We have previously shown that ~1/3 of transepithelial K⁺ flux through the cation-conducting principal cell is via the basolateral NKCC and is regulated by the WNK-SPAK/OSR1 kinase cascade. This pathway is activated under hypotonic conditions. Cl⁻ is a key regulator of WNK activity. Here, we measured intracellular Cl⁻ in the fly tubule using the transgenic Cl⁻ sensor, ChlopHensor.

Methods: The GAL4-UAS system was used to drive tubule expression of ChlopHensor, a pH- and Cl⁻-sensitive GFP linked to a pH- and Cl⁻-insensitive dsRed. Fluorescence after excitation at 488 nm (green), 458 nm (cyan) and 543 nm (red) was quantified using ImageJ. Calibration curves of the green/cyan ratio (to measure pH) and cyan/red ratio (to measure Cl⁻) were generated at varying intracellular pH and Cl⁻ by equilibrating in the presence of 5 mM nigericin, CCCP, valinomycin and 10 mM tributyltinchloride. Fluorescence emission was then measured in the tubule principal cells under varying conditions.

Results: In standard bathing medium (SBM), intracellular Cl⁻ concentration was 27±2 mM (n=21 cells in 7 tubules), similar to previous measurements made with double-barrelled ion-specific electrodes. In hypotonic medium, Cl⁻ decreased to 16±1 mM (p<0.0001, paired t-test). pH_i was unchanged. In a timecourse experiment, initial Cl⁻ was 30±4 mM in SBM, then decreased to 20±3, 16±2, and 15±2 mM at 10, 30 and 60 minutes of hypotonic exposure. The decrease in Cl⁻ in hypotonic conditions was blunted by increasing [K⁺] in the hypotonic medium (Δ , 8±1 mM) and increased by decreasing [K⁺] and [Cl⁻] in the hypotonic medium (Δ , 17±2 mM, p<0.05 compared to usual hypotonic and p<0.001 compared to high-K⁺ hypotonic, one-way ANOVA with Bonferroni correction).

Conclusions: Activation of the WNK-SPAK/OSR1-NKCC pathway in the *Drosophila* renal tubule under hypotonic conditions correlates with decreased intracellular Cl⁻ concentration. The decrease in Cl⁻ is accentuated when bath K⁺ and Cl⁻ are lowered, suggesting KCl efflux in hypotonic conditions, perhaps due to regulatory volume decrease mechanisms.

Funding: NIDDK Support, Private Foundation Support

TH-PO451

Potassium-Induced Dephosphorylation of Renal Sodium Chloride Cotransporter Is NOT Dependent on the Anions Naohiro Nomura, Wakana Shoda, Eisei Sohara, Tatsumitsu Rai, Shinichi Uchida. *Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.*

Background: Dietary potassium intake is strongly associated with blood pressure and cardiovascular death. High-potassium diets decrease phosphorylation of sodium-chloride cotransporter (NCC) and induce lower blood pressure. In many experimental studies using high-potassium diets, potassium chloride was added to make high-potassium diets. On the other hand, there is a recent report that a high-potassium diet made of potassium citrate increased phosphorylation of NCC. It is also known that chloride itself affects NCC phosphorylation. Thus, the accompanying anion might modulate the NCC phosphorylation response to the high potassium diets, and aldosterone also might be involved in the discrepancy. In this study, we clarified the change of NCC phosphorylation with potassium compounds accompanying different anions, and confirmed the association between potassium intake and NCC phosphorylation with acute oral infusion.

Methods: Adult C57BL/6 mice were fed potassium chloride, potassium gluconate, and potassium citrate with oral gavage. Kidneys were collected after 15 min infusion, because plasma aldosterone level did not show significant difference at this time point. Western blotting was performed with anti-phospho-NCC antibody.

Results: All potassium compound infusion showed significant decrease of NCC phosphorylation. Sodium gluconate and calcium gluconate infusion showed very little and no reduction of NCC phosphorylation respectively.

Conclusions: Rapid potassium infusion decreases phosphorylation of NCC. It is not depend on the anions at least in acute potassium infusion.

Funding: Government Support - Non-U.S.

TH-PO452

Association of Birth History and BMI with APOL1 Risk Alleles in CKiD Rebecca C. Hjorten,¹ Kimberly J. Reidy,¹ Derek Ng,² Robert Woroniecki,³ Susan L. Furth,⁴ Bradley Warady,⁵ Craig S. Wong,⁶ Larry A. Greenbaum,⁷ Marva M. Moxey-Mims,⁸ Jeffrey B. Kopp,⁸ Sophie Limou,⁸ Cheryl Ann Winkler,⁸ Frederick J. Kaskel.¹ ¹*Pediatrics/ Nephrology, Montefiore, Bronx, NY;* ²*Epidemiology, Johns Hopkins, Baltimore, MD;* ³*Pediatrics/ Nephrology, Stony Brook Univ, Stony Brook, NY;* ⁴*Pediatrics/Nephrology, Children's Hospital of Pennsylvania, Philadelphia, PA;* ⁵*Pediatric/ Nephrology, Children's Mercy, Kansas City, MO;* ⁶*Pediatrics/ Nephrology, Univ of New Mexico, Albuquerque, NM;* ⁷*Pediatrics/ Nephrology, Emory Univ, Atlanta, GA;* ⁸*NIH, Bethesda, MD.*

Background: In the Chronic Kidney Disease in Children (CKiD), there is a high prevalence of abnormal birth history (BH) and poor growth. African Americans (AA) have increased rates of prematurity. APOL1 risk alleles are associated with risk of glomerular CKD in AA patients, but the association with BH or growth is unknown.

Methods: Children of AA descent were genotyped for APOL1 risk alleles (G1, G2). High risk (HR) was defined as 2 risk alleles (G1,G1; G1,G2 or G2,G2) Low risk (LR) was defined as no risk alleles or one G1/G2 allele. Demographics and growth parameters were compared between APOL1 HR vs. LR groups.

Results: 28/84 AA children with glomerular disease had HRAPOL1, 28 had LRAPOL1 and 28 did not have APOL1 measured. 26.9% (7/28) with HR APOL1 were premature, versus 3.7% (1/28) in AA LR APOL1 patients and 6.9% (13/191) in non-AA LR APOL1 patients (p=0.010). Also in AA children with HR APOL1, 29.2% (7/28) were small for gestational age, vs. 36% (9/28) in AA LR APOL1 patients and 15.4% (27/191) in non-AA LR APOL1 patients (p=0.011). Overall, 48.1% (13/28) AA children with HR APOL1 had an abnormal BH, versus 35.7% (10/28) in AA LR APOL1 patients and 20.5% (39/191) in non-AA LR APOL1 patients (p=0.007). HR APOL1 risk alleles were also associated with increased BMI in patients with FSGS (p<0.04).

Conclusions: HR APOL1 in CKiD is significantly associated with an abnormal BH and higher BMI. Further analysis of the interaction of APOL1 genotype with BH and BMI in CKD is warranted.

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TH-PO453

Relationships of Serum Growth Hormone, Insulin-Like Growth Factor-1 and IGF-1 Binding Proteins (BPs) in Children with CKD on Growth Hormone Therapy Rose M. Ayoob,¹ John D. Mahan,¹ Larry A. Greenbaum,² Amira Al-Uzri,³ Frederick J. Kaskel,⁴ Susan L. Furth,⁵ Bradley Warady.⁶ ¹*Pediatrics, Nationwide Children's/The Ohio State Univ, Columbus, OH;* ²*Pediatrics, Emory Univ, Atlanta, GA;* ³*Pediatrics, Oregon Health & Science Univ, Portland, OR;* ⁴*Pediatrics, Albert Einstein COM, New York, NY;* ⁵*Pediatrics, Univ of Pennsylvania, Philadelphia, PA;* ⁶*Pediatrics, Children's Mercy Hospital, Kansas City, MO.*

Background: We evaluated children with chronic kidney disease (CKD) enrolled in the Chronic Kidney Disease in Children (CKiD) study to determine relationships between Growth Hormone (GH), Insulin-Like Growth Factor-1 (IGF-1) and IGF-1 Binding Proteins (BP's), with/without recombinant GH therapy, to assess values that might be useful to guide individual treatment decisions.

Methods: 266 CKiD children: 206 - normal height; 26 - short stature; 34 [18 short, 16 normal height] on recombinant (r) GH therapy were selected for gender, age and GFR matching. Normal height = Height Standard Deviation Score (SDS) > -1.88. GH, IGF-1, and IGFBP-1 were measured by chemiluminometer and ELISA.

Results: Children with CKD on rGH display lower IGF-1/GH than normal height and short CKD children not on rGH therapy.

	IGF-1/GH*	IGF-1/IGF-1 BP 1*
Children Height SDS < -1.88	356.7 [152.3-1017.2]	0.0056 [0.0012, 0.0161]
Children Height SDS > -1.88	811.8 [168.2, 2360.0]	0.0136 [0.0055, 0.0582]
Children on rGH Therapy	138.8 [66.1, 291.0]	0.0098 [0.0017, 0.0308]
p-value (Kruskal Wallis ANOVA)	0.0002	0.02

* = (median [IQR])

On rGH, IGF-1/IGF-1 BP1 is closer to that in normal height CKD children than in short CKD children. Height SDS correlates with serum IGF-1 in children on rGH better (r = 0.374) than normal height (r = 0.323) and short children (r = 0.048).

Conclusions: IGF-1/IGF-1 BP1 in children on rGH is closer to that in normal height than in short CKD children not on rGH, supporting importance of serum IGF-1 levels achieved in rGH treated children to provide statural growth. Further analyses in samples over time and in paired subjects may provide further insights into effective "therapeutic targets" for rGH treatment in these children.

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TH-PO454

Two-Year Kidney Outcomes of Teen-LABS Participants Edward Nehus,¹ Todd Jenkins,¹ Nianzhou Xiao,² Marc P. Michalsky,³ Anita Courcoulas,⁴ Thomas H. Inge,¹ Mark Mitsnefes.¹ ¹*Cincinnati Children's Hospital Medical Center, Cincinnati, OH;* ²*Children's Hospital of Richmond at VCU, Richmond, VA;* ³*Nationwide Children's Hospital, Columbus, OH;* ⁴*Univ of Pittsburgh Medical Center, Pittsburgh, PA.*

Background: A significant amount of severely obese adolescents undergoing weight loss surgery have evidence of early kidney damage. The objective of this study was to determine if early kidney injury is reversible following weight loss surgery.

Methods: We analyzed data two years following bariatric surgery in the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort, a prospective multicenter study of 242 severely obese adolescents undergoing bariatric surgery. Primary outcomes of albuminuria (urinary albumin to creatinine ratio > 30 mg/g) and cystatin C-estimated GFR (eGFR) were compared to baseline values to determine the effect of bariatric surgery on kidney injury.

Results: At surgery, the mean (± SD) age of the patients was 17 ± 1.6 years, 76% were female, and 72% were white race. Procedures included gastric bypass (67%), sleeve gastrectomy (28%), and adjustable gastric band (5%). Median BMI (IQR) at baseline was 51 (45, 58) kg/m², and this decreased to 35 (30, 43) kg/m² at two years follow-up. Cystatin C-based eGFR was 108 ± 27 mL/min/1.73m² at baseline and by two years post-operatively, eGFR had increased by 10% to 119 ± 27 mL/min/1.73m² (p<0.01). Low eGFR (< 90 mL/min/1.73m²) was observed in 25% at baseline, and this improved to 12% at two years follow-up (p<0.01); 71% with low baseline eGFR experienced normalization of eGFR at follow-up. Alternatively, 7% of subjects with normal baseline eGFR developed incident low eGFR at two years post-op. Albuminuria was observed in 17% at baseline and 12% at two years follow-up (p=0.03). Among those with baseline albuminuria, 69% experienced normalization of albuminuria at follow-up. In contrast, 7% of subjects were observed with incident albuminuria at two years post-op.

Conclusions: Two years following surgery, improvements in kidney function and albuminuria were observed in our cohort. Further study will permit assessment of durability of improvements and longer-term kidney outcomes of severely obese adolescents undergoing bariatric surgery.

Funding: NIDDK Support

TH-PO455

Genetic Variation Underlying Uric Acid Clearance in Hispanic Children: The Viva La Familia Study Geetha Chittoor,¹ Sandra L. Laston,² Nitesh R. Mehta,³ Karin Haack,⁴ Shelley A. Cole,⁴ Anthony Gean Comuzzie,⁴ Nancy F. Butte,³ V. Saroja Voruganti.¹ ¹*Nutrition and Nutrition Research Inst, Univ of North Carolina at Chapel Hill, Kannapolis, NC;* ²*South Texas Diabetes and Obesity Inst and Regional Academic Health Center, UTHSC at San Antonio/ Univ of Texas Rio Grande Valley, Brownsville, TX;* ³*Pediatrics and USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX;* ⁴*Genetics, Texas Biomedical Research Inst, San Antonio, TX.*

Background: Variation in renal excretion of uric acid is a key factor in the development of gout, hyperuricemia, and nephropathy. Hyperuricemia (increased serum uric acid concentrations) and hyperuricosuria (increased urinary uric acid concentrations) can lead to uric acid nephrolithiasis. These are two common multifactorial disorders that have been shown to be associated with progression to kidney disease and have a familial inheritance. The genetic determinants of renal handling of uric acid are poorly elucidated.

Methods: We investigated the genetic factors that influence the excretion of uric acid and its related indices in 769 Hispanic children of the Viva La Familia Study. We conducted a genome-wide association analysis for uric acid clearance after accounting for family kinships. All methods were implemented in SOLAR.

Results: All renal uric acid clearance measures were significantly heritable (p < 2 x 10⁻⁶). We observed a strong association of uric acid clearance with a single nucleotide polymorphism (SNP) in the zinc finger protein 446 (ZNF446) gene on 19q13 [p < 8 x 10⁻⁸, rs2033711 (A/G), minor allele frequency (MAF) of 0.30]. The minor allele (G) was associated with increased uric acid clearance. We also found suggestive associations of uric acid clearance with SNPs in ZNF324, ZNF584, and ZNF132 (within 72kb region of 19q13, p < 1 x 10⁻⁶, MAFs between 0.28 and 0.31).

Conclusions: Our study indicates, for the first time, the importance of the chromosomal region 19q13 in the regulation of renal clearance of uric acid in Hispanic children.

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TH-PO456

Association Between Height and Clinical Outcomes in Children at Time of ESRD Onset Elaine Ku,¹ Richard N. Fine,² Chi-yuan Hsu,¹ David V. Glidden,¹ Barbara A. Grimes,¹ Kirsten L. Johansen.¹ ¹*UCSF;* ²*Stony Brook Univ.*

Background: Short and tall stature are associated with adverse outcomes in the general adult population. The aim of this study was to examine risk of mortality and transplantation in children with short and tall stature at time of ESRD onset.

Methods: Using data from US Renal Data System, we performed a retrospective analysis of children ages 2-19 who began renal replacement therapy during 1995-2011. We used Cox models adjusted for demographic and socioeconomic factors, calendar year, and cause of ESRD to determine the association between short (<3rd percentile) and tall

(>97th percentile) stature and risk of transplantation and death. In sensitivity analysis, we also evaluated mortality and transplant risk in the subset of children with normal BMI (5th-95th percentile).

Results: Among 13,666 children, 26% of children were short and 3% were tall at time of ESRD onset. During a median follow-up of 7.1 years, 10,354 kidney transplants and 1,795 deaths occurred. Risk of death was higher in children with short and tall stature [table 1], and cause-specific mortality differed by height category. The higher risk of death in children with short stature persisted even when analysis was limited to children with normal BMI. Children with short stature were also less likely to receive a kidney transplant (HR 0.83, 95% CI 0.79-0.87).

Outcome (N=13,666)	Short Stature (N=3576)	Tall Stature (N=397)
All-cause mortality	HR* (95% CI)	HR* (95% CI)
Adjusted model (primary analysis)	1.48 (1.33-1.65)	1.30 (1.01-1.67)
Adjusted model among persons with normal BMI (N=9,663)	1.56 (1.36-1.77)	0.98 (0.67-1.44)
Cause-specific mortality		
Adjusted model for cardiac death	1.45 (1.19-1.76)	1.19 (0.76-1.85)
Adjusted model for infectious death	1.77 (1.34-2.33)	1.23 (0.57-2.63)
Adjusted model for malignancy death	0.79 (0.44-1.41)	2.70 (1.11-6.60)

*Reference is children with normal stature

Conclusions: Both extremes of height at ESRD onset were associated with higher risk of all-cause and cause-specific mortality, and short stature was also associated with lower risk of transplantation. Further studies are warranted to determine whether interventions can improve the risk associated with growth failure.

Funding: NIDDK Support

TH-PO457

Genital Organ Anomalies in Female Pediatric Patients with End-Stage Renal Disease Shoichiro Kanda,¹ Naoya Morisada,² Yuji Tomii,¹ Keiichi Takizawa,¹ Naoto Kaneko,¹ Tomoo Yabuuchi,¹ Hirotaka Hama,¹ Eiji Nakano,¹ Norimasa Tada,¹ Kiyonobu Ishizuka,¹ Yuko Akioka,¹ Hiroko Chikamoto,¹ Kazumoto Iijima,² Motoshi Hattori.¹ ¹*Pediatric Nephrology, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan;* ²*Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.*

Background: In the general population, the rate of prevalence of genital organ anomalies in females is 1.3–4.0 per 1000 births. Although female pediatric patients with end-stage renal disease (ESRD) appear to occasionally have genital organ anomalies, the clinical features of them have not been examined.

Methods: We performed a retrospective analysis of female pediatric ESRD patients attending the Department of Pediatric Nephrology, Tokyo Women's Medical University (TWMU) Hospital. The study was in accordance with the ethical guidelines of the Ministry of Health, Labour and Welfare, Japan. The study was also approved by the central ethics board of TWMU and Kobe University.

Results: Eighty-two patients were included in this study. Genital organ anomalies were found in eight (9.7%) patients and consisted of bicornuate uterus in three patients, double uteri with vaginal atresia in two, cicatricial tissue in two, and double uteri in one. Renal phenotypes were congenital anomalies of the kidney and urinary tract in six patients and FSGS in two patients. In seven (87.5%) patients, genital organ anomalies were diagnosed after the start of renal replacement therapy. Two patients complained of acute abdomen associated with their first menstrual period. Genetic and chromosome analyses revealed hypoparathyroidism, deafness, and renal dysplasia syndrome (GATA3, c.1013G>T) in one patient, Turner syndrome in one, Frasier syndrome (46XY, WT1, IVS9+5G>A) in one, and FSGS carrying a mutation of WT1 (c.745C>A) in one.

Conclusions: Our study showed that female pediatric ESRD patients had a frequency of genital organ anomalies of approximately 10%. Additionally, genetic disorders responsible for kidney and genital organ development were detected in four out of eight patients. Therefore, physicians need to be aware of the possibility of genitourinary syndrome and investigate genital organ anomalies in the medical care of female pediatric patients with ESRD.

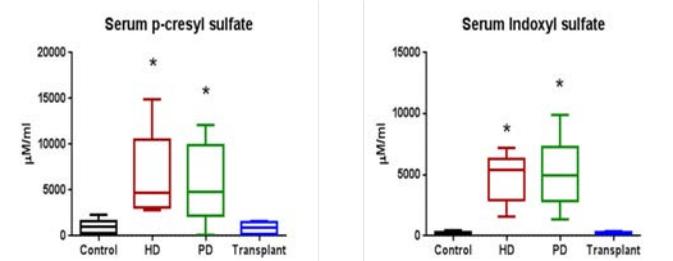
TH-PO458

Intestinal Microbiota in Pediatric Patients with End Stage Renal Disease Janice Crespo-Salgado,¹ Tyrus Stewart,¹ Mike J. Ferris,¹ Mahmood Kallash,² Larry A. Greenbaum,³ V. Matti Vehaskari,¹ Diego H. Aviles.¹ ¹*Pediatric Nephrology, LSUHSC, New Orleans, LA;* ²*Pediatric Nephrology, Women & Children's Hospital of Buffalo, Buffalo, NY;* ³*Pediatric Nephrology, Emory Children's Center, Atlanta, GA.*

Background: Cardiovascular mortality is increased in children with end stage renal disease (ESRD). Studies in adult population suggest that uremia increase intestinal permeability and alters the intestinal microbiota. These changes could facilitate the translocation of endotoxin and bacterial metabolites to the systemic circulation leading to inflammation. We hypothesized that children with ESRD have an altered intestinal microbiota that lead to increased bacterially derived uremic toxins, and renal transplantation will reverse those changes.

Methods: Subjects were divided into 4 groups: ESRD on peritoneal dialysis (PD), ESRD on hemodialysis (HD), post kidney transplant and healthy control. PCR and pyrosequencing analysis of 16S rRNA gene was used to assess stool bacterial composition. Serum levels of CRP, D-lactate, p-cresyl sulfate and indoxyl sulfate were detected.

Results: Children with ESRD showed significant decrease in Firmicutes (p=0.006). HD patients showed significant increase in Bacteroidetes (p=0.017) and PD patients showed significant increase in Proteobacteria (p=0.0006). Bacterial diversity was significantly decreased in ESRD and transplant patients. ESRD patients had significantly increased serum levels of p-cresyl sulfate and indoxyl sulfate (p<0.0002).



Conclusions: ESRD in children results in alteration of the intestinal microbiota favoring bacteria able to metabolize and produce more uremic toxins. Renal transplantation does not restore the decreased bacterial diversity, but results in normalization of bacterially derived uremic toxins. These findings may be associated with the increased cardiovascular mortality seen in children with ESRD.

TH-PO459

Cardiorenal Effects of Exposure to Environmental Chemicals in Children Anglina Kataria,¹ Suzanne M. Vento,¹ Leonardo Trasande,¹ Dov Levine,¹ Debra J. Morrison,² Rachel Brody,² Kurunthachalam Kannan,³ Jingchuan Xue,³ Howard Trachtman.¹ ¹*Pediatrics, NYU Langone Medical Center, New York, NY;* ²*Office of Collaborative Sciences, Human Specimen Resource Center, NYU Langone Medical Center, New York, NY;* ³*Environmental Health Sciences, School of Public Health, State Univ of New York at Albany, Albany, NY.*

Background: Exposure to short-lived organic chemicals such as bisphenol A and S (BPA/BPS) and phthalates is ubiquitous in the US. Graded exposure to BPA and di-(2-ethylhexyl) phthalate (DEHP), based on urinary excretion, is associated with an increased low-grade albuminuria. Oxidant stress is hypothesized as the mediator underlying these associations. We conducted the following study to assess (1) the mechanism of action of these compounds and (2) the impact of exposure on vascular function in children.

Methods: A cross-sectional study recruiting 10-13 year old children was conducted at Bellevue Medical Center. Demographic information was obtained and height, weight and BP were measured. A first morning and spot urine samples were collected for determination of BPA, BPS, phthalate, 8(OH)-deoxyguanosine, and F2-isprostane excretion (normalized to creatinine excretion). Pulse wave velocity (PWV) was measured non-invasively (SphygmoCor). Multivariate analysis was used to evaluate the relationship between exposures and the laboratory tests.

Results: There were 41 participants, 19 M:22 F, age 12±1 yr. 31 Hispanic, 7 Caucasian, and 3 Other. The mean BMI was 21.7±5.0 and albuminuria 11.4±23.6 mg/g. and 10 (25%) were pre-hypertensive (BP≥90th percentile). The degree of exposure to BPS, total bisphenols, DEHP, and high molecular weight (HMW) phthalates correlated with F2-isoprostane excretion (P<0.05). Multivariate regression also showed each unit of DEHP and HMW phthalate exposure was associated with an increase in PWV of 0.034 m/s (p=0.037) and 0.024 m/s (p=0.041), respectively.

Conclusions: This is the first demonstration of oxidant stress and vascular dysfunction related to environmental chemicals in otherwise healthy children. The link with replacement compounds such as BPS suggests that the consequences of exposure to these chemicals will be a long-term public health problem.

Funding: NIDDK Support, Other NIH Support - NIEHS Pilot study Award

TH-PO460

Safety of Eculizumab in Pediatric Patients with Atypical Hemolytic Uremic Syndrome Gema Ariceta,¹ Larry A. Greenbaum,² Jimmy Wang,³ John F. Kincaid,³ Christoph Licht.⁴ ¹*Hospital Univ Vall d'Hebron, Barcelona, Spain;* ²*Emory Univ, Atlanta, GA;* ³*Alexion Pharmaceuticals, Inc, Cheshire, CT;* ⁴*The Hospital for Sick Children, ON, Canada.*

Background: The safety of eculizumab, a terminal complement inhibitor approved for treatment of children and adults with aHUS, was characterized in 4 prospective trials. This post hoc analysis further evaluates its safety in pediatric participants in 3 of the trials.

Methods: Treatment-related adverse events (TRAEs) and serious AEs (SAEs) reported for patients (pts) (<18 yr) after 1 year and by end of study (EOS) in studies C08-002, C08-003, and C10-003 were pooled.

Results: Pediatric pts (N=28) received eculizumab for a mean (SD) of 67 (42) weeks. TRAEs occurred in 13 pts (46.4%) after 1 year (Table). SAEs are listed in the Table. Elevated levels of alanine transaminase and aspartate aminotransferase were noted in some pts before and after receiving eculizumab; levels generally were higher before treatment and normalized over time. By EOS after 433 cumulative months of treatment, there were

no deaths or meningococcal infections; 6 infection-related serious TRAEs occurred in 4 pts: viral upper respiratory tract infection (n=2), influenza, peritonitis (patient was on peritoneal dialysis), respiratory syncytial virus infection, and pyelonephritis (n=1 each).

Conclusions: Eculizumab appears well tolerated in pediatric pts with aHUS. The safety profile of eculizumab in pediatric pts is similar to that in the broader pt population of these studies. Although more infection-related TRAEs were noted, most were mild to moderate in severity, none led to treatment discontinuation, and all pts recovered. Some TRAEs might have been manifestations of underlying aHUS disease.

Medical writing support - Kristen W. Quinn, PhD, of Peloton Advantage, funded by Alexion

Table. Baseline Demographic and Clinical Characteristics and Eculizumab Safety in Pediatric Patients (N=28)

Baseline Demographic and Clinical Characteristics			
Characteristic	Pediatric (<12 y) (n=18)	Adolescent (12-17 y) (n=10)	Total (N=28)
Mean age at baseline, years (SD)	4.3 (3.8)	16.0 (1.5)	8.46 (6.5)
Female, n (%)	9 (50.0)	6 (60.0)	15 (53.6)
Identified complement gene mutation or autoantibody, n (%)			
CFH	9 (50.0)	7 (70.0)	16 (57.1)
MCP (CD46)	2 (11.1)	2 (20.0)	4 (14.3)
CFH autoantibodies, CFHR1-CFHR3 polymorphism	2 (11.1)	1 (10.0)	3 (10.7)
CFI	1 (5.6)	1 (10.0)	2 (7.1)
C3	1 (5.6)	1 (10.0)	2 (7.1)
CFB	0 (0)	0 (0)	0 (0)
CFH, C3	1 (5.6)	1 (10.0)	2 (7.1)
CFH autoantibodies	1 (5.6)	0 (0)	1 (3.6)
CFHR1-CFHR3 polymorphism	1 (5.6)	0 (0)	1 (3.6)
Mean time from diagnosis to screening, months (SD)	6.7 (17.2)	86.7 (75.3)	35.3 (60.0)
Newly diagnosed, n (%)	15 (83.3)	2 (20.0)	17 (60.7)
No PE/PI during the current manifestation, n (%)	11 (61.1)	2 (20.0)	13 (46.4)
Dialysis at baseline, n (%)	9 (50.0)	3 (30.0)	12 (42.9)
History of ≥1 renal transplant, n (%)	0 (0)	2 (20.0)	2 (7.1)
Safety Findings			
AEs, n (%)	1 Year		
	Pediatric (<12 y) (n=18)	Adolescent (12-17 y) (n=10)	Total (N=28)
Any TEAEs	16 (88.9)	10 (100.0)	26 (92.9)
Severe	4 (22.2)	2 (20.0)	6 (21.4)
Serious	10 (55.6)	6 (60.0)	16 (57.1)
Leading to discontinuation	1 (5.6)	0 (0)	1 (3.6) ^a
TRAEs ^b	8 (44.4)	5 (50.0)	13 (46.4)
Severe	0 (0)	1 (10.0)	1 (3.6)
Serious	3 (16.7)	1 (10.0)	4 (14.3)
Leading to discontinuation	1 (5.6)	0 (0)	1 (3.6) ^a
SAEs	10 (55.6)	6 (60.0)	16 (57.1) ^c
Most common TRAEs by organ system			
Skin and subcutaneous tissue	6 (33.3)	1 (10.0)	7 (25.0)
Infections and infestations	5 (27.8)	1 (10.0)	6 (21.4)
Gastrointestinal	2 (11.1)	1 (10.0)	3 (10.7)
Nervous system	2 (11.1)	1 (10.0)	3 (10.7)
Eye	1 (5.6)	0 (0)	1 (3.6)
General and administration site conditions	1 (5.6)	0 (0)	1 (3.6)
Musculoskeletal and connective tissue	0 (0)	1 (10.0)	1 (3.6)
Psychiatric	1 (5.6)	0 (0)	1 (3.6)
Respiratory, thoracic, and mediastinal	0 (0)	1 (10.0)	1 (3.6)
Vascular	0 (0)	1 (10.0)	1 (3.6)

^aOne patient discontinued due to a TRAE (agitation, moderate severity; possibly related to treatment).
^bIncludes TEAEs that were possibly or probably related to treatment. No TEAEs were judged to be definitely related.
^cSAEs included anemia, hypertension, peritonitis, pyrexia, upper respiratory tract infection, viral gastroenteritis (n=2 each), abdominal pain, acute respiratory failure, agitation, back pain, bone marrow failure, catheter removal, cholecystitis, cholelithiasis, device malfunction, device-related sepsis, infection, medical device complication, metabolic disorder, overdose, parainfluenzae virus infection, pharyngitis, respiratory syncytial virus infection, urinary tract infection, uterine polyp, viral enterocolitis, viral upper respiratory tract infection, and wrist fracture (n=1 each).
 AE, adverse event; CFB, complement factor B; CFH, complement factor H; CFHR, CFH receptor; CFI, complement factor I; MCP, membrane cofactor protein; PE/PI, plasma exchange/plasma infusion; SAE, serious AE; SD, standard deviation; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

TH-PO461

Early Renin-Angiotensin System Inhibition in Pediatric Chronic Kidney Disease Patients May Prevent Progression of Renal Failure
 Kazuya Matsumura, Midori Awazu. Dept of Pediatrics, Keio Univ School of Medicine.

Background: While inhibitors of renin-angiotensin system (RASi) are known to slow CKD progression, the optimal timing of their introduction is not established. Some patients with chronic kidney disease (CKD) have nonprogressive GFR periods (stable or increasing GFR). We compared longitudinal GFR trajectories between patients in whom RASi was initiated during stable periods (early-treated) and those during decline periods (late-treated).

Methods: GFR was estimated by equation for Japanese children and adults. Stable GFR periods were defined as GFR slope = 0 or positive. Fifty-three pediatric CKD patients (stage ≥2) were studied (26 males and 27 females, age 3 to 38 years, median 17). Blood pressure (BP) was evaluated as BP index (BP divided by the 95th percentile).

Results: Twenty-seven subjects (11 early- and 16 late-treated) were prescribed with RASi. All of the early-treated subjects showed stable GFR during the follow-up period of 8.5 years (NS vs the late-treated 11.4 years), whereas GFR declined in all the late-treated subjects (P<0.05). Current age and the age at the time of follow up were significantly younger in the early-treated vs the late-treated (12.6 vs 20.6 and 4.1 vs 9.1 years). There was no difference in gender. In the early-treated, 8 of 11 had CAKUT, which was significantly more than the late-treated (4 of 16). The initial GFR tended to be lower in the early-treated than the late-treated (69 vs 92 ml/min/1.73 m²). There was no difference in BP index (0.88 vs 0.86), but urine protein creatinine ratio was numerically lower in the early-treated (median 0.15 vs 0.27 g/gCr). The reason for the initiation of RASi in the early-treated was hypertension (6), albuminuria (4), or accompanying cardiac disease (3). Of all 53

patients, 26 had stable GFR periods during the course. Ten patients with stable periods were not on RASi because of the absence of hypertension or albuminuria and only one of whom subsequently developed GFR decline, proteinuria, and hypertension requiring RASi.

Conclusions: In pediatric CKD patients, initiation of RASi during periods of stable GFR may prevent CKD progression although the influence of age and underlying disease cannot be ruled out.

TH-PO462

Novel Urinary Biomarkers for Detecting Renal Scar in Children with Febrile Urinary Tract Infection
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Background: Recurrent febrile urinary tract infections (fUTI) during infancy cause renal scar. Renal scar can be diagnosed through renal scintigraphy while it seems impractical to perform it for all infants with fUTI. Therefore, exploring biomarkers that can identify the patients at high risk of developing renal scar is worthwhile. Urinary excretions of total proteins, beta-2 microglobulins (BMG), and N-acetyl-β-D-glucosaminidase (NAG) have been traditionally used for assessing kidney injury including interstitial damage. In addition, urinary excretions of neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP), full-length megalin (C-meg) and angiotensinogen (AGT) have recently been reported as sensitive biomarkers for various kidney injuries. This study was undertaken to explore sensitive urinary biomarkers to diagnose renal scar.

Methods: Thirty one infants who underwent renal scintigraphy during the chronic phase after fUTI were enrolled. The following measurements were performed using urine samples; total proteins, BMG, NAG, NGAL, L-FABP, C-meg and AGT. The values were corrected by creatinine and compared between the patients with renal scar (n=20) and these without renal scar (n=10).

Results: Among urinary biomarkers, AGT and C-meg in the group with scar (median value 14.4 mg/gCr and 6.7 pmol/gCr) demonstrated significantly higher levels than those in the group without scar (median value 4.5 mg/gCr and 1.9 pmol/gCr) (P=0.021 and 0.0046). Among the area under the curves in receiver operating characteristic curve calculated for each urinary biomarker, C-meg yielded the highest value as following: C-meg (0.81) > AGT (0.76) > NAGL (0.60) > protein (0.58) > BMG (0.54) > NAG (0.50) > L-FABP (0.46). When using the point on the curve closest to the (0, 1) point, cut-off in the C-meg (AGT) was 3.06 pmol/gCr (10.4 mg/gCr), the test had 80 % (70 %) sensitivity, 72.7 % (81.8%) specificity.

Conclusions: Urinary C-meg and AGT are useful for renal scar screening.

TH-PO463

Prevalence and Distribution of (Micro)Albuminuria in Toddlers: A Sign of Early Endothelial Dysfunction?
 Sophie Van den Belt,¹ Valentina Gracchi,² Eva Corpeleijn,³ Dick de Zeeuw,¹ Hiddo Jan Lambers Heerspink.¹ ¹Dept Clinical Pharmacy & Pharmacology, UMC Groningen, Netherlands; ²Dept Paediatric Nephrology, UMC Groningen, Netherlands; ³Dept Epidemiology, UMC Groningen, Netherlands.

Background: Microalbuminuria is common in the general population with a prevalence of 7% and is an independent indicator of renal/cardiovascular risk. Whether microalbuminuria is acquired during life (as a result of hypertension/diabetes) or is congenital and already present at birth is unknown. We studied the prevalence of microalbuminuria in toddlers and compared distributions of albuminuria with the general adult population. In addition, we looked for possible associations with antenatal, postnatal and maternal factors explaining albuminuria variations.

Methods: The urinary albumin (U_{AC}) was measured in 1352 children (20-40 months old) from the GECKO Drenthe cohort. Albuminuria distribution was compared with the distribution in 40854 participants of the general adult cohort PREVEND. Difference in prevalence of increased albuminuria (U_{AC} ≥20 mg/L) was tested with chi-square. Associations between logarithm of U_{AC} and antenatal, postnatal and maternal factors were tested with linear regression analysis.

Results: The median U_{AC} in GECKO was 2.3 mg/L [5-95th percentile: 2.1-25.5] and in PREVEND 6.0 mg/L [2.3-28.6] (P distribution comparison 0.053). Prevalence of U_{AC} ≥20 mg/L was 6.9% in GECKO and 7.8% in PREVEND (Figure; P=0.195). U_{AC} was lower in boys and not associated with other factors.

Conclusions: The distributions of U_{AC} and the prevalence of microalbuminuria in toddlers and general adult population are comparable. These findings suggest that microalbuminuria is a congenital condition which may predispose those affected at a higher renal/cardiovascular risk later in life.

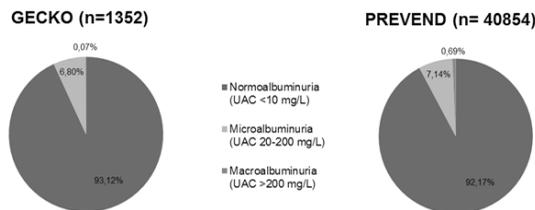


Figure: Prevalence of different U_{AC} levels in toddlers (GECKO) vs adults (PREVEND).

Funding: Pharmaceutical Company Support - Hutchison Whampoa Ltd, Hong Kong, Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO464

Validation of a Novel Device to Collect Urine for Albuminuria Assessment in Young Children Sophie Van den Belt,¹ Valentina Gracchi,² Dick de Zeeuw,¹ Hidido Jan Lambers Heerspink.¹ ¹Dept of Clinical Pharmacy and Pharmacology, UMC Groningen, Netherlands; ²Dept of Paediatric Nephrology, UMC Groningen, Netherlands.

Background: Urine collection for albuminuria measurement in babies and toddlers is cumbersome. Taped plastic bags are complicated and may come loose. Old-fashioned cotton wool (pantyliner) or a felt (PeeSpot®) are used as collection devices in a regular disposable diaper. We compared the analytical performance of these two methods.

Methods: The pantyliner and urine collection felt were placed in the diaper; 81 different standard urines with a wide range of albuminuria were applied by hand (in duplicate); incubated for 3 hours at 37°C (simulating the baby), and 72 hours at room temp (simulating transport); extracted by centrifuging. Urinary Albumin Concentration was measured. Analytical performance of two methods was tested according National Committee for Clinical Laboratory Standards (NCCLS) guidelines for method comparison, and compared with the standard urine. Performance measures assessed were bias, precision and accuracy.

Results: Median albumin concentration was: standard 66.0 mg/L [IQR 25.0–211.0 mg/L]; pantyliner method 32.0 mg/L [4.7–165.0 mg/L], and PeeSpot method 61.0 mg/L [27.0–216.0 mg/L]. Bias and precision were higher in pantyliner (-34.2% and 32.4 mg/L) than in PeeSpot (3.3% and 5.0 mg/L) and accuracy was lower in pantyliner (48.1%) vs PeeSpot (96.3%). Passing-Bablok regression and Bland-Altman plot showed a systemic underestimation for pantyliner method, but not for PeeSpot method (Figure).

Conclusions: The PeeSpot method is a reliable method for the collection of urine in babies and toddlers albuminuria measurement. This technique should be used in future research into this subject.

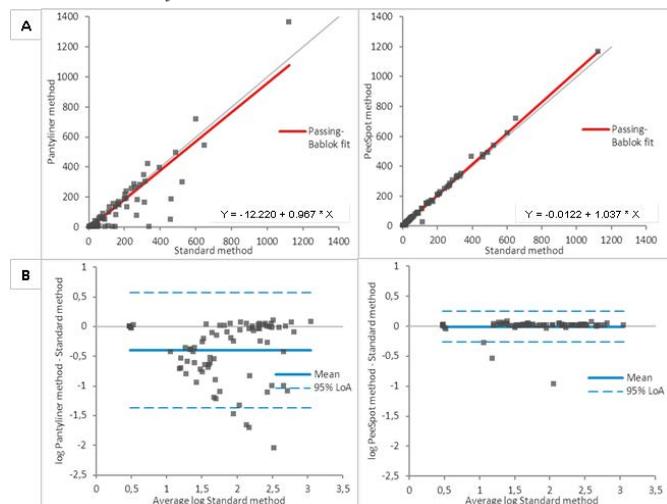


Figure: A; Passing-Bablok regression for pantyliner and PeeSpot. B; Bland-Altman plots for pantyliner and PeeSpot on logarithm of albuminuria. LoA = Limit of Agreement. Funding: Government Support - Non-U.S.

TH-PO465

A Distinct Urinary Lipid Profile in Patients with FSGS Elif Erkan, Xueheng Zhao, Prasad Devarajan. *Pediatrics, Children's Hospital of Cincinnati.*

Background: Focal segmental glomerulosclerosis (FSGS) accounts for the majority of patients with end-stage renal disease (ESRD) during adolescence. Treatment of FSGS has been a great challenge for pediatric nephrologists due to intertwined molecular pathways underlying its complex pathophysiology. In FSGS patient kidney biopsy sections display increased tubular apoptosis a hallmark for tubular injury. We hypothesize that tubulointerstitial injury caused by the uptake of lipogenic mediators in glomerular filtrate contributes to the progressive nature of FSGS.

Methods: We explored urinary lipid profile of patients with FSGS, minimal change disease (MCD) and healthy controls by High Performance Liquid Chromatography. Normalized data from GC/MS and UPLC/MS analysis including 625 metabolites were thereby used for subsequent statistical analysis. A total of 29 metabolites met the significant threshold of p-value (student two samples t test) less than 0.05 and fold changes between FSGS and MCD urine samples bigger than 2.

Results: We discovered a unique signature characterized by increased concentration of fatty acid (FA) and lysophosphatidylcholines (LPC) and a decrease in urinary concentration of phosphotidylcholine (PC) in patients with FSGS. Patients with FSGS had lower urinary acylcarnitine levels. Patients with FSGS were divided into two groups (four patients in each group) based on their estimated GFR, to normal GFR (105.29 ± 4.11 ml/min/1.73m²) and low GFR group (69.25 ± 6.49 ml/min/1.73 m²). Low GFR group had higher urinary FA concentration and lower urinary acylcarnitine concentration (p<0.05).

Conclusions: We speculate that these findings indicate increased metabolism of membrane phospholipid PC by phospholipase A2 (PLA2) resulting in higher urinary concentrations of LPC and FA. We propose that decrease in urinary acylcarnitine levels in FSGS implicates an arrest at mitochondrial fatty acid oxidation despite high FA levels. e

believe increased by products of PC metabolism further potentiate tubular and podocyte toxicity in FSGS. Validation of urinary lipids as a biomarker in predicting the diagnosis and progression of FSGS in a larger patient population is warranted.

Funding: NIDDK Support

TH-PO466

Steroid Dependency in Childhood Steroid-Sensitive Nephrotic Syndrome – Clinical Characterization of a Large Single Center Cohort Anja K. Büscher, Mareen Sadau, Rainer Büscher, Peter F. Hoyer, Stefanie Weber. *Pediatric Nephrology, Univ of Duisburg-Essen, Pediatrics II, Essen, Germany.*

Background: Steroid-sensitive nephrotic syndrome (SSNS) is characterized by preservation of renal function and recurrent disease. Clinical course depends on the number of relapses which is highly variable. A subset of patients presents with relapses during or shortly after steroid therapy (steroid-dependency, SDNS). Mostly, childhood SSNS is of idiopathic origin with minimal change glomerulopathy (MCN) in renal histology. Aim of our study was the characterization of SSNS patients with regard to differences between SDNS and non-SDNS.

Methods: We retrospectively analyzed 100 SSNS patients treated at our hospital. Data collection comprised age at onset, number/trigger of relapses, dose/duration of steroid therapy, time to response, further immunosuppressants, renal function, renal histology, and family history.

Results: 89% of patients experienced relapses (mean 9 (range 0-34)), 55% developed SDNS (after 15 (2-45) months from onset). In 80% of cases trivial infections triggered SSNS relapse. 60% of patients received further immunosuppressants (95% cyclophosphamide, 58% ciclosporinA; sustained disease remission in 24/51%, respectively). Renal biopsy was performed in 70% (93% MCN, SDNS and non-SDNS). SDNS patients were significantly younger at disease onset (4.16ys (SDNS) vs. 5.34ys (non-SDNS), P=0.035; all patients 4.7ys). Mean time to first relapse was significantly shorter in SDNS (6.3months vs. 16.3months non-SDNS; P<0.001; all patients 9.8months). Response to steroids at disease onset was faster in non-SDNS (6.8days vs. 11.7days SDNS; P<0.001). SDNS patients developed secondary steroid resistance in 20% (2% non-SDNS; P<0.01; all patients 12%).

Conclusions: 55% of patients developed SDNS and differed from non-SDNS patients by a younger age at disease onset, a shorter time until first relapse and a slower therapy response. The clinical course in general was influenced by therapy regimen.

Funding: Clinical Revenue Support

TH-PO467

Dyslipidemia in Pediatric CKD Patients from KNOW-PedCKD Study Seong heon Kim,¹ Yo Han Ahn,³ Eujin Park,³ Kyoung Hee Han,² Heeyeon Cho,⁴ Joo Hoon Lee,⁶ Hee Gyung Kang,³ Young seo Park,⁶ Hae Il Cheong,³ Curie Ahn,⁷ IL-Soo Ha.³ ¹Dept of Pediatrics, Pusan National Univ Children's Hospital, Yangsan, Republic of Korea; ²Dept of Pediatrics, Jeju National Univ School of Medicine, Jeju, Republic of Moldova; ³Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Republic of Korea; ⁴Dept of Pediatrics, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea; ⁵Dept of Pediatrics, Yonsei Univ College of Medicine, Severance Children's Hospital, Seoul, Republic of Korea; ⁶Dept of Pediatrics, Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea; ⁷Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea; ⁸Dept of Pediatrics, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea.

Background: Children with chronic kidney disease (CKD) exhibit various comorbidities, including dyslipidemia. We investigated the prevalence and characteristics of dyslipidemia in pediatric CKD patients.

Methods: Seven major pediatric nephrology centers of Korea enrolled children younger than 20 years who had CKD. From July 2010 to December 2013, 322 children (M:F 218:104) were enrolled.

Results: Baseline lipid analysis found a high prevalence of dyslipidemia in 49%. Several factors were analyzed including age, gender, CKD stage, primary renal disease, height, weight, BMI, social economic status, hypertension, co-morbidity, z score of height, z score of weight, z score of BMI, gestational age at birth, birth weight, estimated GFR and duration of underlying diseases. Univariate logistic regression analysis demonstrated that several factors including BMI, co-morbidity, Z score of weight and Z score of BMI were associated with dyslipidemia. After multivariate adjustment, social economic status and Z score of BMI were significantly associated with dyslipidemia.

Conclusions: Among children with CKD, dyslipidemia is quite common and is associated with factors such as social economic status and Z score of BMI.

Funding: Government Support - Non-U.S.

TH-PO468

Self-Management/Transition Readiness and Health Services Utilization Among Adolescents/Young Adults with Chronic Conditions in the Pediatric or Adult Settings from Across the USA Maria E. Ferris,¹ Keisha L. Gibson,¹ Hsiao Ling Lai,² Susan F. Massengill,³ John D. Mahan,⁴ Randal K. Detwiler,¹ Gerald A. Hladik,¹ Mara Medeiros.⁵ ¹UNC at Chapel Hill, NC; ²East Carolina Univ, NC; ³Carolinas Medical Center, NC; ⁴The Ohio State Univ, OH; ⁵Hospital Infantil de Mexico "Federico Gomez", DF, Mexico.

Background: The performance in self-management and/or health care transition readiness measurements by adolescents or young adults with chronic conditions (AYA) needs to be correlated to clinical outcomes and health services utilization.

Methods: The 18-question STAR_x Questionnaire is a self-report survey of self-management (adult-focused setting) and/or transition-readiness (pediatric setting) with 6 factors: Medication Management, Provider Communication, Engagement during Appointments, Disease Knowledge, Adult Health Responsibilities, and Resource Utilization. The total raw score ranges from 0-90, with higher scores reflecting more intact skills (Ferris et al., 2015). Data presented is from 321 AYA with chronic health conditions (including chronic kidney disease, transplant, hypertension and lupus), seen in the pediatric- or adult-focused settings at 6 large health systems in the northeast, southeast, and midwest regions of USA, or who attended Victory Junction Camp (from several states in USA). The outcomes/health services utilization measures were adherence (Morisky et al., 1986) and number/length of hospitalizations in the last year.

Results: Higher STAR_x Questionnaire total score correlated with higher medication adherence ($\beta = .301, p = .000, R^2 = .070$). Higher STAR_x Medication Management Subscale correlated with higher medication adherence ($\beta = .499, p = .000, R^2 = .224$). Greater STAR_x Disease Knowledge Subscale correlated with higher medication adherence ($\beta = .216, p = .001, R^2 = .044$), fewer number of hospitalizations ($\beta = -.453, p = .000, R^2 = .262$) and inpatient days in the past year ($\beta = -.432, p = .000, R^2 = .187$).

Conclusions: The strong reliability of the STAR_x Questionnaire in AYA with a variety of conditions treated in either the pediatric or adult-focused clinics, correlates with health outcomes and health services utilization.

Funding: Private Foundation Support

TH-PO469

Emotional-Behavioral Functioning of Children Enrolled in the Chronic Kidney Disease in Children (CKiD) Cohort Study Rebecca J. Johnson,^{1,2} Matthew Matheson,² Arlene C. Gerson,² Susan R. Mendley,² S. Shinnar,² Marc Lande,² Amy Kogon,² Lyndsay Harshman,² Debbie S. Gipson,² Bradley Warady,^{1,2} Susan L. Furth,² Stephen R. Hooper.² ¹Children's Mercy; ²Chronic Kidney Disease in Children (CKiD) Study Group.

Background: CKiD is a longitudinal study examining medical, neurocognitive, and psychosocial outcomes for children with mild to moderate CKD ages 1-16 years at study entry. Little is known about how CKD affects emotional-behavioral functioning (EBF), although data from the CKiD study indicate that these children are at increased risk of attention and executive functioning deficits. In one of the largest studies to date, we report EBF of participants at baseline and over time.

Methods: Parents of participants completed the Behavior Assessment System for Children (BASC-2) at baseline and every 2 years. 835 participants had BASC-2 data, including 797 at baseline. Linear mixed models predicted participants' scores on BASC-2 summary measures (Internalizing, Externalizing, Behavioral Symptoms Index, Adaptive Skills) and selected clinical scales (Depression, Attention Problems). Analyses controlled for key demographic (age, sex, ethnicity, maternal education, household income, Full Scale IQ) and medical (GFR, hypertension [HTN], low birth weight, anemia, seizures, proteinuria, glomerular diagnosis, time since CKD onset) covariates.

Results: Children with mild to moderate CKD have EBF scores generally within normal limits at baseline and over time. At baseline, the proportion with scores at least 1 SD above the mean was 24% for internalizing problems and 27% for attention problems, higher than would be expected in a typical sample. In an adjusted linear mixed model, persistent hypertension was related to attention problems ($\beta = 1.81, 95\% \text{ CI} = 0.40-3.21, p < .02$).

Conclusions: Children with mild to moderate CKD have parent-reported EBF that is within normal limits, at baseline and over time. However, the proportion with scores more than one SD above the mean is higher than would be expected, suggesting that this population may be at slightly increased risk for internalizing symptoms and attention problems, particularly in the context of HTN, which was associated with increased risk of parent-reported attention problems.

Funding: NIDDK Support, Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI)

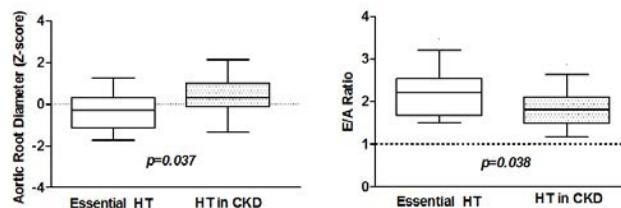
TH-PO470

Echocardiographic Findings in Hypertensive Children with Kidney Disease or Essential Hypertension Gabriel Paris,¹ Wacharee Seeharunvong,² Aura Jeannette Arenas morales,² Marissa J. Defreitas,² Carolyn L. Abitbol,² Michael Freundlich,² Sethuraman Swaminathan,¹ Gaston E. Zilleruelo.² ¹Pediatric Cardiology, Univ of Miami; ²Pediatric Nephrology, Univ of Miami, Miami, FL.

Background: Hypertension (HT) is a major risk factor causing left ventricular hypertrophy (LVH) and diastolic dysfunction. In children with chronic kidney disease (CKD), the cardiovascular morbidity exceeds that of peers without CKD.

Methods: Children with diagnosis of HT underwent echocardiography with concurrent tests of kidney disease were included. LV mass, systolic and diastolic function were reviewed. Diastolic transmitral early (E), late (A), septal E', lateral-mitral E' velocities measured. Calculated E/A < 1 and/or E/E' Z-score (Z) > 2 defined diastolic dysfunction.

Results: 52 HT children (11±5yr), 29 had CKD (CKD-HT) and 23 essential HT (eHT). No differences in age, gender, body mass index (BMI), %obesity, degree HT between groups. Prevalence LVH (25% & 30%) and LVMI-Z were similar. LVMI-Z was strongly correlated with BMI-Z in both groups (each $r + 0.6, p < 0.01$) and to a lesser degree with SBP-Z ($r + 0.3, p 0.05$). No correlation of LVMI-Z with GFR. Diastolic dysfunction was identified in both eHT and CKD-HT (24% vs. 25%) whereas systolic function was preserved in both groups. Changes of E/A and aortic root diameter were subtle but significantly different between eHT and CKD-HT (see figure). Additionally, a significant decline in E/A ($p 0.01$) and Septal E/E' Z ($p 0.03$) was observed with worsening GFR.



Conclusions: High prevalence of LVH and diastolic dysfunction noted in HT children with or without CKD. Severity of LVH associated with obesity and to a lesser extent to high BP. HT children with CKD had subtle but significantly lower E/A ratio and larger aortic root diameter which could be related to poor renal function.

TH-PO471

Glomerular Capillary Injuries in Thin Basement Membrane Disease Yusuke Kajimoto, Michiko Aoki, Go Kanzaki, Kiyotaka Nagahama, Akira Shimizu. *Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.*

Background: Thin basement membrane disease (TBMD) is diagnosed by diffuse reduction of the thickness of glomerular basement membrane (GBM) in electron microscopy (EM), and characterized clinically by benign familial hematuria. However, some cases progress to end-stage renal disease. In the present study, we performed the clinicopathological analyses of TBMD, especially focusing on glomerular capillary injuries, including morphological and qualitative alterations of GBM and glomerular capillaries, and correlated with clinical findings.

Methods: In our department, 27 renal biopsy cases of TBMD (1.9%) was identified. We investigated clinical characteristics using clinical records. We also examined pathological characteristics using light and EM, immunostaining for CD34, which can detect glomerular capillaries, immunostaining for $\alpha 5$ (IV) chains of type IV collagen, which is one of the main component of GBM, and low-vacuum scanning electron microscopy (LV-SEM), which allows detailed three-dimensional observation of GBM surface.

Results: The average age was 37.3±19.5 (5-64) years. 26 cases had hematuria and 21 cases had proteinuria. 17 cases (63.0%) indicated hematuria or proteinuria under 20 years of age. In 6 cases, the eGFR declined in G3a to G4 in clinical CKD stage. In immunofluorescence, $\alpha 5$ (IV) expression was significantly reduced in the GBM with partial enhancement of $\alpha 2$ (IV). In LV-SEM observations, thinning and flatter of GBM was noted with multiple small holes and manufactures in the surface of GBM. In CD34 and PAS staining, narrowed glomerular capillaries increased with accumulation of glomerular extracellular matrix (ECM), associated with glomerular endothelial cell injuries.

Conclusions: In TBMD, narrowing glomerular capillaries developed with increased glomerular ECM, in association with glomerular endothelial injuries. In addition, qualitative (reduced $\alpha 5$ (IV) expression) and ultrastructural alterations of GBM (small holes and manufactures) were noted. These glomerular capillary injuries might be associated with the clinical findings including urinary abnormalities and renal dysfunction.

TH-PO472

Clinical Significance of IgM Disposition in Kidney Biopsy of Paediatric Minimal Change Disease, Single-Centre Case-Control Study Duaa Alromaili, Turki Abdullah Alshareef. *Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*

Background: In many cases of Minimal change nephrotic syndrome, or Minimal change disease (MCD), immunoglobulin M (IgM) is occasionally deposited in the mesangium, and can be seen under the electron microscopy (EM) and immunofluorescence (IF). Based on many studies, the rule of IgM is controversial in minimal change disease MCD which is one of the histopathological types of INS. The aim of this study is to explore the clinical significance of mesangial IgM deposits in paediatric MCD cases.

Methods: We reviewed a sample of 313 cases children with MCD who underwent a native kidney biopsy (NKB) at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia from 2003 to 2014. The sample is divided furtherly according to the presence of IgM deposits under EM and IF to IgM +IF and IgM-IF, which are labeled as case- control groups respectively. We reviewed the clinical course as per the response to the steroid treatment. Initial adjuvant therapies included: Cyclosporine, Tacrolimus and Cyclophosphamide.

Results: MCD IgM+IF has shown a significant association with the presence of hypertension at the time of diagnosis, where a p-value of 0.03. MCD IgM+IF showed

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

statistical significance in association of steroid dependence where p-value of 0.04 in the MCD IgM+IF steroid dependence group and p-value of 0.05 in the MCD IgM+IF steroid resistance cases. Chronic kidney disease is not associated statistically with the presence of IgM. In terms of treatments, cyclosporine (CSA) has shown a significant association in the development of remission of the MCD IgM+IF with a p value of 0.04 for the subtype.

Conclusions: Our results indicate that IgM+IF may be a marker of the initial disease severity of MCD as it correlates with the outcome of steroid response. Cyclosporine shows a better outcome in achieving the remission in MCD IgM+IF. A prospective study is required to support our conclusion.

TH-PO473

Correlation Between Age-Dependent Expression of Oxidant Handling Genes and Sensitivity to Nicotine Exposure in the Mouse Kidney

Istvan Arany, Samuel Hall, Mehul P. Dixit. *Pediatrics, Univ of Mississippi Medical Center, Jackson, MS.*

Background: Studies have shown that childhood exposure to secondhand smoke may increase adulthood renal risk. Other studies also suggest that children may be more vulnerable to secondhand smoke exposure than adults, which may imply augmented sensitivity to renal oxidative stress. Accordingly, we tested the status of oxidant handling genes and extent of oxidative stress in the kidneys of adolescent mice exposed to active or passive smoking-equivalent nicotine and compared to the kidneys of adult mice.

Methods: 4- and 24-week-old male C57BL/6J mice -that are equivalent to early adolescence and early adulthood, respectively- had ad libitum access to NIC in their drinking water (200 or 5 µg/ml) for 4 weeks that results in either active (>150 µg/ml) or passive (<10 µg/ml) smoking-equivalent cotinine (stable metabolite of NIC) levels in their plasma. Renal oxidative stress (4HNE content), injury (KIM-1 expression) and function (plasma creatinine) were determined. Expression of select pro- and antioxidant genes were determined by Western blotting and microarray.

Results: Active smoking-equivalent NIC exposure resulted in 2.5 fold increase in renal 4HNE content in adolescent mice compared to vehicle, which is significantly higher (p<0.05) than in adult mice (1.7 fold). Similarly, renal KIM-1 expression increased 2.2 vs 1.5 fold (p<0.05), respectively, while renal function was unchanged. In contrast, passive smoking-equivalent NIC exposure increased renal 4HNE content only in young (1.4x) but not in adult mice. Interestingly, baseline expression of select pro-oxidant genes (p66shc) was higher, while expression of some anti-oxidant genes (Nrf2, MnSOD) was lower in the young kidney compared to the adult kidney. In vitro experiments confirmed that high level of p66shc or low level of Nrf2 or MnSOD exacerbates NIC-mediated ROS production and consequent mitochondrial depolarization-dependent injury in renal proximal tubule cells.

Conclusions: Our results imply that the young kidney exhibits a more pro-oxidant environment than the adult kidney, which may explain their higher sensitivity to chronic NIC exposure-dependent oxidative stress.

TH-PO474

Maternal Nutrient Restriction Aggravates Renal Tubular Necrosis and Interstitial Fibrosis After Unilateral Ureteral Obstruction in Rat Offspring

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Background: Maternal nutrient restriction not only reduces nephron number but may also affect tubules, interstitium, capillary density, endothelial function, and response to oxidant injury. These changes may become apparent only after a secondary injury to the kidney. We examined the response to unilateral ureteral obstruction (UUO) in the kidney of offspring from control and nutrient restricted rats.

Methods: Six-week old offspring from rats given food ad libitum (CON, n=3) and those subjected to 50% food restriction throughout pregnancy (NR, n=6) were subjected to left ureteral obstruction. After 7 days, blood pressure, serum creatinine, urea nitrogen, and urine from the left kidney were examined. Kidneys were stained with Masson trichrome, elastica van Gieson, or CD31. Collagen was quantified by analyzing the color distribution of whole-slide-images after color classification of the pixels. The expression of nitrotyrosine was assessed by immunoblot of kidney lysate.

Results: There was no difference between CON and NR in body weight, blood pressure, serum creatinine, and urine protein or osmolality. Blood urea nitrogen was significantly higher in NR than CON (20.8±0.8 vs 17.5±0.1 mg/dL, P<0.05). Macroscopically, pelvic dilation of similar degree was noted in the obstructed kidney of CON and NR. Tubular necrosis, however, was more extensively observed in NR. There was no difference in the collagen area ratio of the contralateral kidney between CON and NR. The collagen area ratio of the obstructed kidney was increased compared with the contralateral kidney, and the increase was significantly greater in NR compared with CON (6.8±3.8% vs 2.6±0.5%, P<0.05). There was no difference in immunohistochemical expression of endothelial marker CD31 between CON and NR. The expression of nitrotyrosine, a marker of oxidative stress, was increased in the obstructed kidney in both CON and NR, and the extent was greater in NR.

Conclusions: NR kidneys are more susceptible to ischemia and fibrosis secondary to UUO, which may be due to increased oxidative stress.

Funding: Government Support - Non-U.S.

TH-PO475

Post-Weaning High-Fat Diet Accelerates Kidney Injury, but Not Hypertension Programmed by Maternal Diabetes

Min-Chun Liao,¹ Yessoufou Aliou,¹ Xin-Ping Zhao,¹ Shiao-Ying Chang,¹ Isabelle Chenier,¹ Julie R. Ingelfinger,² Shao-Ling Zhang.¹ ¹CRCHUM, Univ of Montreal, Montreal, QC, Canada; ²Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, MA.

Background: Severe maternal diabetes results in offspring with intrauterine growth restriction (IUGR) phenotype. The long-term outcome of these affected IUGR diabetic offspring who experience overnutrition in early life is incompletely delineated. In the current study, we aimed to establish the underlying mechanisms by which a post-weaning high-fat diet (HFD) accelerates the perinatal programming of kidney injury occurring in the offspring of diabetic mothers.

Methods: Male offspring of non-diabetic and diabetic C57/BL6 dams were fed with standard chow (normal diet, ND) or HFD from 4 to 20 week-old. Biological parameters, renal morphology, and gene expression were assessed. Rat immortalized renal proximal tubular cells (IRPTCs) were used for *in vitro* studies.

Results: As compared to offspring from non-diabetic dams, on ND, the offspring of dams with severe maternal diabetes had IUGR phenotype and developed mild hypertension and evidence of kidney injury in adulthood. Exposing the IUGR offspring to HFD resulted in rapid weight gain, catch-up growth and later, to profound kidney injury with glomerulosclerosis and tubular apoptosis. In adulthood these IUGR animals demonstrated activation of renal TGFβ1 and collagen type IV expression, increased oxidative stress and enhanced renal lipid deposition, but not systemic hypertension. HFD or free fatty acid (FFA) in the diet appear to accelerate the process of perinatal programming of kidney injury, associated with increased CD36 and fatty acid binding protein 4 (Fabp4) expression in proximal tubular cells, which may target reactive oxygen species (ROS), NF-κB and TGFβ1 signaling.

Conclusions: Early postnatal exposure to overnutrition with a HFD appears to increase the risk of development of kidney injury, but not hypertension, in IUGR offspring of dams with maternal diabetes.

Funding: Government Support - Non-U.S.

TH-PO476

Does Anemia Contribute to Growth Delay in Pediatric CKD? Implications from Adenine Mouse Model of CKD-Related Growth Failure

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Background: Growth delay remains common in children with CKD and it worsens their quality of life. The origin of CKD-related growth failure in children is thought to be multi-factorial but the contribution of anemia remains controversial based on the data from the major clinical studies. Experimental investigations of the role of anemia and iron homeostasis in growth and nutrition in juvenile CKD are lacking.

Methods: C57Bl6 mice and hepcidin gene (HAMP) knock-out (KO) pups were started on 0.2% adenine diet at weaning (3 weeks) and sacrificed in 8 weeks. Litter-mate controls were fed a regular diet. Weekly measurements of nose to tip of tail length were used for tracking linear growth.

Results: Adenine fed juvenile mice had statistically significant elevation of BUN, serum creatinine and phosphorus at sacrifice. Adenine fed mice had slower rate of weight gain compared with controls and by 3 weeks they stopped gaining and / or started to lose weight. Linear growth was also significantly slower in adenine fed mice. At sacrifice, adenine fed mice had approximately 40% deficit in body weight and 10-15% deficit in body length, as compared with controls (both differences were statistically significant). Bone histology revealed marrow adiposity in adenine fed mice. While wild type adenine fed mice developed anemia, hemoglobin and hematocrit levels remained unchanged in HAMP-KO mice throughout the experiment. However, no differences in linear growth or serum creatinine were observed between wild-type and HAMP-KO adenine-fed mice.

Conclusions: In this study we demonstrated that 0.2% adenine diet reliably induces CKD-related growth failure and anemia in juvenile mice, resembling those seen in children with CKD. Knocking out HAMP rescues the anemia phenotype but does not affect linear growth and renal function decline, thus providing new insights into the interplay between anemia and other CKD complications in children. Our ongoing experiments are directed towards further characterization of the mineral metabolism and erythropoiesis in this model and testing novel therapies that can improve growth in juvenile CKD.

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TH-PO477

Establishment of Urinary Tract Infections in the Absence of Umbrella Cells and Uroplakin Plaque

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Background: Uropathogenic *Escherichia coli* (UPEC) accounts for 90% of human urinary tract infections (UTI). Urothelial umbrella cells elaborate uroplakin plaques that establish a permeability barrier to urine and pathogens. UPEC attach to Uplk1a within uroplakin plaques, invade umbrella cells, and establish intracellular bacterial communities. We genetically ablated plaques and umbrella cells to test their role in UPEC invasion and establishment of experimental UTI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: Six week old *Upk1b^{RFP/RFP}* and wild type mice were intravesically inoculated with 10^8 cfu UPEC strain UTI89. Upk1a was localized by immunohistochemistry. Bacterial burden and histopathology were analyzed at baseline, 1 and 7 days post infection (dpi). Urothelial permeability was evaluated at baseline using 10,000 dalton FITC-Dextran.

Results: Deletion of *Upk1b* led to absent urothelial plaques and umbrella cells, as well as reduced expression and apical concentration of *Upk1a* protein. UPEC established intracellular bacterial communities in wild type but not *Upk1b^{RFP/RFP}* urothelium 1 dpi. *Upk1b^{RFP/RFP}* bladders demonstrated reduced urothelial neutrophil infiltrates 1 dpi. Whereas bacterial recovery from urine, bladder, ureters and kidneys was significantly reduced in *Upk1b^{RFP/RFP}* versus wild type 1 dpi ($p < 0.05$, Mann-Whitney), comparable burden was observed 7 dpi. *Upk1b^{RFP/RFP}* but not wild type bladder urothelium was permeable to FITC-dextran.

Conclusions: *Upk1b* serves an essential role in plaque assembly and terminal differentiation of umbrella cells. Whereas umbrella cells and uroplakin plaques facilitate initial UPEC colonization of the bladder, these structures are dispensable for maintenance of infection. Comparable UPEC recovery from *Upk1b^{RFP/RFP}* urinary tracts 7 dpi supports the existence of alternative UPEC reservoirs, potentially as a consequence of a disrupted urine permeability barrier. Thus, genetic ablation of umbrella cells provides the opportunity to define alternative pathways for UTI pathogenesis.

Funding: NIDDK Support

TH-PO478

3D Modeling of the Urinary Tract to Better Understand Urothelial Development and Pathogenesis Leah D. Hunter,^{1,2} Claudia F. Mosley,^{1,2} Ashley R. Jackson,^{2,3} Kirk M. McHugh,^{1,2} ¹Div of Anatomy, Ohio State Univ; ²Center for Human and Molecular Genetics, Nationwide Children's Hospital; ³Biomedical Sciences Graduate Program, Ohio State Univ.

Background: Recent evidence implicates a role for urothelium in the pathogenesis of chronic kidney disease (CKD). To better understand these processes, we plan to three-dimensionally (3D) reconstruct and electronically annotate the expression of urothelial markers during development.

Methods: Embryonic day (E)13.5 (undifferentiated), E14.5 (urothelial differentiation onset) FVB/N mice were 3D reconstructed electronically from 10mm serial sections labeled with urothelial antibodies. Molecular annotations were electronically generated using Stereo Investigator software and quantitated using NeuroLucida Explorer.

Results: E13.5 urothelium displayed highly undifferentiated characteristics, lacking keratin (Krt) and uroplakin expression, while E14.5 exhibited significant urothelial identity expressing a wide range of markers. Bladder basal urothelial cells express sporadic Krt5, Krt14 and Ki67. Unexpectedly, Krt5 also localized to intermediate and select superficial cells at E14.5. Shh and p63 uniformly localized to basal and most intermediate urothelial cells. Shh and Ki67 localized to some superficial urothelial cells. Intermediate and superficial bladder urothelial cells expressed uroplakins. Interestingly, uroplakin expression was more prominent in the dorsal urinary tract, while Shh exhibited more ventral patterning, and Krt14 commonly localized to anterior portions of the caudal bladder urothelium. Krt20 was only minimally expressed at E14.5. Overall, E14.5 bladder urothelial cells expressed 13% Krt14, 57% uroplakin, 1% Krt20, 79% p63, 66% Shh, 21% Ki-67, and 34% Krt13, when normalized to E-cadherin.

Conclusions: Molecular annotation and 3D modeling of the entire embryonic urinary tract will provide novel insight into the expression pattern of urothelial-specific proteins temporally and spatially. Future studies will include 3D mapping of these tissues and markers throughout development and disease states. Our work will serve as a vital resource for developing diagnostic and therapeutic measures for CKD.

Funding: NIDDK Support

TH-PO479

Cardiac Hypertrophy Causes Elevation in Circulating c-FGF23 Levels in Mice Isao Matsui,¹ Akihiro Shimomura,² Yasuo Kusunoki,¹ Daisuke Mori,¹ Sayoko Yonemoto,² Masamitsu Senda,² Yusuke Sakaguchi,¹ Takayuki Hamano,² Yoshitaka Isaka,¹ Hiromi Rakugi,¹ ¹Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; ²Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate homeostasis. Besides its phosphaturic effect, intact FGF23 induces left ventricular hypertrophy (LVH). However, it remains unclear whether ventricular hypertrophy affects circulating levels of FGF23.

Methods: The activation of the calcineurin/NFAT (nuclear factor of activated T-cells) pathway plays pivotal roles in the pathogenesis of LVH. Using cardiomyocyte-specific calcineurin A transgenic (CnA-TG) mice, we assessed whether ventricular hypertrophy affects circulating levels of FGF23.

Results: CnA-TG mice at age 6 weeks developed ventricular hypertrophy. Heart weight/body weight ratio was 0.0111 ± 0.0014 in CnA-TG mice and 0.0043 ± 0.0003 in wild type (WT) mice. Real time PCR analyses demonstrated that cardiac tissues of CnA-TG mice had higher levels of atrial natriuretic peptide, brain natriuretic peptide, and β myosin heavy chain. Serum C-terminal FGF23 levels of CnA-TG mice was significantly higher than those of WT mice (214.7 ± 68.7 vs. 137.2 ± 19.8 pg/mL, $P=0.032$), whereas the levels of intact FGF23 were not different between the two groups (CnA-TG mice 27.6 ± 14.4 pg/mL vs. WT mice 24.7 ± 6.1 pg/mL, $P=0.943$). All parameters — body weight, food intake, water intake, urine volume, creatinine clearance, serum phosphate/calcium levels, urinary phosphate/calcium excretion, and fractional excretion of phosphate/calcium

— were not different between the two groups. Although iron deficiency has been reported to be associated with high circulating c-FGF23, but not i-FGF23 levels, CnA-TG mice had higher transferrin saturation than WT mice (91.5 ± 6.3 vs. $71.7 \pm 15.5\%$, $P < 0.001$).

Conclusions: Cardiac hypertrophy causes elevation in circulating c-FGF23 levels through yet-unknown mechanisms.

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TH-PO480

Soluble Klotho and Cardiac FGF23 Modulate Left Ventricular Hypertrophy in CKD Patients Maren Leifheit-Nestler,¹ Christian Faul,² Dieter Haffner.¹ ¹Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; ²Div of Nephrology and Hypertension, Dept of Medicine, Univ of Miami Miller School of Medicine, Miami, FL.

Background: Elevated levels of circulating fibroblast growth factor 23 (FGF23) are strongly associated with chronic kidney disease (CKD) mortality, and left ventricular hypertrophy (LVH), a major cause of cardiovascular death in CKD patients. Existence and role of a paracrine cardiac FGF23/Klotho system in the heart, however, remain elusive.

Methods: We conducted a retrospective case-control study in 25 deceased patients with end-stage renal disease, and 25 age and sex-matched healthy controls. At the time of death 18 patients were on dialysis treatment, and 7 patients were transplanted. Myocardial autopsy samples of the left ventricle (LV) were evaluated for endogenous FGF23 expression, FGFR 1-4, Klotho, calcineurin-NFAT signaling mediated LVH, and genes regulating pathological cardiac remodeling by immunohistochemistry and quantitative real-time PCR analysis. The expression of brain natriuretic peptide (BNP) served as a marker of LVH.

Results: Here, we find that FGF23 is expressed in human cardiomyocytes, and that myocardial expression of FGF23 in concert with Klotho deficiency strongly correlates with the presence of LVH in CKD patients. Enhanced cardiac FGF23 expression is associated with chronic phosphate load, up-regulation of FGFR4 expression, and activation of calcineurin-NFAT signaling, an established inducer of cardiac remodeling and LVH. Most important, these changes are reversed after renal transplantation. Using *in vitro* studies, we observe that cardiomyocytes express and release full-length biologically active FGF23, and that enhanced FGF23 secretion results in cardiomyocyte hypertrophy, which is blocked in the presence of soluble Klotho.

Conclusions: Our results indicate that enhanced levels of FGF23 induce LVH via a paracrine mechanism in settings of Klotho deficiency. In CKD patients, this process is reversed after renal transplantation.

TH-PO481

Role of FGF23 Mediating LVH in a Mouse Model of Klotho Deficiency Maren Leifheit-Nestler,¹ Melis Basaran,¹ Makoto Kuro-o,² Ioana Alesutan,³ Jakob Völk,³ Florian C. Lang,³ Dieter Haffner.¹ ¹Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; ²Center for Molecular Medicine, Jichi Medical Univ, Shimotsuke, Japan; ³Dept of Physiology, Univ of Tuebingen, Tuebingen, Germany.

Background: In patients with chronic kidney disease (CKD), high serum concentrations of the phosphaturic hormone fibroblast growth factor 23 (FGF23) result in high mortality rate and left ventricular hypertrophy (LVH). FGF23 signals via FGF receptors (FGFR) in the presence of its cofactor Klotho. Recent studies reveal a Klotho independent pathway of FGF23 in cardiomyocytes to promote cardiac remodeling and LVH. However, Klotho seems to be cardioprotective. The aim of our study was to investigate the role of cardiac FGF23/FGFR signaling in the activation of pathologic cardiac remodeling and LVH in the Klotho knockout (*kl/kl*) mouse.

Methods: Hearts of 8 weeks old *kl/kl* mice and wild-type (WT) mice were excised and weighted. The left ventricle was isolated and stained with wheat germ agglutinin (WGA) to quantify cross-sectional area of individual cardiomyocytes. Furthermore, cardiac tissue was homogenized and analyzed by quantitative real-time PCR for genes involved in pathological cardiac remodeling, and protein lysates were used to determine FGF23-mediated activation of calcineurin-NFAT pathway mediating LVH.

Results: Relative heart weight of *kl/kl* mice was significantly higher compared with WT, and cardiomyocyte cross-sectional area was increased in *kl/kl* mice indicating LVH. Cardiac Fgf23 gene and protein levels were induced significantly in *kl/kl* mice compared with WT. Interestingly, expression of *Fgfr1*, the physiological receptor for FGF23/Klotho signaling, was unaffected in *kl/kl* mice, but *Fgfr4* was up-regulated significantly. The calcineurin-NFAT protein complex was activated in *kl/kl* mice inducing genes involved in pathological cardiac remodeling and the development of LVH.

Conclusions: Our data suggest that high levels of circulating and cardiac FGF23 contribute to cardiac remodeling and LVH in Klotho deficient mice indicating a direct impact of FGF23 signaling via FGFR4 on cardiovascular disease beyond CKD.

TH-PO482

Cardiac FGF23 in Concert with Klotho Deficiency Affect Myocardial Fibrosis in Dialysis Patients Maren Leifheit-Nestler, Felix Kirchhoff, Dieter Haffner. Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.

Background: Pathologic cardiac remodeling, i.e. left ventricular hypertrophy (LVH) and myocardial fibrosis, is a major cause of cardiovascular (CV) death in patients with chronic kidney disease (CKD). Increased circulating levels of fibroblast growth factor 23 (FGF23) are associated with increased mortality in CKD coinciding with enhanced CV

disease risk factors and LVH. The impact of cardiac FGF23 on myocardial fibrosis in CKD is not known. Here we investigate the association of cardiac FGF23 and its coreceptor Klotho with myocardial fibrosis in autopsy samples of CKD patients on dialysis.

Methods: Myocardial autopsy samples of the left ventricle of 18 deceased CKD patients on dialysis treatment, and age and sex-matched controls were evaluated with human fibrosis *RT² Profile™ PCR Arrays* including genes responsible for fibrotic remodeling. For histological investigation of cardiac fibrosis, samples were stained with picosirius red and quantified by brightfield and polarized light microscopy. Cardiac FGF23 and soluble Klotho in cardiac tissue were assessed by qPCR and immunohistochemistry, respectively.

Results: The degree of cardiac fibrosis was increased in dialysis patients compared with controls, and correlated positively with duration of ESRD, and dialysis treatment. The expression of cardiac *FGF23* was enhanced in the dialysis group, and associated with fibrosis. The amount of circulating Klotho was reduced in myocardial tissue of our patient cohort, and correlated negatively with cardiac fibrosis. Human fibrosis gene array analyses identified 31 genes regulated significantly in dialysis patients. The TGF β pathway, with *TGF β 1*, *TGF β Rs* and *SMAD3*, was up-regulated in patients on dialysis treatment, and *TGF β 1* correlated negatively with circulating Klotho. *BMP7* and *SMAD7*, which attenuate fibrotic activity, were down-regulated in our patient cohort. In contrast, the pro-fibrotic target genes *CTGF* and collagen I and III were up-regulated.

Conclusions: Enhanced cardiac *FGF23* expression in concert with Klotho deficiency is strongly associated with fibrotic cardiac remodeling processes in heart tissue of CKD patients on dialysis treatment.

TH-PO483

FGF23-Induced LVH Is Reversible in Rodents Ansel P. Amaral,^{1,2} Alexander Grabner,¹ Saurav Singh,¹ Karla J. Schramm,¹ Christopher Yanucil,¹ Alexis J. Sloan,¹ Christian Faul.¹ ¹Medicine, Univ of Miami Miller School of Medicine, Miami, FL; ²Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Left ventricular hypertrophy (LVH) contributes cardiovascular disease in chronic kidney disease (CKD). Serum levels of fibroblast growth factor (FGF) 23 rise as patients progress to renal failure. We have previously shown that FGF23 can activate FGF receptor (FGFR) 4 and calcineurin/NFAT signaling in cardiac myocytes and induces LVH in rodents. Administration of a pan-FGFR inhibitor in the 5/6 nephrectomy model of CKD immediately after surgery protects rats from developing LVH. Furthermore, LVH in rats 2 weeks after surgery is reversible by pan-FGFR inhibition.

Methods: To further study FGFR4-dependency and reversibility of FGF23-mediated LVH, we elevated serum FGF23 in FGFR4 knockout (-/-) mice and wild type littermates by administration of a high phosphate (2%) diet for 3 months. Furthermore, a group of wild type mice that received a high phosphate diet for 3 months was returned to normal chow for 3 months. LVH was assessed by histology and analysis of cross sectional area of individual myocytes. Serum levels of cleaved FGF23 were determined by ELISA and kidney function by BUN.

Results: Serum levels of phosphate and FGF23 were elevated in mice on high phosphate diet when compared to mice on normal chow. However, only wild type but not FGFR4/- mice developed LVH after 3 months as evident by significantly increased LV wall thickness and cross sectional myocyte area. When wild type mice were switched from high phosphate to normal chow, the LVH phenotype resolved within 3 months and cardiac parameters were comparable to those of mice that constantly received a normal diet.

Conclusions: FGFR4 is required for the development of LVH in mice with high FGF23. LVH caused by 3 months of FGF23 elevation is reversed when serum FGF23 levels are normalized. We propose that FGF23-induced LVH in CKD is treatable, and that the FGF23/FGFR4 signaling mechanism in the heart provides novel options for pharmacological interventions, including FGFR4 blockade. Progression and reversibility of cardiac injury might depend on the duration of FGF23/FGFR4 activation in the heart.

Funding: NIDDK Support, Private Foundation Support

TH-PO484

FGF23/FGFR4 Signaling Mediates LVH in Aging Mice Alexander Grabner,¹ Karla J. Schramm,¹ Saurav Singh,¹ Christopher Yanucil,¹ Alexis J. Sloan,¹ Ansel P. Amaral,^{1,2} Christian Faul.¹ ¹Medicine, Univ of Miami Miller School of Medicine, Miami, FL; ²Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Serum levels of fibroblast growth factor (FGF) 23 are elevated in patients with chronic kidney disease (CKD) and are independently associated with increased rates of left ventricular hypertrophy (LVH). A recent translational study from our group demonstrated that FGF23 is a causal factor in the pathogenesis of LVH and that FGF receptor (FGFR) 4 mediates the cardiac effects of FGF23. We have shown that constitutive FGFR4 knockout (-/-) mice that were administered a high phosphate diet to elevate circulating FGF23 were protected from LVH. Human studies have shown that serum FGF23 levels increase with age and are associated with LVH in the elderly population. Therefore we wanted to test, if FGF23 is causatively involved in the development of age-related LVH.

Methods: We studied 6 and 18 months old FGFR4/- mice and wild type littermates. LVH was assessed by H&E staining of cardiac cross sections and quantification of LV wall thickness, as well as analysis of cross sectional area of individual myocytes by WGA-fluorochrome labeling. Serum levels of cleaved FGF23 were determined by ELISA and kidney function by BUN.

Results: Serum FGF23 levels continuously increase in wild type mice with age, whereas kidney function is not altered over time. Compared to 6 months old mice, 18 months old wild type mice develop LVH as evident by significantly increased LV wall thickness and

cross sectional myocyte area. Although the increase in serum FGF23 levels in 18 months old FGFR4/- mice is even higher than in wild type littermates, FGFR4/- mice do not develop an LVH phenotype.

Conclusions: Aging wild type mice develop elevated serum FGF23 levels as well as LVH. Since aged FGFR4/- mice are protected from LVH, we postulate that FGF23 mediates age-associated LVH via activation of cardiac FGFR4, similar to the mechanism that we have previously described in animal models of CKD. In our aging model, elevations of serum FGF23 and cardiac effects of FGF23 appear to be independent of reduced kidney function.

Funding: NIDDK Support, Private Foundation Support

TH-PO485

miR-29b and miR-30c in the Regulation of Cardiac Fibrosis by VDRA Sara Panizo,¹ Manuel Naves,¹ Natalia Carrillo-Lopez,¹ Adriana S. Dusso,¹ Amalia Fernandez-Vazquez,² Laura Martinez-Arias,¹ Guillermo Solache-Berrocal,¹ Jorge B. Cannata-Andia,¹ Isabel Rodriguez.¹ ¹Bone and Mineral Research Unit, IRSIN, REDinREN, Hospital Univ Central de Asturias, Univ de Oviedo, Oviedo, Spain; ²Centro Medico de Asturias, Oviedo, Spain.

Background: Cardiac remodeling in chronic kidney disease is associated with increased myocardial fibrosis. miRNAs could have a regulatory role in this process. The aim of the study was to identify the role of some miRNAs in myocardial fibrosis and also their implication in the effect of the vitamin D receptor activation (VDRA) as well as their potential use as biomarkers.

Methods: Male Wistar rats with chronic renal failure (CRF, by 7/8 nephrectomy) were treated intraperitoneally with equivalent doses of two VDRA (10 ng calcitriol and 30 ng paricalcitol/kg/day, 5 days per week, during 4 weeks). A placebo group (CRF + vehicle) and a sham group with normal renal function served as controls. Biochemical parameters, cardiac fibrosis (Sirius red staining), miRNAs (miR-29b and miR-30c) levels in heart and serum, and the expression of target genes (collagen I [COL1A1], matrix metalloproteinase 2 [MMP2], and connective tissue growth factor [CTGF]) in heart were evaluated.

Results: All VDRA prevented cardiac fibrosis, achieving statistically significant difference in the paricalcitol treated group. A reduced expression of miR-29b and miR-30c was observed in heart of CRF rats, which was prevented with all VDRA, observing the better results in paricalcitol group. It is described that miR-29b regulates COL1A1 and MMP2 expression and miR-30c regulates CTGF expression. In the hearts of CRF rats, increases in RNA and protein levels of COL1A1, MMP2 and CTGF were observed, which were prevented with all VDRA. In serum levels of miR-29b and miR-30c, a significant increase was observed, which was prevented by VDRA use. In the heart and serum analyses, the more marked effects were observed with paricalcitol.

Conclusions: The VDRA, particularly paricalcitol, reduced cardiac fibrosis acting on COL1A1, MMP2 and CTGF expression, probably through the regulation of miR-29b and miR-30c. These miRNAs could be useful serum biomarkers for cardiac fibrosis and also potential new therapeutic targets.

Funding: Government Support - Non-U.S.

TH-PO486

Inhibition of FGFR4 Reduces Changes in Cardiac Contraction Induced by FGF23, but Does Not Rescue Impaired Endothelium-Mediated Vasorelaxation Neerupma Silswal,¹ Chelsea Shapland,¹ Matthew J. Hendrix,¹ Chad D. Touchberry,² Alexander Grabner,³ Christian Faul,³ Michael J. Wacker.¹ ¹Univ of Missouri-Kansas City School of Medicine, Kansas City, MO; ²Health and Sport Sciences, Univ of Memphis, Memphis, TN; ³Univ of Miami Miller School of Medicine, Miami, FL.

Background: Fibroblast growth factor 23 (FGF23) is released by bone cells and is an important hormone in bone-kidney crosstalk in the regulation of phosphate. As kidney function declines, plasma FGF23 increases significantly and elevated FGF23 has been correlated with cardiac pathologies. Recently, our laboratory has shown that FGF23 treatment increases intracellular calcium in primary cardiomyocytes, increases contractility of left ventricular muscle strips, and impairs endothelium-mediated relaxation of aortic rings by reducing nitric oxide bioavailability. While FGF receptors (FGFR) 1-4 are expressed in the heart and vasculature, it is currently unknown which FGFR mediates these direct effects of FGF23.

Methods: We tested the effects of FGF23 on adult mouse heart and aortic rings in the presence of an isoform specific FGFR4 blocking antibody (anti-FGFR4; U3 Pharma/Daiichi-Sankyo).

Results: Acute treatment of FGF23 (9000 pg/ml) increased contraction of paced left ventricular muscle strips 1.6 \pm 0.1 fold over vehicle (P<0.01; n=5). Additionally, FGF23 treatment of paced Landendorff-perfused hearts acutely induced contraction abnormalities typically in the form of mechanical alternans. Both the increase in contractility as well as the alternans were eliminated by pretreatment with anti-FGFR4. Using isometric tension myography, preincubation with FGF23 (9000 pg/ml) caused a 35% inhibition of endothelium-dependent relaxation elicited by acetylcholine in PGF_{2 α} -precontracted aortic rings (n=3-5; P<0.05). However, pretreatment with anti-FGFR4 did not improve relaxation (n=5; P>0.05).

Conclusions: FGF23 can directly target cardiomyocytes via FGFR4 to alter cardiac excitation-contraction, but may work through different FGFR isoforms to alter endothelium-mediated relaxation. Our findings have importance for targeting potential mechanisms of arrhythmias and cardiovascular changes directly induced by FGF23.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO487

Differential Expression and Regulation in Uremia of FGF23 in Bone and Kidney Maria Lerche Mace,¹ Eva Gravesen,² Jacob Hofman-Bang,² Klaus Olgaard,² Ewa Lewin.^{1,2} ¹Nephrology B, Herlev Hospital, Copenhagen, Denmark; ²Nephrology P, Rigshospitalet, Univ of Copenhagen, Copenhagen, Denmark.

Background: CKD is associated with increased plasma levels of FGF23 and contribution from extraskelatal sources has been proposed. Our aim was to study the regulation of FGF23 expression in bone and kidney tissues and the potential importance of kidney FGF23 for the increased plasma FGF23 in uremia.

Methods: The remnant kidney model of chronic uremia (8 weeks) in 5/6 nephrectomized rats was used. Groups of uremic and age-matched normal rats (n= 6-9) were treated with a bolus of the FGF receptor (FGFR) inhibitor, PD173074 (PD) 50mg/kg, or calcitriol 200ng or parathyroidectomy (PTX). Intact FGF23 levels in plasma, and FGF23 expression in bone and kidney were studied.

Results: FGF23 was not expressed in the normal kidney, but was induced in injured kidney tissue. FGFR inhibition significantly (p<0.01) decreased iFGF23 plasma levels in normal PD rats from 364±22 to 154±18pg/ml, and in uremic PD rats from 1590±229 to 581±84pg/ml, whereas the plasma levels in the vehicle groups remained unchanged, normal 357±26 and uremic 1004±112pg/ml. In parallel, a decrease in FGF23 mRNA in bone tissue was demonstrated in both normal and uremic PD rats, as compared to their vehicle control (p<0.005); normal vehicle 1.54±0.23 vs normal PD 0.15±0.02, and uremic vehicle 2.38±0.52 vs uremic PD 0.12±0.2. In contrast, kidney FGF23 mRNA remained unchanged in the uremic PD rats 1.19±0.25 vs vehicle 1.13±0.40 (ns). PTX at time of 5/6 nephrectomy prevented the increase in plasma iFGF23 and bone FGF23 expression in uremia (normal 1.0, uremic 3.01±1.28 and uremic-PTX 0.42±0.09), while it had no influence on induction of kidney FGF23 expression in uremia (uremic 3.87±1.61 vs uremic-PTX 3.06±2.27). Calcitriol further stimulated the increased iFGF23 plasma levels in uremia, whereas it had no impact on kidney FGF23 expression.

Conclusions: FGF23 is induced in the injured kidney. In contrast to bone tissue, the kidney expression of FGF23 in uremia is not regulated by FGFR, PTH or calcitriol signaling. The present results indicate that kidney FGF23 is not contributing to the high plasma levels of iFGF23 in uremia.

Funding: Government Support - Non-U.S.

TH-PO488

MEMO1 Deletion Abolishes Renal Responses to FGF23 Matthias B. Moor,¹ Barbara Haenzi,² Nancy Hynes,³ Olivier Bonny.^{1,4} ¹Dept of Pharmacology & Toxicology, Univ of Lausanne, Lausanne, Switzerland; ²Wolfson Centre for Age-Related Diseases, King's College London, London, United Kingdom; ³Friedrich Miescher Inst for Biomedical Research, Basel, Switzerland; ⁴Service of Nephrology, Lausanne Univ Hospital, Lausanne, Switzerland.

Background: Mediator of ErbB2-Driven Cell Motility 1 (Memo) modulates fibroblast growth factor (FGF) signaling in vitro, but its physiological role is unclear. Memo KO mice showed premature aging, insulin hypersensitivity and a deranged mineral metabolism similar to what is observed in FGF23 KO and Klotho mutant mice (Haenzi B, *FASEB J* 2014). Here, we assessed Memo's role in renal FGF23 effects. We attempted to rescue the Memo KO phenotype, and we established kidney-specific Memo KO mice.

Methods: Exon 2 of *MEMO1* was deleted in the full body of Memo^{fl/fl} mice using a tamoxifen-inducible Cre recombinase to obtain cKO mice. Littermates without Cre served as controls. Twelve Memo cKO and 12 control mice were randomized to receive an intraperitoneal FGF23 or vehicle injection, and kidneys were studied by immunoblotting and qPCR. Memo cKO mice were put on 0.2% or 0.8% phosphate diets, and disease-free survival was assessed. Inducible kidney-specific Memo KO mice were established using the PAX8-LC1 Cre recombinase (Traykova-Brauch M, *Nat.Med* 2008).

Results: Memo cKO mice developed a phenotype of premature aging upon tamoxifen treatment. Reducing dietary phosphate content did not alter disease-free survival. Memo cKO mice lacked renal responses to FGF23. Moreover, the vitamin D inhibitory effect of FGF23 on the 24a-hydroxylase (*CYP24A1*) was absent in cKO mice. Kidney-specific Memo KO mice remained viable and had abolished Memo expression in the kidney but not in other organs upon KO induction. These mice showed renal calcium wasting.

Conclusions: Memo is involved in the mediation of renal FGF23 effects and in renal calcium handling. This explains many similarities that Memo cKO mice share with FGF23 or Klotho KO mice. However, the three mouse models differ in phosphate dependence of the eventually lethal phenotype.

Funding: Government Support - Non-U.S.

TH-PO489

Exploring Bacterial Endotoxin as a Promoter of Fibroblast Growth Factor 23 Production in Chronic Kidney Disease Shiqin Zhang, Jason R. Stubbs. *The Kidney Inst, The Univ of Kansas Medical Center, Kansas City, KS.*

Background: Serum fibroblast growth factor 23 (FGF23) is elevated in chronic kidney disease (CKD) and correlates with circulating concentrations of inflammatory cytokines. Low levels of bacterial endotoxin have been detected in the bloodstream of CKD patients and may promote inflammation in this setting. We hypothesized that endotoxemia may stimulate FGF23 production in CKD.

Methods: We first utilized a mouse osteocyte cell line (IDG-SW3) to explore the direct effects of lipopolysaccharide (LPS) on FGF23 production. Next, we tested the *in vivo* effects of low-dose LPS injection on FGF23 production in both wild-type (WT) mice

and mice lacking CD14, a primary LPS receptor. Lastly, we compared the progressive changes in FGF23 production in WT and CD14^{-/-} mice in response to CKD induction by adenine ingestion.

Results: Treatment of IDG-SW3 cells with LPS (1ug/ml) resulted in an 11-fold increase in FGF23 mRNA expression compared to vehicle (p<0.05, triplicate experiments). Moreover, intraperitoneal injection of LPS (2mg/kg) in WT mice resulted in a 35-fold increase in calvarial FGF23 gene expression two hours post-treatment (p<0.001 compared to vehicle-treated WT mice), which was accompanied by a doubling of serum FGF23 (342.9 ± 124.2 pg/ml vs. 166.5 ± 25.9 pg/ml in vehicle-treated WT mice; p=0.001). Identical LPS dosing in CD14^{-/-} mice blunted this response, resulting in only a 10-fold increase in calvarial FGF23 gene expression (p<0.01) and no obvious difference in serum FGF23 (188.9 ± 75.8, p=NS) compared to vehicle-treated WT mice (n≥8 per group). Finally, CKD induction in WT mice led to a marked elevation of serum FGF23 (6862.0 ± 4829.1 pg/ml vs. 251.9 ± 133.3 pg/ml in WT mice fed a control diet). The absence of CD14 failed to mitigate FGF23 increments with CKD progression, as CD14^{-/-} mice with CKD exhibited comparable serum FGF23 concentrations to WT mice with CKD (9958.7 ± 5047.6 pg/ml, p=NS; n≥9 per group).

Conclusions: Bacterial endotoxin stimulates FGF23 production by bone by a mechanism that is partially dependent on CD14 signaling; however, the deletion of CD14 in a CKD mouse model fails to attenuate the rise in serum FGF23 that accompanies kidney injury.

Funding: NIDDK Support

TH-PO490

Inflammation Affects FGF23 Production in Uremia Maria Encarnacion Rodriguez Ortiz,¹ Juan miguel Diaz-tocados,² Juan R. Munoz-Castaneda,² Carmen maria Herencia,² Julio Manuel Martinez Moreno,² Addy Rosa Montes de Oca Gonzalez,² Alberto Ortiz,¹ Escolastico Aguilera-tejero,³ Mariano Rodriguez,² Yolanda Almaden Peña.⁴ ¹IIS-Fundacion Jimenez Diaz, REDinREN, Madrid, Spain; ²IMIBIC. Reina Sofia Hospital. Un. of Cordoba, Cordoba, Spain; ³Dep. Animal Medicine and Surgery, Univ of Cordoba, Cordoba, Spain; ⁴Lipid and Atherosclerosis Unit, IMIBIC/Reina Sofia Hospital/Un. of Cordoba. CIBEROBn, Cordoba, Spain.

Background: FGF23 increases since early stages of chronic kidney disease (CKD). In CKD, other factors as inflammation may affect the phosphaturic action of FGF23, and higher FGF23 may be required to control P. We aimed to determine if the production of FGF23 is affected by LPS-induced inflammation in experimental uremia.

Methods: 5/6Nx Wistar rats on diets with 0.2% or 0.4%P received LPS for 15 days. Sham rats also received LPS. Blood, urine, and kidney samples were collected.

Results: Nx rats on a 0.2%P diet had lower FGF23 compared to sham, whereas a 0.4%P diet increased FGF23 levels. LPS-treated groups had more than a 3-fold increase in plasma levels of FGF23 as compared with their respective controls. Fractional excretion of P in sham and Nx rats was not modified by the administration of LPS. No differences in renal Klotho expression were found between sham and rats on a 0.2%P diet. A 50% reduction in Klotho was seen in 5/6Nx rats on the diet containing 0.4%P. The administration of LPS to sham rats reduced Klotho expression by approximately 25%. In 5/6 Nx rats on 0.2% and 0.4%P, LPS reduced Klotho by 70% and 50%, respectively.

	Sham 0.6%P	Sham 0.6%P+ LPS	Nx 0.2%P	Nx 0.2%P+ LPS	Nx 0.4%P	Nx 0.4%P+ LPS
Serum P (mg/dl)	4.86± 0.33	5.45± 0.94	2.41± 0.31 ^c	6.40± 1.81	5.74± 0.61	6.44± 0.93
Serum PTH (pg/ml)	22± 0.6	21± 0.5	18± 0.4	29± 6	33± 10	24± 0.6
Serum 1,25(OH) ₂ D ₃ (pg/ml)	57± 21	37± 7	55± 31	10± 2 ^{ab}	11.1± 1 ^{ab}	7± 1 ^{ab}
Serum FGF23 (pg/ml)	92± 12	245± 73 ^a	25± 6 ^a	324± 32 ^a	142± 19 ^a	472± 95 ^c
FEP (%)	8.1± 0.6	5.4± 1.4	4.2± 1.7	2.4± 2	16.1± 2.3 ^a	14.9± 2.7 ^a

Conclusions: The prevention of the increase in FGF23 associated with CKD is not possible in the presence of inflammation.

TH-PO491

Dietary Sodium Bicarbonate Decreases Serum Fibroblast Growth Factor 23 in Normal Rats Nancy S. Krieger, Felix M. Ramos, Min Ho Kim, Kevin K. Frick, David A. Bushinsky. *Medicine, Univ of Rochester School of Medicine, Rochester, NY.*

Background: Patients with CKD have a marked increase in serum fibroblast growth factor 23 (FGF23) which is associated with increased mortality. FGF23 is synthesized in osteoblasts and osteocytes; however, its specific regulators are not clear. During CKD there is a fall in renal net acid excretion leading to metabolic acidosis (MET). We have previously shown that MET directly stimulates FGF23 in mouse bone and in primary osteoblastic cells in vitro, suggesting that an *in vivo* increase in serum HCO₃ might reduce serum FGF23 levels. In this study we tested the hypothesis that oral NaHCO₃ would decrease serum FGF23 levels in normal rats.

Methods: Sprague Dawley rats (250 g) were acclimated to a powdered 1.2% Ca, 0.65% P diet, 13 g/d, for 14d. Rats were either continued on this diet supplemented with 3% NaCl (n=9) or 3% NaHCO₃ (n=10) for an additional 8 d. Blood was then obtained by cardiac puncture for measurement of FGF23 by ELISA (intact FGF23, Immotopics) as well as standard metabolic parameters.

Results: Feeding rats NaHCO₃ led to a significant fall in serum FGF23 and an increase in serum HCO₃ compared to feeding NaCl (Table; values are mean±SE; *, p<0.05; **, p<0.01). Serum PO₄ fell with NaHCO₃ as did both serum Cl and K. There were no differences in serum Ca, Na or creatinine with NaHCO₃ compared to NaCl fed rats.

Treatment	FGF23 (pg/ml)	HCO ₃ (mmol/L)	Ca (mg/dL)	PO ₄ (mg/dL)	K (mmol/L)	Cl (mmol/L)
NaCl	391± 27	23.2± 0.68	9.41± 0.09	7.10± 0.21	4.51± 0.26	101.0± 0.67
NaHCO ₃	255± 15**	27.0± 1.49*	9.59± 0.10	6.16± 0.22**	3.95± 0.07*	98.6± 0.40**

Conclusions: Provision of oral NaHCO₃ sufficient to raise serum HCO₃ led to a significant fall in FGF23 in normal rats supporting the hypothesis that pH (or HCO₃) directly regulates FGF23; however, we cannot exclude that a NaHCO₃-induced change in PO₄ contributed to the change in FGF23. If comparable acid-base regulation of FGF23, now demonstrated in vitro and in vivo, is confirmed in humans, it suggests that correction of acidosis in patients with CKD may lower their elevated FGF23 levels.

Funding: NIDDK Support

TH-PO492

Metabolic Acidosis Increases Osteoblastic MEPE Expression in Parallel to the Increase in Fibroblast Growth Factor 23 Nancy S. Krieger, Min Ho Kim, David A. Bushinsky. *Medicine, Univ of Rochester School of Medicine, Rochester, NY.*

Background: Serum fibroblast growth factor 23 (FGF23) increases with the severity of chronic kidney disease (CKD), leading to decreased renal tubular phosphate (Pi) reabsorption and serum 1,25(OH)₂D₃. FGF23 is synthesized in osteoblasts and osteocytes; however, the primary factors regulating its production are not clear. Patients with CKD have decreased renal net acid excretion leading to metabolic acidosis (MET). During MET, acid is buffered by bone with release of mineral calcium and Pi. MET directly stimulates FGF23 in mouse bone and primary osteoblastic cells utilizing the same signaling pathways that lead to MET-induced bone resorption. To further characterize the regulation of FGF23 by MET we utilized primary osteoblasts to study gene expression pathways upstream of FGF23 production, including the major extracellular phosphoglycoprotein, MEPE, and the phosphate-regulating endopeptidase, PHEX.

Methods: Confluent osteoblastic cells isolated from neonatal mouse calvariae were incubated in neutral (NTL, pH=7.50, Pco₂=39 mmHg, [HCO₃]=30 mM) or acid (MET, pH=7.20, Pco₂=39 mmHg, [HCO₃]=14 mM) medium. Specific RNA gene expression was analyzed by real time PCR with expression normalized to RPL13A and calculated relative to non-incubated cells.

Results: Maximal stimulation of FGF23 was found at 24h (MET=7.26±1.55 vs NTL=3.75± 0.64, p<0.05). MET significantly increased MEPE RNA expression as early as 6h compared to NTL (relative expression: MET=2.23±0.41, vs NTL=1.19±0.16, p<0.05) with a further increase at 24h. There were no significant differences in PHEX expression in response to MET compared to NTL, although there was a progressive decrease in PHEX expression in both groups over 24h.

Conclusions: Thus, MET stimulation of MEPE expression may be an initial step by which MET increases FGF23 production in mouse osteoblasts. By better understanding how MET stimulates FGF23, therapeutic interventions directed toward correction of MET, especially in CKD patients, can be devised to not only prevent bone resorption but also lower FGF23.

Funding: Private Foundation Support

TH-PO493

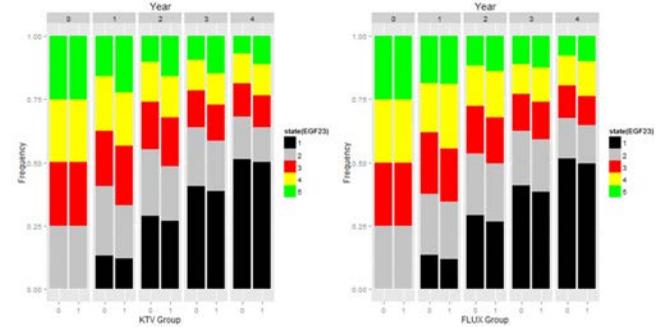
Effect of High-Dose and Flux Hemodialysis on Circulating Markers of Mineral Metabolism in the HEMO Study Anna Jeanette Jovanovich,^{1,2} Alfred K. Cheung,^{3,4} Tom Greene,⁴ Jian Ying,⁴ Michel Chonchol.¹ *Denver VA Medical Center; ²Univ of Colorado Denver; ³VA Salt Lake City; ⁴Univ of Utah.*

Background: There are limited and somewhat contradictory data in the literature on the effects of high versus low dialysis clearance and high versus low flux on circulating markers of mineral metabolism.

Methods: The HEMO Study was a randomized multicenter study of the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Fibroblast growth factor 23 (iFGF23, pre-specified primary endpoint for these analyses), serum phosphorus, and 25-hydroxyvitamin D (25(OH)D) were measured in stored serum samples. We used multi-state analyses to analyze the dose and flux effects on each mineral metabolism marker while accounting for mortality. We estimated the proportions of patients in 5 ordered states (S) for serum phosphorus, 25(OH)D and FGF23: S1= deceased (score=0); S2 = alive in highest quartile (score=1); S2 = alive in 3rd quartile (score =2); S4 = alive in 2nd quartile (score=3); and S5 = alive in lowest quartile (score=4). The average rank was computed over 3 years of follow-up and compared between the randomized groups.

Results: Randomized patients had high rates of coexisting conditions 45% had diabetes, and 80% had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups. The state distributions for FGF23 each year by dose (KTV) group and by flux group

are shown in Figure 1. FGF23 differed significantly between dose groups (p=0.02) but not between flux groups (p=0.17). No significant differences were observed for serum phosphorus or 25(OH)D.



Conclusions: Over 3 years, high-dose of dialysis appeared to reduce FGF23 compared to standard dialysis dose.

Funding: NIDDK Support, Veterans Administration Support

TH-PO494

Factors for Persistent Low or High FGF-23 Levels in Maintenance Hemodialysis Patients Sonoo Mizuiri,¹ Yoshiko Nishizawa,¹ Kazuomi Yamashita,¹ Kohji Usui,² Shigehiro Doi,³ Takao Masaki,³ Kenichiro Shigemoto.¹ *¹Nephrology, Ichiyokai Harada Hospital, Hiroshima, Japan; ²Nephrology, Ichiyokai Ichiyokai Clinic, Hiroshima; ³Nephrology, Hiroshima Univ, Hiroshima, Japan.*

Background: The aim of this study was to assess the association between serum fibroblast growth factor-23 (FGF-23) and mortality, and to determine the factors for persistent low or high FGF-23 levels, in maintenance HD (MHD) patients.

Methods: We examined serum intact FGF-23, age, dialysis vintage, presence of diabetes, BMI, blood pressure, (Ccr+Curea)/2, Kt/Vurea, hs CRP, b2MG, serum albumin, nPCR, geriatric nutritional risk index (GNRI), serum phosphate, serum calcium, iPTH, active vitamin D dosage, and phosphate binders and/or cinacalcet in 332 MHD patients in September of 2012, 2013 and 2014. Coronary artery calcification score (CACS) was measured in a subgroup (n=173). According to quartile (Q) of FGF-23 in 2012, mortality was assessed by Kaplan-Meier and adjusted Cox models. Patients with FGF-23 Q1-Q1-Q1 were categorized in Group 1, patients with FGF-23 Q4-Q4-Q4 in Group 3, and the others in Group 2.

Results: Median age and dialysis vintage were 69 years and 66 months, respectively, at baseline. During the 2 years, 71 patients died and 24 patients left our hospital. Baseline FGF-23 levels (pg/ml) were <310 (Q1), 310-1489 (Q2), 1490-5294 (Q3) and >5294 (Q4) (P<0.05), with cumulative survival rates of 65.4%, 78.9%, 85.1% and 80.6%, respectively (P<0.01), and hazard ratios (HRs) for death of 1.0, 0.6, 0.4 and 0.5, respectively, in univariate model. However, there was no significant association between Q of FGF-23 level and mortality in multivariate model. HR for death of CACS was 1.1 (P<0.01), but there were no differences in CACS in patients based on FGF-23 level. Significant associations between Group 1 and diabetes (OR: 3.5), age (OR: 1.1), serum phosphate (OR:0.4) and vitamin D dosage (OR: 0.2), and between Group 3 and serum phosphate (OR: 2.0), iPTH (OR: 1.004) and vitamin D dosage (OR: 1.9), were observed (P<0.05).

Conclusions: FGF-23 in the lowest quartile showed the lowest 2-year cumulative survival rate in MHD patients, and factors for persistent low FGF-23 levels were diabetes, age, serum phosphate and active vitamin D dosage.

Funding: Private Foundation Support

TH-PO495

Maintenance of Residual Diuresis and Type of Dialysis Can Influence FGF23 Levels Valentina Corradi,^{1,2} Sara Samoni,² Francesca K. Martino,^{1,2} Elisa Scalzotto,³ Ilaria Santolin,³ Elisabetta Galloni,³ Carla Estremadoyro,² Renhua Lu,² Carlo Crepaldi,^{1,2} Monica Zanella,^{1,2} Alessandra Brendolan,^{1,2} Claudio Ronco.^{1,2} *¹Nephrology, San Bortolo Hospital, Vicenza, Italy; ²IRRV, San Bortolo Hospital, Vicenza, Italy; ³Neurology, San Bortolo Hospital, Vicenza, Italy.*

Background: Bone mineral disorders are common in patients (pts) with end stage renal disease (ESRD). In particular, hyperphosphatemia can be frequently seen in pts undergoing peritoneal dialysis (PD) and hemodialysis (HD). Recently, several studies investigated the role of fibroblast growth factor 23 (FGF23) in regulation of renal phosphate excretion in ESRD pts. However, patients with residual diuresis (RD) seem to better control serum phosphorus levels than those without RD. The aim of our study was to determine if the dialysis modality and the preservation of RD influence serum levels of FGF23.

Methods: We performed a cross-sectional study in two groups of pts: HD and PD. The variables analyzed were creatinine, urea, calcium, phosphate (Phosp), i parathormone (intact PTH) and cFGF23 (C-term). The urinary output collection refers to one week. All p value were two sided and statistical significance was set at p<0.05. Statistical analysis was performed by SPSS version 20.

Results: A total of 122 pts were enrolled (58HD,64PD).The mean age of HD pts was 64.45±14.25yrs and of PD pts 62.33±13.86 yrs. RD was present in 78 pts (65.4±

12,87yrs) and the median volume was 5600 (3412-9450 ml/week). The median cFGF23 were significantly higher in HD compared to PD pts (2634 [1192-6880] vs 1395 [609-2660] RU/ml; $p=0,012$) and higher in pts without than in pts with preserved RD (2634 [970-8348] vs 1428 [1042-3047] RU/ml; $p=0,030$). We found a significant correlation between FGF23 and age, Phosp, dialysis modality and RD. Univariable and multivariable adjusted analysis showed that Phosp, dialysis modality and RD are independent predictors of cFGF23 respectively with OR=0,495 [$p<0,001$], OR=-0,184 [$p=0,040$] and OR=-0,189 [$p=0,034$].

Conclusions: In our study, serum cFGF23 levels were lower in patients with preserved RD and those undergoing PD compared to patients without RD and undergoing HD. The dialysis modality and the preservation of RD are independent predictors of cFGF23 levels.

TH-PO496

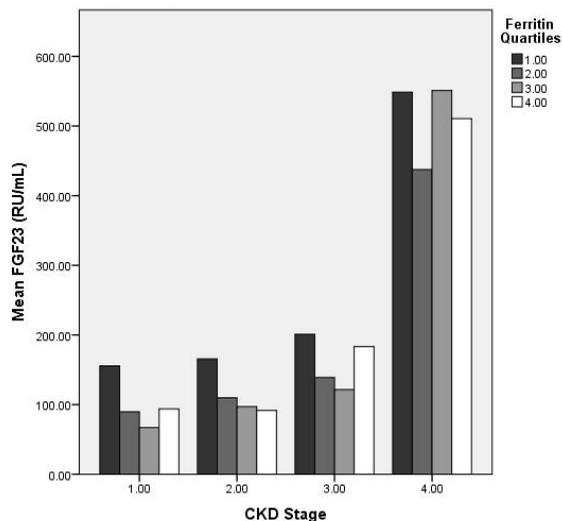
Iron Deficiency Is Associated with Elevated FGF23 Levels in Pediatric CKD

Farah N. Ali,¹ Bradley Warady,² Susan L. Furth,³ Harald Jüppner,⁴ Isidro B. Salusky,⁵ Anthony A. Portale,⁶ Myles S. Wolf.¹ ¹Northwestern Univ; ²Children's Mercy Hospital; ³Children's Hospital of Philadelphia; ⁴MGH; ⁵UCLA; ⁶UCSF.

Background: FGF23 excess contributes to CV disease and death in CKD. Mechanisms of elevated FGF23 levels in CKD are incompletely understood. Iron deficiency is a novel stimulus of FGF23 production. Given high rates of iron deficiency in CKD, we hypothesize that iron deficiency is related to higher FGF23 levels in pediatric CKD and that iron deficiency induced by proteinuria contributes to higher FGF23 levels in glomerular diseases.

Methods: We measured ferritin, TSAT, C-terminal (c) FGF23, CRP, and urine protein/creatinine (pr/cr) in 551 children in the CKiD Study.

Results: Mean age was 10.2 ± 4.4 yrs; 62% were male; mean eGFR was 53 ± 19 ml/min/1.73m²; mean TSAT was 26 ± 13%, median ferritin was 46 ng/mL (IQR 27-81); median urine pr/cr was 0.31 mg/mg (IQR 0.10-1.00); median cFGF23 was 114 RU/mL (IQR 80-185). cFGF23 correlated inversely with ferritin ($p=0,055$) and eGFR ($p<0,001$) and directly with CRP ($p=0,049$), proteinuria ($p<0,001$), and phosphate ($p<0,001$). Grouping proteinuria into low or high grade (pr/cr >3) revealed no differences in ferritin and TSAT, but TIBC was lower (288 vs 310 µg/dL, $p=0,011$) and cFGF23 was higher in the high vs low grade groups (362 vs 184, $p=0,016$). cFGF23 levels were significantly elevated in the lowest ferritin quartile, preferentially in early stages of CKD (Figure).



In multivariate analysis that included proteinuria and CRP, only lower eGFR, glomerular disease, higher phosphate, and lower ferritin were independent predictors of higher cFGF23 levels ($p<0,001$ for all). The relationship between proteinuria and cFGF23 was mitigated when ferritin was added to the multivariable model.

Conclusions: Iron deficiency is associated with higher cFGF23 levels in pediatric CKD and may contribute to the relationship between proteinuria and higher FGF23.

Funding: NIDDK Support, Other NIH Support - NICHD NHLBI

TH-PO497

The Ratio of C-Terminal to Intact Fibroblast Growth Factor 23 Was Elevated in Iron Deficient Patients with Chronic Kidney Disease

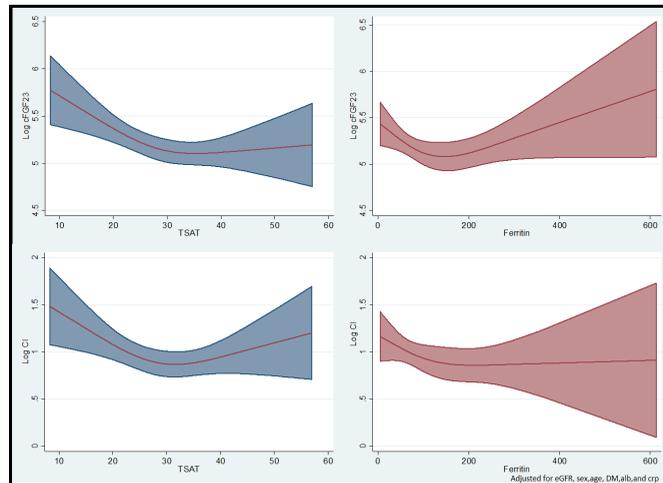
Sayoko Yonemoto,^{1,3} Takayuki Hamano,² Naohiko Fujii,¹ Daisuke Mori,³ Yasuo Kusunoki,³ Akihiro Shimomura,² Isao Matsui,³ Hiromi Rakugi,³ Yoshitaka Isaka.³ ¹Dept of Internal Medicine, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo, Japan; ²Dept of Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; ³Dept of Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka.

Background: A recent study showed iron deficiency was associated with elevated fibroblast growth factor 23 levels by c-terminal assay (cFGF23) but not with intact FGF23 (iFGF23) levels in women without chronic kidney disease (CKD). It remains elusive if

this holds true also in patients with CKD. In this cross-sectional study, we examined the associations between iron deficiency and FGF23 levels by the two assays in predialysis patients.

Methods: The study population consisted of 100 predialysis outpatients of the nephrology department in a hospital in Japan. We measured plasma cFGF23 (Immupoints) and serum iFGF23 (Kainos). Restricted cubic spline analysis was employed to estimate non-linear relationships between iron markers and ratio of cFGF23 to iFGF23 CI ratio. The CI ratio can be regarded as a FGF23 cleavage marker.

Results: The mean age and eGFR was 70.1±15.0 and 26.9±12.9 ml/min/1.73m², and the proportions of female and patients with diabetes mellitus were 30 and 40%, respectively. Only 18 and 6.0% of patients were treated with ESA and oral iron therapy, respectively. The cFGF23 was elevated with the decrease in TSAT and ferritin levels, and the CI ratio was also elevated with the decrease in TSAT and ferritin levels.



Conclusions: In this study, we observed elevation of cFGF23 and CI ratio in iron deficiency patients with CKD. This might be because iron-deficiency stimulates FGF23 transcription and its cleavage simultaneously just as reported in non CKD women.

TH-PO498

Ferric Citrate Hydrate Decreases Circulating FGF23 Levels Independently of Serum Phosphate Levels in Hemodialysis Patients with Iron Deficiency

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Background: Fibroblast growth factor 23 (FGF23) is regulated by dietary phosphate intake and vitamin D receptor activator (VDRA). Iron is another potential modulator for FGF23 metabolism.

Methods: This prospective study enrolled 27 maintenance hemodialysis patients with iron deficiency and hyperphosphatemia who had been treated with sevelamer-HCl. Their phosphate binder was changed to ferric citrate hydrate (FCH), so that their phosphate levels were maintained constant. VDRA, other phosphate binders, and cinacalcet hydrochloride were unchanged. Serum intact-FGF23, C-terminal FGF23, intact parathyroid hormone, 1,25(OH)₂D, and other parameters were prospectively monitored for 12 weeks.

Results: Serum levels of phosphate and 1,25(OH)₂D were unchanged. Serum ferritin levels increased from 25.6 ± 24.3 ng/mL at baseline to 55.8 ± 33.5 ng/mL at 12 weeks with the administration of FCH. Serum intact-FGF23 and C-terminal FGF23 levels were 2000 (1300.0 – 3471.4) pg/ml and 1608.7 (634.8 – 2308.7) RU/ml at baseline, respectively. At 12 weeks, intact-FGF23 and C-terminal FGF23 significantly decreased to 1771.43 (1142.9 – 2342.9) pg/ml ($P=0,0258$) and 1165.2 (626.1 – 1547.8) RU/ml ($P=0,0298$), respectively. Serum intact parathyroid hormone levels significantly increased from 96 (65 – 125) pg/ml at baseline to 173 (114 – 283) pg/ml after 12 weeks ($P=0,0006$).

Conclusions: Oral administration of FCH decreased both serum intact- and C-terminal FGF23 levels and increased intact parathyroid hormone levels, without any change in phosphate and 1,25(OH)₂D. Treatment of iron deficiency with oral FCH may be a useful strategy to reduce serum FGF23 levels independent of phosphate and VDRA.

TH-PO499

Intravenous Iron Leads to Fibroblast Growth Factor 23-Dependent Changes in Calcium-Phosphate Metabolism in Non-Dialysis Patients with Chronic Kidney Disease Stages 3-5

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Background: Iron deficiency is a common phenomenon among patients with chronic kidney disease (CKD) treated with erythropoiesis stimulating agents. Intravenous iron may interfere with calcium-phosphate (Ca-P) metabolism in CKD. Iron infusion may reduce peripheral degradation and clearance of circulating iFGF23 after its secretion by

osteocytes but it is unclear whether it could also modulate FGF23 synthesis. Our research objective was to evaluate the effect of intravenous iron supplementation on the parameters of mineral metabolism in patients with CKD.

Methods: The study included 35 non-dialysis patients with CKD stages 3-5. Each patient received once-daily 100 mg iron solution (Ferric oxide saccharated complex; Vifor, France) for 5 consecutive days. Iron doses were administered in a slow 40-min. intravenous infusion. On day 1 and 3 at baseline and 2 hours after each dose administration, calcium (Ca), phosphorus (P), parathormone (PTH), intact-FGF23 (iFGF23), C-terminal-FGF23 (cFGF23), bonealkaline phosphatase (BAP) were assessed. The measurements were repeated on day 6.

Results: Two hours after the first iron infusion and on day 6 a significant increase in serum iFGF23 was observed (from 257±446.5 to 326.3±529.9 on day 1; p=0.005 and to 451.4±601 on day 6 pg/ml; p<0.05). The concentration of cFGF23 was reduced in parallel only on day 1 (from 654.3±441.3 to 473.6±414 RU/ml; p<0.05). Serum phosphorus concentration decreased significantly on day 1 two hours after iron infusion (from 1.75±0.6 to 1.53±0.35 mmol/l; p=0.005). On following days the changes of cFGF23 and phosphorus concentration were not significant. The serum concentrations of Ca, BAP and PTH were unchanged throughout the study.

Conclusions: Intravenous iron supplementation may interfere with the mechanisms governing both production and degradation of FGF23 thereby leading to transient hypophosphatemia at the beginning of iron therapy.

TH-PO500

The Increase of Fractional Excretion of Phosphorus Induces FGF23 Resistance due to a Decrease in Renal Klotho Juan R. Munoz-Castaneda,¹ Carmen maria Herencia,¹ Maria Encarnacion Rodriguez Ortiz,³ Juan miguel Diaz-tocados,¹ Julio Manuel Martinez Moreno,¹ Addy Rosa Montes de Oca Gonzalez,¹ Yolanda Almaden Peña,² Mariano Rodriguez.¹ ¹*Servicio de Nefrología, Inst Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Univ Reina Sofia, Córdoba, Spain;* ²*Unidad de Lípidos y Aterosclerosis (CIBEROBN), IMIBIC, Hospital Univ Reina Sofia, Córdoba, Spain;* ³*Laboratorio de Nefrología, IIS-Fundación Jiménez Díaz, REDinREN, Madrid, España.*

Background: The maintenance of serum phosphate (P) levels is critical in the context of renal diseases to prevent CKD-MBD, the progression of CKD and mortality mainly caused by cardiovascular events. As renal function declines P levels increases instead of the high FGF23. In these conditions an unsolved FGF23 resistance is produced. The mechanisms whereby FGF23 resistance is produced will be evaluated.

Methods: Renal FGFR1 and klotho were analyzed in normal rats receiving continuously infusion of rat recombinant FGF23 and 5/6 Nx rats with high or low levels of P in the diet. An additional group with anti-FGF23 antibody was also used in 5/6 Nx rats unsolved FGF23 resistance is produced.

Results: In normal rats, high levels of FGF23 increased fractional excretion of P (FePi) and renal FGFR1, whereas klotho was decreased. In 5/6Nx with normal FGF23 (0.6%P diet), the FePi was moderately increased and FGFR1 and klotho was decreased. In 5/6Nx rats with high FGF23 levels (1.2%P diet) there was a severe decrease of klotho and an increase of FGFR1. Anti-FGF23 was administered to check whether renal klotho decreases due to high FGF23 or by the increase of FePi. Anti-FGF23 increased serum P decreasing slightly phosphaturia. In addition we checked that in HEK293 cells high P activated the wnt/b-catenin pathway and decreased klotho expression. Dkk1 administration prevented the drop of klotho in presence of high P. Therefore renal FGFR1 levels results FGF23-dependent, whereas the decrease of klotho is induced by the increase in FePi.

Conclusions: High FGF23 levels increase FGFR1, whereas higher phosphaturia decreases klotho expression through the activation of the canonical wnt/b-catenin pathway, which may induce the resistance to FGF23.

Funding: Government Support - Non-U.S.

TH-PO501

Regulation of α -Klotho Expression by Dietary Phosphate During Growth Periods Shiori Fukuda,¹ Hironori Yamamoto,² Masashi Masuda,¹ Mari Nakao,¹ Yutaka Taketani.¹ ¹*Dept of Clinical Nutrition and Food Management, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan;* ²*Dept of Health and Nutrition, Faculty of Human Life, Jin-ai Univ, Echizen City, Fukui, Japan.*

Background: Phosphate is critically important for biological functions, particularly during growth periods. Phosphate deficiency causes bone diseases such as rickets and osteomalacia. On the other hand, excess intake of dietary phosphate increases secretion of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) to maintain plasma phosphate level. FGF23, is a potent phosphaturic factor, binds to α -klotho /FGFR complex in the kidney to promote excretion of phosphate into urine. In addition, excess intake of dietary phosphate also decrease in renal α -klotho expression. Downregulation or lack of α -klotho induces a premature aging-like phenotype such as ectopic calcification and osteoporosis resulted from hyperphosphatemia. However, the effects of high phosphate diet on renal α -klotho expression just after weaning period are still unknown.

Methods: To investigate that, we used C57BL / 6J mice aged 3-4 week old under a rapid growth phase. Mice were fed 0.02, 0.3, 0.6, 0.9, 1.2, 1.5 or 1.8% phosphate diets for 7 days beginning just after weaning at 3 week old.

Results: As a result, elevation of plasma phosphate and FGF23 levels, and decrease in renal α -klotho expression were observed as the content of dietary phosphate increased. In addition, renal calcification was clearly observed in mice fed 1.5 or 1.8% phosphate diets.

The renal calcification did not observed when the 8 week-old mice were fed with 1.5 or 1.8% phosphate diet for 7 days. These results suggest that the effects of high phosphate diet during growth periods have a much greater adverse effect on renal α -klotho expression and morphology of the kidney as compared to a similar investigation during maturation periods.

Conclusions: In conclusion, excessive dietary phosphate intake during growth periods such as just after weaning period decreases in renal α -klotho expression relating to premature aging-like lesions.

Funding: Government Support - Non-U.S.

TH-PO502

The Secreted Klotho mRNA Transcript Is Continuously Degraded by Nonsense-mediated mRNA Decay and Its Splicing Is Dysregulated After Kidney Damage Rik Mencke, Geert Harms, Jan-luuk Hillebrands. *Pathology and Medical Biology, Univ Medical Center Groningen, Groningen, Netherlands.*

Background: Klotho is an anti-aging gene of which two mRNA transcripts have been identified: one corresponds to the full 5-exon coding sequence and the other, alternatively spliced, consists of exons 1-3 and 50 downstream base pairs, forming a stop codon. The latter mRNA is thought to code for a secreted Klotho protein. While soluble Klotho proteins can be detected in blood, urine, and cerebrospinal fluid, a product of this alternative transcript has never been identified. Nonsense-mediated mRNA decay (NMD) research predicts that the premature stop codon induces continuous degradation during translation.

Methods: We first assessed the mRNA transcripts in human kidney and HK-2 cells by RT-PCR and DNA sequencing. We then blocked NMD in HK-2 cells using cycloheximide (CHX) (100 μ g/ml) for 2, 4, or 6 h, or using XRN1 siRNA for mRNA degrading enzyme exoribonuclease 1, to assess possible accumulation of the alternative mRNA by RT-PCR and densitometry. Then, we assessed whether splicing was different in normal human kidneys (N=11) and in chronic rejection transplanted (CRT) kidneys (N=4).

Results: Expression of both Klotho mRNA transcripts was confirmed in human kidney and in HK-2 cells by RT-PCR and DNA sequencing. CHX-induced inhibition of translation increased the "secreted" / membrane-bound Klotho mRNA ratio from 0.14±0.02 to 0.44±0.06 (p<0.001). Preliminary data show that silencing of XRN1 has the same effect. Furthermore, already in normal kidneys, there was a marked, reproducible variation in splicing ratios, ranging from 0.03±0.01 to 0.20±0.02. In CRT kidneys, Klotho mRNA was expectedly down-regulated and splicing was skewed towards the non-functional alternative splice variant.

Conclusions: The alternative Klotho mRNA contains a premature stop codon and is a likely NMD substrate. Soluble Klotho would therefore be cleaved Klotho only. Furthermore, in damaged kidneys, splicing of the Klotho gene is dysregulated, which constitutes a new mechanism of Klotho down-regulation.

Funding: Government Support - Non-U.S.

TH-PO503

Genetic Deletion of NaPi-2c Rescues Phenotype of Klotho Knockout Mice without Improving Severe Hyperphosphatemia Ai Hanazaki, Hiroko Segawa, Kayo Ikuta, Toru Fujii, Ichiro Kaneko, Shihoko Yuki, Shiori Nishiguchi, Kejiro Notsu, Yuji Shiozaki, Sawako Tatsumi, Ken-ichi Miyamoto. *Molecular Nutrition, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.*

Background: SLC34A3/NaPi-2c is one of the renal sodium dependent phosphate (Pi) transporters. Mutation of human NaPi-2c causes hereditary hypophosphatemic rickets with hypercalciuria (HHRH). Thus, NaPi-2c may have an important role on renal Pi reabsorption and bone mineralization in humans. The physiological role of NaPi-2c, however, has not been completely explained yet. NaPi-2c knockout (NaPi-2c^{-/-}) mice showed hypercalciuria, but did not show any Pi abnormality. Recently, Hernand N. et al. reported that kidney specific NaPi-2c conditional knockout mice did not show any abnormality. These results suggested that NaPi-2c has minor role in the Pi homeostasis. To discover the role of NaPi-2c, we examined genetic inactivation of NaPi-2c in klotho knockout (klotho^{-/-}) mice.

Methods: To obtain the klotho and NaPi-2c double knockout (klotho^{-/-}/NaPi-2c^{-/-}, KL2c DKO) mice, klotho^{+/-} mice and Npt2c^{+/-} mice were crossed. Total body weight of each of wild-type, klotho^{-/-}, KL2c DKO and NaPi-2c^{-/-} mice was taken every week. Urine and blood were obtained for biomedical measurements at the several ages of weeks. Tissues were obtained from each mice for histological and calcification analysis.

Results: Genetic disruption of NaPi-2c significantly increased body weight and extended the life span of klotho^{-/-} mice. KL2c DKO mice were viable and larger in size than klotho^{-/-} mice, but smaller than wild-type and NaPi-2c^{-/-} mice. KL2c DKO mice showed slightly decreased plasma Pi levels at early hood, but not adult hood. Plasma FGF23 levels were extremely high in KL2c DKO mice as well as klotho^{-/-} mice.

Conclusions: Our finding demonstrated that NaPi-2c genetic deletion rescued the phenotype of klotho^{-/-} mice without improving severe hyperphosphatemia.

Funding: Government Support - Non-U.S.

TH-PO504

Klotho/FGF23-Independent and ERα Mediated Direct Downregulation of NaPi-IIa by Estrogen in the Mouse Kidney Proximal Tubule Hassane Amlal, Sulaiman Sheriff, Rose P. Webster. *Internal Medicine, Univ of Cincinnati, Cincinnati, OH.*

Background: Estrogen treatment is associated with renal wasting of inorganic phosphate (Pi) and hypophosphatemia in rats and humans; however the molecular and signaling mechanisms mediating this effect are still not fully understood.

Methods: To determine the roles of estrogen receptor isoforms (ERα and ERβ) and Klotho/FGF23 pathway in these effects, we studied the effects of estrogen on renal Pi handling in the kidneys of mice with null mutations of ERα or ERβ or Klotho and their wild-type (WT) littermates. Accordingly, Females ERα Knockout (KO), ERβ KO and WT mice were placed in metabolic cages and had free access to food and distilled water. After adjustment, mice were injected daily with 17β-estradiol (estrogen) or vehicle for 3 days.

Results: The results indicate that estrogen-treated WT and ERβ KO mice exhibited a significant phosphaturia despite a reduction in food intake. The phosphaturic effect resulted from a significant downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. Interestingly, these effects were abolished in ERα KO mice. Further, the results showed that estrogen-treated Klotho KO mice exhibited hypophosphatemia and a significant downregulation of NaPi-IIa with no change in the abundance of NaPi-IIc. *In vitro* studies showed that estrogen treatment (24 hrs) of a cell line (U2OS) stably co-expressing both ERα and ERβ caused a significant downregulation of NaPi-IIa protein, when cells are transiently transfected with a plasmid containing ORF-3'UTR but not 5'UTR-ORF of the mouse NaPi-IIa transcript.

Conclusions: In conclusion, estrogen causes phosphaturia in mice despite a reduction in food intake. This effect results from the downregulation of NaPi-IIa and NaPi-IIc protein abundance with no change in their mRNA expression levels. This effect is independent of Klotho/FGF23 pathway and is mediated through the exclusive activation of ERα. A Cis-acting element in the 3'UTR region of mNaPi-IIa mRNA likely plays an important role in the inhibition of its translation by estrogen.

Funding: NIDDK Support

TH-PO505

Effect of Calcitriol on Serum Heparin in Individuals with Chronic Kidney Disease Bhupesh Panwar, Orlando M. Gutierrez. *Univ of Alabama.*

Background: Anemia is highly prevalent in CKD. Elevated hepcidin levels are an important mediator of disordered iron metabolism, a key mechanism underlying anemia of CKD. Vitamin D was recently shown to reduce hepcidin levels in healthy individuals. We examined whether treatment with calcitriol reduces serum hepcidin in individuals with CKD.

Methods: 40 participants with stage 3/4 CKD (eGFR 15-60 ml/min) were randomized to placebo or oral calcitriol 0.5mcg daily for 6 weeks. Primary outcome variable was change in hepcidin levels. Secondary outcomes variables included change in iron parameters, calcium and hemoglobin. Samples were drawn at baseline, 3 days, 1 week and 6 weeks after randomization. Repeated measures analysis was used to examine differences in outcome variables over time in the 2 groups.

Results: At baseline, the only differences in the 2 groups were that hemoglobin and creatinine clearance were higher in the placebo vs. calcitriol arm (13.3±1.7 vs 12.2±1.9 mg/dL; and 69.7±26.8 vs 50.9±23.7 ml/min, respectively). Over 6 weeks of follow-up there were no significant differences in serum hepcidin, iron parameters, or hemoglobin between the 2 groups. There was a significant increase in serum calcium at 6 weeks in the calcitriol arm compared to the placebo.

Table 1. Median[IQR] or Mean±SD of outcome variables over a 6 week follow-up.

		Baseline	3 days	1 week	6 weeks
Hepcidin	Calcitriol	72[46,196]	79[39,146]	81[48,151]	91[39,180]
	Placebo	76[46,124]	77[46,121]	73[40,112]	64[39,94]
Ferritin	Calcitriol	140[84,390]	177[91,339]	177[91,339]	177[88,277]
	Placebo	176[73,296]	173[63,238]	173[63,238]	142[57,217]
Transferrin saturation	Calcitriol	25.3±12.5	24.1±7.9	24.9±15.8	23.5±10.5
	Placebo	23.2±8.1	23.6±7.8	22.7±7.6	21.5±5.5
Hemoglobin	Calcitriol	12.3±1.7	12.2±1.7	12.2±1.9	12.1±1.8
	Placebo	13.2±1.6	13.1±1.8	13.2±1.6	13.3±1.7
Calcium	Calcitriol	9.21±0.43	9.28±0.42	9.32±0.48	9.51±0.51*
	Placebo	9.34±0.29	9.39±0.36	9.39±0.36	9.48±0.37

Conclusions: Calcitriol did not reduce serum hepcidin levels among individuals with stage 3/4 CKD. Future studies are needed to assess if nutritional forms of vitamin D affect hepcidin levels in CKD.

TH-PO506

A Double Blind Randomized Trial to Compare the Effect of High-Dose Cholecalciferol versus Placebo on Secondary Hyperparathyroidism in Chronic Kidney Disease Stage 3-4 Per-Anton Westerberg,^{1,3} Gunnar Sterner,² Osten Ljunggren,¹ Torbjorn Linde.¹ ¹Medical Sciences, Univ Hospital, Uppsala, Sweden; ²Nephrology, Skåne Univ Hospital, Malmö, Sweden; ³Internal Medicine, Ryhov County Hospital, Jönköping, Sweden.

Background: Suboptimal levels of calcitriol (25D) may accelerate secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD). The aim of this study is to determine if a substantial increase in 25D has beneficial effects on mineral metabolism, muscle strength or fatigue.

Methods: We conducted a double blind randomized trial (EudraCT 2011-002586-38) of cholecalciferol 8000IU/day versus placebo in 97 adult CKD3-4 patients with mild SHPT and a 25D level below 75 nmol/L. The primary endpoint was the difference in mean change, after 12 weeks, in intact PTH between those treated with cholecalciferol as compared to those receiving placebo. Other endpoints were the proportion of participants having a 30% reduction in PTH, hand grip strength and fatigue, assessed by a questionnaire, and differences in calcium, phosphate, calcitriol and FGF23. The statistical test of treatment effect was based on ANCOVA, with baseline value as covariate.

Results: 95 subjects completed the study. Their median age was 66 years, 64 were males and mean GFR was 32 ml/min/1.73 m². Baseline 25D were 57.5±23 and 56.8±22 nmol/L, and PTH 10.9±5 and 13.1±9 pmol/L in the cholecalciferol and placebo groups respectively. 25D increased to 161.6±49 nmol/L and PTH decreased slightly to 10.5±5 pmol/L in the treatment group, while 25D remained stable and PTH increased to 15.2±11 pmol/L in the placebo group. A significant difference in the mean change in PTH between the groups at 12 weeks (P<0.01) was recorded. There was no significant difference in the proportion of subjects reaching a 30% decrease in PTH. Additionally, there was no effect on grip strength or fatigue. The calcium level was unchanged in the treatment group, calcitriol increased distinctly from 64.5±43 to 101.5±54 pmol/L, while there were no effects on phosphate or FGF23.

Conclusions: High dose cholecalciferol increases calcitriol and alleviates the development of SHPT in CKD, without causing hypercalcemia or influencing muscle strength or fatigue.

Funding: Pharmaceutical Company Support - Renapharma Ab, Government Support - Non-U.S.

TH-PO507

Comparison Between Paricalcitol and Non-Selective Vitamin D Receptor Activator for Secondary Hyperparathyroidism in Chronic Kidney Disease: A Systematic Review and Meta-Analysis Panpan Cai, Zi Li, Wei Qin, Xiaohong Tang. *Nephrology, West China Hospital Sichuan Univ, Chengdu, Sichuan, China.*

Background: Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney diseases (CKD). Paricalcitol is a tissue-selective vitamin D receptor activator (VDRA) with the promising effects of lower risks of hypercalcemia, hyperphosphatemia, and even calciphylaxis. We conducted a systematic review and meta-analysis to compare the efficacy and safety of paricalcitol and non-selective VDRA for the management of SHPT in CKD patients.

Methods: We comprehensively searched MEDLINE, Embase, the Cochrane trials Group's Specialized Register and CENTRAL database, collected all randomized controlled trials (RCTs) on comparison paricalcitol and VDRA in adult CKD patients with SHPT. A quality evaluation to every enrolled RCT was conducted. Analysis was performed using the statistical software Review Manager 5.2.

Results: A total of 8 trials involving 674 patients were identified for this review. The quality of included trials was limited. Except for one trial that mentioned two deaths, all other trials did not report all-cause mortality and vascular calcification. Paricalcitol effectively lowered the level of PTH (MD: -11.27, 95% CI: -18.70 to -3.85, P=0.003) but no significant difference was observed in the proportion of patients that achieved the target reduction of PTH between paricalcitol and non-selective VDRA (OR: 2.22, 95% CI: 0.91 to 5.40, P=0.08). No statistical differences were found among patients in terms of serum calcium, episodes of hypercalcemia, serum phosphorus, calcium×phosphorus products and bone metabolism index. The low quality of enrolled studies, lack of hard outcome, and multiple definitions of target PTH reduction composed the limitation of our systematic review.

Conclusions: Current evidence provides some support for the use of this selective VDRA in lowering PTH. No sufficient evidence is available to prove that VDRA can reduce the burden of mineral loading. Further trials are required given the limitation of current research.

TH-PO508

Paricalcitol and Calcitriol Exhibit Differential Effects on Gene Expression in Human Arteries Tzongshi Lu,¹ Li-lun Ho,² Thomas F. Hiemstra,³ Daniel Zehnder,⁴ Li-Li Hsiao.¹ ¹Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; ²Chemical Engineering, Massachusetts Inst of Technology, Cambridge, MA; ³School of Clinical Medicine, Univ of Cambridge, Cambridge, United Kingdom; ⁴Univ Hospital Coventry and Warwickshire NHS Trust, Coventry, United Kingdom.

Background: Vitamin D deficiency is common in patients with CKD, and therapeutic use of vitamin D receptor activators (VDRAs) may improve cardiovascular outcomes. The molecular targets of the VDRAs calcitriol and paricalcitol are incompletely understood.

Methods: We studied gene expression in human arterial explants from healthy individuals and CKD patients after exposure to calcitriol, paricalcitol or vehicle. We selected the leading differentially expressed genes based on log 2 ratio fold changes (Δ). Analysis utilized KEGG and DAVID.

Results: Calcitriol and paricalcitol exhibited differential effects on gene expression. Calcitriol induced expression of Toll-like receptor 4 (TLR4) (Δ 14369) and Nuclear Factor of Activated T-cells (NFAT) (Δ 3851) in healthy arteries. In CKD arteries, Calmodulin-dependent KinaseII β (CamKII β) (Δ 7972) and HIF1 β (ARNT) expressions were upregulated (Δ 235). Interestingly, TLR4 is involved in the HIF1 pathway, and NFAT is downstream of CamK in the non-canonical Wnt/calcium pathway. In contrast, paricalcitol significant upregulates Peroxisome Proliferator-Activated Receptor Gamma (PPAR γ) (Δ 8461) in healthy arteries and AXIN1 (Δ 1933) in CKD arteries. AXIN1 is also involved in the Wnt signaling pathway.

Conclusions: Our data demonstrate differential effects of calcitriol and paricalcitol on gene expression in human arterial explants. This finding may provide important mechanisms in developing therapeutic strategies for the roles of VDRAs. Further investigation is needed.

Funding: Private Foundation Support

TH-PO509

Paricalcitol and FGF23 Effects on the Progression of Cardiac Disease in Pediatric Hemodialysis Wacharee Seeherunvong,¹ Chryso P. Katsoufis,¹ Arpit Kumar Agarwal,² Sethuraman Swaminathan,² Phillip Ruiz,³ Gaston E. Zilleruelo,¹ Carolyn L. Abitbol,¹ Michael Freundlich.¹ ¹Pediatric Nephrology, Univ of Miami; ²Pediatric Cardiology, Univ of Miami; ³Pathology, Univ of Miami, Miami, FL.

Background: FGF23 induces and Paricalcitol (Pc) attenuates left ventricular hypertrophy (LVH) in uremic animals. In adults CKD, Pc has not yet consistently improved LVH. We hypothesized that in young hemodialysis (HD) patients, Pc improves LVH and function despite \uparrow FGF23 levels.

Methods: Twenty patients (16 \pm 4 years) on HD (31 \pm 17 months) on Pc >6 months underwent longitudinal biochemical and echocardiography (Echo1 and Echo2) measurements. LV mass index (LVMI) reflects LV structure and shortening fraction (SF) systolic function. To assess LV diastolic function, early (E), late (A) diastolic trans-mitral (m), annular Em, septal Es, tricuspid annular Et velocities were measured with E/A, E/Em and E/Et ratios calculated. Values >2 Z-scores defined diastolic dysfunction. Echo results were reported as height-age adjusted Z-scores. The ratio of the cumulative average weekly Pc dose to the prevalent logFGF23 level (Pc/logF) was used as a reflection of the opposing hormonal effects.

Results: Overall Z-LVMI (1.7 \pm 1.3 vs. 2.0 \pm 1.8) was unchanged; LVH prevalence \downarrow from 55% to 45% (Z-LVMI in 35%, p=0.01); SF was normal throughout. Abnormal E, Em and E/Em (in 30-61%) all improved by 25% on Echo2. Z-LVMI correlated with E/Et (r 0.6, p<0.01) suggesting concurrent \uparrow LV mass with diastolic dysfunction. Pc dose correlated with Echo2 LVMI & E/Et (both r -0.5, p<0.05), indicating improved LVMI & diastolic dysfunction. LogFGF23 changes correlated positively with the changes of weekly Pc dose (p<0.05) and serum P (p<0.05). Pc/logF ratio (4.0 \pm 3.2) correlated with LVMI, wall thickness and E/Et (all r -0.5, p<0.05).

Conclusions: Diastolic dysfunction observed in 2/3 of young HD patients and concurrent LVH improved with Pc despite \uparrow FGF23 levels. The Pc/logF ratio associated significantly with LV structure and diastolic dysfunction and may reflect the net mechanistic effects of these hormones on myocardial hypertrophy and function. Studies in larger cohorts with higher and longer dose regimens of Pc are warranted.

TH-PO510

A Phase 2A Pharmacokinetic Study of an Oral Vitamin D Compound (2MD) in Patients on Dialysis with Secondary Hyperparathyroidism Daniel W. Coyne,¹ Richa A. Pandey,¹ Hector F. Deluca,^{2,3} Julia B. Zella,^{2,3} Lori A. Plum,^{2,3} Margaret Clagett-Dame.^{2,3} ¹Renal Div, Washington Univ School of Medicine, Saint Louis, MO; ²Biochemistry, Univ of Wisconsin-Madison, Madison, WI; ³Deltanoid Pharmaceuticals, Inc., Madison, WI.

Background: Dialysis patients frequently receive a vitamin D receptor agonist such as the endogenous hormonal form of the vitamin, calcitriol, or an analog (e.g. paricalcitol) for treatment of secondary hyperparathyroidism. Although effective, these drugs can cause hypercalcemia. 2MD is a new vitamin D analogue that suppresses parathyroid hormone (PTH) at doses that do not adversely affect serum calcium and phosphorus.

Methods: We enrolled 11 hemodialysis patients with secondary hyperparathyroidism for a pharmacokinetic (PK) study of oral 2MD. After a 4-week screening period that

included a 2-week washout of current pharmaceutical vitamin D therapy, patients received 550ng of 2MD orally after each dialysis treatment for the next 4 weeks. PK studies were performed after the first and final dose.

Results: All eleven patients completed the study. At 4 weeks, the half-life (t1/2) of 2MD was 50.8 \pm 25.8h, time to maximum plasma concentration (tmax) was 4.0 \pm 2.4h and concentration maximum (Cmax) was 3.44 \pm 0.89pg/ml, while the area under the curve (AUC (0-96h)) was 148.0 \pm 38.7pg*hr/ml. Similar results were observed after a single dose. Mean PTH was suppressed 32% and calcium and phosphorus did not change significantly.

Parameter (unit) ^a	First dose n = 10 ^b	Week 4 n = 10
Cmax (pg/ml)	2.50 \pm 1.16	3.44 \pm 0.89
Tmax (hr)	2.1 \pm 1.4	4.0 \pm 2.4
AUC (0-t) (pg*hr/ml)	50.7 \pm 18.5	148.0 \pm 38.7
AUC (0- ∞) (pg*hr/ml)	120.8 \pm 59.5	204.3 \pm 75.7
t1/2 (hr)	55.8 \pm 36.8	50.8 \pm 25.8

^a all results are mean \pm SD.

^b One subject was excluded from the PPS because of a major protocol violation.

Conclusions: In hemodialysis patients, 2MD has a much lower Cmax and AUC but a much longer t1/2 than calcitriol and paricalcitol. These characteristics are consistent with its high potency and effectiveness in suppressing PTH without significant perturbations of calcium and phosphorus.

Funding: Pharmaceutical Company Support - Deltanoid Pharmaceuticals

TH-PO511

Effect of a Novel Vitamin D Receptor Analog VS-105 on Chronic Kidney Disease-Mineral Bone Disorder Hideki Fujii, Yuriko Yonekura, Kentaro Nakai, Keiji Kono, Shunsuke Goto, Shinichi Nishi. *Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan.*

Background: VS-105 is a novel vitamin D receptor (VDR) analog to suppress the progression of secondary hyperparathyroidism. Most important clinical problem is hypercalcemia, hyperphosphatemia and vascular calcification. In the present study, we compared the effect of VS-105 on chronic kidney disease-mineral bone disorder (CKD-MBD) to that of paricalcitol (Pari) using CKD model rats.

Methods: We used male Sprague Dawley (SD) rats and CKD was induced by 5/6 nephrectomy at 8 and 9 weeks. At 10 weeks, they were classified into six groups and were administered vehicle (V), low-dose paricalcitol (LP), high-dose paricalcitol (HP), low-dose VS-105 (LV), and high-dose VS-105 (HV) three times a week, except in the sham operation group (C) (the C, V, LP, HP, LV, and HV group). At 20 weeks, the rats were sacrificed and urinary and blood biochemical analyses and calcium contents of the aorta were performed in all the groups.

Results: At 20 weeks, serum calcium levels showed overall comparable results at low doses. However, at higher doses, serum calcium levels were highest in the HP group followed by the HV group. Serum phosphate levels were higher in the Pari treated-group than in the VS-105 treated-group. The urinary excretion of phosphate was greater in the VS-105 treated-group than in the Pari treated-group. Serum parathyroid hormone (PTH) levels were decreased and serum fibroblast growth factor-23 (FGF23) levels were elevated after administering Pari and VS-105; however, despite comparable serum PTH levels, serum FGF23 levels were remarkably elevated in the Pari treated-group compared to the VS-105 treated group. Calcium content of the aorta was higher in the Pari treated-group than in the VS-105 treated-group. The expressions of VDR and Klotho in the kidney were significantly higher in the VS-105 treated-group compared to Pari treated-group.

Conclusions: While serum PTH levels were similar, our data suggested that the effect of VS-105 on CKD-MBD was more favorable compared to paricalcitol. The mechanism appears to be associated with the difference in the expression of VDR and Klotho in the kidney.

TH-PO512

Vitamin D Receptor Modulators Suppress Vascular Remodeling in the Inflammatory State of Subtotally Nephrectomized Rats Masahide Mizobuchi,¹ Keiichi Sumida,² Takashi Inoue,¹ Nozomu Hosaka,¹ Hiroaki Ogata,³ Fumihiko Koike,⁴ Takanori Shibata.¹ ¹Dept of Nephrology, Showa Univ School of Medicine, Tokyo, Japan; ²Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; ³Dept of Internal Medicine, Showa Univ Northern Yokohama Hospital, Yokohama, Japan; ⁴Dept of Medicine, Showa Univ Fujigakka Hospital, Yokohama, Japan.

Background: Vitamin D receptor (VDR) modulators (VDRMs) have been shown to have pleiotropic effects. In this study we focused on this effect of a novel VDRM, VS-105 on the vasculature in 5/6 nephrectomized rats in which inflammation was induced by lipopolysaccharide (LPS).

Methods: Male SD rats were 5/6 nephrectomized and fed a normal diet. Two weeks after the nephrectomy, an infusion mini pump was implanted through a catheter placed into the right jugular vein; saline was infused for 7 days and LPS was infused for another 4 weeks. During the LPS infusion period, rats were treated (i.p. 3 times/week) with vehicle (propylene glycol; UC), calcitriol (0.015 μ g/kg; CAL), or VS-105 (0.9 μ g/kg; VS-105). Normal rats on the normal diet served as control (NC).

Results: The UC showed significant increase in serum TNF α levels (pg/ml) compared with NC (36.9 vs 11.0, P<0.05) suggesting the induction of systemic inflammation in

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

this model. Both VDRMs (CAL: 13.4, $P < 0.05$ vs UC, and VS-105: 6.0, $P < 0.05$ vs UC) significantly suppressed the increase in TNF α . Serum creatinine levels, significantly increased in the UC ($P < 0.05$ vs NC), were not altered by the VDRMs. No statistical significance was observed in serum calcium and phosphorus among all 4 groups. The mRNA expression of PCNA in the aortic tissue was significantly increased in the UC (15.8-fold) compared with the NC ($P < 0.05$), which was significantly suppressed by the VDRMs (CAL: 9.2-fold, $P < 0.05$ vs UC, and VS-105: 5.0-fold, $P < 0.05$ vs UC). A similar observation was made in the Nox4 mRNA levels (7.2-fold in UC, 1.3-fold in CAL, and 1.8-fold in VS-105).

Conclusions: These results demonstrate that VS-105 has a suppressive effect on vascular remodeling in the inflammatory state of 5/6 nephrectomized rats in which oxidative stress is involved, suggesting that VS-105 exhibits anti-inflammatory pleiotropic effects.

Funding: Government Support - Non-U.S.

TH-PO513

Differential Effects of Ergocalciferol and Cholecalciferol Therapies in Chronic Kidney Disease Cassandra A. Kimber,¹ James B. Wetmore,² Jason R. Stubbs.¹ ¹The Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; ²Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN.

Background: Nutritional vitamin D deficiency is common in patients with chronic kidney disease (CKD) and may contribute to a variety of comorbidities. Prospective studies assessing the comparative efficacy of cholecalciferol and ergocalciferol for correction of 25(OH)D deficiency in CKD patients are lacking.

Methods: We conducted a prospective, randomized, double-blinded trial to assess the relative efficacy of ergocalciferol versus cholecalciferol, 50,000 IU weekly for 12 weeks, to raise serum 25(OH)D levels in vitamin D-insufficient CKD patients ($n = 41$). Serum 25(OH)D concentrations were assessed at baseline, during therapy (week 6), immediately post-therapy (week 12), and six weeks following discontinuation of therapy (week 18). The primary outcome was the absolute change in 25(OH)D from baseline to 12 weeks. Secondary analyses included change in 25(OH)D from weeks 12 to 18, as well as changes in PTH and 1,25(OH)₂D from baseline to 12 weeks.

Results: Mean baseline 25(OH)D concentrations were 20.5 ± 5.5 and 20.9 ± 6.3 ng/mL in the ergocalciferol and cholecalciferol groups, respectively. Cholecalciferol therapy resulted in a greater absolute change in 25(OH)D (45.0 ± 16.5 ng/mL) versus ergocalciferol (30.7 ± 15.4 ng/mL) from baseline to week 12 ($p < 0.01$). However, this superiority of cholecalciferol was transient, as the cholecalciferol group had a more pronounced decline in 25(OH)D (-27.7 ± 19.5 ng/mL) compared to ergocalciferol (-13.2 ± 11.5 ng/mL) following the discontinuation of therapy (week 12 to 18; $p < 0.01$). We observed no significant difference between these two therapies with regard to serum PTH or 1,25(OH)₂D changes.

Conclusions: Therapy with cholecalciferol, compared to ergocalciferol, is more effective at raising serum 25(OH)D concentrations in CKD patients while active therapy is ongoing; however, this superiority is offset by a more pronounced decline in 25(OH)D concentrations with cholecalciferol following discontinuation of therapy. We observed no significant difference in serum PTH or 1,25(OH)₂D changes between these two therapies.

TH-PO514

Effectiveness of High Dose Ergocalciferol versus Conventional Dose Ergocalciferol on 25-Hydroxyvitamin D Level in Chronic Kidney Disease Patients with Vitamin D Insufficiency Bancha Satirapoj,¹ Siwimon Areepong,¹ Panbubpa Choovichian,¹ Ouppatham Supasynhdh.¹ ¹Medicine, Phramongkutkiao Hospital and College of Medicine, Bangkok, Thailand; ²Phramongkutkiao Hospital.

Background: Patients with chronic kidney disease (CKD) have an exceptionally high rate of 25-hydroxyvitamin D (25OHD) deficiency. Progression of CKD and the all cause mortality link to 25-OHD deficiency. The KDOQI guideline, modest supplementation with ergocalciferol to raise serum 25-OHD levels and might improve bone and mineral disorders in CKD. There was limitation of evidence for dosage of ergocalciferol supplement in CKD population.

Methods: This was an open labeled, randomized, controlled study in CKD patients with stage III-IV and serum 25-OHD < 30 ng/mL. The patients were randomized into two groups: conventional-group treated with ergocalciferol as recommended by K/DOQI guidelines or high-dose-group treated with double dosage of ergocalciferol from the recommendation. Serum testing including 25-OHD, intact PTH, phosphate, and calcium were performed at baseline and 12th weeks.

Results: Sixty-three patients with average aged 69.23 ± 11.62 years were included. Characteristics of the two groups were similar at baseline. At the end of the 12-week, the mean 25-OHD level significantly increased from 18.98 ± 7.25 to 27.95 ± 10.06 ng/mL in the conventional-group ($p < 0.001$) and increased from 18.15 ± 7.44 to 32.08 ± 9.04 ng/mL in the high-dose-group ($p < 0.001$). There was also a significantly increase 25-OHD levels in high-dose-group compared with conventional-group (13.64 ± 9.87 vs. 8.52 ± 6.77 ng/mL, $p = 0.03$). Moreover, there was a significantly greater decrease in serum PTH level in the high-dose-group than in the conventional-group (-16.75 ± 26.42 vs. -0.25 ± 26.76 pg/mL, $p = 0.03$). Serum calcium and phosphate were not significantly different between the groups. There was no adverse effects associated with the treatment.

Conclusions: The study demonstrated that oral high-dose ergocalciferol had higher efficacy for increasing 25-OHD and decreasing PTH level in patients with CKD than conventional-dose ergocalciferol after 12 weeks of treatment. The high-dose treatment might have potential effects on improved the bone and mineral disorders in patients with CKD.

TH-PO515

A Rapid Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) Method for Measurement of 24,25-Dihydroxyvitamin D for the Identification of Patients with CYP24A1 Mutations Hemamalini Ketha, Ravinder Singh, Rajiv Kumar. *Dept of Laboratory Medicine and Pathology, Dept of Medicine, Mayo Clinic, Rochester, MN.*

Background: Patients with inactivating CYP24A1 gene mutations exhibit elevated serum 1,25(OH)₂D concentrations with resultant hypercalcemia, hypercalciuria and nephrolithiasis. The measurement of serum 25(OH)D to 24,25(OH)₂D ratios permits the identification of patients with CYP24A1 mutations and is clinically valuable in the identification of patients who are candidates for subsequent CYP24A1 gene sequencing. The objective of our study was to validate a LC-MS/MS assay for 24,25(OH)₂D (-D₂ and -D₃), to establish a range for normal serum 25(OH)D/24,25(OH)₂D ratios and demonstrate the utility of such a ratio in patients with CYP24A1 mutations.

Methods: We validated a LC-MS/MS assay for serum 24,25(OH)₂D₃ and -D₂. Inter- and intra-assay imprecision, limits of detection (LOD), limits of quantitation (LOQ), analytical measurement range (AMR) and recovery were determined. Interference, carry over, stability and ion suppression studies were performed. The serum 25(OH)D/24,25(OH)₂D reference interval in 91 normal subjects was established and similar measurements were performed in 34 patients with clinically suspected CYP24A1 mediated hypercalcemia.

Results: The LOD and LOQ were 0.03 ng/mL and 0.1 ng/mL for 24,25(OH)₂D₃ and 0.1 and 0.5 ng/mL for 24,25(OH)₂D₂, respectively. Intra- and inter-assay imprecision was 4-15% across the AMR of 0.1-25 ng/mL. No interference was observed with 25(OH)D and 1,25(OH)₂D. Intra- and inter-assay imprecision was 4-15% across the AMR of 0.1-25 ng/mL. A 25(OH)D/24,25(OH)₂D ratio of 7-35 was observed in normal subjects whereas in patients with CYP24A1 mutations 25(OH)D/24,25(OH)₂D ratios were significantly increased (99-467; $P < 0.01$). A 25(OH)D/24,25(OH)₂D ratio of ≥ 99 identifies patients who are candidates for CYP24A1 genetic testing.

Conclusions: Elevated 25(OH)D/24,25(OH)₂D ratios support the diagnosis of reduced CYP24A1 activity found in patients with mutations of the CYP24A1 gene. A 25(OH)D/24,25(OH)₂D ratio of ≥ 99 in a patient with hypercalcemia of unknown etiology warrants genetic confirmation by sequencing of the CYP24A1 gene.

Funding: NIDDK Support, Private Foundation Support

TH-PO516

Initiation of AMG 416 After Discontinuation of Cinacalcet Kenneth Liss,¹ Geoffrey A. Block,² Glenn Matthew Chertow,³ Bastian Dehmel,⁴ Yan Sun,⁴ David M. Spiegel.⁴ ¹Hypertension and Nephrology Association, Eatontown, NJ; ²Denver Nephrology, Denver, CO; ³Div of Nephrology, Stanford Univ School of Medicine, Palo Alto, CA; ⁴Amgen, Thousand Oaks, CA.

Background: AMG 416 is a novel intravenous calcimimetic agent that has been shown to significantly decrease parathyroid hormone (PTH) without increasing serum phosphate (P) or the albumin-adjusted serum calcium (cCa) in two 26-week placebo-controlled randomized clinical trials.

Methods: This 4-week, multiple-dose single-arm, open-label safety study was conducted to assess the incidence of hypocalcemia (< 7.5 mg/dL and < 8.3 mg/dL; primary and secondary endpoints respectively) in patients treated with the intravenous calcimimetic AMG 416 after discontinuation of daily oral cinacalcet. Subjects on a stable dose of daily oral cinacalcet (30, 60, or ≥ 90 mg) for a minimum of 4 weeks before and during the 4 weeks of screening were enrolled and underwent a cinacalcet washout period of a minimum of 7 days. Subjects who had a serum cCa ≥ 8.3 mg/dL during the washout period were treated with AMG 416, 5 mg TIW after hemodialysis for 4 weeks followed by a safety observation period for 4 weeks. During the treatment period, the dose of AMG 416 could be restarted at 2.5 mg if a dose hold was required for low serum calcium or low PTH (two consecutive predialysis PTH < 100 pg/mL). Dose increases were not allowed.

Results: 158 subjects were enrolled and 148 completed the washout period and received AMG 416. 140 subjects completed the 4-week treatment period. The per-subject incidence (n, %) of low cCa during the 4 week treatment period was as follows: Prior cinacalcet dose cCa < 7.5 mg/dL cCa < 8.3 mg/dL 30 mg (N=63) 0 (0%) 18 (28.6%) 60 mg (N=47) 1 (2.1%) 4 (8.5%) ≥ 90 mg (N=35) 0 (0%) 1 (2.9%) No subject had a post-baseline cCa < 7.0 mg/dL and no subject developed symptomatic hypocalcemia. Eight subjects discontinued AMG 416: 4 due to subject request, 2 due to adverse events, 1 loss to follow up, and 1 due to death.

Conclusions: Treatment with AMG 416 at a starting dose of 5 mg can be safely initiated after a 7-day washout of cinacalcet therapy, provided that cCa is ≥ 8.3 mg/dL.

Funding: Pharmaceutical Company Support - Amgen

TH-PO517

Treatment with Cinacalcet Increases Plasma Sclerostin Concentration in Hemodialysed Patients with Chronic Kidney Disease and Secondary Hyperparathyroidism Andrzej Wiecek, Piotr Kuczera, Marcin Adamczak. *Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.*

Background: Sclerostin (Scl) is a paracrine acting factor which is expressed in the osteocytes and articular chondrocytes. Results of recent clinical studies suggest that Scl may decrease the osteoblast-related bone formation through the inhibition of the Wnt/ β -catenin pathway. The aim of this prospective, single-arm, open-label clinical study was to assess the influence of six-month cinacalcet treatment on plasma Scl concentration in hemodialysed patients with secondary hyperparathyroidism (sHPT).

Methods: In 45 hemodialysed patients with sHPT (PTH>300 pg/ml) plasma Scl as well as serum PTH, calcium and phosphate concentrations were assessed before the first dose of cinacalcet and after 3 and 6 months of treatment. Repeated measures ANOVA with Bonferroni correction was used in the statistical analyses. The results are shown as means and 95% confidence index.

Results: Serum PTH concentration decreased significantly after 3 and 6 month of treatment from 1173 (905-1441) pg/ml to 859 (584-1134) pg/ml and to 700 (432-767) pg/ml; p for trend <0.0001, respectively. Mean serum calcium and phosphate concentrations remained stable during the treatment period. Plasma Scl concentration increased after 3 and 6 months of treatment from 1.39 (1.20-1.58) ng/ml to 1.47 (1.27-1.67) ng/ml and to 1.55 (1.32-1.79) ng/ml; p for trend = 0.04, respectively. There were no significant correlations between the magnitude of the plasma sclerostin increase and the decrease of serum PTH concentration after 3 or 6 months of treatment ($r=-0.006$; $p=0.97$ and $r=0.004$; $p=0.98$), respectively.

Conclusions: In hemodialysed patients with secondary hyperparathyroidism treatment with cinacalcet increases plasma sclerostin concentration which seems to be independent from the concomitant decrease of parathormone concentration.

Funding: Government Support - Non-U.S.

TH-PO518

The Effect of Cinacalcet Persistence on Risk of All-Cause Mortality and Heart Failure Diane Reams,¹ Paul Druzniowski,³ Abhijit V. Kshirsagar,² Brian D. Bradbury,³ Liron Walsh,³ M. Alan Brookhart.¹ ¹UNC Gillings School of Global Public Health, Chapel Hill, NC; ²UNC Kidney Center, Chapel Hill, NC; ³Amgen, Inc., Thousand Oaks, CA.

Background: Cinacalcet (Sensipar®) discontinuation occurs frequently for medical and non-medical reasons, such as parathyroid hormone levels below 150 pg/mL and medication cost. However, the clinical impact of discontinuing calcimimetic therapy is not well studied. We compared the risk of mortality and congestive heart failure (CHF) hospitalization between individuals with persistent cinacalcet use and patients who discontinued therapy for pre-defined non-medical indications.

Methods: Using data from a large dialysis provider merged with data from the USRDS, we identified new users of cinacalcet (2007-2011) from Part D prescription claims. Cinacalcet discontinuation was assessed in 30-day intervals and classified as either for medical or non-medical reasons. CHF hospitalizations were defined as ICD-9 code 428.x in the primary position, with a broader definition used in a sensitivity analysis. Informative censoring was addressed using inverse probability of censoring weighted (IPCW) estimators. The risk differences (RD) and 95% CIs for mortality and CHF hospitalizations were estimated at pre-specified follow-up times by comparing crude and IPCW cumulative risk functions.

Results: We identified 21,827 cinacalcet initiators who contributed 340,622 30-day follow-up intervals. At 12 months, 3,246 initiators (14.9%) had discontinued for medical indications and 12,077 initiators (55.3%) had discontinued for non-medical indications. We observed RDs for all-cause mortality at 12 months and 24 months, RD = -0.03 (95% CI -0.02, -0.03) and -0.04 (95% CI -0.03, -0.05), respectively. For CHF hospitalizations at 12 months and 24 months, RD = -0.00 (95% CI 0.00, -0.00) and -0.00 (95% CI 0.01, -0.01), respectively.

Conclusions: Our results find that approximately 3 extra deaths per 100 persons occur with discontinuation due to non-medical reasons during the first year of treatment. Reduction in risk for CHF hospitalization was evident when a broader definition of hospitalization was used, but no effect was seen with a more specific definition.

Funding: Pharmaceutical Company Support - Amgen, Inc. Thousand Oaks, CA

TH-PO519

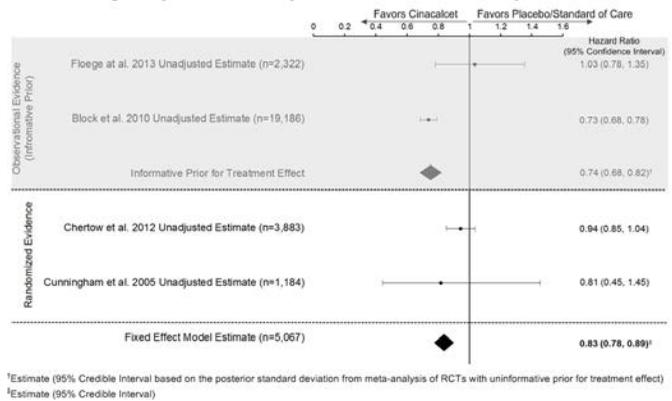
A Bayesian Meta-Analysis of Randomized and Observational Studies on Cinacalcet and Mortality in Secondary Hyperparathyroidism Mark E. Bensink,¹ Greta Lozano-Ortega,² Geoffrey A. Block,³ Glenn Matthew Chertow,⁴ Sarah Goring,² Heather Bennett,² Marie-Louise Trotman,¹ Kerry Cooper,¹ Adrian R. Levy,⁵ Vasily Belozeroff.¹ ¹Amgen Inc., Thousand Oaks, CA; ²ICON plc, Vancouver, BC, Canada; ³Denver Nephrology, Denver, CO; ⁴Stanford Univ, Palo Alto, CA; ⁵Dalhousie Univ, Halifax, NS, Canada.

Background: Conventional meta-analyses of therapeutic effects focus on randomized controlled trials (RCTs) and exclude valuable information captured in observational studies. We conducted a meta-analysis of the effect of cinacalcet in treating secondary hyperparathyroidism (sHPT) in patients with end stage renal disease (ESRD) using methodology that allows for incorporation of non-RCT evidence.

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (2000-February 2014) for RCTs and observational studies in which cinacalcet was compared to placebo or standard of care using all-cause mortality as an endpoint. A high Grading of Recommendations Assessment, Development and Evaluation (GRADE) score was used as an entry criterion. We applied a Bayesian approach where evidence from observational studies was used as the informative prior for treatment effect for the meta-analysis of RCTs.

Results: A total of 616 abstracts were identified. High quality studies meeting inclusion criteria included 2 RCTs and 2 observational. There was insufficient data to estimate between-study variance under a random effects model. The fixed effect hazard ratio estimate (95% credible interval) for the effect of cinacalcet on mortality was 0.83 (0.78, 0.89).

Fig. 1 Bayesian Meta-Analysis Evidence and Evidence Synthesis



[†]Estimate (95% Credible Interval based on the posterior standard deviation from meta-analysis of RCTs with uninformative prior for treatment effect)
[‡]Estimate (95% Credible Interval)

Conclusions: This Bayesian meta-analysis of high quality studies indicates potential beneficial effects of cinacalcet on mortality in ESRD patients with sHPT.

TH-PO520

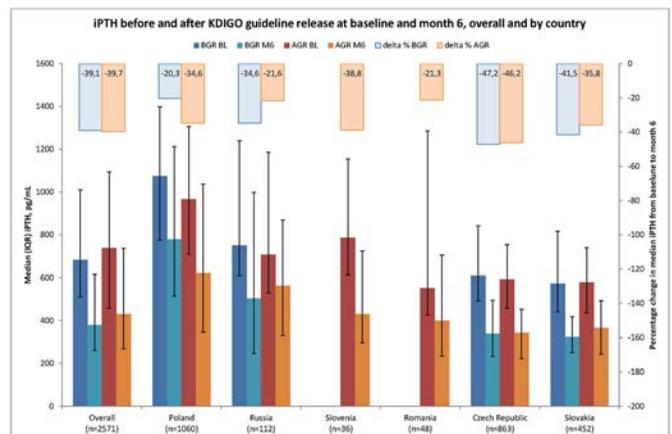
WELCOME – Web-Based Evaluation of Clinical Benefit of Cinacalcet in End-Stage Renal Disease in Central and Eastern Europe Jaroslav Rosenberger,¹ Piotr Mierzicki,² Alexander Selyutin,³ Frantisek Svava,⁴ Kinga Jedynasty,⁵ ¹FMC, Kosice, Slovakia (Slovak Republic); ²SP Wojewodzki Szpital Specjalistyczny, Chelm, Poland; ³Regional Clinical Hospital Orenburg, Orenburg, Russian Federation; ⁴Dept of Medicine, Strahov General Univ Hospital, Prague, Czech Republic; ⁵CEE Headoffice, Amgen GmbH, Vienna, Austria.

Background: Cinacalcet (MIM) is approved for treatment of secondary hyperparathyroidism (sHPT) in ESRD. Study objective: to describe KDOQI target achievement and treatment patterns before release of KDIGO guidelines (BGR; cut-off 08/2009) and thereafter (AGR).

Methods: Design: multicenter, non-interventional, observational study from CEE. Dialysis patients (pts) starting MIM £1 month prior enrollment (BL) were eligible. Primary endpoint: % achieving PTH £300 pg/mL after 6 months. Secondary endpoints: % at KDOQI target for Ca or P at BL and 6 months; MIM dose; vitamin D sterol (VitD) and phosphate binder (PB) use; adverse drug reactions (ADR). The 2nd interim analysis is reported on 12 cohorts enrolling between 01/2007-12/2012. 4 of 6 countries enrolled pts BGR (Figure).
Results: 2571 pts were enrolled, 2172 (84.5%) completed ≥144 days of MIM.

	BGR N=824		AGR N=1747	
	BL	6-mo	BL	6-mo
PTH ≤300 pg/mL (%)	2.8	32.2	1.6	29.1
PTH (pg/mL), median (IQR)	683 (510-1011)	379 (261-615)	739 (547-1094)	430 (269-738)
Ca 8.4-9.5 mg/dL (%)	46.4	58.9	49.5	49.8
P 3.5-5.5 mg/dL (%)	23.7	35.6	32.3	42.5
PB use (%)	82.5	61.7	84.6	61.7
VitD use (%)	59.0	40.5	59.0	43.2

Average median (IQR) MIM dose was 30 (30-42; BGR) and 30 (30-43) mg/day (AGR). Substantial differences in PTH were observed between countries.



110 patients (4.3%) reported ADR (gastrointestinal disorders, n=37; hypocalcemia, n=12); serious ADR: n=2 (cholecystitis, cholelithiasis) in 1 pt. All-cause mortality: 3.1%.

Conclusions: Overall, median PTH was not changed AGR. MIM substantially reduced PTH. Treatment practice varied by country.

Funding: Pharmaceutical Company Support - Amgen

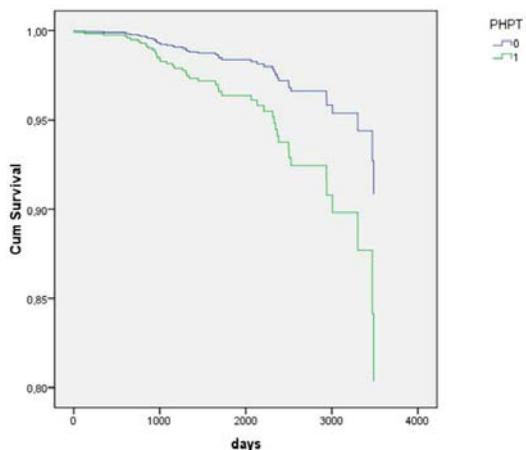
TH-PO521

Persistent Hyperparathyroidism as a Risk Factor for Long Term Graft Dysfunction Maria Julia C. L. N. Araujo, Melani Custodio, Janaina de Almeida Mota Ramalho, William C. Nahas, Rosilene M. Elias, Vanda Jorgetti, Elias David-Neto, Rosa M.A. Moyses. *Nephrology, Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: A successful kidney transplant (KTx) improves most of the mineral disturbances produced by CKD, but some disorders may persist for several years, such as hypercalcemia, elevated PTH and low phosphorus. Previous studies have shown the negative impact of persistent hyperparathyroidism (PHPT) on one year graft function. However, the long term effects of PHPT on renal function are poorly known. Based on that, we aimed to analyze the impact of PHPT on long term graft outcome.

Methods: Retrospective analysis of the isolated adult KTx that occurred between 01/2005 and 12/2014 at the Hospital das Clinicas - USP. Clinical and laboratory data were collected from the charts. Graft failure was defined as return to dialysis. PHPT was considered when, one-year after Ktx, ionized calcium was > 5,3 mg/dl or PTH >100 pg/ml.

Results: From the total of 1708 Ktx occurred in this period, we analyzed 1102 patients that, one year after KTx had an eGFR >30 ml/min and available data for analysis. Of those, 28% (318) had hypercalcemia and 32% (356) had an elevated PTH. PHPT was present in 47% of the patients. The mean follow up time was 1689 days. Graft failure was observed in 47 patients (33 in PHPT and 14 in non-PHPT group, HR = 1,5; p <0,05). Cox-regression analysis showed that graft failure was dependent on PHPT (β=2,3; 1,3-4,1; p= 0,007) even after adjustment for age at KTx, donor age, donor type, PTX and eGFR at 1 year after KTx, as shown in Figure.



Conclusions: Individuals with PHPT one year after KTx, even those with slightly elevated calcium or PTH, have an increased risk of long term graft failure. Our results call our attention for a better management of CKD-MBD before KTx and during the first year of follow-up.

TH-PO522

Epigenetic Alterations in Secondary Hyperparathyroidism Gonzalo Bedia-Diaz,¹ Agustin F. Fernandez,² Jorge B. Cannata-Andia,¹ Adriana S. Dusso,¹ Pablo Roman-Garcia.¹ *¹Bone and Mineral Research Unit, Hospital Univ Central de Asturias, Univ de Oviedo, RedinRen, Oviedo, Spain; ²Epigenetics, Hospital Univ Central de Asturias, Oviedo, Spain.*

Background: Secondary hyperparathyroidism (sHPT) is a complication of CKD characterized by a decreased expression not only of genes such as the VDR, CaSR and Klotho, critical to control parathyroid growth and PTH secretion, but also of 80% of the parathyroid genome. Increased parathyroid DNA methylation in sHPT is an epigenetic change that could account for this widespread down-regulation of gene expression. This work examined the contribution of epigenetic alterations to the severity of sHPT.

Methods: To study methylation patterns in the promoter of the VDR, CaSR, Klotho and PTH genes, the methylation-prone areas in the promoter of each gene were identified and amplified using specific biotin-labelled primers. Parathyroid glands were collected from control and severely uremic rats

Serum biochemical parameters of uremic and control rats. Avg +/- SD

	Urea (mg/dL)	Creatinine (mg/dL)	Ca (mg/dL)	P (mg/dL)	PTH (pg/mL)	FGF23 (pg/mL)
Control	111.67±36.10	1.03±0.38	11.93±0.38	7.55±3.96	255.83±518.22	273.69±76.84
sHPT/Uremic	206.50±53.51	2.10±0.39	10.42±1.14	12.38±1.72	1836.83±495.56	3895.50±385.62
pValue	0.01	0.0001	0.02	0.03	0.0002	0.0008

Parathyroid gDNA was extracted and treated with bisulphite to protect methylated cytosines. Specific PCRs were performed, purified and the PCR product, pyro-sequenced.

Results: Only the Klotho promoter was hyper-methylated (147.2% compared to controls-100%) supporting an epigenetic transcription blockage for this gene. In contrast, the VDR and CaSR promoters were robustly hypo-methylated in sHPT (46.7% and 67%, respectively), thus favouring rather than impairing gene transcription. Importantly, the PTH promoter was also significantly hypo-methylated (50.2%). Taken together, these results support an unrecognized contribution of epigenetic modifications to increase the PTH synthesis in sHPT, and to compensate for the marked reductions in VDR and CaSR expression.

Conclusions: Identification of the regulators of these distinct and gene specific epigenetic changes could provide novel targets for therapeutic interventions to improve outcomes in advanced sHPT.

Funding: Government Support - Non-U.S.

TH-PO523

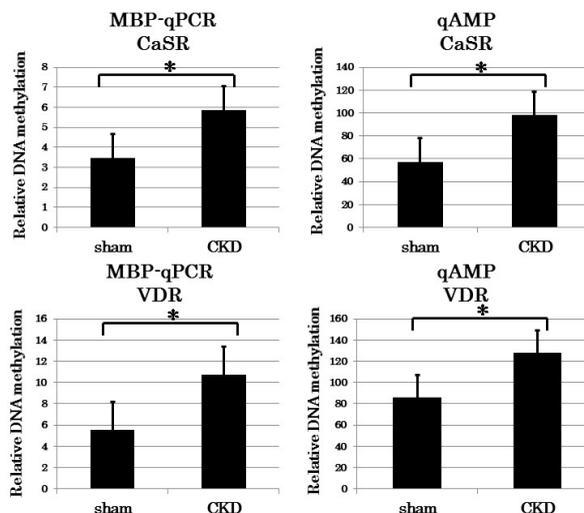
Chronic Kidney Disease Caused Hypermethylations of CaSR and VDR Genes in Parathyroid Glands Takeo Uchiyama,^{1,2} Norifumi Tatsumi,¹ Ichiro Ohkido,² Takashi Yokoo,² Masataka Okabe.¹ *¹Dept of Anatomy, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan; ²Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Background: The stability of mineral homeostasis is the most important for the health of the organism. Secondary hyperparathyroidism (SHPT), a common disorder in patients with chronic kidney disease (CKD), occurs during early course of progressive renal insufficiency. It is well known that the reduction of calcium sensing receptor (CaSR) and vitamin D receptor (VDR) occur slowly and progressively, however the mechanism is largely unknown. Upstream transcription factors of CaSR and VDR are not clear except Glial cells missing 2 (Gcm2), it has affected the CaSR gene directly and transactivates by Gcm2 response elements in the CaSR promoters. In recent years there are reports about epigenetic studies in the field of various diseases including CKD. However, there are few reports related to mineral homeostasis. Here we investigated altered expressions of CaSR, VDR in CKD rats' parathyroid glands. We then demonstrate that the pathogenomic change of SHPT, the reductions of CaSR and VDR expressions proceed from hypermethylations of CaSR and VDR genes.

Methods: Taqman probe (ABI) were used for quantitative real-time PCR. DNA methylation analysis was performed using a restriction digestion and quantitative PCR (qAMP), a combination of methyl-binding protein (MBP) and quantitative PCR (MBP-qPCR). CKD was induced by two-step 5/6 nephrectomy.

Results: The expression level of Gcm2 was not significant both in CKD rats and controls. We then found hypermethylations of CaSR and VDR in CKD rats.

Number : sham 3, CKD 3 * P<0.05



Conclusions: These results suggest that CaSR reduction was independent to the Gcm2 expressions in CKD rats, and chronic kidney disease caused hypermethylations of CaSR and VDR genes in parathyroid glands.

TH-PO524

Proteomic Comparative Analysis of Parathyroid Oxyphil Cell and Chief Cell Nodules of Uremic Secondary Hyperparathyroidism Patients Shensen Li, Qian Zhang, Minmin Zhang, Jing Chen. *Div of Nephrology, Huashan Hospital, Shanghai Medical College, Fudan Univ, Shanghai, China.*

Background: Secondary hyperparathyroidism (SHPT) is the common abnormality in CKD patients. Hyperplasia of the parathyroid gland (PG) was considered to be an important processes in SHPT pathology. Physiologically, PG mainly composed of chief cells (CC, 95-99%) and oxyphil cells (OC, 1-5%). Our previous study shown that OC in PG were significantly increased in uremic SHPT patients and closely related to oral calcitriol dose

and treatment duration. In order to investigate OC proliferation and vitamin D metabolism, we conducted proteomic analysis to compare differences between PG OC and CC nodules from SHPT patients.

Methods: Two pairs of PG OC and CC nodules were selected to conduct proteomic (liquid chromatography tandem mass spectrometry). The protein expression were quantified and filtered by more than 2-fold between two groups. By using bioinformatics analysis, the protein expression profiles were sorted to several terms (cellular component, molecular function and biological process). Vitamin D metabolism were further analyzed in both cell type groups.

Results: 14691 unique peptides were identified and 2675 proteins were quantified. A total of 174 proteins (6.5%) were more than 2-folds up/down expressed in OC nodules compared to CC nodules (40 increased and 134 decreased in OC nodules). Bioinformatics analysis showed that in cell components, membrane structure including mitochondrial (47.89%) were most significantly differences. In molecular function, protein with binding capacity (38.46%) were the major differences. In biological processes, protein and energy metabolism (33.92%), cell replication and cycle regulatory (10.14%) were significantly differences. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules, among which, the decreasing of vitamin D binding protein in OC nodules were the most significantly (0.32 times of CC nodules).

Conclusions: Protein, energy metabolism, cell stress and cell cycle regulation are significant differences in the OC from CC nodules. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules.

Funding: Government Support - Non-U.S.

TH-PO525

Clinical Outcomes in Japanese Chronic Kidney Disease Patients Aged Over 65 Years: A Report from the Gonryo Study *Tae Yamamoto,¹ Mariko Miyazaki,¹ Masaaki Nakayama,² Gen Yamada,¹ Hiroshi Sato,¹ Sadayoshi Ito.¹* *¹Tohoku Univ, Sendai, Japan; ²Fukushima Medical Univ, Fukushima, Japan.*

Background: Japan will become a full-fledged aged society. Aging is a risk factor for progression of chronic kidney disease (CKD) and CKD is common in elderly population. However the information of clinical feature of elder CKD is limited.

Methods: We prospectively followed up 1,750 elder outpatients over 65 years old under the care of nephrologists. Inclusion criteria was the basal age over 65 years, and estimated glomerular filtration rate < 90 mL/min and/or proteinuria. Survival, censored for RRT, was recorded for a follow-up time of 5 years. Patients were divided into 3 age groups, 65-74, 75-85 and over 85 years old, and stratified by CKD stages. The effects on outcomes were evaluated, and assessed in association with body mass index (BMI).

Results: Among 1,750 patients, the median age 74 (min 65- max98) years and males 49.8%, and 118 died and 200 patients started RRT during a median follow-up of 4.60 (quartile 1.84 – 5.00) years. The ESKD incidence did not differ among age groups. While the risk for survival increased in the higher aged groups (Log-Rank $\chi^2=62.93$, $P<0.0001$), and the incidence rate was higher than that of ESKD in the over 85 years group (164.7 vs. ESKD 126.9 per 1,000 persons per year). When patients were divided by CKD stages, patients with G5 progressed mainly ESKD in all groups, on the other hand, the context of all-cause mortality increased even in G3 and G4 in the higher aged groups compared to ESKD. In competing models, the survival risk before developing ESKD associated significantly with high age, smoking, low BMI, low pulse pressure and history of cardiovascular disease, but did not with diabetes, renal function, proteinuria and hemoglobin level. A high BMI, which decreased significantly in the higher aged groups ($P = 0.043$), predicted a better survival in patients over 85 years old, but had no clear effects in patients under 75 years old.

Conclusions: The content of clinical outcomes were different among generations in elder CKD especially in CKD G3-4. In patients over 85 years increased the survival risk before developing ESKD, and the lower BMI associated the higher risk.

TH-PO526

Undocumented Immigrant and Uninsured Status Are Independent Risk Factors for Chronic Kidney Disease Progression *Orlando Nicholas Machado,¹ Ilay Rakhman,¹ Jonathan M. Wyrick,² Brittany Kalosza,² George N. Coritsidis.^{1,2}* *¹Div. of Nephrology, Elmhurst Hospital Center, MSSM, Elmhurst, NY; ²Dept of Surgery, Elmhurst Hospital Center, MSSM, Elmhurst, NY.*

Background: Being uninsured is a risk factor for chronic kidney disease (CKD) progression to end stage renal disease (ESRD). Undocumented immigrants (UI) belong to a vulnerable group in terms of healthcare. Little is known about the association of UI status and CKD progression.

Methods: Records of adult patients admitted to Elmhurst Hospital Center from 2009 to 2014 with CKD stage 4 or 5 as diagnosis or comorbidity were analyzed. ESRD patients were excluded. Covariates analyzed included sex, age, documentation (Social Security Number) and insurance status. Data was analyzed using STATA; Pearson's Chi Squared test was used for bivariate analyses.

Results: Of 703 patients analyzed: 81% had insurance (n=569), 19% were uninsured (n=134), 84% were documented (DOC, n=588), and 16% were UI (n=115). Of the DOC, 89% had insurance (n= 525) vs. 38% (n=44) of UI ($p<0.005$) and were older than UI (71 ± 15 vs. 59 ± 15 , $p<0.005$). 21% of CKD patients progressed to ESRD (n=151): 20% of DOC compared to 30% of UI ($p<0.05$). Analyzed by insurance status, 18% of the insured developed ESRD compared to 36% of the uninsured ($p<0.0001$). On bivariate level, UI was associated with ESRD progression ($p<0.05$). On multivariate level, documentation status lost significance, but insurance status remains significant for ESRD progression.

Likelihood of Progression to ESRD		
	Model 1 OR(95% CI)	Model 2 OR(95% CI)
Documentation Status		
DOC	1.00	1.00
UI	1.18(0.74-1.89)	0.90(0.53-1.53)
Gender		
Male	1.00	1.00
Female	0.82(0.56-1.20)	0.79(0.54-1.16)
Age		
18-59	1.00	1.00
60-79	0.63(0.41-0.94)*	0.70(0.46-1.08)
80-99	0.18(0.10-0.33)**	0.21(0.11-0.39)**
Insurance Status		
Insured		1.00
Uninsured		1.81(1.10-2.10)*
<i>Model 1: Controlling for Documentation Status Gender and Age</i>		
<i>Model 2: Controlling for above and Insurance Status</i>		
* $p<0.05$, ** $p<0.0005$		

Conclusions: Documentation and insurance status are associated with ESRD progression. Once controlling for demographic variables, documentation status is no longer significant, but insurance status remains significant for progression.

TH-PO527

The Impact of Medical Comorbidities on Renal Function following Radical or Partial Nephrectomy *Michael J. Vacchio, Andrew G. Winer, Emily C. Zabor, A. Ari Hakimi, Paul Russo, Jonathan A. Coleman, Edgar A. Jaimes.* *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Background: Increasing utilization of nephron sparing surgery (NSS) for kidney tumors has led to superior renal functional outcomes while maintaining oncologic control. However, the impact of comorbidities on post-nephrectomy renal function is not well understood. Here, we aim to identify patient and disease characteristics which have an adverse impact on renal function following nephrectomy.

Methods: We conducted a retrospective review of data on 440 patients who underwent robotic partial (PN) or radical nephrectomy (RN) for renal tumors by a single surgeon between 2006 and 2014 at our institution. Loess plot was generated to visually assess renal function over time. Univariable and multivariable longitudinal regression analyses incorporated a random intercept and slope to evaluate the association between patient and disease characteristics with renal function following surgery.

Results: Advanced age at surgery, larger tumor size, male sex, history of smoking, hypertension and higher ASA score were significantly associated with lower preoperative estimated glomerular filtration rate (eGFR). On multivariate analysis, independent predictors of reduced renal function following surgery were advanced age, lower preoperative eGFR, and RN. Length of time from surgery was strongly associated with improvement in renal function among all patients.

Table. Multivariable linear mixed effects regression for the association between patient and disease characteristics with eGFR following surgery. Estimates presented are for the fixed effect of the factor of interest.

	Estimate	Std. Error	p-value
Age	-0.389	0.045	0.000
Tumor Size	-0.102	0.186	0.582
Pre-op GFR	0.744	0.030	0.000
HTN	-0.297	1.026	0.773
Radical procedure	-9.590	1.770	0.000
Former smoker	-0.063	1.029	0.951
Current smoker	1.936	1.964	0.325
Months followup	0.120	0.018	0.000

Conclusions: Independent predictors of post-operative decline in renal function include advanced age, lower pre-operative eGFR and RN. A significant number of subjects had recovery in renal function over time following surgery which continued past the 12 month mark. These findings suggest that patients undergoing nephrectomy can experience long-term improvement in renal function. This improvement is greater among younger patients with higher pre-operative eGFR undergoing PN.

Funding: Private Foundation Support

TH-PO528

A Longitudinal Analysis of Chronic Kidney Disease and Related Comorbidities Among Human Immunodeficiency Virus (HIV) Patients

Grace Mccomsey,¹ Nicole M. Meyer,² Xue Song,² Jonathan A. Winston,³ ¹Case School of Medicine, Cleveland, OH; ²Truven Health Analytics, Cambridge, MA; ³Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Patients with HIV infection can present with or develop multiple comorbidities including risk factors for chronic kidney disease (CKD). This study examined CKD and comorbid conditions in HIV patients in the US.

Methods: Adults diagnosed with HIV (ICD-9 code: 042.xx, 795.71, V08) in 2007-2013 were selected from MarketScan Commercial, Medicare, and Medicaid Databases. Patients were continuously enrolled for ≥ 365 days in 2007-2013 and stratified by the presence of CKD based on diagnosis codes. Comorbidities, prevalence (per 1,000 patients), and incidence (per 1,000 patient-years) of CKD in 2007-2013 were assessed.

Results: A total of 31,229 HIV patients (mean age: 42.8; male: 77.9%; mean Deyo-Charlson comorbidity index (CCI): 6.0) were selected from Commercial data, 1,541 (mean age: 71.9; male: 62.7%; CCI: 7.9) from Medicare, and 10,190 (mean age: 42.9; male: 44.1%; CCI: 7.0) from Medicaid. CKD prevalence and incidence were, respectively, 48.6 and 13.1 in Commercial, 242.1 and 61.1 in Medicare, and 114.3 and 28.4 in Medicaid. Prevalence and incidence increased over time. During 2007-2013, end-stage renal disease (ESRD)/dialysis patients accounted for 1.8% of Commercial, 7.7% of Medicare and 4.8% of Medicaid patients. Common CKD risk factors included hypertension (Commercial: 32.5%; Medicare: 77.0%; Medicaid: 55.5%), hyperlipidemia (30.6%, 52.7%, 33.8%), diabetes (11.2%, 36.9%, 25.1%), cardiovascular disease (6.4%, 34.4%, 15.5%), and obesity/overweight (7.0%, 7.5%, 16.9). Annual incremental healthcare costs in 2013 were higher in CKD patients than non-CKD patients (Commercial: \$16,406; Medicare: \$6,879; Medicaid: \$5,663).

Conclusions: We observed an increase in CKD prevalence and incidence over time in HIV-infected person. Because of the potential effects of ART treatment on CKD observed in published data, understanding CKD risk factors of HIV patients will help optimize care of patients, including choice of antiviral regimens and screening and treating of these risk factors.

Funding: Pharmaceutical Company Support - Gilead Sciences

TH-PO529

Association of Short Sleep Duration and Rapid Decline in Renal Function

Ciaran Joseph McMullan, Gary C. Curhan, John P. Forman. *Renal Div, Brigham and Women's Hospital, Boston, MA.*

Background: The kidney, like all other organs in the human body, is influenced by circadian rhythms, allowing renal function to be entrained to the sleep-wake cycle. Coordination of this periodicity in the kidney permits anticipation of the metabolic and physiological demands of the kidney throughout a 24-hour cycle. Unsurprisingly, disruption of the sleep-wake cycle may lead to disruption of renal physiology. Although sleep disruption has been studied extensively in cardiovascular and metabolic disease, its association with chronic kidney disease has not been shown.

Methods: In a prospective cohort study of 4238 participants from the Nurses' Health Study with renal function measured on at least two occasions, we analyzed the association of self-reported sleep duration with decline in renal function over an 11 year period.

Results: Individuals who reported shorter sleep duration were more likely to experience a rapid decline in estimated glomerular filtration rate (≥ 25% decline from 1989 to 2000). Compared with sleeping 7-8 hours per night, the adjusted odds ratios for a rapid decline in renal function were 1.65 (95% CI, 1.06-2.55) for ≤ 5 hours sleep per night, 1.31 (95% CI, 1.06-1.61) for 6 hours sleep per night, and 0.78 (95% CI, 0.48-1.25) for ≥ 9 hours sleep per night. Similarly, adjusted annualized decline in estimated glomerular filtration rate was 1.2 ml/min/1.73m²/year, 0.9 ml/min/1.73m²/year, 0.8 ml/min/1.73m²/year, and 0.8ml/min/1.73m²/year for individuals sleeping ≤ 5 hours per night, 6 hours per night, 7-8 hours per night, and ≥ 9 hours per night, respectively (p-trend = 0.02).

Conclusions: Shorter sleep duration is prospectively and independently associated with faster decline in renal function.

Funding: NIDDK Support

TH-PO530

Impairment of Endogenous Nighttime Melatonin Secretion Relates to Intrarenal Renin-Angiotensin System Activation and Renal Damage in Patients with Chronic Kidney Disease

Sayaka Ishigaki,¹ Naro Ohashi,¹ Shinsuke Isobe,¹ Takayuki Tsuji,¹ Akihiko Kato,² Hideo Yasuda.¹ ¹Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; ²Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.

Background: Activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of chronic kidney disease (CKD) and hypertension. Recently, we have demonstrated that the circadian rhythm of intrarenal RAS activation leads to renal damage and hypertension. Melatonin is considered as a major hormone regulating the circadian rhythm and nocturnal melatonin concentrations are reduced in patients with CKD. However, it has not known whether the impairment of endogenous melatonin secretion is related to BP, intrarenal RAS or renal damage in patients with CKD.

Methods: We recruited 53 patients with CKD stage 1-5 and 24-hour ambulatory BP monitoring (ABPM) and urine collection divided into daytime and nighttime were conducted.

We investigated the relationship among urinary 6-sulphatoxymelatonin (U-aMT6s), that is the major melatonin metabolite, BP, renal function, urinary angiotensinogen (U-AGT), and urinary protein (U-P) in daytime and nighttime, respectively.

Results: The nighttime U-aMT6s levels were decreased according to the progression of CKD stage and those in CKD stage 5 was significantly decreased compared with those in other CKD stages. The U-aMT6s levels were significantly and negatively correlated with the clinical parameters such as renal function (serum creatinine), systolic BP, U-AGT and U-P in both daytime and nighttime. Multiple regression analyses for U-aMT6s levels were performed using age, sex, serum creatinine and each parameter (systolic BP, U-AGT or U-P) in daytime and nighttime, respectively. U-aMT6s levels tended to correlate with systolic BP (β=0.22, p=0.11), and were significantly associated with U-AGT (β=0.31, p=0.040) and U-P (β=0.26, p=0.041) in nighttime. On the other hand, U-aMT6s had no associations with the clinical parameters in daytime.

Conclusions: Impairment of nighttime melatonin secretion may be associated with nighttime intrarenal RAS activation and renal damage in patients with CKD.

TH-PO531

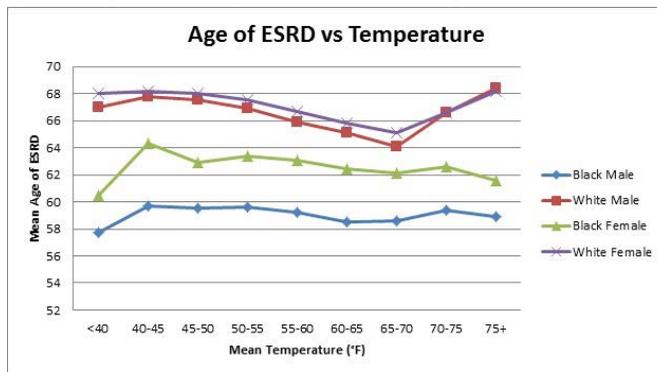
Climate Temperature Affects the Age of Onset of End Stage Renal Disease

Michael E. Bleyer, Marwan M. Abbas, Elizabeth Swain, Kendrah O. Kidd, Anthony J. Bleyer. *Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC.*

Background: Increasing global temperatures is a rising concern. We were interested to see if there was a relationship between climate temperature and the age of onset of end-stage kidney disease.

Methods: We obtained demographic data and cause of ESRD on 1,332,402 individuals who had their first occurrence of ESRD between ages 30 and 90 between June 1971 and October 2012 from the United States Renal Data system (USRDS). We obtained the annual mean temperatures from 1990 to 2010 for weather stations throughout the US and linked a participant's zip code to the nearest weather center. We performed multivariate linear regression for white individuals with age of onset of ESRD as the dependent variable, and independent variables being age, gender, mean income for the participant zip code, baseline estimated glomerular filtration rate at the start of dialysis, and mean temperatures according to participant zip code categorically from 40°F to 75°F in 5 degree intervals.

Results: Figure 1 shows the relationship between age of ESRD and temperature with race/gender combinations. Temperature affects white individuals more than African Americans. The U shaped relationship was similar for PKD, IgA nephropathy and Type 2 diabetes. A multivariate model of whites showed the correlation between temperature and age of ESRD persisted after adjustment for other variables (p<0.0001).



Variable	Type III SS	F value	p value
Gender	107334	760	<0.0001
Temperature	118355	838	<0.0001
Year starting dialysis	242949	1721	<0.0001
Median income by zip code	310045	2196	<0.0001
GFR at start of dialysis	1120868	7940	<0.0001

Conclusions: There is a U-shaped relationship between the age of ESRD and mean temperature for a given region in whites, but not in African Americans. This variation persisted after multivariate regression. Global warming could affect the age of onset of ESRD.

Funding: Clinical Revenue Support

TH-PO532

Prognostic Implications of Anemia in Patients with Chronic Kidney Disease Undergoing Elective Percutaneous Coronary Intervention Yuichiro Kitai,¹ Neiko Ozasa,² Motoko Yanagita,¹ Takeshi Kimura.² ¹Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ²Dept of Cardiovascular Medicine, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: Little is known about the prognostic implications of anemia in patients undergoing elective percutaneous coronary intervention (PCI), especially when they have coexisting chronic kidney disease (CKD).

Methods: We identified 2792 patients with CKD who underwent elective PCI from the CREDO-Kyoto registry cohort-2. The primary outcome was 3-year major adverse cardiac events (MACE); composite of all cause death, heart failure hospitalization, and myocardial infarction.

Results: In total, 738 patients (26.4%) had mild anemia (hemoglobin = 11.0–11.9 g/dL for women and 11.0–12.9 g/dL for men), and 740 patients (17.9%) had moderate-to-severe anemia (hemoglobin < 11.0 g/dL both for women and for men). Compared to the no-anemia group, cumulative incidence of MACE was significantly higher in the mild and moderate-to-severe anemia groups (12.2%, 23.5%, and 37.4%, respectively). The adjusted hazard ratios of mild and moderate-to-severe anemia versus no-anemia for MACE were 1.46 (95% confidence interval: 1.13–1.90) and 1.76 (95% confidence interval: 1.33–2.34), respectively. In addition, the risk for MACE showed an accretive increment with exacerbation in either the renal function or anemia (interaction p < 0.001).

Conclusions: Even mild anemia was associated with significantly worse 3-year clinical outcomes in CKD patients who underwent elective PCI. Anemia and reduced renal function independently and additively increased the risk for MACE in these patients.

TH-PO533

Pathologic Classification of Diabetic Kidney Disease in Prognosticating Time to End-Stage Renal Disease or Death Askia K. Dunnon,¹ A. Gasim,² Fernanda Payan Schober,¹ Yichun Hu,¹ J. Charles Jennette,² Amy K. Mottl.¹ ¹UNC Kidney Center; ²Dept of Pathology, UNC School of Medicine, Chapel Hill, NC.

Background: We performed a retrospective, longitudinal study of patients with diabetic kidney disease (DKD) undergoing renal biopsy to ascertain the prognostic value of histopathologic features when combined with clinical information.

Methods: Specimen from clinical native kidney biopsies performed in 1998-2006 containing diabetic glomerulosclerosis in the final diagnoses were analyzed according to the Renal Pathology Society classification system for DKD. Clinical data were extracted from medical records from time of biopsy until the composite outcome of ESRD or death. Multivariate cox proportional-hazards regression was used to estimate hazard ratios (HR) of the composite outcome according to glomerular class or severity of interstitial fibrosis. Covariates included age, gender, diabetes duration, blood pressure, eGFR and urine protein at the time of biopsy.

Results: Baseline characteristics according to glomerular class are displayed below.

Covariates	Class 2a/2b N = 44	Class 3 N = 67	Class 4 N = 19	p-value
Age, yrs	49±18	48±18	56±10	0.1
Female sex, %	43	47	32	0.5
Diabetes duration, yrs	11±6	15±7	13±7	0.07
HbA1c, %	7.7 ±2.4	8.3 ±2.6	6.7 ±1.1	0.2
Systolic blood pressure, mmHg	141±33	151±22	169±30	0.01
Urine protein*, gm/gm median (IQR)	2.8 (1.5-7.0)	5.2 (2.8-8.7)	5.5 (2.4-9.3)	0.2
estimated GFR, ml/min/1.73m ²	23±24	21±18	12±12	0.07
Interstitial fibrosis severity, %:				
0/1	36	12	0	
2	34	55	16	
3	30	33	84	
Time to ESRD or death, months	23 ±23	18 ±26	6 ±7	0.01

The risk for ESRD/death for glomerular classes 2a/b and 3 versus class 4 was HR=0.12 (0.04-0.42) and HR=0.17 (0.06-0.51), respectively. Analysis of interstitial fibrosis (IF) severity 0/1 versus 3 yielded a HR=0.19 (0.06, 0.63). The HR for IF 2 versus 3 was not significant (p=0.09). The only statistically significant clinical covariate in the analyses was eGFR: HR=0.96 (0.93, 0.99) and HR=0.94 (0.91, 0.97), respectively.

Conclusions: Kidney biopsy significantly improves the prognostication of ESRD or death in patients with diabetic glomerulosclerosis.

Funding: Private Foundation Support

TH-PO534

Progression of Chronic Kidney Disease Stage 3 Over 5 Years in a Prospective Primary Care Cohort Study Adam Shardlow,^{1,2} Natasha Juliette McIntyre,¹ Richard J. Fluck,¹ Christopher W. McIntyre,³ Maarten W. Taal.^{1,2} ¹Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; ²Faculty of Medicine and Health Sciences, Nottingham Univ, Nottingham, United Kingdom; ³London Health Sciences Centre, London, ON, Canada.

Background: CKD stage 3 is commonly diagnosed in primary care. Previous studies indicate that it runs a variable course with only a minority progressing to ESRD. The Renal Risk in Derby study aims to evaluate progression of CKD in a cohort of people with CKD 3 recruited prospectively from primary care in Derbyshire, UK.

Methods: 1741 participants were recruited from local primary care practices. All had eGFR 59-30ml/min on 2 occasions prior to recruitment. At baseline, year 1 and year 5 visits, participants underwent clinical assessment, urine and serum biochemistry. Progression of CKD was defined using KDIGO criteria (25% loss of GFR and an increase in GFR category, or an increase in albuminuria category).

Results: 299 (17.2%) participants died prior to the end of year 5 follow-up. Only 4 participants (0.2%) progressed to ESRD. 1064 participants attended for year 5 visits or submitted blood and urine samples. Mean age was 71 years at baseline. Mean eGFR was 55.3ml/min at baseline and 53.8ml/min at year 5 (p<0.001). Progression occurred in 263 participants (24.6%). Binomial logistic regression identified male gender (HR1.55), baseline eGFR (HR0.97), logUACR (HR1.33), diabetes (HR1.57), haemoglobin (HR=0.81) and the change in GFR at year 1 (HR0.95) as independent determinants of progression at 5 years. Progression in eGFR and albuminuria categories occurred largely independently.

	No Albuminuria Progression	Albuminuria Progression
No eGFR Progression	804 (75.6%)	143 (13.5%)
eGFR Progression	86 (8.1%)	30 (2.8%)

Baseline eGFR and change in eGFR at year 1 were independent determinants of eGFR category progression. Albuminuria progression was independently associated with age, male gender, baseline eGFR, logUACR and diabetes.

Conclusions: Our data confirm that the 5-year risk of ESRD is low in CKD 3 but progression occurred in 24.6% of participants. Change in eGFR over 1 year was an independent predictor of progression over 5 years indicating that annual monitoring is beneficial for assessing prognosis.

Funding: Private Foundation Support

TH-PO535

Change in Albuminuria and Risk of ESRD in a Large Health System Josef Coresh,¹ Yingying Sang,¹ Morgan Grams,¹ Kunihiro Matsushita,¹ Shoshana Ballew,¹ H. Lester Kirchner,² Andrew S. Levey,³ Lesley Inker,³ Hiddo Jan Lambers Heerspink,⁴ Ron T. Gansevoort,⁴ Alex R. Chang.² ¹JHU; ²Geisinger; ³Tufts; ⁴UMCG.

Background: Albuminuria is used in chronic kidney disease (CKD) staging but it is uncertain how change in albuminuria is associated with ESRD risk in primary care and other generalizable settings.

Methods: We included Geisinger Health System participants with multiple albuminuria measurements within a 2-year baseline period, using Cox proportional hazards regression to estimate the association of ESRD with log change in albuminuria (per 2-fold rise in albumin to creatinine ratio, ACR). We tested risk for non-linearity and also analyzed 1- and 3-year baseline periods.

Results: 27,121 participants (6.5% of all primary care patients; 75% of diabetics) had at least 2 ACR measurements during baseline. After the 2-year baseline, 296 ESRD events occurred over a median follow-up of 5.2 years. Change in ACR had a geometric mean (25th-75th percentiles) of 1.1 fold rise (1.9 fold decrease - 2.1 fold rise). A two-fold rise in ACR over 2-years was associated with a subsequent HR (95% CI) of ESRD of 1.42 (1.33-1.51) adjusted for initial eGFR, ACR and 7 other risk factors. The HR was generally similar if the 2-fold ACR rise occurred over 1-year (1.48 (1.36-1.61)) or 3-year (1.42 (1.35-1.51)), as well as across the range of baseline ACR (<10, 10-99, 100+) and diabetes status. There was a suggestion toward non-linearity with 8-fold rise showing a stronger association than an 8-fold fall (HR 3.2 vs. 0.4, reference: stable ACR). Limitations: ACR measurement follows clinical care standards and selection criteria. Replication across other settings will be useful.

Conclusions: In primary care, change in ACR is associated with risk of ESRD. The CKD Prognosis Consortium will expand this investigation to multiple settings to inform use of change in ACR as an outcome in clinical practice, research, and regulatory purposes.

Funding: NIDDK Support

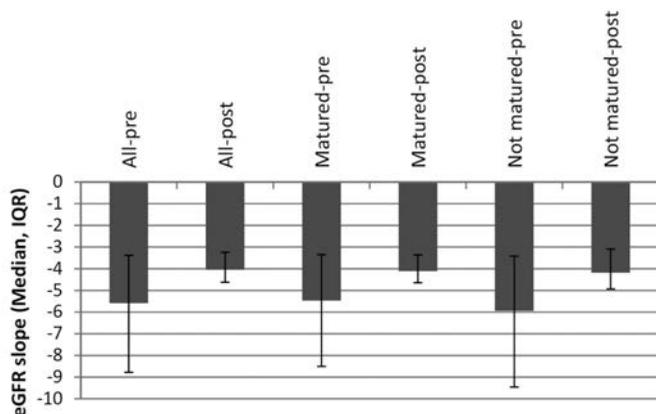
TH-PO536

Association Between Vascular Access Creation and Regression of eGFR Decline in Late-Stage CKD Patients Transitioning to ESRD Keiichi Sumida,¹ Miklos Zsolt Molnar,¹ Praveen Kumar Potukuchi,¹ Fridtjof Thomas,¹ Jun Ling Lu,¹ Jennie Jing,² Vanessa A. Ravel,² Melissa Soohoo,² Connie Rhee,² Elani Streja,² Lawrence Agodoa,³ Kevin C. Abbott,³ Paul W. Eggers,³ Kamyar Kalantar-Zadeh,² Csaba P. Kovessy.^{1,4} ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³NIH, Bethesda, MD; ⁴VA Medical Center, Memphis, TN.

Background: Arterio-venous dialysis access (AVF) creation may be associated with slowing of the decline in eGFR. It is unclear if this is due to physiological benefits of a mature access vs. other confounding factors in late CKD. We hypothesized that the beneficial change in the eGFR would only be seen with a mature AVF.

Methods: From 52,172 U.S. veterans who transitioned to dialysis between 2007-2011, we identified 3,220 who had an AVF created prior to dialysis start, and had at least 3 outpatient eGFR measurements both before the AVF creation and between AVF creation and the initiation of dialysis. We estimated crude and adjusted slopes of eGFR vs. time in multilevel mixed effects models with random intercepts and slopes. Pre- and post-AVF eGFR slopes were compared both overall, and in patients stratified by AVF maturation.

Results: Mean (SD) age was 66.3 (10.8) years, and patients were 98% male, 35% black, and 76% diabetic. Median (IQR) eGFR slope was -5.2 (-8.3 to -3.2) ml/min/1.73m²/year, and 71% had a mature AVF at dialysis start. Compared with the eGFR slopes before AVF, a significant improvement was observed post-AVF (-5.5 [-8.9 to -3.4] vs. -4.0 [-4.6 to -3.2], P<0.001). This association was present to a similar extent in both patients with matured and un-matured AVF (Figure). Results were unchanged in adjusted models.



Conclusions: Regardless of maturation, the creation of AVF is associated with improved eGFR slopes. Clarifying the mechanism behind this warrants additional studies.

Funding: NIDDK Support, Veterans Administration Support

TH-PO537

Presence of Periventricular Hyperintensity in Magnetic Resonance Imaging Is a Predictor for Future End Stage Renal Disease in Predialysis CKD Patients Hideaki Shima,¹ Tatsuhiko Mori,¹ Toshihide Naganuma,² Mika Sonoda,³ Tetsuo Shoji,³ Mikio Okamura,⁴ Eiji Ishimura,³ Masaaki Inaba.³ ¹Nephrology, Osaka Medical College, Takatsuki, Osaka, Japan; ²Urology, Osaka City Univ Hospital, Osaka, Japan; ³2nd Div of Internal Medicine, Osaka City Univ Hospital, Osaka, Japan; ⁴Nephrology, Ohno Memorial Hospital, Osaka, Japan.

Background: In the general population, periventricular hyperintensity (PVH) evaluated by brain magnetic resonance imaging (MRI), is a predictor of future stroke. CKD is a high risk condition of ESRD as well as cardiovascular disease (CVD). However, no longitudinal studies have been performed to determine the clinical significance of PVH in CKD. In the present study, we investigated the influence of PVH as a predictor of future CVD and ESRD in predialysis CKD.

Methods: This is a prospective cohort study. We examined the effect of the presence of PVH for CVD and renal outcome. CVD and renal outcome are defined as the new onset of stroke, ischemic heart disease, amputation as peripheral arterial disease and the doubling of serum creatinine levels or development of ESRD, respectively. We followed up 404 CKD patients without renal replacement therapy, who underwent brain 1.5T-MRI, for 37 months (median survival time, range: 19-56 months). Cox proportional hazard models were performed to each outcome adjusted by several atherosclerotic factors.

Results: At baseline, PVH were detected in 187 of the 404. During follow-up, 124 cases reached outcomes. In the 22 cases of stroke during follow up, the incidence of stroke was significantly higher in the group with PVH than that of without (p=0.0197, Log rank test). The presence of PVH was significantly associated with the increased risk for the future CVD and renal outcome in an unadjusted model. After adjustment, the power to predict CVD but not renal outcome by PVH was diminished (CVD: 1.44, 95%CI 0.66-3.46, renal outcome: HR 1.70, 95%CI 1.05-2.84).

Conclusions: This is the first report clearly showing that the presence of PVH is a strong predictor for future ESRD in predialysis CKD patients, but not CVD. Presence of PVH was a novel predictor for the progression of CKD. These results show one of the evidence of brain-kidney association.

TH-PO538

Telomerase Activity in Patients with Stage 2-5 Chronic Kidney Disease Mehmet Tugrul Sezer,¹ Veysel Kidir,¹ Ayse Aynali,² Atila Altuntas,¹ Salih Inal,¹ Buket Ar?dogan.² ¹Dept of Internal Medicine, Div of Nephrology, Suleyman Demirel Univ, Medical Faculty, Isparta, Turkey; ²Dept of Medical Microbiology, Suleyman Demirel Univ, Medical Faculty, Isparta, Turkey.

Background: The relationship between telomerase activity and stages and progression of Chronic Kidney Disease (CKD) is unknown. The aim of this study is to investigate the association between telomerase activity and stages of CKD.

Methods: A total of 120 patients (30 patients from each stages of 2-5) and 30 healthy volunteers applying to the clinic for their routine examinations were enrolled in the study. The individuals from patient and control groups were matched in terms of age and gender. PBMC telomerase activity was measured by *telomeric repeat amplification protocol*.

Results: PBMC telomerase activity was significantly different between the groups (p < 0.001). Telomerase activity was found to be lowest in healthy controls (0.15 ± 0.02), and highest in patients with stage 5 CKD (0.23 ± 0.04). Telomerase activity was similar between patients with stage 2, 3, and 4 CKD (p > 0.05). There was positive correlation between telomerase activity and CKD stage (r = 0.412, p < 0.001), serum creatinine (r = 0.404, p < 0.001), potassium (r = 0.207, p = 0.023), and intact parathyroid hormone (r = 0.245, p = 0.007) levels and negative correlation between telomerase activity and estimated glomerular filtration rate (eGFR) (r = -0.407, p < 0.001), serum sodium (r = -0.179, p = 0.05), calcium (r = -0.357, p < 0.001), LDL-cholesterol (r = -0.218, p = 0.017), hemoglobin (r = -0.186, p = 0.042), thrombocyte (r = -0.252, p = 0.006), and body mass index (BMI) (r = -0.240, p = 0.008) values. In linear regression analyses, eGFR and BMI were found to be independent predictors of high telomerase activity in CKD group. (Model 1: R² = 0.151, for eGFR β = -0.001, P < 0.001. Model 2: R² = 0.195, for eGFR β = -0.001, P = 0.010; for BMI β = -0.002, p = 0.012).

Conclusions: PBMC telomerase activity is significantly higher in patients with CKD compared to healthy controls. Telomerase activity increases as the CKD stage proceeds, particularly in stage 5. The increase in PBMC telomerase activity is associated with eGFR and BMI.

TH-PO539

Congestive Heart Failure Increases Risk of Long Term Adverse Renal Outcomes Lekha K. George,¹ Santhosh K. Koshy,¹ Miklos Zsolt Molnar,¹ Jun Ling Lu,¹ Kamyar Kalantar-Zadeh,² Csaba P. Kovessy.^{1,3} ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³VA Medical Center, Memphis, TN.

Background: Congestive heart failure (CHF) is associated with poor long term cardiac outcomes and mortality. Reduced cardiac output reduces renal perfusion. It is not known if CHF leads to poor renal outcome including progression to Chronic Kidney Disease (CKD). We hypothesized that a diagnosis of CHF would increase the risk of long-term adverse renal outcome.

Methods: Among 3,570,865 US veterans with eGFR >60ml/min/1.73m² during 2005-2006, we identified 156,743 patients with ICD-9 diagnosis of CHF. We examined the association of the presence of CHF with incident CKD, the composite of incident CKD and mortality, and rapid rate of eGFR decline (slopes steeper than -5 ml/min/1.73m²/year) using Cox proportional hazard analyses and logistic regression, as appropriate. Adjustments were made for age, gender, race, comorbidities, baseline BP, ACEI and statin use, eGFR and cholesterol.

Results: Mean±SD baseline age and eGFR were 68±11 years and 78±14 ml/min/1.73m², in CHF patients vs. 59±14 and 84±16 respectively for patient without CHF. CHF patients had higher prevalence of hypertension, diabetes, cardiac, peripheral vascular and chronic lung diseases, stroke, and dementia. Incidence of CKD was 69/1000 patient years (PY) in CHF patients vs. 14.5/1000PY in patients without CHF, and 22% of patients with CHF had rapid decline in eGFR compared to 8.5% in patients without CHF. A diagnosis of CHF was associated with a two-fold higher risk of incident CKD, composite end point of CKD and mortality and rapid eGFR decline.

	Unadjusted	Adjusted
Incident CKD	4.30 (4.26-4.35)	2.12 (2.10-2.14)
Incident CKD and Mortality	2.96 (3.94-3.99)	2.06 (2.05-2.08)
GFR decline >5ml/min/year	2.96 (2.92-3.00)	2.13 (2.10-2.17)

Conclusions: CHF is associated with significantly higher risk of incident CKD, incident CKD and mortality and more rapid GFR decline. Early diagnosis and management of CHF risk factors before it leads to CHF is warranted to reduce the risk of long-term renal complications.

Funding: NIDDK Support, Veterans Administration Support

TH-PO540

Left Ventricular Global Longitudinal Strain as Early Detection of Subclinical Myocardial Dysfunction in Chronic Kidney Disease Patients
 Secundino Cigarran,¹ Jose Lomban,³ Ana maria Sanjurjo amado,¹ Diego Coronel,¹ Sheila Casas,³ Juan Latorre,¹ M^o milagros López hernández,¹ Jesus Calvino,² ¹Nephrology, Hospital Da Costa, Burela, Lugo, Spain; ²Nephrology, Hospital Lucas Augusti, Lugo, Spain; ³Cardiology, Hospital Da Costa, Burela, Lugo, Spain.

Background: CV mortality is increased in patients with chronic kidney disease (CKD). Little is known regarding the natural longitudinal changes in cardiac structure and function. Global longitudinal strain (GLS) measures myocardial deformation in addition to left ventricular twist. The aim of our cross sectional study is to assess the grade of myocardial dysfunction in CKD stage 1-5ND without previous CV events & normal left ventricular ejection fraction (LVEF).

Methods: 161 pts. 38% F, 47% DM, Age 67.37±6.8yo, not previous CV events and LVEF >55%. All received ACEI/ARB, CCHB & diuretics. Echocardiogram was performed using Vivid 9 (GE Vigmed Ultrasound Horten, Norway). Parameters derived: GLS, left Atrial volume index (LAVI), E/e', E/A & LVEF as recommendations of American Society of Echocardiography. Body composition analysis was performed by BIVA and serum biomarkers of inflammation, anaemia, mineral bone disease, renal function (GFR-EPI) and CV risk markers. AGEs were measured by autofluorescence (AGE's reader, Diagnostic, Kroningen ND). CKD (%) stage: 1 & 2 (20%); 3 (55.5%); 4 & 5 (24.5%). Normal GLS (-20%) LAVI 24 ml/m² were considered as published for general population Rev Esp Cardiologia 2014;67:651-8.

Results: Mean GLS -15.59 ± 4.4%, LVEF 61.5 ± 4.4%. LAVI 40.6 ± 19.8 ml. GFR showed negative significantly correlation to GLS (r: -.228, P<0.016). GLS progress with CKD progression CKD 1&2: -18.1 ± 4.7%; CKD 3: -15.96 ± 4.1%; CKD 4&5: -13.22 ± 5.6% (P adjusted 0.008). LAVI: CKD 1&2: 49.6 ± 29.8 ml/m²; CKD 3: 36.36 ± 42.4 ml/m²; CKD 4&5: 83.33 ± 51 ml/m² (P adjusted = 0.006). 16% pts have GLS > 20% and 60% LAVI > 24 ml/m². GLS correlates negative with cholesterol (r: -.191, p= 0.50). No other correlation were met.

Conclusions: GLS & LAVI are two useful parameters to detect early subclinical myocardial damage (myocardial fibrosis & ischemia) in CKD with normal LVEF. We detect abnormal GLS in 16% pts and LAVI in 60% of CKD pts at early stages. Studies of larger CKD populations are required.

Funding: Other NIH Support - Sergas

TH-PO541

Aortic Stiffness and Change in GFR and Albuminuria in Older People
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Background: Higher aortic stiffness (AS) has a direct effect on microvascular structure and function, and may be an underlying mechanism for progression of CKD in older people.

Methods: Our study included community dwelling Icelandic elderly adults. Linear and logistic regression were used to assess the association between AS measures (carotid-femoral pulse wave velocity [CFPWV], carotid pulse pressure [CPP] and augmentation index [AI]) with the change in creatinine-cystatin C based estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (ACR) by two measurements 5 years apart. Rapid eGFR decline was defined as a decrease of ≥ 3 mL/min/1.73 m²/year.

Results: Of the 629 included, mean age was 75 years at baseline, mean eGFR was 72 mL/min/1.73 m² and median ACR was 2.9 mg/g. The table shows associations of AS parameters to change in eGFR. No significant associations were observed between AS parameters and change in ACR.

Per SD change	Models	eGFR change (ml/min/1.73m ² /year)	Rapid eGFR Decline Odds Ratio (95% CI)
CFPWV	Model 1	-0.2 (-0.4, -0.1)	1.5 (1.1, 1.9)
	Model 2	-0.2 (-0.4, -0.1)	1.7 (1.3, 2.3)
	Model 3	-0.1 (-0.3, 0.1)	1.5 (1.1, 2.1)
CPP	Model 1	-0.3 (-0.4, -0.1)	1.4 (1.1, 1.8)
	Model 2	-0.3 (-0.4, -0.1)	1.4 (1.1, 1.8)
	Model 3	-0.1 (-0.3, 0.1)	1.3 (0.9, 1.7)
AI	Model 1	-0.1 (-0.2, 0.1)	1.2 (1.0, 1.5)
	Model 2	-0.1 (-0.3, 0.1)	1.2 (0.9, 1.5)
	Model 3	-0.1 (-0.2, 0.1)	1.2 (0.9, 1.5)

CFPWV was negatively inverse transformed. SD, standard deviation; Model 1: unadjusted; Model 2: adjusted by age, sex, heart rate, height and baseline eGFR; Model 3: model 2+mean arterial pressure, high dense lipoprotein, hemoglobin A1c and C-reactive protein. **Bold indicates significance at p < 0.05.**

Conclusions: AS is associated with rapid decline in kidney function in older age beyond traditional cardiovascular risks.

TH-PO542

Central Aortic Blood Pressure in Patients with Chronic Kidney Disease
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Background: Central blood pressure (BP) has been suggested as a better predictor cardiovascular outcome than the brachial BP. However, in patients with chronic kidney disease (CKD) the relationship between aortic BP and brachial BP remains to be elucidated. This study compared invasive measurements of central aortic BP with brachial artery BP and the accuracy of estimated central BP obtained non-invasively by radial artery tonometry.

Methods: 83 with stage 3-5 CKD and 41 patients without signs of renal disease undergoing planned coronary angiography for evaluation of ischemic heart disease were included. BP was sequentially measured at the brachial artery with an oscillometric BP device; in the ascending aorta using an invasive catheter; and by radial artery tonometry using the SphygmoCor device for the estimation of the central BP. Arterial stiffness was assessed by pulse wave velocity (PWV).

Results: The difference between estimated central and invasive systolic BP increased with 3.6 (95% CI 1.8; 5.3) mmHg per level increase in CKD stage (P<0.001) and 0.1 (95% CI 0.05; 0.18) mmHg per decrease in eGFR (P=0.001) in unadjusted linear regression. The difference between brachial and invasive systolic BP increased with 3.1 (95% CI 1.3; 4.8) mmHg per level increase in CKD stage (P<0.001) and 0.1 (95% CI 0.03; 0.16) mmHg per decrease in eGFR (P=0.003) in unadjusted linear regression. Multivariate adjustment did not change the results. The difference between brachial and invasive systolic BP was significantly associated with PWV (P=0.01).

Conclusions: Our data shows, that central BP increases more than brachial BP with increasing CKD stage. The differences were significantly associated with increased arterial stiffness. As brachial BP is used for calibration of the tonometry based SphygmoCor device, central BP is increasingly underestimated as CKD stage increases. Thus, in advanced kidney disease the utility of non-invasively obtained central BP seems questionable.

TH-PO543

Correlation of Pulse Pressure to Renal Functional Parameters in a Cross Sectional Study of General Population – The Texas Kidney Study
 Sharma S. Prabhakar, Katherine Kam. *Medicine, Texas Tech Univ Medical Center, Lubbock, TX.*

Background: Chronic kidney disease (CKD) presents an increasing economic burden. Diabetes and hypertension remain the major risk factors for development and cardiovascular complications the leading cause of mortality among patients with CKD. Pulse pressure has been noted to be an important and independent factor for cardiovascular mortality. Effect of pulse pressure (PP) on renal function in the general population has not been well studied. In this study, we examined the relation of pulse pressure to kidney function in a random, cross-sectional study of unselected population in Texas.

Methods: A cohort of 1606 subjects was recruited from the general population using random digit dialing. Detailed history and physical examination were performed and blood and urine samples were taken for renal function assessment. Estimated glomerular filtration rate (eGFR) was derived using both the 4 variable MDRD formula. Subjects were divided into normal PP group (PP≤45), wide PP group (PP>45) and were further subdivided in different age categories (age <50 and age ≥50) and those with and without systolic hypertension. Correlation of PP to eGFR and logarithmically transformed urine albumin to creatinine ratio (UACR_{log}) were analyzed.

Results: A total of 1576 subjects completed the study. There were 976 subjects with normal PP and 603 with wide PP. Among subjects with age ≥50, wide PP was associated with higher UACR_{log} (p<0.001), but not with eGFR (p=0.99). In subjects without systolic hypertension, the group with wide PP compared to normal PP, had a significantly lower eGFR (p<0.0011) and a greater UACR_{log} (p<0.05). In patients with systolic hypertension, no significant differences in these parameters were seen between the PP groups (p=0.234).

Conclusions: In patients without systolic hypertension, wide PP is a predictor of worse kidney function in terms of eGFR and UACR_{log}. This could be attributed to underlying heart disease, severe anemia, thyroid disorders and other factors that lower diastolic blood pressure. Hemodynamic significance of wide pulse pressure on renal functional parameters needs further exploration.

Funding: Other U.S. Government Support

TH-PO544

TNFα Receptor Type 2 Is Not Associated with an Accelerated Age-Related eGFR Decline in the General Middle-Aged Non-Diabetic Population
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Background: TNF-α is an inflammatory cytokine that mediates renal injury in animal studies. Soluble TNFα receptor type 2 (sTNFR2) is a reliable marker of TNFα activity and has emerged as an independent predictor for kidney function decline in persons with diabetes. However, few studies have investigated the effect of sTNFR2 on chronic kidney disease (CKD) risk in the general population. Previous studies have mainly used

estimated GFR which is inaccurate in the near normal range of GFR and biased by non-GFR determinants. We investigated whether sTNFR2 is a risk-factor for GFR decline in the general population using measured GFR.

Methods: We measured GFR by iohexol clearance in a cohort of the general population aged 50-62 years without diabetes, kidney- or cardiovascular disease at baseline. Of the 1594 subjects investigated at baseline, 1299 (81%) had a second measurement after a median observation of 5.6 years in the Renal Iohexol-clearance Survey Follow-Up study (RENIS-FU). Baseline sTNFR2 levels were measured by ELISA.

Results: In a linear mixed regression model adjusted for time-dependent variables including sex, weight, height, smoking, use of NSAIDs, HbA1c and albumin-creatinine-ratio, one standard deviation (SD) increase in baseline sTNFR2 was associated with a slower GFR decline of 0.10 ml/min/year (95% CI: -0.01 to 0.19). There was a strong negative association between the baseline values of sTNFR2 and GFR; one SD increase in sTNFR2 was associated with lower GFR ($\beta = -5.63$ ml/min, 95% CI: -6.87 to -4.40).

Conclusions: Increased sTNFR2 is not a risk-factor for accelerated decline in GFR in the general middle-aged population. The negative baseline association between sTNFR2 and GFR is probably due to renal clearance of sTNFR2. A longer follow-up time may be necessary to fully evaluate whether sTNFR2 influences age-related GFR decline in the general population.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim

TH-PO545

Abstract Withdrawn

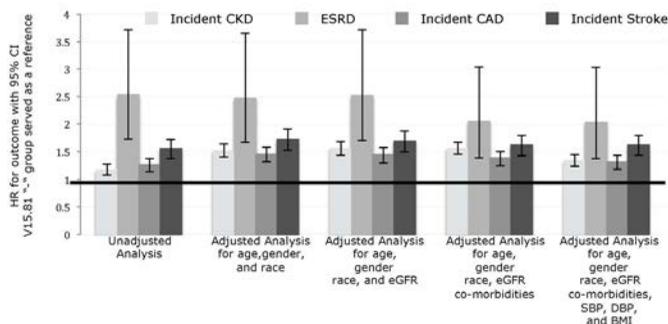
TH-PO546

Diagnosis of Non-Adherence and Renal, and Cardiovascular Outcomes in Newly Treated Hypertensive U.S. Veterans Elvira Gosmanova,¹ Miklos Zsolt Molnar,¹ Ahmed Zeen Alabedeen Alrifai,¹ Jun Ling Lu,¹ Elani Streja,² William C. Cushman,³ Kamyar Kalantar-Zadeh,² Csaba P. Kovacs,^{1,3} ¹Univ of Tennessee, Memphis, TN; ²Univ of California, Irvine, CA; ³VA Medical Center, Memphis, TN.

Background: Adherence is paramount in treating hypertension, yet no gold standard method is available for non-adherence screening delineating high-risk patients. An ICD-9-CM non-adherence diagnostic code (V15.81) has been available for many years; however, its utility is poorly studied.

Methods: We examined the association between V15.81 code assigned prior to HTN diagnosis, with renal (incident CKD and ESRD) and cardiovascular (incident coronary heart disease-CHD and stroke) outcomes in 312,489 incident hypertensive individuals identified from a historical prospective cohort. Baseline mean age was 53.8 years, patients were 91% males and 20% African Americans; 10,401 patients had a V15.81 code. We used crude and Cox models adjusted for baseline demographic characteristics, eGFR, BMI, blood pressure, and co-morbidities.

Results: During a median follow up of 7.9 years, event rates were: for incident CKD 7.1 (7.0-7.2)/1000 patient-years, for ESRD 0.15 (0.13-0.16)/1000 PY, for CHD 4.6 (4.5-4.7)/1000 PY, and stroke 4.0 (3.6-4.5)/1000 PY. The presence of a V15.81 code was associated with a higher risk of all renal and cardiovascular outcomes in unadjusted and adjusted analyses including 2 fold higher risk of ESRD and 70% higher stroke risk.



Conclusions: A diagnosis of non-adherence based on the assignment of a V15.81 code prior to the diagnosis and treatment of hypertension was associated with increased adverse renal and CV outcomes in incident hypertensive US veterans. Further research is warranted to examine interventions targeting modifiable patient characteristics linked to non-adherence with the aim to improve outcomes in hypertensive individuals.

Funding: NIDDK Support, Veterans Administration Support

TH-PO547

Soluble KLOTTHO Negatively Correlates with Low-Grade Inflammation in Chronic Kidney Disease Patients Marek Kuzniewski,¹ Beata Kusniercz-cabala,² Danuta Fedak,² Paulina Dumnicka,³ Magdalena Barbara Kaziuk,¹ ¹Dept of Nephrology, Jagiellonian Univ Medical College, Krakow, Poland; ²Dept of Diagnostics, Chair of Clinical Biochemistry, Jagiellonian Univ Collegium Medicum, Krakow, Poland; ³Dept of Medical Diagnostics, Jagiellonian Univ Collegium Medicum, Krakow, Poland.

Background: Circulating soluble KLOTTHO (sKLOTTHO) is a multifunctional protein, possessing anti-aging properties, recently associated with beneficial modulation of phosphate metabolism, cardiovascular protection and lower oxidative stress. In chronic kidney disease (CKD), sKLOTTHO concentrations decrease along with the decrease of kidney function. Our aim was to study the relationship of low-grade inflammation observed in CKD patients with sKLOTTHO concentrations.

Methods: The studied group consisted of 90 predialysis CKD patients (13 stage 1, 4 stage 2, 13 stage 3a, 19 stage 3b, 32 stage 4 and 9 stage 5), 52 male and 38 female, age 60+/-17. Serum concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) were measured to assess inflammation. Soluble KLOTTHO concentrations were measured in sera of patients using ELISA method.

Results: Median sKLOTTHO concentrations in the whole group of patients were 822 (IQR: 475-1078) pg/ml and was highest in patients with stage 1-2 CKD [1078 (990-1832) vs 704 (469-1034) pg/ml; p=0.002]. Median CRP concentrations were 2.13 (IQR: 0.80-4.97) mg/l. In the whole studied group, log(CRP) and log(IL-6) concentrations negatively correlated with log(sKLOTTHO) (R=-0.33; p=0.002 and R=-0.25; p=0.014, respectively). Such correlations were observed throughout CKD stages, even in patients with CKD stage 1-2 (R=-0.66; p=0.005 and R=-0.75; p=0.001). In the whole group, CRP above the median value was associated with significantly lower sKLOTTHO [713 (412-1031) vs 979 (574-1823) pg/ml; p=0.042]. In multiple analysis, log(CRP), but not log(IL-6) was a significant predictor of log(sKLOTTHO) concentrations (beta=0.22+/-0.10; p=0.045), independently of age and CKD stage.

Conclusions: In CKD patients chronic low-grade inflammation may be one of the factors lowering sKLOTTHO concentrations. It is important to carefully diagnose and treat any inflammatory states in those patients, starting at early stages of CKD.

Funding: Government Support - Non-U.S.

TH-PO548

Inflammasome Activation by Lipopolysaccharide (LPS) and Angiotensin II (Ang II) in CKD Sindhura Bobba, Siddhartha S. Ghosh, Daniel E. Carl, Todd W. Gehr, Richard Krieg. Nephrology, VCU, Richmond, VA.

Background: Inflammasome dependent cytokines, such as IL-1 β play a role in CKD, but their regulation during renal injury is not clearly elucidated. In this study we analyzed the ontogeny of inflammasome markers during the development of CKD in rats. Earlier studies have shown that changes in gut microbiota releases LPS in the circulation of CKD animals. LPS plays a major role in inflammasome activation. In this study we explored if LPS plays a role to activate inflammasome in CKD.

Methods: CKD was generated in Sprague dawley rats by 5/6 nephrectomy (Nx). Rats were sacrificed at 2, 4, 8 and 12 weeks after Nx (n=5/group). The controls were sham operated rats sacrificed on the 12th week. A group of Nx rats received 10 mg/kg losartan from 4 to 8 weeks. Kidney cytosols were taken to measure inflammasome markers (NF κ B, ASC, caspase 1 and IL-1 β) by western blots. Serum LPS was measured by LAL assay. Ang II levels in the kidney were measured by ELISA. Rat mesangial cells were treated with Ang II and LPS to investigate inflammasome activation.

Results: Serum creatinine and urea significantly went up from 2 weeks onwards and glomerulosclerosis was seen from 4 weeks onward. Kidney Ang II concentration increased longitudinally from 2 weeks and plateaued at 8 weeks. Significant increase in caspase 1 and IL-1 β were seen only at 8 and 12 weeks, whereas ASC increased from 4 weeks. However, pNF κ B was significantly activated from 2 weeks onward. Serum LPS significantly increased from 4 weeks onward. Losartan significantly decreased all the inflammasome markers. Mesangial cells were treated with LPS and/or Ang II to investigate inflammasome activation. 50 ng/ml LPS and 10⁻⁶M and 10⁻⁸M Ang II did not affect inflammasome activation. When 50 ng/ml LPS and Ang II (10⁻⁶M) were combined significant increase in all the inflammasome markers were observed and this was blocked by losartan.

Conclusions: Appearance of LPS at 4 weeks is probably due to increased intestinal permeability associated with CKD. Neither LPS or AngII alone could activate inflammasome. By blocking AT1 receptor we could reduce inflammasome activity. This suggest that Ang II is required for LPS mediated inflammasome activation in CKD.

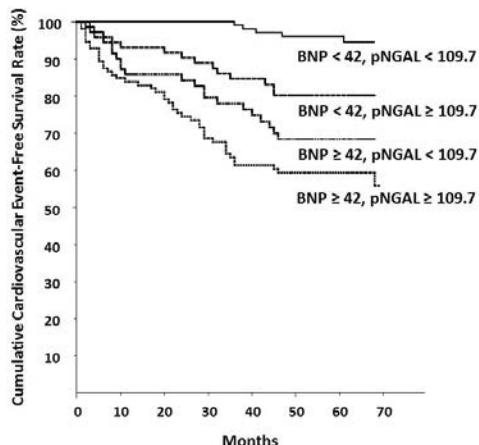
TH-PO549

Plasma Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Cardiovascular Events and All-Cause Mortality in Patients with Chronic Kidney Disease Midori Hasegawa, Kazuo Takahashi, Hiroki Hayashi, Shigehisa Koide, Yukio Yuzawa. Nephrology, Fujita Health Univ School of Medicine, Aichi, Japan.

Background: Elevated neutrophil gelatinase-associated lipocalin (NGAL) levels have recently been reported in patients with heart failure, coronary heart disease, or stroke. Here, we aimed to assess the usefulness of plasma NGAL (pNGAL) as a predictor of cardiovascular (CV) events and mortality in patients with chronic kidney disease (CKD).

Methods: In this prospective cohort study, the pNGAL level was measured in 371 ambulatory patients with CKD not on dialysis with an estimated glomerular filtration rate < 60 mL/min/1.73 m². CV events were defined as CVdeath, acute coronary syndrome, hospitalization for worsening heart failure, stroke, or aortic dissection.

Results: During a median follow-up period of 58 months, 84 CV events (22.6%) and 32 deaths (8.6%) occurred. On Cox stepwise multivariate analysis of all significant variables (p < 0.05) on univariate analysis, pNGAL, B-type natriuretic peptide (BNP), the urinary albumin creatinine ratio, and a history of previous CV diseases were significant predictors of CV events, while pNGAL, BNP, hemoglobin, and age were significant predictors of mortality. Considering both pNGAL and BNP, we stratified patients into four groups, with the median level of each marker as cutoff values (109.7 ng/mL for pNGAL and 42 pg/mL for BNP). Five-year CV event-free survival rates were 94.6%, 80.3%, 68.3%, and 59.4% in the four groups above, respectively (p < 0.0001).



Conclusions: Elevated pNGAL could predict future CV events and mortality in patients with CKD, while the combination analysis of pNGAL and BNP was useful in stratifying CV event risk.

TH-PO550

Clinical Significance of Urinary Liver-Type Fatty Acid Binding Protein as a Predictor of End Stage Renal Disease and Cardiovascular Disease in Patients with Chronic Kidney Disease *Katsuomi Matsui*,^{1,2} Atsuko Ikemori,² Naohiko Imai,^{1,2} Takeshi Sugaya,² Takashi Wada,³ Sayuri Shirai,^{1,2} Kenjiro Kimura,⁴ Yugo Shibagaki.² ¹Dept of Nephrology and Hypertension, Internal Medicine, St. Marianna Univ School of Medicine Yokohama City Seibu Hospital, Yokohama, Kanagawa, Japan; ²Dept of Nephrology and Hypertension, Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; ³Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Kanazawa, Japan; ⁴Dept of Internal Medicine, Tokyo Takanawa Hospital, Takanawa, Tokyo, Japan.

Background: To improve outcomes in patients with chronic kidney disease (CKD), it is important to identify prognostic factors for end-stage renal disease (ESRD) as well as cardiovascular disease (CVD). This study assessed urinary concentrations of albumin, N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP), as predictors of ESRD and CVD.

Methods: A prospective, observational, multicenter study, comprising 244 Japanese outpatients with CKD who had a follow-up period of at least 3 months. The primary endpoint was the first onset of a nonfatal or fatal CVD event and progression to ESRD, defined as myocardial infarction, stroke, or artery revascularization (coronary, carotid or peripheral), and initiation of dialysis.

Results: During a median follow up of 3.8 years, the primary endpoint occurred in 39 (15.8%) patients. Irrespective of diabetes, high urinary L-FABP correlated with the development of ESRD and CVD. The areas under the receiver operator characteristic curves (AUCs) for predicting the primary endpoint for urinary concentrations of L-FABP, albumin, and NAG were 0.825, 0.797, and 0.722, respectively. Cox regression analyses, which were adjusted for factors known to influence the primary endpoint, including patient characteristics, and serum and urinary parameters, demonstrated that the primary outcome was associated with high urinary L-FABP and low eGFR (p = 0.049, hazard ratio = 1.341 [95% CI, 1.005 - 1.790]; and p < 0.000, hazard ratio = 0.953 [95% CI, 0.930 - 0.976], respectively).

Conclusions: Urinary L-FABP may be a useful prognostic marker of progression to ESRD and the onset of CVD in patients with CKD.

Funding: Government Support - Non-U.S.

TH-PO551

Elevated Serum Adiponectin Concentrations Might Predict End-Stage Renal Disease in Japanese Patients with Moderate to Severe Chronic Kidney Disease *Hitomi Tanimoto*,¹ Hirotake Kasuga,¹ Ryo Takahashi,¹ Keiko Kimura,¹ Chieko Matsubara,¹ Mari Maseki,¹ Yasuhiko Ito.² ¹Dept of Nephrology, Nagoya Kyoritsu Hospital, Nagoya, Japan; ²Dept Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: Adiponectin (ADPN) is an adipocyte-derived, anti-inflammatory, anti-atherogenic, insulin-sensitizing polypeptide. However, elevated serum ADPN levels are associated with high mortality rates and more cardiovascular events in patients with chronic kidney disease. In addition, ADPN reportedly helps to protect renal function, whereas others have found that high ADPN levels predict end-stage renal disease.

Methods: We monitored serum ADPN, Cr and eGFR in 215 outpatients during 2008 and assigned 104 of them with eGFR ≤ 60 mL/min/1.73 m² to groups based on ADPN values ≤ 12.3 (L) or > 12.3 (H) mg/mL. These patients were followed for five years or until they started dialysis.

Results: During the study period, 6 patients in the L group (n=55) and 21 patients in the H group (n=49) started dialysis (P < 0.0005). The dialysis-free survival rates at 60 months in groups L and H were 87.4% and 52.2%, respectively (p < 0.0005). Cox multivariate analysis identified low ADPN (HR, 0.35; p < 0.05), age (HR, 0.9; p < 0.05) and eGFR 30 - 60 mL/min/1.73 m² (HR, 0.07; p = 0.00005) as independent risk factors for end stage kidney disease.

Conclusions: High serum adiponectin levels might predict end stage kidney disease in Japanese patients with moderate-to-severe chronic kidney disease.

TH-PO552

The Association Between Direct Measures of Body Fat, Incident Chronic Kidney Disease and Kidney Function Decline: The Health Aging Body and Composition Study *Magdalena Madero*,¹ Ronit Katz,² Linda F. Fried,³ Rachel A. Murphy,⁶ Michael Shlipak,⁴ Carmen A. Peralta,⁴ Joachim H. Ix,⁹ Anne B. Newman,⁸ Suzanne Satterfield,⁷ Kushang V. Patel,⁶ Mark J. Sarnak.³ ¹National Heart Inst Mexico; ²Washington U; ³Tufts; ⁴UCSF; ⁵VA; ⁶NIH; ⁷UTHSC; ⁸Pittsburgh; ⁹UCSD.

Background: We evaluated and compared the association of CT and anthropometric measures of obesity with kidney outcomes in the Health ABC Study. We hypothesized that CT measures, particularly of visceral fat, would confer the highest risk for kidney outcomes in comparison with other measures.

Methods: CT measures included visceral abdominal fat (VAT) and subcutaneous adipose tissue (SAT), anthropometric measures included waist circumference (WC) and body mass index (BMI). Kidney outcomes included incident CKD (follow-up eGFR_{cr} less than 60 ml/min/1.73 m² in individuals with baseline GFR>60 ml/min/1.73m²) and kidney function decline (30% decrease in eGFR_{cr} in follow up at either year 3 or 10). Multivariable logistic regression models were used to evaluate the association with outcomes.

Results: 2489 individuals were included. Mean age was 74±3 y, 49% were male, 39% were black and 15% were diabetic. In continuous models SAT, VAT, BMI and WC were associated with kidney function decline. VAT, BMI and WC were also all associated with incident CKD, but SAT did not reach statistical significance.

	Unadjusted	Adjusted
KF Decline >30%	OR (95% CI)	
VAT (per SD=67)	1.30 (1.17-1.43)	1.19 (1.06-1.33)
SAT (per SD=121)	1.15 (1.04-1.27)	1.18 (1.04-1.34)
BMI (per SD= 4.6)	1.28 (1.15-1.41)	1.20 (1.07-1.34)
WC (per SD= 12.5)	1.32 (1.19-1.46)	1.22 (1.09-1.37)
	Unadjusted	Adjusted
Incident CKD (per SD)	IRR (95% CI)	
VAT	1.36 (1.25-1.47)	1.21 (1.09-1.33)
SAT	1.18 (1.08-1.29)	1.11 (0.99-1.23)
BMI	1.28 (1.18-1.41)	1.15 (1.04-1.27)
WC	1.28 (1.19-1.38)	1.18 (1.06-1.30)

Adjusted for age, gender, race, site, baseline GFR, DM, BP, HTN meds, albuminuria, smoking, LDL and HDL cholesterol, oral estrogen, prevalent CHD and prevalent HF

Similar results were found in categorical analyses using quartiles of the exposure variable

Conclusions: Anthropometric measures of body fat appear to provide as reliable estimates of kidney decline risk as direct measures in elders.

Funding: NIDDK Support

TH-PO553

Gender Dependent Association Between Metabolic Syndrome and Arterial Stiffness in Patients with Chronic Kidney Disease: Findings from the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) Study Yong Un Kang,¹ Eun Hui Bae,¹ Seong Kwon Ma,¹ Kook-Hwan Oh,² Curie Ahn,² Soo Wan Kim.¹ ¹Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; ²Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.

Background: We investigated the relationships of metabolic syndrome (MS) to arterial stiffness in chronic kidney disease (CKD) patients across a wide range of renal function from early CKD to predialysis.

Methods: Risk factors for MS and brachial-ankle pulse wave velocity (baPWV) as measures of arterial stiffness were assessed in 1,256 CKD patients from the KNOW-CKD study. MS was defined by modified National Cholesterol Education Program Adult Treatment Panel III guidelines. Multivariate logistic regression was used to test the association between MS and cardiovascular risk factors, measures of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), and arterial stiffness.

Results: Higher arterial stiffness levels were associated with older age, lower estimate glomerular filtration rate, diabetes, and hypertension. Arterial stiffness was not associated with measures of CKD-MBD including total calcium, intact parathyroid hormone, alkaline phosphatase, and albumin. MS was an important determinant of arterial stiffness in CKD patients after adjustment for demographics, cardiovascular risk factors, and CKD-MBD measures, and medication. Systolic blood pressure (SBP) and fasting plasma glucose were the major determinant of arterial stiffness. In sub-analysis by gender, women had more stronger association between arterial stiffness and MS than men. SBP, waist circumference, and triglyceride were independent determinants of arterial stiffness in women, whereas only SBP predicted arterial stiffness in men.

Conclusions: The presence of MS and its risk factors were associated with increased arterial stiffness and that these relationships were independent of renal function, CKD-MBD measures, and cardiovascular risk factors in CKD patients. Women had more stronger association between arterial stiffness and MS than men and the association between risk factors for MS and arterial stiffness may differ between men and women in CKD patients.

Funding: Government Support - Non-U.S.

TH-PO554

Body Mass Index (BMI) Has a U-Shaped Association with Chronic Kidney Disease (CKD) Progression in Children with Glomerular Diseases Robert H. Mak, Christopher B. Pierce, Nancy MacDonald Rodig, Craig S. Wong, George J. Schwartz, Marva M. Moxey-Mims, Susan L. Furth, Bradley Warady. *Pediatric Nephrology, Univ of California San Diego, La Jolla, CA.*

Background: In adult patients, BMI has a U-shaped association with disease progression in CKD stages II to IV. Data in children have not been reported. We investigated BMI association with disease progression in the Children with CKD (CKiD) Cohort.

Methods: Children with CKD stages II to IV had annual measurements of glomerular filtration rate (GFR), either directly by iohexol clearance or estimated using a CKiD data-derived equation. Stratifying by CKD diagnosis, glomerular (G) and non-glomerular (NG) diseases, GFR decline rate during follow-up was modeled on baseline BMIz-score for height-age and sex using joint shared-parameter models to account for informative censoring associated with renal replacement therapy (RRT). GFR was log-transformed and change was estimated as %/yr.

Results: 866 children with median age 11 [8,15] yrs and median GFR 52 [38,71] ml/min/1.73m² at baseline were followed for a median of 4.6 [2.0,6.9] yrs; 131 children initiated RRT or died (n=2) during follow-up. In 276 children with G diagnoses, expected GFR decline rate exhibited a quadratic relationship with baseline BMIz modeled continuously; high and low ends of the baseline BMIz spectrum showed steeper relative declines in GFR rates compared with patients with slightly above average baseline BMIz. Specifically, G children with BMIz ≤ 25th %tile (10% of G) had expected GFR declines of 13.6%/yr or greater; G children with BMIz between 75th and 90th %tile (20%) had expected GFR declines of 8.5%/yr; G children with BMIz ≥ 98th %tile (15%) had expected GFR declines of 11.3%/yr. Adjusting for sex, age, black race and proteinuria did not change this relationship qualitatively. In contrast, in 590 children with NG diagnoses, BMIz was not associated with expected GFR decline rate, which was 4.5%/yr.

Conclusions: BMIz has a U-shaped association with disease progression in children with CKD stages II to IV with G but not with NG diagnoses. Weight management in CKD children to avoid extremes in BMIz may improve CKD outcomes and await clinical trials confirmation.

Funding: NIDDK Support

TH-PO555

Combination of Low Body Mass Index and Serum Albumin Level Leads to Chronic Kidney Disease Progression: The Chronic Kidney Disease-Research of Outcomes in Treatment and Epidemiology Study Hiroaki Kikuchi,¹ Eiichi Kanda,² Soichiro Iimori,¹ Shotaro Naito,¹ Sei Sasaki,¹ Eisei Sohora,¹ Tomokazu Okado,¹ Tatemitsu Rai,¹ Shinichi Uchida.¹ ¹Nephrology, Tokyo Medical and Dental Univ; ²Nephrology, Tokyo Kyosai Hospital.

Background: The relationship between nutritional deficiency and chronic kidney disease (CKD) progression is unknown. In the present prospective cohort study, we evaluated the hypothesis that a combination of low body mass index (BMI) and serum albumin level leads to rapid CKD progression.

Methods: The study cohort comprised 728 predialysis patients with CKD (stages 2–5) enrolled from 2010 to 2011. Patients were categorized into 4 groups according to their serum albumin levels and BMI: group 1, low serum albumin level (<4 g/dL) and low BMI (<23.5 kg/m²); group 2, high serum albumin level (≥4 g/dL) and low BMI; group 3, low serum albumin level and high BMI (≥23.5 kg/m²); and group 4, high serum albumin level and high BMI. The primary outcome was a 30% decline in estimated glomerular filtration rate (eGFR) or start of dialysis within 2 years. The secondary outcome was an annual GFR decline (mL/min/1.73 m²/year).

Results: Logistic regression analysis adjusted for baseline characteristics (reference, group 4) showed that only group 1 was associated with a high risk of CKD progression; adjusted odds ratio (aOR) 3.07 [95% confidence interval (CI) (1.51, 6.24)]; group 2, aOR 1.81 (95% CI 0.89, 3.70); group 3, aOR 1.97 (95% CI 0.96, 4.03). A multivariate general linear regression analysis adjusted for baseline characteristics showed a significant difference in annual eGFR decline between groups 1 and 4 (β = -3.04, P ≤ 0.001).

Conclusions: This study suggests that combined effects of low body mass index and serum albumin level lead to CKD progression.

TH-PO556

Weight Reduction Has an Additive Effect on the Anti-Albuminuric Effect of Angiotensin II Type I Receptor Blocker in Hypertensive Patients with Chronic Kidney Disease Ho Jun Chin,^{1,3} Chun Soo Lim.^{2,3} ¹Internal Medicine, Seoul National Univ Bundang Hospital; ²Seoul National Univ Boramae Medical Center; ³Seoul National Univ Hospital, Seoul.

Background: We searched the additive anti-proteinuric effect of weight reduction in addition to medication of an angiotensin II type I receptor blocker (ARB) for hypertensive chronic kidney disease (CKD) patients with mild overweight.

Methods: This study is a sub-analysis of data from an open-label, case-controlled, randomized clinical trial including 245 hypertensive CKD patients completed the trial (NCT01552954). We were able to calculate the ratios of estimated daily excretion of sodium (eNa), albumin (eUalb), and urea nitrogen (eUN) in 227 participants during 16 week-trial period with medication of Olmesartan 40 mg a day. The primary outcome of the study was a decrement of eUalb ≥ 25% during 16 weeks. We grouped the participants according to the ratio of weight (WtRatio) during 16 weeks.

Results: The baseline mean values of BMI, GFR, and eUalb were 25.4 ± 3.8 kg/m², 67.0 ± 23.9 ml/min/1.73 m² and 1.0 ± 0.7 g/day, respectively. The proportion of patients that achieved a decrement of eUalb ≥ 25% during 16 weeks with an ARB medication was 93.0% (53/57) in group 1 with a decrement of weight ≥ 1.5%, 83.3% (25/30) in group 2 with WtRatio between -1.4% and -0.1%, and 70.6% (96/136) in group 3 with WtRatio ≥ 0.0% (p = 0.002). The probability of a decrease in albuminuria was 7.405-fold (95% CI: 2.168-25.293, p=0.001) higher in group 1 compared to group 3, as observed in multiple logistic regression analysis as well. The decrement of eUalb was the highest in group 1 (-59.4 ± 47.1%) compared to group 2 (-38.4 ± 70.1%) or group 3 (-26.2 ± 160.4%) (p=0.005). The additive anti-albuminuric effect of weight change in addition to the medication of an ARB was independent from the change in urinary excretion rate of sodium or urea nitrogen calculated using 24-hour urine collection.

Conclusions: The small change of body weight had an additive anti-albuminuric effect in hypertensive CKD patients with albuminuria using an ARB, independent from the change of sodium or protein intake.

Funding: Pharmaceutical Company Support - Daichi-Sancho Korea and Daewoong Pharm.

TH-PO557

Can Exercise-Induced Proteinuria Predict the Onset of Chronic Kidney Disease? A Systematic Review Naushad Ali Junglee,^{1,2} Mahdi M. Jibani,^{1,2} Andrew B. Lemmey,¹ Jamie Hugo Macdonald.¹ ¹Extremes Research Group, School of Sport Health and Exercise Sciences, Bangor Univ, Bangor; Gwynedd, United Kingdom; ²Renal Unit, Ysbyty Gwynedd, Bangor, Gwynedd, United Kingdom.

Background: Post-exercise proteinuria (PeP) shares characteristics with proteinuria of chronic kidney disease (CKD) including its cause (increased intraglomerular pressures) and its consequences (albuminuria and reduction in glomerular filtration rate). The aim of this study was to perform a systematic review to determine if PeP could predict the onset or progression of CKD.

Methods: A systematic review of articles published in Ovid Medline(R), Ovid Medline in process, AMED, EMBASE, Pubmed, Cochrane Library and Web of Science between 1946 and 2014 was conducted. Eligible studies included randomized controlled trials

and prospective observational cohorts whose participants had or were at-risk of CKD and performed an exercise test to elicit PeP. Search terms included: exercise, proteinuria, albuminuria, chronic kidney disease and nephropathy. Primary outcomes examined were biomarkers of CKD (e.g. rise in blood creatinine) during a follow-up period of at least three months.

Results: Five studies (n=351) met inclusion criteria. Full meta-analysis was not possible interventions and PeP measurements varied markedly between studies. Therefore, narrative synthesis was performed. When combining results of the primary outcome in four similar studies (n=318), the presence of PeP was highly associated with elevated resting proteinuria at follow-up (χ^2 test, $P < 0.0001$) and significant odds ratios (OR) of developing CKD following a positive exercise test vs. not developing CKD were noted for each of these four studies (OR 2.3 to 52). However, interventions induced potential bias with notable differences in type of exercise routines between studies. Also, primary outcomes did not factor confounding variables (e.g. use of angiotensin-receptor antagonists). Finally, findings are only generalisable to a young type I diabetics at risk of CKD.

Conclusions: Despite the limited number of studies in the literature and their shortcomings, PeP shows promise as a predictor for CKD progression. However, there is a need to define the most appropriate exercise test for this purpose.

Funding: Private Foundation Support

TH-PO558

Ketoanalog Supplementations Decreases Dialysis and Mortality Risk in Patients with Advanced Chronic Kidney Disease Che-Hsiung Wu,¹ Vincent Wu,² ¹Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taipei, Taiwan; ²National Taiwan Univ Hospital, Taipei, Taiwan.

Background: The benefit of alpha-ketoanalog (KA) supplementation for advanced chronic kidney disease (CKD) patients that followed low-protein diet (LPD) remains undetermined.

Methods: We extracted longitudinal data for all advanced CKD patients in the Taiwan National Health Insurance from January 1, 2000 through December 31, 2010. A total of 1483 patients with advanced CKD treated with LPD, who started KA supplementation, were enrolled in this study. We analyzed the risks of end stage renal disease and all-cause mortality using Cox proportional hazard models with influential drugs as time-dependent variables.

Results: A total of 1113 events of initiating long-term dialysis and 1228 events of composite outcome occurred in patients with advanced CKD after a mean follow-up of 1.57 years. Data analysis using the Cox model suggests KA supplementation is associated with a lower risk for long-term dialysis (table 1) (HR, 0.54 [95% CI 0.47 - 0.62]) and the composite outcome of long-term dialysis or death (HR, 0.49 [95% CI 0.43 - 0.55]) when daily dosage is more than 5.5 tablets. The beneficial effect was consistent in subgroup analysis.

Variables	Hazard Ratio (95% confidence interval)	p value
Diabetes mellitus	1.80 (1.52 - 2.12)	< 0.001
Hypertension	1.25 (1.10 - 1.42)	< 0.001
Age, >60 vs. ≤60 years old	1.29(1.14 - 1.45)	< 0.001
CCI score, >3 versus ≤3	1.26 (1.05 - 1.52)	0.0124
Medicine Hospitalization	8.04 (7.02 - 9.20)	< 0.001
Daily KA dosage (expressed as tablets) larger than 5.5 vs. Unsuitable dose	0.65 (0.43 - 1.00)	0.0492
ACEI use	0.63 (0.49 - 0.81)	< 0.001
ARB use	0.65 (0.56 - 0.76)	< 0.001
KA use	0.54 (0.47 - 0.62)	< 0.001

Conclusions: Among advanced CKD patients that followed LPD, KA supplementation at an appropriate dosage may substantially reduce the risk of initiating long-term dialysis or of developing the composite outcome. KA supplementation represents an additional therapeutic strategy to slow the progression of CKD. The promising results in terms of mortality and commencing chronic dialysis need confirmation with different study designs.

TH-PO559

Serum Fibroblast Growth Factor 21 Is a Significant Predictor for Renal Outcomes in Patients with Chronic Kidney Disease Masashi Kitagawa, Hitoshi Sugiyama, Hiroshi Morinaga, Ayu Akiyama, Toshio Yamanari, Akifumi Onishi, Keiko Tanaka, Yoko Kikumoto, Tatsuyuki Inoue, Jun Wada. *Medicine and Clinical Science, Okayama Univ Graduate School, Okayama, Japan.*

Background: Fibroblast growth factor 21 (FGF21) is a metabolic hormone that plays a significant role in glucose and lipid homeostasis. FGF21 activity depends on its binding to FGF receptors and β-Klotho. Circulating FGF21 levels are independently associated with the renal function. The purpose of this study was to identify the relationship between the serum FGF21 levels and the renal function in patients with chronic kidney disease (CKD) and investigate whether the serum FGF21 levels can predict renal outcomes in patients with CKD.

Methods: We conducted a prospective cohort study. We enrolled 120 CKD patients and measured serum FGF21 levels by a sandwich ELISA. The endpoint was defined as an increase in serum creatinine of 50% or the initiation of renal replacement therapy (median age, 56 years; 62% male; 59% had glomerulonephritis).

Results: At enrollment, the median estimated glomerular filtration rate (eGFR) was 56 (24-73) mL/min/1.73m² and median proteinuria was 0.84 (0.31-2.49) g/gCr. The median serum FGF21 levels were 296 (90-560) pg/mL. The natural logarithm FGF21 concentrations negatively correlated with the eGFR ($r=-0.4940$, $p<0.0001$) and positively correlated with proteinuria ($r=0.2583$, $p=0.0044$). During two years, 29 patients reached the endpoint. The renal survival was significantly lower in patients with serum FGF21 ≥ 296 pg/mL than in those with serum FGF21 < 296 pg/mL ($p<0.0001$). A Cox regression analysis showed that serum FGF21 ≥ 296 pg/mL was significantly associated with an increased risk for the renal endpoint adjusted for age, gender, body mass index, current smoking, eGFR, proteinuria, pulse pressure, fasting plasma glucose, glycoalbumin, non HDL-cholesterol, phosphate, FGF23 and renin angiotensin system blockade.

Conclusions: The data indicate that the serum FGF21 level is significantly associated with the renal outcomes, suggesting that a higher serum FGF21 level may serve as a novel biomarker for CKD progression.

TH-PO560

Serum Phosphorus Independently Predicts Risk of ESRD in an Urban CKD Clinic Jonathan W. Bazeley, Fei He, Sharon M. Moe, Ali Khalil, Ranjani N. Moorthi. *Indiana Univ.*

Background: Serum phosphorus (PO₄) levels have been positively associated with adverse outcomes in chronic kidney disease (CKD) populations, albeit in cross sectional studies of largely Caucasian cohorts. Given differences in vitamin D and PTH homeostasis in African-Americans (AA) and dietary fluctuation, we tested the hypothesis that PO₄ measured over time (as is done in clinical practice) will be associated with the risk of dialysis initiation in our urban, predominantly AA CKD population.

Methods: A retrospective cohort of 754 adult patients with CKD(eGFR <60ml/min at baseline) visiting the nephrology clinic at a large urban county hospital from 2007-10 were followed until death or May 2012. A Cox proportional hazards model adjusted for demographics, comorbidities, medications, and laboratory values was used to study the association of time varying PO₄ with the end point of time to dialysis initiation (days to event from index date). Death before dialysis was a censoring event(n=100; 13.26%).

Results: Of 754 patients, 54% were female, 60% were AA and 57% had diabetes mellitus. The mean age was 58.6 ± 13.6 years (mean ± SD), mean eGFR at the start of follow-up period was 33.4 ± 14.9 ml/min/1.73m². The median PO₄ level was (3.9 mg/dl; IQR 3.3-4.3). PO₄ was measured ≥ 2 times in 437 (58%) of patients. During a median follow up of 714 days, 117 (15.5%) patients were initiated on dialysis. When fully evaluated in a multivariable model, the time varying PO₄ remained a significant in predicting time to dialysis initiation (HR 1.44, 95%CI 1.07-1.93).

	Descriptive Statistics	Model 0 (Univariate)		Model 1		Model 2		Model 3 (Full)	
		Hazard Ratio	95% CI*	Hazard Ratio	95% CI*	Hazard Ratio	95% CI*	Hazard Ratio	95% CI*
Phosphorus (mg/dl) [†]	3.9 (3.3 - 4.3) [‡]	2.55	2.25-2.88	2.41	2.11-2.74	2.45	2.04-2.94	1.44	1.07-1.93
Age (years) [§]	58.6 ± 13.6 [‡]			0.98	0.96-0.99	0.98	0.96-1.00	0.99	0.97-1.01
Female	53.7%			1.03	0.69-1.55	1.07	0.61-1.89	0.60	0.29-1.25
African-American [¶]	60%			1.16	0.76-1.75	1.36	0.77-2.39	1.71	0.89-3.29
Smoking Yes	16.1%					0.88	0.44-1.76	0.94	0.42-2.13
Diabetes Yes	56.6%					1.97	1.05-3.68	1.28	0.63-2.60
CAD and/or CHF Yes	34.5%					1.35	0.77-2.39	1.54	0.77-3.11
ACE-I or ARB Yes [‡]	55.4%					0.43	0.22-0.83	0.57	0.25-1.26
>=3 anti-HTN Yes [‡]	56.6%					1.77	0.86-3.65	0.95	0.39-2.33
BMI (kg/m ²)	33.46 ± 8.92 [‡]					1.00	0.97-1.03	1.03	0.99-1.07
Albumin (mg/dl) [†]	4.1 (3.85-4.3)							0.20	0.08-0.51
Calcium (mg/dl) [†]	9.4 (9.0-9.7) [‡]							1.42	0.94-2.14
MDRD eGFR (ml/min/1.73m ²)	30.7 (19.4-42.2) [‡]							0.87	0.82-0.92
Bicarbonate (mg/dl) [†]	25 (23-28) [‡]							0.94	0.85-1.03
Hemoglobin (g/dl) [†]	12.2 (11.1-13.4) [‡]							0.94	0.76-1.17

* CI = Confidence Interval.
[†] Hazard ratios for laboratory values are per 1mg/dL for phosphorus, albumin, bicarbonate, per 1g/dL for hemoglobin, and per 1ml/min/1.73m² for eGFR. Bicarbonate and hemoglobin were baseline measures, while phosphorus, calcium, albumin and MDRD eGFR were time-varying.
[‡] Descriptive statistics for laboratory values and eGFR are shown in median ± interquartile range. [§] Hazard ratio for age is per year.
[¶] Descriptive statistics for age and BMI are mean ± standard deviation.
[‡] The comparator for African-American is all other races.
[‡] ACE-I or ARB reflects whether the patient picked up an ACE-inhibitor or ARB from pharmacy during observation period.
[‡] >=3 anti-HTN reflects whether subject picked up 2 or more different categories of anti-hypertensive agents (calcium-channel blockers, beta-blockers, ACE-inhibitors, ARB, direct renin inhibitors, diuretics, or miscellaneous) from the pharmacy during the observation period.

Conclusions: An increase in serum PO₄ over time was associated with faster progression to dialysis initiation in an AA urban population of CKD patients, even when adjusted for eGFR. The results suggest PO₄ may have independent negative consequences on CKD progression; testing this would require trials that evaluate lowering serum PO₄ on progression to dialysis.

Funding: Pharmaceutical Company Support - Dialysis Clinic, Inc.

TH-PO561

Serum Phosphorus Is Associated with Increased Risk of Kidney Failure Alex R. Chang,¹ H. Lester Kirchner,¹ Amanda Young,¹ Morgan Grams,² ¹Geisinger Health System; ²Johns Hopkins Bloomberg School of Public Health.

Background: Limited data exists on the association between serum phosphorus and progression to kidney failure.

Methods: Using data from 28,542 outpatients at Geisinger Health System, we examined the association between serum phosphorus and incident kidney failure (dialysis, transplant, eGFR < 15 ml/min/1.73m²). Cox regression analyses were adjusted for demographics,

history of cardiovascular disease, eGFR, fasting status, phosphorus-altering medications (estrogen, testosterone, calcium supplements, and other phosphorus-binding medications), time of day (morning, afternoon, evening), and renal risk factors.

Results: Overall, 25% were fasting lab values and 70% were drawn in the morning (8-12am). Elevated serum phosphorus was associated with increased risk of kidney failure. The highest quartile of serum phosphorus (≥ 3.8 mg/dL) was associated an adjusted hazard ratio of 1.99 (95% CI: 1.65-2.41) compared to the lowest quartile of serum phosphorus. The relationship between serum phosphorus and risk of kidney failure was similar by gender, baseline eGFR, and time of day of measurement. Associations between serum phosphorus and eGFR decline $\geq 30\%$ were similar.

Conclusions: Elevated serum phosphorus is associated with increased risk of kidney failure. Future studies are needed to determine whether lowering phosphorus levels can delay progression to ESRD.

Funding: Private Foundation Support

TH-PO562

Serum Calcification Propensity Signifies Myocardial Injury and Myocardial Structural and Functional Abnormalities in Chronic Kidney Disease Angela Yee Moon Wang,¹ Qizhe Cai,^{1,4} Matthias Bachtler,² Xiuzhang Lu,⁴ Andreas Pasch,³ ¹Medicine, Univ of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong; ²Clinical Research, Univ of Bern, Bern, Switzerland; ³Chemistry, Univ Hospital Bern and Univ of Bern, Bern, Switzerland; ⁴Echocardiography, Heart Center, Beijing Chao-Yang Hospital, Capital Medical Univ, Beijing, China.

Background: A recent novel blood test measuring the maturation time of calciprotein particles or serum calcification propensity (T50) has been shown to predict all-cause mortality in CKD subjects. This study aims to elucidate the mechanisms that explain this association.

Methods: We prospectively recruited 300 stages 3-5 non-dialysis CKD patients (age:60±10yrs, 56%men) & 100 healthy control subjects. Echocardiography with tissue Doppler Imaging & plain cardiac multislice computed tomography were done to evaluate cardiac dimensions, function & coronary artery calcium scores. Their associations with T50 were investigated.

Results: T50 was significantly lower in CKD patients vs control subjects ($P<0.001$). A significant increase in age ($P=0.05$), serum phosphate ($P<0.001$), intact parathyroid hormone ($P=0.001$), C-reactive protein ($P=0.031$), spot urine protein to creatinine ratio ($P=0.001$) as well as a decrease in serum albumin ($P<0.001$) & eGFR ($P<0.001$) were observed across the three tertiles of decreasing T50 in CKD. Adjusting for age & gender, T50 showed significant inverse associations with left ventricular (LV) mass index ($P<0.001$), left atrial volume index ($P=0.012$), early diastolic mitral annular velocity (Em) ($P=0.004$) & the ratio of early transmural flow velocity (E) to Em ($P=0.001$) but not systolic functional parameters. Serum T50 retained significant association with cardiac troponin T ($P=0.027$) in the model adjusting for age, gender, eGFR & LV mass index. T50 however showed no direct association with baseline coronary artery calcium score.

Conclusions: Low T50 may predict adverse outcomes in CKD via its close associations with myocardial injury, myocardial structural & diastolic functional abnormalities. These data suggest T50 may more be a biomarker reflecting myocardial disease rather than calcification of the coronary arteries.

Funding: Pharmaceutical Company Support - Sanofi

TH-PO563

Loss of AT-1 Receptor Regulation in CKD: Role of β -Arrestin2 Siddhartha S. Ghosh, Sindhura Bobba, Daniel E. Carl, Richard Krieg, Todd W. Gehr. VCU, Nephrology, Richmond, VA.

Background: Angiotensin II (A-II) is known to play a major role in renal failure. Studies have proven that A-II down regulates AT-1 receptors via β -arrestin2. In CKD A-II levels increase significantly and mediates its action via ERK signaling. Increased A-II will down-regulate AT-1 receptors in CKD and ERK signaling will decrease. However, regulation of the AT-1 receptor in CKD kidney has not been clearly evaluated. This study was conducted to understand AT-1 receptor regulation in CKD.

Methods: CKD was generated in Sprague dawley rats by 5/6 nephrectomy (Nx). Nx rats were sacrificed at 2, 4, 8 and 12 weeks after Nx (n=5/group). The sham control rats were sacrificed on the 12th week. A group of Nx rats received 10 mg/kg losartan from 4 to 8 weeks. Expression of kidney AT-1 receptor, β -arrestin2, pERK/ERK was measured by western blots. A- II was measured by RIA. Serum from these rats was analyzed for creatinine and urea.

Results: Serum creatinine and urea went up gradually and peaked at 8 weeks. The mean kidney A-II concentration of the control animals was 303 ± 25 fmol/gm. The results shown in the table are expressed as fold change. A-II levels peaked at 8 weeks. AT-1 receptor and ERK signaling went down but was restored by 8weeks. β -arrestin2 expression decreased at 2 weeks and never recovered. Losartan effectively reduced ERK signaling.

	Control	2 weeks	4 weeks	8 weeks	12weeks	Losartan
A-II	1.00± 0.08	1.56± 0.12*	2.68± 0.25*	3.29± 0.27*	3.31± 0.26*	3.15± 0.38
AT-1	1.00± 0.08	0.13± 0.02*	0.45± 0.05*	0.81± 0.14	0.76± 0.05	0.86± 0.13
pERK/ERK	1.00± 0.14	0.18± 0.06*	0.53± 0.06*	0.99± 0.12	0.91± 0.19	0.15± 0.05*, †
β -arrestin2	1.00± 0.17	0.25± 0.11*	0.37± 0.08*	0.20± 0.06*	0.33± 0.10*	0.38± 0.20*

* $p<0.05$ compared to control † $p<0.05$ compared to 8 weeks

Conclusions: β -arrestin2 is known to internalize AT-1 receptor. Our study shows that normal regulation of AT-1 receptor by A-II is lost as CKD progressed which is likely due to the loss of β arrestin2. Losartan neither affected AT-1 receptor expression or β -arrestin2 levels but by blocking ERK signaling it could abate A-II mediated deleterious effect on CKD.

TH-PO564

Sphingosine 1-Phosphate Changes in Patients with Chronic Kidney Disease on Hemodialysis and Peritoneal Dialysis Daria Salata,¹ Malgorzata Marchelek-Myśliwiec,² Marta Budkowska,¹ Wojciech Brzoska,² Barbara Dolegowska,¹ ¹Medical Analytics, Pomeranian Medical Univ, Szczecin, Poland; ²Dept of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical Univ, Szczecin, Poland.

Background: Sphingosine-1-phosphate is involved in the development and pathogenesis of renal function and physiology of many renal diseases including chronic kidney disease. Changes in concentrations of sphingosine-1-phosphate may affect the renal function and appear to be potential indicators of renal damage and renal graft function. The aim of this study was the evaluation of the biochemical parameters and quantitative analysis of the concentrations of sphingosine-1-phosphate in patients with chronic renal failure undergoing peritoneal dialysis, hemodialysis, or pre-dialysis.

Methods: The study included 120 patients with CKD: on peritoneal dialysis (n=30) and hemodialyzed (n=30), in predialysis state (n=60). The concentrations of biochemical parameters in serum were determined by colorimetric methods. The concentrations of S1P in the plasma were measured using the RP-HPLC. Obtained results were statistically analysed using STATISTICA PL v.10.1.

Results: The highest average concentration of S1P has been obtained in patients on peritoneal dialysis (83.83 ± 18.99 mg/dL), and the lowest in patients with pre-dialysis therapy (58.06 ± 20.38 mg/dL). The average concentration of S1P in patients before hemodialysis (71.52 ± 19.86 mg/dL) and after treatment (77.83 ± 26.48 mg/dL) were similar. Significant differences in concentration of S1P were found between patients with peritoneal dialysis and pre-dialysis patients ($p = 0.0002$) and between patients after hemodialysis and pre-dialysis ($p = 0.003$).

Conclusions: Observed higher concentrations of S1P in hemodialysis patients and peritoneal dialysis in comparison to patients treated conservatively. Indicate that activation of cellular lipid sources may be caused by the activation of the coagulation system and increased oxidative stress

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TH-PO565

Renal Elasticity of Patients with Chronic Kidney Disease Evaluated with Real-Time Ultrasound Elastography Hugo You-Hsien Lin,^{1,2,3} Shang-Jyh Hwang,¹ Hung-Chun Chen,¹ Chi-chih Hung.¹ ¹Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; ²Dept of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan; ³Graduate Inst of Medicine, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Ultrasound real-time elastography is a new imaging technique, which provides information about the elasticity of soft tissue. It is widely applied in patients with liver diseases. In patients with chronic kidney disease (CKD), glomerulosclerosis and tubulointerstitial fibrosis could be associated with lower renal parenchymal elasticity. However, little is known about the elasticity of the kidney. We designed a study to evaluate renal elasticity in patients with CKD stage 3-5.

Methods: There were 148 healthy volunteers and 227 patients with CKD in this cohort from Southern Taiwan. Renal sonography was performed on the Hitachi EUB 7500 and HVISION PREVIUS sonographer with elastography and the EUP-C715 (1-5MHz) probe.

Results: There were 143 (63.0%) male, 166 (73.1%) diabetes, with a mean estimated glomerular filtration rate (eGFR) of 33.9 ± 15.8 ml/min/1.73 m² and a median urinary protein-to-creatinine ratio (UPCR) 502 (122-1491) mg/g in the CKD group. Patients with later CKD stages had lower value of renal elasticity, which means more stiff ($p<0.001$), and smaller kidney long length ($p<0.001$). We demonstrated that renal elasticity only correlated with log-transformed UPCR ($\beta = -7.544$, $P<0.001$). Renal long length correlated with age ($\beta = -0.231$, $P<0.001$), sex ($\beta = -3.730$, $P<0.001$), serum albumin level ($\beta = -3.024$, $P=0.001$), body mass index ($\beta = 0.390$, $P=0.009$) and eGFR ($\beta = 0.146$, $P<0.001$). In fully-adjusted logistic regression model, the odds ratio (OR) per 10 unit change of renal

elasticity for rapid renal progression was 0.928 (95% CI, 0.864-0.997; $P = 0.042$). The OR per 1mm change of renal long length for rapid renal progression was 1.022 (95% CI, 0.994-1.050; $P = 0.125$).

Conclusions: Renal elasticity is associated with proteinuria and rapid renal progression in patients with CKD. It may be a useful tool for early detecting renal function change in patients with CKD.

Funding: Clinical Revenue Support

TH-PO566

The Availability of Proteinuria/Urinary Beta2-Microglobulin Combination as a Complementary Marker to Predict Early Progress in Chronic Kidney Disease Chang Hwa Lee, Il hwan Oh, Joon-sung Park. *Internal Medicine, Hanyang Univ College of Medicine, Seoul, Korea.*

Background: Proteinuria as a marker of glomerular damage is of pathogenic importance to the progression of chronic kidney disease (CKD). However, renal tubulointerstitial damage can serve a common pathway of CKD progression. Urinary β_2 -microglobulin excretion, a marker of proximal tubular damage, may reflect the presence of tubulointerstitial damage. We hypothesized that the combination of proteinuria and urinary β_2 -microglobulin may be useful predictor of renal outcome.

Methods: Proteinuria and urinary β_2 -microglobulin excretion were measured in 104 patients with CKD. Based on the value of urine protein-to-creatinine ratio (PCR) or urinary β_2 -microglobulin-to-creatinine ratio (UBCR), a total of 104 patients were divided into four groups: group I ($n = 39$), PCR < 0.5 mg/g and UBCR ≤ 300 ug/g; group II ($n = 16$), PCR < 0.5 mg/g and UBCR > 300 ug/g; group III ($n = 24$), PCR ≥ 0.5 mg/g and UBCR ≤ 300 ug/g; group IV ($n = 25$), PCR ≥ 0.5 mg/g and UBCR > 300 ug/g. Logistic regression analysis was used to compute odds ratio to examine the relationship of proteinuria or increased UBCR with deterioration of renal function (DRF), and Kaplan-Meier analysis was used to compare cumulative renal survivals among the groups.

Results: During a mean follow-up of 71 ± 21 months, renal function deteriorated in 28 of the 104 patients with CKD. Among four groups, there was statistically significant difference in gender ($P < 0.0198$), serum glucose ($P < 0.0147$), serum uric acid ($P < 0.0279$), and eGFR at 12 months ($P < 0.0158$). Logistic regression analysis identified the only combination of proteinuria and high UBCR (OR 7.396; 95% CI, 1.235 to 44.284; $P = 0.028$) as risk factors for DRF. In Kaplan-Meier analyses, group IV had most inferior cumulative renal survival rate and there were statistically significant difference among the groups ($P < 0.008$).

Conclusions: The combination of protein and β_2 -microglobulin in urine of CKD may be useful predictors of long-term renal survival. Proteinuria and urinary β_2 -microglobulin should not be discretely but simultaneously considered to early detect and delay DRF.

TH-PO567

Renal Hyperfiltration Predicts Increased Urinary Albumin Excretion in the General Non-Diabetic Population Toralf Melsom,^{1,2} Vidar T. N. Stefansson,¹ Jørgen Schei,^{1,2} Marit D. Solbu,^{1,2} Trond G. Jenssen,^{1,4} Tom Wilsgaard,³ Bjorn Odvar Eriksen.^{1,2} ¹Metabolic and Renal Research Group, UiT the Arctic Univ of Norway; ²Dep. of Nephrology, Univ Hospital of North Norway; ³Dep. of Community Medicine, UiT the Arctic Univ of Norway; ⁴Dep. of Nephrology, Oslo Univ Hospital, Norway.

Background: In cohort studies, both low and high estimated glomerular filtration rate (eGFR) have predicted cardiovascular disease (CVD) and death. The increased risk associated with high eGFR has been explained by confounding due to a low serum creatinine in persons with chronic illness. However, abnormally high GFR, renal hyperfiltration, has been hypothesized to cause elevated urinary albumin excretion, a known risk factor for CVD and death. We investigated this hypothesis in the non-diabetic general population using measurements of GFR instead of eGFR.

Methods: In 2007-2009 we measured GFR by iothexol clearance in 1552 persons aged 50-62 years from the general population without diabetes or high albumin-creatinine ratio (ACR) (ACR > 3mg/mmol). 1274 (82%) had a follow-up measurement of GFR in 2013-2015. 36 persons with diabetes at follow-up were excluded. Hyperfiltration was defined as an increase in absolute GFR (positive Δ GFR) within the same individual between baseline and follow-up. Since nephron number does not increase with age, this will be a proxy for increased single nephron GFR.

Results: Δ GFR was positively associated with a change in $\log(\text{ACR})$ in multiple linear regression. The ratio $\text{ACR}_{\text{FU}}/\text{ACR}_{\text{BASELINE}}$ increased 7% (95% CI: 0.4 to 13%) per standard deviation (SD) increase in Δ GFR. The top Δ GFR quartile was associated with a 34% (95% CI: 8 - 68%) increased $\text{ACR}_{\text{FU}}/\text{ACR}_{\text{BASELINE}}$ ratio in women, but not in men, $p < 0.05$ for the interaction. The odds ratio (95% CI) of high ACR at follow-up was 2.0 (1.3 - 2.9) per SD increase in Δ GFR. We adjusted for baseline CVD risk factors and change in body weight and use of anti-hypertensive medication.

Conclusions: Hyperfiltration predicts high ACR in the general population without diabetes. Although this may represent a link between hyperfiltration and an increased risk of CVD and mortality, it is unknown whether hyperfiltration is associated with these outcomes.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.

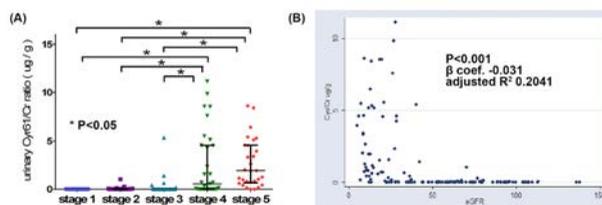
TH-PO568

Elevated Urinary Excretion of Cysteine-Rich Protein 61 Is Associated with Rapid Renal Function Decline in Patients with Chronic Kidney Disease Chun-Fu Lai, Shuei-Liong Lin, Wen-Chih Chiang, Yung-Ming Chen. *Dept of Internal Medicine, National Taiwan Univ Hospital, Taipei City, Taiwan.*

Background: Cysteine-rich protein 61 (Cyr61) has been identified as a proinflammatory factor in animal models of obstructive kidney fibrosis and ischemic kidney injury. We hypothesized that Cyr61 participates to the inflammatory process in injured kidneys and leads to progressive renal failure. The present clinical study aimed to examine urinary Cyr61 excretion in patients with chronic kidney disease (CKD).

Methods: Adult patients with stages 1-5 CKD were recruited from outpatient clinic. Urinary levels of Cyr61 were measured by sandwich enzyme-linked immunosorbent assay. The clinical factors associated with urinary Cyr61 excretion were explored using regression analysis. Rapid renal function decline was defined as estimated glomerular filtration rate (eGFR) decline rate higher than 4 cc/min/year during the follow-up period.

Results: A total of 154 patients were included ($n = 29, 31, 34, 31,$ and 29 in stage 1, 2, 3, 4, 5 CKD, respectively). Their age were 60.9 ± 13.4 years, and there were 57 women (37%). Urinary Cyr61 to creatinine ratio (UCyr61CR) was markedly elevated in patients with stage 4 and 5 CKD (Figure 1A). UCyr61CR was negatively correlated with eGFR (Figure 1B) and positively correlated with urinary protein to creatinine ratio. Furthermore, eGFR was independently associated with UCyr61CR after adjusting age, gender, body weight, body high, and urinary protein to creatinine ratio ($\beta = -0.026, P < 0.001$). Among patients with stage 3-5 CKD, UCyr61CR was significantly higher in those with rapid renal function decline in the following 3 months ($P = 0.02$).



Conclusions: Urinary Cyr61 excretion increases significantly in patients with advanced CKD. Higher UCyr61CR may be associated with following rapid renal function deterioration.

Funding: Government Support - Non-U.S.

TH-PO569

Hyperuricemia Can Be a Risk Factor for the Development of Hypertension and CKD – An 8-Year Follow-Up Study Shinichiro Nishio, Satoru Kuriyama, Naoki Sugano, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine.*

Background: Uric acid (UA) levels correlate positively with the prevalence of CKD and/or hypertension, suggesting that UA can be a progression factor. We tested the hypothesis that UA may also have a link to a new incidence of chronic kidney disease (CKD) and hypertension.

Methods: Study design is a cohort study and the predictor is UA levels. Of the 14,360 screened cases, 7,536 participants without CKD were eligible for the analysis of the incidence of CKD. Among these CKD candidates, 6,475 participants were eligible for the analysis of the new development of hypertension. The observation period was 8 years. UA levels were divided into 4 groups (Group 1:UA < 5mg/dL, Group 2:5.0-5.9mg/dL, Group 3:6.0-6.9mg/dL, Group 4:UA ≥ 7 mg/dL).

Results: Higher UA levels had a closer association with the new development of CKD at year 8; 1.6% (Group 1), 2.3% (Group 2), 3.1% (Group 3), and 4.9% (Group 4), respectively. Cox proportional hazard analysis showed that the estimates of the CKD development were age, UA levels (Hazard Ratio (HR) 1.372, 95% confidence interval (CI) 1.214-1.550), HbA1c and gender, indicating that UA levels can be predictors. The logistic analysis showed that the odds ratio (OR) to estimate CKD incidence in the high UA group (Group 4; OR 3.41, 95% CI, 95%CI 1.99-5.84) was greater than that in the low UA group (Group 1). On the other hand, higher UA levels had a closer association with the new development of hypertension; 6.9% (Group 1), 10.5% (Group 2), 13.0% (Group 3), and 17.0% (Group 4), respectively. Cox proportional hazard analysis showed that the estimates of the hypertension development were BMI, age, HDL-cholesterol, male gender, UA level (HR 1.112, 95% CI, 1.024 to 1.207), and eGFR. The logistic analysis showed that the odds ratio (OR) to estimate hypertension in the high UA group (Group 4; OR 1.33, 95% CI, 1.01 to 1.80) was greater than that in the low UA group (Group 1).

Conclusions: High UA levels are associated with the incidence of CKD and the development of hypertension.

TH-PO570

Associations Between Uric Acid, Adiponectin and Urinary Biomarkers in Persons with and without the Metabolic Syndrome Marit D. Solbu,^{1,2} Jon viljar Norvik,² Jens Kronborg,^{2,3} Bjorn Odvar Eriksen,^{1,2} Toralf Melsom,^{1,2} Trond G. Jenssen.^{2,4} ¹Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; ²Metabolic and Renal Research Group, UiT the Arctic Univ of North Norway, Tromsø, Norway; ³Innlandet Hospital Trust, Lillehammer, Norway; ⁴Oslo Univ Hospital, Oslo, Norway.

Background: In the metabolic syndrome (MetS), serum uric acid (UA) is often increased, and adiponectin is low; UA may cause renal damage, whereas adiponectin may be renoprotective. It is not known whether UA and adiponectin interact in development of renal damage. We assessed the cross-sectional association between UA, adiponectin and two urinary biomarkers (albumin creatinine ratio (ACR) and orosomucoid creatinine ratio (oroCR)) in persons with or without the MetS (NCEP-ATPIII definition).

Methods: From the Tromsø Study 2007-08, 7047 persons were included. Three urine specimens were collected and median values of ACR and oroCR used. The associations between UA, adiponectin and the upper vs. three lower quartiles of each biomarker were assessed by logistic regression analysis adjusted for cardiovascular risk factors, medication use and eGFR in persons with and without the MetS.

Results: Mean age was 63.5 (±SD 9.2) years, 57% were women and 27% had the MetS. UA was associated positively with the upper ACR quartile and negatively with the upper oroCR quartile. The association with ACR was stronger in persons with the MetS than in those without (OR 1.18; 95% CI 1.07-1.31; P=0.002 vs. OR 1.08; 95% CI 1.01-1.16; p=0.04 per 1 mg/dL increase in UA.) Adiponectin was positively associated with ACR and oroCR, but only in persons without the MetS (OR 1.08 (95% CI 1.04-1.13); OR 1.07 (95% CI 1.03-1.12), both P<0.001, per µg/mL). There were no interactions between UA and adiponectin in their associations with the urinary biomarkers.

Conclusions: UA and adiponectin did not interact in their associations with biomarkers of renal damage. Contrary to what we expected, adiponectin was positively associated with ACR and oroCR, but only in persons without the MetS. UA was positively associated with ACR only. The findings should be studied longitudinally before firm conclusions could be made.

Funding: Government Support - Non-U.S.

TH-PO571

The Longitudinal Association Between Uric Acid Level and Progression of Chronic Kidney Disease in Chinese Population Ching-Wei Tsai, Shih-yi Lin, Chin-Chi Kuo, Chiu-Ching Huang. *Div of Nephrology and Kidney Inst, China Medical Univ and Hospitals, Taichung, Taiwan.*

Background: Hyperuricemia is commonly observed in patients with chronic kidney disease (CKD). Although increasing evidence supports the association between hyperuricemia and incident CKD, there are conflicting data about the role of hyperuricemia in the progression of CKD. The main aim of current study was to add empirical evidence to the debate on the direction of the relationship among uric acid levels, allopurinol, and CKD progression in Chinese population.

Methods: We conducted a retrospective cohort study in central Taiwan. Patients who had documented hyperuricemia (defined by uric acid greater than 7 mg/dL) and/or receiving uric acid-lowering agents between 2003 and 2005 were included in the study. They were followed till December 31, 2011. Only patients with at least three available renal function profiles were analyzed. CKD progression was evaluated by the change in eGFR using linear mixed models.

Results: Longitudinal analyses showed patients with a baseline uric acid level greater than 7 mg/dl had faster decline in eGFR, comparing to those with uric acid level less than 7 mg/dl. After adjustment for demographics, comorbidities, proteinuria, allopurinol and ACEI/ARB use, three categories of hyperuricemia (uric acid 7-9, 9-11, >11 mg/dl) remained strongly associated with faster decline in eGFR over the follow-up. In multivariate longitudinal analysis, those receiving allopurinol was associated with a significantly faster decline in eGFR than non-allopurinol users during the follow-up.

	beta	p value
uric acid<7 mg/dl	Ref	
uric acid 7-9 mg/dl	-6.7	0.002
uric acid 9-11 mg/dl	-7.2	0.006
uric acid >11 mg/dl	-10.7	0.001
age at exam	-0.6	<0.0011
sex	1.8	0.9
DM	-2.2	0.2
CAD	-0.5	0.8
SBP	-0.03	0.4
Baseline creatinine	-6.4	<0.001
proteinuria	-10.6	<0.001
Allopurinol	-9.6	<0.001

Conclusions: Our study showed higher uric acid level is strongly associated with an accelerated decline in renal function in Chinese population. However, uric acid-lowering therapy with allopurinol was associated with even faster progression of CKD in this study.

TH-PO572

Revisiting Medullary Tophi: A Link Between Uric Acid and Progressive Chronic Kidney Disease? Salem Almaani,¹ Isabelle Ayoub,¹ Sergey V. Brodsky,² Tibor Nadasdy,² Jason Prosek,¹ Lee A. Hebert,¹ Brad H. Rovin.¹ ¹Div of Nephrology, The Ohio State Univ, Columbus, OH; ²Dept of Pathology, The Ohio State Univ, Columbus, OH.

Background: It is well-established from autopsy studies that gouty tophi can form in the kidney, particularly in the renal medulla. Recently hyperuricemia has been identified as a risk factor for progression of chronic kidney disease (CKD). Because each collecting duct serves more than 2000 nephrons, we postulated that obstruction or disruption of collecting ducts by medullary tophi may explain, at least in part, the association between hyperuricemia and progressive CKD. This work was done to determine the prevalence of medullary tophi in CKD patients.

Methods: We queried our nephropathology database over the last ten years for native kidney biopsies that had medullary tophi. The presence or absence of CKD and uric acid levels around the time of biopsy were determined by chart review.

Results: Predominant medullary tissue was reported in 796 of 7409 total biopsies, and 572 of these were from patients with established CKD. Medullary tophi were seen in 36 patients, 35 of whom had CKD, suggesting a minimum prevalence of tophi in CKD and non-CKD of 6.11% and 0.45%, respectively. Medullary tophi occurred with and without hyperuricemia or a history of gout.

ID	Age ¹	Race ²	Gout	Nephrolithiasis	Serum Creatinine Concentration/eGFR ¹	Serum Uric Acid Concentration ²
1	42	CAU	Yes	No	2.8/26	9.1
2	47	CAU	No	No	1.6/46	7.9
3	37	CAU	No	No	1.5/39	8.7
4	69	CAU	No	Yes	2.9/21	9.1
5	54	CAU	No	No	4.0/19	9.8
6	65	CAU	Yes	No	6.5/6	6.3
7	52	CAU	No	No	2.5/28	7.5
8	60	CAU	No	No	4.2/11.5	Normal ⁶
9	36	CAU	No	No	10.7/5.8	8.8
10	22	H	Yes	NA	13.5/4.9	Normal
11	37	NA	No	No	26/NA	6.0
12	65	CAU	Yes	No	2.5/20.5	5.8
13	67	CAU	Yes	NA	2.2/41	6.8
14	22	H	No	No	2.8/35	10.1
15	51	CAU	Yes	Na	14/NA	17.4
16	40	CAU	No	No	1.5/40	13.5

Conclusions: Medullary tophi appear to be far more likely to occur in CKD compared to non-CKD patients. This cross-sectional study cannot determine whether medullary tophi are a cause or consequence of CKD. However, given their strategic location and bulk, it is possible that medullary tophi contribute to progression of established CKD by causing upstream nephron damage.

TH-PO573

Serum Uric Acid Over 7 mg/dL Is an Independent Risk of Incident End Stage Kidney Disease – A 6-Year Population-Based Cohort Study Uppatham Supasundh, Puvanant Wiputhanuphong, Bancha Satirapoj. *Nephrology Div, Dept of Internal Medicine, Phramongkutklao Hospital and College of Medicine, Thailand.*

Background: Uric acid deteriorates kidney function via crystal and non-crystal dependent mechanisms. However epidemiological evidence for the significance of serum uric acid levels on the risk for developing end-stage kidney disease (ESKD) is scarce in a setting of population-based screening especially in Asian population. The purpose of the study was to evaluate the effect of serum uric acid level on incidence of impaired kidney function and ESKD.

Methods: A total of 23,712 individuals from an integrated health care delivery system in the Thai army who participated for health checkups between July 1, 2006, and December 31, 2012 were screened. Only 18,390 participants (14,686 men, 3,704 women) older than 20 years for whom available for body weight, serum uric acid, and creatinine data with estimated glomerular filtration rate (eGFR) over 60 ml/min/1.73m² were enrolled in the study. The cumulative incidence of chronic kidney disease (CKD, eGFR<60 mL/min per 1.73 m²) and ESKD (eGFR<15 mL/min per 1.73 m²) was calculated according to quartiles of baseline serum uric acid levels and significant high serum uric acid levels (≥7.0 mg/dL).

Results: The mean age of participants was 47.69±6.69 years and body mass index was 24.71 ±3.47 kg/m². Fourteen percent (n=2,648) was diabetes and 65.2% (n=11,998) had high blood pressure. Average serum uric acid and eGFR were 6.29 ± 1.55 mg/dL and 87.84 ± 13.27 mL/min per 1.73 m², respectively. The incidence of CKD at 6 years follow up was 3.64/1000 person-year. A total of 11 patients (0.06%) of ESKD were observed. Participants with highest serum uric acid quartile (>7.3 mg/dL) had a 3.42-fold increase in adjusted hazard ratio (HR) (95%CI; 2.19 to 5.32), compared to those with the lowest serum uric acid quartile (<5.2 mg/dL). Moreover, serum uric acid ≥ 7 mg/dL were significantly increased risk of ESKD (adjusted HR 5.74 with 95%CI; 1.58 to 20.8, P=0.008). Finally, every 1 mg/dL increasing of serum uric acid, eGFR would decline 2.2 mL/min per 1.73 m².

Conclusions: Serum uric acid level is an independent risk of CKD and ESKD in Thai population.

TH-PO574

Proton Pump Inhibitors Are Associated with Increased Risk of Development of Chronic Kidney Disease Pradeep Arora,^{1,2} Mojgan Golzy,³ Anu Gupta,² Rajiv Ranjan,^{1,2} Randy L. Carter,³ James W. Lohr.^{1,2} ¹Nephrology, VA Medical Center, Buffalo, NY; ²Medicine, SUNY, Buffalo, NY; ³Dept of Biostatistics, UB, Buffalo, NY.

Background: Proton pump inhibitors (PPI) are one of the common cause of acute interstitial nephritis in the United States. This frequently goes undiagnosed due to its subacute clinical presentation, which may later present as chronic kidney disease (CKD). We investigated the association of PPI use with the development of CKD and death.

Methods: The population included 99,351 patients who were seen in primary care VISN2 clinics from 4/2001 until 4/2008. For evaluation of CKD outcome, 27,835 patients with baseline CKD were excluded. Study data was obtained from Veterans Affairs Health Care Upstate New York (VISN2) network. Data obtained included use of PPI (Yes/No), age, gender, race, retrospective observation time, laboratory data including eGFR, pre-PPI comorbidity variables: vascular disease, chronic obstructive pulmonary disease (COPD), cancer, diabetes, and hypertension. A prospective logistic analysis of case-control data (Prentice and Pyke) was used to investigate the association of treatment (exposure to PPI) with onset of CKD with propensity score in the model.

Results: A total of 24,149/71,516 patients developed CKD. Of those who developed CKD 25.7% were treated with PPI. Patients receiving PPI were more likely to have vascular disease, COPD, cancer and hypertension. Of the total of 99,251 patients analyzed for mortality outcome, 36,290 died. Propensity score analysis showed higher odds for development of CKD (OR 1.29 95% CI 1.24-1.34) and mortality (OR 1.97, 95% CI 1.88-2.06) among patients taking PPIs versus those not on PPIs. Sensitivity analyses showed a significant effect of the interaction of age and PPI use in models with CKD.

variables	contrast	Odds ratio with 95% CI
PPI	Yes vs No	1.29 (1.24-1.35)
Age	1 Year Increase	1.06 (1.05-1.07)
Race	Black vs white	0.92 (0.87-0.98)
Gender	Female vs Male	0.91 (0.84-0.99)
Time	one quater increase	0.9 (0.89-0.91)
Propensity score	0.1 unit increase	0.45 (0.3-0.66)

Conclusions: Use of proton pump inhibitors are associated with increased risk of development of CKD.

TH-PO575

Influence of Statin on Iron Utilization and Metabolism in Patients with Chronic Kidney Disease Stage 3-4 Anna Masajtis-zagajewska, Michal P. Nowicki. Dept of Nephrology, Hypertension and Kidney Transplantation, Medical Univ of Lodz, Lodz, Poland.

Background: Hepcidin, an acute phase reactant protein is a key regulator of iron homeostasis. Elevated hepcidin levels are expected in the face of decreased glomerular filtration and inflammation. Hepcidin is a potentially modifiable mediator of anemia in patients with chronic kidney disease (CKD). Statins have had potent anti-inflammatory effects in experimental and clinical CKD and may thereby modulate erythropoiesis.

Methods: Thirty-six patients (17 M, 19 F, mean age 58±13 years) with stage 3 and 4 CKD and LDL cholesterol >100 mg/dl not on statin therapy were studied. In a double blind, crossover study all subjects received in a random order either atorvastatin 20 mg/day or placebo for two 6-month periods with 3-month wash-out. Basic biochemistry, serum inflammatory markers such as hsCRP, IL-6, parameters of iron metabolism including iron, serum hepcidin, Total Iron Binding Capacity (TIBC), Unsaturated IronBinding Capacity (UIBC) and hemojuvelin were measured both before and after each treatment period.

Results: TIBC and UIBC did not change during placebo phase but significantly increased after 6 months statin therapy from 255±43 to 267±45µg/dl (p=0.006) and from 186±48 to 196±50µg/dl (p=0.03), respectively. Serum iron tended to increase from 68.8±19.1µg/dl to 72.4±17.8µg/dl (p=0.08) only during statin treatment. Hemoglobin increased after 6 months statin therapy from 11.6±1.6 to 11.8±1.5g/dl (p=0.001) while after placebo period hemoglobin did not change. Hepcidin levels significantly decreased during statin treatment from 241±337 to 160±210pg/ml (p=0.01), while no effect was found during placebo phase. Hemojuvelin levels did not change after both statin and placebo. IL-6

and hsCRP tended to decrease after 6 months only after statin therapy (from 11.5±11.1 to 11.1±15.2pg/ml; p=0.06 and from 52.2±28.9 to 46.2±28.1mg/dl; p=0.06, respectively. Total and LDL-cholesterol decreased significantly only during statin treatment.

Conclusions: The treatment of CKD patients with statin may reduce inflammation and improve iron utilization through decreased serum hepcidin.

Funding: NIDDK Support

TH-PO576

CKD Prevalence and Iron Status: Are They Linked to the Etiology and Ejection Fraction in Chronic Heart Failure Jacek S. Malyszko,¹ Hanna Gajewska,² Slawomir Dobrzycki,² Jolanta Malyszko.³ ¹Ist Nephrology, Medical Univ, Poland; ²Invasive Cardiology, Medical Univ, Poland; ³2nd Nephrology, Medical Univ, Poland.

Background: Kidney disease and cardiovascular disease are tightly associated and there is a mounting evidence of inter-organ cross-talk. Anemia and iron deficiency are frequent in CKD. We performed the cross-sectional study on 273 prevalent patients and investigated a) the prevalence of chronic kidney disease in patients with heart failure due to coronary artery disease, cardiomyopathy or valvular disease undergoing percutaneous coronary interventions-PCI; b) iron status (additionally assessed using circulating soluble transferrin receptor-sTfR, hepcidin, hemojuvelin, GDF-15) in these 3 subpopulations in regard to kidney function.

Methods: GFR was estimated by MDRD formula. sTfR, hepcidin, hemojuvelin, GDF-15 were studied using commercially available kits.

Results: Prevalence of CKD (stage 3 or more) was the highest in in valvular disease (34%), the lowest in coronary artery disease (23%). According to the WHO definition, the prevalence of anemia in the studied cohort was 23.1%. We observed a progressive decline in GFR and hemoglobin concentration together with a rise in NYHA class in the whole cohort. Iron deficiency and anemia were the most often found in patients with heart failure due to coronary artery disease, with the highest hepcidin and GDF15 levels, and highest eGFR. Anemic patients had worse kidney function, except valvular disease subgroup relative to non-anemics. In the latter serum hepcidin was the lowest. Iron status in heart failure was related to the etiology of this clinical setting, but not to kidney function. However, when divided into groups with preserved or reduced ejection fraction-EF, CKD, anemia and iron deficiency was more prevalent in patients with worse ejection fraction. Significant correlations were observed between eGFR and age, NYHA class, hepcidin, GDF-15.

Conclusions: The prevalence of anemia and chronic kidney disease is high and depends on the etiology of heart failure and EF in patients undergoing PCI. Hemodynamic changes and subclinical inflammation seems to play a major role in altered iron status and impaired kidney function in heart failure.

Funding: Government Support - Non-U.S.

TH-PO577

Hormone Replacement Therapy in Post-Menopausal Women Is Associated with Better Kidney Function Andrea G. Kattah,¹ Bradley R. Lewis,² Stephen T. Turner,¹ Vesna D. Garovic.¹ ¹Div of Nephrology and Hypertension, Mayo Clinic; ²Health Sciences Research, Mayo Clinic, Rochester, MN.

Background: The effect of hormone replacement therapy (HRT) on renal function in post-menopausal women is unclear. Experimental models suggest estrogen has a renoprotective effect, but human studies have had variable results.

Methods: We performed a cross-sectional study on 2217 post-menopausal women who participated in the Family Blood Pressure Program, a multi-network study aimed at studying the genetics of hypertension. We compared markers of renal function, including urine albumin/creatinine ratio (UACR) and estimated glomerular filtration (eGFR) using the CKD-EPI equation, between women who were using HRT (n=673, median age 60.2) and those who were not (n=1544, median age 62.9). Clinical characteristics, including body mass index (BMI), medical history, medications, family history and blood and urine tests were measured at a single study visit conducted between 2000-2004.

Results: UACR was significantly lower in those on HRT versus those who were not (3.5 vs. 5.2 mg/g Cr, p<0.001), as was the number of women with eGFR < 60 ml/min/1.73 m² (7% vs. 10%, p=0.003). We performed linear and logistic regression models using generalized estimating equations for log(UACR), UACR > 25 mg/g Cr and eGFR < 60 ml/min/1.73 m² and adjusted for age, race, network, education, smoking, diabetes, hypertension, family history of hypertension, log(BMI), log(HDL), log(LDL) and log(triglycerides). After adjusting for these factors, we found that the use of HRT was still significantly associated with lower log(UACR) (-0.307, p<0.001) and women not on HRT had an odds of 1.6 (95% CI 1.2-2.3) times that of those on HRT of having UACR > 25 mg/g Cr. The association between HRT and eGFR < 60 ml/min/1.73m² was no longer significant after adjustment.

Conclusions: The use of HRT in post-menopausal women was associated with lower UACR after adjusting for known risk factors for renal and cardiovascular disease. Strengths of our study include a large sample size and a comprehensive medical history of subjects. Limitations include that subjects were recruited on the basis of hypertension and that we had limited information on the length of time on HRT.

TH-PO578

Tobacco Smoking and Progression of Chronic Kidney Disease: A Role for Reactive Aldehydes? Gabriel Rezonzew,¹ Phillip H. Chumley,¹ Wenguang Feng,¹ Ping Hua,¹ Huma Fatima,¹ Edgar A. Jaimes.² ¹Univ of Alabama at Birmingham; ²Memorial Sloan Kettering Cancer Center.

Background: Clinical and experimental evidence supports the role of tobacco smoking as a risk factor in the progression of chronic kidney disease (CKD) of different etiologies. Cigarette smoke (CS) contains numerous compounds that could be responsible for the deleterious effects of tobacco smoking. Among these compounds are included large concentrations of reactive aldehydes such as acrolein that react with thiol groups and active NADPH oxidase as we have previously shown (ATVB'04). In these studies we postulated the hypothesis that acrolein (Acr) accelerates the progression of CKD and that these effects are linked to increased oxidative stress.

Methods: Sprague-Dawley rats (n=6-8) rats were divided in the following groups: Sham, Sham+Acr (0.5 mg/kg/day via osmotic minipump), 5/6Nx and 5/6Nx+Acr. Rats were euthanized after 12 weeks and kidneys saved for glomerular injury score (GIS) and tubular injury score (TIS). Urine was collected every two weeks for proteinuria (Bio-Rad). Urinary isoprostanes and TGF-β were measured by Elisa and adjusted for urinary creatinine.

Results: Sham rats on Acr had a significant increase in proteinuria, urinary excretion of isoprostanes and TGF-β, TIS but not GIS. Rats with 5/6Nx had a significant increase in proteinuria, TIS and GIS and a modest increase in TGF-β. The administration of Acr to 5/6Nx resulted in further increases in proteinuria, isoprostanes and TIS but not GIS. The urinary excretion of TGF-β in these rats was also increased and similar to Sham+Acr.

	Sham	Sham+Acr	5/6Nx	5/6Nx+Acr
Proteinuria (mg/24 hours)	51.1± 9.8	122.4± 10.2*	122.7± 13.6*	420.5± 98.5**
Isoprostanes (pg/mg creatinine)	61.4± 10	164.5± 32.4*	51.5± 20	336.5± 126.7**
TIS	2.9± 0.6	6.5± 1.2*	8.26± 2.1*	15.1± 2.5**
GIS	0	0.1± 0.1	36± 22*	36± 20*
TGF-β (pg/mg creatinine)	5.3± 1.8	50.1± 16.7*	10.7± 4.	51.5± 28.1**

* P < 0.05 vs Sham, # P < 0.05 vs 5/6Nx (N=6-8)

Conclusions: These studies suggest that the reactive aldehyde acrolein plays a role as mediator of the deleterious effects of tobacco smoking in the progression of CKD.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

TH-PO579

Intermittent Smoking Associates with Chronic Kidney Disease in U.S. Hispanics: The Hispanic Community Health Study/ the Study of Latinos (HCHS/SOL) Nora Franceschini. *Epidemiology, Univ of North Carolina, Chapel Hill, NC.*

Background: Cumulative smoking exposure is associated with chronic kidney disease (CKD). However, the patterns of exposure, such as the effect of intermittent smoking, on CKD risk are unknown. These patterns may be important given the recent increase in alternative smoking exposures such as e-cigarettes.

Methods: Cross-sectional study of 15,664 participants of a population-based cohort of Hispanic/Latinos aged 18-74 years recruited from four U.S. field centers from 2008 to 2011. Data on current, past and never smoking, and smoking pack-years were obtained through a questionnaire. The association between smoking exposure and CKD (estimated glomerular filtration rate <60 ml/min/1.73 m² or urine albumin to creatinine ratio ≥ 30 mg/g) was estimated using logistic regression models. We tested the interaction between smoking status and cumulative pack-years at the significance level of 0.05.

Results: Approximately 62% individuals were non-smokers, 17% were past smokers and 22% were current smokers, of which 14% were daily smokers and 8% were intermittent smokers. The adjusted prevalence estimates of CKD were 10% for non-smokers, 11% for past smokers, 8% for daily smokers and 12% for intermittent smokers. There was a significant interaction between smoking status with pack-years of exposure (p=0.0002). In adjusted models accounting for this interaction, there were increased odds of CKD among current daily, intermittent, and past smokers by pack-years compared to never smokers. The association of intermittent smokers with CKD was significant at 10 pack-years of smoking, whereas for daily smokers, it was observed only at 40 pack-years of smoking. Past smokers had a 20% increased odds of CKD compared with non-smokers across pack-years of smoking.

Conclusions: This study demonstrates significant effects of current daily and intermittent smoking on prevalent CKD among Hispanic/Latinos, which was significant at lower pack-years of exposure among intermittent smokers. Our research support efforts to aggressively eliminate smoking exposure through public health interventions and extend these current recommendations to prevention of CKD.

Funding: Other NIH Support - R21HL123677, R01ES021367, R01HL118305-01A1

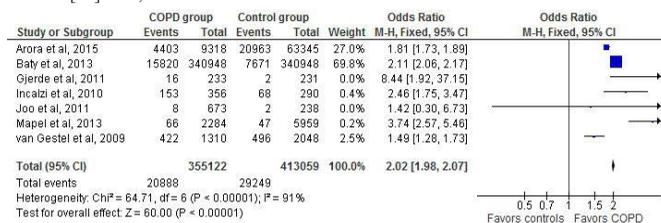
TH-PO580

Incidence of Chronic Kidney Disease in Patients with COPD: Systematic Review and Meta-Analysis Swarna Gouddam,¹ Sameer K. Gunukula,¹ James W. Lohr,² Nader Nader,³ Pradeep Arora.² ¹Medicine, SUNY at Buffalo, Buffalo, NY; ²Medicine, VAMC, Buffalo, NY; ³Anesthesiology, VAMC, Buffalo, NY.

Background: Chronic obstructive pulmonary disease (COPD) is common disease especially in elderly population, and is an important cause of mortality world-wide. Several studies have identified COPD as part of a systemic inflammatory syndrome and reported on the association of comorbidities like lung cancer, osteoporosis, progression of atherosclerosis. However, the relationship between COPD and incidence of chronic kidney disease (CKD) has not been clearly demonstrated in the literature. The focus of our study was to systematically review the medical literature reporting the incidence of renal function disturbances specifically incidence of CKD in patients with COPD.

Methods: We conducted a systematic review using the Cochrane Collaboration Methodology. We searched Medline via Ovid, Pubmed, Embase and ISI web of Science databases from 1950 through 2015. We rated the quality of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Meta-analysis was done using Review Manager Version 5.0.20.

Results: Our search resulted in 8 eligible studies. COPD was found to be associated with a significantly increased incidence of CKD (Odds Ratio [OR]=2.10; 95% Confidence Interval [CI] 2.04, 2.16.



Conclusions: COPD patients are at increased risk of developing chronic kidney disease. The exact reasons for the increase in the incidence of CKD are unclear. Clinical research and practice guidelines usually target disease conditions in isolation. Research into COPD and CKD is scant and there is a need for further studies to delve into the pathophysiological mechanisms and clinical implications of incidence of CKD in patients with COPD.

TH-PO581

Effects of Nicotine on the Severity of Diabetic Nephropathy: Role of α7-Nicotine Receptor Mohammed Siddiqui,¹ Wenguang Feng,¹ Gabriel Rezonzew,¹ Lawrence P. Wennogle,² Edgar A. Jaimes.³ ¹Univ of Alabama at Birmingham; ²Intra-cellular Therapies; ³Memorial Sloan Kettering Cancer Center.

Background: Tobacco smoking plays a major role in progression of chronic kidney disease (CKD) of different etiologies including diabetes mellitus (DM). In previous studies we demonstrated that nicotine is responsible for deleterious effects of smoking in the progression of CKD and pharmacologic blockade of the α7 nicotine receptor subunit (α7-nAChR) reduces the effects of nicotine in a CKD rat model. Whether this receptor also plays a role in the progression of other models of CKD such as diabetic nephropathy is not known.

Methods: DM was induced with streptozotocin (STZ) in eNOS^{-/-} and eNOS^{-/-}/α7-nAChR^{-/-} (DKO) mice. A separate group of eNOS^{-/-} mice also received an α7-nAChR blocker (IC200610, 2 mg/kg IP, 5 days a week for 10 weeks). Mice were given nicotine (100mg/ml in drinking water) or tap water for 10 weeks. Blood pressure (BP) was measured by tail-cuff method and urine collected every 2 weeks for albuminuria.

Results: All mice became diabetic after STZ and had no significant differences in weight or blood glucose at sacrifice. All animals were also hypertensive and nicotine had no effect on BP in any of the groups. Diabetic mice receiving nicotine (DN) had higher albumin excretion as compared to diabetic mice on tap water (DT). Diabetic mice on nicotine lacking the α7-nAChR (DN^{-/-}) or with pharmacologic blockade (DN+B) had urinary excretions of albumin similar to diabetics on tap water (DT). Neither absence of the α7-nAChR (DT^{-/-}) nor pharmacologic blockade (DT+B) had any effect on mice on tap water.

	DN (n=13)	DT (n=10)	DN ^{-/-} (n=9)	DT ^{-/-} (n=12)	DN+B (n=8)	DT+B (n=7)
Body Weight (gm)	26± 1.0	22± 0.9	25± 1.9	23± 0.5	25± 0.5	26± 1.1
Blood Glucose (mg/dL)	442± 48	542± 17	479± 41	516± 26	441± 43	354± 51
Albuminuria (ng/24 hr)	103± 25*	71± 8	42± 14	46± 7	35± 6	50± 13
Systolic BP (mm Hg)	153± 6	147± 6	153± 5	147± 4	142± 13	150± 11

* p<0.05 vs other groups.

Conclusions: These studies demonstrate that α7-nAChR is a critical mediator of the deleterious effects of nicotine in the severity of diabetic nephropathy.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

TH-PO582

Lithium Nephropathy: A Long-Term Complication of Chronic Lithium Therapy

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Background: Lithium is the treatment of choice for bipolar disorder. Lithium-induced nephropathy is a known complication limiting its use. The aim of this study is to establish the prevalence of renal failure in our population. We sought to quantify the contribution of lithium therapy to the risk of developing renal failure.

Methods: We selected 1751 patients on lithium therapy from the laboratory database of the Delta Center for Mental Health Care, Rotterdam. The database contains measurements of lithium and creatinine concentration over a period from 2000 to 2011. eGFR was calculated using the 4-variable MDRD formula. Renal failure was defined as having GFR <60mL/min on at least 2 measurements 6 weeks apart. A comparison was made between patients with and without renal insufficiency regarding gender, mean lithium concentration in serum, lithium intoxication, duration of therapy, age at initiation of therapy, cardiovascular disease, hypertension and diabetes mellitus.

Results: 305 out of 1751 (17.4%) patients were classified as having renal failure. Occurrence of renal failure was positively correlated with female sex, age at initiation of therapy and duration of lithium therapy ($p < 0.001$). Significant correlation was also observed between renal failure and cardiovascular risk factors. Mean lithium serum concentration was 0.68 mmol/l and did not differ between patients with and without renal failure. In 251 patients follow up data was available for a period of more than 10 years. In these patients history of lithium intoxication did not predict occurrence of renal failure.

Conclusions: Prevalence of renal failure in our cohort is similar to other reports. Longer duration of lithium therapy was found to be associated with an increased risk of renal failure. Contrary to our expectation, lithium intoxication was not correlated with renal failure. Although therapy duration was a significant predictor, one should not forget the importance of cardiovascular risk factors in development of renal failure.

TH-PO583

Study of Organochlorine Pesticides in Patients with Chronic Kidney Disease of Unknown Etiology

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Background: An apparently new form of CKD not attributable to diabetes, hypertension or other known causes, i.e. CKD of unknown etiology (CKDu) has emerged in south Asia, especially Sri Lanka, and Sub-Saharan Africa in the last one decade. CKDu affects younger individuals and is asymptomatic until advanced stages. Organochlorine pesticides (OCPs) are implicated in the etiopathogenesis of CKDu. This study aimed at estimating the serum level of various OCPs (α -HCH, β -HCH, γ -HCH, total HCH, Aldrin, Dieldrin, α -endosulfan, β -endosulfan, p,p'-DDT, p,p'-DDE) and total pesticide load (TPL) in patients with CKDu in comparison with patients with CKD of known etiology (CKDk) and to assess their role in etiopathogenesis of CKDu.

Methods: This was a case-control, cross-sectional study conducted in east Delhi. Subjects in the age group 18-60 years of either sex were recruited under 3 groups: Group I: Healthy controls (n=30), Group II: Patients with CKDu (n=30) and Group III: Patients with CKDk (n=30). Detailed history, physical examination, routine investigations and urinary protein excretion estimation were done. Serum OCP levels were estimated by high performance liquid chromatography.

Results: The median serum levels of all OCPs were higher in patients of group II as compared to other study groups and this difference was statistically significant for α -HCH, β -HCH, total HCH, α -endosulfan, p,p'-DDE and TPL. For the same CKD stage, CKDu patients had higher levels of TPL as compared to CKDk patients. Mean blood urea and serum creatinine levels were higher in patients of group II. Significantly greater proportion (66.34%) of CKDu patients had stage V CKD as compared to CKDk patients. CKDu patients had higher urinary protein excretion as compared to CKDk patients though this was statistically insignificant.

Conclusions: Despite some limitations of the study, the presence of higher serum OCPs in individuals with CKDu in comparison to CKDk at corresponding CKD stages suggests their possible role in the etiopathogenesis of CKDu.

Funding: Government Support - Non-U.S.

TH-PO584

Chronic Kidney Disease After Intravenous Colistin Use in Survivors of Severe Infections

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Background: The resurgence of colistin use for multidrug-resistant (MDR) infections has led to an increase of colistin-associated acute kidney injury (AKI). Nevertheless, long-term renal prognosis information is scarce.

Methods: A retrospective cohort study was performed from January 2011 to March 2015. Patients who received colistin for >5 days were included. We excluded cases with CKD, history of kidney transplant, and non-survivors to MDR infection. The primary outcome was the development of CKD after colistin treatment. CKD was defined as eGFR <60mL/1.73m² and/or proteinuria during ³ months.

Results: In all, 132 patients received colistin, of them, 50 (40%) died due to MDR infection. During a median follow-up of 2.1 years (interquartile range [IQR]: 1.2-3.1) in 82 survivors, 28 (35%) progressed to CKD (stage 3: 25, stage 4: 2, and stage 5: 1). Mild AKI occurred in 29 patients during colistin treatment, one patient needed dialysis and 22

progressed to CKD. Independent predictors of colistin-associated progression to CKD in a logistic regression analysis were AKI (odds ratio [OR]: 32.0; 95% confidence interval [CI]: 6.0-87.0), colistin cumulative dose >5 g (OR: 16.0, 95% CI: 2.6-95.0), and age (OR: 1.1, 95% CI: 1.0-1.05).

Conclusions: Patients treated with intravenous colistin had a substantial risk for CKD. Therefore, they should be tightly monitored when cumulative dose is >5 g and AKI is identified.

Table1. Bivariate analyses on factors associated with progression to CKD

Characteristic	Patients without progression to CKD (n=54)	Patients with progression to CKD (n=28)	p value
Age, y (IQR)	38 (25-54)	59 (25-72)	0.024
Male gender, n (%)	25 (47)	15 (53)	0.580
Baseline SCr, mg/dL (IQR)	0.6 (0.5-0.7)	0.7 (0.5-0.9)	0.200
SOFA, score (IQR)	4 (2-5)	4 (3-5)	0.420
Colistin dose, mg/kg	4 (4-5)	4 (3-5)	0.290
Diabetes, n (%)	3 (6)	6 (21)	0.058
AKI, n (%)*	7 (13)	22 (78)	0.001
Colistin cumulative dose, g (IQR)	3.8 (2.1-4.9)	6 (3.9-8.4)	0.001
Final eGFR, mL/min/1.73m ² (IQR)	101 (72-130)	55 (37-64)	0.001

*According to KDIGO

TH-PO585

High-Density Lipoprotein Subfractions and Their Oxidized Subfraction Particles in Patients with Chronic Kidney Disease

Hirokazu Honda,¹ Tsutomu Hirano,² Masashi Ueda,³ Shioh Kojima,³ Shinichi Mashiba,³ Yasuyuki Hayase,³ Tetsuo Michihata,⁴ Takanori Shibata.⁵ *¹Div of Nephrology, Dept of Medicine, Showa Univ Koto Toyosu Hospital, Tokyo, Japan; ²Div of Diabetes, Metabolism, and Endocrinology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan; ³Igakaku Co. Ltd., Kyoto, Japan; ⁴Ebara Clinic, Tokyo, Japan; ⁵Div of Nephrology, Dept of Medicine, Showa Univ school of Medicine, Tokyo, Japan.*

Background: Chronic kidney disease (CKD) may lead to reduced concentrations of high-density lipoprotein (HDL) and its subfractions (HDL2 and HDL3), and damage them via inflammation and oxidative stress. The present study aimed to determine the contribution of such changes to cardiovascular disease (CVD) in patients with CKD.

Methods: Levels of total cholesterol, low-density lipoprotein cholesterol, HDL-C, HDL2, HDL3, apolipoproteins, malondialdehyde-modified LDL (MDA-LDL), oxidized (ox) HDL, oxHDL2 and oxHDL3 were measured in blood samples from patients with CKD (stages 2-5, n = 86) who were not on dialysis and from patients undergoing hemodialysis (CKD stage 5D, n = 25). The patients were followed up for 28 ± 9 months after baseline examinations and CVD events were recorded.

Results: Levels of HDL3 and ApoA1 in HDL3 fraction decreased according to CKD severity, whereas those of HDL2 and ApoA1 in HDL2 fraction did not differ. Levels of oxHDL were similar across CKD stages. Levels of oxHDL3 and MDA-LDL were decreased, whereas those of oxHDL2 increased according to CKD severity. Multivariate analyses using the Cox proportional hazards model selected high levels of oxHDL and its subfractions, and those adjusted with HDL-C and HDL subfractions or ApoA1 in HDL fractions respectively, compared with HDL-C and HDL subfractions or ApoA1 in HDL fractions alone as independent risk factors for CVD events.

Conclusions: Levels of HDL subfractions and their oxidized subfraction particles differed among patients with CKD. Increasing levels of oxHDL subfractions might cause a high frequency of CVD events in those patients.

TH-PO586

The Relevance of Systolic Blood Pressure to Vascular Disease in Chronic Kidney Disease Patients with and without Vascular Disease: Observations from the Study of Heart and Renal Protection (SHARP)

Parminder K. Judge, William G. Herrington. *On behalf of the SHARP Collaborative Group. CTSU, Univ of Oxford.*

Background: Confounding by prior disease may distort associations between systolic blood pressure (SBP) and disease outcomes in people with chronic kidney disease (CKD), causing uncertainty about the effect of low SBP on vascular risk in advanced CKD. Measurement of troponin may allow confounding by subclinical cardiac disease to be reduced.

Methods: SHARP randomized 9270 people with CKD. Over 5 years, SBP and clinical outcomes were recorded at baseline and at 6 monthly intervals. Cox regression, adjusted for relevant confounders, was used to assess the relevance of usual SBP to vascular outcomes. Analyses were stratified by baseline vascular disease (defined as self-reported vascular disease or troponin-I >0.01 ng/mL).

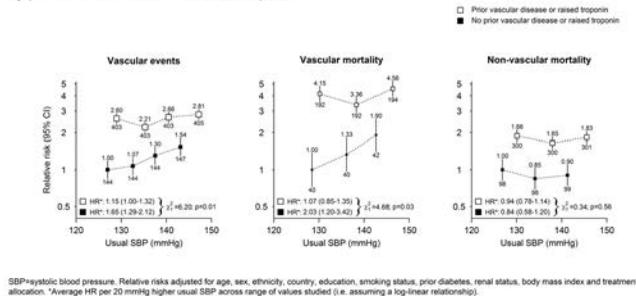
Results: Overall, there was a "U"-shaped association between usual SBP and vascular risk. Among the 4075 participants without baseline vascular disease, there was a log-linear

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

association: each 20 mmHg higher usual SBP was associated with an average 65% increase in risk of vascular events (adjusted hazard ratio [HR] 1.65, 95% confidence interval 1.29-2.12) and 2-fold increased risk of vascular death (HR 2.03, 1.20-3.42). By contrast, among the 4603 participants with baseline vascular disease, the associations between usual SBP and vascular events (HR 1.15, 1.00-1.32; p for heterogeneity=0.01) and vascular death (HR 1.07, 0.85-1.35; p for heterogeneity=0.03) were significantly weaker. There was no clear association between usual SBP and non-vascular mortality (HR 0.96, 0.82-1.13), irrespective of history of prior vascular disease.

Figure: Relevance of systolic blood pressure to vascular events and cause-specific mortality, by prior vascular disease or raised troponin



SBP=systolic blood pressure. Relative risks adjusted for age, sex, ethnicity, country, education, smoking status, prior diabetes, renal status, body mass index and treatment allocation. *Average HR per 20 mmHg higher usual SBP across range of values studied (i.e. assuming a log-linear relationship).

Conclusions: In CKD, the “U”-shaped relationship between usual SBP and vascular risk appears to be explained by confounding by vascular disease. Trials to assess the effect of lower than currently recommended SBP targets are indicated.

Funding: Pharmaceutical Company Support - Merck/Schering-Plough Pharmaceuticals(North Wales,PA,USA), Government Support - Non-U.S.

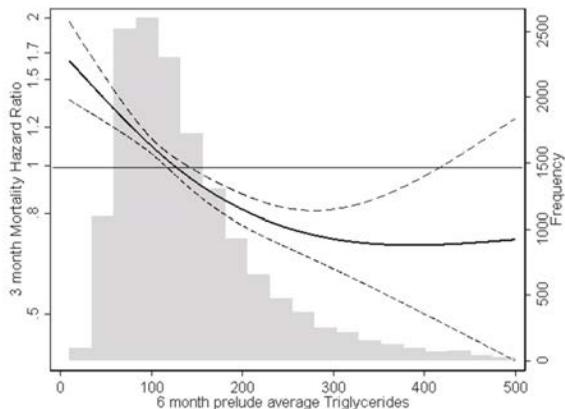
TH-PO587

Serum Triglyceride Levels during Progression to ESRD and Early Dialysis Mortality among U.S. Veterans: A Transition of Care in CKD Study Elani Streja,¹ Melissa Soohoo,¹ Connie Rhee,¹ Yoshitsugu Obi,¹ Jennie Jing,¹ Danh V. Nguyen,¹ Moti L. Kashyap,^{1,2} Csaba P. Kovcsdy,³ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC; ³VA Long Beach.

Background: High triglyceride (TG) levels are an established cardiovascular risk factor in the general population. In a study of non-dialysis dependent chronic kidney disease, higher TG levels (<200 mg/dL) were associated with higher mortality risk, whereas other data show that patients with low TG levels (<115 mg/dL) have even higher mortality risk. The impact of TG levels in the prelude period immediately preceding transition to dialysis on early post-transition outcomes is not known.

Methods: In a cohort of 52,172 US veterans who transitioned to dialysis between October 2007 and September 2011, we identified 15,345 patients with available TG measurements within the last 6 month prelude period (preceding dialysis transition). We examined the association of TG (averaged over 6 months) as a continuous predictor of early all-cause mortality (within the first 3 months post-transition), using restricted cubic spline analysis and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region of residence.

Results: The mean±SD age was 69±11 years, among whom 27% were African-American, 7% were of Hispanic, and 51% had diabetes listed as their primary cause of ESRD. The 6-month averaged prelude TG showed an inverse linear association with post ESRD mortality risk, in which patients with TG<115mg/dL had a higher risk of mortality and patients with TG>115mg/dL had comparatively better survival.



Conclusions: Among veterans transitioning to dialysis, higher TG levels were associated with lower risk of early post-ESRD mortality. Further studies are needed to investigate underlying mechanisms and to determine how lipid-modulating treatments influence these associations.

Funding: NIDDK Support

TH-PO588

Initiation of Statins for Chronic Kidney Disease Patients in the Veterans Affairs Health System Sai Hurrish Dharmarajan,¹ Rajesh Balkrishnan,⁴ Kara Zivin,¹ Tanushree Banerjee,² Neil R. Powe,³ Nilka Rios Burrows,³ Rajiv Saran,¹ Sundar Shrestha.³ ¹Univ of Michigan, Ann Arbor, MI; ²Univ of California, San Francisco, CA; ³Centers for Disease Control and Prevention, Atlanta, GA; ⁴Univ of Virginia, Charlottesville, VA.

Background: The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend cholesterol-lowering treatment with statins for Chronic Kidney Disease (CKD) patients aged 50 years or older, and those aged 30-49 years with elevated risk of cardiovascular disease (CVD). We investigated the predictors of statin initiation in a cohort of CKD patients in the Veterans Affairs Health System between 2010 and 2012.

Methods: Our sample included patients with at least one outpatient visit with a serum creatinine value in 2010 or 2011. Patients were categorized into five stages of increasing severity based on estimated glomerular filtration rate (eGFR). A cohort of these patients not using statins in the baseline year (2010 or 2011) were identified and followed in the subsequent year (2011 or 2012) to determine statin initiation. A multivariate logistic regression model was used to examine the socio-demographic and comorbidity related predictors of statin initiation.

Results: Our sample included 1,676,215 patients in 2010 and 1,778,655 patients in 2011. Of these, 8.77% in 2010 and 9.48% in 2011 initiated statins in the subsequent year. The most significant predictors of statin initiation were diagnosis of CVD in the prior year (adjusted Odds Ratio-aOR: 2.46, 95% CI: 2.43–2.49) and diabetes mellitus (aOR: 1.94, CI: 1.92–1.95). Using patients with eGFR>90ml/min/1.73m² (Stage 1) as reference, CKD Stage 3 patients had a higher odds (aOR: 1.24, CI: 1.23–1.26) of statin initiation, in comparison to stage 4 (aOR: 0.87, CI: 0.83–0.91) and stage 5 (aOR: 0.33; CI: 0.29–0.38) patients.

Conclusions: CVD and diabetes were the most influential predictors of statin initiation in CKD patients in a large cohort of U.S. Veterans. Statin initiation appeared to be lowest in patients with CKD Stage 4 and 5. Future research will consider adherence to statin prescription and its association with CKD progression.

Funding: Other U.S. Government Support

TH-PO589

Association of Urine Kidney Injury Biomarkers with Risk of Cardiovascular Events in CRIC Meyeon Park,¹ Chi-yuan Hsu,¹ Alan S. Go,² Dawei Xie,³ Xiaoming Zhang,³ Sushrut S. Waikar,⁴ Joseph V. Bonventre,⁴ Josef Coresh,⁵ Robert G. Nelson,⁶ Harold I. Feldman,³ Paul L. Kimmel,⁶ Vasani S. Ramachandran,⁷ Kathleen D. Liu.¹ ¹UCSF; ²Kaiser Permanente; ³U. of Pennsylvania; ⁴Brigham and Women's Hospital; ⁵Johns Hopkins Univ; ⁶NH NIDDK; ⁷Boston Univ.

Background: Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease (CVD). We investigated whether kidney injury biomarkers were associated with increased risk of atherosclerotic and non-atherosclerotic CVD events in the Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: Urine kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), and liver fatty acid-binding protein (LFABP) were measured in 2466 CRIC subjects in CRIC. Cox proportional hazards models were used to examine the associations between biomarkers indexed to urinary creatinine and heart failure (HF) or a composite of CVD events (myocardial infarction, ischemic stroke, or peripheral artery disease).

Results: Mean age of study subjects was 59.5 (± 10.8) years; 46% were women, 50% had diabetes mellitus, and 34% had history of cardiovascular disease. NGAL/Cr, NAG/Cr and LFABP/Cr were associated with HF and CV events in unadjusted models, but not in multivariable adjusted models (accounting for baseline eGFR, albuminuria, age, sex, race, comorbidities, and medications). Those in the highest two quintiles [Q5 (>2990.3 pg/g) and Q4 (>1830.9 pg/g)] of KIM-1/Cr levels had an increased risk of HF relative to the lowest quintile (Q1, <661.3 pg/g) [Q5 v. Q1 hazard ratio (HR) 1.7 (1.1-2.9); Q4 v. Q1 HR 1.6 (1.0-2.6)]. KIM-1/Cr was not independently associated with HF in the continuous analysis [HR per log SD increase 1.14 (0.98-1.33)]. Higher KIM-1/Cr was independently associated with CVD events in the continuous analysis [HR per log SD increase 1.21 (1.02-1.41)] after adjustment for confounders.

Conclusions: Select urine biomarkers of kidney injury were independently associated with increased risk of HF and CVD events.

Funding: NIDDK Support

TH-PO590

Cystatin C as a Predictor for Mortality in Elderly Patients with Chronic Kidney Disease Sebastian Bevc,¹ Nina Hojs,¹ Masa Knehtl,¹ Robert Ekart,² Radovan Hojs.¹ ¹Clinic for Internal Medicine, Dept of Nephrology, Univ Clinical Centre Maribor, Slovenia; ²Clinic for Internal Medicine, Dept of Dialysis, Univ Clinical Centre Maribor, Slovenia.

Background: The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum cystatin C, an accurate marker of estimation of kidney function have also prognostic utility in CKD patients. The aim of our study was to determine the prediction for mortality of different markers for estimation of kidney function on long-term survival in elderly CKD patients.

Methods: 103 adult Caucasian patients, older than 65 years (56 women, 47 men; mean age 72.5 years; range from 65 to 86 years), were included. In each patient

⁵¹CrEDTA clearance, serum creatinine (IDMS traceable method), serum cystatin C (immunonephelometric method) and eGFR using the CKD-EPI creatinine formula were determined on the same day and then followed for 10 years or until patient's death.

Results: The mean ⁵¹CrEDTA clearance was 52.2±15.9 ml/min/1.73m², mean serum creatinine 142.1±41.9 μmol/l, mean serum cystatin C 1.79±0.6 mg/l, CKD-EPI creatinine formula 39.7±12.9 ml/min/1.73m², respectively. In the follow up period of 10 years 60 (61.2%) of our elderly CKD patients (32 men and 28 women) died. Cox regression analysis showed different hazard ratios (HR): for ⁵¹CrEDTA clearance HR 0.963 (95% CI 0.592-0.778; P=0.015), serum creatinine HR 1.012 (95% CI 1.007-1.018; P=0.0001), serum cystatin C HR 1.611 (95% CI 1.234-2.105; P=0.0001), CKD-EPI creatinine formula HR 0.957 (95% CI 0.933-0.981; P=0.0001).

Conclusions: Our results indicate that serum cystatin C values at the beginning of follow-up are better in predicting the outcome of elderly CKD patients than other markers for estimation of kidney function.

TH-PO591

The Relationship Between Neutrophil to Lymphocyte Ratio and Cardiovascular Disease in Patients with Chronic Kidney Disease Dede Sit, Hasan Kayabasi, Emel Gokmen, Zehra Sucuoglu, Serhat Sigirci, Suleyman Yildirim, Bennur Esen, Saadet Pilten guzel. *Bagcilar Training & Research Hospital, Istanbul, Turkey.*

Background: Neutrophil to lymphocyte ratio (NLR) is a new, widely-easily available, inexpensive marker calculated from complete blood count is a new addition to the inflammatory markers. In many studies it has been established that NLR is associated with CVD. In this study we evaluated the relationship between NLR and CVD in patients with predialysis CKD.

Methods: In total 172 predialysis CKD patients who were undergone coronary angiography for CAD where studied. GFR of all patients were calculated using MDRD formula, and according to eGFR, the patients were divided into stage 1-5 CKD via K/DOQI guidelines. The patients were divided into two groups as angiography positive and negative group for coronary artery disease. Demographic, biochemical, hematological parameters and NLR of patients were compared.

Results: The mean age of patients was 65.06±10.53 years, 119 were male, and 53 were female. According to eGFR 16 were stage 1, 75 were stage 2, 46 were stage 3, 17 were stage 4 and 18 were stage 5. There was a statistically significant difference in NLR between two groups. In patients with CAD NLR was higher than in patients without CAD (p<0.01). All parameters of patients were detailed in table 1.

	CAD		
	No	Yes	P
Calcium	9,09±0,73	8,6±0,65	0,002
Phosphorus	3,93±1,39	3,79±1,42	0,415
CaxP	35,63±12,37	32,69±12,14	0,195
PTH	156,45±144,7	328,87±476,18	0,238
Albumin	4,05±0,63	3,66±0,5	0,002
CRP	32,26±40,16	42,49±48,58	0,348
Spot Protein/ Creatinin	815,57±1644,7	1501,05±2284,78	0,043
Neutrophil/ Lymphocyte	4,14±4,49	8,46±11,4	0,001

Conclusions: In many studies, NLR is reported as an independent predictor of outcome in coronary artery disease, as well as a predictor of short- and long-term mortality in patients with CVD. We found that NLR is significantly higher among CKD patients with CAD, thus we suggest that it may be used as a new marker to investigate CAD and its results in CKD population.

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TH-PO592

Change in Skin Autofluorescence Over One Year Predicts Mortality at Five Years in a Prospective Cohort of People with Chronic Kidney Disease Stage 3 Adam Shardlow,^{1,2} Natasha Juliette McIntyre,¹ Richard J. Fluck,¹ Christopher W. McIntyre,³ Maarten W. Taal.^{1,2} ¹Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; ²Faculty of Medicine and Health Sciences, Univ of Nottingham, Nottingham, United Kingdom; ³London Health Sciences Centre, London, ON, Canada.

Background: Tissue advanced glycation end product (AGE) accumulation is a marker of cumulative metabolic stress assessed by a simple non-invasive measurement of skin autofluorescence (SAF). This has been shown to predict mortality in haemodialysis patients and in earlier CKD in some studies, but the impact of change in SAF over time has not previously been reported. In this study we sought to investigate the associations of SAF and change in SAF over time with mortality in people with CKD stage 3.

Methods: 1741 people with CKD 3 (confirmed by two eGFR values) were recruited from primary care. Participants attended for baseline, year 1 and year 5 study visits and underwent clinical assessment, blood and serum biochemistry. SAF was recorded at each visit. Dates of death were collected from hospital and national records.

Results: At baseline mean eGFR was 53.5 ml/min/1.73m², mean age 73 years and mean SAF 2.7 arbitrary units. There was a small decrease in mean SAF after 1 year (-0.1 arbitrary units; p<0.001) but 310 (20.1%) participants evidenced an increase of >10%. 299 (17.2%) participants died prior to the year 5 study visit. Cox proportional hazards showed that both baseline SAF (HR 1.38) and change in SAF (HR 1.53) over the first year were independent determinants of mortality at 5 years in addition to age (HR 1.77), male gender (HR 1.53), baseline eGFR (HR 0.98) and previous cardiovascular disease (HR=1.56). In a sensitivity analysis of participants without diabetes, change in SAF at 1 year remained an independent determinant of mortality (HR 1.5), adjusted for age, gender, baseline eGFR, previous cardiovascular disease and baseline SAF.

Conclusions: Our data show for the first time that an increase in SAF over 1 year is an independent predictor of mortality in CKD stage 3 in addition to baseline SAF. Serial measures of SAF may therefore be useful in predicting risk and monitoring interventions for reducing AGE accumulation.

Funding: Private Foundation Support

TH-PO593

Fibroblast Growth Factor 21 Plasma Levels and Future Cardiovascular Outcome Among Non-Dialysis Chronic Kidney Disease Patients Lucie Bauer,¹ Kyryll S. Rogacev,¹ Adam M. Zawada,¹ Sarah Seiler,¹ Insa E. Emrich,¹ Kevin L. Duffin,² James R. Voelker,² Matthew D. Breyer,² Danilo Fliser,¹ Gunnar H. Heine.¹ ¹Internal Medicine IV - Nephrology and Hypertension, Saarland Univ Medical Center and Saarland Univ Faculty of Medicine, Homburg, Saarland, Germany; ²Eli Lilly and Company, Indianapolis, IN.

Background: Patients with chronic kidney disease have substantial metabolic alterations, which comprise insulin resistance, hypertriglyceridemia and low HDL-cholesterolemia. Fibroblast Growth Factor 21 (FGF-21) is a recently discovered hormone which is a central regulator of glucose and lipid metabolism. We examined the effects of chronic kidney disease (CKD) on circulating plasma FGF-21 concentration, and the association of plasma FGF-21 with incident cardiovascular disease.

Methods: We analyzed plasma FGF-21, along with traditional cardiovascular and renal risk factors, in 441 CKD G2 – G4 patients who were recruited into the prospective CARE FOR HOME cohort. Plasma adiponectin (total and subfractions) were measured in 339 patients. All patients were followed for the occurrence of cardiovascular events; defined either as atherosclerotic (acute myocardial infarction, stroke, amputation above the ankle, any surgical or interventional coronary/cerebrovascular or peripheral-arterial revascularization, or death of any cause) or as cardiac events (admission for heart failure, or death of any cause).

Results: Baseline plasma FGF-21 correlated with higher age (r=0.114), body mass index (r=0.116), waist-hip-ratio (r=0.113), triglycerides (r=0.292) and CRP (r=0.149), as well as with lower eGFR (r=-0.272) and HDL (r=-0.134, all p<0.001), but not with total adiponectin or adiponectin subfractions. In univariate Kaplan-Meier-analyses, higher quartiles of baseline FGF-21 were associated with future atherosclerotic (p=0.001) and cardiac (p<0.001) events. However this association lost statistical significance after adjustment for eGFR.

Conclusions: Our study results demonstrate an increase of plasma FGF-21 levels in CKD patients. Despite its role in glucose and lipid metabolism, plasma FGF-21 does not independently predict adverse cardiovascular outcome among CKD patients.

TH-PO594

Graded Increases in Cardiac Biomarkers Across Advancing CKD Stages Elizabeth K. Batchelor, Gates Colbert, Nishank Jain, Beverley Adams-Huet, Xilong Li, James Delemos, Susan Hedayati. *UT Southwestern and VA North Texas Medical Centers, Dallas, TX.*

Background: Elevated cardiac troponin T (cTnT) ³10 ng/L is reported in 80% of ESRD patients and associated with poor outcomes. There are less data on whether cardiac biomarkers are elevated in non-dialysis CKD patients.

Methods: We investigated whether cTnT, high sensitivity cTnT (hs-cTnT), brain natriuretic peptide (BNP), and N-terminal-pro-BNP (NT-pro-BNP) levels increase with worsening CKD in 3,298 asymptomatic, multi-ethnic participants of the Dallas Heart Study.

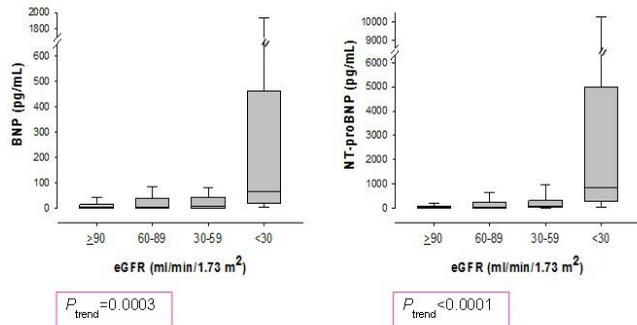
Results: Mean age was 44±10 years. 55% were female, 50% Black, 31% Caucasian, 17% Hispanic, and 2% other races. 288 had CKD, defined as eGFR<60 mL/min/1.73 m² or albumin-to-creatinine ratio ³17 mg/g in men or ³25 in women. Of those with CKD, 37% had diabetes mellitus and 66% hypertension vs. 10% and 33% if without CKD, p<0.05. A higher proportion of CKD vs. non-CKD individuals, 8.0 vs. 0.43%, had elevated cTnT ³10 ng/L and hsTnT ³3 ng/L, 58.3 vs. 24.2%, p<0.0001 for both. Mean BNP was 55.5±314.8 in CKD vs. 10.9±32.5 pg/mL in non-CKD, and NT-pro-BNP was 319.7±1225.7 in CKD vs. 53.4±117.5 pg/mL in non-CKD (p<0.0001 for both). There were graded increases in the proportion with elevated troponins as CKD severity increased across stages.

Group	N (Total=288)	cTnT	hs-cTnT
		% ≥10 ng/L	% ≥3 ng/L
CKD 1	143	3.5	47.6
CKD 2	76	5.3	61.8
CKD 3	59	15.3	74.6
CKD 4/5	10	50.0	90.0
P		<0.0001	<0.0001

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

The same was seen with BNP and NT-pro-BNP levels, with the highest increases in those with eGFR<30.



Conclusions: A higher proportion of CKD vs. non-CKD individuals had elevated cardiac biomarkers, even at early CKD stages. Graded increases in biomarkers were observed across advancing stages. Further research should determine if higher cardiac biomarker cutoffs are warranted to improve diagnostic and prognostic utility in CKD patients.

Funding: Other NIH Support - UL1TR001105 from the National Center for Advancing Translational Sciences, National Institutes of Health. M01-RR00633 from NIH/NCRR-CR., Veterans Administration Support, Private Foundation Support

TH-PO595

Circulating Endothelial Cells and Cardiovascular Risk in Chronic Kidney Disease and Hemodialysis Patients Yasser Ahmed Nienaa,¹ Nahla Mohamed gamal Farahat,² Iman Ezzat Elgohary,¹ Marwa Fathy Oraby,¹ ¹Internal Medicine-Nephrology Unit, Faculty of Medicine, Alexandria, Egypt; ²Clinical and Chemical Pathology, Faculty of Medicine, Alexandria, Egypt.

Background: This work was conducted with the aim to study circulating endothelial cells in CKD patients and correlate this with some cardiovascular risk factors. Cardiovascular disease remains the leading cause of morbidity and mortality in patients with CKD and may account for 50% of all deaths. Endothelial dysfunction is commonly observed along the CKD spectrum. Endothelial dysfunction is a well-documented early phenomenon in atherosclerosis that precedes structural changes and clinical manifestations. The chronic micro inflammation state present in uremia has been proposed as one of the mechanisms causing endothelial dysfunction. Inflammatory circulating endothelial cells (CECs) are thought to be mature cells that have detached from the intimal mono layer in response to endothelial injury. In humans, elevated levels were reported in various cardiovascular disorders, as a result of mechanical injury, ischemic injury or hypertension.

Methods: This study included 50 subjects classified as follows: Group I 20 patients with CKD not yet on dialysis, group II 20 patients on maintenance hemodialysis and 10 age and sex matched individual used as a control (group III). All included individual were subjected to complete blood count, renal function tests, estimation of GFR by MDRD formula, complete lipid profile, high sensitive CRP, ESR and detection of CEC count using flow cytometry.

Results: The study showed increased count of CEC and hs CRP in both CKD groups than the control and it was higher in patients on dialysis than those on conservative treatment. There was a statistically positive correlation between ESR, hs CRP, TG and CECs in the three groups, there was also a statistically negative correlation between estimated GFR and CECs in the three groups.

Conclusions: Measurement of CECs count might offer a mean for recognizing CKD patients at risk of cardiovascular events.

TH-PO596

The Association Between Soluble Klotho and Cardiac Parameters in Chronic Kidney Disease: Korean CKD Patients Hyo Jin Kim,¹ Kyung don Ju,¹ Tsogbadrakh Bodokhsuren Bodokhsuren,¹ Seungmi Lee,¹ Aram Lee,¹ Shin-Young Ahn,² Dong-Wan Chae,² Ho Jun Chin,² Curie Ahn,¹ Kook-Hwan Oh,¹ ¹Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; ²Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Gyeonggi-do, Korea.

Background: Klotho is one of mineral metabolism regulator in chronic kidney disease (CKD). Bone mineral metabolism is important in CKD and it is associated with cardiovascular (CV) complications. We investigated factors determining soluble klotho concentration and the association between klotho and cardiac parameters from Korean CKD patients.

Methods: We analyzed 1,443 CKD patients with soluble klotho at baseline from the prospective KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) study. Left ventricular hypertrophy (LVH) and arterial stiffness were explored as CV parameters. LV mass index (LVMI) was used as a maker of LVH (male > 115 g/m², female > 95 g/m²). Brachial-to-ankle pulse wave velocity (baPWV) was used as a marker of arterial stiffness. Renal outcome (initiation of renal replacement therapy or decline of estimated glomerular filtration rate ≥50% or doubling of creatinine) or composite outcome (renal outcome or death) were analyzed for association soluble klotho level.

Results: Patients were 53.5 ± 12.4 years old and 61.5% were male. In a multivariable linear regression analysis, uric acid and log CRP were positively and hemoglobin was inversely associated with klotho. LVH (OR 0.46; 95% CI, 0.25 to 0.85; P = 0.014) and baPWV (Pearson correlation, -0.099; P = 0.001) were associated with klotho in univariate analysis. However, in multivariable analysis, klotho was not independently associated with LVH and baPWV. 887 (61.5%) patients were investigated for association between klotho and outcomes (23.3±4.7 months follow-up). Analyzed by Cox proportional hazard model, klotho was not associated with renal or composite outcomes.

Conclusions: Soluble klotho was not an independent determining factor for LVH, arterial stiffness, and renal outcomes. Further studies are warranted to elucidate the clinicopathogenic significance of klotho in Korean CKD patients.

Funding: Government Support - Non-U.S.

TH-PO597

Elevated C-Reactive Protein, and Albuminuria Increase Mortality Risk in Metabolic Syndrome Patients Satyesh K. Sinha,¹ Magda Shaheen,¹ Deyu Pan,¹ Keith C. Norris,² Susanne B. Nicholas,² ¹Charles R Drew Univ, Los Angeles, CA; ²David Geffen School of Medicine, UCLA, Los Angeles, CA.

Background: Metabolic syndrome (MetS) is a serious health condition affecting nearly 25% of adults in the United States and places them at higher risk of cardiovascular disease (CVD), chronic kidney disease, and mortality. Studies have shown that the MetS is associated with albuminuria (urinary albumin excretion [UAE] >30ug/ml). Inflammation has been posited as an important link between the MetS and UAE. However, little is known about the added value of UAE and C-reactive protein (CRP) in predicting mortality in patients with the MetS. Therefore, the study objective was to determine the relationship between mortality and the MetS, after adding both CRP & UAE as additional components.

Methods: We analyzed data from the National Health and Nutrition Examination Surveys 1999-2004 of 5,930 adults aged ≥20 years with and without MetS (=>3 components of the MetS according to the definition of National Cholesterol Education Program's Adult Treatment Panel III). We added elevated CRP and UAE as a 6th and 7th criteria, respectively for the MetS. We analyzed data using Cox regression to estimate the hazard ratio (HR) for mortality, controlling for demographics, smoking, and CVD. Data are presented as HR, and 95% confidence interval (CI); p<0.05 was statistically significant.

Results: In the adjusted model, the MetS was not associated with mortality. However, HR for mortality was high with elevated CRP (>0.5 mg/dl; HR=1.84, 95% CI 1.45-2.35, p<0.001) and albuminuria (HR=1.89, 95% CI 1.36-2.63, p<0.001) compared to low CRP (<0.5 mg/dl) and no albuminuria (UAE<30 ug/ml). With addition of elevated CRP to the MetS, HR for mortality was high (HR=1.36, 95% CI 1.05-1.77, p<0.02) vs. low CRP and no MetS. HR for mortality was high when albuminuria was also added to MetS with elevated CRP (HR=1.52, 95% CI 1.12-2.06, p<0.01).

Conclusions: We conclude that elevated CRP and UAE may predict the group at high risk for mortality in MetS patients.

Funding: Other NIH Support - NIH grant U54MD007598, UL1TR000124, and S21-MD-000103.

TH-PO598

Longitudinal Change in Low-Grade Albuminuria Is a Better Predictor of Cardiovascular Disease Than Change in Serum Uric Acid: The Tromsø Study Marit D. Solbu,^{1,2} Bjorn Odvar Eriksen,^{1,2} Toralf Melsom,^{1,2} Hilde Merete Storhaug,² Jon viljar Norvik,² Trond G. Jenssen,^{2,3} ¹Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; ²Metabolic and Renal Research Group, UiT the Arctic Univ of North Norway, Tromsø, Norway; ³Oslo Univ Hospital, Oslo, Norway.

Background: Serum uric acid (SUA) and albuminuria are independent risk factors for cardiovascular disease (CVD), but the joint impact of longitudinal changes in SUA and albuminuria on clinical events is unknown. We assessed the associations between change in SUA and urinary albumin-creatinine ratio (ACR) over 7 years and the occurrence of incident myocardial infarction, ischemic stroke and all-cause mortality.

Methods: We included 3931 participants without CVD from the population-based the Tromsø Study; Tromsø 4 (1994/95) and Tromsø 5 (2001/02). SUA change was categorized into four groups according to upper (high) versus the three lower (low) gender specific quartiles of SUA in Tromsø 4 and 5; persistently high, decreasing, increasing, and persistently low SUA. ACR change was categorized the same way. Percentage of change from baseline in SUA and ACR was calculated.

Results: During follow-up (median 9.3 years for CVD; 11.3 years for mortality) there were 379 myocardial infarctions, 223 strokes and 869 deaths. In multivariable analyses increasing ACR predicted mortality (HR 1.65; 95% CI 1.38-1.96). Persistently high ACR predicted myocardial infarction (HR 1.34; 95% CI 1.03-1.75) and stroke (HR 1.79; 95% CI 1.28-2.51). Increasing and persistently high SUA did not predict any endpoint. A ≥50% increase in ACR from baseline predicted myocardial infarction and death, whereas a 15% increase in SUA did not. Change in SUA and ACR did not interact in their association with CVD. Baseline SUA significantly predicted stroke and mortality.

Conclusions: Longitudinally increasing ACR predicted CVD independently from SUA change. Baseline, but not changes in SUA predicted stroke and mortality. This may have implication for the use of change patterns in risk assessment.

Funding: Government Support - Non-U.S.

TH-PO599

Transient Dipstick-Proteinuria Could Be a Risk of Cardio-Vascular Diseases Kei Nagai,¹ Kunihiro Yamagata,¹ Toshiaki Usui,¹ Koichi Asahi,² Kenjiro Kimura,³ Kunitoshi Iseki,² Toshiki Moriyama,² Ichiei Narita,² Shouchi Fujimoto,² Kazuhiko Tsuruya,² Tsuneo Konda,² Masahide Kondo,² Tsuyoshi Watanabe.³ ¹Univ of Tsukuba; ²Steering Committee for 'Design of the Comprehensive Health Care System for CKD Based on the Individual Risk Assessment by Specific Health Checkups.

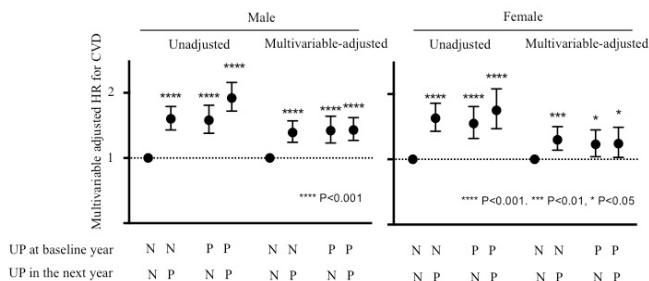
Background: Dipstick-proteinuria is the major method to detect high-risk participants for cardiovascular diseases (CVD). A large part of positive dipstick-proteinuria has gone to negative in the next year, which means transient proteinuria. The aim of this study is to clarify whether transient proteinuria is a risk of CVD comparing to sequentially negative proteinuria with one-year interval measurement.

Methods: By using a population-based 339,172 persons longitudinal cohort receiving annual health checkups sequentially twice or more, we examined presence of dipstick-proteinuria both at baseline year and in the next year. Medical history of CVD was obtained via a self-reported questionnaire. The incidence of CVD event in this study was defined as a negative history at the baseline year and a positive history in the follow-up year. Proteinuria was defined as (+) or more.

Results: Forty-five percent of subjects with positive proteinuria at baseline year in male and 58% of those in female have gone to negative proteinuria in the next year.

At baseline year	Proteinuria in the next year				Subtotal % per Total
	Negative		Positive		
	119,020	95.7%	5,317	4.3%	94.0%
	3,571	45.3%	4,301	54.7%	6.0%
	195,925	97.5%	4,986	2.5%	97.1%
	3,538	58.5%	2,514	41.5%	2.9%

Subjects with proteinuria have higher risk of CVD than those with sequentially negative proteinuria as reference (hazard ratio [HR] and 95% confidential intervals [CI], 1.58 [1.38-1.81] in male and 1.55 [1.32-1.81] in female).



Conclusions: Transient proteinuria could be a risk of the incidence of CVD.

TH-PO600

Urinary Phosphate Excretion Modifies the Association Between Serum Osteoprotegerin and Coronary Calcification in CKD: KNOW-CKD Study Young Youl Hyun,¹ Kyu-Beck Lee,¹ Hyang Kim,¹ Kook-Hwan Oh,² Curie Ahn,² Dong-Wan Chae,³ Yong-Soo Kim,⁴ Woogyung Chung,⁵ Young-Hwan Hwang,⁶ Soo Wan Kim,⁷ Yeong Hoon Kim.⁸ ¹Sungkyunkwan Univ School of Medicine, Kangbuk Samsung Hospital; ²Seoul National Univ Hospital; ³Seoul National Univ Bundang Hospital; ⁴The Catholic Univ of Korea, Seoul St. Mary's Hospital; ⁵Gachon Univ, Gil Hospital; ⁶Eulji General Hospital; ⁷Chonnam National Univ Medical School; ⁸Inje Univ, Pusan Paik Hospital.

Background: High serum osteoprotegerin (OPG) is closely related to coronary calcification, but the exact mechanism is not known well. To understand the underlying pathophysiology, we explored whether this association between OPG and coronary calcification is modified by 24-hr urinary phosphate excretion (UPi) in CKD patients.

Methods: This cross-sectional study analyzed 871 participants from the KNOW-CKD cohort who underwent a coronary MDCT, serum OPG measurement and 24-hr urine collection as baseline examinations between 2011-2013. We evaluated the association between serum OPG and coronary artery calcium scores (CACS) in each group with low and high UPi. Effect modification was evaluated by an interaction term and tested by Wald test.

Results: Percentages of participants with CACS > 0 were different between OPG quartiles (23.4%, 41.1%, 52.5% and 78.8% for the lowest to highest quartiles of OPG, P<0.001). In multivariate-adjusted Tobit models, the CACS ratio (95% confidence intervals) comparing the highest quartile of OPG to the lowest quartile was 19.74 (4.14-94.10) in the low UPi group, whereas the ratio was 1.86 (0.48-7.20) in the high UPi group (P for interaction = 0.003). In multivariate logistic model, the odds ratio of highest quartile for CACS > 0 compared with lowest quartile was 6.56 (2.52-17.11) in the low UPi group, whereas the odds ratio was 1.65 (0.68-3.99) in the high UPi group (P for interaction = 0.006).

Conclusions: Serum OPG was associated with coronary calcification only in CKD patients with low UPi, but not in those with high UPi. Further studies are warranted to verify the role of phosphate excretion in OPG-related coronary calcification.

Funding: Government Support - Non-U.S.

TH-PO601

The Relationship of LV Mass Index and FGF-23/25(OH)D Modulating Phosphaturia Shin-Young Ahn,¹ Ho Jun Chin,¹ Kook-Hwan Oh,² Curie Ahn,² Dong-Wan Chae.¹ ¹Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Republic of Korea; ²Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: As renal function declines, level of fibroblast growth factor-23 (FGF-23) rise and 25-hydroxyvitamin D (25(OH)D) decrease. We evaluate the relationship among 25(OH)D and FGF-23 on cardiovascular risk factors such as LV mass index and vascular calcification (VC).

Methods: KNOW-CKD is an on-going, prospective, university hospital based observational cohort study under the sponsorship of Korean Center for Disease Control and Prevention. Cross-sectional analysis of echocardiography data and other clinical data was performed in 1529 participants of KNOW-CKD. The study participants were divided into 4 groups by FGF-23 and 25(OH)D values below and above the median.

Results: Among the 1529 study participants, the mean of age and estimated GFR were 53.6 ± 12.4 years and 50.9 ± 31.7 ml/min/1.73m². The median FGF-23 concentration was 17.85 RU/ml (interquartile range [IQR] = 0.42, 31.28), and median level of 25(OH)D was 16.52 ng/ml (interquartile range [IQR] = 13.31, 21.04). The patients who had FGF-23 above the median but 25(OH)D below the median had highest level of serum P, iPTH, mean of pulse wave velocity (PWV), and LV mass index. They also had lowest level of hemoglobin, serum albumin, eGFR, corrected Ca, and bone mineral density of femur neck. After multivariate analysis, the result showed significant correlation between LV mass index and FGF-23/25(OH)D ratio (std β=0.176, p=0.021). Decreasing level of 25(OH)D reduced phosphaturia caused by FGF-23. Finally vascular calcification measured by abdominal aorta calcification showed significant negative relationship with phosphaturia after multivariate analysis (stdβ=-0.095, p=0.031).

Conclusions: We observed the significant association between FGF-23/25(OH)D and LV mass index and FGF-23/25(OH)D and degree of phosphaturia which was correlated with vascular calcification. We suggest that FGF-23/25(OH)D may increase LVMI through modification of phosphaturia and vascular calcification.

Funding: Government Support - Non-U.S.

TH-PO602

Fractional Excretion of Phosphorus Is Independently Associated with Left Ventricular Hypertrophy in Chronic Kidney Disease Patients Xiaoyan Zhang. *Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China.*

Background: Left ventricular hypertrophy (LVH) is an important mechanism of cardiovascular disease in chronic kidney disease (CKD). Elevated Fibroblast growth factor-23 (FGF23) levels are independently associated with LVH. The aim of this study is to investigate whether elevated fractional excretion of phosphorus, as one major action of FGF23, is independently associated with LVH in CKD patients.

Methods: LVH was defined as LVMI (Left ventricular mass index) ≥ 50 g m^{-2.7} in men or ≥ 47 g m^{-2.7} in women. The fractional excretion of phosphorus (FePi [%]) was calculated as [urine phosphorus (mg/dl)/serum phosphorus (mg/dl)]/[serum creatinine (mg/dl)/urine creatinine (mg/dl)]×100.

Results: We measured FePi levels in 1,389 individuals who underwent echocardiography within 3 months. The median FePi level was 13.44%. The mean (± SEM) left ventricular ejection fraction was 67% ± 17%, left ventricular mass indexed to height^{2.7}(LVMI) was 42 ± 14 g m^{-2.7}, and LVH was present in 24% of participants. The left ventricular ejection fraction was lower in the highest versus the lower quartiles of FePi levels, while the LVMI increased with increasing FePi quartiles. Each ten percent increase in FePi was associated with a 2.406 g m^{-2.7} greater LVMI (95% CI, 1.022-2.789; P < 0.001). Each ten percent increase in FePi was associated with a 1.363-fold greater relative risk (RR) of eccentric hypertrophy and concentric hypertrophy (95% CI, 1.275-1.456; P < 0.001) compared with normal ventricular geometry. Multivariable analyses that adjusted for age, sex, weight, hypertension, diabetes, GFR, total cholesterol, total triglyceride, hemoglobin, proteinuria, parathyroid hormone (PTH), and serum phosphate demonstrated that elevated FePi was independently associated with increased LVMI (0.745 g m^{-2.7} greater LVMI per ten percent increase in FePi, 95% CI, 0.264-1.226; P < 0.01) and conferred greater risk of eccentric and concentric LVH (RR 1.102 per ten percent increase in FePi; 95% CI, 1.000-1.214; P < 0.05).

Conclusions: FePi is independently associated with left ventricular hypertrophy in patients with CKD across a broad range of kidney function.

TH-PO603

Clinical Significance of Vascular Calcification and Retinopathy on Renal and Cardiovascular Outcomes in Patients with Chronic Kidney Disease
 Hyeon Seok Hwang, Hye Eun Yoon, Yu ah Hong, Suk young Kim. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.*

Background: Vascular calcification and retinopathy is the representative marker of macrovascular and microvascular dysfunction in patients with chronic kidney disease (CKD). While both of them share common pathophysiology, their relationship and combined effects on clinical outcome remained undetermined.

Methods: We included 523 nondialysis-dependent CKD stage 3-5 patients, who had been examined with funduscopy for diabetic or hypertensive retinopathy. Simple X-ray images of the pelvis and the abdomen were analyzed for the presence of intimal or medial arterial calcifications. The clinical significance of intimal calcification and retinopathy was evaluated in terms of the rate of renal function decline and composite of any cardiovascular event or death.

Results: Intimal calcification was observed in 81 (15.5%) CKD patients, medial calcification in 50 (9.6%) CKD patients, and retinopathy in 258 (49.3%) CKD patients. The presence of retinopathy was independently associated with intimal (odds ratio 1.72, 95% CI 1.03-2.89) and medial calcification (OR 3.41, 95% CI 1.68-6.90). The renal function decline rate was significantly steeper in patients with than in those without intimal calcification (-8.1 ± 9.4 mL/min/1.73 m²/yr vs. -4.6 ± 10.4 mL/min/1.73 m²/yr; P = 0.005). However, medial calcification was not associated with rapid renal function decline (P = 0.153). In multivariate analysis, patients with both intimal calcification and retinopathy were independently associated with a rapid decline in renal function (β = -4.21; P < 0.001). The combined status of retinopathy with intimal or medial calcification independently increased the risk of composite events (hazard ratio 3.34, 95% CI 1.41-4.43 for intimal calcification; hazard ratio 3.19, 95% CI 1.62-6.28 for medial calcification).

Conclusions: Coexistence of intimal calcification and retinopathy were independently associated with CKD progression, and the combined status of retinopathy with intimal or medial calcification was an independent predictor for composite cardiovascular event/death.

TH-PO604

Abdominal Aortic Calcification in Patients with Chronic Kidney Disease
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Background: Abdominal aortic calcification (AAC) is independently associated with cardiovascular events in dialysis patients and in the general population. However, data in non-dialysis chronic kidney disease (CKD) patients are limited. We studied determinants and prognostic value of AAC in non-dialysis CKD patients.

Methods: We included patients with CKD not receiving renal replacement therapy who participated in the MASTERPLAN study, a randomized controlled trial that started in 2004. In the period 2008-2009 an X-ray to evaluate AAC was performed in a subgroup of patients. We studied AAC using a semi quantitative scoring system by lateral lumbar X-ray. We used baseline and two year data to find determinants of AAC. We used a composite cardiovascular endpoint and propensity score matching to evaluate the prognostic value of AAC.

Results: In 280 patients an X-ray was performed. In 79 patients (28%) the X-ray showed no calcification, in 62 patients (22%) calcification was minor (<4), 139 patients (50%) had moderate or heavy calcification (≥4). Older age, prior cardiovascular disease, higher triglyceride levels, and higher phosphate levels were independent determinants of a calcification score ≥4. AAC score ≥4 was independently associated with cardiovascular events, with a hazard ratio of 5.5 (95% confidence interval 1.2-24.8).

Conclusions: Assessment of AAC can identify patients at higher cardiovascular risk, and may provide important information for personalized treatment. Whether this approach will ultimately translate into better outcomes, remains to be answered.

TH-PO605

Association of Serum Chloride Level with Mortality and Cardiovascular Events in Chronic Kidney Disease: The CKD-ROUTE Study
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Background: Electrolyte abnormalities, particularly dysnatremias, are increasingly recognized as independent predictors of adverse outcomes in individuals with and without renal failure. However, the association of serum chloride level (Cl⁻) with mortality or risk of cardiovascular (CV) events in patients with chronic kidney disease (CKD) has yet to be clarified.

Methods: This prospective cohort study included 1134 pre-dialysis CKD G2-G5 patients among the participants of the CKD Research of Outcomes in Treatment and Epidemiology (CKD-ROUTE) study, who newly visited 16 nephrology centers. The primary outcome was a composite of death of any cause and CV events, and the secondary outcome

was death of any cause. Data were analyzed with Cox hazards model with adjustment for potential confounders including serum sodium. Patients were followed up until end-stage renal disease, death, transfer, or the end of 3-year follow-up.

Results: Median Cl⁻ was 106.0 mEq/L at enrollment [quartile (Q) 1: 103.9, n = 257; Q2: 104.0-105.9, n = 258; Q3: 106.0-108.0, n = 352; Q4: 108.1, n = 267]. During 33 months' median follow-up, there were 115 CV events, 78 deaths, and 180 composite outcomes. The hazard ratio (HR) for the composite outcome was higher for Q1 than Q3 (unadjusted HR, 1.74; 95% confidence interval (CI), 1.16-2.61; p = 0.007; and adjusted HR, 1.63; 95% CI, 1.05-2.52; p = 0.029). Examined as a continuous variable in a subset of patients whose Cl⁻ was £106.0, higher Cl⁻ was associated with lower risk of the composite outcome (unadjusted HR, 0.88; 95% CI, 0.84-0.93; p < 0.001; and adjusted HR, 0.94; 95% CI, 0.88-1.00; p = 0.038). The HR for all-cause mortality was also higher for Q1 than Q3 (unadjusted HR, 2.90; 95% CI, 1.56-5.41; p = 0.001; and adjusted HR, 2.56; 95% CI, 1.30-5.05; p = 0.007).

Conclusions: Low Cl⁻ was associated with greater mortality and risk of CV events in pre-dialysis CKD patients. Low Cl⁻ may be an additive predictor of adverse outcomes in CKD.

TH-PO606

Association of Urine Potassium with ESRD, Cardiovascular (CVD) Death, and All-Cause Mortality in Chronic Kidney Disease (CKD)
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Background: Low urine potassium excretion is associated with a higher risk of developing hypertension and CVD in the general population. There are few data on the relationship of urine potassium with clinically important outcomes in CKD.

Methods: The association of urine potassium with ESRD (defined as the need for dialysis or transplantation), CVD mortality and all-cause mortality was evaluated in 812 participants enrolled in the MDRD Study. 24-hour urine potassium was measured at the first screening visit (before randomization) and in an average of 22 subsequent visits. Cox-proportional hazards models were adjusted for demographics, CVD risk factors, GFR, proteinuria, randomization assignment, and urine sodium. Interactions were performed with baseline GFR, proteinuria and urine sodium as well as blood pressure randomization.

Results: Mean age at baseline was 52±12 years; 60% were men and 85% were white. Mean 24-hour urine potassium excretion was 61.2±22.7 mEq/day. Median follow up for ESRD and mortality were 6.1(IQR 3.5, 11.7) and 19.2 (10.8, 20.6) years, respectively. Higher urine potassium levels were associated with a lower hazard of CVD mortality and all-cause mortality, but were not associated with ESRD (Table). No significant interactions were noted.

Table: Association of 24-hour urine potassium with clinical outcomes

	Event N (%)	First screening visit urine potassium*		Average time-dependent urine potassium*	
		HR (95% CI)	p-value	HR (95% CI)	p-value
ESRD (per SD ↑)	603 (74)	0.94 (0.86,1.03)	0.17	0.95 (0.84,1.06)	0.36
CVD mortality (per SD ↑)	195 (24)	0.76 (0.63,0.91)	0.003	0.72 (0.58,0.90)	0.004
All-cause mortality (per SD ↑)	430 (53)	0.85 (0.76,0.96)	0.007	0.78 (0.67,0.90)	0.001

*Adjusted for age, sex, race, cause of kidney disease, GFR, urine protein, systolic blood pressure, diabetes, history of CVD, blood pressure and dietary protein randomization group, and urine sodium.

Conclusions: Higher urine potassium is associated with lower risk of CVD mortality and all-cause mortality. It remains to be determined whether higher dietary potassium intake results in improved outcomes in CKD.

Funding: NIDDK Support

TH-PO607

Association Between Serum Bicarbonate and Heart Rate Variability in Hypertensive Adults: The Systolic Blood Pressure Intervention Trial
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Background: Reduced heart rate variability (HRV), a measure of cardiac autonomic dysfunction, has been associated with lower serum [HCO₃⁻] in advanced CKD and ESRD. The purpose of this study is to determine if [HCO₃⁻] is associated with HRV in hypertensive adults with more preserved eGFR.

Methods: We examined the cross-sectional association between baseline [HCO₃⁻] and HRV in 9,265 participants from the Systolic Blood Pressure Intervention Trial (SPRINT). Three sequential 10-second 12-lead ECGs were used to calculate two time domain measures of HRV (standard deviation of all normal RR intervals [SDNN] and root mean square of the successive differences in normal RR intervals [RMSSD]) from the individual durations between normal RR intervals. Linear regression models (adjusted for demographics, smoking, eGFR, ACR, CVD, and SBP) were performed using [HCO₃⁻] as the independent variable and log-transformed SDNN and RMSSD as dependent variables. These models were repeated using [HCO₃⁻] as a categorical variable: < 22, 22.0-24.9, 25.0-29.9 (referent), and ≥ 30 mEq/L.

Results: Mean age was 67.9 (9.4) years, 28.4% had CKD, mean eGFR was 71.8 (20.6) ml/min/1.73m², mean [HCO₃⁻] was 26.3 (2.6) mEq/L, mean SDNN was 21.2 (17.6), and

mean RMSSD was 25.2 (24.6). There was no significant association between [HCO₃⁻] and SDNN (beta coefficient -0.01, p=0.94) or RMSSD (beta coefficient 0.04, p=0.71) in adjusted linear regression models. Results were similar in models using [HCO₃⁻] as a categorical variable. There was no interaction of these relationships by CKD status (p>0.40 for SDNN and RMSSD).

Conclusions: In this large study of trial participants with normal kidney function to moderate CKD, there was no association between [HCO₃⁻] and HRV. The association between lower [HCO₃⁻] and reduced HRV may only exist in more advanced CKD.

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TH-PO608

Serum Alkaline Phosphatase Negatively Affects Endothelium Dependent Vasodilatation in Naïve Hypertensive Patients Carmine Zoccali,¹ Maria Perticone,² Raffaele Maio,² Angela Sciacqua,² Michele Andreucci,² Giovanni Tripepi,¹ Salvatore Corrao,³ Francesca Mammaci,¹ Giorgio Sesti,¹ Franco Perticone.² ¹National Research Council-Inst of Clinical Physiology, Reggio Calabria, Italy; ²Univ Magna Graecia of Catanzaro, Catanzaro, Italy; ³Biomedical Dept of Internal Medicine and Subspecialties Univ of Palermo, Palermo, Italy.

Background: Tissue non-specific Alkaline Phosphatase (Alk-Phos) promotes arterial calcification in experimental models and, independently of other risk factors, high Alk-Phos is a powerful predictor of total and cardiovascular (CV) mortality in the general population and in patients with heart diseases.

Methods: To investigate the relationship between Alk-Phos and atherosclerosis at an early disease stage we tested the association between serum Alk-Phos and the endothelium dependent maximal vasodilatory response to acetylcholine in 500 untreated individuals with uncomplicated essential hypertension without liver disease and with Alk-Phos levels well within the normal range of activity of this enzyme.

Results: The maximal response to acetylcholine was inversely related to Alk-Phos (r=-0.55, P<0.001) and this association was unmodified (r=-0.61, P<0.001) in adjusted analyses including demographic and classical risk factors, the BMI, the eGFR, serum phosphate and calcium as well as serum C reactive protein (CRP) and albuminuria. The steepness of the Ach-max/Alk.Phos relationship was substantially attenuated (P<0.001) in patients with serum phosphate above the median value than in those below the median (-5.0% per Alk-Phos Unit vs -10.0% per Alk-Phos Unit) and this interaction remained highly significant (P<0.001) in adjusted analyses.

Conclusions: Our findings offer a novel interpretative clue to explain the association between serum Alk-Phos and phosphate and all cause and CV mortality in previous observational studies in the general population and in patients with heart disease and suggest that the endothelium may be an early target of raised Alk-Phos.

TH-PO609

Alkaline Phosphatase Lowering by Selective BET Inhibition, a Novel Mechanism for MACE Reduction in High Risk CVD, Diabetes and CKD Patients – A Post-Hoc Analysis of Phase 2b Studies with RVX-208 Kamyar Kalantar-Zadeh,¹ Jan O. Johansson,² Michael Sweeney,² Kenneth E. Lebioda,² Ewelina Kulikowski,² Christopher Halliday,² Norman Cw Wong.² ¹Div of Nephrology and Hypertension, IUniv of California Irvine School of Medicine, Irvine, CA; ²Research and Development, Resverlogix Corp, Calgary, AB, Canada.

Background: RVX-208 development is focused on reducing major adverse cardiovascular events (MACE) in high risk CVD, diabetes and CKD patients. RVX-208 is a first in class select BET inhibitor small molecule that interacts with the second ligand domain found in bromodomain and extra-terminal proteins (BET). It is characterized by reductions in alkaline phosphatase (ALP) and anti-inflammatory effects.

Methods: In the SUSTAIN and ASSURE phase 2b clinical studies, high risk CVD patients were treated with 200 mg b.i.d RVX-208 or placebo for up to 26 weeks duration. Patients with a history of diabetes were analysed as a subgroup.

Results: A significant reduction in MACE in all the RVX-208 treated patients (n=331) compared to placebo (n=168) was observed (p=0.02) as well as in those with diabetes (RVX-208 n=127/placebo n=65) (p<0.01). MACE included death, non-fatal myocardial infarct, and hospital admittance for cardiac reasons. In all patients (n=499), MACE compared to non-MACE patients had higher baseline ALP; 77.0 U/L vs. 72.0 U/L (p<0.05). Similar trends were observed in diabetes patients, 81.0 U/L vs. 75.5 U/L. RVX-208 treatment significantly lowered ALP vs. placebo in all patients (p<0.0001) and especially in those with diabetes (p<0.0001). In addition, in the RVX-208 treated group, patients who did not experience a MACE had greater reductions of ALP compared to those who experienced a MACE (-8.0 U/L vs. +3.0 U/L) (p<0.05).

Conclusions: In phase 2b studies in high risk CVD and diabetes patients treated with RVX-208, a select BET-inhibitor, baseline ALP levels were significantly different between the MACE and non-MACE patients. Furthermore, RVX-208 significantly lowered serum ALP. A prospective phase 3 study currently planned, called BETonMACE, will need to further examine RVX-208's potential in reducing MACE in high risk CVD, diabetes and CKD patients.

TH-PO610

Serum Electrolyte Levels and Risk of Sudden Death in Patients with Moderate CKD Patrick H. Pun, Benjamin A. Goldstein, John Gallis, Sarah H. Timberlake, Midori L. Mccarty, John Paul Middleton, Laura P. Svetkey. *Duke University, Durham, NC.*

Background: Abnormalities in the serum potassium(K), calcium(Ca) and magnesium(Mg) are known to disturb cardiac conduction and are rare causes of sudden death (SD). However, CKD patients are at higher risk for both electrolyte disturbances and SD; the extent to which these processes are related has not been well described. We examined the role of disordered serum electrolyte levels in SD risk among a large cohort of patients with coronary artery disease (CAD) and moderate CKD.

Methods: Retrospective longitudinal cohort study of 38,576 patients undergoing cardiac catheterization at a single institution from 1989 to 2014. Patients with significant CAD were included. Baseline laboratory measures were extracted within 60 days of the time of cardiac catheterization. GFR was estimated using the CKD-EPI equation. The main outcome measures were all-cause death and SD, which was determined by chart review, query of the national death index and information from surviving family members. Cox proportional hazards models were used to determine associations with predictors.

Results: 28% of patients had stage 3-4 CKD (eGFR 15-60). This group had a higher risk of death (HR=2.53, P<0.001), SD (HR 1.80, P<0.001), hyperkalemia (RR=3.5), hypercalcemia (RR=1.7), and hyper- and hypomagnesemia (RR=1.4, RR=1.2) compared to patients without CKD. Elevated K, Ca, and Mg were associated with increased risk of all-cause death among patients with moderate CKD, but not with SD. Hyperkalemia was associated with SD in the absence of CKD.

	No CKD (N=26,992)		CKD 3-4 (N=10,828)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
All Cause Mortality				
Potassium (Normal ref)				
High	1.53 (1.21, 1.94)	<.001	1.17 (1.01, 1.36)	0.042
Low	1.19 (1.06, 1.35)	0.004	1.12 (0.97, 1.29)	0.124
Corrected Calcium (Normal ref)				
High	1.59 (1.29, 1.97)	<.001	1.35 (1.11, 1.64)	0.003
Low	0.91 (0.78, 1.07)	0.253	0.92 (0.77, 1.10)	0.364
Magnesium (Normal ref)				
High	1.18 (1.08, 1.29)	<.001	1.18 (1.08, 1.29)	<.001
Low	1.12 (0.97, 1.29)	0.182	1.09 (0.96, 1.23)	0.182
Sudden Death				
Potassium (Normal ref)				
High	2.48 (1.33, 4.65)	0.004	1.55 (0.89, 2.71)	0.119
Low	1.39 (0.95, 2.04)	0.094	0.97 (0.53, 1.77)	0.917
Corrected Calcium (Normal ref)				
High	0.66 (0.21, 2.06)	0.473	1.60 (0.76, 3.36)	0.214
Low	1.12 (0.65, 1.91)	0.684	1.02 (0.51, 2.05)	0.95
Magnesium (Normal ref)				
High	0.85 (0.60, 1.19)	0.342	1.02 (0.70, 1.50)	0.906
Low	1.24 (0.84, 1.82)	0.273	0.72 (0.40, 1.31)	0.288

Conclusions: Abnormalities in K, Ca and Mg are common among CKD patients and are associated with heightened risk of all-cause death, but are not associated with SD. Targeted management of serum electrolyte abnormalities could reduce overall mortality risk in CKD patients, but other strategies may be needed to protect from sudden death.

Funding: NIDDK Support

TH-PO611

Circulating ACE2 as a Biomarker of Chronic Kidney Disease Progression Lidia Anguiano,¹ Marta Riera,¹ Julio Pascual,¹ Angels Betriu,² Jose M. Valdivielso,² Clara Barrios,¹ Elvira Fernandez,² Maria Jose Soler.¹ ¹Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain; ²Nephrology, Hospital Arnau de Vilanova, Lleida, Spain.

Background: In a CKD population without previous history of CV disease, ACE2 activity from human EDTA-plasma samples directly correlated with the classical CV risk factors namely older age, diabetes and male gender. Objective: To study circulating ACE2 as a biomarker of renal progression and atheromatous disease(AD) in CKD stages 3-5(CKD3-5) patients.

Methods: Prospective study from 930 CKD3-5 patients without history of CVD. Circulating ACE2 activity was analyzed. We evaluated renal function(serum creatinine, glomerular filtrate MDRD-4), carotid/femoral echography, mortality, renal replacement therapy and AD at baseline and 24 months. ACE2 activity was divided in tertiles(£27.64;27.65-46.34;≥46.35RFU/µL/h). Univariate and multivariate(dependent variable ACE2 natural logarithm) were performed.

Results: Patients with ACE2 in the higher tertile doubled creatinine more frequently(61% higher tertile vs 28% lowest tertile,p=0.013). Patients that showed plaques appearance at 24month had a higher ACE2 activity in comparison to patients without(42.0±2.4 vs 34.2±1.2,p=0.009). Patients that presented plaques at baseline had higher ACE2 than those that have never had (48.2±1.7 vs 34.2±1.2,p<0.001). Femoral plaques: ACE2 increased in patients with baseline plaques(48.9±1.9) or with de novo plaques at 24months(46.6±3.2) respect to patients without plaques(35.9±1.5,p=0.002/p<0.001).

Carotid plaques: ACE2 increased in patients with baseline plaques respect to patients without plaques (49.0±2.1 vs 38.5±1.3, p<0.001). Patients with AD2-3 at 24months showed an ACE2 increase as compared to AD0-1 at 24months(47.6±1.6 vs 35.7±1.6, p<0.001). Multivariate analysis demonstrated circulating ACE2 in CKD3-5 as a predictor of doubling creatinine (β=0.069, p=0.034), de novo appearance of femoral plaques at 24months (β=0.087, p=0.016) and presence of femoral plaques at basal and 24months(β=0.199, p<0.001).

Conclusions: In CKD3-5 patients without history of CVD, circulating ACE2 may become a biomarker of CKD progression and AD appearance at 24months of follow-up.

TH-PO612

Blood Pressure and Risk of Cardiovascular Events at Advanced CKD: The CRIC Study Nisha Bansal,¹ Charles E. McCulloch,² Feng Lin,² Cassianne Robinson-Cohen,¹ Mahboob Rahman,³ John W. Kusek,⁴ Amanda Hyre Anderson,⁵ Raymond R. Townsend,⁵ Jackson T. Wright,⁶ Alan S. Go,⁷ Arnold B. Alper,⁸ Radhakrishna Reddy Kalleem,⁵ Chi-yuan Hsu.² ¹UW; ²UCSF; ³UH; ⁴UPenn; ⁵NIDDK; ⁶Case Western; ⁷KPNC; ⁸Tulane.

Background: The association of SBP with cardiovascular events (CVD) among patients with advanced CKD is not known and may be an important modifiable risk factor.

Methods: Participants of the Chronic Renal Insufficiency Cohort (CRIC) Study with advanced CKD (defined as eGFR <30 ml/min/1.73 m²) had SBP measured by standardized methods at yearly in-person visits. We studied the association of SBP with time to physician-adjusted atherosclerotic CVD (defined as myocardial infarction, stroke, peripheral vascular disease) and heart failure (HF) using Cox models.

Results: Among 1,795 participants with eGFR <30 ml/min/1.73 m², mean age was 60±11 years, 46% were women and 46% were African American. Mean eGFR was 26±5 ml/min/1.73 m² and mean BP was 131 (±24)/69 (±13) mm Hg. In models adjusted for demographics, clinical site, tobacco use, body mass index, diabetes, urine proteinuria, statin use and number of classes of anti-hypertensive medications, higher SBP was associated with greater risk of incident atherosclerotic disease and HF. Results were similar when participants with prevalent atherosclerotic CVD and HF were excluded.

Association of SBP and risk of atherosclerotic CVD (MI, stroke, PVD) and heart failure (HF) among patients with eGFR <30 ml/min/1.73 m²

	Atherosclerotic CVD	Atherosclerotic CVD, excluding participants with prevalent atherosclerotic CVD	HF	HF, excluding participants with prevalent HF
	N=1,795 Adjusted HR (95% CI)	N=1,036 Adjusted HR (95% CI)	N= 1,795 Adjusted HR (95% CI)	N= 1,481 Adjusted HR (95% CI)
SBP<120 mm Hg	Ref	Ref	Ref	Ref
SBP 120-140 mm Hg	1.46 (1.05 - 2.02)	1.28 (0.75 - 2.20)	1.21 (0.92 - 1.58)	1.51 (1.08 - 2.12)
SBP >140 mm Hg	2.00 (1.43 - 2.79)	2.28 (1.34 - 3.86)	1.27 (0.96 - 1.68)	1.47 (1.03 - 2.12)

adjusted for demographics, clinical site, tobacco use, body mass index, diabetes, urine proteinuria, statin use and number of classes of anti-hypertensive medications

Conclusions: Among this diverse multi-center cohort of advanced CKD patients, higher SBP was associated with greater risk of atherosclerotic CVD and HF. This is similar to what has been reported in the general population and suggests that treatment guidelines developed for non-CKD populations can be extended to those with eGFR <30 ml/min/1.73 m².

Funding: NIDDK Support

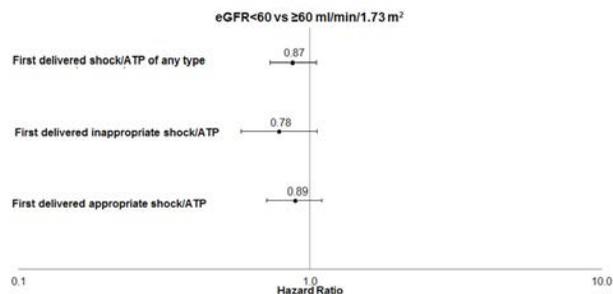
TH-PO613

CKD Does Not Impact Risk and Appropriateness of Device Therapies in Adults with Primary Prevention Implantable Cardioverter Defibrillators Nisha Bansal,¹ Adam Szpiro,¹ Frederick A. Masoudi,² Robert Greenlee,³ Jerry H. Gurwitz,⁴ Kristi Reynolds,⁵ Grace Hsu Tabada,⁶ Sue hee Sung,⁶ Ashveena Dighe,¹ Andrea E. Cassidy-Bushrow,⁷ Romel J. Garcia-Montilla,³ Stephen Hammill,⁸ Alan Kadish,⁹ Param Sharma,³ Humberto Vidaillet,³ Alan S. Go.⁶ ¹UW; ²UC; ³MCRC; ⁴MPCI; ⁵KPSC; ⁶KPNC; ⁷HFH; ⁸MC; ⁹TC.

Background: Implantable cardioverter defibrillators (ICD) reduce the risk of sudden cardiac death (SCD). CKD patients are at high-risk for SCD, but whether CKD is associated with greater risk of delivered shocks/anti-tachycardia pacing (ATP) therapies among those with an ICD remains unclear.

Methods: We studied participants in the Cardiovascular Research Network Longitudinal Study of Implantable Cardioverter Defibrillators (CVRN LS-ICD). CKD was defined as eGFR <60 ml/min/1.73 m² at the time of ICD implantation. Outcomes included number and type of shock/ATP (inappropriate or appropriate, determined by physician adjudication) within 3 years after implant. We evaluated the associations between kidney function and time to first device therapy, burden of device therapy, and inappropriate vs. appropriate device therapy.

Results: Among 2,161 participants, 49.3% had CKD at the time of ICD implantation. During mean follow-up of 2.3±0.9 years, 9.8% and 18.5% of participants had at least 1 inappropriate and appropriate shock/ATP, respectively. CKD was not associated with time to first shock/ATP of any type.



Adjusted for: age, gender, race, site, NYHA class, ischemic heart disease, hypertension, dyslipidemia, previous myocardial infarction, previous coronary artery bypass surgery, previous percutaneous coronary intervention, atrial fibrillation or flutter, ventricular tachycardia, previous valvular surgery, tobacco use, cerebrovascular disease, diabetes, lung disease, liver disease, systolic blood pressure, body mass index, left ventricular ejection fraction, ICD device type, ACE Inhibitors / Angiotensin II receptor blockers, beta-blockers, and diuretics

CKD was not associated with greater overall burden of shock/ATPs (adjusted relative rate 0.93, 95% CI: 0.74-1.17) or inappropriate vs. appropriate shock/ATP (adjusted relative risk 0.88, 95% CI: 0.68-1.14).

Conclusions: In adults receiving a primary prevention ICD, CKD was not associated with the timing, burden or appropriateness of delivered ICD therapies. Concern for more frequent or inappropriate ICD therapies should not preclude ICD implantation among eligible CKD patients.

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TH-PO614

Diagnostic and Prognostic Characteristics of Amino-Terminal Pro B-Type Natriuretic Peptide in Patients with Diminished Renal Function: A Systematic Review and Meta-Analysis Jennifer A. Schaub,¹ Steven G. Coca,² Dennis G. Moledina,¹ Jeffrey M. Testani,¹ Chirag R. Parikh,¹ Mark Gentry.¹ ¹Yale Univ School of Medicine, New Haven, CT; ²Nephrology, Mount Sinai, New York, NY.

Background: Patients with renal dysfunction have higher plasma Amino-terminal pro B-type Natriuretic Peptide (NT-proBNP), which may complicate interpretation for diagnosis of acute decompensated heart failure (ADHF) or prognosis. We sought to systematically review studies on NT-proBNP testing in patients with and without renal dysfunction.

Methods: We searched MEDLINE, EMBASE and Web of Science through August 2014 and selected studies with sub-group analysis by renal function of the diagnostic or prognostic ability of NT-proBNP.

Results: For diagnosis, nine studies were included with 4,287 patients and 1,325 ADHF events. Patients were mostly divided into sub-groups with and without renal dysfunction by an estimated glomerular filtration rate of 60 ml/min/1.73m². In patients with renal dysfunction, the area under the curve (AUC) for NT-proBNP ranged from 0.66 to 0.89 with a median cut-point of 1980 pg/ml while the AUC ranged from 0.72 to 0.95 with a cut-point of 450 pg/ml in patients with preserved renal function. For prognosis, 30 studies with 32,203 patients were included, and mortality in patients with renal dysfunction (25.4%) was twice that of patients with preserved renal function (12.2%). The unadjusted pooled risk ratio (RR) for NT-proBNP and mortality was 3.01 (95% CI, 2.53-3.58) in patients with preserved renal function and was similar in patients with renal dysfunction (3.25 [CI, 2.44-4.32]). There was significant heterogeneity, which was partially explained with meta-regression, if patients with heart failure or coronary artery disease were enrolled.

Conclusions: NT-proBNP retains utility for diagnosis of ADHF in patients with diminished renal function with higher cut-points. Elevated NT-proBNP confers a worse prognosis regardless of renal function.

Funding: Other NIH Support - T32DK007276-36
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TH-PO615

Changes in Urinary L-FABP as a Biomarker for Cardiovascular Events Atsuko Ikemori,^{1,2} Takeshi Sugaya,¹ Katsuomi Matsui,¹ Mikako Hisamichi,¹ Kenjiro Kimura,³ Yugo Shibagaki.¹ ¹Dept of Nephrology and Hypertension, Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; ²Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; ³Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Contrast medium (CM) induces tubular hypoxia via endothelial damage due to direct cytotoxicity or viscosity. Urinary liver-type fatty acid binding protein (L-FABP) is a tubular biomarker which increases along with tubular hypoxia and may be useful as a detector of systemic circulation injury. The aim of this study was to evaluate the clinical usefulness of increase in urinary L-FABP levels due to administration of CM as a prognostic biomarker for cardiovascular disease in patients without occurrence of CM-induced nephropathy undergoing cardiac catheterization procedure (CCP).

Methods: Cross-sectional and retrospective longitudinal analyses of the relationship between urinary L-FABP levels and occurrence of cardiovascular events were performed. Urinary L-FABP was measured by ELISA before, and at 6, 12, 24 and 48 h after CCP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Results: Urinary L-FABP levels were significantly higher at 12h and 24h after CCP compared with before CCP only in the patients with occurrence of cardiovascular events. The difference in urinary L-FABP levels (Δ L-FABP) between before and at 24h after CCP was a risk factor for the occurrence of cardiovascular events.

Conclusions: Measurement of urinary L-FABP before and at 24h after CCP in patients with mild to moderate renal dysfunction may be an important indicator for risk stratification of onset of cardiovascular events in clinical practice.

TH-PO616

Suggested Role of Adiponectin in Reciprocal Relationships Between Pulse Wave Velocity and Bone Mineral Density in CKD Patients Seon Ha Baek,¹ Sung Woo Lee,¹ Shin-Young Ahn,¹ Sejoong Kim,¹ Ho Jun Chin,¹ Ki Young Na,¹ Dong-Wan Chae,¹ Curie Ahn.² ¹Internal Medicine, Seoul National Univ Bundang Hospital, Gyeonggi-do, Republic of Korea; ²Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: Although adiponectin plays a beneficial role in the regulation of insulin action and atherosclerosis in various populations, the role of adiponectin remains a controversy in patients with chronic kidney disease (CKD).

Methods: A total of 1310 patients (male/female = 794/516) with CKD stage 1 to 5 who enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD) from June 2011 to December 2013. We measured serum total adiponectin and examined the association between adiponectin, bone mineral density (BMD) measured by dual energy X-ray absorptiometry, and pulse wave velocity (PWV) calculated by mean value of both brachial-ankle (ba) PWV.

Results: Increasing quintiles of serum adiponectin levels were associated with female gender; lower body mass indices, estimated glomerular filtration rate, triglycerides, BMD and albumin; higher urinary protein creatinine ratios, PWV, phosphorous, intact PTH. T-scores at LS spine (LS), total hip (TH), and femur neck (FN) inversely correlated with ba PWV (LS: $r = -0.075$, $P = 0.010$; TH: $r = -0.097$, $P = 0.001$; FN: $r = -0.111$, $P < 0.001$) in male CKD, however, this association was not significant for female CKD (LS: $r = 0.019$, $P = 0.607$; TH: $r = -0.046$, $P = 0.223$; FN: $r = -0.043$, $P = 0.277$). Adiponectin was inversely associated with T-scores at all sites for both male and female CKD patients (LS: $r = -0.133$, $P < 0.001$; TH: $r = -0.135$, $P < 0.001$; FN: $r = -0.099$, $P < 0.001$). Adiponectin was positively associated with ba PWV for male CKD ($r = 0.074$, $P = 0.016$), but not for female CKD ($r = -0.021$, $P = 0.567$).

Conclusions: Adiponectin, BMD, and PWV were associated with each other in male CKD patients. The findings suggested that adiponectin have the role in reciprocal relationships between PWV and BMD in not female but male CKD patients.

TH-PO617

The Association of High-Sensitivity Troponin I and N-Terminal Pro-Brain Natriuretic Peptide with Plasma Galectin-3 in Chronic Kidney Disease Patients Gek Cher Chan,¹ Rui shian Ao,² Jialiang Li,² Boon Wee Teo.^{1,3} ¹Nephrology, National Univ Hospital, Singapore; ²Statistics and Applied Probability, National Univ of Singapore, Singapore; ³Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore.

Background: Plasma galectin-3 (pG3), a beta-galactoside-binding lectin, regulates inflammation and fibrosis. N-terminal pro-brain natriuretic peptide (NTproBNP), high-sensitivity Troponin I (hsTnI), and pG3 concentrations are elevated in chronic kidney disease (CKD) patients with heart failure. Between hsTnI and NTproBNP, it is unknown which has a better association with pG3. We assessed the relationship of NTproBNP and hsTnI with pG3 in Asian CKD patients and healthy controls.

Methods: We retrieved prospectively collected frozen plasma samples from 163 stable CKD patients and 105 healthy controls. NTproBNP, hsTnI and pG3 were assayed. By univariate analysis, we assessed pG3 for associations with age, gender, ethnicity, systolic (SBP) and diastolic (DBP) blood pressures (mmHg); height, weight, body mass index (BMI, kg/m²), previously diagnosed CKD, diabetes, hypertension, coronary artery disease, estimated glomerular filtration rate (eGFR, mL/min/1.73m²); C-reactive protein (CRP), beta-trace protein (BTP), 24-hr urine protein (TUP), serum albumin, uric acid and cystatin C. We created 2 models predicting pG3 using multiple linear regression by backwards elimination to include hsTnI and NTproBNP. Akaike Information Criterion (AIC) was used for comparison. Significance was taken at $P < 0.05$.

Results: Population averages: Age=52.7±15.3 years; BMI=26.9±5.2, eGFR=75 (IQR:36-102); pG3=19.4 (IQR:14.9-29.9)ng/mL, NTproBNP=27 (IQR:11-71) pg/mL, hsTnI=3.1 (IQR:1.6-6.0) ng/L. Age, SBP, DBP, height, BMI, previous disease diagnoses, Ln CRP, Ln BTP, Ln TUP, Ln albumin, Ln uric acid, Ln creatinine, Ln cystatin C, Ln eGFR, Ln hsTnI, Ln NTproBNP were associated with pG3. The best model included Ln hsTnI, diagnosis of CKD, Ln albumin, Ln cystatin C, Ln uric acid, and height. (AIC: 83.3).

Conclusions: NTproBNP and hsTnI are associated with pG3 in CKD patients. The model including hsTnI is a better predictor of pG3.

TH-PO618

ACE/ARB Use in Patients with Severe Kidney Disease and Heart Failure Is Not Associated with Worsening Renal Function, Acute Kidney Injury and Hyperkalaemia Gowrie Balasubramaniam, Sebastian Vandermolen, Sarah Mapplebeck, Michael K. Almond. *Dept of Medicine, Southend Univ Hospital, Southend, Essex, United Kingdom.*

Background: The role of ACE/ARB in patients with severe kidney disease and heart failure needs clarification. This includes patients with preserved systolic function. ACE/ARB use is associated with better cardiac prognosis but there is a risk of worsening renal function, especially in older and frail people.

Methods: We undertook a retrospective analysis of patients who were diagnosed with heart failure in primary care with BNP testing and Echocardiogram. Our centre serves a population of 350,000, details of hospital admissions, drug information and blood results were obtained from our electronic patient records. A BNP>450 and clinical features of heart failure is the criteria used by general practitioners for diagnosis, an eGFR < 30 was used to identify patients with severe kidney disease. We looked at rates of worsening kidney function, AKI and hyperkalaemia.

Results: 159 patients with raised BNP and eGFR <30 were identified on electronic search from 01/12 to 01/14. Mean age was 81.7year (range 41-96), M:F was (79:80). Average follow-up was 17 months. 27 patients with transient rise in serum creatinine (Cr) or on dialysis were excluded. 87 of the remaining 132 patients had echocardiograms; 13 had ejection fraction (EF) <40%, 7 EF had 40-50% and 67 had preserved ejection fraction (>50%). Comparing with EF<50% vs. EF>50%; mortality was 55% (11/20) vs. 10% (7/67), mean BNP was 12,037 vs. 3645, mean Cr was 235 vs. 201 and 1/20 vs. 1/67 reached ESRD, respectively. 84 patients had drug information available.

	On ACE/ARB (n=62)	Not on ACE/ARB (n=22)
Mortality	21%	23%
Episode of AKI	58%	45%
Worsening CKD at follow-up	53%	45%
Mean potassium	4.2	4.7

Conclusions: Impaired EF was associated with worse mortality. ACE/ARB use was not associated with more adverse events with regards to episodes of AKI, worsening egfr and mean potassium. We feel that ACE/ARB treatment for heart failure should be maintained even in the setting of severe renal disease to reduce cardiovascular mortality.

TH-PO619

Protein-Fiber Intake Ratio and Cardiovascular Risk in Older Men with Chronic Kidney Disease Hong Xu,¹ Megan Rossi,² Katrina L. Campbell,^{2,3} Gloria Lissete Sencion martinez,¹ Johan Arnlov,⁴ Tommy Cederholm,⁵ Per Sjogren,⁵ Bengt Lindholm,¹ Juan Jesus Carrero.¹ ¹Renal Medicine & Baxter Novum, Karolinska Inst, Stockholm, Sweden; ²Princess Alexandra Hosp, Brisbane, Australia; ³Health Sciences & Medicine, Bond Univ, Robina, Australia; ⁴Medical Sciences, Uppsala Univ, Uppsala, Sweden; ⁵Public Health and Caring Sciences, Uppsala Univ, Uppsala, Sweden.

Background: The elevated cardiovascular (CVD) risk in chronic kidney disease (CKD) may be partially alleviated through a healthy diet. While protein intake has been linked to CVD events in CKD patients, dietary fiber may be cardioprotective. Nutrients are not consumed in isolation; we hypothesize that CVD incidence associates with dietary patterns aligned with excess of dietary protein relative to fiber.

Methods: Prospective cohort study from Uppsala Longitudinal Study of Adult Men of 390 elderly men aged 70–71 years with manifest CKD (eGFR<60 mL/min/1.73m² and albuminuria³20 µg/min) and no clinical history of CVD. Protein and fiber intake and its ratio, were calculated from 7-day dietary records. Cardiovascular structure and function was estimated from echocardiographic examination. Fatal and non-fatal cardiovascular events were registered prospectively during median follow-up of 9.1 (IQR 4.5–10.7) years.

Results: The median of protein-fiber ratio was 4.0 (3.5–4.7); dietary protein was 66.7 (60.7–71.1) and dietary fiber was 16.6 (14.5–19.1) grams/day. Protein-fiber intake ratio, rather than separate components, remained strongly associated to left ventricular cardiovascular structure and diastolic function after multivariable adjustment. During follow-up, 164 first-time CVD events occurred (incidence rate 54.5/1,000 py). Protein-fiber intake ratio was an independent risk factor for CVD incidence [adjusted HR per SD increase (95% confidence interval, CI) 1.29 (1.05, 1.57)]. Although in opposing directions, neither dietary protein [1.10 (0.92, 1.33)] nor dietary fiber [0.83 (0.68, 1.02)] associated with this outcome.

Conclusions: An excess of dietary protein relative to fiber intake associated with cardiovascular structural dysfunction and with incidence of cardiovascular events in a homogeneous population of older men with CKD.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO620

Impact of Percutaneous Transluminal Renal Angioplasty (PTRA) on Long-Term Prognosis in Patients with Severe Atherosclerotic Renal Artery Stenosis (RAS) Yasuhiro Mochida, Takayasu Ohtake, Kunihiro Ishioka, Machiko Oka, Hidekazu Moriya, Sumi Hidaka, Shuzo Kobayashi. *Nephrology, Shonan Kamakura General Hospital, Kamakura, Kanagawa, Japan.*

Background: PTRA for the patients(Pt's) with RAS was concluded to be not superior to medical therapy in terms of preserving renal function, renal events, and cardiovascular events in multicenter randomized trial in ASTRAL and CORAL. However, in these studies, approximately 40% of all Pt's had only mild to moderate RAS (50~70%). Therefore, we studied whether PTRA for the Pt's with more severe RAS would be beneficial or not.

Methods: Eligibility of the study included the Pt's with RAS in stenosis more than 75%, who underwent PTRA in our hospital from September 2004 to December 2007. Mean follow-up period was 81±34 months (median 7 years). We investigated the changes of renal function as primary endpoint, and renal event (doubling of serum creatinine(=Scr) or dialysis initiation) and cardiovascular death as secondary endpoint.

Results: Among 80 RAS patients with PTRA treatment, 74 Pt's were followed by April 2015. There were 24 Pt's with 75-89% (moderate group), 38 Pt's with 90-95% (severe group), and 12 Pt's with more than 95% (more severe group) in stenosis. At the time of PTRA, 92% of all the Pt's had ischemic heart disease. The changes of Scr from baseline to the final hospital visit (mean±SD) were from 1.21±0.59 to 1.47±0.91 mg/dl in moderate, from 1.10±0.34 to 1.89±1.84 mg/dl in severe, and from 1.95±1.14 to 1.76±0.80 mg/dl in more severe group, respectively. During the follow-up period, totally four renal events (5.4%) occurred (1 in moderate, 3 in severe). However, none of the more severe group presented renal event, nor renal function worsening in this group (P=0.002). Fourteen Pt's died (19%), of which cardiac death occurred in 6 Pt's (8.1% among all Pt's) during the follow-up period.

Conclusions: In comparison with 5-year cumulative rate of 22% renal events and 11.4% cardiovascular death in medical group in ASTRAL study, the results in our study clearly demonstrated the effectiveness of PTRA in more severe RAS patients in preserving renal function and protecting from cardiac deaths. PTRA is a useful treatment for the Pt's with more severe RAS.

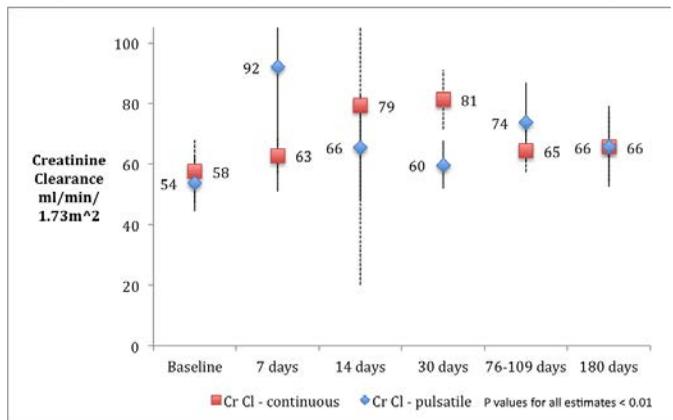
TH-PO621

Changes in Renal Function After LVAD Placement – A Meta-Analysis Reejis Stephen,¹ Chandrashekar Kashyap,² Minesh Rajpal,¹ Sankar D. Navaneethan.¹ *¹Nephrology, Cleveland Clinic, Cleveland; ²Medicine, MetroHealth Medical Center, Cleveland.*

Background: Renal function after Left Ventricular Assist Device (LVAD) placement predicts survival, irrespective of baseline Creatinine Clearance (CrCl). Continuous flow devices have been reported to have better renal outcomes than pulsatile devices. We compared the change in renal function in recipients of both continuous and pulsatile-flow devices at various time points following LVAD placement.

Methods: We searched MEDLINE for all publications with prospective cohorts and trials of LVAD recipients. Studies documenting renal-function at various time points after LVAD placement were included. CrCl at suitable time points after LVAD placement was pooled using an inverse of variance method and analyzed using random-effects models. Changes in CrCl after continuous and pulsatile flow LVAD placement was compared for cohorts with at least 10 subjects.

Results: 33 studies with 23 cohorts including continuous flow devices (n=1262) and 18 including pulsatile flow (n = 678) were included. Baseline CrCl for continuous and pulsatile-device recipients were similar. Continuous flow LVAD recipients showed higher CrCl at 1 month, compared to baseline and pulsatile-flow device recipients. There was a non-significant trend towards improved renal function after LVAD placement (Figure).



Conclusions: In this pooled analysis, we noted a pattern of an initial improvement in renal function followed by later decline with continuous-flow devices. While CrCl appears to improve after LVAD placement, the long-term effect remains unclear. Further studies focused on renal function and risk factors are needed to better understand the phenomenon in LVAD recipients.

TH-PO622

Impact of Kidney Function on Intima-Media Thickness in Patients with Type 2 Diabetes Yusuke Nakade,^{1,3} Tadashi Toyama,² Shinji Kitajima,² Yasuyuki Shinozaki,² Akinori Hara,² Miho Shimizu,² Yasunori Iwata,² Norihiko Sakai,² Kengo Furuichi,² Takashi Wada.^{1,2,3} *¹Clinical Laboratory, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan; ²Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan; ³Dept of Laboratory Medicine, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.*

Background: Carotid echo indexes [intima-media thickness (IMT)] are commonly used surrogate markers for cardiovascular disease; However, the impacts of chronic kidney disease (CKD) on changes in IMT are unclear. We examined associations between CKD and IMT in participants with and without type 2 diabetes through longitudinal analysis.

Methods: In total, 424 subjects were enrolled in this study. IMT was measured as per carotid echo indexes. Relationships between IMT and risk factors were analyzed using multiple linear regression analysis, in which we defined IMT as the dependent variable and atherosclerosis-related factors (age, sex, systolic pressure, total cholesterol, body mass index, estimated glomerular filtration rate (eGFR), uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein levels, past cardiovascular event, glycated hemoglobin, and diabetes duration) as independent variables.

Results: The study population was composed of 70.3 % male subjects. Participants with diabetes accounted for 64.4 % of the total population. The mean follow-up duration was 2.2 ± 1.5 years. Alterations in IMT tended to be associated with systolic blood pressure (+10 mmHg) (β = -0.0084, p = 0.09) and eGFR (+10 mL/min/1.73 m²) (β = -0.0049, p = 0.06) in all participants. In participants without diabetes, alterations in IMT were associated with eGFR (+10 mL/min/1.73 m²) (β = -0.0104, p = 0.03) and tended to be associated with systolic blood pressure (+10 mmHg) (β = 0.0094, p = 0.06). No significant relationships were found in participants with diabetes.

Conclusions: Low eGFR was associated with progression of carotid thickness independent of common cardiovascular risk factors in non-diabetic participants.

TH-PO623

The Number of Arterial Territories with Atheroma Plaque Predicts Cardiovascular Event-Free Survival in Chronic Kidney Disease. Analysis of the NEFRONA Study after 36 Months of Follow-up Jose M. Valdivielso,¹ Montserrat Martinez-alonso,³ Marta Gracia,¹ Angels Betriu,¹ David Arroyo,² Maria Abajo,¹ Mercedes Salgueira lazo,⁴ Jose L. Gorritz,⁵ Elvira Fernandez,² *¹Experimental Nephrology, IRBLleida, Lleida, Spain; ²UDETMA, Arnau de Vilanova Univ Hospital, Lleida, Spain; ³Statistics Unit, IRBLleida, Lleida, Spain; ⁴Unidad Mixta, Hospitales Virgen Macarena y Virgen del Rocío, Sevilla, Spain; ⁵Nephrology, Hospital Dr Peset, Valencia, Spain.*

Background: Cardiovascular disease remains the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD).

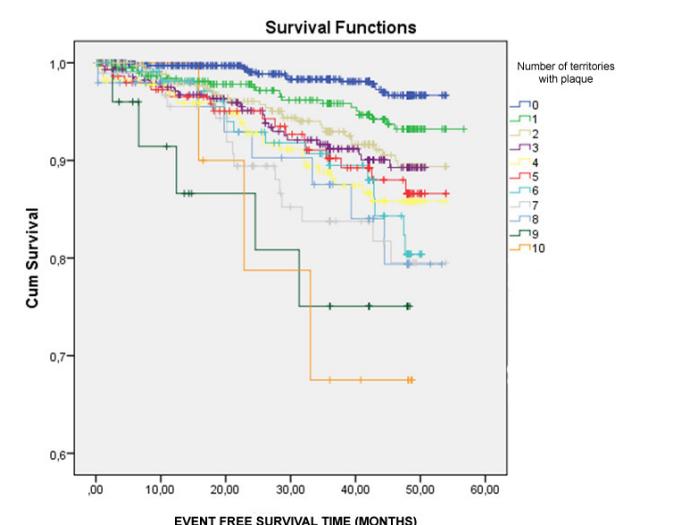
Methods: The NEFRONA study enrolled 2445 patients in different stages of CKD to assess the value of detection of subclinical atherosclerosis by ultrasound in the prediction of cardiovascular risk. This study shows the data on cardiovascular events (CVE) with a minimum follow-up time of three years, and the COX regression analysis of predicting factors.

Results: There have been 67 fatal and 152 nonfatal CVE and 113 deaths from other causes. The number of missings is 648 (593 renal transplants, 1 non renal transplant and 67 changes of center). The cumulative incidence of CVE is of 8.96% (median follow-up=42.09 months); stage 3: 6.95% (48 months), stage 4-5: 9.29% (42.8 months), stage 5D: 11.34% (23.1 months). Kaplan Meier curves of survival free from CVE show that the survival time is inversely proportional to the number of territories with plaque.

Background: Cardiovascular disease remains the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD).

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The COX regression analysis shows that the factors significantly predicting event-free survival time are the number of territories with plaque, being on dialysis, smoking, diabetes, high levels of phosphorus, low albumin and 25OH vitamin D as well as having 1,25(OH)₂ vitamin D below 14 pg/dl.

Conclusions: The severity of arterial atheromatosis estimated by ultrasound predicts the time free from CVE in CKD. Arterial ultrasound is a useful tool to predict cardiovascular risk in CKD patients.

Funding: Pharmaceutical Company Support - ABBVIE, Government Support - Non-U.S.

TH-PO624

The Effects of Diuretics on the Progression of CKD and Incidence of Cardiovascular Events: Results from the CKD-ROUTE Study – A Prospective Cohort Study of Newly Visiting CKD Patients in Japan Shotaro Naito, Soichiro Iimori, Eisei Sohara, Tomokazu Okado, Sei Sasaki, Shinichi Uchida, Tatemitsu Rai. *Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.*

Background: Anti-hypertensive agents are requisite for control of blood pressure in CKD patients. Although diuretics seem to be associated with progression of CKD or incidence of cardiovascular (CV) events, this hypothesis has not been adequately elucidated. To evaluate the association of anti-hypertensive agents prescription and outcomes, we analyzed a cohort study of newly visiting pre-dialysis CKD patients in Japan.

Methods: We recruited 937 newly visiting CKD patients followed for the next 3 years. At 6 months visit, use of RAAS inhibitors (RAASi), calcium channel blockers (CCB), and diuretics was assessed, and the association between these medications and outcomes was evaluated. The outcomes were composite kidney endpoint of ESKD or 50% decline of eGFR from baseline, incidence of CV events and CV related death during three years after first visit to nephrologists. We used multivariate Cox proportional hazards regression adjusted by age, sex, albumin, hemoglobin, eGFR, systolic blood pressure, presence of proteinuria and diabetes, and past history of CV events.

Results: At first visit, mean age was 67 years old, 70.2% was male, mean eGFR was 33.7 ml/min/1.73m², and mean systolic blood pressure was 139 mmHg. During the follow-up period of 3 years, 114 CV events occurred, 24 patients died of CV events, and 220 patients reached the composite kidney endpoint. In multivariable analysis, risk of CV events and CV related death during the 3-year period was higher in the patients using diuretics at six months visit (adjusted hazard ratio 1.55 [95%CI 1.23-2.33] for CV events, 3.09 [95%CI 1.19-8.02] for CV related death.) The patients taking both diuretics and RAASi had comparable risk of CV events with those taking diuretics only (adjusted HR 1.09 [95%CI 0.54-2.2].) However, none of the three kinds of anti-hypertensive agents had associations with CKD progression.

Conclusions: CKD patients using diuretics were more likely to have CV events and CV related death. RAASi might contribute to reduce the risk of CV events by diuretics.

TH-PO625

Rapid Increase in Aortic Stiffness in Patients on Hemodialysis and Peritoneal Dialysis Compared with Non-Dialysis-Dependent Chronic Kidney Disease Patients: A Longitudinal Study Using MRI-Based Pulse Wave Velocity Kazuhiko Tsuruya,¹ Hisako Yoshida,¹ Takanari Kitazono,² *¹Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ²Dept of Medicine and Clinical Sciences, Graduate School of Medical Sciences, Kyushu Univ, Japan.*

Background: Pulse wave velocity (PWV) is a well-established technique for obtaining a measure of arterial stiffness that has the potential to provide information on early atherosclerotic disease. MRI-based PWV measurements have been well validated in comparison with invasive pressure recordings (Grotenhuis et al. J Magn Reson Imaging, 2009). To date, very few studies have reported on MRI-based PWV in patients with chronic kidney disease (CKD), especially in patients with end-stage kidney disease on hemodialysis (HD) and peritoneal dialysis (PD). In the present study, we examined the annual changes in MRI-based PWV from baseline to 2 years and compared them among non-dialysis dependent-CKD (ND), HD, and PD patients.

Methods: A total of 172 CKD patients (ND, n=89; HD, n=47; PD, n=36) were recruited and underwent cardiovascular MRI at baseline and 2 years after. Using cine and phase contrast sequences, the cross-sectional area for distensibility and average blood flow were measured between the ascending and the proximal descending aorta. Annual change in MRI-based PWV was calculated as (MRI-based PWV after 2 years – baseline MRI-based PWV) × 365/interval days between the first and second MRI. Multivariable linear regression was used to evaluate differences in the changes among the 3 patient groups.

Results: The annual changes in MRI-PWV were significantly increased in patients on HD and PD compared with ND patients, even after adjusting various confounding factors including age, sex, and blood pressure (least square means were -0.18, 0.35, and 0.49 in ND, HD, and PD patients, respectively; p < 0.001). Meanwhile, there was no difference in the changes between HD and PD patients (p = 0.736).

Conclusions: Progression of aortic stiffness is more rapid in patients on HD and PD compared with ND patients independent of age and blood pressure, while comparable between those on HD and PD.

TH-PO626

The Recent ADQI Proposal for a Functional Classification System of Heart Failure in Patients with End-Stage Renal Disease Will Substantially Overdiagnose Cardiac Disease Among Chronic Kidney Disease Patients Kathrin Untersteller,¹ Francesca Mallamaci,² Danilo Fliser,¹ Gerard M. London,³ Carmine Zoccali,² Gunnar H. Heine,¹ *¹Saarland Univ Medical Center, Homburg, Germany; ²CNR-Inst of Clinical Physiology, Reggio Calabria, Italy; ³Manhès Hospital, Fleury-Mérogis, France.*

Background: The Acute Dialysis Quality Initiative (ADQI) XI Workgroup has recently proposed a novel classification for HF stages in advanced CKD, which is based upon a broad spectrum of echocardiographic criteria. We hypothesize that these criteria will substantially overdiagnose HF across the whole spectrum of CKD, as echocardiographic changes are a very frequent finding even among patients with mild to moderate CKD.

Methods: Within the ongoing CARE FOR HOME study, we echocardiographically examined 317 patients in GFR categories G2 – G4, following American Society of Echocardiography guidelines. According to ADQI criteria, HF is defined by moderate to severe changes in any of the following criteria: valve function, left atrial volume index (LAVI), left ventricular (LV) or right ventricular systolic function, LV mass index, LV diastolic function, LV diameter, or regional LV wall contractility. Patients were followed for a mean of 3.6 ± 1.5 years until the first admission for decompensated HF.

Results: Among the 317 CKD patients, 209 (66%) fulfilled ADQI criteria. HF was detected more often in advanced CKD (G3b/G4: 114/146; 78%) than in milder CKD (G2/G3a: 95/171; 56%). An increased LAVI (158/317; 50%) and diastolic dysfunction (101/317; 32%) were the most frequent findings within the subcategories of echocardiographic changes. Among all 209 patients with ADQI HF, only 24 patients (11%) suffered decompensated HF during follow-up, and event-free four year survival was 89%.

Conclusions: The proposed ADQI criteria will substantially overdiagnose HF among patients with mild to moderate CKD. We suggest defining more conservative echocardiographic criteria for HF prior to introduction of this new classification in daily clinical practice. The validity and reliability of such revised criteria should subsequently be analyzed across the whole spectrum of CKD.

TH-PO627

Prognostic Value of Pulmonary Hypertension in Combination with Heart Valvular Calcification on Cardiovascular Outcome in Maintenance Hemodialysis Patients Zhilian Li, Zhonglin Feng, Wei Dong, Sijia Li, Wei Shi. *Nephrology, Nephrology Dept of Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China.*

Background: Our previous study had revealed pulmonary hypertension (PH) as a predictor of all-cause mortality, cardiovascular mortality and new onset cardiovascular events in maintenance hemodialysis (MHD) patients. We hypothesize that patients complicated with both PH and heart valvular calcification (HVC) may take higher cardiovascular risk than those suffer from PH or HVC only.

Methods: 304 Chinese MHD patients were enrolled and followed up for 24 months. Each patient underwent Doppler echocardiographic evaluation before entry. A value of Systolic PAP (SPAP) ³⁵ mmHg was defined as PH. HVC was defined as the presence of bright echoes of >1mm on one or more cusps of the aortic valve, mitral valve or mitral annulus. Patients were divided into 3 groups: No risk group (with neither PH nor HVC, n=140), One Risk Factor Group (with PH or HVC, n=121) and Two Risk Factors Group (with PH and HVC, n=43). The endpoints were all-cause mortality, CV mortality and CV events.

Results: A total of 63 (20.7%) patients died during follow-up from all causes; 18 (12.9%) in Group 1, 29 (24.0%) in Group 2, and 16(37.2) in Group 3. 36 died of CV events (57.1% of the causes of death); 7(5.0%) in Group 1, 16(13.2) in Group 2, and 13 (30.2%) in Group 3. All-cause and CV mortality increased significantly in both Group 2 and 3. 101(33.2%) had new-onset CV during the follow-up period; 29(20.7%) in Group 1, 43(35.5%) in Group 2, and 29 (67.4%) in the non-PH group, which was a significant difference (p<0.05).PH in combination with HVC increased risk for all-cause, CV mortality and new onset CV even[HR:4.32(2.01-8.90) versus 1.93(1.03-3.63) for all-mortality, 6.49(2.57-16.39) versus 2.60(1.05-6.44) for CV mortality and 3.51(2.03-6.07) versus 1.40(0.86-2.30) for new onset CV event].

Conclusions: PH in combination with HVC predicts worse outcome than those with either PH or HVC in MHD patients. Echocardiography can easily identify both PH and HVC, and is helpful to stratify risk in this population.

Funding: Government Support - Non-U.S.

TH-PO628

Survival of ESRD Patients Diagnosed with Idiopathic Heart Failure prior to Dialysis Frances M. Yang,¹ Chen chun Chen,¹ Shuang Li,⁴ Adam E. Berman,² Lu Y. Huber,^{2,3} Matthew J. Diamond,^{2,3} Mufaddal F. Kheda,² Jusmin Patel,² N. Stanley Nahman,^{2,3} *¹Biostatistics, Georgia Regents Univ, Augusta, GA; ²Medicine, Georgia Regents Univ; ³Medicine, Norwood VAMC, Augusta, GA; ⁴Statistics, UTMB, Galveston, TX.*

Background: Cardio-renal syndrome type 2 (CRS-2) is defined as chronic abnormalities in heart function leading to kidney injury or dysfunction, and may occur in over 60% of patients admitted for heart failure (HF) (Ronco, Eur Hrt J 31:703, 2010). Idiopathic HF (IHF) may clinically manifest as CRS-2 and progress to ESRD. The prognosis

of patients with pre-dialysis IHF after the institution of dialysis is unknown. We used the USRDS to compare survival between IHF patients diagnosed prior to ESRD (PRE) with patients developing IHF after the institution of dialysis (POST).

Methods: All incident adult ESRD cases from the USRDS from 1967-2012 were queried for a diagnosis of IHF before or after the incident date of dialysis. IHF was defined by the presence of any ICD-9 HF code (428.0 - 428.9), and the absence of other cardiovascular diagnoses. Descriptive statistics and co-morbidities by group were calculated, and survival analysis performed using Cox regression.

Results: 50,052 patients were identified with IHF. 46% and 54% were diagnosed with IHF PRE or POST the incident date of dialysis, respectively. When compared to POST, PRE were older (73% > age 65 vs. 33%), White (61% vs. 59%), diabetic (45% vs. 6%), and female (52% vs. 47%, all $p < 0.001$), and with a hazard ratio (HR) for death of 1.82 (95% CL 1.773-1.861, $p < 0.001$). Diabetes prior to dialysis and age > 44 years also exhibited increased HR for death (1.11 and 1.62, respectively). Non-white race was protective for death in all patients with IHF.

Conclusions: In ESRD, a diagnosis of IHF is common either before or after the incident date of dialysis. PRE is associated with decreased survival, perhaps due to pre-existing heart disease in an older, diabetic population. IHF in POST included younger patients likely with volume overload and an intact ejection fraction; thus with more readily reversible conditions. IHF before and after the incident date of dialysis may be two distinct entities, and suggests unique management strategies for each syndrome may be indicated.

TH-PO629

Association of Sleep Apnea with Mortality in Chronic and End Stage Kidney Disease Patients Manisha Jhamb,¹ Herbert T. Davis,² Mark L. Unruh,² ¹Univ of Pittsburgh; ²Univ of New Mexico.

Background: Presence of sleep apnea and its severity has been associated with increased mortality in the general population. In the dialysis population, limited evidence suggests an association of nocturnal hypoxemia with mortality. We sought to determine the association of sleep apnea and mortality in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Methods: 180 patients (87 CKD stage 4-5, 93 ESKD), underwent 1 night home polysomnography. Sleep apnea severity was measured as number of apneas and hypopneas per hour (apnea-hypopnea index, AHI). Information on patients' demographics, comorbidities and laboratory values was obtained from patient interviews and chart review. Mortality data was obtained from National Death Index. Chi-square and ANOVA were used to test between group differences and Cox proportional hazard model was employed to test association with mortality.

Results: 71% of the patients had sleep apnea (AHI≥5) and 23% had severe sleep apnea (AHI>30). There was no difference in age, race, hypertension, body mass index, smoking status, renal function status (CKD vs ESRD), depression, hemoglobin or albumin levels among patients with no or varying severity of sleep apnea. Males were more likely to have more severe sleep apnea. In both males and females, sleep apnea severity increased with age. Over a mean (SD) follow-up period of 9.0 (3.7) years, there were a total of 31 deaths and 57 patients received kidney transplant. We found no association between sleep apnea severity and all-cause mortality. However, in unadjusted analysis, more percentage of time with SpO₂ < 90% was associated with higher mortality [HR 1.03 (1.01-1.06), $p < 0.001$].

	AHI<5	AHI 5 < 15	AHI 15-30	AHI >30	P - value
AHI (events/hour)	2.4 (1.5)	8.7 (2.8)	21.6 (4.2)	57.7 (28.0)	<0.001
Age	47.7 (15.3)	54.4 (15.2)	58.5 (12.5)	56.4 (11.7)	0.09
Sex (male)	26 (50.0%)	21 (46.7%)	34 (81.0%)	32 (78.0%)	<0.001
Race (Black)	14 (26.9%)	14 (31.1%)	14 (33.3%)	14 (34.1%)	0.97
Diabetes	10 (19.2%)	16 (35.6%)	21 (50.0%)	17 (41.5%)	0.03
Death Rate per 100 person-years (95% CI)	2.15 (0.97-4.78)	4.68 (2.59-8.45)	4.45 (2.31-8.55)	2.24 (0.93-5.38)	-
All-cause mortality, unadjusted HR (95% CI)	1.0	2.48 (0.84-7.37)	2.09 (0.68-6.44)	1.07 (0.30-3.77)	-
All-cause mortality, adjusted HR (95% CI)*	1.0	3.7 (0.9-15.5)	1.7 (0.4 - 7.9)	1.2 (0.3-6.1)	-

*Adjusted for age, sex, diabetes and grp (CKD vs ESRD)

Conclusions: In patients with advanced CKD and ESRD, sleep apnea is common and increases in severity with age. Sleep apnea, as measured by AHI was not associated with all-cause mortality.

Funding: NIDDK Support, Private Foundation Support

TH-PO630

CKD Measures and Segment-Specific Arterial Stiffness: The Atherosclerosis Risk in Communities (ARIC) Study Kunihiro Matsushita,¹ Yuanjie Pang,¹ Yingying Sang,¹ Shoshana Ballew,¹ Hirofumi Tanaka,² Gerardo Nmn Heiss,³ Josef Coresh.¹ ¹Johns Hopkins Univ; ²Univ of Texas; ³Univ of North Carolina.

Background: Several studies have reported an association of CKD with arterial stiffness but generally focus on either, but not both, of eGFR or albuminuria, assess pulse wave velocity (PWV) at limited segments, or investigate clinical populations.

Methods: We studied 3,687 ARIC participants aged 66-90 (mean 75) years during 2011-13 after excluding those with missing variables and clinical conditions potentially biasing PWVs (e.g., morbid obesity). Four PWV parameters were assessed: carotid-femoral (cf, the indicator of central arterial stiffness), heart- and brachial-ankle (ha and ba, respectively, reflecting both central and peripheral stiffness), and femoral-ankle (fa, the indicator of peripheral stiffness). Multiple logistic regression was used to quantify the associations of eGFR and albuminuria with elevated PWV (highest 25% value) at each segment.

Results: There were 57.9% of women and 23.2% of blacks. After accounting for potential confounders, cfPWV was the only PWV parameter consistently and monotonically associated with both low eGFR and high ACR (Table). haPWV also demonstrated positive association with all high ACR categories. baPWV and faPWV were only significantly associated with high normal ACR (10-29 mg/g). None of haPWV, baPWV, and faPWV was significantly associated with low eGFR.

Conclusions: Both low eGFR and high ACR were independently associated with central arterial stiffness, with more robust results for ACR than for eGFR. In contrast, peripheral arterial stiffness tended to relate to high normal ACR but not necessarily to clinical ACR categories or low eGFR. These results suggest central artery stiffness as a pathophysiologic link in the cardiorenal interaction and potentially unique pathophysiology of elevated ACR within normal range.

Table. Adjusted* odds ratios (95% CIs) for high PWV according to CKD measures.

	creatinine-based eGFR, ml/min/1.73m ²					
	90+	75-89	60-74	45-59	30-44	<30
N	319	910	1196	833	353	76
cfPWV	1.14 (0.81, 1.62)	ref	1.18 (0.93, 1.50)	1.28 (0.99, 1.65)	1.41 (1.02, 1.96)	1.45 (0.83, 2.56)
haPWV	1.21 (0.87, 1.69)	ref	1.07 (0.85, 1.35)	1.13 (0.87, 1.45)	0.78 (0.55, 1.11)	0.80 (0.43, 1.51)
baPWV	1.48 (1.07, 2.06)	ref	1.07 (0.85, 1.35)	0.98 (0.76, 1.26)	0.72 (0.51, 1.02)	0.51 (0.26, 0.99)
faPWV	1.01 (0.74, 1.39)	ref	1.02 (0.83, 1.26)	0.89 (0.70, 1.14)	0.57 (0.40, 0.81)	0.63 (0.33, 1.19)
	Urine albumin-creatinine ratio (ACR), mg/g					
	<10	10-29	30-299	300+		
N	1886	1185	545	71		
cfPWV	ref	1.22 (1.01, 1.48)	1.42 (1.12, 1.81)	2.03 (1.18, 3.49)		
haPWV	ref	1.40 (1.15, 1.69)	1.48 (1.16, 1.90)	1.28 (0.71, 2.32)		
baPWV	ref	1.37 (1.13, 1.66)	1.25 (0.97, 1.60)	0.80 (0.42, 1.51)		
faPWV	ref	1.20 (1.00, 1.44)	1.17 (0.92, 1.49)	0.91 (0.48, 1.71)		

*Adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive drugs, cholesterol, history of cardiovascular disease, and each CKD measure

Significantly positive results in red

Funding: Other NIH Support - NHLBI

TH-PO631

Impact of Kidney Failure on Management and Outcome of Patients Admitted with Heart Failure Debasish Banerjee, Juan Carlos Kaski, Lisa J. Anderson. *Renal and Transplantation Unit, St. Georges Hospital, United Kingdom.*

Background: Data from epidemiological studies and intervention trials suggest poor prognosis in heart failure patients with kidney disease. However no study has investigated the impact of severe kidney failure on management and outcome of in-hospital heart failure patients.

Methods: We analysed data on clinical, laboratory, management and in-hospital mortality on 990 patients admitted between 01/03/2013 and 17/03/2013.

Results: Severe kidney failure (eGFR<30 ml/min/1.73m²) was present in 19% of patients and moderate kidney failure (eGFR 30-60 ml/min/1.73m²) was present in 43%. Patients with severe kidney failure, compared to the rest were older (79±11 vs. 75±13 years; $p < 0.001$), with lower haemoglobin (10.5±1.9 vs. 12±1.8 g/dL; $p < 0.001$), higher potassium (4.8±0.8 vs. 4.2±0.6 mmol/L; $P < 0.05$) and higher NT-pro BNP (17915±12911 vs. 9240±9577; $p < 0.001$). Diuretics use in severe kidney failure patients was less (85% vs. 90%, $p < 0.005$); however β blocker use was similar (74% vs. 75%). Furosemide dose was high in severe kidney failure (101±62 vs. 79±43 mg; $p < 0.001$) but dose of bumetanide was similar (3.9±2.3 vs. 4.1±1.9 mg, $p = 0.5$). In the presence of echocardiographic LV dysfunction severe kidney failure patients were less likely to be on ACEi or ARB (24% vs. 74%; $p < 0.001$). 98 patients who died during admission were older (78±10 vs. 76±13 years; $p < 0.05$), with lower haemoglobin (11.1±2.2 vs. 11.8±1.9 g/dL, $p < 0.01$), higher creatinine (191±123 vs. 135±93 μ mol/L; $p < 0.001$), higher NT-pro BNP (16536±12727 vs. 10174±10346, $p < 0.001$) and higher potassium (4.7±0.9 vs. 4.2±0.6 mmol/L, $p < 0.001$). In-hospital mortality was 6% in patients with eGFR>60, 8% with moderate kidney failure and 22% with severe kidney failure. Adjusted for age, haemoglobin, potassium and NT-pro BNP, presence of severe kidney failure was an independent predictor of mortality ($p < 0.01$).

Conclusions: Among hospital admissions for heart failure, patients with severe kidney failure had low haemoglobin, high potassium, high BNP; were less often on ACEi/ARB and diuretics; suffered higher in-hospital mortality. Severe kidney failure is common, adversely affects management and outcomes in admitted heart failure patients.

TH-PO632

Pulse Wave Velocity in Children with Chronic Kidney Disease
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Background: Pulse wave velocity (PWV) is a measure of arterial stiffness associated with CV events in the general population and adults with CKD. However, few data exist regarding PWV in children with CKD. We compared observed PWV to normative data in healthy children and examined risk factors associated with elevated PWV in children enrolled in the CKiD cohort study.

Methods: PWV was assessed via carotid/femoral tonometry using the SphygmoCor device (AtCor, Australia). PWV Z-score for height/gender was calculated from and compared to published pediatric norms (Reusz et al., 2010). Multivariate linear regression was used to assess the relationship between PWV and level of proteinuria (UP/C) adjusted for age, gender, race, height, waist circumference, mean arterial pressure (MAP), and GFR.

Results: 249 PWV studies were performed on 90 participants. 63% were male, 20% African American, 49% had glomerular CKD, 9% UP/C >2mg/mg; median age was 16 years, median MAP was 82mmHg, and median GFR was 67 ml/min. Average PWV was 5.1±0.9 m/s, Z-score= -0.01(1.2). As expected, PWV was significantly associated with age and MAP in multivariate analysis (Table 1). Additionally, the point estimate for UP/C was large but non-significant.

Conclusions: In this pediatric cohort with mild kidney dysfunction, arterial stiffness was comparable to that of normal children. Data collection is ongoing to further assess the effects of BP and proteinuria on arterial stiffness in children with CKD.

Table 1. PWV multivariate analysis.

Variable	Estimate ± SE	P-value
Age (years)	0.09 ± 0.04	0.02
Male	-0.05 ± 0.17	0.79
African American	0.12 ± 0.20	0.55
Height (cm)	-0.01 ± 0.01	0.41
Waist circumference (cm)	0.00 ± 0.01	0.47
MAP (mmHg)	0.03 ± 0.01	0.02
ieGFR (per 10 ml/min/1.73m ²)	-0.02 ± 0.04	0.56
UP/C (mg/mg)	-	-
<0.5	Ref.	-
0.5-2.0	0.03 ± 0.22	0.88
>2.0	0.34 ± 0.32	0.29

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

TH-PO633

The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study: Baseline Data of a Multicentre Prospective Observational Study
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Background: The role of CKD-specific factors in the initiation and progression of cardiovascular disease (CVD) are likely to be characterized with increased sensitivity in the pediatric age group. The Cardiovascular Comorbidity in Children with CKD (4C) Study is a multicentre, prospective, observational study in children with CKD aged 6 to 17 years, initial glomerular filtration rate 10-60 ml/min/1.73m². The prevalence, degree and progression of cardiovascular comorbidity and its association with CKD progression is explored through longitudinal follow-up.

Methods: The morphology and function of the heart and large arteries is monitored by non-invasive methods and compared with age-matched healthy controls.

Results: A total of 705 patients were enrolled in 55 participating centers from 12 European countries. At baseline examination, 30% of children were hypertensive (ambulatory blood pressure monitoring), 40% had left ventricular hypertrophy (echocardiography), 40% showed an increased intima-media thickness of the carotid artery (cIMT; ultrasound), and 23% an increase in aortic pulse-wave velocity (PWV; oscillometry). By multivariate analysis, systolic blood pressure and serum levels of 25-hydroxyvitamin D, parathyroid hormone, and serum calcium- and phosphorus levels showed significant associations with age-corrected IMT and PWV, respectively.

Conclusions: Children aged 6-17 years with CKD stage 3-5 have significant subclinical CVD. At initial examination, surrogate endpoints of CVD were associated with systolic blood pressure and disturbances of mineral metabolism.

TH-PO634

Impaired Systolic and Diastolic Left Ventricular Function in Children with Chronic Kidney Disease: Results from the Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study
Anke Doyon,¹ Pascal Haas,¹ Maria chiara Matteucci,² Francesca Mencarelli,³ Uwe Querfeld,⁴ Franz S. Schaefer.¹ ¹Univ Children's Hospital, Heidelberg, Germany; ²Ospedale Bambino Gesù, Rome, Italy; ³Univ Children's Hospital, Bologna, Italy; ⁴Charité Children's Hospital, Berlin, Germany.

Background: Tissue doppler (TD) velocities are sensitive markers of left ventricular function. The aim of this work was to describe TD velocities in a large cohort of children with chronic kidney disease and to assess risk factors for ventricular dysfunction.

Methods: A standardized echocardiographic exam was performed in 128 patients of the 4C Study aged 6-18 years with eGFR 10-60 ml/min/1.73 m². TD measurements of the left ventricle included early (E') and late (A') diastolic and systolic (S') velocity. Diastolic function was described by E'/A' ratio and left ventricular compliance by early diastolic conventional to tissue doppler (E/E') ratio. Measured values were normalized to z scores using reference data from 325 healthy children.

Results: TD diastolic E' velocity was reduced and A' increased at the mitral and septal annulus, resulting in a reduced E' to A' ratio (z-score -0.14, p<.0001) indicating diastolic dysfunction. Diastolic function (E'/A') was positively correlated with midwall fractional shortening (r=-0.23, p<.01). Reduced diastolic function was independently associated with declining renal function (β=0.006, p=0.005), increased systolic blood pressure (β=-0.04, p=0.045) and pulse wave velocity (β=-0.03, p=0.07). Left ventricular compliance was increased (z-score 0.65, p<.0001), possibly as a result of increased preload. Systolic TD velocities were significantly decreased (z-score -0.24, p=0.001). Reduced systolic velocities in TD imaging were inversely correlated to left ventricular compliance (r=-0.4, p<.0001). The LVMI was not associated to systolic or diastolic TD velocities.

Conclusions: TD evaluation showed alterations of both systolic and diastolic function in children with chronic kidney disease. Renal function and systolic blood pressure are independent predictors for diastolic function. TD velocities are independent of LV mass and provide early information about ventricular dysfunction.

Funding: Private Foundation Support

TH-PO635

Rapid Early Postnatal Growth Increases Blood Pressure Level in 5-Year-Old Children Born with Low Birthweight
Benedicte Stengel,¹ Marion Taine,² Marie-Aline Charles,² Barbara Heude.² ¹Epidemiology of Renal and Cardiovascular Disease Team, Inserm UMR1018, Villejuif, France; ²ORCHAD Team, Inserm UMR1153, Villejuif, France.

Background: Low birth weight (BW) is associated with hypertension and excess ESRD risk in adults, but whether postnatal growth may modify its impact on blood pressure (BP) and albuminuria in children is unknown. We studied the relationship of BW, gestational age (GA), and postnatal growth with BP and albuminuria in 5-year-old children.

Methods: We used data from the EDEN mother-child cohort of 1,119 children followed from birth to age 5. A mean of 17 weights were collected over this period which enabled to predict weights and weight growth velocities at any age. Three standard BP and albumin-to-creatinin ratio were measured at age 5. In order to avoid the reverse paradox phenomenon due to confounding by 5-year corpulence in the analysis of the relationship with BW, we studied BP SD-score preadjusted for age, gender, 5-year BMI and height. BW was also analyzed using age- and gender- specific z-score. We systematically tested interactions between BW categories and weight growth velocities in the relation with BP SD-score at different ages.

Results: Mean BW was 3,285±10 g. At 5 years of age, mean systolic BP was 101.5±0.3 mmHg in boys, and 102.7±0.3 in girls. After adjusting for mothers' pre-pregnancy BMI and hypertension status during pregnancy, the lower the BW z-score the higher the systolic BP SD score (beta=-0.06 ± 0.03, p=0.03), without gender interaction. In children born small for GA, faster weight growth in the first 4 months of life was associated with higher SBP SD-score at 5 years (p for interactions : 0.002 to 0.08 from 1 to 4 months), but not at older ages (p>0.20). Only boys born prematurely had elevated albuminuria level (>1mg/mmol) at age 5 : OR = 2.5[1.2-5.5].

Conclusions: Rapid early postnatal growth associates with higher blood pressure level in 5-year-old children born with low birthweight. They may deserve early monitoring for cardiovascular risk.

Funding: Government Support - Non-U.S.

TH-PO636

Kidney Function and Risk of Subclinical and Clinical Heart Failure in African Americans: The Jackson Heart Study
Ronit Katz,¹ Nisha Bansal, Ian H. De Boer, Jonathan Himmelfarb, Maryam Afkarian, Bryan R. Kestenbaum, Bessie A. Young. *Kidney Research Inst, Univ of Washington, Seattle, WA.*

Background: African-Americans (AA) and those with chronic kidney disease (CKD) have high risk for heart failure (HF). We determined in an AA cohort the association of kidney function with left ventricular disease (LVD) and risk of incident HF accounting for baseline LVD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: We studied Jackson Heart Study participants and calculated eGFR from baseline serum creatinine (CKD-EPI equation) and urine albumin-to-creatinine ratio (ACR) from urine samples. We tested association of eGFR and urine ACR with left ventricular mass (LVM), left ventricular ejection fraction (LVEF) and incident HF.

Results: In 3332 participants, 5% had eGFR<60ml/min/1.73m² and 12% had urine ACR>30mg/g. Mean LVM was higher in those with eGFR<60 (175g vs 147g) and urine ACR>30 (169g vs 143g). Mean LVEF was similar across eGFR and ACR levels. The association of eGFR with LVM was significant adjusting for age, sex, education, blood pressure, BMI, smoking, hypertension, statins, diabetes and cardiovascular disease (β-coefficient 13g[95% CI:7,19]), while association with LVEF was not (β-coefficient -0.9%[95% CI:-1.9,0.1]). Urine ACR>30mg/g was associated with higher LVM in adjusted models (β-coefficient 6g[0.7,11]); however, was not associated with LVEF (adjusted β-coefficient -0.4[95%CI:-1.2,0.4]). Rate of HF events was greater in those with CKD (Table). Higher urine ACR was strongly linked with incident HF after adjusting for LVM and LVEF (Table).

Association of kidney function with risk of incident heart failure among participants in the Jackson Heart Study

	N	#with HF	Rate/year	Model 1* HR (95% CI)	MI + LVM HR (95% CI)	MI + LVEF HR (95% CI)
eGFR (per 10 decrease)	3073	84	0.75	1.03 (0.92, 1.14)	0.99 (0.89, 1.10)	1.03 (0.92, 1.15)
eGFR						
≥ 60	2939	71	0.66	1.00 (ref)	1.00 (ref)	1.00 (ref)
<60	134	13	2.51	1.20 (0.61, 2.36)	0.92 (0.45, 1.86)	1.20 (0.61, 2.36)
ACR (per doubling)	3073	84	0.75	1.14 (1.02, 1.28)	1.11 (0.99, 1.24)	1.14 (1.02, 1.27)
ACR						
<30	2745	61	0.60	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥ 30	328	23	2.01	2.09 (1.14, 3.81)	1.93 (1.03, 3.65)	2.09 (1.10, 3.98)

*adjusted for age, sex, systolic blood pressure, diastolic blood pressure, BMI, tobacco use, hypertension medications, lipid lowering medications, history of CHD, history of stroke, history of diabetes, ACR (for eGFR) or eGFR (for ACR)

Conclusions: LVM was higher in AA with lower eGFR and higher ACR. Higher urine ACR was linked with incident HF and not entirely explained by LVD. We show the importance of mild/early kidney dysfunction with risk of HF among AA. More study is needed to characterize the mechanisms by which kidney disease contributes to worse outcomes in HF in this group.

Funding: NIDDK Support

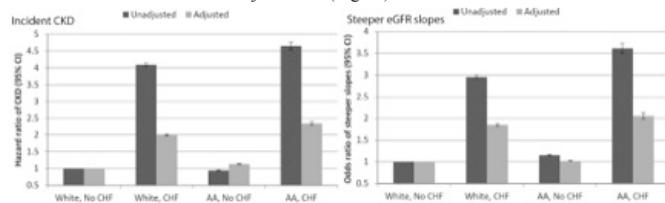
TH-PO637

Racial Differences in Risk of Chronic Kidney Disease in Patients with Congestive Heart Failure Lekha K. George,¹ Santhosh K. Koshy,¹ Miklos Zsolt Molnar,¹ Jun Ling Lu,¹ L. Ebony Boulware,² Keith C. Norris,³ Kamyar Kalantar-Zadeh,⁴ Csaba P. Kovesdy.^{1,5} ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Duke Univ School of Medicine, Durham, NC; ³UCLA, CA; ⁴Univ of California, Irvine, CA; ⁵VA Medical Center, Memphis, TN.

Background: While CKD is more common in African Americans (AA), the prevalence of CV disease is lower in AA patients with CKD. It is unclear if the higher risk of incident CKD associated with AA race is modified by the presence of CHF.

Methods: Among 3,065,749 AA or white US veterans with eGFR>60ml/min/1.73m², we identified 143,229 with a diagnosis of CHF (17% AA), and 2,922,520 with no CHF (18% AA). We examined the interaction of race with CHF for the risk of incident CKD and rapid rate of decline in eGFR (slopes <-5 ml/min/1.73m²/yr) during a median follow up of 7.8 yrs. We examined outcomes in Cox models (for CKD) and logistic regression (for slopes), including interaction terms for race-CHF, and adjusting for baseline age, gender, race, comorbidities, BMI, BP, eGFR and medication use.

Results: Mean±SD baseline age and eGFR were 68±11 yrs and 79±14 ml/min/1.73m² for patients with CHF, vs. 59±14 yrs and 84±16 ml/min/1.73m² for those without CHF. 327,548 (11%) patients developed incident CKD and 253,081 (9%) experienced rapid eGFR decline. AA race showed a significant interaction with HF for both CKD incidence (p=0.009) and loss of kidney function (p<0.001). Compared to white patients with no CHF, AA patients with CHF experienced a >2-fold higher risk of incident CKD and more rapid eGFR loss after multivariable adjustments (Figure).



Conclusions: The increased risk of renal complications associated with AA vs. white race is higher in patients with CHF compared to those with no CHF. Interventions aimed at improving renal outcomes in AA patients with CHF should be further examined.

Funding: NIDDK Support, Veterans Administration Support

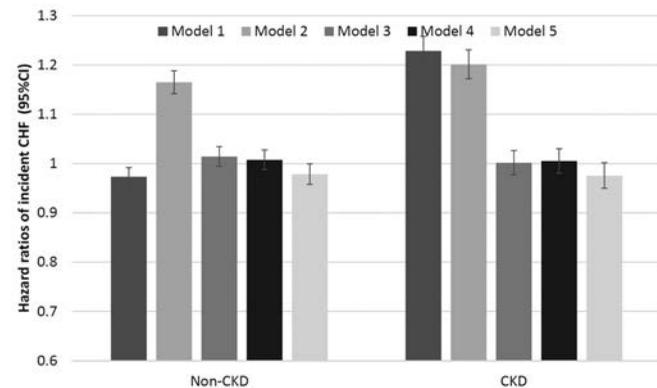
TH-PO638

Incidence of Congestive Heart Failure in African-American versus White Patients with and without Chronic Kidney Disease Csaba P. Kovesdy,^{1,2} Miklos Zsolt Molnar,² Praveen Kumar Potukuchi,² Jun Ling Lu,³ Kamyar Kalantar-Zadeh.³ ¹Memphis VA Medical Center; ²Univ of Tennessee Health Science Center; ³Univ of California Irvine.

Background: African Americans (AA) are at higher risk of cardiovascular disease and its complications, such as congestive heart failure (CHF). CKD is also more common in AA, yet the prevalence of coronary artery disease is lower in AA patients with CKD. It is unclear if the risk of CHF is also lower in AA with CKD, given its more complex pathophysiology in patients with kidney disease.

Methods: Among 2,929,736 AA (N=523,181) or white (N=2,406,555) US veterans with eGFR≥60 ml/min/1.73m² and no CHF at baseline, we examined the association of AA race with incident CHF (hospitalization-based ICD9 codes) during a median follow up of 6.7 yrs. We examined outcomes separately in patients who maintained an eGFR≥60 ml/min/1.73m² (non-CKD group; N=2,632,034), and those who developed 2 eGFR values <60 with >90 days in-between (CKD group; N=286,597). We used Cox proportional hazards models, without adjustments (Model 1) and with sequential adjustments for baseline demographics and eGFR (Model 2), comorbidities (Model 3), BMI and BP (Model 4), and medications and socioeconomic indicators (Model 5).

Results: 71,137 (event rate: 4.8/1000 patient-years, 95%CI: 4.8-4.9) and 42,067 (26.4/1000PY, 26.2-26.7) patients developed CHF in the non-CKD and CKD groups, respectively. Compared to whites, AA race was associated with similar unadjusted risk of CHF in non-CKD (hazard ratio, 95%CI: 0.97, 0.95-0.99), but with higher unadjusted risk among CKD (1.23, 1.20-1.26). After adjustments, the risk of CHF in AA was minimally lower in both non-CKD and CKD patients (Figure1).



Conclusions: The risk of incident CHF is slightly lower in AA US veterans with and without CKD. These qualitatively different associations compared to the non-veteran population warrant additional studies.

Funding: NIDDK Support, Veterans Administration Support

TH-PO639

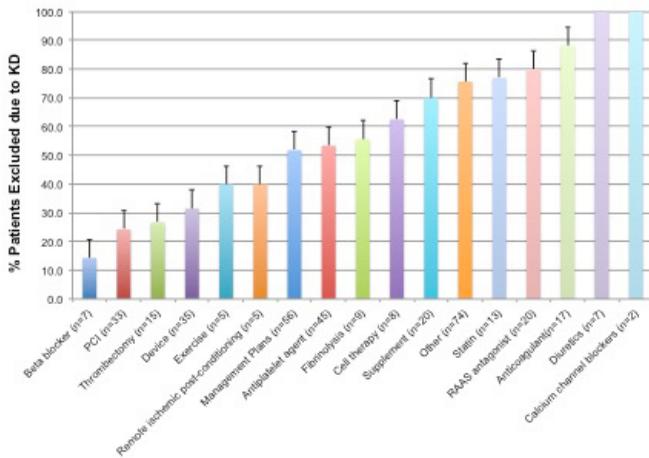
Continued Underrepresentation of Patients with Kidney Disease in Cardiovascular Trials: An Updated Systematic Review After a Decade Ioannis Konstantinidis,¹ Aparna Saha,¹ Priti R. Poojary,¹ Priya Simoes,¹ Rabi Yacoub,¹ Chirag R. Parikh,² Girish N. Nadkarni,¹ Steven G. Coca.¹ ¹Mount Sinai Medicine; ²Yale Univ.

Background: Cardiovascular disease (CVD) is a major cause of morbidity/mortality in kidney disease (KD). Two systematic reviews showed that KD patients are underrepresented in CVD randomized controlled trials (RCTs) using data from 1985-2005 and 1998-2005. We aimed to update estimates of KD patient representation in major CVD RCTs over the past decade.

Methods: We searched MEDLINE for congestive heart failure/acute coronary syndrome RCTs in major journals between 2006-2014. We excluded RCTs not reporting mortality outcomes, with <100 participants, or were subgroup, follow-up, or post-hoc analyses.

Results: We included 371 trials randomizing 590,040 participants. KD patients were excluded in 212 (57.1%) RCTs and were more likely to be excluded from North American (p=0.02) or industry-funded (p=0.01) trials. They were more likely to be excluded in RCTs of anticoagulants, antiplatelet agents, statins or RAAS antagonists compared to trials of PCI (p<0.01).

Figure 1: Proportion of Trials Excluding Patients with Kidney Disease Based on Intervention Type



Of 212 RCTs excluding KD patients, 111 (52.4%) used serum creatinine, 25 (11.8%) used eGFR cut-offs, 23 (10.8%) used creatinine clearance, 60 (28.3%) excluded if on renal replacement and 36 (17.0%) had non-specific kidney-related exclusions. Only 156 (42.0%) trials reported baseline kidney function and only 84 (22.6%) trials reported the proportion of KD patients in each randomization arm. While 197 (53.1%) reported subgroup analyses of >1 non-renal baseline characteristics, only 60 (16.2%) reported subgroup analyses by renal parameters.

Conclusions: Most CVD RCTs continue to exclude KD patients. They neither adequately report nor analyze outcomes by participants' baseline kidney function.

Funding: NIDDK Support

TH-PO640

Effect of Niacin on Markers of Mineral Metabolism in CKD: The AIM-HIGH Trial Joachim H. Ix,¹ Ronit Katz,² Andrew N. Hoofnagle,² Dena E. Rifkin,¹ Andrew Bostom,³ Jeffrey L. Probstfield,² Geoffrey A. Block,⁴ ¹UCSD; ²U Washington; ³Brown Univ; ⁴Denver Nephrology.

Background: Niacin blocks intestinal phosphate (P) transport in vitro. Short-term human studies suggest niacin lowers P in CKD patients. Longer-term effects on P, and on other mineral markers are uncertain. Fibroblast growth factor (FGF) 23 is a phosphaturic hormone that induces left ventricular hypertrophy in vitro and higher levels are associated with heart failure and death in CKD patients. Higher serum P may stimulate higher FGF23. We hypothesized that 3-year treatment with niacin would induce lower plasma P (1^o aim) and FGF23 (2^o aim) in CKD patients.

Methods: AIM-HIGH randomized 3,414 patients with cardiovascular disease (CVD) and dyslipidemia to sustained-release niacin 1500-2000mg vs. placebo (pbo) for prevention of recurrent CVD events (1^o endpoint). Both groups were on a background of statin therapy. Exclusions included serum Cr ≥ 2.7mg/dL. The trial was stopped after 3 yrs mean follow-up due to futility. In 352 patients with eGFR < 60 ml/min/1.73 m², we measured plasma P, calcium (Ca), intact (i) FGF23 (Kainos), intact parathyroid hormone (iPTH), and calcitriol (LC/MS) at baseline, yr 1, and yr 3. Mean levels were compared between arms, and linear mixed models provided summary estimates of the effect of niacin on each.

Results: Demographics, CVD history, and CVD risk factors were well balanced in the pbo (n=174) and niacin (n=178) arms at baseline. Mean eGFR was 47±8 and 45±9 ml/min/1.73 m², respectively. At 3 yrs, P was 0.25mg/dL lower in the niacin vs. pbo arm. No significant differences were noted in iFGF23, Ca, iPTH, or calcitriol between arms at 3 yrs.

	Placebo (n=174)	Niaspan (n=178)	P-value
Phosphate, mg/dL; mean ± SD			
Baseline (n=351)	3.43±0.58	3.44±0.59	0.849
Year 1 (n=291)	3.40±0.60	3.38±0.61	0.762
Year 3 (n=139)	3.57±0.47	3.32±0.53	0.003
Difference in Slopes (95% CI)	-0.08 (-0.13, -0.02)		0.005
iFGF23, pg/mL; median (IQR)			
Baseline (n=352)	74 (60, 97)	72 (54, 101)	0.749
Year 1 (n=297)	80 (60, 102)	73 (60, 102)	0.092
Year 3 (n=140)	71 (54, 94)	75 (57, 102)	0.866
Difference in Slopes (95% CI)	-0.47 (-5.46, 4.53)		0.855
Calcium, mg/dL; mean ± SD			
Baseline (n=344)	9.54±0.55	9.67±0.54	0.032
Year 1 (n=289)	9.55±0.50	9.64±0.58	0.160
Year 3 (n=135)	9.63±0.48	9.66±0.60	0.770
Difference in Slopes (95% CI)	-0.03 (-0.08, 0.03)		0.312
iPTH, pg/mL; median (IQR)			
Baseline (n=349)	53 (38, 76)	51 (36, 71)	0.566
Year 1 (n=295)	54 (34, 75)	44 (29, 65)	0.003
Year 3 (n=140)	51 (34, 79)	45 (36, 67)	0.866
Difference in Slopes (95% CI)	-2.11 (-4.94, 0.71)		0.142
Calcitriol, ng/ml; mean ± SD			
Baseline (n=339)	31.7±11.2	30.5±11.1	0.315
Year 1 (n=280)	31.0±11.1	30.6±10.2	0.797
Year 3 (n=135)	33.3±12.2	32.1±13.1	0.590
Difference in Slopes (95% CI)	-0.17 (0.133, 0.98)		0.769

Conclusions: Niacin lowers serum P in CKD patients, an effect that extends for 3 yrs. We observed no significant effect of niacin on other mineral measures. Regulation of FGF23 may be more complex than simply reflecting changes in serum P.

Funding: NIDDK Support, Veterans Administration Support

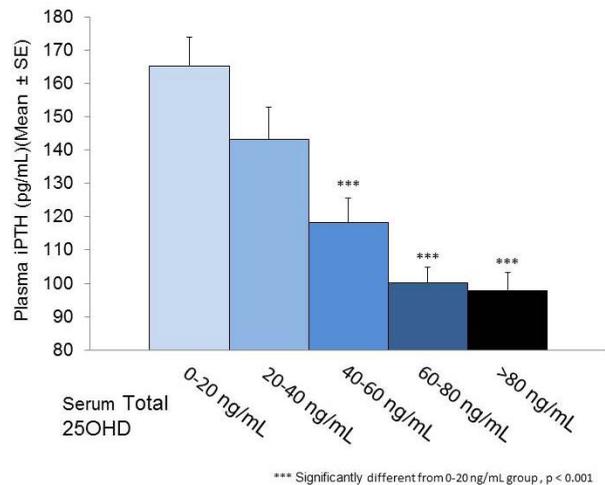
TH-PO641

Efficacy and Safety of Modified-Release Calcifediol in Stage 3-4 CKD Patients with Secondary Hyperparathyroidism and Vitamin D Insufficiency Stuart M. Sprague,¹ Stephen A. Strugnelli,² Joel Z. Melnick,² Jay A. White,² Martin P. Petkovich,³ Charles W. Bishop,² ¹Medicine, NorthShore Univ HealthSystem-Univ of Chicago, Evanston, IL; ²OPKO Health, Miami, FL; ³Queens Univ, Kingston, ON, Canada.

Background: Current approaches to correct vitamin D insufficiency (VDI) in stage 3 or 4 CKD are poorly defined and generally ineffective in controlling secondary hyperparathyroidism (SHPT). The effectiveness of modified-release calcifediol (MRC) at correcting VDI and controlling SHPT was evaluated.

Methods: Two identical, randomized, double-blind, placebo-controlled trials were conducted in patients with SHPT (>85 pg/mL), stage 3 or 4 CKD and VDI (serum 25OHD of 10-29 ng/mL). The trials enrolled a total of 429 subjects from 77 US sites, randomized 2:1 to receive MRC or placebo for 26 weeks. MRC dosing started at 30 mg/d and increased, as needed to lower iPTH, to 60 mg/d after 12 weeks. Subjects were stratified based upon their 25OHD levels (0-20, 20-40, 40-60, 60-80 or > 80 ng/mL) at the end of treatment (EOT). The mean EOT plasma iPTH, serum total 1,25-dihydroxyvitamin D (1,25D), serum Ca and Phos in each group were calculated and compared.

Results: A total of 364 (85%) subjects completed the trials. Serum 1,25D levels progressively increased with increasing 25OHD concentrations, with mean levels 41% higher in the highest quintile compared to the lowest (p < 0.001). Conversely, plasma iPTH progressively decreased with increasing 25OHD concentrations, with mean iPTH levels 40% lower in the subjects with the highest- 25OHD concentrations compared to the lowest concentrations (Figure; p < 0.001). No changes were observed in serum Ca and Phos concentrations independent of 25OHD concentration.



Conclusions: MRC increased serum total 25OHD levels and total 1,25D, while reducing plasma iPTH, without significantly increasing serum Ca or Phos in CKD patients with SHPT and VDI.

Funding: Pharmaceutical Company Support - OPKO Health

TH-PO642

CKD-MBD Indices After 52 Weeks of Sucroferric Oxyhydroxide, an Iron-Based Phosphate Binder, in African American Dialysis Patients Stuart M. Sprague,¹ Anjay Rastogi,² Markus Ketteler,³ Adrian C. Covic,⁴ Jürgen Floege,⁵ Viatcheslav Rakov,⁶ Llera Armando Samuels,⁷ ¹NorthShore Univ Health System, Chicago; ²Univ of California; ³Coburg Clinic and KfH-Dialysis Center, Germany; ⁴Gr.T. Popa Univ of Medicine and Pharmacy, Romania; ⁵RWTH Univ Hospital Aachen, Germany; ⁶Vifor Pharma; ⁷Temple Univ, Philadelphia.

Background: A *post hoc* analysis of data from a randomized, open-label, Phase 3 study and its extension investigated the effects of the iron-based phosphate binder sucroferric oxyhydroxide (SFOH; VELPHORO®) vs sevelamer carbonate (SEV; Renvela®) on chronic kidney disease-mineral bone disorder (CKD-MBD) indices in African American dialysis patients.

Methods: Overall, 1059 patients were randomized to SFOH (1.0-3.0 g/day; n=710) or SEV (2.4-14.4 g/day; n=349) for 12 weeks' dose titration then 12 weeks' maintenance. Eligible patients enrolled in a 28-week extension study.

Results: Of the 549 patients who completed the extension study, 100 were African American patients, (n=48, SFOH; n=52, SEV). Serum phosphorus control was maintained over 1 year; both SFOH and SEV were associated with significant decreases in serum phosphorus from baseline to Week 52 (Table), as well as significant reductions in mean

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

serum fibroblast growth factor-23 (FGF-23). Decreases in mean serum intact parathyroid hormone (iPTH) were seen with both treatments over 52 weeks, but were not significant with SFOH. There were small but statistically significant increases in total calcium levels in both groups over 52 weeks. No significant differences between treatment groups were observed for any of the indices reported here.

Conclusions: SFOH and SEV led to reductions in serum phosphorus, FGF-23 and iPTH over 1-year of treatment in African American dialysis patients. *Post hoc* results so far reflect those from the overall study population.

Table: Serum levels of CKD-MBD indices in African American patients (completers; N=100)

Parameter, mean (SD)	SFOH (n=48)	SEV (n=52)
Phosphorus, mg/dL		
Baseline	7.4 (1.97)	7.3 (1.36)
Δ at Week 52	-2.1 (2.58)	-2.1 (1.58)
P-value	<0.0001	<0.0001
FGF-23, µg/L		
Baseline	234.3 (297.72)	136.5 (242.02)
Δ at Week 52	-174.2 (253.40)	-90.0 (202.84)
P-value	<0.0001	0.0032
iPTH, pg/mL		
Baseline	608.3 (342.95)	494.3 (318.80)
Δ at Week 52	-67.8 (433.59)	-84.0 (296.55)
P-value	n.s.	0.0464
Total calcium, mg/dL		
Baseline	8.8 (0.71)	9.0 (0.70)
Δ at Week 52	0.4 (0.92)	0.4 (0.68)
P-value	0.0114	<0.0001

CKD-MBD, chronic kidney disease-mineral bone disorder; FGF-23, fibroblast growth factor-23; iPTH, intact parathyroid hormone; n.s., not significant; SEV, sevelamer carbonate; SD, standard deviation; SFOH, sucroferriic oxyhydroxide.

Funding: Pharmaceutical Company Support - Vifor Pharma

TH-PO643

Concomitant IV Iron Use Drives Changes in Iron Indices in African American Dialysis Patients Over 52 Weeks of Sucroferriic Oxyhydroxide Treatment *Stuart M. Sprague,¹ Anjay Rastogi,² Markus Ketteler,³ Adrian C. Covic,⁴ Jürgen Floege,⁵ Viatcheslav Rakov,⁶ Llera Armando Samuels.⁷* ¹NorthShore Univ Health System, Chicago; ²Univ of California; ³Coburg Clinic and KfH-Dialysis Center, Germany; ⁴Gr.T. Popa' Univ of Medicine and Pharmacy, Romania; ⁵RWTH Univ Hospital Aachen, Germany; ⁶Vifor Pharma; ⁷Temple Univ, Philadelphia.

Background: A *post hoc* analysis of data from a randomized, open-label, Phase 3 study and its extension investigated iron indices after treatment with the iron-based phosphate binder sucroferriic oxyhydroxide (VELPHORO[®]; SFOH) vs sevelamer carbonate (SEV) in African American dialysis patients who received IV iron vs those who did not.

Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12 weeks' dose titration then 12 weeks' maintenance. Eligible patients enrolled in a 28-week extension study.

Results: Of the 549 patients who completed the extension study, 100 were African American (n=48, SFOH; n=52, SEV). A high proportion of patients in the SFOH and SEV groups received IV iron (95.8 and 92.3%) and erythropoietin-stimulating agents (95.8 and 98.1%) during the 1-year study. Baseline levels of ferritin appeared elevated in both treatment groups with higher levels in the SEV group (Table). Significant increases in ferritin were observed in SFOH 'IV iron' subgroup. Ferritin and TSAT levels increased only in patients receiving IV iron. Hemoglobin was relatively stable over 1 year.

Conclusions: Changes in iron indices in both treatment groups were mainly attributable to concomitant IV iron use. Differences between groups may be due to baseline differences and minimal iron uptake from SFOH, although no signs of iron accumulation were observed over 1 year. *Post hoc* results, in terms of changes in iron indices, reflect those from the overall study population.

Table: Serum levels and changes in iron indices in African American patients by concomitant iron use during the study (completers; N=100).

Parameter, mean (SD)	SFOH (n=48)		SEV (n=52)	
	IV iron (n=46)	No IV iron (n=2)	IV iron (n=48)	No IV iron (n=4)
Ferritin, ng/mL				
Baseline	797.5 (412.57)	1402.0 (420.02)	970.3 (379.50)	1489.5 (389.36)
Δ at Week 52	290.8 (283.61)*	-426.5 (50.20)	44.3 (391.85)*	-489.5 (199.92)
P-value	<0.0001	n.s.	n.s.	0.0163
Transferrin saturation, %				
Baseline	32.0 (16.99)	57.0 (7.07)	29.1 (11.51)	33.3 (8.96)
Δ at Week 52	0.3 (23.45)	-23.0 (11.31)	4.1 (16.21)	-6.8 (7.09)
P-value	n.s.	n.s.	n.s.	n.s.
Hemoglobin, g/L				
Baseline	117.2 (9.83)	115.5 (9.19)	115.4 (7.51)	113.8 (5.12)
Δ at Week 52	-3.9 (12.19)	-5.5 (7.78)	-1.7 (10.52)	2.0 (12.46)
P-value	0.0339	n.s.	n.s.	n.s.

*P<0.05 for SFOH vs SEV. SEV, sevelamer carbonate; SD, standard deviation; SFOH, sucroferriic oxyhydroxide.

Funding: Pharmaceutical Company Support - Vifor Pharma

TH-PO644

The Effectiveness and Safety of Cinacalcet: Randomized, Open Label Study in Chronic Hemodialysis Patients with Severe Secondary Hyperparathyroidism *Paweena Susantitaphong,¹ Teerada Susomboon,² Wanchana Singhan,² Somrattai Vadcharavivad,² Kearkiat Praditpornsilpa.¹* ¹Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand; ²Dept of Pharmacy Practice, Chulalongkorn Univ, Bangkok, Thailand.

Background: Secondary hyperparathyroidism (HPT) results in high incidence of cardiovascular disease, bone fracture, and mortality. This study was conducted to demonstrate the efficacy of treatment with cinacalcet compared to control group for controlling plasma parathyroid hormone (iPTH) levels among hemodialysis (HD) subjects with severe secondary HPT.

Methods: 60 adult HD patients with iPTH > 800 pg/mL and serum calcium > 9 mg/dL was randomized 1:1 for treatment (cinacalcet 25-100 mg/day) and control group for 12 weeks follow up. The patients who previously received cinacalcet and parathyroidectomy were excluded. Achievement of >30% reduction of iPTH from baseline was set up as primary end-point.

Results: The mean baseline iPTH of both groups were comparable (1,435±506 pg/mL in control group and 1,535±965 pg/mL in treatment group). Following 12-week treatment in 30 HD patients, the percentage reductions of iPTH was significantly different (-67% in treatment group and -13% in control group, P=0.02). Regarding the ethic issue, we switched the patients in control group to treatment group and follow up as prospective cohort study to further explore the optimal cinacalcet dose on baseline iPTH. The mean cinacalcet dose was 50±23 mg/day. The mean serum calcium and phosphate were significantly decreased from baseline. On contrary, the dialysate calcium was significantly increased from baseline. Subgroup analysis by baseline iPTH on efficacy of cinacalcet showed that higher iPTH level associated with less reduction of iPTH to achieve primary end-point.

Subgroup by baseline PTH level in cinacalcet group	Equal or greater 30% reduction of PTH from baseline at 12-wk follow up
PTH 801-1600 pg/mL	22/26 (85%)
PTH 1601-2400 pg/mL	8/14 (57%)
PTH 2401-3200 pg/mL	1/2 (50%)
PTH >3,200 pg/mL	1/3 (33%)
P-Value (Linear by linear association)	0.018

Conclusions: The high efficacy of cinacalcet was still demonstrated even in case of severe secondary HPT. However, higher iPTH reduced the efficacy outcome of cinacalcet.

TH-PO645

A Double-Blind, Randomized, Placebo-Controlled Trial of Ergocalciferol with/without Calcitriol in Chronic Kidney Disease with Proteinuria *Paweena Susantitaphong, Siriwan Nakwan, Khajohn Tiranathanagul, Pisut Katavetin, Kearkiat Praditpornsilpa, Somchai Eiam-ong.* *Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.*

Background: These are no available data regarding the role of natural vitamin D with/without active vitamin D on proteinuria and renal function in CKD patients with vitamin D insufficiency/deficiency. This study was conducted to explore the additional effect of both active vitamin D (calcitriol) and natural vitamin D (ergocalciferol) on proteinuria and kidney function in CKD with vitamin D insufficiency/deficiency.

Methods: The first double-blind, randomized placebo-controlled trial was performed to answer this question. Sixty eight patients with eGFR 15-60 mL/min/1.73m², UPCR greater than 1 g/g, and vitamin D insufficiency/deficiency were enrolled. Patients were randomly assigned to receive 12-week treatment with oral ergocalciferol plus placebo (n=36) or ergocalciferol plus oral calcitriol (n=32).

Results: The mean baselines UPCR of both groups were comparable (3.6 ± 3.8 g/g in combined group and 3.5±3.0 g/g in ergocalciferol group). Following 12-week treatment, there were significant reductions in UPCR of both groups from baseline (2.3± 2.1 g/g in combined group and 2.4± 2.0 g/g in ergocalciferol group). The percentage reductions in UPCR of both groups were not significantly different (-25.5% in combined group and -23.7% in ergocalciferol group). These effects were demonstrated in all range of proteinuria, diabetic nephropathy, non-diabetic nephropathy, receiving RAAS blockade and non-receiving RAAS blockade. The mean eGFR and blood pressure did not differ between baseline and 12-week follow up and between both groups. No severe hypercalcemia or serious side effects were noted in both groups.

Conclusions: This is the first RCT which illustrates the lowering proteinuria effect of ergocalciferol in CKD patients with vitamin D deficiency. However, additional calcitriol did not have more effects on proteinuria. Therefore, ergocalciferol should be added for more decreasing proteinuria in CKD patients with proteinuria that cannot tolerate or increase the dosage of RAS blockade due to any side effects. A longer study is required to examine the renal function retardation effects.

TH-PO646

Anemia Correction with Roxadustat Lowers Hepcidin in Chronic Kidney Disease (CKD) Patients Lynda Szczech, Anatole Besarab, Khalil Georges Saikali, Stefan Hemmerich, Lona Poole, Gopal Saha, Kin-Hung Peony Yu, Frank H. Valone, Thomas B. Neff. *FibroGen, San Francisco, CA.*

Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) is being developed for treatment of CKD anemia. Hepcidin regulates iron metabolism and higher levels are associated with greater mortality. This analysis of phase 2 studies was undertaken to explore the consistency of the suppressive effect of roxadustat on hepcidin.

Methods: Among CKD-NDD (017 and 041) & CKD-DD (040 and 053) studies, roxadustat doses, study duration, and comparator (placebo or epoetin) varied. Studies restricted IV iron in general but allowed oral iron. Baseline (BL) hepcidin and change from BL (CFB) are summarized (mean±SD) overall and by BL tertile. Significant differences (p<0.05 vs BL) based on within-group comparisons (*).

Results: Mean BL hepcidin in CKD-NDD roxadustat subjects was 292.8±179.8 and 120.3±107.0 ng/mL (studies 017 & 041). Hepcidin fell with roxadustat treatment by 158.4±179.2 & 45.6±87.7. Mean BL hepcidin in CKD-DD roxadustat subjects was 303.9±172.9 & 91.1±90.0 (040 and 053). Hepcidin fell with roxadustat treatment by 26.7±192.0 & 57.4±68.5. For both groups, the greatest declines were in the highest BL tertiles.

Study	Treatment	Hepcidin at BL	CFB during treatment (4 wks, 8 wks for 041)	CFB: highest tertile BL hepcidin	CFB: middle tertile BL hepcidin	CFB: lowest tertile BL hepcidin
017	Roxadustat (N=38)	292.8±179.8	-158.4±179.2 [^]	-290.7±211.2 [^]	-132.3±67.7	-52.2±106.5 [^]
	Placebo (N=15)	288.7±176.3	-29.0±70.6			
041	Roxadustat (N=139)	120.3±107.0	-45.6±87.7 [^]	-108.3±120.7 [^]	-22.2±63.6 [^]	-14.2±23.1 [^]
040	Roxadustat (N=100)	303.9±172.9	-26.7±192.0	-90.3±247.6	-32.6±166.7	27.7±151.8
	Epoetin alfa (N=34)	283.6±135.2	25.5±147.9			
053	Roxadustat (N=57)	91.1±90.0	-57.4±68.5 [^]	-112.6±93.1 [^]	-45.2±26.5 [^]	-16.7±17.7 [^]

Conclusions: Roxadustat consistently lowered hepcidin in phase 2 studies. The decrement in hepcidin is greatest among those with the highest BL levels. The roxadustat phase 3 trials will include measurements of hepcidin to further define this effect.

Funding: Pharmaceutical Company Support - FibroGen

TH-PO647

Anemia Correction with Roxadustat Increases Soluble Transferrin Receptor (sTfR) in Chronic Kidney Disease (CKD) Patients Lynda Szczech, Anatole Besarab, Khalil Georges Saikali, Stefan Hemmerich, Lona Poole, Kin-Hung Peony Yu, Frank H. Valone, Thomas B. Neff. *FibroGen, San Francisco, CA.*

Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat corrected anemia in phase 2 trials without IV iron. This analysis of 4 phase 2 studies explores roxadustat's effect on sTfR levels.

Methods: In phase 2 studies CKD-NDD 017 & 047 and CKD-DD 040 & 048, subjects were randomized to roxadustat at different doses with comparator arms of placebo or epoetin-alfa. Studies restricted IV iron use in general but allowed oral iron. sTfR at baseline (BL) and % change from BL were summarized by treatment.

Results: Among CKD-NDD subjects (n=125), BL sTfR mean±SD was 1.35±0.56 and 3.58±1.69 mg/L (studies 017 & 047 respectively) in roxadustat groups. sTfR rose with roxadustat treatment in both studies by 86.5% and 101.5%. These increases were greater than the placebo arm (15.3% & 2.6%, p=0.0081 & <0.0001 respectively). Among subjects with CKD-DD (n=199), BL sTfR mean±SD was 3.57±1.41 and 3.33±1.47 mg/L (studies 048 & 040 respectively) in the roxadustat group. In 040, the increase in the roxadustat group was greater than in the epoetin arm (31.1% vs -0.7% respectively, p=0.0013). However, in 048, the changes in sTfR were comparable to epoetin arm (32.1 vs 39.9% respectively).

Study Population (N)	Control (N)	Baseline sTfR mg/L Mean (SD)		EOT	% Change from BL Mean (SD)	
		Roxadustat	Control		Roxadustat	Control
017 CKD-NDD (24)	Placebo (10)	1.35 (0.56)	1.37 (0.43)	Day 26-29	86.5 (92.9)	15.3 (42.7)
047 CKD-NDD (61)	Placebo (30)	3.58 (1.69)	3.47 (1.20)	Week 8	101.5 (72.2)	2.6 (17.8)
040 CKD-DD (78)	Epoetin (26)	3.33 (1.47)	3.52 (1.04)	Day 43	31.1 (60.1)	-0.7 (21.3)
048 CKD-DD (73)	Epoetin (22)	3.57 (1.41)	2.92 (1.21)	Week 7	32.1 (54.6)	39.9 (61.8)

Conclusions: Roxadustat consistently increased sTfR in phase 2 studies with oral iron supplementation. Placebo had little effect on sTfR, and epoetin results varied. The consistent increase in sTfR supports sufficient iron delivery for erythropoiesis during the time periods studied. The coordinated erythropoiesis induced by roxadustat is being evaluated in phase 3 trials.

TH-PO648

Anemia Correction with Roxadustat Lowers Cholesterol in Chronic Kidney Disease (CKD) Patients Lynda Szczech, Anatole Besarab, Khalil Georges Saikali, Stefan Hemmerich, Brian K. Roberts, Lona Poole, Kin-Hung Peony Yu, Frank H. Valone, Thomas B. Neff. *FibroGen, San Francisco, CA.*

Background: Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor roxadustat is being developed for CKD anemia. The HIF pathway affects cholesterol metabolism & ascension to altitude reduces total cholesterol (TC). This analysis of phase 2 studies explores roxadustat's effect on TC in non-dialysis (NDD) and dialysis (DD) CKD.

Methods: In Phase 2 studies 41&47 in NDD & 40,48&53 in DD, roxadustat dose, study duration and comparator (placebo, epoetin) varied. Studies restricted IV iron but allowed oral iron. Baseline (BL) TC and change from BL (Δ) were summarized overall and by BL tertile. Data are mean±SD.

Results: Among roxadustat NDD subjects (n=206), mean BL TC was 170.9±45.2 and 166.8±39.1 mg/dL (studies 41&47). TC fell with roxadustat by 25.8±29.7 and 33.7±31.8. Among roxadustat DD subjects (n=238), mean BL TC was 171.1±35.1, 174.3±57.3, and 171.0±56.7 (studies 48, 53&40). TC fell with roxadustat treatment by 14.2±36.4, 44.4±45.9 and 36.7±37.0. The greatest declines were among the highest BL tertile in both populations.

Study	Treatment (N)	BL TC	CFB during treatment	CFB in highest tertile of BL TC	CFB in middle tertile of BL TC	CFB in lowest tertile of BL TC
041	Roxa (145)	170.9±45.2	-25.8±29.7*	-33.5±37.1*	-28.7±26.8*	-15.9±21.5*
	Placebo (61)	166.8±39.1	-33.7±31.8*	-48.1±38.1*	-33.8±14.3*	-16.4±31.0
047	Roxa (74)	171.1±35.1	-14.2±36.4*	-21.9±39.4*	-14.3±34.5	-7.0±35.2
	Epoetin alfa (22)	158.4±28.4	+18.3±24.3*			
053	Roxa (56)	174.3±57.3	-44.4±45.9*	-66.3±29.2*	-58.0±36.9*	-11.3±48.9
040	Roxa (108)	171.0±56.7	-36.7±37.0*	-59.3±48.6*	-35.4±21.8*	-16.6±19.8*
	Epoetin alfa (36)	168.9±40.5	+4.1±27.4			

*p<0.05 two-sided; within-group comparisons; Δ at wk 9 for 041 and wk 5 for 053.

Conclusions: Roxadustat consistently lowered TC in phase 2 studies. The decrement in TC is greatest among those with highest BL levels. Roxadustat phase 3 trials will include TC to further define this effect and significance.

Funding: Pharmaceutical Company Support - FibroGen

TH-PO649

AKB-6548 Demonstrates Controlled Hemoglobin (HGB) Response in a Phase 2b Study for the Treatment of Anemia in Patients with Chronic Kidney Disease Not on Dialysis (ND-CKD) Volker H. Haase,¹ Bruce S. Spinowitz,² Pablo E. Pergola,³ Tasha Farmer,⁴ Bradley J. Maroni,⁴ Charlotte S. Hartman,⁴ ¹Vanderbilt Univ, Nashville, TN; ²New York Hospital Queens, Flushing, NY; ³Renal Associates PA and Univ of Texas Health Sciences Center, San Antonio, TX; ⁴Akebia Therapeutics, Inc., Cambridge, MA.

Background: AKB-6548 is a novel, once daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) that preferentially stabilizes HIF-2α. Current standard of care for anemia in ND-CKD with recombinant ESAs often results in overshoots and oscillations of HGB levels. It has been suggested that fluctuations in HGB concentrations, rapidly increasing HGB levels, and overshoots of the HGB target are associated with increased risk of cardiovascular events. Presented here are data assessing the control and predictability of HGB response from a Phase 2b study.

Methods: A randomized, double-blind, placebo-controlled study was conducted to assess the HGB response of AKB-6548 over 20 weeks of dosing in ND-CKD subjects with anemia. 210 subjects were randomized 2:1 (138 AKB-6548, 72 placebo) to once daily AKB-6548 (450mg) or placebo. HGB was monitored at each study visit and a protocol-defined dose adjustment algorithm was used to raise and maintain HGB and to minimize excursions ≥13 g/dL.

Results: The starting dose of 450 mg once daily was validated by the final average dose of 450 mg/day in the AKB-6548-treated subjects. Only 15 subjects (11%) had a confirmed HGB ≥12 g/dL and only 2 subjects (1%) had a confirmed HGB ≥13 g/dL. From Weeks 12 to 20, 74% and 81% of all HGB measurements were between 10-12 g/dL and 10-13 g/dL,

respectively. The majority of subjects (120 of 135, 89%) achieved and maintained a stable HGB level with 2 or fewer dose adjustments throughout the 20-week treatment period and 24% (33 of 135) of subjects required no dose adjustment.

Conclusions: AKB-6548 increased and maintained HGB levels in ND-CKD patients in a controlled and predictable manner with minimal dose adjustments. The study provides support that targeting the HIF oxygen sensing pathway is likely to represent a more physiologic and potentially safer approach to treating anemia than currently available therapy.

TH-PO650

Randomized Controlled Trial of Darbepoetin Alfa and Continuous Erythropoietin Receptor Activator Once Every 4 Weeks in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage Tetsuya Furukawa, Kazuyoshi Okada, Ritsukou Tei, Masanori Abe, Noriaki Maruyama. *Div of Nephrology, Hypertension and Endocrinology, Dept of Medicine, Nihon Univ School of Medicine, Tokyo, Japan.*

Background: Subcutaneous injection of Continuous Erythropoietin Receptor Activator (CERA) seems to maintain a stable Hb level than darbepoetin alfa (DA) in CKD patients who are not on dialysis because of its longer half-life. We therefore conducted a randomized controlled trial.

Methods: The cohort consisted of 20 CKD patients at the pre-dialysis stage who were receiving a fixed dose of DA with a Hb level >9.5 g/dL and ferritin level >80 ng/mL in the 12 weeks prior to the study. Patients were randomly assigned to receive subcutaneous CERA or DA once every 4 weeks. The study consisted of a 48-week evaluation period. The target Hb range was from 11.0 g/dL to 12.5 g/dL. Primary endpoints were rate of achievement of target Hb and change of eGFR, and the secondary endpoints were change in Hb level after start of the study and change in dose of DA and CERA.

Results: In both groups, the rate of achievement of target Hb level at week 0 was 70%, which rose to 100% in the interval between weeks 4 to 48, with no significant difference between the groups. Despite the absence of a significant difference in Hb level, it was significantly increased from week 24 and from week 8 relative to those at week 0 in the DA continuation group and CERA changeover group, respectively. In addition, the reticulocyte count was significantly increased at weeks 4, 8 and 12 in the CERA changeover group compared with the DA continuation group. The doses of DA and CERA during the evaluation period were not significantly changed. Because the total administered doses of DA and CERA over 48 weeks were 0.998±0.106 mg/kg/4 weeks and 0.956±0.204 mg/kg/4 weeks, the dose conversion ratio was 1.05:1 mg. There was no significant difference in the levels of eGFR and iron state between both groups.

Conclusions: The present study demonstrated that subcutaneous administration of DA and CERA once every 4 weeks to predialysis patients have similar effects on achievement of target Hb levels but longer acting CERA can increase the Hb level earlier than DA.

TH-PO651

QW or Q2W Darbepoetin Alfa in Pediatric Subjects with Chronic Kidney Disease Bradley Warady,¹ John P. Barcia,² Nadine M. Benador,³ Augustina Jankauskiene,⁴ Kurt Olson,⁵ Ludmila Podracka,⁶ Aleksey Shavkin,⁷ Poyyapakkam Srivaths,⁸ Cynthia Wong,⁹ Jeffrey Petersen,⁵ ¹Children's Mercy; ²UVA Med; ³UCSD; ⁴Vilniaus U; ⁵Amgen; ⁶UPJS; ⁷Children's City; ⁸TX Children's; ⁹Stanford Med.

Background: Minimal data are available on the initiation of erythropoiesis stimulating agents (ESA) for the correction of anemia in ESA-naive pediatric patients with CKD. Additionally, the optimal dosing frequency with darbepoetin alfa (DA) in this setting has not been previously evaluated. This study assessed the ability of DA administered either once weekly (QW) or once every 2 weeks (Q2W) to correct anemia in pediatric patients.

Methods: Multicenter, double-blind, randomized study in pediatric subjects (age 1 to 18 years) with CKD and anemia (hemoglobin; Hb < 10.0 g/dL) on or not on dialysis and not treated with an ESA. The primary endpoint was Hb ≥ 10.0 g/dL at any time after the first dose without receiving a RBC transfusion within 90 days prior to initial Hb measurement or after randomization. Subjects were randomized to DA QW or Q2W at an initial dose of 0.45mg/kg or 0.75mg/kg, respectively. For both treatment groups, subsequent DA doses were titrated to achieve Hb 10.0 g/dL to 12.0 g/dL, inclusive over a 25 week period of observation.

Results: 116 subjects were enrolled: 59 were randomized to DA QW and 57 to Q2W. 114 subjects (58 QW; 56 Q2W) were included in the analyses. Mean (SD) Hb for the QW group increased from 8.6 (0.84) g/dL at baseline to 11.3 (1.33) g/dL at week 10 and remained relatively stable (range: 10.9 [1.10] to 11.7 [1.19] g/dL) through week 25. Mean Hb for the Q2W group increased from 8.7 (0.84) g/dL at baseline to 10.9 (1.38) g/dL at week 12 and remained relatively stable between 10.4 (0.97) and 11.1 (1.00) g/dL through end of study. Hb concentrations were corrected to ≥ 10 g/dL in 98% and 84% of pediatric subjects administered DA QW or Q2W, respectively. 4 (7%) QW and 5 (9%) Q2W subjects received RBC transfusions. Safety results were consistent with the known safety profile for DA.

Conclusions: Hb concentrations were corrected to ≥ 10 g/dL in > 80% of pediatric subjects administered DA QW or Q2W. No new safety signals were identified in this pediatric subject population.

Funding: Pharmaceutical Company Support - Amgen Inc.

TH-PO652

Intravenous (IV) Ferric Carboxymaltose (FCM) versus Oral Iron in the Randomized FIND-CKD Trial of Patients with Non-Dialysis Dependent CKD (ND-CKD): A Safety Analysis Simon D. Roger,¹ Andreas H. Bock,² Fernando Carrera,³ Kai-Uwe Eckardt,⁴ Carlo A. Gaillard,⁵ David B. Van wyck,⁶ Bernard Roubert,⁷ Maureen Cronin,⁷ Iain C. Macdougall.⁸ ¹Renal Research, Gosford, NSW, Australia; ²Kantonsspital, Aarau, Switzerland; ³Eurodial, Leiria, Portugal; ⁴Uni. of Erlangen-Nuremberg, Erlangen, Germany; ⁵Uni. Groningen, Groningen, Netherlands; ⁶Davita Healthcare Partners, Denver, CO; ⁷Vifor Pharma Ltd, Glattpburg, Switzerland; ⁸King's College Hospital, London, United Kingdom.

Background: There are safety concerns, including hypersensitivity reactions, iron overload, increased risk of infection, oxidative stress and mortality risk, in patients with CKD receiving IV iron.

Methods: In the 56-week, open-label, multicenter, prospective, randomized FIND-CKD study, 626 anemic patients with ND-CKD and iron deficiency not receiving ESA therapy were randomized (1:1:2) to IV ferric carboxymaltose (FCM), targeting higher (400–600µg/L) or lower (100–200µg/L) ferritin, or oral iron.

Results: In the IV iron arms, two patients had mild hypersensitivity reactions, neither requiring treatment nor hospitalization. Desired target ferritin levels were achieved and transferrin saturation (TSAT) levels were maintained within KDIGO guidelines (mean TSAT 31% in the high ferritin FCM group). The rate of infections was equivalent within all three groups (33.1%, 34.0% and 30.4% in the high ferritin FCM, low ferritin FCM and oral iron groups, respectively), as was the rate of serious infections (3.9%, 3.3%, 3.8%). As a measure of oxidative stress, estimated GFR values were unchanged during the study. Overall, 4.1% of patients died (4.5%, 2.0% and 4.8% in the high ferritin FCM, low ferritin FCM and oral iron groups, respectively). No death was assessed by the investigator as related to study drug. Most frequent causes of death were cardiovascular events and respiratory infections.

Conclusions: Despite this being the longest RCT of oral vs IV iron in ND-CKD patients, the follow-up was still only 12 months and there was no placebo group. Nevertheless, there was no obvious signal of excess harm in patients targeting a higher ferritin range with IV FCM.

Funding: Pharmaceutical Company Support - Vifor Pharma, Glattpburg, Switzerland

TH-PO653

Recruitment for Clinical Trials of Interventions to Prevent ESRD in T2D Patients Adam Smiles,¹ Melissa Major,¹ Masayuki Yamanouchi,¹ Natalia Z. Nowak,¹ Monika A. Niewczas,¹ Jan Skupien,¹ Marcus G. Pezzolesi,¹ Fergus Fleming,² James Warram,¹ Matthew D. Breyer,³ Kevin L. Duffin,³ Nick Pullen,⁴ Andrzej S. Krolewski.¹ ¹Joslin Diabetes Center, Boston; ²EKF Diagnostics, London, United Kingdom; ³Eli Lilly, Indianapolis; ⁴Pfizer Global R&D, Cambridge, MA.

Background: The current dependence of clinical trials of measures to prevent ESRD, on recruitment of patients with T2D and proteinuria is problematic. The eligible pool, shrunken due to ACE inhibitor treatment, largely consists of non-progressors (due to depletion of rapid progressors) whose participation may be less informative.

Methods: In search of alternatives, we recruited T2D patients attending Joslin Clinic from 2003 to 2009 by screening those age 35-69 (and CKD stage 1-3) for onset of albuminuria (ALB), micro or macro, and identified for each a similar patient in the 3x larger pool with normo ALB. 2/3 granted participation consent. Mean baseline eGFR was 95 for Normo and Micro ALB groups and 68 mL/min/1.73 m² for Macro-ALB group. Patients were examined at baseline and followed to 2013 to ascertain onset of ESRD or death unrelated to ESRD. Baseline and follow-up blood and urine were assayed for serum creatinine and other characteristics.

Results: After 4-6 year follow-up for 1335 patients (excluding 82 incomplete follow-ups) are summarized according to ALB category:

Outcome	Normo-ALB n=695 [2085]*	Micro-ALB n=484	Macro-ALB n=156	All n=1335 [2725]
ESRD onset	2/0.3% [6]*	7/1.4%	32/21%	41 [45]
Loss>40% eGFR	24/3.5% [72]*	54/11%	49/31%	127 [177]
Death	16/2.3% [48]*	23/4.8%	19/12%	58 [90]
Composite	42/6.0% [126]*	84/17%	100/64%	226 [310]

* expected number if all normo-ALB patients were followed

Unfavorable outcomes occurred in an estimated 310 of 2725 patients (including all normo ALB patients). Although incidence was highest in Macro-ALB group, 2/3 occurred in Normo and Micro ALB groups and 1/3 occurred in patients with baseline eGFR >90 ml/min/1.73 m². Circulating levels of TNFR1 and KIM-1 and urinary levels of MCP-1 and KIM-1 at baseline are associated with risk of these outcomes.

Conclusions: In summary increased clinical trial enrollment of patients with outcomes can be achieved by including patients with normal renal function and Micro or Normo ALB.

Funding: NIDDK Support, Pharmaceutical Company Support - Pfizer Pharmaceuticals, Eli Lilly and Company, EKF Diagnostics

TH-PO654

Post Hoc Analyses of the EPPIC Trials to Assess the Effect of AST-120 in Chronic Kidney Disease Patients Gerald Schulman,¹ Tomas Berl,² Gerald J. Beck,³ Giuseppe Remuzzi,⁴ Eberhard Ritz,⁵ Miho Shimizu,⁶ Yuko Shobu,⁷ Mami Kikuchi,⁷ ¹Vanderbilt U., Nashville, TN; ²U. Colorado, Denver, CO; ³Cleveland Clinic, Cleveland, OH; ⁴Mario Negri Inst, Bergamo, Italy; ⁵U. Heidelberg, Heidelberg, Germany; ⁶Mitsubishi Tanabe Pharma Co, Tokyo, Japan; ⁷Kureha Co, Tokyo, Japan.

Background: The orally administered spherical carbon adsorbent AST-120 is approved in Asian countries for delaying the initiation of dialysis and ameliorating symptoms of uremia in patients with progressive CKD. Two randomized, double-blind, placebo-controlled trials (EPPIC trials) investigated the efficacy and the safety of AST-120 in adults with CKD. The benefit of adding AST-120 was not supported by the results of the primary analysis as reported previously. In order to further assess the efficacy of AST-120, we examined clinical and geographic factors by *post hoc* analyses using pooled populations of 2 trials.

Methods: The primary endpoint was a composite of dialysis initiation, kidney transplantation and serum creatinine doubling. The same statistical methods for the efficacy endpoint analysis were applied for these *post hoc* analyses.

Results: In a multivariable analysis using baseline parameters, positive hematuria and elevated UP/UCr were found to be an independent risk factor for the primary endpoint. In the ITT population with positive hematuria, elevated UP/UCr (≥ 1.0) and ACEI/ARB use, a difference between the AST-120 and the placebo treatment groups was observed in primary endpoint occurrence (HR 0.74, 95% CI 0.56-0.96). In subgroup analysis by country, a higher event rate was observed in the USA population than outside the USA. In the ITT population from the USA with ACEI/ARB use, a difference between the AST-120 and the placebo treatment groups was observed in primary endpoint occurrence (HR 0.74, 95% CI 0.56-0.98).

Conclusions: These results suggest that there may be a beneficial effect of adding AST-120 to standard therapy regimens in high risk populations such as patients with hematuria and elevated UP/UCr and in the patients similar to those enrolled in the USA EPPIC trials. Due to its *post hoc* nature of the analysis, further prospective studies are needed to confirm the results.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma Co Kureha Co

TH-PO655

A Phase 2 Study on the Effect of Tenapanor on Albuminuria in Patients with T2DM and CKD Bergur V. Stefansson,¹ David P. Rosenbaum,² Peter J. Greasley,¹ Maria Leonsson Zachrisson,¹ Anna Maria Langkilde.¹ ¹AstraZeneca R&D, Mölndal, Sweden; ²Ardelex Inc., Fremont, CA.

Background: Patients with type 2 diabetes mellitus (T2DM) and CKD are treated with renin-angiotensin-aldosterone system (RAAS) inhibitors to slow the decline in renal function. The effectiveness of RAAS inhibition is limited by high sodium (Na) intake. Tenapanor (AZD1722), an inhibitor of the Na⁺/H⁺ exchanger NHE3, reduces absorption of Na and phosphate from the gut. This trial evaluated the effects of tenapanor on albuminuria levels, which may be associated with renal function decline, in patients with T2DM and CKD stage 3 receiving RAAS inhibitors.

Methods: This was a randomized, placebo-controlled, 12-week study (NCT01847092) in patients with urine albumin-to-creatinine ratio (UACR) 200–3500 mg/g. The starting dose of tenapanor hydrochloride was 15 mg bid; there was a 4-week titration period (dose escalation up to 60 mg bid followed by reduction down to 5 mg bid), based on gastrointestinal tolerability, before fixed-dose treatment with 5–60 mg bid for 8 weeks.

Results: Patients were randomized to tenapanor (n=77; mean±SD urinary Na, 182±81 mmol/day; completed, n=51) or placebo (n=77; mean±SD urinary Na, 189±85 mmol/day; completed, n=66). Reductions from baseline to week 12 in UACR were 16% for tenapanor and 11% for placebo (p=0.36). Tenapanor had no observed effect on systolic or diastolic BP or eGFR. Changes (tenapanor vs placebo) in urinary Na were (LS mean±SE) -9.6±9.7 vs -1.5±9.1 mmol/day (p=0.54) and in urinary phosphorus were (mean±SD) -3.8±14 vs 1.7±9.7 mmol/day. Tenapanor treatment resulted in a softer consistency and increased frequency of stool compared with placebo. The tolerability profile of tenapanor was consistent with that seen in other studies, with diarrhea reported more frequently with tenapanor use.

Conclusions: In patients with T2DM and CKD stage 3, the pharmacodynamic effects of tenapanor were confirmed, as shown by softer consistency and increased frequency of stool, and reduced urinary phosphorus excretion following tenapanor treatment. However, these observations did not translate into effects on albuminuria.

Funding: Pharmaceutical Company Support - AstraZeneca

TH-PO656

Effect of Fluvastatin Treatment on Proteinuria in Diabetic Patients with Chronic Kidney Disease Jin Joo Cha,¹ Kitae Kim,¹ Hye sook Min,¹ Jungyeon Ghee,¹ Yeo-Joo Kim,² Eun-Young Lee,² Shin-Wook Kang,³ Tae-Hyun Yoo,³ Jung Tak Park,³ Yaeni Kim,⁴ Cheol Whee Park,⁴ Ho Jun Chin,⁵ Young Sun Kang,¹ Dae R. Cha.¹ ¹Internal Medicine, Korea Univ, Republic of Korea; ²Internal Medicine, Soonchunhyang Univ Cheonan Hospital, Republic of Korea; ³Internal Medicine, Yonsei Univ College of Medicine, Republic of Korea; ⁴Internal Medicine, The Catholic Univ of Korea Seoul St. Mary, Republic of Korea; ⁵Internal Medicine, Seoul National Univ Bundang Hospital.

Background: Correction of dyslipidemia with statin has shown to be protective and therapeutic in the progression of cardiovascular events. However its association with progression of kidney disease has not been established. In this study, we investigated the efficacy of fluvastatin (Lescol XR) on the progression of diabetic nephropathy in patients with renal insufficiency.

Methods: A total of 75 diabetic patients with CKD (stage 2 to 4) completed this multicenter, randomized 12 month controlled trial. All patients were treated with 20mg fluvastatin for 6 months. At month 6, patients were randomized to either continue or to discontinue fluvastatin for additional 6months. Primary endpoint was the difference in urinary protein to creatinine ratio between the groups at 12months.

Results: Baseline characteristics showed no differences between the groups in HbA1c, HOMA-IR, diabetes duration and estimated glomerular filtration rate (GFR). Majority of patients (81%) were using RAS blockers. After 6months of fluvastatin treatment, there was no significant decrease in urinary protein excretion or microalbumin excretion. Estimated GFR significantly declined at 6months in both groups and continued to decline after discontinuation of fluvastatin, whereas the change was not significant with fluvastatin treatment. Interestingly, HOMA-IR significantly improved in continuation group. Significant decrease in total and low density cholesterol was observed after 6, 12months in patients treated with fluvastatin.

Conclusions: In conclusion, there was no significant reduction in proteinuria with fluvastatin treatment in diabetic patients with chronic kidney disease. However, our study suggests that there might be a role in statin to slow the progression of kidney disease.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals

TH-PO657

Hyperkalemia in the HALT PKD Trial Ronald D. Perrone,¹ Kaleab Z. Abebe,² Peter G. Czarnecki,³ Marie C. Hogan,⁴ Theodore I. Steinman,⁵ Susan Spillane,² Charity G. Moore.² ¹Tufts; ²U Pittsburgh; ³Brigham and Womens; ⁴Mayo Clinic; ⁵BIDMC, for the HALT PKD Investigators.

Background: HALT-PKD was a prospective, randomized trial designed to determine the effects of dual renin-angiotensin system (RAAS) blockade and blood pressure (BP) reduction on ADPKD progression. In view of prior reports of hyperkalemia (HK) with dual RAAS blockade, we describe the frequency and severity of HK in HALT-PKD.

Methods: Study A subjects with eGFR >60 ml/min aged 15-50 were randomized to lisinopril (L) and placebo (P) vs L and telmisartan (T) with two levels of BP control: standard (SBP) (120-130/70-80 mmHg) vs low (LBP) (95-110/65-75 mm Hg). Study B subjects with eGFR 25-60 ml/min aged 18-65 were randomized to L and P vs L and T with SBP only. Serum K was measured every 6 months at study visits, within 1-2 weeks after an increase in L or T dose, and every 3 months when eGFR was less than 30. All elevated serum K values were reviewed on a monthly basis by a quality control committee.

Results: HK was infrequent in Study A; mild, but not moderate or severe HK, was more common in Study B.

Hyperkalemia	STUDY A				:	STUDY B	
	(N)	L/T (273)	L/P (285)	SBP (284)		LBP (274)	L/T (244)
Mild >5.5 - 6	7,7 (3%)	5,4 (1%)	8,7 (3%)	4,4 (2%)	:	61,42 (17%)	60,38 (16%)
Moderate >6 - 6.5	5,4 (2%)	1,1 (0.4%)	3,3 (1%)	3,2 (1%)	:	9,9 (4%)	4,4 (12%)
Severe >6.5	1,1 (.4%)	0,0 (0%)	0,0 (0%)	1,1 (.4%)	:	0,0 (0%)	1,1 (0.4%)

events, # participants, (% participants); L/T: lisinopril/telmisartan; L/P: lisinopril/placebo; SBP: standard BP; LBP: low BP. There were no significant differences in HK due to L/T or LBP

Intervention with dietary K reduction, furosemide, or Kayexalate was successful in reducing serum K in all participants. There was no relationship between HK and serious adverse events (SAEs) and there were no SAEs within 21 days after detection of HK.

Conclusions: HK was infrequent with eGFR>60, despite dual RAAS blockade or intensive BP control. Mild HK was more common with eGFR 25-60, but easily managed. Severe HK was rare. With careful management, dual RAAS blockade and intensive BP control were safe in the HALT PKD trial. Clinical use of dual RAAS blockade or intensive BP control should only be done with close monitoring.

Funding: NIDDK Support, Private Foundation Support

TH-PO658

Chronic Diuretic Therapy Does Not Impair the Effectiveness of Patiromer in Hyperkalemic Patients with CKD Matthew R. Weir,¹ Martha Mayo,² Dahlia Garza,² Yuri Stasiv,² Susan Arthur,² Lance Berman,² David A. Bushinsky,³ Daniel J. Wilson,² Murray Epstein.⁴ ¹Univ of Maryland; ²Relypsa, Inc.; ³Univ of Rochester; ⁴Univ of Miami.

Background: Loop diuretics control volume in advanced CKD and may reduce elevated serum K⁺, but can induce intravascular volume depletion or gout and may not be ideal for long-term hyperkalemia (HK) management. Thus, the efficacy of investigational serum K⁺ binders in HK pts on chronic diuretics is of interest. We compared patiromer's effects in RAASI-treated CKD pts with HK on diuretics to those not on diuretics in the treatment phase of the 2-part OPAL-HK study.

Methods: Pts (n=243) with baseline (BL) s-K⁺ 5.1 to 6.5 mEq/L on RAASI received patiromer (4.2 or 8.4 g BID to start) for 4 wks. For this post hoc analysis, Ds-K⁺ from BL to wk 4 was assessed in pts stratified by diuretic use and type. Pts (n=22) receiving aldosterone antagonists were excluded.

Results: Mean (SD) age was 64 (10.5) yr; 58% were male. Mean s-K⁺ decreased from BL at wk 4 in all subgroups (Table). Reductions in s-K⁺ did not differ in pts receiving any diuretic vs those not on diuretics. Patiromer was well tolerated; mild-moderate GI constipation was the most common AE. Hypokalemia (s-K⁺<3.5 mEq/L) was infrequent.

Conclusions: The s-K⁺-lowering efficacy of patiromer in HK pts was unaffected by concomitant diuretics.

Table: Efficacy, safety, and disease characteristics in pts on patiromer ± diuretics					
	Loop (n=51)	Thiazide/T-like (n=51)	Combination Loop/thiazide (n=15)	Any diuretic (n=117)	No diuretic (n=104)
BL					
HF, %	49.0	25.5	66.7	41.0	32.7
S-Creatinine Mean±SD (mg/dl)	2.4±0.9	2.0±0.8	2.0±0.7	2.2±0.8	2.1±1.2
Mean±SE BL s-K ⁺ , mEq/L	5.61±0.06	5.58±0.07	5.67±0.13	5.58±0.04	5.57±0.05
Wk 4					
Mean±SE Δ s-K ⁺ BL to wk 4 (95% CI), mEq/L [p-value]	-1.02±0.06 (-1.14, -0.89) [<0.001]	-0.97±0.06 (-1.09, -0.86) [<0.001]	-0.69±0.19 (-1.11, -0.28) [0.0037]	-0.95±0.05 (-1.04, -0.86) [<0.001]	-1.03±0.05 (-1.13, -0.93) [<0.001]
Hypokalemia, %	2.0	0	6.7	1.7	3.9

*6 pts without a s-K⁺ value at a weekly visit after day 3 were excluded.

Funding: Pharmaceutical Company Support - Relypsa, Inc.

TH-PO659

Add-On HCTZ Administration to ARB Can Achieve Lower Sodium Balance in CKD Patients Daisuke Fuwa,¹ Michio Fukuda,¹ Toshiyuki Miura,¹ Yoshiaki Ogiyama,¹ Sumiko Abe-Dohmae,¹ Hiroyuki Kobori,² Nobuyuki Ohte.¹ ¹Nagoya City Univ; ²International Univ of Health and Welfare.

Background: Recently, we have reported that angiotensin receptor blocker (ARB) can attain lower sodium balance and resultant restoration of nondipper circadian BP rhythm in patients with augmented intrarenal renin angiotensin system (RAS). It has been established that ARB can enhance renal sodium excretion in subjects with sodium deprivation. We tested whether add-on administration of hydrochlorothiazide (HCTZ) can further achieve a lower sodium balance in patients with CKD under ARB treatment.

Methods: CKD patients (n=20) with previous treatment with valsartan (80mg/day) for 2 months or more, office BP >130/80 on at least one occasion were eligible. Filtered tubular sodium load was defined as PNa x GFR. Ambulatory BP and sodium balance were studied before and 8-week administration with HCTZ (12.5mg/day).

Results: Add-on HCTZ to ARB could attain lower sodium balance: tubular sodium load (13200±9300@11800±7800 mmol/day, p=0.04), and tubular sodium reabsorption (13000±9300@11700±7800 mmol/day, p=0.04) were both decreased, while urinary sodium excretion did not change (160±80@161±60 mmol/day, p=0.9). Decrease in tubular sodium load correlated directly with baseline urinary angiotensinogen excretion (uATG) (r2=0.10), and the decrease in night/day SBP ratio (r2=0.16). uATG was significantly decreased (150±10→80±20 mg/gCre, p=0.02).

Conclusions: Add-on administration with HCTZ to ARB can attain the lower sodium balance and resultant restoration of non-dipper BP rhythm with no acceleration of intrarenal RAS.

TH-PO660

Association of Serum Adiponectin Level with Albuminuria in Chronic Kidney Disease Patients Ha yeon Kim,¹ Eun Hui Bae,¹ Seong Kwon Ma,¹ Kook-Hwan Oh,² Curie Ahn,² Soo Wan Kim.¹ ¹Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; ²Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.

Background: Adiponectin, peptide hormone secreted in an adipocytes, has been known to exert anti-diabetic, anti-atherogenic and anti-inflammatory properties. We aimed at determining the relationship between serum adiponectin levels and albuminuria and evaluate determinant factors for serum adiponectin in patients with chronic kidney disease (CKD).

Methods: A total of 1,474 CKD patients were included and divided into three groups according to their albumin-to-creatinine ratio: patients with normoalbuminuria (N = 232), microalbuminuria (N = 459), macroalbuminuria (N = 783). The serum adiponectin was specifically assayed with a commercially available enzyme-linked immunosorbent assay kit.

Results: Serum adiponectin was significantly higher in patients with macroalbuminuria than those without macroalbuminuria. (9.7±6.06 mg/ml in patients with normoalbuminuria, 12.4±9.07 mg/ml in patients with microalbuminuria, 14.9±11.09 mg/ml in patients with macroalbuminuria). Univariate linear regression analysis showed that the serum adiponectin concentrations correlated with age, albumin-to-creatinine ratio, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, whereas negatively correlated with body mass index, estimated glomerular filtration rate, serum albumin and triglyceride. Multiple backward regression analysis revealed that sex, diabetes mellitus, estimated glomerular filtration rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglyceride, logarithm of albumin-to-creatinine ratio were independently associated with logarithm of serum adiponectin levels (r = 0.55, p < 0.001).

Conclusions: The serum adiponectin concentrations are higher in patients with increasing albuminuria and these levels are also associated with renal insufficiency and lipid profiles.

TH-PO661

Effects of Candesartan on Clinical Remission in IgA nephropathy Treated with Steroid Pulse Therapy and Tonsillectomy (CAST IgA Study) – A Randomized Control Study Kentaro Kohagura,^{1,2} Hisatomi Arima,³ Hitoshi Miyasato,⁵ Tung-Huei Chang,⁶ Hiroyuki Kobori,⁴ Kunitoshi Iseki,⁷ Yusuke Ohya.¹ ¹Dialysis Unit, Univ Hospital of the Ryukyus, Nishihara-cho, Okinawa, Japan; ²Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Nishihara-cho, Okinawa, Japan; ³Center for Epidemiologic Research in Asia, Shiga Univ of Medical Science, Shiga, Japan; ⁴Pharmacology, Kagawa Univ, Kagawa, Japan; ⁵Internal Medicine, Okinawa Chubu Hospital, Okinawa, Japan; ⁶Internal Medicine, Okinawa Heartlife Hospital, Okinawa, Japan; ⁷Clinical Research Center, Tomishiro Central Hospital, Okinawa, Japan.

Background: Angiotensin receptor blockade (ARB) may have additional benefit on the conventional therapy with steroid pulse and tonsillectomy among Japanese patients with IgA nephropathy.

Methods: Seventy seven patients with IgA nephropathy were randomly assigned to regular regimen consists of steroid pulse followed by oral prednisolone for 6 months and tonsillectomy (control group, n=37) regular regimen combined with ARB (candesartan) for 6 months (ARB group, n=40). Among all patients in both groups who did not achieve remission of proteinuria at 12 M, candesartan was initiated and titrated until the 24 M visit. The primary endpoint was the remission of proteinuria (<0.2g/gCr) and hematuria.

Results: Baseline proteinuria (g/gCr, interquartile range) were comparable between the groups (0.90, 0.70-1.20 vs. 0.95, 0.60-1.50, P=0.97). Cumulative remission rate in control group and ARB group at 6, 12 and 24 M were comparable (10.8% vs. 15% [P=0.58], 29.7% vs. 30.0% [P=0.98], 45.9% vs. 42.5% [P=0.76]). The hazard ratio for remission was 1.01 (95% confidence interval, 0.51-1.99; p=0.98). Proteinuria was slightly heavier in control group than ARB group (0.11 vs. 0.21g/gCr, p=0.002) at 6 M, but comparable afterwards (0.20 vs. 0.23 g/gCr at 12 M, 0.12 vs. 0.13 g/gCr at 24 M). Although remission rate of hematuria was comparable until 12M, it was higher in control group than ARB group at 24M (85% vs. 64%, P=0.008).

Conclusions: Early use of ARB regardless of the level of blood pressure combined with steroid pulse and tonsillectomy may not provide benefit for clinical remission among IgA nephropathy.

TH-PO662

Tacrolimus Monotherapy Follows Intravenous Methylprednisolone in Adults with Minimal Change Nephrotic Syndrome: A Prospective, Multi-Centered, Open, Randomized, Controlled Trial Xiayu Li, Jianghua Chen. Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ; Hangzhou, Zhejiang Province, China.

Background: Adults with minimal change nephritic syndrome (MCNS) show excellent responses to glucocorticoid (GC). However, responding patients may suffer relapses and GC related frequent side effects. Tacrolimus (TAC) may serve as an alternative to GC therapy for adult-onset MCNS with less-frequent side effects.

Methods: This randomized, multicentre, controlled study was undertaken in 8 renal units across the China. 119 adult-onset patients were randomly allocated to receive the conventional GC therapy (GC group) or tacrolimus monotherapy (trough blood level of 4 to 8 ng/mL) follows intravenous methylprednisolone for 10 days (TAC group). The

primary outcome variables was remission. The secondary outcome variables included relapse, time to remission, time to relapse, change of serum creatinine (Scr) and eGFR, and adverse events (AEs).

Results: Remission (either complete or partial remission) was attained by 51 of 53 patients (96.2%) in GC group and 55 of 56 (98.3%) of patients in TAC group ($p=0.611$). 51 of 53 patients (96.2%) in GC group and 52 of 56 patients (92.9%) in TAC group experienced complete remission, respectively ($p=0.679$). The mean time to remission in GC group (2.7 ± 2.3 weeks) was similar ($p=0.548$) to TAC group (2.6 ± 2.6 weeks), respectively. Relapse occurred in 25 (49.0%) of GC group versus 25 (45.5%) of TAC group ($p=0.847$), and 7 patients with GC therapy and 4 patient with TAC therapy suffered frequent relapse. The mean time to relapse in GC group (27.6 ± 16.9 weeks) was similar ($p=0.617$) to TAC group (25.2 ± 16.9 weeks), respectively. There was no significant difference of Scr and eGFR between two groups during therapy and follow-up periods. Adverse events were more frequent in GC group than in TAC group (128 events versus 81 events), of which 9 (7 in GC group and 2 in TAC group) were deemed serious AEs.

Conclusions: The regimen with tacrolimus monotherapy follows short-term intravenous methylprednisolone was noninferior to conventional GC treatment in adult-onset MCNS, and could replace steroids as the initial therapy for such patients due to less-frequent side effects.

TH-PO663

Changes in Concentrations of Chemokine Ligands for CCR2 and CCR5 Receptors in Response to Administration of PF-04634817 *Karen M. Page, Julie M. Lee, Amira Quazi, Lori Fitz, Weidong Zhang, Steven A. Gilbert, Nick Pullen, Robert Webster, Jeremy D. Gale. Worldwide Research and Development, Pfizer, Cambridge, MA.*

Background: PF-04634817 is a competitive dual inhibitor of CCR2 and CCR5 receptors. In early clinical studies, administration of this compound to healthy volunteers has been found to elevate circulating levels of the primary CCR2 ligand, CCL2 (MCP-1). The ability of PF-04634817 to reduce albuminuria, compared with placebo, after administration for 12 weeks was tested in a phase 2 study in subjects with diabetic nephropathy and macroalbuminuria. In this study, samples were collected to confirm the previously observed pharmacological effect on CCL2 in this population and to examine the impact on other ligands known to bind to CCR2 or CCR5 receptors.

Methods: CCL2 in serum and urine was measured by ELISA from 226 subjects at Eurofins (The Netherlands) at baseline and during treatment at weeks 4, 8, and 12. CCL5 (RANTES) was measured in plasma and urine as part of a multi-analyte panel at Myriad Rules Based Medicine (Austin, TX) and CCL8 (MCP-2), CCL3 (MIP-1a), and CCL4 (MIP-1b) were measured in plasma using two Luminex assays (Bio-Rad, Berkeley, CA) from 158 subjects at baseline and weeks 8 and 12.

Results: At week 12, serum levels of CCL2 and plasma levels of CCL4 were elevated 9.25 fold ($p < 0.0001$) and 2.11 fold ($p < 0.0001$) respectively following administration of PF-04634817, but not placebo. Elevation of both chemokines was also observed at the earlier time points. Levels of CCL8, CCL5 and CCL3 in circulation and CCL2 and CCL5 in urine did not change in either group.

Conclusions: This study confirms elevation of the CCR2 ligand, CCL2, following treatment with PF-04634817 in diabetic nephropathy subjects. It also identifies the CCR5 ligand, CCL4, as another potential pharmacodynamic marker. The observed lack of apparent change in CCL5 warrants further follow up analysis.

Funding: Pharmaceutical Company Support - Pfizer

TH-PO664

Circulating Tumor Necrosis Factor Receptor Expression in a Phase 2 Study to Evaluate the Efficacy and Safety of PF-04634817 in Adults with Type 2 Diabetes and Overt Nephropathy *Karen M. Page, Lori Fitz, Weidong Zhang, Steven A. Gilbert, George Bashirians, Nick Pullen, Robert Webster, Jeremy D. Gale. Worldwide Research and Development, Pfizer, Cambridge, MA.*

Background: PF-04634817 is a small molecule dual inhibitor of CCR2 and CCR5, chemokine receptors found on the surface of monocytes and T cells that are involved in the development and progression of diabetic nephropathy (DN). Identifying patients with accelerated renal function decline is an important area of research. Circulating TNFRs have been identified as biomarkers with potential to predict accelerated decline. In the current study, we investigated changes in soluble TNFR-1 and TNFR-2 following 12 weeks of treatment with PF-04634817 or placebo in subjects with DN.

Methods: Soluble TNFR-1 and TNFR-2 were measured from 161 subjects in serum by ELISA at baseline, weeks 8 and 12. Urinary albumin and creatinine concentrations were averaged from 3 consecutive first morning voids immediately prior to each visit. Estimated glomerular filtration rate (eGFR) was measured using the abbreviated (4 variable) Modification of Diet in Renal Disease (MDRD) formula. Study subjects were defined at baseline by a mean UACR of 180.78 ± 160.53 mg/mmol Cr and a mean eGFR of 41.46 ± 12.64 mL/min/1.73 m².

Results: Mean concentrations at baseline of soluble TNFR-1 and TNFR-2 were 4.25 ± 1.37 ng/mL and 8.27 ± 2.99 ng/mL respectively. Baseline concentrations were strongly correlated between the receptors ($\text{Corr}_s = 0.90$, $p < 0.0001$). Soluble TNFRs were weakly correlated with UACR at baseline ($\text{Corr}_s = 0.35$, $p < 0.0001$ and $= 0.34$, $p < 0.0001$), in contrast to a stronger inverse correlation with eGFR ($\text{Corr}_s = -0.69$, $p < 0.0001$ and $= -0.61$, $p < 0.0001$). The concentration of neither TNFR was changed from baseline following treatment with PF-04634817 and baseline TNFR concentrations were not able to predict changes observed at week 12 in UACR.

Conclusions: At baseline, TNFR-1 and TNFR-2 in subjects with DN were well correlated to each other and more strongly correlated with eGFR than UACR. Our observations do not support either TNFR-1 or TNFR-2 as pharmacodynamic biomarkers or as predictive biomarkers of clinical response as measured by UACR.

Funding: Pharmaceutical Company Support - Pfizer

TH-PO665

Effects of Intensified Vasodilatory Antihypertensive Treatment on Renal Function, Bloodsupply and Oxygenation in Chronic Kidney Disease *Dinah S. Khatir,¹ Michael Pedersen,² Per R. Ivarsen,¹ Kent L. Christensen,³ Bente Jespersen,¹ Niels Henrik Buus.⁴ ¹Renal Medicine, Aarhus Univ Hospital, Aarhus N, Denmark; ²Comparative Medicine Lab, Aarhus Univ Hospital, Aarhus N, Denmark; ³Cardiology, Aarhus Univ Hospital, Denmark; ⁴Renal Medicine, Aalborg Univ Hospital, Denmark.*

Background: Progression of Chronic kidney disease (CKD) may result from tissue hypoxia induced by small artery structural narrowing, with increased renal vascular resistance (RVR) and impaired blood supply. We investigated whether vasodilating therapy (VT) is superior to non-vasodilating therapy (nonVT) for improvement of RVR, tissue oxygenation, and preservation of kidney function.

Methods: Eighty-two hypertensive grade 3-4 CKD patients (glomerular filtration rate (GFR) 36 ± 15 mL/min/1.73 m²) were randomised to renin-angiotensin inhibition combined with either VT (amlodipine) or nonVT (beta-blocker metoprolol). At baseline and following 18 months of therapy we determined forearm resistance by venous occlusion plethysmography. Using magnetic resonance imaging (MRI) renal artery blood flow was measured for calculation of RVR, and blood oxygen level dependent (BOLD) MRI was used as a marker of renal oxygenation (R₂*). GFR was measured as ⁵¹Cr-EDTA clearance.

Results: The VT and nonVT arms had similar blood pressure levels throughout the study. At follow-up, in the VT group forearm resting resistance had decreased by 7% ($P < 0.05$) and RVR by 12% ($P < 0.05$), while in the nonVT group forearm resistance increased by 39% ($P < 0.01$) while RVR remained unchanged. Cortical and medullary R₂* values were not affected by VT and nonVT. After 18 months GFR decline was similar in the two groups (3.0 vs. 3.3 mL/min/1.73 m²).

Conclusions: In CKD, long-term VT reduced both peripheral and RVR, but was not associated with improved renal oxygenation and did not influence loss of kidney function compared to nonVT.

Funding: Government Support - Non-U.S.

TH-PO666

The Epigenetic BET-Inhibitor RVX-208/Apabetalone Shows Favorable Effects on ALP and eGFR in Chronic Kidney Disease (CKD) Patients – A Post-Hoc Analysis of Phase 2 Clinical Trials *Kamyar Kalantar-Zadeh,¹ Jan O. Johansson,² Michael Sweeney,² Kenneth E. Lebioda,² Ewelina Kulikowski,² Christopher Halliday,² Norman Cw Wong.² ¹Div of Nephrology & Hypertension, I Univ of California Irvine School of Medicine, Irvine, CA; ²Research and Development, Resverlogix Corporation, Calgary, AB, Canada.*

Background: The epigenetic BET inhibitor RVX-208 is a small molecule with anti-inflammatory and apolipoprotein A-I (apoA-I) enhancing effects. It exerts its actions by inhibiting bromodomain extra-terminal proteins (BET) thus inhibiting acetylated lysine, present in histones, from binding to the same site. In this process chromatin structure is altered and activity of select genes inhibited. A subpopulation analysis from the double-blind placebo controlled phase 2b program in cardiovascular disease (CVD) identified 81 subjects with CKD based on eGFR < 60 mL/min/1.73m².

Methods: The effect of selective BET inhibition on key renal parameters in 81 CKD subjects (RVX-208 n=58/Placebo n=23) that were treated with either RVX-208 100mg/day or 150 mg b.i.d or matching placebo for 3 to 6 months were studied. A pooled analysis was performed to assess the changes from baseline for eGFR, ALP and creatinine at 3 and 6 months.

Results: ALP changes for RVX-208 and placebo were -14.2% and -0.34% at 3 months ($p < 0.05$ vs. placebo) and -13.9% vs. -6.28% ($p < 0.05$ vs. placebo) at 6 months. Following 6 months of RVX-208 treatment, eGFR showed an increase of +3.4% ($p = 0.04$ vs. baseline) in the RVX-208 group compared to a decrease of -5.9% in the placebo group. After 6 months treatment serum creatinine was decreased (-2.82%, $p < 0.10$ vs. baseline) compared to increases in the placebo group of +3.0% and +4.85% at 3 and 6 months, respectively. No significant change in eGFR and serum creatinine were observed after 3 months RVX-208 treatment, albeit nominal numbers went in the normalization directions.

Conclusions: Six months treatment with RVX-208, a selective BD2 selective BET-inhibitor significantly lowers serum ALP, and shows trends for eGFR and serum creatinine improvements. A phase 3 study BETonMACE is being planned in which these effects will be assessed in the prospective setting in diabetic CVD patients with or without CKD.

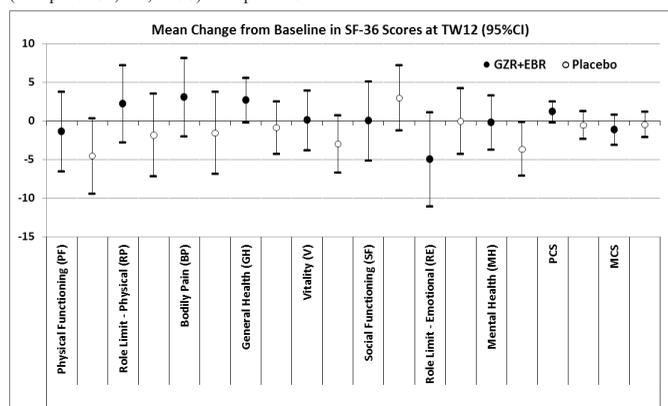
TH-PO667

Impact of Grazoprevir plus Elbasvir on Health-Related Quality of Life in Patients with Hepatitis C Virus Genotype 1 Infection and Chronic Kidney Disease Stages 4 and 5 Jean Marie Arduino,¹ Boshao Zhang,¹ Beth Jackson,¹ David Roth,² Annette Bruchfeld,³ Shazia Khawaja,¹ Elisa Martinez,¹ Chizoba Nwankwo,¹ Chris Mast,¹ Wayne L. Greaves.¹ ¹Merck & Co., Inc.; ²Univ of Miami Miller School of Medicine; ³Karolinska Univ Hospital.

Background: Health-related quality of life (HRQOL) is diminished in patients with hepatitis C virus (HCV) infection and chronic kidney disease stages 4 and 5 (CKD4/5). A randomized, double-blind, placebo-controlled trial of Grazoprevir 100 mg + Elbasvir 50 mg (GZR+EBR) once daily for 12 weeks was conducted among patients with HCV genotype 1 infection and CKD4/5. GZR+EBR was highly effective, with a sustained viral response rate at follow-up week 12 (FW12) of 99.1% (95% Confidence Interval (CI): 95.3%-100.0%). GZR+EBR was well-tolerated, with a safety profile that was comparable to placebo. The aim was to assess whether HCV treatment with GZR+EBR altered the HRQOL profile.

Methods: 224 patients were randomized and received at least one dose of study drug (GZR+EBR: n=111, Placebo: n=113). Patients completed the SF-36v2® Health Survey at baseline, treatment week 12 (TW12), and FW12 (GZR+EBR arm). Mean change from baseline in health domain, mental component summary (MCS) and physical component summary (PCS) scores, with 95% CIs, were estimated. Differences in mean change scores, with 95% CIs, were estimated between treatment groups.

Results: At baseline, mean scores were balanced between treatment groups. At TW12, GZR+EBR had more favorable changes from baseline in PCS and health domain scores (except for SF, RE, MCS) than placebo.



At FW12 for GZR+EBR, GH improved from baseline (mean change score: 4.5 (95% CI: 1.2-7.9)).

Conclusions: Treatment with GZR+EBR had a positive impact on HRQOL as compared to placebo. In addition, changes in HRQOL were substantially more favorable than the large declines in HRQOL historically associated with interferon and ribavirin-containing regimens.

Funding: Pharmaceutical Company Support - Merck & Co., Inc.

TH-PO668

Bortezomib Before, in and After Autologous Hematopoietic Stem Cell Transplantation in Patients with Newly Diagnosed AL Amyloidosis Xiang-hua Huang, Qingwen Wang, Wencui Chen, Dehua Gong, Caihong Zeng, Zhihong Liu. National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.

Background: In previous study, we have demonstrated that the outcome of treating AL amyloidosis with bortezomib with dexamethasone (BD) induction followed by autologous hematopoietic stem cell transplantation (ASCT) was superior to the outcome of the ASCT treatment alone. To further improve the hematologic response rate, we conducted a prospective trial of bortezomib before, in and after ASCT in newly diagnosed AL amyloidosis.

Methods: Newly diagnosed AL amyloidosis patients who met the criteria of ASCT could be included in this trial. Treatment schedule consisted of two cycles of BD induction therapy (bortezomib 1.3mg/m² and dexamethasone 40 mg/d on days 1, 4, 8 and 11 followed by 10 days rest), ASCT treatment (the conditioning regimen consisted of melphalan and bortezomib, the dose of bortezomib was 1mg/m² in day -6, -3, +1, +4), and four additional 21-day cycles of bortezomib treatment (with a dose of 1.6mg/m² on day 1 and 8 of the cycle) will be conducted as consolidation therapy after ASCT. The objectives were hematologic response, tolerability and survival.

Results: 18 patients were enrolled in the study. 9 patients had cardiac involvement. The overall hematologic response rate was 94.4% (17/18), including 13 patients (72.2%) with complete response, 4 patients (22.2%) with very good partial response. The organ response rate was 72.2%. The organ response was reached in 13 patients of the 18 patients with renal involvement and 7 of the 9 patients with cardiac involvement. Peripheral neuropathy and infection were the common adverse events during the treatment, and 4 patients have been discontinued bortezomib for neuropathy. No death occurred in this study. After a median follow up of 24 months, the overall survival was 100%, and the estimated progression free survival was 91% at 48 months.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: In conclusion, our preliminary data suggest that incorporating bortezomib into induction, conditioning and consolidation with ASCT yielded a high rate of hematologic response with tolerable toxicity. (ClinicalTrials.gov Id: NCT01273844).

Funding: Pharmaceutical Company Support - Xi'an Janssen Pharmaceutic Ltd: Research Funding.

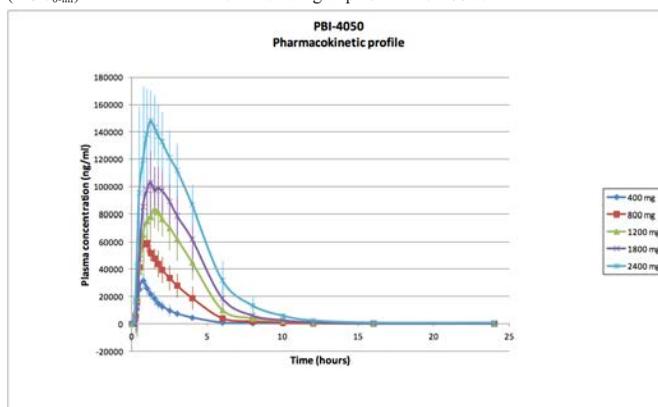
TH-PO669

Phase 1 and 1b Studies of PBI-4050, a Novel Anti-fibrotic Agent for Chronic Kidney Disease John E. Moran,^{1,2} Lyne Gagnon,¹ Pierre Laurin,¹ Vincent Pichette,³ ¹ProMetic Life Sciences, Laval, QC, Canada; ²Nephrology, Stanford Univ School of Medicine, Palo Alto, CA; ³Univ de Montréal, Montréal, QC, Canada.

Background: PBI-4050 is an orally administered new chemical entity with a MW < 300 showing remarkable anti-fibrotic efficacy in multiple pre-clinical models of fibrosis in kidney, liver, lung, and heart. Phase 1 studies in normal volunteers and Phase 1b studies in patients with advanced nephropathy associated with Type 2 diabetes have been successfully completed.

Methods: Single ascending dose (SAD) phase 1 studies were performed in 5 cohorts of healthy volunteers, 6 subjects in each cohort receiving PBI-4050 and 2 receiving identical placebo, at doses of 400 to 2,400 mg po. The 800 mg cohort had studies in both the fasting and fed state. Phase 1b studies were performed in 8 subjects with Stage 3b and 4 nephropathy associated with Type 2 diabetes (eGFR 15-45 mL/min), 2 of whom received placebo; after a single dose of 800 mg po and a washout period, the same patients received 800 mg po daily for 10 days.

Results: In the SAD study all doses were well-tolerated; there were no dose-related adverse events (AE) and no serious AE's. The half-life (T_{1/2}) mean was 3.3-5.0 hours, dependent on dose (See Figure). There was a 34% decrease in the area under the curve (AUC_{0-inf}) after a fat meal. Protein binding in plasma was > 99%.



In the patients with CKD the T_{1/2} mean and AUC_{0-inf} were unchanged and there was no change in plasma protein binding. In the 10 day study there was no significant drug accumulation. One subject experienced diarrhea listed as mild to moderate and possibly related. There were no other significant AE's.

Conclusions: PBI-4050 was found to be safe in normal volunteers and in advanced CKD. The pharmacokinetics and protein binding were unchanged in CKD. Phase 2 studies are underway in patients with CKD associated with Type 2 diabetes.

Funding: Pharmaceutical Company Support - ProMetic Life Sciences

TH-PO670

Immunogenicity and Safety of Quadrivalent Human Papillomavirus (HPV) Types 6/11/16/18 Recombinant Vaccine in CKD Stage IV-V-VD Karkiat Praditpornsilpa, Paweena Susantitaphong, Somchai Eiam-ong. Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Up to 70% of sexually active adults will become infected with HPV during their lifetime. HPV infection can result in anogenital cancer and genital warts. Studies have demonstrated the efficacy of HPV-6/11/16/18 vaccination (GARDASIL®) 3 doses at day1, month2, and month6 to lower the occurrence of high-grade cervical intraepithelial neoplasia. HPV vaccination has been integrated in health care in nonCKD. However, immunogenicity and safety of the HPV vaccine have not been proven in CKD. This study investigated the immunogenicity and safety of quadrivalent HPV-6/11/16/18 vaccination by the current recommended dose/schedule in CKD stage IV-V-VD.

Methods: This is a prospective, open-label study. CKD stage IV-V-VD patients were enrolled. Vaccine was given as a 0.5mL intramuscular injection at day1, month2, and month6. Each dose contains 20gHPV6L1 virus-like-particle (VLP), 40gHPV11L1VLP, 40gHPV16L1VLP, and 20gHPV18 L1VLP. HPV type-specific Ab response was performed by multiplexed, competitive Luminesx immunoassay (LIA) to neutralizing epitopes on HPV6/11/16/18 at day1 and month7.

Results: Sixty CKD cases (male/female: 28/32) received vaccination. Pre-dialysis/HD/CAPD cases were 2/44/14 cases. Mean age was 25.0±4.7 years. Average Cr and eGFR were 10.3±4.5mg/dL and 14.3±12.8mL/min/1.73m² respectively. Five patients underwent kidney transplantation before completing 3 doses of vaccination. At baseline, anti-HPV seropositivity was 3.3-8.3% for HPV genotype 6/11/16/18.

HPV genotype	Day1		Month7	
	%Seropositivity	MeanLIA (mMu/ml)	%Seropositivity	MeanLIA (mMu/ml)
Anti-HPV6	8.3	49.8	100	928.5
Anti-HPV11	8.3	19.4	100	1,136.1
Anti-HPV16	6.6	69.2	100	6,951.0
Anti-HPV18	3.3	12	100	2,196.3

Patients received 3 doses of vaccine had 100% seropositivity for all genotypes. The average cLIA for genotype6/11/16/18 were 928.4±231.1, 1,136±264.6, 6,951.0±1872.3 and 2,196.3±761.2mMu/ml respectively. No serious vaccine related adverse events were observed.

Conclusions: Standard dose/schedule of quadrivalent HPV vaccine provided excellent immunogenicity and safety inCKD stageIV-VVD. HPV vaccination for CKD should be integrated in public health policy.

Funding: Pharmaceutical Company Support - MSD provided vaccine doses, Government Support - Non-U.S.

TH-PO671

Minocycline-EDTA: Good Performance for Catheter Patency Maintenance Marcus Vinicius de Souza Joao Luiz,¹ Cristoforo Scavone,¹ Carmen B. Tzanno-Martins.² ¹Pharmacology, Inst of Biomedical Sciences, Sao Paulo, Brazil; ²Nephrology, Integrated Centre of Nephrology, Guarulhos, Sao Paulo, Brazil.

Background: Poor flow (PF) and catheter-related blood stream infections (CRBSI) are highly prevalent among CKD 5D patients with long-term central venous catheters. Heparin (H) catheter lock solutions are commonly used to maintain catheter patency, however PF and CRBSI incidence remains high. The purpose of this study was to evaluate two lock solutions on reduction of PF and CRBSI: one, a lock solution combining of the tetracycline antibiotic minocycline with the anticoagulant/chelation agent EDTA (M-EDTA) versus H; and other, trisodium citrate (C) versus H. M-EDTA and C were also evaluated as to their safety versus H.

Methods: Thirty CKD 5D patients on high-efficiency hemodialysis (blood flow rate = 350 ml/min) at the Integrated Centre of Nephrology (Guarulhos, Brazil) were randomized 1:1:1 to receive M-EDTA, C or H locks for 15 weeks. Lock solutions concentrations were M-EDTA 30 mg/ml/3 mg/ml, C 30% (C) and H 1,000 U/ml and both investigators and patients were blinded to treatment allocation. The primary end-point was a 10% reduction in HD blood flow rates (35ml). The frequency of CRBSI was recorded. Bleeding and lock solution-related adverse events were the primary safety end points. Logistic Regression was performed to evaluate differences in PF rates among the treatments (SPSS version 13.0, IBM, USA).

Results: PF was significantly higher among patients on H (7/10) compared to C (3/10) and M-EDTA (1/10) locks, according to results of Logistic Regression comparison: H vs C (p=0.082); H vs M-EDTA (p=0.016). Heparin was associated with the highest rate of PF. M and C lock solutions had similar PF rates. Only one CRBSI was identified in a patient on receiving a C lock. No bleeding or adverse events were identified. There was no difference in CRBSI prevention.

Conclusions: M-EDTA and C seem may preserve catheter patency. A larger clinical trial is being conducted in order to confirm these findings and to further evaluate CRBSI rates.

Funding: Government Support - Non-U.S.

TH-PO672

Long-Term Outcomes After Renal Artery Stenting Among Diabetic and Non-Diabetic Patients with Renal Artery Stenosis Happy Farouk Sadiek, Amol Mittal, Shraddha Narechania, Bassel Akbik, Gaurav Kistangari, Arash Rashidi. ¹Internal Medicine, Cleveland Clinic-Fairview Hospital, Cleveland, OH; ²Internal Medicine, Cleveland Clinic-Fairview Hospital, Cleveland, OH; ³Internal Medicine/Nephrologist, Cleveland Clinic-Fairview Hospital, Cleveland, OH.

Background: The current study aims to determine if renal-artery stenting affects mortality and/or delays the onset of Renal Replacement Therapy over a 10 year period in diabetic and non-diabetic patients with renal artery stenosis (RAS).

Methods: Using electronic medical records of Cleveland Clinic Health System, 168 patients with a diagnosis of RAS were identified from 01/01/2000 to 12/31/2004. Patients were categorized into two groups - "stented" for those who underwent renal artery stenting and "medical" for those who were treated with medical therapy alone. The primary outcome was time to death. The secondary outcome was a composite end point of death or the need for renal replacement therapy.

Results: Out of 168 patients, 67 were in 'stented' group and 101 in 'medical' therapy group; diabetic patients represented 24% in the stented group and 38% in the medical group. Overall, a higher percentage of deaths were seen in 'stented' group (64% vs. 42%, p 0.02). Multivariable analysis revealed CKD stage=>3 as the only variable significantly associated with death (HR 2.45, 1.32-4.85, p 0.003). In another analysis - bilateral renal artery stenosis, CKD stage =>3 and DM were found to be significantly associated with the occurrence of composite end point of RRT and/or death. On subgroup analysis among diabetics,

multivariable analysis revealed mortality benefit among patients who underwent renal artery stenting (HR 0.15, 0.03-0.55, p 0.006) when compared to 'medical' therapy alone; and a trend towards delaying the onset of composite end point (HR 0.28, 0.06-1.11, p 0.07).

Conclusions: Renal-artery stenting in RAS did not confer any benefit in terms of survival or delaying the onset of RRT; however stenting of renal arteries in diabetics showed a survival benefit and may have some benefit in delaying the onset of RRT. Further research is warranted to confirm these findings.

TH-PO673

Oral versus Intravenous Hydration to Prevent Contrast Induced Nephropathy Corinne E.A. Balemans,¹ Yvonne R.P. de Waal,¹ Jan A.J.G. van den Brand,¹ Marc A.G.J. Ten Dam,² Louis J.M. Reichert,³ Jack F. Wetzels.¹ ¹Nephrology, Radboud Univ Nijmegen Medical Center, Nijmegen, Gelderland, Netherlands; ²Nephrology, Canisius-Wilhelmina Hospital, Nijmegen, Gelderland, Netherlands; ³Nephrology, Rijnstate Hospital, Arnhem, Gelderland, Netherlands.

Background: Contrast Induced Nephropathy (CIN) complicates the use of iodinated contrast media. Guidelines advise identification of high risk patients and intravenous hydration as preventive measure. We conducted a multicenter randomized controlled trial to compare oral (home) hydration versus standard therapy (NCT01654328). The trial was stopped prematurely because of a low recruitment rate.

Methods: Patients with an eGFR<60ml/min/1.73m² were stratified for risk of CIN based on eGFR and the presence of risk factors (diabetes, peripheral arterial disease, heart failure, age, anemia, use of diuretics or NSAID's) Exclusion criteria were: overhydration, use of ³² diuretics, severe heart failure, CKD stage V. High risk patients were randomized. Arm A: sodiumchloride 1g/10kg of body weight/day per os on day -2 and -1 before contrast exposure. Maximum 10g sodiumchloride/day. Arm B: NaCl 0.9% 1000ml in 4 hrs or (in case of heart failure or severe renal failure) 12 hrs before and after contrast administration. We evaluated the incidence of CIN (defined as a rise in serum creatinine >25% or ≥44umol/L 48-96hrs after contrast) and adverse events.

Results: From Aug 2012 until Nov 2014 there were 1593 radiological procedures in high risk patients. In 1116 the inclusion criteria were met. Only 255 patients gave informed consent. We evaluated 233 procedures (11 missing data, 7 intercurrent hospitalisation, 4 severe nausea and vomiting.) (table 1) provides clinical characteristics and outcome data. Nausea was a frequent complaint during oral hydration. One SAE (overhydration) was related to IV hydration.

	Oral N=154	IV N=79	P
Female	48(31%)	28(35%)	0.56
Age(yrs)	71±9	67±14	0.02
eGFR(ml/min/1.73m ²)	47±16	44±9	0.05
CIN	3(1.9%)	1(1.3%)	1.00
SAE	5	2	1.00

Conclusions: Oral hydration is as effective as intravenous hydration in preventing CIN. Oral hydration obviates the need for hospital admission, and thus reduces costs. Adaptation to the protocol is needed to prevent nausea and vomiting.

TH-PO674

Obstructive Sleep Apnea and Blood Pressure and in Patients with Hypertension and Chronic Kidney Disease, Stage 2 Bodil Gade Hornstrup,^{1,2} Jeppe B. Rosenbaek,^{1,2} Nikolai Hoffmann-petersen,^{1,2} Pia Holland Gjørup,² Jost Wessels,² Erling B. Pedersen,^{1,2} Jesper N. Bech.^{1,2} ¹Univ Clinic of Nephrology and Hypertension, Regional Hospital West Jutland and Aarhus Univ; ²Dept of Internal Medicine, Regional Hospital West Jutland, Holstebro, Denmark.

Background: High nocturnal blood pressure (BP) and non-dipping are important prognostic factors in the evaluation of the risk of cardiovascular disease in patients with hypertension (HT). Many patients with chronic kidney disease (CKD) suffer from high nocturnal BP and non-dipping. The mechanism behind this phenomenon is unknown, but might be related to the presence of obstructive sleep apnea (OSA). In general population, OSA is observed in 10-15% of men and 5-8% of women, only symptomatic in 2-4%.

Methods: From a population study in Holstebro County, 238 subjects diagnosed with HT and CKD stage 2 were invited to participate. 70 subjects were included and underwent conventional 24-h ambulatory BP monitoring (ABPM) and applanation tonometry to monitor central BP (HealthSTATS BPro), 24 h urine collection for microalbuminuria, blood samples for creatinine, and cardiorespiratory monitoring to determine apnea hypopnea index (AHI). HT, nocturnal HT, resistant HT and non-dipping were defined according to current guidelines. OSA was diagnosed when AHI > 5.

Results: Of the 70 subjects, 27 (39%) were diagnosed with OSA (average AHI 16.5). The subjects suffering from OSA were more obese, had lower mean oxygen saturation and longer snoring time during sleep. There were no difference between subjects with and subjects without OSA in regard to age, gender, eGFR, u-albumine, number of antihypertensive agents, weekly alcohol intake, Epworth score, and lung function. Subjects with OSA tended to have higher clinic BP, average 24 h BP, nocturnal BP, central BP both 24 h, day and nocturnal. In addition a tendency was measured towards higher frequency of resistant HT and non-dipping in OSA.

Conclusions: The occurrence of OSA in a population with hypertension and CKD stage 2 was larger than expected in general population. In subjects with OSA, there was a tendency towards higher central and brachial BP. It is suggested, that OSA is the cause of high BP in patients with CKD stage 2.

Funding: Government Support - Non-U.S.

TH-PO675

Structured Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial (NCT01036490) David J. Leehey,^{1,2} Eileen Collins,¹ Holly J. Kramer,^{1,2} Cheryl Cooper,¹ Jolene Butler,¹ Conor McBurney,¹ Christine Jelinek,¹ Susan O'Connell.¹ ¹Research, Hines VA Hospital, Hines, IL; ²Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: Patients with type 2 diabetes, obesity, and chronic kidney disease (CKD) are generally physically inactive and may benefit from an exercise program. However, there have been few randomized controlled trials to determine the benefits of exercise training in this population.

Methods: We hypothesized that exercise training in obese diabetic patients with CKD will improve physical fitness and stabilize renal function. This was a 52-week randomized controlled study. Inclusion criteria were type 2 diabetes, obesity (body mass index > 30 kg/m²), CKD (stage 2-4), and persistent proteinuria (> 200 mg/day for at least 3 months). Subjects were randomized to a control group consisting of dietary management alone (CON) vs. dietary management plus 12 weeks of exercise training followed by 40 weeks of supervised home exercise (EX).

Results: 46 subjects were enrolled, of whom 36 (n=18 in each group) completed at least the 12-week evaluation. At baseline, mean values (± SD) were as follows: age 70.0 ± 8.0 years, body mass index (BMI) 36.9 ± 4.5 kg/m², body fat 41.3 ± 6.6%, glycated hemoglobin (HbA1c) 8.0 ± 1.8%, eGFR 39.9 ± 19.0 mL/min/1.73m², and urinary albumin excretion rate (UAE) 1118 ± 1236 mg/24h. Average symptom-limited treadmill time was 7.8 ± 3.8 minutes and peak oxygen consumption (V_{O₂} peak) was 13.2 ± 3.4 mL/kg/min. Treadmill time was increased from baseline at both 12 weeks and 52 weeks in EX but not in CON (p < 0.05). Change from baseline in eGFR was somewhat less in the EX than in the CON group at both 12 weeks (0.2 ± 4.7 vs. -3.4 ± 8.9 mL/min/1.73m²) and 52 weeks (-2.0 ± 5.8 vs. -3.1 ± 6.0 mL/min/1.73m²), though this did not reach statistical significance. No changes were seen between the groups in the other parameters.

Conclusions: Obese diabetic subjects with CKD have markedly impaired physical fitness. A structured exercise program improved exercise capacity but did not affect renal function.

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TH-PO676

Strength Training Intervention in Patients with Advanced Chronic Kidney Disease: A 20 Week Pilot Study Jordana B. Cohen,¹ Erica D. Palmer,¹ Angela M. Sheridan,¹ Brenden David Connor,¹ Mary B. Leonard,² Kathryn H. Schmitz,¹ Francis Perry Wilson.³ ¹Univ of Pennsylvania, Philadelphia, PA; ²Stanford Univ, Stanford, CA; ³Yale Univ, New Haven, CT.

Background: Although chronic kidney disease (CKD) is highly associated with sarcopenia and poor functional status, the feasibility and impact of longitudinal strength training in subjects with advanced CKD is not well understood.

Methods: Patients took part in a predominantly home-based 20 week program with 60 minutes of resistance training three times per week. We measured dual-energy X-ray absorptiometry (DXA) assessment of appendicular lean mass (ALM), bio-electrical impedance analysis (BIA) of fat free mass (FFM), 1 repetition-maximum (1RM) assessment of maximum quadriceps strength, short-physical performance battery (SPPB) assessment of functional status, 24-hr urine creatinine collection (UCr), and Kidney Disease and Quality of Life Short Form (KDQOL-SF) in individuals >=45 and <80 years of age with baseline eGFR >=15 and <=45 mL/min/1.73m². We used paired t-testing and Wilcoxon sign-rank to assess for changes in within-subject measurements before and after the intervention period as well as change-on-change analyses.

Results: 22 subjects completed the training program. The median age was 71 years, 63% were male, median eGFR was 27.9 mL/min/1.73m², and median BMI was 29.2 kg/m². There was a significant improvement in 1RM (mean difference 15.9 kg +/- 6.5, p=0.03), but no significant change was appreciated in ALM (p=0.99), FFM (p=0.99), SPPB score (p=0.67), 24-hr urine creatinine (p=0.22), eGFR (p=0.26) or KDQOL-SF score (p=0.78). There was a significant decrease in AST (p=0.01), ALT (p=0.01), and total bilirubin (p<0.01). There was also a significant association between within-subject improvement in 1RM and improvement in FFM (p=0.02).

Conclusions: In this small study of patients with advanced CKD, we successfully developed a predominantly participant-driven strength training program. The significant improvement in 1RM indicates that patients were adherent with the protocol, however larger studies are needed to assess for the effect of strength training on anthropomorphic measures, serologic measures, and quality of life.

Funding: NIDDK Support

TH-PO677

Effect of a Medication Management Intervention on Acute Care Utilization After Hospitalization in CKD Katherine R. Tuttle,^{1,2,3} Radica Z. Alicic,^{1,3} Robert Short,^{1,2} Joshua J. Neumiller,² Kenn B. Daratha,^{2,3} Brian J. Gates,² Cynthia F. Corbett.² ¹Providence Health Care; ²Washington State Univ; ³Univ of Washington.

Background: People with chronic kidney disease (CKD) are hospitalized often and incur high risk of readmission. The study objective was to test the effect of a medication management intervention during the hospital-to-home transition on subsequent acute care utilization.

Methods: A single-center, randomized, controlled clinical trial of an intervention to improve medication information transfer (MIT) was conducted by pharmacists in participants' homes within the first week of hospital discharge and compared to usual care. Hospitalized participants with CKD stages 3-5 (not treated by dialysis or transplant) were enrolled. The primary outcome was a composite of hospital readmissions and visits to emergency departments or urgent care centers within 90 days of discharge.

Results: Enrollee (n=182) characteristics included: age 69±11 (mean±SD) years; women 48%; diabetes 56%; hypertension 83%; eGFR (CKD-EPI creatinine) 41±14 mL/min/1.73m²; albuminuria 43 (4,521; median, IQR) mg/g creatinine. The 3 top categories of primary diagnoses for hospitalization were cardiovascular disease (30%), infection (19%), and kidney disease (14%). Enrollees lost before the baseline visit (n=41, mainly due to severe illness) were not included as active study participants. In intent-to-treat analysis (n=141), the primary outcome occurred in 32/72 (44%) of the MIT group and 28/69 (41%) of those in usual care (Kaplan Meier, log-rank p=0.72). At 90 days post-discharge, achievement of guideline-based CKD goals did not differ significantly between MIT and usual care groups: blood pressure <140/90/<130/80 mm Hg in those without/with albuminuria, respectively (43% vs 50%); hemoglobin A1c <7.5% in diabetic participants (69% vs 76%); hemoglobin >11 g/dl (81% vs 83%); and phosphorous <5 mg/dl (97% vs 96%).

Conclusions: A medication management intervention conducted during the hospital-to-home transition did not reduce subsequent acute care utilization for hospitalized people with CKD. This high-risk population may require more comprehensive interventions to improve outcomes after hospitalization.

Funding: NIDDK Support

TH-PO678

Impact of Decision Making Tools Use at the Time of Modality Choice and PD Take on in a Multicentre-Multinational Setting Belen Marron,¹ Janusz Ostrowski,² Delia Timofte,³ Marietta Torok,⁴ Jose C. Divino-Filho.¹ ¹Diaverum Home Therapies. Medical Office, Diaverum, Munich, Germany; ²Wloclawek Diaverum Clinic, Diaverum, Wloclawek, Poland; ³Sema Diaverum Clinic, Diaverum, Bucharest, Romania.

Background: Different factors have been attributed to low PD take on such as late referral, unplanned start, physician bias towards PD, large HD availability and lack of patient's choice. Some references apply for 50% of PD if a good modality information is provided. Objectives: To analyze the impact of a structured modality information program with the use of decision making tools (DMTs) on type of modality choice and start.

Methods: Observational, prospective, multicentre and multinational experience. All patients under ESRD 4-5 and/or after an unplanned dialysis start if non-informed before were recruited to undergo a DMT process for RRT choice. Process included: personal values evaluation, RRTs information with different tools, deliberation and patient's modality election.

Results: 444 patients, mean age 61.5 y. from 31 clinics in Poland, Hungary and Romania underwent a DMTs evaluation between August-December 2014. Staff considered PD as contraindicated in 45% of Polish patients, 32% in RO and 24% in HU. Reasons behind were mix causes and "other" than abdominal or mental. Home orientation was stated for 30% (PL), 40% (RO) and 54% (HU). Written information was largely used for 71 to 97% of patients; DVD in 9-21% and in centre HD/PD touring visits in 31-75%. PD as elected modality varied among countries: 10% (RO), 21% (PL) and 35% (HU). For patients who started dialysis (n= 163), PD was used in 10% (RO), 14% (PL) and 36% (HU).

Conclusions: Use of DMTs at the time of RRT modality choice is encouraging and complies with patient's empowerment. An increase in PD take-on has been observed in our institution after DMTs use. However, when compared with other references, our patient's PD election is still low and factors behind this fact needs to be elucidated with a larger recruitment pool (in process).

TH-PO679

Thrombotic Microangiopathy And Complement Factor C4d Predict Poor Prognosis in IgA Nephropathy and Henoch-Schönlein Purpura Nephritis Jamie S. Chua,¹ Malu Zandbergen,¹ Johan W. De Fijter,² Ron Wolterbeek,³ Jan A. Bruijn,¹ Ingeborg M. Bajema.¹ ¹Pathology, LUMC, Leiden, Netherlands; ²Nephrology, LUMC, Leiden, Netherlands; ³Medical Statistics, LUMC, Leiden, Netherlands.

Background: Thrombotic microangiopathy (TMA) was previously reported to be clinically relevant and underdiagnosed in IgA nephropathy (IgAN). Complement factor C4d is a common denominator of TMA. Aim: to validate the prevalence of TMA and to determine the clinical significance of TMA and C4d in IgAN and Henoch-Schönlein Purpura Nephritis (HSN).

Methods: We included 129 native renal biopsies from 2003-2013; IgAN in 82% and HSN in 18%. Biopsies were classified according to Oxford MEST-scores, scored for vascular lesions including TMA, arterial intimal sclerosis and arteriolar hyalinosis, and immunostained for C4d. Retrospectively collected clinical data included hypertension and renal function. Three groups were distinguished: absence of both TMA and C4d; presence of both TMA and C4d; and presence of either TMA or C4d. Changes in eGFR over time were compared using a linear mixed model. Renal survival was analyzed with Cox regression. Prognostic values of C4d, TMA and hypertension for renal survival were analyzed with multivariable Cox regression.

Results: The prevalence of TMA in this cohort was 20% (n=26). TMA was mainly chronic (65%; 17/26) and was localized in arterioles (81% of TMA cases), glomeruli (15%) or both (4%). TMA was associated with interstitial fibrosis and tubular atrophy, arterial intimal sclerosis, hyalinosis and hypertension (p-values<0.05). TMA was strongly associated with the presence of C4d deposits (p<0.001). Linear Mixed Model analysis: patients with hypertension and both C4d and TMA had significantly lower eGFR (mean decrease 24 and 40 ml/min/1.73m² respectively). Patients with both TMA and C4d had significantly worse renal survival than the two groups without both C4d and TMA (HR 6.33 and 3.38 resp.) corrected for hypertension (HR 4.52 and 3.30 resp.).

Conclusions: The prevalence of TMA in IgAN and HSN is substantial (20%) but lower than previously reported. TMA was mainly chronic, arteriolar and associated with C4d, hypertension and chronic lesions. TMA and C4d mark poor renal function and poor renal survival in IgAN and HSN.

TH-PO680

Glomerular Complement Factor C4d Marks Glomerular Basement Membrane Duplications: C4d Beyond Antibody Induced Injury Jamie S. Chua,^{1,2} A. Gasim,² Ron Wolterbeek,¹ Harsharan Kaur Singh,² Volker Nickleleit,² ¹LUMC, Leiden, Netherlands; ²UNC, Chapel Hill, NC.

Background: C4d deposits along peritubular capillaries (ptc) mark antibody mediated rejection (ABMR) in renal allografts. The diagnostic significance of linear C4d deposits along glomerular basement membranes (GBM-C4d), which can occur as isolated event, is poorly understood. **Hypothesis:** GBM-C4d, especially when isolated, is not a sign of ABMR but rather a marker of structural GBM changes and duplications in native kidneys and renal transplants.

Methods: We analyzed 319 renal allograft biopsies from 219 patients. GBM remodeling was analyzed by light (Banff cg-score) and by electron microscopy. Linear C4d staining by immunohistochemistry (IHC) and immunofluorescence (IF) was scored along the GBM and ptc. Controls: native kidneys with minimal change disease (n=10) and chronic thrombotic microangiopathy with GBM duplications (n=26).

Results: Transplants: GBM duplications/transplant glomerulopathy (TG) occurred in 52/319 biopsies (16%). By IF, 49/52 (94%) TG cases had GBM-C4d; 36/49 (73%) had isolated GBM-C4d lacking ptc-C4d deposits. By IHC, 74% of TG cases had GBM-C4d; 60% of which as isolated event. GBM-C4d staining intensity correlated with Banff cg-scores (IF: rs=0.453, p<0.01; IHC: rs=0.478, p<0.01). 80% of cases (24/30) with GBM duplications present only by electron microscopy revealed GBM-C4d. Association GBM-C4d with TG/GBM duplications: p<0.001. Statistical significance between GBM-C4d staining and structural GBM duplications remained after omitting cases with presumed or definitive ABMR (DSA-positivity, C4d positivity in ptc, transplant glomerulitis). Multivariate logistic regression: GBM duplication/TG was an independent predictor of GBM-C4d positivity. **Native kidneys:** GBM-C4d occurred in 24/26 (92%) cases with thrombotic microangiopathy and GBM duplications; no staining was seen in minimal change disease.

Conclusions: The diagnostic significance of linear C4d deposits along ptc versus GBM differs. C4d along ptc marks ABMR while linear GBM-C4d is associated with structural GBM duplications in native and transplanted kidneys, independent of the etiology or antibody induced injury. In transplants GBM-C4d serves as marker for TG.

TH-PO681

Predicting Outcome in Patients with Anti-GBM Glomerulonephritis Using the Histopathological Classification for ANCA-Associated Vasculitis: Preliminary Results Emma Elisabeth Van Daalen,¹ J. Charles Jennette,² Jan A. Bruijn,¹ Ingeborg M. Bajema,¹ ¹Pathology, Leiden Univ Medical Center, Leiden, Netherlands; ²Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: The renal biopsy in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) is characterized by crescent formation. No histopathological classification has been implemented for the disease. We have applied the histopathological classification for ANCA-associated vasculitis (AAV) to see whether this classification can distinguish patients regarding renal outcome.

Methods: We analyzed biopsies of 20 patients, diagnosed with anti-GBM GN between 1984 and 2014 at a university hospital in the Netherlands. We classified these biopsies according to the histopathological classification for AAV: sclerotic (≥50% sclerotic glomeruli), focal (≥50% normal glomeruli), crescentic (≥50% cellular crescents) or mixed (no dominant lesion) class. We collected data on serology, renal function and end-stage renal disease (ESRD) during 5-year follow-up.

Results: Fourteen biopsies (70%) were categorized as crescentic, three (15%) as focal, two (10%) as mixed and one (5%) as sclerotic. Mean age was 47.4 years (SD: 17.1, range: 17.0-74.9) and differed between classes (P=0.039), with the focal class having the youngest patients with a mean age of 25.4 years. Estimated glomerular filtration rate (eGFR) at time of biopsy differed between classes (P<0.001), focal class having a mean of 80.2 ml/min/1.73m², crescentic 6.9 and mixed 8.7 (no available data for sclerotic class).

Mean eGFR at 1 year was 107.6 in the focal, 10.1 in the crescentic, and 21.8 in the mixed class (P<0.001). The occurrence of ESRD differed between groups (P=0.016), with no occurrence in the focal group.

Conclusions: These preliminary results show that the histopathological classification for AAV is useful for anti-GBM GN, predicting outcome in terms of eGFR at time of biopsy and at 1 year after biopsy. The focal group had more favorable outcomes regarding renal function and development of ESRD.

TH-PO682

The Role of C4d Immunohistochemistry to Highlight Immune Complex Deposition in IgA Nephropathy Umer Sheikh,¹ Hong Qu,² Alton Brad Farris,¹ Thomas E. Rogers,¹ Carla L. Ellis,¹ ¹Pathology, Emory Univ Hospital and School of Medicine, Atlanta, GA; ²Pathology, St. John Hospital and Medical Center, Detroit, MI.

Background: IgA glomerulonephropathy (IgAN) is one of the most common immune complex associated nephropathies worldwide. It may develop de novo or recur in an allograft. Recently, C4d immunohistochemistry has been shown to highlight immune complex deposits in a variety of glomerular diseases. Limited conclusive data is available regarding the utility of C4d immunohistochemistry to highlight mesangial deposits in IgAN despite some authors claim to the contrary. The presence of this finding would be beneficial in cases where immunofluorescence studies are unavailable. Our study seeks to determine the ability of C4d immunohistochemistry to highlight mesangial, IgA dominant immune complex deposition.

Methods: A retrospective study from two institutions is performed. 24 cases (19 native and 5 allografts) from one and 36 native cases from the other of IgAN diagnosed between the years of 2005 and 2012 were selected (n=60). All cases were confirmed IgAN by immunofluorescence and electron microscopy. Paraffin-embedded tissue sections from all biopsies were then stained for C4d immunohistochemistry by each respective institutional protocol. Cases from each institution were reviewed by the respective senior author for the presence, intensity and location of glomerular staining by the C4d antibody.

Results: All native and allograft cases of IgAN from both institutions showed complete absence of mesangial C4d immunoreactivity with some non-specific tubular epithelial staining in some cases and some low intensity, segmental capillary wall staining in others. Control tissue reacted appropriately.

Conclusions: Our results suggest that at least in our small cohort spanning two academic medical centers, the utility of C4d immunohistochemistry to support a diagnosis of IgAN in the native or allograft population is limited despite recent evidence of C4d deposition in immune complex associated disease. Although complement deposition with C3 is typically seen in IgAN, C4d deposits are not identified, suggesting the lack of this specific complement factor in IgAN.

TH-PO683

DNA Methylation as a Biomarker of Disease Status in Patients with ANCA-Associated Vasculitis Britta E. Jones, Jia Jin Yang, Akhil Muthigi, Susan L. Hogan, Joshua Starmer, Candace Henderson, Elizabeth J. Brant, Julie Anne G. McGregor, William Franklin Pendergraft, Ronald J. Falk, Dominic J. Ciavatta. *Univ of North Carolina at Chapel Hill-Kidney Center.*

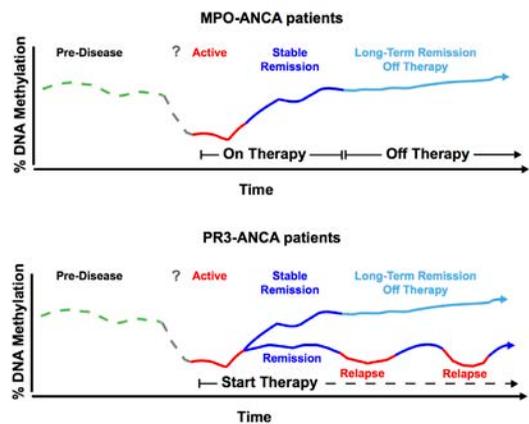
Background: ANCA-associated vasculitis (AAV) is associated with environmental exposures and age, both of which are linked to changes in DNA methylation. We tested whether DNA methylation changes in patients compared to healthy controls and if DNA methylation may be used as a biomarker of disease status.

Methods: AAV patients (67) were followed longitudinally through disease activity and remission (143 leukocyte samples), including 21 patients in long-term remission off therapy and 32 healthy individuals. DNA methylation was measured using mass spectrometry and bisulfite sequencing at myeloperoxidase (MPO) and proteinase 3 (PR3). Expression was measured for MPO, PR3 and DNA methyltransferase 1 (DNMT1).

Results: Patients with active AAV were hypomethylated compared to healthy individuals. Within paired active and remitting patients, MPO-ANCA and half of PR3-ANCA patients showed increased DNA methylation. In PR3-ANCA patients with increased methylation in remission, DNA methylation correlated with expression of MPO and PR3, and stable remission. DNMT1 expression in leukocytes from active and remitting patients was 0.6 fold and 0.8 fold, respectively, of healthy individuals. At MPO and PR3 there is a positive correlation between DNA methylation and DNMT1 expression.

Conclusions: AAV patients are characterized by dynamic changes in DNA methylation; differences in methylation during disease remission suggest these fates have an epigenetic basis.

Changes in DNA methylation at MPO and PR3 genes in patients with AAV



MPO-ANCA patients restore DNA methylation in remission, while chronically relapsing PR3-ANCA patients may benefit from therapies that increase DNA methylation. These data suggest that DNA methylation in leukocytes may function as a biomarker of disease status in AAV.

Funding: NIDDK Support, Private Foundation Support

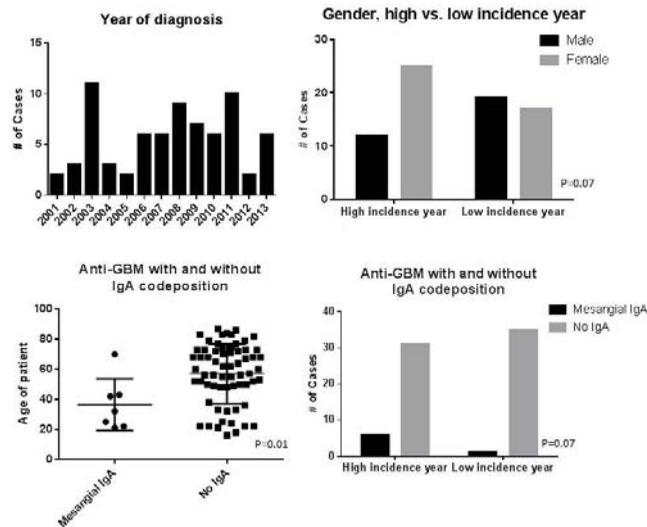
TH-PO684

Epidemiologic Features of Anti-Glomerular Basement Membrane Disease
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Background: Anti-glomerular basement membrane (anti-GBM) disease is a rapidly progressive glomerulonephritis mediated by autoantibodies to the noncollagenous domain of the alpha-3 chain of type IV collagen. Previous reports demonstrated an association with a seasonal or environmental exposures in some cases (PMID: 4604010, 3256901). We sought to understand epidemiologic factors associated with anti-GBM disease.

Methods: Reports from consecutive cases of anti-GBM diagnosed at the University of Washington were retrospectively reviewed, with specific attention to epidemiologic parameters. Statistical analysis was performed on Graphpad Prism using Fisher's exact and Mann-Whitney tests.

Results: Seventy three (M=31; F=42) cases of anti-GBM disease were identified, with a median age of 56 years. Overall, 2 to 11 cases were seen per year (median = 6); a high incidence year was defined as > median number of cases. 60% of cases were diagnosed in winter or spring (95% CI: 48-72%), and 40% in summer or fall (95% CI 28 - 52%). The M:F ratio was 1:2 in high incidence years, but nearly 1:1 with a male predominance in low incidence years (p=0.07). Of variables studied, concurrent deposition of IgA in the mesangium was associated with younger age at diagnosis (p=0.01); 6 of 7 of these were seen in a high-incidence year (p=0.07). No associations among ANCA-positivity vs. respiratory symptoms, age, sex, and/or season of presentation were identified.



Conclusions: There were quantitative and qualitative differences in epidemiologic parameters in anti-GBM disease. Unlike low incidence years, cases diagnosed in high incidence years showed a trend for increased likelihood of concurrent mesangial IgA deposition, and male gender. The findings suggest potential differences in the environmental and/or gender-based triggers in the development of anti-GBM.

TH-PO685

The Lumped System Utilized in the Japanese Histological Grade Classification of IgA Nephropathy May Produce a Score with a Broader Applicability Compared to the Split System of Oxford Classification
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Background: Japanese Histological Grade Classification (JHGC; HG1-HG4) (J Nephrol, 2013) and Oxford classification (Oxford) were compared with a focus on their ability to predict renal functional decline (RFD) and proteinuric remission (PUR).

Methods: 411 Japanese with IgAN (male 49%) were collected from 32 centres in Japan. The patients, whose median age was 36.2 years old, were prospectively followed for a median of 36 months. The average amount of initial proteinuria (PU) was 0.8 g/day. Mean eGFR was 77.9±29.6 ml/min/1.73m² and median rate of decline in eGFR was -0.7 ml/min/1.73m².

Results: 24% and 55% of patients received steroid and RAS blockade, respectively. The ICC among 5 observers on M, E, S, T, and HG scores were fair or good. In multivariate Cox analysis, hazard ratio (HR) of MEST in Oxford for 1.5 time's increase of serum creatinine (sCr) was not significant, whereas HG3 and HG4 in JHGC were significant (HR of 13 and 42, respectively) even after adjustment by steroid, RAS blockade, initial PU, initial eGFR, and initial MAP (p<0.05). When comparing HG, M, E, S and T, HG score was the only independent predictor in isolation or in comparison to varied combinations of MEST parameters. The HR for PUR (an endpoint of proteinuria as 0.3 g/day) was not significant in Oxford, whereas HG3, initial MAP and steroid were independent predictors with HR as 0.4, 0.9, and 1.7, respectively (p<0.05).

Conclusions: HG score was more effective than Oxford in predicting both RFD and PUR in the Japanese cohort consisting of earlier stage of IgAN. The inherent flexibility in a lumped approach (JHGC) as opposed to a split system (Oxford) may make the HG score more robust when being applied to diverse cohorts allowing a wider application of scoring.

Funding: Government Support - Non-U.S.

TH-PO686

Prospective Cross-Sectional and Longitudinal Observational Study of Urinary Podocyte Markers and Urinary Megalin in Kidney Disease of ANCA-Associated Vasculitis
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Background: The purpose of this study is to clarify the significance of urinary podocyte markers (urinary podocyte number (U-Pod/Cr) and urine podocalyxin (PCX) (U-PCX/Cr)) and urinary megalin (A-Meg/Cr, megalin's extracellular domain; C-Meg/Cr, full-length of megalin) in ANCA-associated vasculitis (AAV).

Methods: AAV patients (30 cases) were recruited from August 2009 to April 2014. Presence of proteinuria and/or reduced eGFR or histological renal diagnosis was defined as kidney disease (KD)(+). U-Pod/Cr, U-PCX/Cr, A-Meg/Cr and C-meg/Cr were measured around the treatment start (M0), and at 1 (M1), 3 (M3), 6 (M6) and 12 months (M12) after treatment.

Results: At M0, urinary protein creatinine ratio (U-PCR) was significantly higher, and eGFR was significantly lower in KD(+). CRP was not different between KD(+) and KD(-) at M0. U-Pod/Cr was significantly higher in KD(+), and U-PCX/Cr, A-Meg/Cr and C-Meg/Cr were not different at M0, although there was a trend of high C-Meg/Cr in KD(+), compared with KD(-). After treatment in KD(+), CRP (from M1 on), U-PCR, urinary-NAG (U-NAG)/Cr (from M3 on) significantly improved. U-Pod/Cr and C-Meg/Cr (from M6 on) were significantly improved after treatment in KD(+), and U-PCX/Cr and A-Meg/Cr were not significantly changed. Only the correlation of C-Meg/Cr with U-NAG/Cr (p=0.028, Spearman r:0.46, 95%CI 0.04-0.74) was significant between laboratory data and urinary markers measured at M0.

Conclusions: U-Pod/Cr and C-Meg/Cr are elevated in AAV kidney disease and improve after treatment. U-Pod/Cr and C-Meg/Cr may reflect podocyte and proximal tubular injuries, respectively, in AAV.

TH-PO687

Clinical and Histological Determinants of Renal Outcome in Lupus Nephritis

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Background: The ISN/RPS 2003 histopathological classification of lupus nephritis (LN) is based on lesions historically thought to be relevant for prognosis, but for some lesions the evidence base is lacking. Without preconceptions, we tested a wide range of histologic and clinical features to objectively identify prognostic indicators of renal outcome in patients with LN.

Methods: 42 histological and 7 clinical parameters were determined as candidate predictors of renal outcome. A cohort of patients was identified from the pathology archives of our center, diagnosed with any class of LN between 1990-2011. Renal biopsies were rescored for 42 histologic parameters. eGFR and proteinuria were recorded at time of renal biopsy, as well as during 1, 5, and 10 years of follow-up. For preliminary analyses, variables were tested using univariate mixed models, in which $p < 0.05$ for fixed effects was considered statistically significant.

Results: Interim analysis was performed on 29 patients, of whom none developed end-stage renal disease. Significant associations with eGFR were found for age ($p=0.03$) and eGFR ($p < 0.001$) at time of renal biopsy, percentage of normal glomeruli ($p < 0.01$), percentages of glomeruli with mesangial hypercellularity ($p=0.05$), endocapillary hypercellularity ($p=0.03$), endothelial swelling ($p=0.03$), endocapillary mononuclear cells ($p=0.01$), wire loops ($p=0.02$), and cellular crescents ($p < 0.05$), as well as the presence of an interstitial infiltrate ($p=0.04$). Significant associations with proteinuria were found for eGFR at time of biopsy ($p=0.02$), percentage of glomeruli with mesangial global sclerosis ($p=0.02$), presence of cellular and fibrocellular crescents ($p=0.01$), as well as the presence of an interstitial infiltrate ($p < 0.01$) and tubular atrophy ($p=0.02$).

Conclusions: Besides histological parameters characteristic of the previously established classes of LN, also interstitial and clinical parameters may have prognostic significance. These and other features will be studied in an extended dataset in multivariate analyses of which the outcome may be relevant for future modifications of the LN classification.

TH-PO688

Specificity of Full House Immunofluorescence for Systemic Lupus Erythematosus

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Background: The finding of full house immunofluorescence (IF) in combination with various histological lesions in renal biopsies of patients without overt systemic lupus erythematosus (SLE) poses a diagnostic challenge. We studied the clinical course of these patients as compared to patients who did have SLE at the time of biopsy.

Methods: Patients with full house IF on renal biopsy between 1968-2014 were identified from the pathology archives at our center. Clinical records were reviewed for the presence of ACR or SLICC criteria for the classification of SLE at the time of renal biopsy and during follow-up.

Results: 149 patients with full house IF on renal biopsy were identified. At time of biopsy, 112 had SLE according to >4 ACR criteria (SLE_{ACR}), 7 according to SLICC criteria (SLE_{SLICC}), and 30 did not fulfill criteria for SLE. Of the latter 30, one was classified as SLE_{SLICC} during follow-up. Survival without end-stage renal disease regardless of immunosuppressive therapy was better in the group of patients with $SLE_{ACR/SLICC}$ than in those without SLE ($p < 0.01$). No difference was noted between patients with SLE_{SLICC} or SLE_{ACR} ($p=0.16$). Compared to patients with $SLE_{ACR/SLICC}$, patients without SLE were significantly more often male, had significantly higher serum creatinine, CH50, and C3, and had significantly less frequent anti-ENA, anti-SS-A, anti-RNP70, and anti-C1q. All SLE criteria were significantly more frequent in patients classified as $SLE_{ACR/SLICC}$ except for chronic cutaneous lupus, and oral/nasal ulcers.

Conclusions: This study demonstrates that the presence of full house IF in renal biopsies as a marker of biopsy-confirmed LN, has limited specificity for SLE. This contrasts with the SLICC classification, where biopsy-confirmed LN was seen as a highly specific feature of SLE. Our results show that patients with full house IF without SLE are clinically distinct from SLE patients. Consequently, for clinical and study purposes, a separate classification for these patients is warranted.

TH-PO689

Novel Urinary Tubular Biomarkers for Diagnosis and Predictive Active Lupus Nephritis

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Background: Tubulointerstitial damage is important in the prediction and progression of lupus nephritis (LN). *Novel urinary tubular biomarkers included neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and periostin have been reported to increase in progressive kidney injury.* Therefore, these urinary biomarkers may relate and predict renal activity in systemic lupus erythematosus (SLE) patients.

Methods: We performed a diagnostic and prospective study in SLE patients with biopsy-proven active LN and with inactive LN. All patients were collected urine for NGAL, KIM-1 and periostin measurement by ELISA. After standard treatment in active LN patients, urinary biomarkers were repeated.

Results: A total of 67 patients with SLE including 35 patients with active LN and 32 patients without active LN were included. Urinary levels of KIM-1 was higher in active LN compared to inactive LN (median 2.17 (IQR: 0.92, 5.18) vs.0.29 (IQR: 0.13, 1.11) $\mu\text{g/g}$ creatinine, $P < 0.001$), while no significant difference was found in urinary NGAL and periostin levels. Urinary KIM-1, NGAL and periostin correlated positively with proteinuria, and only KIM-1 and NGAL correlated negatively with renal function. On ROC analysis, urinary KIM-1 (AUC; 0.80, 95%CI 0.69-0.92) outperformed conventional biomarkers (serum creatinine, urine protein, serum complements and anti-dsDNA antibody) in differentiating active LN from non-LN group. On follow-up after treatment in active LN patients ($n = 19$), there was no significant difference in all urinary tubular biomarkers between response and nonresponse LN patients.

Conclusions: Levels of urinary KIM-1, but not of urinary NGAL and periostin may be potentially useful markers of LN activity and urine KIM-1 is better performance than conventional markers of active LN. However, these novel tubular biomarkers are not predictive for a clinical response to treatment of active LN.

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TH-PO690

Revisiting of Anti-Phospholipase A2 Receptor Antibodies and Its Antigen as Specific Biomarkers in Membranous Nephropathy

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Background: M-type phospholipase A2 receptor (PLA2R) as antigen in idiopathic membranous nephropathy (IMN) is a success model of fast-speed translation medicine. The objective of this study was to assess the prevalence and clinical value of serum autoantibodies against the M-type phospholipase A2 receptor (anti-PLA2R) in Chinese MN patients.

Methods: In this prospective study, 195 patients with MN including 37 MN patients with coexisting diseases and 70 patients with other glomerular diseases were enrolled. Anti-PLA2R antibodies in serum were assessed by direct immunofluorescence assay (IFA). The staining of PLA2R in glomeruli was evaluated by standard immunofluorescence microscopy.

Results: Anti-PLA2R was only found in MN patients. PLA2R-related MN rate in MN was 87.23%, the positive rate of the serum anti-PLA2R and glomeruli PLA2R were 68.09% and 83.21%, respectively. PLA2R-unrelated MN patients had more coexisting diseases compared with PLA2R-related MN patients (61.11% vs 21.13%, $p=0.01$), but in MN patients with coexisting diseases, the rate of PLA2R-related MN is 72.97%, thus we regard that PLA2R in glomeruli or anti-PLA2R in circulation is not suitable for discrimination of IMN and SMN. In 54 MN patients who have received treatment the positive rate for Anti-PLA2R was 8.33%, 31.58% and 69.57% in Complete remission (CR), Partial remission (PR), and disease active patients, respectively ($p=0.001$). More Anti-PLA2R positive patients at the start of the study developed nephrotic-range proteinuria (70.31%) compared to Anti-PLA2R negative PLA-related MN (53.85%) ($p=0.004$), but there was no statistical difference in remission rate during follow-up ($p=0.406$).

Conclusions: We confirm that anti-PLA2R antibody measured by IFA is specific detected in serum of MN patients but it is controversy as used in the differential diagnosis of IMN and as a biomarker to predict outcome of disease. the absence of predictive value may be due to the fact that you have not looked at quantitative data (would need ELISA or quantitative expression of IF data).

TH-PO691

Endoplasmic Reticulum Stress Marker Glucose-Regulated Protein 78 Instead of Calcineurin Expression within Kidney Is Predictive of Poor Response to Cyclosporine Treatment in Idiopathic Membranous Nephropathy

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Background: Cyclosporine (CsA) is effective to achieve 60-70% remission rate in treatment of idiopathic membranous nephropathy (IMN). Little is known if Endoplasmic Reticulum stress marker glucose-regulated protein 78 (GRP78) within kidney before CsA treatment could predict post treatment outcome.

Methods: Seventy-six adult biopsy-confirmed IMN patients treated by CsA for at least six months from Peking Union Medical College Hospital from 1996 to 2014 were retrospectively reviewed. They were grouped into non-remission (NR) ($n=12$), partial remission (PR) ($n=12$), or complete remission (CR) ($n=52$) at the end of six month treatment of CsA with an initial CsA dosage ($2.8 \pm 0.7 \text{ Mg/Kg/d}$). GRP78 in kidney and Calcineurin (CAL) expression in the kidney and serum were assayed by immunohistochemistry and ELISA, and their expressions were correlated with clinical outcome.

Results: Serum CAL and kidney CAL expression in IMN patients are significantly increased compared to healthy controls, although there is no difference in either serum or kidney CAL among NR, PR or CR groups. There is a negative correlation between serum CAL activity and renal CAL expression ($p=0.034$). However, glomerular GRP78 expression in NR group is significantly higher than CR group (Bonferroni correction $p < 0.0083$). There is a positive correlation between kidney CAL expression and GRP 78 expression ($p < 0.05$).

Conclusions: ER stress marker GRP78 expression in glomerular section of kidney instead of serum or kidney CAL expression could be an additional marker, which negatively predicts the clinical response to CsA treatment in IMN patients. New drugs targeting to alleviate ER stress in IMN could be developed to treat those non-responders to CsA. (Supported by National Natural Science Foundation of China 81170665 to Dr. Jianling Tao).

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Underline represents presenting author.

TH-PO692

Selected Reaction Monitoring for Quantification of Angiotensin-II Signature Proteins in Urine Ana Konvalinka,¹ Andrei Drabovich,² Xuewen Song,¹ York P. Pei,¹ James W. Scholey,¹ Eleftherios P. Diamandis.² ¹Medicine, Div. of Nephrology, Toronto General Hospital, Toronto, ON, Canada; ²Laboratory Medicine and Pathobiology, Lunenfeld Research Inst, Toronto, ON, Canada.

Background: Angiotensin-II (AngII) mediates polycystic kidney disease progression. However, there are no specific markers of kidney AngII activity. We previously defined 83 AngII-regulated proteins *in vitro*, which reflected kidney AngII activity *in vivo*. We aim to quantify these proteins in urine using a mass spectrometry technique called selected reaction monitoring (SRM), and establish their role as markers of kidney AngII activity in patients with ADPKD.

Methods: We demonstrated that 47 of 83 AngII-regulated genes were differentially expressed in cystic vs normal kidney tissue. We then selected 18 AngII-regulated proteins upregulated in cystic tissue and/or present in urine. We developed SRM assays for 37 peptides corresponding to 18 AngII-regulated proteins. To assess reproducibility and recovery, we spiked in bovine serum albumin (BSA), and the corresponding heavy-labeled peptides. We determined an optimal method for detection of AngII-regulated peptides. Heavy peptides corresponding to 13 identified AngII-regulated peptides were purchased and spiked into urine. Ultimately, 20ug of total protein/sample was concentrated and analyzed on triple-quadrupole mass spectrometer. We quantified AngII-regulated peptides in urine samples of 9 ADPKD and 2 healthy subjects.

Results: Technical replicate CVs were <6% for BSA peptides, and recovery was ~100%. Calibration curves demonstrated linearity (R²>0.99) and CVs<20% in the concentration range of 7/13 peptides in normal and ADPKD urines. Deamidated peptides accounted for 1-40% of total concentration. Peptides were quantified in all urine samples. Peptides corresponding to proteins TSP1, BST1, and LAMB2 had the highest excretion rate in urine of the only ADPKD patient with impaired GFR.

Conclusions: We have developed a protocol for SRM quantification of AngII-regulated proteins in urine. Seven AngII-regulated peptides were quantified in urine samples. Future studies will examine if urine excretion rate of AngII signature proteins is associated with cyst size and GFR in larger cohorts of ADPKD patients.

TH-PO693

Establishment of Proteomic Profiles of Normal Glomeruli Using Laser Microdissection and Mass Spectrometry Ying Sun,¹ Mingxi Li,¹ Yubing Wen,¹ Wei Sun,² Jian Sun,³ Xuemei Li.¹ ¹Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China; ²Dept of Core Instrument Facility, Inst of Basic Medical Sciences, Inst of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; ³Dept of Pathology, Peking Union Medical College Hospital, Beijing, China.

Background: Laser microdissection combined with mass spectrometry (LMD/MS) has become a powerful tool in proteomics study. There is little data of normal glomeruli proteomic profiles which are fundamental in the study of differential proteomics of kidney diseases. Our study aimed on establishing proteomic profiles of normal glomeruli from formalin-fixed paraffin-embedded (FFPE) specimen through LMD/MS.

Methods: Normal kidney cortices were obtained from four patients underwent nephrectomy due to renal carcinoma. 10-mm FFPE sections were prepared for laser microdissection, 4-6 glomeruli were cut out each case and collected for digestion. Peptides were quantified using Thermo Scientific LTQ Orbitrap Velos mass spectrometer. MASCOT software was used for identification of proteins, with tandem mass spectrometry data searching against UniProt. Scaffold 4 software was used to integrate results, taking proteins with credibility of ≥95% and identified peptides number > 1 into statistics.

Results: 67 proteins were identified in normal glomeruli from four cases with LMD/MS analysis. High abundance glomerular structural proteins and blood-related proteins are shown below.

MS/MS View	Accession Number	Molecular Weight
Alpha-actinin-4	O43707	105 kDa
Zinc-alpha-2-glycoprotein	P25311	34 kDa
Na(+)/H(+) exchange regulatory cofactor	Q15599	37 kDa
Uromodulin	P07911	70 kDa
Synaptonemalcomplex protein 2	Q5T4T6	94 kDa
Basement membrane-specific proteoglycan	P98160	469 kDa
Osteopontin	P10451	35 kDa
Peroxisredoxin-2	P32119	22 kDa
Laminin subunit alpha-5	O15230	400 kDa
Tubulin beta chain	P07437	50 kDa

Conclusions: This study obtained proteomic profile of normal glomerular from FFPE samples, which can provide comparison data for differential proteomic study of glomerular diseases. Further study is needed to analyse the function and location of glomerular proteins identified with LMD/MS.

Funding: Government Support - Non-U.S.

TH-PO694

Systemic Lupus Erythematosus/ANCA-Associated Vasculitis Overlap Syndrome in Patients with Biopsy-Proven Glomerulonephritis Noemie Jourde-chiche,¹ Pierre-André Jarrot,² Laurent Chiche,³ Laurent Daniel,⁴ Bertrand Gondouin,¹ Bertrand Dussol,¹ Stephane Burtey.¹ ¹Nephrology, Aix-Marseille Univ, Marseille, France; ²Internal Medicine, Aix-Marseille Univ, Marseille, France; ³Internal Medicine, Hopital Europeen, Marseille, France; ⁴Pathology, Aix-Marseille Univ, Marseille, France.

Background: SLE and AAV are distinct auto-immune diseases with possible renal involvement. Some patients fulfil both SLE and AAV classification criteria, defining the SLE/AAV overlap syndrome. We aimed: 1) to report clinical, biological and pathological characteristics of patients with SLE/AAV overlap syndrome and a biopsy-proven glomerulonephritis (GN), 2) to evaluate the incidence of overlapping auto-antibodies and of the overlap syndrome in a cohort of patients with lupus nephritis (LN) or crescentic GN (CGN).

Methods: A nationwide survey was conducted to identify cases of SLE/AAV overlap syndrome. Data were collected from SLE and AAV French research groups. Inclusion criteria were diagnosis of both SLE and AAV and biopsy-proven GN between 1995 and 2014. An independent cohort of LN and CGN was used to study the prevalence of overlapping antibodies and/or overlap syndrome. Additional cases were identified through a systematic literature review.

Results: The national survey identified 8 cases of SLE/AAV overlap syndrome. All patients were female, median age was 40 years. AAV preceded (n=3), followed (n=3) or occurred concomitantly (n=2) to SLE. Six patients had rapidly progressive GN, and 3 had alveolar hemorrhage. All patients had antinuclear antibodies (ANA), 7 had p-ANCA anti-myeloperoxidase (MPO) antibodies. Renal biopsy showed LN or CGN. Remission was obtained in 6 patients. Literature review identified 31 additional cases with similar profile. Cohort analysis revealed ANCA positivity in 24% of LN, ANA positivity in 55% of CGN, with no correlation with pathological findings, and a prevalence of 2/110 (1.8%) for SLE/AAV overlap syndrome.

Conclusions: In patients with GN, SLE/AAV overlap syndrome may occur but its prevalence seems low. Most patients have an aggressive renal presentation, with usually both ANA and anti-MPO antibodies. Further studies are needed to assess shared pathogenesis and therapeutic options.

TH-PO695

The Effect of Chronic Kidney Disease on Plasma Cell-Free DNA Levels and Apoptosis Alessandra Brocca, Grazia Maria Virzi, Sabrina Milan manani, Massimo de Cal, Claudio Ronco. *S Bortolo Hospital, Vicenza, Italy.*

Background: Cell-free plasma DNA (cfDNA) is composed of circulating extracellular DNA fragment that originates from necrotic and apoptotic cells reflecting inflammation. cfDNA has been found in many conditions, in which apoptosis or necrosis was involved suggesting that such events are the main source for its presence. CfDNA quantification is a possible method to determine cell damage *in vivo*. Caspase-3 is an effector caspase, it is responsible for progression to apoptosis. We focused on plasma cfDNA and Caspase-3 detection in patients with different stages of Chronic Kidney Disease (CKD), as index of inflammation, apoptosis and tissue damage in this population.

Methods: We enrolled 25 CKD patients who came to our center for routine visit and we divided them according to CKD stage (1-5). In addition, 8 healthy volunteers (CTR) were enrolled as control group. cfDNA was extracted from plasma and quantified by Real Time PCR for the β-globin gene. Quantitative plasma level of Caspase-3 was performed by ELISA.

Results: Quantitative analysis of plasma cfDNA and Caspase-3 showed significantly higher levels in CKD patients compared with CTR (both p<0.05). Furthermore, cfDNA and Caspase-3 levels were significantly different comparing CKD stages (both p<0.05). A significant positive correlation was observed between cfDNA and Caspase-3 levels (Sperman's rho=0.66 p<0.001) and Caspase-3 levels were significantly different between CKD stages (p=0.002). Positive correlations were observed between urea/cfDNA (Sperman's rho=0.57 p=0.01) and urea/Caspase-3 (Sperman's rho=0.53 both p=0.02).

Conclusions: In conclusion, our data suggest that cfDNA is increased in the plasma of CKD patients and cell apoptosis is one of the potential source of cfDNA. Plasma levels of cfDNA could be a potential biomarker of cytotoxicity due to uremic status of CKD patients. cfDNA can be considered as a direct marker of cell apoptosis which plays a pivotal role in the pathophysiology of CKD. Its levels increase in case of CKD progression AKI and are correlated to urea and cytotoxicity. Plasma levels of cfDNA could be a potential biomarker of cytotoxicity due to uremic status and progression of CKD in these patients.

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TH-PO696

Correlation of the Quantification Methods of Proteinuria in Glomerular Disease Patients Gabriela Miranda Mu?oz, Carmen Vozmediano Poyatos, Maria Dolores Sanchez de la Nieta Garcia, Francisco Rivera Hernandez, Isabel Ferreras Garcia. *Nephrology, Ciudad Real Univ General Hospital, Ciudad Real, Ciudad Real, Spain.*

Background: This study evaluate the correlation between the measurements of 24-hour proteinuria(P24H) versus protein/creatinine ratio(P/Cr) from patients with glomerular disease(GD) diagnosed histologically in Nephrology's Service in HGUCR. Assess whether

this correlation varies with the GD, age, sex, blood pressure control(BP), body mass index(BMI), glomerular filtration rate(GFR) by MDRD, proteinuria degrees mg/24h(PD), urine output(UO) and ACEi/ARBs treatment.

Methods: Observational cross-sectional study of renal biopsies performed 2010-2014. Spearman's coefficient and multiple linear regression was used to identify the correlation of the two proteinuria determinations.

Results: 148 biopsies collected; 96 were GD. Mean age 54±18 years; 66% male; BMI 27.71±5.75. The GD was: glomerulonephritis(GN) IgA 21%, membranous(MGN)19%, vasculitis 17%, focal segmental(FSGS)13%, minimal change(MCGN)10%, lupus 10%, and others 10%. The GFR was categorized >60 mL/min 37.5%; 30-60mL/min 22.9% and <30mL/min 39% and PD was categorized <300mg 8.3%; 300-3500mg 47.9%; >3500mg 43.8%. The BP was controlled in 60.4%. Median P24H 3.01g/24h(1.18-4.79) and P/Cr 2.72(1.16-5.0). P24H and P/Cr showed significant correlations(r=0.71;P<0.001). An 1g increase in ratio P/Cr resulted in an increased in P24H of 0.7g/24h(95% CI 0.59-0.87;P<0.001). There was no correlation seen in subgroup analysis of UO<1liter/day and vasculitis(r=0.39;P=0.13). The correlation was higher in women than men(r=0.81vs r=0.64), if aged ≤65 than >65(r=0.85vs r=0.50), in controlled BP(r=0.79vs r=0.57), in GFR>60 ml/min(r=0.90) and in PD <300 mg(r=0.71). In group of ACEi/ARBs(r=0.75vs r=0.66) and in BMI group(r=0.83 r=0.59 r=0.76). IgAGN(r=0.67), MGN(r=0.77), FSGS(r=0.78), MCGN(r=0.93) and lupus(r=0.90).

Conclusions: Excellent correlation was observed P/Cr and P24H. The P/Cr is useful in IgAGN, MGN, FSGS, MCGN and lupus, regardless of sex, age, BP, ACEi/ARBs and BMI. The correlation was greater with higher GFR and with lower PD. Perform proteinuria determinations in 24-hour urine in patients with UO<1liter/day and vasculitis.

TH-PO697

Renal Functional Reserve and Electron Microscopy in the Evaluation of Subclinical Lupus Nephritis Renato V. Almeida. *Nephrology, Federal Univ of Paraná, Curitiba, Brazil.*

Background: The aim of this research was to study the renal functional reserve (RFR) and electron microscopy (EM) in patients with subclinical lupus nephritis, and to evaluate the changes in the urinary excretion of albumin, retinol-binding protein and electrolytes induced by amino-acids (AAs) infusion; and their relationship with the renal morphology data.

Methods: In 25 lupus patients (SLE group) and in 15 controls, on the 24-hour urine collection and on urine specimens taken after both an oral water load and an AAs infusion, glomerular filtration rate (GFR: creatinine clearance - ml/min/1.73m²), microalbuminuria (uALB) and sodium excretion (FENa⁺/Na_e) were evaluated. The urinary retinol-binding protein (RBP) was evaluated only in the SLE group which was also divided in subgroups according to the classification of lupus nephritis (ISN/RPS 2003). Biopsies were also analyzed in order to characterize the renal ultrastructural abnormalities (EM).

Results: Both in the SLE group and controls there was a significant increase in GFR, uALB, FeNa⁺ and Na_e after the AAs infusion. The SLE group showed significantly higher stimulated GFR than controls; and higher basal and stimulated values for uALB (ug/min) and uALB (um/mg creatinine), respectively. Urinary RBP showed no basal value above 0.4 ug/ml and after stimulation it resulted significantly decreased. When we compared these data to the renal biopsy findings, we found that class II patients showed higher basal GFR than class I patients. Ultrastructural abnormalities in EM were present in 40% of the cases.

Conclusions: The results suggest that in patients with subclinical lupus nephritis, AAs infusion elicits an increase in GFR which indicates the presence of RFR. Although RFR was not a parameter of disease severity in the SLE group, the presence of higher mean-values for uALB - both basal and stimulated - suggests altered glomerular permeability in these patients. Higher basal GFR in class II patients might suggest that compensatory hyperfiltration precedes the decline of renal reserve in patients with more severe forms of lupus nephritis. Electron microscopy findings showed low sensitivity to predict the severity of disease.

Funding: Government Support - Non-U.S.

TH-PO698

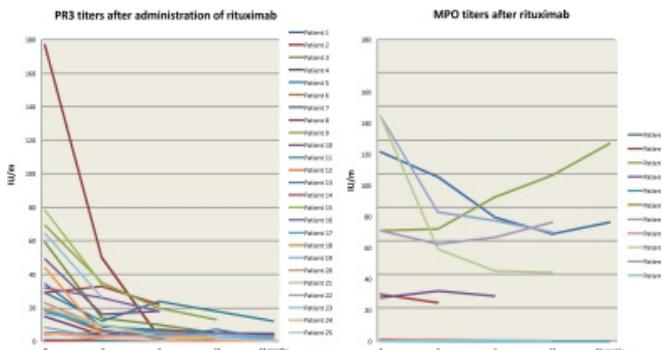
Course of PR3 Titers versus MPO Titers in ANCA Vasculitis Patients After Rituximab Therapy Vega Goedecke, Marcus Hiss, Hermann G. Haller, Annette D. Wagner. *Dept of Nephrology and Hypertension, Medical School Hannover, Hannover, Germany.*

Background: Rituximab has been proven to be an effective therapeutical agent in moderate to severe cases of ANCA vasculitis. B cell depletion plays a major role in suppressing inflammatory processes mediated by granulocytes in ANCA vasculitis. PR3 antibodies are specific for cANCA vasculitis, whereas MPO antibodies are detectable in pANCA vasculitis.

Methods: We compared the time course of anti-PR3 titers in 25 cANCA patients with the course of anti-MPO titers in 11 pANCA patients receiving rituximab induction therapy. We compared anti-PR3 and anti-MPO titers before initiation of rituximab therapy and approximately 3 months, 6 months, 12 months and 24 months after starting therapy. The mean age of both groups was comparable (51,6 in cANCA patients vs. 58,1 years in pANCA patients). The female to male gender ratio was 13/12 in cANCA patients and 6/5 in pANCA patients.

Results: Our results show that rituximab therapy significantly lowers anti-PR3 titers in cANCA vasculitis patients after 3, 6, 12 and 24 months. In contrast, anti-MPO titers are not lowered significantly in pANCA vasculitis patients after rituximab therapy.

	female/male	age	average titer before treatment	average titer after 3 months	average titer after 6 months	average titer after 12 months	average titer after 24 months
cANCA patients	13/12	51,6	anti-PR3 32,4 IU/ml	anti-PR3 15,7 IU/ml	anti-PR3 9,2 IU/ml	anti-PR3 5,1 IU/ml	anti-PR3 3,1 IU/ml
pANCA patients	5/6	58,1	anti-MPO 51,8 IU/ml	anti-MPO 37,3 IU/ml	anti-MPO 40,1 IU/ml	anti-MPO 45,5 IU/ml	anti-MPO 63,1 IU/ml



Conclusions: Clinical experience shows that anti-MPO titers correlate less well with clinical disease activity than anti-PR3 titers. Detailed further analysis of our data will show whether MPO titers correlate with long term clinical patient outcome and FACS analysis data will elucidate involved cell types in pANCA vasculitis.

TH-PO699

Comparison of Urinary Microvesicle Isolation Methods for miRNA Profiling in Nephrotic Syndrome Ilse M. Rood,¹ Thomas Laufer,² Thomas Brefort,² Hannah Schroers,² Johan Van der vlag,¹ Jack F. Wetzels,¹ Jeroen Deegens.¹ ¹Nephrology, RadboudUMC, Nijmegen, Netherlands; ²Comprehensive Biomarker Center GmbH, Heidelberg, Germany.

Background: Urinary microvesicles (uMV) are a promising source for biomarker discovery, including miRNAs (small noncoding single stranded RNAs, which regulate gene expression). UMV can be isolated by different techniques. In healthy subjects, an exosome precipitation protocol yielded the highest quantities of miRNA in uMV. The optimal isolation method of uMV for miRNA profiling in proteinuria is unknown.

Methods: Urine samples were collected from 1 normal control (NC) and 4 patients with nephrotic syndrome (NS1-4). UMV were isolated by 6 different protocols: exoquick(B), Qiagen's exoRNeasy(C), exoquick after additional 17.000g centrifugation step (D), Qiagen's exoRNeasy after additional 17.000g centrifugation step (E), ultracentrifugation (UC) (F), UC followed by size exclusion chromatography(G). The miRNA-profiles were compared with the profile of raw urine (A) to correct for contamination. We determined the expression profiles of all miRBase release v20 human miRNAs using CBC's custom Agilent SurePrintG3 Human miRNA (8x60K) microarrays.

Results: Results are shown in the table. miRNA-analysis was unsuccessful in 5/35 samples (method B/D/G) due to insufficient amount of RNA. Method C and E resulted in highest amount of total miRNAs and in highest percentage miRNAs that were not detected in A. In method F, despite lower amount of total miRNAs, 9-56 additional miRNAs that were not present in A/C/E, were detected.

Sample	Method (# of miRNAs / % not present in A / # of miRNAs in C not present in A/E/F, in E compared to A/C/F and in F compared to A/C/E)						
	A	B	C	D	E	F	G
NC	271	294/34	614/56/53	284/35	554/51/0	312/34/51	156/21
NS1	179	-	477/63/7	134*	480/63/4	324/51/56	214/37
NS2	188	181/25	434/57/7	229/29	441/58/27	305/41/35	-
NS3	130*	-	420	217	341	367	243
NS4	154	208/39	346/58/30	-	400/62/74	236/42/9	-

*analysis is ongoing

Conclusions: Method C, E and F are the most consistent methods. Method C and E had the highest yield of miRNAs that were not detected in raw urine. Method F may be of additional value to detect miRNAs not present in A/C/E.

TH-PO700

Gross Hematuria of Glomerular Origin in Adults Sami Safadi,¹ Samih H. Nasr,² ¹*Nephrology and Hypertension, Mayo Clinic, Rochester, MN;* ²*Anatomic Pathology, Mayo Clinic, Rochester, MN.*

Background: Gross hematuria is a relatively uncommon presentation of glomerulonephritis. Glomerular gross hematuria (GGH) is more frequent in children than adults. IgA nephropathy and Alport syndrome are the most common causes of GGH in children. The clinicopathologic characteristics of GGH in adults have not been systematically evaluated. We investigated the etiology and clinicopathologic characteristics of GGH in a large single-center cohort of adults.

Methods: Adult patients (318) with native kidney biopsy were identified from the pathology database. The electronic medical record (EMR) was searched for the symptom of gross hematuria in these patients. The EMR was then examined manually to select patients with GGH. Patients with a urological cause of hematuria were excluded. Univariate logistic regression was used to test association between age, gender, and diagnosis.

Results: Between 1993 and 2015, 101 patients with GGH were identified. 51% were male and 88% were white. Median age at biopsy was 52 yrs. (18-89). The clinicopathologic causes of GGH were heterogeneous as shown in table 1. The most common causes were: IgA nephropathy/HSP nephritis (IgA/HSP) (36%), thin basement membrane disease (TBMD) (14%), pauci-immune crescentic GN (PICGN) (13%), and monoclonal protein related glomerular disease (amyloidosis, MIDD, PGNMID) (13%). Younger adults were more likely to have IgA/HSP (OR 3.2, p<0.01), and less likely to have PICGN (OR 0.05, p<0.01). Male patients were more likely to be older on presentation (dif 8 years, p<0.05). Female patients were slightly more likely to have loin pain hematuria syndrome (LPHS) and TBMD. Only 30% of patients with IgA/HSP with GGH had crescents on biopsy.

Conclusions: This is the first study to analyze GGH in adults. We show that causes of GGH in adults are very heterogeneous, but most cases are due to IgA/HSP or TBMD disease in younger adults, and PICGN in older adults.

Diagnosis	N
IgA/HSP	36
TBMD	14
PICGN	13
LPHS	5
MIDD	5
Infection-related GN	3
Proliferative Lupus Nephritis	3
Amyloidosis	3
MPGN, immune complex (IC) type	3
Fibrillary GN	3
PGNMID	3
MGN with Renal Vein Thrombosis	3
Anti-GBM Disease	2
C3 GN	2
Proliferative GN, IgG4 related	1
Mesangioproliferative GN, IC type	1
Fabry Disease	1
	101

TH-PO701

IgM Staining in Immunofluorescence Is a Risk Factor for Relapsing in Focal Segmental Glomerulosclerosis Daiiane Silva, Gisele Vajgel Fernandes, Luis H.B.C. Sette, Renata Silva, Denise Maria do nascimento Costa, Maria Alina G.M. Cavalcante, Lucila Maria Valente. *Nephrology, Univ Federal de Pernambuco, Recife, Pernambuco, Brazil.*

Background: Glomerular IgM and C3 deposits are frequently found in idiopathic focal segmental glomerulosclerosis (iFSGS). Some experimental studies have suggested that IgM deposits may play a role in activation of the complement system in the glomeruli. However, the clinical meaning of the IgM deposits is unclear in iFSGS patients. In this study we analyzed outcomes regarding the presence of IgM deposits in biopsies of iFSGS patients.

Methods: We collected data from single center retrospective cohort of patients with histologic diagnosis of iFSGS between 2002-2014 that had a minimum follow-up period of 6 mo. Secondary FSGS, collapsing glomerulopathy (CG), childhood onset of iFSGS and patients with baseline Scr>3.0mg/dL where excluded. Relapsing was defined as new onset of nephrotic proteinuria after remission.

Results: We reviewed data from 96 patients, however 38 were excluded: secondary FSGS (14), CG (20) and patients with baseline Scr>3.0mg/dL (2), leaving 58 patients to analysis. The mean age was 31.3±14.3y, 58.6% were female and 46.5% were self-identified as white. Labs showed: mean Scr 1.2±0.6mg/dL; proteinuria 8.1±4.95 g/d; Salb 1.9±0.9 mg/dL; GFR (MDRD) 81 ±41ml/min. The median follow up period was 34.5 mo. Interstitial fibrosis was moderate to severe in 26%, IgM and C3 deposits were present in 31% and

12% of the biopsies, respectively. ACEI/ARB was used in 81%, prednisone in 96.6% and cyclosporine in 46.6% of the cases. Complete or partial remission was achieved in 79.3% of the patients during follow-up. Relapsing was seen in 17 of 41 cases (41.5%). IgM staining in the glomeruli was the only significant risk factor for relapsing in the multivariate analysis (OR 6.1 [CI 1.02-36.4]; P=0.047). Nevertheless, C3 deposits showed some association but lost strength in the multivariate analysis (OR 8.3 [CI 0.79-87.7] P=0.077).

Conclusions: In a single center retrospective cohort we found that IgM staining in immunofluorescence was a risk factor for relapsing in idiopathic FSGS.

TH-PO702

Targeted Metabolomics Reveals Reduction in TCA Cycle Metabolites in Non-Diabetic Hypertensive Chronic Kidney Disease Stein I. Hallan,¹ Maryam Afkarian,² Leila R. Zelnick,² Bryan R. Kestenbaum,² Shoba Sharma,³ Rintaro Saito,¹ Kumar Sharma,¹ Ian H. De Boer.² ¹*Center for Renal Translational Medicine, UCSD, San Diego, CA;* ²*Kidney Research Inst and Div of Nephrology, Univ of Washington, Seattle, WA;* ³*Clinical Metabolomics Inc, La Jolla, CA.*

Background: Interesting metabolic disturbances have recently been described in DKD using metabolomic analysis. Non-diabetic hypertensive CKD is common and needs to be better characterized.

Methods: Using a targeted quantitative panel of 66 organic acids, we compared plasma concentrations and urine excretion/24h in 22 adults with stage 3-4 non-diabetic hypertensive CKD to those of 10 healthy controls.

Results: After correcting for multiple testing, urinary excretion of 27 metabolites and plasma concentration of 33 metabolites differed significantly (range -68% to +113%). All 27 altered urine metabolites was reduced in CKD, while 27 of 33 altered plasma metabolites were higher in CKD. Pathway analysis based on significantly altered metabolites identified seven metabolic pathways significantly altered in CKD, most strikingly the TCA cycle (6 of 20 measured metabolites significantly different, q<0.001).

Pathway	FDR	Impact
1 TCA-cycle	0.0000	0.25
2 Phenylalanine metabolism	0.0000	0.14
3 Glyoxylate & dicarboxylate-metabolism	0.0001	0.10
4 Propanoate metabolism	0.0015	0.03
5 Butanoate metabolism	0.0023	0.11
6 Tyrosine metabolism	0.0051	0.11
7 Ketone bodies metabolism	0.0284	0.70
8 Alanine, aspartate, & glutamate-metabolism	0.0358	0.00
9 Fatty acid biosynthesis	0.2310	0.00
10 Valine, leucine, & isoleucine degradation	0.7820	0.00

Urinary excretion of citrate, cis-aconitate, isocitrate, oxoglutarate and succinate was reduced 40-68%. Based on data from Nephromine, expression of genes for four TCA cycle enzymes was reduced in human kidney tissues with nephrosclerosis. One transcription factor (TFAP2C) regulating TCA genes was also significantly reduced in nephrosclerosis.

Conclusions: In conclusion, in non-diabetic CKD, targeted metabolomics identified differences in the urinary excretion and plasma concentrations of small molecules that are consistent with both reduced renal excretion and impaired metabolism. Reductions in TCA cycle metabolites and gene expression were also identified and suggested suppressed mitochondrial function in CKD.

Funding: NIDDK Support, Other U.S. Government Support, Pharmaceutical Company Support - Abbvie

TH-PO703

The Application of Laser Microdissection and Liquid Chromatography – Mass Spectrometry in the Diagnosis of Renal Amyloidosis Michiko Aoki, Dedong Kang, Yusuke Kajimoto, Takafumi Kanemitsu, Kiyotaka Nagahama, Akira Shimizu. *Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.*

Background: In our department, renal amyloidosis of kidney biopsies have been diagnosed by congo-red stain, immunofluorescence (IF) for immunoglobulin light (L) and heavy (H) chains, and immunostaining for amyloid A, transthyretin, and b2-microglobulin. Recently, it has been reported that liquid chromatography tandem mass spectrometry (LCMS/MS) is helpful for detection of the amyloid precursor proteins.

Methods: We retrospectively investigated 30 cases of renal amyloidosis, 11 cases (36.7%) of AA and 19 cases (63.3%) of AL amyloidosis, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of serum immunofixation electrophoresis (IEP) and findings of IF.

Results: We retrospectively investigated 30 cases of renal amyloidosis, 11 cases (36.7%) of AA and 19 cases (63.3%) of AL amyloidosis, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of serum immunofixation electrophoresis (IEP) and findings of IF.

Conclusions: LCMS/MS could detect the component proteins in amyloid depositions in all cases, even in the cases that had less than 5% area of amyloid deposition in glomeruli. Furthermore, among AL amyloidosis, which was diagnosed previously, we found 2 cases of AH amyloidosis and 2 cases of AHL amyloidosis. LCMS/MS is very helpful for diagnosis of amyloidosis, especially AHL and AH amyloidosis.

TH-PO704

THSD7A Staining of Membranous Glomerulopathy in Clinical Practice Reveals Cases with Dual Autoantibody Positivity Christopher Patrick Larsen,¹ Larry N. Cossey,¹ Laurence H. Beck.² ¹Nephropath, Little Rock, AR; ²Boston Univ Medical Center, Boston, MA.

Background: The majority of primary membranous glomerulopathy (MG) cases are due to antibodies directed against the podocyte phospholipase A2 receptor (PLA2R) antigen. Recently, thrombospondin type-1 domain containing 7A (THSD7A) was described as a second antigenic target leading to MG. We sought to validate an immunohistochemical stain for the diagnosis of THSD7A-associated MG on renal biopsy material.

Methods: Immunohistochemical staining for THSD7A (Sigma) and PLA2R (Sigma) was performed in all cases of non-SLE associated MG diagnosed in our laboratory between December 2014 and April 2015. This included a total of 258 cases. Both stains were performed on formalin fixed paraffin embedded tissue. PLA2R was performed by immunofluorescence while THSD7A was performed by immunoperoxidase. Serologic testing for PLA2R (ELISA, WB) and THSD7A (WB) antibodies was performed in a subset of cases to determine the specificity of positive THSD7A staining for the diagnosis of THSD7A MG.

Results: MG stained positive for THSD7A-only in 7 (2.7%) cases, PLA2R-only in 141 (54.7%) cases, and showed dual positivity for THSD7A and PLA2R in 2 (0.8%) cases. Staining was negative for both in 108 (41.8%) cases. Serologic testing was performed for antibodies to PLA2R and THSD7A in 9 cases with both serum and biopsy material available and the results are shown in Table 1.

Biopsy result	Serum Anti-PLA2R +	Serum Anti-THSD7A +
MG with PLA2R only (n=3)	3/3	0/3
MG with THSD7A only (n=2)	0/2	2/2
MG with dual PLA2R and THSD7A (n=2)	2/2	2/2
MG negative for PLA2R and THSD7A (n=1)	0/1	0/1
Non-membranous glomerulopathy (n=1)	0/1	0/1

Conclusions: Based on these findings we believe it is possible to specifically diagnose THSD7A-associated MG based on renal biopsy staining. Additionally, we confirm that only a minority (3.5%) of MG cases reflect THSD7A-associated disease. Interestingly, 2 (22%) THSD7A-positive cases showed dual positivity for PLA2R and THSD7A with serologic studies showing evidence of antibodies to both THSD7A and PLA2R antigens in these patients. These cases demonstrate the importance of using a panel based approach to subtyping MG.

Funding: NIDDK Support

TH-PO705

Clinical Characteristics Associate Differently with Single Nephron GFR Than Total GFR in Normal Adults Aleksandar Denic,¹ Lilach O. Lerman,¹ John C. Lieske,¹ Mariam P. Alexander,² Harini A. Chakkera,³ Emilio D. Poggio,⁴ Richard J. Glasscock,⁵ Andrew D. Rule.¹ ¹Div of Nephrology, Mayo Clinic, MN; ²Dept of Pathology, Mayo Clinic, MN; ³Div of Nephrology, Mayo Clinic, AZ; ⁴Dept of Nephrology, Cleveland Clinic, OH; ⁵Dept of Medicine, Geffen School of Medicine, CA.

Background: Total GFR (GFR) is the product of mean single nephron GFR (snGFR) and the number of nephrons. Thus, associations with GFR may be attributable to associations with snGFR, nephron number, or both.

Methods: We identified 1,520 living kidney donors at Mayo Clinic and Cleveland Clinic with pre-donation contrast-enhanced CT scans and iothalamate clearance (GFR), and with kidney biopsies at the time of donation. snGFR was estimated from GFR divided by nephron number (CT bilateral cortical volume x biopsy non-sclerotic glomerular density). GFR, snGFR, and nephron number were associated with clinical and biopsy characteristics (age and sex-adjusted).

Results: Donors were 58% women, mean±SD age of 43±12 y, GFR of 103±20ml/min/1.73m², nephron number of 872,280±390,668 per kidney, and snGFR of 0.073±0.042 ml/min/1.73m². There was a strong decline in nephron number and modest rise in snGFR with age such that the net effect was an age-dependent decline in GFR.

Characteristics	Total GFR =		snGFR ×		Nephron number	
	% diff.	p value	% diff.	p value	% diff.	p value
Age, per y	-0.6	**	0.3	*	-1	**
Female sex	1.5	NS	10.9	**	-8.5	**
Family history of ESRD	1.6	NS	12.3	**	-10	**
Glomerular volume, per SD	0.6	NS	26	**	-20.3	**
Tubular area, per SD	0.8	NS	14	**	-11.4	**
Glomerulosclerosis >5%	0.4	NS	14	**	-12	**
Intimal thickening >50%	2.7	NS	13	**	-7.7	**

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Female gender, family history or ESRD, larger glomerular volume, larger tubular area, glomerulosclerosis, and intimal thickening all associated with fewer nephrons and higher snGFR, with the net effect that none associated with GFR.

Conclusions: Among normal adults, the age-dependent fall in GFR underrepresents the loss of nephrons because of a concurrent increase in snGFR. Total GFR did not associate with many risk factors because of the counterbalancing association of these risk factor with both lower nephron number and increased (likely compensatory) snGFR.

Funding: NIDDK Support

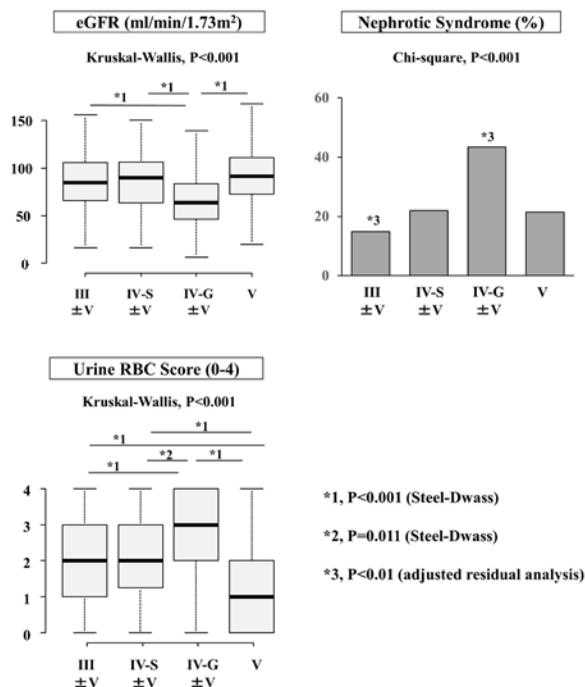
TH-PO706

Clinical and Histological Features of Lupus Nephritis in Japan: An Analysis of the Japan Renal Biopsy Registry (J-RBR) Keiju Hiromura,¹ Ken Kayakabe,¹ Hidekazu Ikeuchi,¹ Hitoshi Sugiyama,² Michio Nagata,³ Hiroshi Sato,⁴ Hitoshi Yokoyama,⁵ Yoshihisa Nojima.¹ ¹Dept of Medicine and Clinical Science, Gunma Univ, Maebashi, Japan; ²Dept of Medicine and Clinical Science, Okayama Univ, Okayama, Japan; ³Kidney and Vascular Pathology, Faculty of Medicine, Univ of Tsukuba, Tsukuba, Japan; ⁴Clinical Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Tohoku Univ, Sendai, Japan; ⁵Div of Nephrology, Kanazawa Medical Univ, Uchinada, Japan.

Background: A cross-sectional study was conducted to examine clinical and histological features of lupus nephritis (LN) in Japan.

Methods: Using the database of J-RBR, a nationwide prospective registry conducted by Japanese Society of Nephrology, we examined 372 LN patients whose ISN/RPS Class was available, out of total 18,463 registered patients who received renal biopsy between 2007 and 2012.

Results: Median age was 37 years old (IQR 27-48); 9.4% of patients were less than 20 years old and 81.2% of patients were female. The frequency of each ISN/RPS Class was as follows; I, 1.3%; II, 7.5%; III±V, 25.3%; IV-S±V, 13.4%; IV-G±V, 30.4%; V 21.2%; VI, 0.8%. Among Class III to V, patients with IV-G±V had lower eGFR, higher urine RBC score and higher incidence of nephrotic syndrome (Figure). In addition, the frequency of mixed proliferative and membranous type (III/IV±V) and chronic lesion (A/C or C) was significantly higher at the second or later biopsy compared to the first biopsy (mixed type, 21.5% vs 43.9%, p=0.003; chronic lesion 51.1% vs 82.1%, P=0.002).



Conclusions: In Japan, patients with IV-G±V LN were significantly associated with decreased renal function and nephrotic syndrome. In addition, the frequency of mixed proliferative and membranous type and chronic lesions was higher at the repeat biopsy, suggesting that these histological features reflect progression of the disease or refractory nature to treatment.

Funding: Government Support - Non-U.S.

TH-PO707

MicroRNA Signatures in Renal Disease: A Meta-Analysis of Tissue and Urine Datasets Christos Argypopoulos, Mark L. Unruh, V. Shane Pankratz. Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: MicroRNA (miRNA) are negative regulators of gene translation and an emerging biomarker in a wide variety of diseases. Little is known about the ability of miRNA to classify patients with renal pathology.

Methods: We undertook a meta-analysis of normalized miRNA profiles from clinical samples in Gene Expression Omnibus. miRNAs in miRBasev20 were scored for kidney relevance according to their experimentally or computationally ability to bind to proteins in the kidney proteome (<http://www.proteinatlas.org>). Elastic Net (EN) regression was then used to select short miRNA signatures according to their ability to classify diseased from healthy samples using 10-fold cross-validation.

Results: Using our systems biology approach we identified 739 miRNAs as potential kidney biomarkers out of 1689 candidates. A total of 8 studies with 178 samples were identified. Of those, 2 studies in patients were lupus (N=30) were excluded due to the incompatibility of the normalization strategy with the other samples. miRNAs profiles from 31 urine samples and 117 biopsy samples were available for analyses.

Dataset	Platform	Source	Normal	Abnormal
GSE53771	Microarray (μA)	Renal Bx (Bx)	28	8 (Transplant, TxP AKI)
GSE30282	μA	Bx	10	30 (TxP Cell Rejection), 11 (TxP AB Rejection), 14 (DGF)
GSE28283	μA	Bx: Cortex	3	5 (Hypertension, HTN)
GSE28344	μA	Bx: Medulla	3	5 (HTN)
GSE48318	qPCR	Urine exosomes	2 (Normoalbuminuria, NA)	2 (Microalbuminuria, MA)
doi: 10.1371/journal.pone.0054662	qPCR	Whole urine	10 NA	17 (MA within 2 years)

The median (IQR) AUC for individual miRNAs to classify diseased samples was 0.59(0.46-0.68) for unselected miRNAs but increased to 0.64(0.54-0.69) in the preselected ones. A short signature of 19 miRNAs achieved a superior classification performance for renal pathology (cross-validated AUC 0.96).

Conclusions: This is the first study to date examining the performance of a panel of miRNAs in classifying patients with kidney disease. A panel of miRNAs may classify patients with native and allograft renal disease aiding the interpretation of elevated creatinine in clinical practice.

TH-PO708

Study into the Effect of Aquaporin-2 on the Efficacy and Predicted Effect of Tolvaptan in Patients of Nephrotic Syndrome Eiichi Sato,¹ Tsukasa Nakamura,² Mayuko Amaha,² Mayumi Nomura,² Daisuke Matsumura,² Akiko Fujii,¹ Yuko Ono,¹ Yoshihiko Ueda.¹ ¹Dept of Pathology, Dokkyo Medical Univ, Koshigaya Hospital, Koshigaya, Saitama prefecture, Japan; ²Div of Nephrology, Dept of Internal Medicine, Shinmatsudo Central General Hospital, Matsudo, Chiba Prefecture, Japan.

Background: A retrospective investigation was conducted into the efficacy and adverse drug reactions of tolvaptan in the treatment of diabetic nephropathy and MCNS (Minimal Change Nephrotic Syndrome) with heart failure.

Methods: The subjects of this study were 56 patients with chronic kidney disease (due to diabetic nephropathy) and MCNS with heart failure who over the last 2 years and who were treated with tolvaptan. We defined effective cases as those showing a 2-fold increase in urinary volume compared to pre-administration levels or a clear improvement in edema or heart failure symptoms. Immunohistochemistry was also used to examine aquaporin-2 expression in the epithelial cells of the collecting duct (the site of tolvaptan action) based on renal biopsy findings. A score of (-) is assigned when the collecting duct shows no staining; a score of (+) is assigned when less than 50% is stained; a score of (++) is assigned when at least 50% of the biopsy specimens is stained.

Results: Of the 56 cases, 49 were tolvaptan responders. No problematic side effects were observed. Comparison of tolvaptan responders and non-responders indicated that serum Cre levels were significantly lower in responders. We conducted immunostaining for aquaporin 2 in the collecting duct. In diabetic cases, findings were positive for the responder but negative for the non-responder. In MCNS cases findings were positive for the responder but weak positive for the non-responder.

Conclusions: Diabetic nephropathy and nephrotic syndrome responders exhibited aquaporin 2 expression in collecting duct epithelial cells. No expression or weak positive expression was observed in diabetic nephropathy and in MCNS non-responders.

TH-PO709

Subclinical Anti-Smith and Anti-Ribonucleoprotein Antibodies Precede Proliferative Lupus Nephritis Diagnosis Stephen W. Olson,¹ Lisa K. Prince,¹ Dustin J. Little,¹ Kevin C. Abbott.³ ¹Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; ²Nephrology, Naval Medical Center San Diego, San Diego, CA; ³NIDDK, National Inst of Health (NIH), Bethesda, MD.

Background: Lupus Nephritis (LN) manifests in approximately 50% of Systemic Lupus Erythematosus cases. Anti-Smith (SM) and Anti-Ribonucleoprotein (RNP) antibodies are associated with proliferative lupus nephritis (PLN) at diagnosis. We hypothesized that prediagnostic anti-SM and anti-RNP antibodies were more common in PLN than SLE without LN.

Methods: This case-control Department of Defense Serum Repository study compared 3 longitudinal prediagnostic quantitative anti-SM and anti-RNP antibody levels in 23 patients with biopsy-proven PLN from the Walter Reed National Military Medical Center with 21 age, sex, race, and age of serum matched SLE without LN disease controls. Immunoassays were performed at Quest Diagnostics.

Results: More PLN patients had an anti-SM antibody level ≥ 4 AI than matched disease controls at any time (52% vs. 5%; $p < 0.001$) and < 2 years (47% vs. 6%, $p = 0.01$) before diagnosis, but not > 2 years before diagnosis (22% vs. 0%, $p = 0.11$). More PLN patients had an anti-RNP antibody ≥ 4 AI than matched disease controls at any time (57% vs. 14%, $p = 0.005$), < 2 years (53% vs. 19%, $p = 0.04$), and > 2 years (39% vs. 0%, $p = 0.008$) prior to diagnosis. Only an anti-SM antibody absolute rise over time of > 4 AI prior to diagnosis was specific for PLN (30% vs. 0%; $p = 0.02$). But, anti-RNP antibody more often preceded anti-SM antibody when there was a clear antecedent antibody (89% vs. 11%, $p = 0.003$).

Conclusions: In a large subgroup of PLN patients, anti-RNP antibodies were consistently elevated prior to anti-SM antibodies, but not rising, years prior to diagnosis. Anti-SM antibodies predominantly elevate in the last two years prior to PLN diagnosis which supports a possible direct contribution to PLN pathogenicity. Our data suggests that SLE patients with baseline RNP antibody along with a rising anti-SM antibody levels may benefit from increased surveillance for early signs of PLN. A more prompt biopsy diagnosis would allow for proactive therapeutic intervention to preserve maximal renal function.

Funding: Other U.S. Government Support

TH-PO710

The Relationship Between Phospholipase A2 Receptor Autoantibody and Idiopathic Membranous Nephropathy Weifeng Lin,^{1,2,3} Hao Li,^{1,2,3} Xuemei Li,^{1,2,3} Yan Qin,^{1,2,3} Ying Su,^{1,2,3} Yang Yu,^{1,2,3} Yin Guan,^{1,2,3} Yubing Wen,^{1,2,3} Xuewang Li.^{1,2,3} ¹Dept of Nephrology, Peking Union Medical College Hospital; ²Peking Union Medical College; ³Chinese Academy of Medical Sciences.

Background: The value of PLA2R autoantibody is still controversial in diagnosis, activity monitoring and prognosis estimation in idiopathic membranous nephropathy (IMN). The test method is non-uniform.

Methods: A total of 233 patients with biopsy-proven IMN at Peking Union Medical College Hospital from 2012 January to 2014 March were enrolled. A control group was set up. The serum antibody titer collected at the time of renal biopsy was measured by quantitative ELISA. 14 IMN patients with detectable antibody at biopsy were followed up to retest antibody 6 months later. Besides, the diagnostic accuracy between ELISA and immunofluorescence (IF) method for IMN was compared. The consistency and difference in antibody detection between two methods were also performed.

Results: The total sensitivity of antibody was 60.0% in IMN. However, it increased to 71.3% if patients didn't receive immuno-suppression therapy before testing. The antibody specificity was 100.0%. Hypoalbuminemia became severe ($P < 0.05$) and the proportion of nephrotic arrange proteinuria rose gradually ($P < 0.05$) as antibody levels increased. The antibody changes were consistent with clinical outcomes. The antibody AUC-ROC for IMN diagnosis was 0.800 by ELISA. There was no significant difference in AUC-ROC between ELISA and IF in IMN diagnosis ($P > 0.05$). The kappa value of antibody detection consistency between ELISA and IF was 0.941 \pm 0.033. The positive rate of antibody detection wasn't significantly different between ELISA and IF ($P < 0.05$).

Conclusions: PLA2R autoantibody has high sensitivity, notable specificity and good diagnostic accuracy for IMN. The antibody positive rate is affected by immunosuppression therapy and disease activity. The antibody could reflect disease activity and predict outcomes. Moreover, there is no significant difference in diagnostic accuracy and antibody detection difference between ELISA and IF. The antibody detection consistency is good between ELISA and IF.

TH-PO711

Factors Related to the Glomerular Volume in Different Cortical Zones of the Human Kidney Yusuke Okabayashi, Go Kanzaki, Nobuo Tsuboi, Kotaro Haruhara, Kentaro Koike, Yoichi Miyazaki, Tetsuya Kawamura, Makoto Ogura, Takashi Yokoo. *Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Recent studies have shown that glomerular enlargement is a surrogate marker of low nephron number in primary hypertension and in people with lower birth weight. To date, however, information is limited regarding the diversity in the distribution of glomerular size within the same kidney of relatively healthy human adults.

Methods: A total of 89 autopsy kidneys without apparent renal diseases were analyzed to measure the glomerular volume (GV) in different parts of the renal cortex. The mean GV was calculated from the measured each glomerular area. Relationships between the GV and the other clinicopathological features were investigated.

Results: The GV showed wide variations between the individuals and showed maximal 7-fold and 4-fold variations in superficial and juxtamedullary cortex, respectively. The GV showed close inverse correlations with the glomerular density in each cortical area. Multivariate analysis revealed that independent factors associated with the mean GV were low glomerular density in the superficial cortex, and hypertension in the juxtamedullary cortex.

Variables	Superficial cortex				Juxtamedullary cortex			
	Univariate		Multivariate		Univariate		Multivariate	
	r-value	p-value	t-value	p-value	r-value	p-value	t-value	p-value
BSA (m ²)	0.217	0.092	1.526	0.133	0.024	0.854	-	-
Weight of left kidney (g)	0.166	0.202	-	-	0.087	0.505	-	-
eGFR (ml/min)	-0.143	0.273	-	-	-0.101	0.438	-	-
Hypertension	0.181	0.163	0.307	0.760	0.340	0.007	2.437	0.018
Interstitial fibrosis/tubular atrophy (%)	0.034	0.794	-	-	0.021	0.875	-	-
Global glomerulosclerosis (%)	0.424	0.001	1.934	0.058	0.104	0.426	-	-
Glomerular density (/mm ²)	-0.463	<0.001	-2.480	0.016	-0.172	0.186	-0.493	0.624

As a whole, compared to the GV in the superficial cortex (2.7±1.0 x 10⁶mm³), the averaged GV in the juxtamedullary cortex (3.1±0.8 x 10⁶mm³) was significantly larger. Of note, in 27 cases (30%), the mean GV in the superficial cortex was larger than that of the juxtamedullary cortex. Such individuals with glomerular enlargement in the superficial cortex were characterized by a low glomerular density and/or large body size.

Conclusions: In each individual kidney, there are considerable variations in the distribution of the GV. Nephron number/body size and hypertension underlie the enlargement of glomeruli in superficial and juxtamedullary cortex, respectively.

TH-PO712

Highly Sensitive Method for Quantification of Iohexol Vera Jankowski, Joachim Jankowski. *Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, Germany.*

Background: Iohexol is used for accurate determination of the GFR in CKD patients. However, high iohexol amounts might lead to adverse effects in organism. In order to minimize the kinetic of iohexol in rats after application of different amounts of iohexol (15 mg-150 µg/rat). Blood sampling was conducted at four time points. Iohexol and the internal standard (iothalamic acid) were separated from serum proteins using centrifugal filtration device with a cut-off of 3 kDa. The chromatographic separation was achieved on an analytical Zorbax SB C18 column. The detection and quantification were performed by ESI-MRM operating in a positive ion mode. Furthermore, the effect of iohexol on early regulated gene expression in thyroid and renal cortex was tested to determine a threshold of physiological active iohexol concentrations.

Methods: In order to test whether a significantly decreased amount of iohexol is sufficient for reliable quantification, a LC-ESI-MRM mass-spectrometric approach was assessed. We analyzed the kinetic of iohexol in rats after application of different amounts of iohexol (15 mg-150 µg/rat). Blood sampling was conducted at four time points. Iohexol and the internal standard (iothalamic acid) were separated from serum proteins using centrifugal filtration device with a cut-off of 3 kDa. The chromatographic separation was achieved on an analytical Zorbax SB C18 column. The detection and quantification were performed by ESI-MRM operating in a positive ion mode. Furthermore, the effect of iohexol on early regulated gene expression in thyroid and renal cortex was tested to determine a threshold of physiological active iohexol concentrations.

Results: A linear correlation of the iohexol amount and mass-signal (MS) intensity was found in the range of 50 pg-40 ng (r² = 0.998). The lowest limit of quantification (LLOQ) was 50 pg. The intra- and inter-day accuracies were between 91.2 % and 98.7 %. The intra- and inter-day precisions were between 2.7 % and 9.2 %. The recovery rate of iohexol was determined in the range of 100.8 % ± 10.9 %. The gene expressions test revealed that iohexol dosages exceeding 0.5 mg/kg induce a group of genes in thyroidal tissue that comprises transcription factors and genes of cellular stress response.

Conclusions: This mass-spectrometric based method has been proved to be sensitive, selective and suitable for the quantification of iohexol in serum. Due to high sensitivity of this novel method the iohexol application dose as well as the sampling time in the clinical routine could be reduced in the future in order to further minimize side effects in humans.

TH-PO713

Proliferative Lupus Nephritis: Are Three Years Enough for Histological Remission? Marcelo Alejandro De Rosa, Federico Fuentes, Gabriel Pedro Alvarez, Graciela Elena De Rosa, Jorge E. Toblli. *Univ of Buenos Aires, Argentina.*

Background: The duration of the treatment in Proliferative Lupus Nephritis (PNL) has not been determined. Almost 30 percent of patients will relapse during or after treatment, in the first 5 years. Furthermore, the factors associated to renal relapses remain unclear. Hence, a prospective histological control study (re-biopsy) performed before the end of the third year of treatment in patients with complete renal remission for a year may contribute to a better understanding on the relapses in PNL.

Methods: A total of 24 patients with PLN were included in this pilot study. All patients presented focal or diffuse PLN in the first renal biopsy, and received induction with cyclophosphamide and corticosteroids by six months. The maintenance therapy was based on mycophenolic acid and low doses of corticosteroids for at least 2 years and 6 months. On those patients who presented total remission during a year (proteinuria ≤0.5g/24h, inactive urinary sediment, and stable creatinine), a second renal biopsy was performed before reduction of treatment. Renal biopsies were classified according to ISN/RPS 2003.

Results: After a media of a 34 (30-42) months of treatment and in complete remission for a year, 70,8% of patients had mesangial or proliferative lupus activity.

Baseline results			
N: 24	mean	median	range
Age (years)	35.5	31	21-64
Gender (M/F)	5/19		
Time of treatment (months)	34	34.2	30-42
Proteinuria g/day	0.2	0.2	0.05-0.43
Creatinine (mg/dl)	0.7	0.73	0.6-1.04
2nd. Biopsy			
Histological class	n 24	IF: IgG, C1q	
Class I	3	-	
Class II	5	+	
Class III (A, A-C)	11	+	
Class III (C)	3	-	
Class IV (A, A-C)	-		
Class IV (C)	1	-	
Class III/V	1	+	
Activity index mean	2 (1-3)		
Chronicity index mean	3 (2-4)		
Histological activity	17	+	70.8 %
No Histological activity	7	-	29.2 %
Total	24		100 %

Conclusions: This study showed that after a satisfactory treatment, most patients with PLN, still presented mesangial or focal proliferative changes with positive IF for IgG and C1q in their second renal biopsy. While data in the present study suggest silent lupus activity, the association of these histological findings with potential relapses in PNL invites to an open discussion.

Funding: Government Support - Non-U.S.

TH-PO714

The Clinical and Renal Pathological Features and Presence of Anti-PLA2R Antibody in 9 Patients with Both Membranous Nephropathy and IgA Nephropathy Xin Zhang, Weifeng Lin, Jianing Li, Yubing Wen, Jianfang Cai, Hang Li, Xuemei Li, Xuewang Li. *Nephrology Dept, Peking Union Medical College Hospital, Beijing, China.*

Background: Both membranous nephropathy (MN) and IgA nephropathy (IgAN) rank top among the primary glomerulonephropathy but they rarely coexist in the same patient. Whether they are accidentally concurrent remains controversial. Here we reported the clinical and pathological features of 9 cases with concomitant biopsy-proved MN and IgAN.

Methods: The 9 patients were admitted to our hospital for renal biopsy between 2009 and 2014, none having apparent secondary causes of renal diseases. 36 age-, sex-, and biopsy-year- matched controls with isolated IgAN or isolated primary MN, respectively, were randomly selected. Clinical features were compared across these groups. Anti-PLA2R antibody was assayed with ELISA test by using the -80° preserved serum samples in 9 cases and 36 controls with isolated MN.

Results: The clinical and pathological features of cases and controls were summarized in table 1. Table 1 the clinical and pathological features among patients with combined IgAN and MN, isolated primary MN, and isolated IgAN.

Group	Combined IgAN and MN	Isolated primary MN	Isolated IgAN
Cases	9	36	36
Male	6	27	26
Age, yrs	40.2±8.4	40.9±7.6	38.6±9.8
24h-Upr, g/24h	5.9±3.7	6.7±5.5	1.6±1.9*
Serum creatinine, mmol/L	74.4±20.2	75.4±17.6	116.5±110.9*
Serum albumin, g/L	29.1±6.9	27.4±7.2	38.8±8.4*
Mesangial proliferation	None	None	All
Lee's grading of IgAN			
Grade I	3	N/A	0
Grade II	0		0
Grade III	6		11
Grade IV	0		25
MN Classification			
Grade I	3	5	N/A
Grade II	6	29	
Grade III or IV	0	2	

* $p < 0.05$ vs concomitant group. A positive anti-PLA2R was detected in 2 patients among the cases and 18 patients among the isolated MN controls. The presence of anti-PLA2R antibody did not differ significantly between the two groups ($p > 0.05$), neither did the grading of MN ($p > 0.05$). However, the pathological lesions in the 9 cases was less severe as compared with the controls with isolated IgAN ($p < 0.05$).

Conclusions: The clinical features and presence of anti-PLA2R of patients with combined MN and IgAN are more likely to mimic isolated primary MN.

TH-PO715

MiRNA Profiling in Urine Exosomes Indicates Renal Tubulointerstitial Fibrosis in CKD Patients Yang Zhou, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Renal fibrosis is an inevitable outcome of chronic kidney disease (CKD). It was reported that various microRNAs regulated the progression of tubulointerstitial fibrosis. However, whether fibrosis-related miRNAs are excreted in urine exosomes, as well as the changes of miRNA profiles in urine exosomes of CKD patients were unknown.

Methods: Morning urine specimens were collected from 10 healthy donor and 16 CKD patients, whose renal biopsy showed mild to moderate tubulointerstitial fibrosis. Urine exosomes were isolated from 2ml samples using urinary exosome isolation kit and observed by transmission electron microscopy. Quantification of miRNA levels in urine exosomes were determined using stem-loop qRT-PCR followed by real-time PCR. CD63 levels in exosomes were analysis by western blot.

Results: Urinary exosomes appeared as clusters of vesicles of 30-200nm in diameter under electron microscope, surrounded by a double-layer membrane. CD63, a major exosome marker associated with membranes of cellular vesicles, in exosomes isolated from same volume of urine indicated that the excretion of exosomes varied among different people. Moreover, the markedly increased CD63 levels in CKD patients suggested that the excretion rate of exosomes was probably upregulated in CKD patients with renal interstitial fibrosis. Most of precisely reported fibrosis-related miRNAs, including miR-21, miR-29 family, miR-30e, miR-192 and miR-200 family were detectable in urine exosomes. However, their contents varied significantly from fmol/L to nmol/L. Furthermore, miRNA levels in urine exosomes were not associated with their levels in kidney. MiR-21 and miR-29c levels in urine exosomes were markedly increased and decreased as their upregulation and downregulation in kidney, respectively. MiR-29b, miR-30e and miR-200b levels in urine exosomes were markedly increased despite their downregulation in kidney. Although miR-192 level in urine exosomes was as large as $\sim 10^4$ nmol/L, its excretion was not significantly changed in CKD patients as compared with healthy control.

Conclusions: Profiling of miRNA in urine exosomes might indicate renal tubulointerstitial fibrosis in CKD patients.

Funding: Government Support - Non-U.S.

TH-PO716

Glucosuria in Normoglycemic Non-Diabetic Kidney Disease: Not Necessarily due to an Isolated Proximal Tubule Defect Abdurrahman M. Hamadah, Kamel A. Gharaibeh, Samih H. Nasr, Nelson Leung. *Nephrology and Hypertension, Mayo Clinic, MN.*

Background: In the absence of hyperglycemia, glucosuria has been classically attributed to either a global dysfunction of the proximal tubule known as the Fanconi syndrome, or familial renal glucosuria which includes inherited defects in the genes that encode the glucose handling kidney transporters. We have investigated the clinical observation that glucosuria is common in other kidney disease entities.

Methods: We analyzed the data for adult patients with native kidney biopsy between January 2014 and January 2015 at our institution that had concurrent urinalysis. We identified the patients who had glucosuria on urinalysis, in the absence of concurrent hyperglycemia (serum glucose > 180 mg/dL) or diagnosis of diabetes mellitus.

Results: 186 adult patients with native kidney biopsy with concurrent urinalysis were identified. Sixty six patients (35%) had evidence of glucosuria on urinalysis. Twenty two (33%) of these patients had either hyperglycemia (serum glucose > 180 mg/dL) or diabetes and were excluded from the analysis. The remaining sub-group of 44 (67%) patients had a median age of 58 (19-81 years), 43% were women, and 81% were Caucasian. Median urinary glucose was 40 mg/dL (range 16-236). Concurrent serum glucose for this group showed a median of 101 mg/dL (range 54-149), with 66% of patients having glucose less than 110 mg/dL. In this subgroup, biopsy findings included 32 (73%) patients with glomerular disease (most commonly glomerular microangiopathy and pauci-immune crescentic glomerulonephritis), 10 (22%) tubulointerstitial disease (most commonly acute tubular necrosis), and 2 (4%) arteriosclerosis as the predominant features on biopsy. No evidence of proximal tubulopathy was found amongst this group.

Conclusions: Glucosuria in the absence of hyperglycemia and diabetes, although classically associated with isolated proximal tubule dysfunction, is common in other kidney diseases and is a frequent occurrence in glomerular disease, which likely reflects a degree of secondary tubular injury. Future delineation of the pathophysiology of this observation may improve the understanding of tubular function in glomerular disease.

TH-PO717

Severe Renal Interstitial Fibrosis Can Be a Predictor of Renal Function in Patients with Lupus Nephritis, Especially in Cases With the International Society of Nephrology/Renal Pathology Society Class IV Daisuke Honda, Kisara Onda-Tsueshita, Isao Ohsawa, Hiroyuki Inoshita, Satoshi Horikoshi, Yasuhiko Tomino. *Div of Nephrology, Dept of Internal Medicine, Juntendo Univ Faculty of Medicine, Tokyo, Japan.*

Background: The ISN/RPS classification of lupus nephritis (LN) pays little attention to the interstitial injuries. We explored the association between irreversible interstitial fibrosis and renal function in patients with LN, especially class IV cases that have not been thoroughly examined in this aspect.

Methods: Forty-three patients of LN were enrolled in this study. All patients were classified using the ISN/RPS classification and were divided into 4 grades according to interstitial fibrosis extent (no, 0%; mild, 1-25%; moderate, 26-50%; and severe, more than 50% fibrosis of the interstitial area, $n = 8, 16, 11$ and 8 , respectively). All 8 patients with severe fibrosis were classified in class IV. Blood and urine analysis was evaluated at the time of renal biopsy and last follow-up period. We compared the data according to both categorizations in all patients, and in only class IV cases ($n = 23$).

Results: In each class categorized with the ISN/RPS classification, renal function showed no significant difference. When all patients were classified according to interstitial fibrosis severity, their renal function at the time of renal biopsy showed no significant difference. However, renal function with severe fibrosis at the last follow-up period was significantly worse than those in the other fibrosis grades (sUN, $p < 0.01$; sCre, $p < 0.05$; and eGFR, $p < 0.05$). Moreover, when we examined only class IV patients, renal function in patients with severe fibrosis at the last follow-up period was significantly worse than that in patients with non-severe fibrosis (sUN, $p < 0.01$; sCre, $p < 0.05$; and eGFR, $p < 0.01$). On the other hand, the serological activities of systemic lupus erythematosus (SLE) significantly improved under all categorizations.

Conclusions: We conclude that severe renal interstitial fibrosis can be a predictor of renal function in patients with LN, independent of glomerular lesions and the serological activities of SLE, especially in cases with ISN/RPS class IV.

TH-PO718

Correlating Biophysical Structure Characteristics with Diagnosis and Phenotypic Severity in Complement-Mediated Renal Disease Jill Johanna Hauer, Fengxiao Bu, Nicolo Ghiringhelli Borsa, Michael Jones, Erika Takanami, Elizabeth Ann Black-Ziegelbein, Diana Kolbe, Yingyue Li, Carla Nishimura, Kathy Frees, Hela Azaiez, Christie P. Thomas, Carla M. Nester, Michael J. Schnieders, Richard J. Smith. *Univ of Iowa, Iowa City, IA.*

Background: Rare genetic variations in the *C3*, *CFH*, and *CFB* genes may lead to dysregulation of the alternative pathway of the human complement system, altering the innate immune response associated with complement activation. The phenotypic consequence includes the thrombotic microangiopathies (TMA) and C3 glomerulopathies (C3G).

Methods: In this study, we compared variants identified in TMA patients to variants identified in C3G patients. Each variant was analyzed in a pipeline that included structural optimization of the wild type and mutant proteins based on molecular mechanics calculations. Initially, the wild type protein structure was optimized using the polarizable AMOEBA force field and dead-end elimination techniques. Each variant was then individually introduced to the wild type structure, which was then re-optimized. Both wild type and variant models were analyzed in molecular dynamics simulations and differences between wild type and variant free energies were calculated.

Results: Overall, for each variant we were able to obtain both: 1) qualitative data describing location and interactions; and 2) quantitative changes to protein conformation and stability relative to the wild type baseline. From these data, we were able to create a spectrum of free energy changes correlating to disease severity and enhance our interpretation of rare and novel variants, as well as identify biophysical characteristics specific to TMA and C3G.

Conclusions: These methods allow us to understand the biophysical consequences of every variant, predict the phenotypic severity of novel variants, and ultimately inform patient diagnosis.

TH-PO719

Urinary EGF Is Associated with Interstitial Fibrosis and Tubular Atrophy in Proteinuric Patients Wenjun Ju,¹ Viji Nair,¹ Michelle R. Smith,¹ S.M. Bagnasco,² L. Barisoni,³ Matthias Kretzler.¹ *¹Medicine, Univ of Michigan, Ann Arbor, MI; ²Pathology, The Johns Hopkins School of Medicine, Baltimore, MD; ³Pathology, Univ of Miami, Miami, FL.*

Background: Interstitial fibrosis (IF) and tubular atrophy (TA) are key morphologic determinants of progression and strong predictors for renal outcome. However, their broader clinical application is limited by the invasiveness of the kidney biopsy procedure. Non-invasive biomarkers predictive of IF/TA have not been reported. Our transcriptome-driven approach identified EGF as a predictor of kidney function, and urinary EGF (uEGF) improved prediction of renal outcome by glomerular filtration rate (GFR) and albuminuria. EGF's expression is limited to tubule epithelium and its role in epithelial cell regeneration suggested that the improved predictive value by uEGF may due to its potential association with chronic tubulointerstitial damage (c-TID). Here we aim to investigate the correlation between uEGF and TID, reflected by the % of cortex affected by IF/TA, and whether uEGF can predict c-TID in adult patients of the NEPTUNE cohort.

Methods: Whole slide images of glass slides stained with Silver, Trichrome and PAS from 102 cases stored in the NEPTUNE digital pathology repository were assessed for % of cortex involved by IF/TA by 5 pathologists. The % of cortex involved by IF/TA was determined in each individual stain and averaged in an overall % value. We derived EGF mRNA levels in the tubulointerstitium using genome-wide expression data and measured uEGF using fully validated ELISA assay. uEGF was normalized by urine creatinine level. A regression model was utilized to predict c-TID using uEGF level.

Results: Both tubulointerstitial EGF mRNA and uEGF correlated significantly (p<0.0001) with IF/TA.

spearman rank correlation	EGF mRNA	uEGF
IF	-0.55	-0.75
TA	-0.53	-0.74

The correlations remain significant after adjusted for eGFR and proteinuria. uEGF predicted patients' c-TID (%IF/TA) using a regression model in 102 adult NEPTUNE patients (r=0.77/0.74, p < 2.2e-16, predicted versus observed IF/TA).

Conclusions: uEGF shows promise as a non-invasive biomarker predictive of the biopsy dependent-IF/TA score in proteinuric patients.

Funding: NIDDK Support

TH-PO720

Considerations in the Use of Urine Protein: Creatinine Ratio (uPCR) and g/24h for Measuring Proteinuria in Nephrotic Patients in a Clinical Study Christine Barrett,¹ Gengqian Cai,² Caroline O.S. Savage.¹ ¹GlaxoSmithKline plc, United Kingdom; ²GlaxoSmithKline plc.

Background: uPCR on spot urine samples is used as an alternative to measurement of g protein/day from 24h urine collections, due to its ease of use and the correlation between the two. Most studies on correlation have concentrated on patients with subnephrotic levels of proteinuria. In a clinical study (BEL116472) to evaluate the mechanism of action of belimumab in idiopathic membranous nephropathy (IMN), uPCR and g protein/24h were assessed, correlation determined and variability in uPCR evaluated.

Methods: Samples from 14 patients with IMN and nephrotic proteinuria (>4g/10mmol uPCR at screening) were tested. On 2 occasions during screening, spot morning samples were tested for uPCR. At key timepoints, consecutive 24h urine collections, or a spot morning sample and post dose 24h collection were used to test uPCR, g protein/24h and g creatinine/24h.

Results: Median uPCR 8.31 mg/10mmol (range 3.21-12.20) or 11.70 g/24h (range 3.99-20.40) at baseline was found in 11 M and 3 F aged 24 to 70y. High correlation (0.88-0.99) was observed between uPCR and g protein/24h within all groups with high, medium or low creatinine excretion. Different slopes were seen in each group: low- 0.93; medium- 1.34; high- 1.77. In individual samples, the ratio of g protein/24h to uPCR ranged from 0.66 to 2.97. In addition, with screening and prior to dosing data, a big range of within subject coefficient of variation for uPCR was observed: 8.5%-57.7%. Analysis of 6 mth history of proteinuria in the absence of immunosuppression prior to screening showed great variability and no specific pattern of worsening or improvement. Values for g protein/24h also varied considerably in consecutive samples.

Conclusions: uPCR values in patients with nephrotic syndrome are heavily influenced by creatinine excretion. This should be considered when setting eligibility criteria in clinical studies, or if basing dosing on levels of protein excretion. Variability in proteinuria in longitudinal samples from patients with nephrotic levels of proteinuria means that caution should be applied to values from single samples within clinical studies, whether using uPCR or g/24h.

Funding: Pharmaceutical Company Support - GlaxoSmithKline plc

TH-PO721

Increasing Incidence of Class V Membranous Lupus Nephritis: A Single Institution Biopsy Experience Parker C. Wilson, Alison G. Obstler, Michael Kashgarian. Dept of Pathology, Yale Univ School of Medicine, New Haven, CT.

Background: Lupus nephritis (LN) contributes significantly to morbidity and mortality in patients with systemic lupus erythematosus (SLE) and is categorized into classes based on the pattern of glomerular injury seen on kidney biopsy. We assessed the proportion of patients presenting with class V or III/IV+V since the advent of systemic immunotherapy for SLE.

Methods: The distribution of patients by LN class at initial presentation was assessed at 5-year intervals from 1998-2013 at our institution. 131 consecutively diagnosed cases of biopsy-proven LN and 54 repeat biopsies were classified using ISN/RPS criteria. Patient information was collected from the medical record. Chi-square test for trend was used to compare the incidence of class V or III/IV+V at 5-year intervals.

Results: The frequency of class V increased from 1998 to 2013 [p = 0.03: 1998 = 9.7%, 2003 = 16.6%, 2008 = 13.0%, 2013 = 29.7%] and was associated with a decreasing incidence of class III/IV [p = 0.0003: 1998 = 78.0%, 2003 = 73.3%, 2008 = 69.5%, 2013 = 37.8%]. Among the 54 patients with a repeat biopsy, 25 individuals who presented with class III/IV underwent a class switch to class V or III/IV+V. These findings showed a tendency for increased use of mycophenolate mofetil at the end of follow-up. Age, gender, race, and BMI were not statistically different over time.

Characteristics (*=Baseline, #=Follow-up)	1998	2003	2008	2013
* Patients (#female)	41 (32)	30 (24)	23 (22)	37 (25)
* with Class V	4	5	3	11
* with Class III/IV+V	1	0	1	7
* with Class III/IV	32	22	16	14
* Mean Age at First Biopsy	31.3	32.5	35.3	35.3
* Non-Hispanic White	17 (65%)	12 (63%)	12 (75%)	14 (58%)
* BMI	29.1	30.3	31.2	29.0
# Mycophenolate Mofetil Use at End of Follow-up (2012-2015)	28.5%	29.4%	66.6%	42.8%

Conclusions: The incidence of class V lupus nephritis increased in the interval 1998-2013. These findings were associated with a decreasing incidence of class III/IV and a tendency for these patients to switch to class V or III/IV+V on repeat biopsy. These changes occurred during a period of increased use of systemic immunotherapy, which may have altered the manifestation of lupus nephritis to a more indolent course.

TH-PO722

Serum Autoantibodies in Membranous Nephropathy Patients with Negative Anti-PLA2R Antibody Jianing Li, Hang Li, Jianfang Cai, Weifeng Lin, Yubing Wen, Xin Zhang, Xuewang Li. Div of Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.

Background: Anti-PLA2R antibodies are negative in up to 30% patients with idiopathic membranous nephropathy (iMN). Autoantibodies against Thrombospondin Type-1 Domain-containing 7A (THSD7A), α-Enolase(αENO) or SOD₂ have also been reported in iMN patients. We evaluated the clinical significance of these autoantibodies in iMN patients with negative serum anti-PLA2R-antibody.

Methods: In this prospective study, we consecutively recruited 97 iMN patients with negative anti-PLA2R antibody, 31 iMN patients with positive anti-PLA2R antibody, 17 patients with secondary membranous nephropathy (sMN), 28 patients with primary glomerular diseases other than MN, and 40 healthy controls. ELISA kits were used to assay serum autoantibodies against THSD7A, SOD₂ and αENO.

Results: A positive anti-THSD7A antibody was detected in 3 of 97 iMN patients with negative serum anti-PLA2R antibody, 1 of 31 iMN patients with positive serum anti-PLA2R antibody, but none of patients with sMN or other glomerular diseases or healthy controls. For titers of anti-SOD₂ antibody, there was no statistical difference among anti-PLA2R antibody-negative iMN, anti-PLA2R antibody-positive iMN, sMN and other glomerular diseases. Result is the same for anti-αENO antibody. iMN patients with negative serum and absent of anti-PLA2R, anti-THSD7A, anti-SOD₂, and anti-αENO antibodies had lighter proteinuria, higher eGFR, and higher serum albumin(all P<0.05) at baseline and shorter duration for remission(P<0.05) as compared with iMN patients with at least one positive above-mentioned antibodies.

Conclusions: In the present study, we found anti-THSD7A may have diagnostic significance for iMN, whereas iMN patients absent of anti-THSD7A, anti-SOD₂, and anti-αENO antibodies may be associated with milder clinical manifestation and better response to treatment as compared with those with positive anti-THSD7A, anti-SOD₂, or anti-αENO antibodies.

Funding: Government Support - Non-U.S.

TH-PO723

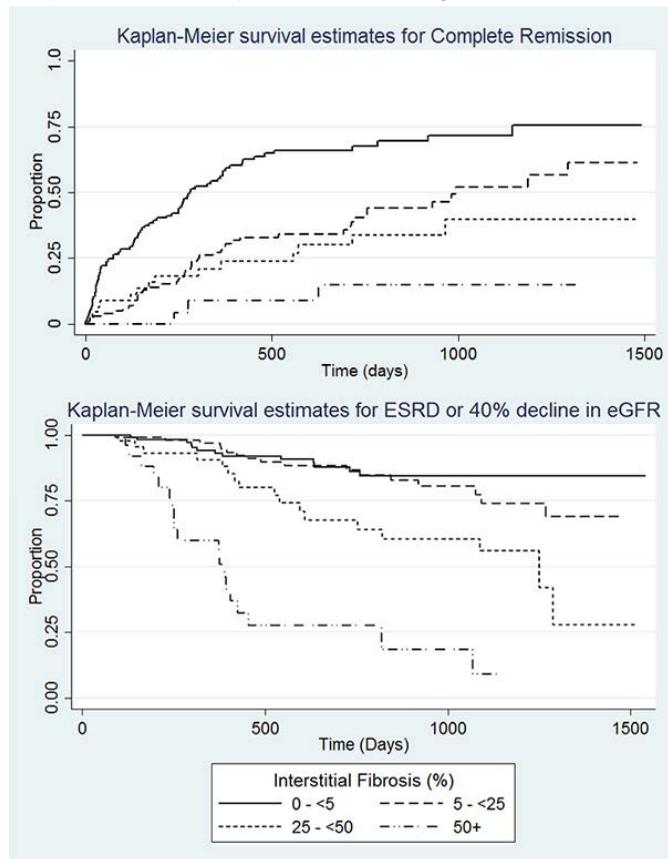
Interstitial Fibrosis Score by Whole Slide Imaging (WSI) Is a Predictor of Outcome in Proteinuric Renal Glomerulopathies Laura H. Mariani,¹ Sebastian Martini,¹ L. Barisoni,² Pietro A. Canetta,³ Jonathan P. Troost,¹ Jeffrey B. Hodgins,¹ Matthew Palmer,⁵ A. Rosenberg,⁷ Kevin V. Lemley,⁶ Chien Hui-Ping,⁴ Gerald B. Appel,³ Howard Trachtman,⁸ Stephen M. Hewitt,⁷ Matthias Kretzler,¹ S.M. Bagnasco.⁴ ¹Univ of Michigan; ²Univ of Miami; ³Columbia Univ; ⁴Johns Hopkins Univ; ⁵Univ of Pennsylvania; ⁶Children's Hosp, Los Angeles; ⁷NIH; ⁸NYU.

Background: Interstitial fibrosis (IF), tubular atrophy (TA), and interstitial inflammation (II) are determinants of progression of renal disease. Standardized assessment could add value to current classification of glomerulopathies.

Methods: NEPTUNE is a multi-center, prospective study of children and adults with >500mg/day of proteinuria and clinically indicated renal biopsy. We studied 310 patients with minimal change disease (MCD n=88), focal segmental glomerulosclerosis (FSGS n=125), membranous nephropathy (MN n=58) and IgA nephropathy (IgAN n=39). IF, TA and II were quantified as % of interstitial space, on digitized whole slide biopsy images (WSI) by 2-5 pathologists (r>0.8 inter-reader agreement). Multivariable cox proportional hazards models were fit to assess hazard of complete remission (CR) and composite of reaching ESRD or 40% drop in eGFR.

Results: IF was highly correlated with TA (r²=0.98, P<0.001) and II (r²=0.66, P<0.001). Median (IQR) for IF was 7(2, 22) and varied by diagnosis [MN 7(4, 13), MCD 1(0, 3), FSGS 17(5, 39), IgA 21(11, 35), P<0.001]. 57% of the cohort had no II. Median II was highest in IgAN (P<0.001). IF was strongly correlated with baseline eGFR (r=-0.71, P<0.001) and

UPCR ($r=0.18$, $P=0.002$). Adjusting for age, race, diagnosis, baseline eGFR and UPCR, each 10% increase in IF score had HR of 0.81 (95%CI 0.67, 0.96, $P=0.018$) for CR and 1.55 (95%CI 1.3, 1.9, $P<0.001$) for ESRD/40% eGFR drop.



Conclusions: IF has predictive value in assessing risk of progression and remission across different types of proteinuric glomerulopathy.

Funding: NIDDK Support, Other NIH Support - NCATS, ORDR

TH-PO724

Study of Relapse Patients with Steroid-Dependent Minimal Change Nephrotic Syndrome following Rituximab Treatment Yuko Iwabuchi, Takashi Takei, Yoei Miyabe, Takahito Moriyama, Kosaku Nitta. *Dept of Medicine, Kidney center, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: In recent years, several clinical trials have shown the efficacy of rituximab (RTX) in patients with steroid-dependent minimal-change nephrotic syndrome (MCNS). We previously reported the efficacy and safety of a single dose of RTX infusions during 24-months at an interval of 6 months for patients with steroid-dependent MCNS in adults (Medicine 93: e300, 2014). But there are few reports about the relapse, and we also had some patients with relapse after RTX treatment. Therefore, the objective of this study was to evaluate the case that relapsed in patients with RTX.

Methods: We conducted a prospective cohort study with a historical control to evaluate the effect of single-dose infusions of RTX at 375 mg/m² BSA per dose at intervals of 6 months during 24-months followed by continuous RTX treatment as a maintenance therapy. 40 patients had RTX treatment, and 11 cases had a relapse during 24-months followed.

Results: In 11 cases with relapses, the patients with CD19 recovery (CD19>10/ μ L) at the time of the relapse were six, and mean CD19 at relapse was 56.4/ μ L, and the mean time to relapse from the RTX infusion was 178 days. On the other hand, three patients had relapse with CD19<10/ μ L, and mean CD19 at the time of the relapse was 2.63/ μ L, and the mean time to relapse from the RTX infusion was 77 days. Two patients were not measured CD19 level at the time of relapse, and the time to relapses from the RTX infusion were 128 days and 146 days each.

Conclusions: The cause of relapse after RTX treatment seemed to be the result of the recovery of CD19. However, we experienced two cases that relapsed without recovery of CD19, so we report it with clinical course.

TH-PO725

Long-Term Outcome in Glomerulonephritis with Organized Microtubular Monoclonal Deposits (Immunotactoid Glomerulonephritis): A Case Series of 25 Patients Léa Dufour,¹ Vincent Javaugue,¹ Guy Touchard,¹ Frank Bridoux.¹ ¹Nephrology, Hospital, Poitiers, France; ²Anatomopathology, Hospital, Poitiers, France; ³Hematology, hospital Saint Louis, Paris, France.

Background: Glomerulonephritis (GN) with organized microtubular monoclonal deposits (GOMMID), also referred to immunotactoid glomerulopathy, is a rare entity distinct from fibrillary GN and type I cryoglobulinic GN. Treatment and outcome in GOMMID remain poorly described.

Methods: Twenty-five adults (17 men, median age: 61 years) from 21 nephrology departments were retrospectively studied. Inclusion criteria were: Congo Red-negative, monotypic IgG glomerular deposits, with microtubular organization (10-60 nm in external diameter) by electron microscopy (EM), without pathological criteria for cryoglobulinic GN.

Results: Renal manifestations included: constant proteinuria (median: 6.0 g/d), nephrotic syndrome (72%), microscopic hematuria (79%), hypertension (79%), median serum creatinine: 130 μ mol/l. Biopsy proven extrarenal manifestations in 2 cases (mononeuritis, nodular hypodermatitis). Eighteen patients had a serum and/or urinal monoclonal component, 12 had a lymphoproliferative disorder (chronic lymphocytic leukemia [CLL] n=9; lymphocytic B cell lymphoma n=3). Kidney biopsy showed atypical membranous GN (n=14) or membranoproliferative GN (n=11), with IgG deposits: IgG1 (n=8/15), IgG2 (n=5/15), IgG3 (n=2/15), mostly kappa (n=15/25). By EM, microtubule mean diameter was 15.6 nm. Intracytoplasmic lymphocyte microtubular inclusions were observed in n=4/11 (CLL n=3, lymphocytic B cell lymphoma n=1). Twenty-one patients received chemotherapy based on alkylating agent (n=17) and/or Rituximab (n=6). Renal response occurred in 15 cases (71%), associated with hematological response in 9 evaluable cases. Eleven patients received a second line of chemotherapy. After a median follow-up of 45 months, 17 patients had a persistent renal response, 5 had reached end-stage renal disease and 5 had died.

Conclusions: GOMMID should be suspected in patients with glomerular disease in the context of CLL or lymphocytic B cell lymphoma. Early chemotherapy, adapted to the underlying B-cell clone, is associated with a favorable renal outcome in 68% of patients.

TH-PO726

PLA2R-Related Membranous Nephropathy in a Patient with Mannan-Binding Lectin Deficiency Stéphane Bally,¹ Hanna Debiec,² Chantal Dumestre-Perard,³ Frédérique Dijoud,⁴ John Rendu,⁵ Pierre M. Ronco,² Denise Ponard.³ ¹Nephrology and Dialysis, CHU Chambéry, Chambéry, France; ²UMR S1155, INSERM, Paris, France; ³Immunology Laboratory, CHU Grenoble, Grenoble, France; ⁴Pathology Center, Hôpitaux de Lyon, Lyon, France; ⁵Biochemistry and Molecular Genetics laboratory, CHU Grenoble, Grenoble, France.

Background: About 75% of patients with primary membranous nephropathy (MN) have autoantibodies against phospholipase A2 receptor (PLA2R), predominantly of IgG4 subclass. C3 and C5b-9 occur in glomerular immune deposits, implicating complement activation as a putative effector mechanism. It was also shown that purified anti-PLA2R IgG4 could activate the mannose binding lectin (MBL) pathway, but the respective role of the three pathways of complement activation remains elusive. Here we report the case of a patient with PLA2R related MN and MBL deficiency who developed MN.

Methods: Kidney biopsy specimens were evaluated for staining for PLA2R, IgG subclasses, and various complement components, including C3, C1q, C4d, factor B, properdin and C5b-9. MBL concentration was assayed by ELISA and its activity was measured from C4 cleavage. Polymorphisms in exon 1 and in the promoter region for MBL2 were detected by direct sequencing.

Results: Kidney biopsy showed MN with intense staining for PLA2R, IgG4, C3, factor B, properdin and C5b-9 and weak staining for C1q, IgG1 and C4d within the subepithelial deposits. Exploration of the lectin pathway revealed a severe MBL quantitative and functional deficiency (concentration 12 μ g/l, normal range 30-3000 μ g/l; and activity < 10% normal range 35-135%). Genotyping revealed a 57 (A/C) heterozygous polymorphism in codon 57 of exon 1 associated with homozygous and heterozygous variation at -550 (L/L) and -1221 (X/Y) respectively in the promoter region, suggesting that the patient harbours the LXA/LYC haplotypes linked to MBL deficiency.

Conclusions: Due to MBL deficiency, binding of anti-PLA2R antibodies to PLA2R could not activate complement by lectin pathway. This is a first case of MN where complement was mainly activated by the antibody independent alternative pathway which does not exclude a direct role for the auto-antibody on receptor function with alteration of podocyte biology.

Funding: Government Support - Non-U.S.

TH-PO727

Alternatively Activated CD163⁺ Macrophages Are a Common Feature in Progressive Interstitial Fibrosis

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Background: Recent studies have shown a disease-specific macrophage (MQ) phenotype in pathologies such as tumor metastasis, arteriosclerosis and diabetes. However, a kidney disease-specific MQ phenotype has not been described. This study examined whether alternatively activated CD68⁺CD163⁺ MQ are associated with interstitial fibrosis irrespective of the nature of the underlying disease.

Methods: Biopsies taken from children with IgA nephropathy (IgAN; n=81), purpura nephritis (HSPN; n=23), lupus nephritis (LN; n=16), minimal change nephrotic syndrome (MCNS) treated with cyclosporine (CyA) for >2 years (n=15), and chronic allograft injury (CAI; n=13, 28 biopsies) were immunostained for collagen I, pan macrophages (CD68) and CD163. Biopsies of thin basement membrane disease (n=9) or MCNS without CyA treatment (n=12) were used as controls. In vitro studies used monocyte-derived MQ from healthy human volunteers.

Results: Significant interstitial fibrosis and accumulation of CD68⁺ MQ was evident in all progressive disease groups. Most interstitial CD68⁺ MQ co-expressed CD163 (89-99%). By contrast, CD163 expression by glomerular CD68⁺ MQ varied from 20-93% across the progressive disease groups, indicating much greater heterogeneity of M1/M2 phenotypes in this compartment. Interstitial CD163⁺M2-type MQ correlated with the degree of interstitial fibrosis in each type of progressive renal disease (all p<0.01), with proteinuria in IgAN (p<0.001), HSPN, and LN (p<0.01), and with kidney function in CAI (p<0.001). In addition, CD163⁺ MQ co-localized in fibrotic lesions with excess type I collagen deposition. In vitro studies showed that dexamethasone (Dex) up-regulated CD163 expression by MQ, and that Dex plus oxidized LDL increased MQ production of pro-fibrotic factors (FGF-1, FGF-2, TGF- β 1, CTGF).

Conclusions: Our study identifies CD163⁺ M2-type MQ as the main MQ population associated with interstitial fibrosis across a range of progressive forms of kidney disease, suggesting a functional role for this MQ subset in renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO728

Increased Urinary Angiotensinogen Is Associated with Crescent Formation in Initial Stage of Henoch Schönlein Purpura Nephritis

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Background: To investigate the relative factors of increased urinary angiotensinogen (uAGT) in children with Henoch Schönlein Purpura Nephritis (HSPN).

Methods: The severity of histopathological changes in HSPN is classified by the International Study of Kidney Disease in Children (ISKDC) into six categories: grade I-VI. 85 inpatient children with HSPN were underwent renal biopsy in our hospital from 2014 June to 2015 March, and their histopathological changes included grade II (mesangial proliferation, n=21) and grade III ((a) focal or (b) diffuse mesangial proliferation or sclerosis with <50% crescents, n=64). The grade III was again divided into IIIa (n=39) and IIIb (n=25) groups, IIIc<25% crescent (n=52) and III>25% crescent (n=12) groups. Morning urine and serum of HSPN patients were collected on the day before renal biopsy. The levels of AGT and collagen type IV (CL-IV) in urinary and serum were detected using ELISA method. The urinary microalbuminuria and IgG levels were measured using immunoturbidimetric method. All indexes mentioned above were corrected with urine creatinine ratio.

Results: The serum AGT and CL-IV concentration had no significant difference among different groups. The uAGT levels were higher in grade III (30.13±13.69ug/gCr) than grade I group (12.09±4.87ug/gCr), and also higher in grade III>25% crescent (57.69±23.31ug/gCr) than grade IIIc<25% crescent group (28.26±12.02ug/gCr). The uAGT level had no significant difference between grade IIIa and IIIb group. The uAGT concentration was positively correlated with uCL-IV (r=0.505) and ulgG (r=0.512) respectively.

Conclusions: The increased uAGT level in initial stage of HSPN was related with the crescent formation. The enhanced uCL-IV suggested the glomerular basement membrane (GBM) may be cleavaged while the crescent formation. On the other hand, the increased ulgG concentration also showed the severe injury of GBM. Therefore, the combined detection of uAGT, uCL-IV and ulgG may contribute to judge the severity of pathological injury of HSPN.

TH-PO729

Ultrasound Microscopy Through a Fine Fiber for Renal Tissues

Takane Ito, Takahiro Kanai, Jun Odaka, Takanori Yamagata. Pediatrics, Jichi Medical Univ, Shimotsuke, Tochigi, Japan.

Background: Renal pathology is a fundamental examination in observations of renal tissue conditions by light microscopy (LM), aiding in precise diagnoses. However, we cannot avoid a bleeding risk in renal biopsies. Additionally, we cannot sometimes make precise diagnoses in cases that the obtained renal tissue includes few glomeruli. Ultrasound (US) microscopy has been already developed, which enables histopathological observations by using the high frequency US. However, it has not been used clinically. We have been developing US microscopy through a fine quartz fiber (1mm in diameter). Our aim is to observe renal tissues in vivo using this method. As a result of this, we could perform safe and precise renal biopsy. For this purpose, we examined that the US microscopy through the fine fiber could obtain equivalent images of renal tissues with LM ex vivo.

Methods: We made the renal tissue slide specimens of patients with glomerulonephritis. Specifically, we made the unstained US microscopic slide specimens and the Periodic Acid-Schiff staining LM slide specimens from the paraffin blocks of renal biopsy tissues. Furthermore, we obtained their images of the US microscopy and LM.

Results: We could make discrimination between glomeruli and renal tubules by the US microscopy. In addition, mesangial cell proliferation and increased matrix, and fibrocellular crescent were detected by the US microscopy, which was enough to evaluate the conditions and lead to diagnoses.

Conclusions: We succeeded in obtaining the images of renal tissues using the US microscopy through a fine quartz fiber ex vivo. Furthermore these images were similar to them of LM. This preliminary study provides a first step toward clinical application of US pathological observation in renal diseases. These high-resolution images through a fine fiber could not only make live images of renal tissues possible, but prevent removing renal tissues which few glomeruli include in. This enables safe and precise renal biopsy, and we can thereby make precise diagnoses of renal diseases. This study provides an important contribution to future diagnoses and treatments of renal diseases, and further studies are warranted.

TH-PO730

Serum Levels of Antigliyan IgG Autoantibodies in Patients with IgA Nephropathy Predict the Oxford Classification Scores S and T

Nicolas Maillard,¹ Hitoshi Suzuki,² Blandine Laurent,¹ Bruce A. Julian,² Christopher R. Mariat,¹ Jan Novak,² Francois C. Berthoux.¹ ¹Nephrology, Dialysis, Transplantation, CHU Saint Etienne, Saint Etienne, France; ²Dept of Microbiology, Univ of Alabama at Birmingham, Birmingham.

Background: IgA nephropathy (IgAN) is driven by mesangial deposition of immune complexes consisting of galactose-deficient IgA1 (Gd-IgA1) and IgG antigliyan autoantibodies, leading to glomerular injury and chronic kidney disease. As serum levels of Gd-IgA1 and IgG autoantibodies have prognostic significance, we evaluated in this study the relationship between these markers and renal histology according to the Oxford classification.

Methods: Ninety-seven biopsy-proven IgAN patients were selected from our to equally represent the absolute renal risk scores from 0 to 3. Gd-IgA1 and IgG autoantibody levels were assessed in the serum samples obtained at the time of diagnosis using ELISA. Oxford classification and global optical scores (GOS) were compiled based on the evaluation of stored kidney tissue sections. A logistic regression analysis and c statistics were performed.

Results: Eighty-six patients were included in the Oxford analysis (biopsies from 11 patients did not have sufficient tissue) and GOS was calculated. IgG autoantibody levels predicted a T score of 1 or 2, using a logistic regression model (estimate 1.04, p=0.01), and an S score of 1 (estimate 1.10, p=0.006), but did not predict a positive M or E score. GOS was predicted by IgG autoantibody levels (linear regression, p<0.001). The ROC curve analysis revealed an areas under curve of 0.68 [0.55-0.81] and 0.68 [0.57-0.80] predicting positive T and S scores from IgG autoantibody levels. Gd-IgA1 levels were not associated with any histological pattern.

Conclusions: IgG autoantibody levels correlated with GOS and predicted positive S and T scores according to Oxford classification in IgAN.

TH-PO731

Comparison of Native and Transplant Percutaneous Renal Biopsy: Safety and Diagnostic Yield

William Luke Whittier, Samuel N. Saltzberg, Stephen M. Korbet. Nephrology, Rush Univ, Chicago, IL.

Background: No prospective studies exist which directly compare the safety and adequacy of the percutaneous native (NRB) and transplant (TRB) renal biopsy. We report a large single-center prospective series comparing the success and complication rate of NRB and TRB over a twenty year period.

Methods: From 01/1995 to 04/2015, 1,705 adult pts underwent NRB (N= 767) or TRB (N=938) by a Nephrology attending or fellow. Data were collected prospectively in all biopsies. Real-time U/S guidance and automated needles were used for all biopsies. NRB was performed with either a 14 or 16 gauge needle while TRB was with a 16 gauge needle. All NRB pts were observed in the hospital for at least 24 hours and TRB pts for at least 3 hours. Complications were defined by the need for an intervention (i.e. transfusion, surgery or embolization), readmission, or death.

Results: At the time of biopsy, NRB pts were younger (47±17 vs. 50±14 years, p<0.0001) and more often female (62 vs. 48%, p<0.0001) compared to TRB. TRB pts had higher blood pressure (systolic BP: 140±22 vs. 133±18 mmHg, p<0.0001), higher serum creatinine (3.1±1.8 vs. 2.3±2.2 mg/dl, p<0.0001), increased aPTT (28±4.3 vs. 27±5 seconds, p<0.0001) as well as lower Hgb (11.2±1.8 vs. 11.7±2.1 g/dl, p<0.0001) compared to NRB. A fellow performed the biopsy in 91% of NRB compared to 63% of TRB (p<0.0001). Adequate tissue for diagnosis was obtained in 99% of NRB and TRB (p=0.71). Total number of glomeruli on light and immunofluorescent microscopy was 33±17 for TRB and 31±13 for NRB (p=0.11). The only factor predictive of a complication in the TRB was pre-TRB Hgb (no complication, 11.2±1.7 vs. complication, 10.1±1.7 g/dl, p<0.0001). Compared to TRB pts, NRB pts had a greater drop in Hgb post-PRB (0.97±1.1 vs. 0.73±1.3 g/dl, p<0.0001), had more complications (6.5 vs. 3.9%, p=0.02) and/or transfusions (5.2 vs. 3.3%, p=0.045). There was 1 death in each group attributed to the biopsy.

Conclusions: The NRB and TRB remain successful and safe procedures. There are more complications with NRB compared to TRB despite TRB pts having more risk factors. Differences in technique, operator (fellow or attending), or needle size may explain this variability.

TH-PO732

Serum Immunoglobulin E Level Is Associated with Renal Progression in Immunoglobulin A Nephropathy Shin yeong Lee, Jin sug Kim, Sang ho Lee, Se yun Kim, Yu ho Lee, Kyung-hwan Jeong, Tae won Lee, Ji hoon Lee, Yang gyun Kim, Ju-Young Moon, Chun-Gyoo Ihm. *Dept of Nephrology, Kyung Hee Univ Medical Center, Seoul, Korea.*

Background: Previous studies reported that serum Immunoglobulin E(IgE) levels are elevated in Immunoglobulin A nephropathy(IgAN) and suggested IgE levels as a prognostic indicator in IgAN. The aim of this study is to explore the association between plasma IgE level of IgAN patients and renal outcome.

Methods: This study is an observational study of IgAN patients undergoing kidney biopsy between 1995 and 2012. We collected the data of patient's demographics and serum IgE levels from routine laboratory examination. We retrospectively analyzed the correlation between serum IgE level and clinical parameters and pathologic findings. We defined renal progression if patient meets the following criteria; 1) negative value of delta estimated glomerular filtration rate(eGFR)(ml/min/1.73m2/months) and 2) a rise in serum creatinine(SCr) an absolute level ≥ 1.3 mg/dl(male) or 1.2mg/dl(female).

Results: A total of 117 patients were included. The mean level of initial eGFR and serum IgE were 84.79 ± 37 ml/min/1.73m2 and 304 ± 607 IU/mL. The distribution in glomerular grades using the H. S. Lee grading was as follows; grade I, 28 patients(23.9%); grade II, 62 patients(53%); grade III, 19 patients(16.2%); grade IV, 6 patients; grade V, 1 patient. Of the 117 patients, twenty-two (22%) had renal progression. Serum IgE level was significantly high in renal progression group compared to nonprogressive group. (590 ± 1247 vs. 238 ± 290 , $p=0.014$). Gender(76% vs 50%, $P=0.011$) and history of gross hematuria (9% vs 29%, $p=0.024$) were significant difference between high and low IgE group. But no significant differences were seen for delta SCr, delta eGFR, delta proteinuria and pathologic findings. Linear regression analysis showed that male gender ($\beta=0.308$, $p=0.028$), initial proteinuria ($\beta=0.617$, $p=0.008$) and delta proteinuria ($\beta=0.404$, $p=0.028$) were significant associated with IgE levels.

Conclusions: These results suggested that serum IgE level is probably associated with renal progression in IgAN patients. Further studies are needed to elucidate immunopathogenesis of the increased IgE level in IgAN.

TH-PO733

Podometric Changes in Perinatal Kidneys (127 to 471 Day Post-Conception) Masao Kikuchi, Larysa T. Wickman, Su Qing Wang, Mahboob A. Chowdhury, Roger C. Wiggins, Raja Rabah. *Div of Nephrology, Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.*

Background: We recently reported that glomerular volume increases and podocyte density decreases with age from 4 to 89 years in man. However the changes that occur before and immediately after 38 weeks gestation are not well defined.

Methods: Podometric parameters (including glomerular volume, podocyte number, density and cell size) were estimated from archival tissue sections with recently developed technology (Venkatarreddy et al. JASN 2014 and Yang et al. JASN 2015) using autopsied kidney samples from newborn and infants without kidney disease as a proximate cause of death (n=25, age 0-240 day-old). Because premature kidneys were included, post-conceptual age (range 127-471 day-old) was used instead of postnatal age.

Results: The younger post-conceptual age was, the greater the proportion of immature glomeruli present ($R^2=0.63$, $P<0.001$). Compared to mature glomeruli, immature glomeruli were smaller (1.4×10^5 vs $4.9 \times 10^5 \mu m^3$, $P<0.001$) and podocytes were smaller (140 vs $320 \mu m^2$, $P<0.001$) and fewer per glomerular tuft (300 vs 520 , $P<0.001$), and present at higher podocyte density ($2,700$ vs $1,400/10^6 \mu m^2$, $P<0.001$). In mature glomeruli podocyte density decreased linearly with age ($R^2=0.54$, $P<0.001$) due to a rapid increase in glomerular volume ($+210\%$ per year, $R^2=0.48$, $P<0.001$). Podocyte number per glomerular tuft did not change with age ($R^2=0.008$, $P=0.68$). Mean podocyte cell volume increased with age ($+140\%$ per year, $R^2=0.39$, $P<0.002$). Glomerular volume correlated with kidney-to-body weight ratio ($R^2=0.49$, $P<0.001$).

Conclusions: Prior to and after term there is a very rapid decrease in podocyte density (increase in glomerular volume and podocyte size without a change in podocyte number or proportion of the glomerulus that constitutes podocytes). These large perinatal adaptations could play a role in triggering glomerular syndromes prevalent early in life.

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TH-PO734

Novel Monoclonal Antibody KM55 Specifically Detected Glomerular Galactose-Deficient IgA1 in Patients with IgA Nephropathy Hitoshi Suzuki,¹ Junichi Yasutake,^{1,2} Yuki Tanbo,^{1,2} Yusuke Suzuki.¹ *¹Nephrology, Juntendo Univ Faculty of Medicine, Tokyo, Japan; ²Nephrology Research Labs, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan.*

Background: Galactose-deficient IgA1 (Gd-IgA1) has been proposed as an important effector molecule in patients with IgA nephropathy (IgAN). Our previous study revealed that Gd-IgA1-specific monoclonal antibody KM55 could be a new tool for detecting circulatory Gd-IgA1 in patients with IgAN, which enabled us to study molecular roles of Gd-IgA1. In this study, we further examined pathophysiological significance of Gd-IgA1 in glomerular deposits of patients with IgA nephropathy by immunohistochemical analysis with KM55.

Methods: Immunostaining of Gd-IgA1 and immunoglobulins (IgA and IgG) was performed with KM55 and anti-immunoglobulin polyclonal antibodies in paraffin embedded sections of renal biopsy specimens from patients with IgAN (n=16), and other renal

diseases (n=19); such as lupus nephritis and membranous nephritis. Area of glomerular deposits of Gd-IgA1 and immunoglobulins were semi-quantitated by spectral imaging using Nuance software.

Results: Glomerular Gd-IgA1 was specifically detected in all patients with IgAN, but not in those with other renal diseases. Gd-IgA1 could not be detected even in patients with lupus nephritis whose glomerular IgA were positive. In patients with IgAN, immunofluorescence with KM55 revealed diffuse and global glomerular staining of Gd-IgA1. Moreover, double staining of Gd-IgA1 and IgA showed that Gd-IgA1 was localized predominantly in the mesangial region; however the localization of IgA was similar to that of Gd-IgA1 but was more broadly observed.

Conclusions: This is the first observation to clearly reveal that Gd-IgA1 could be specifically deposited in glomeruli of IgAN, strongly suggesting the pathophysiological function of Gd-IgA1 in patients with IgAN. Further studies are necessary to clarify the underlying mechanisms of Gd-IgA1 deposition and induction of renal injuries in IgAN. Novel monoclonal antibody KM55 against galactose-deficient IgA1 could be a powerful tool to detect nephritogenic IgA in patients with IgAN.

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TH-PO735

Serum Levels of Galactose-Deficient IgA1 in Patients with IgA Nephropathy Correlate with Serum Levels of IgG Autoantibodies William J. Placzek,¹ Yuko Makita,⁴ Matthew B. Renfrow,¹ Bruce A. Julian,³ Yusuke Suzuki,⁴ Jan Novak,² Hitoshi Suzuki.⁴ *¹Biochemistry and Molecular Genetics, The Univ of Alabama at Birmingham, Birmingham, AL; ²Microbiology, The Univ of Alabama at Birmingham, Birmingham, AL; ³Medicine, The Univ of Alabama at Birmingham, Birmingham, AL; ⁴Internal Medicine, Juntendo Univ, Tokyo, Japan.*

Background: IgA nephropathy (IgAN) is an autoimmune disease in which IgA with some O-glycans deficient in galactose (Gd-IgA1) is recognized by anti-glycan IgG and/or IgA autoantibodies to form pathogenic immune complexes. Some of these immune complexes deposit in the kidney and induce glomerular injury. In this study, we assessed possible associations between serum levels of Gd-IgA1 and IgA, and Gd-IgA1 and IgG or IgA autoantibodies.

Methods: Serum samples from 135 patients with biopsy-proven IgAN, 79 patients with other renal diseases, and 106 healthy controls at Juntendo University, Tokyo, Japan, were analyzed for levels of total IgA and IgG, Gd-IgA1, and Gd-IgA1-specific IgA and IgG autoantibodies and the data assessed for possible associations.

Results: Patients with IgAN had higher total IgA compared to healthy controls and exhibited a significantly stronger correlation between total IgA and Gd-IgA1 levels ($r=0.639$ vs. $r=0.901$, $p<0.0001$). Gd-IgA1 levels strongly correlated with levels of Gd-IgA1-specific IgG autoantibodies in patients with IgAN ($r=0.4909$, $p<0.0001$), but not in healthy controls or disease controls. Levels of Gd-IgA1 did not correlate with the levels of IgA autoantibodies in any of the three groups. Furthermore, among IgAN patients with levels of Gd-IgA1-specific IgG higher than the mean + 2 SD level of healthy controls, only 37% also had an elevated level of Gd-IgA1-specific IgA autoantibody.

Conclusions: Our data revealed a new association between the key autoantigen, Gd-IgA1, and IgG autoantibodies in patients with IgAN, further supporting their key role in the pathogenesis of IgAN.

TH-PO736

Cryoglobulinemic Glomerulonephritis: A Single-Center Experience Insara Jaffer Sathick,¹ Tyler V. Klobucher,² Nelson Leung,^{1,3} Samih H. Nasr.⁴ *¹Div of Nephrology, Mayo Clinic, Rochester, MN; ²Mayo Medical School, Rochester, MN; ³Div of Hematology, Mayo Clinic, Rochester, MN; ⁴Div of Anatomic Pathology, Mayo Clinic, Rochester, MN.*

Background: Cryoglobulinemic glomerulonephritis(CryoGN) is a recognized form of glomerulonephritis. However, the clinical characteristics are not well-established due to lack of large studies with biopsy and serological confirmation. We present our experience with 42 cases of serologically and biopsy-proven CryoGN.

Methods: We conducted a retrospective search for patients with cryoglobulinemia and kidney biopsy and identified patients with CryoGN.

Results: From 2000 to 2014, we identified 569 patients with cryoglobulinemia. Of the 71 patients who underwent kidney biopsy for kidney dysfunction, 42(59%) had CryoGN, the remaining had other pathology, including interstitial nephritis, lupus nephritis, fibrillary GN and amyloidosis. Median age of CryoGN patients was 59 yrs; male/female ratio, 23:19. Median eGFR by MDRD equation was 41ml/min/1.73m2 at onset. 88% had nephritic syndrome and rest had nephrotic syndrome. 74% had Type II, 19%- Type I and 7%-Type III cryoglobulinemia. Hypocomplementemia was present in 83%. 76% had skin involvement, 16% had joint symptoms, 14% had neuropathy and 1% had pulmonary involvement. 4 patients required dialysis. Etiology of cryoglobulinemia was a hematological disorder in 40%(of which 88% lymphoproliferative and 12% MGRS) and hepatitis C in 26% patients.

Etiology of Cryo GN(% total)	Type I(19%)	Type II(74%)	Type III(7%)
Hematological (40%)	23	71	6
Hepatitis C (26%)	9	82	9
Connective Tissue Disease (17%)	14	72	14
Idiopathic (17%)	34	66	

80% patients received immunosuppression for treatment, 54% receiving Rituximab. Median duration of follow up was 18 months. Median overall survival was 36.4 months. At 6 months, median eGFR improved to 48ml/min/1.73m².

Conclusions: Though CryoGN is the most common pathology in cryoglobulinemia, a wide array of other lesions is seen. Most patients with CryoGN have skin lesions while other systemic features of cryoglobulinemia are rare. In this study hematological disorders were the commonest etiology for CryoGN followed by hepatitis C infection.

TH-PO737

The Clinicopathological Impact of Medullary Ray Injury on Early Stage Renal Allografts Takahito Niikura,¹ Akimitsu Kobayashi,¹ Yasuyuki Nakada,¹ Izumi Yamamoto,¹ Yudo Tanno,¹ Ichiro Ohkido,¹ Masayoshi Okumi,² Hideki Ishida,² Kazunari Tanabe,² Hiroyasu Yamamoto,¹ Takashi Yokoo.¹ ¹Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan; ²Urology, Tokyo Women's Medical Univ, Tokyo, Japan.

Background: Interstitial fibrosis and tubular atrophy (IF/TA) constitute an important cause of renal graft loss. Previously, we examined medullary ray injury (MRI) inducing IF/TA via non-immunological mechanisms, classifying the etiology of MRI into calcineurin inhibitor (CNI) toxicity (32.8%), vesicoureteral reflux (50%), and urinary tract infection (8.6%) (Pathol Int. 2010;60:744-9). However, we did not examine the influence of the etiology on the long-term renal allograft prognosis, since the timing of the biopsies differed among the cases. Herein, we focused on MRI observed in protocol biopsies within 3 months, examining the influence on the renal allograft prognosis.

Methods: Retrospectively, we divided 53 protocol biopsies within 3 months into two groups with (n=34) and without (n=19) MRI. The MRI+ cases with isometric vacuolization and aah in the Banff classification were classified as CNI toxicity (MRI+CNI); the cases with Tamm-Horsfall protein casts in the interstitium and thyroid-like appearance were classified as urinary tract system abnormalities (MRI+UT); and the remaining cases as others. We compared the annual change in serum creatinine (sCr) levels over 3 years and the extent of fibrosis (ct+ci) at the 1-year biopsies. Cases with rejection were excluded.

Results: The sCr levels declined in both groups, but were significantly higher in the MRI+ group than the MRI- group at 3 years (p=0.024). Examining three MRI+ subgroups, only MRI+UT had significantly high sCr levels compared to the MRI- group (p=0.019). The observation of IF/TA in the base-line and 1-year biopsies in the MRI+ group indicated the significant development of IF/TA.

Conclusions: Cases developing MRI within 3 months after kidney transplantation were significantly more likely to develop IF/TA at the 1-year biopsies. These cases had higher sCr levels at 3 years. In the cases with MRI in the base-line biopsies, interventions might preserve kidney graft function over the long-term.

TH-PO738

Diagnostic Gene Signature from Urinary Extracellular Vesicles Can Be Used as Biomarker for Non-Invasive Diagnosis of Clear Cell Renal Cell Carcinoma Giuseppe De Palma,¹ Fabio Sallustio,^{1,2} Vanessa Galleggiante,³ Monica Rutigliano,³ M. Battaglia,³ Francesco Paolo Schena.¹ ¹C.A.R.S.O. Consortium, Univ of Bari, Valenzano, BA, Italy; ²Dept of Science, Biological and Environmental Sciences and Technologies, Univ of Salento, Lecce, LE, Italy; ³Urology, Andrology and Kidney Transplantation Unit, Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, BA, Italy.

Background: Clear cell renal cell carcinoma (ccRCC) is one of the most common malignancies and due to its intimate association with urine, it appears well suited for studies to identify non-invasive biomarker in this material. The extracellular vesicles (EV) can be isolated in urine. They transport proteins and nucleic acids that reflect the physiopathological status of renal cells. The purpose of this study has been to analyze the transcripts in the urinary EV from ccRCC patients and to specific transcripts for preventive diagnosis of ccRCC.

Methods: We enrolled 12 patients with a diagnosis of ccRCC undergoing unilateral nephrectomy. We collected pre-intervention urine. A group of healthy volunteers (n = 11) with negative urine analysis was used as control. The EV were isolated from the urine by differential centrifugation. Total RNA was extracted, quantified and qualitatively evaluated. Illumina HumanHT-12 v4 BeadChip was used for microarray analyses. Then, the dysregulated genes were validated by qRT-PCR in independent cohorts of 12 patients and 10 controls.

Results: We identified four genes (GSTA1, CEBPA, PCBD1, RCC2) differentially modulated in ccRCC patients and we investigated whether the functions of these genes could be related to ccRCC through the pathways analysis. The qRT-PCR validated a number of potential diagnostic biomarkers that could be used to distinguish ccRCC patients at an early stage from healthy individuals. Some potential biomarkers were already present in pathways involved in the pathogenesis of cancer as glutathione or arsenate mediated detoxification instead other biomarkers were new.

Conclusions: Using this approach, we have identified a signature of four transcripts that could be used as biomarkers for non-invasive diagnosis of ccRCC.

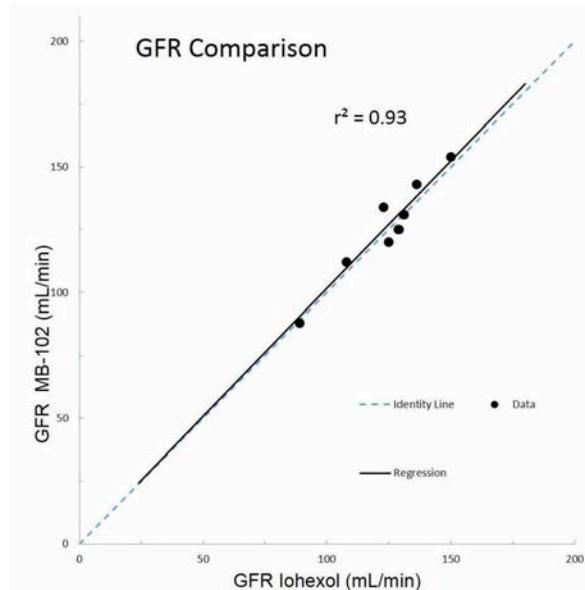
TH-PO739

Initial Clinical Trial Results of a Real-Time Point-of-Care Glomerular Filtration Rate Measurement Utilizing a Novel Fluorescent Tracer Agent Richard B. Dorshow,¹ Martin Debreczeny,¹ Jeffrey C. Fink,³ Thomas C. Dowling.² ¹MediBeacon, LLC, St. Louis, MO; ²College of Pharmacy, Ferris State Univ, Grand Rapids, MI; ³Dept of Medicine, Univ of Maryland Medical System, Baltimore, MD.

Background: A first-in-human clinical study with MB-102, a fluorescent tracer agent engineered to have photophysical and clearance properties for use as a real-time point-of-care measure of glomerular filtration rate (GFR) is reported. The clearance of this agent can be monitored noninvasively by transdermal fluorescence.

Methods: Blood samples were taken over a period of 12 hours post simultaneous administration of MB-102 and iohexol to assess pharmacokinetic parameters including clearance on 32 subjects recruited to have normal renal function. Urine samples were collected concurrently to assess percent injected dose recovered in the urine. A prototype noninvasive fluorescence detection device was employed to simultaneously measure the transdermal fluorescence from MB-102 to assess correlation with the plasma pharmacokinetics.

Results: The plasma pharmacokinetics displayed the expected 2 compartment model of a vascular-tissue equilibrium phase followed by renal excretion only. The GFR measured from the MB-102 plasma pharmacokinetics matched the GFR measured from iohexol.



The % injected dose of MB-102 appearing in the urine (99+/-7%) matched that of iohexol. The MB-102 time-dependence of the transdermal fluorescence monitored by the prototype device matched that of the plasma (r²~0.98). No significant adverse events were reported.

Conclusions: MB-102 was shown to be a GFR tracer agent in humans from the plasma pharmacokinetic match and the % injected dose in urine match to iohexol. The transdermal fluorescence pharmacokinetics mirrored that of the plasma pharmacokinetics thus demonstrating that the validity of this noninvasive GFR measurement.

Funding: Pharmaceutical Company Support - MediBeacon, LLC

TH-PO740

Analysis of Exogenous Near Infrared Fluorescent Markers for the Transcutaneous Measurement of Glomerular Filtration Rate Jiaguo Huang,¹ Stefanie Weinfurter,¹ Johannes Pill,² Norbert Gretz,¹ Rossana Perciaccante,³ Federica Rodeghiero,³ Lepoldo Della ciana.³ ¹Medical Faculty Mannheim, Univ of Heidelberg, Mannheim, Germany; ²Mannheim Pharma & Diagnostics GmbH, Mannheim, Germany; ³Cyanagen S.r.l., Bologna, Italy.

Background: Recently, we developed approaches for the transcutaneous measurement of GFR in lab animals. Using fluorescent markers allows GFR assessment without blood and/or urine sampling. Therefore, there is considerable interest in the development of exogenous fluorescent markers for real-time and accurate measurement of GFR via transcutaneous fluorescent methods using new dye conjugates.

Methods: A near infrared (NIR) cyanine was synthesized by a five-step synthetic procedure. This dye was used to label (2-hydroxypropyl)-β cyclodextrin. The chemical structure was fully confirmed by ¹H-NMR, ¹³C-NMR, and HRMS spectra. Optical properties were characterized by UV-2450 spectrophotometer and fluorescence spectrometer. The percent plasma protein binding (PPB) was determined by equilibrium dialysis of fluorescent marker solutions incubated with rat plasma using a two-chamber dialysis set-up. Elimination half-life was determined in combination with a miniaturized new electronic device for

the transcutaneous fluorescence detection in freely moving rats. Recovery rate in urine was measured in conscious rats after intravenous injection using metabolic cages. Mean \pm S.D are given.

Results: The NIR marker was synthesized in a high yield. It exhibits good water solubility with concentrations reaching more than 200 mg/mL with a molecular weight range from roughly 1200 up to 2700 D. In addition it shows a low plasma PPB, i.e. 3.7 %, which is clearly lower than that of iohalamate (9.5 %). The excitation and emission are 705 nm and 790 nm respectively providing low background and high tissue penetration for in vivo application. The noninvasive real-time monitoring of clearance resulted in a half-life of 33.4 ± 4.6 min and 34.9 ± 6.8 min without and with probenecid treatment, respectively. A high urinary recovery of the marker with $99 \pm 7.3\%$ of the dose given was observed within 24 h.

Conclusions: We identified the marker with a high potential as exogenous fluorescent tracer for GFR measurement. A patent has been filed.

Funding: Government Support - Non-U.S.

TH-PO741

Phospholipase A2 Receptor Antibodies in Membranous Nephropathy: Biopsy, Serum and Urine Findings Aikaterini K. Nikolopoulou, Theresa H. Page, Gurjeet Bhangal, Janet Lee, Paul Brookes, Tom Cairns, Liz Lightstone, Megan Griffith, H. Terence Cook, Charles D. Pusey. *Renal and Transplant Centre, Imperial College London, London, United Kingdom.*

Background: The major target antigen in Membranous Nephropathy (MN) is the phospholipase A2 receptor (PLA2R); its exact role is not yet fully understood. In this retrospective study we examined the presence of PLA2R in biopsy tissue, PLA2R antibodies in serum and urine of patients with MN, and aimed to identify associated clinical variables.

Methods: 120 MN patients were identified from 2008 - 2014: 74 with idiopathic MN (iMN); 12 secondary MN; 9 recurrent MN post transplantation; 25 class V lupus MN (LMN). 27 controls with other GN were also used. Immunofluorescence (IF) for PLA2R was performed on paraffin embedded biopsies and ELISA (EUROIMMUN) for the detection of PLA2R antibodies in serum and urine.

Results: In the iMN group 35/74 (47%) biopsies stained positive, 30 (40%) negative and 9(12%) borderline. Circulating PLA2R antibodies were detected in sera from 30/74(40%) patients within 6 months from biopsy, all of whom had positive or borderline staining on biopsy. In the secondary MN group 5/12 stained positive; 1 had a detectable PLA2R antibody. In the transplant cohort 3/9 stained positive; 1 had a positive serum. Of 25 class V LMN, 3 stained positive and 1 had a positive serum antibody. There was no correlation between staining or the level of PLA2R antibody with proteinuria or creatinine at the time of biopsy. Urine from 5 iMN patients with active disease was positive for PLA2R antibodies; 26 healthy controls and 6 iMN patients in remission tested negative.

Conclusions: Our data suggest that IF for PLA2R in biopsy tissue is more sensitive than serum testing for the presence of PLA2R antibodies. This cross sectional study did not demonstrate a correlation between PLA2R staining or antibody levels and proteinuria at the time of biopsy; however a longitudinal study to assess the variations of PLA2R Ab levels with clinical outcomes is in progress. The presence of PLA2R antibodies in urine of patients with active disease is interesting although further studies are required to determine whether this is due to nonspecific proteinuria.

TH-PO742

Belimumab in Idiopathic Membranous Nephropathy: An Interim Analysis of Exploratory Biomarkers Including Anti-PLA2R Autoantibodies Christine Barrett,¹ Shaun Flint,¹ Robert Brian Henderson,¹ Tim Sebastian Schmidt,¹ Sophie I. Gisbert,¹ Gengqian Cai,² Caroline O.S. Savage.¹ *¹GlaxoSmithKline plc, United Kingdom; ²GlaxoSmithKline plc.*

Background: Belimumab, a B-lymphocyte stimulator (BLyS)-specific inhibitor has been shown to reduce anti-phospholipase A2 receptor (PLA2R) autoantibodies and proteinuria in a mechanistic study (BEL116472) in idiopathic (primary) membranous nephropathy (IMN). Here we report an interim analysis of individual patient responses and analysis of exploratory pharmacodynamic (PD) biomarkers.

Methods: 14 anti-PLA2R autoantibody positive IMN patients with nephrotic range proteinuria received 10mg/kg iv belimumab every 4 wks (or 2 wks if >10g/24h) for up to 100 wks. 11 of these completed at least 28 wks treatment, with 3 withdrawals before wk 16. Assessment of proteinuria, anti-PLA2R antibody levels, belimumab kinetics, BLyS levels and B cell immunophenotypes was performed.

Results: There was a significant reduction in anti-PLA2R antibodies by wk 12 (-46%, p=0.025) and in uPCR by wk 36 (-38%, p=0.022). 9 of 11 subjects showed a reduction of >50% in anti-PLA2R levels at the primary endpoint (wk 28). 6 of 11 achieved at least partial remission of proteinuria and negative or borderline anti-PLA2R levels by last follow-up to date (44-104 wks). Lack of remission was linked to a smaller fall in anti-PLA2R levels, or anti-PLA2R at wk 28 >100 RU/ml, or a shorter follow-up (≤ 36 wks). Week 2 belimumab trough levels showed strong negative correlation with baseline uPCR ($r_s = -0.94$ p<0.0001). The correlation of baseline BLyS level with proteinuria response was weak. Exploratory belimumab PD effects included a reduction in naive B cells and expanded memory B cells.

Conclusions: This mechanistic trial of belimumab in IMN has enabled a novel analysis of PD and PK endpoints, confirming but also extending the PD effects previously reported in studies of SLE. Further analysis of anti-PLA2R antibody kinetics as a predictor of remission may also be informative.

Funding: Pharmaceutical Company Support - GlaxoSmithKline plc

TH-PO743

Diagnostic Performance of M-Type Phospholipase A2 Receptors Autoantibodies (Anti-PLA2R) for the Differentiation of Idiopathic Membranous Nephropathy (iMN) without Mesangial Immunocomplexes in Kidney Biopsy Hugo Enrique Chavez,¹ Juan Carlos Ramirez-Sandoval,¹ Magdalena Madero,² Ricardo Correa-Rotter,¹ Jose Antonio Nino-Cruz.¹ *¹Nephrology and Mineral Metabolism, Inst Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Distrito Federal, Mexico; ²Nephrology, Inst Nacional de Cardiología Ignacio Chávez, Distrito Federal, Mexico.*

Background: The presence of mesangial immunocomplexes in membranous nephropathy without an apparent cause constitutes a controversial element and has been considered a potential indicator of an unidentified secondary cause. The value of anti-PLA2R for diagnosis of iMN and for this specific purpose has not been assessed. **Objective:** Assess the diagnostic performance of anti-PLA2R to differentiate iMN (without mesangial deposits) and MN with presence of mesangial deposits as well as from other glomerulonephritis (GM).

Methods: We prospectively enrolled 108 cases with biopsy proven GM: 40 iMN, 33 systemic lupus erythematosus (23 with proteinuria >1 g/day), and other. In 27 MN, we found proteinuria >1 g/day, of which 21 had typical granular deposition along the basement membrane (iMN cases); the 6 other had mesangial deposits without a diagnosed secondary cause of MN. Serum anti-PLA2R was assessed by ELISA (euroimmun, Germany).

Results: 21/108 patients had anti-PLA2R >9 RU/mL, all of them had iMN. Among patients with MN and proteinuria >1g/day, 19/27 had anti-PLA2R >9 RU/mL. The area under the ROC curve (AU-ROC) of anti-PLA2R was 0.87 (95% CI: 78-0.96) when cases of MN and proteinuria >1 g/day were compared vs. other cases. At a cutoff of 9 RU/mL, sensitivity and specificity were 70% and 99% respectively. When we predefined cases of iMN and presence of mesangial deposits as probably not idiopathic, the AU-ROC was 0.95 (95% CI: 0.87-1.00). In this analysis, at the cutoff of 9 RU/mL, the sensitivity and specificity were 91% and 99% respectively. All clinically diagnosed MN that had mesangial immunocomplex deposition were negative for Anti-PLA2R.

Conclusions: Anti-PLA2R levels had an excellent diagnostic performance to detect iMN. Anti-PLA2R >9 RU/mL may be sufficient to diagnose iMN precluding the need of a renal biopsy.

TH-PO744

Declining Renal Function in Idiopathic Membranous Nephropathy: A Report from Two Tertiary London Renal Units Sanjana Gupta,¹ Kieran McCafferty,² Horia Stanescu,¹ Stephen H. Powis,¹ Alan D. Salama,¹ John Connolly,¹ Stephen B. Walsh,¹ Robert Kleta,¹ Muhammad M. Yaqoob,² Neil Ashman.² *¹UCL Centre for Nephrology; ²Royal London Hospital.*

Background: Idiopathic Membranous Nephropathy (iMN) is a major cause of nephrotic syndrome in adults. Renal function may deteriorate (progressor) or be preserved (non-progressor patients).

Methods: We performed a retrospective analysis of patients with biopsy proven iMN between 2000-2015.

Results: We identified 188 patients with biopsy proven iMN.

Median age	58 (44-71)
Male %	68
Ethnicity (White / Black / Asian / Unknown) %	48 / 17 / 24 / 11
Diagnosis Serum creatinine (sCr) (μmol/L)	86.5 (64 – 111)
Diagnosis Serum albumin (sAlb) (mmol/L)	25 ± 7
Diagnosis urine protein creatinine ratio (PCR)	900 (485 – 1255)
Spontaneous remission %	34
Renal replacement therapy %	34
Deceased %	12

20% of patients were progressors (increase in sCr >50%, no RRT). There was no statistical difference between sCr (101 ± 6 vs 92 ± 9 μmol/L, ns), sAlb (25.2 ± 1.3 vs 26.2 ± 0.8 mmol/L, ns) or PCR (893 ± 87 vs 895 ± 94, ns) at diagnosis between progressors and non-progressors, respectively. Progressors were more likely to be Asian (36% vs 21%, p=0.058) and non-progressors black (32% vs 20%, p=0.058). Of the 37 patients that spontaneously remitted, 5% relapsed. 65% of patients were treated with immunosuppressives. 60% received prednisolone, the most used first line agent was cyclophosphamide 35%, then anti-proliferatives 34% and calcineurin inhibitors (CNI) 23%. There was a significant difference between treatment between progressors and non-progressors; progressors were treated with CNI (38% vs 15%, p=0.04). Rituximab was used 3 times. The complication rate from immunosuppression was 25%. The most common was diabetes from steroid therapy at 10%. Infection occurred in 2% and drug specific complications in 7%. Thromboembolism rate from nephrosis was low at 14%.

Conclusions: At diagnosis there was no significant difference in sCr, sAlb or PCR between progressors and non-progressors. Progressor patients with iMN may benefit from immunosuppression, but this is associated with risks. It is important to identify progressor patients; there is an unmet need for a biomarker to do this.

TH-PO745

End-Stage Renal Disease from Membranous Nephropathy in the United States, 1995 to 2010

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Background: While management has evolved substantially, it is unknown whether the burden of end-stage renal disease from membranous nephropathy (end-stage membranous nephropathy, ESMN) has declined.

Methods: Here retrospective United States Renal Data System data were used to enumerate incidence trends and outcomes of ESMN in the US between 1995 and 2010 ($n = 7035$, overall rate 1.9 per million per year).

Results: When adjustment was made for demographic shifts, adjusted incidence ratios (AIR, compared to 1995-1996) rose to 1.15 in 1997-1998 and remained stable between 1.09 and 1.14 in subsequent biennia. Other associations of ESMN included older age (AIR 4.08 for age 40-64 (Vs. < 20 yrs.), 9.55 for 64-79, and 8.09 for ≥ 80 male sex (AIR 2.20) and Black/African American race (AIR 3.15 Vs. White). Incidence trends differed by age group: AIR fell for age 40-64 (0.84 in 2009-2010 [Vs. 1995-1996]) and rose for age ≥ 80 (AIR 2.63). ESMN patients were more likely than matched controls to be listed for transplant (9.8 vs. 7.5 per 100 person years [PHPY]) and to receive a transplant (7.4 vs. 4.6 PHPY) and less likely to die (9.8 Vs. 15.9 PHPY). Among patients with ESMN, African American patients were as likely as whites to be listed for transplant (adjusted hazards ratio [AHR] 1.05), less likely to receive a transplant (AHR 0.61) and less likely to die prematurely (AHR 0.85).

Conclusions: While ESMN has not declined meaningfully in the last two decades, trends differ by age and racial disparities in outcomes on renal replacement therapy are apparent.

TH-PO746

42 Cases of Primary Sjögren Syndrome with Membranous Nephropathy: Clinicopathologic Features and Ectopic Germinal Center Formation

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Background: To study the clinicopathologic features of primary Sjögren Syndrome (pSS) with membranous nephropathy (MN) from a single hospital center. Pathogenesis including the formation of ectopic germinal center (EGC) was explored.

Methods: From 1990 to 2014 in Peking Union Medical College Hospital, all pSS patients who underwent renal biopsy with a diagnosis of MN were reviewed. CD21 immunohistochemistry study was used to characterize EGC formation.

Results: Among 154 pSS patients with a renal biopsy, 94 (61%) were diagnosed with glomerulonephritis, including 42 (45%) cases of MN. The majority were female (76.2%) with an age of 52.3 ± 15.0 years. At the time of renal biopsy, the patients presented with microscopic hematuria (80.9%), proteinuria (4.57 ± 3.11 g/24h), hypoalbuminemia (26.5 ± 7.3 g/L) with normal eGFR (92.8 ± 26.3 ml/min). Hypergammaglobulinemia and hypocomplementemia were present in 26.8% and 20.5% patients respectively. Pathologically, 17 (40.5%) cases had atypical MN, featured by mesangial electron-dense deposit or C1q staining. On immunofluorescent study, C3 was positive in 43.9% cases and C1q positive in 34.1%. IgG subtype staining showed positivity of IgG4 (95%), IgG1 (55%), IgG3 (50%) but not IgG2. Most patients showed clinical improvement on prednisone (1mg/kg/d) and/or immunosuppressant (cyclophosphamide or cyclosporine), while 2 patients had progression of CKD with persistent or recurrent proteinuria. CD21 staining on 36 available biopsy samples revealed the presence of EGC in 11 (31.4%) cases, and EGCs were notably abutting or surrounding the glomeruli in 7 cases. Grading of interstitial lymphocyte infiltration revealed the percentage of G0 (absent), G1 (scattered), G2 (focal) and G3 (EGC formation) to be 5.7%, 34.3%, 28.6% and 31.4%, respectively, which was negatively correlated with eGFR ($p=0.008$) and positively correlated with glomerulosclerosis index ($p=0.001$).

Conclusions: MN is the most common type of glomerulonephritis among pSS patients. Interstitial lymphocyte infiltration and EGC formation may be pathologically related to glomerular damage.

Funding: Government Support - Non-U.S.

TH-PO747

In Primary Membranous Nephropathy, Relapse After Partial Remission Is Predicted by Serum Albumin Level

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Background: In primary membranous nephropathy (MN), partial remission (PR), defined as 50% reduction of proteinuria+attaining <3.5 g/day with stable GFR, is associated with decreased risk of ESKD, compared to No remission. However, PR is associated with greater risk of relapse (46%, median 8 months) compared to complete remission (proteinuria <0.3 g/day) (23%, median 25 months). Relapses are associated with increased risk of ESKD. We investigated risk factors of relapse among patients who achieve PR by 18 months, thus simulating the setting of a clinical trial.

Methods: From the Glomerular Disease Collaborative Network cohort, we identified 135 patients who had a minimum of 24 months of follow up from biopsy. Patients who reached a PR at 18 months were included for the analysis. Patients with a relapse (proteinuria

>3.5 g/day) were compared to those with no relapse. Risk factors for relapse were explored by logistic regression analysis. A threshold of serum albumin (salb) associated with risk of relapse was evaluated using a receiver operator curve (ROC).

Results: Among 86 patients who met inclusion criteria, 30(35%) relapsed over a median follow up of 33months. Patients with relapse were similar to those with no relapse with respect to baseline demographics, proteinuria, salb, eGFR and immunosuppressive treatment. Relapsers had significantly lower salb level at 18 months compared to non relapsers (3.47 ± 0.68 vs 3.89 ± 0.46 respectively; $P=0.002$). C-statistics from the ROC for salb as a predictor of relapse was 0.75. 22% of patients with salb >3.5 g/dl at 18 months relapsed (median time to relapse 174 months; 0.7/100 patient-month), compared to 72% of patients with salb ≤ 3.5 g/dl (median time 42months; 2.4/100 patient-month).

Conclusions: Attaining a PR and a salb >3.5 g/dl at 18 months after biopsy is associated with a low risk of relapse. We suggest that a definition of PR should include attaining a salb >3.5 g/dl in addition to the target decrease and level of proteinuria. This definition should be evaluated as a possible surrogate endpoint for clinical trials in MN.

TH-PO748

Clinical Significance and Risk Factor of Relapse in Proteinuria in Primary Membranous Nephropathy

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Background: Achieving complete remission (CR) of proteinuria (<0.3 g/day) in primary membranous nephropathy (MN), is associated with excellent long-term renal outcome. Patients achieving partial remission (PR), defined as $>50\%$ reduction in proteinuria to <3.5 g/day with stable renal function, also show favorable prognosis compared to patients with no-remission (NR). Relapse in proteinuria is associated with a higher risk of ESKD. We investigated the risk factors of relapse in patients who have achieved a PR at any point.

Methods: To identify variables associated with relapse we studied 466 patients with primary MN registered in the Glomerular Disease Collaborative Network. 293 patients with at least 12 months of follow up were included. Time-to-event analysis from the time of PR to relapse was performed to evaluate risk factors for development of relapse. We incorporated various changes of remission status (PR, CR, and NR) during follow-up as time-dependent variable along with baseline patient characteristics.

Results: Of 293 patients, 213(83%) achieved PR and 80 (17%) had NR. Among patients with PR, 95 patients (45%) reached CR, and 118 (55%) remained in PR until the last follow-up or relapse. A total of 63 relapses were observed (48 from PR and 15 from CR). By univariate analysis, older age, male sex, higher baseline proteinuria, PR (vs CR) and lower serum albumin (sAlb) at PR were significantly associated with increased risk of relapse. Higher sAlb at PR was associated with a lower risk of relapse (HR, 0.49 [95% CI, 0.289-0.831]) adjusted for age, sex, proteinuria at baseline, and immunosuppressive therapy. 34% of patients with sAlb ≤ 3.5 g/dl at PR had a relapse (median time to relapse 7.4 months) compared to 20% relapsers among patients with sAlb >3.5 g/dl (median time 21.8 months; $P<0.001$).

Conclusions: A serum albumin level >3.5 g/dl when patient achieve first PR is associated with a low subsequent risk of relapse. We suggest that incorporating a normalized serum albumin level into the definition of PR would improve its predictive value of subsequent outcome.

TH-PO749

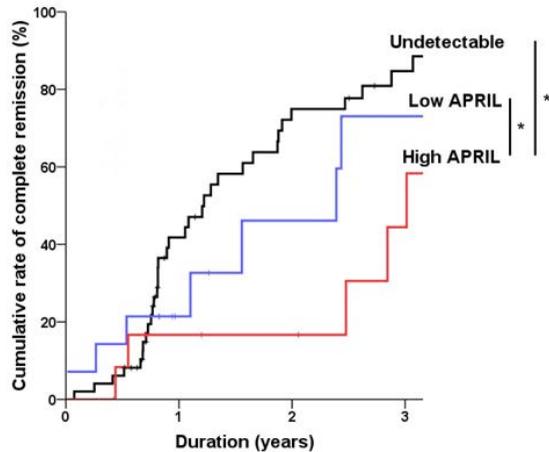
Clinical Implication of BAFF and APRIL in Membranous Nephropathy

Seung Seok Han, Eunjin Bae, Kwon Wook Joo, Yon Su Kim, Dong Ki Kim. *Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.*

Background: BAFF and APRIL have a role in B cell development. Additionally, these are related with several autoimmune diseases. However, the clinical implication of BAFF and APRIL remains unresolved in patients with membranous nephropathy (MN).

Methods: 84 patients with primary MN were recruited, and their plasma BAFF and APRIL levels at the time of diagnosis were compared with the data on patients with secondary MN ($n=13$) and healthy individuals ($n=111$). The time to complete remission was used as primary outcomes and the hazard ratios (HRs) by plasma BAFF and APRIL levels were calculated after adjustment of multiple variables.

Results: The plasma BAFF levels in primary MN (0.94 ± 0.26 ng/mL) were significantly higher than those of healthy individuals (0.54 ± 0.16 ng/mL) and lower than of secondary MN (1.59 ± 1.09 ng/mL). For the APRIL, a substantial number of primary MN patients ($n=51$) had undetectable plasma level. The APRIL levels of primary MN (0.73 ± 2.50 ng/mL) were similar to the levels of healthy individuals (0.54 ± 0.16 ng/mL), but lower than those of secondary MN (8.07 ± 25.68 ng/mL). The BAFF levels were positively associated with the auto-PLA₂ antibody titers, but the APRIL levels were not. The cumulative rates of complete remission were significantly different between APRIL groups (undetectable, low level, and high level) (Figure 1), in contrast to the similar remission rates between the BAFF tertile groups. Patients with high plasma APRIL attained the complete remission lower than patients with undetectable level: adjusted HR, 0.29 (0.089-0.921); $P=0.036$.



Conclusions: The present study first demonstrates the plasma levels of BAFF and APRIL and their predictability for outcome in patients with membranous nephropathy.

TH-PO750

The Clinical and Prognostic Significance of Segmental Glomerulosclerosis Among Patients with Idiopathic Membranous Nephropathy *Hala M. Kfoury, Sufia Husain, Abdulkareem Alsuwaida, Mohammed A. Al-Ghonaim, Saad S. Alobaili, Tariq Aljohani, Tameem Ashry, Jamal S. Al Wakeel. College of Medicine, King Saud Univ, Riyadh, Saudi Arabia.*

Background: Idiopathic membranous nephropathy (iMN) is a main cause of nephrotic syndrome in adults. In this study, we attempt to examine the relationship between segmental glomerular sclerosis in iMN and progression towards chronic kidney disease.

Methods: The study included 89 patients with iMN, followed over sixteen years, to evaluate the prognostic significance of glomerular segmental sclerosis in terms of renal survival. In the two groups (one with and one without segmental sclerosis), we analyze the various factors that are prognostic in iMN (eg. serum creatinine, proteinuria, etc.) and the histologic parameters.

Results: Segmental glomerulosclerosis was noted in 41 (46.1%) of 89 cases with iMN, representing cases from 57 (64.0%) males and 32 (36.0%) females. The prevalence of interstitial fibrosis and tubular atrophy did not contrast substantially between the two respective groups (3.38 ± 7.8 versus 1.22 ± 3.3 , $p=0.137$). Only IgM positivity among the sclerosis group, compared to the non-sclerosis group was statistically significant (48.8% versus 25.0%, $p=0.02$). The median serum creatinine was significantly different among the two groups of $101 \mu\text{mol/l}$ in cases with sclerosis vs. $92 \mu\text{mol/l}$ among cases without sclerosis, $p=0.059$. The baseline proteinuria recorded was 2.2 gm and 2.9 gm per day in the two respective groups, $p \text{ value}=0.9$. At last follow up, the median serum creatinine was similar among the two groups (median $90 \mu\text{mol/l}$ and $81 \mu\text{mol/l}$, respectively).

Conclusions: Our study revealed that segmental glomerulosclerosis was not associated with the severity of interstitial fibrosis. Although baseline serum creatinine was higher in patients with glomerulosclerosis at the time of biopsy, there was no impact on longterm outcome of the patients. Further studies are needed to outline the therapeutic regimen in iMN with segmental glomerulosclerosis.

TH-PO751

Clinical Features and Outcomes of Membranous Nephropathy with Crescents *Jia Wang,¹ Ping Zhu,² Zhao Cui,¹ Minghui Zhao.¹ ¹Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, Beijing, China; ²Renal Div, Dept of Medicine, The First College of Clinical Medical Science, China Three Gorges Univ, Yichang, Hubei, China.*

Background: Cases of membranous nephropathy with crescents have been reported, in the absence of lupus, HBV-associated glomerulonephritis, anti-glomerular basement membrane nephritis, or antineutrophil cytoplasmic antibody. Disease presentation and outcomes of these patients are unclear.

Methods: All patients with biopsy-proven MN, diagnosed from 2008 to 2014 and followed up, were enrolled retrospectively. Patients with ANCA, anti-GBM antibodies, lupus, malignancy or HBV infection were excluded. Clinical features and outcomes were compared between patients with crescentic MN and non-crescentic MN.

Results: In 401 consecutive patients with primary MN, 28 (6.9%) patients having crescent formation. All patients presented with proteinuria ($6.5 \pm 4.8 \text{ g/24 h}$) and hematuria. 21.4% of patients had declined eGFR ($<60 \text{ ml/min/1.73m}^2$) on biopsy. Glomeruli showed on average 4.9% (range, 2.2-16.7%) involvement by crescents. Tubular atrophy was more common in these patients (96.3% vs. 78.6%, $P=0.031$). 12 (42.9%) patients received immunosuppressive therapy, similar to those with non-crescentic MN (41.33%). Fewer patients achieved remission in those with crescentic MN (67.9% vs. 86.7%, $P=0.029$). Crescent formation was a risk factor for no remission of treatments ($RR=3.079$, $P=0.033$). Higher percentage of crescents in glomeruli was also susceptible for no remission

($RR=1.166$, $P=0.038$). During follow-up, more patients with crescentic MN presented with eGFR decline (10.7% vs. 1.3%, $P=0.031$). Crescent formation was a risk factor for worse renal outcome ($RR=10.24$, $P=0.046$).

Conclusions: MN patients with crescent formation showed inferior response to treatments and worse renal outcome during follow-up, although the baseline clinical characters were similar on biopsy. The crescent was a risk factor for poor prognosis of MN patients.

Funding: Government Support - Non-U.S.

TH-PO752

Prevalence of Cancer in Membranous Nephropathy Patients *Yasuyuki Nagasawa, Sayuri Kawada, Mana Yahiro, Yuki Morikami, Tomoko Kimura, Kiyoko Yamamoto, Aritoshi Kida, Masayoshi Nanami, Yukiko Hasuike, Takahiro Kuragano, Takeshi Nakanishi. Dept of Internal Medicine, Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.*

Background: Membranous Nephropathy is one of major primary glomerulonephritis. This disease was known to have high prevalence of cancer. Recent meta-analysis reported that estimated prevalence of cancer in membranous nephropathy patients was 10%[95%CI, 6.1-14.6] (Leeaphorn-N et al, Am J nephrol,2014). The aim of this study is to reveal the prevalence of cancer with image investigation information.

Methods: This study is retrospective cohort study. Among 720 cases who receive renal biopsy from 2000 to 2012 in Hyogo College of Medicine University Hospital, 73 membranous nephropathy patients were enrolled sequentially in this study. Exclusion Criteria is secondary membranous nephropathy induced by collagen diseases, such as Lupus nephritis. Information about cancer and image scanning was collected from medical records.

Results: Mean age was 60.2 ± 15.2 years old. Male was 49% and Female was 51%. Patients with smoking was 55% (Current 24%, Past 31%), and alcohol Drinking was 48%. Chest Xp and fecal occult blood examination were done for all patients. Gastroscopy was done for 20 cases (27%), abdominal CT was done for 33 cases (45%), and chest CT was done for 31 cases (42%) according to the risk factors. At renal biopsy, 6 patients had past history of cancers; larynx, uterine body, renal, epipharynx, and colon cancers (2 cases). 3 patients were diagnosed as cancer around renal biopsy; thyroid, gastric, and colon cancers. 7 patients were suffering from cancers after renal biopsy; lung renal, cervical cancer, breast, tongue, and colon cancers. The prevalence of all cancers (both at renal biopsy and after diagnosis of membranous nephropathy) was 20.8%. Prevalence of cancer in membranous patients seemed to be higher than Caucasian membranous cohort. The previous review reported that only 20% cancers were found at renal biopsy, although our result suggested 46% cancers were diagnosed at renal biopsy, probably because of high prevalence of advanced imaging check-up of cancers.

Conclusions: The prevalence of cancer in membranous patients was 20.8%.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

TH-PO753

Efficacy of Low-Dose Prednisone Treatment Combined with Mizoribine on Idiopathic Membranous Nephropathy and Nephrotic Syndrome *Yoshihiro Matsumoto, Yasushi Shimada, Youichi Nojima, Kimitoshi Shiratori. Nephrology and Dialysis, Shizuoka City Hospital, Shizuoka, Japan.*

Background: Idiopathic membranous nephropathy (IMN) patients with persistent high-grade proteinuria are at the highest risk for developing end-stage renal failure. We previously reported the effects of treatment with mizoribine followed by low-dose prednisone in 4 IMN patients. The purpose of the present study was to further assess the effects of this combined treatment in a larger study group.

Methods: Twenty-two patients with IMN and nephrotic-range proteinuria received combined treatment. Mizoribine was initiated at a dose of 150 mg/day, and 1-3 months later, 20 mg/day prednisone was added to mizoribine regimen. The dosage of prednisone and/or mizoribine was tapered according to the urinary protein-to-creatinine ratio (P/C). We evaluated patient responses for up to 36 months after initiation of combination therapy.

Results: Before treatment, patient urinary P/C ranged from 2.8 to 15.9 g/g. Although these values did not decrease during mizoribine monotherapy, all patients showed P/C decreases over the course of combination therapy. At 12, 24, and 36 months after combination therapy, 55% (12/22), 70% (14/20), and 79% (11/14) of patients attained complete remission, respectively. The 21 patients of 22 (95%) attained partial or complete remission at 12 months after combination therapy. Side effects including fracture were observed in 4 patients.

Conclusions: The addition of prednisone after mizoribine monotherapy can be beneficial for most of all IMN patients with nephrotic syndrome. The risks associated with immunotherapy can be decreased by initially prescribing mizoribine alone, which might act as a base for establishing therapy, followed by low-dose prednisone treatment.

TH-PO754

Response to Immunosuppressive Therapy in PLA₂R-Associated IMN and Non-PLA₂R-Associated IMN *Jia Wang, Qionghong Xie, Chuanming Hao. Div of Nephrology, Huashan Hospital, Shanghai, China.*

Background: According to the renal PLA₂R immunohistochemistry, iMN could be categorized into PLA₂R-associated and non-PLA₂R-associated iMN. We conducted a retrospective, multicenter cohort study of 99 patients to compare the effect of immunosuppressive therapy on PLA₂R-associated and non-PLA₂R-associated iMN patients.

Methods: 99 biopsy-proven iMN patients were collected from Huashan hospital and People's hospital of Wuxi in past 5 years. The iMN with positive PLA2R immunohistochemistry in kidney biopsies were designated as PLA2R associated MN. 79 of the 99 iMN patients were PLA₂R-associated iMN and 13 were non-PLA₂R-associated iMN. 49 patients were treated with prednisone plus CTX, and fifty with prednisone plus CNIs. 95% of the patients were on ACEI/ARB. The patients were followed for 15 months.

Results: The baseline characteristics between the PLA2R-associated and non-PLA2R-associated iMN was demonstrated in Table 1 (left part). In patients with non-PLA₂R-associated MN, the remission rate at 3-month was significantly higher than that in PLA₂R-associated group (table 1 right part). Relapses were observed in 8 patients of PLA₂R-associated group and none of non-PLA₂R-associated group.

	PLA2R (+) (n=78)	PLA2R (-) (n=13)	P		PLA2R (+) (n=78)	PLA2R (-) (n=13)	P
CTX%	47.4% (37/78)	61.5% (8/13)	0.346	3 month-remission	44.9%	76.9%	0.032
gender (M:F)	52:26	5:8	0.102	3 months-CR	2.6%	30.8%	0.003
age	53.81±14.64	53.54±17.52	0.953	6 month-remission	64.1%	76.9%	0.557
urine protein (g/24h)	5.51 (4.02, 7.72)	5.23 (2.34, 12.51)	0.829	6 months-CR	11.5%	46.2%	0.007
albumin (g/L)	19.45±5.05	21.58±9.07	0.423	9 month-remission	77.3%	91.7%	0.455
creatinine (μmol/L)	78 (61.65, 93.75)	68.6 (60, 132.5)	0.875	9 months-CR	24.2%	50.0%	0.140
cholesterol (mmol/L)	7.86±2.69	6.93±1.88	0.238	12month-remission	79.7%	100%	0.197
triglyceride (mmol/L)	2.1 (1.77, 3.21)	1.82 (1.57, 2.98)	0.434	12month-CR	27.1%	50%	0.222

Conclusions: The non-PLA₂R-associated iMN responded quicker to the immunosuppressive therapy compared with PLA₂R-associated iMN, and relapses were more frequent in PLA₂R-associated iMN. Non-PLA₂R-associated iMN may have a better response to immunosuppressive therapy.

Funding: Government Support - Non-U.S.

TH-PO755

Prevalence of Enhanced Granular Expression of Thrombospondin Type-1 Domain-Containing 7A in Glomeruli in Japanese Patients with Idiopathic Membranous Nephropathy Takamasa Iwakura,¹ Naro Ohashi,¹ Akihiko Kato,² Hideo Yasuda,¹ ¹Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; ²Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.

Background: Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults. Autoantibodies against M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) were reported as the primary causes of MN. Although PLA2R is a major pathogenic factor for idiopathic MN, the prevalence of MN patients seropositive for PLA2R in Japan is lower than in other countries. In this study, we conducted immunohistochemical analysis of the presence of THSD7A and PLA2R in renal specimens of MN patients to estimate the prevalence of THSD7A/PLA2R-related idiopathic MN in Japan.

Methods: All patients with the histologic diagnosis of MN in adults made in our institution between 1995 and 2015 were included in this study. Immunohistochemical analysis for THSD7A and PLA2R were performed to these patients, and samples showing enhanced granular staining along capillaries of glomeruli were recognized as histologically positive for THSD7A and/or PLA2R. We collected the clinical information and laboratory data at the time of biopsy in order to classify MN patients into primary and secondary, and in order to compare characteristics of patients with enhanced expression of THSD7A and that of PLA2R.

Results: Enhanced granular expression of THSD7A and PLA2R was detected in 9.1% and 52.7%, respectively, of the patients with idiopathic MN. Although none of patients with secondary MN displayed enhanced granular expression of THSD7A, 5.4% of them had enhanced granular expression of PLA2R.

Conclusions: The prevalence of enhanced granular expression of THSD7A in glomeruli in Japanese patients with idiopathic MN was higher than the prevalence of MN patients seropositive for THSD7A in USA and Europe. This higher prevalence of THSD7A-related MN is likely associated with the lower prevalence of PLA2R-related MN in Japan.

TH-PO756

PLA2R Autoantibodies and Glomerular PLA2R Deposit in Membranous Nephropathy: How to Evaluate the Roles They Played? Huazhang Qin, Wei-bo Le, Ming-chao Zhang, Caihong Zeng, Hao Chen, Qiang Ren, Da cheng Chen, Ke Zuo, Feng Xu, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Higher Glomerular PLA2R-Antigen deposit (GAg) rates compared with the serum Phospholipase A2 receptor-Antibody (SAb) positive rates were reported. However, the exact roles played by this two biomarkers remained unknown.

Methods: A total of 572 patients diagnosed iMN were included. Both SAb and GAg were detected. Fifty-two iMN patients received repeat renal biopsy were also included.

Results: In the 572 patients, 401 (70.1%) were SAb positive (SAb+) while 171 (29.9%) were SAb negative (SAb-). In SAb+ patients, the glomerular PLA2R-Antigen deposition (GAg+) was observed in 99.1% (397/401). Interestingly, the GAg+ was observed in 68.4% (117/171) SAb- patients. Patients with SAb manifested more severe proteinuria (3.9 g/24h vs 2.8 g/24h, P<0.001) and lower eGFR (104 ml/min.1.73m2 vs 110 ml/min.1.73m2, P=0.002) than patients without SAb. Further comparison between patients with SAb+/GAg+ and SAb-/GAg+ showed a similar profile (more severe clinical manifestation in patients with SAb). Patients with SAb+/GAg+ also showed lower chance of proteinuria remission and higher chance of renal function decline in the follow up when compared to patients with SAb-/GAg+. Changes of SAb and GAg were observed in patients with repeat renal biopsy, in 11 patients the SAb+ turned into SAb-, among them 1 patients failed to achieve remission, 7 patients achieved remission and 4 remitted during the interval but relapsed at the time of repeat biopsy. While the GAg+ turned into GAg- in only 3 patients, all achieved remission at the repeat biopsy. The proportion of GAg disappearance was lower than SAb (P=0.016).

Conclusions: The GAg deposit can be detected in a large proportion of SAb negative patients, which can be explained by the lag of GAg disappearance in the follow up. The SAb was more tightly correlated to disease activity, treatment response and prognosis than the GAg. We recommend adopting GAg deposit detection as a supplement to SAb in iMN diagnosing and keeping on monitoring SAb in the follow up.

Funding: Government Support - Non-U.S.

TH-PO757

Phospholipase A2 Receptor Autoantibody in Membranous Nephropathy Complicated with HIV Infection Weifeng Lin,^{1,2} Xin Zhang,¹ Jianing Li,¹ Hang Li,¹ Jianfang Cai,¹ Xuemei Li,¹ Yubing Wen,¹ Xuewang Li.¹ ¹Dept of Nephrology, Peking Union Medical College Hospital; ²Peking Union Medical College.

Background: When membranous nephropathy (MN) complicated with HIV-infection, it's difficult to discriminate the relationship between them. MN is idiopathic or secondly to HIV-infection? The therapy should cover MN, HIV or both? Although PLA2R autoantibody is a potential biomarker for the differential diagnosis of idiopathic and secondly MN, its role in MN complicated with HIV-infection is unknown.

Methods: 6 patients with biopsy-proven MN complicated with HIV-infection admitted to Peking Union Medical College Hospital from 2011 January to 2015 March were recruited in this study. 5 HIV-infection patients without nephropathy were selected as control group. Serum PLA2R autoantibody in all patients were detected by ELISA method. The serum samples of MN group were collected at renal biopsy. The medical records were retrospectively reviewed.

Results: The antibody was found in most patients with MN complicated with HIV-infection (5/6). However, the antibody in HIV-infection without nephropathy were all negative (5/5). The basic line of clinical data in 6 MN complicated with HIV-infection patients were as follows: all males, 24h-UP (12.62±6.65)g/d, serum albumin (19.16±5.49) g/L, and serum creatinine (81.7±30.17)mmol/L. Table1 shows antibody test results, treatments and renal outcomes in 6 MN patients. Table1 6 patients with MN complicated with HIV-infection.

Patient	NO.1*	NO.2	NO.3	NO.4	NO.5	NO.6
Nephrotic Syndrome	(+)	(+)	(+)	(+)	(+)	(+)
PLA2R antibody	(-)	(+)	(+)	(+)	(+)	(+)
Treatment	HAART ^b ACEI ^c GCS ^d	HAART ACEI GCS+ CsA ^e	HAART ACEI GCS+ CTX ^f	HAART ACEI	ACEI	HAART ACEI
Renal outcome	PR ^g	CR ^h	CR	PR	PR	SR ⁱ

* also had HBV infection. ^bhighly active antiretroviral therapy. ^cangiotensin converting enzyme inhibitors. ^dglucocorticoids. ^eCyclosporine A. ^fcyclophosphamide. ^g partial remission. ^h complete remission. ⁱ spontaneous remission before HAART and ACEI therapy.

Conclusions: MN complicated with HIV-infection seems to be two independent diseases if PLA2R autoantibody is positive. First line immunosuppressive therapy is likely necessary for MN complicated with HIV-infection if antibody is positive.

TH-PO758

Comparison of Outcomes Between Individuals with Pure and Mixed Lupus Nephritis: A Retrospective Study Nosayaba Enofe,¹ Anju A. Oommen,¹ Jason Cobb,¹ Jose E. Navarrete,¹ Demilade Adedinsowo,² Oluwatobiloba A. Osikoya,³ Helene B. Fevrier,⁴ Alton Brad Farris,⁵ Laura Plantinga,¹ Titilayo O. Ilori.¹ ¹Dept of Nephrology, Emory Univ School of Medicine, Atlanta, GA; ²Morehouse School of Medicine, Atlanta, GA; ³Lee Univ, Cleveland, TN; ⁴Dept of Epidemiology, Rollins School of Public Health, Emory Univ, Atlanta, GA; ⁵Dept of Pathology and Laboratory Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: Lupus nephritis (LN) is divided into six classes (ISN/RPS Class I to VI) but can occur as a mixture of two classes. Pure proliferative LN (PPLN) comprises Class III or Class IV only while mixed proliferative and membranous LN (MPLN) comprises combinations of Class III & V or Class IV & V. Our aims were to compare individuals with biopsy-proven PPLN vs. MPLN in terms of clinical presentation and outcomes of complete or partial remission at 2 years and end-stage renal disease (ESRD) and clinical predictors of outcomes.

Methods: A retrospective review of all adult (>18) LN patients (n=278; PPLN (n=60) and MPLN (n=96)) identified from a native renal biopsy registry at a hospital network performed January 2000-December 2011. We assessed associations of LN category (MPLN vs. PPLN) with: time to remission (define as ≥ 25% improvement in eGFR if baseline abnormal and urine protein creatinine ratio <0.5) and ESRD (defined using ICD-9 diagnosis code - 585.6 or the onset of chronic renal dialysis) using multivariable Cox proportional hazards analysis.

Results: The population was predominantly female (84.0%) and African American (71.8%), with a mean age of 33.4. Over follow-up (median, 1.5 years), using the PPLN group as the reference group, we did not find any associations between MPLN and time to remission (HR=0.13, 95% CI = 0.01-1.36) or ESRD (HR=0.30, 95% CI = 0.07-1.26). Baseline eGFR was significantly associated with time to remission (HR = 0.90, 95% CI = 0.84 - 0.98).

Conclusions: We found no significant differences in remission or progression to ESRD between patients with PPLN and MPLN. We, however, demonstrated that higher baseline eGFR at presentation were important factors in achieving remission in individuals with LN.

TH-PO759

Pure Class V Lupus Nephritis: Towards a Better Understanding of Lupus Membranous Nephropathy Compared to Its Proliferative Counterparts Fernanda Payan Schober, Keisha L. Gibson, Taewoo Lee, Caroline J. Poulton, Mary Anne Dooley, William Franklin Pendergraft. *UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC.*

Background: Class V lupus nephritis, also known as lupus membranous nephropathy, accounts for approximately 10-20% of patients with lupus nephritis. There is not a consensus on the best treatment for isolated class V lupus nephritis, so providers often turn to the proliferative lupus nephritis and idiopathic membranous nephropathy (IMN) literature to extrapolate treatment approaches and outcomes. Here we compare clinical data between patients with lupus membranous, proliferative lupus nephritis and IMN.

Methods: Clinical and treatment data for lupus membranous patients were extracted from electronic medical records starting at the time of diagnosis until date of chart review.

Results: Patients with lupus membranous resembled the lupus nephritis population more than the IMN population as they were more likely to be African American women in the fourth decade of life. At presentation, lupus membranous patients had preserved kidney function but significant proteinuria, much like patients with IMN. Almost all of these patients (94%) received immunosuppression. At mean follow up of 7.1 years, the mean serum creatinine remained 1.1 mg/dl, but proteinuria improved to a mean of 1.6 gram/day.

	Lupus Membranous (n=41)	Lupus Nephritis (n=601)	Idiopathic Membranous (n=558)
Female:Male (%)	37:4 (90:10)	510:90 (85:15)	216:342 (39:61)
Age (mean)	34 ± 16	34 ± 16	53 ± 15
Ethnicity (%)			
Caucasian	3 (7)	200 (33)	412 (74)
African American	35 (85)	297 (49)	92 (16)
Asian	1 (2)	8 (1)	1 (0.1)
American Indian	1 (2)	9 (1)	1 (0.1)
Other	1 (2)	25 (4)	12 (2)
Unknown	0 (0)	62 (10)	38 (7)
Serum Creatinine (mg/dl)	1.1 ± 0.6	1.56 ± 2.3	1.4 ± 1.3
Serum Albumin (mg/dl)	3.2 ± 4	1.5 ± 1.8	2.6 ± 0.8
Proteinuria (gm)	8.4 ± 13	4.3 ± 26	8.2 ± 16

Conclusions: Patients with lupus membranous make up a substantial portion of patients with lupus nephritis. They present with significantly more proteinuria than patients with proliferative lupus nephritis, but have less kidney impairment. There's a clear need for more prospective multi-center randomized controlled studies to determine the most effective treatment in this population.

Funding: NIDDK Support

TH-PO760

Necrotizing Glomerular Lesions Portend a Worse Prognosis for Patients with Lupus Nephritis Fernanda Payan Schober,¹ Keisha L. Gibson,¹ Mary Anne Dooley,¹ Elizabeth R. Blyth,¹ Caroline J. Poulton,¹ Harsharan Kaur Singh,² Volker Nickleit,² William Franklin Pendergraft.¹ ¹UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC; ²UNC Pathology, UNC Chapel Hill, Chapel Hill, NC.

Background: Necrotizing glomerular lesions on kidney biopsy are uncommonly found in patients with lupus nephritis (LN) and are similar in appearance to those lesions found in patients with ANCA glomerulonephritis. The presence of these lesions portends a worse prognosis and has been reported previously to be more common in patients of African descent¹. Here we describe the clinical and histologic features of 48 patients with lupus nephritis and necrotizing glomerular lesions on native kidney biopsy.

Methods: Patients with lupus nephritis who had necrotizing and crescentic lesions were identified from the UNC Division of Nephropathology database. Clinical, histologic, treatment, and long-term outcome data were obtained from the electronic medical record.

Results: Demographic and histologic data are shown in the following table. Most notably, these patients were predominantly African American women with class IV lupus nephritis high overall disease activity.

	Tuft Necrosis (n=48)
Female	41 (87%)
Male	7 (14%)
Ethnicity	
Caucasian	11 (23%)
African American	32 (67%)
Hispanic	3 (6%)
Asian	1 (1%)
American Indian	1 (1%)
Age	34 ± 12
Serum creatinine (mg/dl)	1.64 ± 1.3
Proteinuria (gm)	3.71 ± 3.1
LN Histologic class	
II	2 (5%)
III	4 (5%)
IV	24 (56%)
V	3 (7%)
Mixed	10 (23%)
Activity Index	10.9 ± 3.6
Chronicity Index	3.5 ± 2.8
ESLEDAI	11.1 ± 9.6

Conclusions: This cohort represents one of the largest of its kind in the literature to date. Necrotizing lesions are more characteristic of pauci-immune ANCA vasculitis, but have been described in patients with lupus nephritis as well. This rare variant is an understudied glomerular disease that portends a poor prognosis with an increased risk of progression to ESKD. There is a need for prospective multi-center treatment studies to determine durable therapeutic avenues. †Korbett, et al. Severe lupus nephritis: Racial differences in presentation and outcome. *JASN*. 18:244-254.2007.

Funding: NIDDK Support

TH-PO761

Membranous Lupus Nephritis: Immunoglobulin Deposits and Clinical Correlations Eduardo J. D. de Sa Carneiro Filho, Alcino Gama, Leonardo Abreu Testagrossa, Denise M. Malheiros, Luis Yu, Cristiane B. Dias, Leticia Jorge, Viktoria Woronik. *Nephrology Div, Univ of São Paulo, São Paulo, Brazil.*

Background: Lupus nephritis histological hallmark, mostly in proliferative classes, is a “full house” (FH) pattern of immunoglobulin deposition and complement. However, Haas showed that membranous lupus nephritis (MLN) depicted this pattern only in 65% of the patients. The importance of FH deposition in MLN disease is still a matter of debate. It remains to be determined association between immunoglobulin deposition with clinical disease aggressiveness or transformation into proliferative forms.

Methods: All MLN patients submitted to kidney biopsies from July 1999 to August 2007 were included and biopsy tissue was studied by light microscopy and immunofluorescence. Patients were classified according to immunoglobulin glomerular capillary wall deposition in rich (rIF), with two or more deposited immunoglobulins, and poor (pIF) with a single and exclusive IgG deposition. Clinical and laboratorial data were collected at baseline, after one year and at the end of follow-up. Treatment was decided based on literature protocols.

Results: We included 15 patients in pIF group and 46 in rIF. At baseline, groups were similar regarding age, complement level, ANA, anti-DNA and proteinuria. Interestingly pIF was significantly associated with a lower eGFR at baseline that persisted after one year follow-up. At the end, the pIF showed a not significant tendency to lower eGFR.

	rIF	pIF	p
N	46	15	
Age	33±10	34±12	
MDRD Baseline	96±34	78±40	0.04
MDRD after 1 year	103±32	76±40	0.01
MDRD Final	80±39	63±33	ns
PTN Baseline (g/day)	4.6±3.6	4.4±5.7	ns
PTN Final (g/day)	1.2±1.8	2.1±3.8	ns
C3 (mg/dL)	85±32	96±52	ns
Hematuria Baseline	39%	46%	ns
ACLIgG Baseline	54%	71%	ns
ACLIgM Baseline	45%	64%	ns
Mesangial Hypercellularity	76%	53%	ns
Immunosuppression			
Pred	22%	50%	ns
Double	78%	50%	ns

Conclusions: We found 25% of MLN patients with only one deposited immunoglobulin. The poor IF group compared to rich IF showed lower MDRD at baseline and even after one year. Studies are needed to elucidate the role of different patterns of deposits in the pathogenesis of MLN.

TH-PO762

Segmental versus Global Subclasses of Proliferative Lupus Nephritis: Clinical Correlations Eduardo J. D. de Sa Carneiro Filho, Alcino Gama, Mariana Pin de Andrade, Beatriz Holanda, Leonardo Abreu Testagrossa, Denise M. Malheiros, Luis Yu, Cristiane B. Dias, Leticia Jorge, Viktoria Woronik. *Nephrology Div, Univ of São Paulo, São Paulo, Brazil.*

Background: The International Society of Nephrologists and Renal Pathology Society classification of lupus nephritis proposes a subclassification of proliferative forms into segmental (S) and global (G). Data comparing renal outcomes between these two subclasses is controversial and pathogenesis also seems to differ (Bariaty J, 2005). We aimed to compare histopathology with clinical correlations.

Methods: Seventy-one biopsy-proven patients with proliferative (classes III or IV) lupus nephritis data were retrospectively analyzed. Twenty-nine of them were classified as global and 42 as segmental. All procedures were performed in one single center between 2004 and 2014.

Results: All patients received induction therapy with steroids plus either intravenous cyclophosphamide monthly pulses or daily oral mycophenolate mofetil. Although there was no difference in age, eGFR and hemoglobin levels at baseline (see *table*), after a median follow-up of 3.6 years the global subgroup had worse renal outcome (final eGFR 59.6 ± 37.6 vs 78.9 ± 28.4, p 0.02). During follow-up, there was also a tendency for faster eGFR recovery rate in segmental subgroup after treatment (5.2 vs 1.8 ml/min/year, p 0.2). Interestingly, the prevalence of males in global subgroup was significantly higher (20% vs 4%, p 0.03).

	Global	Segmental	p
N	29	42	
Baseline features			
%Male	20%	4%	0.03
Age (y)	31.8±12	31.5±9	ns
Hb (mg/dL)	10.9±1.4	11±1.1	ns
MDRD Baseline (ml/min/1.73m ²)	55.2±26	63.9±27	ns
Follow-up features			
Follow-up (y)	3.63	3.62	ns
MDRD Final (ml/min/1.73m ²)	59.6±37.6	78.9±28.4	0.02
MDRD Delta per year	+1.8±2.3	+5.2±2.9	0.2

Conclusions: In global compared to focal proliferative lupus nephritis patients: male sex prevailed and renal function decreased on 3.6 years follow-up in spite of similar MDRD on baseline. Prospective studies are necessary to determine if histological pattern is relevant to guide the clinician's therapy choice.

TH-PO763

Renal Pathological Classification in Lupus Nephritis: What Else We Can Tell? Yang Jing, Dandan Liang, Haitao Zhang, Zheng-zhao Liu, Wei-bo Le, Minlin Zhou, Weixin Hu, Caihong Zeng, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: To observe the discrepancy between class III and class III+V, between class IV and class IV+V, and between subclass IV-S and IV-G on clinicopathological features and renal outcomes and explore the pathological lesions associated with poor renal outcomes in patients with different classes.

Methods: The records of all adult patients with biopsy-proven proliferative lupus nephritis followed for at least 1 year were reviewed. All patients were pathologically classified according to the 2003 ISN/RPS classification of lupus nephritis and each pathological lesion was semiquantitatively scored.

Results: Patients with class III+V (class IV+V) presented with more severe proteinuria and chronic pathological lesions and milder acute pathological lesions than patients with class III (class IV); patients with subclass IV-G presented with more severe hypertension, proteinuria and hypocomplementemia, lower ANCA positivity rate, more severe glomerular cell proliferation and hyaline deposit, and milder fibrinoid necrosis and crescent than patients with subclass IV-S. The renal outcomes between patients with class III and class III+V, between class IV and class IV+V, and between subclass IV-S and subclass IV-G were not different respectively. Global glomerulosclerosis, cellular crescent, fibrous crescent, glomerular cell proliferation, tubular acute injury, interstitial inflammation and TMA were predictors for ESRD.

Conclusions: LN patients with proliferative lesions combined with membranous lesions presented with both clinicopathological characteristics of the two types of lesions, but their renal outcomes were not different from patients with pure proliferative lesions. Patients with subclass IV-S and subclass IV-G LN had their own clinicopathological characteristics respectively, but the division of class IV into the two subclasses was not meaningful for predicting renal outcomes. In addition to glomerular lesions, tubulointerstitial and vascular lesions were also predictors for poor renal outcomes.

Funding: Government Support - Non-U.S.

TH-PO764

Ability of Spot Urine Protein/Creatinine Ratio (Spot PCR) to Correctly Identify the Proteinuria Endpoints of Complete Remission (CR), Partial Remission (PR), and Treatment Failure (TF) as Determined by 24 Hour Urine PCR (24 PCR): Experience of the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study (ACCESS) Ganesh B. Shidham,¹ Daniel J. Birmingham,² Brad H. Rovin,³ Lee A. Hebert,⁴ *¹Div of Nephrology, OSUWMC, Columbus, OH; ²Div of Nephrology, OSUWMC, Columbus, OH; ³Div of Nephrology, OSUWMC, Columbus, OH; ⁴Div of Nephrology, OSUWMC, Columbus, OH.*

Background: Spot PCR is an inherently highly variable estimate of 24 hour proteinuria magnitude, compared to 24 PCR (Ann Rheum Dis, 73, 475, 2014). So, it is likely that using spot PCR rather than 24 PCR to guide management increases the risk of management error. The present work is the first to rigorously test this hypothesis. ACCESS is a prospective randomized phase 2 trial of Abatacept or placebo added to the Euro-Lupus regimen of cyclophosphamide and prednisone followed by azathioprine and low dose prednisone. A unique feature of ACCESS was concurrent testing for spot PCR (monthly) and 24 PCR (each three months). ACCESS proteinuria endpoints were CR, PR, and TF assessed at 6 months and 12 months of follow-up (Arth Rheum 66, 3096, 2014).

Methods: Evaluable data (spot PCR measured within one month of the 24 PCR) was present at six months in 100 patients, and at twelve months in 54 of the 100 patients. Spot PCR was deemed correct if it was concordant with the 24 PCR determination of whether CR, PR, or TF was present, and deemed incorrect if discordant with the 24 PCR determinations of whether CR, PR, or TF was present.

Results: At 6 month follow up, spot and 24 PCR were concordant in 36 CR, 25 PR, 10 TF, and discordant in 10 CR, 11PR, and 8 TF. At 12 month follow up, spot and 24 PCR were concordant in 36 CR, 11 PR, and 2 TF, and discordant in 4 CR, 2 PR, 0 TF. Totals: Concordant 120, Discordant 35. P < 0.001 (null hypothesis that concordance is 95% is rejected).

Conclusions: The error rate of spot PCR in identifying ACCESS proteinuria endpoints (defined by 24 PCR) was 23%. Proteinuria endpoints in LN trials are broad targets and mainly involve low level proteinuria. This minimizes the impact of spot PCR variability.

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TH-PO765

Induction Treatments for Proliferative Lupus Nephritis: A Network Meta-Analysis Suetonia Palmer,¹ David J. Tunnicliffe,² Allison Tong,² Dimitris Mavridis,³ Jonathan C. Craig,² Marcello Tonelli,⁴ David W. Johnson,⁵ Giovanni F.M. Strippoli.^{2,6} *¹Univ of Otago Christchurch; ²Univ of Sydney; ³Univ of Ioannina; ⁴Univ of Calgary; ⁵Univ of Queensland; ⁶Univ of Bari.*

Background: Intravenous cyclophosphamide has been standard care for inducing remission among patients with proliferative lupus nephritis (class III and IV). More recently, several agents have been trialed, however, given the numerous treatment options and head-to-head trials, there is uncertainty about the comparative effectiveness of all available treatment options.

Methods: Immunosuppressive treatments to induce remission of kidney disease among patients with proliferative lupus nephritis were all compared using network meta-analysis of parallel-group randomized controlled trials. Outcomes were complete disease remission, treatment failure, all-cause mortality, end-stage kidney disease, major infection, alopecia, ovarian failure and malignancy. Effect sizes for treatments were calculated using random-effects network meta-analysis and compared to intravenous cyclophosphamide (referent). Trials were critically appraised using Cochrane risk of bias.

Results: 47 studies involving 3510 patients were eligible. Mycophenolate mofetil was superior to intravenous cyclophosphamide for inducing disease remission (network odds ratio 1.60, 95% CI 1.07-2.41), and resulted in lower risks of treatment failure (0.48, 0.26-0.87), and alopecia (0.22, 0.13-0.39). Mycophenolate mofetil had uncertain risks of death (OR 1.14, 0.49-2.65), major infection (1.30, 0.88-1.92) and ovarian failure (0.48, 0.11-2.08) versus intravenous cyclophosphamide. Comparative effects of other treatments including azathioprine and calcineurin inhibitors alone or in combination were uncertain. Information for end-stage kidney disease and malignancy endpoints for all treatments was sparse. Treatment effects were generally consistent within networks. Methodological reporting in trials was frequently unclear.

Conclusions: Mycophenolate mofetil is more effective than intravenous cyclophosphamide for induction treatment of proliferative lupus nephritis.

TH-PO766

A Systematic Review on Tacrolimus Treatment in Lupus Nephritis
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Background: Recently, 2 large randomized controlled trials (RCTs) have been published on the efficacy of tacrolimus (TAC) in Asian LN patients. Both trials used different treatment regimens and efficacy was not consistent between the trials. Therefore, the role of TAC in the treatment of LN remains unclear. Thus, we performed a systematic review on TAC treatment for LN.

Methods: We searched multiple databases for all human studies investigating TAC treatment in LN. Then studies were selected on clinical relevance and results were analysed on renal response and adverse events.

Results: We found 26 clinical studies from which data were extracted from all controlled studies: 6 RCTs and 3 case-control studies involving a total of 888 patients. As induction treatment, TAC with steroids resulted in 82% responders of which 56% complete responders (CR). Induction with steroids, mycophenolate (MMF) and TAC resulted in 85% responders, of which 46% CR. Data from 1 RCT performed with TAC in combination with steroids as maintenance treatment, resulted in 100% responders of which 56% CR. Generally, control patients receiving induction treatment with cyclophosphamide achieved 66% response of which 29% CR. Those receiving induction treatment with MMF achieved 76% response of which 53% CR. Overall infections were observed in 26% of TAC treated patients compared to 26% of control patients treated with cyclophosphamide and 29% in MMF treated control patients. A rise in serum creatinine was observed in 5% of all TAC treated patients compared to 2% in the cyclophosphamide control group and 0% in the MMF control group.

Conclusions: This systematic review suggests that TAC-based treatments can achieve comparable renal responses in LN as conventional regimens. Currently, limitations of the available studies are the heterogeneity of TAC-based regimens, lack of studies in non-Asian LN patients and lack of long-term safety data. Altogether, these data warrant further RCTs on TAC-based regimens for LN. At this time, TAC can only be advised as consideration in difficult LN patients, such as therapy-refractory patients (especially if severe proteinuria is present) and in preparation or during pregnancy.

TH-PO767

Predicting Chronic Kidney Disease (CKD) in Lupus Nephritis (LN)
Ana Malvar,¹ Valeria Gabriela Alberton,¹ Bruno Jorge Lococo,¹ Haikady Nagaraja,² Brad H. Rovin.³ ¹Hospital Fernandez, Buenos Aires, Argentina; ²Ohio State Univ, Columbus, OH; ³Ohio State Univ Wexner Medical Center and the CKD Biomarker Consortium.

Background: Early identification of LN patients likely to develop CKD may permit therapy to be adjusted and CKD to be avoided. Clinical and histologic parameters measured after completing induction therapy were associated with long-term kidney outcomes in a cohort of LN patients to define predictors of new CKD.

Methods: Patients (n=69) with biopsy-proven class III/IV LN were induced with steroids and MMF (53%) or cyclophosphamide (44%) for 6 months, had repeat kidney biopsy (biopsy 2, 6.6±0.7 months), and were put on maintenance therapy. Long-term (median 73 months) follow-up was available on 87% of the cohort. Multivariate linear regression was used to develop a predictive model for future serum creatinine (SCR) based on clinical and histologic variables obtained after induction.

Results: No difference was seen in CKD at last follow-up among patients who did or did not achieve a complete clinical renal response after induction (19% vs 18.4%, respectively). Among patients with complete histologic renal remission after induction, 36% had a final SCR of 1.3-2.9 mg/dl. There was no relationship between the NIH activity index at biopsy 2 and long-term kidney function. However, the median NIH chronicity index (CI) at biopsy 2 of patients who developed CKD was 6 (range 2-8) compared to 4 (range 0-7) in patients who did not develop CKD (p<0.02). Regression analysis showed a significant linear correlation between CI ≥ 4 at biopsy 2 and log(SCR) at long-term follow-up (R²=0.36, p < 0.0001). In multivariate analysis CI and SCR at biopsy 2 were independent predictors of long-term SCR (R²=0.48, p < 0.0001). For a given level of SCR at biopsy 2, a 1 unit increase of CI in the range of 4-8 corresponded to a 20% increase in last SCR.

Conclusions: Neither clinical nor histologic remission after induction predicts long-term renal function in LN. However, the combination of SCR and chronic damage on kidney biopsy after induction accounts for 48% of the long-term variability of renal function in those patients who reach a threshold level (CI=4) of chronic kidney damage.

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TH-PO768

Clinical and Histologic Remission in Class IVG and IVS Lupus Nephritis (LN) After Induction Therapy Ana Malvar,¹ Bruno Jorge Lococo,¹ Valeria Gabriela Alberton,¹ Diego Morales,¹ Brad H. Rovin.² ¹Hospital Fernandez, Buenos Aires, Argentina; ²Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: The ISN/RPS classification of LN distinguishes class IV with predominantly segmental lesions (IVS) from class IV with global (IVG) lesions. It has been suggested that IVS may have a lower remission rate than IVG, possibly because it is more like a vasculitis than IVG. However several studies found no significant difference in long-term kidney survival between these subclasses. We examined differences in histologic and clinical remissions between IVG and IVS in our LN cohort with serial kidney biopsies.

Methods: SLE patients (n=43) were biopsied at first presentation of kidney involvement (Bx1) and again at 6 months after completing induction therapy (Bx2). Class IVG and S patients were treated identically with steroids plus MMF or cyclophosphamide. NIH activity (AI) and chronicity (CI) indices, proteinuria and serum creatinine (SCR) were compared. Complete clinical response (CCR) was defined as normal SCR and proteinuria < 500 mg/d. Complete histologic remission was defined as an AI=0 at Bx2.

Results: Clinical outcomes and histologic data are shown in the Table. All patients were ANCA negative. Final SCR and proteinuria were determined after a mean follow-up of 54±7 months. Only 4 patients were lost to long-term follow-up.

Bx1	CRR Bx2	Final SCR ≤1 (mg/dl)	Final Proteinuria (g/d)	AI Bx1	AI Bx2	CI Bx1	CI Bx2
IVG (n=33)	39%	87%	0.32± 0.24	10.3± 2.9	3.7± 2.8	3.5± 1.9	4.9± 1.9
IVS (n=10)	80%	89%	0.26± 0.19	8.5± 2.2	0.1± 0.3	2.6± 1.8	4.4± 0.7
P (IVG vs IVS)	0.034	1.00	0.43	>0.05	<0.05	>0.05	>0.05

Conclusions: Class IVS LN has an excellent early clinical and histologic response to standard-of-care LN induction therapy. Class IVG takes longer to respond, but over time there are no differences in long-term renal outcomes between Class IVG and IVS LN as assessed by SCR and proteinuria. This suggests that these subclasses may be treated similarly. These results also raise the possibility that class IVS patients who have complete clinical and histologic remission after induction may do well with an abbreviated course of maintenance therapy.

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TH-PO769

Complete Remission Rate and Outcome in Severe Lupus Nephritis: The Impact of Baseline Serum Creatinine Stephen M. Korbet, William Luke Whittier, Edmund J. Lewis. Rush Univ Medical Center, Chicago, IL.

Background: A complete remission (CR) in severe lupus nephritis (SLN) is associated with a favorable long-term outcome. Numerous factors including level of serum creatinine (SCR) at baseline have been shown to impact on CR rate and outcome. We assess the impact of baseline SCR on CR rate and outcome in SLN.

Methods: We evaluated the 86 adult patients in the prospective, controlled trial of plasmapheresis in SLN and compared them based on SCR level at baseline (£1.0, 1.01-1.5, 1.51-2.0, 2.01-3.0 and >3.0 mg/dl; n= 22, 23, 16, 12, 13 respectively). The CR rate (defined by a serum creatinine (SCR) of ≤ 1.4 mg/dL and UPro of £0.33 g/day) and long-term outcomes (stable renal function, dialysis and death) were compared. Pts were followed for 121±64 mo.

Results: Baseline clinical features (age, gender, race and UPro) were similar among the groups. All pts had ISN/RPS class IV lesions and while the activity index was similar among the groups, the chronicity index (2 vs 3 vs 3 vs 5 vs 5, respectively, P 0.007) was significantly higher with increasing levels of SCR. At follow-up, CR rates (86% vs 52% vs 19% vs 25% vs 0, respectively, P <0.0001) were significantly higher and occurred in a shorter period of time (6 vs 12 vs 23 vs 18 mo, respectively, P 0.33) in pts with lower levels of SCR. Pts with a baseline SCR of £1.0 mg/dl were >16 times as likely (odds ratio, 16.2; 95% confidence interval, 4.2-61.5) to attain a CR and >6 times as likely (odds ratio, 6.1; 95% confidence interval, 1.9-18.6) to have stable renal function at last follow-up compared to pts with a SCR >1.0 mg/dl. The 15-yr renal survival (76% vs 57% vs 48% vs 25% vs 10%, respectively, P <0.0001) and patient survival without ESRD (76% vs 40% vs 42% vs 25% vs 8%, respectively, P <0.0001) was greatest in the patients with a SCR of £1.0 mg/dl at baseline.

Conclusions: The CR rate and outcome in SLN are significantly affected by baseline serum creatinine. The CR rate is highest and long-term prognosis most favorable in pts with a baseline SCR £1.0 mg/dl; the group with the least amount of chronic disease on biopsy. This emphasizes the importance of early diagnosis and treatment in pts with SLN.

TH-PO770

Urine Adiponectin Isoforms and Kidney Lesions in Lupus Nephritis (LN)
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Background: Human adiponectin isoforms exert different effects on inflammation. Urine adiponectin is increased at LN flare, but the relationship between adiponectin isoforms and kidney lesions in LN has not been studied.

Methods: Urine and plasma total and high molecular weight (HMW) adiponectin isoforms were measured by specific ELISAs in samples from 39 normal controls and 97 biopsy-diagnosed LN patients. Urine adiponectin levels were normalized and log-transformed, and then examined for associations with histologic lesions on kidney biopsy by ANOVA, nonparametric Wilcoxon ranked-sum testing and multiple linear regression analysis.

Results: The HMW to total adiponectin ratio was increased in plasma (p=0.022) and urine (p=0.0004) of LN patients compared to controls. Total and HMW adiponectin levels were highly correlated within the plasma (R²=0.91, p < 0.0001) and urine (R²=0.64, p < 0.0001) in LN, but between plasma and urine only HMW adiponectin showed a correlation, and this was minor (R²=0.21, p<0.037). Urine adiponectin levels increased with the severity of ISN/PRS class. The highest total and HMW urine adiponectin levels were found in patients who had combined class III or IV + V LN. Using urine HMW adiponectin levels to differentiate between control and LN patients, and between single and combined LN classes, receiver-operating characteristic analysis showed areas under the curve of 0.96 and 0.85, respectively. Urine HMW adiponectin was significantly increased when glomerular proliferation, cellular crescents or interstitial inflammation were present on the biopsy, and HMW adiponectin correlated with the biopsy activity index (R²=0.31, p < 0.0001), but not chronicity index. Using HMW adiponectin plus urine hemopexin plus serum creatinine, an equation to predict biopsy activity index was constructed with a R²=0.46.

Conclusions: Urine adiponectin isoforms increase with the severity of active kidney lesions in LN. The increase in urine adiponectin is not simply a reflection of changes in systemic adiponectin, and may be due to intra-renal processing.

Funding: NIDDK Support

TH-PO771

Significance of Serum Cystatin C as a Biomarker for Clinical Practice in Patients with Lupus Nephritis
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Background: Serum Cystatin C (sCysC) as a novel biomarker of renal function has been studied in many primary glomerular diseases. However, sCysC was barely reported in lupus nephritis (LN). We aim to compare the changes of sCysC and traditional biomarkers in LN patients.

Methods: 106 patients with LN proven by renal biopsy were studied. sCysC, serum creatinine (sCr), BUN, 24 hr total urinary protein (uTP), serum albumin (sAlb), systemic lupus erythematosus disease activity index (SLEDAI), C3, C4, IgG, ANA, DsDNA, C-reactive protein (CRP), and ESR were examined before and 1, 3, 6, 12, 24 months after treatment with steroid and immunosuppressants. estimated glomerular filtration rate (eGFR) was calculated by EPI-sCysC, EPI-sCr, and EPI-sCysC + sCr. The strength of correlation was compared between sCysC and sCr with uTP, sAlb, SLEDAI, and CRP before and after treatment.

Results: sCysC and eGFR (EPI-sCysC+sCr) showed stronger correlation with uTP, sAlb, SLEDAI, and CRP before the treatment (table). During treatment, a similar trend was seen in sCysC and eGFR (EPI-sCysC). sCysC also showed a better statistical p value than sCr/BUN in response to treatment with steroid plus either all kinds of immunosuppressants or cyclophosphamide.

Index	sCysC	sCr	BUN	eGFR (EPI-sCysC)	eGFR (EPI-sCr)	eGFR (EPI-sCysC+ sCr)
uTP r (p value)	0.25 (p= 0.03)	0.16 (p= 0.097)	0.24 (p= 0.012)	-0.23 (p= 0.06)	-0.11 (p= 0.29)	-0.31 (p= 0.014)
sAlb r (p value)	-0.44 (p< 0.0001)	-0.28 (p= 0.004)	-0.29 (p= 0.0012)	0.40 (p= 0.0008)	0.17 (p= 0.08)	0.47 (p< 0.0001)
SLEDAI score r (p value)	0.41 (p= 0.0004)	0.29 (p= 0.003)	0.36 (p= 0.0001)	-0.42 (p= 0.0004)	-0.14 (p= 0.16)	-0.45 (P= 0.0001)
CRP r (p value)	0.28 (p= 0.02)	0.25 (p= 0.012)	0.10 (p= 0.31)	-0.25 (p= 0.046)	-0.14 (p= 0.19)	-0.26 P= 0.036

Conclusions: sCysC and eGFR based on sCysC might be useful early biomarkers to diagnose LN and better to monitor the treatment of LN. sCysC will likely help in clinical decision making for early intervention and the timing of reducing key treatments. Prospective study is needed to investigate the effect of early treatment based on sCysC increase (sCr normal) in large cohort of LN patients.

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TH-PO772

Neutrophil Modular Blood Transcriptional Signature Is Associated with Lupus Nephritis and Its Severity in SLE
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Background: Lupus nephritis (LN) is a severe complication of SLE. The aim of this study was to assess the link between blood transcriptional signatures and LN, comparatively with other pathological conditions associated with renal injury.

Methods: 102 patients were included: 62 SLE patients, 40 controls with various conditions (10 with crescentic GN due to ANCA-associated vasculitis (AAV), 15 with severe bacterial sepsis, 15 with non-proliferative glomerular diseases), and their matched healthy controls. SLE samples were split in those at the time of: a biopsy-proven active LN (group 1, n=24); an extra-renal flare (group 2, n=11); a clinically quiescent visit (group 3, n=34). Microarray data were generated using Illumina beadchips and analyzed using modular repertoire analyses.

Results: Modular repertoire analysis in SLE patients revealed, in addition to the activation of IFN-related modules, a strong upregulation of M5.15, a module of 24 transcripts annotated "neutrophil". There was no correlation between M5.15 and SLEDAI, anti-dsDNA level or IFN modules activity. M5.15 was strongly associated with active LN (p=0.009), but not with non-renal manifestations. The neutrophil modular signature was present in 67%, 18% and 47% of patients from group 1, 2 and 3 respectively. In group 2 and 3, its presence was associated with a past history of LN or the occurrence of LN during the follow-up. M5.15 was correlated with acute renal failure (p=0.03) and serum albumin (p=0.01). In group 1, the median value of M5.15 was higher in patients with proliferative than non proliferative LN (66.7 vs 18.8 %, p=0.04). AAV and sepsis patients shared the neutrophil signature observed in SLE, but displayed no IFN signature, while those with non-proliferative GN had none of these signatures.

Conclusions: Modular repertoire analysis demonstrates that neutrophil signature is correlated with occurrence and severity of LN in SLE. This result could allow the design of new biomarkers in LN.

TH-PO773

Anticoagulation and Longterm Outcomes in Patients with Renal Artery Stenosis and Antiphospholipid Syndrome
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Background: Our previous data showed renal artery stenosis (RAS) is more prevalent in antiphospholipid syndrome (APS) (26%) compared to the general hypertensive population (8%), and anticoagulation with INR>=3 was associated with initial reduction of chronic kidney disease (CKD) and hypertension.

Methods: We identified 37 patients with RAS and APS fulfilling Sapporo criteria: anticardiolipin IgG/IgM titer>40 units or >99th percentile (or +lupus anticoagulant) on >=2 occasions >=6 weeks apart AND vascular thrombosis (or pregnancy morbidity). RAS was diagnosed by magnetic resonance angiography (MRA).

Results: 15 patients had APS alone and 22 APS associated with autoimmune conditions (13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37 (83.8%) were female and median follow-up was 10.4 years. 25/37 (67.6%) had previous thrombosis. 7/37 (18.9%) had bilateral RAS, 3 artery occlusion. 6/37 (16.2%) had coeliac stenosis. Recanalization of RAS occurred after hydroxychloroquine in 3/37 and 9/37 (24.3%) underwent angioplasty +/-stenting. MRA was repeated in 11/37 (29.7%) after 2 years. 23/37 (62.2%) were anticoagulated, with 9/37 (24.3%) on antiplatelet therapy. 13/37 (35.1%) received hydroxychloroquine, 10/22 (45.5%) immunosuppressives and 18/37 (48.6%) antihypertensives. 9/37 (24.3%) died after a median of 10 years since RAS diagnosis. 21/37 (56.8%) developed CKD: 6 endstage renal failure (ESRD) and 15 with median eGFR 39 ml/min.

Patient Group	CKD	ESRD	Death
Anticoagulation(23)	15/23	4/23	5/23
No anticoagulation(14)	6/14	2/14	4/14
p value	0.3	1.0	0.7
APS(15)	7/15	3/15	1/15
APS+autoimmune disease(22)	14/22	3/22	5/22
p	0.3	0.7	0.4
Medical therapy(28)	13/28	3/28	7/28
Angioplasty (9)	8/9	3/9	2/9
p	0.05	0.14	1

Conclusions: The majority of patients with RAS and APS were female, developed CKD and did not benefit from angioplasty. Anticoagulation was not associated with longterm reduction of ESRD or death, suggesting a non-thrombotic pathogenic process underlying

RAS, e.g. intimal hyperplasia. Treatment of associated vascular risk factors and autoimmune disease is paramount. Anticardiolipin antibodies and renal MRA are useful for screening hypertensive lupus patients.

TH-PO774

A Prospective Study to Investigate Mycophenolic Acid Pharmacokinetics and Its Clinical Correlations in Lupus Nephritis Patients Desmond Y.H. Yap,¹ Chun-Hay Tam,² Sunny Sze ho Wong,² Maggie Kam Man Ma,¹ Susan Yung,¹ Daniel Tak Mao Chan.¹ ¹Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong; ²Medicine and Geriatrics, United Christian Hospital, Hong Kong, Hong Kong.

Background: The dosing regimen of mycophenolate mofetil (MMF) in the treatment of lupus nephritis (LN) is adopted from the kidney transplant experience. The role of therapeutic drug monitoring of mycophenolic acid (MPA) level in managing LN remains undefined.

Methods: We prospectively studied LN patients on maintenance treatment with prednisolone and MMF. Blood MPA level at 1, 2, 4, 8, 10 and 12 hours (i.e. C1, C2, C4, C8, C10 and C12) after MMF administration was measured with an enzymatic assay upon recruitment and repeated at 6-month intervals for 24 months, and at occurrence of clinically significant events, to investigate their clinical correlations.

Results: 51 patients were included, with prednisolone and MMF dose of 6.2±1.8mg/d and 1284±493mg/d respectively at baseline. C1, C2 and C12 MPA levels were 9.9±8.7mg/L, 8.6±6.2mg/L, 1.9±1.4mg/L during disease remission. C1, C2 and C12 MPA levels correlated with AUC₀₋₁₂ (r= 0.52, 0.85 and 0.77; p=0.004, <0.001 and <0.001 respectively). C12 correlated inversely with hemoglobin, white cell and platelet counts (r= -0.359, -0.226, -0.20; p=0.001, 0.010 and 0.024 respectively). There was no association between C12 and anti-dsDNA, serum creatinine or 24-hr urine protein excretion (p=0.53, 0.07 and 0.37 respectively). C1 and C2 showed no association with clinical or serological parameters. Clinically significant events included infection in 2 patients, gastrointestinal upset in 3 patients, and renal flare in 5 patients. C12 MPA level at the time of these events were 1.7±1.6mg/L, 2.6±1.7mg/L and 1.5±0.9mg/L respectively.

Conclusions: C12 MPA level showed good correlation with drug exposure, and may be associated with renal flare and haematological side-effects but not infection.

Funding: Private Foundation Support

TH-PO775

Long-Term Prospective Study of Tacrolimus-Based Treatment in Lupus Nephritis Patients Kazunori Karasawa, Keiko Uchida, Yukari Asamiya, Takahito Moriyama, Mitsuyo Itabashi, Takashi Takei, Kosaku Nitta. Dept Medicine, Kidney Center, Tokyo Women's Medical Univ, 8-1 Kawada-cho, Shinjyuku-ku, Tokyo, Japan.

Background: This study aimed to examine whether long-term maintenance treatment with tacrolimus for patients with lupus nephritis (LN) is effective and safe.

Methods: A total of 27 adult patients with LN after induction therapy were enrolled. Tacrolimus was initiated at a dose of 3 mg/day. Patients treated with other immunosuppressive agents were also switched to tacrolimus. Prednisolone doses were tapered throughout the period according to individual disease activity. Prospective data on renal response, lupus nephritis disease activity index (LNDAI) including hematuria, proteinuria, C3 and anti-ds DNA antibody (score range: 0-10), and prednisolone dose, were collected.

Results: Four patients discontinued tacrolimus treatment due to its ineffectiveness, complications including acute myeloblastic leukemia, or their personal intention to become pregnant or discontinue medication. A total of 23 patients (mean age 52.6 ± 11.8 years and mean duration of LN 15.6 ± 8.7 years) were treated with tacrolimus throughout a 5-year period and their data were analyzed. The mean urinary protein/creatinine ratio significantly decreased from a baseline of 1.12 ± 1.47 to 0.33 ± 0.78 at 1 year (p = 0.005) and 0.40 ± 1.54 at 5 years (p = 0.016), while mean eGFR levels were unchanged throughout the 5 years of tacrolimus treatment. The mean LNDAI was significantly decreased from a baseline of 3.54 ± 2.53 to 1.96 ± 1.40 at 1 year (p = 0.021) and 2.08 ± 1.44 at 5 years (p = 0.022). Similarly, the mean prednisolone dose significantly decreased from a baseline of 0.35 ± 0.21 mg/kg/day to 0.22 ± 0.15 mg/kg/day at 1 year (p = 0.022) and 0.17 ± 0.09 mg/kg/day at 5 years (p = 0.001). The mean blood concentration of tacrolimus was 4.0 ± 2.3 ng/ml. Only one patient experienced a disease flare, and there were no deaths during the study period.

Conclusions: Our results suggest that tacrolimus can be potentially effective for the treatment of LN; moreover, the current dosage appeared to be generally well-tolerated for long-term maintenance treatment in patients with LN.

TH-PO776

Comparison of Kidney Function and Mortality of Mexican Children versus Adults with Lupus Nephritis Luis Gerardo Gonzalez-Correa, Enrique Rojas-Campos, Benjamin Gomez-Navarro, Alfonso M. Cueto-Manzano, Petra Martinez. Unidad de Investigación Médica en Enfermedades Renales, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.

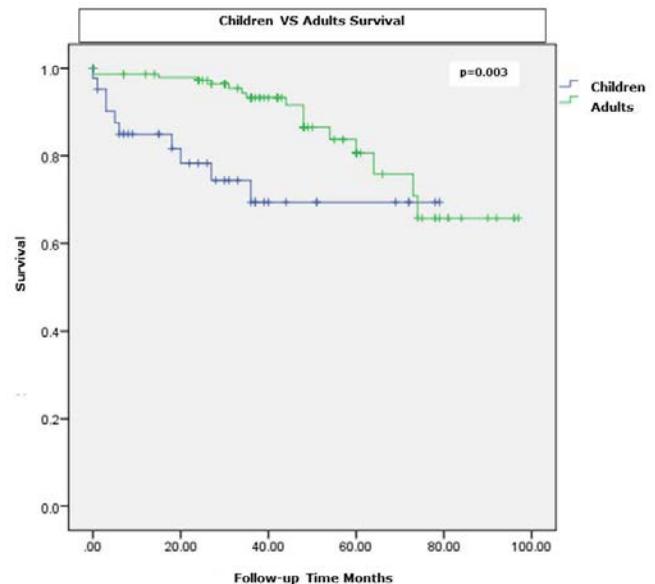
Background: Childhood-onset lupus nephritis (CLN; onset before 16 years of age) has been associated with a more aggressive disease course as compared to adulthood-onset lupus nephritis (ALN). Kidney factors such as LN Class and Activity and Chronicity Indexes are related to renal prognosis. No information is available in our setting. **Aim:** To compare kidney function and mortality of CLN vs ALN.

Methods: Retrospective cohort study. Medical records of patients with LN biopsy proven performed Jan/2005 – Dec/2012 were reviewed. Clinical, kidney function and sociodemographical variables were recorded. Kidney biopsy findings, LN class, Activity and Chronicity Indexes, and patient status (alive=deceased) were also analyzed.

Results: There were 53 patients with CLN and 188 with ALN, with a follow-up of 24±23 vs 43±22 months, and age 12±2 vs 32±11 years, respectively. Main results are shown in the table.

Variable	CLN		ALN	
	Baseline	Final	Baseline	Final
Proteinuria g/day	2.0 (1.0-5.0)	0.5 (0.2-1.4)	2.1 (0.6-4.3)	0.5 (0.2-1.5)
CrCl (ml/min/1.73m ²)	85±42	98±45	80±29	76 ±34*
Activity Index	10±4	4±3	8±3	7±4
Chronicity Index	2±1	5±2	3±2*	4±2
LN Class		Loss of Kidney function		Loss of Kidney function
	N (%)	N (%)	N (%)	N (%)
Class II	12 (23)	1 (8)	23 (12)	1 (4)
Class III	12 (23)	1 (8)	42 (22)	5 (12)
Class IV	22 (41)	8 (36)	54 (29)	10 (18)
Class V	4 (7)	0	48 (25)	1 (2)
Mixed Class	3 (6)	0	21 (12)	5 (24)
Death	10 (19%)		14 (7%)*	
Death Sepsis	30%		36%	

*p<0.05 vs CLN



Conclusions: Patients with CLN had higher mortality and those with ALN had lower CrCl at the end of follow-up. Children died mainly due to infectious causes which might be related to the immunosuppression used because of the high prevalence of class IV LN.

TH-PO777

Determining Long-Term Outcomes in Lupus Nephritis Through Molecular Analysis of Serial Kidney Biopsies Samir Parikh,¹ Ana Malvar,² Huijuan Song,¹ Jianying Zhang,¹ Lianbo Yu,¹ Brad H. Rovin.¹ ¹Div of Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH; ²Nephrology, Hospital Fernandez, Buenos Aires, Argentina.

Background: Most patients with proliferative lupus nephritis (LN) achieve a partial remission (PR) after induction therapy. With time some patients will attain complete remission (CR) while others will not improve. We tested whether gene expression in serial kidney biopsies could identify markers of long-term kidney outcome in patients who achieved a PR after induction.

Methods: The expression of 511 immune response genes was evaluated for 9 pairs of proliferative LN biopsies. A kidney biopsy was done at flare (bx1) and after induction therapy was completed (bx2). All patients achieved a clinical PR prior to bx2. At 3 year follow-up 4 patients were in CR and 5 patients did not improve or worsened (NR). Gene

expression profiles were compared at bx1 and at bx2 between these CR and NR patients. Transcripts were considered differentially expressed only if they met both criteria of at least a 1.5-fold change (FC) and p-value < 0.01.

Results: At flare, 2 transcripts were differentially expressed between CR and NR. IL-28a, a type 3 interferon gene was decreased 2.6-fold (p=0.006) and mannose-binding lectin serine peptidase 1 (MASP1), a member of the complement lectin-pathway, was decreased 1.8-fold (p=0.009) in CR versus NR. From bx1 to bx2, 8 genes were differentially expressed in the CR group. Expression of adhesion molecule VCAM1 and macrophage regulator CEBPB was decreased while expression of TGF-β activator SMAD3, inhibitor of TLR signaling, TOLLIP, and inhibitor of NF-κB signaling, TRAF4 was increased. In NR, from bx1 to bx2, 9 genes were differentially expressed. Expression of the type 3 interferon, IL28b and the TNF-receptor TNFRSF13b (TACI) was decreased while expression of complement C2 and CFB and the TNF cytokine TNFSF8 was increased.

Conclusions: Molecular characterization of kidney biopsies at LN flare along with the change in expression after treatment identifies differentially-expressed genes among patients who eventually have or do not have a CR. Some of these genes may be candidate biomarkers of long-term renal outcomes in LN.

Funding: Other NIH Support - NIDDK U01: DK096927, Pharmaceutical Company Support - Mallinckrodt/Questcor Fellowship Grant: 00033990

TH-PO778

Evaluation of Healthcare Resource Utilization and Costs by Immunosuppressant Pattern of Use in Lupus Nephritis Shih-Yin Chen, Ning Wu, Jie Ting, Fei Shih. *Biogen.*

Background: US-based treatment guidelines recommend 6 months of immunosuppressant (IS) therapy before continuing or switching regimen for class III/IV lupus nephritis (LN) patients. Literature suggested that management of LN is costly, but published data on how costs and healthcare resource utilization (HRU) may vary by IS pattern of use are limited.

Methods: We identified LN patients initiating cyclophosphamide (CYC) or mycophenolate mofetil (MMF) in 2010-2013 from a US commercial/Medicaid claims database. All-cause costs and HRU during the year post-IS initiation were examined. Comparison was made between the following four groups based on their IS utilization during the first 6 months and 7-12 months post-IS initiation: 1) patients who used the same IS continuously for at least 7 or up to 12 months (reference group), 2) patients who switched/added-on IS after 6 months, 3) patients who switched/added-on IS within 6 months, and 4) patients who discontinued IS within 6 months.

Results: Final sample included 1,567 LN patients (mean age=37 years; 86% female) initiating CYC (16.1%) or MMF (83.9%). Patients who remained on the same IS throughout had significantly lower costs and HRU compared to other three groups.

	Overall (N=1,567)	Patient groups			
		Remained on the same treatment (reference group; N=833)	Switched/ added-on after 6 months (N=223)	Switched/ added-on before 6 months (N=206)	Discontinued before 6 months (N=305)
<i>Annual per patient costs (mean)</i>					
Total	\$37,636	\$25,261	\$44,308*	\$59,437*	\$51,832*
Inpatient	\$13,564	\$6,407	\$17,085*	\$23,442*	\$23,867*
Emergency room	\$1,771	\$1,407	\$2,238*	\$1,998*	\$2,272*
Outpatient	\$16,543	\$11,567	\$17,942*	\$28,080*	\$21,319*
Pharmacy	\$5,757	\$5,880	\$7,043*	\$5,916	\$4,374*
<i>HRU (%)</i>					
Hospitalizations	26%	19%	35%*	39%*	30%*

*Significantly different from reference group at P < 0.05

Conclusions: In LN patients, those who required additional IS or discontinued before 6 months incurred more than twice the annual total costs compared to those who continued the same IS through 7-12 months. Identifying safe and efficacious therapies early for LN patients may have economic implications. Future study supplemented with clinical markers to understand the economic impact of achieving early renal response is warranted.

Funding: Pharmaceutical Company Support - Biogen

TH-PO779

Retrospective Analysis of 65 Pregnancies in Patients with Lupus Nephritis in France Jean-charles Puthet,¹ Noemie Jourde-chiche,² Dominique Chauveau,³ Eric Daugas,⁴ Laurent Juillard.¹ *¹Hôpital Edouard Herriot - Hospices Civils de Lyon, France; ²Hôpital La Conception - CHU Marseille, France; ³Hôpital Rangueil - CHU Toulouse, France; ⁴Hôpital Bichat - APHP, on behalf of the French Cooperative Group on Lupus Nephritis, France.*

Background: Lupus nephritis (LN) mostly affects women of childbearing age. Despite the improvement in care over the last decades, pregnant women with LN are still at high-risk of maternal and foetal complications.

Methods: The aim of this study is to outline retrospectively the care and pregnancy prognosis carried out after 24 weeks of gestation between 2004 and 2014, in patients with LN diagnosed before or during pregnancy.

Results: Data was collected from 65 pregnancies in 44 patients across nine French hospitals centres. LN was revealed by pregnancy in five cases. A preparation phase preceded the pregnancy in 90% of the cases, and complete remission from the disease was obtained for more than 24 months in 74% of them. Corticosteroids and hydroxychloroquine were generally continued (68% and 73% respectively). Azathioprine and aspirin were administered in 37% and 65% of pregnancies. Maternal complications occurred in 40% of pregnancies, mainly preeclampsia (18%) and LN flares (20%). The risk factors associated with LN flares during these pregnancies were: the presence of positive anti-native DNA antibodies (p < 0.0001), low C4 (p = 0.004), the absence of complete remission of LN at conception (p < 0.001), or inactivity of LN inferior to 12 months (p = 0.003). Preeclampsia occurred more frequently with the degradation of kidney function or an increase in proteinuria at conception (p = 0.01 and p = 0.001). The perinatal death rate was calculated at 6.8%. We observed 25% premature births and 15% intrauterine growth retardation (IUGR).

Conclusions: We found encouraging results. The incidence of maternal and foetal complications during pregnancy was reduced compared to previous European studies including lupus patients. Risk factors of major maternal complications are best characterized.

TH-PO780

Nephrotic Syndrome and Pregnancy Iris C. De Castro,¹ J. Ashley Jefferson,¹ Thomas R. Easterling,² *¹Div of Nephrology, Dept of Medicine, Univ of Washington School of Medicine; ²Dept of Obstetrics and Gynecology, Univ of Washington School of Medicine, Seattle, WA.*

Background: In the absence of hypertension or renal insufficiency, some consider the perinatal outcomes in pregnant women with nephrotic syndrome to be good. However, the diagnosis and management of both maternal and fetal well-being is challenging.

Methods: We describe the presentation, management, and maternal and fetal outcomes of 31 pregnancies in 24 women with biopsy proven nephrotic syndrome during pregnancy. We include hemodynamic data from UltraCOM cardiac output measurements. All patients had nephrotic-range proteinuria (>3.5g/24hr and or >3.5g/g on spot urine protein: creatinine ratio) during pregnancy, a kidney biopsy diagnosis, and serum creatinine <1.5mg/dL at presentation.

Results: There were 24 subjects (9 primiparas) with 31 pregnancies and 32 offspring. Mean age was 27.6 years (range 16- 39 years) and mean gestational age at presentation was 18.7 weeks (range 5- 40 weeks). Labs revealed a mean creatinine 0.85mg/dL (range 0.4- 1.4mg/dL), mean serum albumin 1.97g/dL (range <1- 3.2g/dL), and mean proteinuria 8.96g/24h (range 3.6- 32g). UltraCOM data was available for 18 pregnancies. Mean cardiac output at presentation was markedly elevated at 8.38L/min. 14 of 31 pregnancies were known to have kidney disease before pregnancy. Nephrotic syndrome was newly diagnosed in 16 patients. Biopsy was performed during pregnancy in 10 subjects (median age of gestation 20.5 weeks (range 2-27 weeks)) changing management in 70%. 6 were biopsied postpartum. Biopsy diagnoses were FSGS(11), IgAN(3), lupus nephritis(3), membranous nephropathy(3), and 1 case each of Fibrillary GN, MPGN, C3GN, and minimal change disease. Maternal complications included preeclampsia(10/31), acute kidney injury(3/31) and cellulitis(3/31). Mean age of gestation at delivery was 35.4 weeks (range 25-40 weeks). 17 delivered via caesarean section. Fetal complications included birth weight <2,500g(18), IUGR(3), and 10 were admitted to NICU.

Conclusions: Pregnant women with nephrotic syndrome are at high risk for developing maternal and fetal complications despite the absence of significant hypertension or renal insufficiency.

TH-PO781

The Relationship Between Serum Cholinesterase, Number of Organ Involvement and Fibrotic Markers in Japanese Patients with IgG4-Related Disease Hirofumi Nishikawa, Yoshinori Taniguchi, Tatsuki Matsumoto, Kazu Hamada-Ode, Yoshiko Shimamura, Koji Ogata, Kosuke Inoue, Taro Horino, Shimpei Fujimoto, Yoshio Terada. *Kochi Univ, Japan.*

Background: To evaluate the relationship between cholinesterase, number of organ involvement and serum fibrotic markers in Japanese patients with IgG4-related disease (IgG4-RD) including kidney involvement.

Methods: The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=20) were assessed. Several laboratory data of IgG4-RD with multiple organs' involvements (IRDMOI) (n=10), IgG4-RD with limited organ's involvement (IRDLOI) (n=10), ANCA-associated vasculitis (AAV) (n=10) and Sjögren Syndrome (SjS) (n=10) were comparatively examined. Furthermore, we studied the relationship between the numbers of organ involvement (NOI) and several fibrotic markers (ELF score and serum Dkk-1) in IgG4-RD group.

Results: Serum cholinesterase (ChE) levels were significantly lower in IRDMOI group than IRDLOI, AAV and SjS groups. All cases did not show hepatic dysfunction in laboratory examinations. Serum albumin and IgG levels were significantly lower and CRP levels were significantly higher in AAV group, compared with IgG4-RD and SjS group. There were no significant differences in these levels between IRDMOI and SjS. In total IgG4-RD cases, ChE levels inversely correlated with NOI and fibrotic score, and fibrotic score positively correlated with NOI. Finally, Dkk-1, one of Wnt inhibitors, levels in IRDMOI were significantly lower than IRDLOI and healthy subjects (p<0.05).

Conclusions: The ELF score and serum Dkk-1 level might be a clinically useful indicators of active fibrosis and the extent of disease in Japanese patients with IgG4-RD. Notably, serum ChE levels could predict these phenomena.

TH-PO782

Crescentic IgA Nephropathy – A Prospective Study Krishan L. Gupta,¹ Prabhakar Doddi,¹ Ritambhara Nada,² Raja Ramachandran.¹ ¹*Nephrology, PGIMER, Chandigarh, India;* ²*Pathology, PGIMER, Chandigarh, India.*

Background: Crescentic IgA nephropathy (cIgAN) carries a very poor prognosis and the initial creatinine at presentation predicts long-term outcome. The present prospective study was carried out to evaluate the clinico-pathological correlation and outcome of cIgAN.

Methods: Patients ³12 yrs with Crescentic IgAN were included in the study. Patients with infection with evidence of systemic disease like HSP, SLE, hepatitis B surface antigen, anti hepatitis C antibody and HIV-I/II were excluded from the study. Patients were followed prospectively monthly for a period of 12 months or till end stage renal (ESRD) or death. Primary objective of the study was to evaluate percentage of patients achieving remission/ESRD and the secondary outcome to see for histological correlation with clinical outcome.

Results: A total of 60 cases of crescentic IgAN were enrolled in the study. The mean age of the patients was 28.91±10.14 (12-60) years. The study included 46 (76.67%) males and 14 (23.33%) females. The mean 24 hour-urine protein (UP), serum creatinine and serum albumin were 2.22±1.33 gm, 6.37±4.13 mg/dl and 3.39±0.78 gm/dl respectively. Active sediments were present in 44 (74.57%) patients at presentation. The clinical presentation was RPRF in 34 (56.66%) cases, nephrotic syndrome in 04 (6.66%) and CKD in 20 (33.33%) and 2 (3.33%) cases presented with only subnephrotic proteinuria. Seventeen (28.33%) patients received combination of pulse cyclophosphamide and steroids, 29 (48.33%) received only steroids and 14 (23.34%) cases with tubular atrophy and interstitial fibrosis >70% were not treated with any immunosuppressive. At the end of 12 months 03 (5%) achieved CR, 08 (13.33%) had PR progressive CKD in 09 (15%) and 02 (3.33%) had persistent NS. Thirty-eight (63.33%) cases progressed to ESRD by the end of 12 months. Serum creatinine at presentation and IFTA> 50% and presence of fibrous crescent on biopsy was risk factor for ESRD.

Conclusions: Crescentic IgAN carries a very poor prognosis, with majority of the cases progressing to ESRD by 12 months. Serum creatinine at presentation and presence of diffuse IFTA and fibrous crescents on biopsy predicts development of ESRD.

TH-PO783

Comprehensive Microbiome Analysis of Tonsillar Crypts in IgA Nephropathy Hirofumi Watanabe, Shin Goto, Masafumi Tsuchida, Ichiei Narita. *Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: IgA nephropathy (IgAN) is the most prevalent primary chronic glomerular disease, in which the mucosal immune response, especially elicited in the tonsils or intestine, has been estimated to be involved with the development of the disease. To explore the relationship between IgAN and bacterial flora in the tonsils, we conducted a comprehensive microbiome analysis.

Methods: We enrolled 21 IgAN patients, 14 recurrent tonsillitis (RT) patients without urine abnormalities and 20 children with tonsillar hyperplasia (TH) who had been performed with tonsillectomy. Genomic DNA from tonsillar crypts of each patient was extracted, and V4 regions of the 16S ribosomal RNA (rRNA) gene were amplified and analyzed using a high-throughput multiplexed sequencing approach. Differences of the genus composition among three groups were statistically analyzed by PERMANOVA, and visualized by principal component analysis (PCA).

Results: In 16S rRNA analysis, substantial diversity of bacterial compositions was detected in each sample. *Prevotella*, *Fusobacterium*, *Sphingomonas*, and *Treponema* were dominated in IgAN. The proportion of the *Haemophilus* spp., *Porphyromonas* spp., and *Treponema* spp. of IgAN was different from that of TH. However, there was no bacterial genus that differs significantly in the frequency of between IgAN and RT. The PCA did not separate IgAN from RT, although it was discriminated from TH. In addition, we compared the bacterial composition between IgAN patients with higher and lower serum IgA levels; however, no difference in composition of microbiome between the two groups was observed.

Conclusions: Similar pattern of bacteria are present in tonsillar crypts of both IgAN and RT, suggesting that the host responsiveness to these bacteria is important in the development of IgAN.

TH-PO784

Urinary N-Acetyl-β-D-Glucosaminidase Level Is Associated with Tubulointerstitial Fibrosis and Therapeutic Response in Immunoglobulin A Nephropathy Yosuke Yamada, Makoto Harada, Akinori Yamaguchi, Koji Hashimoto, Makoto Higuchi, Yuji Kamijo. *Dept of Nephrology, Shinshu Univ School of Medicine, Matsumoto, Nagano, Japan.*

Background: Therapeutic response in Immunoglobulin A nephropathy (IgAN) patients has been shown to be affected by the severity of chronic renal lesion, such as tubulointerstitial fibrosis. Urinary N-acetyl-β-d-glucosaminidase (U-NAG) is a known biomarker of tubulointerstitial injury. The present study aimed to clarify if U-NAG level was associated with the severity of tubulointerstitial fibrosis and whether it could predict the effectiveness of combined steroid pulse and tonsillectomy therapy (ST), which is the primary treatment for IgAN in Japan.

Methods: Among the 81 IgAN patients who were diagnosed by kidney biopsy and treated with ST between March 2005 and April 2015 at Shinshu University Hospital, the U-NAG data of 77 patients were investigated for relationships between clinical and histological data. To search for associations between U-NAG level and clinical remission

(CR) rate, we examined 39 of the above 77 patients who were observed for 3 years following ST. CR was defined as proteinuria of less than 0.3 g/gCre and urinary erythrocytes of less than 5 /high-power field.

Results: Multiple linear regression analysis adjusted by age and estimated glomerular filtration rate (eGFR) indicated that U-NAG level was significantly associated with tubulointerstitial fibrosis score (p<0.001) and the percentage of global sclerotic glomeruli (p=0.008). Multiple logistic regression analysis adjusted by age, sex and eGFR indicated that the CR rate 3 years after ST was significantly associated with tubulointerstitial fibrosis score (Odds Ratio [OR] 0.092, 95% Confidence Interval [CI] 0.009-0.914, p=0.042) and U-NAG level (OR 0.713, 95%CI 0.530-0.958, p=0.025).

Conclusions: U-NAG is a potentially useful biomarker of the severity of renal tubulointerstitial fibrosis and global glomerular sclerosis percentage in IgAN. U-NAG measurement may also aid in the prediction of therapeutic response to ST in IgAN.

TH-PO785

Beneficial Effect of Immunosuppressive Therapy for IgA Nephropathy with Moderately Impaired Renal Function Kyung sun Park,¹ Jongha Park,² Jong Soo Lee,² Hyun Chul Chung.² ¹*Div of Nephrology, Dept of Internal Medicine, Dongkang Medical Center, Ulsan, Korea;* ²*Div of Nephrology, Dept of Internal Medicine, Ulsan Univ Hospital, Ulsan, Korea.*

Background: A variety of treatment has been attempted to slow progression of IgA nephropathy (IgAN) such as renin-angiotensin system inhibitors and adding corticosteroid for patients with impaired renal function. We compared clinical outcomes of IgAN patients who were treated with vs. without immunosuppressive therapy (IST), and explored identified risk factors associated with progression of renal dysfunction.

Methods: Patients who were diagnosed as IgAN between 2001 and 2014 were screened. Among them, patients who had initial estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m² and had followed up for at least 12 months were included in this analysis.

Results: A total of 92 patients were analyzed. 39 patients received IST (Group 1) and 53 did not (Group 2). Median follow-up (59 vs. 77 months) and mean age (46.6 vs. 47.4 years) were not different. In Group 1, mean arterial pressure (MAP, 99 vs. 93 mmHg, P=0.019), serum creatinine (1.66 vs. 1.45 mg/dL, P=0.003), and median amount of proteinuria (2033 vs. 1115 mg/day, P<0.001) were significantly higher, but mean eGFR (43.7 vs. 50.1 mL/min/1.73 m², P<0.001) and serum albumin (3.5 vs. 4.0 g/dL, P=0.009) were lower than Group 2 at baseline. Three patient of Group 1 and 7 of Group 2 progressed to end-stage renal disease (ESRD). ESRD-free survival was comparable between two groups (P=0.639). For 1 year, the change of mean eGFR was significantly different between 2 groups (3.8 of Group 1 vs. -1.3 mL/min/1.73 m² of Group 2, P=0.027).

	Group 1 (n=39)	Group 2 (n=53)	P
Mean eGFR, mL/min/1.73m ²			
·baseline	43.7	50.1	
·at 1 year	47.5*	48.8*	0.027
·change	3.8	-1.3	

*P=0.069, *P=0.179 compared to baseline

In multivariate linear regression, age at diagnosis (standardized beta, 0.212; P=0.041), MAP (standardized beta, -0.227; P=0.027), baseline eGFR (standardized beta, 0.566; P<0.001) and IST (standardized beta, 0.273; P=0.013) were independent predictors of last-visit eGFR.

Conclusions: IST may have a beneficial effect for slowing progression of IgAN with moderately impaired renal function.

TH-PO786

Longitudinal Study of a Kindred with Familial IgA Nephropathy Reveals Stable Serum Levels of Galactose-Deficient IgA1 Hiroyuki Ueda,^{1,2} Yoshimi Ueda,^{1,2} Zina Moldoveanu,¹ Stacy D. Hall,¹ Karen Hart,¹ Krzysztof Kiryluk,³ Ali G. Gharavi,³ Dana Rizk,¹ Bruce A. Julian,¹ Jan Novak.¹ ¹*Univ of Alabama at Birmingham, Birmingham, AL;* ²*The Jikei Univ School of Medicine, Tokyo, Japan;* ³*Columbia Univ College of Physicians and Surgeons, New York, NY.*

Background: Patients with IgA nephropathy (IgAN) have elevated levels of circulatory galactose-deficient IgA1 (Gd-IgA1). Familial form of IgAN has been reported among people of all ancestries. Serum Gd-IgA1 levels are heritable in patients with familial and sporadic IgAN. Moreover, 50% of first-degree relatives of patients with familial IgAN have high serum Gd-IgA1 levels (≥95th percentile of healthy controls) without clinical signs of IgAN. This study is a longitudinal follow-up of a large kindred with familial IgAN.

Methods: Pedigree includes 4 men with biopsy-proven IgAN. Members recruited in 2005 and 2014 included 2 IgAN patients, 13 relatives, and 7 genetically unrelated individuals (marry-ins). Blood samples were drawn to determine for total IgA and Gd-IgA1 levels. Gd-IgA1 was measured using lectin ELISA and expressed relative to a standard Gd-IgA1 in U/100 ng of serum IgA. Spot urine sample was obtained for urinalysis and protein/creatinine ratio. Abnormal urinalysis was defined by hematuria (≥2+ blood) and/or protein/creatinine ratio ≥0.5 g/g.

Results: Mean (± SD) ages of IgAN patients, blood relatives, and marry-ins were 48 (±3), 43 (±16), 61 (±12) yr in 2014. Two patients had multiple kidney transplantations. Except for the 2 IgAN patients, no individual had an abnormal urinalysis. Serum Gd-IgA1 levels for marry-ins were similar to other healthy controls. Serum Gd-IgA1 levels were higher in blood relatives and IgAN patients than in marry-ins at each sampling time (P = 0.03). Serum Gd-IgA1 levels demonstrated longitudinal stability in most individuals (Intraclass correlation coefficient = 0.812; 95% CI 0.604-0.917).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Serum Gd-IgA1 levels in 22 individuals in this multiplex IgAN pedigree were stable over a 9-year period. No blood relative developed IgAN or exhibited a urinary abnormality during the 9-year follow-up.

Funding: NIDDK Support, Private Foundation Support

TH-PO787

Childhood IgA Nephropathy with Nephrotic Syndrome (NS-IgAN) at Onset Yuko Shima,¹ Koichi Nakanishi,¹ Taketsugu Hama,¹ Masashi Sato,¹ Hiroko Togawa,¹ Hironobu Mukaiyama,¹ Hiroshi Kaito,² Kandai Nozu,² Ryojiro Tanaka,³ Kazumoto Iijima,² Norishige Yoshikawa.⁴ ¹*Pediatrics, Wakayama Medical Univ, Wakayama, Japan;* ²*Pediatrics, Kobe Univ, Kobe, Japan;* ³*Pediatric Nephrology, Hyogo Childrens' Hospital, Kobe, Japan;* ⁴*National Center for Child Health and Development, Tokyo, Japan.*

Background: Clinical characteristics and long term outcomes of childhood NS-IgAN are not fully clarified.

Methods: We retrospectively analyzed 426 consecutive biopsy-proven samples of childhood IgAN from July 1976 to June 2013. There were 30 cases with NS-IgAN (7.0%) at onset. We compared clinical and pathological findings between NS- and other IgAN.

Results: Clinical findings showed significant differences (NS vs non-NS) in males (77 vs 53%, $p=0.008$), gross hematuria (77 vs 51%, $p=0.006$), and duration from onset to renal biopsy (1.5 vs 8.4 months, $p<0.001$). Pathological findings had significant differences in mean mesangial hypercellularity score (M, 1.5 vs 0.8, $p<0.0001$), median endocapillary hypercellularity (E, 27.3 vs 3.9%, $p<0.0001$), and median crescents (C, 15.2 vs 3.6%, $p=0.006$). Logistic analyses showed a significant relation between M, an acute lesion, and NS-IgAN. Although Kaplan-Meier analysis showed significantly lower renal survival rate in cases with NS-IgAN than other cases ($p=0.02$), the 10-year renal survival rate of NS-IgAN was 92.7% (95%CI=75.0–98.2). The prognostic factors for renal survival were proteinuria disappearance, M, E, tubular atrophy/interstitial fibrosis (T) and C, but not presence of NS at onset. Combination therapy including PSL and immunosuppressants was given to 20/30 NS-IgAN patients, and 21 showed disappearance of proteinuria. Three cases (9.7%) developed chronic renal failure (eGFR<60) during the observation period (6.2±3.2 years). All three cases received combination therapy and showed heavy proteinuria after 2 years of treatment. The factor T, a chronic lesion unmodifiable by treatment, was identified in patients refractory to treatment.

Conclusions: Renal outcome of childhood NS-IgAN was good. Modifiable acute lesions are the dominant pathological findings in childhood NS-IgAN.

TH-PO788

Predictive Factors of Spontaneous Remission in Patients with Immunoglobulin A Nephropathy Tae-Hyun Yoo,¹ Kyoung Sook Park,¹ Tae ik Chang,² Shin-Wook Kang.¹ ¹*Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea;* ²*Dept of Internal Medicine, NHIC Ilsan Hospital, Gyeonggi-do, Korea.*

Background: Although immunoglobulin A nephropathy (IgAN) is commonly considered as a lifelong disease, incidences of spontaneous remission (SR) have been occasionally reported. We investigate the incidence as well as the clinical predictors of SR in IgAN.

Methods: Medical records of biopsy-proven IgAN in Severance hospital from 2006 to 2014 were reviewed. SR was defined as complete remission reached without any immunosuppressive therapy. Two different SR criteria were used to classify the patients into SR or non-SR (NR) group. A criteria proposed in previous reports was chosen as criteria I [urine red blood cell (RBC) count<5/HPF and random urine protein-to-creatinine ratio (UPCR)<0.3 g/g]. Criteria II was defined to better represent a normal renal function state [urine RBC<3/HPF, UPCR<0.2 g/g, and estimated glomerular filtration rate (eGFR)>60 mL/min/1.73m²]. Cox proportional hazard analysis was performed to identify independent predictors of SR.

Results: A total of 488 patients were investigated. The mean age was 36.9±12.2 years and 43.2% were male. SR was defined as complete remission reached without any immunosuppressive therapy. Two different SR criteria were used to classify the patients into SR or non-SR (NR) group. A criteria proposed in previous reports was chosen as criteria I [urine red blood cell (RBC) count<5/HPF and random urine protein-to-creatinine ratio (UPCR)<0.3 g/g]. Criteria II was defined to better represent a normal renal function state [urine RBC<3/HPF, UPCR<0.2 g/g, and estimated glomerular filtration rate (eGFR)>60 mL/min/1.73m²]. Cox proportional hazard analysis was performed to identify independent predictors of SR.

Conclusions: The incidence of SR in IgAN was substantially frequent. UPCR levels may be an independent predictor of SR in patients with IgAN.

TH-PO789

Comparison of the Effect of Oral Steroid and Tonsillectomy Combined with Steroid Pulse Therapy for IgA Nephropathy Yoshie Hoshino,¹ Takahito Moriyama, Mitsuyo Itabashi, Takashi Takei, Ken Tsuchiya, Kosaku Nitta. *Dept of Medicine, Kidney Center, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Recently, in Japan, IgA nephropathy (IgAN) has been often treated by tonsillectomy combined with steroid pulse therapy (TSP) instead of traditional oral steroid therapy (oPSL). However, there are few reports described about the comparison of them.

Methods: We identified the 68 IgAN patients who were diagnosed in our institution between 1991 and 2013, and met the following criteria: (1) age≥16 years old; (2) proteinuria >1 g/day; (3) estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m²; (4) treated by TSP or oPSL with our standard protocol; (5) follow-up period >1 year; (6) interval from renal biopsy to initiation of therapy ≤3 years; (7) not combined with other renal disease. We compared the clinical findings at the time of renal biopsy, histological findings, renal function and urinary findings during the follow-up period between both groups. We defined complete remission (CR) as proteinuria <0.3 g/g creatinine and urinary red blood cells <5 counts/HF.

Results: After adjusting clinical findings by propensity score, each 20 patients were selected in both groups. Almost of all clinical and histological findings at baseline between both groups did not differ (TSP vs. oPSL group; eGFR: 77.5 vs. 75.7 mL/min/1.73m² and proteinuria: 1.9 vs. 2.2 g/day). The CR rate was increased significant earlier (mean duration: 17.7±3.4 vs. 43.9±10.8 month, $p<0.001$) and higher (at 3 years: 61 % vs. 5 %, $p<0.001$) in TSP than oPSL group by Kaplan-Meier analysis. Renal function was decreased from baseline in both groups, however the ratio of patients with renal dysfunction (25% decreasing from baseline eGFR) was significantly lower in TSP than oPSL group during 3 years (at 3 years: 7 vs. 50 %, $p<0.001$). TSP (HR 4.00, 95%CI 1.03-21.06, $p=0.04$, higher eGFR (HR 2.43, 95%CI 1.10-5.80, $p=0.03$), lower triglyceride (HR 1.44, 95%CI 1.05-2.10, $p=0.02$) were the contributive factors to CR in multivariate analysis.

Conclusions: TSP therapy is useful for reaching CR and protecting renal function rather than oPSL therapy for IgAN with moderate to severe proteinuria.

TH-PO790

Evaluation of KDIGO Clinical Practice Guidelines for IgA Nephropathy by Japanese Multicenter Large Cohort Study Kyoko Watanabe,¹ Kentaro Koike,² Akihiro Shimizu,² Nobuo Tsuboi,² Keita Hirano,¹ Makoto Ogura,² Sayuri Shirai,³ Yoshinari Yasuda,⁴ Takashi Yasuda,⁵ Shoichi Maruyama,⁴ Tetsuya Kawamura,² Seichi Matsuo,⁴ Takashi Yokoo.² ¹*Ashikaga Red Cross Hospital, Ashikaga, Tochigi, Japan;* ²*Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Minato-Ku, Tokyo;* ³*Div of Hypertension and Nephrology, St. Mariana Univ, Kanagawa, Japan;* ⁴*Nephrology, Nagoya Univ, Nagoya, Japan;* ⁵*Nephrology, Kichijoji Asahi Hospital, Musashino-shi, Tokyo, Japan.*

Background: Current KDIGO clinical practice guidelines for IgA nephropathy (IgAN) neither advocate tonsillectomy nor steroid therapy for patients with eGFR<50ml/min. However, IgAN patients referred to nephrologists often have reduced eGFR at the time of referral. Therefore, we evaluated the KDIGO guidelines to assess and further develop their clinical significance for treatment of IgAN with reduced eGFR by a large multicenter cohort study in Japan.

Methods: Of 1,174 patients registered for the multicenter cohort study led by the Progressive Kidney Disease Study Group funded by Japan Ministry of Health, Labor, and Welfare in 2012, cases with eGFR<50ml/min at the time of biopsy were selected. Primary outcome was defined as 1.5 times increase in creatinine concentration from baseline.

Results: Enrolled 201 patients showed 36.8 ml/min as mean eGFR and 1.15 g/day as median level of proteinuria. During the median follow up of 4 years, 70 patients (34.8%) reached primary outcome. Like KDIGO recommendations, multivariate analysis adjusted with eGFR, proteinuria, and blood pressure at baseline revealed that steroid therapy alone did not significantly improve renal prognosis compared with no steroid therapy (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.43 to 1.25). By contrast, combining steroid therapy with tonsillectomy demonstrated significantly improved renal survival compared to no steroid therapy (HR 0.25; 95%CI 0.06 to 0.71).

Conclusions: In keeping with KDIGO recommendations, our results did not suggest improvement in renal prognosis by steroid therapy alone for IgAN with eGFR <50ml/min. However, they indicated that combining steroid therapy with tonsillectomy could be associated with a significantly better renal outcome.

TH-PO791

The Effect of Renin-Angiotensin System Blockade on the Incidence of End-Stage Renal Disease in IgA Nephropathy Shigeru Tanaka,¹ Toshiharu Ninomiya,^{1,5} Ritsuko Katafuchi,² Kosuke Masutani,¹ Masaharu Nagata,¹ Akihiro Tsuchimoto,¹ Hideki N. Hirakata,³ Kazuhiko Tsuruya,^{1,4} Takanari Kitazono.^{1,5} ¹*Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan;* ²*Kidney Unit, National Fukuoka-Higashi Medical Center, Fukuoka, Japan;* ³*Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan;* ⁴*Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan;* ⁵*Div of Research Management, Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.*

Background: The impact of renin-angiotensin system blockade (RASB) on the incidence of end-stage renal disease (ESRD) remains unclear in IgA nephropathy (IgAN). This study assessed associations between RASB treatment and the incidence of ESRD in IgAN using propensity score approaches.

Methods: We retrospectively analyzed 1267 patients with IgAN biopsied between 1979 and 2010. Propensity scores were calculated using logistic regression. Associations between RASB and ESRD were examined using a Cox regression model adjusted by inverse probability of treatment weighted, regression, stratification and matching.

Results: During follow-up (median 5.1 years), 130 patients developed ESRD. With Cox regression adjusted by inverse probability of treatment weighted, RASB use was significantly associated with a lower risk of ESRD (hazard ratio, 0.57; 95% confidence interval, 0.41–0.79). Significant associations were observed for other propensity score-based

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

approaches. In stratified analysis, a beneficial association between RASB and ESRD was observed in patients ≥ 35 years, with hypertension, reduced estimated glomerular filtration rate (<60 mL/min/1.73 m²), mesangial proliferation and segmental glomerulosclerosis (P for interaction <0.05), and tended to be greater in patients with proteinuria (≥ 1.0 g/24 h), extracapillary proliferation, and receiving methylprednisolone pulse therapy (P for interaction <0.10).

Conclusions: Treatment with RASB was associated with a lower incidence of ESRD in the real-world practice of IgAN.

TH-PO792

Long-Term Outcome in 56 Patients with Assumed Benign IgA Nephropathy Thomas Knoop, Bjorn Egil Vikse, Einar Svarstad, Sabine Leh, Rune Bjørneklekt. *Renal Research Group, Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway.*

Background: Patients with IgA nephropathy (IgAN) presenting with mild to moderate proteinuria and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m² are assumed to have excellent renal prognosis. There is however limited data on very long-term outcome (>15 years) in such patients.

Methods: Patients with biopsy proven IgAN were retrieved from the Norwegian Kidney Biopsy Registry when fulfilling the following criteria; biopsy taken at Haukeland University Hospital 1988-1999, eGFR ≥ 60 mL/min/1.73m² and proteinuria < 1 gram/24 hours at presentation. Patients were invited for a medical examination and the following data were recorded: responsible physician during follow-up period (none/primary physician/nephrologist), antihypertensive treatment (any/ angiotensin converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB)), blood pressure (BP), eGFR, urinary albumin creatinine ratio (UACR) (0-2.5 mg/mmol creatinine (negative) / 2.5-30 (microalbuminuria) / 30-100 (manifest albuminuria) / >100 mg/mmol creatinine) and hematuria.

Results: We report data for 56 patients with a median follow-up time of 22 years after diagnosis. Nine patients (16 %) had no medical follow-up, thirty-five patients (63 %) were followed by a primary physician on a regular basis, and twelve patients (21 %) were followed by a nephrologist. Thirteen patients (23 %) had eGFR < 60 mL/min/1.73m² (eight with eGFR 30-45 and five with eGFR 45-60). Fifteen patients (27 %) had microalbuminuria, six patients (11 %) had manifest albuminuria and three patients (5 %) had UACR > 100 mg/mmol creatinine. Twenty-three patients (41 %) were treated with an ACE-I/ARB. Fifteen patients (27 %) had hypertension (BP $> 140/90$ mmHg), nine of these had antihypertensive treatment and six were untreated. Nineteen patients (34 %) had hematuria. Ten patients (18 %) had no medication, normal BP, eGFR ≥ 60 mL/min/1.73m² and normaloalbuminuria. Of notice, several patients with no medical follow-up had microalbuminuria, hypertension and/or decreased eGFR < 60 mL/min/1.73m².

Conclusions: Prognosis in patients with assumed benign IgAN is not always favorable and adequate medical follow-up is needed.

Funding: Government Support - Non-U.S.

TH-PO793

J-Curve Effects of Uric Acid on the Progression of IgA Nephropathy Yuta Matsukuma,¹ Shigeru Tanaka,¹ Kosuke Masutani,¹ Akihiro Tsuchimoto,¹ Ritsuko Katafuchi,² Hideki N. Hirakata,³ Kazuhiko Tsuruya,^{1,4} Takanari Kitazono.¹ ¹Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; ²National Fukuoka Higashi Medical Center, Fukuoka, Japan; ³Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; ⁴Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ, Fukuoka, Japan.

Background: Recently, low uric acid (UA) as well as high UA has been emerged as a risk factor for cardiovascular disease (CVD). However the impact of low UA on the outcome of IgA nephropathy (IgA-N) remains unknown.

Methods: We retrospectively investigated 1226 patients with IgA-N diagnosed between 1978 and 2010. Patients were divided into three groups by tertile of UA: low (T1), middle (T2), and high (T3) tertiles (<6.1 , $6.1-7.1$, and >7.1 mg/dL in men and <4.4 , $4.4-5.4$, and >5.4 mg/dL in women, respectively). The risk factors of developing end stage kidney disease (ESKD) were assessed using a Cox proportional hazards model.

Results: After an average of 5.2 years of follow-up, 145 patients (11.8%) developed ESKD. High UA was an independent risk factor for ESKD after adjusting for potential confounding factors, hazard ratio (HR) for men, 1.27; 95% confidence interval [CI], 1.07 to 1.49, and HR for women, 1.41; 95% CI, 1.11 to 1.78, for every 1-mg/dL increase in UA, respectively. We also found that the HR showed a J-shaped trend with tertile of UA in both men (HR for T1, 1.24; 95% CI, 0.56 to 2.67, T2 [reference], HR for T3, 1.78; 95% CI, 1.03 to 3.21) and women (HR for T1, 2.64; 95% CI, 1.08 to 6.67, T2 [reference], HR for T3, 2.16; 95% CI, 1.06 to 4.86). Notably, low UA in women was significantly associated with the progression to ESKD.

Conclusions: UA showed a J-shaped trend with the progression of IgA-N. Not only high UA but also low UA is a risk factor for ESKD, and the trend was more clearly observed in women.

TH-PO794

Remission of Urinary Protein at 2 Years After Diagnosis with Normal Renal Function and Remission of Urinary Protein at 1 Year After Diagnosis with Decreased Renal Function as an Accurate Prognostic Marker in IgA Nephropathy Takayuki Fujii,¹ Junichi Hoshino,² Joichi Usui,³ Satoshi Suzuki,¹ Yoshifumi Ubara,² Kunihiro Yamagata.³ ¹Seirei Sakura Citizen Hospital, Sakura, Japan; ²Toranomon Hospital, Tokyo, Japan; ³Univ of Tsukuba, Tsukuba, Japan.

Background: Level of proteinuria (UP) has a strong association with poor renal prognosis in IgA nephropathy. Recent studies reported that the level of UP, especially, remission of UP (CR) defined as less than 0.3 g/d, during the follow-up was a more accurate prognostic factor than at diagnosis. In this multicenter study, we evaluated which post-diagnosis measurement point achieving CR strongly associated with the renal prognosis.

Methods: 1,077 patients diagnosed with IgA nephropathy between March 1981 and December 2013, and could be followed-up for at least 3 years or reached end-stage kidney disease (ESKD) were enrolled. We performed a retrospective cohort study among 2 divided groups: 638 with eGFR ≥ 60 mL/min/1.73m² (A) and 439 with eGFR < 60 mL/min/1.73m² (B). The endpoint of this study was a 50% decrease in eGFR or ESKD. The annual daily UP level until 3 years after diagnosis was categorized into 2 grades: <0.3 g/d and ≥ 0.3 g/d and its association with the renal prognosis was investigated. The hazard ratio of the endpoint adjusted with clinical and pathological findings and treatment was examined.

Results: Regarding CR as a reference, UP ≥ 0.3 g/d was not a significant poor prognostic factor at diagnosis, but at 1 year, especially at 2 years, it became a significant factor in group A. On the other hand, in group B, UP ≥ 0.3 g/d was already shown to be a significant factor at diagnosis and the strongest factor at 1 year.

Measurement point	eGFR ≥ 60 mL/min/m ²		eGFR < 60 mL/min/m ²	
	UP < 0.3 g/d	HR(95%CI) with UP ≥ 0.3 g/d	UP < 0.3 g/d	HR(95%CI) with UP ≥ 0.3 g/d
at diagnosis	reference	1.97(0.96-4.58)	reference	2.33(1.26-5.26)
after 1 year	reference	4.91(2.03-14.64)	reference	16.54(6.76-54.82)
after 2 years	reference	10.84(3.68-48.33)	reference	4.91(2.62-10.11)

Conclusions: CR within 2 years after diagnosis with normal renal function and CR within 1 year after diagnosis with decreased renal were the most accurate predictors for a favorable outcome in IgA nephropathy.

TH-PO795

Copeptin, a Surrogate Marker for AVP, Is Associated with Disease Severity and Progression in IgA Nephropathy Patients Debbie Zitterma,¹ Jan A.J.G. van den Brand,² Jack F. Wetzels,² Ron T. Gansevoort.¹ ¹Nephrology, Univ Medical Center Groningen, Groningen, Netherlands; ²Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: The disease course of IgA Nephropathy (IgAN) is difficult to predict. Copeptin, a surrogate marker for AVP, has been described to cause kidney damage in various renal diseases. We investigated therefore the associations of copeptin with disease severity and progression in IgAN.

Methods: Included were 60 biopsy proven IgAN patients from the Radboud UMC Nijmegen, of whom urine and blood samples were available. Urinary excretion of a1M, b2M, KIM-1 and NGAL and plasma copeptin was measured at baseline. Survival analyses was performed for the composite outcome death, end stage renal disease (ESRD), doubling of serum creatinine, start of immunosuppressive therapy and the individual components.

Results: In IgAN patients (male: 72%, age: 42 ± 13 years, eGFR: 48 ± 21 mL/min/1.73m², copeptin: 9.4 (5.5-18.1) pmol/L) copeptin was associated at baseline with proteinuria (St. $\beta = 0.34$, $p = 0.05$), a1M (St. $\beta = 0.41$, $p = 0.003$) and b2M (St. $\beta = 0.38$, $p = 0.005$), adjusted for age, sex and eGFR, and with NGAL when adjusted for age and sex (St. $\beta = 0.34$, $p = 0.01$). During a follow-up of 7 ± 3 years, copeptin (divided in tertiles) was positively associated with the composite outcome ($p = 0.03$) and with start of immunosuppressive therapy ($p = 0.04$) using a log rank test. When patients who started immunosuppressive therapy during follow up ($n = 14$) were excluded, copeptin (as continuous variable) was furthermore associated with the incidence of ESRD ($p = 0.01$, HR = 1.09; i.e. a 9% increase in risk of ESRD per 1 pmol/L increase in copeptin), doubling of serum creatinine ($p = 0.004$, HR = 1.07) and the composite outcome ($p = 0.003$, HR = 1.07) in Cox regression models, adjusting for proteinuria and sex. After additional adjustment for eGFR, which is debatable as eGFR decline could be part of the causal pathway between copeptin and outcomes, the survival analyses lost significance.

Conclusions: Copeptin is a promising disease severity marker in IgAN with additive predictive value for future kidney function loss over proteinuria, but not over eGFR, the strongest predictor of disease progression in this study.

Funding: Government Support - Non-U.S.

TH-PO796

Clinical Outcomes of Nephrotic Syndrome in IgA Nephropathy
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Background: Uncommonly, IgA nephropathy can be complicated by nephrotic syndrome. In such cases, although, corticosteroid therapy should be recommended, the response to steroid treatment has been variable, and spontaneous remission without steroid treatment can occur in some cases. Here, we report our experience of clinical outcomes of nephrotic syndrome in patients with IgA nephropathy.

Methods: Thirty-three patients with biopsy-proven IgA nephropathy with nephrotic syndrome were enrolled between March 1990 and March 2009 in Dong-A university hospital. We retrospectively analyzed the data, including demographic, clinical, and laboratory records.

Results: The mean follow-up duration were 62 ± 45 months (10-204) in 33 patients. Complete remission occurred in 10 patients with steroid therapy and 2 patients without steroid therapy. Partial remission occurred in 7 patients with steroid therapy and 8 patients without steroid therapy. There were 6 patients with progressive deterioration of kidney function during follow-up periods.

Conclusions: Of IgA nephropathy patients with nephrotic syndrome, 36% of patients have complete remission, 45% of patients have partial remission. Steroid treatment may effectively reduce proteinuria. However, spontaneous remission occurs in some cases. Large-scale studies may be necessary in the future.

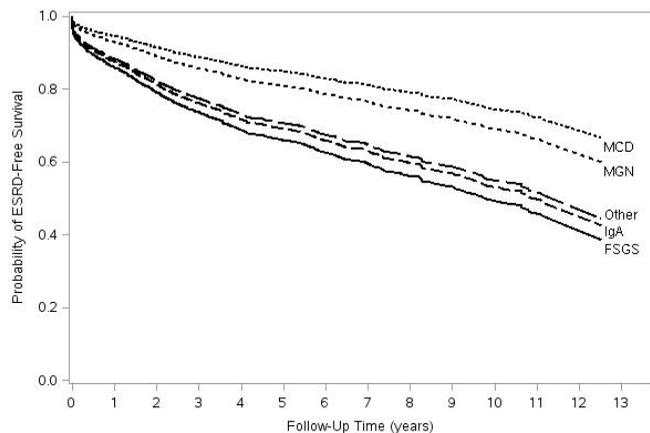
TH-PO797

Comparative Outcomes in Primary Glomerulonephritis Among a Large Diverse United States Population John J. Sim,¹ Michael Batech,² Teresa N. Harrison,² Taurino N. Avelar,¹ Aviv Hever.¹ ¹Nephrology and Hypertension, Kaiser Permanente Los Angeles Med Ctr, Los Angeles, CA; ²Research and Evaluations, Kaiser Permanente Southern California, Pasadena, CA.

Background: Glomerulonephritis (GN) remains an important cause of end stage renal disease (ESRD) in the United States and the world. Within a large diverse population of an integrated health system, we sought to evaluate rates of primary GN and then compare ESRD and mortality outcomes within different GN's.

Methods: Retrospective longitudinal cohort study in the period 1/1/2000 through 12/31/2013 among patients within Kaiser Permanente Southern California. Patients who had biopsy proven primary GN were characterized and followed until they reached the outcome of ESRD or mortality. ESRD was defined as receiving dialysis or renal transplant.

Results: 2,849 patients were identified with biopsy proven GN. The mean age of the cohort was 47 yrs with 48% females, 37% Hispanics, 30% whites, 17% blacks, and 12% Asians. Focal segmental glomerulosclerosis (FSGS) was the most common GN among all race/ethnic groups (36% overall) followed by membranous GN (MGN) (12%), minimal change disease (MCD)(11%), IgA nephropathy (IgAN) (10%), and others (31%). The mean follow up was 3.8 yrs. ESRD occurred in 26% (704 required dialysis and 38 had a renal transplant). Mortality occurred in 18%. ESRD occurred among 35% of FSGS, 19% among IgAN, 12% among MGN, 10% among MCD, and 29% among other GN's.



Conclusions: Among a large racially/ethnically diverse United States population, FSGS was the most prevalent GN and was associated with the highest rate of progression to ESRD among all race/ethnic groups. This diverse cohort may give insight into characterizing and risk stratifying different GN's which may pave the way for more optimal management strategies.

Funding: Pharmaceutical Company Support - Questcor Pharmaceuticals

TH-PO798

A Specific Transcriptomic Profile Characterizes Peripheral Blood Mononuclear Cells (PBMCs) from Uremic Patients (pts) Treated with On Line Hemodiafiltration (OL-HDF) Compared to Those Treated with Bicarbonate Dialysis (BHD) Simona Simone,¹ Annarita Chieti,¹ Matteo Accettura,¹ Roberto Corciulo,¹ F. Rascio,² Paola Pontrelli,¹ Giovanni Stallone,² Loreto Gesualdo,¹ Giuseppe Grandaliano,² Giovanni B. Pertosa.¹ ¹Dept of Emergency and Organ Transplantation, Univ of Bari, Italy; ²Dept of Medical and Surgical Sciences, Univ of Foggia, Italy.

Background: Recent studies suggest that OL-HDF can reduce the progression of dialysis-related cardiovascular diseases, but the molecular mechanisms underlying this improvement are not yet known. The aim of our study was to identify, through a high-throughput approach, differences in gene expression profiles of PBMCs from pts undergoing OL-HDF compared to BHD.

Methods: The transcriptomic profile was evaluated in PBMCs isolated from 10 pts regularly dialyzed with OL-HDF (convective volume³22 L) and 10 pts treated with BHD using microarray analysis (Agilent Technologies). The results were evaluated by statistical (unpaired t test) and functional pathway analysis (Ingenuity Pathway Analysis).

Results: We observed that 868 genes were differentially expressed in the comparison between OL-HDF and BHD (fold change>1.5). Thirty-seven functional gene networks were identified and atherosclerosis signaling was the top canonical pathway associated with BHD (p=2.45x10⁻⁴). Among the downregulated genes in OL-HDF there were PDGF (FC -2.13) and Clusterin (FC -2.14), involved in vascular injury and Monoamine Oxidase A (MAO-A, FC=-2.43), an important source of oxidative stress and a major contributing factor to the development of ventricular hypertrophy and hearth failure. Interestingly, Apolipoprotein E (Apo-E) gene, an anti-oxidant/inflammatory protein, was upregulated (FC=+1.7) by OL-HDF. qPCR, performed in an independent testing-group [15 BHD, 15 OL-HDF] confirmed that PDGF, Clusterin and MAO-A were down-expressed in OL-HDF (p=0.01), whereas APO-E resulted higher expressed (p<0.01).

Conclusions: The OL-HDF can contribute to cardiovascular risk reduction through the modulation of pathways involved in the progression of atherosclerotic disease. This observation could open new perspectives in the prevention of cardiovascular risk in dialysis pts.

TH-PO799

Twice-Weekly versus Thrice-Weekly Hemodialysis in Patients with or without Residual Kidney Function Hyeon Seok Hwang,¹ Suk young Kim,¹ Su Hyun Kim,² Yong-Lim Kim,³ Yon Su Kim,⁴ Shin-Wook Kang,⁵ Chul Woo Yang.¹ ¹College of Medicine, The Catholic Univ of Korea, Korea; ²Chung-Ang Univ College of Medicine, Korea; ³Kyungpook National Univ School of Medicine, Korea; ⁴Dept of Internal Medicine, Seoul National Univ College of Medicine, Korea; ⁵Yonsei Univ College of Medicine, Korea.

Background: Residual kidney function (RKF) accounts for large solute removal and significantly contributes to survival benefits in hemodialysis (HD) patients. However, there are no reliable outcome data suggesting that the frequency of HD might be safely reduced in patients with substantial RKF.

Methods: A total of 685 patients receiving more than 3 months HD therapy were included from the CRC registry for ESRD. The presence of RKF was defined as more than 100 ml/day of urine volume, and patients were classified into twice-weekly HD with RKF (n = 113), thrice-weekly HD with RKF (n = 137) and thrice-weekly HD without RKF (n = 435).

Results: The baseline RKF was significantly higher in twice-weekly HD patients with RKF than in thrice-weekly HD patients with RKF, and it remained higher at 12 months follow-up. The sum of weekly renal Kt/V and delivered-standard Kt/V per week was similar pattern between twice-weekly and thrice-weekly HD patients with RKF. The thrice-weekly HD patients with RKF showed significantly higher survival rate than twice-weekly HD patients with RKF or thrice-weekly HD patients without RKF (P = 0.002). In multivariable analyses, compared with thrice-weekly HD patients without RKF, thrice-weekly HD patients with RKF were associated with lower risk for all-cause mortality (HR 0.11; 95% CI 0.02-0.53). However, twice-weekly HD treatment with RKF did not reduce the risk of mortality (HR 0.65; 95% CI 0.22-1.87). For hospitalization of cardiovascular events, thrice-weekly HD therapy with RKF was independently associated with lower risk, (HR 0.40; 95% CI 0.16-0.98), but twice-weekly HD patients with RKF were not associated (HR 0.80; 95% CI 0.38-1.71).

Conclusions: Twice-weekly HD patients with RKF have similar outcome compared to thrice-weekly HD patients without RKF. However, thrice-weekly HD patients with RKF were more advantageous for mortality and CVE than those without RKF.

TH-PO800

Comparison of Outcomes Between Incremental and Abrupt Initiation of Hemodialysis: A Propensity-Matched Analysis of a Prospective Cohort Study in Korea Ji In Park,^{1,2} Yong-Lim Kim,^{2,3} Shin-Wook Kang,^{2,4} Chul Woo Yang,^{2,5} Yon Su Kim,^{2,6} Jung Pyo Lee,^{2,7} ¹Kangwon National Univ; ²Clinical Research Center of End Stage Renal Disease in Korea; ³Kyungpook National Univ; ⁴Yonsei Univ; ⁵The Catholic Univ of Korea; ⁶Seoul National Univ; ⁷Seoul National Univ Boramae Medical Center.

Background: When patients are diagnosed as end-stage renal disease (ESRD) and initiate hemodialysis (HD), thrice-weekly HD is a very common format. Recent report suggested possible benefit from beginning HD therapy less than three times weekly and incremental increase of dialysis dose, but there are not sufficient data. We compared outcomes of thrice-weekly and incremental HD.

Methods: A total of 1273 patients who were diagnosed as having ESRD and initiated hemodialysis from 2008 to 2014 were prospectively enrolled. The patients were classified into the abrupt initiation group (3 sessions/week) or the incremental initiation group (1-2 sessions/week). We compared HRQOL evaluated by KDQOL-SF and Beck's depression inventory (BDI) score at 3 months and 12 months after HD, and residual renal function by daily urine volume at 12 months after HD and all-cause mortality between the groups.

Results: Before propensity score matching, the abrupt group tends to be younger and showed smaller daily urine volume, higher modified Charlson comorbidity index (mCCI), and higher serum blood urea nitrogen and creatinine level compared to incremental group. A total of 432 patients (288 for abrupt and 144 for incremental group) were selected by propensity score matching. HRQOL tends to be better in incremental group for every domain of KDQOL-SF and BDI, but none of them showed significant difference at 3 months. At 12 months after HD, only cognitive functioning domain was better in incremental group. Daily urine volume at 12 months after HD was similar in two groups. All-cause mortality was comparable between two groups before and after propensity score matching.

Conclusions: Incremental initiation of HD showed comparable results with abrupt group regarding HRQOL, residual renal function and all-cause mortality. Incremental HD might be considered as another format of initiating HD for selected ESRD patients.

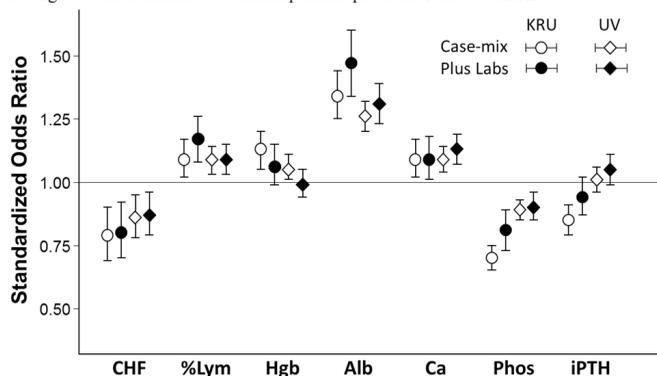
TH-PO801

Predictors of Substantial Residual Kidney Function in the First Year of Hemodialysis Treatment Yoshitsugu Obi,¹ Elani Streja,¹ Connie Rhee,¹ Anna Mathew,² Joline L.T. Chen,¹ Wei Ling Lau,¹ Steven M. Brunelli,³ Csaba P. Kovessy,⁴ Rajnish Mehrotra,⁵ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²Hofstra North Shore-LIJ Health System; ³DaVita Clin Research; ⁴UTHSC; ⁵UW.

Background: Residual kidney function (RKF) plays a critical role in dialysis adequacy, quality of life, and survival in hemodialysis (HD) patients. Therefore, identifying predictors related to preservation of RKF may contribute to improving patient management and developing novel strategy for preserving RKF.

Methods: In a longitudinal cohort of 18,091 patients who initiated conventional HD over four years (1/2007-12/2010), we examined the association of baseline characteristics during the first 3 months of their dialysis treatment with RKF [renal urea clearance (KRU) and urinary volume (UV)] after one year. We employed multivariate logistic regression analyses using ≥ 3 mL/min/1.73m² of KRU or ≥ 600 mL/day of UV as outcomes with 2-level adjustments for case-mix variables and laboratory measurements in addition to baseline RKF values.

Results: Patients were 62±14 years old, 37% female, 29% non-Hispanic Black, and 67% diabetic. Median KRU and UV were 2.95 (IQR, 1.63-4.64) mL/min/1.73m² and 800 (IQR, 500-1,300) mL/day, respectively. High %lymphocyte, higher serum concentrations of albumin and calcium, and lower serum concentrations of creatinine and phosphorus were consistently associated with better preserved RKF indices irrespective of models. A history of congestive heart failure was an independent predictor for loss of RKF.



Conclusions: Better nutritional and CKD-MBD indices were associated with preserved RKF while a history of congestive heart failure were associated with loss of RKF at 1 year of hemodialysis initiation in this large national cohort. Additional studies to preserve RKF in dialysis patients are warranted.

Funding: NIDDK Support

TH-PO802

Clinical Determinants of Ultrafiltration Rates in Hemodialysis Adam K. Horeish, Jeffrey M. Rimmer. *Univ of VT Med Ctr, Burlington, VT.*

Background: High rates of ultrafiltration (UFR) are associated with adverse events. Approaches to reduce UFR other than fluid restriction alone are needed.

Methods: We examined characteristics associated with ultrafiltration rates (UFR) in patients dialyzed at UVMC. Ultrafiltration rates (volume removed/pre-dialysis weight/treatment time) are followed electronically. Charts of 233 patients treated in October 2015 were examined with IRB approval. Patient characteristics and laboratory values were determined for 177 patients receiving three treatments during each of 4 consecutive weeks. These include average weight (PWt), treatment duration (RxT), and inter-dialytic weight gain (WtG); age, gender, dialysis vintage, sequence (TThS vs MWF), treating unit, diabetes, heart failure, prescribed diuretics, difference between serum and dialysate sodium (DifNa), percent urea reduction (PRU), absolute urea reduction, serum potassium, albumin, hemoglobin and pre and post dialysis blood pressure. The relation of weight, weight gain and treatment length were examined with descriptive statistics. Other potential explanatory variables were explored with multivariable regression models using both average UFR and average UFR for first weekly treatment as dependent variables.

Results: The range and median for PWt, RxT, and WtG respectively are 41.6 to 226, 81 Kg, 3 to 5.5, 4 hrs; and 0.63 to 8.38, 2.69 kg. When the values of PWt, RxT and WtG are below the median, 48.4%, 44.8% and 19.1% of patients respectively have a UFR > 10 ml/kg/hr and 15.6%, 23.9% and 48.9% if above the median. Variables significantly associated with UFR by regression are enumerated in table 1.

	1st UFR		AVG UFR	
R Square	0.321		0.317	
	BETA	P	BETA	P
Age	-0.042	0.007	-.045	0.002
Vintage	0.014	0.025	NA	NA
PreBP	0.022	0.037	0.020	0.042
DifNa	0.327	0.000	0.300	0.000
PRU	0.154	0.000	0.136	0.000
Sequence	-1.452	0.000	-1.525	0.000
Unit 5	1.258	0.030	1.525	0.005
Potassium	0.502	0.000	0.596	0.000
On Lasix	-0.765	0.117	-0.844	0.054

Variables not listed did not reach significance.

Conclusions: The large effect of low PWt requires long RxT to avoid high UFR with moderate WtG. Other prescribed variables that could be used to modify UFR include TThS vs MWF schedule, DifNa and possibly diuretic use.

TH-PO803

Study on Hemodialysis (HD) Time and Prognosis in Maintenance HD Patients: The Q-Cohort Study Kiichiro Fujisaki,¹ Shigeru Tanaka,¹ Masatomo Taniguchi,¹ Kazuhiko Tsuruya,¹ Hideki N. Hirakata,² Takanari Kitazono.¹ ¹Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; ²Div of Nephrology, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.

Background: HD time has been recognized as an important factor of dialysis adequacy. However, there have been few reports on studying the associations between HD time and prognosis in maintenance HD patients. We present some findings from a prospective cohort study, the Q-cohort Study, which was set up to explore the risk factors for mortality in Japanese HD patients. In the present study, we examined the associations between HD time and mortality in Japanese HD patients.

Methods: A prospective multicenter cohort study (Q-Cohort Study) was conducted between December 2006 and December 2010. A total of 3,459 Japanese HD patients were prospectively followed for 4 years. We examined the association of HD time and prognosis using a Cox proportional hazards model. Propensity scores were calculated using logistic regression.

Results: During follow-up period, 566 patients died from any causes. Patients with HD of 5 hours or more (n = 2,144) showed significantly lower mortality risk for all cause death at hazard ratio = 0.82 (95% confidence interval: 0.68 to 0.99) compared with those with HD of less than 5 hours (n = 1,315) after adjusting for confounding risk factors. This association remained significant using a propensity score-based approach. We stratified the analysis by patient age in 10-year increments, this finding remained significant only in patients with older than 80 years.

Conclusions: Our results suggest that HD time of 5 hours or more improves all-cause mortality especially in older HD patients.

TH-PO804

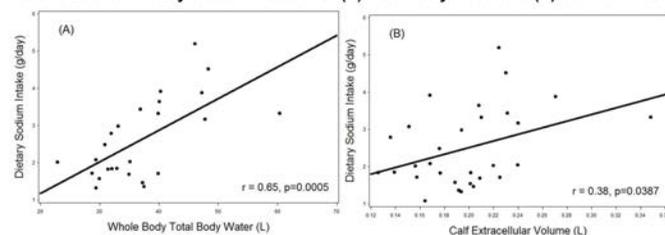
Salt Taste Sensitivity, Sodium Intake, and Fluid Status in Hemodialysis
 Panduranga S. Rao,¹ Robin L. Padilla,¹ Linton Cuff,¹ Tanu P. Verma,¹ Debra Peterman,¹ Michael Heung,¹ Scott L. Hummel,¹ Peter Kotanko,² Brenda W. Gillespie,¹ Rajiv Saran.¹ ¹Univ of MI, ²Renal Research Inst.

Background: Dietary Sodium intake (SI) contributes to volume status and blood pressure (BP) control in hemodialysis (HD) patients. Salt taste sensitivity (STS) may drive sodium intake, and has not been systematically studied in HD. We sought to assess the relationship between STS, SI, fluid status (as determined by bioelectrical impedance spectroscopy (BIS)) and pre-dialysis BP in HD patients.

Methods: As part of an ongoing randomized trial involving a low sodium diet, adults receiving outpatient HD were assessed for STS using commercial taste strips impregnated with 0-1.6% sodium chloride (NaCl); mean SI was estimated from 3-day food diary. Total Body Water (TBW) and Extracellular Volume (ECV) were estimated using whole-body and segmental (calf-resistivity) BIS, respectively.

Results: Baseline data on 33 enrolled patients (16 male, 17 black, 13 white, mean age 52 ± 15yr) were analyzed. Mean monthly pre-HD systolic BP was 151 ± 16 mmHg. Mean SI was 2.5 g/day (range: 1.1-5.2). Mean estimated SI was 0.8 g/day higher in patients without STS compared to those with STS (1.6% NaCl) (p=0.06). Higher SI correlated with higher calf ECV (r=0.38, p=0.04), whole body-BIS TBW (r=0.65, p=0.0005) and ECV (r=0.34, p=0.09). Mean Calf ECV was significantly lower in those with STS vs those without STS at 1.6% (0.19 vs 0.23 L; p=0.04). There was no correlation between SI and pre-dialysis BP (in-center routine or standardized).

Correlation of Dietary Sodium Intake with (A) Total Body Water and (B) Calf ECV BIS



Conclusions: Salt taste sensitivity and measures of hydration status by bioelectrical impedance spectroscopy are correlated with sodium intake in hemodialysis. These findings suggest that patients with low salt taste sensitivity may be particularly at risk for fluid excess. Future research should examine mechanisms of Salt taste sensitivity and its role in management of hemodialysis patients.

Funding: Private Foundation Support

TH-PO805

Arrhythmic Risk in Patients with Type II Diabetes on Hemodialysis: Preliminary Results from the Monitoring in Dialysis (MiD) Clinical Study
 Prabir Roy-Chaudhury,¹ Don E. Williamson,² James A. Tumlin,³ David M. Charytan,⁴ Kowdle Chandrasekhar Prakash,⁵ Vijay K. Kher,⁶ ¹Univ of Cincinnati; ²Nephrology Associates; ³Univ of Tennessee; ⁴Brigham and Womens Hospital, Boston; ⁵Apollo Hospitals-Chennai; ⁶Medanta-Medicity.

Background: 40% of the overall ESRD population has diabetes and these patients are considered to be at increased risk of cardiac events. The goal of this analysis was to describe the pattern of both clinically significant events and documented arrhythmias in a subset of patients with Type II diabetes from the Monitoring in Dialysis (MiD) study.

Methods: The MiD study is a prospective, multi-center, observational study designed to characterize the type and frequency of documented and adjudicated arrhythmias in hemodialysis patients during a 6-month period, using an implanted continuous cardiac monitoring device (Medtronic Reveal XT or Reveal LINQ). All documented arrhythmias and clinically significant arrhythmias (CSA) defined as bradycardia ≤40 bpm for ≥6 sec, asystole ≥3 sec, sustained ventricular tachycardia ≥130 bpm for ≥30 sec and symptomatic arrhythmias during this period were then correlated temporally to the dialysis cycle (first, second or third dialysis session of the week; during or after hemodialysis; how long after hemodialysis).

Results: Type II Diabetes was present in 39/66 (59%) of the MiD patients. The mean age was 62 (36-76) years, 72% male, mean years on HD 2.8 (1-15), 36% with a history of cardiac arrhythmias with a mean follow-up of 8.6 months (range 0.6-13.9). Arrhythmic risk in the Type II diabetic patients was similar to the previously reported data on the entire study population, with the highest incidence of documented arrhythmias occurring in the 12 hour period starting with each dialysis session (particularly in the 8 hours after the end of the session). The incidence then decreased, followed by a gradual rise during the rest of the interdialysis period. Interestingly, the incidence of CSA in the 12 hour period starting with the first dialysis session of the week was much greater than in the overall study population.

Conclusions: The increase in the incidence of CSA in diabetic ESRD patients suggests that these patients could be a target population for the use of the Reveal implant.

Funding: Pharmaceutical Company Support - Medtronic

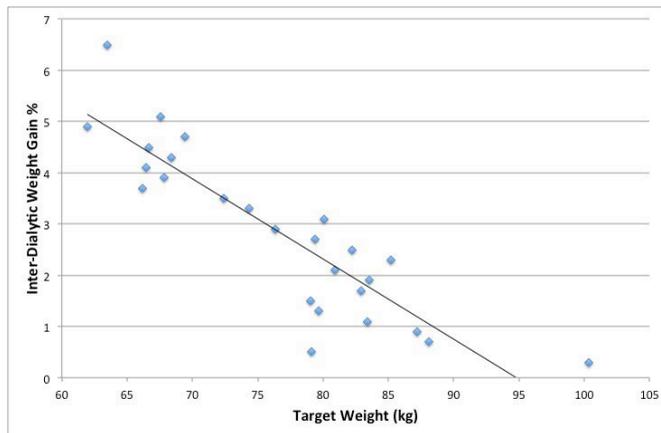
TH-PO806

Individualising Fluid Restriction Based on Target Weight Can Prevent a High Ultrafiltration Rate
 Emily See, John W. MacD. Agar. *Nephrology, Univ Hospital, Geelong, VIC, Australia.*

Background: Fluid restriction (FR) in haemodialysis patients has traditionally been advised by residual urine output and an arbitrarily defined oral intake, commonly 750ml/day. Surprisingly, little attention has been paid to individualising FR according to target post-dialysis weight (TW), despite the logical argument that smaller patients require less fluid. Excessive inter-dialytic weight gain (IDWG), when calculated as a percentage of TW (IDWG%), results in a high ultrafiltration rate (UFR) if session length (t) is constant [$UFR(\text{ml/kg/hr}) = \text{IDWG}(\text{ml}) \div \text{TW}(\text{kg}) \div t(\text{hr})$]. Since a high UFR has been linked to a poor clinical outcome, these patients must be identified and targeted. We aim to determine if a high IDWG% can be predicted from TW and then be used to individualise FR.

Methods: Data were prospectively collected from 14,112 sessions in 139 patients undergoing in-centre thrice-weekly haemodialysis between Jan-Dec 2014. Mean age was 68.9yr, 56% were male. Mean TW and IDWG% were calculated every 6 weeks. Results were divided into IDWG% cohorts, within each of which an average TW was calculated.

Results: Mean IDWG% was 2.30% (range 0.1-6.4). IDWG% was inversely proportional to TW ($r^2=0.78$).



From this data, we devised a formula that calculates an individualised FR based on the desired UFR (dUFR), the session duration (t), TW, and interval days between sessions (n). As $[\text{IDWG} = \text{FR} \times n]$; and $[\text{IDWG} = \text{dUFR} \times t \times \text{TW}]$; therefore $[\text{FR}(\text{ml}) = \text{dUFR} \times t \times \text{TW} \div n + \text{residual urine output}]$.

Conclusions: Patients with low TW are most at risk of high IDWG% and, consequently, a high UFR. A high UFR leads to rapid intravascular volume contraction which triggers post-dialytic thirst and reinforces the inevitable cycle of further high IDWG%. As TW provides a readily accessible clinical end-point that predicts at-risk patients, we propose that FR be individualised according to TW to enable patients to remain below the desired UFR.

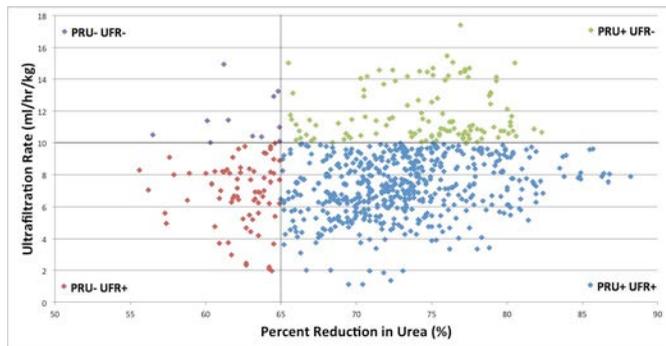
TH-PO807

Ultrafiltration Rate Should Be Independently Targeted as a Marker of Haemodialysis Adequacy
 Emily See, John W. MacD. Agar. *Dept of Nephrology, Univ Hospital, Geelong, VIC, Australia.*

Background: For 30 years, solute clearance has been the key determinant of dialysis adequacy. This emphasis has marginalised the critical contribution of safe rates of fluid removal to “adequate” dialysis. Ultrafiltration rate (UFR) has been proposed as an easily measurable marker of volume management (Agar 2015 HDI) and several studies have demonstrated a correlation between high UFR and poor clinical outcomes. Despite this association, UFR is not routinely targeted and the proportion of patients who meet percentage reduction in urea (PRU) but not UFR targets is unclear. While a “safe” UFR_{MAX} is yet to be conclusively defined, current literature supports an escalating clinical risk beyond a UFR of 10ml/hr/kg and an absolute risk above 13ml/hr/kg.

Methods: Data were prospectively collected from patients undergoing in-centre thrice-weekly conventional haemodialysis over a 12-month study period (Jan-Dec 2014). PRU and mean UFR were calculated every 6 weeks. $\text{UFR} < 10\text{ml/hr/kg}$ was defined as “volume-adequate” and $\text{PRU} > 65\%$ was considered “solute-adequate”.

Results: 720 episodes were collected from 115 patients. The mean age was 68.9yr and 56% were male. 73% of episodes met both adequacy targets ($\text{PRU} + \text{UFR} +$). 10% met the UFR but not the PRU target ($\text{PRU} - \text{UFR} +$). 16% met the PRU but not the UFR target ($\text{PRU} + \text{UFR} -$). 1% met neither ($\text{PRU} - \text{UFR} -$). In patients who met the PRU target 18% did not meet the UFR target.



Conclusions: Adequacy of solute removal does not equate to adequacy of volume removal. When a solute marker is used as the sole determinant of dialysis adequacy, a significant number of patients undergo “volume-inadequate” dialysis. These patients were more likely to be female and have a lower post-dialysis weight. Given the potentially substantial clinical implications, we propose that UFR be independently targeted allowing composite solute and volume markers to together define truly “adequate” dialysis.

TH-PO808

Fluid Management with Technology-Assisted Probing Peter B. De Ore,¹ Mary Kay Deck,² Anne M. Brumfield.² ¹Medical Affairs, Centers for Dialysis Care 1, Shaker Heights, OH; ²Systems, Intelomed 2, Wexford, PA; ³Clinical Services, Intelomed 2, Wexford, PA.

Background: Intradialytic hypotension (IDH) is associated with mortality. Rapid fluid removal is associated with cardiovascular (CV) morbidity and mortality. Decreased pulse pressure during HD is associated with improved outcomes. A focused intervention approach assisted by monitoring technology was used to assess fluid management as defined by 1) achievement of post weight within 1 kg around dry weight, 2) avoidance of IDH [SBP<90], 3) decrease in pulse pressure (PP) from pre-post dialysis.

Methods: 24 patients (16 controls, 8 intervention) were included. Control data: 18 treatments (txs) with same staff, room, time interval. Intervention data: 36 baseline txs prior to protocol along with 18 txs during active monitoring and guided probing. The protocol required setting goal to .2 KG < dry weight OR < .2 KG last post weight with small goal changes early in treatment, set of defined actions based on CV physiologic monitoring via CVInsight™ (CVI) [Intelomed, Wexford, PA] and relative plasma volume (RPV) via Crit-Line III® [Fresenius, Kaysville, UT]. Interventions were employed based on monitoring data, with a goal to increase UF tolerance without increasing IDH events. BP was measured every 15 minutes.

Results: Intervention patients demonstrated significant improvement in all three fluid management parameters during the protocol compared to preceding txs.

	PW<DW-1 KG*	PW<DW+1 KG*	SBP < 90 [†]	Pre PP [‡]	Post PP [‡]	UFR [‡]	PW/DW [‡]
Baseline	.09 ± .02	.24 ± .02	.07 ± .01	71 ± 1.3	68 ± 1.2	5.73 ± .19	.01 ± .001
Protocol	.34 ± .04	.15 ± .04	.01 ± .02	66 ± 1.6	63 ± 1.6	7.74 ± .32	.028 ± .001

* p < .0001, † p < .05

Intervention patients also demonstrated significant improvement in IDH compared to Control patients that dialyzed without guided probing.

Conclusions: A focused effort to improve fluid management through technology guided probing supported by CVI measures of cardiovascular stress and RPV, was successfully executed by chair-side staff. Optimizing fluid removal goals while simultaneously avoiding IDH events illustrates the benefit of patient monitoring.

Funding: Pharmaceutical Company Support - Intelomed

TH-PO809

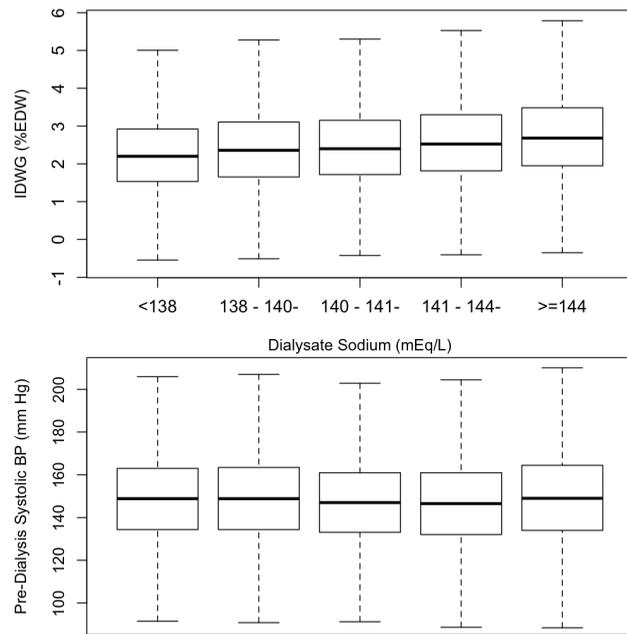
Increased Mortality Associated with Higher Dialysate Sodium Concentrations Is Not due Solely to Higher Interdialytic Weight Gains and Blood Pressure Ambreen Gul,¹ Ronald Schrader,¹ Susan Paine,¹ Philip Zager.^{1,2} ¹DCI, Albuquerque, NM; ²UNM, Albuquerque, NM.

Background: There is ongoing controversy regarding the optimal DNa. Many investigators have urged the use of DNa of 134 to 138 mEq/L, to limit interdialytic weight gain (IDWG) and improve control of hypertension. In contrast, others have cautioned that low DNa may be associated with increased hospitalization and mortality.

Methods: We conducted a retrospective observational study of 26,000 chronic hemodialysis (HD) patients treated in facilities operated by Dialysis Clinic Inc. from 2009-2013 to assess the relationships of DNa to IDWG and predialysis systolic BP (SBP) and their effect on mortality. We fit a time-varying Cox proportional hazards regression model for mortality, which included all incident and prevalent patients. There were over 630,000 patient-months of follow-up. Multiple data values for each patient were aggregated by month. Predictor variables in addition to DNa included demographics, monthly lab values, and session-level data including IDWG and pre- and post-dialysis BP. Individual clinic effects were fit as random effects. Time-varying predictors were lagged by 2 months.

Results: Higher DNa concentrations were associated with only modest increases in IDWG and predialysis SBP [figure]. Moreover, neither predialysis SBP ≥ 150 mm Hg or IDWG < 4.2% of estimated dry weight were associated with increased mortality.

Nevertheless, higher DNa concentrations were associated with increased mortality (HR [95%CI] = 1.09 [1.02, 1.16]) for DNa > 140 mEq/L (Referent DNa = 140 mEq/L) after adjusting for all other variables including IDWG and BP.



Conclusions: Although reducing DNa to < 140 mEq/L may have only a modest impact on IDWG and predialysis SBP it has the potential to significantly decrease mortality.

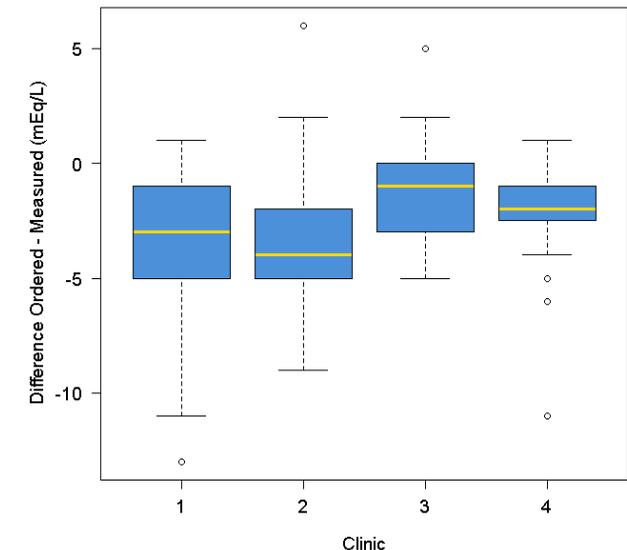
TH-PO810

Comparison of Ordered versus Measured Dialysate Sodium Concentrations Ambreen Gul,¹ Dana Miskulin,³ Leonard A. Arbeit,⁴ Sriram Narsipur,⁵ Susan Paine,¹ Ronald Schrader,¹ Philip Zager.^{1,2} ¹DCI, Albuquerque, NM; ²UNM, Albuquerque, NM; ³Tufts, Boston, MA; ⁴SUNY, Stony Brook, NY; ⁵SUNY, Syracuse, NY.

Background: There is controversy regarding the optimal dialysate sodium concentration (DNa). Many investigators have urged the use of DNa of 134 to 138 mEq/L, while others have cautioned that low DNa may be associated with increased hospitalization and mortality. Unfortunately, throughout this debate, little attention has been paid to how closely delivered DNa matches ordered DNa.

Methods: We studied 333 hemodialysis (HD) patients at 4 DCI facilities. We sampled dialysate from the arterial dialyzer port prior to the start of HD for measurement of DNa. Units 1 and 2 used Fresenius 2008 K and 2008 K² machines and Fresenius Granuflo® Dry Acid and NaturaLyte® mixed onsite from dry concentrates. Units 3 and 4 used Gambro Phoenix machines and pre-mixed acid concentrates obtained from Rockwell and bicarbonate cartridges from Baxter or Gambro. The online clearance feature was off.

Results: Measured DNa was usually higher than ordered DNa. The magnitude of difference varied by clinic (p < .0001).



Least squares mean differences (95% CI) were larger at Clinics 1 [-3.27 (-4.02, -2.53) mEq/L] and 2 [-3.77 (-4.49, -3.05) mEq/L] vs. with Clinics 3 [-1.44 (-2.10, -0.78) mEq/L] and 4 [-1.78 (-2.47, -1.10) mEq/L]. The percentages of measured DNa concentrations within ± 2 mEq/L of the ordered DNa at Clinics 1, 2, 3 and 4 were 47, 25, 71 and 77%, respectively.

Conclusions: Measured DNa concentrations were often significantly higher than ordered DNa in facilities using Fresenius machines and dialysate concentrates mixed onsite. Routine measurement of DNa should be incorporated into facilities' QAPI programs. Future studies looking at clinical outcomes associated with differences in prescribed DNa, should include measurements of delivered DNa concentrations.

Funding: Clinical Revenue Support

TH-PO811

Successful Use of Bivalirudin Protocol to Prevent Extracorporeal Thrombosis in Hemodialysis Patients with Heparin Induced Thrombocytopenia
 Abdullah Hamad, Fadwa S. Al-Ali, Hoda Tolba, Rania Abdelaziz Ibrahim, Mohamed Elsayed. *Nephrology, Fahd Bin Jasim Kidney Center, Hamad General Hospital, Doha, Qatar.*

Background: Heparin Induced Thrombocytopenia (HIT) has been reported in hemodialysis (HD) patients with a variable prevalence of 1-13%. There have been few reports using Lepirudine, Argatroban and Danaparoid in the management of extracorporeal thrombosis (ECT) during dialysis in these patients as heparin is contraindicated. We are reporting use of Bivalirudin to prevent ECT.

Methods: Our Study was done in Fahad Bin Jassim Kidney Center in Doha, Qatar (a large outpatient HD clinic of 300 patients). All patients diagnosed with HIT were included. HIT was diagnosed by ELISA method.

Results: 8 patients had confirmed positive HIT AB, 2 were receiving warfarin for atrial fibrillation with no ECT events and were excluded. One patient had a negative repeat test for HIT AB with no ECT events so he was excluded too. 5 patients with HIT AB and recurrent ECT events during dialysis were included. 3 patients had fistula and 2 had permanent catheter. A protocol was developed to start and adjust Bivalirudin based on **activated partial thromboplastin time (aPTT)** value. Table 1 summarize patients dosing and adjustment on protocol.

Bivalirudin Infusion Protocol for HIT in Hemodialysis Patients

1. Initial Infusion Rate 0.02 mg/Kg/hr.
2. Baseline aPTT should be checked and then 2 hours after infusion initiated
3. aPTT should be checked 2 hours after infusion every session until a PTT in therapeutic range with no further clotting then once per week.
4. Risk for bleeding versus thrombosis must be evaluated to determine safe and effective dose: In high risk of bleeding, adjust aPTT to 1.5 - 2.5 X normal, In high risk of clotting or active HITTS, adjust aPTT to 2.0 - 2.5 X normal

aPTT Ratio	Dose Adjustment
< 1.2	Increase dose by 20% and repeat aPTT after 2 hrs.
1.2 - 1.4	Increase dose by 10% and repeat aPTT after 2 hrs.
1.5 - 2.5	No dose change and monitor aPTT as protocol
2.6 - 3.5	Decrease dose by 10% and repeat aPTT after 2 hrs.
3.6 - 4.4	Decrease dose by 20% and repeat aPTT after 2 hrs.
> 4.5	Hold therapy until aPTT ratio < 3.5 then restart at a reduced dose and repeat aPTT after 2 hrs.

Patient	Dialysis access type	Duration on Bivalirudin	Starting dose	Final dose	Adjustment of dose
1	fistula	5 months	1.8 mg/hour	3.4 mg/hour	6 times
2	fistula	4 months	1.6 mg/hour	2.1 mg/hour	2 times
3	permcath	2 months	2 mg/hour	4 mg/hour	4 times
4	fistula	4 months	1.5 mg/hour	1.8 mg/hour	1 time
5	permcath	8 months	1.7 mg/hour	3 mg/hour	3 times

Conclusions: We are reporting a successful use of Bivalirudin protocol to prevent ECT in HD patients with HIT. It provided a simple dosing initiation with easy adjustment based on weight, aPTT and ECT events. The protocol provided excellent safety where no bleeding complications occurred in these patients throughout the study.

TH-PO812

(1@3)- β -Glucans and Endotoxins in Hemodialysis
 Jonathan P. Wong,¹ Yonglong Zhang,² Enric Vilar,¹ Malcolm A. Finkelman,² Ken Farrington.¹ ¹Lister Renal Unit, United Kingdom; ²Associates of Cape Cod.

Background: Endotoxemia is widely reported in dialysis patients and proposed to be related to systemic inflammation. Endotoxins are detected using the Limulus Amoebocyte Lysate (LAL) assay. However, the LAL assay is prone to interference and can be activated by (1@3)- β -glucans (BG), a component of fungal cell wall, through an alternative LAL

enzymatic pathway leading to falsely high endotoxin signals. High endotoxin content reported in dialysis patients may be due, to an unknown extent, to BG-based activation of LAL.

Methods: Predialysis blood samples were collected from 10 hemodialysis (HD) patients with systemic inflammation and 10 HD patients without inflammation and tested for endotoxin using the kinetic turbidimetric LAL assay (KTA2, Charles Rivers). Endotoxin measurements were performed with and without a BG blocking buffer. The buffer prevents the activation of the LAL assay by BG, to ensure that LAL activation is endotoxin-specific. The same samples were also assayed for BG content using an FDA-cleared BG detection assay (Fungitell[®], Associates of Cape Cod). Differences in endotoxin and BG content were compared between inflamed and non-inflamed patients. Differences in endotoxin content in samples assayed with and without a BG blocking buffer were compared.

Results: Blood endotoxin was higher in patients with systemic inflammation although this did not reach statistical significance (0.027 vs 0.013 EU/ml, p=0.579). Endotoxemia was detected in 55% of patients. On repeat measurement with a BG blocking buffer, no patients had detectable endotoxemia. Both inflamed and non-inflamed patients were found to have similarly significant elevated blood BG (60 vs 81.3 pg/ml, p=0.29). There was no significant correlation between levels of BG and endotoxin (r=-0.435, p=0.055). No endotoxin and very low concentration of BG (3pg/ml) was detected in saline washout from the blood compartment of the dialyser.

Conclusions: Elevated blood endotoxin reported in HD patients may be due to BG interference. This suggests that endotoxin measurements should be carried out with BG blocking buffers. The source and clinical significance of elevated BG levels in HD patients is unknown and requires investigation.

Funding: Clinical Revenue Support

TH-PO813

The Correlation of BNP and hANP in Hemodialysis Patients and Their Prediction Ability of Life Prognosis
 Koji Takemura, Fumitaka Fujino, Yoshihiro Miyauchi, Takashi Watanabe. *Nephrology, Asahi General Hospital, Asahi, Chiba, Japan.*

Background: B-type natriuretic peptide (BNP) and human atrial natriuretic peptide (hANP) have been reported to be useful for assessment of the volume status, cardiovascular risk, or life prognosis in hemodialysis patients. However, correlation or superiority of the two parameters are not clear. The aims of this study were to assess whether BNP and hANP have correlation, and whether they are predictive.

Methods: Two hundred and twenty-eight hemodialysis patients at one hospital were assessed in March 2012. BNP and hANP were measured at the end of hemodialysis. And we observed the patients' survival until May 2015.

Results: This study analyzed 228 patients. Results showed that BNP and hANP had strong correlation in patients without chronic heart failure (EF>40%): R²=0.70 in those with atrial fibrillation (Af), R²=0.57 without Af. 69 deaths occurred in about 3 years; in univariate analysis, BNP and hANP were significant predicting factors (p=0.004 and p=0.013 for each) and in multivariate analysis, age and hANP were significant predicting factors in multivariate analysis (p=0.019 and 0.011).

Conclusions: BNP and hANP had strong correlation in hemodialysis patients without chronic heart failure. They also predicted life prognosis, and especially hANP had independent prediction ability. In hemodialysis patients, BNP and hANP are useful for assessment of life prognosis in spite of various known or unknown confounding factors.

TH-PO814

Intracranial Fluid Shifts During Hemodialysis Measured Using VIPS (Volumetric Integral Phase-Shift Spectroscopy) Is Influenced by Osmolarity, Sodium and Less So by Urea Nitrogen
 Chethan P. Venkatasubba rao,¹ Sreedhar A. Mandayam,² Eric Bershad,¹ Eusebia Calvillo,¹ Jose Ignacio Suarez.¹ ¹Neurology, Baylor College of Medicine, Houston, TX; ²Nephrology, Baylor College of Medicine, Houston, TX.

Background: End Stage Renal Disease (ESRD) patients undergoing hemodialysis(HD) experience a drop in serum osmolarity. This may result in cerebral edema. Cerebral edema has been measured by invasive monitors or imaging studies. We used Volumetric Integral Phase-shift Spectroscopy(VIPS), a non-invasive technology that detects fluid-induced phase shifts in low-energy radio waves transmitted through the brain.

Methods: The protocol was approved by the IRB of Baylor college of Medicine. ESRD on HD subjects without intracranial illnesses were enrolled. VIPS monitoring was performed pre, intra and post HD. Measured and calculated serum osmolarity(osm) and mini mental state examination was performed pre and post HD.

Results: 19 patients (12 males) were enrolled. Median age was 50 years. 1 patient withdrew. Of the 31 HD runs, 21 complete data sets were analyzed. There was a mean increase of 10.6% in the total Intracranial fluid(ICF) value from baseline corresponding to an average of 7 mOsm reduction. The ICF change measured by VIPS correlated with osm changes (r=0.31), best with change in Sodium change [Post HD - pre HD](r= 0.51), less so with the BUN change (r=0.14) and least with glucose (r=0.01). Subjects with sodium < 135 at baseline had a tendency to develop lower ICF change (3% n=5) as compared to eunatremic subjects (12%, n=16, p=0.22).

Conclusions: VIPS provides real-time non-invasive monitoring of intracranial fluid shifts. Subjects develop serum osmolar reductions during HD, which can potentially be a model for studying cerebral edema. Sodium shifts had a higher correlation to ICF change in our study. Further research to confirm our findings are warranted.

Funding: Pharmaceutical Company Support - Cerebrotech Medical Systems, Inc.

TH-PO815

Online Hemodiafiltration Using Citrasate® Dialysis Solution – An Alternative to Systemic Anticoagulation? Pavlina Richtrova, Lukas Kielberger, Jan Mares, Tomas Reischig. 1st Medical Dept, Charles Univ Medical School and Teaching Hospital, Plzen, Czech Republic.

Background: Citrasate® is a dialysis solution using citrate (contrary to more common acetate) as the acidifying buffer compound. According to recently published data, its application could decrease or even obviate the need for systemic anticoagulation in hemodialysis (HD) patients. Particularly so during online hemodiafiltration (HDF) as in this setting predilution should provide yet higher in-dialyzer citrate concentrations resembling regional citrate anticoagulation (RCA).

Methods: In a prospective, randomized, cross-over study, 10 long-term HD patients were examined during 4h HDF procedure using Citrasate® (0.8 mmol/l citrate) in a predilution setting without additional systemic anticoagulation. Standard HDF procedure using acetate-buffered solution together with fractionated heparin was applied as a control. Along the session, blood and dialysate were sampled to enable analysis of thrombogenicity, acid base balance, calcium metabolism, and dialysis efficacy. Data are given as means±SD, statistical significance was calculated by ANOVA.

Results: No HDF session was terminated prematurely though the semiquantitative dialyzer clotting score showed increased clotting under citrate solution ($p=0.001$). At the same time, procedure efficacy assessed by spKt/V , as well as serum calcium, bicarbonate and pH did not differ significantly. While in controls the thrombin-antithrombin (TAT) levels remained unchanged, during citrate-buffered HDF a steady increase of TAT was demonstrated: from 3.6 ± 2.36 and 5.6 ± 3.85 $\mu\text{g/l}$ at 0h to 7.8 ± 7.65 and 38.9 ± 23.25 $\mu\text{g/l}$ at 4h for acetate and citrate respectively ($p<0.001$).

Conclusions: From a clinical standpoint, HDF using Citrasate® excluding heparin may serve as a viable alternative to RCA where systemic anticoagulation is to be avoided. No issues were detected in terms of safety, tolerability, and dialyzer performance. Even then, increased laboratory markers of thrombogenicity suggest inferiority of such approach precluding its use for regular HD.

Funding: Government Support - Non-U.S.

TH-PO816

Hypertension in Hemodialysis Patients: Dialysis Techniques and Hormonal Regulation Guido Gatti, Chiara Lanzani, Marco Simonini, Simona Pozzoli, Stefano Tentori, Elena Brioni, Lorena Citterio, Elisabetta Messaggio, Simona Delli carpini, Nunzia Casamassima, Teresa Arcidiacono, Maria Teresa Sciarone Alibrandi, Rita Quartagno, Marco Melandri, Giorgio Slaviero, Donatella Spotti, Paolo Manunta. Nephrology, Dialysis and Hypertension, IRCCS San Raffaele Scientific Inst, Milan, Italy.

Background: Hypertension in hemodialysis patients has a prevalence of 50-80% and is associated to increased cardiovascular mortality. Endogenous ouabain (EO), a digitalis-like cardiotonic steroid produced by adrenal glands, in hemodialysis patients is associated to left ventricular mass, volume and eccentric hypertrophy remodeling. N-terminal pro B-type natriuretic peptide (NT-proBNP) is associated with heart failure and fluid overload. Hemodiafiltration (HDF) improves cardiovascular survival than bicarbonate hemodialysis (HD). The aim is to explore the relationship between BP values, hormonal regulation (EO and NT-proBNP) and hemodialysis techniques.

Methods: We enrolled 93 chronic hemodialysis patients; we performed ABPM of 24 hours, blood and effluent dialysis fluid analysis. 42 patients were treated with HDF, 51 with HD.

Results: NT-proBNP is directly associated with SBP of 24h and indirectly with EF of left ventricle; it is removed by HDF by convective clearance (decrease of 57%), as medium molecular weight compounds, and not by HD (increase of 21%). EO is directly associated with interdialytic weight gain and interventricular septum; it decreases with dialysis session independently of dialysis technique (decrease of 20%). Patients with cardiopathy have higher EO plasma levels than patients without cardiopathy. Beta-2 microglobulin is directly associated with NT-proBNP and SBP of 24h.

Conclusions: These data show that NT-proBNP is an index of hypertension and heart failure, while EO is linked to fluid overload and left ventricular hypertrophy. NT-proBNP is removed by convection, while EO decreases with dialysis independently of dialysis technique (may ultrafiltration determine the decrease?). Convective clearance, expressed indirectly by beta-2 microglobulin, may influence BP control through the modulation of NT-proBNP.

TH-PO817

NT-proBNP Is a Useful Biomarker to Identify Cardiac Dysfunction in Japanese Hemodialysis Patients Minako Shimizu,¹ Ayumu Nakashima,² Shigehiro Doi,³ Takao Masaki.⁴ ¹Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan; ²Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan; ³Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan; ⁴Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) is a well-established diagnostic biomarker of heart failure in populations without kidney dysfunction. However, the clinical significance of NT-proBNP in hemodialysis (HD) patients remains unclear.

Methods: We enrolled 1428 HD patients from 14 dialysis centers in Hiroshima, Japan and performed cross-sectional analysis. Blood samples for measurement of serum NT-

proBNP were collected at pre- and post-HD sessions. Among all participants, ultrasonic cardiography (UCG) was performed in 395 patients (27.7%). We evaluated whether serum NT-proBNP levels were associated with left ventricular hypertrophy (LVH) on the electrocardiogram (ECG), and LVH and ejection fraction (EF) on UCG. We also used multiple regression analysis to investigate the clinical factors that correlated with the reduction ratio of NT-proBNP levels due to HD.

Results: The mean pre- and post-HD NT-proBNP levels were 8789 ± 15311 and 5257 ± 8939 pg/mL, respectively. Multivariate regression analysis revealed that the post-HD NT-pro-BNP was significantly correlated with LVH on ECG as well as EF and LVH on UCG ($P < 0.001$). When both pre- and post-HD NT-proBNP were evaluated in the same patients, the odds ratios (ORs) for LVH on ECG, and LVH and EF on UCG were lower at pre- than post-HD (ORs: 1.36, 2.16, 3.47 versus 1.19, 1.54, 2.37, respectively). However, the sensitivity and specificity of pre- and post-HD NT-proBNP to predict LVH and EF were similar. In multiple linear regression analysis, the reduction ratio (%) of NT-proBNP due to HD was correlated with Kt/V ($P < 0.001$), membrane area ($P < 0.001$), membrane type ($P < 0.001$), modality ($P < 0.001$), % body weight gain ($P < 0.001$), treatment time ($P < 0.001$) and ultrafiltration rate ($P = 0.003$).

Conclusions: NT-proBNP is a useful biomarker to identify LVH and LV dysfunction in HD patients. Blood samples should be taken post-HD despite the NT-proBNP reduction due to HD.

Funding: Pharmaceutical Company Support - Roche

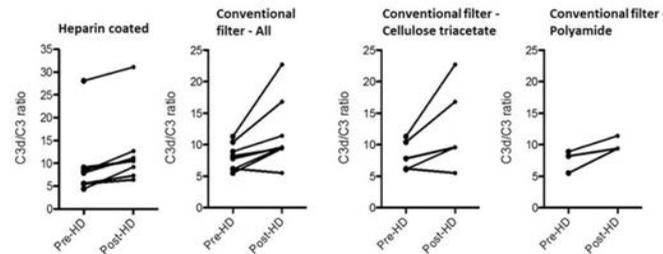
TH-PO818

Similar Complement Activation by Heparin-Coated Dialyzer Compared with Heparin-Free Dialysis Using Predilution Susan J. Logtenberg,^{1,2} Casper F.M. Franssen,¹ Marc Maj Seelen.¹ ¹Nephrology, Univ Medical Center, Groningen, Netherlands; ²Internal Medicine, Diakonessenhuis, Utrecht, Netherlands.

Background: Heparin-coated dialyzers have been shown to be an effective method for heparin-free hemodialysis and are increasingly used. Conflicting reports on complement activation by heparin have been published, however. Complement activation could therefore be potential harmful for patients that are scheduled for transplantation shortly after hemodialysis (HD). We investigated the difference in complement activation between heparin-coated dialyzers and heparin-free HD using conventional filters with predilution.

Methods: We measured C3 and C3d levels in 16 (5 F) consecutive patients that were treated with either a heparin coated filter ($n=8$ (Evodial®)) or a conventional filter ($n=5$ cellulose triacetate, $n=3$ polyamide) with predilution 1-2l/h. C3 and C3d were measured before and at the end of a single HD treatment session. C3d to C3 ratios were calculated.

Results: Mean age was 58 ± 16 years. The figure shows C3d/C3 ratios before and after HD for individual cases in the different filter groups. Mean C3d/C3 ratios increased during HD with all types of dialyzers. Mean C3d/C3 ratio in the heparin-coated dialyzer group increased from 9.7 ± 7.6 before HD to 12.4 ± 7.8 after HD ($p=0.001$). Mean C3d/C3 ratio in the conventional filter group increased from 8.0 ± 2.1 to 11.8 ± 5.4 ($p=0.03$). C3d/C3 ratio increased during HD with both the polyamide (from 7.5 ± 1.8 to 10.0 ± 1.2 ; $p=0.09$) and the cellulose triacetate dialyzer (from 8.3 ± 2.4 to 12.9 ± 6.9 ; $p=0.02$). There was no significant difference in the change of C3d/C3 ratio between the heparin coated filter group and the conventional filter group (2.7 ± 1.4 vs. 3.7 ± 3.7 , respectively ($p=0.5$)).



Conclusions: Heparin-coated dialyzers induce similar complement activation during HD when compared to conventional dialyzers.

TH-PO819

A Heparin-Grafted Membrane plus Citrate Containing Dialysate versus Regional Citrate Anticoagulation: Results of the CiTED Study Christoph Metalidis, Ruben Poesen, Annelore De winter, Dirk R. Kuypers, Pieter Evenepoel, Bjorn Meijers. Nephrology, Univ Hospitals Leuven, Belgium.

Background: Heparin is the mainstay anticoagulant during dialysis. Alternative anticoagulant strategies include regional citrate anticoagulation (RCA), heparin-grafted dialyzers or saline flushes. Of these, RCA is the most efficacious, although technical complexity and labor intensiveness preclude widespread use. Heparin-grafted membranes are easy to use, but dialyzer patency is inferior to RCA. Whether combination of citrate-containing dialysate plus heparin-grafted membranes is non-inferior to RCA is unknown.

Methods: The CiTrate plus Evodial in Dialysis (CiTED) study is a prospective, open-label randomized cross-over study comparing citrate-containing dialysate plus heparin-grafted membranes vs. RCA. In the study arm, we scheduled 750 dialysis sessions using combination of a heparin-grafted AN69ST dialyzer (Evodial 180®, BAXTER) and 1 mmol/L citrate-containing dialysate (Selectbag Citrate®, BAXTER). In the control arm, 750 sessions of RCA were scheduled using Polyflux 170 (BAXTER) dialyzers and calcium-containing dialysate. In all sessions, scheduled treatment duration was 4 hours.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

No systemic heparin was used. Primary endpoint was non-inferiority for clotting events of the combination of a heparin-grafted membrane plus citrate-containing dialysate vs. RCA, with a prespecified non-inferiority margin of 10%.

Results: We included 25 patients, receiving 1285 study dialysis sessions in total, 636 in the study arm and 649 in the control arm. Both anticoagulation strategies were safe. Overall, clotting rates were low: 37/636 (5.82%) in the study arm and 42/649 (6.47%) in the control arm. The primary endpoint of non-inferiority was met ($P < 0.0001$). In secondary analysis, using Cox proportional hazard analysis, time to clotting did not differ between study arms ($P > 0.62$).

Conclusions: Combination of a heparin-grafted dialyzer with citrate-containing dialysate is non-inferior to conventional RCA. The procedure is easy to perform without additional pumps or calcium measurements. Combination of a heparin-grafted dialyzer and citrate-containing dialysate is a valid alternative to RCA in patients requiring heparin-free dialysis.

Funding: Pharmaceutical Company Support - Gambro - Baxter

TH-PO820

Effect of L-Carnitine on Markers of Mineral Bone Disease in the CARNIDIAL trial Lucile Mercadal,¹ Michel Chonchol,² Messaoud Ouziala,⁴ Christine Fumeron,⁵ Aude Servais,⁶ Sophie Tezenas du montcel,⁹ ¹Nephrology, AP-HP, Pitié-Salpêtrière, Paris, France; ²Nephrology, Univ of Colorado, Denver; ³CMC Pantin, Aubervilliers; ⁴AURA Paris; ⁵Nephrology, AP-HP, Necker; ⁶Statistics, AP-HP, Pitié-Salpêtrière, Paris.

Background: Previous studies suggested that L-carnitine in hemodialysis patients decreases intact parathyroid hormone levels (iPTH). We studied the effects of L-carnitine on markers of mineral bone disease (MBD), including fibroblast growth factor (FGF23) in a randomized, double-blind trial.

Methods: We evaluated the effects of 1 g of intravenous L-carnitine after each dialysis session for 1 year when compared to placebo in a randomized and double-blind trial. C-terminal FGF23 (cFGF23) were measured at baseline, every 3 months and end of study in 91 chronic hemodialysis patients. Serum calcium, phosphate and iPTH were available at similar time points. The effect of L-carnitine on serum calcium, phosphate, iPTH and plasma cFGF23 was studied by mixed linear models for repeated measurements in intent-to-treat. We also examined the relation of cFGF23 with intravenous (IV) iron and EPO dose.

Results: Serum calcium and phosphate increased more in the L-carnitine than in the placebo group (calcium: β of L-carnitine \times time 0.005 ± 0.002 mmol/L.month, $p=0.03$; phosphate: β of L-carnitine \times time 0.02 ± 0.006 mmol/L.month, $p=0.001$). In both groups, serum iPTH was stable over time and plasma cFGF-23 increased (β log FGF23 0.05 ± 0.01 rHu/mL.month, $p<0.0001$). In multivariable analyses on 166 measurements, cFGF23 was positively correlated with serum calcium (β 1.5 ± 0.6 , $p=0.01$), serum phosphate (β 1.2 ± 0.2 , $p<0.0001$) and negatively correlated with EPO dose (β -0.41 ± 0.17 , $p=0.02$). No association was observed between cFGF23 and IV iron administration ($p=0.13$), serum ferritin ($p=0.7$) and iron saturation ($p=0.7$).

Conclusions: L carnitine treatment slightly increased serum calcium and phosphate without an effect on iPTH or cFGF23. FGF23 was inversely correlated with ESA dose but not with IV iron dose.

Funding: Government Support - Non-U.S.

TH-PO821

Clinicopathological Characteristics of Lanthanum Deposition in the Gastrointestinal Tract of Dialysis Patients Shigeo Hara,^{1,2} Akira Fujimori,³ Shinichi Nishi,⁴ ¹Dept of Diagnostic Pathology, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan; ²Div of Pathology, Ako City Hospital, Ako, Hyogo, Japan; ³Div of Nephrology, Konan Hospital, Kobe, Hyogo, Japan; ⁴Dept of Nephrology, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.

Background: Lanthanum carbonate (LC) is a phosphate binder for dialysis patients with hyperphosphatemia. Recent studies have reported gastric lanthanum deposition in patients treated with LC (Haratake J et al. Am J Surg Pathol 2015; Makino M et al. Pathol Int 2015); however, clinicopathological features of LC deposition have not been fully evaluated. The present study was conducted to elucidate the clinicopathological characteristics of LC deposition in the gastrointestinal (GI) tract.

Methods: Pathological specimens of the GI tract ($n = 60$) obtained from the patients ($n = 28$) being administered LC were retrospectively reviewed. Prevalence, distribution, and duration from initiation of administration of LC to the detection of lanthanum deposition were evaluated.

Results: Among 28 patients (male:female = 17:11; mean age, 68.5 years), LC deposition was observed in 11 (39.3%). Pathological specimens were obtained from the pharynx ($n = 1$), esophagus ($n = 5$), stomach ($n = 40$), duodenum ($n = 1$), colon ($n = 12$), and appendix ($n = 1$). LC deposition was confined to the stomach ($n = 16$) and the duodenum ($n = 1$). The duration from the initiation of administration to the first histological detection of LC ranged from 0.35 to 5.39 years (mean, 1.91 ± 0.45 years). In 4 patients, follow-up biopsy revealed no improvement in the gastric LC deposition.

Conclusions: Lanthanum deposition occurs in approximately 40% of dialysis patients and is mostly confined to the stomach. Its deposition can be seen histologically within a couple of months from the commencement of LC administration.

TH-PO822

Comparative Effectiveness of Oral and Injectable Vitamin D Receptor Activator on Infectious Mortality in Hemodialysis Patients: The Q Cohort Study Shigeru Tanaka,¹ Toshiharu Ninomiya,^{2,5} Masatomo Taniguchi,² Masanori Tokumoto,¹ Hideki N. Hirakata,³ Hiroaki Ooboshi,¹ Kazuhiko Tsuruya,^{2,3} Takanari Kitazono,^{2,5} ¹Div of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; ²Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ³Div of Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; ⁴Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ⁵Div of Research Management, Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Vitamin D receptor activator (VDRA) has recently been reported to be associated with better survival after infection in hemodialysis patients. The optimal administration route of VDRA to prevent infection death remains unclear. The aim of this study is to investigate the comparative effectiveness of VDRA between oral route and injectable form on infectious mortality in hemodialysis patients registered in a prospective cohort study.

Methods: A total of 3,278 subjects were divided into 3 groups by the administration type of VDRA: oral group ($n=1,835$), injectable group ($n=459$) and non-user ($n=984$). Impacts of VDRA on infectious mortality were examined using a Cox regression model adjusted with propensity score-based approaches.

Results: During follow-up (median 3.9 years), 534 patients died and 115 patients developed infection death. The use of injectable VDRA was associated with a significant lower infectious mortality compared to non-user, while oral VDRA did not significantly reduce the risk of infection mortality compared to non-user (hazard ratio [HR] for injectable VDRA, 0.40; 95% confidence interval [CI], 0.18–0.91, and HR for oral VDRA, 0.78; 95% CI, 0.53–1.15, respectively). Direct comparison between oral and injectable VDRA revealed that the injectable group was also significantly associated with better survival than oral group (HR, 0.33, 95% CI, 0.13–0.83).

Conclusions: Treatment with injectable VDRA has a more favorable impact on the infectious mortality compared to oral VDRA in the real-world practice of hemodialysis patients.

TH-PO823

Aldosterone Levels in Patients on Hemodialysis/Relationship with the Metabolic Syndrome María Jose Fernandez Reyes,¹ Manuel M. Heras,¹ Maria Gonzalez,² Olaia Rodriguez fraga,² Ramiro Callejas,¹ Alvaro Molina,¹ Vanesa Lopes-martin,¹ Maria astrid Rodriguez gomez,¹ Leonardo Calle,¹ ¹Nephrology, Hospital General Segovia, Segovia, Spain; ²Biochemistry, Hospital Univ La Paz, Madrid, Spain.

Background: Recently it has been shown that serum aldosterone (SA) levels are correlated with several components of the metabolic syndrome (MSyn). **OBJECTIVE:** to establish SA levels on hemodialysis (HD) patients and its possible association with insulin resistance (homeostasis model assessment of insulin resistance HOMA-IR), excess body fat and/or serum adipocytokines levels.

Methods: 44 stable patients on HD, not taking ACE inhibitors/angiotensin receptor blockers. Mean age: 72.5 ± 12.5 years; 52.3% men; 34.1% diabetics. Mean time on HD: 43.2 ± 49 months. 28 patients were anuric. All measurements were done prior to the midweek HD session.

Results: SA levels were above the normal range (1.17-23.6 ng/dl) in 63.6% of patients. Plasma Renin Activity (PRA) was above the normal range (0.23-3.32 ng/mL/hour) in 27.3% of patients. SA median: 31.15 (p25: 5.6; p75: 411 ng/dl); PRA median: 1.14 (p25: 0.04; p75: 20.9 ng/mL/hora). There were not statistically significant difference (Student's-t) in SA levels between anuric and non-anuric; male and female; presence and absence of myocardialopathy or diabetes. There were no statistically significant correlations (Spearman) of SA levels or PRA with urine volume; residual renal function; dose or length of time on HD; age; or Charlson Comorbidity Index. SA levels were positively correlated (Spearman) with ARP ($r=0.72$; $p<0.0001$); body fat mass in kg/m² ($r=0.32$; $p=0.045$); serum leptin levels ($r=0.30$; $p=0.05$); HOMA-IR ($r=0.36$; $p=0.017$) and negatively with serum adiponectin levels ($r=-0.31$; $p=0.041$). Multivariate logistic regression analysis showed that SA levels above its median level were independently associated to PRA and HOMA-IR.

Variables Independientes	Odds ratio	95% CI	Valor de p
HOMA-IR	1,236	1,025-1,452	0,01
Plasma renina Actividad	2,664	1,136-6,248	0,024

Conclusions: SA levels are elevated in a high percentage of HD patients and such elevation is associated with PRA and several components of MSyn (insulin resistance; body fat mass; and serum levels of adipocytokines).

Funding: Government Support - Non-U.S.

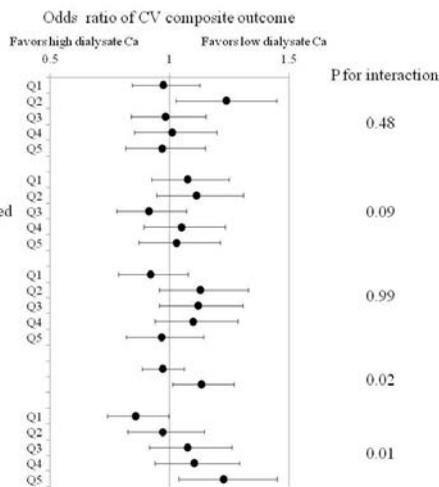
TH-PO824

Dialysate Calcium Concentration Was Significantly Associated with Cardiovascular Diseases in Diabetics and Patients with High Body Mass Index among Hemodialysis Patients Miho Tagawa,¹ Takayuki Hamano,² Shinichi Sueta,³ Seiji Hashimoto,² Satoshi Ogata.² ¹Nara Medical Univ, Nara, Japan; ²Patient Registration Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan; ³Kyoto Univ, Kyoto, Japan.

Background: Previous studies showed that higher dialysate calcium (Ca) concentration was positively associated with cardiovascular (CV) diseases. Which patient characteristics modify this association has not been studied.

Methods: This was a longitudinal study based on the Japan Renal Data Registry (JRDR) from 2008 to 2009. Predictor variables were dialysate Ca concentration (3.0 mEq/L vs 2.5 mEq/L). Primary outcome was CV composite event (either myocardial infarction, stroke, amputation, or CV death). Statistical analyses were performed using multivariable logistic regression model, adjusted for potential confounders.

Results: Among 300,660 patients on JRDR database, data for 38,697 patients were available for analyses after excluding patients with missing data. Serum albumin corrected Ca was significantly higher (9.27±0.77 vs 9.18±0.79 mg/dL) and intact parathyroid hormone (iPTH) was significantly lower (135[65-236] vs 164[85-274] pg/ml) among high dialysate Ca users compared with low dialysate Ca users. The odds ratio of CV composite outcome among high dialysate Ca users was higher among diabetics and patients with higher body mass index (BMI) (p for interaction 0.02 and 0.01, respectively).



Additional adjustment for pre-dialysis serum albumin corrected Ca and iPTH did not change the effect size of high dialysate Ca among diabetics and patients with high BMI.

Conclusions: Diabetes and BMI, but not serum phosphate, Ca, or iPTH were effect modifiers for the association of high dialysate Ca and CV composite outcome. High dialysate Ca was significantly associated with CV composite outcome among diabetics and patients with high BMI.

TH-PO825

Association of Serum and Dialysate Electrolytes with Arrhythmic Risk in Incident Hemodialysis Jacqueline Watt,¹ Esther D. Kim,² Larisa Tereshchenko,³ Stephen M. Sozio,³ Bernard G. Jaar,³ Lucy A. Meoni,³ Michelle M. Estrella,³ Rulan S. Parekh.^{2,3} ¹McMaster Univ; ²Univ of Toronto; ³Johns Hopkins Univ.

Background: Arrhythmias and sudden cardiac death (SCD) may occur during or shortly after receiving dialysis treatment. The extent to which serum and dialysate concentrations of potassium (K) and calcium (Ca) are associated with the risk of arrhythmias in incident hemodialysis is unclear.

Methods: In 402 patients from the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study, we analyzed the association of serum (ionized Ca[iCa], K, magnesium [Mg]) and dialysate (dCa and dK) electrolyte concentrations with prolonged QTc interval (Bazett's formula) and heart rate variability (HRV). Outcomes were measured by a 5-minute signal-averaged ECG. Prolonged QTc was defined as >460ms in women and >440ms in men. Baseline associations were examined using linear and logistic regression, and repeated measures were analyzed using mixed-effects models.

Results: At baseline, 86.3% had QTc prolongation, of whom 68.5% had persistent QTc prolongation at the follow-up visit. In the baseline analysis, higher iCa was associated with a shorter QTc interval and lower odds of having QTc prolongation, independent of demographic and cardiovascular risk factors, CRP, and pH.

Adjusted Associations	Baseline	Repeated Measures
	β or OR (95% CI)	β or OR (95% CI)
QTc Interval	-10.6(-17.7, -3.6)*	-10.6(-17.5, -3.7)*
Heart Rate Variability	2.9(0.6, 5.1)*	2.9(0.7, 5.1)*
QTc Prolongation	0.1(0.0, 8.1)	

*p<0.05

Higher iCa was also associated with higher HRV. The association of iCa with QTc interval and HRV remained significant in the repeated measures analysis. Associations with serum K, Mg, dCa, and dK were not significant at baseline or over follow-up. Serum-to-dialysate Ca gradient, but not K gradient was associated with higher HRV at baseline and over follow-up ($\beta=0.3(0.0, 0.6)$ and $0.3(0.0, 0.6)$ respectively).

Conclusions: Serum iCa, but not K and Mg, is consistently inversely associated with QTc prolongation and the serum to dialysate gradient is also associated with HRV. This suggests that the absolute serum level as well as the lower dCa concentration increases arrhythmic risk.

TH-PO826

Phosphorus Kinetics During Hemodialysis: Further Validation of a Pseudo-One Compartment Model J. Ken Leygoldt,¹ Baris U. Agar,² Alfred K. Cheung,³ Angelito A. Bernardo.¹ ¹Medical Products (Renal), Baxter Healthcare Corporation, Deerfield, IL; ²Medical Products (R&D), Baxter Healthcare Corporation, Round Lake, IL; ³Nephrology, Univ of Utah, Salt Lake City, UT.

Background: A pseudo-one compartment model has been proposed to describe phosphorus kinetics during hemodialysis (HD) and postdialysis rebound. This model suggests that phosphorus mobilization from tissues is proportional to the difference between the predialysis serum (C_{pre}) and instantaneous serum concentration. The current study evaluated the ability of a pseudo-one compartment model to describe the kinetics of phosphorus during two short HD treatments on the same day separated by a 1-hr inter-treatment period without dialysis. The latter is the postdialysis rebound period for the first treatment.

Methods: Serum was collected frequently during both HD treatments and the inter-treatment period to assess phosphorus kinetics in 21 chronic HD patients. Phosphorus mobilization clearance (K_{phos}) and predialysis central distribution volume (V_{pre}) were estimated for each patient during the first HD treatment and the inter-treatment period. Assuming those kinetic parameters remained constant for each patient, phosphorus concentrations during the second HD treatment were used to estimate the driving force concentration (C_{dr}) for phosphorus mobilization during that treatment.

Results: Treatment times (117±14 vs. 117±14 min), dialyzer phosphorus clearance (151±25 vs. 140±32 mL/min) and net fluid removal (1.44±0.74 vs. 1.47±0.76 L) were similar during both HD treatments. Phosphorus concentration at the start of the second HD treatment (3.3±0.9 mg/dL) was lower ($P<0.001$) than at the start of the first or C_{pre} (5.4±1.9 mg/dL). K_{phos} and V_{pre} were 98±44 mL/min and 11.0±4.2 L, respectively. Calculated C_{dr} was 4.9±2.0 mg/dL, not significantly different from C_{pre} ($P=0.12$). C_{dr} and C_{pre} were correlated ($R=0.72$, $P<0.001$).

Conclusions: The results from this study demonstrate that the driving force concentration for phosphorus mobilization during HD is constant and equal to that predialysis, consistent with a fundamental assumption of the pseudo-one compartment model.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO827

Association of Sleep Apnea and Sleep Quality with Left Ventricular Mass in Hypertensive Hemodialysis Patients in the Blood Pressure in Dialysis-SLEEP study Manisha Jhamb,¹ Cynthia A. Kendrick,² Dana Miskulin,³ Lavinia A. Negrea,⁴ David W. Ploth,⁵ Jennifer J. Gassman,² Mark L. Unruh,⁶ Philip Zager.^{6,7} ¹Univ of Pittsburgh; ²Cleveland Clinic; ³Tufts; ⁴Case Western; ⁵MUSC; ⁶UNM; ⁷DCI.

Background: Sleep apnea (SA), short and fragmented sleep may contribute to cardiovascular disease in hemodialysis (HD) patients. However, the relationship of sleep quality with left ventricular mass (LVM) is not well described.

Methods: Chronic HD patients joined an ancillary study during the baseline period of the Blood Pressure in Dialysis (BID) trial. SA was monitored for 1 night with a portable home monitor (ApneaLink with oximetry) and measured as Apnea Hypopnea Index (AHI). Sleep-wake behavior was assessed by actigraphy over a 5-day period. LVM was measured by MRI.

Results: We studied 42 patients. SA was present in 84% and was moderately severe (AHI >15) in 48%. 61% of patients slept <6 hrs/night and 89% had poor sleep efficiency. Patients with AHI>15 had longer dialysis vintage, lower hemoglobin, and lower Kt/V than those with AHI<15. BMI, systolic BP, diastolic BP, heart rate, number of antihypertensive medications, inter-dialytic weight gain, history of myocardial ischemia, and MRI characteristics did not differ between the two groups. LVM index was inversely correlated with sleep duration and efficiency (Pearson's $r=-0.35$, $p \leq 0.04$ for both, AHI ($r=-0.01$) and hypoxemic index ($r=-0.04$)).

	No-mild SA (n=22)	Mod-Severe SA (n=20)
	Mean ± SD	Mean ± SD
LV Mass (g)	154 ± 50.0	153 ± 57.4
LV Mass Index (g/m ²)	78.2 ± 23.8	76.8 ± 30.4
LV End Diastolic Volume (ml)	195 ± 52.6	200 ± 69.1
LV End Systolic Volume (ml)	89.6 ± 29.2	102 ± 51.7
RV End Diastolic Volume (ml)	154 ± 45.2	156 ± 60.1
RV End Systolic Volume (ml)	76.4 ± 26.1	82.2 ± 37.3
LV Ejection Fraction (%)	53.3 ± 12.4	50.8 ± 11.1
Inferior Vena Cava diameter (mm)	21.4 ± 8.2	23.3 ± 7.5

Conclusions: SA and poor sleep quality were common among hypertensive HD patients. Short sleep duration and poor sleep efficiency, but not the severity of SA, were associated with higher LVM indices.

Funding: NIDDK Support, Clinical Revenue Support

TH-PO828

Role of Nicotinic Acid as Phosphate Lowering Agent in End Stage Renal Disease Patients on Maintenance Hemodialysis Khalid Tahir,¹ Hafiz I. Ahmad,¹ Syed Rizwan Bokhari,¹ Syed A. Khalid,¹ Arif Asif,² ¹Dept of Nephrology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, Pakistan; ²Div of Nephrology and Hypertension, Albany Medical College, Albany, NY.

Background: Hyperphosphatemia is associated with higher risk of mortality and morbidity in End Stage Renal Disease (ESRD) patients. Use of Nicotinic Acid as phosphorus lowering agent has been studied in many countries but available data is sparse and limited. We conducted a study to determine the mean decrease in serum Phosphorous level with Nicotinic acid use in our dialysis patients.

Methods: Nicotinic acid, in a dose of 250 mg twice a day with food for 4 weeks, was given to 45 ESRD patients with serum Phosphorous level more than 5.5 mg/dl. Serum phosphorus level was measured at the start and then at the end of study. Data was analyzed for decrease in serum phosphorus level with Nicotinic acid use.

Results: Mean age of 45 patients was 44.6 ± 13.9 years and 57.8% were male. Serum Phosphorus level before treatment was 5.6 - 10.8 mg/dl (mean 6.91 ± 1.33) and after treatment for one month it was 2.60 - 8.70 mg/dl (mean 5.82 ± 1.40). Mean decrease in phosphorus level with Nicotinic acid after one month of treatment was 1.08 ± 1.16 mg/dl (p value < 0.001).

Conclusions: Nicotinic acid is an effective and cheaper phosphate lowering agent in dialysis patients. Further larger and Randomized Controlled Trials are needed to establish the role of this cheaper phosphate lowering agent.

Funding: Private Foundation Support

TH-PO829

Cerebral and Cognitive Effects of Short- and Long-Term Hemodialysis – A Pilot Study Xiufeng Li,¹ Yelena Slinin,² Gregory J. Metzger,¹ Lynn E. Eberly,¹ Donald R. Dengel,¹ David Tupper,³ Anne M. Murray,³ ¹Univ of Minnesota, MN; ²Veterans Affairs Medical Center, MN; ³Hennepin County Medical Center, MN.

Background: The short- (<=6 months) and long-term (³12 months) effects of conventional hemodialysis (HD) on brain structure, cerebral blood flow and cognitive function are not well understood.

Methods: We conducted a small longitudinal pilot study to investigate the effects of HD initiation on brain MRI and cognitive function in 4 HD patients by obtaining pre- and post- initiation brain MRIs and cognitive testing. The MRIs were obtained at 3-6 months before HD initiation (baseline), and at ~6 and ~12 months after HD initiation. The Modified Mini-Mental State Examination (3MSE) was performed within one month of the baseline and 12 month MRI examinations. MR diffusion tensor imaging (DTI) measured white matter (WM) fractional anisotropy (FA)(connectivity), and pseudo-continuous arterial spin labeling (PCASL) imaging was used to evaluate grey matter (GM) cerebral blood flow (CBF). A two-tailed paired t-test was used to compare pre- and post- initiation results. Patients provided written informed consent to participate in the IRB- approved protocol.

Results: Progressive and significant declines in frontal and temporal WM FA (Fig. 1), prefrontal CBF (Fig. 2), and cognitive function (Fig. 3, left) were found following HD initiation (Table 1 for p values). The decline in frontal WM FA on MRI was correlated with the 3MSE decline (R = 0.42)(Fig. 3, right).

	6 months	12 months	
FA	Frontal	0.031	0.025
	Temporal	0.048	0.044
CBF	Prefrontal	0.038	0.048
	Anterior Hippocampus	0.042	0.013

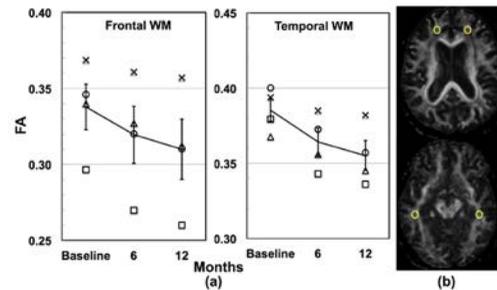


Figure 1. Results from longitudinal DTI studies performed about 3 to 6 months before (baseline), 6 and 12 months after hemodialysis initiation (N=4): (a) regional fractional anisotropy (FA) measurements over time in frontal (left) and temporal (right) white matter (WM), and (b) bilateral regions of interests used for FA measurements overlaid on FA maps. Error bars represent standard errors.

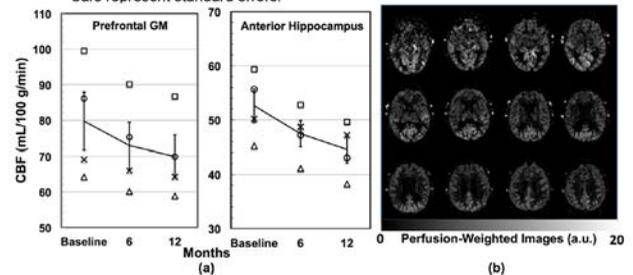


Figure 2 Results from longitudinal PCASL imaging studies performed about 3 to 6 months before (baseline), 6 and 12 months after hemodialysis initiation (N=4): (a) regional cerebral blood flow (CBF) measurements across time in prefrontal grey matter (GM) (left) and the anterior portion of the hippocampus (right), and (b) one subject's perfusion-weighted images covering middle part of the brain from the study before hemodialysis initiation. Error bars represent standard errors.

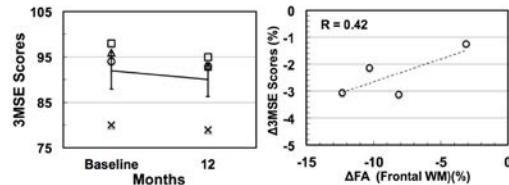


Figure 3. The 3MSE test scores from the baseline and annual visits (left), and the scatter plot for relative percent changes of 3MSE test scores and fractional anisotropy (FA) measurements in frontal WM (N=4). Error bars represent standard errors.

Conclusions: Our results suggest that HD may adversely alter cerebral vascular function and progressively induce cerebral structural abnormalities and associated cognitive decline.

Funding: NIDDK Support

TH-PO830

Patient and Dialysate Temperature Characteristics in Incident Hemodialysis Patients: Results from a Large U.S. Population Xiaoling Ye,¹ Len A. Usvyat,² Yue Jiao,² Peter Kotanko,^{1,3} Franklin W. Maddux,² ¹Renal Research Inst, New York, NY; ²Fresenius Medical Care North America, Waltham, MA; ³Icahn School of Medicine at Mount Sinai, New York, NY.

Background: In chronic hemodialysis (HD) patients the use of dialysate at a temperature below the patient's core temperature ("cool" dialysate) has been associated with improved outcomes in observational and prospective randomized studies [Odudu et al., CJASN 2015; Eldehni et al., JASN 2015; Selby, Sem. Dial 2008]. Little is known about temperature profiles in large US populations.

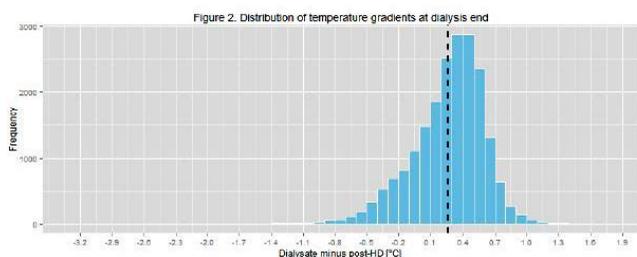
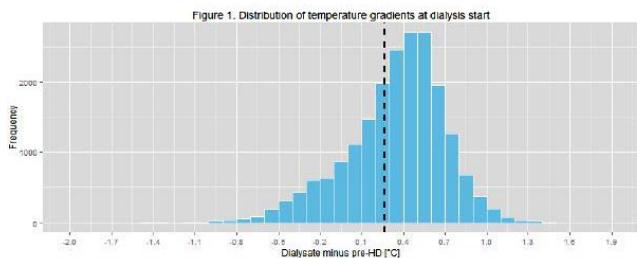
Methods: We include a subset of incident HD patients who were treated in Fresenius Medical Care North America facilities from 1/2010 to 12/2014 and who survived the first year of HD. Pre- and post-HD body temperatures were measured with thermometers. The dialysate temperature was measured by the HD machine. The dialysate-to-patient temperature gradient was computed as dialysate temperature minus patient temperature.

Results: We studied 20,360 incident HD patients (age 62.5 (SD 14.5) years; 57.6 % males; 68.1% White, 29.2 Black, 2.7% others). The vast majority (83.8 %) had a dialysate temperature above body temperature at the start, and at the end (80.6%) of HD.

Table 1. Patient and dialysate temperatures

Temperatures [C°]	Mean (SD)	Range	95% CI
Pre-HD body	36.37 (0.23)	35.13 to 37.40	36.36 to 36.37
Post-HD body	36.45 (0.21)	35.21 to 39.04	36.44 to 36.45
Post-HD minus pre-HD body	0.08 (0.16)*	-1.00 to 2.97	0.07 to 0.08
Dialysate (actually delivered)	36.71 (0.31)	35.00 to 37.57	36.71 to 36.72
Dialysate minus pre-HD	0.34 (0.36)*	-1.86 to 1.79	0.34 to 0.35
Dialysate minus post-HD	0.26 (0.33)*	-3.16 to 1.70	0.26 to 0.27

* different from zero (P=0.0001)



The prescribed dialysate temperature was 36.87±0.31 °C. We observed a small yet significant rise in body temperature during HD.

Conclusions: Delivered dialysate temperature exceeds the body temperature in majority of patients. This may provide potential opportunities for dialysate temperature reduction to improve intradialytic stability and outcomes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO831

Effect of a Single Hemodialysis Session on Visual Evoked Potentials Savas Sipahi,¹ Ahmed Bilal Genç,¹ Yalcin Solak.¹ ¹Nephrology, Sakarya Univ Research and Training Hospital, Sakarya, Turkey; ²Neurology, Sakarya Univ Research and Training Hospital, Sakarya, Turkey.

Background: Some studies have shown that visual evoked potentials (VEPs) may be a marker of dysfunction in visual pathways in uremic subjects. However, data are scarce regarding effect of hemodialysis procedure on VEPs. We aimed to compare VEPs of hemodialysis patients with healthy volunteers and in particular to assess the impact of a single hemodialysis session on VEPs.

Methods: Thirty hemodialysis patients were included in the study. We also recruited 30 age and gender matched control subjects. Patients with diabetes mellitus, cataracts, glaucoma, and stroke were excluded. Demographic characteristics, midweek predialysis and postdialysis laboratory values, amount of ultrafiltration at that dialysis session were recorded. Patients underwent VEP measurement through which P100 latency values were determined just before hemodialysis session and 24 after hemodialysis session. We assessed the changes in P100 values with single hemodialysis session. We also investigated effect of ultrafiltration on VEPs in maintenance hemodialysis patients.

Results: There was no difference between the groups in terms of age and gender (mean age 49 ± 12 and 48 ± 11 years, respectively). Median duration of hemodialysis was 78 months (range 12-192). At baseline there was no difference with respect to P100 values between the groups (100.6 ± 8.8 vs 99 ± 5.8, p=0.4, for hemodialysis and controls respectively). Both right and left eye VEPs showed a significant decrease measured 24 hours after dialysis session compared with baseline values (right VEP; 100.6 ± 8.8 predialysis and 97 ± 8.7 postdialysis, p<0.001, left VEP; 101.9 ± 9.2 predialysis and 97.3 ± 8.1, p<0.001). There was no correlation between baseline predialysis P100 values and age, serum urea, hemoglobin, and dialysis vintage. Amount of ultrafiltration was not significantly correlated with postdialysis P100 latency values.

Conclusions: Our results did not show a significant difference in P100 latency values between hemodialysis patients and healthy controls. A single hemodialysis session significantly shortened P100 latency values compared with baseline values.

TH-PO832

²³NaMRI Detects Bound versus Soluble Tissue Sodium Content in Hemodialysis Patients Anke Dahlmann,¹ Carolin Maier,¹ Christoph Kopp,¹ Peter Linz,² Daniela Amslinger,² Matthias Hammon,³ Kai-Uwe Eckardt,¹ Friedrich C. Luft,⁵ Jens Titze.⁴ ¹Nephrology and Hypertension, Univ Hospital Erlangen, Germany; ²Junior Research Group II, Interdisciplinary Center for Clinical Research, Erlangen, Germany; ³Radiology, Univ Hospital Erlangen, Germany; ⁴Clinical Pharmacology, Vanderbilt Univ, Nashville; ⁵Experimental and Clinical Research Center, MDC, Berlin, Germany.

Background: Tissue sodium content is elevated in patients with end-stage renal disease and can be corrected by hemodialysis treatment. Until now no data are available concerning the extent of water free sodium storage in muscle and skin tissue in humans. ²³Na magnetic resonance technique (MRI) can offer options to distinguish non-invasively between soluble and bound (water free) tissue sodium content.

Methods: We used ²³Na magnetic resonance spectroscopy and imaging at 3Tesla (T) to quantify Na⁺ content in skeletal muscle and skin of the lower leg. Analysis of specific MRI echo times (2ms vs. 4ms during sodium signal decay) allowed determination of bound vs. total and soluble sodium content. 39 hemodialysis patients were measured before and after regular dialysis treatment with ²³Na MRI.

Results: Initial bound sodium content of M. triceps surae in dialysis patients was 1.58±0.78 mmol/l, which represents 7.5±4.1% of total detectable sodium signal in this tissue. While parts of soluble sodium content were removed during dialysis treatment, its bound fraction was unaffected by HD (1.63±0.54 mmol/l). Therefore the ratio of bound to total sodium significantly increased up to 10.0±4.1% (p<0.05) post dialysis. Initial bound sodium content in skin was 2.19±1.19 mmol/l, which represents 9.4±4.2% of total sodium signal in this tissue. This value was significantly higher compared to muscle tissue. During hemodialysis its content decreased significantly to 1.63±0.89 mmol/l (p<0.05). Due to the simultaneous reduction of soluble skin sodium, the ratio of bound to total sodium was unchanged by hemodialysis (9.3±5.0%).

Conclusions: Reduction of tissue sodium content by hemodialysis treatment differs in skin and muscle tissue: While bound sodium content in muscle was unaffected by hemodialysis, bound sodium content in skin tissue could be mobilized by HD.

TH-PO833

Blood Pressure in Hemodialysis Patients: Which Measurement Is More Reliable? Jose Mora-Macia, Francesc J. Moreso, Jose Ignacio Merello, Rosa Ramos. Hemodialysis, Fresenius Medical Care, Spain.

Background: The reliability of blood pressure (BP) measurements during the hemodialysis (HD) is controversial. The aim of this study was to evaluate which interval of intradialytic BP has less Bias in comparison with home BP monitoring (HBPM).

Methods: A cross-sectional study was done with interdialytic HBPM as reference standard and interdialytic BP measurement as test. Index BP recordings tested were predialysis (pre-HD), postdialysis (post-HD) and intradialysis (intra-HD). Dialysis unit BP recordings were averaged over 1 week: 2 pre-HD, 2 post-HD and 7 intra-HD (every 30 min); and HBPM over 1 week (the same days): 3 morning and 3 evening readings. BP measurements during dialysis were measured by dialysis nurses using the validated oscillometric BP monitor OMRON M3 (HEM 7051 E, Omron Healthcare), and the same device was used for the patient at home. Patients were instructed to bring the device to the dialysis. Patients with symptomatic hypotension during dialysis were excluded. To measure Bias, average HBPM was subtracted from each of these three index BP intradialytic recordings. Bias was defined as the mean difference in BP (pre-HD, intra-HD, post-HD) compared with HBPM.

Results: 192 patients, mean age 63.8±14.8 y.o. (70% male), of 11 HD clinics of Fresenius Medical Care of Spain were included, 33% diabetic. All patients were on thrice times weekly HD. The mean time on HD was 46±57 months.

	HBPM	Pre-HD	Intra-HD	Post-HD
SBP	135±21.4 (80,194)	143.0±21.6 (92,225)*	130.7±20.9 (83,204)*	136.1±23.2 (84,207)‡
DBP	69.3±11.2 (44,97)	71.1±11.1 (46,117)*	68.4±10.4 (49,105)**	70.2±10.4 (48,98)‡
Bias SBP	reference	-7.97±12.1 (-48,+22)&	4.35±13.16 (-37,+44)&	-1.08±15.95 (-52,+42)&
Bias DBP	reference	-2.08±6.18 (-35,+16)&	0.90±6.67 (-23,+21)&	-0.92±7.44 (-25,+21)&

Data are expressed as mean±SD (range). * p<0.001 vs HBPM. ** p=0.062 vs HBPM. ‡ NS vs HBPM. & p<0.0001 ANOVA between HD

Conclusions: BP at the end of the HD, in not hypotensive symptomatic patients, not differ from HBPM and have less Bias that predialysis or intradialysis BP measurements. So, the postdialysis BP measurements are the most reliable BP readings.

TH-PO834

End-Dialysis Overweight and Chronic Inflammation: A Dangerous Association – A 36-Month Prospective Observational Study Ezio Movilli. *U.O. of Nephrology, Spedali Civili and Section of Nephrology Univ of Brescia, Brescia, Italy.*

Background: Attaining dry body weight is paramount in dialysis practice, but this goal is not always reached. We hypothesized that the amount of end-dialysis overweight (edOW), could be associated to increased chronic inflammation and mortality. Aim of the study: to evaluate the effect of edOW on serum C-reactive protein(hsCRP) concentrations and on survival in a cohort of 182 prevalent HD patients (pts) followed for 36 months.

Methods: In 182 pts (117 men, age 65±12 years, vintage 48 months; range 6-336), edOW was present in 98/182 (54%) pts. Mean value was 0.4±0.2 Kg (range: 0.1-1.4). In the 98 pts with edOW (Group 1) and in the other 84 (Group 2) we evaluated: Ultrafiltration rate(UFR), hsCRPdry body weight (dBW), Kt/V, protein catabolic rate (PCRn), interdialytic weight gain (IDWG), mean arterial pressure (MAP). Unpaired Student's t test was employed to compare groups, linear regression analysis to test correlations, log-rank test and Kaplan-Meier curves to evaluate survival.

Results: Mean UFR was 11.7±2.8 ml/Kg/hour, dBW 64±12 Kg, hsCRP 6.6 (0.2-36) mg/L, Kt/V 1.27±0.09, PCRn 1.06±0.10 g/Kg/day, IDWG 2.8±0.4 Kg, MAP 97±6.5 mmHg. edOW and hsCRP were directly and significantly correlated (r= 0.67; p<0.0001). Comparison between pts with (Group 1) and without (Group 2) edOW showed significant differences in: UFR (12.7±2.6 vs 10.9±2.6 ml/Kg/hour; p< 0.0001), hsCRP (13.0±8.1 vs 5.2±5.3 mg/L; p< 0.0001), and PCRn (1.03±0.09 vs 1.08±0.10 g/Kg/day; p<0.004). 98 pts (54%) died during follow-up for cardiovascular complications in 69% of cases. Survival curves showed significantly greater mortality in Group 1 vs Group 2 in relation to the amount of edOW, and hsCRP (p<0.0001).

Conclusions: : edOW and chronic inflammation are directly correlated in HD pts, and both are associated to a greater long-term risk of mortality.

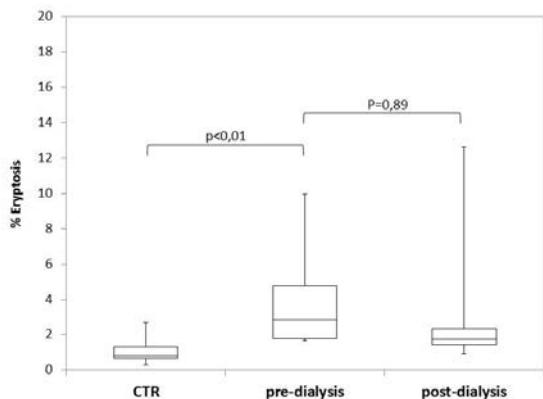
TH-PO835

Suicidal Erythrocyte Death in Hemodialysis Patients Anna Clementi,¹ Grazia Maria Virzi,² Alessandra Brocca,² Massimo de Cal,² Antonio Granata,¹ Claudio Ronco.² *¹Nephrology, Agrigento; ²Nephrology-IRRI, Vicenza.*

Background: Even though anemia in ESRD results mainly from the lack of erythropoietin, compelling evidence points to the contribution of accelerated erythrocyte death/eryptosis, which is characterized by phosphatidylserine (PS) exposure at surface, cell shrinkage and cell membrane scrambling. Eryptosis may be stimulated both by uremic toxins and the mechanical stress induced by hemodialysis (HD). We investigated the possible difference in terms of eryptosis levels between healthy subjects and HD patients before and after HD session.

Methods: We enrolled 15 patients (4F, mean age 65±16yrs, 33% with diabetes) undergoing chronic HD and 15 healthy subjects (CTR). Blood samples were collected prior to and after 4h standard HD session. Measurements were made in isolated erythrocytes (RBCs). PS exposure was estimated from AnnexinV binding in flow cytometer.

Results: The percentage of AnnexinV reflecting the percentage of RBCs exposing PS at RBC surface was significantly higher (more than twice) in HD patients than CTR (2.2%; IQR 1.2-4.1 versus 0.8%; IQR 0.7-1.3; p<0.05). The average forward scatter reflecting cell volume was significantly higher in RBCs from HD patients than in CTR. There was no statistically significant relationship between urea levels and eryptosis in HD patients. The percentage of AnnexinV and cell volume were measured prior to and after 4h of HD: no significant differences were observed between pre and postdialytic eryptosis.



Conclusions: Our data suggest that HD may lead to a significant increase in eryptosis, but no differences in its level were observed before and after HD session. Although dialytic procedure is known to be responsible for cytokines and inflammatory mediators release, because of the interaction between blood and circuit lines and filters, it does not seem to induce eryptosis. Further studies are needed to compare different types of HD treatments.

TH-PO836

Deployment of a Dialysis Hospitalization Reduction Program Is Associated with Lower Hospitalization Rates Hanjie Zhang,¹ Dugan Maddux,² Karen G. Butler,² Len A. Usvyat,² Yue Jiao,² Brian Scott Ash,² John W. Larkin,² Terry Ketchersid,² Peter Kotanko,^{1,3} Franklin W. Maddux.² *¹Renal Research Inst, New York, NY; ²Fresenius Medical Care North America, Waltham, MA; ³Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The aim of this study was to investigate the potential effect of a Dialysis Hospitalization Reduction Program (DHRP) on hospital admissions.

Methods: We deployed DHRP to 69 patients between 1/1/2014 and 5/5/2015 in a network of Fresenius Medical Care North America (FMCNA) dialysis clinics. These patients were identified as being at high risk for hospitalization based on FMCNA's data driven predictive modeling efforts and clinical assessments. The DHRP encompasses multiple interventions, targeting malnutrition, non-compliance, mental status issues, fluid overload, and others. Each patient is identified to have one or more "clinical tags"; 88 tags were identified for 69 patients. Interdisciplinary teams were deployed to design and implement interventions. Hospitalization rates were measured 90 days before and after the program.

Results: DHRP was associated with a reduction of all-cause hospitalization from 7.5 to 4.4 per patient year (ppy) (-42%) (Figure 1A). Interventions targeting patients with "malnutrition" tag were associated with a reduction of hospitalizations from 9.3 to 4.1 ppy (-56%) (Figure 1B).

Figure 1 A. Overall intervention outcomes

	Before	After	Difference
Number of clinical tags	88	88	
Hospital admissions	7.5	4.4	-42%
Hospital days	58	30	-49%
Missed treatments	7.9	7.4	-6%
Albumin (g/dL)	3.52	3.51	0%
Catheters	31%	30%	-3%
Pre-dialysis SBP (mmHg)	146.5	147.1	0%
IDWG (kg)	2.49	2.47	-1%

B. Intervention outcomes targeting malnourished patients

	Before	After	Difference
Number of clinical tags	21	21	
Hospital admissions	9.3	4.1	-56%
Hospital days	76	38	-50%
Missed treatments	4.4	4.1	-7%
Albumin (g/dL)	3.22	3.28	2%
Catheters	43%	34%	-20%
Pre-dialysis SBP (mmHg)	144.2	144.4	0%
IDWG (kg)	2.3	2.34	2%

SBP, systolic blood pressure; IDWG, interdialytic weight gain

Conclusions: DHRP was associated with reductions in hospital admissions and days. Reductions in overall hospital admissions were even higher in patients specifically identified to have malnutrition issues.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO837

The Long Inter-dialytic Period Is Not Associated with Inferior BP Control in Stable Hemodialysis Patients Mohamed Shantier, Rajneet Singh, Paul Mcdermott, Sami Suleiman, Donal N. Reddan, Louise Giblin, David W. Lappin, Matthew D. Griffin. *Nephrology Dept, Saolta Univ Healthcare Group, Galway, Ireland.*

Background: 3-day-a-week hemodialysis (HD) involves one long (72hr) and two short (48hr) inter-dialytic periods (IDP) with higher death risk after the long IDP. We investigated BP and CV biomarker patterns in clinically stable HD patients to determine whether BP control during the final 24 hrs of the long IDP is inferior to that of the short IDPs.

Methods: In an initial retrospective study, in-center BP readings over 1 month were analyzed for 81 adult HD patients with stable regimen and medical status for 33 mths. Next, 23 patients completed a prospective study in which ambulatory BP monitoring was performed for the final 24hrs of the long and one short IDP in the same week. Blood was collected for CRP, Troponin T, BNP following each ABPM.

Results: In the retrospective study, mean pre-dialysis systolic and diastolic BP (SBP/DBP) did not differ for the long and short IDPs despite greater weight gain during the long IDP. This observation was confirmed in the ABPM study and applied to both day- and night-time readings. Pre-dialysis CV biomarkers were not significantly higher following the long IDP. Inter-dialytic weight gain showed no correlation with BP indices.

Index	Long-IDP	Short-IDP	P value
24hr SBP (mmHg, mean± SD)	148.4±18	146.8±19.2	0.4
24hr DBP (mmHg, mean± SD)	80.8±10.3	80.5±11.2	0.5
24hr MAP (mmHg, mean± SD)	103.3±11.6	102.6±12.8	0.4
Day-time SBP(mmHg, mean± SD)	150.7±17	147.8±18.2	0.3
Night-time SBP (mmHg, mean± SD)	141.9±24.6	143.3±25.8	0.4
Inter-dialytic weight gain (kg, mean± SD)	2.7±1.4	1.8±0.8	0.002
Pre-dialysis Troponin T(ng/mL,mean± SD)	76±57	72±50	0.4
Pre-dialysis BNP (pg/mL, mean± SD)	9801±10805	8628±9822	0.1
Pre-dialysis CRP (mg/L, mean± SD)	9.5±12	6.6±9	0.2

Conclusions: In stable HD patients, BP control and CV biomarkers were similar during long compared to short IDP despite greater fluid gain. The adverse influence of excessive inter-dialytic fluid gain is unlikely to be mediated directly through a hypertensive effect.

TH-PO838

Notch Signaling in Bone Marrow-Derived FSP-1⁺ Cells Mediates a Phenotypic Change in Smooth Muscle Cells Leading to AVF Failure Ming Liang,^{1,2} Jinlong Luo,¹ William E. Mitch,¹ Jizhong Cheng.¹ ¹Medicine, Baylor College of Medicine, Houston, TX; ²Nephrology, Guangzhou Medical Univ, Guangzhou, Guangdong, China.

Background: sociological and economic costs of failed arteriovenous fistulas (AVF) are well known but mechanisms of AVF losses are controversial. We have shown that smooth muscle cells (SMCs) from anastomosed artery compose of ~50% of neointima cells in AVF. Arterial anastomoses are also infiltrated by bone marrow (BM)-derived FSP-1⁺ cells, potentially linking FSP-1⁺ cells to SMC activation. However, whether Notch/RBP-JK signaling involves in BM-derived FSP-1⁺ cells activation has not been studied. We propose that Notch/RBP-JK activation in BM-derived FSP-1⁺ cells causes a phenotype-switch of SMCs, resulting in SMC translocation from the artery to the venous anastomosis, forming neointima.

Methods: we created CKD and AVFs in wild type and Notch knock out mice. The role of Notch signaling in activation and function of BM-derived FSP-1⁺ cells was explored. Activated SMCs were characterized by a loss of differentiation markers plus a gain in proliferation (PCNA+). Using BM transplantation, we examined if FSP-1⁺ cells lacking RBP-JK in CKD mice would suppress SMC phenotype switch and neointima formation in AVFs.

Results: BM-derived FSP-1⁺ inflammatory cells in AVFs from CKD mice were 45% greater vs. results in pair-fed, control mice. In the artery anastomosis, increased infiltration of FSP-1⁺ cells led to loss of SMC differentiation markers, SMMHC, SM-22 and SMA- α . Activation of Notch signaling (NICD⁺ and RBP-JK⁻) raised expression of cytokines (IL-1 β , MCP-1) and growth factors (PDGF-BB, bFGF2 and TGF- β 1) in FSP-1⁺ cells. The cytokines and growth factors caused a SMC phenotype switch (characterized by loss of SMC markers), resulting in SMC migration and proliferation. RBP-JK KO in BM-derived FSP-1⁺ cells significantly decreased the production of cytokines and growth factors, suppressed SMC activation of and neointima formation in AVFs.

Conclusions: Thus, Notch signaling in BM-derived FSP-1⁺ cells can induce a phenotypic switch in SMCs stimulating neointima growth. Targeting Notch signaling in FSP-1⁺ cells could improve AVF function.

Funding: NIDDK Support

TH-PO839

Cytoglobin Is Upregulated in Failed Arteriovenous Fistula from Hemodialysis Patients and Exerts Survival Functions in Medial Smooth Muscle and Neointimal Cells David Jourde'heuil, Frances L. Jourde'heuil, Yongfeng Liu, Julia Steppich, Roman G. Ginnan, David J. Conti, Harold A. Singer, Arif Asif. *Center for Cardiovascular Sciences and Nephrology Group, Albany Medical Center, Albany, NY.*

Background: Arteriovenous fistulae (AVFs) suffer significant problems with high incidence of both early and late failures. Interventions that may prolong access patency are still very limited and require strategies that may impair or regress neointimal hyperplasia. In the cardiovascular system, globins such as hemoglobin are thought exclusively to regulate O₂ and nitric oxide (NO) levels. However, recent studies suggest that this model might be incomplete and that non-canonical mammalian globins including cytoglobin (CYGB) have survival functions independent of the regulation of O₂ and NO. Our goal was to understand the function of CYGB in the hyperplastic response associated with AVF failure.

Methods: Histomorphometric, immunostaining, and protein analysis were performed on samples obtained from the venous segments of AVFs collected from patients undergoing surgical access creation/revision. The functional significance of CYGB was studied in vivo in rodent models of injury-induced neointimal formation and in sub-cultured human smooth muscle cells (SMCs) derived from primary placement and revision veins.

Results: CYGB was upregulated in revision compared to primary placement veins with significant expression in both medial smooth muscle and neointimal cells. Injury-induced neointimal formation in vivo was attenuated by CYGB deficiency and associated with increase apoptosis and medial VSMCs loss. Human venous medial and neointimal SMCs derived from failed AVFs maintained high levels of CYGB in culture in contrast to

medial SMCs from placement veins. Molecular strategies to modulate CYGB expression levels revealed that CYGB promotes SMC cell survival by inhibiting the mitochondrial pathway of apoptosis.

Conclusions: Our results challenge the current dogma on globin functions and demonstrate a role for CYGB in regulating venous VSMCs survival. Strategies aimed at regulating CYGB anti-apoptotic functions might represent important therapeutic options to control for AVF maturation and limit stenosis.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund, Private Foundation Support

TH-PO840

Identification of Ca²⁺/CaM-Dependent Protein Kinase (CaMKII) Isoforms and Their Selective Regulation by NADPH Oxidases in Failed Arteriovenous Fistula from Hemodialysis Patients Roman G. Ginnan,¹ Ravi S. Shah,¹ David J. Conti,³ Arif Asif,² David Jourde'heuil,¹ Harold A. Singer.¹ ¹Center for Cardiovascular Sciences, Albany Medical College, Albany, NY; ²Div of Nephrology and Hypertension, Albany Medical College, Albany, NY; ³AMC Surgery Group-Transplantation, Albany Medical College, Albany, NY.

Background: Placement of an arteriovenous fistula (AVF) provides vascular access for lifesaving hemodialysis to patients with severe and chronic kidney disease. A significant percentage of AVFs initially mature; serve as successful hemodialysis access points; but fail at some later time due to neointimal hyperplasia that occludes the vein. The causative underlying molecular, biochemical, and cellular factors that contribute to AVF failure are incompletely understood. CaMKII is a positive regulator of VSM cell proliferation and migration that results in occlusion of carotid arteries in both mice and rats. Currently, there is little known regarding the role of CaMKII in either physiological or pathophysiological venous function.

Methods: Cephalic veins from patients prior to AVF placement and after AVF failure were obtained. Immunohistochemical studies were performed on OCT embedded frozen sections. Molecular analyses were performed on RNA extracts from these venous segments and protein analyses were performed on protein extracts.

Results: Our results indicate that there is an increase in CaMKII δ and CaMKII γ expression in failed AVFs as compared to cephalic vein prior to AVF placement. CaMKII activity is regulated by both phosphorylation and oxidation. NADPH oxidases (Noxs) generate reactive oxygen species (ROS) that increases CaMKII activity. Analysis of failed AVFs shows an upregulation of Nox4 and Nox5. Further studies show an increase in CaMKII activity. Interestingly, our data indicates that only a subset CaMKII isoforms are oxidized under these conditions.

Conclusions: These findings lead us to conclude that increases in [Ca²⁺] and [ROS] after AVF placement may result in increases of CaMKII expression and sustained activity that contribute to AVF failure. They also identify CaMKII as a rational target for therapeutic manipulation to prevent AVF failure.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund

TH-PO841

Combined RNA seq and gDNA Methylation Analysis for AVF Maturation Begoña Campos, Sonia Bhati, Nikhil Grandhi, Ashish Verma, Amanda B. Naciff-Campos, Gagan Deep Singh, Keith Louis Saum, Mario Medvedovic, Amy Pflum, Timmy C. Lee, Prabir Roy-Chaudhury. *Univ of Cincinnati.*

Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction. In order to understand the cellular and molecular mechanisms involved in early AVF failure we evaluated the gene methylation profile (epigenetics) in conjunction with the gene expression profile (RNA Seq) from venous segment tissue samples obtained at the time of AVF creation. This approach allows us to identify genes that have altered expression (RNA Seq analysis) as a result of epigenetic changes (DNA methylation). The latter can be induced by different factors, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD).

Methods: Genomic DNA (gDNA) and RNA were isolated from venous segments collected at the time of AVF creation. We divided the samples into 2 groups, THICK (n=5) and THIN (n = 5), based on a histological evaluation of the amount of neointimal hyperplasia. Deep sequencing technologies were then used to identify differentially regulated levels of gene expression between the THICK and THIN groups, that also had significant differences in the degree of methylation. Standard bioinformatic techniques were used to identify/interrogate these changes.

Results: We were able to identify a number of genes that were differentially regulated, either at the level of the transcriptome or at the level of DNA methylation (epigenetics) between the THICK and THIN groups. However, we were not able to identify individual genes that had changes in both the RNA Seq and DNA methylation analyses, at a high level of statistical significance.

Conclusions: While we were unable to identify differences in both gene expression and the level of DNA methylation for individual genes, between our two groups (perhaps because of a small sample size), we do believe that these techniques and technologies could be used in larger studies, to dive deep into the mechanisms of AVF failure at a molecular and genetic level.

TH-PO842

Computational Fluid Dynamic Analyses in a Uremic Mouse Model of AVF Stenosis: Of Surgery, Techniques and Computation Begoña Campos,¹ Yang Wang,¹ Yong He,² John M. Pearce,³ Richard Scott Dunn,³ Keith Louis Saum,¹ Janaka Wansapura,³ Charles L. Dumoulin,³ Scott A. Berceci,² Prabir Roy-Chaudhury.¹ ¹Univ of Cincinnati; ²Univ of Florida; ³CCHMC.

Background: Although arteriovenous fistulae (AVF) are the preferred form of vascular access for hemodialysis patients, over 50% of AVFs fail to mature (inability to increase blood flow and diameter adequately to support dialysis). Work performed in our laboratory suggests that AVF maturation failure is due to an interaction between “upstream hemodynamics” and “downstream vascular biology”. In order to better elucidate the mechanisms involved in both these processes, we herein describe the techniques needed to develop a shear stress profile within a uremic mouse AVF.

Methods: In order to create a uremic mouse model, C57Bl/6 animals underwent an initial cauterization of the left kidney followed 2 weeks later by a contralateral nephrectomy. Four weeks later AVFs were created in the neck. In order to generate different shear stress profiles, we created AVFs between the carotid artery and jugular vein in the following surgical configurations (a) end of carotid artery to end of jugular vein (b) end of jugular vein to side of carotid artery and (c) end of carotid artery to side of jugular vein. Mice were then perfused with a silicone rubber casting agent (Microfil). Fistulae were harvested, stored in 4% paraformaldehyde, and treated with Lugol solution as a micro-CT contrast agent. Each AVF was then scanned using micro-CT imaging to create a 3D reconstruction of AVF geometry. In order to obtain blood flow parameters we have developed an MRI technique that allows us to quantify blood flow within the carotid artery. We then use software to develop a complete shear stress profile in the mouse AVF.

Results: We have described for the first time a hybrid surgery-fluid dynamics approach, which could allow us to identify the differential impacts of different surgical configurations, with or without the impact of uremia on AVF fistula functionality (with the promise of also being able to use genetically manipulated animals in the future).

Conclusions: We firmly believe that teasing out the relative roles of upstream hemodynamics and downstream uremic vascular biology will allow us to identify target(s) for future therapeutic interventions.

TH-PO843

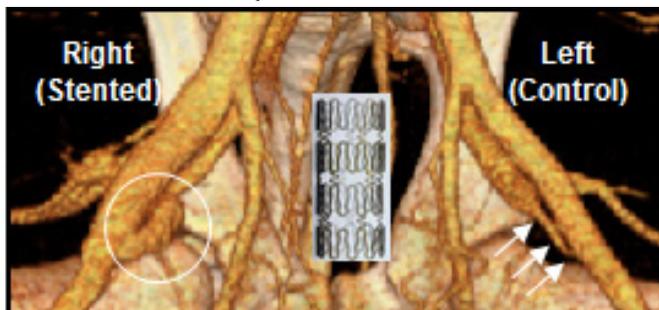
Biodegradable Stents Improve Arteriovenous Fistula (AVF) Maturation Begoña Campos, Yang Wang, Zhangzhang Yin, Keith Louis Saum, Diego Celdran-Bonafonte, Mark J. Schulz, Vesselin Shanov, Prabir Roy-Chaudhury. *Univ of Cincinnati.*

Background: Arteriovenous fistula (AVF) maturation failure is currently a huge clinical problem with no effective therapies. At a pathogenetic level the three main causes of AVF maturation failure are (a) small veins (b) abnormal non-laminar flow profiles and (c) abnormal local endothelial function. We therefore, hypothesize, that the placement of a malleable, biodegradable magnesium based maturation enhancing stent (bMES) within the venous segment, at the time of surgical AVF creation would dilate small veins, optimize the anatomical configuration, and serve as a conduit for the future delivery of therapies to improve local vascular biology during the critical initial 4-8 week period with an absence of long term side effects (no stent after 4-8 weeks).

Methods: bMES were fabricated using pure Mg foil (125 mm) and Mg-Zn alloy wire. Bilateral AVFs were created between the femoral artery and vein of Yorkshire pigs. A bMES was inserted on one side and dilated to 8mm. A control AVF was created on the contralateral side. CT angiograms and ultrasounds were performed to document blood flow and diameter for the control and stented AVF.

Results: Preliminary data documents almost complete degradation of the bMES at 4-8 weeks with an initial increase in diameter of the stented AVFs on CT angiograms at 2 weeks (Figure). Histological examination performed on both the stented and control AVFs did not reveal any evidence of necrosis or inflammation.

Conclusions: These initial results clearly demonstrate technical feasibility and safety for the bMES, and also provide us with an efficacy signal based on our CT angiogram data (Figure). We believe that this technology could significantly reduce the huge morbidity and mortality associated with AVF maturation failure and also expand the patient population considered to be suitable for AVF placement in the future.



Funding: Other NIH Support - R21EB016150

TH-PO844

Abstract Withdrawn

TH-PO845

Association Between Clinical Outcomes and Type of Vascular Access in Elderly End-Stage Renal Disease Patients Initiating Hemodialysis Kyoung Sook Park, Mi Jung Lee, Tae-Hyun Yoo, Shin-Wook Kang. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Although dialysis initiation via arteriovenous fistula (AVF) is the best strategy in incident hemodialysis (HD) patients. Elderly patients with HD are compelled to use HD catheter (HC) due to maturation failure after AVF operation. Therefore, we investigated the association of vascular access (VA) type and clinical outcomes in elderly incident HD patients.

Methods: A prospective cohort of incident HD patients from the Clinical Research Center for End-stage renal disease in Korea between 2009 and 2013 was used. Patients who were 65 years or older were defined as elderly. The patients were classified into three groups according to VA type at HD initiation. Since the hazard ratio (HR) according to type of VA was not proportional, time-dependent Cox regression analysis was performed to determine all-cause mortality.

Results: Among the 511 enrolled patients, 303 (59.3%) were male and the mean age was 72.3±5.4 years. HD was initiated with AVF, arteriovenous graft (AVG), or HC in 86 (16.8%), 36 (7.0%), and 389 (76.1%) patients, respectively. During a median follow up of 12 months, all-cause death was observed 12 (14.0%) in AVF, 13 (36.1%) in AVG, and 107 (27.5%) in HC. Multivariate time-dependent Cox regression analysis demonstrated that AVG (AVF as reference, HR=1.719, 95% confidence interval [CI]=1.274-2.319, P<0.001) and HC (HR=1.304, 95% CI=1.036-1.640, P=0.023) were significant risk factors for all-cause mortality after adjustment of age, sex, diabetes mellitus, previous cardiovascular disease, timing of referral to nephrologist, hemoglobin, serum albumin, and C-reactive protein levels.

Conclusions: Patients with successful AVF were associated with better survival compared to those with AVG or HC. In addition, survival was comparable between elderly patients initiating HD with AVG and HC. Although vascular problems are common in elderly patients, AVF may be the best strategy to improve clinical outcomes in this population.

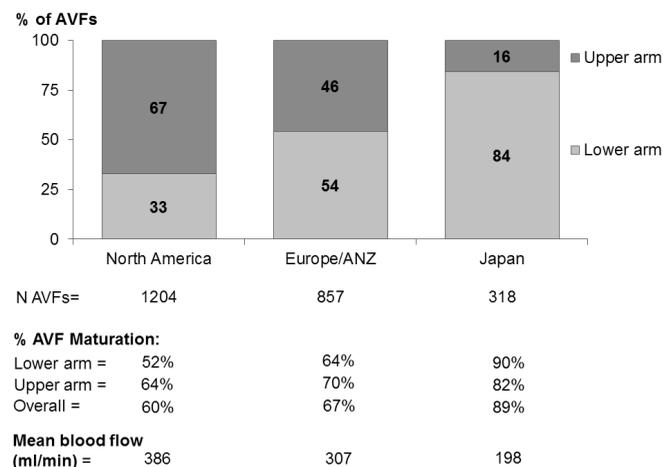
TH-PO846

International Variability in Arteriovenous Fistula Maturation and Placement: The Dialysis Outcomes and Practice Patterns Study Ronald L. Pisoni,¹ Lindsay Zepel,¹ Francesca Tentori,^{1,2} Yun Li,³ Jarcy Zee,¹ Richard J. Fluck,⁴ Loreto Gesualdo,⁵ Hideki Kawanishi,⁶ Gültekin Süleymanlar,⁷ Bruce M. Robinson.¹ ¹Arbor Research; ²Vanderbilt Univ; ³Univ of Mich.; ⁴Nat. Health Service England; ⁵Azienda Ospedaliero Univ Consorziabile Policlinico; ⁶Tsuchiya Gen. Hosp.; ⁷Akendiz Univ.

Background: Prior Dialysis Outcomes and Practice Patterns Study (DOPPS) findings demonstrate international variability in vascular access practices, and association with outcomes. Here we describe international practices in arteriovenous fistula (AVF) placement and predictors of AVF maturation.

Methods: We studied 2,230 patients with an AVF created during DOPPS phases 4-5 (2009–2015) in North America, Europe/Australia-New Zealand (ANZ), and Japan. AVF maturation was defined as access use ≥ 30 days. Generalized estimating equations with a logit link were used to assess predictors of AVF maturation adjusting for country, phase, patient characteristics, and accounting for facility clustering.

Results: No significant association was found between many patient characteristics (e.g., age, diabetes, peripheral vascular disease) and AVF maturation. AVF maturation was more likely for males vs. females (OR = 1.49 [95% CI = 1.25-1.79]) and for AVFs placed in the upper vs. lower arm (OR = 1.40 [95% CI = 1.15-1.70]). Even though upper arm AVFs were more common in North America, AVF maturation was lowest in this region (Figure).



Conclusions: There is large international variability in site of AVF placement and AVF maturation. Differences in blood flow used (much higher in the US vs. Europe and Japan) may lead to different interpretation of the term “maturation” internationally, and may influence maturation rates.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGfN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

TH-PO847

Vascular Access in Acute Kidney Injury: Results from the ATN Study Kavitha Ganta, Yue-Harn Ng, Herbert T. Davis, Mark L. Unruh. *Department of Internal Medicine, Univ of New Mexico, Albuquerque, NM.*

Background: Acute kidney injury requiring renal replacement therapy (RRT) portends a poor prognosis. Currently, the decision regarding catheter placement is based solely on physician discretion. Limited data exist to guide catheter placement. The Acute Renal Failure Trial Network (ATN) study was a multicenter, prospective, randomized trial on the effects of dialysis dose on mortality in critically ill patients. Using data from this study, we assessed the complications rates and the adequacy of dialysis based on different catheter locations.

Methods: Baseline characteristics were gathered. The outcomes of interest include catheter related infections, cardiac arrhythmias, excessive bleeding, local thrombosis and dialysis adequacy. Categorical variables were analyzed using Chi-square test while continuous variables were analyzed using the Student T test. The SAS software was used for analysis.

Results: There were 242 (11.7%) subclavian (SC), 951 (46.1%) internal jugular (IJ) and 861 (41.7%) femoral (FC) catheters inserted. The baseline characteristics based on catheter location is shown in Table.1.

Baseline Characteristics	Catheter Location			P
	SC (%)	IJ (%)	FC (%)	
Age	61.3 ± 14.3	61.3 ± 14.7	59.1 ± 15.8	<0.01
Gender (Male)	170 (70.3)	686 (72.1)	618 (71.8)	0.84
BMI	27.3 ± 6.0	28.6 ± 6.0	27.9 ± 5.6	<0.01
Platelet (000/mm ³)	141 ± 138	144 ± 113	130 ± 114	0.04
INR	1.6 ± 0.8	1.7 ± 1.6	1.9 ± 1.8	<0.01
Diabetes	78 (32.2)	286 (30.1)	235 (27.3)	0.23
PVD	75 (31.0)	197 (20.7)	113 (13.1)	<0.01

The rate of bacteremia was comparable between the 3 groups. (5.4% (SC) vs. 3.5% (IJ) vs. 3.5% (FC); p = 0.34) The IJ group experienced more cardiac arrhythmias (2%) compared to the SC (0.8%) and FC (0.5%) group [p = 0.01] while the FC group had more venous thrombosis (0.7%) compared to none in the SC and IJ group [p = 0.02]. Overall, complication rates were low. There was no clinically significant difference in the adequacy of dialysis between the 3 groups.

Conclusions: There was no significant differences in complication rates amongst the 3 catheter locations hence decision on catheter location should be based on operator experience and comfort level.

TH-PO848

Vascular Access at Dialysis Initiation in the United States Renal Data System (USRDS): Strong Agreement between CMS 2728 Medical Evidence Form and CROWNWeb Purna Mukhopadhyay,¹ Jeffrey Pearson,¹ Kenneth J. Woodside,² Sarah Bell,² Ronald L. Pisoni,¹ Douglas E. Schaebel,² Kaitlyn Ratkowiak,¹ Rajiv Saran.² ¹Arbor Research Collaborative for Health, Ann Arbor, MI; ²Univ of Michigan, Ann Arbor, MI.

Background: The USRDS has long reported vascular access (VA) at the start of hemodialysis (HD) using the CMS-2728 Form. In 2012, CMS rolled out the CROWNWeb (CW) system to collect clinical treatment and laboratory data monthly for all dialysis patients. As CW data are fully integrated into the USRDS database, it is critical to evaluate the level of completeness and consistency between these two data sources.

Methods: We compared VA used at the first HD session reported on the CMS-2728 form for new ESRD patients in 2013 (n = 96,936) in USRDS database with VA used at the end of the 1st month of HD reported through CW. To evaluate the potential for data lag, we also compared to the 2nd month of HD reported through CW. Completeness and consistency was assessed at the patient level by 2x2 tables. The level of agreement was evaluated by kappa statistics. Logistic regression models were fit to identify patient characteristics associated with the level of agreement.

Results: 89% of patients had at least one monthly VA report in CW among which 0.23% was missing VA data from the CMS-2728 and 32.8% did not have a VA reported in CW for their 1st month of HD. However, completeness of CW data improved when either 1st or 2nd month of HD was considered as only 12.6% of patients did not have a VA reported. Among patients with VA reported from both data sources, kappa statistics was 0.88 using the 1st month of ESRD and 0.84 using first two months of ESRD. Agreement was highest for catheter (97-98%) and lowest for graft (78-81%). Age, sex, race were associated with the level of agreement; Hispanic ethnicity and cause of ESRD were not.

Conclusions: CW data has VA information for the vast majority of patients; however, coverage is not complete and may be lowest at start of ESRD. However, there is very strong agreement in VA reported on the CMS-2728 and in CW. This study also demonstrates near completeness of CMS Form 2728 with respect to VA information at start of HD.

Funding: NIDDK Support

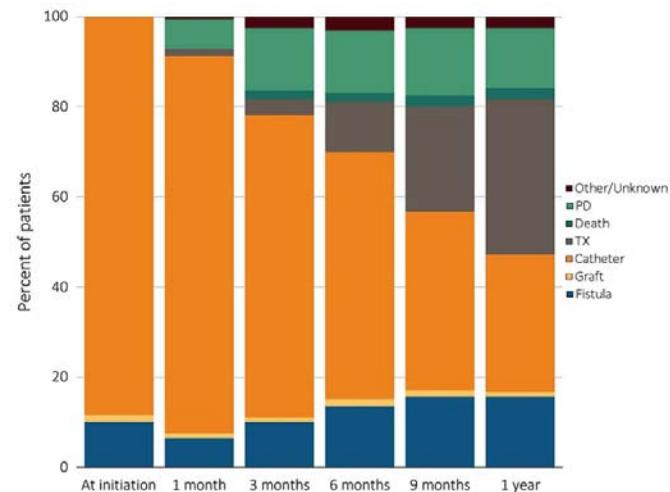
TH-PO849

Vascular Access and Trends in Pediatric End-Stage Renal Disease: Results from the USRDS Brett W. Plattner,¹ Yee Lu,² David T. Selewski,² Xue Dietrich,⁴ Nan Ji,⁴ Alissa Kapke,⁴ Douglas E. Schaebel,³ Debbie S. Gipson,² Rajiv Saran.¹ ¹Internal Medicine, Univ of Michigan, Ann Arbor, MI; ²Pediatrics, Univ of Michigan, Ann Arbor, MI; ³Biostatistics, Univ of Michigan, Ann Arbor, MI; ⁴Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Policy to improve outcomes for End-Stage Renal Disease (ESRD) patients (pts) may be less widely adopted in children. We describe vascular access (VA) in incident and prevalent pediatric ESRD pts and examine changes in the first year.

Methods: Pediatric ESRD was defined as 0-17 yrs at diagnosis of ESRD. Data was from the 2728 and CROWNWeb. For pts incident during 2006-2013, data on VA at hemodialysis (HD) initiation (n=2,851) was categorized as catheter only (CVC), AV Fistula (AVF), AV Graft (AVG), CVC with maturing fistula, or CVC with maturing graft. Pts initiating HD between 6/1/2012-12/31/2012 (N=197), were tracked over 12 months. For prevalent pts, AVF & AVG groups include CVC/maturing fistula and CVC/maturing graft, respectively.

Results: From '06-'12, incident pts began ESRD care using HD 39%, PD 36%, and transplant 25%. In 2013, in pts starting HD, 90% had a CVC, an increase from 84% in 2006. CVC was lower for the older pts (<4yrs: 99% vs. 14-17yrs: 83%, p <.05). VA trends over a year in a 7-month incident cohort showed the proportion of CVC decreased from 84% at 1 month to 31% at 1 year, while 16% were using or maturing an AVF. 1% were using or maturing an AVG. 13% of pts transitioned to PD and 35% received a TX by 1 year.



Conclusions: Our analysis confirms the large CVC burden among pediatric HD pts. Conversion to AVF were observed over the first year in an incident cohort where nearly 50% of pts transitioned to PD or TX. Further study will assess the impact of CVC dependence among pediatric ESRD pts with respect to future VA options and patient outcomes.

Funding: NIDDK Support

TH-PO850

In Search of an Optimal Screening Program for Containing Graft Thrombosis Nicola Tessitore,¹ Giuseppina Pessolano,¹ Valeria Bedogna,¹ Albino Poli,² Antonio Lupo.¹ ¹Emodialisi Borgo Roma, Verona, Italy; ²Dept Public Health, Verona, Italy.

Background: K/DOQI guidelines recommend regular screening for >50% stenosis (ST) in graft by surveillance (access blood flow (Qa) &/or static venous pressure ratio (sVPR) or Duplex Ultrasound to reduce the risk of thrombosis. Analysis of the literature suggests that the best predictor of thrombosis is sVPR>0.5, with an area under curve (AUC) of 0.81[95%CI:0.75-0.85] significantly higher than that of Qa<600 ml/min (0.72[95%CI:0.68-0.77]) & ST (0.49[95%CI:0.45-0.53]), but no study has compared vis-a-vis all of the tools.

Methods: To identify an optimal screening program, in 2013 we compared the diagnostic performance of the available tools for incipient thrombosis (within 3 mo) in the same population of 42 grafts (5 forearm loop & 37 straight upperarm), that underwent 18 thrombotic episodes.

Results: Qa by Ultrasound Dilution proved to be the best screening tool (AUC:0.81[0.69-0.93]); optimal thresholds between Qa<1000 ml/min(63% sensitivity[SE], 18% false positives[FPR]) & Qa<1200 ml/min (83% SE, 27% FPR). Its AUC was higher than that of ST (0.69[95%CI:0.54-0.84]: 78% SE, 39% FPR), monitoring (0.62[95%CI 0.45-0.79]: 33% SE, 9% FPR), & VAPR (0.58[95%CI:0.42-0.74]: VAPR>0.8:72% SE, 58% FPR). At GLM analysis Qa was the only significant predictor of thrombosis, with 18%[95%CI 7-29] lower risk for each 100 ml/min above a Qa 400 ml/min. From January

2014 onward we adopted a monthly Qa screening program using a Qa<1000 ml/min for stenosis repair & a drop inQa>25% for detecting & repairing restenosis. This led to a significant drop of thrombosis rate from 0.70[95%CI 0.41-1.11] (during the 2012-2013 period in which screening was based on bimonthly VAPR and quarterly Qa measurements and stenosis repair triggered as per guidelines, by a VAPR>0.5 or a Qa<600 ml/min) to 0.11[95%CI 0.01-0.40] event/graft-y (p=0.005), at a comparable elective angioplasty rate (0.71[95%CI 0.46-1.04] vs 0.77[95%CI 0.43-1.27] event/graft-y, p=ns).

Conclusions: Our comparative study suggests that Qa is the best predictor of graft patency & Qa surveillance using a Qa<1000 ml/min threshold allows for appropriate and timely stenosis repair & may contain the risk of thrombosis.

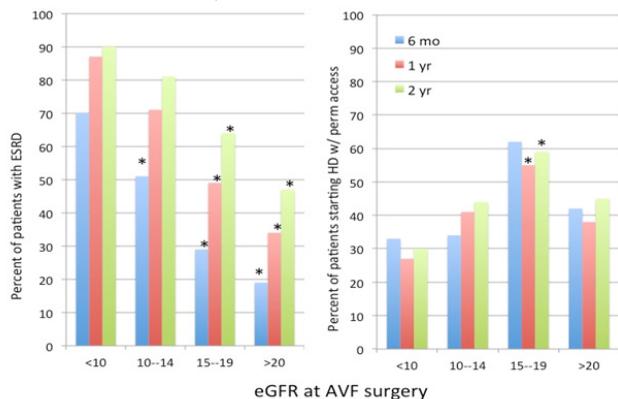
TH-PO851

The Impact of eGFR at Pre-HD Access Surgery on the Likelihood of Starting Hemodialysis with a Mature Vascular Access Alian Albalas, Timmy C. Lee, Michael Allon. *Nephrology Dept, UAB, Birmingham, AL.*

Background: The optimal timing of pre-dialysis vascular access surgery is uncertain. If the access is placed too late, it may not be ready for use; if it's placed too early, it may not be needed. The optimal timing may differ for AVF vs AVG. We evaluated the association of eGFR at access placement with (1) likelihood of starting HD, and (2) likelihood of a mature access at HD initiation.

Methods: We retrospectively queried a prospective computerized access database to identify patients with pre-HD access surgery (301 AVF and 64 AVG placed between 2006-12) with an eGFR recorded on the surgery date. Patients were stratified into 4 eGFR groups (<10; 10-14; 15-19; >20 ml/min). For each patient we determined:(1) whether dialysis was initiated within 2 years, and (2)whether the permanent access was used on the first HD session.

Results: Overall, 208 (or 69%) of pts with pre-HD AVF surgery initiated HD within 2 years, but the proportion varied by eGFR at surgery (90, 81, 64, and 47% for eGFR <10, 10-14, 15-19, and >20 ml/min).



Among the 208 pts with pre-HD AVF who started HD, 47% used the AVF on the first HD session, but the proportion varied by eGFR (30, 44, 59 and 45% for eGFR <10, 10-14, 15-19, and >20 ml/min). Among pts with pre-HD AVG surgery, HD was initiated within 6 months in 90, 62, and 50% for eGFR <10, 10-14, and 15-19 ml/min. The AVG was used for the HD session in 78, 89, and 88% of pts with eGFR of <10, 10-14, and 15-19 ml/min.

Conclusions: There are tradeoffs in the timing of pre-HD AVF surgery. A higher eGFR is associated with a lower likelihood of initiating HD in 2 years, but a higher likelihood that the AVF will be used on the first HD session. The optimal balance is achieved at an eGFR of 15-19 ml/min. In contrast, the optimal timing for pre-HD AVG surgery is an eGFR of 10-14 ml/min. Late placement of an AVG may be a catheter-sparing strategy.[figure]

TH-PO852

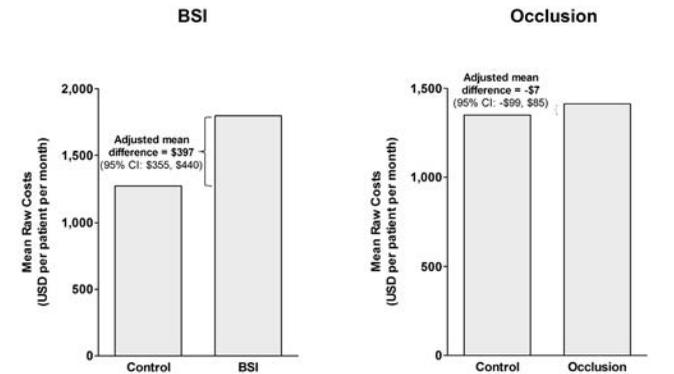
Economic Burden to Dialysis Providers of Central Venous Catheter (CVC)-Related Blood Stream Infections (BSI) and Occlusions Among Incident Hemodialysis (HD) Patients Steven M. Brunelli,¹ Wendy Turenne,¹ Scott Sibbel,¹ John Alan Laich,¹ Antony E. Pfaffle,² ¹DaVita Clinical Research, Minneapolis, MN; ²CorMedix Inc, Bedford, NJ.

Background: Complications of CVCs may have economic consequences for dialysis providers derived from opportunity costs for missed dialysis treatments and increased use of bundled medications. We sought to quantify this financial burden among incident patients at a large dialysis organization (LDO).

Methods: We considered patients who began HD via a CVC between Jan 2013 and Dec 2014. In parallel analyses, patients who developed BSI (N=3269) or occlusion (N=676) during the first 6 months of dialysis were matched to control CVC-HD patients who did not. Missed HD treatment rates and medication utilization were considered from date of BSI/occlusion (or corresponding date for controls) for 180 days or until censoring for death, modality change or loss to follow up. Costs were derived using payor-specific remuneration rates (missed treatments), LDO acquisition costs (IV iron, ESA) and average wholesale prices (antibiotics, thrombolytics). Differences were estimated using linear mixed models including fixed effects for exposure status and month, adjusted for covariates that were imbalanced at baseline.

Results: CVC-related BSI was associated with significantly greater ESA utilization (59,339 vs 49,515 U/month, cases vs controls), IV antibiotic use (41.8% vs 6.0%) and missed HD treatment rate (1.95 vs 1.36 missed treatments/patient-month). This translated to a mean incremental cost of +\$397 per patient per month. CVC occlusion was associated with increased thrombolytic use (10.9% vs 4.2%) but no significant difference in costs.

Conclusions: CVC-related BSI is a potent cost driver for dialysis providers with incremental costs of ~\$400/month over a 6-month time horizon. No appreciable economic consequences of CVC occlusion were observed.



Funding: Pharmaceutical Company Support - CorMedix Inc

TH-PO853

Obesity Related Decrease in Intraoperative Blood Flow Is Associated with Maturation Failure of Radiocephalic Arteriovenous Fistula Jwa-kyung Kim,¹ Sun Ryoung Choi,² ¹Internal Medicine, Dept of Internal Medicine, Kidney Research Inst, Anyang, Korea; ²Internal Medicine, Shamyook Medical Center, Seoul, Korea.

Background: Successful arteriovenous fistula (AVF) maturation is often challenging in obese patients. Optimal initial intraoperative blood flow (IOBF) is essential for adequate AVF maturation. This study was conducted to elucidate the effect of obesity on IOBF and radiocephalic AVF maturation.

Methods: Patients who newly created radiocephalic AVF were included (n=252). Obesity was defined as a baseline BMI≥25 kg/m², and primary maturation failure was defined as the failure to use AVF successfully by 3 months after its creation. IOBF was measured immediately after construction of AVF using a VeriQTM system.

Results: The mean BMI was 24.1±3.9 kg/m², and the prevalence of obesity was 31.3%. Particularly, 8.3% (21 patients) were BMI ≥ 30 kg/m². Primary maturation failure occurred in 100 (39.7%) patients and an IOBF< 190 mL/min was closely associated with the risk of maturation failure (relative risk,3.05; 95% CI,1.52-6.11). Compared to non-obese patients, obese subjects had a significantly higher prevalence of diabetes and elevated hs-CRP levels, whereas diameters of vessels were similar. When the patients were further divided into 3 groups as the BMI <25, 25-29.9, and >30 kg/m², patients in higher BMI group showed significantly lower IOBF and higher maturation failure rate. According to multivariate analysis, the statistically significant variables that determined maturation failure were obesity, previous vascular disease, increased hs-CRP levels, and IOBF < 190 mL/min.

Conclusions: Obese patients had a significantly lower IOBF, and both obesity and low IOBF contributed to the primary maturation failure of AVF. Obesity-associated inflammation and atherosclerosis might play roles in this association.

TH-PO854

The Impact of Vascular Access on Hemodialysis Patient Survival and Risk Analysis Ping chin Lai,¹ Le mei Yeh,¹ Yueh hsia Chiu,² Ling yin Chiu.¹ ¹Renal Dept, Chang Gung Memorial Hospital, Taoyuan, Taiwan; ²Health Care Management, Chang Gung Univ, Taoyuan, Taiwan.

Background: Hemodialysis is the most common dialysis modality worldwide. However, the impact of different types of vascular access on hemodialysis patient survival has not been investigated in a large scale study. Therefore, we retrospectively reviewed the survival of hemodialysis patients in our center and analyzed the impact of vascular access on their survival. Other potential risk factors were also studied.

Methods: From 2001 to 2010, patients, who aged more than 40 years old and received regular hemodialysis in our center for at least 3 months, were included into this study. A total 916 patients were enrolled. The mean followed up interval were 4.4± 2.5 years. Among them, 51.1% were male, while 48.9% were female. These patients were divided into three groups according to their vascular access. Group A: patients used either native arteriovenous fistula or arteriovenous graft at the all time and dialysis catheter had never been used during the whole study period. Group B: patients used either native arteriovenous fistula or arteriovenous graft as their vascular access most of the time but they had used dialysis catheter at least once during study period. Group C: patients used dialysis catheter as their vascular access and arteriovenous shunt had never been established during the study period. Other survival associated factors were analyzed by using univariate and multivariate factor analysis.

Results: The results showed that group C patients had significantly worst survival rate (P<0.0001). The group B patients also had significantly worse survival rate when compare

with group A patients ($P < 0.0001$). The hazard ratio was 1.71 (1.31-2.24) for group B and 3.56 (2.08-6.08) for group C when compared to group A patients. Multivariate analysis showed that the associated risk factors for patient survival were male sex, diabetes mellitus, low albumin, high hsCRP, and abnormal AST level.

Conclusions: The use of dialysis catheter imposed high risk for patient mortality on top of other associated risk factors. Early establishment of vascular access can eliminate this risk factor and improve patient outcome.

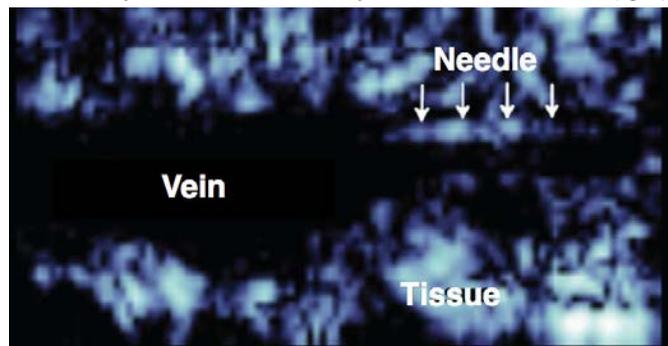
TH-PO855

Early Experience with a Novel Device for Ultrasound-Guided Management and Cannulation of Hemodialysis Vascular Access William D. Paulson,¹ Deborah J. Brouwer-Maier,² Lillian A. Pryor,² John Jason White,¹ Laura L. Mulloy,¹ Lu Y. Huber,¹ Matthew J. Diamond,¹ ¹Charlie Norwood VAMC & Georgia Regents Univ, Augusta, GA; ²Fresenius Medical Care, Waltham, MA.

Background: The vascular access continues to be the Achilles Heel of dialysis. Methods that facilitate easier management and cannulation of accesses are needed. We describe early experience with a novel ultrasound device.

Methods: The Sonic Window (Analogic Corp, Peabody, MA, USA) is designed to assist management of vessels in a variety of contexts. It differs from conventional ultrasound in that it provides a coronal view of vessels that yields determination of characteristics such as depth and luminal diameter, and assists in cannulation for dialysis. We have initiated a program in 4 FMC dialysis units which is designed to identify its role and limitations.

Results: Two experts in the use of the Sonic Window have trained dialysis staff in the 4 FMC units. Staff have successfully cannulated 33 AV fistulas and synthetic grafts. Set up and use of the device generally adds an extra 1-3 minutes to cannulation time. Staff are able to easily visualize advancement of dialysis needles into the vessel lumen (figure).



We plan to evaluate the following potential uses of the device: 1. Assessing fistula maturation by measuring increase in luminal diameter over time; 2. Evaluating accesses that are difficult to cannulate; 3. Evaluating accesses with low blood flow, or high negative arterial or positive venous dialysis pressure; 4. Identifying alternative access sites for cannulation. Possible disadvantages to be addressed: potential staff & patient reluctance to accept new technology and additional cannulation time, to be assessed in surveys.

Conclusions: Our early experience supports the concept that Sonic Window is a significant advance in managing and cannulating accesses in both routine and difficult situations.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

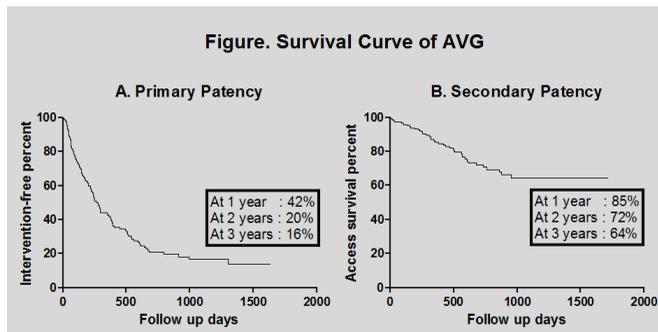
TH-PO856

Modifiable Risk Factors Affecting the Outcome Hemodialysis Graft Jee eun Park, Jin Hae Kim, Subin Hwang, Do Hee Kim, Hye Ryoung Jang, Jung eun Lee, Woosong Huh, Yoon-Goo Kim, Ha Young Oh, Dae Joong Kim. Nephrology Div, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.

Background: Arterio-venous graft (AVG) for hemodialysis has poorer outcome than arterio-venous fistula (AVF) with its frequent stenosis and thrombosis. We investigated modifiable risk factors affecting the outcome of AVG.

Methods: A single-center cohort of 254 patients (pts) receiving AVG for hemodialysis access from Sep 2010 to Oct 2014 were included. Demographics, laboratory data, comorbidities, and medications were collected from the medical records. Surgical factors related to AVG operation including the type and diameter of connected vessels, graft site, and type of operation (elective or emergent) were also recorded. End points was the interval from initial access formation to any intervention intended to restore patency (primary patency, days) and the total access survival duration (secondary patency, days).

Results: Data of 225 pts were analyzed. During the follow-up period, 139 (62%) pts received intervention and 45 (20%) pts underwent permanent failure. Survival analyses using Kaplan-Meier method was shown in the figure. In multivariate analysis, primary patency duration was associated with RAS inhibitor (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.13-2.46), and upper arm graft (HR 0.62, 95% CI 0.40-0.94). Secondary patency duration was associated with serum albumin level (HR 0.28, 95% CI 0.13-0.61), diastolic blood pressure (BP) (HR 0.93, 95% CI 0.89-0.98) and warfarin (HR 5.80, 95% CI 2.04-16.46).



Conclusions: Patients' nutritional status reflected by serum albumin levels and diastolic BP could be modified for favorable outcome of AVG.

TH-PO857

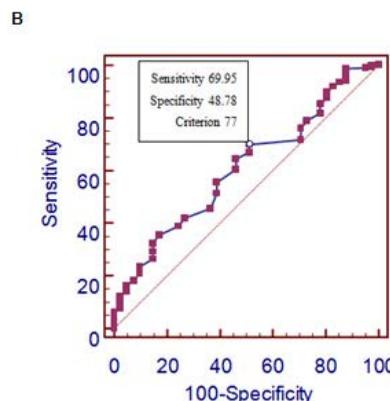
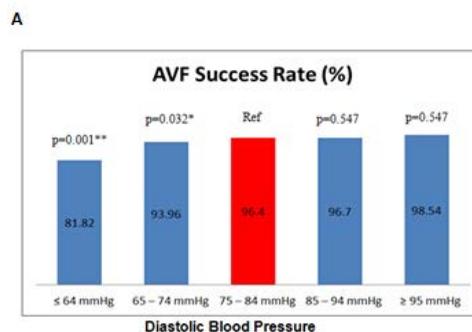
Effects of Diastolic Blood Pressure on the Patency of Brescia-Cimino Arteriovenous Fistula for Hemodialysis Access Yan Yan. Nephrology Dept, The First Affiliated Hospital of Nanchang Univ, Nan Chang, China.

Background: To evaluate the relationship of diastolic blood pressure (DBP) with the patency of the Brescia-Cimino arteriovenous fistula (AVF), and to determine DBP levels that predict the success of this procedure.

Methods: Data was collected from 986 patients with end-stage kidney disease (ESKD) who had Brescia-Cimino AVFs from March 2007 to December 2013. DBP was measured twice a day, at 6 AM and 5 PM, starting 3 days before surgery until 3 days post-procedure. A receiver operating characteristic (ROC) curve was constructed to determine the cutoff value of pre-operative DBP, which predicts an increased chance of AVF patency during the first 7 days after surgery.

Results: Only 41 out of the 986 patients enrolled in this study developed AVF failure within the first 7 days following surgery, resulting in a 95.8% success rate in the procedure. This rate was increased by pre-operative DBP levels ($P = 0.007$). When the cutoff value was 77 mmHg, ROC analysis showed DBP was a pre-operative indicator for predicting AVF patency in the early postoperative period ($P = 0.012$; AUC = 0.607) with a sensitivity of 69.5% and specificity of 48.8%.

Figure



A: AVF early success rate by preoperative DBP level. **B:** ROC curve of the average diastolic blood pressure level prior to AVF construction. AUC was 0.607 (95% CI 0.576-0.638, $P = 0.012$) when a cutoff value of average DBP was 77 mmHg. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Ref is comparison object.

Conclusions: A DBP > 77 mmHg prior to surgery may be considered as a key prognostic indicator of the Brescia-Cimino procedure.

Funding: Government Support - Non-U.S.

TH-PO858

Vascular Access Outcomes following Peritoneal Dialysis to Hemodialysis Transition Timmy C. Lee,¹ Mae Thamer,² Qian Zhang,² Yi Zhang,² Michael Allon.¹ ¹Univ of Alabama at Birmingham; ²Medical Technology and Practice Patterns Inst.

Background: Few studies have evaluated vascular access (VA) use following transition from PD to HD. Our goal was to examine short-term VA utilization following PD to HD transition.

Methods: Using USRDS and Medicare claims data from July 2010-December 2012, we identified 3,565 incident Medicare-insured PD patients who were ≥18yrs and initiated dialysis between July 2010-June 2011. Patients had at least one dialysis claim within 90 days of dialysis initiation and were followed for 1 year until one of the following events: switched to HD, kidney transplant, death, or end of follow-up. We used Cox-regression models to examine the association of risk factors and switching to HD, with death and transplantation used as competing events.

Results: 991 (27.8%) patients switched from PD to HD during the 1 year follow-up. Of these, 46% switched to HD within 90 days of dialysis initiation and 66% by 6 months. The median switch time was 114 days (IQR: 32-226). Patients with cardiovascular disease (Adjusted Hazard Ratio (HR) 1.25, 95% CI 1.10-1.43), COPD (HR 1.29; 95% CI 1.01-1.66), and without pre-dialysis nephrology care (HR 1.46; 95% CI 1.21-1.76 versus those with >12 months nephrologist care) were more likely to switch from PD to HD. After switching from PD to HD, 89% used a catheter, 6.6% AVF, and 1.9% AVG. 90 and 180 days after switching to HD, 71% and 50% of patients, respectively, who remained on HD still used a catheter as their VA.

Type of VA	1st Switch	90 Days After 1st Switch*	180 Days After 1st Switch**
N pts Remaining on Hemodialysis	991	709	653
Catheter Only	868 (87.6)	476 (67.1)	299 (45.8)
Catheter with other VA	9 (0.9)	28 (3.9)	27 (4.1)
AVF only	65 (6.6)	130 (18.3)	224 (34.3)
AVG only	19 (1.9)	50 (7.1)	67 (10.3)
Missing	30 (3.0)	25 (3.5)	36 (5.5)

*Transplantation:41; death:127; switched back to PD:114
 **Transplantation:50; death:160; switched back to PD:128

Conclusions: The majority of patients transitioning from PD to HD initiate HD with a catheter. 50% dialyze with a catheter at 6 months. This highlights the need for VA planning in patients with failed PD to ensure timely transition to permanent VA.

Funding: Private Foundation Support

TH-PO859

Temporal Trends in Pre-Hemodialysis Vascular Access Creation in Elderly Patients with CKD Timmy C. Lee,¹ Mae Thamer,² Qian Zhang,² Yi Zhang,² Michael Allon.¹ ¹Univ of Alabama at Birmingham; ²Medical Technology and Practice Patterns Inst.

Background: Optimal timing of pre-dialysis vascular access (VA) creation remains unclear. Elderly CKD patients with high co-morbidity are more likely to die before starting HD, so deferring VA creation may be reasonable. We assessed whether nephrologists have started selecting healthier elderly patients for pre-HD VA surgery.

Methods: Using Medicare claims data we identified 3418 elderly patients (aged ≥70 years) with CKD undergoing pre-HD VA creation in 2004 to 2009, and divided them into 3 time cohorts (2004-05, 2006-07 and 2008-09). For each temporal cohort, we assessed the likelihood of initiating dialysis during 2 years of follow-up after VA surgery. We collected data on cardiovascular co-morbidities and cardiovascular events prior to VA surgery and after dialysis initiation to determine if there were significant changes in these variables during the 3 time cohorts.

Results: During the 3 consecutive time periods, the proportion of patients dying before initiating HD decreased by 28%, the proportion surviving without HD increased by 31%, whereas the proportion initiating HD remained constant (p<0.005).

Year of VA Insertion	N of Patients	Initiated HD within 2 Years (%)	Died before HD (%)	Survived without HD(%)
2004-2005	1178	68.0	17.5	14.5
2006-2007	1222	66.0	14.8	19.2
2008-2009	1018	68.5	12.6	19.0

Concomitantly, during the 3 consecutive time periods there was a progressive decrease in patients with history of PVD (66.5 to 59.7%, p<0.005), CHF (47.0 to 35.8%, p<0.005), and prior MI (6.5 to 3.3%, p<0.001). Among patients who initiated dialysis, there was a progressive decrease in the proportion of patients with a CHF (38.8 to 26.0%, p<0.001) or MI (5.4 to 2.6%, p<0.01) event in the first year after dialysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: From 2004-2009, there has been a progressive decrease in cardiovascular co-morbidities in elderly CKD patients undergoing pre-HD VA surgery, and this has been associated with a decrease in patients dying before HD and in patients with cardiovascular events after starting HD. Clinicians are becoming more selective in pre-HD placement of VA in this patient population.

Funding: Private Foundation Support

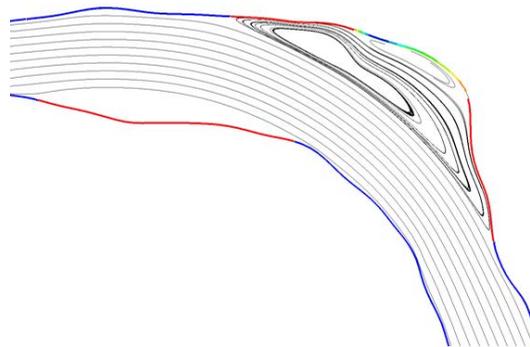
TH-PO860

Hemodynamic Changes in Arteriovenous Fistula During Dialysis Mary S. Hammes,¹ Vikash Kumar Sinha,¹ Tom Blicharski,¹ Michael Boghosian,² Jane E. Hines,¹ Sydeaka Watson,³ Kevin Cassel,² S.M. Javid Mahmoudzadeh A.² ¹Medicine/Nephrology, Univ of Chicago; ²Dept of Mechanical, Materials and Aerospace Engineering, Illinois Institute of Technology; ³Dept of Public Health Sciences, Univ of Chicago.

Background: Optimal blood flow velocity (BFV) in arteriovenous fistulas (AVF) to prevent neointimal hyperplasia is yet to be determined. We have hypothesized that changes in BFV and diameter in a brachiocephalic fistula (BCF) are affected by fistula maturation and blood flow induced during hemodialysis.

Methods: Eight subjects with primary BCF participated. Doppler BFV was measured pre-dialysis and during dialysis at 250, 350 and 450 mL/min blood flow for up to 14 months. BFV was measured in the straight portion of the cephalic vein 10 cm proximal to the cephalic arch. The relationship between BFV and diameter was examined using a linear mixed effects model. Computational modeling using venography was performed at 3 and 12 months.

Results: The change in measured diameter and BFV showed an inverse relationship with a significant association at baseline (p<0.0074) and 350 mL/min dialysis blood flow (p<0.0092). The computational model of the cephalic arch in one subject showed a 4 fold increase in Reynolds number with a dramatic recirculation region shown by a swirling eddy at the upper elbow of the arch.



This region, present at baseline and 3 months is much deeper at 12 months and with increased dialysis blood flow rate of 450 mL/min.

Conclusions: In patients with BCF, as the AVF matures and with increased dialysis blood flow, an increase in diameter of the cephalic vein with subsequent decrease in BFV is observed. Increased blood flow during hemodialysis evokes recirculation eddy's which may result in endothelial damage and subsequent intimal hyperplasia unless the arterialized vein is able to adapt and remodel to the pressures and flows that are generated during hemodialysis.

Funding: NIDDK Support

TH-PO861

Arteriovenous Fistula (AVF) Maturation Among Hemodialysis (HD) Patients: Results from the USRDS Rajiv Saran,¹ Sarah Bell,¹ Brett W. Plattner,¹ Douglas E. Schaubel,¹ Sudipta Dasgupta,¹ Purna Mukhopadhyay,² Jeffrey Pearson,² Ronald L. Pisoni,² Kenneth J. Woodside.¹ ¹Univ of Michigan; ²Arbor Research Collaborative for Health.

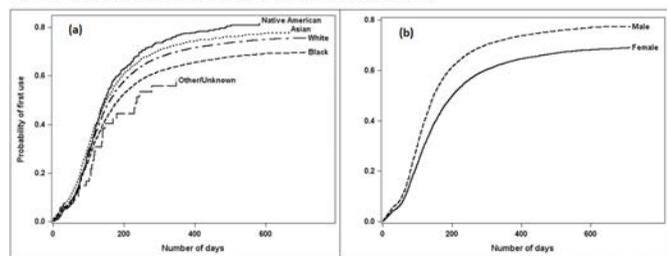
Background: AVF are considered the gold standard for HD vascular access, but require time to mature and may not adequately develop, resulting in prolonged central venous catheter (CVC) use. We describe AVF survival from placement until time to first use for prevalent HD patients in the US.

Methods: We examined HD patients with new AVF placements during 2013 using Medicare claims. Failure of maturation was identified by non-use following placement using CROWNWeb (CW) where patient access use is reported monthly by the facility. Patients were followed until end 2014. We assessed the relationship between patient characteristics and time-to-first-use of AVF with a Cox model.

Results: In 2013, 51,561 AVF were placed among 42,160 HD patients followed through 2014. No subsequent evidence of use occurred in 44.3% of the placements. Of successfully used AVF, median time to first use was 113 days. Older age groups were incrementally associated with lower probability of using AVF. Pts in the 0-21 and 22-44yr groups (HRs=1.23 [95% CI=1.06-1.44], and 1.06 [1.03-1.11], respectively), were more likely to use AVFs compared to the 45-64yr group (ref.). Sex (Female; Fig. 1a), race (e.g., Black; Fig. 1b), comorbidity (cardiovascular disease, peripheral artery disease, diabetes, needing assistance or institutionalized status), vintage <1year, CVC and/or AV Graft use at incidence, were also associated with lower probability of AVF use.

Conclusions: We have characterized AVF maturation in a national US sample and identified important associations with multiple patient-level factors. Research is urgently required into the importance of patient, region and practice factors that could improve AVF placement and maturation, decrease CVC use, to improve patient outcomes and experience.

Figure 1. Probability of first use of fistula placed in 2013 by race (a) and by sex (b)



Funding: NIDDK Support

TH-PO862

Elderly Age Does Not Affect Long-Term Survival of Non-Transposed and Transposed Upper Extremity Arteriovenous Fistulae Neville R. Dossabhoj,^{1,2} Peter Van,^{1,2} Renu Gupta,^{1,2} Clifton Frilot.² ¹Nephrology, Veterans Affairs Medical Center, Shreveport, LA; ²LSU Health, Shreveport, LA.

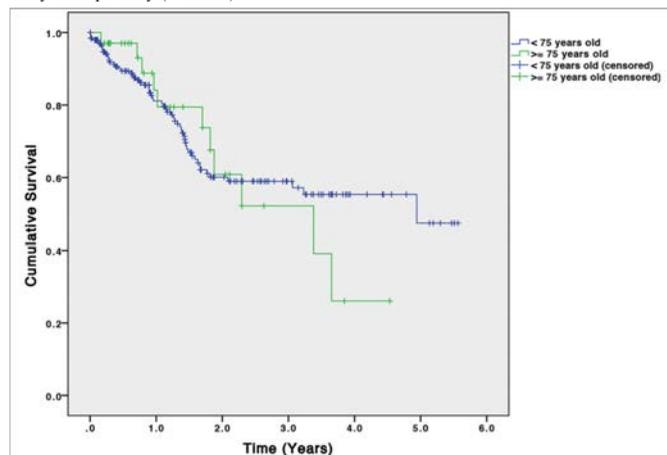
Background: The Fistula First initiative has successfully increased the placement of arteriovenous fistulae (AVF) for vascular access. Some authors have suggested that there is a higher failure rate of AVFs in elderly patients. The purpose of this study was to determine if elderly age influences the overall survival of transposed brachial-basilic fistulae (TBBF) and non-transposed AVFs (NT) placed in the upper extremity (UE).

Methods: Our prospective, computerized clinical database was queried retrospectively to identify the survival outcomes of all upper extremity (UE) fistulae placed in CKD and ESRD patients over a 6-year period at our VA hospital. All fistulae were placed by a single surgeon, hence eliminating inter-operator variability. Patient demographics and comorbid conditions were noted from the electronic record. The primary end point was permanent failure of the access. Kaplan Meier survival analysis was performed using SPSS.

Results: 230 UE fistulae were placed, which were categorized into two groups by patient age at the time of AVF placement: < 75 years and 75 years and older. The table shows the distribution by access type and age.

Age	Type of AVF	TOTAL NUMBER OF AVFs	TOTAL NUMBER OF FAILED AVFs
< 75 years	NT	124	40
< 75 years	TBBF	72	19
≥ 75 years	NT	15	6
≥ 75 years	TBBF	19	5

The figure shows that there was no difference in the Kaplan-Meier survival curves for the two age groups when NT and TBBF were analyzed collectively (P=0.833). Furthermore, there was no statistical difference between the survival curves when each group above was analyzed separately (P=0.996).



Conclusions: In conclusion, overall survival was similar for TBBF and NT AVF in our study and was not influenced by elderly age. This finding is contrary to popular opinion and some other reports.

TH-PO863

Peripherally Inserted Central Catheter (PICC) Placement in Hemodialysis Patients with Central Venous Catheters (CVC) Rita L. McGill, Robin Ruthazer, Klemens B. Meyer, Dana Miskulin, Daniel E. Weiner. *Tufts Medical Center, Boston, MA.*

Background: PICC insertion threatens opportunities for AVF creation and may reduce achievement of AVF. Accordingly, we evaluated the incidence of PICC placement in ESRD patients after starting dialysis and in the 2 years prior to starting dialysis, and recognizing that AVF rates are lower in women, whether PICC rates differed by sex.

Methods: After restricting to patients with pre-dialysis Medicare claims, we used CPT codes to ascertain all PICCs placed during the 2 years before HD initiation and up to 12/31/2012 in the subset of adult HD patients entering USRDS in 2010 or 2011 with CVC as sole vascular access. Accounting for censoring due to death and ESRD modality treatment change, and using Poisson regression to adjust for age, race, BMI, diabetes and peripheral vascular disease, we calculated sex-based incidence ratios (IRR) using PICC per 100,000 patient months.

Results: PICC were placed in 2437 (14.6%) of women and 2260 (12.2%) of men.

	Women	Men
N	16686	18494
# PICC placed during the 2 years prior to HD	1983	1469
# PICC placed during first year of HD	1438	1330
# PICC placed after first year of HD	567	532
# PICC TOTAL	3988	3331

Compared to men, crude and adjusted IRR of PICC for female sex were 1.35 [1.28-1.41] and 1.34 [1.27-1.41]. Multiple PICC (range= 2 to 14) were placed in 648/2260 (29%) men and 803/2437 (33%) women who had any PICC.

Conclusions: Despite persuasive indications for PICC avoidance, people dialyzing via CVC frequently receive one or more PICC before and even after starting dialysis. The PICC rate was 35% higher in women, a difference not attenuated by adjustment for demographic and clinical factors. More frequent PICC placement may explain some of the lower fistula rate in women. Eliminating frequent PICC placements in patients with CVC may improve achievement of AVF.

Funding: Other NIH Support - NIH/NIDDK T32 DK007777 "Epidemiology, Clinical Trials and Outcomes Research In Nephrology" Tufts CTSI Grant [UL1 TR001064]

TH-PO864

Arteriovenous Fistula Outcomes in an Elderly UK Population Agnes Masengu,^{1,2} Jennifer B. Hanko,¹ Alexander P. Maxwell.^{1,2} ¹Regional Nephrology Unit, Belfast City Hospital, Belfast, County Antrim, United Kingdom; ²Nephrology Research Group, Queen's Univ Belfast, Belfast, County Antrim, United Kingdom.

Background: The merit of placing arteriovenous fistulas (AVFs) in the elderly is debated in the literature. We sought to investigate AVF outcomes in the population aged ≥ 65 years in our region.

Methods: The Northern Ireland Vascular Access Database incorporates vascular access data on patients with chronic kidney disease stage 4 and 5. The database includes information on all patients ≥ 65 years who had an AVF created during January 2009-December 2014 and had a functional outcome by the 1st March 2015. Functional AVF patency was defined as sustained 2-needle use on haemodialysis for at least 6 sessions. Failure to mature (FTM) was defined by either by clinical examination or failure to sustain 6 sessions of 2-needle dialysis.

Results: During the study period 344 patients ≥ 65 years had an AVF created. One AVF failed immediately, three AVFs were ligated due to steal, 56 patients had not started dialysis by the study end-point and records were incomplete for 30 patients. A total of 254 patients (98% White) remained included for functional AVF patency analysis. Table 1: Clinical Characteristics of Patients ≥ 65 years with AVF Patency Outcomes (n=254)

Clinical Characteristics	Number (%)
Age (mean, median, range)	74, 74, 65-92
Male gender	170 (67)
Diabetes	102 (40)
Peripheral vascular disease	30 (12)
Ischaemic heart disease	102 (40)
Lower arm AVF	134 (53)

A total of 150 AVFs (59%) achieved functional patency and 105 (41%)FTM. Binary logistic regression revealed that a lower arm AVF in this elderly population was associated with FTM (p < 0.001, OR 0.23, CI 0.13- 0.40).

Conclusions: Given their shorter life-expectancy, the goal of vascular access creation in the elderly should be to create one functional AVF using the best vessels identified. The greater risk of FTM with lower arm AVFs may mean preferential creation of an upper arm AVF if these vessels are better on clinical and ultrasound assessment.

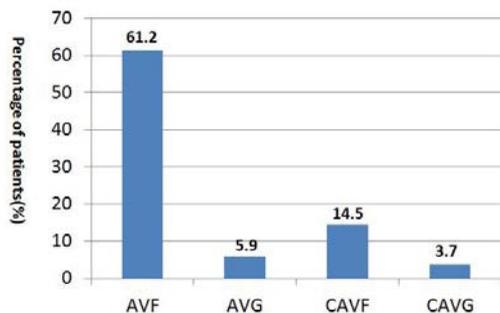
TH-PO865

Type of Vascular Access and Mortality in Japan Toshikazu Ozeki,¹ Shun Minatoguchi,¹ Yukako Ohyama,¹ Hideaki Shimizu,¹ Yoshiro Fujita,¹ Daijo Inaguma,² ¹Nephrology, Chubu Rosai Hospital, Nagoya, Japan; ²Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Japan.

Background: The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) guidelines have recommended the use of AVFs at dialysis initiation of dialysis. However, it has been reported that the dialysis environment has been significantly different between Japan and the United States, and there are few people who continue hemodialysis with CVCs in Japan. The aim of this study is to examine the association between type of vascular access at dialysis initiation and mortality in Japan.

Methods: This study is retrospective, multicenter, cohort study which data was collected by "Aichi Cohort study of Prognosis in Patients" (AICOPP) newly initiated into dialysis. 18 tertiary care centers in Japan participating in the "AICOPP". This study enrolled 1,525 patients who started maintenance dialysis between October 1, 2011 and March 31, 2014. After exclusion of 129 patients who started peritoneal dialysis or without data, 1329 (87.1%) patients were enrolled. Cox regression was used to determine the effect of access type on total mortality. Type of vascular access was divided into four categories: AVFs, AVGs, CVCs changed to AVF during the course (CAVF), CVCs changed to AVG during the course (CAVG).

Results: This research showed prevalence of type of blood access in Japan.



Under multivariate analysis, CAVGs had a higher risk of mortality compared with AVFs group [hazard ratio (HR): 2.408, p value: 0.003]. No significant differences were observed compared AVFs with AVGs [hazard ratio (HR): 1.466, p value: 0.219] and CAVFs [hazard ratio (HR): 1.223, p value: 0.389].

Conclusions: As it is known, high AVF use was seen in Japan. Compared with AVFs, using CVCs changed to AVG during the course is associated with higher risks of mortality.

TH-PO866

Comparison of Arteriovenous Fistula and Arteriovenous Graft on Patient Survival and Access Patency in Non-Elderly versus Elderly Population Hoon suk Park, Min Seok Choi, Woo Jeong Kim, Sung jun Kim, Hyung Wook Kim, Cheol Whee Park, Bum soon Choi, Byung ha Chung, Chul Woo Yang, Dong-Chan Jin. ¹Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ, Korea.

Background: Arteriovenous fistula (AVF) is generally known to be the ideal option as a vascular access. However, this consensus can be challenging in elderly population.

Methods: From August in 2008 to April in 2014, 1452 adult incident hemodialysis patients were included from Clinical Research Center registry for ESRD prospective cohort, from 31 centers in the South Korea.

Results: In the whole population, AVF vs. AVG use was associated with the better patient survival only in male (p < 0.001) and DM (p = 0.004) patients. Multivariate Cox regression analysis showed AVG (vs. AVF; odds ratio [OR] 2.308, 95% confidence interval [CI]: 1.013–4.829; p = 0.026), catheter (vs. AVF; OR 10.658, 95% CI: 5.379–21.119; p < 0.001) and age (OR 1.035, 95% CI: 1.012–1.058; p = 0.003) were significantly associated with poor patient survival. In the elderly patients (≥ 65 years old), the survival benefit by AVF use also existed in only male (p < 0.001) and DM (p = 0.009) patients, but AVF compared with AVG showed better access patency only in female (p < 0.001) and DM (p = 0.01) patients. Multivariate Cox regression analysis in the elderly population showed AVG (vs. AVF; OR 3.158, 95% CI: 1.080–9.238; p = 0.036), male (vs. female; OR 3.941, 95% CI: 1.031–15.066; p = 0.045) and the presence of peripheral vessel disease (OR 4.659, 95% CI: 1.389–15.626; p = 0.013) were significantly associated with poor patient survival. AVF showed the survival benefit compared with AVG in the even septuagenarian patients (≥ 70 years old), which is contrast to the previous reports about western population (p = 0.01). However, the superior access patency of AVF in comparison with AVG began to decrease from septuagenarian population.

Conclusions: In the Korean septuagenarian patients, AVF placement can be considered because of its survival benefit. However, it seems appropriate that AVG is preferentially placed in the septuagenarian patients with multiple comorbidities.

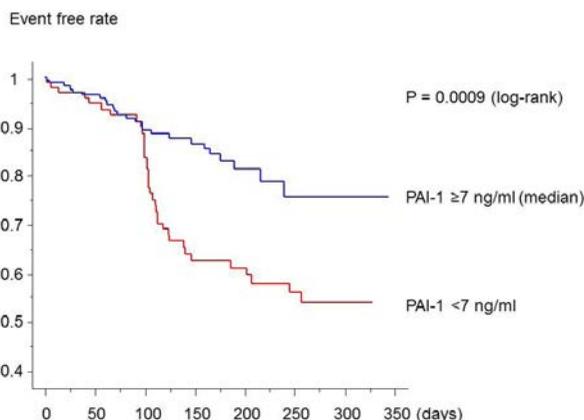
TH-PO867

Abnormality of Fibrinolysis as well as Coagulation Were Associated with Second Patency Rates of Vascular Access in Hemodialyzed Patients Yukiko Hasuike,¹ Naoto Kakita,² Takeshi Nakanishi.¹ ¹Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; ²Vascular Access Center, Tanaka-Kitanoda, Japan.

Background: Vascular access (VA) is essential for the HD patients. However, VA is often occluded even after the percutaneous-transluminal angioplasty (PTA). There is increasing evidence indicating the importance of the fibrinolysis system (i.e., plasminogen activator inhibitor-1 (PAI-1) level) in the progression of vascular disease. We intended to clarify whether coagulation and fibrinolysis might be associated with VA failure after PTA.

Methods: Blood samples were taken from 262 HD patients at the PTA. Thrombin/anti-thrombin (TAT) as a marker of coagulation, PAI-1, FDP, D-dimer as markers of fibrinolysis system, and laboratory data were measured. Blood flow volume of VA was evaluated by Doppler ultrasonography before PTA. The end point was the re-vascularization or re-operation of VA during the observational period after PTA. The results were analyzed using univariate (Kaplan-Meier methods) and Cox regression analyses.

Results: Age of patients was 70.6±9.7 years, and 121 patients (46.2%) have native arteriovenous fistula (AVF). During follow-up period, re-PTA was performed in 33 patients and re-operation in 28 patients. Native AVF, higher blood flow volume (≥500 ml/min), lower TAT (<3 ng/ml), and higher PAI-1 (≥7 ng/ml) were associated with good patency rates. The Kaplan-Meier analysis showed both higher TAT (p=0.0026) and lower PAI-1 (Figure 1) were significantly associated with VA failure. Cox regression analysis revealed that higher TAT (HR 2.140, 95%CI 1.288-3.556, p=0.0033) and lower PAI-1 (HR 2.322, 95%CI 1.390-3.880, p=0.0013) were related to VA failure event.



Conclusions: The present research indicates that VA failure after PTA might be associated with abnormality in the fibrinolysis system as well as activated coagulation.

TH-PO868

Early Hemodynamic and Geometric Changes in Brachiocephalic Fistula Access Mary S. Hammes,¹ Kevin Cassel,² Michael Boghosian,² Jane E. Hines,¹ Sydeaka Watson,³ S.M. Javid Mahmoudzadeh A.² ¹Medicine/Nephrology, Univ of Chicago; ²Dept of Mechanical, Materials and Aerospace Engineering, Illinois Inst of Technology; ³Dept of Public Health Sciences, Biostatistics Laboratory, Univ of Chicago.

Background: An arteriovenous fistula is the optimal vascular access for hemodialysis. A brachiocephalic fistula (BCF) is often placed in the upper arm to provide effective dialysis, but unfortunately cephalic arch stenosis (CAS) commonly develops leading to access failure. We hypothesized that a contribution to fistula failure is low wall shear stress (WSS) resulting from changes that occur in the cephalic arch because of alteration in post-fistula creation hemodynamics.

Methods: Twenty-two subjects with advanced renal failure had BCF placed. The following procedures were performed at mapping (pre-operative) and fistula maturation (8-32 weeks post-operative): venogram, Doppler to measure venous blood flow velocity, and whole blood viscosity. Geometric and computational modeling was performed to determine WSS and other parameters that represent the curve of the cephalic arch. The relationship between parameters was examined using univariate analysis and linear regression.

Results: Blood flow velocity, venous diameter, and regions of low WSS were shown to increase in subjects by the time of maturation (p < 0.05). The percent of low WSS was linearly related to an increase in blood flow velocity (p = 0.01). Although the mean global measures in curvature and asymmetry remained unchanged from baseline to time to maturation, the change fell for shorter time to maturation and rose for longer time to maturation (r = 0.52; p = 0.01), crossing the regression line at 15–16 weeks.

Conclusions: The maturation process of an AVF introduces geometric effects in arch curvature and asymmetry. Hemodynamic changes increase the percentage of low WSS regions within the cephalic arch by the time of fistula maturation. Low WSS may contribute to endothelial cell damage, subsequent intimal hyperplasia, and resultant CAS. If this hypothesis remains tenable with further studies, ways of protecting the arch through control of flow during maturation of the fistula, or alternatives to the BCF, may need to be developed.

Funding: NIDDK Support

TH-PO869

Dilator-Assisted Banding and Beyond: Proposing an Algorithm for Managing Dialysis Access-Associated Steal Syndrome

Shouwen Wang, AKDHC Access Centers, Arizona Kidney Disease and Hypertension Center, Phoenix, AZ.

Background: Dialysis Access-associated Steal Syndrome (DASS) is a major complication of arteriovenous dialysis accesses and its proper management is of critical clinical importance. However, the reported approaches are diverse and general consensus is lacking. Recently, guided banding approaches have gained popularity, as they are minimally invasive. This report analyzes the clinical outcome of Dilator-assisted Banding (DAB), a simple technique initially described by the author for managing DASS.

Methods: This series included 30 patients that underwent DAB for DASS due to excessive dialysis access flow.

Results: Of the 30 patients: 29 had upper arm fistulas or grafts and 1 had a forearm fistula; 23 had arteriogram - 3 of which required angioplasty ± stent for feeding artery stenosis. The DAB procedures included: intraluminal DAB (12/30), extraluminal DAB (14/30) and open fistula reduction plus DAB (4/30). After DAB, the average severity scores of ischemic symptoms was reduced from 2.8 ± 0.4 to 0.2 ± 0.4 for the fistula group ($n=24$, $p<0.001$) and from 3.0 ± 0.0 to 1.2 ± 1.2 for the graft group ($n=6$, $p=0.041$). Of the 24 patients with fistula, 19 had resolution of ischemic symptoms and 5 had minimal residual symptoms while 3 had finger necrosis that healed after DAB. Of the 6 patients with graft, 2 had resolution, 2 had minimal residual and 2 had no change of ischemic symptoms. These two DAB-ineffective patients underwent proximalization of arterial inflow (PAI) revisions that resulted in resolution of ischemic symptoms. During follow-up of 18.7 ± 14.5 months (range 1-50), all dialysis accesses remained functional. At 24-month post-DAB, the primary patency, primary-assisted patency and secondary patency rates of the fistula group were 72%, 91% and 100%, respectively.

Conclusions: DAB is a simple, effective and versatile approach for managing DASS due to excessive flow, especially in patients with fistula. In patients with failed banding, PAI can be effectively used for rescue. Based on the data in this series and the literature, an algorithm is proposed for managing DASS.

TH-PO870

Outcomes of Vascular Access Creation in Incident Hemodialysis Patients in Singapore

Nicholette Goh,¹ Chieh-suai Tan,² Shaam Achudan,¹ Yi liang Tan,¹ Kian Guan Lee,² Hui-Lin Choong,² Tze tec Chong,³ ¹National Univ of Singapore; ²Renal Medicine, Singapore General Hospital; ³Vascular Surgery, Singapore General Hospital.

Background: Hemodialysis is the main modality of renal replacement therapy for end-stage renal disease (ESRD) patients in Singapore. Vascular access is critical for effective therapy. This study evaluates the impact of pre-operative vein mapping on vascular access creation in patients newly initiated on hemodialysis in Singapore General Hospital.

Methods: Data of ESRD patients initiated on hemodialysis from January 2010 to December 2012 were retrospectively collected from electronic medical records. 708 patients (mean 62.8 ± 12 years old, 61% male, 71.3% Chinese) who underwent surgical creation of their first vascular access were followed up for a mean of 2.3 ± 1.2 years.

Results: 694 (98%) arteriovenous fistulae (AVF) and 14 (2%) arteriovenous grafts (AVG) were created. Successful AVF cannulation was established in 543 patients (78.2%). After 1 year, 511 (73.6%) remained patent with 43.5% (302/694) primary and 30.1% (209/694) secondary patency. 216 upper arm and 478 forearm AVFs were created. Upper arm AVFs had significantly higher maturation rates (85.0% vs 76.4%, $p = 0.011$). Pre-operative vein mapping was performed in 42.5% (295/694) of patients. The mean vein diameter was 2.44 ± 0.82 mm. Maturation rates with and without vein mapping were 72.2% and 82.7% respectively ($p = 0.001$). Between vein diameters of <2 and ≥ 2 mm, there was no statistical difference in maturation rates (71.3% vs 72.6%; $p = 0.887$) or median maturation time (66.5 vs 77 days; $p = 0.280$). There was no statistical difference in maturation rates between veins of <2 and ≥ 2 mm in both forearm ($p = 0.076$) and upper arm AVFs ($p = 0.722$). On univariate analysis, male gender ($p = 0.001$) and the presence of good post-operative thrill ($p < 0.001$) were associated with successful maturation in newly created AVF. AVFs created by trainees also had better maturation rates compared to consultants (83.5% vs 76.2%; $p = 0.027$).

Conclusions: In conclusion, successful vascular access creation can be accomplished in majority of ESRD patients. This is independent of vein size or the need for pre-operative vein mapping.

TH-PO871

Uremia Induced Gene Expression in a Mouse Model of Arteriovenous Fistula Stenosis

Keith Louis Saum, Begoña Campos, Neil Batra, Yang Wang, Prabir Roy-Chaudhury. Univ of Cincinnati.

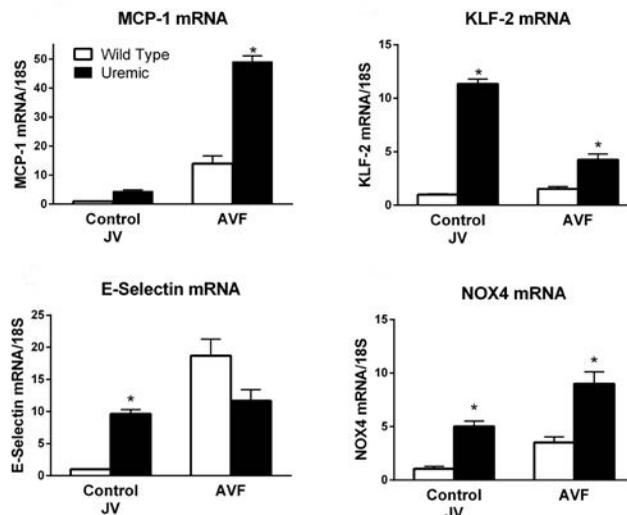
Background: Arteriovenous fistula (AVF) non-maturation remains a huge clinical problem resulting in significant morbidity and mortality. Unfortunately most animal models of AVF stenosis do not incorporate uremia. As a result, the molecular mechanisms by which uremia contributes to AVF dysfunction remain unknown. The aim of this study was to assess the impact of uremia on the expression of genes associated with the pathogenesis of AVF dysfunction using a uremic mouse model of AVF stenosis.

Methods: Mice were made uremic by cauterization of one kidney, followed by contralateral nephrectomy. After 4 weeks, an end to side anastomosis was created between the jugular vein and carotid artery. Contralateral vessels served as controls. Vessels were harvested after

14 days, and RNA isolated from the AVF venous segment. Gene expression of different mediators was measured with qPCR. Data was analyzed from control vein; uremic vein; veins of non-uremic AVFs; and veins of uremic AVFs.

Results: Significant upregulation in the expression of monocyte chemoattractant protein-1 (MCP1), NADPH Oxidase (NOX4), and E-Selectin were found within the veins of AVFs compared to wild-type control vessels ($P<0.017$ for each gene). Compared to normal vein, MCP1 expression was increased 4.4, 14.0, and 49.1 fold in uremic vein, the non-uremic AVFs, and uremic AVFs respectively. Paradoxical increases in Krüppel-like factor-2 (KLF-2) were also seen in uremic vessels compared to wild-type veins ($P<0.017$).

Conclusions: In summary, marked upregulation of the proteins MCP-1, NOX4, and E-Selectin were seen with uremia, and some of these (MCP-1) were further elevated within the AVF. Of note, the flow sensitive gene KLF2 was also elevated in uremia, but was attenuated in the setting of an AVF. These preliminary findings suggest key pathways by which uremia could exacerbate AVF dysfunction and future targets for the prevention and treatment of AVF maturation failure.



TH-PO872

Chlorhexidine-Impregnated Transparent Dressing for Prevention of Catheter-Related Bacteremia in Hemodialysis Patients: A Quality Improvement Study

Vandana Nijyar,¹ Ibironke W. Apata,¹ John Hanfelt,² ¹Nephrology/ Internal Medicine, Emory Univ, Atlanta, GA; ²Rollins School of Public Health, Emory Univ, Atlanta, GA.

Background: CRBSI are a major cause of morbidity in HD patients dialyzing with a CVC. A major route of catheter contamination is introduction of organisms from the skin to the catheter. Tegaderm-CHG is a transparent catheter dressing with an integrated gel containing chlorhexidine, designed to combine the benefits of transparent dressings; and the bactericidal and bacteriostatic benefits of chlorhexidine. We conducted a QI project to assess the rates of catheter-related bloodstream infection (CRBSI) in three dialysis units following the introduction of chlorhexidine-impregnated transparent catheter dressings.

Methods: Our study was conducted in two phases. In the first phase (9/12 through 10/13), we introduced the intervention, Tegaderm-CHG, to EDC, one of the three Emory hemodialysis units. EDGB and EDNS were the control sites where standard gauze catheter dressings were maintained. The rates of CRBSI at each dialysis units during the 12-month intervention were compared against the rates of CRBSI for the 12 month pre-intervention period. CRBSI rates were also compared between the dialysis units. The second phase of the study started in 11/2013, with the extension of Tegaderm-CHG dressing to EDGB and EDNS (the control sites in Phase 1). Tegaderm-CHG was maintained at EDC.

Results: The three dialysis units were comparable in terms of age, sex, and race of patients. In phase 1, the catheter infection rate (per 1,000 catheter days) in EDC decreased by 51% (pre: 1.69, post: 0.82). At EDGB, the infection rate increased by 12% (pre: 1.80, post: 2.02) while the infection rate increased by 35% (pre: 0.91, post: 1.23) at EDN. However, none of these increases in infection rates were significant (i.e., $p > 0.05$). The infection rates at EDGB and EDN decreased significantly in phase 2 by 86% (pre: 1.86, post: 0.26), and 53% (pre: 1.89, post: 0.88), respectively. At EDC, the catheter infection rate did not change significantly in phase 2.

Conclusions: The use of Tegaderm CHG dressing was associated with decreased rates of CRBSI at Emory outpatient dialysis units.

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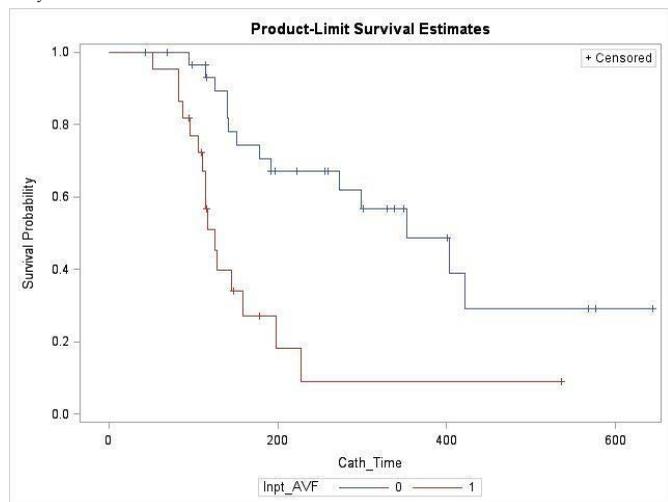
TH-PO873

In-Patient Permanent Access Is Associated with Reduced Catheter Time for Emergent Start Hemodialysis Patients Catherine A. Moore,¹ Richard E. Wing,¹ Scott E. Liebman.¹ ¹Medicine- Nephrology Div, Univ of Rochester, Rochester, NY; ²Aurora Medical Group, Marinette Menominee Clinic, Marinette, WI.

Background: Hemodialysis initiation with a tunneled catheter carries increased risk of morbidity and mortality. Conversion from a hemodialysis catheter to permanent access at any time is associated with improved outcomes. This study investigates whether a strategy of placing permanent dialysis access in incident HD patients without permanent access while still hospitalized is associated with reduced exposure to hemodialysis catheters.

Methods: We conducted a retrospective cohort study of ESRD patients initiating Hemodialysis with a catheter while hospitalized at a single University Hospital Medical Center from October 2010 through June 2013. Patients were divided into two groups: those with permanent access placed during the hospitalization (N = 22) vs. those discharged without permanent access (N = 67). Our primary endpoint was removal of the hemodialysis catheter.

Results: Subjects who underwent permanent access placement while still hospitalized had a median catheter exposure time of 114 days compared with 241 days for those who did not. The median time with HD catheter in place was shorter by 127 days in the Inpatient Access group. There was no significant difference in length of hospital stay or early access loss.



Conclusions: The practice of placing permanent access while the patient is still admitted to the hospital is associated with greater likelihood of hemodialysis catheter removal.

TH-PO874

Factors Affecting Haemodialysis Arterio-Venous Fistula Maturation Hannah R. Wilson, Salman Ahmed, Joseph Russell, Nicola Ding, Maggi Steele, Ayesha Irtiza-Ali, David Makanjuola, Nihil Chitalia. Renal Unit, St. Helier Hospital, Surrey, United Kingdom.

Background: Arterio-venous fistulae (AVF) are the preferred access for haemodialysis (HD). Many AVFs however, fail to mature. We investigated the factors affecting maturation of AVFs in order to identify any characteristics which were predictive of AVF maturation.

Methods: All AVFs created between 2006 and 2014 were reviewed. Data analysis was performed using GraphPad. AVFs were deemed to have failed to mature if by 90 days post-creation, it was not possible to use them for HD. The patients were divided into 2 groups – those who had the AVF created pre-emptively (group 1) and those already on HD at the time of AVF creation (group 2). Characteristics reviewed were age, gender, ethnicity, co-morbidity score, diabetes status and site of AVF.

Results: There were 1876 AVFs created. 954 in group 1 and 922 in group 2. In group 1, 597 patients started HD; 469 (79%) used their AVF for the 1st HD session. In group 2, 330 (36%) used their AVF within 90 days from creation. Group 1 AVFs were more likely to mature than those in group 2. Co-morbidity scores, age, diabetes status and ethnicity had no impact on AVF maturation rates.

Variable	Mature AVF (n=745)	Non-mature AVF (n=833)	p value
Pre-emptive	415 (55.7%)	241 (28.9%)	*
Non pre-emptive	330 (44.3%)	592 (71.1%)	*
Age in years [mean(SD)]	63 ±15.6	64 ±15.6	ns
Gender	69% M, 31% F	59% M, 41% F	0.0002
Ethnicity			
Caucasian	56%	55%	ns
Asian	12%	13%	
Afro-Caribbean	8%	9%	
Not stated	24%	24%	
Upper arm AVF	54%	52%	ns
Diabetic	35%	37%	ns
Davies co-morbidity score			
0 (no co-morbidities)	18%	15%	ns
1 (1-2 co-morbidities)	68%	68%	
2 (3 or more co-morbidities)	14%	17%	

*p<0.0001 for percentage of mature AVFs in pre-emptive vs non-pre-emptive groups.

Conclusions: Our data show that the timing of AVF creation is important; those formed pre-emptively are more likely to mature than those created when the patient is on dialysis. It is possible that the presence of a dialysis line might delay maturation, especially if it is ipsilateral to the AVF.

It highlights the importance of prompt referral to nephrology services so that AVFs can be created in a timely manner.

TH-PO875

Hand Held Ultrasound Device Solves Vascular Access (VA) Cannulation Problems Beth Adams, Vivek Soi, Jerry Yee, Lalathaksha Murthy Kumbhar. Henry Ford Hospital, Detroit, MI.

Background: The Fistula First Catheter Last workgroup coalition identifies VA cannulation as a fundamental “failure” point in optimizing arteriovenous fistula (AVF) usage. Infiltration from cannulation difficulties result in significant morbidity including loss of VA and cost. Cannulation success is reliant on cannulators’ skill and VA characteristics. Surface marking of VA to aid cannulation is frequently used but lacks real time information. Traditional ultrasound devices are expensive and need skilled operators rendering inapt for routine use in hemodialysis units. Sonic Window© (Analogic Ultrasound) is a coronal mode ultrasound device (CMUD) approved for VA cannulation. We present our early experience in using this novel hand held CMUD for real time guidance of AVF cannulation.

Methods: Three patients with cannulation failure defined as inability to achieve 3 needle cannulations leading to tunnel cuffed catheter (TCC) removal were identified. AVF was evaluated initially for 1-2 dialysis sessions with CMUD for course, depth from skin, optimal site for cannulation, needle length and size. Infiltration rates, subsequent procedures and hospitalizations were noted before and after CMUD use and cannulation failure days (days from initial VA clearance for use to TCC removal).

Results:

AVF		Pre-events			Post-events		
Type	Cannulation failure days	Infiltration	Interventions	Hospitalization	Infiltration	Interventions	Hospitalization
Brachio-basilic	210	1	1	6	0	0	0
Brachio-cephalic	206	3	6	0	0	0	0
Radiocephalic	153	3	4	0	0	0	0

All 3 AVF were successfully cannulated leading to TCC removal within 21 days of CMUD guidance. CMUD usage resulted in no cannulation related complications and no subsequent revision procedures

Conclusions: CMUD guided cannulation of dialysis access is feasible and safe. Real time ultrasound guidance mitigates cannulation failure and catheter removal.

TH-PO876

Reaching First Dialysis Quickly and Unassisted with Sirolimus Treated Fistulae – Serial Ultrasound Results and Clinical Outcomes
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Background: Neointimal hyperplasia (NH) resulting in a flow limiting stenosis within the juxta-anastomotic segment (JAS) of an AV Fistula (AVF), impairs increase in upstream vein diameter (VD), often requires supplementary procedures and prolongs time to 1st cannulation for dialysis (D). Sirolimus delivered locally to the vessel wall can suppress NH and preserve lumen patency ("sirolimus effect").

Methods: 30 pts (29 on D) undergoing AVF surgery [22 Radiocephalic (RCF), 8 Brachiocephalic fistulae (BCF)] received a Sirolimus eluting collagen implant at and around the JAS. 1st cannulation was based on clinical evaluation.

Results: 18 males, mean age 50.8y, 20% diabetic. Analysis excludes 4/22 RCF that thrombosed ≤2 weeks; 18/22 RCF (88%) and all 8 BCF maintained Primary Patency (PP) prior to first cannulation (mean 49 days); 13 AVF were cannulated ≤6wks, 74% AVF maintained suitability for D with PP at 12mos. Table shows serial Ultrasound results.

Characteristic	Pre op	6-8 hours Post op	2 weeks	4 weeks	6 weeks	8 weeks
RCF (n=18)						
VD Mean (±SD)	2.7 (0.5)	4.4 (0.5)	5.1 (0.8)	5.8 (0.7)	6.1 (0.4)	6.4 (0.4)
VD change from prior time point	-	63%	16%	14%	5%	5%
VD ≥6mm n=		0	2 (11%)	8 (44%)	13 (72%)	18 (100%)
VD ≥4mm n=		14 (70%)	16 (89%)	17 (94%)	18 (100%)	
BCF (n=08)						
VD Mean (±SD)	3.9 (0.6)	5.4 (0.8)	6.8 (0.8)	7.5 (0.9)	7.9 (1.71)	8.45 (1.38)
VD change from prior time point		38%	26%	9%	5%	8%
VD ≥6mm n=		2 (25%)	6 (75%)	8 (100%)		
VD ≥4mm n=		8 (100%)				

Conclusions: 1.Maximum % increase in VD occurred within 8hrs of surgery with gradual continued increments thereafter. 2.At 4, 6 and 8wks, VD of 6mm was attained by 62%, 81% and 100% of the AVF respectively. 3. 26/30 AVF(87%) maintained PP before first cannulation; time to first dialysis for 13 AVF(50%) was ≤6wks and at 12mos 75% were functional with PP. 4.Results signal a "sirolimus effect" and will be tested in an upcoming randomized trial.

Funding: Pharmaceutical Company Support - Vascular Therapies, Inc

TH-PO877

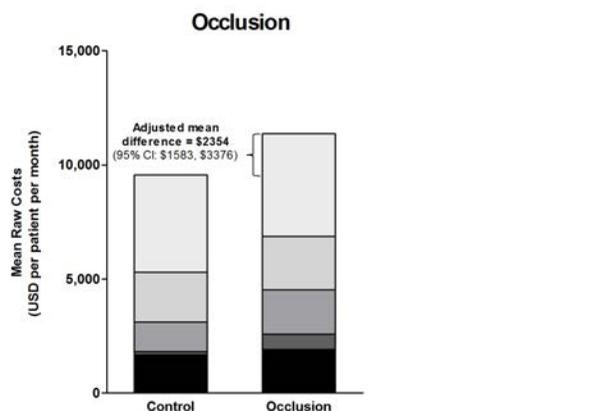
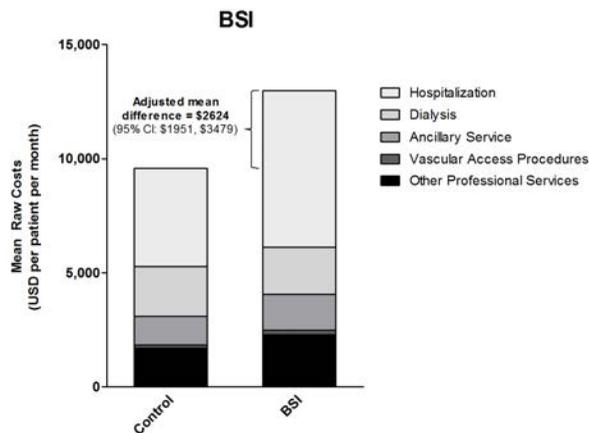
Economic Burden to Medicare of Central Venous Catheter (CVC)-Related Blood Stream Infections (BSI) and Occlusions Among Incident Hemodialysis (HD) Patients Scott Sibbel,¹ Steven M. Brunelli,¹ Abigail Hunt,¹ Wendy Turenne,¹ Antony E. Pfaffle,² ¹DaVita Clinical Research, Minneapolis, MN; ²CorMedix Inc, Bedford, NJ.

Background: Episodes of CVC-related BSI and occlusion in HD patients result in hospitalizations and vascular access-related procedures, with attendant increases in costs. We sought to quantify this burden to the payor among Medicare-enrolled patients at a large dialysis organization.

Methods: Patients received HD via CVC during 2011 and were enrolled in Medicare Parts A and B. In parallel analyses, patients who developed BSI (N=1413) or occlusion (N=793) were matched with controls who did not, on the basis of entry month and incident/prevalent dialysis status. Outcomes were assessed from date of BSI/occlusion (or corresponding date for controls) for 6 months or until censoring for modality change, transfer of care, loss of Medicare benefits or death. Comparisons were made using linear mixed models including fixed effects for exposure status and month, adjusted for covariates that were imbalanced at baseline.

Results: CVC-related BSI was associated with greater rate of hospitalization (incidence rate difference [IRD], 1.07 events/patient [pt]-year) and vascular-related procedures (IRD, 2.87 events/pt-year). Mean per patient per month (PPPM) costs were \$2624 higher for BSI patients versus controls, driven primarily by increased inpatient costs. CVC occlusion was associated with modestly greater rate of hospitalization (IRD, 0.29 events/pt-year), but substantially greater rate of ambulatory procedures (IRD, 4.00 events/pt-year). Mean PPPM costs were \$2354 greater for occlusion patients versus controls, driven by higher ancillary service and procedure costs.

Conclusions: CVC-related BSI and occlusion are potent cost drivers for Medicare. Risk mitigation strategies to prevent BSIs and occlusions should prove to reduce systemic health care costs.



Funding: Pharmaceutical Company Support - CorMedix Inc

TH-PO878

Arteriovenous Fistula Maturation and Medial Collagen Organization Assessed by Second Harmonic Generation Microscopy Yan-Ting E. Shiu,¹ Michael Allon,² Daniel Pike,¹ CS Jason Tey,¹ Silvio H. Litovsky,² Alfred K. Cheung,^{1,3} ¹U of Utah; ²U of Alabama; ³VASLCHCS.

Background: Arteriovenous fistula (AVF) maturation entails vascular dilation to allow increases in AVF blood flow. The required vascular wall distention is likely affected by its microstructure. We hypothesized that the organization of collagen fibers in the medial layer affects vascular dilation and hence AVF maturation. State-of-the-art second harmonic generation (SHG) microscopy and image-analysis algorithms were used to visualize and assess collagen-fiber organization.

Methods: Arteries and veins used for anastomosis were sampled during AVF creation from 128 participants with chronic kidney disease (CKD). Collagen SHG signals in unstained paraffin-embedded tissue sections were acquired under a two-photon microscope at 850 nm excitation, and analyzed for fiber pattern, anisotropy index (AI) and dominant angle (DA) by 3 independent observers blinded to AVF outcomes. AI ranged from 0 (random fiber network) to 1 (completely aligned fiber network). DA ranged from 0° (parallel to lumen) to 90° (perpendicular to lumen).

Results: Arterial and venous medial collagen fibers demonstrated a total of 5 patterns: parallel to lumen, perpendicular to lumen, track, web, or random (Fig. 1). The parallel and perpendicular patterns had a similar AI (~0.3) which was higher than the AI of the other patterns. However, the parallel pattern had a smaller DA than the perpendicular pattern in arteries (18° vs 70°, p=0.001). AVF non-maturation rate was lower in patients with a perpendicular vs parallel arterial fiber network (15 vs 40%, p=0.04). Likewise, AVF non-maturation rate was lower in patients with venous DA >30° vs DA <30° (17 vs 36%, p=0.03).

Conclusions: We have characterized novel vascular medial collagen fiber organization in CKD patients. Moreover, these patterns appear to be associated with the likelihood of AVF maturation.

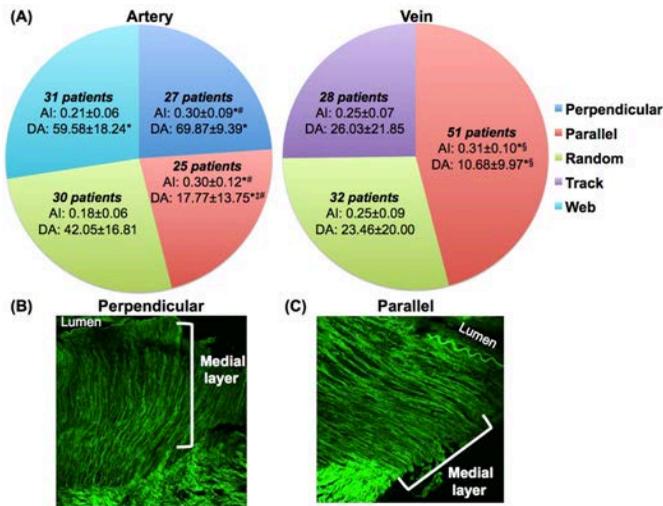


Fig. 1. (A) Characteristics of the medial layers. Data are shown as average ± S.D. Statistical analysis was performed using ANOVA with Bonferroni post-hoc analysis. *P<0.05 when compared to Random in the same pie chart. **P<0.05 when compared to Web. †P<0.05 when compared to Perpendicular. ‡P<0.05 when compared to Track. (B,C) Representative SHG images of the perpendicular and parallel patterns in the arterial medial layers.

Funding: NIDDK Support

TH-PO879

Polyurethane Prosthesis for Early Cannulation as an Alternative to Central Venous Catheter Irena Glowinska,¹ Jerzy Glowinski,² Jolanta Malyszko.¹ ¹Dept of Nephrology and Hypertension, Medical Univ, Bialystok, Poland; ²Dept of Vascular Surgery and Transplantation, Medical Univ, Bialystok, Poland.

Background: Autologous arterio-venous fistulae is an optimal vascular access for haemodialysis. Arterio-venous fistula is not faultless and up to 40% of fistulae never mature. In patients with no possibilities to create effective native arterio-venous fistulae haemodialysis with using a proper prosthesis gives a chance to avoid a central venous catheter (CVC).

The aim of the study was to evaluate of usefulness polyurethane prosthesis as an emergency vascular access for haemodialysis.

Methods: The study involved 23 patients, 18 men and 5 women, at 29 – 83 years. Eight patients were in predialysis period, for 17 patients (2 in predialysis) it was a secondary procedure. All patients had implanted AvFlo prosthesis (Nicast, Israel). There were 5 loops in the forearm and 18 straight segments in the arm. Six patients underwent an urgent operation, because of lack of any vascular access. For others it was an elective operation.

Results: The longest observation period was over 36 months. Twenty one grafts were used for hemodialysis within 1-42 days, one prosthesis was removed due to infection, one patient died before initiation of dialysis. All grafts implanted for urgent indications were successfully cannulated within 24 hours. No differences were observed between diabetic and non-diabetic patients.

Conclusions: Implantation of polyurethane prosthesis provides an effective vascular access for dialysis and enables avoidance of CVC. Low infection rate improves the final outcome.

TH-PO880

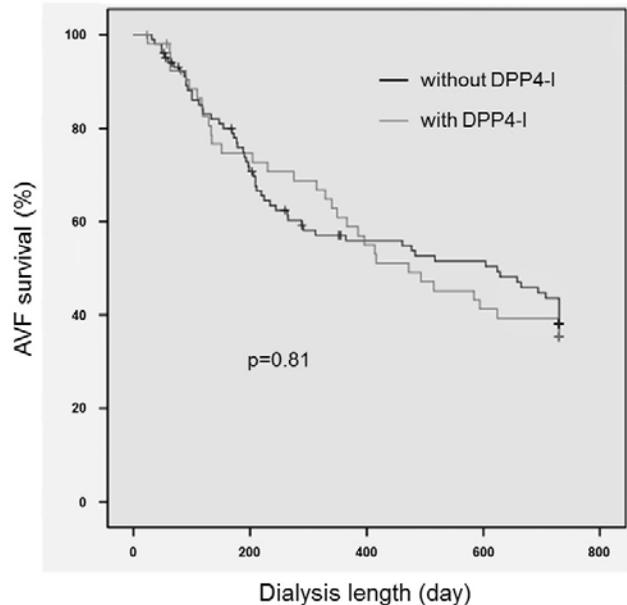
Impact of DPP-4 Inhibitors on Hemodialysis Vascular Access Dysfunction Hiroki Ito, Yuki Nakamura, Satoru Sanada, Kozo Sato, Atsuhiko Kanno, Yasunori Miyasaka, Mitsuhiro Sato, Yoshio Taguma, Toshinobu Sato. *Nephrology, Japan Community Health Care Organization Sendai Hospital, Sendai, Miyagi, Japan.*

Background: The maintenance of arteriovenous fistula (AVF) is crucial for hemodialysis patients and reduction of complications remains a challenge. Previous reports show that patients with diabetes mellitus are more likely to have AVF dysfunction than those with other underlying diseases. Also, elevated inflammatory cytokine such as IL-6 is known to be associated with AVF dysfunction. Recently, dipeptidyl peptidase 4 inhibitors (DPP4-I) were known to have pleiotropic action including anti-inflammation that decrease IL-6. Thus, we hypothesized that DPP4-I could improve AVF outcome by decreasing inflammatory cytokines.

Methods: The study population included 157 consecutive patients newly starting hemodialysis between 2011 and 2012 with diabetic nephropathy. AVF dysfunction was tracked for 2 years; criteria of which include complete obstruction, insufficient inflow and uniform thrill. AVF survival between patients treated with DPP4-I (n=54) and without DPP4-I (n=103) was investigated using Kaplan Meier and Cox regression analysis. Serum IL-6 level was analyzed by ELISA.

Results: Baseline characteristics were identical between 2 groups in age, sex, blood pressure, body mass index, history of congestive heart failure and coronary artery disease. There was no difference in AVF survival between the groups (DPP4-I: 455±36 vs without DPP4-I: 464±28 days, p=0.81, Log-rank), although serum IL-6 levels were significantly

lower in patients with DPP4-I (with DPP4-I: 5.0±1.9 vs without DPP4-I: 10.5±7.2 pg/ml, p=0.03). Among other drugs, no correlation was indicated between AVF dysfunction with insulin, RAS blocker, other antihypertensive drugs nor antiplatelet agents.



Conclusions: DPP4-I did not show any advantage in AVF outcome despite anti-inflammatory effect of lowering serum IL-6 level.

TH-PO881

Drug-Eluting Balloon: New Endovascular Treatment for Haemodialysis Arteriovenous Fistula Carmen Gonzalez corvillo, Alejandro A. Suarez benjumea, Alfonso Lara Ruiz, Mercedes Salgueira lazo. *Nephrology, Virgen Macarena-Rocio, Sevilla, Spain.*

Background: The purpose of this article is to report our experience with drug-eluting balloon (DEB) for the treatment of failing Arteriovenous Fistula (AVF). Mean life expectancy of the vascular access after the procedure, influence on adequate dialysis parameters postintervention and percentage of complications.

Methods: DEB procedures made in our hospital were evaluated. Main objective was to analyze: a) Reason of consulting and vascular lesion found. b) Hemodialytic arteriovenous shunt type. c) Kt/V, Qb, PV d) Survival of the vascular access at the end of the study e) Complications related to the procedure.

Results: 9 angioplastics were made by DEB. Mean age: 74.6 years, 50% male. 5 left native radiocephalic fistula and 1 humero-axillary prosthetic. Most of the patients had at least 4 previous interventions. Principal reason of consultation was low flow, being the most frequent arterial stenosis. No complications were found related to any procedure. Every vascular access is permeable at the actual time, mean life since the intervention: 24 months, being necessary only one reintervention in the target lesion. Blood flow, venous pressure and Kt/V improvement regarding to the basal was observed, after the procedure and at the end of the study.

Conclusions: There is limited experience with the use of drug-eluting balloon in haemodialysis arteriovenous fistula, an increase in average life expectancy of the vascular access with bad prognosis (led to a new vascular access) was found, an improvement on adequate dialysis parameters was observed, preserving vascular system of the patient, decreasing costs and with no complications. More studies would be needed.

TH-PO882

Alteplase Infusion as Rescue Therapy for Central Venous Haemodialysis Catheter Dysfunction Sanjana Gupta,¹ Stephen B. Walsh,² Karlene Thomas,¹ Ravindra Rajakarar.¹ ¹Barts Health NHS Trust; ²UCL Centre for Nephrology.

Background: Central venous haemodialysis catheters (CVHC) can become occluded or have poor blood flow (Qb). CVHC complication estimates are 35% and result in hospitalisation and interventional procedures. This study aimed to review alteplase infusion success and patency rates.

Methods: We undertook a retrospective review of all patients that had an alteplase infusion at the Royal London Renal Unit over a 15-month period. Patients had failed an alteplase lock and 4mg alteplase was used in both lumens. Data was collected using the renal database.

Results: There are 1002 haemodialysis patients; 412 dialyse via a CVHC.

Total uses / total patients (n)	94 / 74
Repeat Alteplase, same CVHC n (%)	20 (21)
Median age of CVHC (IQR)	147 days (77 - 300)
Indication (occlusion / Poor Qb) n	31 / 63

CVHC age was statistically different depending on the indication; occluded CVHC age was 124 ± 22 vs 244 ± 27 days for low Qb (p=0.01). Rescued CVHC age was significantly lower than those in whom the alteplase was unsuccessful (147 ± 18.4 vs 269 ± 35.8, p=0.004). In 48% of patients with an occluded CVHC, flow was restored; the remaining 52% required further intervention. Low Qb CVHC success rate was 60% compared to 38% requiring further intervention, 2% were removed (arteriovenous fistula or transplant). There was no significant difference between success rates depending on the indication (p=0.34). Alteplase infusion significantly increased litres processed in subsequent dialysis sessions, in whom the indication was low Qb (6.2 ± 1.16 litres, p < 0.0001). Overall of all infusions undertaken; 1 month patency was 56%, 3 months 45% and 6% removed. No patient had an adverse bleeding event as a result of the alteplase infusion.

Conclusions: Alteplase infusion use is common; approximately once a week in our centre. Interestingly, complete occlusion of CVHC occurs early, possibly suggesting rapid growth of fibrin following insertion. Total litres processed improves after an alteplase infusion in over half of patients. This study demonstrates the safety and success rates of an alteplase infusion, providing evidence for its role prior to replacing the CVHC and importance in saving resources.

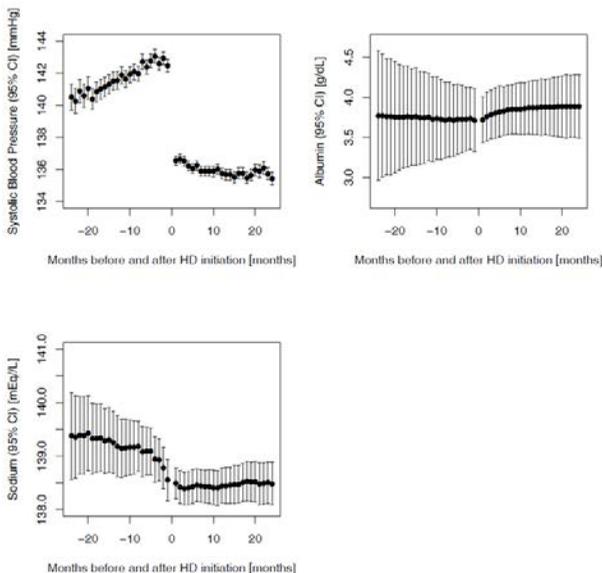
TH-PO883

Temporal Evolution of Parameters Before and After Initiation of Hemodialysis Jochen G. Raimann,¹ John W. Larkin,² Carly R. Van Zandt,² Len A. Usvyat,² Jeroen Kooman,³ Frank van der Sande,³ Barbara Cannon,² Chad Sowers,² Mark Stuart,² Terry Ketchersid,² Dugan Maddux,² Peter Kotanko,^{1,4} Franklin W. Maddux.² ¹Renal Research Inst; ²Fresenius Medical Care North America; ³Maastricht Univ Medical Center; ⁴Icahn School of Medicine at Mount Sinai.

Background: Little is known about the dynamics of clinical and laboratory parameters during the transition between pre-dialysis chronic kidney disease and end stage kidney disease (ESKD). The goal of our research was to explore the temporal evolution of albumin (Alb), systolic blood pressure (SBP) and serum sodium (SNa) by analyzing monthly data before and after hemodialysis (HD) initiation.

Methods: We analyzed all available data from the de-identified Fresenius Medical Care CKD Data Registry to understand progression of clinical and laboratory markers before and after HD initiation. Average values of Alb, SBP and SNa were compared for 12 months prior and after HD initiation using t-test. To estimate the trends of the average values, we fitted a linear regression function through monthly averages.

Results: We studied 136846 patients (64±14 years, 56% male) over 48 months. Average SBP increased prior to HD initiation (1.2 mmHg/year), immediately decreased following HD initiation, and remained lower for the following 12 months (142.4±22.8 vs. 136.1±23.2 mmHg; P<0.05). Before starting HD, Alb was found to be relatively unchanged, but increased after HD initiation (average Alb increased by 0.14 g/dL per year; levels were slightly higher 12 months after HD initiation [3.7±0.5 vs. 3.8±0.4 g/dL; P<0.05]). Average SNa pre-ESKD had a declining trend (-0.5 mEq/L per year) and was lower compared to the HD period (139.0±3.4 vs. 138.4±3.5 mEq/L; P<0.05).



Conclusions: Our study demonstrates a trend toward improvement in SBP and Alb following HD initiation. The etiology of the SNa decrease after HD initiation requires further investigation.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO884

Accelerated Arterial Stiffening in Vitamin-K-Antagonist Treated Hemodialysis Patients Christian D. Peters, Krista D Kjaergaard, J. Dam Jensen, Bente Jespersen. *Dept of Renal Medicine, Aarhus Univ Hospital, Aarhus, Denmark.*

Background: Many hemodialysis (HD) patients are treated with vitamin-K-antagonists (VKA) in order to prevent thromboembolic events. A potential side effect to VKA treatment is an increase in soft tissue calcification due to the inhibitory effect of VKAs on the central (liver) and peripheral (e.g. vascular) carboxylation cycle synthesis of several vitamin K-dependant calcification-inhibiting factors. The aim of the present study was to investigate the impact of VKA-treatment on arterial stiffness in a longitudinal, prospective comparative study.

Methods: Seventy-five HD patients from the SAFIR study with urine output >300 mL/day and HD-vintage <1 year were divided into controls (n=67) and VKA-treated (n=8) and followed for one year. The groups were well matched according to age, sex, comorbidity, and intervention (placebo/irbesartan). Arterial stiffness was assessed with carotid-femoral pulse wave velocity (PWV) and pulse wave analysis using the SphygmoCor device.

Results: Blood pressure (BP), PWV, and glomerular filtration rate (GFR) were similar at baseline (controls/VKA-treated) systolic BP: 148±20/145±17 mmHg; PWV: 11.6±3.2/11.0±3.9 m/s; GFR: 5±3/5±3 ml/min/1.73m². Dialysis treatment and BP-medication were also similar. During follow up, GFR decreased similarly in both groups (P=0.2). There was no significant difference in BP between the two groups over time although BP tended to decrease more in the controls. PWV decreased in the controls -0.9(-1.4; -0.3) m/s; P=0.004 and increased in the VKA-treated 1.6(0.0; 3.2)m/s; P=0.05. Mean difference after 12 months between the groups (DPWV) was 2.5(0.7; 4.2) m/s; P=0.006. DPWV remained significant after adjustment for ΔGFR, ΔMAP, age at baseline, and ΔBP-medication: 2.2(0.4; 4.0) m/s; P=0.02. Mean differences after 12 months between the groups in heart rate adjusted augmentation index and time to pulse wave reflection were: 7(-2; 15) %; P=0.11 (AIxHR75) and -14(-27; -2) ms; P=0.03 (TR).

Conclusions: Our findings indicate that VKA-treatment increases arterial stiffening significantly. We speculate that vitamin K-dependant calcification-inhibiting factors in HD patients may be inadvertently affected by VKA treatment.

Funding: Private Foundation Support, Government Support - Non-U.S.

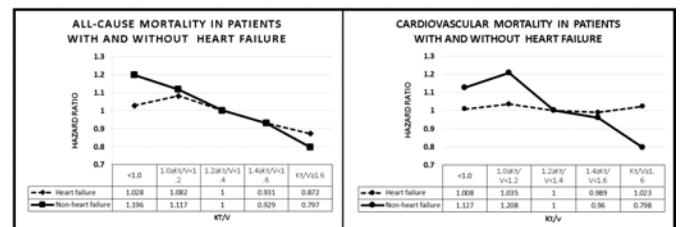
TH-PO885

Associations of Kt/V with Mortality in Hemodialysis Patients by Heart Failure Status Parva Hatamizadeh,¹ Brian Bieber,² Keith McCullough,² Bruce M. Robinson.² ¹Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI; ²Arbor Research, Ann Arbor, MI.

Background: Kidney failure and heart failure (HF) frequently coexist, a condition called cardiorenal syndrome (CRS). Though HF patients on maintenance hemodialysis (mHD) have high risk of poor outcomes, there is a paucity of data to guide their care. Given the role of uremic toxins in the pathogenesis of CRS, we hypothesized that mortality for mHD patients is lower at higher Kt/V targets.

Methods: Cox regression was used to estimate associations of baseline Kt/V with all-cause mortality (ACM) and cardiovascular mortality (CVM) in phases 1-4 of the Dialysis Outcome and Practice Patterns Study (DOPPS), an international prospective cohort study of mHD patients. Separate models for patients with and without HF (by clinical diagnosis) were stratified by country and DOPPS phase and adjusted for age, gender, race, diabetes and hypertension as comorbidities, dialysis vintage, serum albumin, pre-dialysis systolic blood pressure, and weight. SAS 9.4 was used for analyses.

Results: Among 51,678 mHD patients, mean age was 62.5±14.8 yrs, 41.5% female and 32% had HF. In non-HF patients, Kt/V was inversely associated with ACM and CVM, following a monotonic pattern. In HF patients, the association was similar for ACM but generally flat for CVM. A sensitivity analysis of Kt/V by sex showed a monotonic decline in mortality in women, but little decline at Kt/V >1.4 in men [consistent with prior literature]. HF did not clearly modify associations by sex.



Conclusions: Contrary to our hypothesis, higher dialysis adequacy was not associated with longer survival in HF patients. Confounding by health status (patients with more advanced HF may achieve lower Kt/V because they tolerate dialysis poorly) may be an explanation for this finding. Additional study is needed to identify ways to improve outcomes for these high-risk patients.

TH-PO886

Different Impact of Malnutrition-Inflammation and Metabolic Syndrome on Long-Term Mortality and Cardiovascular Events in Hemodialysis Patients Naoki Nakagawa. *Renal Div, Dept of Internal Medicine, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan.*

Background: Metabolic syndrome confers an increased risk of cardiovascular disease (CVD) in the general population. The relationship between adiponectins, and clinical outcomes in hemodialysis patients remains controversial. We investigated whether adiponectins, biomarkers of inflammation, nutrition status and clinical features predict the mortality of hemodialysis patients for 6 years.

Methods: We measured baseline plasma total and high-molecular-weight (HMW) adiponectins, tumor necrosis factor (TNF)- α , serum high sensitivity C-reactive protein (hsCRP), and clinical characteristics including visceral fat area (VFA) and the Geriatric Nutritional Risk Index (GNRI) in 133 hemodialysis patients.

Results: During the 6-year follow up period, 41 (30.9%) patients died (heart failure, $n = 13$; acute myocardial infarction, $n = 11$; stroke, $n = 2$; infection, $n = 10$; and malignant cancer, $n = 5$). The deceased patients were significantly older, had more prior CVD and diabetes, higher TNF- α and hsCRP levels but lower GNRI, VFA, and total and HMW adiponectin did not significantly differ between the two groups. TNF- α and hsCRP levels and GNRI score were significant for predicting all-cause and cardiovascular mortality in receiver operating curve analyses. The present ROC curve analysis for all-cause 6-year mortality found the predictive value of GNRI for mortality was 96. When stratified by a GNRI score of 96, Cox proportional hazards analyses identified TNF- α as a significant predictor of all-cause mortality (hazard ratio [HR] 1.23; $P = 0.038$) and hsCRP as a significant predictor of all-cause and cardiovascular mortality (HR, 2.32, $P = 0.003$; HR 2.30, $P = 0.012$, respectively) after adjusting for age, sex, diabetes mellitus, and prior CVD, only in malnourished patients.

Conclusions: These results demonstrate that malnutrition and the inflammatory markers TNF- α and hsCRP, but not metabolic markers, including VFA and adiponectins have a significant impact on 6-year all-cause and cardiovascular mortality in hemodialysis patients.

Funding: Government Support - Non-U.S.

TH-PO887

Associations of the Malnutrition-Inflammation Complex Syndrome with Depression Symptoms, Kidney-Disease Targeted Quality of Life Measures and Mortality in a Hemodialysis Population of Predominantly African Descent Marcelo Barreto Lopes,¹ Raissa B. Peixoto,¹ Priscila S. Carvalho,¹ Jean M. Monteiro,¹ Jéssica S. Fernandes,¹ Pedro Guimarães Silva,¹ Luciana Ferreira Silva,² Gildete Barreto Lopes,¹ Antonio Alberto Lopes.¹ ¹Univ Federal da Bahia; ²Univ do Estado da Bahia, Salvador; BA, Brazil.

Background: The malnutrition-inflammation score (MIS) has been used to assess protein-energy wasting (PEW), also named malnutrition-inflammation complex syndrome, in maintenance hemodialysis (MHD) patients. Higher MIS has been associated with poorer outcomes in MHD patients but remains unclear if MIS expands the predictive power for outcomes in relation to its ten components and if the published results may be generalized for populations not targeted by previous investigations. We assessed associations of MIS and its components with mortality and patient-reported outcomes, i.e., health-related quality of life (HRQOL) and depression symptoms in a MHD population predominantly of African descent.

Methods: Prospective cohort (PROHEMO) of 632 MHD patients (92% Black or mixed race) treated in Salvador, Brazil. The predictor was MIS (range: 0-30, higher worse) and its ten components. Outcomes were mortality, HRQOL by KDQOL-SF and depression symptoms by CES-D. Multivariable linear regression was used for differences in scores and Cox regression for mortality.

Results: After extensive adjustments for covariates, MIS ≥ 6 was significantly ($P < 0.05$) associated with higher mortality (hazard ratio=1.52; 95% CI=1.13, 2.05), higher depression symptoms and poorer HRQOL, including physical, mental and kidney-disease targeted HRQOL scales with differences > 4 points. Four of the 10 MIS components were independently associated with mortality, but not with patient-reported outcomes.

Conclusions: The consistent associations of MIS with mortality, HRQOL and depression symptoms despite the distinct association of MIS components with mortality and patient-reported outcomes support the importance of combining PEW components to assess health status and risks of outcomes in MHD patients. The observed results in a predominantly African descent population expand support to MIS as a valid predictor of outcomes in different MHD populations.

TH-PO888

Non-Traditional Risk Factors Predict Atherosclerotic Events in Haemodialysis Patients – Post-Hoc Analyses of the AURORA Trial Marit D. Solbu,^{1,2} Geir Mjøen,³ Patrick B. Mark,^{1,4} Hallvard Holdaas,⁵ Bengt C. Fellstrom,⁶ Alan G. Jardine.^{1,4} ¹Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom; ²Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; ³Dept of Nephrology Ullevål, Oslo Univ Hospital, Oslo, Norway; ⁴Renal and Transplant Unit, South Glasgow Univ Hospital, Glasgow, United Kingdom; ⁵Dept of Transplantation Medicine, Oslo Univ Hospital Rikshospitalet, Oslo, Norway; ⁶Div of Nephrology, Uppsala Univ Hospital, Uppsala, Sweden.

Background: Patients on haemodialysis are at high risk for cardiovascular events, but heart failure and sudden death dominate and atherosclerotic events are less common. The AURORA trial was designed to assess the effect of rosuvastatin on myocardial infarction and death from any cardiac cause in haemodialysis patients. We studied predictors of the atherosclerotic, and not all cardiovascular, events in AURORA.

Methods: We readjudicated all deaths and presumed myocardial infarctions according to stricter criteria to separate atherosclerotic from non-atherosclerotic cardiovascular events. The readjudicated atherosclerotic endpoint included non-fatal myocardial infarction, fatal coronary heart disease, non-fatal and fatal non-haemorrhagic stroke, revascularisation procedures and death from ischaemic limb disease. Baseline predictors were assessed for the 2776 participants of the AURORA trial, and step-wise Cox regression analysis was applied.

Results: During a mean follow-up of 3.2 years, 716 patients experienced a readjudicated atherosclerotic event. Baseline phosphate (HR 1.33; 95% CI 1.16-1.53 per 1 mmol/L increase), albumin (HR 0.93; 95% CI 0.91-0.96 per 1g/L increase) and high sensitive CRP (HR 1.07; 95% CI 1.00-1.14 per mg/L increase) were significant predictors in addition to female sex, age, prevalent diabetes and cardiovascular disease. LDL cholesterol was not a significant risk factor.

Conclusions: Even with the use of strict criteria for endpoint definition, non-traditional risk factors, but not lipid disturbances, predicted atherosclerotic events in haemodialysis patients.

Funding: Pharmaceutical Company Support - AstraZeneca, Government Support - Non-U.S.

TH-PO889

Proteomic Studies of Blood Plasma Using 2DE and Mass Spectrometry for Deeper View into the Mechanisms Involved in Atherosclerosis in Chronic Kidney Disease Maria Wanic-Kossowska,¹ Dorota Formanowicz,² Elzbieta Pawliczak.¹ ¹Dept of Nephrology, Transplantology and Internal Medicine, Poznan Univ of Medical Sciences, Poznan, Poland; ²Dept of Clinical Biochemistry, Poznan Univ of Medical Sciences, Poznan, Poland.

Background: The exact participation and association of particular risk factors and specific mechanisms that promote cardiovascular complications (CVD) in patients with chronic kidney disease (CKD) remain unclear. The close relationship between CVD and CKD is most likely due to the co-existence of both traditional and novel risk factors. To gain insight into better recognition of the mechanisms of CKD-related accelerated atherosclerosis, a comparative proteomic analyses have been performed.

Methods: Blood samples were taken from 90 patients (CKD1-2, CKD3-4, CKD5), 30 patients with CVD, but without CKD and 30 healthy volunteers. Plasma samples were depleted using affinity chromatography and divided into three fractions: high-abundance protein, low-abundance protein and low molecular weight protein. The first two fractions were analyzed by two dimensional gel electrophoresis and mass spectrometry, the last one has been subjected to direct MS/MS analysis. Differential accumulated proteins were confirmed by selected reaction monitoring analysis.

Results: 49 proteins (13 high and 36 low molecular mass) showed differences in accumulation levels. The proteomic profiles in CKD5 and CVD patients differed in the accumulation of four LAPs the relative accumulations of alpha -2-macroglobulin, second isoform of alpha 1 microglobulin and were higher in CKD5 compared with CVD; fold changes 1.77, 4.14, 2.68 and 1.79, respectively. Moreover, the relative abundances of these proteins were up-regulated in CKD3-4 compared with CVD. CKD1-2 and CVD group differed in the accumulation of apolipoprotein A-4 and apolipoprotein A-1.

Conclusions: Our results definitely indicated similar proteomic profiles in CKD1-2 and CVD patients, in contrast to CVD and CKD5 patients, suggesting that mechanisms of CVD acceleration may be different in initial and advanced stages of CKD. It seems that it is related to chronic inflammation and immune disturbances, typical for CKD.

TH-PO890

Hemodialysis-Induced Release of Microparticles Liina Vassil,¹ Inga Soveri,¹ Fariborz Mobarrez,² Tora Almquist,³ Bengt C. Fellstrom.¹ ¹Dept of Medical Sciences, Uppsala Univ, Uppsala, Sweden; ²Dept of Medicine, Karolinska Inst, Stockholm, Sweden; ³Dept of Clinical Sciences, Danderyd Hospital, Karolinska Inst, Stockholm, Sweden.

Background: Microparticles (MPs) are 0.1 -1.0 μ m vesicles that are released from cells upon activation or during apoptosis. MPs are believed to be involved in the pathophysiology of atherosclerosis and thrombosis. Patients with cardiovascular risk factors have significant MP elevation. Measurements of MPs may uncover new insight into mechanisms behind the severely increased cardiovascular disease (CVD) risk in hemodialysis (HD) patients. The aim was to study whether a hemodialysis session affects MP formation and release.

Methods: Plasma samples from 20 HD patients were drawn before and 1h after the start of a HD session. MPs derived from platelets (CD41+), monocytes (CD14+), endothelial cells (CD62E+), and their expression of phosphatidylserine (PS) and tissue factor (CD142) were analyzed using flow cytometry. P-selectin (CD62P) and CD40 ligand (CD154) were measured on platelet-MPs. In addition, Klotho and the receptor for advanced glycation end products (RAGE) expression were measured on MPs. Paired t-test was used.

Results: Mean age was 73.6 years (range 54-91), 5 patients were female, 14 had central dialysis catheter, 8 patients had diabetes and 14 had CVD.

Marker (x10 ⁶ /L)	Before HD	1h after start of HD	P-value
Lactadherin (PS+MPs)	3645(1960-9784)	4388(1966-12672)	0.08
Lactadherin + CD41	464(153-2321)	774(169-3000)	0.04
Lactadherin+CD41+CD62P	186(50-1098)	550(70-1369)	0.01
Lactadherin+CD41+CD154	205(33-992)	365(52-1236)	0.05
Lactadherin+CD14	216(175-443)	337(205-584)	0.00
Lactadherin+CD62E a	713 (±233)	845 (±348)	0.03
CD41+CD142 a	467 (±262)	541 (±337)	0.30
CD62E+CD142	135(15-392)	171(26-900)	0.06
CD14+CD142	31(11-121)	58(17-193)	0.00
Klotho a	2260 (±276)	2612 (±414)	0.00
RAGE	154(122-1356)	252(178-1491)	0.00

Mean (± SD) a or Median (range)

Conclusions: The majority of MP levels increase significantly after the start of a HD session. Whether this is driven by patient or dialysis specific factors remains unclear. The clinical significance of MP release during HD needs to be evaluated.

Funding: Government Support - Non-U.S.

TH-PO891

The Monocyte Subset of CD14+CD16+ Cells Plays a Key Role of Promoting Atherosclerosis in Hemodialysis Patients Miki Nishida,¹ Minoru Ando,² Yusuke Iwamoto,³ Ken Tsuchiya,¹ Kosaku Nitta.¹ ¹Dept Medicine, Kidney Center, Tokyo Women's Medical Univ, Tokyo, Japan; ²Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; ³Saitou Memorial Hospital, Tokyo, Japan.

Background: Atherosclerosis is closely associated with morbidity and mortality in hemodialysis (HD) patients. The scavenger receptors (SR) in circulating monocytes play a key role in promoting foam cell formation by binding and internalizing oxidized low-density lipoprotein. In addition, heterogeneity of monocytes and macrophage-colony stimulating factor (M-CSF) may facilitate the atherosclerotic process by SR over-expression.

Methods: Subjects included 62 HD patients and 30 healthy controls. Peripheral monocytes were isolated using magnetically labeled Whole Blood CD14⁺ micro-beads. Transcriptional levels of CD16 and SR-A were measured in monocytes by quantitative real-time RT-PCR, using the comparative threshold (Ct) method. The gene expressions were compared between HD patients and controls, and between HD patients who had cardiovascular disease (CVD) and those who did not. Plasma concentration of M-CSF was measured with M-CSF ELISA kit. Additionally, CD16 protein expression was analyzed by a flow cytometry.

Results: SR-A gene expression was higher in monocytes from HD patients than in those from controls (2.35 vs 1.29, p=0.0006). Moreover, it was higher in HD patients with CVD than in those without (2.79 vs 1.64, p=0.0023). Plasma concentration of M-CSF was 8-fold higher in HD patients than in controls (1173±517.3 vs 152±55.1 pg/ml, p<.0001). It was significantly correlated with the gene expression of SR-A (r²=0.129, p=0.0007). The CD16 gene expression was higher in CD14⁺ monocytes from HD patients than in those from controls (1.28 vs 1.07, p=0.0310), and was significantly correlated with the gene expression of SR-A (r²=0.051, p=0.0467). In a flow cytometry, the proportion of CD14⁺CD16⁺ cells was 2.2-fold higher in HD patients than in controls (34.60 vs 15.85, p=0.0034). In addition, this proportion was related with M-CSF (r²=0.354, p=0.0118) and SR-A gene expression (r²=0.540, p=0.0240).

Conclusions: The CD14⁺CD16⁺ cells are important subset of monocytes in HD patients, which may prime and increase SR expressions.

TH-PO892

Active Ghrelin Enhances the Association Between BMI and Clinical Outcome in Hemodialysis Patients Irrespective of Appetite Ilija Beberashvili,¹ Inna Sinuani,² Ada Azar,³ Leonid Feldman,¹ Shai Efrati.¹ ¹Nephrology, Assaf Harofeh Medical Center, Zerifin, Israel; ²Pathology, Assaf Harofeh Medical Center, Zerifin, Israel; ³Nutrition, Assaf Harofeh Medical Center, Zerifin, Israel.

Background: Ghrelin, a gastric orexigenic peptide, and BMI are known as inversely associated to each other and have both been linked to cardiovascular (CV) risk and mortality in hemodialysis (HD) patients. However, it is unclear whether ghrelin and BMI interact modifying risk of all-cause and CV death in this population.

Methods: We investigated the interactions between BMI and ghrelin as predictors of death over a 3 years of follow-up (median - 28 months, interquartile range - 17-34 months) in 261 maintenance HD patients (39% women, mean age of 68.6±13.6 years).

Results: A significant interaction effect of high ghrelin and high BMI (defined as their levels higher than median) on all-cause mortality was found: crude Cox hazard ratio (HR) for the product termed Ghrelin x BMI was 0.52, with a 95% confidence interval (CI): 0.29 to 0.95 (P=0.04). Across the four ghrelin-BMI categories, the group with high ghrelin and high BMI exhibited the better outcome in both all-cause and cardiovascular mortality (multivariable adjusted hazard ratios were 0.30, 95% CI 0.15 to 0.59, P<0.001, and 0.33, 95% CI 0.13 to 0.86, P=0.02, respectively). Compared to patients from other ghrelin-BMI categorized groups, patients in the high ghrelin-high BMI group were more surprisingly anorexic, were predominantly non-smokers, with lower incidence of diabetes and had higher Kt/V levels. These variables consequently were inserted in all multivariable models. Data analyses carried out by stratifying patients according to ghrelin-fat mass, but not to ghrelin-lean body mass categories, provided similar results.

Conclusions: We observed interactions between high ghrelin and BMI that were associated with decreased mortality risk in our cohort, especially those due to cardiovascular causes. Interestingly, the orexigenic effect of ghrelin does not seem involved in described interaction.

TH-PO893

Serum Procollagen Type I Carboxy-Terminal Propeptide Is Associated with Left Ventricular Hypertrophy and Dysfunction, and May Predict Cardiovascular Event in Incidental Dialysis Patient Sung jun Kim,¹ Hye Eun Yoon,¹ Sungjin Chung,² Seok Joon Shin.¹ ¹Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Incheon, Korea; ²Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.

Background: Serum procollagen type I carboxy-terminal propeptide(PICP) is a marker of myocardial fibrosis in hypertensive heart disease. However the clinical significance of this biomarkers is less determined in end-stage renal disease (ESRD) patients. This study was to evaluate the association of predialysis serum PICP levels with echocardiographic markers in ESRD patients.

Methods: Serum PICP, albumin, CRP, iPTH levels were obtained from predialysis blood samples of 123 incidental dialysis patients. Echocardiographic parameters included left ventricular mass index (LVMI) and ejection fraction, ratio of peak early transmitral flow velocity to peak early diastolic mitral annular velocity (E/E' ratio), ratio of peak early transmitral flow velocity to peak late transmitral flow velocity (E/A ratio), and mitral valve-deceleration time (DT).

Results: A direct correlation was found between PICP and Left ventricular mass index (r=0.308, P=0.002), between PICP and E/E' ratio (r=0.236, P=0.009), between PICP and ratio of peak early transmitral flow velocity to peak late transmitral flow velocity (E/A) (r=0.285, P=0.002). A negative correlation was found between PICP and Left ventricular ejection fraction (r=-0.289, P=0.001), between PICP and mitral valve-deceleration time (r=-0.203, P=0.026). In the multivariate linear regression analysis, the PICP was independently positive associated with LVMI and E/e' and negative associated with Left ventricular ejection fraction. In the multivariate cox regression analysis, previous CV event (HR 15.224, CI 3.26-71.04), and High PICP group (vs low PICP group) (HR 9.478, CI 1.10-81.82) were the significant prognostic factors cardiovascular event.

Conclusions: Serum procollagen type I carboxy-terminal propeptide (PICP) is associated with left ventricular hypertrophy and dysfunction, and may predict cardiovascular event in incidental dialysis patient.

TH-PO894

Associations of Soluble Receptor for Advanced Glycation End Products (s-RAGE) and S100A12 (EN-RAGE) with Mortality in Long-Term Hemodialysis Patients Ji Yong Jung,¹ Eul Sik Jung,¹ Byoungcho Choi,¹ Yun Jung Oh,² Chungsik Lee,² Ae jin Kim,¹ Han Ro,¹ Jae Hyun Chang,¹ Hyun Hee Lee,¹ Wookyung Chung.¹ ¹Div of Nephrology, Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea; ²Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea.

Background: Hemodialysis (HD) patients have been associated with vascular calcification and ultimately with high mortality rates. Formerly, we reported association of soluble receptor for advanced glycation end products (s-RAGE) and S100A12 (EN-RAGE) with vascular calcification. We extended our observation whether those biomarkers could be proposed for predicting cardiovascular morbidity and mortality in these subjects.

Methods: This is a prospective observational cohort study in 199 HD patients from extended analyses of our previous study. Serum S-RAGE, S100A12, comorbidities, and other traditional risk factors were also investigated. The cumulative incidences for death using Cox proportional-hazards regression were evaluated in multivariable analyses. A mean observation period was 29 months.

Results: The patients were 57.1 ± 13.7 years of age; 54.3% were male, 49.2% were diabetic, and 36.2% had a history of cardiovascular disease. During the observation period, 27 patients (13.6%) were died. Univariate analysis demonstrated that S100A12 was correlated with diabetes (P = 0.04) and hs-CRP (P = 0.01). In multivariable analyses, serum s-RAGE (HR [hazard ratio], 1.16; 95% CI [confidence interval], 0.61-2.19; P = 0.65) and S100A12 (HR 1.05; 95% CI, 0.62-1.77; P = 0.87) were not associated with mortality in hemodialysis patients, though traditional predictors for mortality including age, history of cardiovascular diseases, serum albumin and serum high-sensitivity C reactive protein (hs-CRP) were related to mortality. Powerful predictors for mortality were age, previous cardiovascular disease and serum albumin level.

Conclusions: Serum S-RAGE and S100A12 may be weak surrogate markers to predict all-cause mortality in patients receiving hemodialysis, even though S100A12 was partly related with diabetes and inflammation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO895

Impact of Sodium-Dependent Phosphate Co-Transport, Pit-1, in Peripheral Blood Mononuclear Cells on Cardiac Calcification in Maintenance Hemodialysis Patients *Minwen Ding, Mengjing Wang, Minmin Zhang, Jing Chen. Huashan Hospital, Fudan Univ.*

Background: Vascular calcification (VC) is an importance risk factor for cardiovascular disease in MHD patients, however, the mechanisms of which are still under investigation. The aims of this study were to explore the risk factors of VC in MHD patients, and to identify the expression of sodium-dependent phosphate co-transporter (Npt) in peripheral blood mononuclear cells (PBMCs) and assess its association with cardiac calcification and its possible impact factors.

Methods: This is a cross-sectional analysis of adult MHD patients who received at least 6-month regular MHD in our dialysis center. The coronary artery calcification (CAC) was measured by cardiac MSCT. The gene expression of Npt in PBMCs was measured by Real-time PCR and we tested serum TNF- α and IL-6 by ELISA. Multivariate logistic analysis was used to determine the risk factors of CAC. Correlation between the gene expression of Npt and other parameters was examined by Pearson relativity analysis.

Results: 1.68 eligible patients were enrolled. 2. Three kinds of Npts were detected in PBMCs of MHD patients. They were typeIINpt,Npt2b,type III Npt,Pit-1 and Pit-2, among which Pit-1 mRNA expression was significantly associated with extent of CAC. 3. The results of the logistic regression analysis were listed in Table 1. 4.Pearson relativity analysis showed Pit-1 mRNA expression of PBMCs was significantly correlated with serum phosphorus ($r=0.43, P=0.002$), CAC score ($r=0.63, P<0.001$) and Pit-2 mRNA expression of PBMCs ($r=0.53, P=0.001$).

Table 1. Multiple logistic regression analysis of factors associated with CAC score tertile in MHD patients

Variable	Unadjusted		Adjusted	
	OR(95% CI)	P	OR (95% CI)	P
Female gender	0.36	0.037		
Age(y)	1.03	0.062		
Dialysis vintage(m)	1.02	0.007	1.03 (1.01-1.05)	0.003
Smoking	2.38	0.074		
Diabetes mellitus	5.56	0.004	7.14 (0.03-0.75)	0.021
Laboratory parameters				
Ferritin(ug/l)	1.01	0.080		
TNF- α (pg/ml)	1.20	0.019	1.29 (1.01-1.66)	0.044
IL-6 (pg/ml)	1.06	0.030		
Triglyceride(mmol/l)	1.48	0.038		
PBMC Pit-1 mRNA(exp.AU)	1.79	0.055	2.52 (1.08-5.88)	0.032
Therapy				
ACEI/ARB	0.35	0.075		
Lipid-lowing drugs	0.44	0.098		

Longer dialysis vintage ($P=0.003$), diabetes ($P=0.021$), higher concentration of serum TNF- α ($P=0.044$), and Pit-1 mRNA expression of PBMCs ($P=0.032$) were significantly associated with higher tertile of coronary artery calcification.

Conclusions: Our result showed that longer dialysis vintage, diabetes, higher concentration of serum TNF- α and Pit-1 mRNA expression of PBMCs are the risk factors of CAC in MHD patients. Pit-1 mRNA expression of PBMCs was significantly correlated with serum phosphorus, CAC score and Pit-2 mRNA expression of PBMCs.

Funding: Government Support - Non-U.S.

TH-PO896

HDL Not as Predictive as apoA-1:apoB Ratio of Dialysis Patients in Predicting Death *Yuji Sato,¹ Shouchi Fujimoto,² Tatsunori Toida,² Yasuhiro Yamashita,³ Takashi Iwakiri,³ Akihiro Fukuda.¹* ¹Dialysis Div, Univ of Miyazaki Hospital, Miyazaki, Japan; ²epartment of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, Univ of Miyazaki, Miyazaki, Japan; ³Dept of Internal Medicine, Div of Circulatory and Body Fluid Regulation, Faculty of Medicine, Univ of Miyazaki, Miyazaki, Japan.

Background: In dialysis patients, the risk extended by the apolipoprotein profile to all-cause or cardiovascular (CVD) mortality is obscure. Our aim was to investigate the association between the apolipoprotein profile and the incidence of death in chronic dialysis patients.

Methods: A prospective observational study of mortality incidence in dialysis patients was conducted.

Results: Prevalent dialysis patients (n=1088) were enrolled and followed for 4 years. Of the 194 deaths recorded, 82 were of CVD origin. For the regular lipid markers (HDL, non-HDL, and TG), +1 mg/dl of HDL was significantly associated with all-cause mortality [HR and 95% CI, 0.986 (0.974-0.999)] but not for CVD mortality by multivariable Cox analysis adjusted for sex, age, basal kidney disease, dialysis vintage, dry weight, and pre-dialysis systolic blood pressure. For apolipoprotein lipid markers (apoA-1:apoB ratio, apoCIII:apoE ratio, and apoB48:TG ratio), +1 digit of the apoA-1:apoB ratio was significant for all-cause [0.279 (0.102-0.765)] and CVD [0.165 (0.036-0.750)] mortality.

When participants were divided into quartiles, the highest quartiles of the apoA-1:apoB ratio were significantly associated with both categories of death when compared with the lowest quartiles by multivariable Cox analysis.

Conclusions: Although controversies persist regarding whether lipids affect the prognosis of dialysis patients, our data revealed that the apoA-1:apoB ratio was significantly associated with all-cause and CVD mortality in dialysis patients.

Funding: Government Support - Non-U.S.

TH-PO897

HDL Subfractions in End-Stage Renal Disease (ESRD) Patients *Anna Gluba-Brzozka, Beata Franczyk-Skora, Jacek Rysz. Dept of Nephrology, Hypertension and Family Medicine, Medical Univ of Lodz, Poland.*

Background: Chronic kidney disease is a common disease associated with high cardiovascular risk. Recent studies have suggested that HDL not LDL may play the more important role in the progression of atherosclerosis in CKD patients. HDL from CKD patients was shown to become dysfunctional, lose its vasoprotective properties and begin to promote endothelial dysfunction and inflammation.

Methods: The aim of this study was to analyze which HDL fractions were more abundant in ESRD patients and are associated with advanced atherosclerosis. This study included 50 ESRD patients (16 women, 34 men) on dialysis (WAM University Hospital, Lodz, Poland) and 20 healthy volunteers (14 women, 6 men). Blood samples were collected from all subjects and HDL subfractions were analyzed with the use of Lipoprint system. Moreover, all patients had IMT measured.

Results: This study revealed statistically significant differences in HDL subfractions between control and study group: HDL1 [5.6 (2.0-7.1) vs. 13.0 (8.2-15.8), $p<0.0001$], HDL2 [13.1 (7.8-14.9) vs.17.7 (15.2-21.0), $p=0.009$], HDL3 [5.5 (0.4-8.6) vs. 9.4 (7.8-11.3), $p<0.0001$], HDL4 [8.5 (0-10.4) vs.10.6 (9.5-12.0), $p=0.003$], HDL5 [9.2 (3.3-10.5) vs. 11.4 (9.9-12.1), $p=0.01$], HDL7 [7.6 (7.2-8.4) vs. 5.3 (4.2-7.2), $p<0.0001$], HDL8 [8.7 (8.0-9.5) vs. 4.8 (3.5-5.8), $p<0.0001$], HDL9 [7.0 (5.9-8.2) vs. 3.8 (3.0-4.8), $p<0.0001$], HDL10 [15.9 (7.6-28.7) vs. 4.3 (2.6-7.1), $p<0.0001$] and large HDL [26.5 (17.5-29.2) vs. 40.3 (33.0-47.0), $p<0.0001$] and HDL Small [30.8 (22.3-43.2) vs. 12.8 (9.4-17.9), $p<0.0001$]. Significant differences were also observed in HDL1 [9.3 (6.6-12.9) vs. 13.4 (8.7-16.9), $p=0.014$], HDL6 [20.2 (18.0-23.2) vs.17.6 (15.2-20.1), $p=0.020$], HDL Large [35.0 (23.7-40.0) vs. 41.4 (33.6-48.0), $p=0.017$] and HDL Intermediate [50.2 (45.8-51.7) vs.45.8 (40.0-49.1), $p=0.017$] between HD patients with IMT > 0.9 mm and <0.9 mm].

Conclusions: This study revealed that ESRD influences HDL subfractions. Subfractions of large HDL are more abundant in patients with ESRD while small HDL fraction is more frequent in healthy persons. It is possible that the shift in HDL subfractions may be responsible for the increased risk of atherosclerosis in CKD patients.

TH-PO898

High Non-HDL Cholesterol as an Independent Risk Factor for Coronary Restenosis in Hemodialysis Patients Undergoing Percutaneous Coronary Interventions *Shoko Hasegawa,¹ Toshiaki Nakano,¹ Yasushi Mukai,² Yuta Matsukuma,¹ Ryusuke Yotsueda,¹ Akihiro Tsuchimoto,¹ Kiichihiro Fujisaki,¹ Kazuhiko Tsuruya,^{1,3} Takanari Kitazono.¹* ¹Dept of Medicine and Clinical Science, Kyushu Univ Graduate School of Medical Sciences, Fukuoka, Japan; ²Dept of Cardiovascular Medicine, Kyushu Univ Graduate School of Medical Sciences, Fukuoka, Japan; ³Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ Graduate School of Medical Sciences, Fukuoka, Japan.

Background: It has been reported that patients with end-stage kidney disease (ESKD) have a higher risk of restenosis after percutaneous coronary intervention (PCI). The aim of this study was to investigate the risk factors of restenosis after PCI in hemodialysis (HD) patients.

Methods: From January 2007 to December 2014, we enrolled 54 consecutive ESKD patients undergoing HD (mean age: 66.5 +/- 10.1 years; 15 women, 39 men; mean HD duration: 3.7 years), who received PCI and follow-up coronary angiography (CAG) after about 6 months. The coronary restenosis was defined by the patient having target lesion revascularization on follow-up CAG.

Results: Of 54 patients who had received PCI, restenosis occurred in 22 patients (40.7%) within 5-12 months after PCI. In the univariable logistic analysis, serum levels of low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, serum levels of non-high-density lipoprotein cholesterol (non-HDL-C), and history of major adverse cardiovascular events (MACE) were significantly associated with the occurrence of coronary restenosis; odds ratio (OR) [95% confidence interval (CI)] was 1.89 [1.02-3.50], 1.22 [1.01-1.47], and 5.79 [1.59-20.99], respectively. In the multivariable logistic analysis, non-HDL-C and the history of MACE were significantly associated with the coronary restenosis; OR [95% CI] was 1.35 [1.08-1.69](per 10 mg/dL increase in non-HDL-C) and 8.55 [1.88-38.85], respectively.

Conclusions: Non-HDL-C was an independent risk factor for the occurrence of coronary restenosis in HD patients undergoing PCI. This result suggests the significance and necessity of strict management of lipid metabolism after PCI in even HD patients.

TH-PO899

Galectin-3 Does Not Correlate within Markers of Cardiac Structure and Function on Cardiac MRI: A Study in Haemodialysis Patients

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Background: End-stage renal failure patients undergoing haemodialysis (HD) suffer disproportionate rates of death due to heart failure. Accurate tools to help predict those at highest risk are therefore desirable. Galectin-3 is a soluble β -galactoside binding protein secreted by activated macrophages that promotes cardiac fibroblast proliferation, collagen deposition and as a result ventricular dysfunction. Galectin-3 is the only FDA approved test for assessing prognosis in chronic heart failure. Our study explored the relationship between Galectin-3 and cardiac structure and function in a dialysis population.

Methods: We measured Galectin-3 (G3) levels in a multiplex assay (Merck Millipore) in HD patients enlisted in a clinical trial. Results were correlated with tagged cardiac magnetic resonance imaging to assess left ventricular structure and function.

Results: A total of 65 patients had G3 levels taken. The mean age of the cohort was 60±24 years. The overall mean G3 level was 17.7ng/mL±0.07. The mean Left Ventricular Mass Index was 77.09g/m²±20.4, mean ejection fraction 57.47%±11.7 and mean End-diastolic volume 143.4ml±39.4. In the whole cohort there was no significant correlation between G3 levels and any of the measure of left ventricular structure and function including LVMI (r=-0.22 p=0.24), LVEF (r=0.08 p=0.65) or LVEDV (r=0.012 p=0.94). The previously recommended upper limit of normal for G3 levels is 17.7ng/mL. 32 patients had a G3 level greater than this. In this group the mean G3 level was 23.2ng/mL, however there remained no significant correlations with age (r=0.10 p=0.38), LVEF (r=0.23 p=0.26), LVEDV (r=-0.01 p=0.95), LVMI (r=0.11 p=0.59) or global peak diastolic and systolic strain rates (r=0.3 p=0.14 and r=0.16 p=0.41).

Conclusions: In HD patients, Galectin-3 is not associated with structural and functional markers of systolic dysfunction seen on tagged cardiac MRI. Our results suggest that Galectin-3 does not have a role in risk stratification of this patient group.

Funding: Government Support - Non-U.S.

TH-PO900

Association of Klotho and FGF23 with Frailty in Patients Initiating Hemodialysis

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Background: Frailty at dialysis initiation is associated with higher mortality. Both FGF23 and its co-receptor, klotho, have been implicated in the development of frailty. We aimed to evaluate the independent association of FGF23 and soluble klotho (sKlotho) with frailty in hemodialysis (HD) patients.

Methods: We conducted a cross-sectional study of incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Events in ESRD (PACE) Study. Frailty was defined by ³ of the following: unintentional weight loss ³10 lbs in prior year, self-reported exhaustion, weakness (by hand grip strength), slowness (by walking distance) and self-reported low physical activity. Logistic regression was used to examine the associations of sKlotho and FGF23 with odds of frailty and frailty subcomponents.

Results: Of 336 individuals, 71% were black; 59% were male. Mean age was 55y. All had hypertension and 56% had diabetes, 38% CAD, and 37% obesity. Median sKlotho level was 364.4 pg/ml (IQR 272.5-494.6); mean FGF23 level was 656.2 U/ml (SD: 498). 40% of participants were frail. Adjusting for demographic factors, obesity, Charlson Comorbidity Index, hsCRP, serum albumin and Kt/V, higher sKlotho was associated with lower odds of frailty (Table).

Model	sKlotho, per 1-log pg/mL higher			FGF-23, per 100 ru/mL higher		
	OR	95% CI	P-value	OR	95% CI	P-value
Frailty						
Unadjusted	0.67	0.41 – 1.10	0.12	0.96	0.92 – 1.00	0.06
Adjusted*	0.58	0.33 – 1.01	0.05	0.96	0.91 – 1.01	0.09
Frailty Subcomponents*						
Weight loss ≥10 lbs	1.19	0.65 – 2.18	0.58	0.93	0.88 – 0.98	0.01
Exhaustion	0.53	0.31 – 0.95	0.03	1.04	0.99 – 1.10	0.11
Weakness	0.60	0.33 – 1.08	0.09	1.00	0.95 – 1.05	0.98
Slowness	0.92	0.51 – 1.66	0.78	0.98	0.93 – 1.03	0.43
Low physical activity	0.66	0.38 – 1.13	0.13	1.01	0.96 – 1.06	0.72

*Adjusted for age, gender, race, obesity, Charlson Co-morbidity Index, hsCRP, serum albumin and Kt/V. This remained robust after also adjusting for FGF23. Conversely, FGF23 was not associated with frailty. In adjusted analyses of the frailty subcomponents, higher sKlotho was only associated with self-reported exhaustion (OR=0.54, 95%CI: 0.30-0.95) while higher FGF23 was only associated with unintentional weight loss (OR=0.93; 95%CI: 0.88-0.98).

Conclusions: sKlotho, but not FGF23, was inversely associated with odds of frailty in incident HD patients, although both hormones appear to be associated with different individual subcomponents of the frailty phenotype.

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TH-PO901

FGF23 Is Not Associated with Arterial Stiffness in Patients with CKD5D

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Background: Arterial stiffening is thought to be a key determinant of excess Cardiovascular mortality in CKD patients. In CKD, the bone-derived phosphatonin fibroblast growth factor (FGF) 23 is elevated and has been implicated in the development of Cardiovascular disease. In this study, we sought to determine whether FGF23 is a predictor of arterial stiffness in dialysis-dependent CKD patients.

Methods: In this cross-sectional study, we enrolled 352 patients with advanced CKD and 150 healthy controls. Pulse wave velocity (PWV) was recorded by applanation tonometry, and blood pressure and biochemical parameters including plasma intact-FGF23 concentrations determined.

Results: Patients with CKD were significantly younger than controls (46±14 versus 49±11 years, p=0.02), had a higher blood pressure (MAP 97±14 vs 94±10 mmHg, p=0.003), and were more likely to be male (61% versus 49%, p=0.008). CKD patients had significantly higher FGF23 (3095 pg/ml, IQR 612-12726 versus 40 pg/ml, IQR 33-49, p<0.001) and parathyroid hormone (25 pmol/l, IQR 13-56 versus 3.8 pmol/l, IQR 3-5, p<0.001). PWV was elevated in patients with CKD (8 m/sec, IQR 6.9-9.6 vs 7.3m/sec, IQR 6.6-8.4, p=0.0002). In a regression model adjusted for known predictors of PWV, FGF23 did not predict PWV (β =-0.15, p=0.063), but was positively associated with the presence of CKD (p=0.009), age (p<0.001), mean arterial pressure (p<0.001) and heart rate (p=0.001).

Conclusions: In this prospective cohort study, FGF23 did not predict arterial stiffening beyond known risk factors of age, mean arterial pressure, heart rate and the presence of diabetes. Our findings suggest that the excess cardiovascular mortality observed with elevated FGF23 in CKD is not primarily driven by effects on arterial stiffening.

TH-PO902

Differential Association of Fibroblast Growth Factor-23 and Soluble Klotho with Left Ventricular Hypertrophy

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Background: Fibroblast growth factor-23 (FGF23), a phosphaturic hormone, has been implicated in the pathogenesis of left ventricular hypertrophy (LVH) among patients with chronic kidney disease. Whether FGF23's co-receptor, klotho, is independently associated with LVH is unclear.

Methods: To determine whether soluble klotho (sKlotho) is independently associated with LVH among incident hemodialysis patients, we conducted a cross-sectional study among participants who underwent baseline 2D echocardiograms in the Predictors of Arrhythmia and Cardiovascular Events (PACE) Study. Multivariable logistic regression models with FGF23, sKlotho, and both as primary predictors were constructed to estimate the odds of LVH (defined as LV mass index >116 g/m² in men and >104 g/m² in women).

Results: Of 391 participants who underwent echocardiogram, 371 and 387 had sKlotho and FGF23 levels available, respectively; 72% had LVH. Mean age was 54 years and 72% were black. All participants had hypertension with mean systolic BP 154 mm Hg. Median volume removed per HD session was 2.6L (IQR: 1.6 – 3.7). FGF23 was not associated with LVH after adjusting for age, race, gender, BMI, systolic BP, serum albumin level, and ultrafiltration volume. In contrast, higher sKlotho was independently associated with lower odds of LVH (OR=0.51 per 1 log higher; 95% CI: 0.29-0.96); this association remained robust with additional adjustment for FGF23 and Charlson Co-Morbidity Index.

Conclusions: sKlotho, not FGF23, is associated with a lower odds of LVH among incident hemodialysis patients.

	OR	95% CI	P-value
FGF23, per 100 rU/mL higher*	1.03	0.98 – 1.10	0.20
sKlotho, per 1 log pg/mL higher*	0.51	0.28 – 0.96	0.04
sKlotho, per 1 log pg/mL higher†	0.51	0.27 – 0.95	0.03

*Adjusted for age, race, gender, BMI, systolic BP, serum albumin level, ultrafiltration volume
†Additionally adjusted for FGF23 and Charlson Co-Morbidity Index

Funding: NIDDK Support

TH-PO903

Predictors of Arterial Stiffness in Incident Hemodialysis Patients

Stephanie M. Toth-Manikowski,¹ Esther D. Kim,² Lucy A. Meoni,¹ Bernard G. Jaar,¹ Tariq Shafi,¹ Michelle M. Estrella,¹ Rulan S. Parekh,^{1,2} Stephen M. Sozio.¹ *¹Johns Hopkins Univ; ²Univ of Toronto.*

Background: Premature vascular aging and arterial stiffening characterize CKD progression to ESRD and are associated with increased cardiovascular (CVD) morbidity and mortality. We identified predictors of arterial stiffness over time in HD patients.

Methods: In 339 incident HD patients in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) study, we examined the associations of baseline age, sex, race, comorbidities, CVD medications, and dialysis characteristics with longitudinal vascular stiffness measured by carotid-femoral pulse wave velocity (PWV) using generalized estimating equations. Annual change in PWV for up to 3 years was analyzed using linear regression.

Results: Mean age was 54, 58% male, 74% African-American, mean (SD) baseline PWV 10.7 (3.4) m/s, and annual PWV change 0.1 (2.6) m/s. Several factors were associated with higher PWV in univariate and multivariate longitudinal models. None were associated with PWV change.

	Univariate β (95%CI)	Multivariate β (95%CI)
Demographics		
Age (/10y)	1.03 (0.81-1.24) [‡]	0.88 (0.66-1.09) [‡]
Female	-0.35 (-1.03-0.32)	-0.61 (-1.1--0.07)*
African-American	-0.62 (-1.39-0.14)	0.34 (-0.29-0.98)
Comorbidities		
Diabetes	2.62 (2.00-3.24) [‡]	1.58 (0.99-2.16) [‡]
Coronary Disease	0.87 (0.17-1.56) [‡]	-0.24 (-0.87-0.39)
Congestive Heart Failure	0.93 (0.26-1.60) [‡]	-0.14 (-0.72-0.45)
LV Mass Index	-0.03 (-0.10-0.04)	-
Tobacco Use	-0.51 (-1.18-0.17)	-
Medications		
Renin-Angiotensin Inhibitor	-0.01 (-0.70-0.67)	-
Beta Blocker	0.83 (0.16-1.51) [‡]	0.99 (-0.45-0.65)
Clinical Characteristics[‡]		
Pulse Pressure (/10mmHg)	1.12 (0.88-1.37) [‡]	0.77 (0.54-1.00) [‡]
Phosphorus (/10mg/dL)	-0.24 (-0.57-0.10)	-
iPTH (/10mg/dL)	-0.01 (-0.02-0.00)*	0.00 (-0.01-0.01)
Albumin (mg/dL)	-0.38 (-1.11-0.34)	-

P-value:
[‡]<0.05
^{*}<0.01
[‡]<0.001
[‡]1st 3 month average

Conclusions: Although PWV did not change significantly over time in incident HD patients, age, male sex, diabetes, and pulse pressure were independently associated with higher PWV. It may be difficult to modify PWV after HD initiation and clinical factors should be optimized prior to starting HD.

TH-PO904

Differences in Risk Factors for Coronary Artery Calcification Between Nondiabetic and Diabetic Hemodialysis Patients

Yoshiko Nishizawa,¹ Sonoo Mizuiri,¹ Kyoka Ono,¹ Mariko Asai,¹ Kazuomi Yamashita,¹ Kenichiro Shigemoto,¹ Kohji Usui,² Michiko Arita,³ Kiyoshi Fujita,⁴ Takao Masaki.⁵ *¹Div of Nephrology, Ichiyokai Harada Hospital, Hiroshima city, Japan; ²Ichiyokai Ichiyokai Clinic, Hiroshima city, Japan; ³Ichiyokai East Clinic, Hiroshima city, Japan; ⁴Ichiyokai Yokogawa Clinic, Hiroshima city, Japan; ⁵Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima city, Japan.*

Background: The differences in risk factors for coronary artery calcification between nondiabetic and diabetic hemodialysis (HD) patients have not been fully explored.

Methods: We examined Agatston coronary artery calcium score (CACS) using MDCT, age, sex, presence of diabetes, dialysis vintage, smoking history, administration of phosphate binders, geriatric nutritional risk index (GNRI), HbA1c, serum calcium, phosphate, iPTH, CRP, b2MG, LDL-cholesterol and triglyceride (TG) in 355 HD patients: 242 nondiabetics and 113 diabetics. Factors related to CACS were assessed by multivariate regression analysis using all of the above independent variables. Differences in the above parameters according to quartile (Q) of CACS were also assessed.

Results: Mean age (years), dialysis vintage (months), CACS (H) and serum phosphate (mg/dl) were 63±14 vs. 66 ±12 (ns), 125±100 vs.71±50 months (P<0.01), 1651±2173 vs. 2377±2513 (P<0.05), and 5.3±1.3 vs. 5.0±1.4 (ns) in nondiabetics and diabetics, respectively. Patients with CACS Q4 showed higher prevalence of diabetes (40 vs. 19%),

age (68±12 vs. 58±14 years), and CRP (0.7±1.3 vs. 0.2±0.4 mg/dl), but lower iPTH (146±133 vs. 193±131 pg/ml) levels than patients with CACS Q1 (P<0.05), and other parameters were not significantly different except HbA1c. Significant associations were observed between CACS and age (P<0.001, β: 0.21), female (P<0.001, β: -0.21), dialysis vintage (P<0.001, β: 0.31), CRP (P<0.05, β: 0.16), TG (P<0.05, β: 0.15) in nondiabetics. However, CACS was significantly associated only with age (P<0.05, β: 0.30) and HbA1c (P<0.05, β:0.26) in diabetics.

Conclusions: Risk factors for coronary artery calcification differ between nondiabetic and diabetic HD patients, and poor glycemic control is the main factor in the latter.

TH-PO905

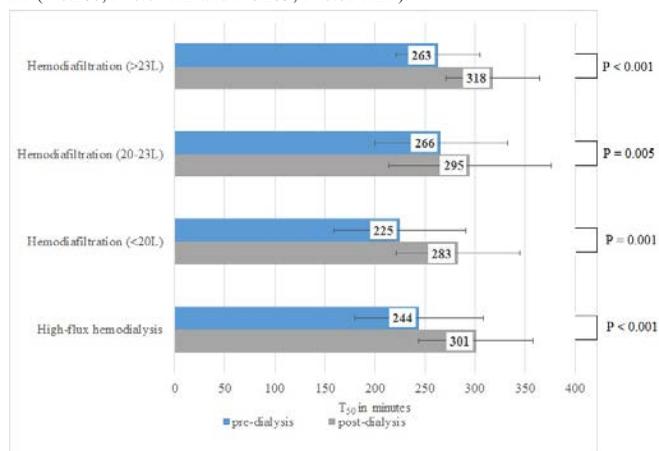
Hemodialysis and Hemodiafiltration Improve Serum Calcification Propensity

Marijke J.E. Dekker,² Andreas Pasch,³ Frank van der Sande,¹ Constantijn Konings,² Matthias Bachtler,⁴ Mauro Dionisi,⁴ Jeroen Kooman,¹ Bernard J. Canaud.⁶ *¹Maastricht Univ Medical Center; ²Catharina Hospital Eindhoven; ³Univ Hospital Bern; ⁴Calisco AG; ⁵Fresenius Medical Care.*

Background: Calciprotein particles (CPPs) may play an important role in the calcification process. The calcification propensity of serum (T₅₀) is highly predictive of all-cause mortality in chronic kidney disease patients. Whether T₅₀ is therapeutically improvable, by hemodialysis (HD) or even further by hemodiafiltration (HDF), has not been studied yet.

Methods: We designed a cross-sectional single center study, and included prevalent patients on HD or HDF. Patients were divided into two groups based on dialysis modality. We included patients on a thrice-weekly schedule, with a dialysis vintage of >3 months and vascular access providing a blood flow rate of >300 ml/min. Calcification propensity of serum was measured by the time of transformation from primary to secondary CPP (T₅₀ test), by time-resolved nephelometry.

Results: In total 64 patients were included and, T₅₀ was measured in 376 pre- and post-dialysis samples of all in-center dialysis sessions during one week. T₅₀ levels improved in both the HD and HDF group with pre- and post-dialysis (mean (SD)) of 244(64)-301(57) and 253(55)-304(61) min respectively (P=0.43). The mean improvement of T₅₀ was 26.29% in the HD group and 21.97% in the HDF group (P=0.61). The delta values (Δ) of calcium, phosphate (P) and albumin were equal in both groups. The DT₅₀ was mostly influenced by DP (r² 0.280; P=0.01 HD and r²-0.239; P=0.02 HDF).



Conclusions: HD and HDF patients present with same baseline vascular calcification risk values pre-dialysis. Calcification propensity is significantly improved during both HD and HDF. T₅₀ might be a useful guide to optimize renal replacement strategy to improve the individual calcification risk in dialysis patients.

Funding: Pharmaceutical Company Support - Unrestricted Grant from Fresenius Medical Care

TH-PO906

Association of Circulating Biomarkers with Vascular Stiffness and Coronary Artery Calcium in Incident Hemodialysis

Esther D. Kim,¹ Stephen M. Sozio,² Bernard G. Jaar,² Lucy A. Meoni,² Michelle M. Estrella,² Rulan S. Parekh.^{1,2} *¹Univ of Toronto, Canada; ²Johns Hopkins Univ.*

Background: Vascular calcification and stiffness are associated with higher mortality in hemodialysis. Studies examining the role of circulating biomarkers – specifically, FGF23, desphospho-uncarboxylated matrix Gla protein (dpuCMGP), Fetuin A, osteoprotegerin (OPG), and C-reactive protein (CRP) – in vascular calcification have reported contradictory findings, and the independent association of the biomarkers remains inconclusive.

Methods: In 392 incident hemodialysis patients in the Predictors of Arrhythmic and Cardiovascular Risk End Stage Renal Disease (PACE) study, we examined the associations of baseline FGF23, dpuCMGP, Fetuin A, OPG, and CRP with total coronary calcium score (Agatston) at baseline and vascular stiffness (pulse wave velocity [PWV]) at baseline and over 4 study visits. Baseline associations were determined using linear regression and repeated measures over visits were examined using mixed-effects models.

Results: At baseline, higher OPG was associated with increased odds of having a high coronary calcium score (>257), independent of other biomarkers (OR=1.11, 95%CI: 1.06,

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

1.16). The remaining biomarkers were not associated with high coronary calcium. Higher OPG was associated with higher PWV, and higher FGF23 was associated with lower PWV after adjusting for demographic factors, body mass index, comorbidity index, calcium phosphorus product, systolic blood pressure, and albumin.

Adjusted association with PWV	β (95% CI)
OPG (1 pmol/l)	0.10 (0.02, 0.19) [†]
FGF23 (100 RU/ml)	-0.10 (-0.18, -0.02) [*]
dpucMGP (1-log pm)	0.07 (-0.38, 0.53)
Fetuin A (1 g/l)	-0.79 (-2.77, 1.19)
CRP (1-log μ g/ml)	0.02 (-0.27, 0.30)

*P<0.05
†Adjusted for all biomarkers

OPG and FGF23 remained associated with PWV over follow-up and after additionally adjusting for all biomarkers ($\beta=0.08$, 95%CI: 0.01, 0.15 and $\beta=-0.07$, 95%CI: -0.13, -0.01).

Conclusions: Several vascular and phosphate biomarkers are associated with vascular calcification at baseline and/or stiffness longitudinally in incident dialysis patients. Further studies assessing interventions on these biomarkers are warranted.

Funding: NIDDK Support

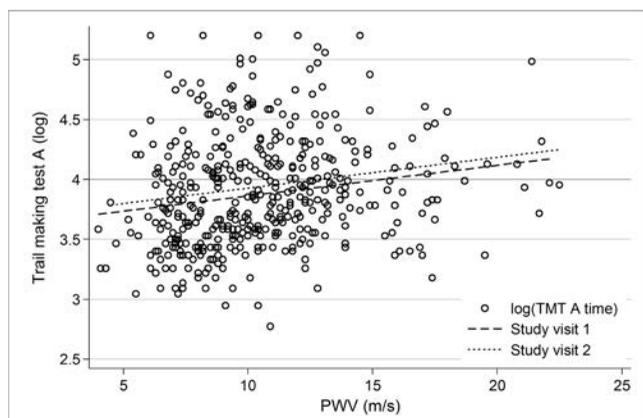
TH-PO907

Association of Arterial Stiffness with Cognitive Impairment in Incident Hemodialysis Esther D. Kim,¹ Lucy A. Meoni,² Bernard G. Jaar,² Tariq Shafi,² Michelle M. Estrella,² Rulan S. Parekh,^{1,2} Stephen M. Sozio.² ¹Univ of Toronto, Canada; ²Johns Hopkins Univ.

Background: Cognitive impairment is common in hemodialysis and places a significant burden on patients and healthcare system. Though vascular stiffness is implicated in the pathogenesis of cerebral microvascular disease, few have examined the relationship between arterial stiffness and cognitive function in dialysis patients.

Methods: This study included 390 incident hemodialysis patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study. Arterial stiffness was measured using aortic pulse wave velocity (PWV) and augmentation index (AIx). Cognitive function was measured using time to complete Trail making tests A and B (TMT A and TMT B) and the modified mini-mental state exam (3MS) score. Log-linear, Tobit, and logistic regression models were used to examine the baseline association of PWV with TMT A, TMT B, and 3MS, respectively. Changes in the scores over visits and mixed-effect models were used to examine association over time at 1 year follow-up.

Results: At baseline, higher PWV was associated with longer time to complete TMT A after adjusting for demographic factors, reading comprehension score, comorbidity index, systolic blood pressure, and atrial fibrillation (%TMT A=3.12, 95% CI: 0.37-5.87). In the repeated measures analysis, higher PWV was still associated with longer TMT A time (%TMT A=2.05, 95% CI: 0.00-4.11), and higher AIx was associated with longer TMT B time ($\beta=0.80$, 95% CI: 0.01-1.58).



Measures of arterial stiffness were not associated with 3MS.

Conclusions: Vascular stiffness is associated with longer time to complete TMT A and TMT B suggesting that arterial stiffness may lead to subclinical cerebrovascular events and decline in executive function among incident hemodialysis patients.

Funding: NIDDK Support

TH-PO908

Close Relationship Between Vascular Endothelial Function and Serum Uric Acid Level in Hemodialysis Patients Makoto Harada,¹ Wataru Tsukada,² Yosuke Yamada,¹ Akinori Yamaguchi,¹ Koji Hashimoto,¹ Makoto Higuchi,¹ Yuji Kamijo.¹ ¹Dept of Nephrology, Shinshu Univ School of Medicine, Matsumoto, Nagano, Japan; ²Dept of Nephrology and Urology, Ueda Kidney Clinic, Ueda, Nagano, Japan.

Background: Vascular endothelial function (VEF) impairment is often detected in hemodialysis (HD) patients and has been associated with atherosclerosis and cardiovascular disease (CVD). Although avoidance of VEF impairment is therefore desirable in preventing such complications, the precise factors that influence VEF remain unknown. The present study evaluated VEF for associating factors in HD patients.

Methods: We enrolled 48 patients undergoing maintenance HD at Ueda Kidney Clinic in Japan. No patient had a history of CVD. Reactive hyperemia index (RHI) as evaluated by Endo-PAT (Itamar Medical, Ltd., Caesarea, Israel) was used to assess VEF, whereby a higher RHI was indicative of better function. We also assessed for correlations between the natural logarithm of RHI (LnRHI) and clinical parameters.

Results: The median age of our patients was 67 years, the male-to-female ratio was approximately 2:1, and median LnRHI was low at 0.36. Analysis of Spearman's rank correlation coefficient revealed a significant positive correlation between serum uric acid level (sUA) and LnRHI ($r_s=0.372$, $p=0.009$). As sUA is influenced by dialysis efficiency and dietary intake, we also performed multivariable linear regression analysis adjusted by age, body mass index, dialysis efficiency by Kt/V, and normalized protein catabolic rate, and observed that sUA was significantly related to LnRHI ($B=0.042$, 95% CI: 0.007-0.078, $\beta=0.396$, $p=0.021$).

Conclusions: The current study suggests that VEF is closely associated with sUA in HD patients. Although the precise mechanism is unknown, a marked decrease in sUA might be correlated with VEF impairment and should be avoided in individuals undergoing HD.

TH-PO909

Ambulatory Arterial Stiffness Index: An Early Marker of Cardiovascular Disease in Young Hemodialysis Patients Alicia D. Edwards-Richards, Chryso P. Katsoufis, Wacharee Seeherunvong, Nao Sasaki, Marissa J. Defreitas, Gaston E. Zilleruelo, Michael Freundlich, Carolyn L. Abitbol. *Pediatric Nephrology & Cardiology, Univ of Miami/ Holtz Children's Hospital, Miami, FL.*

Background: Cardiovascular disease (CVD) is the leading cause of death in pediatric hemodialysis (HD) patients. Ambulatory arterial stiffness index (AASI) may be an earlier measure of vascular compliance in young patients than pulse pressure (PP). Our objective was to evaluate AASI as a marker of increased vascular stiffness in young HD patients and to compare it with other non-invasive indicators of CVD risk.

Methods: Retrospective review of 24-hour ambulatory blood pressure monitoring (ABPM) was performed in 11 pediatric patients on chronic HD (16±3.6yrs) and dialysis vintage of 32±18 months. AASI was calculated as 1-regression slope of the diastolic over systolic BP. Echocardiogram and bilateral carotid artery ultrasounds were performed to assess left ventricular mass index (LVMI) and carotid intimal medial thickness (cIMT). Carotid artery stiffness indices included distensibility coefficient (DC), stiffness index- β (SI- β) and PP. These were compared with reference values for healthy pediatric controls.

Results: AASI was significantly increased in HD patients compared to controls (0.42±0.1 versus 0.20±0.2; $p=0.01$). When matched to controls with similar BP's and PP's, the AASI detected increased vascular stiffness independent of PP, cIMT, LVMI, and DC were also significantly increased in HD patients ($p<0.01$).

Echocardiography & Carotid Ultrasound & 24-Hr ABPM			
Variable	HD	Controls	p-Values
cIMT (mm)	0.60±0.1	0.38±0.1	0.01
LVMI (g/m ^{2.7})	40±9	34±11	0.01
DC (kPa ⁻¹ 10 ³)	43±13	53±17	0.04
Stiffness Index β	4.2±10	5.3±3	0.13
PP (mmHg)	49±10	40±7	<0.05
24-hr PP (mmHg)	43±9	43±5	1.00
AASI	0.42±0.1	0.20±0.2	0.01

Conclusions: Young HD patients demonstrate early surrogate markers of CVD including increased LVMI, cIMT and decreased vascular compliance. Increased AASI detected vascular stiffness that was independent of BP's and PP's. AASI may be an early non-invasive marker of vascular disease in young HD patients that merits further investigation.

TH-PO910

Endovascular Renal Denervation Ameliorates Pathological Left Ventricular Dilatation in Dialysis Patients Neil A. Hoye,¹ J. Christopher Baldi,¹ David L. Jardine,² John B.W. Schollum,¹ Gerard T. Wilkins,¹ Luke C. Wilson,¹ Robert J. Walker.¹ ¹Dunedin School of Medicine, Univ of Otago; ²Christchurch School of Medicine and Health Sciences, Univ of Otago.

Background: Endovascular renal denervation (RDN) ameliorates left ventricular hypertrophy and improves contractile function in resistant hypertension. Its cardiac effects on a dialysis population are unknown. We hypothesized RDN would improve blood pressure (BP) control and sympathetic overload, resulting in improved ventricular function.

Methods: Nine dialysis patients with uncontrolled office BP (>140/90mmHg despite two or more agents at maximal tolerated dosages) were recruited into this feasibility study. Office and ambulatory BP monitoring (ABPM) were performed at baseline, one and three months post RDN, along with supine muscle sympathetic nerve activity (MSNA). Echocardiography was performed at baseline and three months. Bilateral RDN was undertaken with an EnligHTN™ catheter.

Results:

	Baseline	1 Month	3 Months	P value
Office Systolic BP (mmHg)	179±28	156±24	152±25	<0.05
Office Diastolic BP (mmHg)	90±17	76±13	82±12	0.137
Mean Systolic ABPM (mmHg)	173±19	173±23	166±24	0.544
Mean Diastolic ABPM (mmHg)	92±11	89±13	88±11	0.906
MSNA Burst Frequency (bursts/min)	59±12	59±15	59±13	0.872
LVIDD (mm)	54±6		50±7	<0.05
LV EDV (mL)	168±43		150±42	0.391
LV ESV (mL)	102±41		80±29	0.397
LV EF (%)	41±14		47±11	0.801
LVd mass/BSA (g/m2)	97±16		91±9	0.490
Diastolic Dysfunction Grade	2.0±0.7		1.1±0.4	0.063

Similar to previous, office systolic BP reduced and the effect on ABPM was attenuated. MSNA did not change, a novel finding. Despite lack of change in MSNA, LVIDD reduced with an improving trend in diastolic dysfunction, another novel finding. There was no correlation between change in office systolic BP and ventricular dilatation (R²=0.255) or dysfunction (R²=0.034), suggesting BP-independent effects.

Conclusions: RDN in dialysis patients improves office systolic BP and leads to a BP-independent improvement in ventricular dilatation and probably dysfunction. Further controlled studies are warranted in this population.

TH-PO911

Effects of Music and Exercise during Hemodialysis on the Cardiac Autonomic Nervous System Activity Maria Mitsiou,¹ Evangelia J. Kouidi,¹ Vassilios Liakopoulos,² Asterios P. Deligiannis.¹ ¹Laboratory of Sports Medicine, Aristotle Univ of Thessaloniki, Thessaloniki, Greece; ²Renal Unit, 1st Dept of Internal Medicine, Aristotle Univ of Thessaloniki, Thessaloniki, Greece.

Background: Cardiac autonomic nervous system (CANS) dysfunction is a common complication in Chronic Kidney Disease (CKD), linked with increased cardiovascular morbidity and mortality. It is known that exercise training during hemodialysis (HD) improves physical function and quality of life in HD patients. Exercise training can suppress the sympathetic over-excitation, restoring the sympathetic (SNS) to parasympathetic nervous system (PNS) balance. Music can positively affect CANS activity. The combination of music and physical training has never been used in CKD. The aim of this study was to investigate the effectiveness of a 6-month, music and physical training combined protocol during HD.

Methods: Heart rate variability (HRV) data were collected from 40 free of any systemic disease HD patients (age 50±14.7 yrs). Patients were randomly assigned to four equally numbered [n=10] groups, employing a joint music and exercise training program for Group A, a sole exercise training program for Group B, a sole music program for Group C and none of the above-mentioned interventions for Group D. At entry and at the end of the study all patients underwent a 6-minute walking test (6MWT) and ambulatory 24-hour Holter monitoring for time- and frequency-domain HRV calculation. The HRV indices obtained were: mean heart rate (HR); standard deviation of NN intervals (SDNN); root mean square of successive differences (RMSSD); proportion of NN50 divided by total number of NNs (pNN50) and very low frequency (VLF).

Results: All indices were significantly better for Group A: 6MWT [F(3,36)=13.095, p=0.000], HR[F(3,36)= 1.910, p=0.145]; SDNN [F(3,36)=11.671, p=0.000]; RMSSD [F(3,36)=12.395, p=0.000]; pNN50 [F(3,36)=45.752, p=0.000]; and VLF [F(3,36)=3.141, p=0.037].

Conclusions: Musical auditory stimulation when jointly used with exercise training during HD has the strongest influence on CANS activity, improving the dynamic interaction between the SNS and PNS. These favorable changes may positively affect cardiovascular morbidity and mortality.

TH-PO912

Temporal Loss of Bone Mineral Density Is Associated with Cardiovascular Diseases in Japanese Patients Starting Renal Replacement Therapy Sawako Kato,¹ Shoichi Maruyama,¹ Bengt Lindholm,² Yukio Yuzawa,³ Yoshinari Tsuruta,⁴ Seiichi Matsuo.¹ ¹Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; ²Baxter Novum & Renal Medicine Karolinska Inst, Stockholm, Sweden; ³Nephrology, Fujita Health Univ School of Medicine, Toyoake, Japan; ⁴Meiyo Clinic, Toyohashi, Japan.

Background: Atherosclerosis, vascular calcification and alterations of bone metabolism are common aging disorders, which may be biologically linked via bone-vascular interactions. However, clinical studies on associations of temporal bone loss with cardiovascular disease (CVD) in dialysis patients are limited.

Methods: Seventy-six incident Japanese dialysis patients (46 males, age 60 ± 10 years) were enrolled and followed for a median of 3.8 years (range 1-5.8 years). Bone mineral density (BMD) of the lumbar spine was measured by dual X-ray absorptiometry at baseline and after 1 year.

Results: Baseline BMD, median value 1.05 (0.67-1.56) g/cm², negatively correlated to age (rho = -0.28, P = 0.015) and iPTH (rho = -0.14, P = 0.0002). When dividing patients into two groups according to delta BMD (defined as baseline - 1 year), those with high delta BMD had an increased mortality risk (Log rank 6.36, P = 0.012) and time from dialysis initiation to the first CVD event appeared, although not significant, shorter in patients with high delta BMD (Log rank 2.81, P = 0.094). Patients with high delta BMD had a significantly increased relative risk (RR; Cox hazard model) of mortality (10.9, 95% CI; 1.34-250.6) even after adjustments for age, gender, diabetes and smoking, compared with those with low delta BMD. RR of the first CVD event was 5.52 (95% CI; 1.15-7.83) with adjustment for age and gender.

Conclusions: Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.

Funding: Government Support - Non-U.S.

TH-PO913

First in Man: Reduction of Inflammation with Medium Cut-Off (MCO) Membranes Daniel Zickler,¹ Ralf Schindler,¹ Markus Storr,³ Kevin Willy,¹ Bogusz Trojanowicz,² Peter Martus,⁴ Christof Ulrich,² Kristin Liehr,⁵ Christian Henning,⁵ Torsten Böhler,³ Marcus A. Glomb,⁵ Roman Fiedler,² Matthias Girndt.² ¹Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin, Germany; ²Dept of Internal Medicine II, Martin-Luther-Univ, Halle, Germany; ³Research & Development, Gambro Dialysatoren GmbH, Hechingen, Germany; ⁴Inst for Epidemiology and Applied Biometry, Eberhard-Karls-Univ, Tübingen; ⁵Inst for Chemistry / Food Chemistry, Martin-Luther-Univ, Halle.

Background: High mortality in dialysis patients may be related to reduced clearance of cytokines with conventional dialysis membranes. Attempts to provide a better clearance with high cut-off membranes also leads to albumin loss. A new Medium-Cutoff membrane with better permeability for molecules up to 45 kDa but with limited permeability for albumin was tested clinically for the first time.

Methods: 50 patients were dialyzed with MCO and conventional high-flux (HF) membranes for four weeks following a randomized cross-over design. After the second phase, another 12-week-period was conducted to test for long-term effects. Serum samples were tested for inflammatory effects and cytokine concentrations. Support was granted by the German Federal Ministry of Education and Research (FKZ 13N11796-99).

Results: The primary end point mRNA content of TNF-alpha in leucocytes was reduced to a higher degree and significantly better after 4 weeks on MCO compared to HF membrane (p<0.001). Interleukin-6 mRNA was markedly reduced with MCO (p<0.001). After a significant drop after four weeks of MCO dialysis, albumin concentrations stabilized after 12 weeks.

	Before HF	After HF	Before MCO	After MCO
TNF mRNA Log 10 ¹	1.19 ± 0.57 0.03 ± 0.21	1.02 ± 0.49 -0.03 ± 0.18	0.92 ± 0.34 -0.06 ± 0.16	0.75 ± 0.31 -0.16 ± 0.19
IL6 mRNA Log 10 ¹	0.86 ± 0.68 -0.18 ± 0.33	0.84 ± 0.67 -0.25 ± 0.34	0.79 ± 0.79 -0.19 ± 0.31	0.60 ± 0.43 -0.32 ± 0.31
Albumin (g/l)	36.6 ± 3.2	37.5 ± 2.7	37.0 ± 3.6	35.2 ± 3.7

¹Significance testing was based on log transformed values for TNF mRNA and IL6 mRNA. Note that both crossover phases were pooled.

	HF Before extension period	HF After extension period	MCO Before extension period	MCO After extension period
Albumin(g/l)	37.6 ± 2.3	37.9 ± 3.5	35.7 ± 4.5	36.4 ± 3.9

Note that the dialysator before extension period was the dialysator of the 2nd cross over phase.

Conclusions: MCO membranes modulate inflammation in dialysis patients. Albumin concentrations stabilize after an initial drop. These results encourage further investigations with longer treatment periods and clinically relevant endpoints.

Funding: Pharmaceutical Company Support - Gambro, Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO914

Vitamin D and Cardiac Autonomic Tone in End-Stage Kidney Disease: A Blinded, Randomized Controlled Trial Sofia B. Ahmed,¹ Michelle C. Mann,¹ Brenda Hemmelgarn,¹ David A. Hanley,¹ Tanvir Chowdhury Turin,¹ Jennifer M. MacRae,¹ David C. Wheeler,² Sharanya Ramesh,¹ Darlene Y. Sola,¹ Derek Exner.¹ ¹Univ of Calgary, Canada; ²Univ College London, United Kingdom.

Background: Importance: End-stage kidney disease (ESKD) patients are at high cardiovascular (CV) risk. Vitamin D deficiency is associated depressed heart rate variability (HRV), a risk factor for CV death. Both vitamin D deficiency and depressed HRV are highly prevalent in ESKD.

Methods: Objective: To determine the effects of activated vitamin D (conventional) compared to activated and nutritional vitamin D (intensive) on HRV (low to high frequency spectral ratio; LF:HF) in patients with ESKD on hemodialysis (HD). **Design:** 2x2 crossover, blinded, randomized controlled trial in outpatient HD units. Fifty-six patients were randomized 1:1 to begin either conventional (0.25mcg alfalcidol and placebo 3 times/week) or intensive vitamin D therapy (0.25mcg alfalcidol 3 times/week and 50000IU ergocalciferol weekly) for 6 weeks. **Main Outcomes:** HRV is a surrogate index of cardiac autonomic nerve function and independently predicts CV mortality. The primary outcome was the change in LF:HF from the 1st to 6th week HD session. Secondary endpoints included individual changes in LF and HF, parameters of mineral metabolism and renin angiotensin system (RAS) activity.

Results: There was no difference in LF:HF from baseline to 6 weeks for either vitamin D treatment (conventional p=0.9; intensive p=0.07). There were no significant changes in any other measure of HRV, mineral metabolism or RAS activity. On exploratory subgroup analysis, participants who remained vitamin D deficient (25-hydroxyvitamin D<50nmol/L) after treatment had a significant increase in LF:HF (conventional: n=13, p<0.001 vs. insufficient and sufficient groups; intensive: n=8, p<0.001 vs. sufficient group).

Conclusions: Six weeks of treatment with conventional or intensive vitamin D did not alter LF:HF in ESKD patients. However, improved LF:HF was observed in the vitamin D-deficient subgroup. This finding may translate into decreased CV risk and should be considered hypothesis-generating and deserving of further study. **Trial Registration:** ClinicalTrials.gov NCT01774812.

Funding: Private Foundation Support

TH-PO915

The Validity of Left Ventricular Mass as a Surrogate Endpoint for Mortality Outcomes in Chronic Kidney Disease Sunil V. Badve,^{1,2} Suetonia Palmer,³ Giovanni F.M. Strippoli,⁴ Matthew A. Roberts,⁵ Armando Teixeira-Pinto,¹¹ Neil Boudville,⁶ Alan Cass,⁷ Carmel M. Hawley,⁸ Swapnil Hiremath,⁸ Elaine M. Pascoe,¹ Vlado Perkovic,⁹ Gillian A. Whalley,¹⁰ Jonathan C. Craig,¹¹ David W. Johnson.¹² ¹Univ of Queensland; ²Princess Alexandra Hospital; ³Univ of Otago; ⁴Univ of Bari; ⁵Monash Univ; ⁶Univ of Western Australia; ⁷Menzies School of Health Research; ⁸Univ of Ottawa; ⁹The George Inst for Global Health; ¹⁰Unitec Inst of Technology; ¹¹Univ of Sydney.

Background: Left ventricular mass (LVM) is increasingly used as a surrogate endpoint in trials involving chronic kidney disease (CKD) patients, as intervention-induced reductions in LVM are assumed to lower cardiovascular (CV) risk.

Methods: The aim of this systematic review was to determine the validity of LVM as a surrogate endpoint for all-cause and CV mortality in CKD. Randomized controlled trials evaluating pharmacological and non-pharmacological interventions with follow-up ≥3 months were included. The outcomes of interest were LVM change from baseline to last measurement and all-cause and CV mortality. Standardized mean differences (SMD) in LVM change and relative risk of mortality were estimated using random-effects models. Correlations between LVM change and mortality endpoints were summarized across all interventions using a bivariate random-effects Bayesian model together with 95% credible intervals (CrI).

Results: Seventy trials (6420 participants) were eligible. Among 23 interventions, only 3 significantly reduced LVM [erythropoiesis-stimulating agents (SMD -0.13, 95%CI -0.23 to -0.03), renin-angiotensin-aldosterone-system inhibitors (SMD -0.28, 95%CI -0.44 to -0.11) and isosorbide mononitrate (SMD -0.43, 95%CI -0.72 to -0.14)]. There were weak and imprecise associations between LVM change and all-cause mortality (30 trials, 4749 participants, correlation coefficient [r] 0.28, 95%CrI -0.15 to 0.60) and CV mortality (13 trials, 2327 participants, r 0.22, 95%CrI -0.60 to 0.75).

Conclusions: In CKD, it is uncertain whether an intervention-induced LVM change correlates with reduced mortality. Evidence for LVM as a valid surrogate endpoint in CKD is currently lacking.

TH-PO916

Non-Invasive Left Ventricular End-Diastolic Pressure (LVEDP) Measurement in Hemodialysis Patients: A Pilot Study Tariq Shafi, Bernard G. Jaar, Luis F. Gimenez, Alison G. Abraham, Chloe F. Knight, Naya El Hage, Paul J. Scheel, Josef Coresh, Harry A. Silber. Johns Hopkins Univ.

Background: Optimal volume status in dialysis patients is difficult to assess. The Valsalva maneuver is recognized as an bedside marker of central volume overload. A novel handheld device that combines finger photoplethysmography with Valsalva maneuver can reliably estimate LVEDP (normal: <12mmHg). (Silber H. PMID: 22389389). The goal of our pilot study is to determine the role of this non-invasive LVEDP measurement in managing volume in hemodialysis patients.

Methods: The LVEDP-Guided Volume Management Study is being conducted at 2 dialysis units in Baltimore. Baseline data collected includes demographics, medical history, KDQOL-36, NYHA dyspnea scale, intra/post dialysis symptoms, predialysis metrics [LVEDP, bioimpedance, blood pressure (BP)] and echocardiogram. We assessed the cross-sectional association of predialysis LVEDP with dyspnea symptoms and intradialytic hypotension (IDH, defined as ≥20mmHg drop in systolic BP + nursing interventions).

Results: In the first 28 participants (mean age 56 years, 71% male, 82% black), median (25th, 75th percentiles) for predialysis LVEDP was 14 mmHg (12, 19), interdialytic weight gain (IDWG) was 1.7 kg (0.9, 2.9) and systolic BP was 150 mmHg (133, 164). LVEDP was significantly higher in patients with dyspnea vs. those without. (Mean, 19.9 vs. 14.6; p=0.03). IDH occurred in 5 (18%) patients and all had LVEDP ≥14 mmHg (Table). The unadjusted odds ratio for IDH per SD decrease in LVEDP was 4.37 (p=0.08). There was no significant association between IDH and predialysis systolic BP or IDWG.

Table: Associations of IDH	IDH		P
	No (n=23)	Yes (n=5)	
Predialysis Factors	Mean (SD)	Mean (SD)	
LVEDP	16.2 (4.7)	11.8 (2.8)	0.05
Systolic BP	153.8 (22.3)	135 (15.5)	0.10
Interdialytic weight gain	1.97 (1.5)	1.92 (0.8)	0.93

Conclusions: Non-invasive LVEDP measurements can identify hemodialysis patients with volume overload associated with symptoms (high LVEDP) and patients at risk for IDH (low LVEDP). Our ongoing study may help confirm these initial findings and define the role of this measurement for volume management in dialysis patients.

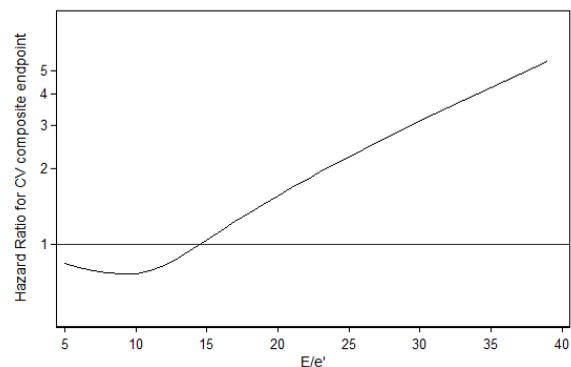
TH-PO917

E/e' Calculated by Tissue Doppler Echocardiography and Cardiovascular Outcome in Incident Dialysis Patients Jongha Park,¹ Jongmin Lee,¹ Kyung sun Park,² Sung Hyun Son,³ Shin-Jae Kim,¹ Jong Soo Lee,¹ Hyun Chul Chung.¹ ¹Ulsan Univ Hospital, Ulsan, Republic of Korea; ²Dongkang Medical Center, Ulsan, Republic of Korea; ³BHS Han-Seo Hospital, Busan, Republic of Korea.

Background: The ratio of early diastolic peak mitral flow velocity (E) to early mitral annulus velocity (e'), called E/e' is a less volume dependent, non-invasive index to estimate left ventricular (LV) filling pressure. However, the prognostic value of E/e' has not been evaluated sufficiently in patients with end-stage renal disease (ESRD).

Methods: The patients who newly started maintenance dialysis therapy between 2009 and 2012, had survived for at least 3 months after dialysis initiation, and had E/e' data, were analyzed. E/e' was calculated by pulse and tissue Doppler echocardiography. Cardiovascular (CV) composite endpoint comprised hospitalization for heart failure (HF), acute coronary disease (ACD) requiring intervention, ventricular arrhythmia, cerebral infarction or hemorrhage, and CV death. The patients were followed up until 2013.

Results: A total of 206 patients were analyzed (mean age 55.0±13.7 years old, female 51.5%). Median follow-up duration was 29.2 months (range 3.1-61.3). Forty-two CV events occurred during follow-up (15 HF, 17 ACD, 1 cerebral infarction, and 9 CV deaths). Mean E/e' was 13.6±5.4 (range 5-39). After adjusting age, sex, diabetes, mean arterial pressure, LV ejection fraction, hemoglobin, serum albumin, C-reactive protein and volume status, one unit increase in E/e' ratio was associated with 7% increase in the risk of CV composite endpoint (hazard ratio 1.07, 95% confidence interval 1.02-1.13, p=0.009). Adjusted hazard ratio linearly increased above 15 of E/e' in Cox regression with cubic splines.



Conclusions: A higher E/e' ratio, reflecting high LV filling pressure which is the main physiological finding of diastolic HF, may be associated with a higher CV risk in patients with ESRD.

TH-PO918

Tallium-201 Washout Rate of Single Photon Emission Computed Tomographic Myocardial Perfusion with Pharmacologic Stress as a Predictor of Mortality in CKD Patients Undergoing Hemodialysis: An Observational, Follow-Up Study Toshihide Hayashi, Nobuhiko Joki, Masaki Iwasaki, Ai Matsukane, Takasuke Asakawa, Yuri Tanaka, Hiroki Hase. *Div of Nephrology, Toho Univ Ohashi Medical Center, Tokyo, Japan.*

Background: Thallium-201 (²⁰¹Tl) washout rate of single photon emission computed tomography (SPECT) has been reported to correlate with coronary flow reserve which is an index of myocardial microcirculation and be useful to detect coronary artery disease and evaluate the severity. However, the evidence for its use in chronic kidney disease (CKD) has been lacking, and the association between ²⁰¹Tl washout rate and mortality is unknown. Therefore, a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of ²⁰¹Tl washout rate for mortality in CKD patients undergoing hemodialysis.

Methods: A total of 156 patients who had been started on maintenance hemodialysis undergoing pharmacologic stress thallium-201 SPECT within 1 year, 107 men and 49 women, with a median age of 67 years, were studied. The endpoint was defined as all-cause death. The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Results: During the mean follow-up period of 3.2 ± 2.4 years, 30 (19.2%) deaths occurred. The median (interquartile range) of ²⁰¹Tl washout rate was 45.1 (37.4 - 50.8)%. Cumulative survival rates at 5 years after starting dialysis, with ²⁰¹Tl washout rate levels above and below the median, were 76.7% and 63.8% (p = 0.992, log-rank test), respectively. Overall, the multivariate Cox regression analysis revealed that ²⁰¹Tl washout rate remained an independent predictor of death after adjusting by confounding variables (HR 0.95, 95% CI 0.90 to 0.99).

Association of ²⁰¹Tl washout rate with Death (Cox proportional hazard model)

	HR (95% CI)	p value
Unadjusted	0.95 (0.93 - 0.99)	0.009
Adjusted	Model 1 ^{a)}	0.95 (0.91 - 0.99)
	Model 2 ^{b)}	0.94 (0.90 - 0.98)
	Model 3 ^{c)}	0.95 (0.90 - 0.99)

Covariates: a) perfusion defect and left ventricular ejection fraction.
 b) Model 1 + age, sex, diabetes and cardiovascular disease.
 c) Model 2 + serum Alb and CRP.

Conclusions: Among CKD patients undergoing hemodialysis, ²⁰¹Tl washout rate seems to be useful for predicting death.

TH-PO919

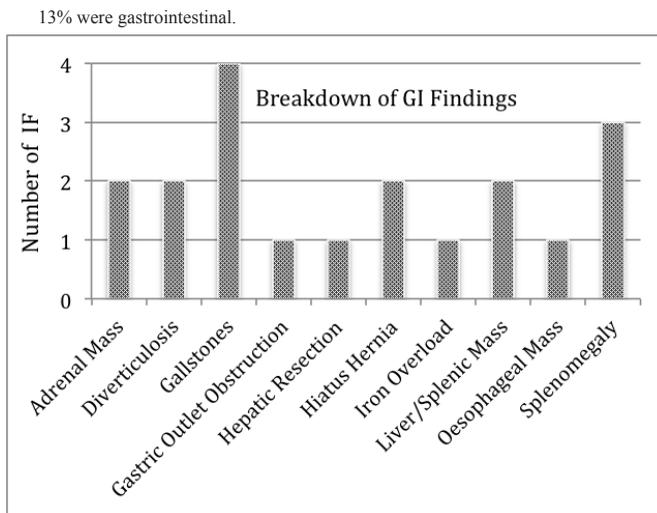
Research Cardiac Magnetic Resonance Imaging in Chronic Kidney Disease – Incidence, Significance and Implications of Unexpected Incidental Findings Elaine Rutherford,¹ Jonathan Weir-mccall,¹ Rajan K. Patel,² John Graeme Houston,¹ Giles Roditi,² Allan Struthers,¹ Alan G. Jardine,² Patrick B. Mark.² *¹Div of Cardiovascular & Diabetes Medicine, Univ of Dundee; ²Inst of Cardiovascular & Medical Sciences, Univ of Glasgow.*

Background: Left ventricular (LV) mass on cardiac magnetic resonance imaging (CMR) is a common end point of clinical trials in nephrology. Incidental findings (IF) on research images have ethical & clinical implications. We retrospectively investigated the incidence of IF in research CMR & reviewed their impact on patient care.

Methods: 161 CKD5 patients underwent CMR for a 2002-2006 research study into transplant assessment. Images were used to assess LV mass & function. In our study a radiologist reviewed the scans for IF. Abnormalities in mass, perfusion or function were not considered IF. The clinical significance of every IF was determined by patient record review.

Results: There were 150 IF. 59% of patients had one or more IF. 68% were extra-cardiac, 56% were new diagnoses.

	Lung/Mediastinal	Pleural Effusion	GI Tract	Cysts (Not PKD)	Other	Total
Number of IF	11	15	19	50	7	102
New Diagnosis	9	4	12	18	7	50
Should have changed management but clinical course not altered	6	3	1	1	3	14
Identification may have altered clinical course	1	1	3	0	0	5



16 IF were suspicious of malignancy. 17 unidentified IF would have changed patient management if known, but a review of patient records showed these IF had no later clinical impact. In 6 cases earlier identification of an important IF may have improved quality of life or survival.

Conclusions: Without radiology support clinically important IF may be missed on CMR. A suitably trained radiologist should prospectively review all CKD CMR research studies & obtained images. Patients undergoing CMR in trials should be counselled about the frequency & implications of possible IF.

TH-PO920

A Significance of Cardiothoracic Ratio for Mortality in Hemodialysis Patients: The Q-Cohort Study Ryusuke Yotsueda,¹ Masahiro Eriguchi,¹ Shigeru Tanaka,¹ Masatomo Taniguchi,¹ Hideki N. Hirakata,³ Kazuhiko Tsuruya,^{1,2} Takanari Kitazono.¹ *¹Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ²Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ³Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.*

Background: Cardiothoracic ratio (CTR) of chest X-ray is commonly used to determine the volume status in hemodialysis (HD) patients. Thus, the present study was conducted to evaluate the significance of CTR in terms of longitudinal prognosis of HD patients.

Methods: A total of 3,437 Japanese HD patients aged ³18 years were followed for 4 years. Patients were divided into four groups according to quartiles of CTR levels by sex. Risk estimates were calculated by a Cox proportional hazards model, adjusting for potential confounders. We investigated stratified analysis by sex, age, etiology of end-stage kidney disease, history of major adverse cardiac events (MACE) and blood pressure for subanalysis.

Results: The median values (interquartile range) of CTR were 0.49 (0.46-0.53) in male and 0.52 (0.48-0.56) in female. During the follow-up period, 564 patients (16%) died from any causes and the 4 years survival rate decreased significantly with higher CTR levels (p for trend <0.001). Compared with the lowest CTR quartile, the multivariable-adjusted hazard ratios (HRs) for all-cause mortality were 0.89 (95% confidence intervals, 0.66-1.21), 1.41 (1.07-1.86), and 1.52 (1.17-2.00) in subjects with low-intermediate, high-intermediate and highest quartile, respectively. Furthermore, the combination of higher CTR levels and history of MACE or lower blood pressure before HD (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) synergistically increased the risk of all-cause mortality.

Conclusions: A higher CTR level is closely related to increased mortality in HD patients. This association is more remarkable in patients with history of MACE or without high blood pressure.

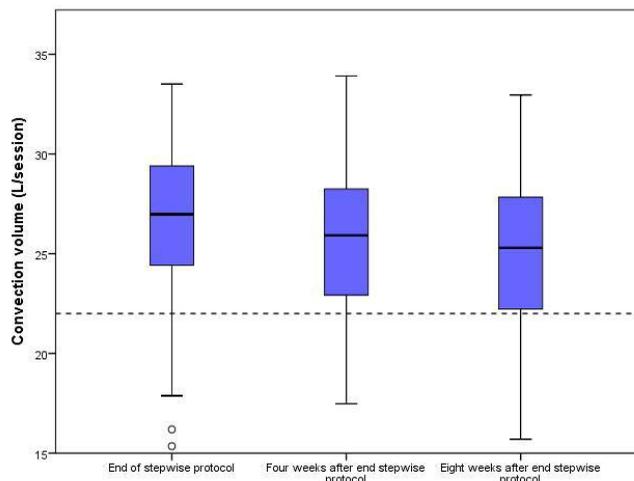
TH-PO921

High Convection Volumes in Postdilution Online Hemodiafiltration (HDF) Are Feasible in the Vast Majority of ESKD Patients Camiel LM de Roij van Zuijdewijn,¹ Isabelle Chapdelaine,¹ Menso Jan Nubé,¹ Peter J. Blankestijn,² Constantijn Konings,³ Tonnis K. Kremer Hovinga,⁴ Neelke C. Van Der Weerd,⁵ Pieter M. Ter Wee,¹ Muriel P. Grooteman.¹ *¹Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; ²Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands; ³Internal Medicine, Catharina Hospital, Eindhoven, Netherlands; ⁴Internal Medicine, Martini Hospital, Groningen, Netherlands; ⁵Nephrology, Academic Medical Center, Amsterdam, Netherlands.*

Background: Available evidence suggests a survival benefit for patients treated with high volume postdilution HDF (hvHDF) when compared to HD. Since these studies are limited by an observational design, we investigated whether hvHDF (>22L/session) is feasible in the majority of patients (>75%).

Methods: A prospective, multicenter study was performed (NCT01877499). HD(F) patients (¹18y) were eligible if treated 3x/week for ≥6 weeks. Non-participating eligible patients formed a reference group to examine the representativeness of the study group. Treatment-related determinants of the convection volume were optimized in a stepwise fashion (treatment time [TT] up to 4 hours, blood flow rate [BFR] up to 400 mL/min and filtration fraction [FF] up to 33%). At the end of this protocol (T0) and 4 (T4) and 8 (T8) weeks thereafter, the convection volume was determined.

Results: Baseline characteristics were comparable in participants (n=86) and references (n=58). At T0 and at T4, 79/86 (92%) and 68/86 (79%) patients achieved hvHDF (mean 26.9±3.56 and 26.3±3.36L/session, resp). Hereafter, 2 patients died and 1 was transplanted. 83 patients remained; 66 (80%) reached hvHDF (mean 25.9±3.53L/session, fig 1). Study discontinuation (n=9), TT <4h (n=4) or BFR ≤300 mL/min (n=4) caused a convection volume <22L/session.



Conclusions: hvHDF is feasible in the vast majority of ESKD patients. As TT remained virtually unaltered, these findings were mainly due to a higher BFR and FF.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

TH-PO922

Physical Activity Among Patients with End-Stage Renal Disease: Use of the Exercise Vital Sign Shayna L. Henry,¹ Yi-Lin Wu,¹ John J. Sim,² Michael K. Gould.¹ ¹Dept of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA; ²Dept of Nephrology, Kaiser Permanente Southern California Los Angeles Medical Center, Los Angeles, CA.

Background: Exercise has been shown to improve physical functioning among ESRD patients. However, ESRD patients report exceedingly low levels of physical activity (PA) with only 13-34% engaging in recommended levels of PA. Although ESRD is characterized by substantial barriers to PA, low PA puts patients at risk for serious complications and higher mortality. Within Kaiser Permanente (KP), patients are administered the Exercise Vital Sign (EVS) – self-reported weekly minutes of PA – during each office encounter. The EVS has been validated in multiple KP regions, with roughly one-third each of the membership reporting no, insufficient, and sufficient PA, or ¹150 minutes exercise/week. Although the relationship between EVS reports and cardiometabolic status has been examined, levels of PA reported by ESRD patients using the EVS have not yet been explored.

Methods: EVS reports of all KP patients with a diagnosis of ESRD between January 2013 and July 2014 (N=8,187; Female=3,534, Mean Age=63.3 years) were assessed.

Results: Patients were 25% White, 38% Black, 23% Hispanic, 12% Asian, and the remainder Other, consistent with the regional patient catchment; just over 50% were married. The majority (88%) had comorbid HTN, 65% had comorbid DM, and 37% comorbid CHF. On average, patients had four other comorbid illnesses. During the study period, patients presented for 135,562 encounters. The mean reported PA frequency was 1.4 times per week (SD=2.2), for a mean 12.3 minutes/bout (SD=22.4), or an average of 49.0 minutes/week (SD=103.2) and a median zero minutes/week. The majority of ESRD patients did not achieve sufficient levels of PA during this period; 75% of the sample exercised for ≤60 minutes/week.

Conclusions: Self-reported rates of PA among ESRD patients at KP are critically low. Implications of low PA for cardiovascular and other outcomes as well as for interventions to improve rates of PA in this diverse population will be discussed.

TH-PO923

The Association of RAS Inhibition with Cardiovascular Events in Patients Undergoing Hemodialysis in Japan Masahide Mizobuchi,¹ Hiroaki Ogata,² Yoshihiro Onishi,⁴ Shingo Fukuma,³ Tadao Akizawa,¹ Shunichi Fukuhara.³ ¹Dept of Nephrology, Showa Univ School of Medicine, Tokyo, Japan; ²Dept of Internal Medicine, Showa Univ Northern Yokohama Hospital, Yokohama, Japan; ³Dept of Epidemiology and Healthcare Research, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ⁴Inst for Health Outcomes & Process Evaluation Research (iHope International), Kyoto, Japan.

Background: Pharmacological inhibition of the renin-angiotensin system (RAS) contributes to cardiovascular protection in predialysis patients. However, definitive evidence of whether RAS inhibition is beneficial on cardiovascular event (CVE) among hemodialysis (HD) patients is lacking. The objective of this study was to investigate the association of RAS inhibitors usage with CVEs in patients enrolled in the Dialysis Outcomes Practice Pattern Study in Japan (J-DOPPS).

Methods: HD patients enrolled in J-DOPPS were eligible for analysis. Association of RAS inhibitors prescription with outcomes including all-cause death, death caused by CVE, and hospitalization due to cardiac failure was investigated by using a multivariable Cox proportional hazards model.

Results: Of the 3848 patients enrolled, 1784 (45 %) patients were treated by RAS inhibitors. The prevalence of male, diabetes, and other anti-hypertensive agent usage was higher in patients with RAS inhibitors compared to those without RAS inhibitors. Dialysis vintage was shorter and systolic blood pressure was higher in patients with RAS inhibitors. After adjusting for potential cofounders by Cox proportional hazards models, we did not find statistically significant associations of RAS inhibitors with all-cause death (HR: 1.19, 95%CI: 0.93-1.53, p=0.16), death caused by CVE (HR: 1.32, 95%CI: 0.80-2.18, p=0.28), and hospitalization due to cardiac failure (HR: 1.30, 95%CI: 0.89-1.89, p=0.18). A similar trend was observed when patients were stratified by the presence or absence of cardiovascular disease history.

Conclusions: RAS inhibition was not associated with CVEs suggesting that RAS inhibition alone is insufficient to reduce the risk of cardiovascular complications. Strategies in addition to RAS inhibition are needed to protect against CVEs in HD patients.

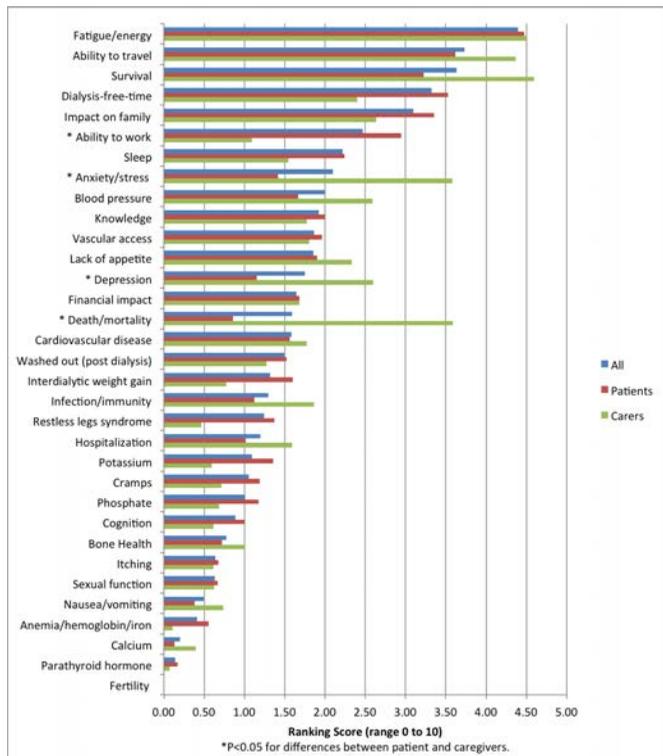
TH-PO924

Patient and Caregiver Priorities for Outcomes in Hemodialysis: A Multinational Nominal Group Technique Study Allison Tong,¹ Rachel Urquhart-Secord,¹ Brenda Hemmelgarn,² Braden J. Manns,² Kevan Polkinghorne,³ David C. Harris,¹ Peter G. Kerr,³ Helen Tam-Tham,² Stephanie E. Thompson,⁴ Kara Schick-Makaroff,⁴ Martin Howell,¹ Jonathan C. Craig.¹ ¹Univ of Sydney; ²Univ of Calgary; ³Monash Univ; ⁴Univ of Alberta.

Background: In the context of clinical trials, researchers have historically selected the outcomes they consider to be important. However, there is a growing awareness that they are often discordant with patient priorities. Efforts to define and report patient-centered outcomes are gaining momentum but have largely been outside of nephrology. We aimed to identify patient and caregiver priorities for outcomes in hemodialysis (HD).

Methods: Structured discussions using a nominal group technique were conducted with patients on HD and caregivers purposively sampled from 5 dialysis units in Australia (Sydney, Melbourne) and Canada (Calgary), who identified and ranked outcomes for HD. A mean rank score out of 10 was calculated for each outcome.

Results: 12 nominal groups involving 82 participants (patients n=58, caregivers n=24) aged 24–88 yrs (mean 58.3) identified 69 outcomes. The top 10 were: fatigue/energy (mean rank 4.4), ability to travel (3.7), survival (defined by patients as daily well-being and coping) (3.6), dialysis-free time (3.3), impact on family (3.1), ability to work (2.5), sleep (2.2), anxiety/stress (2.1), blood pressure (2.0), and knowledge (1.9). Mortality ranked 15th and participants distinguished this from survival. Caregivers ranked mortality, anxiety, and depression higher; patients ranked ability to work higher (P<0.05).



Conclusions: Patient prioritized outcomes are focused on maintaining a quality lifestyle above the usual outcomes in HD trials i.e. death, adverse events, and biological markers. Researchers need to consider interventions that could improve these outcomes, and measure and report patient-relevant outcomes in trials.

TH-PO925

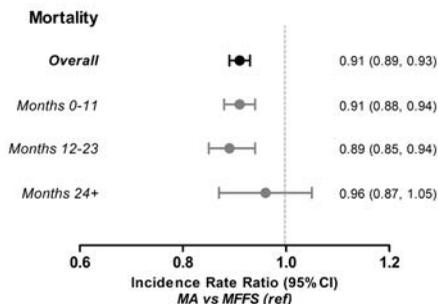
Medicare Advantage (MA) Is Associated with Lower Rates of Mortality versus Medicare Fee-For-Service (MFFS) Among Incident End-Stage Renal Disease (ESRD) Patients Steven M. Brunelli,¹ Carey Colson,¹ Scott Sibbel,¹ Abigail Hunt,¹ Allen R. Nissenson,² Mahesh Krishnan.² ¹DaVita Clinical Research, Minneapolis, MN; ²DaVita HealthCare Partners Inc, Denver, CO.

Background: Patients with ESRD have a high burden of comorbid illness and are complex to manage and may therefore benefit from programs like MA that facilitate care coordination. Currently, ESRD patients are barred from enrolling in MA after onset of ESRD; however, those already enrolled at the time of ESRD onset may remain enrolled. To understand the potential impact of MA among ESRD patients, we compared mortality rates among patients who began dialysis enrolled with MA versus MFFS.

Methods: Adult patients initiating hemodialysis (HD) or peritoneal dialysis (PD) between 01 Jan 2009 and 30 Jun 2011 and who were enrolled with MA or MFFS as of ESRD onset were considered. MA patients were matched 1:1 to MFFS controls based on initial modality, access type, and propensity score (based on 26 demographic and clinical characteristics). Patients were followed from dialysis initiation until death, transplant, loss to follow up, change in benefits status, or end of study (31 Dec 2011). Mortality rates were compared using negative binomial models. Sensitivity analyses considering early and latent effects were performed using piecewise methods.

Results: Compared to MFFS, MA was associated with lower rates of mortality (64.3 vs 70.7 deaths/100 patient-years; incidence rate ratio, 0.91). Mortality effects were limited to HD patients and were attenuated after the first 24 months of dialysis.

Conclusions: Enrollment in MA was associated with substantially lower rates of mortality during 2009-2011.



Funding: Pharmaceutical Company Support - DaVita HealthCare Partners Inc

TH-PO926

Characteristics of Patients Receiving Dialysis at a Comprehensive Cancer Center and Outcomes Ala Abudayyeh,¹ Jai prakash babu Thippaiah Jadegondanahalli,² Rima N. Pai,¹ Maria del Pilar Fernandez,² Alvin H. Moss.³ ¹Section of Nephrology, UT MD Anderson Cancer Center; ²Nephrology and Hypertension, UT at Houston Medical School; ³Section of Nephrology, West Virginia Univ School of Medicine.

Background: With the increasing therapeutic options from the traditional cytotoxic therapies, small molecules for targeted therapies and more recently immunotherapies, cancer patients have been given a massive arsenal to tackle their cancer. With the associated renal toxicities from the chemotherapies, sepsis, infections, antibiotics, and obstruction we are often faced with decisions about the utility of dialysis. This is often the situation in the patients with advanced solid tumors that have failed multiple lines of treatment and are admitted with renal failure necessitating hemodialysis. Our hypothesis for this study is offering dialysis to advanced solid tumor patients will not improve overall survival and is not cost effective.

Methods: All patients diagnosed with Acute Kidney Injury in their last hospital admission with solid tumor and nephrology consult between 01/01/2005 through 12/31/2014 were identified using billing data. Patient demographic data for those records was extracted: date of birth, gender, race, financial class, vital status and last contact date. Our final study cohort is a total of 2,268 unique patient records.

Results: Out of 2,268 patients, 392 patients (17.28%) received dialysis and 1876 patients (82.72%) did not. A total of 1470 patients (64.81%) were discharged alive and 798 patients (35.19%) resulted in a hospital death. The hospital deaths included 269 patients (33.71%) that received dialysis and 529 patients (66.29%) that did not receive dialysis in the hospital.

Conclusions: Our preliminary data indicates that patients who survived their last hospitalization were less likely to have undergone dialysis (8.36%) when compared to patients that died during their last hospitalization (33.71% were dialyzed). Therefore, reaffirming that dialysis in advanced cancer patients would not likely add further benefit to their mortality.

TH-PO927

Emergency Room Utilization by Dialysis Patients: A Population Based Study Claudio Rigatto,^{1,2} James M. Zacharias,^{1,3} Bing Hu,⁴ Brett M. Hiebert,¹ Navdeep Tangri,^{1,2} Paul Komenda.^{1,2} ¹Internal Medicine, Univ of Manitoba, Winnipeg, MB, Canada; ²Renal Health/Dialysis, Seven Oaks General Hospital, Winnipeg, MB, Canada; ³Renal Health/Dialysis, Winnipeg Health Sciences Centre, Winnipeg, MB, Canada; ⁴Manitoba Renal Program, Winnipeg Regional Health Authority, Winnipeg, MB, Canada.

Background: Patients with kidney failure are frail and have high rates of cardiovascular and infectious comorbidities. As a result, they are heavy users of non-dialysis acute health services such as the emergency department (ED). Despite this, accurate population based data on rates and patterns of ED visits by dialysis patients are lacking. The objective of the current study was to determine rates and patterns of ED utilization by adult dialysis patients vs. the adult general population.

Methods: We linked two large regional databases in Winnipeg, Manitoba, Canada (population 1.3 million), the Manitoba Renal Program Patient Registry and the Winnipeg Regional Emergency Program Admission Discharge Triage database. Data were analyzed for the years 2000-2010. Poisson Regression was used to compare rates.

Results: Over the study period, the linked dataset comprised >2.0 million visits in 1.2 million non-dialysis patients, and 17,738 visits in 3260 dialysis patients. Our key findings were 1) Age and Sex adjusted rates of ER visits were 8.5X higher among dialysis patients [153 vs 18 visits per 100 patient-years, p<0.001], with negligible variation year to year over the study period; 2) Rate of ER visits were 25% higher on Mondays and Tuesdays overall; this “post-weekend” risk phenomenon was more pronounced in dialysis patients vs. the general population (p<0.001 for interaction); 3) among dialysis patients, ER visits were 8X higher during the two weeks before and after initiation of dialysis, reflecting a period of heightened vulnerability for patients with kidney disease.

Conclusions: Our population based rates of ED utilization will help health administrators predict the “collateral” impact of a typical dialysis unit on the health system. Strategies to mitigate the high risk of ED utilization “post weekend” and around the time of transition to dialysis are urgently needed and should be a focus of future health systems research.

Funding: Private Foundation Support

TH-PO928

Development of a Clinical Risk Prediction Tool for Six-Month Mortality After Dialysis Initiation Among Older Adults James Wick,¹ Tanvir Chowdhury Turin,¹ Peter D. Farris,¹ Jennifer M. MacRae,¹ Robert G. Weaver,¹ Brenda Hemmelgarn. ¹Univ of Calgary, Calgary, AB, Canada.

Background: Early mortality after dialysis initiation is common among older adults. We sought to develop a tool to predict mortality within 6 months of dialysis initiation in an older adult population.

Methods: We linked administrative and dialysis registry data to define a cohort of older adults (age 65+) in Alberta, Canada who initiated chronic dialysis between May 2003 and March 2012. The outcome was all-cause mortality within 6 months of dialysis initiation. Potential predictors included demographics, comorbidities, health-system use,

laboratory measurements and dialysis-related information. We used logistic regression and 10-fold cross validation to identify and validate a model of significant predictors. Model discrimination and calibration were measured by c-statistic and Hosmer-Lemeshow goodness-of-fit respectively. A point system was created based on regression coefficients of predictors in the final model.

Results: 2,211 adults initiated dialysis, of whom 386 (17.4%) died within 6 months. Significant predictors of 6-month mortality were: age ≥ 80 , vascular access with central venous catheter, baseline eGFR 10-14.9 or $>15\text{mL}/\text{min}/1.73\text{m}^2$, normal proteinuria, atrial fibrillation, lymphoma and congestive heart failure (CHF). Model discrimination (C-Statistic: 0.73) and calibration (Hosmer-Lemeshow χ^2 : 6.09; $p=0.64$) were good. A 40-point scale for 6-month mortality was created based on model coefficients with points assigned based on strength of each predictor as specified in Table 1.

Category		Points
Age	65-79.9	0
	80+	2
Vascular Access	Central Venous Catheter	10
	Arteriovenous Fistula/Graft	0
	PD Catheter	3
eGFR	<10	0
	10-14.9	2
	15+	5
Proteinuria	Normal	6
	Mild	4
	Heavy	0
	Unmeasured	5
Atrial Fibrillation		4
Lymphoma		9
CHF		4
TOTAL		0 - 40

Conclusions: We derived and internally validated a clinical risk prediction tool for 6-month mortality for older adults initiating dialysis, using age, vascular access, eGFR, proteinuria, atrial fibrillation lymphoma and CHF as predictors. The results require external validation prior to use in clinical practice. A tool such as this can guide decision making for older adults with kidney failure.

TH-PO929

Coping Strategies and Outcomes Among Hemodialysis (HD) Patients in the DOPPS Elodie Speyer,¹ Hal Morgenstern,^{1,2} Peter G. Kerr,³ Antonio Alberto Lopes,⁴ Hugh C. Rayner,⁵ Bruce M. Robinson,¹ Ronald L. Pisoni.¹ ¹Arbor Research, USA; ²Univ of Michigan, USA; ³Monash Health & Monash Univ, Australia; ⁴Federal Univ of Bahia, Brazil; ⁵Birmingham Heartlands Hospital, UK.

Background: Although HD presents numerous psychological and physical challenges for patients, how they cope with dialysis therapy and its impact on quality of life (QoL) and mortality is poorly understood.

Methods: Patients from 6 DOPPS countries completed the Coping Strategies Inventory-Short Form (CSI-SF), which we found to be reliable and valid in those countries for measuring 4 coping strategies: problem-focused engagement (PFE) and disengagement (PFD), and emotion-focused engagement (EFE) and disengagement (EFD); and summary measures of engagement (actions to confront stressors) and disengagement (avoiding exposure to stressors). Outcomes were QoL (from SF-12 and KDQoL-SF), depression symptoms (from the CES-D), and all-cause mortality. Mixed linear and logistic models were used to estimate coping effects, adjusting for country and potential confounders.

Results: The sample included 2,262 HD patients from the US, UK, Australia/New Zealand, Canada, and Sweden in DOPPS4 (2009-11). In general and whatever the instrument, both engagement coping strategies and the summary score were positively associated with better QoL scores and inversely associated with depression symptoms. In contrast, disengagement strategies were inversely associated with better QoL scores and positively associated with depression symptoms. The PFE score was inversely associated with mortality (HR =0.78 per 4 points higher score; 95% CI: 0.66-0.9).

Association between coping strategies and patient-reported outcomes (QoL and depression symptom)

	Coping Scores		Quality of Life measures [§]		Depression measure [¶]	
	Mean	Range	Adjusted difference in means (95% CI)	Adjusted difference in means (95% CI)	Odds Ratio (95% CI) (>10 vs =10)	
Model 1^{**}						
PFE	13.6	4-20	4	2.15 (1.5; 2.8)	4.62 (3.9; 5.3)	0.42 (0.36; 0.49)
PFD	11.1	4-20	4	0.03 (-0.6; 0.6)	-1.84 (-2.5; -1.2)	1.43 (1.27; 1.61)
EFE	12.0	4-20	4	-0.12 (-0.7; 0.5)	0.02 (-0.6; 0.7)	0.97 (0.86; 1.10)
EFD	5.0	2-10	2	-0.34 (-0.8; 0.2)	-2.37 (-2.9; -1.9)	1.62 (1.46; 1.79)
Model 2^{**}						
E	25.6	8-40	7	1.69 (1.1; 2.3)	3.92 (3.3; 4.6)	0.48 (0.42; 0.54)
D	16.1	6-30	6	-0.50 (-1.2; 0.2)	-4.55 (-5.3; -3.8)	2.39 (2.06; 2.77)

¹IQR=interquartile range
[§]PCS and MCS=SF-12 physical and mental component summary scores;
[¶]Analysis modeling the probability that CES-D score>10 (symptom of depression)
^{**}All analyses were adjusted for country

Conclusions: Engagement strategies appear to be beneficial and disengagement detrimental for HD patients. A better understanding of the coping strategies used by patients may have prognostic implications and may help to improve disease management by providing tailored care for each patient.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGFN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

TH-PO930

Intradialytic Aerobic Cycling Exercise Improve Inflammation Status, Endothelial Progenitor Cells and Bone Density in Patients with End Stage Renal Disease on Maintenance Hemodialysis Chia-chao Wu,¹ Kuo-cheng Lu,² ¹Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; ²Dept of Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic Univ, New Taipei City, Taiwan.

Background: Inflammation, endothelial dysfunction and mineral bone disease play critical roles of morbidities and mortalities in the hemodialysis (HD) patients. Physical exercise can improve inflammatory status and bone density reverse protein-energy wasting (PEW) and bone loss. We investigate the effects of intradialytic aerobic cycling exercise (IACE) during HD.

Methods: Forty end-stage renal disease patients undergoing HD will be randomly allocated into an exercise or control group for 3 months. The cycling session consisted of 5 minute warm-up, 20 minutes cycling at desired workload and 5 minutes cool-down during the three weekly dialysis sessions. Biochemical markers, inflammatory cytokines and nutritional status as well as serum endothelial progenitor cells (EPCs) count, bone mineral density and functional capacity were checked.

Results: There were no statistically differences in the baseline characteristics between groups. Biochemical and anthropometric parameters revealed improvement in serum albumin, body mass index and inflammatory cytokines in the exercise group. Statistically significant changes in numbers of CD133/CD34/KDR cells were observed in exercise group, whereas EPCs increased significantly during the study. The patients in exercise group showed a significantly greater 6-minute walk test than at baseline. Subjects who were able to walk faster showed greater increases in EPCs than other subjects. Bone loss at the femoral neck was significantly greater in the control group compared with the exercise group which essentially showed no change. The bone mineral density (BMD) change at the lumbar spine (L1 to L4) was not significantly different between the treatment groups.

Conclusions: In conclusion, an intradialytic aerobic cycling exercise program can decrease inflammation, increase nutritional status and bone mass index, improve 6-minute walk distance, and increase the number of EPCs in HD patients.

TH-PO931

Multicenter Trial of Aerobic Exercise in Maintenance Hemodialysis Patients Misa Miura,¹ Aki Hirayama,¹ Shigeru Owada,³ Yo Hirayama,⁴ Osamu Ito,² Masahiro Kohzaki.² ¹Dept of Health, Tsukuba Univ of Technology, Tsukuba, Ibaraki, Japan; ²Dept of Internal Medicine and Rehabilitation Science, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; ³Asao Clinic, Kawasaki, Kanagawa, Japan.

Background: Hemodialysis patients show reduced physical function and greater risk of arteriosclerosis because of hypertension, metabolic disturbances, and vascular calcification. Meanwhile, exercise training in hemodialysis patients improves fitness, physical function, quality of life, and markers of cardiovascular disease such as arterial stiffness. This study aimed to determine whether aerobic training and electrical stimulation to skeletal muscles for 12 weeks could improve physical function and dialysis efficacy in patients with end-stage renal disease (ESRD).

Methods: This was a multicenter trial. A total of 35 ESRD patients on three occasions (20 males, 15 females; age: 70.2±11.7 years) were randomized to receive 12 weeks of aerobic training exercise during hemodialysis session (Ex-group: n=19), electrical stimulation to the lower limbs (ES-group: n=6), or no specific intervention (Cont-group: n=10). The Borg

scale was used to control the intensity of training. At baseline and study completion, the primary outcome measures were grip strength, quad muscle torque, workout time, activities, dialysis efficacy, HDL, LDL, CRP, IL-6 and blood pressure.

Results: In the Ex-group, handgrip, quad torque, and workout time increased significantly ($P<0.05$). Dialysis efficacy, HDL-cholesterol, LDL-cholesterol, CRP, and blood pressure on the morning of the dialysis day also improved significantly ($P<0.05$). These effects were not observed in the Cont-group. In the ES-group, quad muscle torque and dialysis efficacy increased significantly ($P<0.05$), IL-6 decreased significantly ($P<0.05$), compared to the other two groups.

Conclusions: In this study, the safety and efficacy of training and electrical stimulation during hemodialysis were confirmed without sudden drop of blood pressure or any other side effects. Therefore, training during hemodialysis session for 12 weeks might improve physical function with specific whole-body effects as well as local effects in ESRD patients.

TH-PO932

Glycemic Markers and 2-Year Non-Diabetic Hemodialysis Outcomes from the Glycemic Indices in Dialysis Evaluation Study Mark E. Williams,¹ Neal Mittman,² Lin Ma,³ Julia I. Brennan,⁴ Curtis D. Johnson,⁴ Franklin W. Maddux,³ Eduardo K. Lacson,^{3,5} ¹Joslin Diabetes Center, Boston, MA; ²Kidney Care of Brooklyn and Queens, Brooklyn, NY; ³Fresenius Medical Care North America, Waltham, MA; ⁴Spectra Laboratories, Rockleigh, NJ; ⁵Physician, Lexington, MA.

Background: The ongoing GIDE (Glycemic Indices in Dialysis Evaluation) study includes data on nonDM hemodialysis (HD) patients (confirmed by HgbA1c <6.5%). Because nonglycemic factors may lower HgbA1c levels in ESRD, we previously reported their glycemic status/1-year outcomes using alternative glycemic markers [albumin-adjusted and unadjusted fructosamine (AlbF:F) and glycated albumin (GA) or percent GA (%GA)]. We now report 2-year study data.

Methods: 970 nonDM HD patients from 26 FMCNA facilities with glycemic markers from Jan-March 2013 were followed until April, 2015. Baseline AlbF, F, GA and %GA were used to classify patients as high or low glycemia using thresholds of AlbF \geq 974 μ mol/g, F $>$ 285 μ mol/L, %GA $>$ 15.7%, and GA $>$ 300 μ mol/L. Standard and Time-dependent (TD) Cox models with case-mix adjustment for age, sex, race, ethnicity, vintage, BMI, HD catheter and baseline comorbidity were used to determine associations between each glycemic index and hospitalization/death risk.

Results: While 1% had HgbA1c $>$ 7%, high glycemic status was more commonly detected using F (59%), AlbF (4%), GA (15%) and %GA (29%). Elevated AlbF was significantly associated with 2-year mortality [Standard Cox: Hazard Ratio (HR)=2.53, 95% CI (1.31, 4.92), $p=0.006$; TD Cox: HR=3.55, 95% CI (1.97, 6.38), $p<0.0001$] and hospitalization [TD Cox: HR=2.49, 95% CI (1.70, 3.67), $p<0.0001$]. For all other glycemic markers, no such associations were evident at the proposed thresholds using adjusted analyses in the Cox model.

Conclusions: These data support our previous findings of an association between poor glycemic status (high AlbF) and hospitalization/mortality outcomes in nonDM HD patients. High AlbF-glycemic status may have prognostic implications in nonDM HD patients.

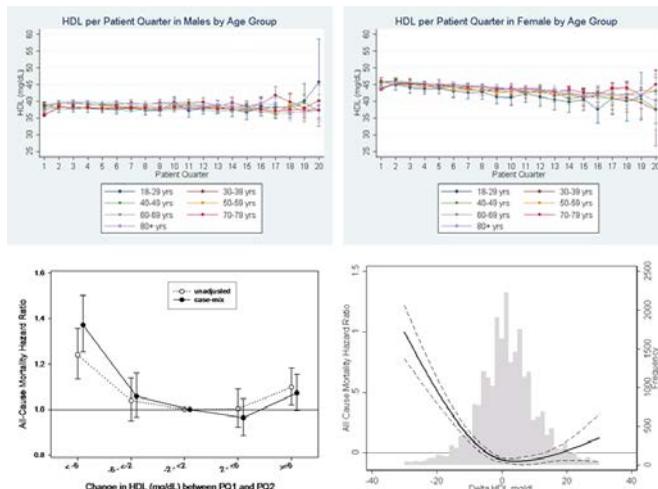
TH-PO933

Association of Change in Serum HDL Cholesterol with Mortality in Hemodialysis Patients: Role of Gender Sheila Mazdyasni,¹ Elani Streja,¹ Tae Hee Kim,¹ Connie Rhee,¹ Steven M. Brunelli,² Moti L. Kashyap,^{1,3} Nosratola D. Vaziri,¹ Kamyar Kalantar-Zadeh,¹ Hamid Moradi.^{1,3} ¹UC Irvine; ²DaVita Clin Research; ³VA Long Beach.

Background: Elevated high-density lipoprotein cholesterol (HDL) levels, though protective in the general population, can be associated with higher mortality in hemodialysis (HD) patients. Association of HDL change over time with mortality has yet to be examined. Based on previous studies, we hypothesized that upward trends in HDL levels may be associated with higher mortality risk in HD patients.

Methods: We examined HDL change over time in 24,400 incident HD patients receiving care from a large dialysis organization in 2007-2011. Association of delta HDL (HDL change between the 1st and 2nd 91 day interval from dialysis start) and HDL trajectory with all-cause mortality were examined using mixed effect and Cox regression models and adjusted for demographics, comorbidities and baseline HDL. Delta HDL was treated both as a continuous variable using restricted cubic splines and in categories: <-6 , -6 <-2 , -2 <-2 (Ref), 2 <6 , and ≥ 6 mg/dL.

Results: Patients were 65 \pm 15 years old, 44% female, 31% black, 66% diabetic with a mean baseline HDL 40.5 \pm 13.9 mg/dL and HDL change 1.7 \pm 10.4 mg/dL. While male patients had no significant change in HDL over time, females had a significant decrease in HDL (mean -0.6mg/dL/year). A ≥ 6 mg/dL increase or decrease in delta HDL was associated with a 7% and 37%, respective increase in all-cause mortality compared to reference group. Delta HDL-mortality associations did not differ across gender.



Conclusions: Decreased HDL over time was associated with worse outcomes and increased HDL was paradoxically associated with higher mortality. While HD treatment can be associated with a decrease in HDL, this effect was magnified in younger females. The novel and intriguing role of age and gender in association of HDL and survival needs further evaluation.

Funding: NIDDK Support

TH-PO934

Differences in Perceived Kidney Disease Burden on Quality of Life by Race/Ethnicity in a Diverse Cohort of Hemodialysis Patients Anna C. Porter,¹ Rani Gallardo,² Linda A. Schiffer,³ Denise M. Hynes.^{2,3,4} ¹Dept of Medicine, Div of Nephrology, Univ of Illinois Hospital and Health Sciences System, Chicago, IL; ²Dept of Medicine, Div of Academic General Internal Medicine and Geriatrics, Univ of Illinois at Chicago, Chicago, IL; ³Inst for Health Research and Policy, Univ of Illinois at Chicago, Chicago, IL; ⁴Center of Innovation for Complex Chronic Healthcare, Edward Hines Jr, VA Hospital, Hines, IL.

Background: Low health-related quality of life (HRQOL) has been well-documented in patients with end-stage renal disease on hemodialysis (ESRD). While African Americans and Hispanics remain at increased risk for ESRD, HRQOL has been less well-described in these individuals compared to non-Hispanic whites.

Methods: Baseline HRQOL data was analyzed for participants enrolled in the Patient-Centered Medical Home for Kidney Disease study (PCMH-KD), a trial of a multidisciplinary, patient-centered primary care intervention in a population of hemodialysis patients at two dialysis facilities in Chicago. The Kidney Disease Quality of Life (KDQOL-36) instrument was used to assess HRQOL at baseline, and the following subscale scores were obtained: Physical, Mental, Burden of Kidney Disease, Symptoms and Problems, and Effects of Kidney Disease.

Results: Baseline data were available for 95 patients. Approximately, 52% of patients were African-American, and 45% were Hispanic. Significant racial/ethnic differences were observed among subscales of self-reported HRQOL.

KDQOL Subscale	Mean Score for African American Participants	Mean Score for Hispanic Participants	P value
Physical	35.8	34.5	>0.05
Mental	51.4	47.1	0.040
Burden	57.4	33.6	<0.001
Symptoms/Problems	76.6	76.0	>0.05
Effects	74.9	66.8	0.048

Conclusions: Hispanic patients with ESRD on HD report disproportionate burden and effects of kidney disease on HRQOL and worse mental HRQOL compared to African American patients with ESRD on HD. Further exploration of these disparities may lead to strategies for improvement of HRQOL in Hispanic patients.

Funding: Private Foundation Support

TH-PO935

Relative Blood Volume and Mortality in Hemodialysis Patients Linda H. Ficociello,¹ Paul Balter,¹ Mark Costanzo,¹ Patrice B. Taylor,¹ Claudy Mullon,¹ Robert J. Kossmann.¹ ¹Fresenius Medical Care North America (FMCNA), Waltham, MA; ²Renal Research Inst (RRI), New York, NY.

Background: A quality improvement project on fluid management using Crit-Line® Monitors (CLM) was conducted across multiple RRI facilities. Percent change in relative blood volume (RBV) was measured during routine hemodialysis (HD). Previous analyses of the same cohort have shown associations between RBV reduction and reduced hospital admission rate; the current analysis assesses mortality.

Methods: A retrospective analysis of HD treatments with RBV measurements was conducted over 6 months. RBV was calculated using: RBV = [(Hematocrit₇₀₀/Hematocrit_{(t-1)X100}]. Average RBV at the end of HD was calculated for 1099 patients (22,579 treatments with RBV). Patient deaths were recorded as part of routine clinic procedures over the same 6 months. Mortality rate per patient month was calculated as #deaths/patient months. Time to death was modeled using Cox proportional hazards model.

Results: Patients were divided into RBV categories by 5% increments and compared on risk of death during the 6 months (Table). There was an increased risk of death with less reduction in RBV. For example, using patients with the greatest reduction in RBV (< -15%) as the reference, patients with the least reduction in RBV by the end of HD had 16 times the risk of death. Modeling time to death, there is a 15% increase risk of mortality for each 1% increase in the end of HD blood volume (p<0.0001). Similar results were obtained after controlling for age, gender, and race (11% increased risk, p=0.002).

% Relative Blood Volume	Total # Patients	Patient Months	Mortality Rate	Mortality Ratio
≤-15%	47	730	0.004	1 (Reference)
-14.9 to -10%	254	41821	0.006	1.34
-9.9 to -5%	507	80408	0.010	2.45
-4.9 to 0%	263	39098	0.017	3.96
>0%	28	3081	0.068	15.97

Conclusions: In a large cohort of HD patients with relative blood volume measured, patients with less reduction in percent change in relative blood volume at the end of dialysis had higher risk of death over 6 months when compared to patients with greater reduction. These patients may represent a subset of patients at high risk for adverse outcomes and may benefit from fluid management programs.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO936

The Effect of Altitude on Erythropoiesis-Stimulating Agent Dose, Hemoglobin Level, and Mortality in Hemodialysis Patients Scott Sibbel,¹ Donna E. Jensen,¹ John Alan Laich,¹ Sarb Shergill,² Bradley J. Maroni,² Steven M. Brunelli.¹ ¹DaVita Clinical Research, Minneapolis, MN; ²Akebia Therapeutics, Cambridge, MA.

Background: Prior studies have shown that hemodialysis (HD) patients residing at high elevations have lower erythropoiesis-stimulating agent (ESA) utilization, possibly due to activation of hypoxia-regulated genes. We sought to better understand the impact of altitude on dosing of anemia medications and mortality following 2011 changes to the US epoetin alfa label and reimbursement policy.

Methods: We studied a cohort of prevalent nonveteran HD patients (vintage >6 months) treated at a large dialysis organization between 1 Jan 2012 and 31 Dec 2012. Patients were compared across categories of altitude for longitudinal hemoglobin (Hb) level, ESA and intravenous (IV) iron dose, and mortality risk using mixed linear models. Associations were adjusted for baseline demographic and clinical characteristics.

Results: Compared to altitude of 0-1499 ft, higher altitude was incrementally associated with higher mean Hb and lower mean ESA dose; mean IV iron utilization did not differ. Altitude >4500 ft (vs 0-1499 ft) was independently associated with lower mortality risk: incidence rate ratio (IRR) was 0.74 with 95% confidence interval (CI) 0.63-0.88.

	Altitude (feet)			
	0-1499 n = 92,490	1500-2999 n = 3118	3000-4499 n = 1659	>4500 n = 2027
ESA utilization, U/treatment				
Adjusted mean difference (95% CI) ^a	0 (ref)	-324 (-361, -218)	-400 (-519, -316)	-723 (-834, -554)
IV iron utilization, mg/month				
Adjusted mean difference (95% CI) ^a	0 (ref)	-2.34 (-5.08, 0.40)	-4.62 (-8.79, -0.45)	-2.93 (-7.44, 1.59)
Hemoglobin, g/dL				
Adjusted mean difference (95% CI) ^a	0 (ref)	-0.01 (-0.04, 0.02)	0.15 (0.11, 0.20)	0.23 (0.19, 0.27)
Mortality				
Adjusted IRR (95% CI) ^a	1 (ref)	1.07 (0.95, 1.21)	1.05 (0.88, 1.24)	0.74 (0.63, 0.88)

^a CIs were generated using a bootstrapping method. Bootstrap estimates were generated with 100 replicates, using unrestricted replacement sampling. Adjustments were made for baseline age, race/ethnicity, etiology of end-stage renal disease, postdialysis weight, vintage, vascular access, Charlson comorbidity index, ferritin, Kt/V, and albumin, as well as baseline diabetes, congestive heart failures, coronary artery disease, cerebrovascular disease, cancer, and peripheral vascular disease. Percent of patients using (yes/no) IV iron and ESA were 10% and 13.9% lower, respectively, in the >4500ft vs. 0-1499 ft groups.

Conclusions: Among contemporary HD patients receiving treatment at altitude >1500 ft, higher altitude was independently associated with greater Hb level despite lower ESA doses and comparable IV iron utilization. Altitude of >4500 ft was independently associated with a 26% lower mortality risk.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

TH-PO937

Achieved Iron Stores and Clinical Efficacy in a Trial of Ferric Citrate as a Phosphate Binder Kausik Umanath,¹ Molly Mcfadden,² Diana I. Jalal,³ Yoram Yagil,⁴ Erwin Antonio Aguilar,⁵ Anas Abou-Ismael,⁶ Mohammed Sika,⁶ Robert M. Niecestro,⁷ Mark Koury,⁶ Julia Lewis,⁶ Tom Greene,² Barbara A. Greco,⁸ Stephen Z. Fadem,⁹ Jamie P. Dwyer,⁶ The Collaborative study group.⁷ ¹Henry Ford Hosp; ²U of Utah; ³U of CO; ⁴Ben-Gurion U; ⁵LSU; ⁶Vanderbilt; ⁷CSG; ⁸Baystate Med Ctr; ⁹Baylor College of Med.

Background: Adequate Fe stores are needed for hematopoiesis in ESRD pts on ESA, but optimal Fe stores assuring efficacy/safety are unknown. PO Fe preparations have been unable to do this. In a Ph3 RCT we showed ferric citrate (FC) as a Phos binder ↑Fe stores and ↓IV iron/ESA use. We studied IV iron/ESA use in the trial based on achieved Fe stores.

Methods: 441 pts randomized 2:1 to FC or non-Fe-containing active control (AC) were followed for 52 wks. IV iron use was at a site's discretion while ferritin 1000ng/mL and TSAT ≥30%. Generalized estimating equations related ↑IV Iron/ESA dose to trailing 4-mo means of ferritin/TSAT to IV iron by randomized group, adjusting for age, sex, black race, CHF and DKD, giving odds ratios (OR) for ESA use >75th %ile (10,611 Units/wk) or IV iron use >median for visits with nonzero dose (47.7 mg/wk) to compare middle and highest TSAT/ferritin tertiles to lowest.

Results: 398 subjects for ESA, 409 pts for IV iron were analyzable. In AC, ORs for ↑ESA dose were 0.63 (0.42-0.95, p=0.03) for middle TSAT, 0.53 (0.31-0.93, p=0.03) for highest TSAT tertile. FC group was similar, Table 1. Ferritin did not predict ESA dose. In AC, ORs for ↑IV iron dose were 0.51 (0.34-0.78) for middle TSAT, 0.39 (0.20-0.76) for highest TSAT tertile; FC was similar, Table 2. ferritin trended to ↓IV iron use, Table 2.

Table 1. Ability of TSAT and ferritin at higher tertiles to predict ESA usage >75th percentile. TSAT 1-28, ferritin 11-529 are reference groups. AC: active control; FC: ferric citrate

TSAT (%)	AC	28-37	OR (95% CI)	p
		37-83	0.53 (0.31-0.93)	0.03
FC	28-37	0.68 (0.48-0.97)	0.03	
	37-83	0.62 (0.40-0.95)	0.03	
Ferritin (ng/mL)	AC	529-825	1.45 (0.84-2.52)	0.18
		825-3212	1.50 (0.79-2.84)	0.22
	FC	529-825	0.92 (0.58-1.48)	0.74
		825-3212	0.90 (0.53-1.54)	0.70

Table 2. Ability of TSAT and ferritin at higher tertiles to predict IV iron use > median use for visits with non-zero dose. TSAT 1-28, Ferritin 11-529 are reference groups. AC: active control; FC: ferric citrate

TSAT (%)	AC	28-37	OR (95% CI)	p
		37-83	0.39 (0.20-0.76)	0.006
FC	28-37	0.51 (0.35-0.74)	0.0004	
	37-83	0.22 (0.13-0.38)	<0.0001	
Ferritin (ng/mL)	AC	529-825	0.71 (0.43-1.17)	0.18
		825-3212	0.49 (0.27-0.90)	0.02
	FC	529-825	1.01 (0.68-1.51)	0.96
		825-3212	0.67 (0.38-1.18)	0.17

Conclusions: TSAT predicted ↓IV Iron/ESA, TSAT>37% showing lowest use. In these ranges no TSAT limit existed over which further ↓IV Iron/ESA did not occur. ferritin levels predicted ↓IV Iron, not ↓ESA use. TSAT may better predict ESA responsiveness in ESRD.

Funding: Other U.S. Government Support, Pharmaceutical Company Support - Keryx Biopharmaceuticals, Inc.

TH-PO938

Sotatercept Improves Anemia, Vascular Calcification, and Bone Loss in Patients with End-Stage Kidney Disease on Hemodialysis John Havill,¹ Nelson P. Kopyt,² Daniel W. Coyne,³ Michael Weiswasser,⁴ William T. Smith.⁴ ¹Kidney Specialists of Southern Nevada, Las Vegas, NV; ²Lehigh Valley Health Network, Allentown, PA; ³Washington Univ, St. Louis, MO; ⁴Celgene Corporation, Warren, NJ.

Background: This ongoing, randomized, single-blind, placebo (PBO)-controlled study evaluated the pharmacokinetic (PK), safety, and hemoglobin (Hb) effect of sotatercept, an ActRIIA-IgG1 fusion protein ligand trap, in hemodialysis (HD) subjects and explored its effects on vascular calcification (VC) and bone mineral density (BMD) using quantitative computed tomography (QCT).

Methods: Subjects were washed out of erythropoietin-stimulating agent (ESA) effects until Hb was <10 g/dL and randomized to PBO or sotatercept given subcutaneously every 28 days for up to 8 dose cycles. Treatment failures (Hb <9 g/dL) were rescued with ESA or transfusion; intrasubject dose escalation was not permitted. QCT scans of the hip, lumbar spine, and abdominal aorta were obtained at baseline and after the 225-day treatment phase. Interim results are reported for PK, safety, home BP, Hb, VC, and BMD effects in the 0.3, 0.5, and 0.7 mg/kg dose groups.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Results: Among subjects treated with PBO (n=9) or sotatercept 0.3 mg/kg (n=9), 0.5 mg/kg (n=8), and 0.7 mg/kg (n=9), adverse events were mostly mild/moderate, unrelated to study drug, relatively similar in type/severity between groups, and generally consistent with subject medical histories. Two deaths occurred in the PBO group. There were no dose-dependent changes in home BP. In the 225-day treatment phase, Hb was >10 g/dL in 33%, 33%, 63%, and 78% of subjects treated with PBO or sotatercept 0.3, 0.5, or 0.7 mg/kg, respectively. Paired QCTs obtained in 4, 6, 5, and 6 subjects treated with PBO or sotatercept 0.3, 0.5, or 0.7 mg/kg showed <15% progression of VC in 33%, 80%, 80%, and 100%, and >2% increase in femoral neck cortical BMD in 0%, 20%, 40%, and 75%, respectively.

Conclusions: Sotatercept appears to be well tolerated with an acceptable safety profile in HD, without increases in home BP. There are beneficial dose-related responses to sotatercept in Hb, VC, and BMD. A larger dataset, with an ongoing 14-day dose group, will further substantiate these results.

Funding: Pharmaceutical Company Support - Study was sponsored by Celgene Corporation.

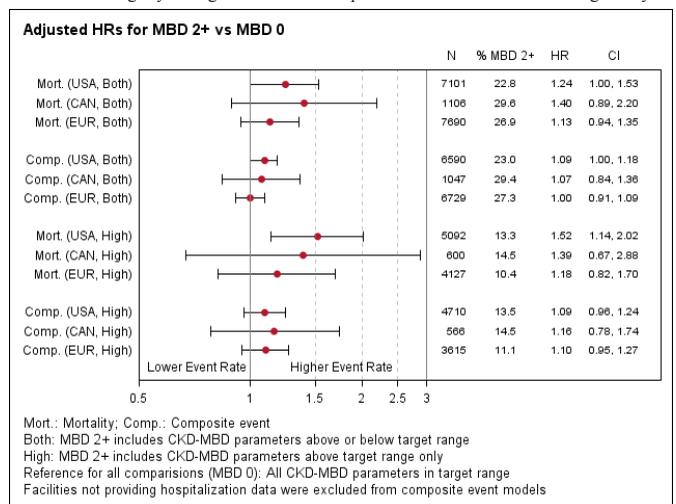
TH-PO939

Impact of CKD-MBD Composite Score on Mortality and Hospitalization: Dialysis Outcomes and Practice Patterns Study (DOPPS) Douglas S. Fuller,¹ Paul Druzynski,² Kerry Cooper,² Brian D. Bradbury,² Mark D. Danese,³ Bruce M. Robinson,^{1,4} Francesca Tentori,^{1,5} *Arbor Research Collaborative for Health, Ann Arbor, MI;* ²Amgen, Thousand Oaks, CA; ³Outcomes Insights, Inc., Westlake Village, CA; ⁴Univ of Michigan, Ann Arbor, MI; ⁵Vanderbilt Univ, Nashville, TN.

Background: The biochemistries associated with chronic kidney disease-mineral and bone disorder (CKD-MBD), parathyroid hormone (PTH), calcium (Ca), and phosphorus (P), are physiologically interrelated. We evaluated the impact of combinations of CKD-MBD parameters outside target ranges in HD patients (pts).

Methods: We identified DOPPS 3-5 (2005-2014) pts in the US, Canada, and Europe (France, Germany, Italy, Spain, Sweden, and the UK) with >12 mos of follow-up. We assessed demographic and clinical covariates in study mos 9-12 and used Cox models to generate disease risk scores (DRS) by region based on pts with CKD-MBD parameters in target (MBD 0; P 3.5-5.5 mg/dL, Ca 8.4-10.2 mg/dL, PTH 150-600 pg/mL) and to compare event rates, adjusted for DRS, of mortality and a composite of death or hospitalization between MBD 0 and pts with 2-3 values outside target (MBD 2+).

Results: MBD 2+ prevalence, primarily due to high PTH and P, was 22.8%, 29.5%, and 26.9% in the US, Canada, and Europe, respectively. PTH above target was higher in the US (52%) compared to Canada (42%) and Europe (28%). Compared to MBD 0, MBD 2+ was associated with moderately higher mortality in the US and Canada but not Europe; MBD 2+ was weakly associated with higher composite rates in all three regions. We observed slightly stronger associations in pts with 2+ MBD labs above target only.



Conclusions: Distributions of CKD-MBD parameters varied by region, perhaps resulting in differential risk of adverse outcomes. Our findings in this international cohort highlight the importance of simultaneous, rather than independent, control of MBD parameters within clinical guidelines ranges.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGfN, Shire, WiNe Institute, Societa' Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

TH-PO940

US DOPPS Practice Monitor: Comparisons with CMS ESRD Databases Douglas S. Fuller, Lindsay Zepel, Keith McCullough, Brian Bieber, Ronald L. Pisoni, Francesca Tentori, Bruce M. Robinson. *Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: Since August 2010, the Dialysis Outcomes and Practice Patterns Practice Monitor (DPM; www.dopps.org/DPM) has leveraged its US hemodialysis (HD) sample (now >200 facilities) to provide timely and detailed (>750 data tables) updates on national trends in HD care. Here we compare DPM estimates to available results from end-stage renal disease (ESRD) data sources collected by the Centers for Medicare and Medicaid Services (CMS).

Methods: Pearson correlations (r) were used to compare contemporary trends since Aug 2010 between DPM and the 2014 US Renal Data System Annual Data Report (ADR, through Dec 2012) and the Nov 2014 CMS Claims-Based Monitoring Project (CBMP, through Jun 2014). We also compared monthly DPM estimates with cross-sectional estimates from 2014 CrownWEB (CW; Dec 2013).

Results: DPM trends in ESA use and dose, IV iron use, and hemoglobin levels were highly correlated (r's: 0.89-0.98) with ADR and CBMP trends. Compared to CW, DPM showed slightly higher fistula use, but slightly lower percent of patients with adequate Kt/V and URR values.

Table: Comparisons of US DPM national estimates to CMS ESRD data sources

	Reference Estimate	DPM Estimate (SE)	Pearson r
Reference data: USRDS 2014 ADR			
Epoetin dose (u/wk, Dec 2012)	10,490	10,550 (422)	0.96
IV iron use (% , Dec 2012)	61.4%	69.8% (1.9)	0.91
Mean Hb* (g/dl, Dec 2012)	10.6	10.74 (0.04)	0.98
Reference data: CW 2014			
Fistula use (% , Dec 2013)	64.8%	67.5% (1.4)	--
Catheter use (% , Dec 2013)	16.1%	12.6% (0.8)	--
Kt/V ≥1.2 (% , Dec 2013)	97.0%	94% (0.8)	--
URR ≥65% (% , Dec 2013)	96.0%	94% (0.8)	--
Reference data: CBMP Nov 2014			
ESA use (% , Jun 2014)	80.7%	85.6% (1.2)	0.89
Median Hb* (g/dl, Jun 2014)	10.5	10.68 (0.03)	0.96

Abbreviations: DPM, Dialysis Outcomes and Practice Patterns Study Practice Monitor; CMS, Centers for Medicare and Medicaid Services; USRDS, US Renal Data System; ADR, USRDS Annual Data Report; CW, CrownWEB; CBMP, CMS ESRD Claims-based Monitoring Project; Hb, hemoglobin; URR, urea reduction ratio; ESA, erythropoiesis-stimulating agent
*Among ESA-treated patients

Conclusions: DPM reports IV medications use as prescription at the end of the month (before Apr 2012) or anytime during the month (Apr 2012 and after), rather than administration. Thus, estimates for ESA and IV iron utilization each month may be somewhat different due to spontaneous or withheld dosing. Differences with CW cross-sectional estimates may result from differences in calculation methods. DPM includes non-Medicare patients that are not necessarily present in claims-based sources. DPM now includes >4 years of monthly estimates for indicators of US HD care. Although differences in data sources and specifications may influence direct comparisons, DPM data remain an important resource for identifying important trends in HD care before confirmations from CMS ESRD databases are available.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGfN, Shire, WiNe Institute, Societa' Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

TH-PO941

Reduced Free Triiodothyronine Is an Independent Predictor of Clinical Outcomes in Hemodialysis Patients with Low Albuminemia Akihiko Kato,¹ Masafumi Ono,¹ Takayuki Tsuji,² Naro Ohashi,² Hideo Yasuda,² *¹Blood Purification Unit, Hamamatsu Univ Hospital, Hamamatsu, Shizuoka, Japan;* *²Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.*

Background: Low free triiodothyronine (fT3) and free thyroxine (fT4) are both related to malnutrition, inflammation and mortality in dialysis patients. Upper-normal thyrotropin (TSH) levels are also associated with a higher risk of total mortality in hemodialysis (HD) patients. However, it remains unclear which of thyroid-related hormones is most useful in predicting clinical outcomes. So, we aimed this study to compare the prognostic value of different hormones in prevalent HD patients.

Methods: We enrolled 339 HD patients (age: 64±13 years old, time on HD: 129±114 months), and measured basal fT3, fT4 and TSH. We then followed the patients for the next 42 months, and assessed the impact of fT3, fT4 and TSH on all-cause mortality and cardiovascular (CV) events or hospitalization. Patients were divided into the 4 groups based on the quartiles of fT4, fT4 and TSH. The associations of basal levels with clinical outcomes were examined with Cox proportional hazards models adjusted for demographic and classical factors and comorbidities.

Results: Mean serum fT3 and fT4 were 2.01±0.37 [0.95-3.73] pg/mL and 0.86±0.20 [0.35-1.67] ng/dL. Serum levels of fT3 and fT4 were lower than those of reference ranges in 85.0% and 56.0% of the patients, respectively. In contrast, TSH levels were within the reference range in most patients (92.9%). Cox hazards analyses revealed that the lowest quartile of fT3 (<1.75 pg/mL) was an independent predictor of all-cause mortality (HR 3.55 [95%CI: 1.17-4.09, p<0.01]), all-cause mortality plus CV events (HR 2.19 [95%CI: 1.53-8.23, p=0.01]), and all-cause mortality plus hospitalization (HR 2.16 [95%CI: 1.28-3.67, p<0.01]) when compared with those with the top quartile (fT3>0.98 pg/mL). However, the significant impact of low fT3 on prognosis was observed only in patients with serum albumin lower than 3.8 g/dL (n=195). In contrast, serum fT4 and TSH levels did not relate to prognosis.

Conclusions: These findings suggest that low fT3 became an independent predictor of clinical outcomes in HD patients with low albuminemia.

TH-PO942

Low Socioeconomic Status and Co-Morbidity Are Associated with Limited Health Literacy in RRT Patients – Results from the ATTOM Study
 Dominic Taylor, The ATTOM investigators. *Southmead Hospital, Bristol, United Kingdom.*

Background: Limited health literacy(LHL) is a risk factor for poor outcomes in chronic disease patients. Studies with limited patient numbers in RRT patients associate LHL with low socioeconomic status(SES), comorbidity and ethnicity.

Methods: This cross-sectional study used baseline data from the ‘Access to Transplantation and Transplant Outcome Measures’(ATTOM) cohort. ATTOM recruited incident dialysis and transplant patients aged 18-75 years in the UK during 2011-2013 and also wait-listed patients similar to those transplanted(matched controls). Health literacy was measured by the question ‘How often do you need someone’s help to read instructions, leaflets, or other written material from your doctor or pharmacy?’ answered on a scale from 1-Never to 5-Always. LHL was defined as a score greater than 2. The three groups were analysed for associations between LHL and demographics, SES factors and comorbidity, using univariate and multivariate analysis, p<0.05.

Results: 6842 patients were recruited: 2621 incident dialysis (ID), 2262 incident transplant (IT) and 1959 matched controls (MC). 6373/6842(93%) completed the health literacy assessment. Prevalence of LHL was 20% in the ID, 12% in the IT and 15% in the MC group. In univariate analyses, in all groups, English not as first language, Asian ethnicity, low educational level, unemployment, absence of car or home ownership, increased comorbidity by modified Charlson index and mental illness were associated with LHL. In adjusted models, in all groups, the following factors were associated with LHL: English not as first language(OR>3), modified Charlson index (OR 1.2 for each point above zero), low level of education (OR>2 for no qualifications compared to any), unemployment (OR>3.0 compared to employed) and absence of car ownership (OR 1.7). Age and sex were not associated with LHL after adjustment.

Conclusions: In this large nationwide study, low SES and co-morbidity are associated with LHL in patients receiving dialysis or at the point of transplantation, independent of first language. LHL may impact upon patients’ ability to engage with shared decision making and their capacity to cope with the burden of disease and treatment.

Funding: Other NIH Support - NIHR(UK)

TH-PO943

Comparing Dialysis Facility Compare (DFC) Star Rating to QIP Payment Categories
 Claudia Dahlerus,¹ Christopher J. Harvey,¹ Joseph M. Messina,¹ Richard Hirth,¹ Cindy Liao,¹ Natalie Scholz,¹ Tempie H. Shearon,¹ Zezhi (zac) Zhang,¹ K. A. Wisniewski,¹ Casey Parrotte,¹ Ji Zhu,¹ Elena K. Balovlenkov,² Joel S. Andress,² Yi Li.¹ ¹*Biostatistics, Kidney Epidemiology and Cost Center, Univ of Michigan, Ann Arbor, MI;* ²*Centers for Medicare and Medicaid Services.*

Background: CMS star ratings summarize DFC quality measures, giving each facility 1 to 5 stars to help consumers compare facilities. The ESRD QIP, a value based purchasing program, applies performance-based payment reductions. We describe differences between the star rating and QIP payment reduction categories and how each distinguishes average facility performance.

Methods: We obtained the fixed percentile star rating (5-Star 10%, 4-Star 20% 3-Star 40%, 2-Star 20%, 1-Star 10%) and QIP payment reduction for each facility from the Jan 2015 DFC file. We calculated star rating mean final scores (MFS) for each tier and used t-tests to assess differences between adjacent tiers.

Results: Differences in MFS between adjacent star rating tiers are similar (~9 pts, p<.0001) (Table 1). In the QIP system, the difference between payment reduction tiers 0.5% to 2% is small (~1 to 3 pts) and not statistically significant and the difference between the 0.5% and 0% categories is ~15 pts, p<.0001.

Star Rating	Facility N(%)	MFS (SD)	QIP Payment Reduction	Facility N(%)	MFS (SD)
1	563(10)	31.8 (0.2)	2.0%	37(0.6)	33.3 (2.1)
2	1127(20)	41.4* (0.1)	1.5%	23(0.4)	34.0 (1.6)
3	2255(40)	50.2* (0.1)	1.0%	41(0.7)	36.9 (1.4)
4	1127(20)	58.7* (0.1)	0.5%	242(3.9)	36.3 (0.6)
5	563(10)	67.7* (0.2)	0%	5795(94.4)	50.9* (0.1)

* p<.0001 vs. previous tier

Conclusions: Differences in MFS between adjacent DFC star tiers were larger and potentially clinically meaningful. QIP categories primarily distinguish between the top tier (0% reduction) and all lower tiers (.5% to 2% reduction). Programs evaluating facility performance have different goals, and methods for categorizing quality are informed by these goals. Further research and debate will help inform what is optimal.

Funding: Other U.S. Government Support

TH-PO944

Association of Socioeconomic Characteristics with Readmission Among Dialysis Patients
 Claudia Dahlerus,¹ John Wheeler,¹ Deanna Chyn,¹ Yanming Li,¹ Richard Hirth,¹ John Kalbfleisch,¹ Jennifer Sardone,¹ Zhi He,¹ Tempie H. Shearon,¹ Joel S. Andress,² Elena K. Balovlenkov,² Yi Li.¹ ¹*UM Kidney Epidemiology & Cost Center;* ²*Centers for Medicare & Medicaid Services.*

Background: CMS recently developed hospital readmissions measures to reflect quality of care provided by nursing homes, long-term care hospitals, inpatient rehabilitation facilities, home health agencies and dialysis facilities. The intent is to encourage care coordination as patients transition between care providers. All measures adjust for patient characteristics. CMS has not adjusted quality measures for patient socioeconomic status (SES), so as not to condone disparities in care delivery. However, not including such adjustments may result in inappropriate assessments about quality of care. We present preliminary analyses assessing the association of SES and readmission among dialysis patients.

Methods: Using 2013 Medicare claims data, we model the probability of readmission, defined as an unplanned readmission within 30 days of a hospital discharge, adjusted for patient characteristics including age, sex, BMI, comorbidities, discharging hospital, and several measures of SES, plus measures reflecting SES of the patient’s area of residence.

Results: Patients with Medicare secondary payer (MSP) were less likely to experience a readmission (OR 0.92; CI 0.90-0.93); patients with dual Medicare and Medicaid coverage (OR 1.08; CI 1.08-1.09), unemployed at ESRD incidence (OR 1.07; CI 1.06-1.08) and living in ZIP codes with high unemployment, low education and income disparity were more likely to experience a readmission.

Conclusions: Insurance status and area of residence are strong proxies for SES and are associated with readmissions. MSP, largely reflective of private insurance coverage, can be an indicator of higher SES and perhaps better health. Dual eligibility for Medicare and Medicaid can be an indicator of lower SES, as can being unemployed at ESRD incidence. As interest in risk adjusting for indicators of SES has grown, the association between SES and readmission suggests further analysis may be appropriate. However, caution must be exercised in efforts to distinguish between SES factors that may or may not be related to quality of care.

Funding: Other U.S. Government Support

TH-PO945

Co-Morbidities (CM) Do Not Predict Adverse Outcomes in Peritoneal Dialysis (PD) versus Hemodialysis (HD) in a Multi-Ethnic Asian ESRD Cohort
 Gekhsiang Lim,¹ Khuan yew Chow,¹ Vathsala Anantharaman.² ¹*Health Promotion Board, Singapore;* ²*National Univ Health System.*

Background: There is conflicting data on outcomes following HD vs PD. USRDS data for ESRD in 2002-2004 suggested similar outcomes for HD and PD over 5 years of followup. This study evaluated outcomes for HD vs PD from a multi ethnic Asian ESRD population and evaluated the impact of CM on worse outcomes in either modality.

Methods: 3279 HD and 1330 PD patients who were included in the Singapore Renal Registry(SRR) in 2001-2007 and followed up till death or 31 Dec 2012 comprised the study population. Data on patients’ demographics, CM and survival were collected. Patients were stratified by age, presence of diabetes(DM) and occurrence of 1 or more vascular(V) vs non-vascular(NV) CM. 5-year survival was compared using Kaplan-Meier and regression analyses.

CM	Age	No.	Median Survival (Yrs) [^]		HR(95% CI)
			PD	HD	
0	All	999	-	-	1.3(0.9-1.6)
Non-DM	<65	1217	11.0	-	1.1(0.9-1.4)
Non-DM+No CM	<65	810	-	-	1.0(0.7-1.4)
Non-DM+V		286	7.8	9.1	1.1(0.8-1.6)
Non-DM+NV		121	7.9	-	1.1(0.5-2.6)
Non-DM		496	3.4	4.9	1.5(1.2-1.9)
Non-DM+No CM	≥65	189	3.8	6.7	2.1(1.4-3.1)
Non-DM+V		265	3.3	3.9	1.3(1.0-1.8)
Non-DM+NV		42	7.2	3.6	0.6(0.2-1.9)
DM		1838	3.2	5.6	1.8(1.6-2.0)
DM+No CM	<65	545	4.8	6.8	1.7(1.3-2.1)
DM+V		1212	2.9	4.9	1.8(1.5-2.0)
DM+NV		81	3.8	7.2	2.1(1.1-2.3)
DM	>65	1058	2.2	3.3	1.7(1.5-2.0)
DM+No CM		224	2.4	4.3	1.7(1.2-2.3)
DM+V		802	2.2	3.0	1.7(1.4-2.0)
DM+NV		32	-	4.1	0.5(0.1-3.8)

[^] -: Not reached

Results: Overall, survival was comparable for HD vs PD for ESRD patients with no CM(HR:1.3;95% CI:0.9-1.6). Likewise, for non-DM patients <65 years, neither V nor NV CM impacted on outcomes for PD vs HD. However, DM had worse survival on PD regardless of age or presence of V vs NV CM.

Conclusions: Median life expectancy for HD is superior in this Asian population relative to USRDS (SRR vs USRDS: 73.5 vs 38.4 months for HD; 42.8 vs 36.6 months for PD) Of note, outcomes for young, non-DM ESRD patients was comparable between HD and PD. CM did not confer additional risk for adverse outcomes for PD in any subgroup.

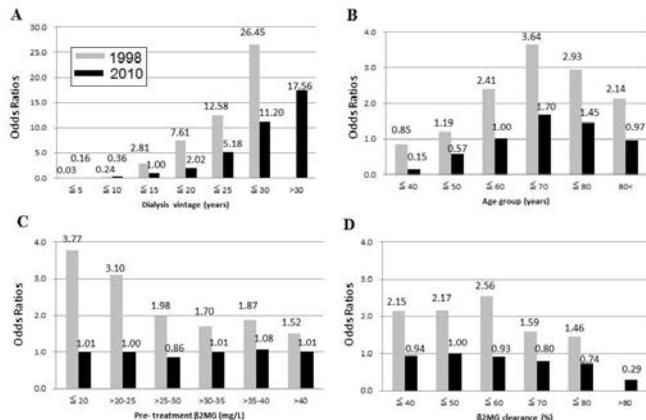
TH-PO946

Significance of the Decreased Risk of Dialysis-Related Amyloidosis Now Proven by Results from Japanese Nationwide Surveys in 1998 and 2010 Junichi Hoshino,^{1,2} Kunihiro Yamagata,² Shinichi Nishi,³ Kunitoshi Iseki,² Ikuto Masakane.² ¹Nephrology Center, Toranomon Hospital, Tokyo, Japan; ²Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan; ³Div of Nephrology, Kobe Univ, Kobe, Japan.

Background: Although dialysis technology greatly improved in recent years, it remained unclear whether those improvements helped decrease the incidence of dialysis-related amyloidosis (DRA). Accordingly, we retrospectively compared the incidence of first-time carpal tunnel surgery (CTS)—as proxy for DRA onset—in two cohorts of hemodialysis patients, the second cohort studied after dialysis methods (especially dialysate quality) had greatly improved.

Methods: We used the 1998 and 2010 Japan Renal Data Registries to compare crude risk of first-time CTS the following year. After adjusting for patient background and laboratory data, odds ratios (ORs) for CTS in the whole cohorts and the populations matched by propensity score for hemodialysis and hemodiafiltration were calculated.

Results: 202,726 patients were analyzed. In the 1998 cohort, 1.77% experienced first-time CTS compared with 1.30% of the 2010 cohort (p<0.001); with 2010 as referent, the adjusted 1998 OR was 2.22 (1.68-2.95). Both crude risks and adjusted ORs were analyzed by dialysis vintage, age, pre-dialysis b2-microglobulin (b2m) and b2m clearance, risk of CTS trending 1.5-2.0 higher in 1998 than 2010.



Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

The reduction was most prominent in patients with longer dialysis vintage, patients who were younger, and those with lower pre-dialysis b2m levels. Similar results were obtained by propensity score-matched analysis. We also found that b2m clearance >80% may reduce risk of CTS.

Conclusions: The incidence of first-time CTS as proxy for DRA decreased significantly from 1998 to 2010. Several factors may have contributed to this decrease, including improved dialysis methods.

TH-PO947

Twice Weekly Hemodialysis and Clinical Outcomes in the China DOPPS Yucheng Yan,¹ Mia Wang,² Jia Qi Qian,¹ Brian Bieber,² Mei Wang,¹ Nan Chen,³ Bruce M. Robinson,² Shuchi Anand.⁴ ¹Shanghai Renji Hospital; ²Arbor Research; ³Shanghai Ruijin Hospital; ⁴Stanford Univ.

Background: Outcomes related to 2 times weekly hemodialysis (HD), substantially practiced in China, remain understudied. Small, single-center studies have indicated better preservation of residual kidney function (RKF) and similar survival for 2 vs. 3 times weekly HD. We used data from the China Dialysis Outcomes Practice Patterns study (DOPPS) to evaluate survival and hospitalizations by frequency of HD.

Methods: We studied 1433 patients from 45 HD units in China (2012-2015). Cox regression was used to model the association of 2 vs. 3 times weekly HD with clinical outcomes adjusting for patient and treatment characteristics.

Results: 270 patients (19%) were undergoing 2 times weekly HD in China. Compared with 3 times weekly HD, patients on 2 times weekly HD were more likely to be female and have shorter time on dialysis (4.3 vs. 2.6 yrs), more urine output, shorter dialysis session length (238 vs. 250 min) and longer travel times to facility. They were less likely to have diabetes or cardiovascular disease. Insurance coverage was similar in the two groups. During follow-up (median=1.7 years), 184 (13%) deaths and 516 (38%) hospitalizations occurred. No differences in mortality or hospitalization were found between the two frequency groups (Table). No interaction was observed with vintage (p=0.43).

Table: Progressive adjustment of mortality with twice weekly dialysis, in China

2 times weekly (vs 3 times weekly)	HR (95% CI)	p
model 1: unadjusted	0.90(0.61-1.33)	0.61
model 2: model 1+patient demographics ^a	0.95(0.63-1.42)	0.79
model 3: model 2+residual kidney function	0.99(0.66-1.50)	0.97
model 4: model 3+insurance	0.98(0.66-1.44)	0.90
model 5: model 4+comorbidities	1.08(0.72-1.61)	0.72
model 6: model 5+ktv, average intra-dialytic weight loss	1.00(0.59-1.69)	0.99
model 7: model 6+labs (hgb, albumin)	1.06(0.61-1.85)	0.84

^a1393 patients, 184 events.

^bage, gender, BMI, standardized, and vintage.

Conclusions: In this multi-center study with well-characterized patient and treatment data, outcomes of 2 vs. 3 times weekly HD were similar. Thus, it is possible that among carefully selected patients 2 times weekly HD may provide acceptable outcomes. An additional study is also need due to residual confounding, small sample size, and the changes in results with progressive adjustments.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGFN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

TH-PO948

Initiation of a Chronic Kidney Disease Case Manager Program Is Associated with Better Outcomes in Incident Hemodialysis Patients Joseph A. Kuhn, Patrick Bridge, John W. Larkin, Hao Han, Sheetal Chaudhuri, Len A. Usvyat, Terry Ketchersid, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: The Renal Care Coordinator (RCC) Program places chronic kidney disease (CKD) case managers in the Nephrology Practice to co-manage late stage CKD (4 and 5) patients for an optimal outpatient start to Renal Replacement Therapy (RRT). This program is performed through both physical and virtual RCCs. We compared outcomes in patients starting hemodialysis (HD) who were previously enrolled in the RCC program to CKD patients cared for in the Nephrology practice, but were not in the RCC program.

Methods: All CKD 5 patients who transitioned to end stage renal disease (ESRD) requiring RRT between 1/1/2012 and 10/1/2014 at the nephrology practices that adopted the RCC were analyzed. We compared outcomes in patients enrolled into the RCC program versus patients considered to have a "Timely Referral" for dialysis (i.e. were followed in a

nephrology practice for >4 months before starting RRT), but received no RCC interaction. The access type, albumin (Alb), and hemoglobin (Hgb) was collected at the first outpatient HD treatment. We also computed the rates of hospital days and mortality in the first 120 days of HD.

Results: 1,404 CKD 5 patients were identified for the analysis, where 51% of the population was enrolled in the RCC. Patients in the RCC had a lower % of catheters, higher % of Alb ≥ 4.0 g/dL, and higher % of Hgb 10-11g/dL at the first HD treatment compared to patients with a "Timely Referral", but no RCC care. During a 120 day follow up after initiating HD, patients in the RCC program had significantly lower hospitalization rates.

Patient group	Number of patients	120 Day hospital admissions (ppy)	120 Day hospital days (ppy)	Catheters at start of HD	Hgb 10-11 at start of HD	Alb ≥ 4.0 at start of HD
TIMELY, Non-RCC	685	1.9	13.7	52.2%	26.9%	21.5%
TIMELY, RCC	719	1.5*	9.3*	31.5%*	30.9%*	27.8%*

P<0.05 (*)

Conclusions: This analysis demonstrates that placement of CKD case managers is associated with better outcomes, including anemia, access type, nutritional status and hospitalizations in the first 120 days of HD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO949

Extracellular Overhydration Measured by Multifrequency Bioelectrical Analysis Is Associated with Increased Postdialysis Systolic Blood Pressure in Hemodialysis Patients Hae Yeul Park,¹ Seok-hyung Kim,¹ Ah Ran Choi,¹ Jung eun Lee,² Hyung Jong Kim,³ Hoon Young Choi,¹ Sung-Kyu Ha,¹ Hyeong cheon Park.¹ ¹Nephrology, Gangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea; ²Nephrology, Yongin Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea; ³Nephrology, Bundang CHA Hospital, Pochon CHA Univ College of Medicine, Seoul, Korea.

Background: Postdialytic hypertension is associated with increased morbidity and mortality for hemodialysis (HD) patients. Recent studies suggest that increased postdialysis extracellular volume may account for the rise in postdialysis systolic blood pressure (PDSBP). The aim of this study was to assess the relationship between volume status and PDSBP in HD patients.

Methods: Volume status assessments were performed after mid-week HD using multifrequency bioelectrical impedance (BIA, Inbody S10) in supine position. Demographic and routine biochemical data were collected and pre- and post-dialysis B-type natriuretic peptide (BNP) level was measured (Triage BNP test, Alere).

Results: We enrolled clinically stable 99 HD patients from 3 dialysis centers. Patients were divided into 3 groups based on a fall in SBP of 20mmHg or more (Hypotensive, 24.2%), an increased SBP of 10mmHg or more (Hypertensive, 32.3%), and a stable group (43.4%). The mean age was 55.1 \pm 13.3 years in hypotensive, 58.3 \pm 11.6 years in stable, and 65.2 \pm 7.2 years in hypertensive group. Postdialysis BNP was 267.8 \pm 251.1 pg/mL in hypotensive, 669.8 \pm 915.9 pg/mL in stable, 1124.2 \pm 1197.8 pg/mL in hypertensive group. There were no differences in gender, dialysis prescriptions, and subjective global assessment score among the patient groups. The ECW/TBW ratio was significantly higher in the hypertensive group and positively correlated with PDSBP and delta SBP. The only independent risk factor affecting PDSBP was ECW/TBW ratio after dialysis.

Conclusions: HD patients who demonstrate increase in PDSBP should have their volume status reassessed and target dry weights adjusted using BIA, with emphasis on increased the ECW/TBW ratio.

TH-PO950

Novel Phosphate Binder, Ferric Citrate Hydrate, Can Reduce Serum Phosphate Levels and Doses of Erythropoiesis Stimulating Agents in Japanese Patients on Hemodialysis Hirotake Kasuga,¹ Ryo Takahashi,¹ Keiko Kimura,¹ Chieko Matsubara,¹ Hitomi Tanimoto,¹ Mari Maseki,¹ Yasuhiko Ito.² ¹Nephrology, Nagoya Kyoritsu Hospital, Nagoya, Japan; ²Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: Ferric citrate hydrate (FC) has been available in Japan as a phosphate binder for patients on dialysis (HD) since 2014 although its effects have not been evaluated in detail in such patients. The present study aimed to determine the effects of FC on serum phosphate levels and anemia control in patients on HD.

Methods: Thirty-eight outpatients (mean age, 62.5 y; male, n = 28 [73.7%]; mean HD vintage, 7.2 y; hypertension, n = 29 [76.3%]; diabetes, n = 19 [50.0%]; secondary hyperparathyroidism, n = 15 [39.5%]) on maintenance HD were treated with FC for six months to control hyperphosphatemia. Serum concentrations of phosphate, calcium, hemoglobin, and ferritin levels, transferrin saturation (TSAT), and weekly epoetin (EPO) doses were evaluated.

Results: Mean phosphate levels were significantly decreased from 7.05 \pm 1.11 to 6.19 \pm 0.91 (p < 0.00001), 6.14 \pm 1.16 (p < 0.005) and 6.01 \pm 1.11 (p < 0.005) mg/dL at one, three and six months, respectively. Calcium, hemoglobin and ferritin levels did not significantly

differ during the same periods. Transferrin saturation was significantly increased (26.7 \pm 10.9% vs. 20.0 \pm 9.5%, p < 0.05) and the weekly EPO dose was significantly decreased (2750 \pm 2699 vs. 6801 \pm 7406 IU/week, p < 0.05) after six months of FC therapy.

Conclusions: FC can decrease serum phosphate levels and the weekly EPO dose. Therefore, FC is useful for treating hyperphosphatemia and renal anemia in Japanese patients on HD.

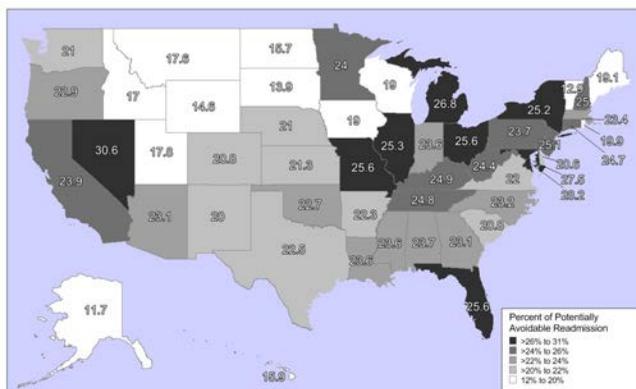
TH-PO951

Geographic Variation of Potentially Avoidable Readmissions in Hemodialysis Patients Daniel W. Ross,¹ Kamyar Kalantar-Zadeh,² Steven Fishbane,¹ Anna Mathew.¹ ¹Div of Nephrology, Hofstra North Shore -LIJ School of Medicine, New York, NY; ²Harold Simmons Center for Kidney Disease Research and Epidemiology, Div of Nephrology, Univ of California, CA.

Background: In 2011 in the United States, 36.3% of prevalent hemodialysis patients were readmitted within 30 days of an index hospitalization. These rates are approximately twice that of the general U.S Medicare population. While some readmissions to hospital are unavoidable, it is probable that a substantial number could be prevented. In the present study, we describe inter-state variability in 30-day potentially avoidable readmissions (PAR).

Methods: The United States Renal Data System (USRDS) was used to identify prevalent hemodialysis patients (vintage >90 days) with acute hospitalizations in 2008. Exclusion criteria were transfer to rehabilitation or skilled nursing facility, unknown dialysis start date, and renal function recovery. PAR were identified using a validated, computerized algorithm (SQLape), and displayed geographically by state using Pitney Bowes MapInfo.

Results: 250,606 index hospitalizations were identified, with 37% readmissions within 30 days (n = 84,279). Nationwide, 24% of index hospitalizations were followed by a 30-day PAR (64.9% of all readmissions) (n = 59,803). PAR ranged from 12% to 31% by state. The figure shows the geographic distribution of potentially avoidable readmissions.



Conclusions: There is inter-state variability in PAR among chronic hemodialysis patients and that may be related to regional differences in practice patterns or patient demographics. Further characterization of risk factors associated with PAR is the focus of our ongoing research.

TH-PO952

Unravelling the Relationship Between Mortality, Hyponatremia, Inflammation and Malnutrition in Hemodialysis Patients: Results from the International MONDO Initiative Marijke J.E. Dekker,¹ Daniele Marcelli,³ Bernard J. Canaud,³ Constantijn Konings,¹ Karel M. Leunissen,² Nathan W. Levin,⁴ Jochen G. Raimann,⁴ Frank van der Sande,² Len A. Usvyat,^{3,4} Peter Kotanko,⁴ Jeroen Kooman.² ¹Catharina Hospital Eindhoven; ²Maastricht Univ Medical Center; ³Fresenius Medical Care; ⁴Renal Research Inst.

Background: Hyponatremia is a risk factor for mortality in hemodialysis patients. However, it is not well known to which extent comorbidities, such as malnutrition, fluid overload and inflammation are related to hyponatremia and influence the association between hyponatremia and outcomes.

Methods: We studied 8892 patients from the European subset of the MONDO Initiative. Nutritional and fluid statuses were assessed by multifrequency bioimpedance spectroscopy. Based on pre-dialysis fluid status, fluid depletion was defined as an extracellular water volume < -1.0L and fluid overload > +2.5L. Malnutrition was defined as a lean tissue index below the 10th percentile of age- and gender matched healthy controls. Hyponatremia and inflammation were defined as serum sodium levels < 135 mEq/L and C-reactive protein levels > 10 mg/L, respectively.

Results: Hyponatremia was predicted by the presence of malnutrition (odds ratio (OR) 1.48 (95%CI 1.30-1.69) and inflammation (OR 1.44 (95%CI 1.26-1.64)), but not by fluid depletion (OR 1.38 (95%CI 0.98-1.93)) or fluid overload (OR 0.99 (95%CI 0.85-1.14)). Malnutrition (hazard ratio (HR) 1.39 (95%CI 1.23-1.58)), inflammation (HR 2.31 (95%CI 2.04-2.62)), fluid overload (HR 2.17 (95%CI 1.90-2.47)) and hyponatremia (HR 1.63 (95%CI 1.39-1.90)) were independent predictors for all-cause mortality.

Conclusions: In hemodialysis patients hyponatremia is associated with malnutrition and inflammation but not with deranged fluid status. Hyponatremia maintained predictive for all-cause mortality after correction for malnutrition, inflammation and fluid status abnormalities. Hyponatremia may aid efforts to identify hemodialysis patients at increased risk of death.

TH-PO953

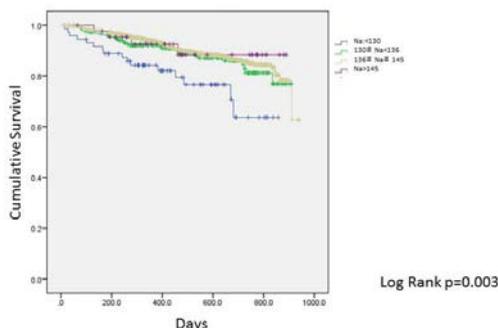
Low Serum Sodium Concentration at the Induction of Maintenance Hemodialysis Predicts Higher Risk of Mortality Yukako Ohyama,¹ Hideaki Shimizu,¹ Daijo Inaguma,² Yoshiro Fujita.¹ ¹Nephrology and Rheumatology, Chubu Rosai Hospital, Nagoya, Japan; ²Nephrology, Red Cross Nagoya Daini Hospital, Nagoya, Japan.

Background: Low serum sodium concentrations are associated with an increased risk of death in the general population because of underlying diseases such as congestive heart failure and cirrhosis. However some papers report hyponatremia itself further increases the mortality risk. The prevalence of hyponatremia and the mortality risk of hyponatremia at the induction of maintenance hemodialysis (HD) haven't been reported before.

Methods: This study is a retrospective cohort study which data was collected from "Aichi Cohort study of Prognosis in Patients" (AICOPP) newly initiated dialysis. After the exclusion of peritoneal dialysis (PD) patients, this study enrolled 1395 patients (mean age; 68 ± 13 years, mean eGFR level; 5.4 ± 2.2 ml/min/1.73m²) who started maintenance HD between 10/1/2011 and 11/30/2013. We divided the cohort to 4 groups by serum sodium concentration at the induction of HD adjusted by serum glucose concentration (Severe hypo:Na<130, Mild hypo:130≤Na<136, Normal :136≤Na<145, Hyper:Na>145 mEq/L). The proportional hazard model was used to examine the association between serum sodium level and mortality.

Results: The prevalence of hyponatremia, defined as Na<136 mEq/L and <130 was at 23% and 5%, respectively. During 15.5 months' mean follow up, 159 patients (11%) died. The lowest Na group was significantly associated with higher risk of mortality.(figure1) Patients with serum sodium levels of <130 mEq/L were more likely to have multivariable-adjusted mortality hazard ratios (95% confidence interval) of 2.34 (1.31-4.15) compared to patients with serum sodium levels of 136-145 mEq/L.

Kaplan-Meier curves



Conclusions: Hyponatremia at the induction of HD is an independent predictor of higher risk for mortality.

TH-PO954

Frequency of Hyperkalemia Events in Dialysis Patients in a Large Dialysis Organization Akeem Yusuf,¹ Yan Hu,¹ Bhupinder Singh,² Alex Yang,² James B. Wetmore.¹ ¹Chronic Disease Research Group, MMRF, Minneapolis, MN; ²ZS Pharma, Inc, Redwood City, CA.

Background: Hyperkalemia is a major problem in dialysis patients. It is associated with increased risk of cardiac arrhythmias and sudden cardiac death. However, few studies have examined frequency of hyperkalemia episodes in a large population of dialysis patients. We present a characterization of the magnitude of hyperkalemia prevalence in a large hemodialysis population and examine the role of interdialytic interval in its occurrence.

Methods: We derived annual cohorts of hemodialysis patients (2007-2010) from linked DaVita and USRDS databases. Included patients were those receiving thrice-weekly hemodialysis. On a monthly basis, hyperkalemia case was defined as a serum potassium level greater than or equal to 5.5 mEq/L. Hyperkalemia prevalence was calculated as the cumulative number of monthly episodes divided by cumulative follow-up time. Hyperkalemia prevalence was also reported separately by long and short interdialytic interval.

Results: Hyperkalemia prevalence in 2010 was 16.3 per 100 patient-months. Overall, hyperkalemia prevalence was stable between 2007 and 2010. The prevalence of hyperkalemia events occurring on day after the long interdialytic interval was about 2.0 to 2.4 times as high as events occurring on the day after the short interdialytic interval.

Cohort	Cohort Size	Number of events per 100 patient-months	
		Events on day after long interdialytic interval	Events on day after short interdialytic interval
2007	28,769	58.74	28.84
2008	34,785	62.16	27.63
2009	34,567	62.94	26.26
2010	36,879	61.61	26.22

Conclusions: The findings from this study show that hyperkalemia is highly prevalent among hemodialysis patients, especially on the day after the long-interdialytic interval. Further studies are warranted.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

TH-PO955

Serum Potassium Levels and Mortality in Hemodialysis Patients Akeem Yusuf,¹ Yan Hu,¹ Bhupinder Singh,² Jose A. Menoyo,² Alex Yang,² James B. Wetmore.¹ ¹CDRG/MMRF, Mpls, MN; ²ZS Pharma, Inc, Redwood City, CA.

Background: Hyperkalemia is common in patients receiving maintenance hemodialysis (HD) and is associated with sudden cardiac death. However, few studies have examined the association between serum potassium (K) level and death in a large population of dialysis patients.

Methods: A cohort of patients receiving thrice-weekly HD in 2010 was constructed using data linked between USRDS and a large dialysis organization (LDO). Patients were followed from first serum K measurement until death, transplant, change in dialysis modality, change in dialysate K concentration, loss of Medicare eligibility, loss to follow up, or Dec 31, 2010. Hyperkalemia was defined by serum K levels 5.5-6.0 mEq/L at 0.1 mEq/L intervals. Time-dependent Cox proportional hazards modeling was used to estimate the association between hyperkalemia occurrence and all-cause and cardiovascular mortality.

Results: Hyperkalemia defined as serum K ≥5.7 mEq/L was associated with all-cause mortality (adjusted hazard ratio [AHR] 1.1, 95% CI 1.01-1.28, P = 0.037, compared to K ≥5.0 mEq/L) after adjustment for demographic and clinical factors in time-dependent models; the AHRs increased progressively as the threshold for hyperkalemia rose (AHRs 1.18, P = 0.014, for K=5.8 mEq/L; 1.29, P = 0.001, for K=5.9 mEq/L; 1.37, P = 0.0002, for K=6.0 mEq/L). The pattern of the point estimates was similar for cardiovascular mortality, although the results did not reach statistical significance (AHRs 1.09 for K=5.7 mEq/L, 1.13 for K=5.8 mEq/L, 1.20 for K=5.9 mEq/L, 1.28 for K=6.0 mEq/L).

Conclusions: Hyperkalemia is associated with all-cause mortality beginning at K level ≥5.7 mEq/L, with mortality risk point estimates increasing in ordinal fashion through K level ≥6.0 mEq/L. A similar pattern was observed in the point estimates for cardiovascular mortality. This study may have identified a threshold at which point serum K becomes dangerous.

Fig.1 Adjusted hazard ratio for all cause death by different definitions of hyperkalemia

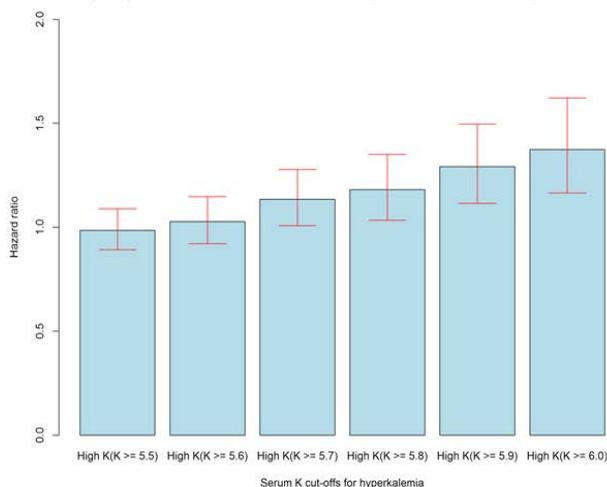
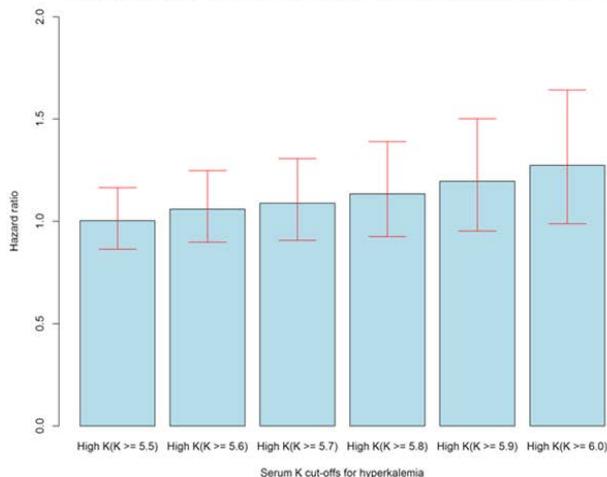


Fig.2 Adjusted hazard ratio for CV specific death by different definitions of hyperkalemia



Funding: Pharmaceutical Company Support - ZS Pharma, Inc

TH-PO956

A Multicenter, Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial of Nalbuphine ER Tablets for the Treatment of Uremic Pruritus: Baseline Population Characteristics Vandana S. Mathur,¹ Jayant Kumar,³ Paul W. Crawford,⁵ Howard Hait,⁴ Thomas Sciascia.² ¹MathurConsulting, Woodside, CA; ²Trevi Therapeutics, New Haven, CT; ³Renal Medicine Associates, Albuquerque, NM; ⁴Biostatistics, Edenridge Consulting, Wilmington, DE; ⁵Research by Design, Evergreen Park, IL.

Background: Uremic pruritus (UP) afflicts 30-40% of hemodialysis patients (HDP) and is associated with greater use of ESA and antibiotics. UP is hypothesized to be centrally-mediated via the reduction in endogenous κ/μ opioid ligand ratio. Nalbuphine ER tablet (NAL), a κ-opioid agonist and μ-opioid antagonist, is being developed for treatment of UP.

Methods: 373 HDP with moderate or severe UP (Numerical Rating Scale, NRS itch intensity scores ≥4.5) were randomized to blinded placebo or NAL (60 or 120 mg BID) X 8-wks.

Results: Worsening itch intensity by baseline NRS quartile was monotonically associated with impaired QOL on all instruments as well as with sleep onset latency, anxiety, and depression, but not with age, gender, BMI, ethnicity, itch duration, iPTH, URR, or Kt/V. Black race appeared to be associated with higher NRS.

Itch Intensity Numerical Rating Scale (NRS) Quartile [N]	Q1 [97] (4.5-5.6)	Q2 [97] (5.7-6.8)	Q3 [104] (6.9-8.0)	Q4 [75] (>8.0)
NRS (0, no itch; 10, worst possible itch)	5.1 (0.4)	6.3 (0.3)	7.5 (0.4)	8.9 (0.6)
White/Black race	53/43%	49/47%	47/53%	44/55%
Self-Assessed Disease Severity Patient Type C [most severely affected]	20%	33%	46%	67%
Skindex-10 (0 - 60) [0 (least); 60 (greatest) QOL impact of pruritus]	26.0 (11.1)	32.4 (13.1)	39.7 (12.4)	43.5 (13.3)
HADS - Depression	5.6 (3.6)	6.1 (3.6)	6.8 (4.0)	7.8 (4.5)
HADS - Anxiety	6.2 (3.9)	7.7 (4.1)	7.7 (4.4)	9.4 (4.6)
Time to fall asleep >60 minutes	20%	22%	36%	42%
iPTH (pg/mL)	492 (451)	336 (304)	433 (334)	463 (439)
Serum phosphate (mg/dL)	5.6 (1.7)	5.4 (1.7)	5.7 (2.0)	5.6 (1.8)
Urea Reduction Ratio (%)	74 (5)	74 (5)	73 (6)	74 (6)
spKt/V	1.6 (0.3)	1.6 (0.3)	1.5 (0.3)	1.7 (0.6)

Conclusions: In addition to the 1° endpoint hypothesis that NAL will reduce itch intensity, the apparent associations between itch intensity and QOL measures at baseline warrant examination by treatment. Unblinded results will be presented.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

TH-PO957

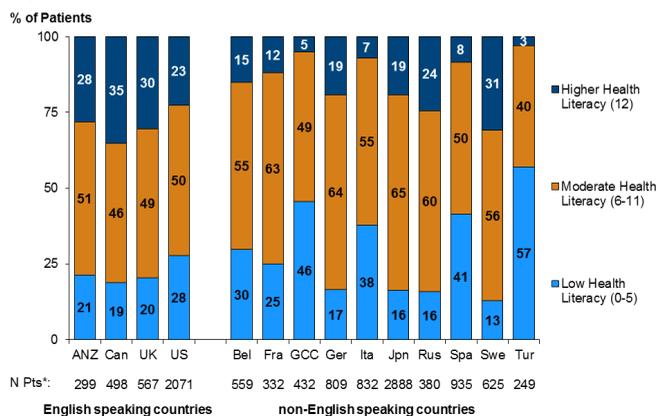
International Variation of Characteristics of Health Literacy and Its Association with Mortality in Dialysis Kerri L. Cavanaugh,¹ Mia Wang,² Ken Wallston,¹ Russell Rothman,¹ Ali AlSahow,³ Patricia De Sequera,⁴ Takeshi Hasegawa,⁵ Brian Bieber,² Bruce M. Robinson,² Ronald L. Pisoni,² Francesca Tentori.^{1,2} ¹Vanderbilt Univ; ²Arbor Research; ³Jahra Hospital; ⁴Hospital Infanta Leonor; ⁵Fukushima Medical Univ.

Background: In patients receiving hemodialysis (HD), low health literacy (LHL) has been associated with greater use of emergency care, more hospitalizations and higher mortality. Little is known about the characteristics of LHL in HD patients outside of the United States.

Methods: A total of 11,476 DOPPS participants completed the Brief Health Literacy Screen (BHLS) [0-12]. Descriptive statistics were performed overall and by country. Participant characteristics were examined between three health literacy categories using mixed, GEE, and multinomial logistic models. Cox models were applied to examine associations of LHL with mortality adjusting for the above variables and also potential effects of study phase, country, and facility clustering.

Results: LHL prevalence varied across countries (Figure). LHL was more likely in patients who were older, female, unemployed and in those who had fewer years on HD, lower education, and lower income (all P for trend<0.001). LHL was significantly associated with mortality when examined as a continuous score (HR=1.05; 95%CI=1.03-1.08 for each point decreased) or as a category (HR=1.65; 95%CI=1.28-2.12 Low vs. High), and no interaction with country was observed.

Figure. Distribution of Health Literacy by Country



*Total of 11,476 patients (6,143 from DOPPS 4 2009-2012 and 5,333 from DOPPS 5 2012-2015).

Conclusions: LHL is common worldwide among HD patients. Variability in LHL prevalence across countries may be in part explained by cultural differences as well as health care systems. Vulnerable patients are at highest risk of LHL, and LHL is an independent predictor of mortality. Further examining by country the role of health system practices may help to overcome LHL-related barriers to patient engagement and improve outcomes in hemodialysis.

Funding: Pharmaceutical Company Support - The DOPPS Program is supported by Amgen, Kyowa Hakkō Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. Additional support for specific projects and countries is also provided in Canada by Amgen, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support); in Germany by Hexal, DGfN, Shire, WiNe Institute; for PDOPPS in Japan by the JSPD. All support is provided without restrictions on publications.

TH-PO958

Evaluation of a Vancomycin Weight-Based Dosing Protocol in Patients Undergoing High-Flux Hemodialysis Katherine Desforges, Marieme N'Diaye, Robert Zoel Bell, Jean-Philippe Lafrance, Vincent Pichette, Michel Vallee. *Nephrology, Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.*

Background: Hemodialysis patients are frequently subject to Gram-positive infections including Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus (MRSA). Vancomycin is an antibiotic of choice in this population to treat these infections. The objective of this project was to validate the performance of a pre formulated individual prescription protocol of vancomycin in its capacity to reach target vancomycin serum concentrations of 10 to 30 mg/L for Gram-positive infections and 15 to 20 mg/L for MRSA infections.

Methods: The records of 84 patients diagnosed with end-stage renal disease undergoing a 4-hour, three times weekly high-flux hemodialysis treatment were analyzed retrospectively. All patients received vancomycin according to a weight-based dosing protocol between 2011 and 2014. Patients < 70 kg received a 1000 mg loading dose followed by a 500 mg maintenance dose at each dialysis session. Patients between 70 and 100 kg received a 1500 mg loading dose followed by a 750 mg maintenance dose. Patients > 100 kg received a 1500 mg loading dose followed by a 1000 mg maintenance dose.

Results: We collected and analyzed 189 dosages of 84 patients. For all assays, 95.2% achieved levels between 10 and 30 mg/L and 50.3% achieved levels between 15 and 20 mg/L. Stratified by weight categories, for the 10 to 30 mg/L target, 93.3% of patients < 70 kg, 100% of patients between 70 and 100 kg and 89.5% of patients > 100 kg achieved the target serum concentrations. For the 15 to 20 mg/L target, 49.3% of patients < 70 kg achieved the target serum concentrations (mainly below), 61.3% of patients between 70 and 100 kg achieved the target serum concentrations and 31.6% of patients > 100 kg achieved the target serum concentrations (mainly higher, but below 30 mg/L).

Conclusions: The vancomycin weight-based dosing protocol achieved target serum concentrations of 10 to 30 mg/L in 95.2% of patients. However, because half the dosages of patients < 70 kg were below the target of 15 to 20 mg/L, vancomycin bolus and maintenance doses should be adjusted upward in this subgroup. No dose change is suggested in the other subgroups.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO959

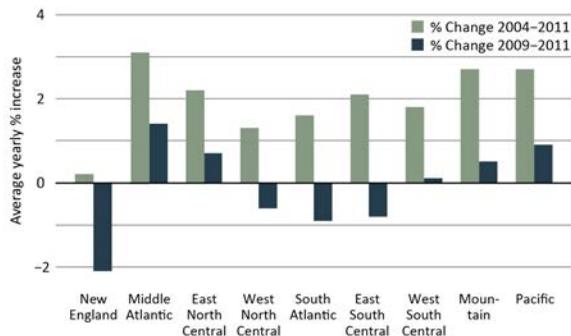
Trends in Incident ESRD Counts Initiating Dialysis in Freestanding Facilities Have Regional Variation David T. Gilbertson,¹ Peer Kidney Care Initiative Investigators.² ¹CDRG, MMRF, Minneapolis, MN; ²Peer Kidney Care Initiative.

Background: Overall rates of incident end-stage renal disease (ESRD) patients initiating dialysis in freestanding units have stabilized, and the growth in counts of incident ESRD patients begun to slow by the beginning of this decade. We assessed trends in incident ESRD counts from 2004–2011, overall and geographically by the 9 US Census Divisions.

Methods: Data were ascertained from the Centers for Medicare & Medicaid Services ESRD database. For annual incident cohorts, we identified patients with their first outpatient dialysis within 3 months of initiating chronic dialysis in a freestanding facility.

Results: Yearly counts increased through 2010, with an average annual percent increase of 2.7% from 2004 to 2011. Between 2009 and 2011, this average percent increase was relatively unchanged (-0.1%). However, there were regional differences, with the New England Census Division experiencing the largest proportionate decrease in incident patients between 2009 and 2011, while the contiguous Middle Atlantic division averaged the highest increase during the same period by 2011.

Conclusions: Overall trends in dialysis incidence reveal substantial geographic variation that has not been explained, suggesting that an assessment based on overall U.S. counts may mask important regional differences. Whether these trends will continue in the face of increasing diabetes rates, an aging population and shifts in social demographic changes is uncertain and will require more detailed analysis.



Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota., Private Foundation Support

TH-PO960

Association of Intradialytic Hypoxemia with Hospitalization and Mortality: Results from a Large U.S. Hemodialysis Cohort Anna Meyring-Wosten,¹ Hanjie Zhang,¹ Xiaoling Ye,¹ Doris H. Fuertinger,¹ Franz Kappel,² Mikhail Artemyev,¹ Nancy Ginsberg,¹ Yuedong Wang,³ Stephan Thijssen,¹ Peter Kotanko,^{1,4} ¹Renal Research Inst, New York, NY; ²Univ of Graz, Austria; ³Univ of California - Santa Barbara, CA; ⁴Icahn School of Medicine at Mount Sinai, New York, NY.

Background: While intradialytic hypoxemia is recognized since the early days of hemodialysis (HD), its associations with hard clinical outcomes have not yet been assessed.

Methods: We analyzed arterial oxygen saturation (SaO₂) data obtained by Crit-Line™ monitor (CLM) in chronic HD patients treated between 1/2012 and 1/2015. An individual 6-month baseline with at least 10 CLM measurements preceded a 12-month follow-up. Prolonged intradialytic hypoxemia (PIH) was defined as SaO₂ ≤ 90% for more than 1/3 of treatment time. Patients were stratified based on the presence or absence of PIH. We conducted Cox proportional hazards analysis with adjustment for age, gender, race, vintage, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes, albumin, hemoglobin, erythropoietin (EPO) dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain, post-HD systolic blood pressure, and ultrafiltration rate.

Results: We studied 983 patients (59% males; 53% whites) with 30.5±12.5 baseline SaO₂ measurements. 100 patients (10.2%) had PIH. PIH patients showed a higher prevalence of CHF and COPD required significantly more EPO, and resembled an inflammatory phenotype. During the follow-up, 2.21 and 1.55 hospitalizations per patient-year were recorded in patients with and without PIH, respectively (P=0.009). Eighty-nine patients died during follow-up. The mortality rate was 24.1 per 100 patient years in the PIH group and 10.2 in the non-PIH group (P=0.0008). Cox proportional hazards analysis corroborated the increased probability of death in PIH patients (hazard ratio 1.98 [95% CI: 1.14 to 3.43]).

Conclusions: Prolonged intradialytic hypoxemia (PIH) is associated with increased risk for hospitalization and mortality. A better understanding of the pathophysiology of PIH, its clinical consequences and its medical management requires future basic and clinical research.

Funding: Pharmaceutical Company Support - Renal Research Institute

TH-PO961

A New Polymethyl Methacrylate Membrane (PMMA) Improves the Membrane Adhesion of Blood Components and Clinical Efficacy Ikuto Masakane. *Yabuki Hospital, Nephrology, Yamagata, Japan.*

Background: Polymethyl methacrylate (PMMA) is a unique dialysis membrane which has protein adsorption property and it has been reported to effective to reduce the pruritus and maintain nutritional status on chronic dialysis patients. The newly launched PMMA membrane (NF) has been modified in order to improve hemo-compatibility as well as maintaining the protein adsorptive capacity. The aim of the current study is to evaluate the solute removal performance, peripheral circulation during dialysis session and clinical efficacy on patient's subjective symptoms in the comparison with conventional PMMA (BG).

Methods: The six subjects were treated with NF and BG for 3 months each in a crossover design. We evaluated the solute removal properties by the clearance of urea, beta-2 microglobulin (B2MG), removed amount of alpha-1 microglobulin (A1MG) and albumin loss in spent dialysate. The hemo-compatibility was evaluated by changes in platelet count. The peripheral circulation was estimated by the Skin Perfusion Pressure (SPP) by PAD-3000® (Kaneka Medix, Osaka, Japan) Dialysis-related complaints, including itching, distraction, malaise, headache, hypotension, fatigue after dialysis, and appetite, were compared.

Results: The total amount of removal in each urea, B2MG, A1MG and albumin leakage was not different in both NF and BG. During dialysis, the percent changes in platelet count were (for NF and BG, respectively) 97.1% and 86.1% after 15 min of dialysis, 96.5% and 85.1% after 30 min, 97.3% and 88.3% after 1 h, and 99.6% and 90.1% after 4 h. The changes in platelet count during dialysis were significantly smaller with the NF than with the BG. The SPP was well maintained in NF but time-dependently deteriorated in BG. There were no significant differences in any subjective symptoms, but the mean score of the seven items tended to be lower in NF.

Conclusions: The new PMMA (NF) membrane may improve the QOL of chronic dialysis patients by stabilizing the platelet and peripheral circulation.

TH-PO962

Outcomes of Infants Receiving Chronic Peritoneal Dialysis Keia Sanderson,¹ Hongying Dai,² Laurel K. Willig,¹ Bradley Warady,¹ ¹Nephrology, Children's Mercy Hospital, Kansas City, MO; ²Research Development and Clinical Investigation, Children's Mercy Hospital, Kansas City, MO.

Background: Outcome data for infants receiving chronic peritoneal dialysis (CPD) is limited and has been reported primarily by small voluntary registries. The impact of treatment era has also been poorly studied.

Methods: The USRDS database was reviewed for demographic features and outcomes of patients who initiated CPD at 12 months of age from 1990-2014.

Results: A total of 1,730 infants (575 £1 month and 1155 >1-12months) who initiated CPD at 12 months from 1990-2014 were identified. Overall, 68% of the infants were male and the most common primary diagnoses were obstructive uropathy (31.8%) and congenital renal dysplasia/hypoplasia (29.9%). Mean age at initiation of CPD was 0.4 months (+/-0.3 months) in infants £1 month and 5.2 months (+/-3.1 months) in infants >1-12months. Overall, 1066 infants received at least one kidney transplant during the follow up (333 infants £1 month and 733 infants >1-12months. Mean age at first kidney transplant was 2.9 years (+/-1.6yrs) in infants £1 month and 2.5 years (+/-2.15yrs) in infants >1-12months. Crude all cause mortality rates were higher among infants who initiated CPD at £1 month (276 per 1000 persons at 3 years) versus infants who initiated CPD at >1-12 months of age (185 per 1000 persons at 3 years). Mortality rates at 5 years were 28.7% for infants initiated on CPD at £1 month and 20.7% for infants at >1-12 months of age. Multivariable Cox proportional hazards modeling of factors associated with mortality demonstrated a statistically significant adjusted HR of 4.027 (95% CI 3.274-4.952) for initiation era (1990-2000 vs 2001-2014) and an HR of 1.42 (95% CI 1.15-1.744) for age at initiation of dialysis (£1 month vs >1-12months). Patient sex, race, and primary ESRD diagnosis were not significantly associated with mortality in this model.

Conclusions: In the largest cohort of infants on CPD reviewed to date, the probability of mortality among infants initiating CPD in the first year of life appears to be greater during the prior initiation era (1990-2000) and greater among infants who initiated dialysis at £1 month of age.

TH-PO963

ESRD from Scleroderma in the United States 1995-2010 Donal J. Sexton, Scott Reule, Robert N. Foley. *Medicine, Univ of Minnesota, Minneapolis, MN.*

Background: Though the management of scleroderma continues to evolve it is unknown whether the burden of ESRD from scleroderma has changed.

Methods: We examined United States Renal Data System data (N = N = 1,557,117) for the years 1995-2010 to calculate incidence rates and outcomes of ESRD due to scleroderma treated with renal replacement therapy (RRT, N=2342).

Results: ESRD rates due to scleroderma in 1995-1996 were 0.6 per million per year in the overall population, with higher rates in age 40-64 (0.9) and ≥ 65 (1.4) years, females (0.8) and African Americans race (0.9). Standardized incidence ratios declined between 1995-1996 and 2009-2010 in the overall population (ratio 0.55), in those aged 40-64 yrs (0.49), 65+ yrs (0.62), in male (0.56) and female sex (0.55), in white (0.6) and AA race (0.37). Characteristics of ESRD from scleroderma included age 40-64 (57.9% Vs. 41.3% yrs.), female sex (76.6% Vs. 45.1%) and white race (78.1% Vs. 65.2%). 74.3 % of patients with scleroderma died over a mean observation period of 3.3 years, while 16.9% were

listed for renal transplant and 10.1% received a renal transplant. With matching for age, sex and race, overall mortality rates were higher in scleroderma cases than controls (22.3 Vs. 15.5 per 100 person-years, P < 0.001). Overall rates of listing for renal transplant (8.4 Vs. 8.5 per 100 person-years, P = 0.92) and rates of transplantation (4.1 Vs. 4.3 per 100 person-years, P = 0.66) were similar in scleroderma cases and controls.

Conclusions: The incidence of ESRD from scleroderma appears to have declined in the United States since 1995. Mortality rates on RRT are higher in scleroderma cases than controls taken from ESRD from other causes. However, listing for and receiving a renal transplant were as likely in scleroderma patients as matched controls.

TH-PO964

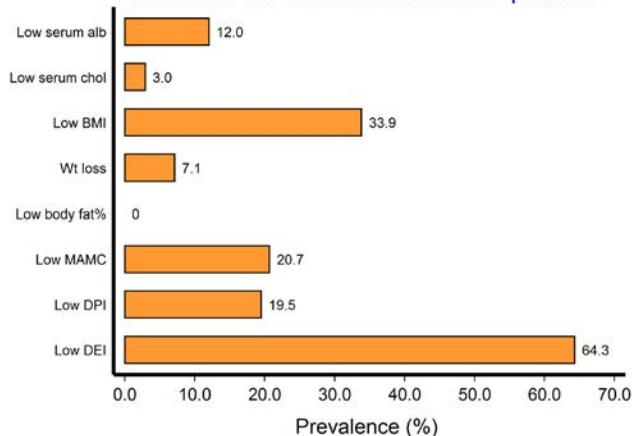
Prevalence and Mortality Associations of Protein-Energy Wasting Syndrome Criteria in Maintenance Hemodialysis Patients Srini Beddhu,^{1,2} G. Wei,¹ Xiaorui Chen,¹ Kalani L. Raphael,^{1,2} Robert E. Boucher,¹ Dominique Ferranti,¹ Tom Greene,¹ Michel Chonchol.³ ¹U of Utah; ²VA SLC; ³UC Denver.

Background: As the prevalence and mortality associations of protein-energy wasting (PEW) syndrome criteria in the MHD population are not well established, we examined these in 1480 MHD pts in the HEMO Study, a multi-center RCT to examine the effects of dialysis dose and dialyzer flux on mortality.

Methods: The prevalence of International Society of Renal Nutrition and Metabolism panel PEW criterion (listed in the table) at the 12 m follow-up visit were examined. Subsequent mortality associations were examined in Cox models adjusted for demographics, duration of ESRD, Kt/V and flux groups, smoking and alcohol use.

Results: There were 632 deaths / 3390 yrs of follow-up. The prevalence of PEW criterion varied widely: 0% for low body fat% to 64% for low DEI (figure).

Prevalence of PEW criterion in MHD patients



Low serum albumin and cholesterol, low BMI, weight loss and low mid-arm muscle circumference (MAMC) were strongly associated with higher risk of mortality (Table 1). However, dietary criteria were not associated with mortality.

PEW Criterion*	All cause mortality HR* (95% CI)
Serum Alb < 3.5 (g/dl)	2.12 (1.68, 2.69)
Serum Chol < 100 (mg/dl)	3.68 (2.46, 5.50)
BMI < 23 (kg/m ²)	1.51 (1.23, 1.86)
Wt loss >10%	1.95 (1.47, 2.58)
Muscle mass category	
Low MAMC [†]	2.00 (1.60, 2.50)
Dietary protein intake (DPI) < 0.60 (g/kg/day)	1.00 (0.80, 1.24)
Dietary energy intake (DEI) < 25 (kcal/kg/day)	0.87 (0.72, 1.05)

*as none had body fat% < 10%, this variable could not be examined, [†]10% or more lower than the 50th percentile of reference population

Conclusions: As there is a wide variability in the prevalence of PEW criteria, the thresholds used in their definition need to be further refined. Dietary variables were not associated with mortality and the validity of these variables as PEW criteria also needs further study.

Funding: NIDDK Support

TH-PO965

Primary Care Physician Involvement in the Care of Chronic Dialysis Patients in the U.S. Vahakn B. Shahinian, Deanna Chyn, Yi Li, John Z. Ayanian, Richard Hirth, William H. Herman, Rajiv Saran. *Univ of Michigan.*

Background: Current health reform efforts aimed at improving quality and value center around delivery of good primary care. However, national patterns of primary care physician (PCP) involvement along with a nephrologist in the care of chronic dialysis patients are unknown.

Methods: Patients on chronic dialysis during 2010-11 with Medicare as the primary insurer were identified using US Renal Data System (USRDS) data. PCP involvement was defined based on a claim for an outpatient (non-dialysis) visit with a physician specializing in family practice, general internal medicine or geriatrics. Patients were characterized with respect to two aspects of preventive care: influenza vaccination and diabetes care.

Results: The sample included 179,645 patients, 81,272 of whom were diabetic. In 2010, 59% of patients had evidence of PCP involvement based on [≥]1 outpatient visit. Patients with PCP involvement were older and more likely to be female, white and with diabetes as cause of ESRD (Table). Rates of vaccination and diabetes care were higher in those with PCP involvement, even after adjustment (ORs: 1.48 [1.45-1.51] for vaccination and 1.53 [1.48-1.58] for a composite of diabetes care).

Patient Characteristics or Delivered Care	PCP Involvement (1+ Visit in 2010)	
	No (n=73,597)	Yes (n=106,048)
Mean age at ESRD (SD)	52.1 (17.0)	57.8 (16.0)
Sex		
Female	40.2	48.7
Male	59.8	51.3
Race		
White	48.6	55.3
Black	45.4	38.3
Other	6.0	6.4
Primary Disease Causing ESRD		
Diabetes	35.8	45.7
Hypertension	31.0	27.7
Glomerulonephritis	15.7	12.0
Influenza Vaccination	59.2	68.4
Diabetes-related care (among diabetic patients)	No (N=29,524)	Yes (N=51,748)
1+ HbA1C test	75.9%	83.5%
1+ Lipid test	65.5%	74.3%
1+ Diabetic eye exam	36.3%	46.3%
All 3 tests	24.1%	33.6%

By a more restrictive definition of [≥]2 visits in 2010, 47% had PCP involvement; under a looser definition of [≥]1 visit over 2 years (2010-11), vs 70% had PCP involvement.

Conclusions: Even under the loosest definition of PCP involvement, over one quarter of dialysis patients have no evidence of PCP involvement. Patients with PCP involvement have higher rates of preventive care, but further study should examine the impact on outcomes and costs.

Funding: NIDDK Support

TH-PO966

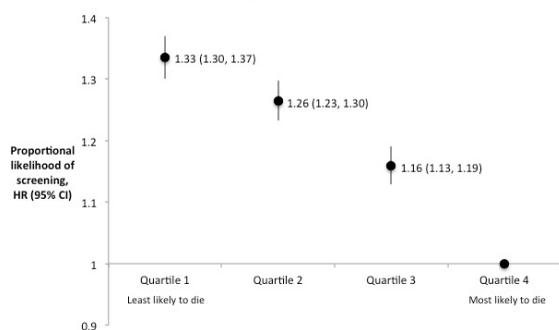
Are We Choosing Wisely? A Study of Colon Cancer Screening Practices Among Dialysis Patients in the United States Christopher A. Carlos,¹ Chi-yuan Hsu,¹ Meda E. Pavkov,³ Nilka Rios Burrows,³ Vahakn B. Shahinian,² Rajiv Saran,² Neil R. Powe,¹ Kirsten L. Johansen.¹ ¹Univ of California, San Francisco, San Francisco, CA; ²Univ of Michigan, Ann Arbor, MI; ³Centers for Disease Control and Prevention, Atlanta, GA.

Background: Because estimated net gains in life expectancy are very small, the American Society of Nephrology recommended against routine cancer screening in asymptomatic dialysis patients. We aimed to determine how often colon cancer screening is performed in the U.S. and whether colon cancer screening is targeted toward healthier dialysis patients. **Methods:** We performed a retrospective cohort study of patients aged [≥]50 years on dialysis between January 1, 2007 and September 30, 2012 using data from the United States Renal Data System (USRDS). Using multivariable Cox regression models, patients were divided into quartiles based on the risk of death and the likelihood of receiving a kidney transplant and, according to these quartiles of risk, we then assessed the likelihood of colon cancer screening (CCS) by fecal occult blood testing, sigmoidoscopy or colonoscopy from Medicare claims data.

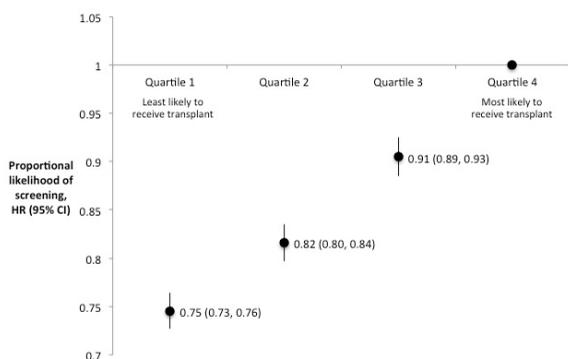
Results: Of 391,616 patients, 13% received CCS over a median follow-up of 1.5 years (interquartile range 0.7-2.9). Screening was most common in patients with the lowest mortality risk (16%), compared with 9% of those with the highest mortality risk (HR 1.33;

95% CI 1.30-1.37). Overall, 41% of CCS occurred in those whose risk of death was above the median. Patients least likely to receive a transplant were less often screened (10%) than those most likely to receive a transplant (HR 0.75; 95% CI 0.73-0.76).

Colon cancer screening among ESRD patients according to mortality risk



Colon cancer screening among ESRD patients according to likelihood of transplantation



Conclusions: Our findings suggest that screening was appropriately targeted to dialysis patients with longer life expectancies and away from those with the lowest chances of receiving kidney transplantation.

Funding: NIDDK Support, Other U.S. Government Support

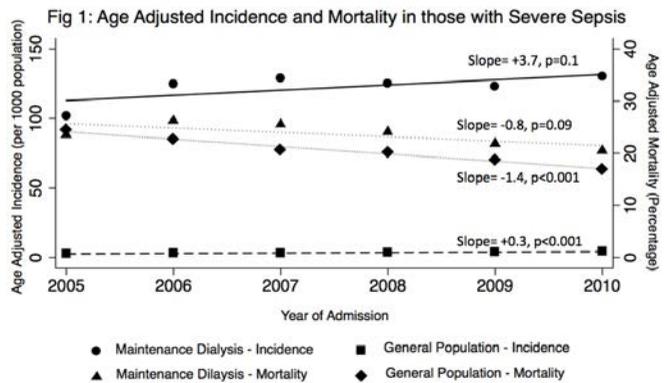
TH-PO967

Severe Sepsis Hospitalizations in Those on Maintenance Dialysis – National Trends and Outcomes Ankit Sakhuja,¹ Kianoush Banaei-Kashani,² Hatem Amer,² Robert C. Albricht.² ¹Nephrology, Univ of Michigan; ²Nephrology and Hypertension, Mayo Clinic.

Background: Severe sepsis (SS) is a life-threatening condition requiring early diagnosis and management. Incidence of SS is increasing in general population (GP) and mortality is declining; however, epidemiology and outcomes of SS have not been well studied in those on maintenance dialysis (MD). We designed this study to look at incidence and outcomes of SS in those on MD.

Methods: Using Nationwide Inpatient Sample database we included all hospitalizations (age ≥20 yr) with SS based on ICD-9-CM codes of severe sepsis, septic shock or blood stream infection with organ dysfunction from 2005 to 2010. Those on MD were identified based on ICD-9-CM codes. Age adjusted incidence of SS and mortality in subgroups was calculated by direct standardization to 2000 standard US population. Linear regression was used to assess trends over time and logistic regression to assess independent effect of MD on mortality.

Results: Of estimated 5,000,152 (95% CI: 4,798,520-5,201,784) hospitalizations with SS, 6.4% were on MD. Unadjusted incidence of SS was 145.4/1000 in MD compared to 3.5/1000 in GP with incidence rate ratio 40.9 (95% CI: 40.8-40.9). Age adjusted incidence of SS seems to be increasing in both subgroups though trend was not significant in MD (Fig 1).



Unadjusted in-hospital mortality is higher in MD (30.3% vs 26.2%; p<0.001). Age-adjusted mortality is decreasing in both subgroups though trend was not significant in MD. Age-adjusted mortality continues to be higher in MD (Fig 1). MD is an independent risk factor for mortality with OR 1.26 (95% CI: 1.23-1.29).

Conclusions: Hospitalizations with SS are over 40 times more common in MD. Mortality is higher in MD and being on MD is an independent predictor of mortality in those admitted with SS. Though incidence of SS seems to be increasing, there is a trend towards decrease in mortality even in MD.

TH-PO968

Trends in Colorectal Cancer Screening in U.S. End-Stage Renal Disease Population Kevin C. Abbott,¹ Chyng-Wen Fwu,² Paul L. Kimmel,¹ Paul W. Eggers,¹ ¹Div of Kidney, Urologic Hematologic Diseases, NIDDK, NIH, Bethesda, MD; ²Social & Scientific Systems, Inc., Silver Spring, MD.

Background: Screening for colorectal cancer (CRC) has been recommended for those over 50 years old. Medicare coverage of CRC screening began in 2000. Dialysis patient care is shared by many practitioners, perhaps leading to therapeutic nihilism and insufficient screening. CDC data show almost 2/3 of patients at risk report CRC screening. We determined rates of CRC screening in ESRD hemodialysis (HD) patients, compared to a 5% Medicare sample, and to assess secular trends.

Methods: We used data from the 2001-2011 USRDS to describe trends in percentages of HD patients receiving CRC screening tests per year. We limited our study population to patients with Medicare Part A and B as primary payer to ensure complete Medicare claims data for CRC screening. Current Procedural Terminology /Healthcare Common Procedure Coding System (CPT/HCPCS) codes identified Medicare physician and supplier billing data for screening: colonoscopy (G0105 and G0121), sigmoidoscopy (G0104), and fecal-occult blood test (FOBT; G0107, G0328, and 82270). We compared HD data to a 5% Medicare sample.

Results: Overall, the proportion of HD patients having CRC screening decreased from 6.1% annually in 2001 to 3.5% in 2011 due to decreased use of FOBT. There was a persistent increase in the proportion of patients with colonoscopy or sigmoidoscopy for CRC screening in the 11-year study period, from 0.3% to 1.0% annually. In most years, male, black and age 50-75 patients were more likely to receive colonoscopy or sigmoidoscopy than female, white, and other age subgroups. In 2006, the most recent available comparable year, CRC screening in HD patients was less than that of the general Medicare population; 0.8% vs. 1.6% annually for colonoscopy and sigmoidoscopy, 6.0% vs. 8.1% including FOBT.

Conclusions: Screening for CRC in ESRD HD patients is less frequent than in the general Medicare population, and considerably less than CDC recommendations. Differences in ascertainment methods (CDC uses self-report) may account for most of the disparity from CDC estimates.

Funding: NIDDK Support

TH-PO969

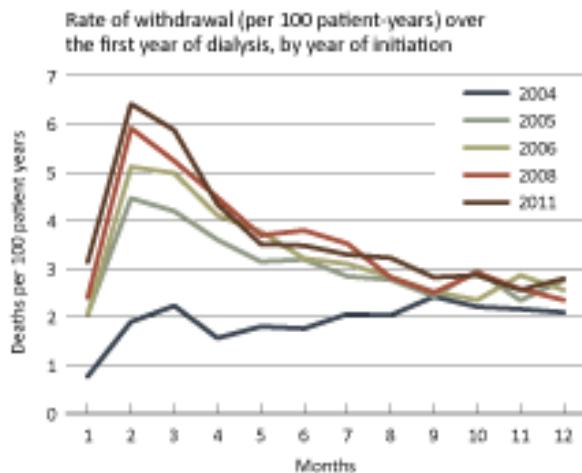
Increasing Prevalence of Withdrawal from Dialysis: Trends from 2004-2011 James B. Wetmore,¹ Peer Kidney Care Initiative Investigators.² ¹CDRG, MMRF; ²Peer Kidney Care Initiative.

Background: Voluntary withdrawal from dialysis, which frequently occurs when a patient perceives dialysis as having become unduly burdensome, is an area of increasing interest. How early withdrawal, defined as that occurring within 1 year of dialysis initiation, has changed over the past decade has not been fully explored.

Methods: Patients initiating dialysis between 2004 and 2011 were selected from the Centers for Medicare & Medicaid Services End-Stage Renal Disease (ESRD) database. Information on withdrawal was ascertained from the ESRD Death Notification Form by the presence of code 104 (“withdrawal”) in the 1st or 2nd position. The unadjusted cause-specific monthly mortality rate (deaths per 100 pt-years) was calculated for patients initiating in each year.

Results: Annual incident counts ranged from 87,174 (2004) to 100,665 (2011). Overall, during the first year of dialysis, the withdrawal rate was highest soon after initiation, peaking at month 2 for all years except 2004. Rates then decreased until approx. month 9, stabilizing through month 12. Additionally, early rates more than tripled over the study period, from 1.9 per 100 pt-years at month 2 in 2004 to 5.9 in 2008 to 6.4 in 2011.

Conclusions: Withdrawal rates are high in the weeks immediately after dialysis initiation, a pattern more marked in recent years. Because patients who withdraw soon after initiation may be suboptimal dialysis candidates, future work should focus on determining whether a tailored approach, designed to identify individual patient goals and present the risks and benefits of dialysis and viable alternatives such as conservative care, might provide optimal patient-centric care.



Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc., DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, MN., Private Foundation Support

TH-PO970

The Dialysis Sodium Gradient – A Modifiable Risk Factor for Fluid Overload Emilie Trinh, Catherine L. Weber. *Nephrology, McGill Univ Health Centre, Montreal, QC, Canada.*

Background: Fluid overload in patients on conventional hemodialysis is a frequent complication associated with increased hospitalizations, cardiovascular morbidity and all-cause mortality. There are multiple patient and physician-related factors that lead to fluid overload. Individualizing dialysate sodium prescription and minimizing the sodium gap are potential modifiable risk factors.

Methods: We performed a cross-sectional study on 111 prevalent stable conventional hemodialysis patients at the McGill University Health Center. The associations of sodium gradient with various hemodialysis parameters of fluid status including interdialytic weight gain percentage (IDWG%), ultrafiltration (UF) rate, blood pressure (BP), intradialytic hypotension and intradialytic hypertension were analyzed.

Results: The mean serum sodium gradient was 4.6 ± 3.6 mEq/L, with a mean pre-dialysis sodium of 137.4 ± 2.5 mEq/L and a mean dialysate sodium of 142.0 ± 3.0 mEq/L. There was a direct correlation between sodium gradient and interdialytic weight gain percentage ($r=0.49, p<0.01$) as well as ultrafiltration rate ($r=0.44, p<0.01$). The average sodium gradient was significantly higher in patients with IDWG > 3% (6.36 vs. 3.16 mEq/L, $p<0.01$) and in patients with UF rate > 10ml/kg/h (6.01 vs. 4.23 mEq/L, $p=0.03$). In a univariate logistic regression model, a higher sodium gradient was associated with increased risk of IDWG% > 3% (OR 1.34, $p<0.01$) and increased risk of UF rate > 10 ml/kg/h (OR 1.16, $p=0.03$), but there was no associations with intradialytic hypotension (OR 1.01, $p=0.87$) or intradialytic hypertension (OR 1.07, $p=0.21$). Also, no significant associations were found between sodium gradient and blood pressure (pre-dialysis or post-dialysis) or number of antihypertensive medications.

Conclusions: A higher sodium gradient was associated with significant increases in IDWG and UF rate which are associated with poor outcomes. Sodium gradient was not associated with intradialytic hypotensive episodes. With the parameters we measured in this study, it appears that individualizing dialysate sodium prescription to minimize sodium gap leads to less fluid overload in conventional hemodialysis patients.

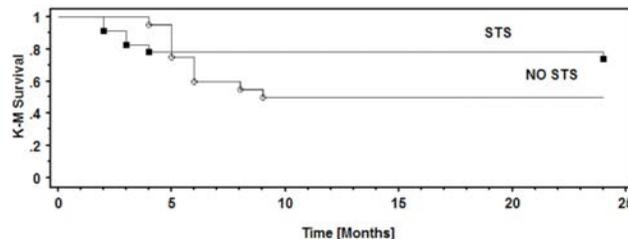
TH-PO971

Calcific Uremic Arteriopathy: Mortality Outcomes with and without Sodium Thiosulfate Therapy Chamberlain I. Obialo, Alexander Quarshie. *Dept of Medicine, Morehouse School of Medicine, Atlanta, GA; Clinical Research Center, Morehouse School of Medicine, Atlanta, GA, Venezuela.*

Background: Calcific uremic Arteriopathy (CUA) or Calciphylaxis is commonly seen in patients with end stage kidney disease (ESKD) and carries a high mortality risk. There is no definite therapy for this condition but promising results have been reported in patients treated with intravenous sodium thiosulfate (STS). However, the mortality advantage of therapy with STS over therapy without STS remains unknown.

Methods: We retrospectively reviewed our ESKD patient's records over a 10-year period and identified 45 biopsy confirmed cases of CUA. Associations between patients who received STS therapy and those who did not and various categorical end points were assessed using the Pearson chi-squared tests while differences in continuous end points were examined using Mann-Whitney- U tests. Survival analysis utilized Kaplan-Meier plots. All statistical tests were two-sided, and level of significance set at 0.05.

Results: The mean age of the 45 cases was 63, 60% female, mean body mass index was 34 and mean dialysis vintage was 4 years. Of the 45 cases, 23 (51%) received STS while 22 (49%) did not. The mean level of serum albumin, phosphorus and parathyroid hormone was 2.8 g/dl, 6.7 mg/dl and 989 pg/dl respectively. One-year mortality was 22% in STS vs. 50% in no STS cases, $p = 0.05$. The overall survival of the patients over the 2-year study period was significantly superior in the recipients of STS than in those who did not receive STS, $p = 0.03$.



Patients who did not receive STS were also more likely to have major surgeries than those who received STS, 86% vs. 52%, $p = 0.01$.

Conclusions: Sodium thiosulfate therapy appears to confer both short term and long term survival advantage over no STS. We encourage hospitals and dialysis companies to procure and make this agent more available to physicians.

Funding: Clinical Revenue Support

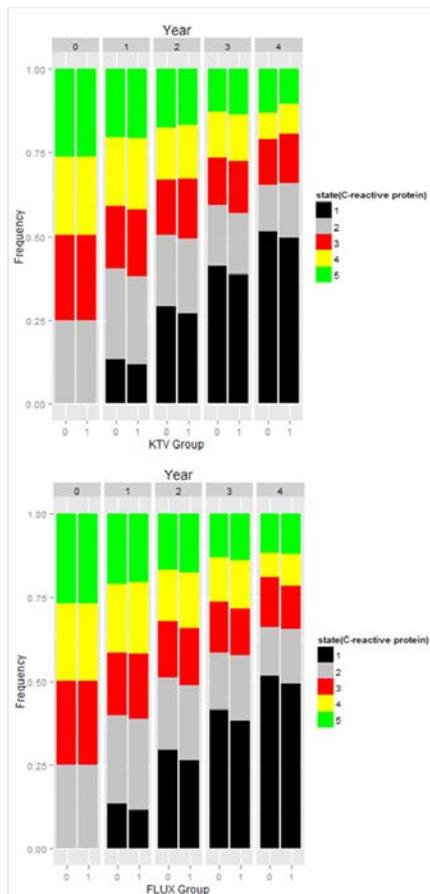
TH-PO972

Effect of High-Dose and High-Flux Hemodialysis on Markers of Inflammation in the HEMO Study Kristen L. Nowak,¹ Tom Greene,² Jian Ying,² Alfred K. Cheung,² Michel Chonchol.¹ ¹Univ of Colorado Denver; ²Univ of Utah.

Background: Hemodialysis treatment induces markers of inflammation, which could affect clinical outcomes. This study sought to determine whether high-dialysis dose and high-flux dialysis would improve markers of inflammation compared with standard dialysis dose and low flux dialysis.

Methods: The HEMO Study was a randomized multicenter study of the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum high sensitivity C-reactive protein (hs-CRP, pre-specified primary outcome for this set of analyses) and interleukin-6 (IL-6) were measured in stored serum samples in 1,846 HEMO participants. For each inflammatory marker we used a joint multi-state modeling approach to estimate the proportion of patients in 5 ordered states (S) over 3 annual assessments while accounting for mortality: S1=deceased (score=0); S2=alive in highest quartile (score=1); S3=alive in 3rd quartile (score=2); S4=alive in 2nd quartile (score=3); and S5=alive in lowest quartile (score=4). The average rank was computed over 3 yrs of follow-up and compared between the randomized groups.

Results: Randomized patients had high rates of coexisting conditions: 45% had diabetes, and 80% had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups. The state distribution of hs-CRP in each year by dose (KT/V) group and by flux group for hs-CRP are shown in Figure 1.



hsCRP did not differ significantly between dose ($p=0.83$) or flux groups ($p=0.53$). Similar results were obtained for IL-6.

Conclusions: Over 3 years, neither high-dose nor high-flux dialysis exhibited a beneficial effect on markers of inflammation.

TH-PO973

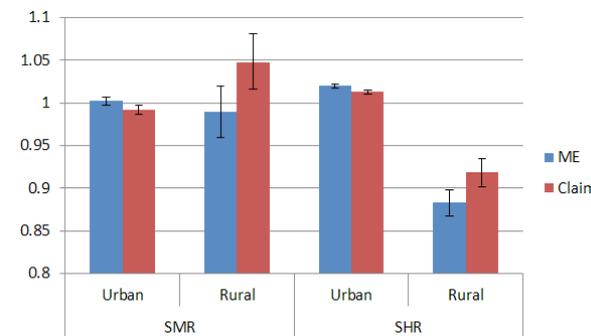
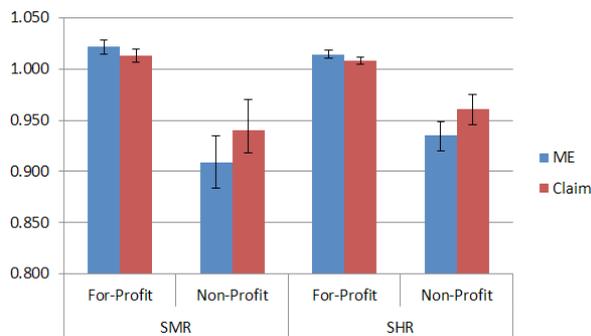
Comorbidity Data Source May Impact SMR/SHR Calculation

Jiannong Liu,¹ Mahesh Krishnan,² Jincheng Zhou,¹ Kimberly M. Nieman,¹ Yi Peng,¹ David T. Gilbertson.¹ ¹CDRG, MMRF, Mpls, MN; ²DaVita Healthcare Partners, Denver, CO.

Background: Standardized mortality and hospitalization ratios (SMRs and SHRs) are used to measure dialysis facility performance, with adjustment for demographics and comorbidities derived from the end-stage renal disease (ESRD) Medical Evidence (ME) Report. Sensitivities are low for ME-based comorbidities. We investigated the effect on SMR and SHR calculations by comparing ratios adjusted for claims-based comorbidities.

Methods: Using the USRDS ESRD database, we included US hemodialysis patients who initiated dialysis July 1-December 31, 2006-2010, had Medicare as primary payer, were aged ≥ 66 years, and had no prior transplant (TX). Patients were followed from dialysis initiation to the earliest of death, TX, modality change, or 1 year. SMRs and SHRs were calculated for patients in for-profit/non-profit and rural/urban facilities for ME-based and claims-based comorbidity, separately. Cox models were used for expected number of deaths and piecewise Poisson models for expected number of hospitalizations. Agreement of comorbidity between the two sources was measured by a kappa statistic.

Results: 73,950 incident hemodialysis patients were included. Kappas for comorbidity agreement were low, less than 0.5, except for diabetes (0.77). Percent of patients with claims-based comorbidity was similar for for-profit and non-profit facilities; ME-based comorbidity was lower for for-profit facilities. Differences between ME-based and claims-based SMR/SHRs were statistically significant. Compared with ME-based SMR/SHR, claims-based ratios decreased 0.9/0.6% for for-profit and 1/0.7% for urban facilities and increased 3.4/2.8% for non-profit and 5.9/4.1% for rural facilities



Conclusions: Comorbidity data source may impact performance evaluation. The impact is larger for smaller groups, and may increase with prevalent patients included.

Funding: Pharmaceutical Company Support - DaVita Clinical Research, DaVita HealthCare Partners Inc., Denver, Colorado

TH-PO974

Thematic Analysis of the Medical Records of a National Cohort of Patients Who Initiated Maintenance Dialysis: 2000-2009

Susan P.Y. Wong,¹ Elizabeth Vig,¹ Nilka Rios Burrows,² Chuan-fen Liu,¹ Desmond Williams,² Paul L. Hebert,¹ Ann M. O'Hare.¹ ¹Univ of Washington; ²Center for Disease Control.

Background: Little is known about how decisions to initiate dialysis take shape in clinical practice.

Methods: We performed a qualitative thematic analysis of the medical records of patients who initiated maintenance dialysis to understand factors that impact decisions to initiate maintenance dialysis as they occur in clinical context. We analyzed key care processes, patient-provider interactions and patient and/or provider concerns and considerations relevant to the decision to initiate dialysis as documented in the electronic medical records of a national random sample of patients for whom the decision to initiate maintenance dialysis was made at the Department of Veteran Affairs between 2000 and 2009 (n=1,691).

Results: We identified three dominant, overlapping themes pertaining to the decision to initiate dialysis: 1) dialysis initiation as *process*, which describes the decision to initiate dialysis as integrated with other treatment decisions and unfolding over time rather than an isolated decision occurring at a fixed point in time; 2) sources of *momentum* for dialysis initiation, which describes factors that appeared to hasten the process of dialysis initiation and included hospitalization for acute illness and efforts to optimize patients' clinical status for future medical interventions; and, 3) *push-pull* dynamics between patients and providers, which describes the sometimes adversarial relationship between patients and providers during the process of dialysis initiation in which patients were often portrayed by providers as "resistant" to dialysis initiation while providers appeared paternalistic and safety conscious in their approach towards treatment decisions.

Conclusions: Our analysis of the medical record underscores the complexity of treatment decisions about dialysis initiation in real-world clinical settings and supports a re-conceptualization of dialysis initiation as a *process* that unfolds over time rather than as a discrete treatment decision occurring at a fixed point in time.

Funding: Other U.S. Government Support, Veterans Administration Support

TH-PO975

Trends in 30-Day Readmission Rates in Dialysis Patients During an Era of Medicare Payment Policy Changes, 1996-2012

Allan J. Collins,¹ Peer Kidney Care Initiative Investigators.² ¹MMRF; ²Peer Kidney Care Initiative.

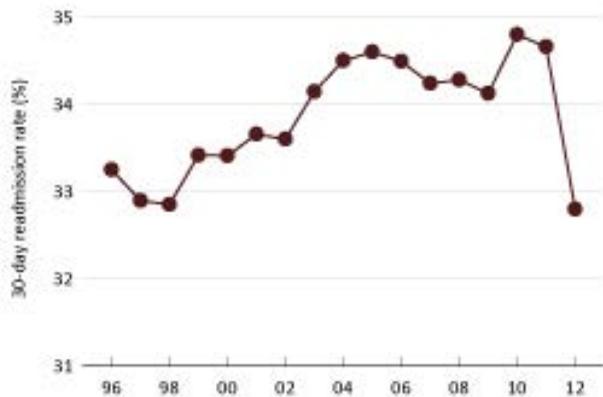
Background: High hospital readmission rates, which may indicate inadequate quality of care and result in unnecessary expenditures, have been a recent focus for Medicare. Medicare has enacted payment-related policy changes: freezing the inpatient payment rate (1997), expanding "disproportionate share" hospital payments (early 2000s), tying

reimbursement for outpatient hemodialysis services to the number of monthly visits (2004), introducing the new Medicare prospective payment system (2011), and instituting the “hospital payment penalty” (2012). Given evidence demonstrating links between these changes and readmission rates in the general population, we sought to examine changes in 30-day readmission rates in dialysis patients 1996–2012.

Methods: Data were obtained from the Centers for Medicare & Medicaid Services End-Stage Renal Disease database. Dialysis patients were assessed for discharges from short-term or critical access hospitals. Thirty-day readmission rates were calculated, without adjustment for differences in patient case-mix or hospital characteristics.

Results: All-cause readmission rates increased modestly over the period studied except for 2012. The nadir was 32.8% in 1998; the rate increased to 34.6% in 2005, fell to 34.1% in 2009, and peaked at 34.8% in 2010. Discharge data in the first 6 months of 2012 showed further decrease (32.8%). In comparison, other studies show that the rate in the general Medicare population was relatively stable 2007–2011 (19.0%), and decreased in 2012 (18.4%).

Conclusions: Thirty-day readmission rates were substantial in dialysis patients compared with general Medicare patients, possibly reflecting case-mix. How public policy changes may have affected potentially avoidable readmissions should be more fully explored. Cause-specific readmission rates might provide a better reflection of quality of care and should be examined.



For 1996 – 2011, the 30-day readmission rate was calculated for live discharge from January 1 to December 31;
For 2012, the 30-day readmission rate was calculated for live discharge during January 1 to June 30.

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TH-PO976

The Impact of Volume Status on Nocturnal Hypoxemia in Patients Undergoing Maintenance Hemodialysis Farhanah Yousaf, Mitesh K. Patel, Sherbeth Marie C. Young, Chaim Charytan, Alla Goldberg, Bruce S. Spinowitz. *New York Hospital Queens, Flushing, NY.*

Background: Hemodialysis patients experience changes in volume status according to hemodialysis schedule. Excess fluid volume may shift to the neck upon assuming a recumbent position during sleep, leading to engorgement of the great veins of neck and peripharyngeal edema. We explored the impact of volume status on nocturnal hypoxemia in the hemodialysis population.

Methods: Following local IRB approval, adult hemodialysis patients who were undergoing regular chronic hemodialysis (HD) for at least 3 months were consented to complete two nights of nocturnal oximetry using Pulsox 300i wristwatch. HD night was defined as the night of HD treatment whereas non-HD night was defined as the night on which no HD was performed. The first hour of recording was deleted in efforts to capture oximetry reading from sleep time only. Motion artifacts and aberrant data were also excluded from the analysis. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds, per hour. Paired t-test was used to compare HD and non-HD night related data.

Results: Twenty HD patients (11 males and 9 females) aged 54 ± 13 years with a mean body mass index of 25.5 ± 4.6 kg/m² and neck circumference of 38.4 ± 5.8 cm participated in the study. Mean ODI was 21.2 ± 21.1 on HD night versus 20.0 ± 19.8 on non-HD night (p=0.6) with a mean interdialytic weight gain of 1.9 ± 1.3 Kg. The lowest recorded mean saturation was 76 ± 10 % on HD night versus 73 ± 11 % on non-HD night (p=0.3). Eleven of 20 patients, with a mean interdialytic weight gain of 2.1 ± 1.5 Kg, experienced worsening

of ODI on non-HD night (16.9 ± 17.9) versus HD night (11.6 ± 13.8) [p=0.008]. Meanwhile, nine patients, with a mean interdialytic weight gain of 1.5 ± 0.9 Kg, exhibited improvement in ODI on non-HD night (23.8 ± 22.4) versus HD night (32.9 ± 23.1) [p=0.04].

Conclusions: Volume status alone does not explain HD to non-HD variation in nocturnal hypoxemia seen in ESRD population. Both central and obstructive mechanisms are likely involved. Additional research is warranted to further explore this phenomenon and develop preventive strategies.

TH-PO977

Hospital Readmission within 30 Days of Discharge Among Adults Receiving Dialysis Lorien S. Dalrymple,¹ Barbara A. Grimes,² Patrick S. Romano,¹ Yi Mu,¹ Danh V. Nguyen,³ Kirsten L. Johansen.^{2,4} ¹UC Davis; ²UCSF; ³UC Irvine; ⁴San Francisco VA.

Background: Hospital readmission is common in adults receiving dialysis. Few studies have examined the timing or causes of 30-day hospital readmission.

Methods: We used the USRDS to examine adults initiating dialysis Jan 2009 through Dec 2010 who had Medicare as the primary payer. The cohort was followed from day 90 of dialysis for up to one year, with censoring for death, renal recovery or transplant. We classified the principal cause of the index hospitalization and hospital readmission using Clinical Classification Software.

Results: Our cohort consisted of 103,381 patients. During follow-up, 50,639 patients experienced 89,728 index hospital admissions; 5% resulted in in-hospital death. Of the 85,284 live hospital discharges, 25,792 (30%) were associated with 30-day readmission. The median time to readmission was 11 [5, 19] days. Leading causes of readmission by cause of index hospitalization are in Table 1.

Cause of Index Admission	Causes of Readmission				
	Leading Cause	2 nd Leading Cause	3 rd Leading Cause	4 th Leading Cause	5 th Leading Cause
All-Cause N=89728	Complication of device, implant or graft	Septicemia	CHF	DM	HTN
Complication of device, implant or graft N=14195	Complication of device, implant or graft	Septicemia	DM	CHF	HTN
Septicemia N=6049	Septicemia	Complication of device, implant or graft	DM	Pneumonia	CHF
HTN* N=5380	HTN	Complication of device, implant or graft	CHF	DM	Fluid and electrolyte disorders
CHF† N=5322	CHF	HTN	Complication of device, implant, graft	Fluid and electrolyte disorders	Septicemia
DM‡ N=4986	DM	Complication of device, implant or graft	Septicemia	HTN	Complications of surgical procedures or medical care

*HTN: Hypertension with complications and secondary hypertension; †CHF: Congestive heart failure - nonhypertensive; ‡DM: Diabetes mellitus with complications

For the 5 most common causes of hospitalization, the principal cause for readmission was in the same category as the initial admission, accounting for 18-32% of readmissions.

Conclusions: Thirty-day hospital readmission in Medicare recipients on dialysis is frequently for a cause related to the initial admission.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.

TH-PO978

Racial/Ethnic and Age Differences in Cause-Specific Deaths Among U.S. Dialysis Patients Alison J. Yu,¹ Keith C. Norris,² Alfred K. Cheung,³ Guofen Yan.⁴ ¹Univ of Southern California; ²UCLA; ³Univ of Utah; ⁴Univ of Virginia.

Background: Recent research reported that Hispanics have the lowest all-cause mortality, African Americans (AAs) intermediate, and Whites the highest among U.S. dialysis patients over 30 years old. The objective of this study is to examine whether this risk pattern varied depending on the cause of death.

Methods: The study included 1,255,640 adult incident dialysis patients between 1995 and 2010 in the USRDS, with no prior kidney transplantation. We examined 5 major cause-specific deaths: cardiovascular (CVD), infection, malignancy, others, and unknown. Cause-specific hazards for each cause-specific death were compared among AAs, Hispanics, and Whites for overall and stratified by age groups.

Results: After adjustment for multiple covariates (Table), compared with Whites, in all age groups, Hispanics consistently had lower risks of cause-specific deaths for all major causes examined (HRs<1), while AAs also had lower risks except for the cause of infection, for which AAs had significantly higher risks in age groups of <50 and >80 years (HRs from 1.07-1.94).

Table. Adjusted cause-specific hazard ratios (HRs) for AAs and Hispanics vs. Whites

Age Groups	CVD		Infection		Malignancy		Others		All-cause	
	AA	Hispanic	AA	Hispanic	AA	Hispanic	AA	Hispanic	AA	Hispanic
18-30	0.99*	0.52	1.94	0.81	0.52	0.60*	1.06*	0.62	1.17	0.60
31-40	0.85	0.61	1.51	0.95*	0.82*	0.65	0.75	0.63	0.97	0.68
41-50	0.74	0.60	1.07	0.79	0.75	0.66	0.59	0.56	0.79	0.63
51-60	0.69	0.63	0.83	0.71	0.86	0.61	0.54	0.56	0.72	0.64
61-70	0.74	0.70	0.84	0.81	0.82	0.62	0.50	0.59	0.73	0.69
71-80	0.78	0.78	0.98*	0.90	0.92	0.70	0.54	0.60	0.78	0.76
>80	0.84	0.84	1.07	1.01*	1.06*	0.89*	0.57	0.65	0.83	0.83

Note: all significant at p<0.05 except the ones indicated by *.

Conclusions: The racial difference observed in all-cause mortality, in which Hispanics have the lowest risk, AAs intermediate, and Whites the highest, was also noted for major cause-specific deaths in most age groups, except for the cause of infection. Both younger and older AAs are at the greatest risk of death due to infection. Further studies are needed to explore the specific reasons responsible for the higher risk of infection-related death in AAs.

Funding: NIDDK Support

TH-PO979

Dialysis Therapy and Mortality in Older Heart Failure Patients with Advanced Chronic Kidney Disease: The Kaiser Permanente MATCH Study
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Background: Heart failure (HF) and chronic kidney disease (CKD) often coexist and those with both have much worse outcomes than having either alone, with limited data to guide optimal management. We evaluated the outcome of dialysis therapy in a diverse elderly cohort with HF and advanced CKD.

Methods: In Kaiser Permanente Northern California, a large integrated healthcare system, we identified members ≥70 years with HF and estimated glomerular filtration rate (eGFR) £20 ml/min/1.73 m² between 2008-2012 and no prior renal replacement therapy, cancer, cirrhosis or organ transplant. Through 2013, we identified patients who started chronic dialysis and individually matched controls who were alive on the dialysis start date of the matched case along with age, gender, diabetes status, and high-dimensional propensity score to start dialysis. Demographics, clinical features and drug use were obtained from electronic records. We calculated rates of death through 2013 and examined the impact of dialysis on mortality using Cox regression.

Results: We identified 334 eligible HF-CKD cases who initiated dialysis and 899 matched control HF-CKD patients. Mean age was 80.1±4.8 yrs, with 51% women, 33% black and 72% diabetic. Case and control patients were well-matched across characteristics, except for controls being less likely to be Hispanic or have proteinuria, or to receive alpha or calcium channel blockers or thiazide diuretics; and more likely to have prior intracranial bleed, liver disease, dementia and higher blood pressure, hemoglobin and mean eGFR (16.4 vs. 12.0 ml/min/1.73 m²). Incidence of death was 32 per 100 p-y in combined case and control patients. Among matched patients, after further adjustment for residual differences in patient features, dialysis was independently associated with a 47% lower rate of death (hazard ratio 0.53, 95%CI:0.41-0.67).

Conclusions: In older adults with HF and advanced CKD, dialysis was independently associated with a lower mortality. Randomized trials are needed to determine the net outcomes of dialysis related to both length and quality of life in the elderly with HF and advanced CKD.

Funding: Private Foundation Support

TH-PO980

Gender, Poverty, and Dialysis Mortality in Adults with Sickle Cell Disease
Tanjala S. Purnell, Xun Luo, Carlton Haywood, Sophie Lanzkron, Lauren Marie Kucirka, Sunjae Bae, Morgan Grams, Dorry L. Segev. *Johns Hopkins Univ.*

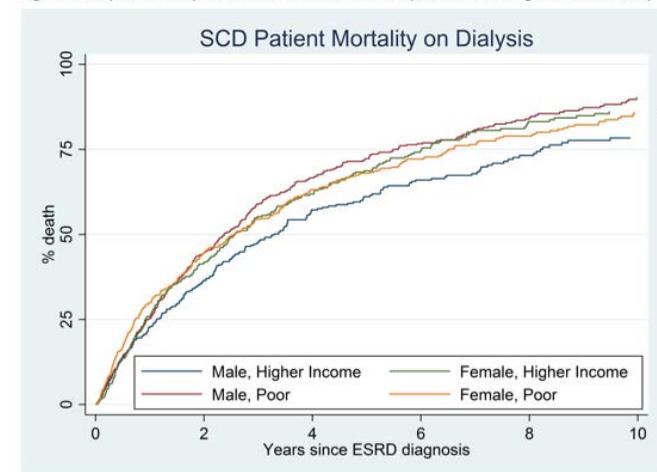
Background: Chronic dialysis patients with sickle cell disease (SCD) have increased risk of mortality compared with the general US dialysis population. The contributions of gender and neighborhood poverty to dialysis mortality in SCD patients are largely unknown.

Methods: Using USRDS data, we linked all US adults with SCD who initiated dialysis between 1995-2012 with zip-code level US Census neighborhood data. We performed multivariable Cox regression models with adjustment for age, dialysis type, BMI, and diabetes status to compare mortality between men and women, stratified by neighborhood poverty level. Neighborhoods with ≥20% of households living below the federal poverty level were defined as poor.

Results: The study cohort included 1,681 SCD patients on dialysis with 52% male, 94.7% black, mean age 42.5, and 55.9% living in poor neighborhoods. 1-, 5-, and 10-year mortality in this population were 26.1%, 67.9%, and 85.5%. Overall, men had similar mortality to women (aHR: 0.96, 95% CI: 0.86-1.07, p=0.45). However, men living in poor neighborhoods had higher risk of death than women (aHR: 1.20, 95% CI: 1.04-1.40,

p=0.015). (Figure 1) The median survival time from dialysis initiation for poor men with SCD was 2.37 years. In comparison, the median survival time for poor men without SCD was 3.77 years.

Figure 1. Dialysis Mortality in Sickle Cell Disease Patients by Gender and Neighborhood Poverty



Conclusions: Men with SCD who live in poor neighborhoods were at highest risk of death. Efforts to address socioeconomic barriers may be an important target for improving survival in this population.

Funding: NIDDK Support, Other NIH Support - NHLBI

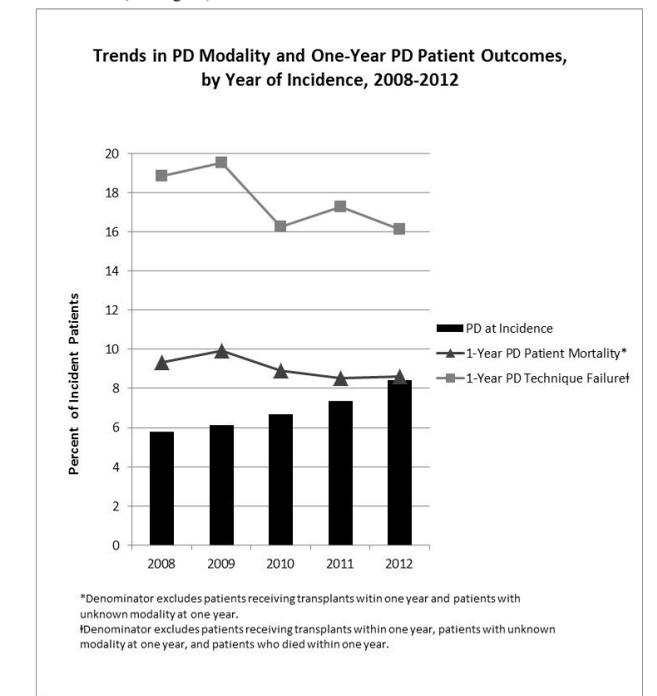
TH-PO981

Peritoneal Dialysis (PD) Patient Outcomes Under the Dialysis Prospective Payment System (PPS)
Marc Turenne, Regina M. Baker, Jeffrey Pearson, Chad M. Cogan, Purna Mukhopadhyay, Elizabeth L. Cope. *Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: The use of PD was expected to be incentivized by the expanded Medicare PPS that was implemented in 2011. There is early evidence under the PPS of additional incident ESRD patients and dialysis facilities using PD (Hirth et al 2013; Turenne et al 2014). More widespread PD use could have implications for PD outcomes due to potential changes in PD selection or in the experience of dialysis providers with PD. This study assessed PD patient outcomes before and after the new PPS was implemented.

Methods: This study included n=36,582 incident ESRD patients for whom PD was identified as the intended initial dialysis modality on the CMS ESRD Medical Evidence Form during 2008-12. We evaluated 1-year PD technique failure and PD patient mortality using data from Medicare claims, the Standard Information Management System, CROWNWeb, and the CMS Death Notification Form. PD technique failure was ascertained when hemodialysis was used for at least 60 days.

Results: Selection of PD increased from 5.8% to 8.4% of incident patients between 2008 and 2012 (see Figure).



*Denominator excludes patients receiving transplants within one year and patients with unknown modality at one year.
†Denominator excludes patients receiving transplants within one year, patients with unknown modality at one year, and patients who died within one year.

During this period, 1-year PD technique failure decreased from 18.8% to 16.1% of patients and 1-year PD patient mortality decreased from 9.4% to 8.6% (see Figure). Outcomes were relatively stable or improving across patient age, race, and Hispanic ethnicity subgroups and for patients in both urban and rural areas.

Conclusions: In the context of expanding PD use under the new PPS, there is no early evidence of worsening overall PD patient outcomes or of growing disparities in PD patient outcomes by demographic group or by urban/rural location. Instead, there were lower levels of PD technique failure and PD patient mortality in the initial years of the new payment system.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities (NIH-NIMHD)

TH-PO982

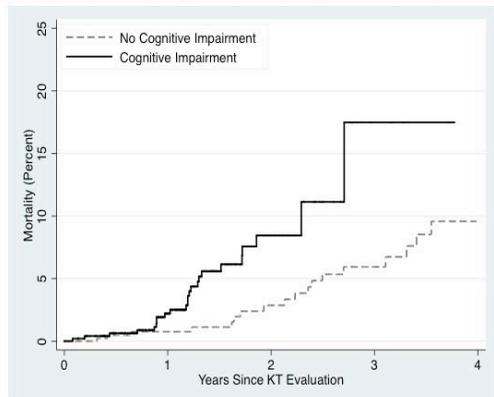
Cognitive Impairment and Mortality in Adults on the Kidney Transplant Waitlist Mara McAdams-DeMarco, Hao Ying, Israel O. Olorundare, Dorry L. Segev. *Johns Hopkins.*

Background: Older adults with poor cognitive function are at increased mortality risk. It is unclear whether ESRD patients of all ages with cognitive impairment are at increased mortality risk of while on the kidney transplant (KT) waitlist.

Methods: 918 ESRD patients being evaluated for and waitlisted for KT (no previous listings) at Johns Hopkins were enrolled in a prospective cohort study (11/2009-5/2014). The Modified Mini Mental Status (3MS), a test of global cognitive function (range 0-100, higher scores represent better function) was assessed at KT evaluation. Global cognitive impairment was defined as 3MS score<80). Mortality risk by 3MS score and cognitive impairment (separately) was estimated using an adjusted Cox proportional hazards model; participants were censored at the waitlist removal, time of KT or administrative end of follow-up.

Results: At KT evaluation, the mean (SD and range) age was 54 (14; 18-86), 57% were male, and 46% were African American. The mean (SD and range) 3MS score was 82.6 (11, 47-100) and 52% were classified as having cognitive impairment. 45 participants died over an average of 1.7 years of follow-up. Mortality risk was greater for adults on the KT waitlist who had worse 3MS scores (1 point decrease in 3MS score: HR=1.05, 95% CI: 1.02-1.08, P=0.003) and those with cognitive impairment (HR=2.51, 95% CI: 1.26-4.99, P=0.009) after adjusting for sex, age, race, education, and dialysis factors. The risk of mortality associated with cognitive impairment was similar for older (age≥65) and younger (age<65) participants (P=0.73).

Waitlist Mortality by Global Cognitive Impairment.



Conclusions: Among adults ESRD patients, impairment in global cognitive function more than doubled the risk of waitlist mortality. A simple screener for global cognitive function scores at the evaluation for first listing would not only identify adults with ESRD who have unrecognized cognitive impairment but also identify a high-risk population.

Funding: Other NIH Support - NIA, Private Foundation Support

TH-PO983

Indications, Technique, and Outcome of Plasmapheresis in a Large Pediatric Dialysis Center Rainer Büscher, Lübbert Lübbers, Anja K. Büscher, Peter F. Hoyer. *Pediatric Nephrology, Univ of Duisburg-Essen, Pediatrics II, Essen, Germany.*

Background: Plasmapheresis (PP) is a established therapeutic option for various indications in pediatric patients. However, there are only few reports with only little information on clinical outcome.

Methods: We performed a retrospective analysis involving 86 children and adolescents undergoing PP in our pediatric dialysis unit from 1997 to 2013.

Results: Within the observation period, 86 children (41 male), mean age 8.7±3.2 years (3 months to 18.9 years) received PP for a total of 652 sessions (1-33 sessions/patient; mean 6.4±3.1 sessions/patient). Most patients (30.2%) were treated for hemolytic-uremic syndrome (HUS), 18.6% for liver failure and 7.8% for rejection following renal transplantation. Other indications included encephalitis (5.9%), thrombotic thrombocytopenic purpura (4.9%), autoimmune hepatitis (3.9%), rapid progressive glomerulonephritis (3.9%) and nineteen other indications (24.8%). Membrane filtration

was used in all patients, fresh frozen plasma (64.7%) the most frequently used substitution fluid and heparin the most frequently used anticoagulant (85.5%). Complications during PE included emesis (17.4%), seizures (13%), hypotension (8.7%), diarrhea (8.7%), mild allergic reactions (4.4%) and headaches (4.4%). All complications could be resolved. Overall, PP achieved full disease remission in 52 patients (60.4%), 14 patients showed a partial response (16.3%) and 20 patients (23.3%) did not respond at all. Among these, 12 patients (15.1%) died within the following 30 days. When stratified by diagnosis, 65% of all HUS patients (n=17/26) achieved complete remission and 5 out of 6 patients with encephalitis (85%) showed no relapse. Only poor results could be achieved in 16 patients with liver failure, where PP was used as bridging therapy prior to liver transplantation (LTX). Ten patients (62.5%) died prior or post LTX and 6 could be successfully transplanted.

Conclusions: Plasmapheresis is a safe method in children with a high efficacy in patients with hemolytic uremic syndrome, neurological autoimmune diseases and other primary renal diseases. Patients with liver failure who receive PP as bridging therapy show an infaust outcome.

TH-PO984

Who Makes the Best Exit Site: Nephrologist or Surgeon? Vaibhav S. Keskar, Mohan B. Biyani, Brian Blew, Jeffrey Warren, Brendan McCormick. *The Ottawa Hospital, Univ of Ottawa, Ottawa, ON, Canada.*

Background: Buried peritoneal dialysis(PD)catheters are placed months before dialysis is needed and the exit site is created at the initiation of dialysis by the nephrologist. In contrast, the exit site of an unburiated catheter is created by the surgeon at the time of insertion. Our PD unit uses both methods of catheter placement. We undertook this study to compare the outcomes of the two methods of exit site creation.

Methods: The charts of all patients who initiation PD between Jan 2012 and Dec 2013 were reviewed. At each clinic visit, exit sites were graded by the PD nurse into standard predefined groups: perfect, good, equivocal and infected. Primary outcome was the frequency of perfect exit sites at 2, 6, and 12 months after initiation of PD. Secondary outcomes were exit site infections, peritonitis and technique failure due to exit site infection.

Results: 119 patients started PD during the period of interest and 114 remained on PD at 2 months. 52 patients had buried catheters exteriorized at the time of starting PD (group A) and 62 patients had unburiated catheters (Group B). Group A had more males (71% vs 48%), had higher mean age (65±14 vs 59±15) and had most of the patients as incident dialysis patients. Diabetic nephropathy was the most common underlying disease in either group (61.53% and 51.61%). Group B had a higher frequency of perfect exit sites at 2 months but this difference disappeared by 6 and 12 months. There was a trend towards more exit site infections in Group A but this did not translate into more technique failure.

		Group A (Buried, n=52)	Group B (Unburied, n=62)	p
% of perfect exit sites	2 months	40%	56%	0.02
	6 months	57%	62%	0.34
	12 months	62%	53%	0.65
Exit site infections		8	3	0.06
Tunnel infections		0	1	NS
Peritonitis		6	5	NS
Technique failure		2	1	NS

Conclusions: Buried catheters are less likely to have perfect appearance at two months compared to unburiated catheters; however this is no longer significant at six and 12 months. The trend towards more exit site infections with buried catheters suggests that there may be clinical consequences of the tissue trauma at time of exteriorization. Consideration should be given to the use of prophylactic antibiotics at exteriorization.

TH-PO985

Prevention of Peritoneal Dialysis Catheter-Related Infections – A Multicenter Randomized Controlled Trial Mercedes L. Velo, Paula López, Carmen Felipe, Jose Ramon Rodriguez-Palomares, Gloria Del peso, Francisco Javier Ahijado, Fernando Tornero, Mar?a Jose Fernandez Reyes, Ana M. Tato, Maria Rosario Luque, Jose M. Portoles. *Grupo Centro Diálisis Peritoneal, Spain.*

Background: Peritonitis, tunnel and catheter exit site (CES) infections are the most serious complications of peritoneal dialysis (PD). We studied the effect of antibiotic ointment (EUDRAC: 2009-016835-36) on catheter-related infections (CRI) and morbidity.

Methods: Allocation was stratified in blocs of 4/center. Ointment containing 2% colistin, tobramycin, amphotericin B and 4% vancomycin or normal saline were applied to the CES over 1 year. Follow-up period was 3 months after the last dose. Exit site infection (ESI) was defined as erythema, edema or local pain with purulent secretion and positive culture. Antimicrobial therapy was given according to local protocols.

Results: 140 patients were included, 6 didn't meet entry criteria. Characteristics and dialysis parameters of the 65 in the control group (CG) and 69 intervention group (IG) patients were comparable.

	Study	Control
Age, mean (SD)	56.5	58.9
Gender, male, %	65.2	53.1
Diabetes, %	24.6	26.6
Charlson index	3.2	3.3
Prior cardiovascular events, %	27.5	23.4
Time in PD, mean, years	1.3 (1.5)	2 (2.2)
APD/CAPD, %	30.4	25
Residual renal function, ml/min	4.5 (4.4)	6.3 (4.2)
KTv	2.2 (0.6)	2.3 (2.5)

Mean study duration was 0.6 (IG) vs 0.6 (CG) years (ns). 26 episodes of CRI (11 ESI, 4 tunnel, 11 peritonitis) occurred in the CG and 12 in the IG (3 ESI, 0 tunnel, 9 peritonitis) ($p < 0.001$). Etiology of ESI was *Staphylococcus aureus* (x7), *Corynebacterium* spp, *Pseudomonas aeruginosa*, *E. coli*, *Serratia* spp., coagulase-negative *S. (x2)* and 1 negative culture in the CG and *S. aureus* (x1), 1 Gram-negative bacillus and 1 negative culture in the IG. Systemic or topical antibiotics were given for ESI in 11 (CG) and 2 patients (IG) ($p < 0.01$), respectively. Hospital admissions were 23 (CG) and 15 (IG). Local side effects were significantly increased in the IG.

Conclusions: Local prophylaxis with a broad-spectrum antimicrobial ointment is associated with a significant reduction in ESI and systemic antibiotic use without associated bacterial resistance. Significant local side effects were observed.

Funding: Private Foundation Support

TH-PO986

Association Between Plasma Fibroblast Growth Factor-23 and Carotid Artery Atherosclerosis in Peritoneal Dialysis Patients Nanmei Liu, Jimin Hospital of Shanghai.

Background: We investigate the association between plasma fibroblast growth factor-23 (FGF-23) level and carotid artery atherosclerosis of 125 stage 5 chronic kidney disease (CKD5) patients, who are doing continuous ambulatory peritoneal dialysis (CAPD) at renal division of Shanghai Jimin Hospital in China.

Methods: A retrospective cohort study of individuals 15 years of age and older, divided into two cohorts according to carotid intima-media thickness (CIMT) : CIMT normal cohort (CIMT<0.9mm) and CIMT thickening cohort (CIMT≥0.9mm). Plasma FGF-23 concentrations were determined by ELISA. CIMT thickness and atherosclerotic plaques were measured by carotid ultrasound.

Results: Of the 125 PD patients, the CIMT was thickened in 82 patients (65.6%). Compared with the CIMT normal patients, plasma FGF-23 concentration was significantly increased ($p < 0.01$) in the CIMT thickening cohort (Table 1). Linear regression analysis discovered an obvious positive correlation between plasma FGF-23 and CIMT ($r = 0.416$, $P = 0.006$) (Table 2). Multiple regression analysis indicated that plasma FGF-23 level was independent risk factor for CIMT ($\beta = 0.421$, $t = 2.607$, $P < 0.01$) (Table 3).

Conclusions: The level of plasma FGF-23 was positively correlated with CIMT and played an important role in development of carotid artery atherosclerosis in peritoneal dialysis patients.

Funding: Government Support - Non-U.S.

TH-PO987

Atherogenic Index of Plasma Is Associated with Insulin Resistance in Non-Diabetic Peritoneal Dialysis Patients Mi Jung Lee,¹ Jae Eun Um,² Meiyan Wu,² Tae ik Chang,³ Tae-Hyun Yoo.¹ ¹Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; ²Brain Korea 21 PLUS, Severance Biomedical Science Inst, Yonsei Univ College of Medicine, Seoul, Korea; ³Dept of Internal Medicine, NHIC Ilsan Hospital, Gyeonggi-do, Korea.

Background: Insulin resistance (IR) is an independent risk factor for cardiovascular morbidity and mortality. Although many factors including uremia, chronic inflammation, and abnormal adipokine levels are known to contribute to the development of IR, the role of pro-atherogenic lipoprotein on IR remains unknown in peritoneal dialysis (PD) patients. Therefore, we investigated the independent association between pro-atherogenic lipoprotein and IR in non-diabetic PD patients.

Methods: We conducted a cross-sectional study in 75 non-diabetic PD patients. Pro-atherogenic lipoprotein was assessed by the atherogenic index of plasma (AIP, log transformed triglyceride to high-density lipoprotein cholesterol ratio). IR was determined by homeostatic model assessment-IR (HOMA-IR). Patients were divided into the higher and lower HOMA-IR group according to the median value of HOMA-IR. Independent association between AIP and HOMA-IR was ascertained by multivariate linear regression analysis.

Results: The mean age of the patients was 52.1±11.2 years, 35 patients (46.7%) were male. The mean value of AIP was 0.38±0.33 and the median value of HOMA-IR was 1.58 (interquartile range, 0.88 to 2.76). AIP was significantly greater in the higher HOMA-IR group (0.25±0.27 vs. 0.53±0.32, $P < 0.001$). AIP was negatively correlated with systolic blood pressure ($r = -0.32$, $P = 0.005$) and log adiponectin ($r = -0.42$, $P = 0.001$) and positively correlated with sagittal abdominal diameter ($r = 0.25$, $P = 0.033$), residual renal function

($r = 0.29$, $P = 0.012$), serum albumin ($r = 0.26$, $P = 0.026$) and log HOMA-IR ($r = 0.54$, $P < 0.001$). In multiple linear regression analysis, AIP ($\beta = 0.251$, $P = 0.037$) was independently associated with HOMA-IR after adjustment for confounding factors.

Conclusions: Pro-atherogenic lipoprotein abnormality determined by high AIP might be implicated with development of IR in non-diabetic PD patients.

TH-PO988

Reducing Mortality in CAPD Patients by Statin Yong kyu Lee, Tae ik Chang, Sug kyun Shin. *Nephrology Div, Dept of Internal Medicine, National Health Insurance Corporation, Ilsan Hospital, Goyang, Korea.*

Background: Patients who are on CAPD (Continuous Ambulatory Peritoneal Dialysis) shows higher serum LDL cholesterol and Triglyceride compared to patients who are on hemodialysis. But higher cholesterol level does not seem to effect on raising mortality or cardiovascular morbidity and PD failure. On the contrary, lower serum cholesterol level in CAPD patients tends to raise mortality and morbidity due to poor nutritional status.

Methods: This study is a retrospective study designed to evaluate the effect of cholesterol level, statin on CAPD outcome and mortality. Patients who were on peritoneal dialysis for at least 6 months since March 1st, 2000 were included. A total of 467 patients were enrolled in this study. Patients' biological parameter, biochemical parameter and morbidity/mortality during CAPD maintenance period were collected.

Results: Patients whose initial cholesterol level were above 240 mg/dL shows significantly low CAPD failure rate compared to patients whose initial cholesterol level were below 200 mg/dL (OR= 0.469, $p = 0.049$). Patients whose average LDL-cholesterol during CAPD period were over 100mg/dL showed significantly higher mortality compared to patients whose initial LDL-cholesterol level were below 100mg/dL (OR=1.848, $p = 0.024$). Patients whose compliance to statin during CAPD period was over 80% showed significantly low mortality compared to patients who did not take statin during CAPD period (OR=0.556, $p = 0.020$). Patients showed no significant difference in mortality due to total cholesterol, HDL cholesterol levels and patients showed no significant difference in CAPD failure due to HDL/LDL cholesterol, statin usage.

Conclusions: In CAPD patients, serum total cholesterol level should be targeted higher than HD or CKD patients. On the contrary, similar to HD or CKD patients, Statin should be administered and LDL cholesterol should be lowered during CAPD period to lower mortality. To identify the difference in cholesterol mechanism of CAPD patients further, in depth study over adequate cholesterol level in CAPD patients needs to be proceeded.

TH-PO989

Using Daily Remote Biometric Monitoring in Peritoneal Dialysis Susie Q. Lew,¹ Manya Magnus,² Neal Sikka.³ ¹Medicine, George Washington Univ, Washington, DC; ²Epidemiology and Biostatistics, George Washington Univ, Washington, DC; ³Emergency, George Washington Univ, Washington, DC.

Background: Peritoneal dialysis (PD) requires self-monitoring with daily blood pressure (BP), weight, & physical examination. Patients (Pts) don't always perform procedures or record results. We aim to determine associations between daily remote biometric monitoring (RBM) & clinical and pt satisfaction outcomes.

Methods: Pts were provided with BP monitoring equipment & scale which were capable of announcing the results, transmitting the results via Bluetooth technology to a hub located in the pt's home & via 2G/3G cellular signal to a Telehealth call center. PD nurses viewed results or alerted to abnormal results.

Results: 300 subjects (subjs) from 10 PD units were followed over at least 12 months. Demographics include male (56%), African American (AA) (62%), & median age 56 yrs (IQR 44-64) and 1.86 yrs on dialysis (IQR 0.62-3.73). AA subjs were more likely to use than non-AA (69% vs 55%, $p < 0.05$). 51% of subjs used RBM, with 66% consistently using the equipment. RBM was associated with reduced risk of hospitalization (Coef -0.27, SE 0.10, $p = 0.006$). Subjs became increasingly less likely to breach any upper or lower alert threshold (OR 0.995, $p = 0.004$). Subj satisfaction of RBM equipment for BP monitoring was 87% & scale 90%. Rural exceeded non-rural subjs in utilizing RBM (OR 4.77, 95% CI 1.34-16.98, $p < 0.02$) Use of RBM was associated with improved perception of confidence with self-care requirements of PD: easier to collect measurements (OR 2.69, 95% CI 1.52-4.76, $p < 0.001$); more secure in their measurements (OR 3.28, 95% CI 1.71-6.26, $p < 0.001$); getting more support from their PD doctors and nurses (OR 2.03, 95% CI 1.01-4.12, $p < 0.05$).

Conclusions: RBM was associated with increased frequency, accuracy, and communication of measurements to medical personnel, enhanced perception of autonomy and confidence in measurements, & reduction of hospitalizations & out of range measurements for BP. RBM was acceptable & satisfactory to PD pts. RBM offers additional tools to support PD pts in maintaining their measurement regimens & reduce negative health outcomes.

Funding: Other U.S. Government Support

TH-PO990

Impact of Patient-Centric Automated Peritoneal Dialysis User-Interface on Operator Learning and Confidence Catherine Firanek, Mary Gellens, James A. Sloand. *Medical Affairs, Baxter Healthcare, Deerfield, IL.*

Background: Automated peritoneal dialysis (APD) is an underutilized therapy for patients with end-stage renal disease (ESRD). The perception patients may not be able to manage their own treatment setups comes into play in choice of this treatment modality. Improvements to cyclor technology may help to further simplify therapy for patients,

reducing barriers to uptake. This study aimed to determine whether a cyclor-embedded, patient-centric interface offered an enhanced user experience compared to a conventional APD cyclor.

Methods: 30 study participants (ages 29-84, mean 50 yrs, 67% male) diagnosed with ESRD were randomized into 2 groups using cyclor with patient-centric user interface with advanced technology in development and a conventional APD cyclor. Participants evaluated cyclors on 2 non-consecutive days using a different cyclor each day. Each participant was given a brief orientation, setup task, training session, break, followed by a setup task and questionnaire. Study results were analyzed via Fisher's exact, Mann-Whitney and Exact binomial tests.

Results: The cyclor with patient-centric user interface and advanced technology (in development) scored better on reduced reliance on printed instructions ($p < 0.0001$). Patients committed fewer deviations on the cyclor in development vs the conventional cyclor (2 of 19 steps vs 14 of 19 respectively) after training ($p = 0.004$), including disinfecting hands ($p = 0.02$) and line handling ($p = 0.01$), and were more confident that they set up the cyclor according to specifications ($p = 0.043$). The new cyclor scored higher in overall preference among study participants: The cyclor with a patient centric user interface was rated easier to learn ($p = 0.005$) and to use ($p = 0.016$), preferable to use ($p = 0.03$), and users felt more confident about using the new cyclor at home compared to conventional cyclor ($p = 0.001$).

Conclusions: A cyclor with embedded, patient-centric interface was rated higher in terms of overall reliance on instructions, task competency, ease of use and learning, preference and overall confidence of using the cyclors. These findings indicate that APD operator learning and confidence can be enhanced with a patient-centric user-interface.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO991

Single-Site Trans-Umbilical Peritoneal Dialysis Catheter Insertion
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Background: Traditional laparoscopic peritoneal dialysis catheter placement requires two ports insertion and this could lead to complications like leak and hernia at the port sites. We describe a novel approach of using single-site trans-umbilical ports that is associated with small scar (less than 1cm) and reduced complications.

Methods: Under general anaesthesia pneumo-peritoneum was created as per standard method. One 10mm port and one 5mm port was inserted through trans-umbilical route to guide peritoneal dialysis catheter insertion. Hernial orifices were inspected and if there was any adhesion present that was released to facilitate free fluid movement. The catheter was inserted through a small incision 1 inch below umbilicus. The catheter was positioned in the pouch of Douglas using lap instrument passed through the trans-umbilical port. The other end of catheter was tunneled in the standard manner and brought out though the exit site and the titanium adaptors were fixed as usual. To prevent the migration of catheter from the pelvic cavity a trans-facial loop was placed around the catheter (freely mobile but remains in pelvis). Omentum was folded and pulled upwards to the left upper quadrant and fixed to anterior abdominal wall using a trans-facial loop. The latter prevented the omentum from wrapping dialysis catheter and causing malfunction. Then the port site was closed in three layers (Video available).

Results: 10 cases underwent catheter insertion with this approach (Male 7, Female 3) and the mean follow up period is 11 months. None of them developed leak or catheter migration or any mechanical complication that might require catheter reposition or change.

Conclusions: Combined method of Single-site port placement, omentopexy and loop fixation of intra-abdominal segment of catheter offers the following advantages -small incision; hence risk of leak when catheter was used early after placement is low. The risk of hernia through port site is reduced and small scar will be welcome to image conscious patients. If there was any adhesion present that could be released with minimal trauma to peritoneal membrane. Placing a loop around the catheter prevented catheter migration. Omental wrapping was prevented by fixing this in the upper quadrant by trans-facial loop.

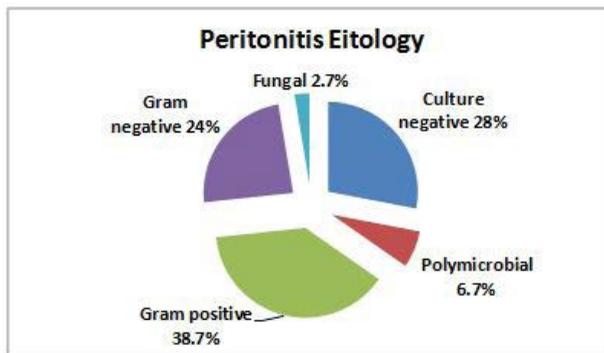
TH-PO992

Peritonitis and Survival following PD Catheter Insertion in Infants
Joshua Zaritsky, Coral D. Hanevold, Troy Richardson, Jonathan Rodean, John P. Lawlor, Raymond P. Quigley, Alicia Neu, Bradley Warady. *SCOPE Collaborative, CHA, Overland Park, KS.*

Background: Chronic peritoneal dialysis (PD) is the dialysis modality of choice for children. However, there are limited outcome data in those who undergo PD catheter (cath) insertion in the 1st year of life. Using data from the Children's Hospital Association Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (ESRD) Collaborative (SCOPE), we examined peritonitis rates and survival in 156 infants who had a PD cath placed in the 1st yr of life.

Methods: Data on pt demographics, PD cath characteristics, peritonitis risk factors and outcomes from 157 cath insertions from 29 North American pediatric dialysis centers were reviewed and analyzed using chi square test for association or a Wilcoxon rank-sum test.

Results: In hospital and overall peritonitis rates during the 1st year post cath insertion were 1.73 and 0.76 per pt-year, respectively. Gram + organisms were responsible for 38.7% of infections (**figure**); 28% were culture negative. Polycystic kidney disease and pulmonary hypoplasia were more frequent in infants with peritonitis, whereas anuria did not differ between groups (**table**). Use of a curled catheter or plastic adaptor, nephrectomy prior to or concurrent with cath insertion, and G-tube insertion after cath placement were more common in pts with peritonitis, while number of cuffs, surgical technique, cath use within 14 days and cath revision did not differ between groups. Infants with peritonitis had longer initial hospital stays and lower survival compared with those without peritonitis.



	No Peritonitis (N=91)	Peritonitis (N=65)	p
DEMOGRAPHICS (median with IQ range)			
DOL at cath placement	32 (9, 129)	21 (8, 88)	NS
Gestational age (weeks)	36 (34, 38)	37 (34, 38.5)	NS
Weight (KG)	3.3 (2.6, 5.2)	3.3 (2.6, 4.6)	NS
Initial hospitalization (days)	60 (21,90)	83 (48,130)	<0.02
RISKS/OUTCOMES for Peritonitis (% Insertions)			
	No Peritonitis (N=91)	Peritonitis (N=66)	p
Polycystic Kidney Disease	2.2	16.9	<0.01
Pulmonary Hypoplasia/CLD	21.4	36.2	<0.05
Anuria at time of placement	19.1	30.6	NS
Curled Catheter	82.4	95	<0.02
Plastic Adaptor	32.6	48.4	<0.05
Nephrectomy prior/at time of placement	3.6	18.6	<0.01
G-tube insertion after placement	23.1	42.4	<0.03
Single Cuff	33	45	NS
Open surgical placement	60	51	NS
Use w/in 14D	52.5	62.5	NS
Cath revision	18.1	29	NS
Survival: Initial hospitalization	96.7	87.9	<0.03
Survival: 1 Year	95.6	86.3	<0.04

Conclusions: In this large cohort of infants with ESRD, we found a high rate of peritonitis and identified several risk factors associated with peritonitis. Given that peritonitis was associated with increased initial hospital stay and mortality, attention to the potentially modifiable factors is needed.

TH-PO993

Risk Factors for All-Cause Unexpected Hospitalization After Peritoneal Dialysis Catheter Implantation Zi Li,¹ Zita C. Abreu,² Joanne M. Bargman,² ¹Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China; ²Nephrology, Toronto General Hospital Univ of Toronto, Toronto, ON, Canada.

Background: Implantation of the peritoneal dialysis catheter (PDC), usually an elective procedure, may necessitate unexpected hospitalization due to multiple co-morbidities and inherent instability of the end-stage renal disease patient. This information is important for administrative planning for a PD program. However, information on hospitalization after PDC implantation is limited and details about the reason for hospitalization are lacking.

Methods: We performed a prospective cohort study in consecutive patients who underwent PDC implantation at a single institution from 2007 to 2013. Clinical characteristics of enrolled patients, technique of the implantation procedure and all-cause unexpected hospitalization and morbidity within 14 days after implantation were analyzed.

Results: A total of 246 patients receiving 252 PDC implantations during the 6 years were studied. After 39 procedures (15.5%), patients had an unexpected hospital stay due to operative complications (33.3%), worsening of comorbid disease (35.9%), or a single-night hospital stay for observation (30.8%). Compared to discharged patients, the unexpected hospitalization ones were older ($P = 0.001$), had higher rates of previous episodes of heart failure ($P = 0.006$) and heart disease ($P < 0.001$), had more use of general anesthesia ($P = 0.046$), had more added procedures during the implantation ($P = 0.02$) and had more episodes of flow obstruction and peritonitis ($P = 0.012$ and $P < 0.001$). Multivariable logistic regression showed that age, cardiac morbidity, use of general anesthesia, PDC flow problems and peritonitis after implantation were independent predictors of all-cause unexpected hospitalization.

Conclusions: For the first time, our study has analyzed the rate of unexpected hospitalization after PDC implantation and identified the salient risk factors. Increased focus to identify patients at greatest risk for hospitalization, evaluation of processes of care, and implementation of preventive strategies may be helpful to reduce unplanned hospitalization after catheter insertion.

TH-PO994

Early Mechanical and Infective Complications in First Time Blind, Bedside, Midline Percutaneous Tenckhoff Catheter Insertion with Ultra Short Break-in Period: Setting New Standards *Suceena Alexander,¹ Ninoo G. George,² Santosh Varughese.¹* ¹Nephrology, Christian Medical College, Vellore, Tamil Nadu, India; ²Nephrology, Billroth Hospitals, Chennai, Tamil Nadu, India.

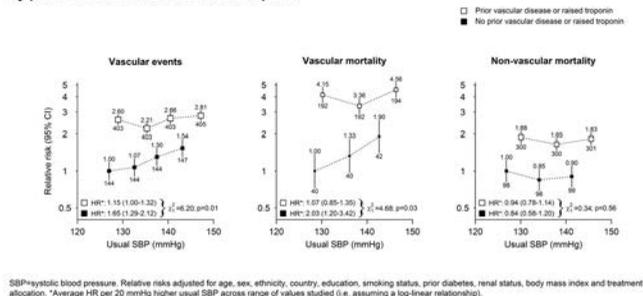
Background: There are no large studies that have looked into ultra-short break-in period with blind, bedside, midline approach of Tenckhoff catheter insertion.

Methods: 284 consecutive adult patients underwent catheter insertion for chronic peritoneal dialysis at our centre from January 2009 to December 2013. Those with history of midline laparotomy scars and hernias were referred for open surgical insertion. 245 patients (86.3%) underwent the percutaneous and 39 patients (13.7%) underwent surgical insertions.

Results: The mean break-in period for the percutaneous group (PG) was 2.68 ± 2.63 days and for the surgical group (SG) was 11.19 ± 6.96 days, p < 0.001. Poor catheter outflow was present in 22 (9%) of PG and in 4 (10.3%) of SG (p = 0.80). Primary catheter non-function was present in 24 (9.8%) of the PG and in 4 (10.3%) of the SG (p = 0.73). Catheter survival at one year was 164/241 (89.1%) in the PG. The various outcomes are:

Outcomes	Percutaneous N=245	Surgical N=39	P value
Failed Catheter Insertion,n(%)	2(0.8)	0	0.74
Poor outflow,n(%)	22(9)	4(10.3)	0.8
Dialysate leak,n(%)	16(6.5)	6(15.4)	0.055
Mesentric tear,n(%)	2(0.8)	0	0.74
Paralytic ileus,n(%)	0	1(2.6)	0.01
Exit site bleeding,n(%)	1(0.4)	0	0.69
Early peritonitis,n(%)	3(1.2)	0	0.49
Overall early mechanical complications,n(%)	40(16.3)	11(28.2)	0.07
Primary catheter non-function,n(%)	24(9.8)	4(10.3)	0.73
Mortality,n(%)	68/241(28.2)	17/36(47.2)	0.02
Catheter survival at one year,n(%)	164/184(89.1)	29/35(82.9)	0.29
Median patient survival(mts)	43(95%CI:28.5-57.5)	35(95%CI:24-46)	0.60

Figure: Relevance of systolic blood pressure to vascular events and cause-specific mortality, by prior vascular disease or raised troponin



Conclusions: The significantly shorter break-in period and smaller wound incisions reduce hospitalization and the need for bridging hemodialysis as well as having good patient and catheter outcomes.

TH-PO995

Comparing Outcomes of Percutaneous Peritoneal Dialysis Catheter Insertion by Nephrologist versus Open Surgical Insertion – Large Single Centre Experience *Louise E. Ross, Bhriju Raj Sood.* *South West Thames Renal and Transplantation Unit, Carshalton, Surrey, United Kingdom.*

Background: Several studies suggest that percutaneous insertion of peritoneal dialysis (PD) catheters by nephrologists improves the uptake of PD. Percutaneously inserted PD catheter has the advantage of being less invasive, removing the need for general anaesthetic, reducing hospital stay, facilitating acute PD, therefore making PD more accessible. There are only a few small studies directly comparing the outcomes of patients who have had a percutaneous versus open method of implantation, with some suggesting poorer outcomes.

Methods: We retrospectively reviewed data on all patients who had a percutaneous or open surgical PD catheter inserted between August 2011 and December 2014 at a single renal centre, to identify the patients who developed an exit site infection (ESI) or episode of PD peritonitis within two and four weeks of catheter insertion. We also looked at patients who developed a functional catheter problem requiring manipulation or replacement of the catheter within the first year. Chi-squared test was used to assess statistical significance.

Results: 276 PD catheters were inserted in the said time period. 152 were inserted percutaneously and 124 with open surgery. There were less ESI (at 2 weeks - 2.6% versus

6.5%; p=0.122, and at 4 weeks - 2.6% versus 10.5%; p=0.007) and less peritonitis (at 2 weeks - 0.7% versus 3.2%; p=0.112, and at 4 weeks - 1.3% versus 5.6%; p=0.044) episodes in the percutaneous versus open surgical group. PD catheters requiring manipulation or replacement within the first year due to a functional problem was comparable in the percutaneously inserted catheters (9.2% versus 12.9%; p=0.327). There were no major complications in the form of viscus perforation or major haemorrhage in either group.

Conclusions: In our study, we found that infection related complications were better with percutaneous PD catheter insertion and mechanical failure rate was comparable to open surgical PD catheter insertion. In our practice we have found that percutaneously inserted PD catheters are a safe means of increasing patient access to PD, enabling more patients to have a home-based therapy.

TH-PO996

Shared Decision-Making in Chronic Kidney Failure: The Retrospection of Early-Stage Dialysis Patients in Germany *Maxi Robinski,¹ Wilfried Mau,¹ Andreas Wienke,² Matthias Grindt.³* ¹Inst of Rehabilitation Medicine, Martin Luther Univ Halle-Wittenberg, Halle (Saale), Germany; ²Inst of Medical Epidemiology, Biostatistics, and Informatics, Martin Luther Univ Halle-Wittenberg, Halle (Saale), Germany; ³Dept of Internal Medicine II, Martin Luther Univ Halle-Wittenberg, Halle (Saale), Germany.

Background: To date, little is known about the extent to which patients with chronic kidney failure feel involved in decision-making regarding the life-changing dialysis treatment. Previous studies on mortality yielded equivalence of peritoneal (PD) and hemodialysis (HD). However, only 5% of the patients in Germany choose PD, even though many patients are eligible for both options and entitled to receive unbiased counselling.

Methods: In a nationwide multicenter study with federal funding ("CORETH-project"), we surveyed 781 patients on dialysis since 6 to 24 months with regard to their rating of shared decision-making (SDM) with their physician concerning the choice of renal replacement therapy. We used the "Shared Decision-Making Questionnaire" (Kriston et al. 2010), which is a highly reliable and well accepted measure. Furthermore, patients indicated the dominating reason for choosing their treatment as well as their treatment satisfaction (TS). Data were compared between propensity score-matched groups of patients (n_{PD}=n_{HD}=246).

Results: PD patients rated all aspects of SDM (for example, consideration of patient-preferences or shared weighing of options) significantly more positive than HD patients (SDM-total score, p<.0001). PD patients predominantly (73%) indicated their independency as a motivator for the choice, whereas HD patients were largely (30%) subject to medical decisions only. Moreover, compared to HD, PD patients were more satisfied with the information received (p=.013). The SDM- and TS-total scores correlated significantly positive in the matched overall sample (r=.19, p<.0001).

Conclusions: Our findings heighten awareness for an unbiased nephrological counselling-culture and provide indications for a successful SDM-process when choosing dialysis modality. According to the results, an effective SDM can pave the way for dialysis patients' quality of life and treatment success.

Funding: Government Support - Non-U.S.

TH-PO997

Depression and Cognitive Impairment in Peritoneal Dialysis: A Multi-Center Cross-Sectional Study *Jie Dong,¹ Hai-chen Pi,¹ Zuying Xiong,² Jinlan Liao,³ Li Hao,³ Gui-ling Liu,³ Ye-Ping Ren,⁴ Qin Wang,⁴ Li-ping Duan,⁵ Zhao-xia Zheng.⁵* ¹Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China; ²Renal Div, Peking Univ Shenzhen Hospital, Shenzhen, China; ³Renal Div, The Second Hospital of Anhui Medical Univ, Hefei, Anhui, China; ⁴Renal Div, The Second Affiliated Hospital of Harbin Medical Univ, Harbin, Heilongjiang, China; ⁵Renal Div, Handan Central Hospital, Handan, Hebei, China.

Background: Depression and cognitive impairment have been identified as independent risk factors for mortality in peritoneal dialysis (PD) patients. The relationship between depression and cognitive functions in PD patients was investigated in this multi-center cross-sectional study.

Methods: Study design: multi-center cross-sectional study. Setting & Participants: A total of clinically-stable 458 patients who performed PD for at least 3 months from 5 PD units were enrolled in this study. Factor: Depression. Outcomes: Global and specific cognitive impairment. Measurements: Global cognitive function was measured by using the Modified Mini-Mental State Examination (3MS), specific cognitive function by executive function, immediate memory, delayed memory, visuospatial skill and language ability by subtests of Repeatable Battery for the Assessment of Neuropsychological Status. Depression was diagnosed if the depression severity index > 0.5 by using Zung's Self-rating Depression Scale.

Results: The prevalence of depression and cognitive impairment evaluated by 3MS were 52% and 28.4% respectively. Patients with mild or moderate/severe depression had higher prevalence of general cognitive impairment, executive dysfunction, impaired immediate and delayed memory. After adjusting for demographic, comorbidity data and clinical parameters, depression scores were independently associated with lower scores of 3MS, immediate and delayed memory, and language ability, and longer completion time of trails A and B. Even mild depression could independently predict higher risk of CI, executive dysfunction, impaired immediate and delayed memory after multivariable adjustments.

Conclusions: Even mild depression plays an important role in global and specific cognitive functions in PD patients.

Funding: Government Support - Non-U.S.

TH-PO998

Proposed Model for the Care of Hospitalized Peritoneal Dialysis Patients

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Background: Peritoneal dialysis (PD) has been prescribed throughout the United States, yet the optimal model of care for hospitalized PD patients remains unknown. With a growing interest in home modalities and emphasis on quality, it is imperative that we identify an effective and efficient way to care for this patient population during hospitalization.

Methods: We describe a model successfully implemented at Vidant Medical Center (VMC) in 2008. Prior to this date, the primary hospital nurses performed PD care. Due to the high risk, low volume nature of inpatient PD, this resulted in inconsistent care as well as decreased physician, nursing, and patient satisfaction. In 2008, an inpatient PD nursing team was created. This team, consisting of nephrology nurses with specialized PD training, is managed by VMC's self-maintained dialysis unit. Staffed with 2 nurses during the day and 1 at night, they provide 24/7 care throughout the hospital, including the ICU and ED. Responsibilities include patient education, exit site care, catheter flushes, and all manual and automated PD exchanges. Upon discharge, the outpatient unit is contacted to ensure appropriate transition back to the outpatient setting.

Results: This model provides several benefits: 1) PD treatments are consistently completed and charted, 2) Increased physician, nursing, and patient satisfaction, 3) Continuity of care, and 4) Cost reduction (personnel and supplies). Since inception, this team has grown to 13 nurses. During FY2014, 2568 (1572 adult / 996 pediatric) PD treatments were performed, the majority CAPD. To ensure appropriate utilization of nursing resources, most are cross-trained to perform hemodialysis.

Conclusions: In conclusion, the creation of a specialized nursing team has been instrumental in optimizing the care of our hospitalized PD patients. This sustainable model provides effective, efficient care and should be considered for implementation by hospitals providing PD services.

TH-PO999

Elderly Peritoneal Dialysis Compared with Elderly Hemodialysis Patients and Younger Peritoneal Dialysis Patients: Competing Risk Analysis of a Korean Prospective Cohort Study

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Background: The outcomes of peritoneal dialysis (PD) in elderly patients have not been thoroughly investigated. We aimed to investigate the clinical outcomes and risk factors associated with PD in elderly patients.

Methods: We conducted a prospective observational nationwide adult end-stage renal disease (ESRD) cohort study in Korea from August 2008 to March 2013. Among incident patients (n=830), patient and technical survival rate, quality of life, and Beck's Depression Inventory (BDI) scores of elderly PD patients (≥65 years, n=95) were compared with those of PD patients aged ≤49 years (n=205) and 50-64 years (n=192); and elderly hemodialysis (HD) patients (n=315). The patient death and technical failure were analyzed by cumulative incidence function.

Results: The patient survival rate of elderly PD patients was inferior to that of younger PD patients (P<0.001). However, the technical survival rate was similar (P=0.097). Compared with elderly HD patients, the patient survival rate did not differ according to dialysis modality (P=0.987). Elderly PD patients showed significant improvement in the BDI scores, as compared with the PD patients aged ≤49 years (P=0.003). Low albumin, diabetes and low residual renal function were significant risk factors for the PD patient survival; and peritonitis was a significant risk factor for technical survival. Furthermore, low albumin and hospitalization were significant risk factors of patient survival among the elderly.

Conclusions: The overall outcomes were similar between elderly PD and HD patients. PD showed the benefit in BDI and quality of life in the elderly. Additionally, the technical survival rate of elderly PD patients was similar to that of younger PD patients. Taken together, PD may be a comparable modality for elderly ESRD patients.

TH-PO1000

Phosphorus Control and Phosphate Binder Pill Burden During Real-World Use of Sucroferic Oxhydroxide in Peritoneal Dialysis Patients

Linda H. Ficociello, Vidhya Parameswaran, Mark Costanzo, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America (FMCNA), Waltham, MA.*

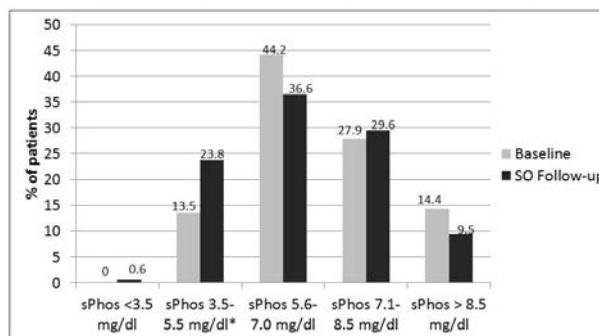
Background: Achieving serum phosphorus (sPhos) control can be a challenge for dialysis patients (pts). This retrospective database analysis examined the real-world effectiveness of sucroferic oxhydroxide (SO), an iron-based phosphate binder (PB), in adult peritoneal dialysis (PD) pts.

Methods: A cohort of PD pts prescribed SO as part of routine clinical care at FMCNA clinics was analyzed. Pts had ³¹SPhos measured during SO and had been previously treated with sevelamer, calcium acetate, calcium carbonate or dual therapy. Changes in sPhos,

serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pills per day (PPD) were assessed 3-months before SO (baseline) and 3-months during SO (follow-up).

Results: Pts (n=328) were, on average, 53 years old, with a dialysis vintage of 3.9 years. At baseline, 56% of pts used sevelamer, 29% calcium acetate, 11% calcium carbonate, and 5% dual therapy. Pts in-range increased from 13.5 to 23.8% (76% increase). Mean sPhos decreased from 6.92 to 6.67 mg/dl, p<0.001. PB PPD was reduced from 8.4 to 3.8 pills (4.6 fewer pills, p<0.001). There was no significant change in sCa (9.1 to 9.0 mg/dl) or iPTH (535 to 555 pg/ml). TSAT and FER increased from 35.4 to 36.6% and 752.1 to 814.9 ng/ml, respectively. In pts not receiving IV iron (n=127), TSAT and FER did not change significantly (36.3 to 37.3% and 797.9 to 743.3 ng/ml, respectively).

Distribution of serum phosphorus during baseline compared to sucroferic oxhydroxide (SO)-treated follow-up for PD patients (N=328)



*Change in %in-range and %out of range baseline compared to SO Follow-up, p<0.001

Conclusions: In this large cohort of PD patients prescribed sucroferic oxhydroxide as part of routine clinical care, a significant reduction in serum phosphorus (p<0.001) and a 76% increase in patients achieving in-range serum phosphorus (p<0.001) was observed. This was accomplished with a mean of 3.8 pills per day, a reduction of 4.6 pills (p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO1001

Laparoscopic Findings of Visceral Peritoneal Injury in Patients Treated with Neutral pH Peritoneal Dialysis Solution

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Background: Encapsulating peritoneal sclerosis (EPS) is caused by a visceral peritoneal lesion, i.e., intestinal tract adhesion and encapsulation, it is important to evaluate changes in the visceral peritoneum. It has been reported that there was a decreasing trend of peritoneal injury with the use of PD solution with neutral pH as compared with acidic pH in the histopathological evaluation of the parietal peritoneum; however, there is no report evaluating changes in the visceral peritoneum, which is essentially important and should be evaluated. We previously reported laparoscopic approach for evaluation of EPS (KI 2012) in patients treated with PD solution with acidic pH. In this study, we examined macroscopic findings of the visceral peritoneum in patients treated with neutral pH solution alone for 4 years or more by laparoscopy.

Methods: 19 patients underwent laparoscopy at the time of PD catheter removal. Duration of PD in these patients was 64.5±18.8 months. Clinically, none of these patients had developed EPS by the time of the investigation. The findings of both parietal and visceral peritoneal tissues were categorized according to color changes, presence of neovascularizations and adhesions.

Results: It was found that longer the duration of PD, the worse the peritoneal injury. Although changes in the parietal and visceral peritoneum had heterogeneous distributions, the changes in the visceral peritoneum were milder, showing a discrepancy with the findings of the parietal peritoneum. As compared with laparoscopic findings in patients treated with PD solution with acidic pH, the degrees of color changes, presence of neovascularizations, and adhesions were all mild, however, severe adhesions were noted in patients with a history of PD peritonitis.

Conclusions: Although changes in the visceral peritoneum resulting from the use of PD solution with neutral pH show a decreasing trend as compared with acidic pH, there is a certain level of peritoneal change, suggesting the possibility of progression of peritoneal deterioration by long-term continuous use.

TH-PO1002

“Composite” Encapsulating Peritoneal Sclerosis: A New Presentation in a Long Time of Renal Replacement Therapy

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Background: Encapsulating peritoneal sclerosis (EPS) is the more dangerous complication of peritoneal dialysis (PD). The EPS can occur during PD (classic EPS), after kidney transplantation (TX) or rapid shift to hemodialysis (HD) as the mode of renal replacement therapies (RRTs).

Methods: single-center retrospective analysis of PD transplanted patients in 35 years. Evaluation of the characteristics of the EPS presentation.

Results: From July 1979 to December 2014, 173 PD patients underwent kidney transplantation (TX). Were diagnosed 5 cases (2.9%) of EPS: one after 6 months from the TX (typical posttransplant EPS), but the other 4 cases have occurred after more than 20 years of different renal replacement therapy (medium 346±20 months, range 327-366) and at least a long time of TX (medium 227±24 months, range 207-259), also after many years of cessation from the last period in PD. The medium time in PD was 71±31 months (range 36-99). Two patients died after 10 and 41 months after diagnosis, respectively after 332 and 367 months in RRT. In our center during the same period other 21 EPS cases (2.8%) are occurred among the 747 PD patients never transplanted. No cases of EPS was manifested after direct transfer from PD to HD.

Conclusions: in our experience EPS prevalence in transplanted PD patients is not greater than not transplanted PD patients. In patients for many years in RRTs, EPS occurs even after a long time of the cessation of DP, especially after many treatments and long periods in TX. It is possible that the PD is acting only as a side event on the tissues affected by fibrotic processes formed for a long time in RRTs and/or due to the immunosuppressive therapy. To its features this form can be defined "composite EPS" and should also be considered in PD patients transplanted since many years.

TH-PO1003

Delta Neutrophil Index Is a Predictive Marker of Catheter Removal in Peritoneal Dialysis Patients with Peritonitis Jae Eun Um,¹ Sul A Lee,² Shin-Wook Kang,^{1,2} *Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea; ²Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Severe and prolonged peritonitis leads to peritoneal membrane failure and is the most common cause of technique failure in patients treated with peritoneal dialysis (PD). Recent studies reported that delta neutrophil index (DNI), which reflects the fraction of circulating immature granulocytes in the blood, is a practical severity marker of infection. This study investigated whether DNI could be a predictive marker of catheter removal in PD patients with peritonitis.

Methods: Patients treated with PD peritonitis at Severance Hospital between January 2012 and January 2015 were enrolled. Demographic data, clinical, and laboratory parameters including DNI were collected at the time of peritonitis. DNI was calculated by automatic analyzer.

Results: A total of 125 PD peritonitis episodes in 92 patients were investigated. The mean age was 59.1±12.0 years and 55 (44.0%) were male. PD catheter was removed in 31 (24.6%) patients. The median value of DNI in patients undergone PD catheter removal was significantly higher compared to that of patients who maintained PD catheters [DNI (interquartile range), 3.30 (0.0-65.0) vs. 0.70 (0.0-22.5), P=0.001]. DNI is significantly associated with percentage of segmented neutrophil ($r=0.28$) and serum albumin ($r=-0.32$), and dialysate leukocyte counts ($r=0.20$), but not with C-reactive protein (CRP) levels ($r=0.08$). Multivariate logistic regression analysis revealed that DNI was an independent predictor for PD catheter removal in patients with PD peritonitis (odds ratio=1.08, 95% confidence interval=1.01-1.12, P=0.04) after adjustment for serum albumin, CRP, leukocyte count of dialysis effluent, and septic shock. The area under the ROC curve (AUC) of DNI for PD catheter removal was 0.69 (P=0.001), whereas the AUC of dialysate leukocyte count was not statistically significant (0.52, P=0.70).

Conclusions: DNI levels reflected the severity of PD peritonitis. Higher levels of DNI could be an independent predictor for PD catheter removal in patients with PD peritonitis.

TH-PO1004

Peritonitis Rates Among African Americans and Caucasians Undergoing Peritoneal Dialysis Aceela Muqri, Russell Griffin, Eric L. Wallace. *Univ of Alabama at Birmingham.*

Background: African Americans (AA) are under-represented in the prevalent peritoneal dialysis (PD) population in the United States. There is relatively little conclusive data to explain the cause of this. One explanation is that AA may have higher rates of peritonitis than Caucasians leading to increased technique failure. This study aimed to determine if differences between AA and Non-AA rates of peritonitis at the University of Alabama at Birmingham Home Dialysis existed.

Methods: This is a single center retrospective cohort analysis on data from November 2012 to November 2014. Baseline demographics as well as data on peritonitis episodes were analyzed. Peritonitis rate was defined as the absolute number of distinct peritonitis episodes divided by the number of patient months at risk. Relapsing peritonitis episodes were excluded. Chi-square analysis was used to compare baseline categorical variables and independent t test to compare length of time on dialysis. Rates of peritonitis were analyzed with Fischer exact test. Peritonitis free survival, hospitalization free survival and technique failure were analyzed by log rank comparison of Kaplan Meier curves.

Results: Between 2012 and 2014, 90 AA and 70 non-AA were treated at the UAB home dialysis units. Baseline demographics between the two groups were similar in Gender and cause of ESRD ($p > 0.2$ in all causes ESRD). Non-AA were older than AA with an average age of 58 vs 50 respectively ($p=0.003$). Average time on dialysis were similar ($p=0.27$) AA had an 82% increased rate of peritonitis over the time period (RR 1.82, 95% CI 0.99-3.37). This association no longer remained after adjustment for age at time of PD start (RR 1.66, 95% CI 0.89-3.10). There was no interaction with age and race in regards to the rate of peritonitis infection rate ($p=0.4637$). Technique survival was not different between AA and Caucasians. ($p=0.44$).

Conclusions: AA when compared to non-AA, trended towards a higher risk of peritonitis than Caucasians. Despite this, technique survival between races did not differ. This study does not support the hypothesis that the underlying cause of decreased prevalent AA PD patients is due to increased technique failure from disproportionate peritonitis rates.

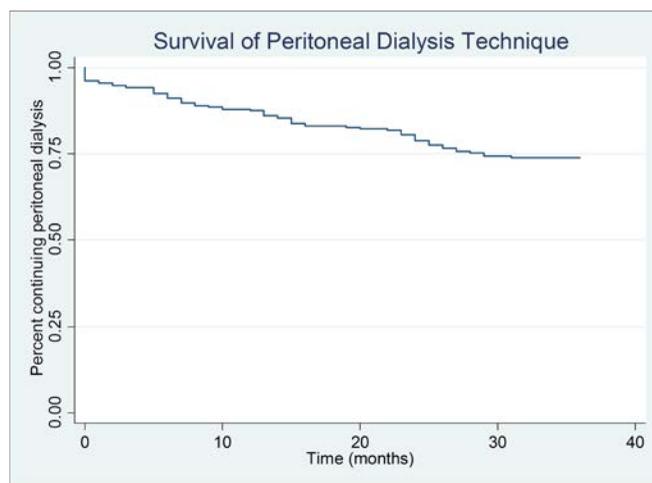
TH-PO1005

Factors Associated with Peritoneal Dialysis Technique Failure: A Single Center Study Anoop Sheshadri, Ramesh Saxena. *Dept of Nephrology, UTSW Medical Center, Dallas, TX.*

Background: To review peritoneal dialysis (PD) technique survival and assess factors associated with PD technique failure at our center.

Methods: We performed a retrospective analysis of 315 patients with PD catheters placed between 01/2001 and 09/2009, reviewing medical records for demographic and clinical information. Primary outcome was PD technique failure, defined as permanent discontinuation of PD due to infectious or non-infectious complications, inadequate dialysis, or miscellaneous factors such as pain. Patients were followed at least 36 months after PD initiation. Survival analysis was performed using Kaplan-Meier methods. Covariates influencing survival were analyzed using Cox proportional hazards regression models.

Results:



There were a total of 70 failures, 31 (44.3%) related to infectious complications, 22 (31.4%) to non-infectious complications (e.g. obstruction, leaks), 8 (11.4%) to inadequate dialysis, and 9 (12.9%) to miscellaneous factors. Overall survival at 36 months was 78.81%. Covariates significantly affecting technique failure include prior HD (1.83; 1.14-2.92), non-infectious complications (1.82; 1.28-2.59), DM (1.62; 1.00-2.63), HIV (2.52; 1.01-6.24), peritonitis (1.94; 1.20-3.12), and exit site infections (1.79; 1.09-2.92). Previous abdominal surgeries (.90; .758-1.08) and BMI (1.005; .971-1.04) were not significantly associated with failure.

Conclusions: This is one of the largest single center studies of its type from a US PD program. It shows excellent 3 year PD technique survival, better than reported in similar studies. Our results confirm that diabetes mellitus, PD related infections, and non-infectious mechanical problems are independent risk factors for PD technique failure. Conversely, BMI, abdominal surgeries, and demographic characteristics such as race and gender do not have significant association and should not be considered barriers to PD initiation.

Funding: Clinical Revenue Support

TH-PO1006

Effect of Early Peritonitis on Clinical Outcomes Kristin M. Corapi,¹ Julia Beth Wenger,¹ Jeffrey Perl,² Sharon Nessim,³ Ishir Bhan,¹ Joanne M. Bargman.⁴ *¹Nephrology, Massachusetts General Hospital, Boston, MA; ²Nephrology, St. Michael's Hospital, Toronto, ON, Canada; ³Nephrology, Jewish General Hospital, McGill Univ, Montreal, QC, Canada; ⁴Nephrology, Toronto General Hospital, Toronto, ON, Canada.*

Background: Infection is a source of significant morbidity and mortality for peritoneal dialysis (PD) patients. Previous studies suggest that early peritonitis is associated with shorter technique survival; however these studies are limited by small samples, restricted generalizability, and a lack of standardized definitions. We used data from a large dialysis database to determine if the timing of the first peritonitis episode is associated with adverse clinical outcomes.

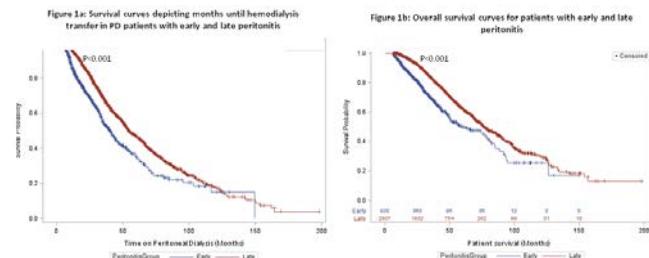
Methods: US and Canadian data from 1996 to 2005 in the Baxter POET (Peritonitis, Organism, Exit sites, Tunnel infections) database was analyzed. Patients who developed peritonitis within 6 months of PD initiation were identified as cases. Controls were patients whose first peritonitis occurred after 6 months. Patients who never developed peritonitis or who were on PD for less than 6 months were excluded. Patients were censored at the time of transplant, transfer to hemodialysis, or death.

Results: 920 cases and 2607 controls were identified.

	Early (n=920)	Late (n=2607)	p value
Age (years)†	57	58	0.7
% Male	54	46	0.6
% on CAPD	66	71	0.006
% with diabetes	47	40	<0.001
% New to PD	50	49	0.5
% Transfer from HD	26	25	
% Other *	24	26	

Presented as %, †= mean, * failed transplant or moved from another unit

Patients with early peritonitis had a significantly higher peritonitis rate than controls (1.26 and 0.67 episodes/patient year, p<0.001). Early peritonitis was also associated with shorter technique and patient survival.



Conclusions: Our results suggest that patients with early peritonitis are at increased risk of adverse clinical outcomes such as future infection, technique failure, and death.

TH-PO1007

Underweight Predicts Technical Failure: A Retrospective Cohort Study of Incident Peritoneal Dialysis Patients Xiaoyan Huang, Xiuqin Zeng, Qing Wang, Zibo Xiong, Yumei Liao, Zuying Xiong. Div. of Nephrology, Peking Univ Shenzhen Hospital, Shenzhen, Guangdong, China.

Background: Technical failure is more common in peritoneal dialysis (PD) than in hemodialysis. High body mass index (BMI) increases mortality in the general population, but it may improve survival in hemodialysis patients. In PD patients, yet, reports regarding the association of BMI with technical survival are scarce and remain controversial.

Methods: In this retrospective cohort study, 348 incident PD patients (aged 48.2 ± 15.5 years, 62% men) at Peking University Shenzhen Hospital from 2000 to 2014 were included. BMI was calculated with height and weight first recorded within 2 to 6 months after initiation of PD. Patients were categorized according to the World Health Organization recommendation for Asians. All patients were followed until October 31, 2014. Primary outcome was technical failure, defined as death or permanently transferred to hemodialysis. Secondary outcomes included all-cause mortality, cardiovascular and cerebrovascular mortality, occurrence of coronary heart disease and stroke, and incidence of peritonitis. Data were analyzed using Cox proportional hazards models.

Results: BMI in this cohort was 22.1 ± 3.0 kg/m². During 2.5 (interquartile range: 1.0-4.0) years, 60 cases of technical failure occurred. Incidence of technical failure was higher in patients with low BMI (13.4/100 person-years) than those with normal BMI (5.2/100 person-years) and with high BMI (6.3/100 person-years). After adjustment of age, sex, education, primary disease, and heart failure, hazard ratios (95% confidence intervals) were 3.60 (1.53, 8.45) and 0.93 (0.49, 1.76) for patients with low and high BMI, respectively, as compared to those with normal BMI. Similarly, the low BMI group had significantly higher rates of total as well as cardiovascular and cerebrovascular mortality than the normal BMI group, but such relationships did not exist in the high BMI group. No associations of BMI with occurrence of coronary heart disease and stroke and incidence of peritonitis were observed.

Conclusions: In incident PD patients, low BMI is associated with technical failure, all-cause mortality, and cardiovascular and cerebrovascular mortality.

Funding: Government Support - Non-U.S.

TH-PO1008

The Association Between Body Mass Index and Mortality in Peritoneal Dialysis Patients Jin Ho Hwang,¹ Geun joo Choi,² Hyun Kang,² Su Hyun Kim.¹ ¹Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; ²Anesthesiology and Pain Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea.

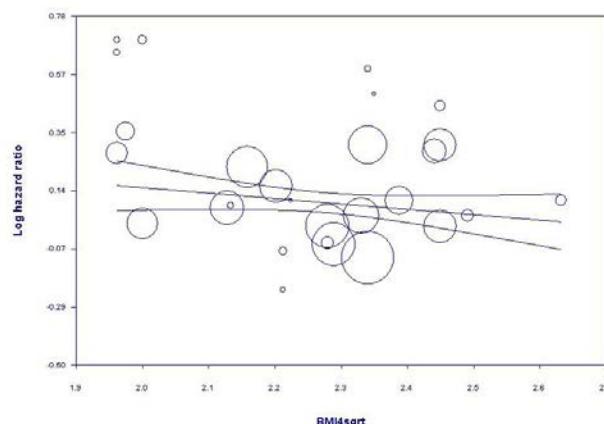
Background: Unlike the general population, a higher body mass index (BMI) was consistently found to be a strong predictor of decreased mortality in patients with end-stage renal disease who receive maintenance hemodialysis (HD). This phenomenon has been referred to as the “Obesity paradox” or “reverse epidemiology”. Similar tendency has been observed in several studies with peritoneal dialysis (PD) patients, but the studies have reported conflicting results. We conducted this study to evaluate the association between BMI and all-cause mortality in PD patients.

Methods: A systematic search was conducted for published studies in Medline, EMBASE, and the Cochrane library databases from 1970 to April 2015. We identified studies

evaluating the impact of BMI on mortality among PD patients. Data of hazard ratios and 95% confidence intervals (CIs) were obtained for respective BMI groups provided by each study. We performed meta-regression analysis using unrestricted maximum likelihood model.

Results: The Medline, EMBASE, and the Cochrane library search provided a total of 3,047 articles. After screening of all titles, 513 abstracts were selected. Finally, 9 cohort studies with 33,090 patients were included in the final analysis. Log hazard ratio for all-cause mortality showed a trend negatively associated with increasing four square root of BMI (slope coefficient: -0.1976, 95% CI -0.4110 to 0.0158, p= 0.0695).

Regression of Log hazard ratio on BMI4sqrt



Conclusions: In PD patients, BMI was inversely associated with mortality as in HD patients. Other outcomes such as cardiovascular death, peritonitis incidence, and technical failure will be additionally evaluated.

TH-PO1009

Is Obesity a Poor Prognostic Factor in Incident Peritoneal Dialysis Patients? Hyunjeong Cho,¹ Hyo Jin Kim,¹ Miseon Park,² Dong Ki Kim,¹ Kwon Wook Joo,¹ Yon Su Kim,¹ Curie Ahn,¹ Kook-Hwan Oh.¹ ¹Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; ²Clinical Research Inst, Seoul National Univ Hospital, Seoul, Korea.

Background: Obesity is associated with an increased risk of death in the general population. Previous studies have demonstrated a discrepancy in the impact of body mass index (BMI) on mortality among peritoneal dialysis (PD) patients. We examined the effect of BMI on patient and technique survival in a prospective, incident PD cohort at a single center.

Methods: Subjects who started PD between 2000 and 2012 were enrolled in the study. Demographic and laboratory data were prospectively collected. Patients were categorized into four BMI groups: obese, ≥25 kg/m²; overweight, 23 –24.9 kg/m²; normal, 18.5 –22.9 kg/m² (reference category); and underweight, <18.5 kg/m². Patient and technique survival were compared using Cox proportional hazards model.

Results: A total of 632 incident PD patients were included in final analysis. The median follow-up period was 40 months (interquartile range, 19–64 months). In Kaplan–Meier survival curve, patient survival was not statistically different among all BMI categories (p = 0.641, by log-rank test). The hazard ratio (HR) adjusted for age, sex, diabetes, comorbidities, albumin, hemoglobin for patient survival was not significant among BMI groups (p = 0.837). In contrast, technique survival was significantly poorer in obese patients than in patients having a normal BMI (p = 0.029, by log-rank test). The HR for technique failure was significantly greater for obese PD patients in comparison with the reference category [1.8; 95% confidence interval (CI): 1.2 to 2.8; p = 0.008]. The reasons for technique failure included recurrent peritonitis (34%), inadequate dialysis (17%), mechanical problem (17%) and refractory exit-site/tunnel infection (11%) in obese patients.

Conclusions: In our PD patients, patient survival was similar in all BMI categories. Therefore, obese patients should not be discouraged from receiving PD purely on the basis of BMI. However, technique survival was significantly poorer for obese PD patients. Further study is warranted to improve technique survival in obese patients.

TH-PO1010

Phosphate Clearance in Peritoneal Dialysis: Residual Renal Function and Dialysis Modality Carmen Gonzalez corvillo, Mariangeles Rodriguez Perez, Alejandro A. Suarez benjumea, Nuria Areste, Mercedes Salgueira lazo. Nephrology, Virgen Macarena-Rocio, Sevilla, Spain.

Background: Evaluate urinary and peritoneal excretion of phosphate and related factors in peritoneal dialysis (PD). Analyze phosphate clearance depending on PD modality and peritoneal membrane type.

Methods: Observational study in a sample of 37PD patients. Mean age: 60±14 years. 24 patients on APD (16CCPD, 8NIPD) 13 on CAPD. Mean Kt/V: 2.64±0.6. Mean residual renal function (RRF) 6.3±4.4 ml/min. Transmembranous peritoneal transport: 6high(H), 26high-average(HA) and 5low-average(LA). Renal and peritoneal phosphate clearance (ultrafiltration(UF) and diffusion(D)) was analyzed. Urinary and dialysate P/Cr. Weekly peritoneal P clearance(WPCI). Serum P.PTH. Use and dosage of phosphate binders and vitaminD analogs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Results: Mean total P clearance: 460±192mg/d. Mean renal P clearance: 286±201mg/d and mean peritoneal P clearance: 21±88mg/d. Mean P clearance through UF: 22±15mg/d(9%) and by D 194±85mg/24h(91%). Mean urinary and dialysate P/Cr were 0.4±0.15 and 0.59±0.24. Mean WPCl: 31.4±13.1L/week. Mean serum P: 4.9±1mg/dl and PTH294±166pg/ml. 86% of patients were on Sevelamer and 22% calcium based binders. 43% were on vita minD (55% calcitriol, 45% paricalcitol). Positive correlation between peritoneal P clearance and UF ($r=0.45$, $p=0.004$) as well as between RRF and renal P elimination ($r=0.83$, $p<0.001$) was observed. WPCl was higher in patients on CAPD than on APD (39.4±7 vs 27.1±13L/week $p<0.05$) being the main difference patients subjected to continuous vs discontinuous modality (CAPD 39.4±7 vs CCPD 31.4±12 vs NIPD 18.4±12 L/week $p<0.001$). Regarding to the membrane, WPCl was higher in H patients vs. HA and LA (46.5±6 vs 28.7±12 vs 27.1±12L/week $p<0.05$). Negative correlation was detected between WPCl and serum P ($r=-0.51$, $p=0.001$). Positive correlation was noted between WPCl and P clearance by D ($r=0.87$, $p<0.001$).

Conclusions: A substantial percentage of daily P elimination took place through urinary excretion, that is why preservation of RRF is crucial. There is a correlation between peritoneal clearance and increase of UF. P removal is higher on continuous modalities, CAPD shows better results. H patients would have better P clearance. Therefore, D would be the main mechanism of P peritoneal elimination, aided by long dwell time.

TH-PO1011

Proteinuria at PD Initiation May Predict Residual Renal Function Loss in the Automated Peritoneal Dialysis Patients Using Biocompatible Solution Yoshifumi Hamasaki,¹ Kent Doi,² Rei Isshiki,¹ Haruki Kume,³ Masaomi Nangaku,¹ Eisei Noiri.¹ ¹*Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan;* ²*Emergency and Critical Care Medicine, The Univ of Tokyo, Tokyo, Japan;* ³*Urology, The Univ of Tokyo, Tokyo, Japan.*

Background: Residual renal function (RRF) has a significant impact on the prognosis of dialysis patients. Peritoneal dialysis (PD), especially using biocompatible PD solution (BPDS) with neutral-pH and reduced glucose degradation products, has advantageous to preserve RRF (Kidney Int., 2013). It is still unclear what factors predict RRF loss in the PD patients using BPDS. We investigated the relationship between clinical parameters at PD initiation and the change of RRF in the PD patients using BPDS.

Methods: The data from patients who started PD as their first dialysis modality from 2001 to 2014 at The University of Tokyo Hospital were collected retrospectively. All patients were treated by automated PD (APD) using BPDS. To identify predictors of RRF decline, we analyzed data including clinical parameters measured at PD initiation. Residual GFR was calculated as the average of 24-hour urinary urea and creatinine clearances. The rates of urine volume and residual GFR decline were calculated by the least squares linear regression formula. The outcome of dialysis modality change was defined as switching APD to hemodialysis (HD) or combined therapy of PD and HD due to RRF loss.

Results: 96 patients were analyzed in this study. On multiple regression analysis, the decline rates of urine volume and residual GFR were significantly correlated with proteinuria at PD initiation. When patients were divided into two groups according to urinary protein level, Kaplan-Meier analysis revealed the lower proteinuria group had higher persistence rate of APD and lower rate of dialysis modality change (Log rank; $p=0.001$ and 0.004 , respectively). On ROC analysis, urinary protein predicted the need of dialysis modality change within 2 years after PD initiation with statistical significance (AUC [95%CI]=0.78 [0.66-0.90]).

Conclusions: Proteinuria at PD initiation may predict RRF loss and the need of dialysis modality change in the APD patients using BPDS.

TH-PO1012

Urgent Start versus Traditional Start Peritoneal Dialysis: Does Race Influence Outcomes? Vinay Narasimha Krishna, Manish K. Saha, Leslie J. Jackson, Gaurav Jain, Eric L. Wallace. *Univ of Alabama at Birmingham.*

Background: Although urgent start (US) peritoneal dialysis (PD) and traditional start (TS) PD have similar outcomes, it is not known if differences in outcomes exist based on race. The objective of this study was to determine if differences in PD outcomes exist when stratified based on race and type of PD start.

Methods: Retrospective data from an electronic database on incident PD patients collected between November 2012 and March 2015 was analyzed. Patients were analyzed by US vs TS and then stratified into 4 groups: African American (AA) TS, Non-AA TS, AA US and Non-AA US. Chi-square analysis was used to compare categorical variables, while ANOVA was used to compare means across groups. Exact mid-p was used to compare rates of hospitalization, peritonitis and catheter revisions. Survival curves were used to evaluate the probability of hospital free, peritonitis free, and technique survival. Patients were censored in the technique survival analysis for death or transplant.

Results: 114 patients were started on PD during the study period, 33 of which were US. When comparing US to TS, patients were matched for age, gender, and average days on study (All p values >0.05). No significant differences were observed in rates of peritonitis, timing of peritonitis, technique failure, catheter revision or hospitalization rates between TS and US groups. Sub-group analysis based on race stratification showed that age at PD start was younger in AA TS vs Non AA TS (50±13 vs 60±14 years respectively, $p=0.003$). AA TS patients were 60% more likely to have technique failure than Non-AA US ($p=0.03$). Non-AA US patients were more likely to be free of hospitalizations than AA TS ($p=0.03$). Peritonitis rates for AA TS, Non-AA TS, AA US, and non-AA US were 0.3, 0.14, 0.33, 0.36 per patient year respectively; catheter revision rates were 0.49, 0.3, 0.42 and 0.3 per patient year respectively with no significant difference among the subgroups.

Conclusions: There were no significant differences in outcomes among TS and US groups. Sub-group analysis showed that non-AA US patients have the least technique failure and hospitalization rates while AA TS have the worst technique failure and hospitalization rates.

TH-PO1013

Reasons for Dialysis Modality Changes in an Integrated Healthcare System Leonid Pravoverov, Sijie Zheng, Joanna Mroz. *The Permanente Medical Group, Oakland, CA.*

Background: In-center HD and PD are the 2 most common types of dialysis utilized in US. Few studies have examined characteristics of patients who changed dialysis modality. Kaiser Permanente Northern California is an integrated health care delivery system with 3.7 million members. We retrospectively examined the characteristics and disease burden of patients who switched from modalities.

Methods: Retrospective examination of EMR from Jan 2009 – Oct 2014. Disease burden was assessed by internally developed comorbidity point score, which predicts negative outcomes in the next 12 months, based on documented comorbidities and hospitalizations.

Results: From 2010-2014, dialysis population in our integrated health system increased from 4005 to 4491 patients, and PD population grew from 621 to 1033. In this period, 11% of patients who initiated dialysis switched modality. Majority of modality changes occurred within a year after dialysis initiation. 8% of HD patients switched to PD and 24% of PD patients switched to HD. Majority of patients who switched from HD to PD do so within 6 months of initiation. They have less comorbidities than those who stay on HD. They have a higher comorbidity score when they switch to PD but lower than repeated score of those who switched from PD to HD. They were younger than those remained on HD. Most patients who switched from PD to HD did so within a year. They have more comorbidities than those who stay on PD and have a higher comorbidity score when they switch to HD, even higher than the repeat score of those who switch from HD to PD. The difference in co-morbidity scores between the first and second measurement is higher for the PD to HD pattern. They have similar age to those who didn't switch.

Conclusions: Patients who switched from HD to PD remain at approximately the same comorbidity score before and after switch. Comorbidity scores of patients who switched from PD to HD significantly increased, suggesting that change was influenced by decline in their overall condition. In our patient population, the switch from HD to PD is likely a patient's decision, while the switch from PD to HD may be due to inability to continue PD.

TH-PO1014

Impact of Pre-Dialysis Immunosuppressive Treatment Time on Infectious Complications and Survival of Systemic Lupus Erythematosus (SLE) Patients on Peritoneal Dialysis Junbao Shi,^{1,2} Joanne M. Bargman.² ¹*Dept of Nephrology, Peking Univ Third Hospital, Beijing, China;* ²*Div of Nephrology, Univ Health Network, Toronto General Hospital, Toronto, ON, Canada.*

Background: SLE patients on peritoneal dialysis (PD) have a significant risk of infectious complications and poor outcomes. However, few studies have examined the relationship between pre-dialysis exposure to immunosuppressive (IS) therapy and the outcome on dialysis. The objective of this study was to investigate whether pre-dialysis IS treatment time influences the infectious complications and outcomes of SLE patients on PD.

Methods: Twenty-six SLE patients were treated with PD in a major academic centre from May 1996 to May 2014. Demographics, diagnostic tests and IS treatment, comorbid illnesses, biochemistry and clinical data upon initiation of PD and lupus activity, infective complications, hospitalizations and clinical outcomes during the study period were collected. Three years was chosen as the discriminant between longer and shorter duration of IS therapy.

Results: Two patients were lost to follow-up during the study period. Therefore, a total 24 patients were included for analysis. The SLE patients with longer duration of pre-dialysis IS ($n=17$) were older than patients with shorter pre-dialysis IS ($n=7$) (38.6±11.0 vs 27.1±7.8, $P<0.05$), but there were no significant differences in sex, race, PD duration, PD sub-modality and biochemistry between the two groups ($P>0.05$). Seven patients died during the follow-up period and all the deaths were from the group with longer pre-dialysis IS time ($P<0.05$). Three patients died from infections, two patients from cardiovascular disease, and two had sudden death at home. However, there were no significant differences in the incidence of peritonitis, exit site infection, other infections, or hospitalizations.

Conclusions: SLE patients undergoing PD with longer pre-dialysis exposure to IS drugs have a greater mortality that appears to be related to both infectious and noninfectious causes. Although incident to PD, they should be considered a high-risk subgroup.

TH-PO1015

Predicting Peritoneal Dialysis Prescriptions with a Fast Peritoneal Equilibration Test Using PD Adequest Ken Leybold,¹ Baris U. Agar,² James A. Sloand,¹ Mary Gellens.¹ ¹*Medical Products (Renal), Baxter Healthcare Corporation, Deerfield, IL;* ²*Medical Products (R&D), Baxter Healthcare Corporation, Round Lake, IL.*

Background: The fast peritoneal equilibration test (PET) is often used to determine peritoneal membrane transport status, but its accuracy in predicting parameters of peritoneal dialysis (PD) therapy adequacy using computer software, like PD Adequest, has not been quantified. In the current study, the ability of a new version of PD Adequest was

examined to 1) compare mass transfer-area coefficients (MTACs) for urea, creatinine and glucose during fast and standard PETs and 2) use those parameters to predict PD therapy prescription adequacy.

Methods: Data from 104 PD (41 CAPD, 63 APD) patients who underwent a 4-hour standard PET and an overnight exchange with the same glucose concentration were used to determine fluid and solute transport parameters. Calculated MTAC values for standard PET were compared with those for fast PET by using only data obtained at 4-hours during the standard PET and assuming a 200 mL residual volume in the prior exchange. The calculated membrane parameters were used to predict net ultrafiltration (UF), urea Kt/V and creatinine clearance (CrCl), and those predictions of therapy adequacy were also compared with the mean of 3 actual measurements of net UF, Kt/V and CrCl for each patient.

Results: Median urea, creatinine and glucose MTACs were 20.9, 10.1, and 9.1 mL/min during standard PET, and 21.0, 10.1 and 9.0 mL/min during fast PET; the corresponding median absolute difference between MTACs for urea, creatinine and glucose were 0.6, 0.3 and 0.6 mL/min. Comparing predictions using standard and fast PETs, 81% of net UF were within 150 mL, 94% of Kt/V were within 0.1/wk and 93% of CrCl were within 2 L/wk/1.73m². The percent of predicted and actual measured values of net UF within 300 mL, Kt/V within 0.2/wk and CrCl within 8 L/wk/1.73m² were 44%, 63% and 77% for standard PET and 38%, 64% and 77% using fast PET; these differences were not statistically significant.

Conclusions: These results suggest that the predictions of PD therapy adequacy using PD Adequacy are clinically equivalent when either fast or standard PET is employed.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO1016

The Loss of Residual Diuresis Increases in Eryptosis in PD Patients
 Grazia Maria Virzi, Carla Estremadoyro, Sabrina Milan panani, Alessandra Brocca, Massimo de Cal, Ilaria Tantillo, Carlo Crepaldi, Claudio Ronco.
Nephrology-IRRV.

Background: Anemia in ESRD is attributed to impaired erythrocyte formation due to erythropoietin and iron deficiency. The accelerated clearance of erythrocytes may at least partially be due to enhanced eryptosis, a suicidal death of erythrocytes characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine(PS)-externalization at the erythrocyte (RBC) surface. Exposed PS is recognized by macrophages that engulf and degrade the affected cells. Little is known about mechanisms underlying enhanced eryptosis in ESRD. At least in theory, eryptosis may be stimulated by some uremic toxins. The present study investigated eryptosis in peritoneal dialysis (PD) patients.

Methods: 46 PD patients (31 M, mean age:64±14yrs) and 17 healthy subjects (CTR) were enrolled. All measurements were made in isolated RBCs. PS exposure was estimated from FITC-AnnexinV binding by flow cytometric.

Results: 27 patients were treated with CAPD and 19 with APD. The mean length of treatment was 39±29months. The PS externalization on surface was significantly higher in PD patients than in CTR (2.6%; IQR 1.6-3.7 versus 0.8%; IQR 0.7-1.3 p<0.01). The median percentage of eryptosis showed no significant differences between patients with(n=18) and without diabetes, treated with CAPD or APD and with a negative or positive (n=18) history of peritonitis. Eryptosis showed significantly lower levels in PD patients with residual diuresis (n=23) than in patients without (3.7%, 2.6-5.6 versus 5%, 3.1-16; p=0.03). A significant negative correlation was observed between percentage of eryptosis and Body Composition Monitor-BCM for hydration status (Spearman's rho= -0.4, p<0.05). There was no a statistically significant relationship between eryptosis and months of PD, urea, albumin and creatinine levels.

Conclusions: In conclusion, eryptosis has been shown to be significantly higher in PD patients than CTR. Our data suggest that the type and the length of PD treatment do not enhance eryptosis. On the contrary, the loss of residual diuresis lead to a significant increase in eryptosis; the residual diuresis may contribute to the elimination of potential uremic toxins that induce increased eryptosis.

Funding: Private Foundation Support

TH-PO1017

The Pattern of T Helper Lymphocytes Has No Clinical Implications in Peritoneal Dialysis Patients
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Background: It has been reported that the imbalance between type-1 T helper lymphocytes (Th1) and type-2 T helper lymphocytes (Th2) exist in uremic patients. Th1 dominance leads to increased cardiovascular risks and Th2 dominance to allergic diathesis and pruritus. In this study, we investigated the pattern of Th lymphocyte differentiation in peritoneal dialysis (PD) patients.

Methods: Peripheral blood mononuclear cells were isolated from venous blood using Ficoll gradient methods. Isolated lymphocytes were stimulated with ionomycin and phorbol myristic acetate in the presence of brefeldin A, and then stained with CD3-, CD8 surface markers, interferon-gamma (IFN-gamma) and interleukin-4 (IL-4) for flow cytometry analysis. CD3-positive/CD8-negative cells were assumed as CD4-positive Th lymphocytes.

Results: We recruited 23 PD patients and 10 healthy controls. Th lymphocytes accounted for 68.9% of total T lymphocytes in PD patients and 72.9% in controls (p=non-significant). IFN-gamma positive T lymphocytes (Th1) accounted for 15.8% of Th lymphocytes in PD patients and 15.3% in controls (p=non-significant). IL-4 positive T lymphocytes (Th2) accounted for 2.6% in PD patients and 2.8% in controls (p= non-significant). The percentage of Th1 or Th2 lymphocytes did not correlate with any of the demographic and laboratory findings including diabetes, PD vintage, PD regimens, Kt/V, left ventricular ejection fractions, serum chemistries and hematologic values. The patients

who suffered from cardiovascular diseases (n=6) showed a similar percentage of Th1 and Th2 lymphocytes compared with those who did not (n=17). The patients who had significant pruritus requiring medications (n=11) showed a similar percentage of Th1 and Th2 lymphocytes compared with those who did not (n=12).

Conclusions: The pattern of Th lymphocyte differentiation was similar between PD patients and healthy people, and it did not have an association with clinical findings in PD patients.

TH-PO1018

Hemostatic Profile of Patients on Automated Peritoneal Dialysis by Thromboelastography
 Thalita Moura Braga, Erica Adelina Guimarães, Rodrigo Souza Adao, Rosilene M. Elias, Hugo Abensur. *Nephrology, Univ de São Paulo, São Paulo, Brazil.*

Background: It's believed that hypoalbuminemia induces hemostatic disorders in peritoneal dialysis (PD) patients. Beside to this lipid profile may also contributes to atherogenicity. Thromboelastography (TEG®) is a skilled and snapshot method that provides a global hemostasis evaluation. We objective to investigate whether TEG profile of patients in automated PD (APD) reflects the coagulation factors abnormalities and it is influenced by peritoneal transport of small solutes, macromolecules, and lipid profile.

Methods: A cross-sectional study included 15 patients (5 men) with age 43±18 years on APD for 26±15 months. Serum, effluent peritoneal fluid, and urinary values of: urea, creatinine, albumin, and total protein were obtained. Kt/V, ultrafiltration (UF), complete lipid profile, serum coagulation factors, and TEG were also performed.

Results: The TEG revealed that 7 patients were hypercoagulant according to coagulation indices (IC) (2.9±0.6, normal range-NR:-3 to 3) and 14 patients presented high maximum amplitude (MA) (68.1±4.2 mm, NR:27 to 49 mm), that reflects fibrin strength and platelet aggregation. Hypercoagulant patients presented UF less than normal patients (926±499 vs. 1896±750 ml, p=0.01). Accordingly, MA and IC correlated negatively with UF (r=-0.545, p=0.04 and r=-0.725, p=0.002, respectively). Factor IX (high in 8 patients) correlated with non-HDL (r=0.639, p=0.02), LDL (r=0.612, p=0.03), and negatively with HDL cholesterol (r=-0.771, p=0.002). D-Dimer (high in 11 patients) correlated with serum urea (r=0.569, p=0.03) and clot elasticity (G) (r=0.589, p=0.03). Unexpectedly, both fibrinogen (high in 12 patients) and D-dimer did not correlate with protein loss. There were no patients with severe hypoalbuminemia in this sample.

Conclusions: The TEG demonstrates an unfavorable hemostatic profile in PD patients characterized by mainly major platelet aggregation, which corresponds to abnormal dosages of clotting factors and degradation products. This panorama did not depend on protein loss and serum albumin. Lipid metabolism alterations, uremia, and low UF can be implicated in this finding.

TH-PO1019

Dialysate Looses of Vitamin 25(OH)D in a Cohort of Patients Treated with Peritoneal Dialysis
 Juan Carlos Ramirez-Sandoval, Maria Luisa Safar-Boueri, Jorge Jesus Silva, Olyinka Vega-Vega, Ricardo Correa-Rotter, Reynerio Fagundo. *National Medical Sciences and Nutrition Inst Salvador Zubiran, Mexico City, Mexico.*

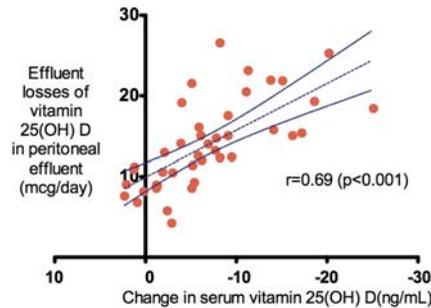
Background: Peritoneal dialysis (PD) is associated with 25(OH)vitamin D deficiency. To our knowledge, there are no cohort studies about 25(OH)vitamin D dialysate losses in PD. Objective: To characterize 25(OH) vitamin D losses in peritoneal effluent (PE) and their relation with changes in serum 25(OH)vitamin D levels during 4 months in a cohort of incident PD patients.

Methods: 52 patients with <6 mths but >1 mth on PD were invited from 2011 to 2014. Those with severe infections, hospitalizations, and oral intake of D3 or D2 during follow up were excluded. Basal vitamin 25(OH) D in 24h PE and serum were measured. After 4 months, a 2nd assessment was performed. The principal outcome was the change in serum vitamin 25(OH) D levels.

Results: 43 patients were included, 22 (51%) men, median age was 39 y (Interquartile range [IQR] 31-62), 29 (68%) had diabetes and 29 (67%) had some degree of renal residual function during all study. After 4 months of PD initiation, all patients had vitamin 25(OH) D levels <20 ng/mL, 13 of them with levels less than 10 ng/mL.

Characteristics, (n=43) *n(%) or median (IQR)	Initial	After 4 months	p
Serum 25(OH)D, ng/mL	14.2 (10.3-20.2)	8.6 (8-9.3 ng/mL)	<0.001
Peritoneal effluent 25(OH)D, ng/mL losses, mcg/day	13 (9.2-17) *All detectable at this timepoint	10 (6-11) *Not detectable in 35/43	<0.001
PTH, pg/mL	521 (343-845)	590(288-791)	0.6
Ca, mg/dL	9.2 (8.5-9.6)	9.14(8.5-9.5)	0.6
P, mg/dL	4.9 (3.6-6.1)	5.4 (3.8-6.1)	0.3

The mean decrease of vitamin 25(OH)D levels was 5.8 ng/mL/6 months (IQR 2-9.3 ng/mL). Basal PE losses in mcg/day and delta in serum vitamin 25(OH) D had a significant correlation



Conclusions: High effluent losses of vitamin 25(OH) D are observed in patients on PD and may explain very low levels observed during follow up in this cohort.

Funding: Government Support - Non-U.S.

TH-PO1020

Peritoneal Protein Excretion Was Lower in Nocturnal Intermittent Peritoneal Dialysis as Compared with Continuous Ambulatory Peritoneal Dialysis Not Associated With Peritoneal Transport Status in the Same Individual Hironori Nakamura, Anayama Mariko, Yasushi Makino, Masaki Nagasawa. *Dept of Nephrology, Shinonoi General Hospital, Nagano, Japan.*

Background: Recent studies have reported that peritoneal protein excretion (PPE) during peritoneal dialysis (PD) therapy is associated with cardiac disease and patient survival. However, little is known regarding the extent to which PPE can be influenced by PD prescription or peritoneal transport status.

Methods: The aims of this study were to compare PPE in the same individual with different PD prescriptions of either continuous ambulatory PD (CAPD) or nocturnal intermittent PD (NIPD), and to evaluate the correlation between PPE and dialysate to plasma creatinine ratio (D/P Cr). Seventeen patients, of whom 58.8% were male, were included in the study. A peritoneal equilibrium test was performed and the amount of total protein (TP) loss in the dialysate was measured during CAPD or NIPD therapy in the same patient.

Results: The mean age of the patients was 59.4 ± 18.0 years, body mass index was 21.5 ± 3.4 , serum TP (s-TP) was 5.8 ± 0.8 g/dL, serum albumin (s-Alb) was 3.0 ± 0.7 g/dL, C-reactive protein (CRP) was 0.4 ± 0.7 mg/dL, and D/P Cr was 0.76 ± 0.15 . During NIPD therapy, PPE was correlated with peritoneal clearance ($\gamma = 0.63$, $p = 0.006$), effluent volume ($\gamma = 0.69$, $p = 0.002$), and PPE to effluent volume ratio ($\gamma = 0.80$, $p = 0.000$), but not with s-TP, s-Alb, CRP, or D/P Cr. During CAPD therapy, PPE was negatively correlated with s-TP ($\gamma = -0.62$, $p = 0.007$) and s-Alb ($\gamma = -0.58$, $p = 0.014$), positively correlated with effluent volume ($\gamma = 0.50$, $p = 0.037$) and PPE to effluent volume ratio ($\gamma = 0.72$, $p = 0.001$), but not with CRP or D/P Cr. On comparing NIPD and CAPD, there was no difference in effluent volume (7341 mg vs. 7209 mg, respectively); however, both PPE and PPE to effluent volume ratio were significantly lower during NIPD than during CAPD [5586 mg vs. 7779 mg ($p = 0.004$) and 0.74 mg/mL vs. 1.09 mg/mL ($p = 0.004$), respectively].

Conclusions: The current study demonstrated that PPE and PPE to effluent volume ratio were lower during NIPD than during CAPD in the same individual, independent of the peritoneal transport status.

TH-PO1021

Fungal Peritonitis in the Standardizing Care to Improve Outcomes in Pediatric ESRD (SCOPE) Collaborative Raj P. Munshi,¹ Christine B. Sethna,² Sushil Gupta,² Samhar I. Al-Akash,³ John P. Lawlor,⁶ Bradley Warady,⁴ ¹Seattle Children's; ²Kosair Children's Hospital; ³North Shore-LIJ Medical Group; ⁴Childrens Mercey Hospital; ⁵Driscoll Childrens Hospital; ⁶Children's Hospital Association.

Background: The SCOPE Collaborative is a multicenter QI initiative with the 1^o aim to reduce dialysis catheter associated infections. The objective of this study was to describe the epidemiology of fungal peritonitis (FP) among pediatric patients with an indwelling peritoneal dialysis (PD) catheter enrolled in SCOPE.

Methods: PD characteristics and patient outcome were collected between 10/11-12/14 from 29 centers participating in SCOPE. Data was stratified based on fungal, bacterial/culture-neg peritonitis and no peritonitis. Peritonitis was defined as any episode that was treated for peritonitis. Differences among groups were assessed by chi-square analysis.

Results: Of 880 patients, there were 416 peritonitis episodes of which 37(8.9%) were fungal. 36 individual (median age 28.3 months; 56% male) were responsible for the FP episodes, with 22(59.4%) episodes occurring in patients <2 years of age. 21(56.8%) episodes were preceded by a documented peritonitis episode, with 12(32.4%) of the peritonitis episodes diagnosed within 90 days of the fungal infection. Culture neg (28.6%) and Staph species (23.8%) were the predominant causes of the prior peritoneal infections. Presence of a G-tube (48.3%, $p=0.003$), vesicostomy (10.3%, $p=0.036$), upward orientation of the PD catheter exit site (13.3%, $p=0.031$), and history of touch contamination (10.3%, $p=0.027$) were more common in children with FP as compared to the other groups. FP resulted in 1(2.9%) death, 33(89.2%) catheter removals, and 29(78.4%) hospitalizations. 1 child (2.9%) had successful treatment of a fungal peritonitis episode while leaving the PD catheter in place.

Conclusions: FP were responsible for 8.9% of peritonitis episodes with the majority of the episodes occurring in children <2 years of age. Additional risk factors included presence of a G-tube, vesicostomy, upward orientation of the exit site and history of touch contamination. The majority of the PD catheters were removed, with a preponderance of patients requiring hospitalization.

TH-PO1022

Relation of Central and Brachial Blood Pressure to Volume Status in Peritoneal Dialysis Patients Yun Jung Oh,¹ Su mi Lee,² Ji Yong Jung,³ So Mi Kim,⁴ Chungsik Lee.¹ ¹Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea; ²Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; ³Dept of Internal Medicine, Gacheon Univ Gil Hospital, Incheon, Republic of Korea; ⁴Dept of Internal Medicine, Jeju National Univ Hospital, Jeju, Republic of Korea.

Background: Euvolemia is an important predictor of outcome in peritoneal dialysis (PD), but chronic subclinical volume overload occurs frequently in PD patients. Even though volume overload is associated directly with hypertension, blood pressure (BP) not always reflect volume overload. Central BP has been shown to be a better predictor for target organ damages compared with brachial BP in general population. In this study, we evaluated comparative values of central BP and brachial BP for determining volume status in PD patients.

Methods: We enrolled 52 prevalent PD patients, and accessed volume status using Body Composition Monitor (BCM). Central BP was estimated using radial artery tonometry, and brachial BP measurement at office and 24-hour ambulatory blood pressure monitoring (ABPM) were performed. Volume overload was defined as an overhydration (OH) ≥ 1.1 L.

Results: Average office central systolic BP (cSBP), office brachial systolic BP (bSBP), and ambulatory brachial systolic BP (24-bSBP) were 139.8 ± 26.3 , 140.7 ± 19.2 , and 142.5 ± 22.0 mmHg, respectively. In overall, 41(78.8%) patients were in volume overload status. A stronger association of central BP with volume overload compared with brachial BP was observed in the receiver operating curve analysis (area under the curve (AUC) of cSBP, bSBP, and 24-bSBP were 0.87 ± 0.06 , 0.78 ± 0.09 , and 0.83 ± 0.06 respectively). In multivariate analysis adjusted for age, sex, PD vintage, diabetes, and cardiovascular disease, the odds ratio (OR) for central BP (OR 1.110; 95% CI 1.019-1.210) was higher than those for brachial BP (OR 1.085; 95% CI 1.014-1.161 for bSBP and OR 1.094; 95% CI 1.021-1.173 for 24-bSBP).

Conclusions: Office central BP was more strongly related to volume status than out-of-office ambulatory brachial BP as well as office brachial BP, suggesting that central BP was more valuable than brachial BP in assessing volume status in PD patients.

TH-PO1023

Novel Regimen for Intraperitoneal Cefazolin and Ceftazidime in Peritoneal Dialysis Patients Sadudee Peerapornratana,¹ Pisut Katavetin,¹ Pajaree Chariyavilaskul,² Talerngsak Kanjanabuch,¹ Kearkiat Praditponsilpa,¹ Somchai Eiam-ong,¹ ¹Div of Nephrology, Dept of Medicine, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand; ²Dept of Pharmacology, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Current guideline suggested that intraperitoneal (IP) antibiotics should be administered only in a long peritoneal dialysis (PD) dwell (≥ 6 hours), which is not always practical because the long dwell might result in low ultrafiltration and volume overload. The objectives of this study were to develop a novel regimen for IP antibiotics in short dwell (≤ 2 hours) during the automated PD cycling and examine the dialysate and plasma level of the most used empirical antibiotics for PD-related peritonitis, cefazolin and ceftazidime.

Methods: In the novel regimen, cefazolin and ceftazidime (20 mg/kg each) were added in a 5-liter bag of 2.5% dextrose PD fluid which was placed on the warmer of the PD cycling machine. Another 5-liter bag of PD fluid was connected to the machine, off the warmer. Patients underwent 5 exchanges of 2-liter PD fluid over 10 hours by the PD cycling machine without last fill or additional dwell. Cefazolin and ceftazidime concentrations in plasma and dialysate were determined by high performance liquid chromatography.

Results: Six PD patients without peritonitis were participated in the study. Dialysate cefazolin and ceftazidime were consistently high throughout the PD session in all patients (26-360 mg/L). Plasma cefazolin and ceftazidime exceeded the minimal inhibitory concentration (MIC) for susceptible organisms (8 mg/L) within 2 hours (cefazolin 28.5 ± 8.0 and ceftazidime 12.5 ± 3.4 mg/L at 2 hours), peak at 10 hours (51.1 ± 14.1 and 23.0 ± 5.2 mg/L) and then sustained well above the MIC at 24 hours (42.0 ± 9.6 and 17.1 ± 3.1 mg/L).

Conclusions: The novel regimen for IP cefazolin and ceftazidime in short dwell (≤ 2 hours) during the automated PD cycling could provide adequate dialysate and plasma concentration and would become a standard regimen for peritonitis in PD patients already using PD cycling machine as well as those who temporarily need shorter dwells during peritonitis due to increasing peritoneal solute transport.

Funding: Government Support - Non-U.S.

TH-PO1024

Is Automated Peritoneal Dialysis Better Than Continuous Ambulatory Peritoneal Dialysis in Quality of Life, Depression, and Renal Treatment Satisfaction? A Prospective Multicenter Propensity-Matched Study
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Background: Health-related quality of life (HRQOL) is an important variable in the selection of dialysis modality among incident dialysis patients. However, relative superiority in HRQOL between automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) are not clearly known. The objective of this study was to compare HRQOL, depression, and renal treatment satisfaction over time between APD and CAPD patients.

Methods: Incident patients initiating APD and CAPD were prospectively enrolled from nationwide multicenters in Korea. HRQOL, depression, and renal treatment satisfaction were assessed at 1 and 12 months after the start of dialysis by Kidney Disease Quality of Life Short Form 36 (KDQOL-36), Beck's Depression Inventory (BDI), and Renal Treatment Satisfaction Questionnaire (RTSQ), respectively. The mean changes of scores in APD and CAPD were compared by propensity score matching analysis.

Results: All 260 incident patients starting peritoneal dialysis (PD) from 11 centers were included in this study. A total of 170 patients were matched from 208 patients who completed all questionnaires and did not change PD modality during the 1-year follow-up period. The total scores at 1 month showed better HRQOL for APD than CAPD patients in symptom, patient satisfaction, pain, and social function domains. No differences were observed between the two groups in total scores of KDQOL-36 at 12 months. However, CAPD patients had a significantly greater improvement in symptom and health status domains. A significant improvement also occurred in BDI and RTSQ in CAPD patients.

Conclusions: APD is not better than CAPD in HRQOL, depression, and renal treatment satisfaction during initial first one year on dialysis. The relative positive effect of CAPD compared with APD on improvement of HRQOL, depression, and renal treatment satisfaction was confirmed.

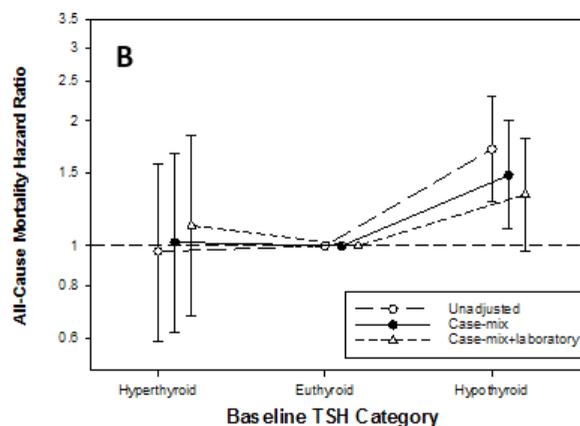
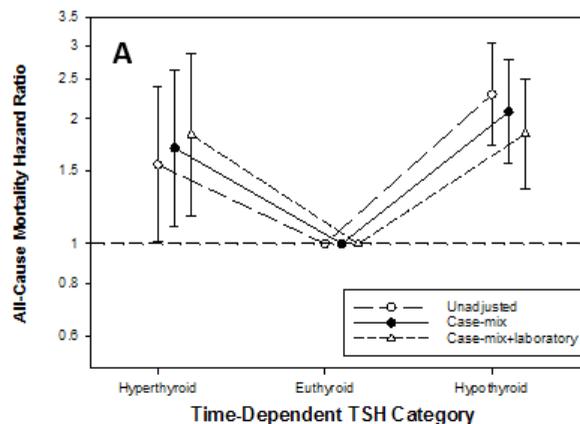
TH-PO1025

Thyroid Functional Disease and Mortality in a National Peritoneal Dialysis Cohort
 Connie Rhee,¹ Vanessa A. Ravel,¹ Elani Streja,¹ Rajnish Mehrotra,² Steven B. Kim,¹ Jiayi Wang,¹ Danh V. Nguyen,¹ Steven M. Brunelli,³ Csaba P. Kovacs,⁴ Gregory Brent,⁵ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UW; ³DaVita Clin Research; ⁴UTHSC; ⁵UCLA.

Background: Peritoneal dialysis (PD) patients have a high prevalence of thyroid dysfunction which may be due to 1) peritoneal effluent losses (vast majority of thyroid hormone is protein-bound) and 2) frequent exposure to povidone-iodine cleaning agents leading to iodine-induced hypo- and hyperthyroidism. In the general population thyroid dysfunction is associated with higher risk of cardiovascular (CV) disease and death. There has not been study of the association between hypo- or hyperthyroidism defined by TSH with mortality in PD patients.

Methods: We examined the association of thyroid functional status with all-cause mortality in a 5-year national cohort (1/2007-12/2011) of PD patients with at least one TSH measure. Thyroid functional status was defined as: hyper-, eu-, and hypothyroidism (TSH <0.5, 0.5-5, >5mIU/L). We examined time-dependent and baseline thyroid function to determine short- and long-term exposure-mortality associations, respectively, using Cox models with 3 adjustment levels: unadjusted, case-mix, and case-mix+laboratory adjusted.

Results: Among 1484 patients, 7% and 18% had hypo- and hyperthyroidism, respectively. In time-dependent analyses, hypo- and hyperthyroidism were each associated with higher mortality risk in all 3 Cox models (ref: euthyroidism). In baseline analyses, hypothyroidism was associated with higher death risk in unadjusted and case-mix models, but associations were attenuated to the null in case-mix+laboratory models.



Conclusions: Time-dependent hypo- and hyperthyroidism were each associated with higher mortality, suggesting short-term risk in PD patients. Further studies are needed to determine if CV pathways are implicated, and if thyroid-modulating therapies ameliorate mortality in this population.

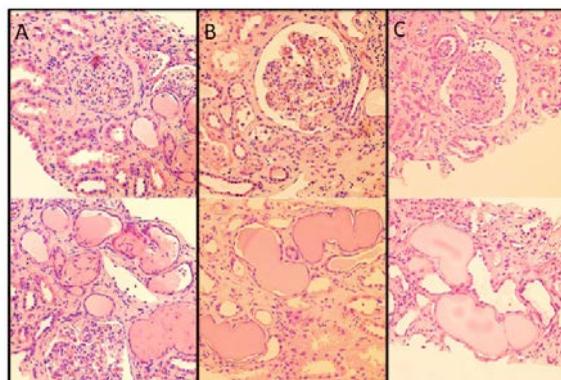
Funding: NIDDK Support, Private Foundation Support

TH-PO1026

A Tale of APOLI Mutation and Parvovirus Infection
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Introduction: We present a case of a first trimester pregnant woman with nephrotic range proteinuria and fetal demise in the setting of an acute parvovirus infection. Kidney biopsy revealed collapsing FSGS, and exome sequencing revealed mutations in APOLI. The relationship between Parvovirus and FSGS is one that clinicians might overlook, and perhaps may play a more prominent role in these progressive cases especially with APOLI mutations.

Case Description: 37 yo Caribbean female presented at 8 weeks gestation with progressive swelling. Her daughter developed fifth's disease one month prior. On presentation her BP was 146/95, HR 77 with pitting edema. Her creatinine was 6.3, BUN 43, albumin 1.5, and spot prt/crt 20.8. Parvovirus PCR was 2000 copies. Biopsy demonstrated collapsing FSGS secondary to Parvovirus B19 [Fig 1A 1B]



The hope was that this injury would improve with improvement in titers, so IVIG was started. A follow up PCR showed improvement to 200 copies but she remained nephrotic with proteinuria of 20-60 g. Re-biopsy revealed significant scarring and dialysis was initiated [Fig 1C]. Patient is now being evaluated for transplant. Given the unusual severity of this case, and her possible African ancestry, a genetic susceptibility to podocyte injury was entertained. Whole exome sequencing identified the patient to have two *APOL1* risk alleles.

Discussion: Parvovirus has been linked with collapsing FSGS, and in one study viral PCR was detected in 78% of kidney tissue with this diagnosis. The combination of B19 infection and *APOL1* mutation likely made our patient particularly susceptible to injury. Our case raises the question of how often subclinical parvovirus infection may be involved in collapsing FSGS, and highlights how sudden and devastating it can be to the life of a prior healthy young woman.

TH-PO1027

Podocyte Myeloid Bodies without Confirmed Genetic Mutation in a Female: Fabry's Disease? Pravir V. Baxi,¹ David J. Cimbaluk,² David G. Warnock,³ Robert J. Desnick,⁴ William Luke Whittier.¹ ¹Nephrology, Rush Univ MC, Chicago, IL; ²Pathology, Rush Univ MC, Chicago, IL; ³Nephrology, UAB, Birmingham, AL; ⁴Genetics, Mt Sinai, New York, NY.

Introduction: Fabry's disease (FD) is a X-linked lysosomal storage disorder caused by deficient alpha-galactosidase activity. A renal variant has been described with the R363H mutation. Due to random X-chromosomal inactivation, heterozygous females can present a diagnostic challenge. We report a case with a renal limited presentation, biopsy findings characteristic of FD but a negative whole blood DNA analysis.

Case Description: A 46 year-old Hispanic woman was evaluated for proteinuria. She was asymptomatic with no prior medical history or family history, and no exposure to silica, amiodarone, or hydroxychloroquine. Her exam was unremarkable: no neuropathy, skin changes, or corneal dystrophy. SCr was 0.6 mg/dL, UA 2+ protein with P/C ratio of 1.94 g/g. Biopsy revealed diffuse enlargement of the podocytes with a foamy cytoplasm appearance and on EM, prominent podocyte lamellated lipid inclusions with foot process effacement and minimal endothelial deposits.

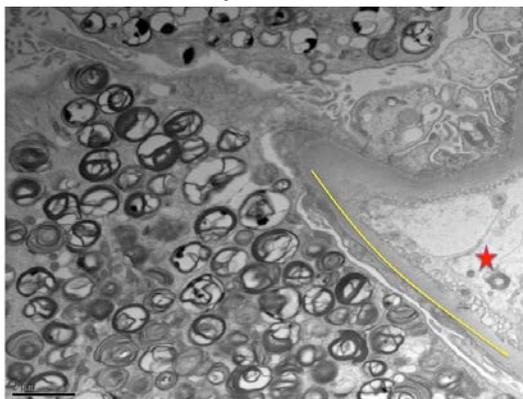


Figure 1: Podocyte myeloid bodies; yellow line denotes foot process effacement, red star shows limited endothelial inclusions. Alpha-galactosidase activity was 0.187 U/L (lower limit of nl) and genomic sequencing of the GLA gene was negative. EKG, Echo, cardiac MRI, and brain MRI with and without gadolinium were nl.

Discussion: We present a pt with renal limited manifestations mimicking FD in the absence of known toxic exposure and a negative whole blood DNA mutation analysis. Treatment with enzyme replacement is not warranted without a positive genetic analysis. This case highlights the variable genotypic and phenotypic presentation, and raises the possibility that tissue-specific mosaicism could explain phenotypic variation in females with Fabry's Disease.

TH-PO1028

Relapsing Thrombotic Microangiopathy following Persistent Intravenous Use of Reformulated Oxycodone Melissa S. Nataatmadja, Dakshinamurthy Divi. Dept of Nephrology, Gold Coast Univ Hospital, Southport, Queensland, Australia.

Introduction: Thrombotic microangiopathy (TMA), resembling thrombotic thrombocytopenic purpura (TTP), with normal ADAMTS13 activity has recently been observed in persons injecting Opana ER (oxycodone), an oral opioid available in the United States. This phenomenon had not been reported outside the US, however, and the mechanism of inducing TMA is not yet known.

Case Description: A 29-year old female presented with hemolytic anemia and thrombocytopenia, with a hemoglobin of 70g/L and platelet count of $17 \times 10^9/L$. She was treated with therapeutic plasma exchange (TPE) for a working diagnosis of TTP and recovered, with no ongoing TPE requirement. She represented two weeks later, with a hemoglobin of 81g/L, platelets of $8 \times 10^9/L$, and additional renal impairment. She again commenced TPE and also prednisone. Her ADAMTS13 activity was >94%, atypical hemolytic-uremic syndrome (aHUS) was therefore considered, and genetic testing was ordered. She then admitted to a two-month history of injecting Oxycodone and

for the previous month had been using reformulated Oxycodone. TPE and prednisone were discontinued and she experienced physical and hematological recovery. Genetic testing for aHUS subsequently returned as negative.

Discussion: To our knowledge, this is one of only two documented cases of TMA following IV Oxycodone use, both of which were observed in Australia soon after reformulated Oxycodone replaced original Oxycodone. This report supports polyethylene oxide (PEO), a tamper-proof coating added to the reformulated Oxycodone and Opana ER, as the causative agent, as TMA has now been observed following the use of two different medications but with the same PEO coating. Additionally, our case is the first to demonstrate relapse of TMA following persistent intravenous drug use of either of these medications. Given the rarity of this illness, it is possible that an unidentified genetic or immunologic susceptibility causes some individuals to develop TMA in response to these drugs, whilst others do not. We encourage clinicians to consider IV drug use in all patients presenting TMA, as treatment approach may differ and the role of plasma exchange is not yet clear.

TH-PO1029

Ipilimumab Associated Kidney Injury Andinet Gizaw, Jason M. Kidd. Nephrology, VCUHS, Richmond, VA.

Introduction: Melanoma is the most fatal form of skin cancer. Patients without surgically resectable disease require chemotherapy. Ipilimumab, a human monoclonal antibody against anti-CTLA-4 is an Immunomodulation agent, with proven benefit in overall survival in patients with unresectable, advanced (Stage 3,4) Melanoma. Cytotoxic T Cell Lymphocyte Antigen-4 (CTLA-4) is a negative regulator of T-Cell mediated anti-tumor immune response working as immune check points (down regulation). We present a case of acute kidney injury due to interstitial nephritis and minimal change disease from this drug.

Case Description: A 55 year old man with metastatic melanoma with right atrial mass, status post resection, was seen for evaluation of acute kidney injury and nephrotic range proteinuria. He developed lower extremity swelling with rash about 02 weeks after receiving a third dose of ipilimumab. He had a baseline serum creatinine of 1.2mg/dl. At the time of consultation, his serum creatinine was 2.97mg/dl, 9 grams of proteinuria on 24 hours collection and serum albumin of 2.2. He was initially fluid resuscitated, however, creatinine increased to 5.2 mg/dl and he became oliguric. Urine microscopy was without casts and serology markers were negative. Renal biopsy was performed that showed an interstitium with eosinophil rich inflammatory cell infiltration and severe edema. Almost half of glomeruli were globally sclerotic, the others had minimally altered composition. Immunofluorescence was unremarkable. Electron microscopy showed diffuse effacement of podocyte foot processes. He was treated with high dose (2mg/kg) steroid and oral diuretics. Renal function has returned to his prior baseline and he has subnephrotic proteinuria.

Discussion: This describes a case of nephrotic syndrome and interstitial nephritis related to the monoclonal antibody, Ipilimumab. Interstitial nephritis has been described with this drug before. However, this is the first case to our knowledge of the administration of ipilimumab leading to acute kidney injury from interstitial nephritis and severe proteinuria from diffuse podocyte foot process effacement. Prompt recognition of this presentation is necessary to preserve renal function.

¹"kidney injury related to ipilimumab", Invest New Drugs (2014) 32:769-773.

TH-PO1030

Kappa Light Chain-Associated Crystal-Storing Tubulopathy, Podocytopathy, and Histiocytosis in GI Tract, in a Patient with Multiple Myeloma Michifumi Yamashita,^{1,3} Albert Q. Lam,^{2,3} Joseph V. Bonventre,^{2,3} Vanesa Bijol.^{1,3} ¹Pathology, Brigham and Women's Hospital, Boston, MA; ²Renal Div, Internal Medicine, Brigham and Women's Hospital, Boston, MA; ³Harvard Medical School, Boston, MA.

Introduction: Multiple myeloma manifests with variety forms of kidney disease, such as AL amyloidosis, cast nephropathy, and light chain deposition disease. Among them, crystal-storing disease is a rare entity. We report an interesting case of a patient with extramedullary IgG/k multiple myeloma, who presented with crystal-storing histiocytosis in GI tract, and subsequently developed crystal-storing tubulopathy and podocytopathy.

Case Description: A 65-year-old man with type 2 DM and HTN was found to have a 1 cm large cecal polyp on screening colonoscopy in 2009. The polyp showed diffuse infiltration by a plasma cell neoplasm and crystal-storing histiocytosis with κ light chain (LC) restriction. At that time, the patient showed intact bone marrow, normal renal function and proteinuria of 0.5 g/24h. He was subsequently closely followed with endoscopy, SPEP, and renal function tests. In 2014, he developed nephrotic range proteinuria (>4g/24h), slightly rising Cre to 1.12 mg/dl, and increased serum free κ LC (216 mg/L). Kidney biopsy was performed, revealing many proximal tubular epithelial cells containing PAS-negative granular materials in the cytoplasm. The glomeruli were unremarkable except for mild mesangial expansion. No significant immune deposits were present in glomeruli or tubulointerstitium, but there was slightly stronger background IF reactivity for κ LC than λ LC on frozen tissue sections. IF studies on protease-digested paraffin sections revealed strong κ LC reactivity of the materials aggregated in the tubular epithelial cells and podocytes, while λ LC was negative. EM revealed extensive intracytoplasmic accumulation of crystalline material of rhomboid and rectangular shapes in proximal tubular epithelial cells and podocytes.

Discussion: LC-associated crystal-storing disease is a rare kidney disease. To our knowledge, this is the first reported case of coexisting crystal-storing tubulopathy, podocytopathy, and histiocytosis in the GI tract in a patient with multiple myeloma.

TH-PO1031

Parvovirus B19-Preceding Collapsing Glomerulopathy in Renal Allograft Michifumi Yamashita,^{1,3} Martina M. McGrath,^{2,3} Anil K. Chandraker,^{2,3} Vanesa Bijol,^{1,3} ¹Pathology, Brigham and Women's Hospital, Boston, MA; ²Renal Div, Internal Medicine, Brigham and Women's Hospital, Boston, MA; ³Harvard Medical School, Boston, MA.

Introduction: Collapsing glomerulopathy (CG) is a distinct clinicopathologic entity with proliferation of glomerular epithelial cells and capillary collapse. It has been classically associated with HIV infection, but other predisposing conditions and etiologic factors include parvovirus and CMV infections, autoimmune diseases, hematologic malignancies, and certain drugs. The pathomechanism of CG in renal allograft is unclear. Here we report a case of parvovirus infection-preceding CG in allograft.

Case Description: A 72-year-old man with ESRD due to DM and HTN, status post DORT in June 2014, who presented with rising Cre from 1.6 to 2.0 without viral illness, 3 months after transplantation. The 1st biopsy showed several mesangial deposits with organized spherical substructural organization, averaging 18 nm in diameter, without evidence of allograft rejection. Extensive immunohistochemistry (IHC) workup revealed positive staining only for Parvovirus in mesangial area. 3 weeks after the biopsy, he developed Parvovirus B19 viremia with 4.8×10^9 IU/mL. 6 weeks later, he presented with rising Cre to 3.4, proteinuria 1.5 g/24hr, and improved Parvovirus viremia (3.3×10^5 IU/mL). The 2nd biopsy revealed severe podocyte injury with features of CG: (1) Collapse of the tuft and prominent epithelial cells with intracytoplasmic protein reabsorption granules, (2) extensive effacement of foot process and other degenerative changes of podocytes, and (3) coarse protein reabsorption granules in tubular epithelial cells. Parvovirus could not be detected anymore by EM or IHC.

Discussion: This case clearly showed: (1) for the first time, Parvovirus B19 particles in glomeruli immunohistochemically and ultrastructurally, (2) Parvovirus B19 infection systemically and histologically preceding CG, and (3) when CG developed, serum Parvovirus B19 titer was significantly decreased, and the virus could not be detected in the kidney tissue by EM or IHC. The evidence suggests that the direct or the indirect association between Parvovirus B19 infection and CG in kidney allograft.

TH-PO1032

A Case Report of Obstructive Nephrolithiasis Secondary to Atazanavir Dina Abdelwahab, Anushree C. Shirali. *Internal Medicine, Section of Nephrology, Yale Univ School of Medicine, New Haven, CT.*

Introduction: Atazanavir, a protease inhibitor used in the management of human immunodeficiency virus (HIV), is associated with crystalluria and nephrolithiasis. While crystalluria is seen in 10-20% of patients on atazanavir treatment, frank nephrolithiasis is less common. We report a case of nephrolithiasis associated with atazanavir in an HIV patient on long-term highly active anti-retroviral therapy (HAART).

Case Description: A 56-year-old male with a past medical history of HIV on HAART, HCV, DM type 2 and proteinuric CKD stage III presented with rise in serum creatinine from 2.6 to 5.7 mg/dL over the preceding year. His CD4+ T-cell count was 514 and his viral load was less than 20 copies/ml on treatment with atazanavir, ritonavir and raltegravir, a regimen that had remained stable for 10 years. He had no history of diabetic retinopathy and his proteinuria was stable around 5.2 gm. Prior abdominal CT imaging had revealed bilateral non-obstructive nephrolithiasis 1 year prior to presentation. Evaluation of the decline in renal function included a CT scan of the abdomen, which showed a left-sided obstructive stone. The patient had no symptoms of renal calculi. He underwent ureteroscopy, laser lithotripsy and stent placement. Stone analysis revealed calculi composed of atazanavir and its metabolites. His HAART regimen was switched to dolutegravir, lamivudine and abacavir. Despite an initial stabilization in creatinine, the patient eventually progressed to ESRD.

Discussion: This case highlights the fact that patients treated with atazanavir may develop nephrolithiasis with chronic therapy. Evaluation of renal disease in patients on atazanavir should include renal imaging for detection of calculi, even in the absence of symptoms, in susceptible patients who have an unexplained drop in GFR. The risk of nephrolithiasis is particularly heightened in patients on ritonavir-boosted atazanavir and those with pre-existing chronic kidney disease. Other types of renal disease associated with atazanavir include acute interstitial nephritis and chronic interstitial nephritis and should prompt kidney biopsy in those patients without evidence of obstructive nephropathy.

TH-PO1033

Paraneoplastic Tumor-induced Osteomalacia (TIO) in Small Cell Carcinoma: First Report of Positive Immunostaining for Fibroblast Growth Factor-23 in Small Cell Carcinoma Smिता Mahendrakar, Hone S. Kaw, Hiba M. Ahmed, Suneet Verma, Mandeep Samra, Jennine Michaud, Donghong Cai, Michael Yudd. *Nephrology, Dept of Veterans Affairs NJ Healthcare System, East Orange, NJ.*

Introduction: We report a case of hypophosphatemia due to Fibroblast Growth Factor(FGF)-23 in small cell carcinoma (SCCA). This is the first reported case of positive immunohistochemical staining for FGF-23 in SCCA.

Case Description: 60 yr old male was admitted with abdominal pain, anorexia and weight loss. Labwork showed normal renal function, serum phosphorus (PO4) 0.8 mg/dl, bilirubin 4 mg/dl, increased LFT's, and elevated fractional excretion of PO4 82%, with high serum FGF-23, 577 RU/ml. No lab findings of Fanconi Syndrome. CT showed pulmonary nodules and a massively enlarged liver with no focal lesions. Liver biopsy showed metastatic SCCA with diffuse sinusoidal pattern. Despite PO4 replacement, hypophosphatemia was

difficult to correct. Chemotherapy was started, but patient died in 2 weeks. Tissue sections from the tumor and controls were stained separately using antibodies directed against epitopes comprising amino acid residues located within the C-terminal portion of FGF23.

Discussion: Immunostaining of tumor cells from the lung and liver were positive for FGF-23. This is the first case with documented elevated serum FGF-23 and positive FGF-23 immunostaining of SCCA. Tumor-induced osteomalacia (TIO), is usually associated with benign tumors of mesenchymal origin, rarely with adenocarcinomas or small cell carcinoma. The syndrome is characterized by renal PO4 wasting due to excess FGF-23 from the tumor, leading to hypophosphatemia. There are at least 10 cases of SCCA with phosphate wasting, but without FGF23 levels. Only four cases of TIO with documented elevated FGF-23 associated with tumors other than mesenchymal tumors: 2 cases of stage D2 prostate adenocarcinoma, one with metastatic colon cancer, and one with stage 4 ovarian cancer. All of these were advanced, metastatic disease. Of these, only the metastatic colon adenocarcinoma case was documented by FGF-23 immunohistochemical staining in the hepatic metastases. Our case is the first case of FGF-23-positive immunostaining in tumor cells of small cell CA.

TH-PO1034

Relapse of Kappa Restricted Chronic Lymphocytic Leukemia Associated with a Lambda Restricted Plasma Cell Clone Causing Renal Amyloid Sunil Rangarajan, James C. Harms, Huma Fatima, Randall S. Davis, Eric L. Wallace. *Univ of Alabama at Birmingham.*

Introduction: Chronic lymphocytic leukemia (CLL) has been associated many glomerular diseases. Rarely, it has been associated with amyloidosis either as the sole clone responsible, or in association with a plasma cell clone possessing the same light chain as the CLL clone, or in very rare cases, a different light chain. We present a case of adult onset nephrotic syndrome secondary to amyloid-lambda light chain due to a small lambda-restricted plasma cell population, temporally associated with a relapse of a kappa-restricted CLL.

Case Description: A 66 year old male, diagnosed with kappa-restricted CLL in 2009 achieved complete remission after 6 cycles of fludarabine, cyclophosphamide and rituximab. 5 years later, he presented with foamy urine, generalized swelling, and weight gain. Serum creatinine was 1.1. Initial spot urine protein / creatinine ratio showed proteinuria of 5g/g which later increased to 10g/g. During the previous year serum albumin fell from 3.8 to 1.5 g/dL and the white blood cell count rose from 7.4 to 30 x10³/cmm. While the lymphocyte frequency rose from 45% to 88%, serum free light chains were 45.1mg/L lambda, 21.5 mg/L kappa with a ratio of 0.48. Kidney biopsy showed AL-amyloidosis with immunofluorescence positive for lambda. Due to discrepancy in the clonality of previous circulating CLL expansion (kappa restricted) and renal amyloidosis (lambda restricted), a bone marrow biopsy was done. This showed a relapse of CLL with low level (<10%) plasma cell dyscrasia. Flow cytometry confirmed that the relapsed CLL population was kappa-restricted while the clonal plasma cell population expressed lambda. After 8 months of treatment with velcade, dexamethasone and revlimid, he showed minimal improvement in proteinuria.

Discussion: Though the co-existence of clonal plasma cells and CLL is known, the temporal association of this patient's nephrotic syndrome secondary to amyloidosis from a unique plasma cell clone expressing a different light chain supports the hypothesis that, in CLL, sharing the same microenvironment as non-tumor cells may activate bystander B-cells to express free light chains and in this case lead to amyloidosis.

TH-PO1035

Recurrent 2,8-Dihydroxyadenine Deposition Successfully Treated with Kidney Transplantation Paula A. Duran, Mohanram Narayanan. *Div of Nephrology, Baylor Scott & White Healthcare, Temple, TX.*

Introduction: Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive purine metabolism disorder where adenine is oxidized by xanthine dehydrogenase to 2,8-dihydroxyadenine (2,8-DHA), forming insoluble urinary crystals, nephrolithiasis, CKD and ESRD. Literature reveals diagnosis of APRT deficiency is rare before kidney transplantation. Delay in diagnosis and xanthine oxidase inhibitor treatment predisposes to recurrent disease in renal allograft, with allograft loss in over 25% cases. Though APRT is ubiquitous in all cells, extrarenal symptoms are uncommon in affected individuals. Our patient presented with crystalline keratopathy resolving completely after kidney transplantation.

Case Description: 41 y/o Caucasian female with recurrent 2,8-DHA nephrolithiasis since age 23 was maintained on Allopurinol. Clinical course was significant for obstructive uropathy requiring multiple stent placements; continued decrement in renal function and blurry vision, intense photophobia, excessive tearing in both eyes. Corneal examination showed crystalline keratopathy. Genetic analysis indicated patient had mutant APRT alleles inherited from her parents. With progressively declining renal function she was evaluated for preemptive renal transplantation. She received a 0-antigen mismatched deceased donor renal allograft with uneventful post-transplant course. Allopurinol dose was increased to 600 mg daily with complete resolution of disabling visual symptoms. Allograft function has been excellent with nadir creatinine of 0.82 and urine microscopy negative for DHA crystals.

Discussion: APRT deficiency is a rare genetic disorder not readily diagnosed but easily treated with Allopurinol to prevent urinary DHA crystallization. Typical recommended daily dose of Allopurinol is 200-300 mg, but reports from Iceland have shown excellent results in transplant recipients taking 600 mg that lacked statistical significance due to the small sample size. Allopurinol 600 mg should be considered post-transplant to prevent allograft loss. Our patient's post-transplant dose was increased to 600 mg with remarkable resolution of crystal keratopathy and crystalluria while maintaining excellent allograft function.

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TH-PO1036

Minimal Change Disease Diagnosing Relapsing Mantle Cell Lymphoma

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Introduction: Glomerular lesions are linked with hematologic malignancies, with minimal change disease (MCD) commonly associated with Hodgkin's lymphoma. Diagnosis of the underlying hematologic disorder often precedes development of the glomerulopathy; however, in rare cases, MCD precedes discovery of the lymphoma by several months. We present a case of new onset nephrotic syndrome and AKI in association with undetected relapsing mantle cell lymphoma (MCL).

Case Description: A 74 y/o man with history of stage IV mantle cell lymphoma in remission developed AKI and new onset edema. Chemotherapy completed 1 year prior to presentation induced complete remission on bone marrow and follow-up PET scans. On presentation he denied B symptoms, had no new lymphadenopathy, and only noted decreased appetite. The patient was edematous and hypertensive. Serum Cr was 2.4 mg/dl up from 1.3 mg/dl. High-grade, non-quantifiable urine protein was noted by the lab. Urine sediment was remarkable for numerous granular casts, oval fat bodies, and few uric acid crystals. Serum uric acid was 13.2 mg/dl. Therapy for tumor lysis syndrome was instituted due to concern for relapsing lymphoma in the setting of AKI. However, PET/CT scan was completely normal with no evidence for lymphoma. Furthermore, LDH was within normal limits. Kidney biopsy revealed normal glomeruli on light microscopy with acute tubular injury. EM revealed global effacement of foot processes. A diagnosis of MCD with focal tubular injury was made and steroid therapy was started. Peripheral flow cytometry and later a bone marrow biopsy confirmed a 23% tumor burden compatible with relapsed MCL. Targeted chemotherapy for MCL was initiated.

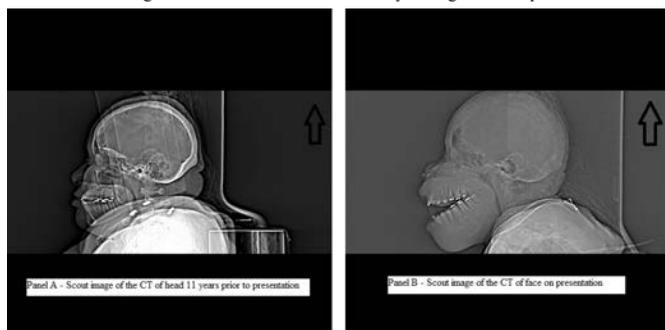
Discussion: We present the first report of MCD associated with relapsing MCL. Oncologic surveillance including PET scan failed to detect recurrent MCL. BM biopsy and flow study was pursued following the diagnosis of MCD. Initial therapy with steroids alone was associated with a reduction in proteinuria. This improved further with therapy directed at the relapsed MCL suggesting a pathophysiologic relationship between these two disorders. Clinicians must remain cognizant of the possibility of malignancy when a suspicious glomerular lesion develops.

TH-PO1037

Renal Osteodystrophy Hitarth S. Dave, Daniel E. Carl. *Dept of Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ School of Medicine, Richmond, VA.*

Introduction: It is believed that mineral metabolism changes start as early as stage II chronic kidney disease (CKD). The spectrum of CKD-mineral and bone disorder (MBD) ranges from low-turnover adynamic disease to high-turnover osteitis fibrosa.

Case Description: A 37-year-old female with end-stage renal disease (ESRD), currently undergoing hemodialysis, presented complaining of a 1-day history of inability to eat or drink. Prior to presentation, she had noticed 2-week history of difficulty speaking, and 8-month history of increasing facial size. On presentation, the blood pressure was 180/68 mm Hg, and the oxygen saturation 98% while breathing ambient air. The physical examination revealed significant bony hypertrophy of the maxilla and mandible with edema of the overlying soft tissue. Computed tomographic (CT) scans of the maxilla and mandible showed severe expansion of the mandible and hard palate with complete replacement of the osseous matrix and surrounding mass effect on the maxillary sinuses and oropharynx with narrowing of the airway most severe at the angle of the mandible (Panel B). Panel A shows a scout image of the CT of head done eleven years ago for comparison.



Laboratory data showed calcium 10.2 mg/dL (8.9-10.7 mg/dL), phosphorus 4.7 mg/dL (2.5-4.6 mg/dL), alkaline phosphatase 2784 units/L (0-120 unit(s)/L), intact PTH 5707.8 pg/mL (12-65 pg/mL). She underwent tracheostomy and four-gland parathyroidectomy with autotransplantation in the subcutaneous abdominal tissue. Biopsy of the left maxillary bone revealed osteitis fibrosa consistent with renal osteodystrophy.

Discussion: Hyperparathyroidism can cause extraosseous calcification in arteries, joints, and viscera. Osteitis fibrosa cystica is characterized by increased bone turnover caused by secondary hyperparathyroidism. The prevention of a positive phosphate balance is the mainstay of treatment of high-turnover bone disease.

TH-PO1038

Bevacizumab Nephrotoxicity: Case Report and Literature Review

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Introduction: Bevacizumab (BCZ), an inhibitor of vascular endothelial growth factor (VEGF), is approved for the treatment of various cancers. We are reporting a case of BCZ induced acute kidney injury (AKI) with proteinuria (PTN) and thrombotic microangiopathy (TMA) and providing a summary of evidence after systematic review of reported cases in literature.

Case Description: A 57-year-old Caucasian woman with no history of kidney disease presented with abdominal pain 4 weeks after completing most recent cycle of BCZ (first dose 2 months before hospitalization) for colon cancer. She presented with new onset of hypertension (HTN), diffusely tender abdomen and a significantly low hemoglobin of 4.6 g/dL. A non-contrast CT showed hemorrhagic pancreatitis. Her serum creatinine at presentation was 2.93 mg/dL (baseline: 0.5 mg/dL). Further workup showed platelets of 45,000/ μ L, haptoglobin of <10 mg/dL and LDH of 947 U/L. Peripheral blood smear showed 3 schistocytes/hpf. Urinalysis was positive for protein and 4 RBCs/hpf. 24 hour urine had 2.1 gms of protein. Hepatitis panel, ANCA and SPEP were negative. ADAMTS 13 activity was normal. Based on clinical diagnosis of AKI, PTN and TMA related to BCZ, the drug was discontinued and patient was managed conservatively without plasma exchange (PE). The creatinine gradually improved to 1.5 mg/dL while platelet count and hemoglobin returned to baseline at discharge.

Discussion: We identified 24 cases reported in literature with mean age of 62 years. All patients presented with AKI and PTN with 61% being nephrotic range. The onset of PTN ranged from 2 weeks to 28 months after initiation of BCZ. HTN occurred among 62% while TMA among 57% of patients. Most of the patients had partial or complete recovery of AKI and PTN with only 1 patient progressing to end-stage renal disease on follow up ranging from 2 to 33 months. The proposed mechanism of nephrotoxicity is thought to be related to low free VEGF levels leading to endothelial dysfunction and podocyte dysregulation. Treatment includes withholding the drug if PTN exceeds 2g/day or permanent discontinuation for nephrotic syndrome and ACEI or thiazide diuretics for treatment of HTN. Drug induced TMA with normal ADAMTS 13 levels rarely requires PE.

TH-PO1039

5-Oxoprolinuria: A Rare Cause of High Anion Gap Metabolic Acidosis due to Acetaminophen Ingestion

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Introduction: Acquired 5-oxoprolinuria is a rare cause of high anion gap metabolic acidosis due to excessive acetaminophen ingestion. It largely goes unrecognized because an assay for 5-oxoprolinuria is not widely available. The malnourished and chronically ill women with history of chronic acetaminophen ingestion are commonly affected. Acetaminophen levels are rarely in toxic range.

Case Description: A 57-year-old woman with a history of adipos dolorosa was admitted for acute osteomyelitis. She was chronically taking acetaminophen containing pain medication. Her hospital course was complicated by anion gap metabolic acidosis and cardiorespiratory failure. Her acetaminophen level was not elevated. Usual causes of anion gap acidosis were ruled out. Finally, a urine organic acid screen showed elevated 5-oxoprolinuria levels. Acetaminophen containing pain medication was stopped, she was given IV hydration and sodium bicarbonate. Her anion gap metabolic acidosis would quickly resolve.

Discussion: Acute and chronic acetaminophen ingestion can lead to high levels of 5-oxoprolinuria. The pathophysiology behind acquired 5-oxoprolinuria has been mostly explained by reduced glutathione in prior case reports. 5-oxoprolinuria is an intermediate in the gamma-glutamyl pathway, the metabolic cycle responsible for creating glutathione and shuttling amino acids into the cytosol. When glutathione levels are diminished, feedback inhibition ceases, causing an overproduction of 5-oxoprolinuria. Sepsis, amongst others etiologies, have been implicated in glutathione depletion. 5-Oxoprolinuria clinically presents with altered mental status. One of the key aspects of diagnosing this disorder is the detection of 5-oxoprolinuria in urine. N-acetylcysteine may be an effective treatment that acts to restore intracellular glutathione levels. Extracellular fluid expansion with dextrose containing saline promptly improves symptoms. In conclusion, 5-oxoprolinuria should be considered in any patient with unexplained metabolic acidosis and recent acetaminophen ingestion. Overlooking the diagnosis can be costly.

TH-PO1040

Severe Tubulointerstitial Nephritis with Lymphoid Follicles in Sjögren's Syndrome Maiko Nagata, Takehiko Kawaguchi, Mao Watanabe, Takafumi Yamakawa, Moritoshi Kadomura, Hiroshi Kitamura, Toshiyuki Imasawa. *Internal Medicine, National Hospital Organization Chiba-East-Hospital, Chiba, Japan.*

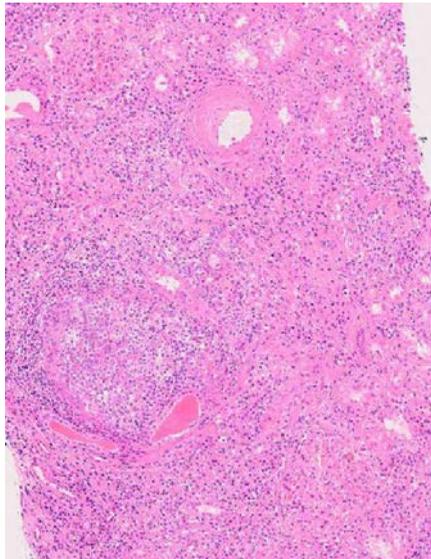
Introduction: Patients with Sjögren's syndrome (SS) are at increased risk for the development of lymphoma. The prolonged state of immunologic and lymphoid hyperactivity in SS may predispose patients to the development of lymphoid neoplasm. However, biopsy specimens from some of these patients do not meet histologic criteria for frank malignancy. We report a rare case of severe tubulointerstitial nephritis with lymphoid follicles in SS.

Case Description: A 66-year-old woman, who had developed general malaise for a few years, was admitted to our hospital, because of the rapid rise in the serum creatinine

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Underline represents presenting author.

level in the past two months. Four months before the admission, she was found to have hypergammaglobulinemia, and a bone marrow–biopsy specimen revealed no hyperplasia of plasma cells. In the admission, the main laboratory values showed the following values: serum creatinine 1.8 mg/dl, IgG 6634 mg/dl, urinary b₂MG 7829 mg/l, anti-SS-A \geq 500 U/ml. Renal biopsy showed tubulointerstitial nephritis with marked lymphoplasmacytic infiltration. Most of the cells were plasma cells; some were immature. Immunostain studies showed plasma cells with a polyclonal pattern. Some lymphoid follicles were also present in the interstitial tissue.



Additionally, lip biopsy showed microsialivary gland with concentrated lymphocyte infiltration. Most of the cells were B lymphocytes. Plasma cells with a polyclonal pattern were present in the peripheral germinal centers. Thus, the diagnosis was primary SS. Immunopathologic analysis of renal and lip biopsy specimens showed no features of malignancy. Steroid therapy led to prompt resolution of the infiltration.

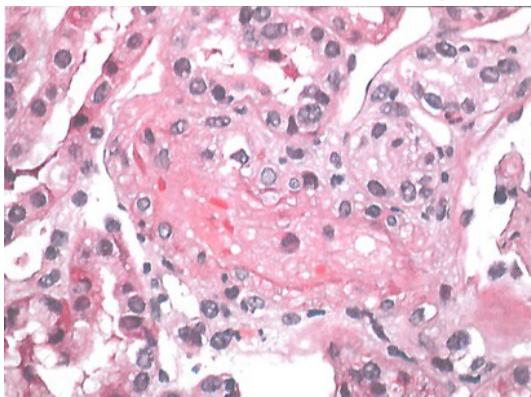
Discussion: This is a rare case of severe tubulointerstitial nephritis with lymphoid follicles in SS. It may show a spectrum of lymphoproliferative disease in SS.

TH-PO1041

Scleroderma Renal Crisis with Normal Blood Pressure and Normal Serum Creatinine Natanong Thamcharoen,¹ Raquel M. Rosen,¹ Vivette D. D'Agati.²
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Introduction: A serious complication of systemic sclerosis is scleroderma renal crisis (SRC) usually presenting with acute onset of high blood pressure, kidney failure and thrombotic microangiopathy. 10% of patients may not have hypertension known as normotensive scleroderma renal crisis but mostly presenting with elevated creatinine. We introduce a case of scleroderma renal crisis with normal blood pressure and normal serum creatinine.

Case Description: A 61 year-old woman was admitted with dysphagia, proximal muscles weakness and tightening of skin. She was diagnosed with systemic sclerosis from the findings. She later developed oliguria without elevation of creatinine (baseline creatinine 0.4 increased to 0.8). Her blood pressure was in normal range. The urinalysis showed 5-10 cell/HPF of red blood cell, no dysmorphic red blood cell or cast. She had proteinuria of 441 mg/day. Kidney ultrasound did not show abnormalities. Anti-dsDNA, MPO antibody and proteinase-3 antibody were performed, they were all negative. Free light chain disease and amyloidosis were ruled out by normal serum protein electrophoresis and normal free light chain. Kidney biopsy was performed revealing arteriolar mucointimal edema and concentric intimal sclerosis, consistent with thrombotic microangiopathy.



Scleroderma renal crisis was diagnosed according to the pathology result. Lisinopril 20 mg oral daily was started but kidneys continued deteriorating leading to hemodialysis.

Discussion: Recognizing the early signs of kidney injury is important to initiate the treatment scleroderma renal crisis(SRC). Physicians should suspect for SRC once patients have signs of acute kidney injury regardless of elevated blood pressure or creatinine.

TH-PO1042

Acetaminophen Associated 5-Oxoproline Acidosis in an Anuric End-Stage Renal Disease Patient Michael Pham,¹ Leslie F. Thomas,² Christine Snozek.³
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Introduction: Also known as pyroglutamic acid, 5-oxoproline is an intermediary in glutathione antioxidant metabolism. Reports of acetaminophen associated 5-oxoproline high-anion gap metabolic acidosis (HAGMA) has been slowly growing in the literature but remains under recognized in clinical practice.

Case Description: A 57 year old male with anuric end-stage renal disease (ESRD) was admitted for confusion and hypotension secondary to sepsis from infected lower extremity ulcers, poor oral intake, and excessive peritoneal dialysis. Laboratory evaluation revealed a depressed bicarbonate level of 17 mEq/L and an elevated albumin-corrected anion gap of 30 mEq/L. Despite correction of an elevated L-lactate with fluid resuscitation and antibiotics, his HAGMA persisted. An exhaustive investigation was unable to find a convincing etiology including commonly attributable organic acids, D-lactate, paraproteinemias, toxic exposures, and medications. Further inquiry revealed a protracted course of therapeutic acetaminophen ingestion with a weighted average daily dose of ³1.3 grams in the four weeks leading to presentation. Serum 5-oxoproline was elevated to >100.0 mmol/L (normal <70.0 mmol/L). Serum acetaminophen was undetectable. All acetaminophen containing medications were subsequently stopped. His clinical course improved with supportive care and he was discharged home. After 5 weeks of acetaminophen cessation, his serum 5-oxoproline normalized to 27.1 mmol/L with anion-gap and bicarbonate levels returning to baseline.

Discussion: To our knowledge, we report the first case of acetaminophen associated 5-oxoproline acidosis in an anuric ESRD patient. Risk factors are thought to be related to glutathione deficiency which in turn favors the 5-oxoproline pathway of the γ -glutamyl cycle and results in accumulation. These risk factors include reactive acetaminophen metabolites, alcohol abuse, malnutrition, sepsis, renal dysfunction, and liver disease. As an under recognized entity in clinical practice, 5-oxoproline should be considered in adults with unexplained HAGMA and the above risk factors.

TH-PO1043

Renal Amyloidosis Associated with Apolipoprotein C-II Deposition Lohit Garg,¹ Gerta Mane,¹ Sami S. Zarouk.² ¹Dept of Internal Medicine, Beaumont Health, Royal Oak, MI; ²Dept of Nephrology, Beaumont Health, Royal Oak, MI.

Introduction: A 62-year-old female with no family history of renal disease presented with a creatinine at 2.3 mg/dL and hypertension. Baseline creatinine was 1.2 mg/dL one year prior to presentation and she had 1+ proteinuria on urinalysis 3 years earlier. Serologic work up was negative for ANA, C3, C4, hepatitis B and C, HIV and SLE. Monoclonal gammopathy evaluation showed IgA kappa monoclonal protein as two bands in the beta globulin region. Random urine for protein electrophoresis showed a small amount of IgA and free kappa monoclonal protein. Her random urine for protein/creatinine ratio was 6.3.

A renal biopsy was consistent with amyloidosis in the mesangium that exhibited apple green birefringence on polarization microscopy after Congo Red staining. Immunofluorescent stains for kappa and lambda light chains were negative. Electron microscopy showed randomly arranged fibrils in the mesangium with features characteristics of amyloid fibrils. Bone marrow biopsy showed 6% plasmacytosis and minimal involvement with amyloidosis. Laser micro dissection and liquid chromatography mass spectrometry (LCMS) were performed on peptides extracted from Congo-red positive dissected areas. LCMS detected high levels of apolipoprotein C-II while analysis for lambda or kappa light chains, transthyretin and serum amyloid A were negative. It was concluded that these findings are unequivocally consistent with apolipoprotein C-II amyloid. Genetic testing was performed by direct sequencing of apolipoprotein C-II and showed mutation in patient as well as her son but not her daughter.

Discussion: Apolipoprotein C-II is a component of very low density lipoprotein and readily aggregates in lipid free conditions to form homogenous amyloid fibrils due to their intrinsic structure. To the best of our knowledge, this is the first case of apolipoprotein C-II renal amyloidosis. This case highlights the importance of performing DNA sequencing of exons of interest and LCMS on known amyloidogenic proteins to accurately diagnose and type the renal amyloidosis, which is critical for prognosis, treatment and genetic counseling.

TH-PO1044

Membranous Nephropathy in a Young Child with IPEX-Like Phenotype and a Novel Foxp3 Mutation Olga Charnaya, Sun-Young Ahn, Asha Moudgil.
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Introduction: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome typically presents with heterogeneous manifestations. The syndrome is characterized by numerous auto-immune diseases due to dysfunction in the *Foxp3* gene, which plays a critical role in maintaining immune tolerance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Case Description: A 14-month-old male with a history of failure to thrive (FTT), eczema and diarrhea presented with cough and wheezing for 4 months. Pertinent findings on physical exam included weight < 2%ile, length 10%ile, BP 103/83 mmHg, and diffuse wheezing. Laboratory evaluation showed nephrotic range proteinuria (urine protein-to-creatinine ratio of 6.3), low serum albumin 1.8 gm/dL, normal serum creatinine 0.3 mg/dL, elevated LDL cholesterol 195 mg/dl, elevated serum glucose 303-426mg/dl, normal urine calcium-to-creatinine ratio 0.25, low C3 46 and C4 9.7, and negative ANA and anti DNA. Thyroid function tests were normal; islet cell antibodies were elevated at 80 (normal <1.2). A renal biopsy revealed membranous nephropathy with mild mesangial proliferative changes. Upon further evaluation, he was found to have fat malabsorption and numerous food allergies. Genetic sequencing identified a novel missense mutation, c.767T>C leading to substitution of the highly conserved amino acid threonine with methionine at position 256 in the *Foxp3* gene. This mutation was predicted to be deleterious by in silico analysis thereby suggesting the diagnosis of IPEX syndrome. Of note, *Foxp3* protein expression was borderline low. The patient was treated with prednisone and tacrolimus with partial resolution of extra-renal symptoms, improvement in proteinuria and is currently awaiting bone marrow transplant.

Discussion: Infants with IPEX syndrome usually present with auto-immune enteropathy, FTT, eczema, type 1 diabetes mellitus and thyroid dysfunction. Renal involvement is rare and includes proteinuria, hematuria and renal insufficiency. Some children with novel mutations may have partial features as seen in this case. A diagnosis of IPEX should be considered in any male infant or young child with proteinuria in association with systemic features of autoimmunity.

TH-PO1045

Acute Rejection of a Kidney Transplant in a Patient with Common Variable Immunodeficiency Syndrome Omar Mousa Al Nimri, Rakesh Malhotra, Pamsit Pauksakon, Beatrice P. Concepcion. *Vanderbilt Univ Medical Center, Nashville, TN.*

Introduction: Common Variable Immunodeficiency (CVID) is a primary immunodeficiency characterized by hypogammaglobulinemia. Clinical manifestations include recurrent bacterial infections, autoimmune disorders, chronic lung disorders, hepatitis and lymphoma. We report a case of a patient with known CVID whose post-transplant course was complicated by acute cellular and humoral rejection which ultimately led to graft loss.

Case Description: A 44 y.o. male with ESRD was diagnosed in 11/2010 with CVID after developing peritonitis. He had a history of recurrent sinopulmonary infections and pneumococcal pneumonia. Immunoglobulin levels were undetectable and B, T and NK cell numbers normal. He was treated with monthly IVIG infusions. In 3/2012, he underwent living unrelated kidney transplantation (KT). Immunosuppression consisted of basiliximab, methylprednisolone (MP), FK, MMF and prednisone. Baseline creatinine (Cr) post KT was 1.3 mg/dL. In 8/2014 Cr was 3.6 mg/dL. Renal biopsy showed diffuse lymphoplasmacytic infiltrate with edema, frequent tubulitis and interstitial eosinophils. C4d and donor specific antibodies (DSA) were negative. He received IV MP 2.5 g and thymoglobulin 10.5 mg/kg as therapy for acute cellular rejection (ACR), CCTT Type 1. In 9/2014 Cr was 5 mg/dL. Rebiopsy showed resolution of ACR. However, he had chronic vascular rejection, focal acute tubular injury and transplant glomerulopathy with new diffuse (100%) C4d positivity. Class I DSA was positive at moderate levels. He was treated for acute humoral rejection with plasmapheresis and IVIG 2 g/kg. Renal function did not improve. In 11/2014 he was declared ESRD due to uremic symptoms and volume overload.

Discussion: To our knowledge, this is the first reported case of a patient with diagnosed CVID on maintenance IVIG who then underwent KT. The main concern for patients with CVID undergoing KT is the risk of infectious complications. However, this case illustrates that rejection can occur and adequate immunosuppression remains essential. Balancing immunosuppression with the risk of infection can be quite challenging in this patient population, making them high risk for transplantation.

TH-PO1046

Reverse Pseudohyperkalemia in a Patient with Non-Hodgkins Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia Chawmay Aye, Mitesh K. Patel, Farhanah Yousaf, Bruce S. Spinowitz, Alla Goldberg, Ritesh Raichoudhury. *New York Hospital Queens.*

Introduction: Distinguishing pseudohyperkalemia from hyperkalemia is often challenging. Simple pseudohyperkalemia is common and is represented by a falsely increased serum potassium whereas reverse pseudohyperkalemia is characterized by a falsely elevated plasma potassium level. We report a case of reverse pseudohyperkalemia in a patient with non-Hodgkin's mantle cell lymphoma and chronic lymphocytic leukemia.

Case Description: A 74 year old South Asian female with a past medical history of non-Hodgkin's mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL), presented to the emergency department with a chief complaint of dizziness. She underwent chemotherapy session with Imbruvica one week prior to her presentation. Her initial vital signs included a blood pressure of 105/73, a pulse of 116 beats/min, a respiratory rate of 17, and a temperature of 36.7 degrees Celsius. Physical exam was unremarkable. Her initial hematology panel consisted of a white blood count of 0.82 K/ μ L, hemoglobin of 10.2 g/dL, and platelets of 40 K/ μ L. Patient was admitted with neutropenic sepsis and was started on Vancomycin, Meropenem, and Valtrex. Subsequent lab tests revealed a rising serum creatinine of 2 mg/dL and greater. One month into hospitalization, lab results showed a plasma potassium concentration of 8.22 mmol/L and a serum potassium concentration of 5.6 mmol/L. Repeat testing four hours later was consistent and showed a plasma potassium

concentration of 7.2 mmol/L and a serum potassium concentration of 5.4 mmol/L. Based on the blood plasma potassium results, the patient received emergent hemodialysis and potassium lowering agents.

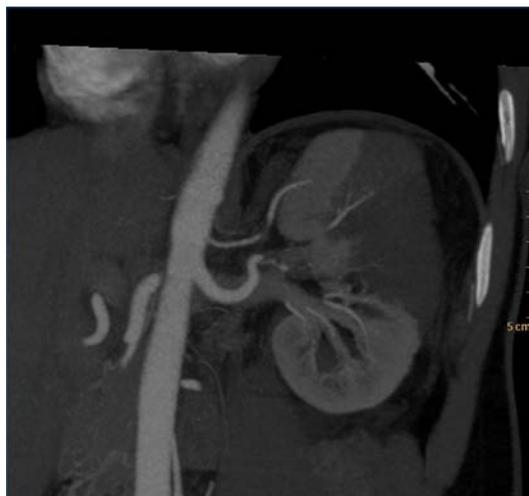
Discussion: Reverse pseudohyperkalemia has been reported in adults with CLL but remains relatively an under-recognized entity among clinicians. The mechanisms producing reverse pseudohyperkalemia are unclear but potassium may be released from leukocytes due to hyperin-induced cell damage and/or impaired Na-K ATPase activity in the presence of hematological malignancy. Early identification of reverse pseudohyperkalemia is crucial in preventing potassium lowering intervention related morbidity and mortality.

TH-PO1047

An Unusual Presentation of Fibromuscular Dysplasia Omar Mousa Al Nimri,¹ Murray J. Mazer,² Margaret L. Burks,³ Gerald Schulman,¹ Rachel B. Fissell,¹ ¹Nephrology, *Vanderbilt Univ Medical Center, Nashville, TN;* ²Radiology, *Vanderbilt Univ Medical Center, Nashville, TN;* ³Internal Medicine, *Vanderbilt Univ Medical Center, Nashville, TN.*

Introduction: Fibromuscular dysplasia typically presents in middle aged women, often with hypertension. Depending on which arteries are involved, patients may present with transient ischemic attack, stroke [carotid artery FMD], or intractable hypertension [renal artery FMD]. We report an atypical case of fibromuscular dysplasia (FMD) in a male, that presented with renal infarction and no other symptoms.

Case Description: The patient is a 47yo male with no significant past medical history, including no history of Ehlers-Danlos syndrome or Marfan's syndrome, who developed sudden left flank pain while driving. No urinary symptoms. No tenderness on exam. The pain was so severe that he went to a local ER. Initial evaluation notable for BUN 10 mg/dL, Cr 1.06 mg/dL, urinalysis negative for blood, protein, and white blood cells. CT angiography revealed beading consistent with FMD at the distal main renal artery at the junction of the bifurcating branches, and tapered narrowing and occlusion most likely caused by spontaneous dissection with intramural hematoma, with upper pole infarct.



Subsequent transthoracic echo showed no vegetation or shunt, appearing to exclude embolus from heart or lungs. Hypercoagulable work-up was negative. Patient is being managed conservatively with no anticoagulation, and is doing well. His Cr has drifted down from a peak of 1.16 mg/dL to a new baseline of 0.99 mg/dL, he has not developed hypertension, and his flank pain has resolved.

Discussion: This case is notable because the FMD occurred in a male, and because renal infarction is a rare presentation of FMD. The actual cause of the infarction is most likely arterial dissection, with or without peripheral emboli.

Funding: Clinical Revenue Support

TH-PO1048

Clotting Filter Might Be an Early Clue to Fat Embolism Syndrome: Case Report and Literature Review Deepak Jasuja, Melissa D. Anderson. *Div of Nephrology, Indiana Univ, Indianapolis, IN.*

Introduction: Non traumatic causes of Fat Embolism Syndrome (FES) have been reported with bone marrow transplantation, osteomyelitis, pancreatitis, alcoholic fatty liver, and with liposuction. Etiology likely is fat particles entering the circulation with damage to capillary beds. Regardless of the mechanism initiating fat embolism, the end result is an intense inflammatory response. In the lungs, this induces lung injury that is indistinguishable from ARDS. FES can cause cerebral edema with raised intracranial pressure along with multi-organ failure and AKI.

Case Description: We present a 40-year-old African American lady who underwent non-myeloablative bone marrow transplant for Myelodysplastic anemia. One week after engraftment she developed sudden onset of respiratory distress leading to a cardio-respiratory arrest. She developed ARDS, multiple organ dysfunction syndrome and CVVH was initiated for oliguric AKI and Metabolic acidosis. Soon after initiating CVVH her filter clotted with white, creamy plaque which cleared after 2 successive filters. Patient met Gurd and Wilson's criteria for diagnosis of Fat Embolism Syndrome. She had abundance of

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inflammatory cells on Broncho alveolar lavage including neutrophils and macrophages. Oil Red-O stain (stain for lipid) was performed to quantify macrophages displaying positivity. The initial Prep yielded 5 of 5 and the repeat prep yielded 11 out of 12 macrophages positive for Oil-Red-O. CT brain was performed which revealed large acute strokes with midline shift compatible with subfalcine herniation. No cerebral blood flow was identified on nuclear scan and patient was declared brain dead and terminally weaned.

Discussion: With the absence of specific tests or criteria the diagnosis of FES is dependent on the clinical acumen of the physician. Lipid inclusion in 30-70% of macrophages / inflammatory cells is most suggestive of FES . Only proven treatment is supportive care. We propose that a clotting filter might be an earlier clue to diagnose fat embolism syndrome and sending the filter for pathological analysis looking for lipid laden inflammatory cells is a less invasive approach as compared to quantification using Broncho-alveolar lavage.

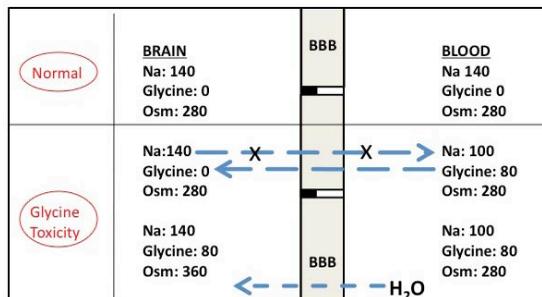
TH-PO1049

Fatal Hyponatremia with Glycine Solution During Hysteroscopy – Proposal for New Mechanisms of Hyponatremia and Cerebral Edema
Suchita J. Mehta, Subodh J. Saggi, Andrea Roche-Recinos, Man S. Oh. *Nephrology, SUNY Downstate, Brooklyn, NY.*

Introduction: We report a fatal case of severe symptomatic hyponatremia and cerebral edema following hysteroscopy.

Case Description: 39 y/o woman underwent 70 mins hysteroscopic myomectomy, 6L of glycine solution used for distension, without documented deficits. 3 hours later she developed pulmonary edema. Hyponatremia of 117mEq/L first noted 4 hours post surgery, baseline normal sodium. Course further complicated by agitation, vomiting, lethargy due to cerebral edema confirmed on C.T. Head 8 hours post-op, remained without brain stem reflexes. Post-op day 2 she also developed central diabetes insipidus. Remained brain dead, extubated and died after 12 days.

Discussion: Hyponatremia with glycine is iso-osmolar occurring as a result of dilution effect since glycine is retained in extra-cellular fluid before its metabolism by glycine cleavage enzyme. Two main questions with our postulated explanations: 1) How does cerebral edema develop with iso-osmolar hyponatremia? 2) Why is hyponatremia often more severe than predicted? Proposed mechanisms: 1) Glycine can cross blood brain barrier (BBB) by passive diffusion, as shown in rats and cats. Sodium, however, does not exit brain via BBB as sodium transport across BBB occurs only inward. With glycine toxicity, glycine accumulates in the brain cells after crossing BBB followed by water resulting in brain edema. Possibility of glycine metabolism to ammonia leading to cerebral edema cannot be ruled although high levels were not seen in our case.



2) The greater reduction in serum sodium than expected can be explained by a smaller initial volume of distribution of glycine than the extracellular volume, which is attributed to rapidity of accumulation of glycine solution and the reduced muscle blood flow during surgery.

TH-PO1050

Cytomegalovirus-Induced Atypical Hemolytic Uremic Syndrome After Renal Transplant Taranpreet Kaur,¹ Andres G. Chiesa-vottero,² Leal C. Herlitz,² Richard A. Fatica.¹ *¹Nephrology, Cleveland Clinic; ²Pathology, Cleveland Clinic, Cleveland, OH.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) may occur as de novo disease and recurrence of primary renal disease in kidney transplant recipients. Causes of de novo HUS includes immunosuppressive drugs, ischemia reperfusion injury, acute humoral rejection, and viral infections. Some patients have a genetic susceptibility to the disease from underlying mutations in the complement regulatory proteins. Cytomegalovirus (CMV) has been rarely reported as a trigger for de novo post-transplant aHUS.

Case Description: A 61 year old male underwent deceased donor kidney transplant for ESRD from presumed FSGS. 1 year following transplant he was admitted with profound diarrhea and weight loss due to CMV colitis and high grade CMV viremia (410,462 copies/ml). His immunotherapy was reduced and he was discharged home on oral valganciclovir with near resolution of symptoms. He was re-admitted 1 week later with nausea, abdominal pain, and acute kidney injury (Creatinine of 3.8 mg/dl, baseline of 1.8 mg/dl). His repeat CMV viral load was significantly better at 70,000 copies/ml. Labs were suggestive of microangiopathic hemolytic anemia: Hb 8 g/dl, platelets 58 K/uL, LDH 586 U/L, haptoglobin <20 mg/dl, and ADAMTS13 activity >67%. He received 4 sessions of plasmapheresis without improvement and required initiation of dialysis. Histologic features of acute and subacute endothelial injury, including segmental fibrin thrombosis of 2 arterioles were present on

transplant kidney biopsy. His aHUS genetic panel revealed several mutations in different gene loci but no disease-associated mutation was identified. He was started on eculizumab. His hemolysis labs improved and he was taken off dialysis.

Discussion: CMV infection by way of endothelial injury can provoke aHUS in kidney transplant recipients and possibly be enhanced by genetic predispositions. Postulated mechanisms of CMV endothelial injury include increased leukocyte and platelet adhesion, endothelial expression of Von Willebrand factor, E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1. In our case, the aHUS process was halted by use of eculizumab.

TH-PO1051

Acute Interstitial Nephritis from Anti-PD-1 Therapy with Pembrolizumab in Two Patients with Advanced Non-Small Cell Lung Cancer
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Introduction: Immune checkpoint inhibition with monoclonal antibodies (mAb) targeted against programmed cell death receptor 1 (PD-1) is emerging immunotherapy for various cancers. Pembrolizumab, an anti-PD-1 mAb, is being used in clinical trials with promising anti-tumor responses, but renal-specific adverse events are not clear. We report 2 cases of acute interstitial nephritis (AIN) in patients who received Pembrolizumab for advanced non-small cell lung cancer (NSCLC).

Case Description: Two female patients, both 69 years of age, with metastatic NSCLC were seen in outpatient nephrology clinic for acute kidney injury (AKI). Both patients were enrolled in a clinical trial with Pembrolizumab, and their cases had been complicated previously by auto-immune adrenalitis. On labs, Patient A had an increase in creatinine to 2.1 mg/dL prior to cycle 16, up from a baseline of 0.9 mg/dL. Patient B had a creatinine peak of 1.9 mg/dL after cycle 6, up from a baseline of 1.1 mg/dL. Medications were significant for long-standing pantoprazole use in both patients. Urine sediment showed many WBC clumps without casts or RBCs. Renal ultrasound was unremarkable. Volume expansion with normal saline and cessation of potential nephrotoxins failed to reverse renal dysfunction in either case. Each patient underwent CT-guided renal biopsy, which showed diffuse AIN. Steroid therapy with prednisone 60 mg/day with a slow taper was started and creatinine improved to baseline.

Discussion: These two cases highlight a new association between AIN and Pembrolizumab, which to the best of our knowledge has not been previously reported. While both patients were on pantoprazole therapy prior to their AKI, this medication was not new. Rather, the time course of AKI best fits with initiation of pembrolizumab. Additionally, their pre-existing drug-related auto-immune adrenalitis suggests a possible auto-immune component to AIN from anti-PD-1 therapy. With increasing use of these agents, clinicians should maintain a high index of suspicion for AIN as a cause of AKI and have a low threshold for kidney biopsy to confirm diagnosis and initiate early treatment.

TH-PO1052

Concurrent Anti-PLA2R and ADAMTS 13 Inhibitor – Coincidence or a Clue to Pathogenicity? Laith Al-Rabadi,¹ Moshe Shashar,¹ Parikshit Duriseti,² Ami Patel,¹ Aala Jaber,¹ Ashish Upadhyay,¹ Joel M. Henderson,¹ Vipul C. Chitalia,¹ David J. Salant,¹ Laurence H. Beck.¹ *¹Boston Univ Medical Center; ²Mamata Medical College, India.*

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a hematologic emergency associated with a decrease in ADAMTS13 activity, most often due to the presence of an inhibitor. Severe proteinuria is an unusual feature of TTP. The concurrent presence of anti-PLA2R and ADAMTS13 inhibitor has never been previously reported until now.

Case Description: Herein, we present a case of a 70 year old male who presented with generalized anasarca. Physical exam was remarkable for BP 180/100, and 2+ peripheral edema. Workup revealed Hgb 7.4, Plt 36, Creatinine 1.43, LD 742 and undetectable haptoglobin. His peripheral smear showed many schistocytes. These findings were consistent with thrombotic microangiopathy. Urine analysis showed 2+ blood, 3+ protein. Examination of the urinary sediment revealed oval fat bodies, and some RBCs. The patient was started on plasma exchange and prednisone (1 mg/kg). Further studies revealed a serum albumin of 2.2 and urine protein/Cr of 9. Kidney biopsy showed features of membranous nephropathy with many subepithelial deposits flanked by new basement membrane material (spikes). The deposits were immunoreactive for PLA2R, with IgG1 but no IgG4 reactivity. In addition, there was moderately severe arterial and arteriolar sclerosis and segmentally prominent double contour formation in the glomeruli. These vascular changes suggest a primary form of endothelial injury and consistent with chronic thrombotic microangiopathy. VWF protease activity came back as less than 3% with an elevated inhibitor titer of 1.3 (reference <0.4 BEU). Anti-PLA2R was detected in the serum at titer of 40.3 RU/ml. Both were exclusively of the IgG1 subtype by western blotting, atypical of the usual IgG4 predominance for both autoimmune disorders.

Discussion: Although prednisone, plasmapheresis, and supportive therapy have thus far stabilized both diseases, rituximab would be our first choice for more definitive treatment of these concurrent autoimmune disorders. This unique case may help to further our understanding of the mechanistic pathways underlying both of those clinical entities.

TH-PO1053

Carfilzomib Associated Acute Kidney Injury Vladimir Liberman,¹ Vivette D. D'Agati,² Naveed N. Masani,¹ Joseph Mattana,¹ James Drakakis.¹ ¹*Medicine, Winthrop-Univ Hospital, Mineola, NY;* ²*Pathology, Columbia Univ Medical Center, New York, NY.*

Introduction: Carfilzomib is a selective proteasome inhibitor approved in 2012 for the treatment of relapsed and refractory multiple myeloma. A phase 2 trial of the drug showed an increased serum creatinine in 17.7% of patients but the mechanism has been incompletely understood. We report a case of biopsy proven acute tubular injury one week after carfilzomib administration.

Case Description: A 60 year old man with IgG lambda multiple myeloma who received an autologous stem cell transplant 2 years ago presented to the hospital complaining of shortness of breath and chest discomfort. Physical examination revealed a blood pressure of 141/74, clear lungs, normal heart sounds with no murmurs and pitting edema of both lower extremities. Serum potassium was 6.3 mEq/L and creatinine was 3.4 mg/dL (baseline 0.8 mg/dL). Serum free lambda light chains were 3630 and free kappa light chains were 5.55. The patient had received an injection of carfilzomib 7 days prior to his arrival. He had no other exposure to nephrotoxic medications. Spot urine protein/creatinine ratio was 3g/g with an albumin/creatinine ratio of 140mg/g. Obstruction was excluded by ultrasonography and he received isotonic saline with only minimal improvement in kidney function at which point a kidney biopsy was performed. Renal biopsy showed focal mild myeloma cast nephropathy with diffuse acute tubular injury out of proportion to the sparse casts. The close temporal association with the initiation of carfilzomib suggests that it could have been responsible for the severe tubular injury given no other obvious insults.

Discussion: Carfilzomib has been associated with kidney injury as one of its adverse effects in its phase 2 trial. Most of the kidney injuries were reported as grade 1 or 2 based on the NIH grading system. Grade 3 and 4 renal impairment was reported in 38 patients (7.2%). This case of biopsy proven acute tubular injury suggests a mechanism by which carfilzomib may cause acute kidney injury in patients with multiple myeloma.

TH-PO1054

Podocyte Infolding Glomerulopathy in a Patient of African Descent Laith Al-Rabadi,¹ Cathryn J. Byrne-dugan,² David Olafsson,³ Saif Alrabadi,⁴ Laurence H. Beck,¹ Helmut G. Rennke,² Stanley D. Crittenden.¹ ¹*Boston Medical Center;* ²*Brigham and Women's Hospital;* ³*Univ of Iceland;* ⁴*Jordan Univ.*

Introduction: Podocyte infolding glomerulopathy (PIG) is a rare entity primarily described in Japan which is frequently associated with autoimmune diseases like lupus. It is not known whether PIG represents a new disease entity or a transient morphologic state of well-known diseases (i.e. a subset of membranous nephropathy or lupus nephritis). PIG has been exclusively described in Asian populations, with no cases reported in patients of African descent. PIG is distinguished by its histologic features of podocyte membrane infolding into the basement membrane and the formation of microspheres and microtubules. The majority of cases do not contain electron-dense deposits, nor do they show any reactivity with IgG. Here we present the first reported case of PIG in a patient of African descent.

Case Description: A 58 year old Africa female from Ghana with history of systemic lupus erythematosus presented to the nephrology clinic for the evaluation of proteinuria. She was found to have a serum creatinine of 1.5 mg/dL and random urine protein to creatinine ratio of 1.5 g/g. Microscopic examination of the urine sediment did not reveal RBCs or cellular casts. Other notable lab findings include anti nuclear antibody titer of 1:2560 and positive anti double stranded DNA. She underwent kidney biopsy. Light microscopy revealed thickened glomerular peripheral capillary walls, with numerous crater-like defects. Immunofluorescence was negative other than trace IgM and C3 reactivity along the peripheral capillary walls and in the mesangium. No electron dense deposits were found on electron microscopy (EM). However, widespread aggregates of spherical structures within the lamina rara externa and lamina densa along with diffuse invaginations of the podocytes at the subepithelial aspect of the basement membrane, with deposition of spherical microparticles were seen on EM.

Discussion: Further studies are warranted to investigate whether this represents a unique primary disease with a specific underlying pathology or if it is simply a morphologic reflection of a transition point for a previously discovered disease entity.

TH-PO1055

Amyloidosis due to R554L Fibrinogen A α -Chain Mutation Matthew R. Lynch,¹ Ian Mccoy,³ Isaac Ely Stillman,² Stewart H. Lecker.¹ ¹*Div. Nephrology, Beth Israel Deaconess Medical Center, Boston, MA;* ²*Pathology, Beth Israel Deaconess Medical Center, Boston, MA;* ³*Medicine, Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Cases of systemic amyloid caused by mutations in the fibrinogen A-alpha chain (A α) were once thought to be quite rare, but may be more common than initially thought. Mutations in A α leading to hereditary amyloidosis, primarily with renal manifestations, was first described in 1993. A significant minority of A α amyloid patients have the R554L variant. To date, about 20 such cases have been published. Small sample sizes have limited definitive conclusions regarding genotype-phenotype correlation.

Case Description: A 66-year-old man with a history of hypertension, hyperlipidemia, and prior heavy NSAID use was referred for two years of stable, nephrotic-range proteinuria. Besides lower extremity edema managed with compression stockings, he was asymptomatic. He had no family history of kidney disease. His medications included losartan, torsemide, and simvastatin. His exam was unremarkable except for pitting edema to the knees. Laboratory studies revealed a stable serum creatinine of 1.1 mg/dL. A 24 hour urine protein

measured 4180 mg. Urine sediment showed lipiduria but no cells or casts. Testing for hepatitis B and C, HIV, and ANCA was negative. Serum and urine protein electrophoresis showed no monoclonal protein. Renal ultrasonography was unremarkable. Kidney biopsy showed massive glomerular deposition of Congo Red positive and apple-green birefringent material. Liquid chromatography tandem mass spectrometry detected mutant R554L amino acid sequence in the fibrinogen A-alpha chain.

Discussion: A α patients progress from presentation to ESRD over a mean of 4.6 years with mean survival of 9.3 years after ESRD. Recurrent amyloidosis occurs in renal allografts, but this process takes several years. While orthotopic liver transplantation may cure the amyloidosis by replacing the source of the mutant fibrinogen, the procedure-related mortality is high, making the benefit of preemptive liver transplantation unclear. With increasing recognition of this disease, further investigation into curative therapy is needed.

TH-PO1056

Diabetes Insipidus Induced by Excessive Intake of Melatonin Rahul N. Pawar, Savneek S. Chugh, Amy R. Patel. *Nephrology, Westchester Medical Center, Valhalla, NY.*

Introduction: Melatonin is produced by the pineal gland and regulates the sleep/wake cycle in humans. Specific over the counter melatonin formulations can be used to treat circadian-rhythm-related sleep disorders and age-related insomnia. Acute intoxication of melatonin and its deleterious effects have rarely been reported.

A 24 year old female, with no known medical history, was brought to the hospital for altered mental status and possible drug overdose. Her vital signs were a Tmax of 101.8 F, HR 170, BP 150/103, and a pulse oximetry of 98% on 2L NC. On physical exam, she had mildly dilated and sluggish pupils. Due to an altered sensorium, she was intubated for airway protection. Initial lab tests showed a sodium of 140 mEq/L, potassium 3.9 mEq/L, chloride 113 mEq/L, bicarbonate 25 mEq/L, BUN 8 mg/dL, and a creatinine of 0.6 mg/dL with no osmolar gap, but elevated AST 74 U/L, ALT 37 U/L and creatine phosphokinase of 2,460. Urine toxicology screen was negative for PCP, cocaine, MDMA, and opioids with an undetectable blood alcohol level. On day 1, she developed polyuria with a urine output of more than 13.5 liters, a serum sodium of 147 mmol/L and urine osmolality of 65 mOsm/kg concerning for diabetes insipidus (DI). CT head and MRI of the brain were negative for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 8L/day. Her urine osmolality increased to 444 mOsm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After extubation, the patient reported ingestion of an excessive amount of melatonin for insomnia, but no other medications. She received DDAVP for 4 days with complete resolution of hyponatremia and polyuria.

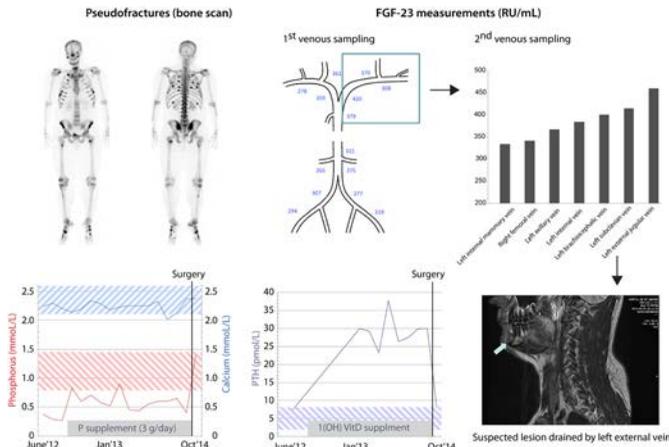
Discussion: Extensive literature review revealed that rat studies show how melatonin regulates the glomerular filtration of both sodium and water. It stimulates sodium tubular transport in the proximal tubules but its receptor or action on the distal tubule is unknown. Only a handful of cases have shown that it can cause polyuria. This rare case of polyuria from the acute ingestion of melatonin, which responded to DDAVP, may suggest its role in causing partial central DI.

TH-PO1057

Localization of Ectopic Fibroblast Growth Factor 23 Production in Tumor-Induced Osteomalacia Using a 2-Step Selective Venous Sampling Method Karyne Pelletier, Veronique Bienvenue, Myriam Lessard, Stephan Troyanov. *Medicine, Hôpital du Sacré-Coeur, Univ of Montreal, Montreal, QC, Canada.*

Introduction: Tumor-induced osteomalacia (TIO) is a rare syndrome characterized by hypophosphatemia, impaired renal phosphate reabsorption and inappropriate reduction of serum 1,25(OH)₂vitamin D usually caused by benign mesenchymal tumors secreting FGF23. Affected individuals present severe osteomalacia with bone pain, pseudofractures and muscle weakness. Although TIO is cured by the resection of the causative tumor, definitive treatment is often delayed because current imaging techniques (MRI and bone, octreotide and PET scans) fail to localize the offending lesion. We propose localization of ectopic FGF23 tumors using 2-step selective venous sampling method.

Case Description: A 37-year-old patient presented with bone pain and hypophosphatemia. An initial workup showed >75% fractional excretion of phosphate, normal serum calcium and intact PTH, low 25(OH) vitamin D. Peripheral blood FGF23 level was 310 RU/mL (N:19-114). Initial imaging failed to localize an obvious lesion. A 1st venous sampling suggested FGF23 drainage from the left subclavian vein. A second focused sampling pointed to the left external jugular vein. The excision of an initially unsuspected small mandibular lesion cured the patient.



Discussion: A recent cases review (Andreopoulou, J Bone Min Research 2011) supports the benefits of systemic venous sampling in locating FGF23 tumors in TIO. However, up to 30 samples are needed when using a single venous sampling method. Since lesions are small and may arise anywhere, we propose a 2-step approach simplifying the localization of causal lesions.

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TH-PO1058

Renal Transplant Dysfunction due to Calcium Casts following Parathyroidectomy Maharajan Raman,¹ Rajkumar Chinnadurai,¹ Grahame N. Wood,¹ Jamil Choudhury,² Philip A. Kalra.¹ ¹Renal Medicine, Salford Royal NHS Foundation Trust, Salford, Manchester, United Kingdom; ²Cellular Pathology, Salford Royal NHS Foundation Trust, Salford, Manchester, United Kingdom.

Introduction: Parathyroidectomy for renal hyperparathyroidism can lead to significant drop in calcium levels due hungry bone syndrome, which can lead to seizure, coma or fractures. Current practice is to pre-load patients with hydroxycholecalciferol and calcium supplements to maintain safe calcium levels in the post-operative period. We report a case of calcium cast nephropathy causing significant renal dysfunction following parathyroidectomy.

Case Description: A transplant patient on Cinacalcet for tertiary hyperparathyroidism underwent parathyroidectomy (PTX). Post operatively her calcium levels were managed according to local protocol. Patient sub-acutely developed renal dysfunction and the trends in creatinine (Cr), corrected calcium (C.Ca) and parathyroid hormone levels (PTH) pre and post surgery are shown in the table below.

	Pre PTX	1 month post	2 months post	3 months post	4 months post	6 months post
Cr (umol/L)	113	167	132	169	284	103
C.Ca (mmol/L)	2.73	2.62	2.55	2.71	2.67	2.38
PTH (ng/L)	329	-	54	-	-	-

Virology screen, immunology screen, urine culture, urine PCR, DSA, Cyclosporin levels and renal ultrasound were normal with no change in patients haemodynamic status. Hence a kidney biopsy was performed to identify the cause, which showed evidence of calcium casts with surrounding inflammation with no evidence of rejection. Her steroid dose was transiently increased due to the inflammation seen on the biopsy and all her calcium and hydroxycholecalciferol supplements were suspended, which lead to recovery of her renal function to baseline.

Discussion: Our patient had mild hypercalcaemia prior to parathyroidectomy with a stable renal function and following parathyroidectomy patient developed renal dysfunction despite similar levels of calcium, which can only be explained by iatrogenic calcium supplementation based on the renal biopsy. Perhaps routine monitoring of urinary calcium may help us guide the amount of calcium given to such patients and aiming for lower levels of calcium post parathyroidectomy rather than normal levels may prevent such phenomenon.

TH-PO1059

Severe Ketoacidosis After Bariatric Surgery in a Patient Treated with Canagliflozin Hossein Ghofrani, Christopher C. Wong, Miroslaw Smorzewski. Div of Nephrology, Keck Hospital of USC, Los Angeles, CA.

Introduction: Euglycemic diabetic ketoacidosis is relatively uncommon and is usually caused by starvation and a lack of caloric intake. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been very recently implicated as a cause of severe ketoacidosis. We report a case of euglycemic diabetic ketoacidosis in a patient who underwent bariatric surgery while taking an SGLT-2 inhibitor, canagliflozin.

Case Description: A 38 year old male with a history of DM type 2 and morbid obesity presented with fatigue, acute dyspnea, decreased exercise capacity and 2-3 pillow orthopnea for two days. Canagliflozin 300 mg daily was initiated 3 months prior to his

current presentation due to poorly controlled DM-2. Ten days prior to his hospitalization, he underwent gastric sleeve bypass surgery and was discharged on post-op day 1. Upon admission in the ICU, his physical exam was benign except for a PR 108/min, RR 29/min, and a normal BP 128/69 mmHg. ABG showed pH 6.9, pCO2 13mmHg, pO2 99mmHg, bicarbonate 5mg/dL. His anion gap was 37, and serum glucose 152 mg/dL, with normal kidney function. Urine toxicology and blood levels of lactic acid and alcohol were negative. Urinalysis revealed pH 5.0, glucose >1000 mg/dL, and ketones >150 mg/dL. During the first day, he received 150 meq of sodium bicarbonate; his canagliflozin was held. He was intubated and started on a regular insulin drip along with 5% dextrose solution. He remained intubated and on an insulin drip for 7 days, receiving a total of 1266 units of insulin and extensive electrolyte replacement; blood glucose never exceeded 200 mg/dL while glycosuria persisted until day 7. C-peptide increased from 0.29 to 2.26 ng/mL. Once anion gap was closed and patient stabilized, he was extubated and weaned off the insulin drip.

Discussion: We present a new case of severe euglycemic DM ketoacidosis, induced by a combination of SGLT-2 inhibitor use and low caloric intake after bariatric surgery. Despite withdrawal of canagliflozin, its effect on glycosuria persisted for 7 days. Considering long biological effect of SGLT-2 inhibitors, they should be stopped weeks before a bariatric surgery to avoid ketoacidosis.

TH-PO1060

Severe Hypercalcemia in Erdheim-Chester Disease: A Rare Clinical Scenario David H. Slade,¹ Esho Georges,² Ahmer Farooq,³ Kavitha Vellanki.² ¹Dept of Medicine, Loyola Univ Medical Center, Maywood, IL; ²Dept of Nephrology, Loyola Univ Medical Center, Maywood, IL; ³Dept of Urology, Loyola Univ Medical Center, Maywood, IL.

Introduction: Erdheim-Chester disease (ECD) is a rare form of histiocytosis with highly variable clinical manifestations. Only a few hundred cases have been reported in the literature to date. It is characterized by proliferation of non-Langerhans cells that can infiltrate all vital organs. Infiltration of the retroperitoneal space and subsequent fibrosis may cause bilateral ureteral obstruction leading to progressive renal failure. Here, we present a case of severe hypercalcemia, work up of which eventually led to the diagnosis of ECD.

Case Description: A 58 year old Polish male with chronic kidney disease due to obstructive uropathy from bilateral ureteral obstruction was transferred to our center for suspected pyelonephritis. His course was complicated by persistent fevers with repeatedly negative infectious work up and severe hypercalcemia with ionized calcium levels peaking at 1.66 mm/L. Parathyroid hormone levels were appropriately suppressed. Work up for multiple myeloma showed no lytic lesions on bone scan, however, bilateral, symmetric, sclerotic lesions in the distal femurs and proximal tibias were incidentally noted. Based on these findings, ECD was suspected. This was confirmed with bone marrow biopsy which revealed multiple histiocytic and lymphocytic aggregates positive for the histiocytic marker CD68, but negative for CD1a (pathognomonic of the disease). He was subsequently started on BRAF (v-raf murine sarcoma viral oncogene homolog B1) inhibitor, vemurafenib with marked improvement in clinical symptoms. While he received pamidronate for hypercalcemia during the hospital stay, his ionized calcium levels have since normalized and continue to be within normal range 6 months after the initial presentation.

Discussion: In conclusion, ECD is a rare disorder with varied clinical manifestations and diagnosis is often elusive, requiring a high level of clinical suspicion. Although skeletal involvement is seen in 96% of the patients with ECD, there have been no reported cases of hypercalcemia, and our case is the first to report such an association.

TH-PO1061

APOL1 Polymorphisms in Deceased Donors and Primary Glomerular Disease Post-Kidney Transplant: First Case Report Pratik B. Shah, Alexander C. Wiseman, James E. Cooper. Renal Diseases and Hypertension, Univ of Colorado Medical Center, Aurora, CO.

Introduction: Genetic polymorphisms in APOL1 (G1/G2) are associated with glomerular disease and ESRD. An emerging issue is whether screening for APOL1 (G1/G2) should be performed in living or deceased kidney donors.

Case Description: A 46 year-old Caucasian male with a history of SLE received a deceased donor kidney transplant. The deceased donor was a 12-year old African American male. 9 months post-transplant, he presented with acute kidney injury following an elective laparoscopic cholecystectomy (CCK). 2 weeks prior to surgery his SCR was at baseline, 1.5 mg/dl with no proteinuria. On postop day 0-CCK, his SCR was 7.9 mg/dl, with spot UPC of 2 g/g Cr, platelet count of 58000, LDH of 2022 U/L, haptoglobin of <14 mg/dl. Renal transplant biopsy showed collapsing glomerulopathy with no evidence of thrombotic microangiopathy or rejection. Plasma CMV PCR was positive at 2340000 copies/ml. The patient's acute kidney injury was attributed to collapsing glomerulopathy in the setting of acute CMV infection. The patient ultimately did not recover kidney function. The patient's deceased donor DNA was analyzed for APOL1 risk variant genotyping and was positive for two APOL1 risk variants: compound heterozygosity for APOL1 G1, c.1024A>G; p.Ser342Gly and APOL1 G2 c.1164delTTATAA. The sister kidney from the same deceased donor had been transplanted to a 63 year old female with ESRD from diabetes. Six months post-transplant, she had new onset proteinuria of 2.5 g/d, and a renal biopsy demonstrated focal segmental glomerulosclerosis (FSGS). Her renal function and proteinuria remain stable 14 months post transplant.

Discussion: To our knowledge, this is the first case report of high risk variant APOL1 in a deceased donor with subsequent primary glomerular disease in both the recipients. This suggests that deceased kidney donor APOL1 genotyping may be informative in predicting graft outcomes. This also highlights the important question of whether routine screening of African American donors for high risk APOL1 variants before renal transplant is warranted. This consideration must be balanced against the significant limitations in kidney availability.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

TH-PO1062

Atypical HUS in an Infant due to a Novel Gene Mutation Mohamed Alsciari,¹ Robin Amy Kremendorf,² M. Khurram Faizan,² ¹Rhode Island Hospital; ²Hasbro Children's Hospital; ³Hasbro Children's Hospital.

Introduction: Atypical HUS (aHUS) is a rare genetic renal disease associated with over-activation of the alternative pathway of complement. A variety of mutations have been described in the complement pathways genes in patients with aHUS. We report a case of aHUS with a novel genetic mutation in the Complement Factor B (CFB) gene.

Case Description: 10 months old Caucasian girl who presented with diarrhea, vomiting, and swelling in her extremities and face for 2 weeks preceded by an episode of cough, runny nose with non-bloody diarrhea. Upon presentation her BP was 150/90 mm Hg. Lab data showed Hgb 4.4 g/dl, Platelets, 46 x10exp9/L, Cr elevated to 0.46 mg/dl from baseline of 0.3, Albumin 2.6 g/dl, LDH 632 IU/L, normal ADAMTS13 and C3 level 7.9 mg/dl. Urine revealed 32RBC/hpf with proteinuria, Urine protein Creatinine ratio 19 g/g. Peripheral blood smear revealed schistocytes. Stool was negative for Shiga toxin. Clinical presentation was strongly suggestive of aHUS and patient was treated with Eculizumab. She developed worsening anasarca with neck edema, requiring a tracheotomy after failed intubation. She required RRT for volume management during her hospital course after failing diuretics. Renal biopsy showed acute and chronic thrombotic microangiopathic changes consistent with aHUS. Genetic testing revealed a novel mutation in the complement Factor B gene in the region of binding to Von Willebrand factor. It also showed a heterozygous deletion of CFHR1 and CFHR4. Patient recovered renal function 3 weeks after presentation. C3 remained low after recovery of renal function. RRT was stopped after two weeks and she was discharged on ACEI with Eculizumab every 2 weeks.

Discussion: Gain of function mutations in CFB are extremely rare in aHUS and occur in only 1% to 2% of cases of familial aHUS. There is increased C3b affinity and form hyperactive C3 convertase that is resistant to dissociation, thus increasing C3b formation. Anti C5 Antibody Eculizumab has revolutionized the care of aHUS, improving the overall prognosis of these patients. This case is the first case reported with this novel CFB gene mutation. No long term data available regarding the outcomes of aHUS with Eculizumab therapy.

TH-PO1063

Oxymorphone-Induced Thrombotic Microangiopathy and Acute Kidney Injury Girish Singhanja, Shriharsha Kallahalli Jayaramu, Dara N. Wakefield, Amir Kazory. *Nephrology, Univ of Florida, Gainesville, FL.*

Introduction: Intravenous (IV) administration of oral oxymorphone represents an emerging pattern of drug abuse with increasing popularity and unforeseen adverse consequences. Here, we present a case of IV Oxymorphone abuse associated with thrombotic microangiopathy (TMA) and acute kidney injury (AKI).

Case Description: A 32-year-old man with a history of IV drug abuse presented with non-healing left arm wound. Physical examination was unremarkable except for a left forearm abscess. However, laboratory studies revealed a serum creatinine (SCR) of 2.3 mg/dL. He was found to have severe anemia with a Hb level of 5.8 g/dL, platelets of 135,000/μL and evidence of hemolysis (LDH of 579 U/L, undetectable serum haptoglobin, and schistocytes on peripheral blood smear). He had proteinuria of 4.1 gm/day and the urine drug screen was positive for oxymorphone. Serum complement levels were normal as were all other immunologic studies. ADAMTS13 level was >100%. Kidney biopsy showed evidence of TMA supported by glomeruli filled with focal extravasated and crenated RBCs. Immunofluorescence (IF) was negative for immune complex deposition but C4d staining was positive. Conservative management including platelet transfusion, without plasma exchange (PE), was followed by stabilization of renal function.

Discussion: This patient presented with TMA, acute kidney injury, and normal serum ADAMTS13 activity. His urine oxymorphone was positive and he admitted to IV abuse of pulverized oxymorphone pills, which represents an emerging pattern of illicit drug abuse. The mechanism of oxymorphone-induced TMA remains unclear but it is suggested that the drug or some ingredients mixed in it triggers a cascade of immunological pathways leading to TMA. Previously reported cases had negative IF on kidney biopsy but positive C4d staining in this patient implies some degree of complement activation. Although PE was initially used in some cases, it has recently been shown that oxymorphone-induced TMA could successfully be managed without it. Based on this case coupled with previous reports, we suggest that health care providers should inquire about IV Oxymorphone abuse in the setting of unexplained TMA and acute kidney injury.

TH-PO1064

IgG-4 Related Tubulointerstitial Nephritis in a Young Patient with Enlarged Kidneys Valerie Jorge Cabrera,¹ Shirin Shirani,² Joni H. Hansson,³ ¹Yale Nephrology, Yale School of Medicine, New Haven, CT; ²Nephrology, Yale New Haven Hospital/St. Raphael Campus, New Haven, CT; ³Nephrology, Yale New Haven Hospital/St. Raphael Campus, New Haven, CT.

Introduction: IgG-4 related disease is a recently recognized entity characterized by the infiltration of tissues with IgG-4 positive plasma cells. It occurs more commonly in middle age men and affected organs can be diffusely enlarged, sometimes with nodular lesions that can mimic tumors. We present the unique case of a young patient with a two year history of recurrent cellulitis, parotid gland enlargement, diffuse lymphadenopathy and nephromegaly.

Case Description: A 27 year old African American male presented with a rash and edema of his right lower extremity. He also reported night sweats and weight loss over 4 months. His past medical history included hypertension, recurrent cellulitis,

nephrolithiasis, chronic kidney disease of unclear etiology, antithrombin III deficiency and pulmonary embolism. Prior imaging had shown bilateral hilar, retroperitoneal and mesenteric lymphadenopathy. However, lymph node and parotid gland biopsies were non diagnostic. On examination, he was afebrile but tachycardic. Parotid glands were enlarged and cardiovascular, lung and abdominal examination were unremarkable. His creatinine was 2.5 mg/dL, elevated from 1.8 mg/dL without significant proteinuria. A C3 level was 41 mg/dL and C4 was less than 10 mg/dL. An IgG-4 level was elevated to 2045 mg/dL. A renal biopsy was obtained and although the lack of glomeruli was limiting, the tissue revealed a dense plasma cell rich infiltrate in the interstitium consistent with an interstitial nephritis. Immunostains were positive for IgG4 in the infiltrating plasma cells. Treatment was initiated with prednisone 40 mg daily. His creatinine decreased to 1.3 mg/dL with resolution of his symptoms.

Discussion: A number of conditions can lead to kidney enlargement. Diabetes, HIV, amyloidosis and leukemia/lymphoma are commonly included in the differential diagnosis. IgG-4 related disease should also be considered in the differential diagnosis of patients presenting with kidney enlargement and recurrent infections.

TH-PO1065

Karyomegalic Interstitial Nephritis: A Rare Cause of Kidney Disease Lindsay Sanders,¹ Maxwell L. Smith,² Ibrahim Qaqish,¹ Sumi Sukumaran Nair,¹ Leslie F. Thomas.¹ *¹Nephrology and Hypertension, Mayo Clinic Arizona, Phoenix, AZ; ²Pathology, Mayo Clinic Arizona, Scottsdale, AZ.*

Introduction: Karyomegalic interstitial nephritis (KIN) is a rare, progressive kidney disease associated with Fanconi-associated nuclease 1 (FAN1) mutation as well as exposure to heavy metal, ochratoxin, or viral pathogens. Less than 50 cases have been reported in the literature. Onset of the disease is often in the third decade and may be associated with a history of recurrent upper respiratory tract infections. There is no known treatment.

Case Description: A 45-year-old male was seen for renal impairment first noted at age 40, with a serum creatinine of 1.6 mg/dL (eGFR 53 mL/min/1.73 m²). He had no known risk factors for chronic kidney disease. His only other personal medical history was for skin changes of his lower extremities consistent with pigmented purpuric dermatosis. He had no known exposures to heavy metals or toxins. He reported renal disease of unclear etiology in one sister. At time of consultation, he had a combined eGFR of 46. Urinalysis and serologic studies were normal, and ultrasound demonstrated kidneys of normal size with echogenic parenchyma. Renal biopsy demonstrated KIN. Significant findings by light microscopy included 1) 8 of 33 glomeruli appearing normal with the remaining 25 glomeruli being globally sclerosed, 2) moderate to severe fibrosis of the tubulointerstitial compartment with associated tubular atrophy, 3) marked pleomorphism of tubular cells with prominently enlarged nuclei, pleomorphic nuclei, and multinucleation, and 4) moderate predominately lymphocytic and plasma cellular inflammatory cell infiltrate. Electron microscopy showed a hypodense chromatin pattern with slight nuclear membrane irregularities.

Discussion: The diagnosis of KIN should be considered especially when there is a family history of kidney disease of unclear etiology. Karyomegalic cells can be found elsewhere in the body, including the brain, lung, and liver. Testing for heavy metals and ochratoxin may be useful. Urine cytology may identify atypical cells. Genetic testing should be considered, including for mutation of FAN1. Literature to date suggests steroid treatment may be of use in some cases.

TH-PO1066

Hypodipsic Hypernatremia: An Unusual Manifestation of Paraneoplastic Syndrome Sahar Siddiqui, Sun-Young Ahn, Asha Moudgil. *Nephrology, Children's National Medical Center, Washington, DC.*

Introduction: Hypernatremia usually results from increased free water losses or impaired thirst perception.

Case Description: A 17-year-old female presented to the emergency room after an episode of syncope while waiting for school bus on a summer morning. She had intermittent episodes of slurred speech over the previous 2 weeks but denied polyuria, polydipsia, dizziness or headaches. She was diagnosed with primary amenorrhea one year ago. Physical Exam: Weight 46 kg (5%ile), height 150 cm (<3%ile), BP 92/58 mmHg and afebrile. She was slow to respond and had slurred speech. She was Tanner III for breast & I for pubic hair. The remainder of her exam was normal. Laboratory evaluation showed hemoglobin 11.2g/dl, hematocrit 37.8%, platelet 100x10⁹/L, sodium 177 mmol/l, potassium 4.3 mmol/l, chloride 139 mmol/l, CO₂ 32 mmol/l, BUN 55 mg/dl, creatinine 2.5mg/dl, glucose 91 mg/dl, calcium 9.7 mg/dl, serum Osm 375 mOsm/kg, urine Osm 678 mOsm/kg, ADH level 2.2 pg/ml(nl). Urinalysis: specific gravity 1.016, pH 5.5, 1+ protein, trace blood. A renal ultrasound showed a right suprarenal mass which was confirmed to be an adrenal mass on CT scan. Despite adequate intravenous hydration, her hypernatremia persisted. Due to low LH & FSH there was a concern for hypogonadotropic hypogonadism. However, brain MRI was normal. DDAVP was initiated with partial response. The patient underwent a right adrenalectomy; pathology was consistent with ganglioneuroma. At the time of discharge, her serum sodium was 138mmol/l and her serum creatinine 0.8 mg/dl.

Discussion: The cause of hypernatremia in this case was likely an impaired thirst mechanism in a cognitively normal child. Her partial response to DDAVP suggests an additional contribution from partial diabetes insipidus. Essential hypernatremia and an adrenal ganglioneuroma expressing sodium level sensors (Nax) were reported in a 6 year old child by Hiyama et al. (Neuron 2010; 66(4): 508-522). The mechanism of hypernatremia was postulated to be impaired thirst due to antibodies to Nax in the brain. A diagnosis of paraneoplastic syndrome should be considered in a patient with hypodipsic hypernatremia without structural hypothalamic lesions.

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Underline represents presenting author.

TH-PO1067

IgG4 Mediated Isolated Retroperitoneal Fibrosis Causing Obstructive Uropathy in a Patient with Subclinical Ankylosing Spondylitis
 Ayman H. Morgan, Vikram Aggarwal. *Internal Medicine/ Nephrology Div, SUNY Upstate Medical Univ, Syracuse, NY.*

Introduction: Retroperitoneal fibrosis is a rare manifestation of systemic autoimmune disease, characterized by the presence of inflammatory and fibrous retroperitoneal tissue that often encases the ureters causing obstructive uropathy. Idiopathic retroperitoneal fibrosis is recently being recognized manifestation of IgG4-related disease. We report a case of histologically confirmed IgG4 related retroperitoneal fibrosis in a patient with subclinical Ankylosing spondylitis. This association has been rarely reported.

Case Description: A 70 year old male with PMH of HTN, diabetes and baseline creatinine of 1.2 mg/dl presented with weakness, vomiting and decreased urine output. Physical examination was unremarkable. Further evaluation revealed serum creatinine of 13.3 mg/dl and BUN=106 mg/dl. He also has mild hyperkalemia and anion gap metabolic acidosis. Urine analysis was negative for protein or RBC cast. A CT scan of the abdomen and pelvis, showed retroperitoneal mass, Aortitis, ankylosis of SI joint bilaterally with osseous fusion and bilateral mild hydronephrosis. Bilateral nephrostomy tubes were placed with excellent urine output as well as improvement of creatinine to baseline in 48 hours. He subsequently had a CT guided biopsy of the retroperitoneal mass. Histopathology revealed dense fibrous tissue with significant IgG4 positive plasma cell infiltrate. Immunological workup showed elevated level of IgG4 as well as positive HLA-B27. Hence this obstructive uropathy was confirmed to be due to IgG4 related retroperitoneal fibrosis. He also met the clinical and imaging criteria for Ankylosing spondylitis. Treatment with oral corticosteroids was initiated by rheumatology.

Discussion: Our hypothesis is that the patient had a subclinical Ankylosing Spondylitis which triggered IgG4 mediated disease that lead to retroperitoneal fibrosis which caused bilateral obstructive uropathy. Hence role of ankylosing spondylitis in development of idiopathic retroperitoneal fibrosis via IgG4 mediated pathways warrants further consideration and for nephrologists to be aware of this rather unusual presentation.

TH-PO1068

IgG4-Related Tubulo-Interstitial Nephritis with Low Complement C4, Circulating Immune Complexes and an Elevated IgG4, Presenting as Unilateral Hydronephrosis and Prostatitis
 Cornelius J. Doorenbos,¹ Annemarie A. Van norel,¹ Christiaan F.M. Klok,² M.m. Smits,³ Peter Van den Tillaar.⁴ *¹Nephrology, Deventer Hospital, Deventer, Netherlands; ²Radiology, Deventer Hospital, Deventer, Netherlands; ³Pathology, Deventer Hospital, Deventer, Netherlands; ⁴Urology, Deventer Hospital, Deventer, Netherlands.*

Introduction: IgG4-Related Disease is characterized by infiltrates of IgG4-positive plasma cells and eosinophils in different organs and is a rare cause of tubulointerstitial nephritis (TIN) and idiopathic retroperitoneal fibrosis.

Case Description: A 67 year old white male had a creatinine increase from 0.90 to 2.06 mg/dl. He had fatigue and dyspnea. Complement C3 was normal, C4 low 0.06 g/l, C1Q-BA 28% (N <8%), but ANA/ENA, DsDNA, AST, ANCA, HBV, HCV and M-protein were negative, IgG4 3.0 g/l (N 0.08-1.40 g/l). Urine showed 3 RBC/HPF, protein 0.36 g, albumin 61 mg per 24h. On ultrasound both kidneys were 13 cm with right sided hydronephrosis and 300 ml urinary retention. CT-Urography showed obstruction of the right ureter at the iliac artery. A bladder catheter and ureteral stent did not improve renal function. A MAG-III scan showed a non-functioning right kidney without hydronephrosis on ultrasound. On revision, the CT showed soft tissue surrounding the aorta and the right iliac artery. A kidney biopsy showed TIN with a dense infiltrate of IgG4-positive plasma cells and eosinophils with impressive fibrosis, a vein showed obliterative phlebitis, consistent with IgG4-related TIN. He was treated with prednisolone 40 mg daily and after 1 week he reported a dramatic clinical improvement, his creatinine decreased to 1.7 mg/dl.

Discussion: Hydronephrosis first dominated the clinical picture, delaying diagnosis, but the low C4, positive C1Q-BA and large kidneys suggested IgG4-related TIN. We found only one report of IgG4-related TIN with hydronephrosis, but that was after urinary tract tuberculosis. Rare cases were reported of IgG4-related segmental ureteritis or prostatitis without TIN and the cases of IgG4-related TIN had no hydronephrosis. The present case is the first with coincident biopsy-proven IgG4-related TIN, ureteral obstruction and prostatitis. Hydronephrosis does not exclude, but may be part of IgG4-related disease.

TH-PO1069

Monoclonal Light Chain Proximal Tubulopathy with Unique Ultrastructural Microtubular Inclusions
 Hiba M. Ahmed,¹ Hone S. Kaw,¹ Mandeep Samra,¹ Smita Mahendrakar,¹ Suneet Verma,¹ Jennine Michaud,¹ Fang Bu,² Nicholas Cassai,² Rosemary Wiczorek,² Michael Yudd.¹ *¹Nephrology, Dept of Veterans Affairs (VA) NJ Health System, East Orange, NJ; ²Pathology, New York Harbor Healthcare System, New York, NY.*

Introduction: Renal disease related to monoclonal gammopathies is common and varied. An uncommon lesion is proximal light chain tubulopathy (PLCT), which may present with Fanconi syndrome (FS) and variable degrees of renal failure. Most have ultrastructural (US) findings of proximal tubule damage with crystalline inclusions of κ LC's within proximal tubular cells (PTC). A minority of PLCT do not have crystals; these may have λ LC restrictions. We describe a patient with a rare finding: PLCT with light chain (LC)-related microtubular inclusions.

Case Description: 74 year old man had progressive CKD over 2 years with serum creatinine 2.1 mg/dl. A serum M spike, 1.0 g/dl of IgG κ , was present. Urine protein, 1200 mg/day, contained 13% albumin, and 45% M spike of IgG κ . No findings of FS. Renal biopsy abnormalities were limited mainly to the proximal tubules (PT). The PTC's were bright red on trichrome stain and showed granular cytoplasmic changes and marked cell shedding. Congo red stain was negative. On immunofluorescence, the cytoplasm of PTC's stained 3-4+ for total Ig and κ . IgG, IgM, IgA and λ were negative. On EM, non-branching microtubules, ranging in size from 26- 36 nm were membrane bound within PT lysosomes. No amyloid filaments or crystalline structures were seen. Bone marrow subsequently showed a low grade B cell lymphoma with clonal κ B cells and small population of κ plasma cells.

Discussion: Two large biopsy reports of monoclonal renal disease found PLCT to be very uncommon, 0.5 – 4%. Most have findings of crystalline inclusions, less without crystals. To our knowledge, there are only 2 other cases with inclusions similar to our findings. Free LC's are freely filtered and rapidly endocytosed into PTC's via the tandem receptors megalin/cubulin for catabolism in the lysosomes. The variable domain of the abnormal LC's may be resistant to proteolysis. Specific characteristics of the LC's and their resistance to metabolism may determine the varied US appearances.

TH-PO1070

IgG1-kappa Monoclonal Membranous Nephropathy Associated with Systemic Lupus Erythematosus
 Stephen W. Roderer, Anjali A. Satoskar, Tibor Nadasdy, Isabelle Ayoub, Brad H. Rovin, Samir Parikh. *The Ohio State Univ, Columbus, OH.*

Introduction: Monoclonal gammopathy of renal significance is a recently described condition in which monoclonal protein is found in the kidney but often without a circulating clone. This has not been previously associated with SLE. Here, we describe two cases of monoclonal immune deposition causing membranous nephropathy in SLE.

Case Description: Case 1: An 18 year old female with SLE developed nephrotic syndrome with 4g/d proteinuria and normal serum creatinine. Immunofluorescence (IF) on renal biopsy showed diffuse IgG1-kappa staining in the mesangium and along the capillary loops. Lambda staining was negative. Electron microscopy (EM) showed intramembranous and subepithelial electron-dense deposits. Work up for systemic monoclonal gammopathy including bone marrow biopsy was negative. She was diagnosed with IgG1-kappa monoclonal membranous nephropathy associated with SLE. She was treated with mycophenolate mofetil and prednisone and achieved partial remission. **Case 2:** A 38 year old female with SLE developed proteinuria of 2.5g/d and microscopic hematuria. Similar to case 1, IF on renal biopsy showed diffuse granular IgG1-kappa deposition in the mesangium and along the capillary loops. Lambda staining was negative. EM revealed mesangial and subepithelial electron-dense deposits. Work up for a systemic monoclonal gammopathy, including serum and urine immunofixation and serum free light chains was negative. A diagnosis of IgG1-kappa monoclonal membranous nephropathy associated with SLE was made. She was started on an ACEi and prednisone with improvement in proteinuria from 2.5g/d to 800mg/d.

Discussion: These 2 cases represent a newly described form of monoclonal membranous nephropathy associated with SLE. In both cases the monoclonal protein was restricted to the kidney. The pathogenesis is unclear but may be due to autoreactive b-cells producing an abnormal clone locally in the kidney. The clinical significance must still be elucidated but it may impact treatment and long-term outcomes so clinicians caring for SLE patients should be aware of this association. Further, these patients may develop a systemic monoclonal gammopathy, so close monitoring is necessary.

TH-PO1071

IgG1- κ Anti-Glomerular Basement Membrane Disease
 Jehan Z. Bahrainwala,¹ Afshin K. Hannani,² Jonathan J. Hogan.¹ *¹Renal, Electrolyte and Hypertension Div, Hospital of the Univ of Pennsylvania, PA; ²Mercer Renal Insts Inc, Trenton, NJ.*

Introduction: Anti-GBM disease is caused by polyclonal IgG that binds to the NC1 domain of the $\alpha 3$ chain of type IV collagen on glomerular and pulmonary capillary walls. It presents with severe glomerulonephritis and/or pulmonary hemorrhage and typically does not relapse. A recent case report described relapsing, necrotizing and crescentic glomerulonephritis associated with linear IgG1- κ antibody staining on IF. Here, we report a second case of this entity.

Case Description: A 38 year old African American woman presented 4 years ago with respiratory (cough, hemoptysis) and gastrointestinal (emesis, diarrhea) symptoms. She had severe AKI (peak Cr 8.6 mg/dL), microscopic hematuria and a urine protein/creatinine ratio (UPCR) of 3.3 g/g. A kidney biopsy showed focal necrotizing and crescentic glomerulonephritis with linear IgG1 κ GBM staining and moderate-severe interstitial inflammation. No electron dense deposits were noted on EM. Anti-GBM (ELISA), ANCA and paraprotein studies were negative. She had a C3 level of 76(88-201) mg/dL and a normal C4. She underwent induction therapy with pulse methylprednisolone and oral prednisone 60 mg/day, PLEX x 4 sessions and oral cyclophosphamide (150 mg/day) for 6 months; followed by azathioprine for 1 year. Her Cr improved to 1.2 mg/dL, UPCR to 55mg/g and her hematuria resolved. 4 years after her initial presentation, she developed respiratory symptoms (cough, sinus congestion), RUQ pain, emesis, gross hematuria and AKI (Cr 2.4 mg/dL). A second kidney biopsy again demonstrated focal necrotizing and crescentic glomerulonephritis with linear IgG1 κ GBM staining with mild interstitial fibrosis. Her serologic workup was again negative for Anti-GBM antibodies, ANCA or paraprotein. She was treated with pulse steroids and rituximab 1000 mg IV x 2.

Discussion: This is the second reported case of necrotizing and crescentic glomerulonephritis associated with IgG1-κ anti-GBM antibody. It is unknown if this disease is driven by an underlying autoimmune process or monoclonal gammopathy. Both cases are atypical for classic anti-GBM disease due to their relapsing nature.

TH-PO1072

First Reported Case of Collagenofibrotic Glomerulopathy in a Patient with Multiple Myeloma Arun Rajasekaran,¹ Indraneel Mogara,² Lillian W. Gaber,³ Jai Radhakrishnan,⁴ Ala Abudayyeh,⁵ ¹Internal Medicine, UCF College of Medicine, FL; ²Div of Renal Diseases & Hypertension, UT- Medical School at Houston, Houston; ³Pathology, The Methodist Hospital, Houston; ⁴Div of Nephrology, Columbia Univ Medical Center, New York; ⁵Section of Nephrology, The Univ of Texas MD Anderson Cancer Center, Houston.

Introduction: Collagenofibrotic glomerulopathy is an extremely rare idiopathic glomerular disease characterized by abnormal accumulation of atypical spiraled and frayed type III collagen fibrils in mesangial and subendothelial areas, and elevated serum procollagen III and hyaluronan levels. Proteinuria (commonest feature), edema, hypertension, and occasional progression to ESRD are commonly seen. We report the first published case of Collagenofibrotic glomerulopathy in Multiple Myeloma.

Case Description: A 54 year old male with recent history of IgG Kappa Multiple Myeloma (May 2011); with underlying CKD stage 3 and baseline Creatinine at 2 mg/dl; in remission status-post autologous stem cell transplant (January 2012) and on Lenalidomide maintenance therapy, presented with proteinuria of 4g. Kidney biopsy revealed Nodular and Focal glomerulosclerosis with IF weakly (+) for IgG, IgA, IgM, c3, c4, c1q, Kappa and Lambda light chains with +3 staining for IgM and c1q. EM showed patchy foot process effacement with massive deposition of collagen-III fibers. The weak and non-specific staining, along with massive collagen-III fiber deposition fitted with the description of Collagenofibrotic glomerulopathy, and made an immune mediated kidney injury less likely.

Discussion: Discussion: Collagenofibrotic glomerulopathy is an extremely rare disease characterized by massive intraglomerular atypical type III collagen fiber deposition. Proteinuria is the cardinal manifestation of this disease. Clinically, patients present with edema and hypertension and often progress to ESRD. Etiology and pathogenesis remains elusive. Most cases are seen in Japan and an autosomal-recessive mode of inheritance has been described. Definitive diagnosis is established by identifying collagen-III fibrils by IF and EM with special staining. No specific treatment is available unfortunately.

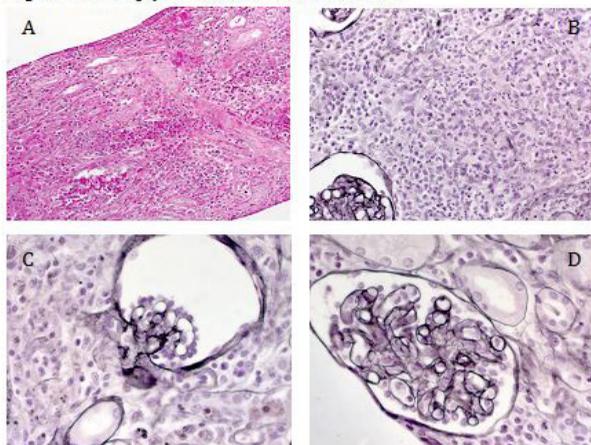
TH-PO1073

Severe Acute Kidney Injury (AKI) with Organomegaly in a 17 Days Old Newborn: When Pathology Makes the Difference Marie-Michele Gaudreault-Tremblay, Catherine Litalien, Natalie Patey, Aicha Merouani. CHU Sainte-Justine, Montreal, QC, Canada.

Introduction: Acute tubulointerstitial nephritis (ATIN) is a significant cause of AKI in children and is often due to allergic drug reactions or infections. Diagnosis of ATIN is usually clinical and renal biopsy not routinely performed.

Case Description: A previously healthy 17 days old baby presented with decreased oral intake, vomiting and oligoanuria. His first laboratory results showed an elevated creatinine (1.7mg/dL) with metabolic acidosis, hyponatremia (Na107mEq/L), hyperkalemia (K 8.8 mEq/L) and thrombocytopenia (platelets $16 \times 10^{12}/L$). His urinalysis was abnormal (proteins 3gr/L, WBC >50/hpf, RBC 21-3/hpf, positive nitrites). An ultrasound revealed bilateral kidney enlargement with a heterogeneous parenchyma and hepatosplenomegaly. Intravenous fluid, broad-spectrum antibiotics, calcium chloride and sodium bicarbonate were started. He was intubated for respiratory failure and required dialysis for fluid overload. With worsening of his condition, a kidney biopsy was performed and showed a massive and polymorph infiltrate with destruction of tubular structures [Fig.1, A-B]. Ischemic glomeruli, double glomerular membranes and mesangial oedema [Fig.1, C-D] were observed. Administration of steroids were followed by improvement of his renal function and cessation of dialysis after 6 days. The patient has been disease-free since.

Fig. 1: Renal biopsy in a newborn with severe AKI



Renal biopsy findings were consistent with severe ATIN. The most likely etiology for his ATIN was a urinary tract infection as this patient was not taking any medication and a follow-up cystography revealed a left grade III vesicoureteral reflux.

Discussion: ATIN is rare in neonates and usually drug-induced. This is the first report of a renal biopsy-proven ATIN in a neonate. Even if procedural risks of a renal biopsy are not negligible, it can make the difference in certain cases by dictating appropriate management.

TH-PO1074

AL Lambda Amyloidosis in Kidney Transplant Allograft as a Cause of Massive Nephritic Syndrome with AKI That Responded to Chemotherapy Noaman Siddiqi,¹ Manish K. Saha,¹ ¹Dept of Nephrology, Univ of Alabama, Birmingham, AL; ²Dept of Nephrology, Univ of Alabama, Birmingham, AL.

Introduction: This interesting case showed AL lambda amyloidosis in kidney transplant allograft as a cause of massive nephritic syndrome with AKI that responded to chemotherapy. 51 year old African American female with history of ESRD secondary to APKD s/p DDKT in Oct 2010 with Thymoglobulin induction, maintained on 3 drug immunosuppression including tacrolimus, mycophenolate and prednisone with baseline creatinine of 1.5, presented with anasarca and orthostatic hypotension. Her serum albumin was 1.2mg/d. She underwent extensive investigations including Echo, transplant allograft ultrasound all of which came back unremarkable. She has sudden onset sub nephritic range proteinuria in Aug 2013 which progressed to nephritic range in Feb 2014. She has 34g of protein on a 24h urine collection 90% of which was albumin. Her UPCR gradually got worse from 10 to 32 with worsening in serum Cr from 1.5 to 5.5. She has poor response to IV Lasix with albumin infusion and has severe orthostatic symptoms. Her SPEP and UPAP were negative. Serum IFE was also negative. Urine IFE showed lambda light chain. Serum free light chain showed elevated lambda levels. Due to worsening and explosive proteinuria with worsening anasarca renal allograft biopsy was done that showed lambda AL amyloidosis involving glomeruli, arterioles and arteries along with light chain proximal tubulopathy. Congoophilic casts consistent with light chain cast nephropathy. Pt underwent bone marrow biopsy that did not show MM. She was treated with bortezomib combined with cyclophosphamide and dexamethasone and has good response with improvement in orthostatic hypotension, serum albumin level and lambda light chain got normal.

TH-PO1075

Granulomatous Interstitial Nephritis Caused by T-Cell Lymphoma Yoshitatsu Ohara,¹ Namiko Kobayashi,^{1,2} Yohei Kono,¹ Tomoharu Yoshimine,¹ Mariko Ichijo,¹ Toshiyuki Hirai,¹ Keiko Suzuki,³ Takayuki Toda,¹ Michio Nagata,² Noriaki Matsui,¹ ¹Dept of Nephrology, Tsuchiura Kyodo General Hospital, Tsuchiura, Ibaraki, Japan; ²Renal Pathology, Univ of Tsukuba, Tsukuba, Ibaraki, Japan; ³Dept of Pathology, Tsuchiura Kyodo General Hospital, Tsuchiura, Ibaraki, Japan.

Introduction: Granulomatous tubulointerstitial nephritis (GTIN) occurs 0.5-1.3% in renal biopsy samples. Granuloma is basically caused by type IV allergy; T cell-mediated mechanism against drug, foreign bodies and microorganisms such as Mycobacterium. We here present, a rare case of GTIN associated with T cell lymphoma.

Case Description: Sixty-year-old man with uncontrolled diabetes complained right chest pain. Chest and abdominal CT revealed multiple abscesses formations in the right lung, right chest wall, liver and right retroperitoneum. Although no distinct bacterium was identified from the liver abscess, the patient was treated by antibiotics, tazobactam/piperacillin(TAZ/PIPC). It was not effective. During the antibiotics treatment, renal dysfunction and skin rashes on extremities occurred. Renal biopsy revealed GTIN with collapsing glomeruli. Light microscopy showed diffuse interstitial inflammatory infiltrates predominantly with mononuclear cells including some atypical cells, which invaded tubular basement membrane resulting in tubular atrophy. Immunohistochemistry revealed hypercellularity of monotonous atypical lymphocytes stained with T-cell markers, CD3 and CD5, and then diagnosed as GTIN caused by T-cell lymphoma. Although CHOP chemotherapy induced remission of lymphoma and disappearance of multiple abscess formation, the kidney dysfunction was unimproved.

Discussion: The case reminds us T-cell lymphoma as an additional cause of GTIN.

TH-PO1076

Pauci-Immune Glomerulonephritis and Escherichia Coli Bacteremia: A Mere Coincidence or a True Causal Association? Marwan M. Abu Minshar, Whib A. Gebregeorgis. Nephrology, Wayne State Univ S.O.M, Detroit, MI.

Introduction: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides are systemic autoimmune diseases affecting small to medium sized blood vessels. Pauci-immune necrotizing glomerulonephritis (GN) is one of the manifestations. Triggering factors for ANCA associated vasculitides are not well-defined. Systemic infections have been implicated in the pathogenesis.

Case Description: A 67 year old patient was admitted to the hospital from a nursing home for a Foley catheter associated Escherichia coli (E. coli) urinary tract infection & bacteremia leading to septic shock and acute kidney injury/acute tubular necrosis with a peak serum creatinine (Cr) of 3.8 mg/dl. She had recently been hospitalized for subarachnoid hemorrhage that was treated conservatively and her serum Cr at that time was 0.9 mg/dl.

She promptly responded to standard treatment of septic shock and her serum Cr improved to 1.6 mg/dl on discharge. Ten days later, she was readmitted to the hospital after a follow up visit to her primary physician where a routine blood work showed her serum Cr to be elevated to 6.8 mg/dl. Urine sediment revealed several RBCs and few granular casts. Anti-myeloperoxidase antibody was positive with a titer of 1:640. Other serological tests were negative. Her renal function declined further and she was initiated on hemodialysis. A renal biopsy was consistent with pauci-immune necrotizing and crescentic GN. She was treated with steroids, intravenous cyclophosphamide and plasmapheresis following which she came off dialysis & her serum Cr stabilized around 1.8 mg/dl.

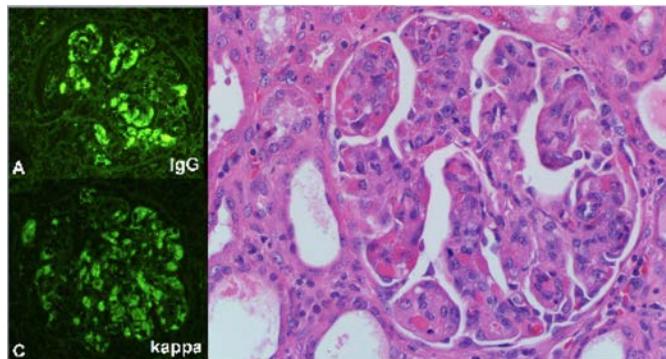
Discussion: Anti-LAMP-2 antibodies, a subtype of ANCA antibodies directed against lysosome-associated membrane protein-2 (LAMP-2) have been reported in patients with pauci-immune necrotizing GN, often in coexistence with anti-PR3 & anti-MPO antibodies. Infections with bacteria that express the bacterial adhesin FimH (mostly *E. coli*), which has 100% homology with the human LAMP-2 epitope, are believed to trigger autoimmunity via molecular mimicry. In our patient, the onset of ANCA positive necrotizing GN in a close temporal association with *E. coli* bacteremia suggests a possible causative relationship.

TH-PO1077

Cryoglobulinemic Vasculitis and Glomerulopathy Associated with Chronic Lymphocytic Leukemia Narottam Regmi, Albert Braverman, Swaty Arora, Raavi Gupta, Subodh J. Saggi. *Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.*

Introduction: Cryoglobulinemia manifests as ischemic or occlusive vasculopathy with or without renal involvement. Early stage Chronic lymphocytic leukemia (CLL) has not been reported with vasculitic lesions as its first manifestation. We report a rare case of Stage I CLL with cutaneous, renal and cerebral lesions due to monoclonal Type I cryoglobulinemia.

Case Description: A 60-year-old woman presented with abdominal pain due to retroperitoneal hematoma from a ruptured right gonadal artery, which was embolized. Labs included leukocytosis, anemia with mild azotemia. Flow cytometry was consistent with CLL. The patient was readmitted with a serum creatinine of 11.2 mg/dL and proteinuria and required hemodialysis. There were extensive lesions on her lower extremities and a necrotic left forearm ulcer. Renal biopsy revealed membranoproliferative glomerulonephritis with deposition of IgG kappa light chain cryoglobulins as intraluminal hyaline deposits (Figure 1), infiltrates consistent with CLL and thrombi in intrarenal arteries. Biopsy was complicated by hematoma leading to left nephrectomy. Plasmapheresis was initiated for cerebral infarcts related to cryoglobulinemia. Despite leukemia treatment and regular hemodialysis her clinical condition deteriorated and patient expired.



The pathophysiology of GN in CLL is possibly due to glomerular deposition of immune complexes and/or paraproteins. Review of the literature reveals a small number of cases of MPGN associated with CLL and cryoglobulinemia.

Discussion: Vasculitic presentations, bleeding or thrombotic and/or renal failure in the setting of CLL may be manifestations of cryoglobulinemia. Because of potential rapid progression, as in this case, regular urinalysis and testing for cryoglobulins should be considered in all stages of CLL, with possible renal biopsy when cryoglobulinemia and proteinuria are detected.

TH-PO1078

PGNMID in a Patient with Hepatitis C Mohamed Alseiyari, Susie L. Hu. *Alpert Medical School of Brown Univ.*

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is infrequently associated with hematological disease but more commonly presents like an immune-complex glomerulonephritis. Few have reported cases associated with viral infections such as hepatitis C. We report a case of PGNMID in a patient with active HCV infection.

Case Description: A 56 year-old male with refractory hepatitis C (post treatment with interferon and Ribavirin), HTN and coronary artery disease presented with rising creatinine (peak 5.3 mg/dl) from baseline (0.9 ml/dl a year ago) and no kidney disease in family. He reported months of progressive fatigue, dyspnea on exertion, nausea, vomiting, and dark urine. He endorsed chronic Ibuprofen use for leg pain. On examination BP was normal with clear lungs and no edema. Urinalysis revealed blood but minimal proteinuria with urine protein to creatinine ratio of 0.5 g/g and albumin 4.2 g/dL. Complements were low (C3 83 mg/dL, CH50 <10 U/mL). HCV-RNA quantification was 1.7 million copies. SPEP, plasma light-chains, ANA, ANCA, Anti GBM, HIV, Hep B serologies were normal. Bone

survey was negative. Renal biopsy revealed diffuse linear staining of glomerular basement with monoclonal IgG1/Kappa immunoglobulin and endocapillary focal glomerulonephritis, chronic interstitial nephritis with ATN. Renal function did not improve until Prednisone was initiated, down to 3.3 mg/dL. Cyclophosphamide was started after discussion with his gastroenterologist. Antiviral therapy has been delayed until further improvement of renal function.

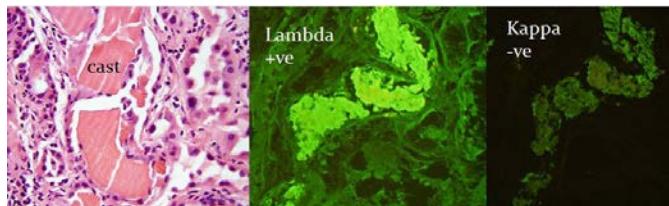
Discussion: We report a case of PGNMID associated with HCV. There are 2 other reports of HCV associated PGNMID however with membranous glomerulonephritis pathology. 30% of PGNMID patients have same heavy- and light-chain isotypes as the glomerular deposits. Membranoproliferative (57%) or endocapillary proliferative (35%) are the most two common histological variants. Nasr et al in a series of 32 patients reported after an average of 30.3 months of follow-up, 38% had complete or partial recovery, 38% had persistent renal dysfunction, and 22% progressed to ESRD. Viral infection such as HCV associated immune disorders could be implicated in the pathogenesis. Currently, there is no consensus regarding the management of this entity.

TH-PO1079

Myeloma Cast Nephropathy with Acute Renal Failure, Skin Rash, Eosinophilia, and Low Complement C4 Level Mustafa G. Aly,¹ Mamoun Elsir Bashir,¹ Irfan Warraich,² Aumyot Prongdong,¹ Weeraporn Srisung,¹ ¹Internal Medicine, Nephrology Dept, Texas Tech Univ Health Science Center, Lubbock, TX; ²Pathology Dept, Texas Tech Univ Health Science Center, Lubbock, TX.

Introduction: We here report myeloma cast nephropathy with skin rash, eosinophilia and low complements which is a very atypical presentation of this renal condition.

Case Description: A 53y Caucasian female was admitted with 3 day confluent erythematous skin rash, acute renal failure with s.Cr 17.6 with a normal baseline renal function of s.Cr 0.7mg/dL. Five days prior, she was prescribed cephalexin for root canal infection. Initial diagnosis of acute interstitial nephritis was made but patient didn't respond after stopping antibiotics and steroid course trial. Urine exam showed WBC clumps and no casts. Serological biomarkers were done and reported Negative ANA, ANCA, cryoglobulins, Hepatitis B, Hepatitis C and HIV. Complement C4 was low with normal C3. Patient's laboratory workup showed normocytic normochromic anemia and pseudohyponatremia per osmolality check, SPEP and SFELC ordered and was positive for M-spike with free light chain analysis showing predominant Lambda more than 4 g/L. Renal biopsy showed myeloma cast nephropathy.



Bone marrow biopsy confirmed MM with 80% plasma cell. Patient received bortezomib + dexamethasone + cyclophosphamide chemotherapy and her renal function completely improved after being dialysis dependent for about 12 weeks with. Patient is being evaluated for BM transplant after chemotherapy response.

Discussion: Multiple Myeloma can cause renal damage in many ways which sometimes can be misleading and very uncharacteristic. Up to our knowledge, this presentation is quite uncommon in literature and hence we suggest including myeloma related kidney injury in such clinical presentation.

TH-PO1080

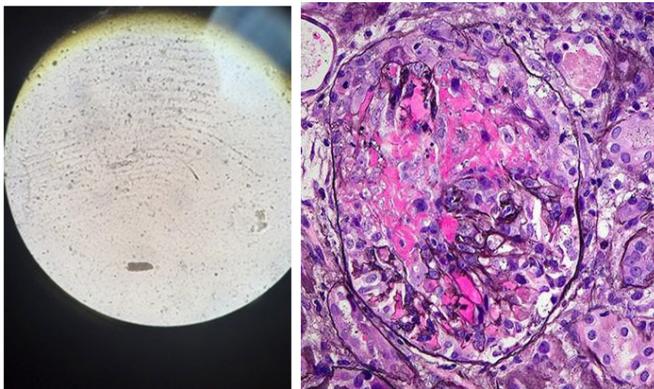
A Rare Case with ANCA-Related Necrotizing Glomerulonephritis without Nephritic Features or Systemic Vasculitis Mustafa G. Aly,¹ Faisal Jamal,¹ Maria Gabriela Suarez,¹ Irfan Warraich,² Aumyot Prongdong,¹ ¹Internal Medicine, Nephrology Dept, Texas Tech Health Science Center, Lubbock, TX; ²Pathology Dept, Texas Tech Health Science Center, Lubbock, TX.

Introduction: We report an atypical and unusual case of ANCA necrotizing glomerulonephritis with no significant nephritic features or systemic vasculitic picture.

Case Description: A 78 year-old African American female with history of controlled hypertension was admitted with diagnosis of pneumonia and renal failure and was treated empirically with antibiotics. Despite antibiotic treatment, she had persistent leukocytosis and pneumonia was ruled out by negative WBC scan and CT chest. Urine had pre-renal pattern and urinalysis was bland twice. Renal ultrasound was unremarkable except for hypercholeic kidneys. Despite aggressive hydration for 10 days, renal function continued to worsen. Patient was never oliguric. Serum biomarkers were checked due to unexplained renal failure which reported negative hepatitis B, C and HIV as well as normal Complement C3, C4, ANA, dsDNA and antiphospholipid panel. Normal SPEP with no M spike. UPEP showed faint IGG monoclonal band in the ALPHA-2 region. SFELC was negative. Bone marrow biopsy showed normal cellularity. Although patient had no obvious systemic vasculitic features, but due to renal failure and persistent non-specific respiratory symptoms, ANCA was checked and was positive for anti-MPO antibodies. Renal biopsy showed pauci-immune acute necrotizing glomerulonephritis (Figure 1) with negative Ant-GBM and immune fluorescence. Patient was treated with cyclophosphamide, high dose steroids and plasmapheresis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.



Discussion: The patient had advanced necrotizing GN but never developed nephritic or systemic vasculitic features and UA was persistently bland. The probability of diagnosing ANCA associated GN based upon above clinical presentation was significantly low, making this an unusual case.

TH-PO1081

Bilateral, Multifocal Renal Tumors Diagnosed as Birt-Hogg-Dubé Syndrome Confirmed by Genetic Analysis Seokwoo Park,¹ Sehoon Park,¹ Eunjeong Kang,¹ Hae Il Cheong,² Dong Ki Kim,¹ Yon Su Kim,¹ Kwon Wook Joo,¹ Hajeong Lee.¹ ¹Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; ²Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Korea.

Introduction: Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant disorder characterized by skin fibrofolliculomas, pulmonary cysts and spontaneous pneumothorax, and renal cancers. The syndrome is caused by germline mutations of the FLCN gene located in 17p11.2 encoding folliculin. The risk of renal cancer is seven times higher in BHD patients. Bilateral, multifocal and chromophobe renal cell carcinoma is characteristic of renal cancers in BHD. Among about 110 pathogenic mutations reported in BHD, only twenty six of them have been associated with renal cancer. In this study, we described a case of 50-year-old woman with chromophobe renal cell carcinoma who had c.1557delT mutation in the FLCN gene which is novel in BHD-associated renal cancer.

Case Description: A 50-year-old woman presented with flank pain. A CT scan of abdomen showed multifocal tumors in both kidneys. To differentiate the origin of the tumors, a chest CT and a whole body PET-CT were carried out, although there was no other lesion except a few lentiform cysts at basal lungs. Histologic evaluation through a needle biopsy revealed that the mass was chromophobe type renal cell carcinoma. The patient underwent partial nephrectomy. Given multifocal distribution of the renal cell carcinoma, we suspected an inherited form of kidney cancer. Although she denied any specific familial history, the cystic change of both lungs and chromophobe renal cell carcinoma pointed towards the possibility of BHD. DNA sequencing of the entire FLCN gene identified a heterozygous c.1557delT mutation in exon 14 [p.Phe(TTT)519Leu(TTA)fs*18].

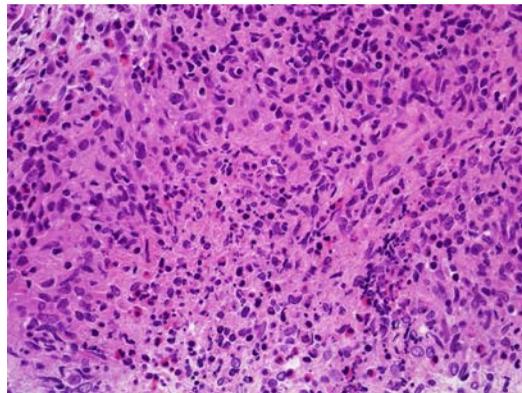
Discussion: Once multifocal renal masses are diagnosed as renal cell carcinoma, histologic subtype, family history and other clinical features should be considered to recognize familial renal cancer syndromes. Multifocal chromophobe renal cell carcinoma should prompt genetic test for BHD even in a patient without typical skin lesion. In our patient, c.1557delT mutation was found out which has been first reported in BHD-associated renal cancers.

TH-PO1082

The First Case of Steroid Responsive Renal Involvement of Mycosis Fungoides without Sezary Syndrome Jinuk Jeong, Kitae Bang, Jongho Shin. Dept of Internal Medicine, The Eulji Univ School of Medicine, Daejeon, Korea.

Introduction: Mycosis fungoides (MF) is a mature T cell non-Hodgkin lymphoma with presentation in the skin but with potential involvement of the nodes, bloods and viscera. Renal lymphomatous involvement in MF has received limited attention. We present a rare case of moderate dose steroid responsive lymphomatous renal involvement with acute renal injury which occurred in solitary kidney.

Case Description: A 39-year-old man presented with fever, right flank pain with a rise of creatinine 10.54mg/dl, one month prior being 1.4mg/dl. He donated his left kidney 10 years ago. He had recurrent pruritic rash before MF was diagnosed by skin biopsy. 4 years prior to his presentation, he received several different course of chemotherapy, including cyclophosphamide, adriamycin, vincristin, and prednisone (CHOP), alpha-interferon. Ultrasound revealed normal echogenicity with right kidney 14 cm. Urinalysis showed protein 1+, WBC cast and no hematuria. He was treated first with antibiotics in case of acute pyelonephritis. He defervescence within two days. However, his renal function kept declining. Hemodialysis was performed. On the 6th day. Renal biopsy was performed. Renal biopsy showed that Numerous atypical lymphocytes with hyperchromatic, indented, variably sized nuclei were infiltrated in the tubulointerstitium.



After treatment with methylprednisolone 40mg, level of creatinine improved up to baseline.

Discussion: To our knowledge, this is the first report of steroid responsive renal involvement of MF. Renal involvement in non-Hodgkin lymphoma has been reported, including AKI, glomerulonephritis, and infiltration of renal parenchyma by lymphoma cell. Renal manifestations of MF are especially rare and there are only few cases published to date. But there has been no case which showed steroid response except this case.

TH-PO1083

A Case of Cryoglobulinemic Nephropathy with Successful Childbirth After Recurrent Episodes of Nephrotic Syndrome During Pregnancy Miho Karube, Kazuhito Fukuoka, Yoshihiro Arimura. The First Dept of Internal Medicine, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan.

Case Description: A 35-year-old woman was admitted to our hospital because of massive proteinuria that developed during the third pregnancy. The previous two pregnancies had been terminated because of similar episodes of nephrotic syndrome. No history of hypertension was observed, but during the course she presented cryoglobulinemia, a high titer of RF and low serum complements. The renal biopsy performed 10 days after the third termination revealed MPGN-like lesions with lobulation in glomeruli, double contour of GBM, endotheliosis, and moderate mesangial cell proliferation. Immunofluorescence study showed IgG, IgA, IgM, C3, C4, and C1q all positive mainly along the glomerular capillaries, and subendothelial deposits were confirmed by EM, thus she was diagnosed as cryoglobulinemic nephropathy. Because the histological findings of repeated renal biopsy were not improved two months after the disappearance of proteinuria, treatment with 30 mg/day of PSL was started, followed by intravenous cyclophosphamide 6 times and plasma exchange, since she had a desire for baby. Finally at the fourth pregnancy, she bore a healthy baby weighing 2,342g on vaginal delivery at 36 weeks despite of recurrent appearance of nephrotic syndrome. After delivery, she was given 30 mg/day of PSL and proteinuria subsided.

Discussion: We experienced a rare case of the type III cryoglobulinemic nephropathy that repeatedly developed nephrotic syndrome during pregnancy, but finally bore a baby after immunosuppressive therapy. The pathogenesis of pregnancy-induced nephrotic syndrome in cryoglobulinemia in this patient was not known, aggressive treatment may be helpful for ameliorating nephropathy, leading to successful delivery.

TH-PO1084

A Case of Glomerular Lipidosis with Type III Hyperlipoproteinemia Exhibiting Nephrotic Syndrome Rei Miura,¹ Kaori Fujimoto,¹ Aya Sakanashi,¹ Tomoaki Onoue,¹ Kengo Kajiwara,¹ Masao Tomita,¹ Taku Miyoshi,² Masataka Adachi,² Yukimasa Koda,² Masashi Mukoyama.² ¹National Hospital Organization Kumamoto Medical Center; ²Kumamoto Univ.

Introduction: Lipid deposition and accumulation in glomeruli are sometimes recognized in kidney biopsy specimens, especially in focal segmental glomerulosclerosis and diabetic glomerulosclerosis, but glomerular lipidosis other than such conditions is rarely seen.

Case Description: A 77-year-old woman was admitted to our hospital because of nephrotic-range proteinuria. She was diagnosed as chronic thyroiditis 8 years before, after which she started to have levothyroxine and remained uneventful. Three weeks before coming to our hospital severe edema developed rapidly, and she gained 10 kg of body weight in 6 months. Laboratory examinations showed nephrotic syndrome with mild renal dysfunction (s-Alb 2.1 g/dL, urinary protein 7.97 g/gCr, s-Cr 0.95 mg/dL), marked dyslipidemia (T-Chol 712 mg/dL, TG 1191 mg/dL) and poorly controlled hypothyroidism (TSH 45.2 μ IU/mL, free T4 0.83 ng/mL). Genetic test for *APOE* revealed homozygosity of apoE2 and immunoelectrophoresis for lipoprotein showed type III hyperlipoproteinemia. Renal biopsy revealed the presence of intracapillary lipid thrombi and foam cells; electron microscopy demonstrated lipid droplet accumulated mainly in mesangial cells, whereas podocytes, endothelial cells and tubular cells were rather unremarkable. Immunofluorescent studies showed no significant deposits in glomeruli. Intense lipid-lowering therapy with bezafibrate and ezetimibe improved hyperlipidemia, with only a partial effect on proteinuria (~5 g/gCr).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Discussion: We report here a case of glomerular lipidosis associated with type III hyperlipoproteinemia exhibiting nephrotic syndrome. We suggest that hyperlipidemia with glomerular lipid accumulation would have a pathogenic role for glomerulopathy, but other factors might be involved in causing nephrotic syndrome.

TH-PO1085

Successful Treatment of Crescentic Glomerulonephritis (GN) in Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS) Ramchandur Bakhtiani, Mark G. Parker. *Nephrology, Maine Medical Center, Portland, ME.*

Introduction: HUVS is a rare autoimmune systemic disorder characterized by chronic urticaria, low complements and extracutaneous organ involvement. Kidney involvement is not uncommon (50% of cases), usually of benign nature. The glomerular injury pattern varies from mesangial proliferation to membranoproliferative glomerulonephritis (MPGN). Crescentic MPGN in HUVS is rare; only six cases have been reported in world literature, many with poor outcomes. We present a case of crescentic GN successfully treated with substantial remission.

Case Description: A 55-year-old Caucasian female with a previous episode of HIVS was admitted to hospital with features of both acute nephritic and severe nephrotic syndrome. She had 6 months history of persistent hives, fatigue, fevers, arthralgia, self-limited recurrent angioedema episodes, and generalized lymphadenopathy. Lymph node biopsy displayed reactive hyperplasia. Her serum creatinine was 4 mg/dl, urine protein to creatinine ratio was 23, serum albumin was 1.4 gm/dl and urinary sediment showed > 100 RBCs, > 10 hyaline casts/HPF. Serologic workup was positive for very low C3 and C4 and ANA titer of 1:80. Anti-dsDNA, cryoglobulins, anti-SSA, anti-SSB, chronic hepatitis panel, and workup for paraproteinemia all were negative. C1q levels were undetectable. Anti C1q antibody was not performed. Renal biopsy revealed immune complex crescentic MPGN with IgG, IgA, IgM, C3 and C1q deposits on immunofluorescence. Treatment was started initially with high dose glucocorticoids followed by addition of mycophenolic acid and losartan. Her systemic symptoms and acute kidney injury resolved completely. Nephrotic syndrome improved slowly. After 6 months of therapy her proteinuria decreased to 4.5g per day and serum albumin increased to 3.8 g/dl.

Discussion: Crescentic GN associated with HUVS appears to convey a poor renal prognosis. Based on available information in five of six reported cases, three progressed to end stage renal disease; one had near complete renal recovery and another had partial recovery with persistent nephrotic range proteinuria. Relatively good outcome in our case may aid to our understanding of this uncommon and newly recognized disease process.

TH-PO1086

An Unusually Early Presentation of Pre-Eclampsia David Bennett, Renu Regunathan-Shenk, Maya K. Rao. *Medicine, Div of Nephrology, Columbia Univ Medical Center, New York, NY.*

Introduction: Pre-eclampsia affects approximately 3-6% of pregnancies in the United States. It is defined as new onset hypertension and proteinuria in pregnancy. By definition, it occurs after 20 weeks gestation. However, earlier cases have been reported in the literature.

Case Description: The patient is a 45 y/o woman, 16 weeks + 4 days pregnant with twins (IVF with donor embryo), with a PMHx significant for obesity and borderline HTN who presented with 6 weeks of progressive swelling that had worsened in the past week. 3 weeks prior to presentation, the pregnancy was complicated by worsening hypertension, ranging 140's-160's/90's-100's, for which she was started on labetalol. On presentation, her exam was notable for BP 193/122, 1+ upper extremity edema, 2+ lower extremity edema, and bibasilar crackles on lung exam. On labs, Cr 0.85, 3+ protein on UA (previously negative) with 3 RBC's and 6 WBC's, ~12g of protein on 24hr urine collection, and serum albumin 2.3. Serologic work-up including ANA, C3, C4, HIV, Hepatitis B, Hepatitis C, SPEP, UPEP, and Kappa and Lambda Free Light Chains was negative. Platelet count 202, LDH 334 (elevated), and indirect bilirubin 0.2. AST, ALT, and Alkaline phosphatase were normal. The patient underwent a kidney biopsy which demonstrated subacute glomerular thrombotic microangiopathy with prominent endotheliosis, characteristic of pre-eclampsia. Termination of pregnancy was advised and performed. On post-discharge follow-up, spot urine protein-to-creatinine ratio (in mg/mg) decreased to 1.52 after ~1.5 months, 0.32 after ~3.5 months, and 0.13 after ~6 months. BP improved as well and she is now off anti-hypertensives.

Discussion: This patient had multiple risk factors for pre-eclampsia including age, multiparity, obesity, IVF, and ovum donor pregnancy. Although kidney biopsies are associated with a higher complication rate in pregnant women, they often change management, as was the case for this patient. Given this case and others reported in the literature, the gestational age criteria for the diagnosis of pre-eclampsia should be reconsidered.

TH-PO1087

A Case of Autosomal Dominant Polycystic Kidney Disease and C3 Glomerulonephritis Conor Patrick Moran, Mamoun S. Elawad. *Dept of Nephrology, Altnagelvin Hospital, Western Health and Social Care Trust, Londonderry, United Kingdom.*

Introduction: Autosomal Dominant Polycystic Kidney Disease, (AD-PKD), is the most common form of inherited renal disease. Proteinuria has been reported, however, nephrotic range proteinuria and nephrotic syndrome are rarely reported in the literature. Only 30 cases of patients with AD-PKD and glomerulopathy have been reported. The most common

have been FSGS and Membranous Nephropathy. Two cases of Mesangioproliferative Glomerulonephritis and one case of Membranoproliferative Glomerulonephritis have been reported.

Case Description: We present a 47 year old female with Autosomal Dominant Polycystic Kidney Disease with C3 Glomerulonephritis. The patient had been under regular and unremarkable Nephrology clinic follow-up for many years. In March 2014, she presented to with new proteinuria, (Urinary ACR 375.4mg/mmol), and evidence of C3 hypocomplementaemia, (0.3 g/L, normal: 0.8-1.7 g/L). Kidney function was newly impaired, (Creatinine 118, eGFR: 45.3 mL/min/1.73m²). C3 Nephritic factor was normal and a minute Cryoglobulin band was detected. ACE inhibitor therapy was commenced. Renal biopsy showed markedly enlarged and lobulated glomeruli with marked endocapillary proliferation. Widespread thickening of the glomerular basement membranes, (GBM), with numerous double contours was observed. Immunofluorescence revealed strong diffuse coarse positivity for C3 along the GBM with some focal mesangial C3. There was some IgM, but no IgG, in the GBM. In July 2014, there was no clinical response to ACE inhibition. Corticosteroids were commenced, (Prednisolone 1mg/kg), which achieved partial remission, (urinary ACR fell from 650.5mg/mmol to 79.7 mg/mmol), however, in August 2014 she developed nephrotic syndrome requiring aggressive diuretic therapy. Addition of Rituximab therapy induced complete remission of proteinuria, (UACR 25-30 mg/mmol), with normalisation of C3 levels. Renal function remains stable.

Discussion: In a disease where CKD progression is predictable, glomerular pathology can accelerate this decline and histology should be sought. This is the second reported case of AD-PKD associated with Membranoproliferative C3 Glomerulonephritis in the literature to date.

TH-PO1088

To Deliver or Not to Deliver: The Dilemma of a Pregnant Patient with Medullary Cystic Kidney Disease Who Develops Acute Kidney Injury Sweta Carpenter, Rozina B. Ali, Sandeep Aggarwal. *Nephrology, Drexel Univ.*

Introduction: Achieving maternity is quite a challenge for women with chronic kidney disease (CKD). Pregnant patients with CKD of any stage but especially stages 3-5 are at increased risk for fetal loss, prematurity and pre-eclampsia.

Case Description: We present a case of a 31 year old pregnant female with a past medical history of CKD stage 3B secondary to medullary cystic disease (MCD) who presented with acute kidney injury at 31 weeks gestation. Her other co-morbidities include a history of diabetes and idiopathic thrombocytopenia (ITP). On admission, the patient had a creatinine of 2.32 mg/dL and was found to have 7 gm proteinuria. During this pregnancy, her baseline creatinine was 1.6-1.8 mg/dL and prior to pregnancy she had baseline proteinuria of 2 gm. Given her elevated creatinine and degree of proteinuria, there was concern that the patient could have pre-eclampsia. A management dilemma occurred and it was unclear whether the patient should have an emergency C-Section for questionable pre-eclampsia. Unfortunately, the usual markers of pre-eclampsia such as proteinuria, elevated creatinine, hypertension, low platelets, and elevated uric acid levels were all present in our patient. These markers however could be present in our patient due to her underlying medical conditions of CKD, ITP, and MCD. After a multidisciplinary meeting with the obstetrician, nephrology, and hematology occurred, it was felt that the patient truly did not have pre-eclampsia. A key decision was made and she was not induced. Her AKI was attributed to volume depletion and progression of CKD. Her creatinine eventually declined to 1.9-2 mg/dL and her proteinuria decreased to 3-5 grams. The patient is now 34 weeks pregnant and her pregnancy has been maintained. As the weeks progress, there are increased chances of fetal development.

Discussion: Our case highlights that in patients with multiple co-morbidities and CKD, the diagnosis of pre-eclampsia can be challenging. Incorrectly labeling a patient as pre-eclamptic can lead to pre-term delivery and risks to the fetus. A multidisciplinary team effort along with fetal monitoring can help differentiate pre-eclampsia from other diagnoses, prolonging delivery.

TH-PO1089

Development of Aggressive De Novo Henoch-Schönlein Purpura, 10 Years Post-Kidney Transplant Kamel Hatahet,¹ Swati Rao,¹ Avrum Gillespie,¹ Mythili Ghanta,¹ Serban Constantinescu,¹ Xu Zeng,² Iris J. Lee.¹ *¹Nephrology, Temple Univ School of Medicine, Philadelphia, PA; ²Temple Univ School of Medicine, Philadelphia, PA.*

Introduction: Histologic recurrence of IgA deposits in renal allografts is as high as 60% in recipients with primary IgA nephropathy, however significant nephritis presenting as de novo Henoch-Schönlein Purpura (HSP) post-kidney transplant (KT) is rare with only a few cases reported. Our patient had biopsy proven diabetic nephropathy (DN), yet presented with severe HSP with multi-system involvement 10 years post-KT.

Case Description: A 63 y/o Hispanic female with DN received a living related KT in 2005 and was stably maintained on tacrolimus, prednisone, without mycophenolate mofetil (MMF) due to recurrent infections. 10-yrs post-KT, she developed diarrhea, melena and acute renal failure (Cr of 4.19 from 1.5) after completing a course of antibiotics for pneumonia. She developed diffuse purpuric rash and had hematemesis with severe abdominal pain. Abdominal CT scan showed enteritis of the small bowel. EGD demonstrated necrotic lesions in the esophagus and severe ulcerative duodenitis with biopsies showing leukocytic infiltration of vessels, and submucosa. Skin biopsy showed leukocytoclastic vasculitis. Urine had 4+protein, leukocytes, red blood cells, but no casts. Extensive infectious and serologic workup was negative. KT biopsy demonstrated membranoproliferative changes without crescents, coupled with findings of DN and advanced interstitial fibrosis and tubular atrophy. Immunofluorescence showed +4 deposits for IgA and C3 and the patient was diagnosed with HSP. Due to severe GI involvement the patient was treated with pulse

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

steroids. Given renal fibrosis and comorbidities, no further therapies were pursued. Repeat EGD showed improved duodenal lesions after steroids, however renal function declined and the patient required dialysis.

Discussion: IgA nephropathy histologically recurs post-KT but rarely impacts graft survival. De novo HSP with significant nephritis is infrequently described and treatment strategies in adults with aggressive disease remain unestablished. Interestingly MMF is used for severe HSP in children. Whether lack of MMF maintenance contributed to HSP in our patient remains unknown.

TH-PO1090

Harvoni Induced Acute Interstitial Nephritis *Jyotsana Thakkar, Kenar D. Jhaveri, Rimda Wanchoo. Nephrology, North Shore-LIJ Hospital, NY.*

Introduction: Harvoni is a new combination pill consisting of ledipasvir with sofosbuvir approved by FDA in October 2014 for the treatment of chronic Hepatitis C genotype 1 virus infection. No cases of Acute Kidney Injury (AKI) have been reported with this agent thus far. We report the first case of Harvoni associated biopsy proven acute interstitial nephritis (AIN).

Case Description: A 64 year old AA female with chronic Hepatitis C, hypertension, diabetes mellitus came to our clinic for evaluation of AKI superimposed on chronic kidney disease. Laboratory data revealed serum creatinine of 2.24 mg/dl (baseline Cr 1.5 mg/dl), hypoalbuminemia (3.2 gm/dL) with a spot urine protein/ creatinine ratio of 3.3 (baseline of 1). Her AKI coincided with peripheral eosinophilia. Home medications included hydralazine, lantus, lisinopril and simvastatin. She had recently completed eight weeks of treatment for Hepatitis C with Harvoni and her most recent viral load was undetectable. She denied using any NSAID, antibiotics, PPI or herbal supplements. Physical exam was normal. AKI workup revealed negative ANCA, normal complement, normal serum free immunoglobulin light chain ratio and negative ANA panel.

Patient underwent kidney biopsy. Light microscopy showed 11 glomeruli, 3 were globally sclerosed, 3 had cellular crescents with mesangial nodular matrix expansion and moderate tubular atrophy. Interstitium showed moderate fibrosis with severe lymphocytic inflammation. Immunofluorescent microscopy was normal and electron microscopy showed diffusely thickened glomerular membrane and moderately effaced foot processes. A final diagnosis of acute interstitial nephritis with chronic diabetic nephropathy was made. Her clinical picture, pathology findings and time course of renal impairment coincided with Harvoni use and is suggestive of Harvoni induced AIN. She was initiated on steroid therapy and advised to stop further use of Harvoni. Her renal function is stable with no further deterioration after stopping offending agent.

Discussion: Harvoni has a cure rate of up to 94-100% in patients with Hepatitis C genotype 1. We report first case of biopsy proven AIN with Harvoni. Hepatologists and nephrologists need to be aware of the potential side effect of this novel agent.

TH-PO1091

Thrombotic Microangiopathy Secondary to Smoldering Myeloma: A Form of MGRS *Jyotsana Thakkar, Rimda Wanchoo, Kenar D. Jhaveri. Nephrology, North Shore-LIJ Hospital, NY.*

Introduction: Thrombotic microangiopathy syndrome (TMA) is not a usual presentation of paraproteinemic diseases. We report a case of TMA secondary to smoldering myeloma presenting as monoclonal gammopathy of renal significance (MGRS).

Case Description: A 69 year old male with past history of hypertension, diabetes mellitus, prostate cancer, Chronic Kidney disease (CKD) (baseline creatinine 1.3-1.5 mg/dl), chronic back pain was referred to our clinic for evaluation of CKD. Home medications included enalapril, humalog, pioglitazone and acetaminophen as needed. Physical exam was normal except for elevated BP of 160/80 mmHg. Workup showed serum creatinine 1.5 mg/dl, Spot urine protein/creatinine ratio of 0.2, Hb 15.5 gm/dl and platelets 113K/UL. Serum free light chain ratio was suggestive of elevated IgA kappa light chain and elevated K/L ratio. Bone marrow biopsy showed mild plasmacytosis (10% plasma cell). Skeletal survey was negative for lytic lesion. Patient was diagnosed with smoldering myeloma. Kidney biopsy was done to rule out MGRS.

Light microscopy showed 24 glomeruli, 11 of which were sclerotic. Immunofluorescence was negative. On Electron microscopy, extensive glomerular basement membrane (GBM) duplication with sub endothelial widening was seen. Between the duplicated GBM, two types of electron dense deposits were seen, consisting of short fibrils and well demarcated dense material giving bubbly appearance consistent with thrombotic microangiopathy. Serological workup for secondary causes of TMA including HIV, Hepatitis, CMV PCR, Parvovirus B19 PCR, antiphospholipid antibody, cryoglobulin, complement (C3, C4), HTLV I/II immunoassay, beta 2 glycoprotein IgA Ab were negative. Given the smoldering nature of MM and the finding of TMA on kidney biopsy with no secondary cause, patient was considered to have MGRS presenting as renal limited TMA and is currently being treated with anti plasma cell agents.

Discussion: Case series of cancer related microangiopathic hemolytic anemia and TTP as initial presentation of multiple myeloma have been described before but not biopsy proven chronic renal limited TMA secondary to smoldering myeloma. We report first case of biopsy proven TMA likely secondary to smoldering myeloma.

TH-PO1092

A Case of Leukocyte Chemotactic Factor 2 Associated Amyloidosis *Nada Bader, Saeed Kamran Shaffi. Nephrology, Univ of New Mexico.*

Introduction: Leukocyte chemotactic factor 2-associated amyloidosis (ALECT2) is a newly described form of nonhereditary amyloidosis. The disease usually presents with chronic kidney disease and bland urinary sediment with variable degrees of proteinuria. We describe a case of a young Hispanic female who presented with nephrotic syndrome without renal insufficiency.

Case Description: A 40 year old Hispanic female with history significant for uncontrolled type 2 diabetes, hypertension and rheumatoid arthritis, was referred to renal clinic for evaluation of nephrotic syndrome. Physical examination revealed periorbital and bilateral lower limb edema. Pertinent diagnostic data are shown in figure 1.

Urinalysis	3+ protein
Urine microscopy	Bland
Spot urine protein/creatinine (g/g)	20
Serum creatinine (mg/dl)	0.5
Serum albumin (g/dl)	1.4
SPEP	No M component
Serum Keppa/Lambda	Normal
Hepatitis panel	Non-reactive
ANA	Non-reactive
Renal ultrasound	Normal kidney size with mild echogenicity

Renal biopsy showed extensive amyloidosis involving the glomeruli, interstitium and arterioles. Immunofluorescence was negative for immunoglobulins and amyloid associated protein. Proteomic typing of the amyloid revealed ALECT2 associated amyloidosis. The patient was started on lisinopril and spironolactone, but her proteinuria failed to improve and she had progressive deterioration of renal function. Two years later, she developed ascites and elevated liver enzymes. Her presentation was concerning for hepatic amyloidosis; therefore, she was transferred to a liver transplant center for further evaluation.

Discussion: Based on two large renal biopsy series, ALECT2 accounts for 2.5-2.7% of all cases of renal amyloidosis. In a multicenter study involving 72 patients with renal ALECT2, 92% were Hispanic, 2.8% were below the age of 50 and 91.4% had a serum creatinine > 1.2mg/dl. One third had nephrotic range proteinuria, but only 10% of all patients presented with nephrotic syndrome. Pathogenesis is not clear. It is postulated that inflammatory processes lead to excessive production of an amyloidogenic variant of ALECT2. Accurate identification of the amyloid protein is essential as disease modifying treatments are available for certain types of amyloidosis.

TH-PO1093

Complement Polymorphisms in Patients with Thrombotic Microangiopathy Associated with Intravenous Abuse of Oral Formulation of Extended-Release Oxymorphone (OPANA-ER) *Joe Ghata, Lukas Haragsim, Satish Kumar. Nephrology, Univ of Oklahoma Health Science Center, Oklahoma City, OK.*

Introduction: In 2012, the CDC reported 15 cases of unexplained renal failure and thrombotic microangiopathy (TMA) in which all patients reported dissolving and intravenously injecting an oral preparation of oxymorphone (Opana ER) prior to presentation. Since then, 30 additional cases have been reported in the U.S. The mechanism of IV Opana-associated TMA is unclear. ADAMTS13 levels were normal. We report two patients with genetic polymorphisms of complement system proteins as a possible mechanism for Opana-associated TMA.

Case Description: Two patients, a 26 yo WM (Pt 1) and a 38 yo WM (Pt 2) presented with unexplained renal failure (serum creatinine 8.2 and 4.6 mg/dl respectively) in the setting of IV Opana Abuse. Both displayed a hematological constellation of microangiopathic hemolytic anemia, thrombocytopenia, consumed haptoglobin and elevated LDH. Both patients had normal INR/PT/PTT, ADAMTS13 (both > 55%) and fibrinogen levels. ANA, HIV, and hepatitis profiles were negative. Renal biopsy showed intermediate sized vessel TMA in both patients. Both received plasmapheresis for 5 days. Hematological microangiopathy resolved in Pt 2 but persisted in Pt 1. Both remained dialysis dependent. Genetic studies for complement-mediated HUS demonstrated both to be positive for a heterozygous polymorphism (IVSP-78 G>A) within an intron of the membrane cofactor protein (MCP/CD 46) and for a homozygous polymorphism (p.His402Tyr) in the complement factor H (CFH). In addition, both patients had an additional CFH polymorphism (p.Val62Ile; Pt 1 homozygous, Pt 2 heterozygous).

Discussion: Our patients suggest a 2 hit mechanism for IV Opana-associated TMA. Both had polymorphisms in complement system proteins MCP and CFH with a potential predisposition for complement-mediated HUS. The MCP/CD 46 polymorphism has been shown to be enriched in patients with complement-mediated HUS. Polymorphisms in complement system proteins could cause hyperactivation and dysregulation of the complement system and provide a genetic predisposition for thrombotic microangiopathy, with IV Opana abuse acting as a trigger.

TH-PO1094

Acute Kidney Injury due to an Excessive Dose of Rivaroxaban Sandar Win,¹ Kevin G. Lazo,² Jordan L. Rosenstock.¹ *¹Nephrology, NSLIJ/Lenox Hill Hospital, New York, NY; ²Internal Medicine, .*

Introduction: Recently, over-anticoagulation with warfarin has been recognized as a cause of acute kidney injury (AKI) and has been termed warfarin related nephropathy (WRN). We report a patient who developed AKI and gross hematuria while taking the new oral anticoagulant (NOAC) rivaroxaban.

Case Description: A 45 y/o man presented to his physician's office with abdominal pain. Computed tomography (CT) of the abdomen was done and thrombosis of the portal, splenic, and mesenteric vein was identified. He was admitted to the hospital and discharged on rivaroxaban 10mg 2 tablets daily. After 6 weeks, he was given a prescription for rivaroxaban 20 mg tab and told to take 1 tablet daily. He mistakenly took 2 tablets daily. After 5 days, he noticed painless gross hematuria for several days. He reported to his physician's office and his serum creatinine had increased to 2.7 mg/dL from a baseline of 1.5. He had a previous history of splenic vein thrombosis of unclear cause 2 years previously (treated with course of warfarin), hypertension, and diabetes. His medications included metformin, glipizide, gemfibrozil, valsartan, sitagliptin, and rivaroxaban. His vital signs were normal. Physical examination showed splenomegaly but was otherwise unremarkable. Urinalysis revealed many red blood cells with trace proteinuria. The urine protein to creatinine ratio was 257 mg. Serologies were negative and there was no evidence of intravascular hemolysis. Antiphospholipid antibodies were negative as was a hypercoagulable work-up. A bone marrow biopsy was unremarkable and paroxysmal nocturnal hemoglobinuria was ruled out. Renal dopplers were negative for renal vein thrombosis. Renal function remains stable after 3 months. Renal biopsy was not performed in the setting of required anticoagulation and likely diagnosis of anticoagulant related AKI.

Discussion: WRN is a newly recognized form of AKI in the setting of excessive anticoagulation with warfarin. This appears to be the first reported case of a WRN-like AKI due to the NOAC rivaroxaban, and was likely caused but inadvertent doubling of the patient's dose. WRN can often be irreversible and in this patient as well no renal recovery was evident at 3 months.

TH-PO1095

Irreversible Acute Kidney Injury due to Oxalate Nephropathy from Intravenous Vitamin C Tarvinder S. Matharu, Satish Kumar. *Nephrology, Univ of Oklahoma Health Science Center, Oklahoma City, OK.*

Introduction: High doses of vitamin C are widely used in alternative medicine for treatment of cancer, viral illness and fatigue. Vitamin C is metabolized to oxalic acid in the body. High doses of vitamin C have the potential to cause hyperoxaluria, nephrolithiasis and oxalate nephropathy. We report a patient who developed severe, irreversible, acute kidney injury due to acute oxalate nephropathy from high dose intravenous vitamin C.

Case Description: 75 yo male with a history of hypertension, hypothyroidism, and mild pancytopenia, presented to a wellness clinic with fatigue and weight loss. He had a normal metabolic profile except hypercalcemia (corrected Ca, 12 mg/dl). He received IV vitamin C 30 g/d for 7 days. Serum creatinine was 1.3 mg/dl prior to Vitamin C administration. One month following treatment, he was admitted to our hospital with serum Cr 9.1, Na 110, K 3.1, Cl 70, CO2 16, BUN 152, Glucose 131, Ca 8.4, Uric Acid 12.1, CPK 175, Phos 11.9, and Mg 3.3. LFTs were normal. Urine vitamin C level was 40. An abdominal CT revealed diffuse mesenteric and retroperitoneal lymphadenopathy with hepatosplenomegaly and ascites. Liver was without cirrhosis. A renal ultrasound revealed normal sized, echogenic kidneys. Serum free light chains and serum and urine protein electrophoresis were normal. A renal biopsy demonstrated diffuse acute tubular injury and abundant tubular calcium oxalate deposits consistent with acute oxalate nephropathy. Bone marrow biopsy was normal and culture negative. A lymph node biopsy demonstrated diffuse T Cell Lymphoma. Patient was started on dialysis and remained dialysis-dependent at last follow up.

Discussion: Our patient developed severe, irreversible acute kidney injury from high dose intravenous vitamin C. The hypercalcemia was likely a contributing factor for the extensive deposition of calcium oxalate crystals in the kidney. A literature search identified 2 previous reports of oxalate nephropathy from intravenous vitamin C. High dose vitamin C is a common component of alternative medical regimens for cancer and other illnesses. We urge caution in using high dose vitamin C especially in patients with pre-existing renal insufficiency or hypercalcemia.

TH-PO1096

Atypical Hemolytic Uremic Syndrome (aHUS) due to a Novel Sequence Variation of Diacylglycerol Kinase Epsilon (DGKE) Shoba Narayan,¹ Rupa A. Udani,² Stefanie Dugan,² Matthew W. Anderson,² Dorit Ben-Ezer,¹ Kenneth Dale Friedman.² *¹Nephrology, Children's Hospital Orange County, Orange, CA; ²Hematology, Blood Center of Wisconsin, Milwaukee, WI.*

Introduction: aHUS is a congenital disease characterized by hemolytic anemia, thrombocytopenia, and organ dysfunction (e.g. renal failure). Genetic alterations resulting in uncontrolled activation of the complement system are found in 50-60% of aHUS cases. Recently autosomal recessive mutations in DGKE have been identified, indicating that intrinsic abnormalities in the signaling pathways controlling endothelial and platelet procoagulant tendency and podocyte function can also lead to aHUS. Patients with DGKE-associated disease tend to present at earlier age, have nephrotic range proteinuria, fail to respond to eculizumab, and may develop renal failure, but do well after renal transplantation.

Case Description: We identified a novel homozygous sequence variation c.1344C>A, p.N448K in the kinase accessory site of DGKE in a family with aHUS. The index case

presented at 1 year of age with nephrotic range proteinuria and hypertension. Renal biopsy at the time revealed TMA. Clinical course was complicated by ongoing proteinuria despite ACE-I and ARB therapies. At age 10, she does not have thrombocytopenia, schistocytes, abdominal or CNS manifestations, as typically noted in patients with complement-mediated aHUS. Genetic testing was sent to identify mutations previously not available to guide further treatment. The patient also carries heterozygous sequence variation ADAMTS13 c.3287G>A, p.R1096H, associated with decreased ADAMTS13 function and is heterozygous for CFHR5. Subsequently, a younger sister presented with hypertension, hematuria and nephrotic range proteinuria. The symptomatic sister is also homozygous for this variant in DGKE and is heterozygous for CFHR5, but lacks the ADAMTS13 variant. Parents and siblings with heterozygous DGKE variants are healthy.

Discussion: This case is the first reported case of a kinase accessory domain of DGKE associated with aHUS. Additional studies are needed to determine the impact of DGKE mutations on the clinical course of patients with aHUS and their appropriate management.

TH-PO1097

Membranoproliferative Glomerulonephritis with Mixed Cryoglobulinemia in Patients with Autoimmune Hepatitis Olorunkemi O. Oluwole, Anand Achanti, Jalal E. Hakmei, Sally Self, Milos N. Budisavljevic. *Nephrology, MUSC, Charleston, SC.*

Introduction: Autoimmune hepatitis (AIH) is frequently associated with extrahepatic manifestations; however, glomerulonephritis is rarely seen. We describe two patients with biopsy proven AIH who developed membranoproliferative glomerulonephritis (MPGN) despite treatment with prednisone and azathioprine. Screening for hepatitis B and C virus was negative and neither patient had SLE.

Case Description: Case 1: A 56 year old female presented with microscopic hematuria (6-10 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serology revealed mixed type III IgG/IgM cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with cryoglobulinemic MPGN. She was treated with plasma exchange and rituximab, with disappearance of cryoglobulins, normalization of urinary findings and resolution of AKI. Case 2: 18 year old female presented with proteinuria (1.7 g), hematuria (44 RBC) and serum creatinine 0.8 mg/dl. Mixed type III cryoglobulins consisting of IgG/IgM were detected in the serum. Kidney biopsy revealed mesangial hypercellularity reduplication of GBM with subendothelial, mesangial and scattered subepithelial deposits. She was treated with plasma exchange, one dose of 1000 mg intravenous cyclophosphamide and 1 gram of rituximab 4 weeks later. Treatment led to the disappearance of cryoglobulins and normalization of urinary findings. Serologic tests at presentation are presented in (table 1).

	Case 1	Case 2
C3 (88-201 mg/dL)	27	42.2
C4 (16-47 mg/dL)	<10	<10
ANA (Negative)	Negative	1:160
Anti dsDNA (<30 IU/ml)	20	28.7
RF (0-24 IU/ml)	1770	Negative
ANCA (Negative)	Negative	1:640

Discussion: Patients with AIH should be monitored for proteinuria and active urinary sediment due to the risk of glomerulonephritis, despite treatment with prednisone and azathioprine. MPGN is a rare, but important, complication of AIH. Prompt diagnosis by kidney biopsy and aggressive treatment of AIH associated MPGN with rituximab and/or cyclophosphamide may result in a favorable renal outcome.

TH-PO1098

A Case of Chinese Herb (Aristolochic Acid) Nephropathy Leading to ESRD Complicated by Bladder Cancer Melin Joe Narayan, Bahar Bastani. *Dept of Nephrology, St. Louis Univ, St. Louis, MO.*

Introduction: Chinese Herb (aristolochic acid) Nephropathy, is a rapidly progressive interstitial nephritis leading to ESRD with a high frequency of urothelial malignancy.

Case Description: We report a 59 year old white female who had received Chinese herbs for one and half years before she developed progressive renal insufficiency that over a six month period lead to ESRD requiring hemodialysis. A renal biopsy showed extensive tubular loss and collapse associated with interstitial edema and interstitial fibrosis consistent with the effects of tubular toxic damage caused by aristolochic acid. After one week of hemodialysis, the patient underwent a living unrelated kidney transplant from a friend. Alemtuzumab induction, steroid free maintenance on tacrolimus and mycophenolate (MMF) were started. She had no history of diabetes, hypertension or use of NSAIDs. She underwent monthly urinalysis and screening cystoscopy every six months to rule out urothelial malignancies. Twenty months post transplant she underwent right breast lumpectomy and radiation for intraductal carcinoma. Two and a half years after kidney transplant routine cystoscopy revealed a bladder mass, a biopsy of which showed high grade urothelial carcinoma with squamous differentiation invading into subepithelial connective tissue for which she underwent bilateral native nephrectomy, ureterectomy, cystectomy and transplant kidney ileal loop urinary diversion. One year later the patient was admitted with shortness of breath and was found to have a malignant pleural effusion of unidentified primary which led to her demise. A sample of the Chinese herb that she had used was found to contain aristolochic acid.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Discussion: There has been a high risk of urothelial malignancies associated with Chinese herb/aristolochic acid exposure with 40 - 45% of these patients developing multifocal high grade transitional cell carcinoma leading to a suggestions for either prophylactic bilateral native nephrectomy and ureterectomy at the time of renal transplantation or screening cystoscopies every 6 months to identify early stage urothelial carcinoma. Our patient is a classic example of aristolochic acid associated nephropathy complicated with urothelial cancer.

TH-PO1099

Anti-Tumor Necrosis Factor Therapy – A Trigger for Anti-Glomerular Basement Membrane Disease Carlos Antonio Cortes Sanchez, Hector R. Cordova, Krystahl Z. Andujar. *Medical Service, VA Caribbean Healthcare System, San Juan, PR.*

Introduction: Tumor necrosis factor (TNF) has a key pathological role in diseases such as rheumatoid arthritis (RA). Vasculitis and other autoimmune diseases have been associated with the use of anti-TNF agents such as Adalimumab.

Case Description: A 73-year-old man with of RA, Hypertension, Diabetes Mellitus type 2 and Non-Hodgkin's Lymphoma in remission for 3 years complained of decreased urine output, dark urine, poor appetite, weight loss and peripheral edema for three weeks. He was on chronic low dose Prednisone and Adalimumab intermittently during the previous 21 months. Physical exam revealed bilateral lower extremity pitting edema but no skin lesions. Laboratories showed a serum creatinine of 9.3mg/dl (baseline of 1.3mg/dl). Urinalysis exhibited many RBC's, proteinuria (2+) and pyuria without casts. The clinical picture suggested acute glomerulonephritis. Hemodialysis (HD) was started.

Test	Upon Admission	After Plasmapheresis	After Reexposure to Adalimumab
ANA	1:80 Speckled		
C3/C4	Normal		
Anti-GBM (N < 1.0 AI)	7.9	2.4	4.3
Atypical PANCA (N < 1:20)	Negative	Negative	Negative
P-ANCA (N < 1:20)	1:20	Negative	Negative
MPO (N < 1.0 AI)	4.6	1.1	2.2
C-ANCA (N < 1:20)	Negative	Negative	Negative
Prot3Ab (N < 1.0 AI)	Negative	Negative	Negative
ASO Titer	Normal		

Serology tests were compatible with Anti-Glomerular Basement Membrane (GBM) Disease. Alveolar hemorrhage was not present. Plasmapheresis therapy decreased anti-GBM titers but there was no recovery of renal function. The patient continued using Adalimumab after discharge. He later returned with hemoptysis due to alveolar hemorrhage, which resolved after the discontinuation of Adalimumab. The patient remained HD-dependent.

Discussion: The temporal association of the illness with anti-TNF therapy and worsening of symptoms upon reexposure suggest an etiologic role of Adalimumab in the development of Anti-GBM Disease in our patient. Patients receiving anti-TNF therapy should have renal function closely monitored to allow early detection of this infrequent but life-threatening side effect.

TH-PO1100

Severe Pauci Immune Crescentic Glomerulonephritis Mimicking ANCA Related Vasculitis Caused by Clinically Silent Dental Abscess Leading to Bacterial Endocarditis Anil K. Chunduri, Maria Saleem Khan, Anthony Alvarado, Tibor Nadasdy, Lee A. Hebert. *Nephrology, OSUMC, Columbus, OH.*

Introduction: Severe crescentic GN is usually categorized based on the cause if it is Anti GBM or IC mediated disease. However, it is not widely appreciated that some instances of pauci immune GN are actually the result of severe occult systemic infections. We present a case of severe pauci immune crescentic GN whose initial assessment for infection was negative. The patient was assumed to have idiopathic AAV and was treated with high dose steroids. Despite no obvious signs of infection, bacteremia was on our differential due to pancytopenia. These findings are rarely common, if ever, associated with AAV.

Case Description: 55 year old male with PMH of CAD presented to an outside hospital with fatigue. Initial labs revealed Hb: 7.6g/dl, WBC: 2.8 K/ μ L, Plt: 44 K/ μ , Creat: 2.26 mg/dl. Infectious work up was negative. Autoimmune workup revealed: ANA positive (1:40), Anti GBM (<0.2), Anti PR3 (0.6), ANCA and Anti MPO: negative. C3 : 77mg/dL, C4 :16.9 mg/dl (wnl). Cryoglobulin (<5), Urine PC ratio was 1.2. Further workup included a bone marrow biopsy and kidney biopsy, which was suggestive of pauci-immune crescentic and necrotizing GN. He received treatment with steroids and was discharged on steroid taper. His creatinine upon discharge was 1.5 mg/dl. On follow up his creatinine was elevated to 3.5 mg/dl. He was transferred to our institution. Repeat Infectious work up revealed streptococcus viridians bacteremia, tricuspid and aortic valve endocarditis. A panoramic radiograph of his teeth showed periapical abscess. He was subsequently diagnosed with infection related acute pauci-immune crescentic necrotizing GN. Unfortunately this patient remained dialysis dependent at the time of discharge.

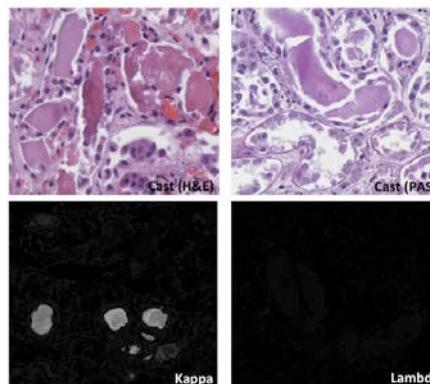
Discussion: It is well established but not widely appreciated that severe pauci-immune crescentic GN can be the direct result of infection. Thorough investigation is warranted even if the initial infectious workup is negative, if the patient does not have a positive response to conventional therapy to improve morbidity and mortality.

TH-PO1101

POEMS Syndrome with Cast Nephropathy Amanda K. Hall,¹ Josephine Abraham,¹ Monica Patricia Revelo Penafiel,² Frederic Clayton.² ¹Div of Nephrology and Hypertension, Univ of Utah, Salt Lake City, UT; ²Div of Pathology, Univ of Utah, Salt Lake City, UT.

Introduction: POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is a plasma cell disorder with peripheral neuropathy and any of the following features osteosclerotic bone, Castleman's disease, increased levels of serum vascular endothelial growth factor(VEGF), organomegaly, endocrinopathy, edema or skin changes. We report a case of POEMS presenting with acute renal failure due to cast nephropathy.

Case Description: A 63-year-old Caucasian female presented with a 3 month history of increasing weakness and was diagnosed with chronic inflammatory demyelinating polyneuropathy. She was also noted to have new onset diabetes mellitus and hypothyroidism. She was treated with intravenous immunoglobulin(IVIG) with minimal response. She was admitted with acute renal failure initially thought to be secondary to IVIG, progressive weakness, and shortness of breath. Serum beta 2 microglobulin was elevated and kappa/lambda ratio was abnormal with Bence-Jones proteinuria. Renal biopsy was deferred as the patient developed respiratory failure, subarachnoid hemorrhage, and a left middle cerebral artery stroke. Comfort measures were initiated. Bone marrow biopsy confirmed multiple myeloma with 20% clonal plasma cells. Autopsy showed hepatomegaly, splenomegaly, and peripheral nerve demyelination with active axonal loss. Renal examination showed cast nephropathy with monoclonal kappa light chains.



These features are characteristic of POEMS given the multiple myeloma with neuropathy, organomegaly, rash and new onset diabetes mellitus and hypothyroidism.

Discussion: POEMS is a paraneoplastic syndrome associated with plasma cell dyscrasia. Polyneuropathy with plasma cell disorder should prompt evaluation for POEMS as outcomes have been excellent with diagnosis and treatment.

TH-PO1102

Acute Interstitial Nephritis Associated with a New Breast Cancer Chemotherapy Regimen Cory Handelsman,¹ Michael T. Tanoue,² Amy Kwon,² Steven Salvatore,³ Jeffrey I. Silberzweig.^{2,4} ¹Div of Nephrology, Weill Cornell Medical College; ²Dept of Medicine, Weill Cornell Medical College; ³Dept of Pathology, Weill Cornell Medical College, New York, NY; ⁴The Rogosin Inst, New York, NY.

Introduction: Acute interstitial nephritis (AIN) as a direct consequence of chemotherapy is infrequently described. A recent review implicated ifosfamide, tyrosine kinase inhibitors, and pemetrexed as culprits in this process. We describe a case of AIN related to the recently approved chemotherapy regimen of pertuzumab, trastuzumab, and docetaxel for HER-2 positive metastatic breast cancer. While diarrhea, rash, and pruritis are well-known side effects, this report is the first to show AIN as a consequence of this combination regimen.

Case Description: A 69-year-old woman recently diagnosed with HER-2 positive breast cancer and treated with six cycles of neoadjuvant pertuzumab, trastuzumab, and docetaxel was hospitalized for acute kidney injury after two days of diarrhea and vomiting. Admission labs demonstrated leukocytosis to 26,000/uL, serum creatinine of 5.9 mg/dL (baseline of 1.55 mg/dL), and elevated anion gap metabolic acidosis with a lactic acid of 4.5 mmol/L. Urinalysis showed pyuria with occasional granular casts. Fractional excretion of sodium was 1.88%. Renal sonogram showed normal resistive indices with no evidence of hydronephrosis or calculi. Infectious workup, including blood, urine, and stool studies, was unrevealing. Despite aggressive hydration and resolution of diarrhea and vomiting within 48 hours, her renal function worsened; her creatinine peaked at 9.0 mg/dL on hospital day 3. She was non-oliguric throughout the admission. A renal biopsy revealed moderate to marked, diffuse acute and subacute, interstitial inflammation characterized by lymphocytic infiltration with moderate eosinophilia and diffuse tubular injury. Some endothelial injury

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was present as well. The patient was diagnosed with AIN secondary to chemotherapy and treated with prednisone. Two weeks later, her symptoms had fully resolved and her serum creatinine had returned to baseline.

Discussion: This is the first documented case of AIN related to combination chemotherapy with docetaxel, pertuzumab, and trastuzumab.

TH-PO1103

Sarcoidosis-Lymphoma Syndrome Presenting with Severe Refractory Hypercalcemia Osita W. Okechukwu,¹ Barry M. Wall,² Elvira Gosmanova,¹ Deepak NANDikanti,¹ ¹Nephrology Div, UTHSC, Memphis, TN; ²Nephrology Section, VAMC, Memphis, TN.

Introduction: Sarcoidosis-lymphoma syndrome (SLS) is rare. Sarcoidosis (S) usually precedes lymphoma (L) by many months. Constitutional symptoms and hilar lymphadenopathy are typical initial manifestations of SLS. We report a SLS case presenting with severe acute hypercalcemia and acute kidney injury (AKI).

Case Description: Case Report: A 70 yr-old Caucasian male was hospitalized with symptoms of generalized weakness, poor oral intake, and altered mental status. Examination was significant for dry mucus membranes, depressed mentation, evidence of bilateral pleural effusions, mild ascites, and 2cm well-delineated hyper-pigmented erythematous plaques on anterior chest wall. Laboratory findings included a corrected serum Ca 19.4mg/dL (2 months prior- 9.3mg/dL), ionized Ca 2.5 mmol/L, BUN 56mg/dL, serum creatinine 2.9mg/dL (baseline 1.4 mg/dL), and mild anemia. Further work up revealed suppressed PTH (6.2pg/mL) normal LFT, PTHrP, serum and urine electrophoresis, calcidiol, calcitriol, ACE, CEA, PSA, and TSH. A working diagnosis of hypercalcemia of malignancy was made. Intravenous fluids, calcitonin, prednisone, and low dose pamidronate were initiated; however, hypercalcemia and AKI remained poorly responsive to conservative measures and hemodialysis was required. Skin biopsy of chest wall lesion demonstrated non-caseating granulomatous dermatitis consistent with sarcoidosis. Thoracentesis was performed and pleural fluid cytology showed occasional plasmacytoid/lymphoid cell and polyclonal T-cells on flow cytometry. However, flow cytometry of ascitic fluid was positive for monoclonal B cells. Computed tomography (CT) demonstrated diffuse soft tissue lung masses and abdominal carcinomatosis. Osseous survey was normal. CT-guided omental mass biopsy showed dense fibrous tissue with lymphoplasmacytic infiltrate. The diagnosis of SLS with associated B-cell lymphoma was made. Given poor functional status and widespread disease, the patient and his family opted for hospice care.

Discussion: Severe refractory hypercalcemia leading to AKI is unusual for sarcoidosis and should prompt investigation for concomitant lymphoma.

TH-PO1104

End Stage Renal Disease Secondary to Oxalate Nephropathy in a Patient with Undiagnosed Chronic Pancreatitis Kalyani Chandra, Burl R. Don. Div of Nephrology, UC Davis Medical Center, Sacramento, CA.

Introduction: Oxalate nephropathy is a rare, underdiagnosed, devastating disease characterized by extensive oxalate deposition, acute kidney injury and rapid progression to end stage renal disease (ESRD). Secondary hyperoxaluria occurs in enteric disorders associated with increased intestinal oxalate absorption and renal tubular injury. Chronic pancreatitis is a rare cause of oxalate nephropathy.

Case Description: A 66 year-old white man with history of diabetes mellitus, hypertension and recurrent kidney stones, was noted on routine labs to have an elevated serum creatinine level (6.88 mg/dL; baseline 1.17 mg/dL, 6 months prior). He reported having chronic diarrhea, fatigue, loss of appetite and weight loss over the past 6 months. Workup revealed pancreatic calcifications consistent with chronic pancreatitis. Urinalysis and renal ultrasound were normal. Renal biopsy revealed acute tubular necrosis with extensive oxalate deposition. A 24 hr urine collection noted increased oxalate and reduced citrate excretion. Despite a 6 month course of a low oxalate diet, pancreatic enzymes, calcium supplementation, and sodium citrate to alkalinize the urine, the patient's renal function failed to improve, and he is preparing for home hemodialysis.

Discussion: Enteric hyperoxaluria can lead to acute oxalate nephropathy. It has been described in patients with post-gastric bypass surgery and inflammatory bowel disease. There are rare reports noting the association between chronic pancreatitis and oxalate nephropathy leading to chronic kidney disease (CKD) and rarely ESRD. The pathogenesis of hyperoxaluria in chronic pancreatitis remains uncertain, but it is postulated that fat malabsorption may increase free fatty acids that competitively inhibit the formation of calcium oxalate in the GI tract, combined with increased colonic mucosal permeability, leading to hyperoxalemia, hyperoxaluria and oxalate crystallization in the kidney. Treatment remains largely empiric, aiming at decreasing oxalate burden to the kidney as was done in this patient. Oxalate removal with dialysis has not been shown to be beneficial. Oxalate nephropathy can be a late complication of chronic pancreatitis leading to CKD and ESRD.

TH-PO1105

mRNA Expression of Proinflammatory Mediators in Common Variable Immunodeficiency with Granulomatous Interstitial Nephritis: Case Report Giacomo Mori, Giulia Ligabue, Sara De biasi, Milena Nasi, Andrea Cossarizza, Gianni Cappelli. Univ Hospital - Modena.

Introduction: Common Variable Immunodeficiency (CVID) impact on kidney function is poorly understood. We present a case of a woman, 39years old, affected by CVID, expressing as hypogammaglobulinemia, anemia and chronic kidney failure secondary to granulomatous interstitial nephritis(IN).

Case Description: In 2013 serum creatinine(s-cr)rose from 0.8 to 2.6mg/dL, without urinary abnormalities or signs of inflammation. A kidney biopsy showed an IN, with granulomatous aspects. PolyomaBK, HIV1/2, ParvovirusB19, SV40 resulted negative, urinary PolyomaJC was positive. A PET-CT ruled out occult infections or reactive lymph nodes. Pathology of several purple-brownish skin lesions demonstrated a lymphocytic infiltrate and perivascular macrophages containing melanin pigment. ACE level was doubled. A course of methylprednisolone(350mg i.v. for 3 days, followed by oral tapering) was started; anemia improved with iron, vitamins and EPO; s-cr decreased to 1.9mg/dL. Along 2014 relevant metabolic acidosis persisted and s-cr gradually rose to 3.8mg/dL. Before starting a new course of steroids we evaluated mRNA expression of a panel of proinflammatory mediators in circulating monocytes.

Among the considered mediators AIM2, PTGS2 and IL1B genes were overexpressed. AIM2 is central in innate immune response, recognizing cytosolic double-stranded DNA and inducing caspase-1-activating inflammasome formation in macrophages; PTGS2 (or Cyclooxygenase) is the key enzyme in prostaglandin biosynthesis, with two isozymes: PTGS1 (constitutive) and PTGS2 (inducible). PTGS2 upregulation leads to the prostanoid biosynthesis involved in flogosis and mitogenesis. IL1B (Interleukin 1) is involved in cell proliferation, differentiation and apoptosis. IL1B induces PTGS2, mediating pain hypersensitivity. Steroids allowed a regression of s-cr to 2.4mg/dL and of ACE to normality range.

Discussion: Innate immune response over activation could be the cause of a pathologic monocyte-macrophage stimulation responsible for tubulointerstitial damage. Further studies are needed to understand the therapeutic potential of biologic therapy of CVID related interstitial nephritis, with the aim of stopping the inflammatory cascade.

TH-PO1106

Nephrotic Range Proteinuria without a History of Penicillamine Therapy in a Patient with Wilson's Disease Hideki Matsumura,¹ Akira Ashida,¹ Yuko Fujii,¹ Akihiko Shirasu,¹ Hyogo Nkakura,¹ Motoshi Hattori,² Hiroshi Tamai.¹ ¹Pediatrics, Osaka Medical College, Osaka, Japan; ²Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.

Introduction: Wilson's disease (WD) is a rare autosomal recessive genetic disorder of copper metabolism, characterized by hepatic and neurological abnormality. Although penicillamine is one of the key drugs for treatment of WD, in rare cases it may have a nephrotoxic effect leading to nephrotic syndrome due to membranous nephropathy. Here, we report a case of WD in a patient who showed nephrotic range proteinuria clinically and focal segmental glomerulosclerosis (FSGS) histologically, without a history of treatment with penicillamine.

Case Description: We treated an 18-year-old girl who had been diagnosed as having WD at the age of 6 years and treated with trientine. She had normal liver function and normal urinalysis parameters. At the age of 16 years, she had developed acute liver failure due to poor drug compliance. Although her liver function subsequently recovered after plasma exchange and medications including zinc and trientine, slight proteinuria began to appear. As the proteinuria increased gradually to within the nephrotic range, we performed a kidney biopsy one year later. The patient had normal blood pressure, no edema, and her body mass index was 26.9. Blood examinations demonstrated no hypoproteinemia, no immunological abnormalities and normal kidney function. Although urinalysis revealed no hematuria, the urine protein:creatinine ratio was increased to 2.98. A kidney biopsy demonstrated perihilar FSGS and arteriolar intimal thickening, without tubular-interstitial or glomerular basement membrane changes. We diagnosed the patient as having secondary FSGS and began administration of an angiotensin receptor blocker.

Discussion: Although the kidney manifestations in WD include aminoaciduria and nephrocalcinosis, these were not observed in our patient. As her symptoms were relatively milder than those of typical FSGS and she had several known causes of secondary FSGS including arteriolar intimal hyperplasia and obesity, our histological diagnosis was secondary FSGS. To our knowledge, this is the first report of histologically confirmed FSGS in a patient with WD.

TH-PO1107

Denosumab for the Treatment of Bisphosphonate Refractory Hypercalcemia of Malignancy Theresa L. Nilson, Tammy Wan, Erik Lawrence Lum. Div of Nephrology, Univ of California, Los Angeles, Los Angeles, CA.

Introduction: Hypercalcemia is common in malignancy, occurring in 20-30% of patients. Volume expansion with normal saline is the mainstay of therapy, with the addition of bisphosphonates in cases of severe hypercalcemia. Here we describe a case of bisphosphonate resistant hypercalcemia of malignancy and discuss potential treatment options for refractory cases.

Case Description: A 62 year-old male with T2 paraplegia following a fall 24 years ago presented to the ER for evaluation of a decubitus ulcer. On arrival his vital signs were unremarkable, and physical examination demonstrated a 10x10 cm stage IV decubitus ulcer with purulent drainage and exposed bone. Initial laboratory data demonstrated white blood cell count 18.7, hemoglobin 4.9 g/dL, normal basic metabolic panel and calcium 8.8mg/dL. He was transfused blood products and given antibiotic therapy. Bone biopsy demonstrated invasive squamous cell carcinoma. His calcium increased to 14.1mg/dL with elevated PTHrP 71pg/mL. He was diagnosed with humoral hypercalcemia of malignancy and treated with intravenous normal saline and pamidronate 90mg. His calcium initially reduced to 11mg/dL, but rose again to 13.4mg/dL. He received a second dose of pamidronate, but the calcium continued to rise to 15.3mg/dL. He was given a single dose of denosumab 120mg and his calcium decreased to 9.32 mg/dL over the next four days. The response was sustained without additional need for administration over the next two months before the patient expired due to complications related to his decubitus ulcer.

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Discussion: This case illustrates the potential effectiveness of denosumab for the treatment of hypercalcemia refractory to bisphosphonates. Denosumab is a human monoclonal antibody against RANK-Ligand (RANKL) whose use has previously been described for management of hypercalcemia, but required multiple infusions. Recognition of this additional treatment, with effectiveness from a single infusion, is critical in managing refractory hypercalcemia, as the only other known option is hemodialysis. Increasing availability of options for management of refractory hypercalcemia may allow patients to avoid complications associated with hemodialysis.

TH-PO1108

Collapsing and NOS Focal Segmental Glomerulosclerosis (FSGS): Progression Along a Spectrum or Different Diseases? *Suzanne L. Katsanos, Patrick H. Nachman, JulieAnne G. McGregor, Volker Nickleit. UNC Kidney Center, Chapel Hill, NC.*

Introduction: Minimal change disease (MCD) and some variants of FSGS (tip lesion and not otherwise specified NOS) are thought to represent a histologic spectrum of a similar autoimmune pathogenic process (Habib, R. Proceedings IXth Int Cong of Neph). This contention has never been proven, however. Some cases of MCD are thought to be “unsampled” FSGS. A “transition” from MCD to FSGS is common in steroid-resistant forms (Tejani, A. Nephron 39). It has been proposed that collapsing FSGS is pathogenetically and clinically distinct from other FSGS variants based on morphology, demographics, severity of nephrotic syndrome, and renal prognosis. The etiology has not been identified but viral agents, drugs, and cyclosporine toxicity have all been proposed.

Case Description: We present the case of a 37-year-old African American male with a complicated course of nephrotic syndrome. He was diagnosed with biopsy-proven MCD when 9 years old. He was treated with steroids followed by chlorambucil and then cyclophosphamide over the next several years. He was in complete remission off therapy for about 2 years until he re-presented with increased edema, proteinuria (3.8 g/d), hypoalbuminemia, and acute kidney injury (AKI). A repeat biopsy (25 glomeruli) showed FSGS NOS. He was treated with steroids followed by mycophenolate mofetil and cyclosporine, resulting in complete remission. 7 years later, he developed edema, proteinuria (21 g/d) and AKI. Repeat biopsy showed 25 glomeruli demonstrating segmental tuft collapse, activation of endothelial cells, and segmented marked activation and crowding of podocytes consistent with collapsing FSGS. HIV, hepatitis B, and hepatitis C were negative.

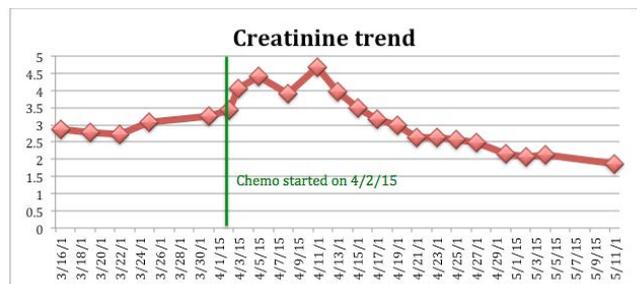
Discussion: The transition from MCD to FSGS NOS is common in the literature. However, the transition from FSGS NOS to collapsing FSGS is rarely reported. This patient’s case raises questions about this transition from NOS to collapsing variant. Glomerular undersampling is unlikely given 25 glomeruli were examined each time. This could represent a progressive, patient-related pathogenetic process versus a *de novo* lesion (either related to a viral infection or medication, for example).

TH-PO1109

Lymphoma Associated Monoclonal Cryoglobulinemia in a Patient with Hepatitis C *Sangeeta Mutnuri,¹ Marjan Afrozian,² Hania Kassem.¹ ¹Dept of Nephrology, UTMB, Galveston, TX; ²Dept of Pathology, UTMB, Galveston, TX.*

Introduction: We present a case of type I cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN) in a patient with hepatitis C infection (HCV), leading to the diagnosis of a marginal zone lymphoma.

Case Description: A 47 year old male with HCV and hypertension presented with two month duration of shortness of breath and decreased urine output. On examination he was hypertensive (blood pressure: 183/111 mm of Hg), had lung crackles, lower extremity edema and hepatosplenomegaly. Laboratory tests were significant for pancytopenia, hypoalbuminemia and an elevated creatinine of 2.8mg/dl (0.8mg/dl four months ago). Urine exam revealed red blood cell (RBC) casts, dysmorphic RBC’s and nephrotic range proteinuria (9.5 gm). Immunochemistry revealed elevated rheumatoid factor, hypocomplementemia and cryoglobulinemia. These findings led to a suspicion of HCV induced cryoglobulinemic glomerulonephritis. Kidney biopsy was performed revealing MPGN type III with deposits. Fluorescence microscopy favored Kappa monoclonality. Electron microscopy of the deposits was consistent with cryoglobulins. Serum immunoelectrophoresis also confirmed IgM/Kappa monoclonality. As HCV is more commonly associated with polyclonal cryoglobulinemia this finding of monoclonality prompted a search for malignancy. A bone marrow biopsy showed lymphoid aggregates indicating marrow involvement by marginal zone lymphoma. The patient was initiated on rituximab/dexamethosone based regimen. The creatinine trended down to 1.87 mg/dl.



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Discussion: Monoclonal cryoglobulinemia is related to lymphoproliferative diseases whereas HCV is associated with polyclonal cryoglobulinemia. This case stresses the importance of differentiating between the two entities especially in patients with co existing disorders. Making this crucial distinction helps predict the underlying etiology and treatment.

TH-PO1110

A Lupus Nephritis Patient Accompanied with Storiform Fibrosis Characteristic in IgG4-Related Kidney Disease in the Absence of Serum IgG4 Elevation and IgG4-Positive Plasma Cell Infiltration *Mamiko Imada, Naoki Takahashi, Daisuke Mikami, Seiji Yokoi, Kenji Kasuno, Hideki Kimura, Masayuki Iwano. Div of Nephrology, Univ of Fukui, Fukui, Japan.*

Introduction: IgG4-related kidney disease (IgG4-RKD) usually presents as tubulointerstitial nephritis with IgG4-positive plasma cell (PC) infiltration and serum IgG4 elevation. IgG4-RKD has characteristic histological findings called storiform fibrosis and radiological findings showing multiple low-density lesions on contrast-enhanced CT scan. Recently, Hara et al. reported a case of IgG4-negative IgG4-RD (Mod Rheumatol, 2014) which had a condition closely mimicking IgG4-RD despite the absence of serum IgG4 elevation and IgG4-positive PC infiltration. Here we report a patient diagnosed with lupus nephritis (LN) with IgG4-negative IgG4-RD.

Case Description: A 59-year-old Japanese man was referred to our hospital with chest pain and mild proteinuria. Thoracic biopsy was performed for abnormal lung shadow and interstitial pneumonia was diagnosed. Although ANA titer was elevated to 2560-fold, anti-DNA, anti-Sm, and anti-SS-A/-B antibodies were all negative. Serum C3 and C4 levels and complement activity were decreased. Serum IgG and IgE levels were elevated, but serum IgG4 level was within normal limits. On contrast-enhanced CT, multiple low-density lesions were observed in kidney. Renal biopsy findings revealed lymphoplasmacytic infiltration with storiform fibrosis and small numbers of eosinophils. Immunostainings revealed CD138- or IgG-positive PC infiltration without IgG4-positive PC. Immunofluorescence microscopy showed granular mesangial positivity for a “full-house” pattern. Electron microscopy disclosed mesangial and subendothelial dense deposition accompanied with virus-like particles. We diagnosed this patient with IgG4-negative IgG4-RD and LN (ISN/RPS II). After administration of 20 mg prednisolone, laboratory data was drastically improved.

Discussion: To our knowledge, this is the first report of a patient with LN and IgG4-negative IgG4-RD. IgG4-negative IgG4-RD may be a chronic burnout phase of IgG4-RD. Further studies gathering similar cases would be needed to clarify whether or not IgG4-negative IgG4-RD is included in a category of IgG4-RD.

TH-PO1111

A Case of Acute Phosphate Nephropathy in a Kidney Transplant Recipient *Hetal Shah, M. Lee Sanders, Kelly A. Birdwell, Anthony J. Langone, Paisit Pauksakon, Beatrice P. Concepcion. Vanderbilt Univ Medical Center, Nashville, TN.*

Introduction: Acute phosphate nephropathy has been described after large doses of phosphate, typically in laxatives and bowel cleansing preparations. We present a case of acute phosphate nephropathy in a kidney transplant recipient who was taking oral phosphorus supplementation for hypophosphatemia.

Case Description: A 26 year-old man with a living related donor kidney transplant in 2011 complicated by recurrent IgA nephropathy with a baseline creatinine of 1.9 mg/dL presented with nausea, vomiting, diarrhea, fatigue and elevated creatinine. Two weeks prior to presentation, he had been started on K-Phos-Neutral 500 mg three times a day for a phosphorus of 1.6 mg/dL. Intact parathyroid hormone (iPTH) was 58 pg/mL. He soon after developed diarrhea and ten days later developed nausea and vomiting. He was found to have a creatinine of 10.4 mg/dL, phosphorus 9.7 mg/dL, calcium 9.6 mg/dL and iPTH 761 pg/mL. Urinalysis had a urine pH of 5, no red blood cells and trace protein. Renal biopsy was performed, and pathology revealed 30 foci of intratubular calcium phosphate crystals with associated acute tubular injury involving 30-40% of tubular profiles, along with known recurrence of IgA nephropathy. The patient underwent acute hemodialysis for oliguric acute kidney injury. Given the high serum phosphorus, he was dialyzed for four consecutive days until phosphorus level was less than 4 mg/dL and did not rebound. Patient was discharged requiring intermittent hemodialysis for an additional three weeks until he demonstrated renal recovery. His new baseline creatinine is 2.2 mg/dL and he has remained off hemodialysis.

Discussion: Hypophosphatemia is common in kidney transplant recipients. Although rare, acute phosphate nephropathy can occur in the setting of phosphorus repletion. This patient also had multiple risk factors, including baseline renal dysfunction, volume depletion and angiotensin receptor blocker use. Acute phosphate nephropathy can potentially lead to irreversible loss of renal function. While no specific treatment exists, in this case, aggressive hemodialysis to decrease serum phosphorus may have played a role in this patient’s eventual renal recovery.

TH-PO1112

Unusual Membranous Nephropathy in a Patient with Lupus *Iheanyichukwu Ogu, Julia Lewis, Agnes B. Fogo. Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.*

Introduction: Membranous nephropathy (MN) is an immunologically mediated glomerular disease. Distinguishing between primary and secondary MN is important in guiding diagnosis and treatment. We present a case of a patient with systemic lupus with pathologic features in a repeat biopsy suggestive of primary MN.

Case Description: A 32 year old African American woman presented in 1998 with nephrotic range proteinuria (8g), edema and serum creatinine 0.6. She had negative work up for secondary causes including lupus. Renal biopsy showed mild matrix expansion, diffuse global basement membrane (GBM) spikes, preserved tubulointerstitial compartment; fine granular IgG(3+), C3(1+) IgM(trace), C1q(trace), IgA(negative) capillary loop staining with focal mesangial IgM and C1q staining; numerous subepithelial deposits, 90% foot process effacement, and unremarkable endothelial cells. She was started on an angiotensin receptor blocker but was lost to follow up. In 2011 she was diagnosed with Lupus and in July 2014, had proteinuria (1.9g). Repeat renal biopsy showed persistent MN with features concerning for lupus, with reticular aggregates, mildly increased mesangial matrix and cellularity, and 20% interstitial fibrosis. After referral to our clinic, additional testing on the 1998 biopsy (fig 1,2) showed diffuse global capillary wall Ig G1(1-2+), IgG2(2+), IgG3(negative), IgG4(3+), PLA2R(negative); and the 2014 biopsy (figs 3,4) showed diffuse global granular capillary wall IgG1(2+), IgG2(1-2+), IgG3(negative), IgG4(3+) and PLA2R near global(1-2+) granular capillary loop staining.

Discussion: The PLA2R staining and the dominance of IgG4 currently are consistent with primary MN. The negative PLA2R in 1998 may indicate early disease or epitope change. The mesangial deposits are nonspecific and could possibly represent a low grade lupus-related nephropathy. The presence of reticular aggregates is a marker of high interferon levels in patients with lupus, and does not necessarily mean lupus nephritis.

TH-PO1113

A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits Exhibiting Marked Nephrotic Syndrome Who Responded Well to the Renin-Angiotensin System Blockade Alone Yoshihiko Nishiguchi, Hideki Inoue, Tomoaki Onoue, Yutaka Kakizoe, Yuichiro Izumi, Takashige Kuwabara, Taku Miyoshi, Masataka Adachi, Yushi Nakayama, Masashi Mukoyama. *Nephrology, Kumamoto Univ Hospital, Kumamoto, Japan.*

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a newly recognized entity of glomerulonephritis caused by glomerular deposition of monoclonal IgG. The clinical and pathological features, treatment and prognosis of this entity remain elusive.

Case Description: A 79-year-old woman was admitted to our hospital due to hematuria and marked nephrotic-range proteinuria. Her serum creatinine level was 0.75 mg/dL and urinary protein excretion was 20.8g/g creatinine. Renal biopsy showed a membranoproliferative feature without nodular formation. Immunofluorescence study showed capillary and mesangial deposits of IgG, C1q and C3. Moreover, IgG-kappa deposits were strongly stained and IgG3 deposits were restrictedly stained for IgG heavy-chain subclass analysis. Electron microscopy revealed amorphous electron-dense mesangial and subendothelial deposits. Monoclonal proteins were not detected in serum or urine samples. Serum cryoglobulin titer was negative. Serum free light-chain assay showed a normal kappa/lambda ratio. These findings were consistent with the diagnostic criteria for PGNMID. Considering her age and tolerability, we started monotherapy with angiotensin II receptor blocker. This case showed drastic reduction in proteinuria with stable renal function within several months after the treatment with the renin-angiotensin system (RAS) blockade alone.

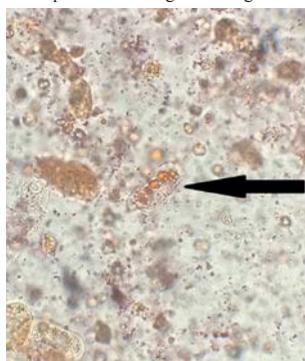
Discussion: We report here an exceptional case of PGNMID associated with the membranoproliferative feature successfully treated with RAS blockade alone, without steroid or other immunosuppressive agents. Further studies are needed to clarify clinical spectrum and prognosis of this newly described disease entity.

TH-PO1114

Brentuximab Induced Renal Steatosis – The Hint Is in the Urine Akhil Hegde, Ronald J. Falk, Abhijit V. Kshirsagar. *UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.*

Introduction: We describe the onset of acute kidney injury (AKI), lipiduria and multi-organ steatosis after the use of Brentuximab, a monoclonal antibody targeting CD30, in patients with recurrent Hodgkin Lymphoma (HL).

Case Description: A 61 year old female with recurrent HL, treated with Brentuximab 180mg (4 and 2 weeks prior to admission), was admitted with a 1-month history of nausea and vomiting. She was found to have AKI, creatinine 1.7 - baseline 0.9 mg/dl, elevated liver enzymes (AST 324, ALT 282 U/L), a urine protein/creatinine ratio of 1.0g with a total cholesterol and HDL of 152 and 32 mg/dl. Urine microscopy revealed numerous free fatty droplets and fatty casts that did not have a maltese cross appearance under polarizing light. Sudan black dye demonstrated positive staining indicating non-cholesterol fat in the urine.



Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PET/CT imaging did not show malignancy, but revealed severe fatty infiltration of multiple organs not present 4 months earlier. The patient’s clinical course worsened and the patient died on hospital day #6. An autopsy revealed hepatomegaly with severe steatosis, fatty infiltration of the pancreas and proximal renal tubular epithelial cell macro/microvesicular steatosis with intra-glomerular lipiduria.

Discussion: The development of AKI, lipiduria, transaminitis and multi-organ steatosis after 2 doses of Brentuximab is concerning for a drug-induced injury. Sudan dye attaches to neutral lipids and is helpful in distinguishing the 2 categories of lipids. Only 2 weeks after the last dose of Brentuximab, the patient was found to have new fatty infiltration and a subsequent autopsy revealed intra-glomerular lipidosis. The first hint to systemic steatosis was the presence oval fat bodies in the urine. Typically, charged lipids have the appearance of a maltese cross under polarizing light, while neutral lipids do not refract polarized light in this manner.

TH-PO1115

Pheochromocytoma: An Unusual Cause of Thrombotic Microangiopathy Induced Acute Kidney Injury in Pregnancy – Wolf in Sheep’s Clothing Yenkat Sainareesh Vellanki,^{1,2} Sachin V. Kodgire,² Anila Abraham,³ *¹Nephrology, Manipal Superspecialty Hospital, Visakhapatnam, Andhra Pradesh, India; ²Nephrology, Univ of Toronto, Toronto, ON, Canada; ³Renal Pathology, Center for Renal and Urological Pathology, Chennai, Tamil Nadu, India.*

Introduction: Hypertensive disorders during pregnancy result in substantial maternal and fetal morbidity. Pheochromocytoma in pregnancy is extremely rare with a reported frequency of 0.002% and 50% maternal and fetal mortality.

Case Description: 25 year old female, 26 weeks of gestation with gestational diabetes presented with antenatal hemorrhage, confusion and uncontrolled hypertension with BP190/124mmHg. Investigations revealed hemoglobin 9 gm/dl, platelets 76000/microliter, serum creatinine 2.4 mg/dl, LDH 245U/L, AST 30U/L, ALT 39U/L, urine dipstick protein 1+. Ultrasound confirmed abruptio placenta and intrauterine death of fetus needing emergency surgical evacuation. She developed intraoperative hypotension needing multiple blood transfusions and ventilatory support. Her renal function worsened needing initiation of hemodialysis. Septic and hemolytic work up were negative. She had paroxysmal episodes of uncontrolled hypertension and flash pulmonary edema needing frequent rescue hemodialysis and parenteral antihypertensives. Renal doppler was negative for renal artery stenosis. CAT scan showed left adrenal mass. Plasma normetanephrine was elevated at 1223 pg/ml suggestive of pheochromocytoma. BP was stabilized with four drugs and surgical resection of the tumor was done. A wedge kidney biopsy showed thrombotic microangiopathy (TMA). The tumor histopathology confirmed pheochromocytoma, positive for chromogranin and synaptophysin staining. Post operative, her creatinine stabilized at 1.6mg/dl, BP and glycemic status returned to normal.

Discussion: Pheochromocytoma in pregnancy is an extreme rarity with a frequency of 0.002%. It is often mistaken for other hypertensive disorders of pregnancy. This is the first case report of a patient with acute kidney injury in pregnancy from TMA secondary to pheochromocytoma. Patient made good renal recovery after resection of the tumor.

TH-PO1116

Immune Reconstitution Inflammatory Syndrome and Hypercalcemia with Acute Kidney Injury following Stribild Therapy Christine A. Garcia, Kelly H. Beers, Catherine Miranda, Kamran Karimi, Yezina T Nigatu, Nand K. Wadhwa. *Nephrology/Medicine, Stony Brook Medicine, Stony Brook, NY.*

Introduction: Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory disorder with paradoxical worsening of preexisting infectious processes following HAART in HIV-infected individuals. We describe a case of IRIS following Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir) resulting in hypercalcemia.

Case Description: A 33 year-old woman with acquired immunodeficiency syndrome (AIDS) who had been on Stribild for two months presented to the ED with acute kidney injury with a serum creatinine of 2.93 mg/dL and Ca of 15.2 mg/dL. Her CD4 count was 145 /uL and viral load 35 copies/mL. Four months prior, she was treated with amphotericin for cryptococcal lung infection and Cryptococemia. One month prior, a right lower lobe mass histology had revealed necrotic tissue with inflammatory cells. On examination, she was alert, in no acute distress, with unremarkable physical examination. Her temperature was 36.7 degrees Celsius, heart rate 72/minute, BP 108/64 mm Hg, respiratory rate 16/minute, and oxygen saturation 100% on room air. Chest X-ray showed an interval decrease in the right lower lobe mass. Serum intact PTH was 9.7 pg/mL. PTHr peptide, SPEP and UPEP were negative. Serum 25 (OH) D was 37 ng/mL, 1,25 (OH)₂ D3 was 17 pg/mL, and 24 hour urine Ca was 270 mg. Urine fractional excretion phosphorus was 28% with no glucosuria. She was diagnosed with IRIS and Stribild was discontinued. She was treated with IV fluids and calcitonin with an improvement in her renal function and normalization of her serum calcium over a period of 4 weeks. Lab data summarized.

	Serum Creatinine mg/dL	Serum Ca mg/dL	CD4 /uL	HIV viral load copies/mL
Base level	0.70	9.0	40	119,698
2 weeks on Stribild	1.45	11.8	122	220
8 weeks on Stribild	2.93	15.2	145	35
6 weeks off Stribild	1.00	9.4	93	178,362

Discussion: IRIS is thought to be due to increased T-lymphocyte proliferation after HAART in AIDS patients. IRIS typically manifests as a granulomatous inflammation. Corticosteroids are treatment of choice in IRIS in the setting of excess 1,25 (OH)₂ D3. In our case, serum 1,25 (OH)₂ D3 was low suggesting possible other mechanisms.

TH-PO1117

IgA-Dominant Postinfectious Glomerulonephritis: A Case Series
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Introduction: IgA dominant post-infectious glomerulonephritis (PIGN) is a distinct clinico-pathologic entity that typically occurs in diabetic patients and in association with a recent or active staphylococcal infection. Patients usually present with hematuria, proteinuria, and AKI. Renal pathology shows an immune-complex GN with varying light microscopic patterns and IgA-dominance or co-dominance with IgG on immunofluorescence. Here we report the clinical characteristics and outcomes of 10 patients with IgA dominant PIGN.

Case Description: After obtaining approval from the local IRB, retrospective, single-center review of data was performed and 10 patients with IgA dominant PIGN were identified.

Majority was white males, and 6/10 were diabetic. Eight patients had a Staphylococcal infection and one had active Hep C infection. Only 3/10 had low complements. 6/10 required RRT and 4 developed ESRD, of which 2 died at 2 and 5 months after initiation of RRT. Five were left with varying degree of CKD and one was lost to follow up. Three patients were treated with immunosuppression in addition to antibiotics-all had significant improvement in renal function; one patient who was initially RRT-dependent was able to come off dialysis.

Patient	Infection	C3/C4	Hematuria	Proteinuria/ d	Peak SCr	RRT	Follow Up
1	Hep C	N/N	Y	7.5	1.6	No	CKD
2	MSSA	L/L	Y	0.6	6.9	Y	CKD
3	MRSA/Pseudomonas	N/N	Y	1.16	3.9	No	NA
4	MRSA	N/N	Y	6.5	5	Y	Died
5	MRSA	N/N	Y	3.7	10.9	Y	CKD
6	MSSA	L/L	Y	1.2	7.5	Y	ESRD
7	MRSA/VRE	N/N	Y	4.1	7	Y	ESRD
8	MSSA	N/N	Y	NA	6.5	Y	Died
9	MRSA	N/N	Y	NA	3.9	No	CKD
10	Clostridium subterminalis	N/L	Y	2.8	5.2	No	CKD

N=Normal,L=Low;Y=Yes

Table 1. Clinical features and outcomes of pts with IgA-dominant PIGN

Discussion: IgA-dominant PIGN is an increasingly recognized disorder that occurs most commonly in diabetic patients with Staphylococcal infections. Overall renal prognosis is poor. Treatment with immunosuppression in addition to antibiotics may be considered.

TH-PO1118

Hematuria in a Young Female: This Was a Hard Nut to Crack
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Introduction: Flank pain with hematuria usually indicates urolithiasis but in its absence, renal vascular abnormalities should be considered.

Case Description: A 27-year old female with history of sickle cell trait, was admitted for gross hematuria. She had flank pain at the end of her urine stream but denied associated fever, chills or dysuria. She was treated with ciprofloxacin for presumed UTI but due to weakness she presented to our hospital. Her vital signs were stable and had a normal physical exam. Her hemoglobin was 5 gm/dl, creatinine at 0.6 mg/dl and urinalysis was evident for 3 plus proteinuria with >25 RBC/hpf and >50WBC /hpf. Her total protein to creatinine ratio was 2 and had a negative urine culture. She had normal complement, ANA screen and negative serology work up for autoimmune disease. Renal ultrasound (US) showed 10 cm (right) X 9.5 cm (left) kidneys. Her non-contrast CT abdomen and cystoscopy was non-diagnostic. To further evaluate her hematuria she underwent renal US with Doppler which showed narrowing of the left renal vein at the level of the superior mesenteric artery (SMA) with a peak velocity gradient greater than 10:1, consistent with left renal vein(LRV) stenosis or “nutcracker” syndrome (NCS). She subsequently underwent exploratory laparotomy with evidence of aortic and SMA scissoring compression of renal vein at its confluence with inferior vena cava (IVC). The IVC and left renal vein were mobilized and the compression was relieved. Patient continued to have hematuria with persistent proteinuria for few months postoperatively but eventually had resolution of both hematuria and resolution of proteinuria and hematuria.

Discussion: NCS refers to compression of left renal vein by abdominal aorta and SMA in fork-like fashion resulting in renal and pelvic venous congestion. The usual manifestations are microscopic to gross hematuria, pelvic or flank pain and orthostatic proteinuria. Hematuria results from the rupture of thin blood vessels into the collecting

system due to elevated renal venous pressure. Symptomatic patients usually need surgical repair, LRV transposition and renal auto-transplantation in rare cases. NCS is an important differential in patient with hematuria-proteinuria and flank pain in young patients.

TH-PO1119

ANCA Negative Pauci-Immune Necrotizing Crescentic Glomerulonephritis in a Patient with Non Hepatitis C Mixed Essential Cryoglobulinemia
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Introduction: Mixed essential cryoglobulinemia (MC) is associated with a hepatitis C infection in 70-90% of patients and presents as membranoproliferative glomerulonephritis or rapidly progressive glomerulonephritis (RPGN) with or without crescents. We report an unusual presentation of type II MC without hepatitis C infection presenting as ANCA negative pauci-immune necrotizing and crescentic glomerulonephritis (CrGN).

Case Description: A 64 year old male presented with AKI (creatinine of 5.4 from a baseline of 0.8 mg/dl, 2 weeks earlier), 12-18 month history of arthralgias, fatigue, joint pains, petechial and purpuric spots on his extremities. His symptoms were exacerbated in the winter months. Lab tests revealed elevated cryoglobulin level (338mg/dL), low C4 (5 mg/dl), positive rheumatoid factor, IgG monoclonal gammopathy (0.37g/dl), MPO ANCA, PR3 ANCA, ANA, hepatitis B and C and HIV serologies were negative. Urinalysis showed 20-50 RBCs, no casts and proteinuria of 2.5 g. Bone marrow biopsy showed < 5% plasma cells and no T cell aberrancy or B cell monoclonality. A kidney biopsy revealed pauci-immune necrotizing CrGN. Electron microscopy (EM) showed no deposits or fibrillar or tubular structures in the glomeruli. The patient was treated with hemodialysis (HD), 5 sessions of plasmapheresis and oral cyclophosphamide for 3 months. He responded to treatment with near complete resolutions of his symptoms and near normalization of kidney function.

Discussion: Pauci-immune CrGN is associated with either microscopic polyangiitis or granulomatosis with polyangiitis. These can present as RPGN and have either a positive MPO or PR3 ANCA but have no deposits on immunofluorescence and EM. CrGN in patients with MC is an immune complex disease, has distinct immune deposits in glomerular capillaries and fibrillar and tubular structures on EM. Our case was an unusual combination of 2 different pathologically and pathogenically distinct disease entities. To our knowledge this is the first reported case with these unusual manifestations.

TH-PO1120

Fibrillary Glomerulonephritis Presenting as Rapidly Progressive Crescentic Glomerulonephritis
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Introduction: Fibrillary glomerulonephritis is a rare disease of unclear etiology, known to be associated with malignancy, autoimmune disorders, lymphoplasmacytic disorders and hepatitis C. It is seen in 0.5 to 1.0% of native kidney biopsies.

Case Description: We report a case of a 62 year old Caucasian male veteran who had a past medical history of hepatitis C, hyperlipidemia, s/p coronary bypass, multiple colon polyps s/p colectomy and CKD stage 3. Patient, on a routine follow up appointment, was noted to have rapid worsening of kidney function, with creatinine increase from baseline of 1.4-1.8 up to 3.2 mg/dL. He was also noted to have 24 RBCs per HPF on urine microscopy. Urine protein:creatinine ratio was 4.5. Hepatitis C related membranous glomerulonephritis (GN) was high on the differential list. Hepatitis B and HIV serologies were negative. Complements, cryoglobulins, ANCA and serum protein electrophoresis were within normal limits. Patient underwent kidney biopsy, which showed crescentic GN, with linear pattern immunoglobulin deposition along the GBM (glomerular basement membrane) on light microscopy and immunofluorescence suggestive of anti-GBM disease. However, patient’s anti-GBM titer was negative! Electron microscopy showed thickening of GBM due to fibrillary deposits. Similar fibrillary deposits were also seen in the mesangium, with haphazard distribution of fibrils measuring about 15 nm, consistent with fibrillary GN. Congo red stain for amyloid was negative. Patient was also found to have a 2.8 x 2.5 cm well-circumscribed solid & cystic mass in right kidney on ultrasound, suspicious for renal cell carcinoma (RCC). A fine needle aspiration of the mass yielded cells consistent with RCC.

Discussion: Fibrillary GN is known to be associated with malignancy. It can rarely present clinically as rapidly progressive, crescentic GN, and masquerade as anti-GBM disease on immunofluorescence. Electron microscopy and serologic workup are needed to clinch the definitive diagnosis.

TH-PO1121

Pauci-Immune Necrotizing Crescentic Glomerulonephritis as the First Manifestation of Chronic Lymphocytic Leukemia Relapse
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Introduction: The association between hematological malignancy and auto-immune disease is a well-documented phenomenon. Chronic lymphocytic leukemia (CLL) patients have 5-10% risk of developing autoimmune cytopenias, and a rare subset of these CLL patients express anti-neutrophil cytoplasmic antibodies (ANCA) in the setting of a vasculitis. Here, we present a case of a patient with treated CLL whose relapse was identified by the new diagnosis of ANCA-associated pauci-immune glomerulonephritis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Case Description: A 73-year-old female with history of CLL, status post chemotherapy five years prior, presented with complaints of dyspnea on exertion, fatigue, oral ulcers, hemoptysis, rash, arthralgias, edema, and tea-colored urine for 3 months duration. Exam showed BP 157/94, bibasilar rales and gingival ulcers. Labs showed Hb 5.4g/dL, platelets 113K, WBC 4.6K, S. creatinine 4.4mg/dL. Urinalysis showed 2+ protein, many RBCs and WBCs with granular casts. ANA, anti-PR3 and MPO were strongly positive. Kidney biopsy showed necrotizing crescentic pauci-immune glomerulonephritis in more than 50% of glomeruli. Taking into consideration the patient's prior history of CLL, bone marrow biopsy was performed and showed scattered nodular lymphoid proliferation with flow cytometry confirming relapse of CLL. Given this finding, our patient was treated on the lines of CLL relapse with steroids and rituximab instead of using steroids, cyclophosphamide and plasmapheresis for the treatment of ANCA-associated vasculitis alone.

Discussion: The prevalence of ANCA positivity in CLL patients has been documented to be <2%. In our patient, ANCA-associated pauci-immune glomerulonephritis was the first manifestation of CLL relapse. Discovering CLL relapse mandated a change in the management from the standard treatment of pauci-immune glomerulonephritis to a regimen more appropriate for both conditions. Clinicians should be aware of this rare association of CLL with ANCA-associated vasculitis to choose the most appropriate treatment regimen for these patients.

TH-PO1122

Multiple Recurrences of Anti-GBM Disease: Diagnosis or Treatment Risk Lamya Boujelbane, Patricia Liu, Sana Waheed, Laura J. Maursetter. *Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Introduction: Anti-GBM disease is commonly a monophasic illness. We present a case of a woman who had two recurrences of anti-GBM disease after her initial diagnosis in 2001.

Case Description: 33-year-old woman with history of tobacco use was diagnosed with anti-GBM disease after presenting with hematuria. A renal biopsy showed crescentic glomerulonephritis with linear IF staining for IgG. Serum anti-GBM and anti neutrophilic cytoplasmic antibodies (ANCA) levels were undetectable at diagnosis. Five years later, she presented with dyspnea and hemoptysis. She had a hemoglobin of 8.5 g/dL and a chest x-ray suggestive of diffuse alveolar hemorrhage. Her anti-GBM antibody level was 122 AU/ml. She was treated as a relapse of anti-GBM disease and, her anti-GBM antibody had decreased to 0 AU/ml and she had no hematuria. Now at 47 years of age, she presented with dyspnea. Her chest x-ray demonstrated bilateral perihilar opacities consistent with diffuse alveolar hemorrhage and urinalysis revealed 1+ hemoglobin. Anti-GBM antibody was not detected but she was treated for a presumed anti-GBM disease recurrence. With each recurrence of anti-GBM disease, her symptoms resolved with 7 sessions of plasmapheresis, 3 days of IV methylprednisolone and 6 months of oral cyclophosphamide 2mg/kg/day. Her creatinine remains low at 0.7 mg/dl but she suffered a complication of osteonecrosis of the knee.

Discussion: Relapses are infrequent in anti-GBM disease but have been reported. Our case is unique because the patient had three episodes of presumed anti-GBM disease. Smoking has been linked to recurrent disease and could have been the trigger in this case. It is interesting that our patient had varying presence of circulating anti-GBM antibodies with each recurrence which poses the question of the accuracy of the diagnosis. One possible explanation is that only local antibodies were reactivated by smoke exposure without a systemic antibody production and we may be missing low level recurrences. An important question is whether the risk of exposure to immunosuppression is higher than the risk of repeat biopsy to confirm diagnosis to avoid treatment related complications.

TH-PO1123

Nephrotic Syndrome, Nodular Glomerulosclerosis and Impaired Glucose Tolerance (IGT) – A Case Report Daniel Taiwo Adeneye, Mary C. Mallappallil, Gary R. Briefel. *Nephrology, Down State Medical Center, Brooklyn, NY.*

Introduction: Diabetic nodular glomerulosclerosis is a recognized complication of overt diabetes but is hardly diagnosed in patients with IGT. Diabetic nephropathy (DN) without overt hyperglycemia vindicates other etiological factors. Pathogenesis of DN is poorly understood but the trigger is still hyperglycemia. Advanced DN without overt diabetes is rare and 3 case reports have been published. This is a 48 yr old AA woman who presented with nephrotic syndrome, renal failure, IGT and renal biopsy with nodular glomerulosclerosis.

Case Description: 48 yr old AA woman referred for elevated creatinine and proteinuria. No gestational diabetes, tobacco, etoh and drug use history. BP -164/77mmhg, Pulse 70/min with pedal edema. BMI-28; funduscoply not done. Urine protein 3+ and normal sediments, no cast. UPCr- 6G/G. (FPG)-118mg/Dl; Bun - 42mg/Dl, Creatinine 3.9mg/dl, Albumin 2.4mg/Dl, Total protein- 4.6g/dl, Cholesterol- 278mg/dl, LDL 191mg/Dl. Hepatitis B, C, HIV, ANA, C3,C4, SSA, ANCA, Cryoglobulin, Spép/Upep- negative.USS; kidneys 13/12cm, increased echogenicity. biopsy-glomeruli; 25% globally sclerosed, moderate interstitial fibrosis and tubular atrophy. I/F :negative staining for Igm,igg,iga,lambda,kappa, albumin,c3 and C1q. E/M ;no deposits in glomerular capillary walls or mesangium. GBM;diffuse thickening,focal podocytes effacement and nodular mesangial matrix.

Discussion: Nodular glomerulosclerosis is usually seen in advanced DN with overt diabetes after 15yrs in Type 1 and variable in Type 2. Our patient did not have a prior diagnosis of diabetes. A causal relationship can be established between IGT and DN;nodular glomerulosclerosis found on renal biopsy is usually seen in overt diabetes of long duration. Animal studies have shown that brief postprandial elevation of glucose may trigger renal injury viaTGFb that results in DN. The CKD was advanced and biopsy was undertaken at her insistence even after she was told;it may not impact outcome or treatment.

This was an unexpected learning case that shows that the occurrence of diabetic nephropathy may correlate more with presence and not the intensity or duration of hyperglycemia. Further studies are needed to elucidate this phenomenon.

TH-PO1124

A Case of Catastrophic Antiphospholipid Syndrome Treated with Plasma Exchange Takeyuki Takamura, Fumihiko Furuya, Tetsuharu Oku, Kenichiro Kitamura. *Third Dept of Internal Medicine, Univ of Yamanashi.*

Introduction: Catastrophic antiphospholipid syndrome (CAPS) is characterized by diffuse vascular thrombosis, leading to multiple organ failure within a few days and resulting to poor prognosis. Antiphospholipid syndrome (APS) is an autoimmune thrombotic syndrome with recurrent thrombosis and occurs in both artery and vein, and from large to micro vessels. CAPS is also defined as a fetal variant of APS and develop thrombosis of three different organ systems with histopathologic evidence of multiple small vessel occlusions and high titers of antiphospholipid antibodies. Treatment for CAPS has not been established, and intensive anticoagulation or immunosuppressive therapy is carried out.

Case Description: A 68-year-old female who had been diagnosed as lupus erythematosus and APS complicated with multiple cerebral infarctions and treated with 5 mg of oral prednisolone. After her admission, she developed de novo cerebral infarction and colonic perforation with ischemic enteritis. Following a partial colectomy, she developed gram-negative bacteremia, subsequently, multiple strokes, non-ST elevation myocardial infarction, renal failure, and pathological findings with multiple thrombi. These clinical findings indicated that patient's features were consistent with CAPS. She was maintained with anti-bacterial agent, anticoagulant, and prednisolone. However, since renal failure and anuria had continued, she was treated with plasma exchange (PE) and hemodialysis. Thereafter the volume of urine output was gradually increased and her renal function was recovered.

Discussion: We report a case of CAPS with multiple organ failure and successfully treated with anticoagulant, prednisolone, and PE. The clinical manifestation of CAPS depends on the release of inflammatory cytokines from the affected organs by thrombosis and small vessel occlusion. Our patient's successful course could be attributed to beneficial role of PE through the removal of excessive inflammatory cytokines.

TH-PO1125

Acute HIVAN in a HIV-Naïve Patient During Primary HIV Infection and High Viral Load Amit N. Shah, Adam G. Winkler, Claude Bassil, Donald E. Wheeler, Jacques A. Durr. *Div of Nephrology, Univ of South Florida, Tampa, FL.*

Introduction: A hitherto healthy 42 yo AA male felt chilly 6 days earlier. He took a NyQuil and skipped next day's shift for body aches/GI cramps. He improved but again felt bad by HS, 48h later. Next AM in a local ER, his UA showed WBC/RBC, 3+ protein, and a SG of 1.030. Physical exam, chest X-ray, contrast abdominal CT, and eGFR, were normal. He improved and worked full capacity again, but got admitted 48h later after a brief syncope.

Case Description: Vital signs: T 103 °F, BP 100/60 mm Hg, and HR 76 bpm. He had transient mild diarrhea. Serum albumin (Alb) was 2.1 g/dl, creatinine (cr) 2 mg/dl, and WBC 3•103/ml. UA had WBC/RBC and >0.5 g/dl protein. UNa was 21 mmol/l. His urine protein was >12 g/24h. CRP was >2 (<0.5 ng/dl), and ESR 50 mm/h. CPK was 8717 U/l and < half by 48h. Hep B, C, and HIV-1/2 Ab screens were (-), but (+) for HIV p24 Ag. He had >3•106 HIV copies/ml, and 213 CD4+ cells/ml. US showed normal-sized kidneys, no obstruction, but some cortical echogenicity.

His cr first improved for 72h, but then rose to >8 mg/dl in 1w. Dialysis and HAART were initiated. By then he had edema and Alb was

1.2 g/dl. Renal biopsy showed collapsing GN, podocyte hypertrophy/hyperplasia, microcystic tubular dilatations, 3+ acute tubular injury, 2+ patchy (mostly lymphocytic) infiltrate with focal tubulitis, and no signs of chronicity. Prednisone was added. He seroconverted (HIV-1) 2w after his first chills.

Discussion: Of the case reports of primary renal HIV infection only 2 had biopsy-proven HIVAN. One was HIV Ab (-) but had 700,000 HIV copies/ml (Levin ML et al. 2001); the other was HIV Ab (+) by EIA but not by Western blot, and had 70,000 HIV copies/ml (Szabo S et al. 2002). Both had advanced RF and already other infections. Our patient had normal eGFR until his acute HIV infection. The high HIV Ag load alone, not replication, is the sole likely cause for HIVAN, consistent with the view that a direct toxic effect of some HIV gene product causes podocyte dedifferentiation, since viral particle endocytosis readily occurs in podocytes (as their normal filter cleaning role?), but lack of HIV entry receptors precludes local replication (Khatua AK et al. 2010).

FR-PO001

A Case of Hypercalcemia with Renal Failure: Renal Sarcoid?

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Introduction: Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by noncaseating granulomas in involved organs. Renal involvement occurs in 35-50%, manifested by hypercalciuria, hypercalcemia, nephrocalcinosis, and nephrolithiasis. Granulomatous interstitial nephritis is the most typical histological finding, usually in the setting of systemic disease and rarely in the absence of extrarenal sarcoid.

Case Description: A 54 y/o male presented with AKI superimposed on CKD and severe hypercalcemia (Calcium 13.5mg/dl, Cai=1.7mmol/L, creatinine=7.59mg/dl). Six months prior he had a kidney stone removed at which time his creatinine was 2.4mg/dl with Ca=11 but no further work up was performed. He was taking no medications and complained of back pain. Physical exam was unremarkable. A CT scan was negative for nephrolithiasis or hydronephrosis, chest X-ray revealed no abnormality. He was aggressively treated with IV NS and then Lasix with minimal improvement in the creatinine or the serum calcium. Work up for hypercalcemia included normal serum and urine immunofixation, negative PPD, normal PSA and normal skeletal survey. 25 Hydroxyvitamin D 27.8ng/ml (30-95ng/mL), PTH suppressed at <3pg/ml, total 1, 25 Hydroxyvitamin D 79pg/ml (18-72pg/mL), and Angiotensin Converting enzyme 82 (9-67U/L). A formal ophthalmologic exam and PFTs were normal. A diagnostic kidney biopsy was performed.

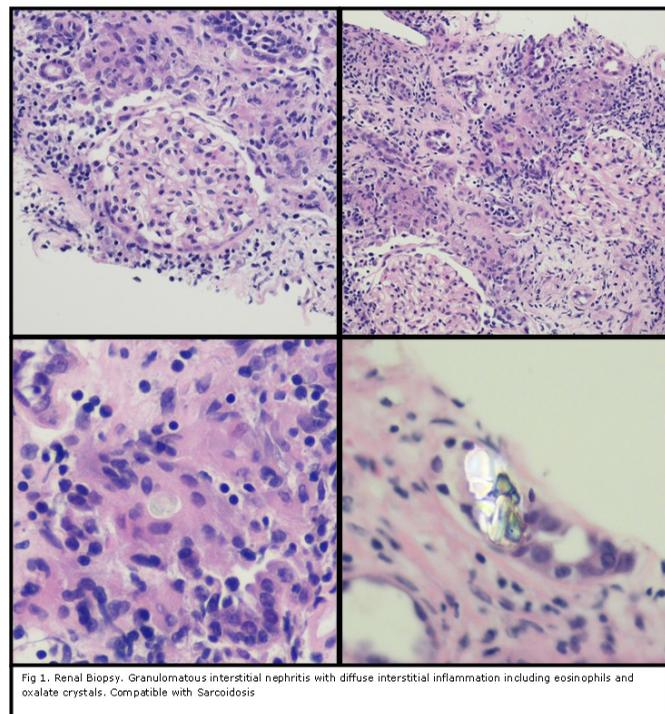


Fig 1. Renal Biopsy. Granulomatous interstitial nephritis with diffuse interstitial inflammation including eosinophils and oxalate crystals. Compatible with Sarcoidosis

Discussion: The diagnosis of sarcoid interstitial nephritis was strongly suggested by the renal biopsy given that other causes of granulomatosis were ruled out. The patient was started on prednisone 60mg/d with rapid resolution of the hypercalcemia and slow improvement in renal function (Creatinine 2.9mg/dl). A slow steroid taper over 1 year is planned.

FR-PO002

Pediatric Chronic Refractory SIADH: Use of Tolvaptan Cristin Kaspar, Nianzhou Xiao, Timothy E. Bunchman, Megan M. Lo. *Pediatric Nephrology, Children's Hospital of Richmond at Virginia Commonwealth Univ, Richmond, VA.*

Introduction: The syndrome of inappropriate antidiuretic hormone (SIADH) is the most common cause of euvolemic hyponatremia in hospitalized patients, and standard therapies can be limited in their effectiveness. Arginine vasopressin receptor antagonists (AVR-A) oral tolvaptan and intravenous conivaptan have been FDA approved in adults, but reports on long-term use in pediatrics are lacking. We report on the dosing and safety of chronic AVR-A treatment in two patients with chronic SIADH. Dosing regimen was extrapolated from current pediatric and adult literature.

Case Description: Case A is a 13 year old, 43.5 kg female with a 12-year history of pituitary astrocytoma treated with an experimental chemotherapy agent. She developed chronic refractory SIADH and was treated with IV conivaptan load and continuous infusion of 0.2-0.5 mg/kg/day, discontinued after 74 hours. Oral tolvaptan for outpatient treatment was then started at 0.7 mg/kg/day (15 mg twice daily) which induced nausea and thirst but [Na⁺] rose only to 129 mmol/L. Dosage was titrated and weaned off after 82 days. Case B is a 13 year old, 47.3 kg female who developed refractory SIADH as her initial presentation

of an olfactory neuroblastoma. She was treated with conivaptan load and infusion of 0.2 mg/kg/day, titrated off after 32 hours. She received tolvaptan starting at 0.15 mg/kg/day and discontinued once the mass was excised after 27 days.

Discussion: Stable tolvaptan dosing was reached at 0.15-0.3 mg/kg/day (7.5 mg daily or twice daily) and weaned to 0.08 mg/kg (3.5 mg) daily or every other day before being discontinued in both patients. Case B had elevation of serum creatinine when on IV conivaptan and fluid restriction. Neither patient had complications of hypokalemia, hyponatremia, or liver dysfunction. Both patients required frequent monitoring of serum sodium and regular titration of dose and oral fluid intake. We recommend starting tolvaptan at 0.15-0.3 mg/kg/day. The use of tolvaptan in an outpatient setting for chronic hyponatremia is safe and effective in adolescent patients with close monitoring.

FR-PO003

Methylmalonic Acidemia: An Unexpected Consult for an Adult Nephrologist: A Case Report Yogita Lakhera, Seyed-ali Sadjadi. *Nephrology, JI Pettis VA Medical Center, Loma Linda Univ School of Medicine, Loma Linda, CA.*

Introduction: Organic acidemias are caused by deficiencies of enzymes involved in the breakdown pathways of amino acids, fatty acids and carbohydrate metabolism. Methylmalonic acidemia (MMA) is a heterogeneous group of disorders of impaired metabolism of methylmalonic acid. We present a patient with MMA who was admitted with severe metabolic acidosis.

Case Description: A 21 year old male with past medical history of end stage renal disease on peritoneal dialysis, chronic pancreatitis, diabetes mellitus and coeliac disease presented to emergency room with diarrhea. He denied fever, abdominal pain and vomiting. He was hypotensive. Laboratory tests showed metabolic acidosis with anion gap of 33 mMol/L and absence of leukocytosis. Arterial blood gas result was, pH:7.38, pCO₂:18 mmHg, paO₂: 108 mmHg and HCO₃: 10 mMol/L. Patient was kept NPO and acidosis worsened the next day.

Labs (mMol/L)	Day 1	Day 2	Day of discharge
Na	144	156	133
K	3.9	2.5	3.9
Cl	96	104	89
CO ₂	15	5	22
Lacate	8.2	20.4	5.5

Initial treatment included fluid boluses with NS, bicarbonate drip and broad-spectrum antibiotics for suspected sepsis. Further history revealed that patient had MMA and then iv fluid was changed to D20NS with insulin drip. He was started on special formula feed for MMA. Daily peritoneal dialysis was continued. Serum ammonia, β-hydroxybutyrate and lipase levels were normal. Blood and stool cultures grew salmonella enteritidis and antibiotics were switched to iv ciprofloxacin and metronidazole. With assistance from metabolic specialist, nephrologist and endocrinologist, patient was treated successfully.

Discussion: MMA is a rare autosomal recessive disorder (incidence of 1:48,000), caused by deficiency of methylmalonyl-CoA mutase or its cofactor, cobalamin. It is associated with anion gap metabolic acidosis, hypoglycemia, ketonuria and hyperammonemia. Metabolic decompensation can occur during episodes of increased catabolism such as prolonged fasting. Treatment of acute illness includes, providing hydration with high caloric supplementation, stopping all protein intake for 1-2 days and reintroduction of a low protein diet later. Severe acidosis may require dialysis.

FR-PO004

Congenital Pituitary Stalk Interruption Syndrome (PSIS) Newly Diagnosed in Case of Hyponatremia in the Elderly Kenji Kajitani, Takahito Ito, Kaori Takaori, Yoko Tomiyama, Ikue Nagayama, Masafumi Yamato, Akira Wada, Hirotsugu Iwatani. *Nephrology, Osaka National Hospital, Osaka, Japan.*

Introduction: There are many diseases that cause hyponatremia. Among them, adrenal insufficiency (AI) is important due to its urgency. We present an extremely rare case of elderly-onset AI in congenital PSIS, which is highly suggestive of the mechanism of AI progression.

Case Description: A hyponatremic episode (Na 117 mEq/L) occurred in a 76 year-old Japanese man in conjunction with common cold. Laboratory analyses revealed a low serum cortisol level. He was short-statured, had no hair growth on his axilla and pubis, and had unusual pale pigmentation in skin. He presented with gynecomastia and micropenis. CT scan revealed anorchism. He was not mentally retarded. Serum hormonal analyses showed AI, hypothyroidism, growth hormone deficiency, hypogonadism and hyperprolactinemia. A set of CRH/TRH/GHRH/LHRH stimulation test disclosed hypothalamic panhypopituitarism. Brain MRI visualized severely pressed 2-mm thick pituitary, but not the pituitary stalk, indicating PSIS.

Discussion: We concluded that his PSIS was not an acquired but a congenital anomaly based on his episode of intrauterine growth retardation and anorchism in the light of embryology. In PSIS patients, the functions of pituitary are sometimes maintained even if partially, although hypophyseal portal vessel snaps apart. This is because hypothalamic hormones reach pituitary through the superior hypophyseal artery (SHA), the nutrient artery of both hypothalamus and pituitary. In this case, the echogram of the internal carotid artery, from which SHA branches showed severe atherosclerosis. We speculate that the progression of atherosclerotic changes impaired the blood flow of SHA and then decreased

the delivery of hypothalamic hormones to pituitary, resulting in elderly-onset AI. Thus, blood flow disturbance of SHA can induce AI in PSIS. In conclusion, a congenital disorder can be the cause for elderly-onset adrenal insufficiency. This case suggests that pituitary stalk interruption syndrome should be taken into account as a differential diagnosis for hyponatremia, even in the elderly, especially in short-statured patients.

FR-PO005

A Family Case of Hypoparathyroidism, Deafness, and Renal Dysplasia Syndrome with a Novel Mutation of GATA3 Tomoo Yabuuchi,¹ Shoichiro Kanda,¹ Naoya Morisada,² Keiichi Takizawa,¹ Yuji Tomii,¹ Naoto Kaneko,¹ Hirota Hama,¹ Eiji Nakano,¹ Norimasa Tada,¹ Kiyonobu Ishizuka,¹ Hiroko Chikamoto,¹ Yuko Akioka,¹ Kazumoto Iijima,² Motoshi Hattori.¹ ¹Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Shinjyuku-Ku, Tokyo, Japan; ²Dept of Pediatrics, Kobe Univ Graduate School of Medicine, Chuo-ku, Kobe, Japan.

Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT), a major cause of end-stage renal disease in children, often present as a systemic disorder with extrarenal symptoms. Extrarenal symptoms and family history are helpful in the genetic diagnosis of CAKUT. We report here a family case of hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome with a novel mutation of *GATA3*.

Case Description: Soon after birth, a female patient was diagnosed as having bilateral cystic dysplastic kidneys by renal ultrasonography. She also had hearing impairment at the infancy. She received peritoneal dialysis at the age of 3 years and received a cadaveric kidney transplant at the age of 10 years. When she was 14 years old, she visited the emergency department because of acute abdomen. Detailed examinations showed hematometra associated with vaginal atresia. Branchio-oto-renal syndrome was considered as her diagnosis based on her hearing impairment, bilateral cystic dysplastic kidneys, and normocalcemia. However, we suspected that she had an HDR syndrome because we found that her mother had hypoparathyroidism after determining a detailed family history. Genetic analysis was approved by the central ethics board of Tokyo Women's Medical University and Kobe University. This analysis showed a novel mutation, c. 1013G>T (C338F) of *GATA3*, the causative gene for HDR syndrome.

Discussion: Our patient did not show any symptoms of hypoparathyroidism. However, based on the family history, we performed a genetic analysis and found a novel mutation of *GATA3*. She was then diagnosed with atypical HDR syndrome. Therefore, determining a detailed family history is important in the precise diagnosis of CAKUT patients.

FR-PO006

Hypocomplementemic Urticarial Vasculitis Syndrome Resistant to Corticosteroid and Plasma Exchange Therapy Yasuhiro Kawai,¹ Kenji Ueki,¹ Yuta Matsukuma,¹ Hiroto Hiyamuta,¹ Akihiro Tsuchimoto,¹ Kiichiro Fujisaki,¹ Kumiko Torisu,¹ Kosuke Masutani,¹ Kazuhiko Tsuruya,² Takanari Kitazono.¹ ¹Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka City, Japan; ²Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ, Fukuoka City, Japan.

Introduction: We present a case of HUVS resistant to corticosteroid and plasma exchange.

Case Description: A 36-year-old Japanese man with the history of diffuse pan-bronchiolitis developed microscopic hematuria, proteinuria, and kidney dysfunction. Percutaneous kidney biopsy was performed at the other hospital, and the diagnosis was non-IgA mesangial proliferative glomerulonephritis. In spite of the administration of angiotensin II receptor blocker, progressive kidney dysfunction was evident. Then he was transferred to our hospital 4 months later. He also had a history of urticarial rash on his leg, and pigmentation was evident at the time of transfer. Urinalysis revealed 3+ proteinuria and 3+ hematuria, and urinary sediment showed red blood cells of 50-99/high power field. Urinary protein/creatinine (Cr) ratio was 2.9 g/gCr. Blood tests revealed a serum Cr level of 2.4 mg/dL, complement (C) 3 level 18 mg/dL, and C4 level 23 mg/dL. We performed kidney biopsy again, and found membranoproliferative glomerulonephritis with crescents. Since additional blood test revealed serum anti-C1q antibodies of 51,965 U/mL, the diagnosis of HUVS was made. We treated him with methylprednisolone pulse therapy followed by oral prednisolone, but his kidney function was unchanged and he developed bacterial pneumonia. Next, we added plasma exchange, and found a temporal decrease in proteinuria accompanied by a decrease of serum anti-C1q antibody level. But his kidney function did not recover, and the level of anti-C1q antibody raised again.

Discussion: HUVS is a small vessel vasculitis associated with recurrent urticarial rash, hypocomplementemia, and anti-C1q antibodies. Safe and effective treatment for HUVS has not been established. Although corticosteroid and plasma exchange showed temporal efficacy, it was impossible to suppress the progressive kidney dysfunction in this case.

FR-PO007

Acquired Fanconi Syndrome in a Patient with Acetaminophen Overdose Deepak Jasuja, Jay B. Wish. *Div of Nephrology, Indiana Univ, Indianapolis, IN.*

Introduction: Acquired Fanconi syndrome is described in patients receiving antiretrovirals, aminoglycosides, platinum compounds and with proximal tubulopathies due to light chain disease/paraneoplasias. We describe a case of acetaminophen induced acute tubular necrosis (ATN) presenting as Fanconi syndrome with hypophosphatemia, normoglycemic-glucosuria, aminoaciduria, and uric acid, potassium and bicarbonate wasting.

Case Description: A 35 year old woman with borderline personality disorder, depression, alcohol abuse, multiple suicide attempts, and previous acetaminophen overdose was transferred from outside hospital with fulminant hepatic failure secondary to acetaminophen poisoning. Nephrology was consulted for metabolic acidosis and AKI. On exam she was oriented to person only and following minimal commands. She had acute fulminant hepatic failure as evidenced by transaminase elevations, encephalopathy, and coagulopathy. On presentation her serum creatinine was 2.95 which rose over the next 3 days to 9.06. Initial blood gas was consistent with metabolic acidosis and respiratory compensation. Serum potassium (K) was low (2.9-3.5) despite large doses of K supplements. Her K requirements abated when bicarbonate supplementation was discontinued. Acetaminophen level was elevated on transfer at 21 and urine drug screen was positive for opiates and benzodiazepines; toxic alcohols were negative. Serum uric acid was <1.5 mg/dL and phosphorus <1 mg/dL. Glucose was 1-2+ on urinalysis with normal blood glucose. The following amino acids were elevated in her urine: aspartic acid, beta alanine, citrulline, gamma amino acid butyric acid, glutamic acid, leucine, ornithine, proline, taurine and valine. This was a non-specific pattern of generalized aminoaciduria consistent with proximal tubulopathy and acquired Fanconi syndrome. The patient subsequently recovered renal function and the proximal tubulopathy resolved.

Discussion: It is important for nephrologists to be aware that ATN (in this case acetaminophen induced) can lead to acquired Fanconi syndrome and proximal tubulopathy which seem to resolve as ATN resolves. Aggressive treatment with bicarbonate supplements can exacerbate urinary K wasting and should be avoided.

FR-PO008

Spontaneous Remission of Non-Parasitic Chyluria Hillel Sternlicht,¹ Lakshmi V. Ramanathan,² Martin Fleisher,² Edgar A. Jaimes,² Ilya Glezerman.² ¹Div of Nephrology and Hypertension, Weill Cornell Medical Center, New York, NY; ²Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

Introduction: Chyluria is a medical condition characterized by the presence of chyle in the urine. The disease is most prevalent in South East Asian countries mostly caused by parasitic (*Wuchereria bancrofti*) infections. Chyluria presents as a cloudy milk-colored urine accompanied by systemic symptoms such as weight loss, fatigue, and rarely, flank pain from retained clots.

Case Description: A 72 year-old woman presented to Nephrology clinic complaining of milky urine (Figure 1) and painless hematuria with clots for two months as well as twenty-pound weight loss. Physical exam was unremarkable. Cystoscopy and urine cytology were unremarkable. Serum albumin was 3.2 g/dL. A urinalysis showed 3+ protein and 50 red blood cells per HPF. Urine sediment had no dysmorphic cells or casts. A 24-hour urine collection revealed 8.8 grams of protein. Chyluria screen was positive for chylomicrons and triglycerides. Midnight blood smears were negative for filarial parasites. Urine culture was negative for mycobacteria or schistosomes. Serologic studies including IgG western blot for cysticercus and IgG ELISA for filariasis were negative. The rapid plasma reagin (RPR) was also negative. Imaging for a lymphatic leak by lymphoscintigraphy was unrevealing. The patient was managed conservatively and underwent spontaneous remission with disappearance of chyluria several months of her initial diagnosis.



Discussion: The most common cause of chyluria is parasitic infection with granulomatous diseases or structural etiologies less frequently encountered. Sclerotherapy of the renal pelvis is the definitive treatment. Idiopathic chyluria as shown in this case is rare. Conservative management of idiopathic disease may be warranted due to the possibility of spontaneous remission.

FR-PO009

Rebound Hypertension and Hypokalemia After Stopping Drospirenone Kalyani Chandra, Shubha Ananthkrishnan. *Nephrology, UC Davis Medical Center, Sacramento, CA.*

Introduction: Drospirenone is the fourth generation oral contraceptive with antimineralocorticoid effects, which are reported to be generally mild. There have been several warnings issued for drospirenone, in relation to adrenal insufficiency and hyperkalemia. But, no reports thus far of the rebound effects like hypertension (HTN) and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

hypokalemia, following the discontinuation of the medication, especially after prolonged use. Review of literature, to our best knowledge, suggests this to be the first case report demonstrating the association between HTN, hypokalemia and drospirenone.

Case Description: A 54 year-old Indian woman, previously normotensive, noted a new rise in home BP to 200/100 mm Hg and presented to the emergency department, where she was also noted to have mild hypokalemia to 3.1 mg/dL. Given the rather new onset of severe HTN and hypokalemia, work-up for secondary causes of HTN was done, which revealed normal aldosterone level (9 ng/dL), low plasma renin activity (PRA) (0.15 ng/mL/hr) and high aldosterone/PRA ratio (60). Looking back into her history, it was noted that, the timing of symptoms was closely related to discontinuing Yasmin® (30 µg ethinyl estradiol and 3 mg drospirenone), which she was taking for over 6 yrs. She was thought to have rebound effect with relatively excess mineralocorticoid activity, precipitated by the abrupt discontinuation of drospirenone. With the introduction of low dose spironolactone, her symptoms significantly improved.

Discussion: Drospirenone (an analogue of spironolactone), which has antiminerocorticoid and antiandrogenic activities similar to endogenous progesterone, counteracts the estrogen-mediated stimulation of the renin-angiotensin-aldosterone system (RAAS). Due to these effects, it has the potential to decrease blood pressure and also cause hyperkalemia. At a dosage that suppresses ovulation, drospirenone induces mild natriuresis, which is followed by compensatory stimulation of the RAAS (comparable to a low sodium diet). When the prolonged ongoing suppression for the RAAS is removed, there might be a potential rebound effect with (relatively) high aldosterone state, resulting in sodium retention, leading to HTN. Spironolactone appears to be useful in this situation.

FR-PO010

Acthar Induced Hypokalemic Metabolic Alkalosis Imran Quyyum, Neil W. Lyman. *Dept of Nephrology, St. Barnabas Medical Center, Livingston, NJ.*

Introduction: Acthar, an ACTH formulation from porcine pituitary gland, is an effective therapy for Membranous Nephropathy (MN). A rare adverse effect of hypokalemic alkalosis has been described in infants only. We present a case report of an 84 y/o Caucasian female who developed severe hypokalemia and metabolic alkalosis with Acthar therapy and concomitant diuretic use.

Case Description: The patient presented with severe bilateral leg edema. Lower extremity doppler was negative for DVT. Echo revealed normal EF. UA showed 4+ protein and 2+ blood. Spot protein/creatinine ratio was 20g. Urine sediment had no RBC casts. Her scr was 1.99 mg/dL (baseline 1.34 mg/dL). Albumin was 2.3 g/dL. Workup for malignancy was negative. Her serologies were unremarkable and a renal ultrasound was negative. Anti-PLA2 Ab was positive. Renal biopsy was consistent with MN. Acthar therapy was preferred due to her advanced age. Acthar 80 units 2x/week was added to her regimen of furosemide, amiloride, losartan and hydrochlorothiazide. Protein excretion decreased from 20g to 5g. Scr and albumin improved to 1.16 mg/dL and 3.4 g/dL, respectively. Follow up labs revealed potassium of 2.1 mmol/L and serum bicarbonate of 40 mmol/L. Acthar and diuretics were held and K+ was repleted. Acthar at 40 units 2x/week was later restarted due to worsening renal function and proteinuria. However, patient was readmitted three weeks later with K+ of 2.3 mmol/L and bicarbonate of 35 mmol/L which prompted termination of Acthar. She currently remained in partial remission with less than 5g of proteinuria.

Discussion: ACTH increases endogenous steroid production via MelanoCortin Receptor (MCR) type 2. It also exerts direct beneficial effects on podocytes and glomerular cells via other MCR subtypes. ACTH is an effective, alternative therapeutic modality for MN as well as other causes of nephrotic syndrome. Importantly as our case report demonstrated, the concomitant use of ACTH and diuretic therapy can result in severe hypokalemic metabolic alkalosis. Clinicians should closely monitor serum electrolytes after initiating Acthar.

FR-PO011

Polycythemia in a Patient with Bartter's Syndrome and Medullary Nephrocalcinosis Girlie Singian Merdegia. *Medicine, Philippine General Hospital, Manila, Metro Manila, Philippines.*

Introduction: Bartter's syndrome is a tubular salt wasting disorder presenting with severe hypokalemic alkalosis, hypochloremia, and hyperreninemia with normal blood pressure. Medullary nephrocalcinosis in this disorder is an infrequent finding and is still generally unrecognized. Polycythemia is an unusual presentation in patients with renal diseases, but has been described in literature among patients with nephrotic syndrome and distal tubular acidosis. It is noteworthy, however, that reports on secondary erythrocytosis among patients with Bartter's syndrome is lacking. The exact mechanism for the polycythemia is still uncertain, although postulates include hypoxia induced by nephrocalcinosis causes stimulation of oxygen receptors thus increasing erythropoietin secretion, and stimulation of prostaglandin production may be contributory.

Case Description: A 27 year old Filipino male with recurrent bouts of severe hypokalemia since childhood presenting as bilateral lower extremity weakness necessitating recurrent hospital admissions was diagnosed with Bartter's syndrome based on metabolic alkalosis, hypokalemia, hypochloremia, slight hyponatremia with normal serum calcium and magnesium levels. He had normal blood pressure and no frank hypercalcemia. His creatinine was elevated at baseline and his ultrasound revealed normal sized kidneys with bilateral nephrocalcinosis. He has elevated hemoglobin of 190 g/L, slight leukocytosis with no thrombocytosis. JAK2 mutation was negative and a bone marrow biopsy revealed mildly hypercellular marrow with trilineage hematopoiesis, mild plasmacytosis for which polycythemia vera was ruled out. Findings were said to be consistent with a reactive marrow. He underwent as needed phlebotomy and was maintained on potassium replacement, spironolactone and an ace-inhibitor.

Discussion: The association of Bartter's syndrome with medullary calcinosis and secondary erythrocytosis is a rare entity with very limited data in literature. The mechanism leading to secondary erythrocytosis, as well as nephrocalcinosis among patients with Bartter's syndrome remains uncertain. Clinicians should be aware of potential complications of this disorder so as to institute appropriate management.

FR-PO012

Homozygous Deletion of CFHR3-CFHR1 as a Cause for Atypical Hemolytic Uremic Syndrome in a Patient with Systemic Lupus Erythematosus Salem Almaani,¹ Tibor Nadasdy,² Samir Parikh.¹ ¹Div of Nephrology, The Ohio State Univ, Columbus, OH; ²Dept of Pathology, The Ohio State Univ, Columbus, OH.

Introduction: Thrombotic microangiopathy (TMA) is a rare but devastating condition associated with systemic lupus erythematosus (SLE). In SLE, renal TMA is typically associated with the anti-phospholipid syndrome (APS) or TTP. Here we report a case of atypical hemolytic uremic syndrome (aHUS) associated with SLE that was confirmed by complement genetic studies and treated successfully with Eculizumab.

Case Description: A 21 year old African American female with a history of SLE and class II+V lupus nephritis was hospitalized after presenting with AKI, thrombocytopenia (TCP), and a microangiopathic hemolytic anemia (MAHA). Initial lab values revealed a serum creatinine of 3.5 mg/dl, platelet count of 58, hemoglobin of 7.3, and LDH of 1484. Plasmapheresis and IV solumedrol was started empirically for presumed TTP and SLE flare. ADAMTS13 enzyme activity was normal and APS antibodies were negative. There was no improvement and the patient was started on dialysis. The patient required multiple blood transfusions as TCP and MAHA persisted. A kidney biopsy was performed and findings were consistent with severe TMA. The patient was empirically started on Eculizumab and after the first dose, TCP improved rapidly, with a platelet counts increase from 77K of 170K. Complement mutation studies were obtained and revealed a homozygous deletion of CFHR3-CFHR1 genes. The patient continued on Eculizumab, and after 4 months she recovered renal function and was liberated from dialysis.

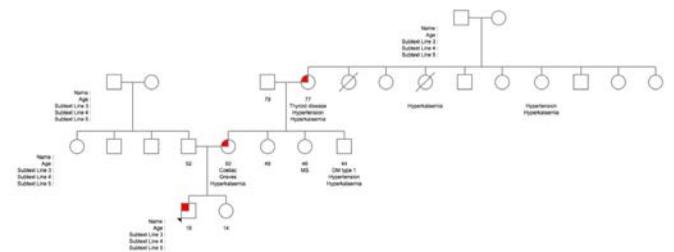
Discussion: This is the first report of aHUS associated with SLE in a patient with an identified complement mutation. Our patient had a homozygous deletion of CFHR3-CFHR1, which has previously been linked to aHUS. CFHR3-CFHR1-deficient plasma is thought to contribute to defective regulation of complement activation on the cell surface and occurs despite the presence of normal factor H and I levels. Treatment with Eculizumab is effective and should be started promptly so disease can be halted and chronic damage limited.

FR-PO013

A Novel Mutation in KLHL3 Gene Causes Familial Hyperkalemic Hypertension Mohd Radzi Rodzlan Akib,¹ Dearbhla Kelly,¹ Xavier Jeunemaitre,² Catherine A. Wall.¹ ¹Nephrology, Adelaide & Meath Hospital, Dublin, Ireland; ²Département de Génétique et Centre de Maladies Vasculaires Rares Hôpital Européen Georges Pompidou, Paris, France.

Introduction: Familial hyperkalemic hypertension is an autosomal dominant disorder where mutations in the regulators of the thiazide-sensitive NaCl co-transporter (NCC) cause salt-dependent hypertension. Implicated genes include WNK1, WNK4, KLHL3 and CUL3. These lead to increased activity of the NCC in the distal nephron, excessive chloride and sodium reabsorption, and volume expansion. We describe a novel disease-causing variant in KLHL3 not previously reported in the literature.

Case Description: An 18 year-old man with no prior medical history presented with an incidental finding of serum potassium of 7.3mmol/L. He was hypertensive with blood pressure 150/90mmHg. His mother, maternal uncle and grandmother also had a history of early onset hypertension and unexplained hyperkalemia.



His labs showed serum sodium 139mmol/L, chloride 103mmol/L, creatinine 83mmol/L. His arterial blood pH was 7.37 with bicarbonate 21. His plasma renin activity was suppressed at 0.2ng/ml/H and his serum aldosterone was raised at 534.4pmol/L. The transtubular potassium gradient was 3.87. Genetic analysis of the patient and affected family members revealed a missense mutation affecting exon 13 of the gene KLHL3 (c.1492C>T p.His498Tyr) affecting a residue located in the 5th kelch motif of the protein. The patient was treated with dietary salt restriction and a thiazide diuretic.

Discussion: This man illustrates classic findings in familial hyperkalemic hypertension including hypertension, hyperkalemia, metabolic acidosis and positive family history. Cases such as this give us further insight into the molecular pathophysiology of blood pressure control. KLHL3 gene products play a key regulatory role in distal nephron Na reabsorption and may have potential as anti-hypertensive drug targets.

FR-PO014

Renal Failure Run A-FUOwl: Disseminated Histoplasmosis Eileen Smith, Rajeev Raghavan, Sreedhar A. Mandayam. *Baylor College of Medicine, Houston, TX.*

Introduction: In patients with fever of unknown origin (FUO) and glomerulonephritis, *Histoplasma capsulatum* should be considered.

Case Description: A 37-year-old man presented to the hospital with 3 weeks of fatigue, 15-pound weight loss, intermittent chest pain, dyspnea on exertion and 3 day history of erythematous pruritic rash on his neck. PMH included congenital aortic stenosis with AVR, complicated by endocarditis requiring repeat AVR. Physical exam found splenomegaly and a lacy erythematous rash on the neck and torso. On admission, creatinine was 3.15 mg/dL (baseline 1mg/dL last year) with gross hematuria, and new pancytopenia. Initial work-up for glomerular disease was non-diagnostic. He developed persistent cyclical fevers to 102°F during his hospital stay. Blood cultures, tagged WBC scan and TEE were negative. Kidney biopsy showed numerous electron-dense deposits suggestive of Membrano-Proliferative Glomerulonephritis with active interstitial inflammation. Further history revealed the patient regularly cleaned a chicken coop. An infectious work-up found the patient to be strongly positive for the *Histoplasma capsulatum* urinary antigen. With itraconazole for histoplasmosis and concomitant steroid therapy for glomerulonephritis, he defervesced and his creatinine improved to 1.4 mg/dL.

Discussion: Infection Related Glomerulonephritis (IRGN) is an immune-mediated disease caused by non-renal pathogens. The incidence is higher in developing countries: for example, per 100,000 individuals, the incidence of cases per year is 39 in India and 0.78 in the United States. It is believed that sub-clinical IRGN is common and underdiagnosed. In a study of 1012 kidney biopsies, 10% had evidence of disease, such as subepithelial humps. Hematuria is present in > 80% of cases, and patients usually present with Nephritic Syndrome. Endemic mycoses as a cause of glomerular disease in humans are rare. An infection due to *H. capsulatum* can result from inhalation of aerosolized spores after disruption of chicken droppings harboring the fungus. We suspected endocarditis given his cardiac history, and kidney biopsy findings also supported infection. However, the splenomegaly, FUO, and exposure to fowls (FUOWs) established the diagnosis.

FR-PO015

Next Generation Sequencer Driven Exome Analyses Identified a MCKD1 Family with New Mutation Before VNTR Of MUC1 DNA Sequence, Suffering from Mucosal Dysfunctions Satoko Yamamoto,² Jun-Ya Kaimori,¹ Masaki Hatanaka,² Naotsugu Ichimaru,¹ Shiro Takahara,¹ Hiromi Rakugi,² Yoshitaka Isaka.² *¹Dept of Advanced Technology of Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; ²Dept of Geriatrics & Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.*

Introduction: Hereditary tubulo-interstitial nephritis (h-TIN) is characterized by family history, bland urine, normal size kidney, hyperuricemia, renal fibrosis and gradual renal function loss. MCKD1 type h-TIN is also recognized by the difficulty to identify mutant sequence by conventional Sanger Sequencer or next generation sequencer, because the cytosine insertion mutation locates in the GC rich valuable number tandem repeat (VNTR) region. The mutant MUC1 DNA sequence is supposed to produce truncated type protein, which is inhibited to be trafficked to the cell membrane. Because of the difficulty of identification, there may be lots of unknown symptoms in MDCK1.

Case Description: We identified 5 hereditary TIN patients in a family, three of those are renal transplant recipients, one is under dialysis, and the other was CKD. The CKD patient is 23 y.o female, whose renal function is gradually reducing for 10 years. Now her serum creatinin is over 3. Her renal MRI images showed normal size kidneys with no cysts. The patients are suffering from mucosal dysfunctions including GI ulcer, sinusitis, and dysphagia. We analyzed genome DNA sequence of hereditary TIN family by next generation sequencer driven trio exome analyses. They revealed that the 2 bp deletion mutation were located before VNTR. Interestingly, consequently produced mutant MUC1 protein is a truncated protein with almost the same a.a. sequence repeats with previously reported mutant protein. The results were confirmed in the further analyses of other family members by conventional Sanger sequencer.

Discussion: We could identified the totally new mutation sequence of MDCK1 family, because it located before the GC rich VNTR sequence of MUC1. The newly identified mutant protein showed the almost same a.a. repeats sequence, suggesting these repeat sequence is implicated in the pathophysiology of MDCK1 type h-TIN.

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FR-PO016

Propofol-Induced Hyperkalemia in a Hemodialysis Patient Ibrahim M. El-Ali, Chandana Shekar, Sarthak Virmani, Ruchir D. Trivedi. *Dept of Medicine, Div of Nephrology, Univ of Connecticut Health Center, Farmington, CT.*

Introduction: Propofol induced hyperkalemia and propofol infusion syndrome are well described in the intensive care literature. Propofol induced sudden cardiac arrest, however, may be under recognized. We report a case in which a large bolus of propofol was associated with an acute increase in serum K⁺ precipitating potentially fatal cardiac arrhythmia.

Case Description: 59 y/o male on maintenance hemodialysis (HD), having missed 2 HD sessions, presented with altered mental status and hyperkalemia. Patient required intubation for airway protection. Serum K⁺ was 8.2 mEq/L and confirmed with repeat of 8.8 mEq/L. Propofol bolus was used as premedication for intubation followed by infusion at 20 mcg/kg/min. Ventricular fibrillation and cardiac arrest ensued soon after propofol bolus. Patient was managed with repeated calcium chloride bolus totaling 10 grams and

urgent hemodialysis. Post-HD Serum K⁺ level was 4.5 mEq/L. Repeat K⁺ 10 hours after HD, with no other parameters being changed, was 7.1 mEq/L, increasing to 7.9 mEq/L within the next hour. Cardiac monitor showed widening QRS interval. No concurrent evidence of hemolysis, DIC or rhabdomyolysis. No exogenous K⁺ was given. HD was re-initiated emergently to avoid recurrent cardiac arrhythmias. Propofol was discontinued with no recurrence of hyperkalemia.

Discussion: Direct mitochondrial respiratory chain inhibition similar to mitochondrial myopathy is the most plausible explanation for propofol infusion syndrome (PRIS); a rare but significant adverse effect of propofol. Impaired mitochondrial fatty acid metabolism leads to lactic acidosis causing trans-cellular potassium shifts to ECF resulting in hyperkalemia. Rapid rise of serum K⁺ is more closely correlated with onset of arrhythmia than absolute K⁺ levels. Propofol bolus can also cause sudden worsening of hyperkalemia via depressed beta adrenoceptor-agonist effect and acute transcellular shift of potassium. This complication can be fatal in ESRD patients who may have baseline hyperkalemia. Hence, propofol should only be used with extreme caution in ESRD patient population on HD.

FR-PO017

A Curious SLE Tangled Case: Systemic Lupus Erythematosus as the Unifying Diagnosis for Fibrillary Glomerulopathy and Toxic Epidermal Necrolysis Kawan A. Swain, Hao Liu, Volker Nickenleit, Patrick H. Nachman. *Nephrology, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.*

Introduction: Fibrillary glomerulopathy is a rare cause of glomerular disease. Most cases are idiopathic but can be associated with autoimmune diseases.

Case Description: 58 yo Caucasian male with a past history of hypertension presented a week after developing an acute erythematous rash associated with fever, encephalopathy, and AKI. This was preceded by an 8 month history of intermittent night sweats, fever, and joint pain. The desquamating rash encompassed >30% BSA with mucosal involvement. Skin biopsy revealed acute vacuolar interface dermatitis consistent with toxic epidermal necrolysis (TEN). Labs showed pancytopenia without evidence of hemolysis. Serum Cr was 2.14 mg/dl (recently 0.9) and urine Protein/Cr was 1.1g. Urine microscopy showed numerous acanthocytes and a few RBC casts. Serologies revealed low C3 and C4, positive ANA 1:640 and ENA screen, but negative ANCA, cryoglobulins, infectious work up and antibodies to ds-DNA, Sm, RNP, Ro/SSA, La/SSB, Jo1 and Scl70. A kidney biopsy showed acute tubular injury and mild mesangial and endothelial proliferation without crescents or tuft necrosis. Immunofluorescence revealed diffuse 1-2+ staining for IgG, IgA, IgM, C3, C1q, kappa and lambda in the mesangium and capillary walls. Electron microscopy showed mesangial and capillary deposits with 20nm non-branching fibrils. Congo red stain was negative and IgG subclass stain did not reveal monoclonality. The findings were classified as a fibrillary glomerulonephritis. After initial methylprednisolone pulse, treatment with oral prednisone and mycophenolate mofetil resulted in resolution of rash, encephalopathy, and recovery of renal function and cell counts. The unifying diagnosis is new onset SLE, with TEN (possibly precipitated by naproxen) and fibrillary glomerulopathy.

Discussion: This case illustrates an uncommon presentation of an immune complex mediated fibrillary glomerulopathy consistent with SLE in an older male patient who presented with TEN. SLE has been rarely implicated as a cause of SJS/TEN when associated with initial photodistribution, absence of genital involvement, and a prolonged course.

FR-PO018

An Unusual Case of Renal Failure in an Adult: "Prune Belly Syndrome" Juan Antonio Medaura, Jeffrey D. Wallach, Sudhanshu Jain. *Nephrology, Harlem Hospital Center, New York, NY.*

Introduction: Prune Belly Syndrome is a rare congenital disease characterized by hypoplastic abdominal wall musculature, severe urinary tract dilatation and bilateral undescended testes. The complete syndrome is seen only in males affecting 3.8 per 100,000 live births. While the cause is unknown several aspects suggest an influence of genetic factors. Very few patients survive adulthood and all of them progress to ESRD.

Case Description: A 25-year-old male from Burkina Faso presented with a 10-day history of fever, rigors and right-sided flank pain. On exam he was found to have an empty scrotum and a distended bladder. He reported history of several urinary tract infections and urological surgeries during childhood. He was found to have azotemia (Sr. creatinine 10.8 mg/dl and BUN 82 mg/dl) and an eGFR of 8 ml/ min/ 1.73m². Urinalysis was cloudy with 2+ protein, 3+ leucocyte esterase, 2-5 WBC's and moderate bacteria. Urine culture grew *Enterococcus fecalis*. CT of the abdomen showed a massively distended urinary bladder with diffuse wall thickening and calcification, severe bilateral hydronephrosis, mild left hydronephrosis, right renal atrophy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.



He received intravenous antibiotics and improved clinically.

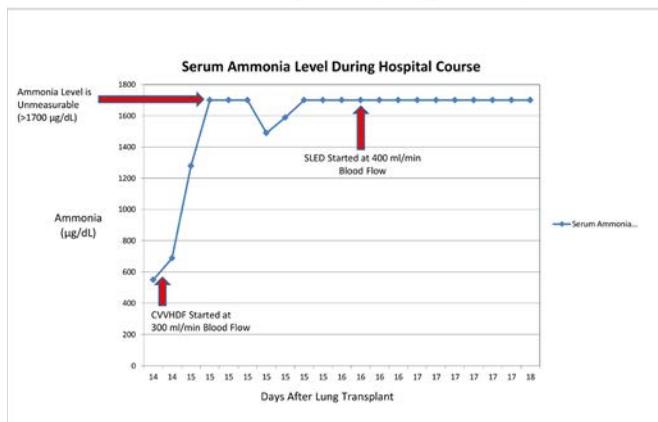
Discussion: Although lower urinary tract and kidney malformations account for 40% of childhood ESRD it is a rare cause of kidney failure in adults. Mutation in the *HNF1β* gene and homozygous loss-of-function mutation of muscarinic receptor M3 (*CHRM3*) were described. *CHRM3* is the major receptor mediating urinary bladder contraction upon micturition. These patients have normal urethral patency on cystogram and detrusor hyporeflexia with high residual volumes after micturition seen on cystometry, identical to the findings in our report. This diagnosis in a 25 year old is rare, as most patients do not survive until adulthood or they are already ESRD.

FR-PO019

How ‘Idiopathic’ Is Idiopathic Hyperammonemia? Esho Georges, Kavitha Vellanki. *Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Introduction: Idiopathic hyperammonemia is characterized by progressive elevations in serum ammonia of unknown etiology, ultimately leading to cerebral edema and death. It is a rare fatal syndrome described in transplant setting; lung transplant recipients having the highest risk. Calcineurin inhibitors are thought to play a role but the exact mechanism is not known. Here we report an unusual case of severe hyperammonemia that has been linked to donor transmitted Ureaplasma infection.

Case Description: A 59 yr old Hispanic man with idiopathic pulmonary fibrosis received bilateral lung transplant at our center. His induction regimen included thymoglobulin and methylprednisolone and was maintained on tacrolimus, mycophenolate and prednisone. His post-operative course was fairly uncomplicated until he was found unresponsive due to seizure on day 14. Work up revealed serum ammonia level of 549 μg/dL. Tacrolimus was discontinued and he was started on lactulose, sodium benzoate, phenyl acetate and broad spectrum antibiotics and started on CVVHDF to help in management of hyperammonemia. Despite all these measures, ammonia levels remained persistently elevated at > 1700 μg/dL (Figure 1) and patient expired within 4 days. At autopsy, bronchoalveolar lavage (BAL) of transplanted lung tested positive for Ureaplasma urealyticum. On further testing, donor’s pre- transplant BAL was positive for the same organism. Lysis of urea by Ureaplasma generates free ammonia and when left untreated, can cause hyperammonemia. But the rise in serum ammonia levels of such a magnitude despite aggressive dialysis is unheard of.



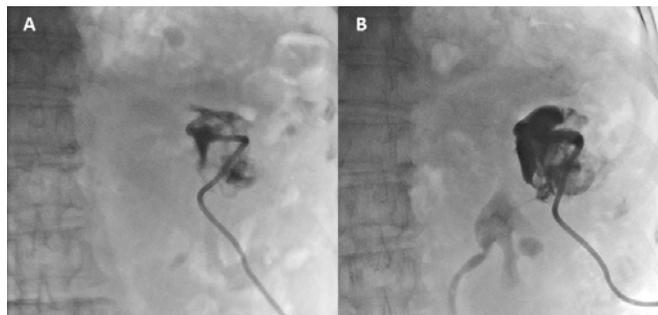
Discussion: In conclusion; underlying infection with urea splitting organisms need to be considered when there is a high rate of ammonia production. And while we are in need of further studies, it may be worthwhile to empirically treat with azithromycin for Ureaplasma infection in so called “idiopathic hyperammonemia”.

FR-PO020

Pelvicocalyceal Leakage on Ethanol Sclerotherapy for Recurrent Infected Renal Cyst in ADPKD Eunyoung Lee, Joo-Hark Yi, Sang-Woong Han, Ho-Jung Kim. *Division of Nephrology, Dept of Internal Medicine, Hanyang Univ Guri Hospital, Guri-si, Gyeonggi-do, Republic of Korea.*

Introduction: Though sclerotherapy has been commonly considered as a valid and safe therapeutic option for symptomatic renal cysts, it’s effectiveness in recurrent infected renal cyst in autosomal dominant polycystic kidney disease (ADPKD) is rarely reported.

Case Description: A 76-year-old woman with ADPKD was again admitted by infected (Lt) renal cyst (7.3 cm) on ultrasonography (US) with similar episode, 1 yr ago. She presented with a fever, dysuria and left CVA tenderness. Despite clinical and laboratory improvement with sensitive antibiotics against Klebsiella pneumonia for 14 days, the size of the infected renal cyst was paradoxically enlarged (8.9 cm) on follow-up US. Thus, percutaneous catheter was inserted for drainage and after 1 wk, tubogram showed no evidence of dye leakage (figure1-A). Following complete clinical recovery, absolute ethanol sclerotherapy was performed to prevent further recurrent cyst infection. However, she complained of severe burning pain in low abdomen at the beginning of the procedure. Tubogram dye was shown in pelvicocalyceal system and ureter (figure1-B). Sclerotherapy was immediately stopped and saline irrigation was followed. Then, percutaneous catheter was remained into the cyst for further draining, and double-J catheter was inserted at ureteropelvic junction to prevent a ureteral stricture. Then, she underwent uneventful hospital course, and discharged on hospital day 42.



Discussion: Infected renal cyst wall, despite clinical recovery, could consist of already damaged tissue that may be easily broken by ethanol. Through this unexpected adverse complication, we learned that cyst ablation therapy with ethanol may not be an appropriate modality to prevent recurrent renal cyst infection in ADPKD.

FR-PO021

A CD2AP Mutation (p.T374A) Associated with Cognitive Decline and Focal Segmental Glomerulosclerosis in Young Adulthood Dmitry Tsvetkov,¹ Yoland Marie Anistan,¹ Christian Harteneck,² Maik Gollasch.¹ ¹Charité Univ Medicine Berlin, Nephrology/Intensive Care, Experimental and Clinical Research Center (ECRC) and Max Delbrück Center for Molecular Medicine, Berlin, Germany; ²Dept of Pharmacology and Experimental Therapy, Inst of Experimental and Clinical Pharmacology and Toxicology, Eberhard Karls Univ Hospitals and Clinics, and Interfaculty Center of Pharmacogenomics and Drug Research, Univ of Tübingen, Tubi.

Introduction: Mutations in CD2-associated protein (CD2AP) gene have been identified in patients with focal segmental glomerulosclerosis (FSGS); however, reports of CD2AP mutations remain scarce.

Case Description: We performed Sanger sequencing in a 32-year old patient with steroid-resistant FSGS presented with a nephrotic syndrome (proteinuria >3.5 g/day). The patient reported that his mother and his only brother also have a kidney disease. Neurological examination showed a remarkable cognitive decline within the last 5 years. Therapy with steroid and low-intermediate doses of cyclosporine A led to a persistent reduction of proteinuria. Serum creatinine levels and glomerular filtration rate (eGFR) did not decline during this treatment.

Discussion: Our patient displayed mild cognitive decline, a phenotypic characteristic not previously associated with CD2AP-associated FSGS. His proteinuria was remarkably reduced by treatment with cyclosporine A. Our findings expand the genetic spectrum of CD2AP-associated disorders and broaden the associated phenotype with the co-occurrence of cognitive decline. Our case shows that cyclosporin A is a treatment option for CD2AP-associated nephropathy.

FR-PO022

Acute Motor and Sensory Axonal Neuropathy-Associated Syndrome of Inappropriate Antidiuretic Hormone Secretion Weeraporn Srisung,¹ Aumyot Prongdong,¹ Pavis Laengvejkaj,² Camilo Pena,¹ Mustafa G. Aly,¹ Sorot Phisitkul.¹ ¹Internal Medicine, TTUHSC; ²Neurology, TTUHSC.

Introduction: SIADH is associated with various conditions including Guillain-Barre’ syndrome (GBS). We report a case of SIADH associated with acute motor and sensory axonal neuropathy (AMSAN), a variant of GBS.

Case Description: A 36-year-old man presented with a 6-week history of progressive ascending weakness. Physical examination showed hypovolemia with asymmetric motor weakness, more severe in the LEs, muscle wasting, absent LE reflexes, dysesthesia and no cranial nerve involvement. MRI head/spine was unremarkable. CSF analysis showed albuminocytologic dissociation and ruled out infection. HIV, viral hepatitis and paraproteinemia were absent. Anti GM1 and GQ1b were negative. Nerve conduction study showed axonopathic pattern on motor and sensory fibers bilaterally. AMSAN was diagnosed. He received IV immunoglobulin with gradual improvement of his weakness. On admission, serum chemistry panel showed Na 115 mmol/L with normal Cr. Urine showed Na <20 mmol/L, and specific gravity 1.045. Urine Osm was not available initially. He received NS infusion for volume expansion. Interestingly, Na did not significantly improve after he became euvolemic. Fluid restriction was then tried with mild improvement. Endocrine work-up ruled out hypothyroidism and adrenal insufficiency. Repeat labs showed serum Na 124 mmol/L, urine Na 191 mmol/L and urine Osm 531 mOsm. Hence, SIADH was diagnosed. Other well-established causes of SIADH were ruled out thus AMSAN was believed to be the most likely cause of SIADH. Tolvaptan was started at 15 mg and resulted in significantly increased urine output (300-500 ml/hr). Na increased rapidly so D5W was started to prevent osmotic demyelination syndrome. Tolvaptan was restarted at 7.5 mg 2 days later with good response. He was discharged on tolvaptan 7.5 mg daily with Na 130 mmol/L.

Discussion: Although GBS is a well-established cause of SIADH, but to our knowledge, AMSAN-associated SIADH has only been rarely reported in literature. We suggest that SIADH should be high on the differential diagnosis for hyponatremia in patients with AMSAN, especially in the setting of euvolemia.

FR-PO023

Severe Renal Osteodystrophy as a Result of Fanconi Syndrome
 Rabie I. Adam-Eldien, Charles W. Heilig. *Nephrology, Univ of Florida, Jacksonville, FL.*

Introduction: Fanconi syndrome is a disease of the proximal renal tubules in which glucose, amino acids, uric acid, phosphate, bicarbonate and other substances are not reabsorbed and lost in the urine.

Case Description: 22 year old African American female with an autosomal dominant Fanconi syndrome. Her disease is clinically manifested by severe rickets and short stature. Her short stature has not responded to growth hormone. She has multiple stress fractures, and she ambulates with a walker. Her disease is manifested chemically by generalized aminoaciduria, hyperchloremic metabolic acidosis, hyperphosphaturia, glucosuria, bicarbonaturia, and proteinuria. Her life compliance with the medication has been poor. She has a gastrostomy tube for medications administration. Her medications include Calcium Carbonate, Neutra-Phos, Rocaltrol, Polycitra and Zantac. Her physical examination showed: Height 98.5 cm, weight 15.8 kg, blood pressure 106/57, pulse 80. She can stand up with hips flexed and her trunk slightly forward because of the anterior and lateral bowing of the femur. She has widening metaphyses of the knees and the wrists. She has ricket changes, ankle prominence, and she has good range of motion. Extremities: Have severe ricket changes. Lower extremities are deformed with prominent femur curve bilaterally. The rest of her exam was unrevealing.

Urinanalysis shows glucose 100 mg/dL, ketones 40 mg, blood trace, pH 7, protein greater than 300 mg. Chemistry showed, Sodium 134, potassium 3.4, bicarbonate 13, chloride 114, glucose 142, BUN 5, creatinine 0.6, calcium 7.9, phosphorus 3.8. Osmolality 268. Alkaline phosphatase 865. White count 7.3, hemoglobin 14, hematocrit 41.3, platelets 385.

Discussion: Fanconi syndrome lead to multiple defects and impair proximal tubular reabsorption of glucose, phosphate, amino acids, HCO₃, uric acid, water, K, and Na. It can be caused by a drug or accompanies another genetic disorder. In hereditary Fanconi syndrome, proximal tubular acidosis, hypophosphatemic rickets, hypokalemia, polyuria, and polydipsia usually appear in infancy. If a patient is unable to keep up with the replacement of these substances secondary to compliance or lack of access, adverse permanent skeletal effects might result from that.

FR-PO024

An Unusual Organism with Unusual Renal Manifestations
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Introduction: Infective endocarditis can cause renal failure due to immune complex mediated glomerulonephritis. We present a case of Nontuberculous mycobacterium (NTM) endocarditis associated with acute glomerulonephritis with tubulointerstitial nephritis.

Case Description: Our patient was a 59 y/o Venezuelan man with a history of cocaine use who presented with generalized weakness, intermittent nausea, and a 40lbs weight loss. He denied taking any medications or illicit drugs for the previous month. On examination, he was afebrile, HR 85, BP 112/43mmHg. Pulmonary exam was unremarkable, and heart auscultation revealed a 3/6 holosystolic murmur at the right upper sternal border. JVP was normal and there was no edema. Serum creatinine was 4.7mg/dL; BUN 56mg/dL; Hemoglobin 8.9g/dL; U/A revealed 2+ protein, 3+ blood, 65 RBCs/HPF, and no casts; Urine Pr/Cr 1.93g/g; HCV IgG positive; HCV PCR negative; low C3; urine drug screen negative. Blood cultures one-day after admission identified Staphylococcus and Corynebacterium species; on hospital day seven the pathogen identification was changed to Mycobacterium chelonae/abscessus complex. Renal biopsy revealed an acute diffuse mesangial proliferative and exudative glomerulonephritis associated with significant tubulointerstitial nephritis. Focal red blood cell casts were also seen on biopsy. TTE revealed a dilated left ventricle with severe aortic insufficiency and possible vegetations. Unfortunately, the patient died on hospital day seventeen from cardiogenic shock.

Discussion: Renal pathology associated with infective endocarditis is rare and typically associated with hematuria, proteinuria, and a mild rise in serum creatinine. Two prior case reports described glomerulonephritis associated with NTM, both of which showed

improvement in renal function with treatment of the underlying infection. Additionally, interstitial nephritis in association with NTM has been reported in two immunosuppressed patients. Our case is the first to describe both glomerulonephritis and acute tubulointerstitial nephritis in association with nontuberculous mycobacterium. This serves as a reminder that infectious endocarditis can have varied renal manifestations whether the causative pathogen is common or uncommon.

FR-PO025

Severe Hyponatremia in a Young Patient with Recurrent Abdominal Pain
 Dimpu M. Patel, Manish K. Saha, Ashita J. Tolwani. *Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.*

Introduction: Acute intermittent porphyria (AIP) is a rare metabolic disorder. Hyponatremia due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) during acute attacks of AIP requires prompt diagnosis and treatment of both AIP and hyponatremia.

Case Description: A 21yo Asian female presented to the ED with sharp intermittent abdominal and flank pain. Upon arrival to the ED, she had a generalized tonic-clonic seizure requiring intubation for airway protection. Her only medications were trimethoprim-sulfamethoxazole and ibuprofen prescribed 2 days prior. Previous ED visits for similar episodes of abdominal pain included an extensive workup with negative urine drug screen, abdominal CT scan, pelvic ultrasound, and surgical evaluation. Prior episodes were noted to occur during menstruation. Physical examination was unremarkable apart from tachycardia. Laboratory data was significant for sodium 113mEq/L, urine osmolality 282 mOsm/kg, and serum osmolality 225 mOsm/kg. Renal function, cortisol, TFTs, LFTs, and CBC were normal. Her hyponatremia was initially corrected slowly with 3% saline and later with sodium chloride tablets after a diagnosis of SIADH was made. The constellation of recurrent abdominal pain and unexplained cause of SIADH in a young menstruating female led to the diagnosis of AIP. Studies sent for AIP demonstrated elevated urine total porphyrin 3,374 (normal 0-300 nmol/24 hr), urine porphyrin 115 (normal 0-4 mg/24hr), 5-aminolevulinic acid (ALA)-delta 79.8 (normal < 7mg/24hr), and RBC protoporphyrin 162 (normal 0-80 mcg/dl). She was treated with a carbohydrate based diet and avoidance of medications known to precipitate an acute attack.

Discussion: AIP results from a deficiency of PBG deaminase, leading to accumulation of ALA and PBG. Acute abdominal pain and involvement of supraoptic nuclei of hypothalamus by the metabolites may trigger constant ADH secretion. Rarely renal and gastrointestinal sodium loss may also cause hyponatremia. Our patient likely had an acute attack triggered by her pain crisis, sulfonamide antibiotic and her menstrual cycle. In the appropriate clinic setting in young patients with hyponatremia, AIP should be considered in the differential diagnosis.

FR-PO026

A Case of Solute Diuresis
 Muhammad K. Qaseem,¹ Elizabeth A. Gilliams,¹ James L. Bailey.¹ *¹Emory Univ School of Medicine, Atl; ²EUH.*

Introduction: Polyuria is a common manifestation of many primary medical disorders. Here we present a case of Arigininosuccinate Lyase Deficiency(ASLD)who presented with altered mental status and later developed polyuria.

Case Description: A 24-year old male with history of ASLD was admitted to the Intensive Care Unit (ICU) for altered mental status with an ammonia level of 347mcmol/L. He was started on Ammonia Scavenger therapy with Ammunol(arginine, Na-benzoate and Na-phenylacetate). On hospital day 10 he developed hypokalemia, hypernatremia and polyuria of 5L. His labs are listed below.

Day-1	Day-14
Na=140 mmol/L	Na=148 mmol/L
K=3.8 mmol/L	K=2.6 mmol/L
Cl=112 mmol/L	CL=118 mmol/L
CO2= 20 mmol/L	CO2=26 mmol/L
Creatinine = 0.68 mg/dL	Creatinine= 0.5 mg/dL
BUN= 3 mg/dL	BUN= 2 mg/dL
Ammonia= 347 mcmol/L	Ammonia= 47 mcmol/L

Urine studies showed urine Sodium of 253mmol/L,urine Potassium of 59mmol/L,urine chloride of 175 mmol/L,urine anion gap of 137,urine osmolality of 637 mOsm/kg and urine Creatinine of 63 mg/dL with a 5.3L of urine in 24 hours. He was receiving 1/2Normal Saline, Ammunol and Total Parenteral Nutrition(TPN). It was recommended to decrease the dose of ammunol to decrease the non-measured anions in the urine, stopping 1/2normal saline and change the TPN to have less solute load. With these interventions his urine output and hypokalemia improved to almost back to normal.

Discussion: Argininosuccinate lyase activity results in the breakdown of argininosuccinic acid to arginine and fumarate. ASLD can result in severe hyperammonemia. Treatment of acute decompensations with hyperammonemia involves discontinuing oral protein, using intravenous arginine and ammonia scavenging therapy. Polyuria in ASLD could be due to different mechanisms such as low BUN leading to poor urine concentrating ability with loss of free water or due to solute diuresis. Our patient's high urine osmolality and high urine sodium indicated a mechanism other than Diabetes insipidus. After the solute content was decreased his urine osmolality decreased significantly along with his urine output. Hypokalemia also improved. Management of solute diuresis in this case was to reduce the solute intake of the patient but first and foremost requires an accurate diagnosis.

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FR-PO027

Life Threatening Hypokalemia and Metabolic Alkalosis Related to Paraneoplastic Cushing's Syndrome Chyi Chyi Chong,¹ Pallavi D. Shirsat,¹ Ramesh Marahatta,¹ Cherinet S. Adgeh,^{1,2} Neville R. Dossabhoy,^{1,2} *LSU Health Science Center, Shreveport; ²VA Medical Center, Shreveport.*

Introduction: Paraneoplastic Cushing's syndrome (CS) develops secondary to tumoral ATCH and less often CRH production. Classical stigmata of CS are often absent, and purple striae and buffalo hump are uncommon. Hypokalemia associated with metabolic alkalosis are more common with ectopic ACTH. We report a case of severe hypokalemia with metabolic alkalosis related to ectopic ACTH production.

Case Description: A 58 y/o African American male presented with complaints of feeling unwell, weight loss and frequent diarrhea for at least one month. On admission, he was noted to be hypertensive with BP 157/87 mmHg. On physical exam, patient had mild wheezes at bases. Laboratory data was significant for Na 144 mEq/L, K 1.1 mEq/L, Cl 82 mEq/L, HCO₃ 50 mEq/L, BUN 14 mg/dL and Cr 1 mg/dL. Blood gas revealed pH 7.34, PCO₂ 92 mmHg, PO₂ 92.4 mmHg and HCO₃ 47 mmol/L. Pt unfortunately developed acute respiratory failure requiring intubation shortly after albuterol nebulizer treatment. He was also receiving Diamox in ICU. He required potassium supplement on average of 120 meq per day (Maximum 300 meq/day). Once diarrhea resolved and with discontinuation of Diamox, patient was still noted to be hypokalemic. Urine electrolytes performed: Na 31 mmol/L, K 107 mmol/L, Cr 41 mg/dL. Additional lab data: Renin <0.15 ng/ml/hr, Aldosterone <1 ng/dl, ACTH level 126 pg/ml and 24hr urine cortisol 3846 mcg. In addition, patient has positive dexamethasone suppression test. CT abdomen and pelvis performed - suggestive of metastatic disease with lesions in liver, left adrenal gland and bone. He had liver biopsy, which revealed neuroendocrine carcinoma. Patient was started on Spironolactone and Triamterene for hypokalemia, and Ketoconazole to decrease ACTH and cortisol level. Potassium supplement requirement decreased to 40 meq/day.

Discussion: This is a rare case of paraneoplastic CS associated with neuroendocrine carcinoma. Early recognition and appropriate treatment for this syndrome are important, although overall clinical outcome remains poor.

FR-PO028

Overcorrection of Hyponatremia Secondary to Diuresis in Postpartum Maria Berenice Nava,¹ Maya K. Rao,² *Div of Nephrology, Columbia Univ, New York, NY; ²Div of Nephrology, Columbia Univ, New York, NY.*

Introduction: Previous case reports have described hyponatremia in pre-eclampsia particularly with twin gestations. Overcorrection in the post-partum period is a potential risk and complicates management.

Case Description: Case report.

30 yo woman G1P0 with intrauterine insemination with triplets presented at 30 weeks gestation with pre-eclampsia and nephrotic syndrome for emergent cesarean section. On presentation she was hypertensive, massively edematous found to have a serum sodium of (sNa) 126 mEq/L (no prior values), serum creatinine 0.5 mg/dl, albumin was 2.4 g/dl. Urine osmolality was 159 mOsm/kg and the serum osmolality was 263 mOsm/kg, urine sodium 21mmol/L. Spot urine protein:creatinine ratio 3.5 grams. By POD 2, her sNa decreased to a nadir of 119 mEq/L and spot protein: creatinine ratio was 0.458 grams, free water restriction was started. She soon began to auto-diurese (2.6L in 4hrs) resulting in a rise in sNa to 127 mEq/L in 5 hrs with a urine osmolality of 159 mOsm/kg. She was started on DDAVP to slow down correction and sNa levels were checked every 4 hours. Her subsequent sodium levels remained at 127 mEq/L over the next 12 hrs. On POD # 3 her sNa corrected to 133 mEq/L, she continued to have a urine output of 200-300 ml/hr, therefore D5W was initiated and DDAVP was again administered. Her urine output decreased to <100ml/hr on POD#4, urine osmolality was 217 mOsm/kg, therefore D5W was discontinued. She received 4 additional doses of DDAVP. The patient was ultimately discharged on POD#10 with a sNa of 143 mEq/L and off DDAVP.

Discussion: Hyponatremia in pre-eclampsia with nephrotic syndrome has been reported in the literature and is thought to be secondary to low effective circulating plasma volume. In this case, we report rapid correction of serum sodium post-delivery likely due to volume redistribution and removal of ADH stimulus. Awareness of potential rapid correction and frequent monitoring of serum sodium is important in order to intervene early and prevent consequences of rapid sodium correction. Serum sodium post-delivery should be monitored very closely in cases such as these.

FR-PO029

Severe Hypocalcemia in a Hemodialysis Patient Manish K. Saha, Maria E. Taylor, Alian Albalas, Denyse Thornley-Brown. *Nephrology, Univ of Alabama, Birmingham.*

Introduction: Severe hypocalcemia in a hemodialysis patient is rare in the absence of parathyroidectomy, vitamin D deficiency or calcimimetic drugs.

Case Description: A 58 year-old man was found to have severe asymptomatic hypocalcemia (5.9 mg/dL) with prolonged QTc (547 ms) four weeks after starting hemodialysis. He had a history of prostate cancer treated with radical prostatectomy, bisphosphonates and a GnRH analogue. Serum calcium prior to starting hemodialysis was 8.6 mg/dL; serum albumin 3.2 gm/dL, PTH 352 pg/mL, 25OH-Vitamin D₂ <4ng/mL, 25OH-Vitamin D₃ 12 ng/ml, and phosphorus 6.3 mg/dL. His intravenous doxercalciferol dose was titrated to 20 mcg thrice weekly; oral calcium carbonate and 1,25-dihydroxycholecalciferol were titrated up. Dialysate calcium concentration was increased to 3.5 mEq/L. However, despite these measures, pre-dialysis calcium was 6 mg/dL. On further review, it was found that he had been started on denosumab six weeks prior to initiation of hemodialysis for

bone pain due to skeletal metastases. Denosumab is a monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand). Tumor cells in patients with skeletal metastases stimulate osteoblast to secrete RANKL, which stimulate osteoclast to promote osteolysis and increase calcium levels. Even after replenishing Vitamin D stores, our patient continues to need higher dialysate calcium.

Discussion: Common causes of hypocalcemia in dialysis patients include: vitamin D deficiency, autoimmune or surgical hypoparathyroidism, severe hyperphosphatemia due to tumor lysis or rhabdomyolysis and medications such as cinacalcet. Denosumab is an easily overlooked cause of hypocalcemia. Our patient had Vitamin D deficiency but had normal calcium level prior to starting denosumab. It is important to replete vitamin D and calcium stores prior to initiating denosumab in patients with chronic kidney disease as they may have resistance to standard therapy for hypocalcemia. It is also recommended to check calcium levels regularly while on this medication.

FR-PO030

Central Diabetes Insipidus with Pituitary Atrophy from Chronic Lithium Use Joe Ghata, Satish Kumar. *Nephrology, Univ of Oklahoma Health Science Center, Oklahoma City, OK.*

Introduction: Lithium use is commonly associated with nephrogenic diabetes insipidus (NDI) and rarely with central diabetes insipidus (CDI). The mechanism of Lithium associated CDI is unclear. We report a patient on chronic lithium therapy who developed CDI and partial NDI and who had atrophy of posterior pituitary atrophy on MRI.

Case Description: A 62 yo woman with diabetes mellitus 2 for 5 years, hypertension for 10 years, and bipolar disorder on lithium for 40 years was admitted to the ICU for altered mental status. ROS was negative for nausea, vomiting, diarrhea, acute intoxication or infectious prodrome. Physical exam was normal; she was clinically euvolemic. Urine output was 4-8 l/d and a serum Na was 178 mEq/l. Serum creatinine was 4.84 mg/dl, elevated from a baseline of 1.5 in 2012. Urine osmolality (U osm) was < 100 mosm/l. Intravenous D5W at 200 ml/h caused improvement in serum creatinine to 1.7 mg/dl but minimal reduction in serum Na. Water restriction produced a submaximal rise (<250 mosm/l) in U osm from 157 to 176. ADH levels were undetectable by RIA when serum Na was 165-175. Intravenous desmopressin produced submaximal elevation in urine osmolality from 80 to 153 (91.25%), consistent with partial NDI (U Osm < 250 mosm/l) and partial CDI (>15 to 99%). MRI demonstrated atrophy of the posterior pituitary, with non-specific volume loss, straightening of the infundibulum, and absence of bright spot corresponding to the posterior pituitary. Final diagnosis was both partial central and nephrogenic DI associated with lithium use. Eunatremia was eventually achieved with intranasal DDAVP and liberal fluid intake.

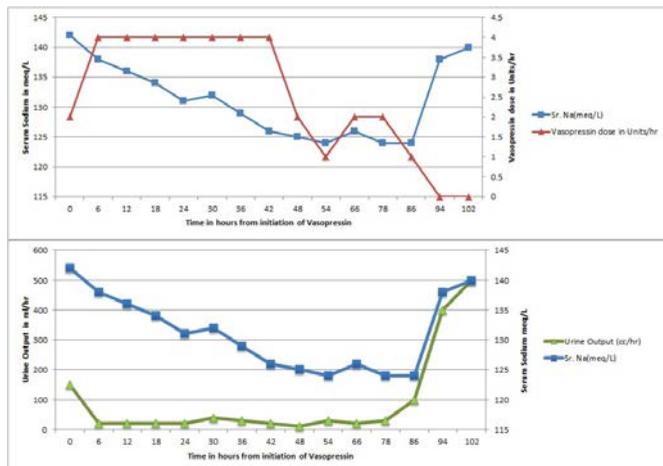
Discussion: This is the first report of radiological evidence of posterior pituitary atrophy with lithium-associated central DI. Possible mechanisms of posterior pituitary atrophy may include "burn-out" from chronic hypersecretion of ADH caused by lithium induced nephrogenic diabetes insipidus or autoimmune hypophysitis from circulating autoantibodies developed in response to chronic high ADH levels.

FR-PO031

Introgenic Hyponatremia Isha Gupta, Eduardo J. Zouain, Karim El Hachem, Anip Bansal, Steven D. Smith, Germaine Z. Chan. *Dept of Nephrology, Mt. Sinai St. Luke's Hospital, New York, NY.*

Introduction: Vasopressin acts in the kidney via V2 receptors to regulate water resorption and on the vasculature via V1 receptors to regulate smooth muscle tone. It is often used in the management of shock, but rarely causes hyponatremia in hemodynamically unstable patients. We present here a case of a man who developed marked hyponatremia during vasopressin infusion.

Case Description: A 58 year old man with history of hypertension and coronary artery disease was admitted to intensive care unit for un-witnessed cardiac arrest. He was intubated and started on vasopressin and norepinephrine for cardiogenic shock. His lab data on admission revealed normal serum sodium, blood urea nitrogen and creatinine. His inpatient course was significant for development of hyponatremia within 2 hours of initiation of vasopressin infusion. Patient's sodium dropped from 142 meq/L (normal range 136-146 meq/L) to lowest value of 124 meq/L associated with oliguria (urine output 20ml/hr). With cessation of vasopressin, urine output increased significantly to 500ml/hr and serum sodium increased from 124 meq/L to 142 meq/L. Dextrose infusion was started to prevent overly rapid correction. Please refer to graph for the changes in the serum sodium and urine output with vasopressin infusion over time. Patient had normal cortisol levels and thyroid function.



Discussion: Vasopressin does not usually result in hyponatremia when used in management of shock. Possible explanations include lack of renal responsiveness secondary to renal hypoperfusion/acute kidney injury, or lack of intake of hypotonic fluids. In this case, the patient developed marked hyponatremia in setting of preserved renal function.

FR-PO032

Hyperkalemia Secondary to Octreotide Use in a Patient with Normal Kidney Function Dron P. Bhandari, Jyotsana Thakkar, Hitesh H. Shah. *Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY.*

Introduction: Octreotide, a somatostatin analogue works by reducing blood levels of a variety of hormones (e.g. growth hormone, insulin) and chemical messengers (e.g. gastrin, vasoactive intestinal peptide). Octreotide therefore has been used as an effective medication for the treatment of sulphonylurea-induced hypoglycemia, acromegaly, VIPoma and carcinoid syndrome. Octreotide-induced hyperkalemia has rarely been reported in the literature. We report a patient with normal renal function who developed hyperkalemia secondary to octreotide use.

Case Description: A 70-year-old male with long standing history of DM (since 20 years), HTN, and metastatic neuroendocrine pancreatic cancer was referred by his oncologist for evaluation of severe hyperkalemia (serum potassium level of 6.6 mmol/L). Patient was diagnosed with pancreatic neuroendocrine tumor approximately 2 years prior to his presentation for which he underwent Whipple procedure. He was also receiving subcutaneous octreotide monthly for nearly 1.5 years prior to his presentation. There was no history of kidney disease or any urinary complaints. Other medications included aspirin, insulin, creon, levothyroxine and HCTZ. BP was normal and patient was noted to have bilateral lower extremity pitting edema on examination. Other labs done 5 days prior to presentation showed normal serum bicarbonate (25 mmol/L) level, normal serum creatinine (1.23 mg/dL) level, and elevated serum glucose (263 mg/dL) level. On reviewing medical records, our patient was noted to have chronic and persistent hyperkalemia over the previous six months that was medically managed by intermittent oral sodium polystyrene and low potassium diet. All other causes of hyperkalemia were clinically excluded. Serum potassium normalized after receiving medical management and holding octreotide treatment.

Discussion: We present a rare case of octreotide-induced hyperkalemia in a patient with normal renal function. We believe that hyperkalemia in our patient occurred as a result of octreotide-induced insulin suppression and resultant impaired cellular potassium uptake. Based on our experience, one should be aware of this potential life-threatening side-effect of octreotide therapy.

FR-PO033

Hypercalcemia and Acute Kidney Injury due to Immune Reconstitution Syndrome in an HIV Patient on HAART and MAC Therapy Anand Achanti, Omar M. Shahateet, Karl Berthold Pembaur, Nithin Karakala, Juan Carlos Q. Velez. *Nephrology, Medical Univ of South Carolina, Charleston, SC.*

Introduction: Hypercalcemia can occur in HIV-infected patients due to several conditions such as granulomatous diseases, lymphomas, and solid tumors. HIV patients are also susceptible to causes found in the general population, such as primary hyperparathyroidism, medications, and vitamin D supplementation.

Case Description: A 48 year old male with history of HIV and disseminated *Mycobacterium avium complex* (MAC) was sent to the hospital after being found to have a serum calcium of 15.5 mg/dl and serum creatinine of 5.8 mg/dL on routine labs. His only complaint was weakness. Five months prior to presentation, patient had an adjustment of his highly active antiretroviral therapy (HAART) with a viral load of 76,000 copies/mL, CD4 count of 36/CUMM, serum calcium of 9.6 mL/dL, and serum creatinine of 2.6 mg/dL at that time. Previous renal dysfunction was caused by interstitial nephritis diagnosed 6 weeks prior. Patient reported increased compliance to his new regimen for several weeks prior to presentation, reflected by an increase in CD4 count of 138 /CUMM earlier and undetectable viral load upon presentation. Workup for hypercalcemia included: low PTH of 5.8 pg/mL, low PTH-rp of 0.7 pmol/L, and a high 1,25 Vitamin D of > 200 pg/mL. Serum and urine protein electrophoresis showed a restricted kappa light chain band, but

serum kappa/lambda ratio and bone marrow biopsy were normal. Imaging was negative for lymphoma. The patient was managed with volume repletion, prednisone 60 mg/d, and IV pamidronate 60 mg with gradual improvement of his calcium to 8.8 mg/dL and creatinine to 2.8 mg/dL in 9 days. Steroids were tapered and the patient remained stable 6 months later.

Discussion: Our patient developed acute kidney injury secondary to severe hypercalcemia, likely due to renal vasoconstriction and volume depletion superimposed over interstitial nephritis. The etiology of hypercalcemia was likely immune reconstitution syndrome caused by the restoration of HAART. In patients with HIV and AIDS with history of granulomatous disease, it is important to monitor for hypercalcemia when initiating HAART therapy or adjusting therapy.

FR-PO034

Hypocalcemia in Severe Malnutrition, and Acute Pancreatitis Veils Vitamin D Intoxication Kamran Karimi, Catherine Miranda, Yezina T. Nigatu, Kelly H. Beers, Nand K. Wadhwa. *Nephrology, Stony Brook Univ Medical Center, Stony Brook, NY.*

Introduction: Although vitamin D has a wide therapeutic index, a routine use of high doses of vitamin D intake can cause toxicity. We report a case with severe hypocalcemia likely due to malnutrition and pancreatitis related to alcoholism followed by hypercalcemia from vitamin D toxicity.

Case Description: A 43 year-old woman with alcoholism was admitted with rhabdomyolysis and alcohol induced acute pancreatitis. On initial examination she was in moderate distress with altered mental status and diffuse abdominal pain. Her blood pressure was 102/67 mmHg, heart rate 136/min and temperature 38.3°C. Her lab data revealed WBC 54.71 mm³, Hb 16.9 g/dL, PLTs 186 mm³, serum Na 129 mEq/L, K 3 mEq/L, bicarbonate 19 mEq/L, BUN 32 mg/dL and creatinine 1.3 mg/dL, Ca 4.4 mg/dl, Mg 1.1 mg/dl, phosphorus 1.7 mg/dL, CPK 1089 IU/L, albumin 2.9 g/dL. She received intravenous Ca, Mg, K and phosphorus in addition to oral supplements. On day 4, her serum Ca was 8.7 mg/dl, albumin 2.5 g/dl, phosphorus 4.0 mg/dl and K 3.9 mmol/l without any supplement. Her serum Mg remained low and continued to receive oral and intravenous Mg supplements. Serum Ca was not checked between days 9-14 of her hospitalization. On day 15, her serum Ca was 12.8 mg/dl, ionized Ca 6.4 mg/dl, vitamin D 25OH 370 ng/ml, vitamin D 1-25 OH₂ 149 pg/ml and intact PTH 11.8 pg/ml. Her TSH, T4, ACE and vitamin A levels were normal. Her 24 hours urine revealed Na 140 mmol, K 70 mmol, creatinine 1110 mg, UN 4.1 g, Ca 462 mg, Mg 403 mg, phosphorus 931 mg. She admitted taking vitamin D 50,000 units daily for many months for her psoriasis on her own. Her hypercalcemia was treated and her serum calcium stabilized over one week to 9.4 mg/dl while her vitamin D 25OH and vitamin D 1-25 OH₂ remained elevated over the next 6 weeks.

Discussion: Her unusual presentation of hypocalcemia masked vitamin D toxicity till she resumed regular nutrition. Her hypocalcemia was likely related to malnutrition due to chronic alcoholism and possible calcium deposition due to acute pancreatitis. With proper nutrition during her hospitalization and improvement of her underlying condition led to hypercalcemia due to vitamin D toxicity.

FR-PO035

Re-Defining the Speed Limit in Osmotic Demyelination Syndrome? Mahrukh Rizvi, Rebeca D. Monk. *Nephrology, Univ of Rochester Medical Center, Rochester, NY.*

Introduction: Osmotic demyelination syndrome (ODS) is a severe, debilitating, possibly fatal neurological condition that results from rapid correction of severe chronic hyponatremia. Imaging reveals central pontine myelinolysis (CPM). Potential added risk factors for ODS include Sodium (Na) < 120 mmol/L, alcoholism, malnutrition and liver transplant. Current recommendations advise raising serum sodium by less than 9 mmol/L in 24 hours. We present a case of ODS in a patient presenting with severe hyponatremia corrected at a maximum rate of 8meq/dL in 24 hrs.

Case Description: A 37 year old man with a history of alcohol abuse was sent in to the hospital by police after a car accident for jaundice. He endorsed two weeks of worsening jaundice and right upper quadrant (RUQ) pain. Admission vital signs were stable. Physical exam revealed marked jaundice, abdominal distention and RUQ pain. Work up revealed severe alcoholic hepatitis with cirrhosis and metabolic derangements including a Na of 105 mmol/L, chloride of 69 mmol/L, urea nitrogen of 45 mg/dL, creatinine of 2.13 mg/dL with unknown baseline. 3% saline with ddAVP was initiated for cautious correction of severe hyponatremia. Na increased at the desired rate, with maximum of 8 mmol/L over 24 hours on day 1. Hospital course was complicated by altered mental status on day 3 for which he was initiated on CIWA. Over the course he had protracted encephalopathy with difficulty moving bilateral lower extremities, trouble swallowing and dysarthria. On day 9 of his stay, a magnetic resonance imaging of the brain was obtained revealing CPM.

Discussion: Defining a safe rate of serum sodium correction that the brain can tolerate has been difficult. It has evolved to more cautious values over the past few decades. Our case adds to the available pool of data in the literature shedding further light on what may be "overcorrection." Despite strict observance of therapeutic guidelines, a maximum correction of 8 mmol/L proved to be a sizeable enough increment to lead to ODS. This leads to reconsideration of a "safe" speed limit. Treatment should be tailored to individual patients and sodium corrected at a rate as low as possible, especially in the presence of other risk factors for ODS.

FR-PO036

A Case of Axenfield-Rieger Syndrome Presenting with Elevated Serum Bicarbonate Rudrick V. Ledesma, Maureen E. Brogan, Venkata Buddharaaju, Rahul N. Pawar, Rajat Lamba. *Westchester Medical Center, NY.*

Introduction: Elevated serum bicarbonate can be often misdiagnosed as metabolic alkalosis leading to improper management. Chronic respiratory acidosis caused by central hypoventilation can lead to elevated bicarbonate secondary to renal compensation. We present a case of central hypoventilation caused by cerebello-pontine lesion in a patient with Axenfield-Rieger syndrome (ARS).

Case Description: A 25 yo man with PMH of glaucoma, developmental delay, schizoaffective disorder sent to the ED for respiratory failure. He was seen earlier in renal clinic for evaluation of elevated serum bicarbonate. He was complaining of fatigue and insomnia. Arterial blood gas was done and showed a pH of 7.30, pCO₂ of 79, PO₂ of 63 and HCO₃ of 38.9. He was eventually admitted for further management. While in the hospital, he continuously needed bilevel positive airway pressure. Chest ultrasound showed little to no movement of his diaphragm. EMG was negative. PFT was suboptimal as he wasn't able to follow the instructions. MRI brain showed a mass on his right cerebello-pontine angle. He was also diagnosed with ARS during his hospital stay. The mass was resected and progressive improvement was observed in his respiratory status. He was eventually weaned off bilevel positive airway pressure and was discharged home without any need for respiratory support.

Discussion: Elevated serum bicarbonate can often pose a diagnostic challenge. Evaluation should start with an ABG which would differentiate a primary metabolic alkalosis from a renal compensation of respiratory acidosis. Differential diagnoses for respiratory acidosis include central hypoventilation, primary lung pathology, neuromuscular disease and airway pathology. Central hypoventilation could be secondary to lesions in the respiratory center. ARS presents as a spectrum of developmental disorders resulting from abnormal migration and differentiation of neural crest cells with both ocular and systemic manifestations. The regions in the brain that are usually affected are forebrain and pituitary gland. Our case is interesting as he had ARS with epidermoid cyst which we believe has led to central hypoventilation and elevated bicarbonate as compensatory mechanism.

FR-PO037

Signet-Ring Cell Carcinoma Presenting as Frequency of Urination Haya Waseem Siddiqi, Daniel E. Carl, Todd W. Gehr. *Nephrology, Virginia Commonwealth Univ, Richmond, VA.*

Introduction: Urinary tract obstruction may occur at any site in the urinary tract and is important to recognize early since it is readily reversible if quickly corrected.

Case Description: 45 year old male with obesity, history of gastric bypass surgery, hypertension and obstructive sleep apnea who presented to our institution for evaluation of frequency of urination. He developed progressively worsening frequency of urination, occurring every hour during the day and night for 3 months prior to presentation. During this time, his serum creatinine was 1.6 mg/dL. He had been seen multiple times by an Urologist and Primary Care Providers outside our institution, and was diagnosed with prostatitis despite negative urine cultures and no pyuria. During the work up, an out-patient CT scan revealed mild bilateral hydronephrosis and mild left hydronephrosis. Furthermore, an office cystoscopy revealed diffuse inflammatory cystitis of the bladder and no definitive bladder outlet obstruction. Over the ensuing 3-4 weeks, he developed acute kidney injury, with a serum Cr that peaked at 6mg/dL. This prompted an admission to an outside facility. He was again found to have mild bilateral hydronephrosis, however, ureteral stents were attempted, but unsuccessful. A repeat cystoscopy revealed severely inflamed bladder tissue, the ureterovesical junction was not visualized, and urinary bladder biopsy was done. Patient was transferred to VCU for placement of percutaneous bilateral nephrostomy tubes by interventional. He had successful stent placement by IR followed by post obstructive diuresis treated with intravenous fluid hydration in the form of saline. His AKI improved as did the hydronephrosis evident on follow-up imaging study. His serum Cr improved to 1.3 mg/dL and repeat CT scan with intravenous contrast was obtained for staging which showed circumferential bladder wall thickening with asymmetric soft tissue prominence along the right anterior dome most consistent with bladder neoplasm. Outside pathology report was consistent with signet ring cell carcinoma of bladder.

Discussion: Signet-ring cell carcinoma a rare bladder tumor can result in acute kidney injury secondary to bilateral ureteral obstruction.

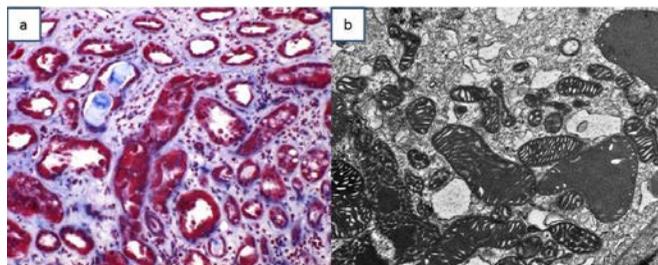
FR-PO038

A Case of Tenofovir-Induced Nephrotoxicity Keerti K. Bhanushali, Girish Singhania, Abhilash Koratala, Radhika Vemuri, William L. Clapp, Dara N. Wakefield, Saraswathi Gopal. *Nephrology, Univ of Florida, Gainesville, FL.*

Introduction: Tenofovir (TFV) is a nucleotide reverse-transcriptase inhibitor used for treatment of HIV and hepatitis B. Most studies suggest that TFV has only a modest effect on estimated glomerular filtration and severe nephrotoxicity is uncommon. We describe a case of severe renal failure and mitochondrial tubulopathy related to TFV.

Case Description: A 55-year-old woman with HIV on TFV for several years, presented with vomiting and abdominal pain for 4 days. Physical exam was unremarkable. Laboratory data showed BUN 65 mg/dL, creatinine 9.07 mg/dL (baseline: normal), bicarbonate 12 mmol/L, glucose 137 mg/dL, HIV RNA: 21 copies/mL and CD4: 292 cells/uL, glycosuria and proteinuria (157mg/24 hours). Serological tests for autoimmune processes were negative. Kidney biopsy showed proximal tubule (PT) injury and eosinophilic oval cytoplasmic inclusions on trichrome stain (fig. a) with no definite glomerular or mesangial abnormalities. Electron microscopy (EM) showed PT cells with cytoplasmic swelling, loss

of membrane integrity, accumulation of enlarged dysmorphic mitochondria with intra-cristal widening and the matrix appearing as electron-dense bands, and focal loss of cristae (fig. b) consistent with mitochondrial injury (MI) seen in TFV nephrotoxicity. Despite discontinuing TFV, she remained dialysis dependent.



Discussion: Currently available data supports renal safety of TFV in HIV patients. Severe renal dysfunction has only been reported sporadically. Although nucleoside reverse transcriptase inhibitors (adeфовир) are known to impair mitochondrial replication by interfering with DNA polymerase- γ , evidence linking TFV specifically to MI is limited. Our case implies that TFV can cause significant renal failure and MI. Monitoring renal function and urinalysis during TFV treatment is key for early detection of nephrotoxicity.

FR-PO039

A Case of Severe Hypomagnesaemia in a Patient Treated with Trastuzumab Saifullah Kazi, Ghulam Akbar, Paul Robbins. *Nephrology, Lankenau Medical Center, Wynnewood, PA.*

Introduction: A case of invasive ductal carcinoma that was treated with chemotherapy including Trastuzumab found to have severe hypomagnesemia requiring very aggressive repletion strategies.

Case Description: A 36 y/o non-alcoholic female with past medical history of hypertension well controlled on diet therapy, was diagnosed with invasive ductal carcinoma of the breast requiring initiation of chemotherapy with docetaxel and carboplatin with Trastuzumab. She received a total of 6 cycles of chemotherapy every three weeks and Trastuzumab 2gm weekly infusions. After completion of chemotherapy, the dose of Trastuzumab was increased to 6gm per infusion every three weeks. Her serum magnesium level which was 2.1mg/dl in the beginning of chemotherapy was noted to be low at 0.5mg/dl when she presented with generalized weakness to the hospital six months into the treatment. At this time, she had completed her chemotherapy 2 months ago and now on Trastuzumab only. She was on lasix and proton pump inhibitors at that time, both of which were stopped immediately. However her serum magnesium remained low between 0.6-1.0 mg/dl persistently for next few months requiring intravenous infusions every week. On repeated testing, fractional excretion of magnesium remained high indicating renal magnesium wasting. Although patient was hypokalemic initially, it corrected immediately after stopping loop diuretics and remained normal ruling against tubulopathies such as Gitelman or Barter syndrome. She remained hypomagnesemic despite completing one year course with Trastuzumab. She is receiving once a week intravenous infusions of magnesium and oral supplements three times a day and serum magnesium remains at 1.4-1.5mg/dl.

Discussion: Trastuzumab is a human epidermal growth factor (HER-2) inhibitor which belongs to the family of epidermal growth factor receptor (EGFR). EGFR is involved in increasing the magnesium absorption in the distal nephron by increasing the transcription of the genes regulating TRPM6 channels. Hypomagnesemia has been well reported in other EGFR inhibitor with Cetuximab used in colon cancer and Erlotinib used in lung cancer, but not reported in patients taking Trastuzumab, especially after escalating to higher doses.

FR-PO040

Capecitabine Induced Acquired Bartter's-Like Syndrome Eric A. Kirk, Jennifer Thompson, Juan Carlos Q. Velez, Nithin Karakala. *Nephrology, MUSC, Charleston, SC.*

Introduction: Many forms of chemotherapy carry a risk of electrolyte abnormalities. Capecitabine is an antimetabolite of the fluoropyrimidine carbamate class of chemotherapeutic agents. Phase I and II trials have reported hypomagnesemia, hypokalemia and hypocalcemia as isolated electrolyte imbalances, and there are case reports of isolated hypomagnesemia and reports of a relatively large number of patients with hypokalemia. A Fanconi like pattern of electrolyte disorders has also been reported with capecitabine.

Case Description: A 68 year old female with neuroendocrine pancreatic cancer treated with capecitabine and temozolomide developed back spasms and was found to have severe hypokalemia (2.4mmol/L), hypomagnesemia (0.7mg/dL) hypocalcemia (6.4mg/dL) and metabolic alkalosis (bicarbonate 30mmol/L) in the absence of vomiting or diarrhea 5 weeks after starting a 2 week course of capecitabine (1400mg/m² divided twice daily). She had evidence of renal salt wasting with sodium 256.5mEq, potassium 51.8 mEq, and calcium 500mg in a 24 hr urine collection. No evidence of hypoparathyroidism, with intact PTH 67.3pg/mL, 1,25 hydroxy vitamin D was 33pg/mL. Further capecitabine therapy was withheld. 24 hr urine collection was completed 1 week later with decreased renal loss of sodium, potassium and calcium and normalization of electrolytes.

Discussion: We present a case of life threatening hypokalemia caused secondary to capecitabine. As the patient had metabolic alkalosis it was unlikely that the patient had Fanconi's as described in some case reports. Our case is unique as this patient developed a combination of hypokalemia, hypocalcemia, hypomagnesemia and metabolic alkalosis

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

caused by capecitabine. The patient exhibited Bartter's like physiology with increased renal loss of potassium, calcium, and magnesium and evidence of metabolic alkalosis. Unlike the proximal tubulopathy associated with capecitabine, the pathophysiology of acquired Bartter's with is unknown but could be caused by direct inhibition of apical NaKCC or ROMK, or activation of the calcium sensing receptor on the basolateral surface in the thick ascending loop of Henle.

FR-PO041

Uncommon Case of Severe Hypercalcemia After Renal Transplantation Rapeepat Lekham, Gitana Bradauskaitė. *Nephrology, Einstein Medical Center, Philadelphia, PA.*

Introduction: Following renal transplantation, hypercalcemia is frequently caused by persistent hyperparathyroidism, but other causes should be kept in mind. We report a case of hypercalcemia after renal transplant from unregulated extrarenal 1,25-dihydroxyvitamin D synthesis from disseminated tuberculosis and cryptococcosis.

Case Description: The patient was a 59-year-old male with unknown etiology of ESRD who received a living unrelated kidney transplant. He was stable on low dose immunosuppressive agents for history of BK virus infection. At 10 months post-transplant, the patient diagnosed with disseminated cryptococcosis with granulomatous mesenteric mass and positive serum cryptococcal antigen. High dose oral fluconazole was started. 10 days later, he readmitted with severe hyponatremia, severe hypercalcemia (corrected serum Ca peak at 14.72 mg/dl) and acute renal failure (serum Cr peak at 5.8 mg/dl from baseline 1.6 mg/dl). The iPTH level was suppressed to 2.8 pg/ml. The serum 1,25(OH)₂D level was elevated and levels of 25(OH)D fell. Serum phosphate rose and ALP levels were elevated. PTH-related peptide was negative. Serum immunoelectrophoresis with immunofixation showed slightly elevated IgG kappa monoclonal gammopathy with normal ratio of free kappa and lambda light chain. Kidney biopsy revealed acute tubular necrosis, no evidence of granulomatous or lymphoproliferative disease. CT chest revealed right upper lobe mass with calcified granuloma at lung base. Culture from lung biopsy showed strongly positive for Mycobacterium Tuberculosis. Anti-tuberculosis drugs were started and mycophenolate mofetil was held. Elevated calcium levels were unresponsive to calcitonin, fluid neither diuretic. After his sputum AFB became negative, the oral prednisone was increased to 20mg/day. Hypercalcemia and hyperphosphatemia normalized upon one month follow up and remained stable until finished 6 months course of anti-tuberculosis drugs and the creatinine returned to baseline.

Discussion: Unlike persistent hyperparathyroidism, underlying diseases of PTH independent hypercalcemia after renal transplantation like a granulomatous disease can lead to significant morbidity and mortality. Early recognition and prompt treatment is necessary.

FR-PO042

Treatment of Malignancy-Associated Hypercalcemia with Low Calcium Hemodialysis Yields Several Benefits for Cancer Patient Rozina B. Ali, Akshatha Rao, Suzanne Boyle, Jesse M. Goldman. *Div of Nephrology and Hypertension, Drexel Univ College of Medicine, Philadelphia, PA.*

Introduction: Hypercalcemia of malignancy can be fatal. In literature, primary treatment remains forced saline diuresis while dialysis is seldom considered. We present a case of severe, refractory hypercalcemia associated with diffuse large B-cell lymphoma that was treated with low calcium (Ca) hemodialysis (HD).

Case Description: A 56 year-old male presented with 3 weeks of weakness and confusion. Labs noted a serum creatinine (Cr) of 1.45mg/dL, Ca of >18mg/dL, and ionized Ca of >2.3. Urine microscopy had pigmented granular casts. Cause of acute kidney injury (AKI) was attributed to hypovolemia, acute tubular necrosis and Ca-induced vasoconstriction. He had a PTH of 7pg/ml, PTH-rp of 2.1pmol/l, vitamin D 25,OH of 25.4ng/ml and 1,25OH of 18.6pg/ml. Non-contrast CT chest demonstrated diffuse lymphadenopathy with LN biopsy showing diffuse large B-cell lymphoma. On day 1, patient received several liters of normal saline, calcitonin, and pamidronate. Despite maximal medical therapy, he had delirium, persistent AKI with Cr peak to 2.6 mg/dL and elevated Ca at 15mg/dL. On days 3, 4, and 5, he received consecutive 4-hour sessions of intermittent HD with low Ca (2meq/L) dialysate using a 0180 high flux dialyzer with blood flow of 400mL/hr. On day 6, Ca decreased to 10.4 mg/dL and mental status improved. He received induction chemotherapy on day 13 with cyclophosphamide, doxorubicin, rituximab, and vincristine. At discharge, Cr was 1.66mg/dL and Ca level was 12mg/dL.

Discussion: Management of refractory severe hypercalcemia with low Ca HD is potentially underutilized. Conventional methods of management have therapeutic and temporal limitations. We found low Ca HD to be a useful adjunctive tool for treatment in our case of malignancy-related severe hypercalcemia. With low Ca HD, care must be taken to avoid hypotension from volume depletion and vasodilation from high Ca flux. Our patient tolerated dialysis without adverse events. Adding low Ca HD to other treatment modalities likely contributed to rapid symptom improvement and mitigation of further Ca-mediated renal injury, allowing for timely chemotherapy induction.

FR-PO043

A Curious Case of PPI Induced Renal Magnesium Wasting Minesh Rajpal, Taranpreet Kaur, Reejis Stephen, Fahad Saeed. *Cleveland Clinic, Cleveland.*

Introduction: Proton pump inhibitors (PPI) are known to impair absorption of magnesium (Mg) by inhibition of transient receptor potential melastatin-6 (TRPM6) and TRPM7 channels on the intestinal epithelium. We present a case of PPI induced hypomagnesaemia from renal Mg wasting.

Case Description: 41 year old female with history of thyroidectomy for cancer, parathyroidectomy, hypothyroidism, and gastro-esophageal reflux disease (GERD) referred to our nephrology clinic for severe symptomatic hypokalemia for a decade. She has poor appetite and weighs around 330 pounds but denies vomiting or diarrhea. Home BPs is low 90's/60's mmHg. She denies licorice, diuretic or excessive alcohol use. She was adopted as a child with unknown family history. She was admitted for further work up. Her serum potassium (K) was 3.5 and Mg was 1.2. 24 hour urine collection was done and levels of sodium, K, Mg and aldosterone were found to be 48 mmol, 21 mmol, 49.6 mmol, and 7.5 ng/dl respectively. Fractional excretion of Mg using the formula $FEMg = 100 * (\text{UrineMg} * \text{PlasmaCr}) / (0.7 * \text{PlasmaMg} * \text{UrineCr})$ was 121% confirming renal Mg wasting. Her serum bicarbonate of 22mmol/L and absence of salt wasting ruled out Gitelman syndrome. Review of medications revealed that she was chronically on esomeprazole 40 mg daily for presumed GERD. Esomeprazole was stopped, and with continued magnesium supplementation her repeat K and Mg were within normal range as outpatient. Repeat 24 hour urinary Mg was pending at the time of abstract submission.

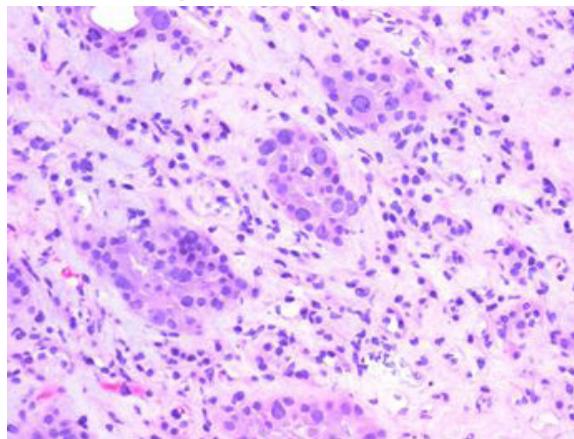
Discussion: The kidneys are highly efficient organs in Mg conservation with most of filtered Mg being reabsorbed in the thick ascending limb of the loop of Henle. It is speculated that patients who develop hypomagnesaemia on long-term PPI treatment may harbor one or more heterozygous mutation(s) of the gene Tmpr6, Fxyd2, Kcnj10, or Kcna1 involved in the modulation of Mg reabsorption in the distal nephron, leading to diminished efficiency of the encoded protein(s). This situation could involve a continuous low-grade Mg leak and facilitate the development of Mg depletion when combined with factors that decreases intestinal magnesium absorption.

FR-PO044

Viral Inclusions Excluding BK: Case Report of JC Virus Renal Allograft Nephropathy Deanne Leonard,¹ Cherise M. Cortese,¹ Xochiquetzal J. Geiger,¹ Lynn D. Cornell,² D. Jane Hata,¹ Mary B. Prendergast.¹ ¹Mayo Clinic, Jacksonville, FL; ²Mayo Clinic, Rochester, MN.

Introduction: JC virus, a DNA polyomavirus, infects 70-80% of asymptomatic adults with clinical significance in immunocompromised hosts; known for causing progressive multifocal leukoencephalopathy, a fatal disease resulting in demyelination from infected oligodendrocytes. The paucity of data on JC virus nephropathy makes it essential to report this case.

Case Description: 76 year old male with diabetes mellitus and end stage renal disease underwent a deceased donor kidney transplant with basiliximab induction and a standard steroid taper. He experienced self-limited diarrhea with negative work up. Maintenance immunosuppression included mycophenolate mofetil, prednisone and tacrolimus, with levels 4.5-8.2. Serum CMV PCR: negative. Year 1, serum creatinine: 1.4mg/dL, urine protein to creatinine ratio 0.05 gm, negative urinalysis. Allograft biopsy: normal glomeruli, 5% tubular atrophy, mild tubulitis not meeting criteria for rejection and several large medullary viral inclusions but minimal plasma cells, C4D negative.



Serum/urine BK PCR: consecutively negative. Immunohistochemistry on tissue sections: positive for BK (SV40 T antigen which cross reacts with JC). In-situ hybridization for JC and BK viruses: positive in medullary tubular epithelial cell nuclei. Reduction in immunosuppression resulted in renal improvement.

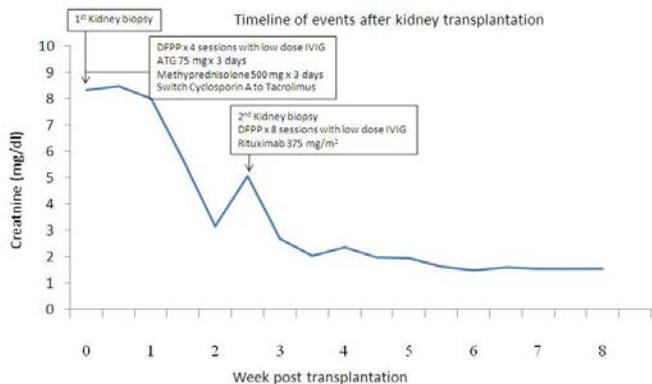
Discussion: Kantarci et al, 2011 summarized only 9 cases ever in existence. It is important to note that the scarcity of cases results in a small pool of patients from which to draw direct correlations. This case emphasizes the importance of other polyoma viruses in biopsy positive "BK" with minimal plasma cells and negative serum/urine thus broadening the differential on viral nephropathy and emphasizing the existence of non BK viral nephropathy.

FR-PO045

Successful Treatment of Anti-Angiotensin II Type 1 Receptor Antibodies Associated with Refractory Antibody-Mediated Rejection and Acute Cellular Rejection in Kidney Transplantation: A Case Report Punlop Wiwattanathum, Atiporn Ingsathit. Nephrology Unit, Faculty of Medicine Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand.

Introduction: Angiotensin II type 1 receptor (AT1R) antibody has been proved that it can be detrimental to kidney allograft. Similar to HLA-antibody, patients who have AT1R antibody are at risk for rejection and poor allograft outcome. There is no standard treatment in this situation but the aim is to remove pathologic antibodies and suppress antibodies production. Outcomes after treatment are unsatisfied and not well established. Herein we present a successful treatment kidney transplant patient who experienced AT1R antibody associated rejection.

Case Description: A 50-year-old male with hypertension and ESRD underwent a disease donor kidney transplantation using a graft from acute kidney injury donor with peak serum creatinine of 1.24 mg/dl. No intraoperative complication occurred, urine flow rate of 300 ml/hr was observed immediate postoperative but abruptly decreased to 20 ml/hr at 8 hours posttransplantation. Acute rejection was suspected, thus allograft biopsy was done. The histopathological findings were compatible with acute cellular rejection combined with antibody-mediated rejection (ABMR). AT1-R antibody was detected at level of 15.0 u/ml. Anti-rejection therapies were offered with steroid, IVIG, plasmapheresis, anti-thymocyte globulin and rituximab. At 8 weeks posttransplantation, rejection was well controlled with stable serum creatinine of 1.5 mg/dl.



Discussion: Although AT1R antibody associated rejection has rarely been reported, the outcomes after rejection are unsatisfied. Early detecting rejection and rapid antibody removal seem to be the most effective treatment that prolong allograft function in present time. There are limited and controversial data about long term graft survival by treating patient with angiotensin receptor blocker.

Funding: Government Support - Non-U.S.

FR-PO046

Hemodiafiltration for Hepatic Encephalopathy Induced by Budd-Chiari Syndrome in a Patient with End-Stage Kidney Disease Takuya Wakamatsu, Suguru Yamamoto, Takeshi Nakatsue, Junichiro J. Kazama, Ichiei Narita. Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Introduction: Budd-Chiari Syndrome (BCS) is defined as portal hypertension caused by obstruction of the inferior vena cava at the liver. Severe BCS induces hepatic encephalopathy, and has known to be exacerbated during hemodialysis (HD) treatment in end-stage kidney disease (ESKD) patients, probably due to lowering branched-chain amino acid (BCAA)/aromatic amino acid (AAA) ratio and reducing blood flow in the portal vein. Hemodiafiltration (HDF) has been proposed be effective for some dialysis-related complications due to better removal of middle sized uremic toxins and preservation of plasma osmolality, compared with HD. Here, we present a patient with ESKD who developed hepatic encephalopathy after progression of BCS, which was ameliorated by HDF.

Case Description: The patient was a 36-year-old woman complaining of a consciousness disorder. She was diagnosed with BCS as a consequence of antiphospholipid syndrome presented at 21 years of age. Her kidney function impaired gradually, and progressed to ESKD. After initiation of HD, transient loss of consciousness due to hepatic encephalopathy occurred frequently. After her blood purification therapy was changed to online HDF, her hepatic coma improved dramatically (West Haven grade, 0.07±0.27 vs. HD, 0.95±1.11). Compared with HD, increased the removal of AAAs (phenylalanine: 43.6% vs. HD, 10.7%; tyrosine: 73.0% vs. HD, 35.3%), contributing to the increased BCAA/AAA ratio was observed after HDF session.

Discussion: In this case, hepatic encephalopathy was worsened by HD treatment in a patient with ESKD due to BCS, and was improved by HDF, with increased removal of AAAs. Hepatic encephalopathy is thought to be exacerbated by HD due to portal systemic bypass or shunting and/or perturbation of the amino acid profile. Tryptophan, one type of AAA, has especially a high protein-binding rate (50%-80%), and only a small amount

of protein-bound tryptophan is removed by HD. Therefore, one of the reasons why HDF ameliorates hepatic encephalopathy is increased removal of protein-bound AAAs, leading to increased BCAA/AAA ratio.

FR-PO047

De Novo Lupus Nephritis in a Stable Kidney Transplant Recipient Laura Panarey, Karthik M. Ranganna, Alden Michael Doyle. Div of Nephrology & Hypertension, Drexel Univ Hahnemann Hospital, Philadelphia, PA.

Introduction: De Novo Lupus Nephritis (LN) is an exceedingly rare complication in kidney transplant recipients, previously reported only twice, neither recipient noted to have clinical manifestations of SLE. The scarcity of autoimmune disease in this population is not fully understood, but has been attributed to the maintenance immunosuppression used to prevent allorecognition and rejection.

Case Description: Herein, we present de novo LN in a 55-year-old woman with post streptococcus glomerulonephritis and HTN; 28 years status-post living-related kidney transplant. The patient had no personal or family history of autoimmune disease at time of transplant. Three years ago, she began complaining of episodic carpo-pedal spasm and scleritis; laboratory abnormalities included mildly low albumin and stable 1g proteinuria. Medications were stable and no potentially provocative antigens, vaccines or transfusions, were given during this period. Immunosuppression included cyclosporine and low dose prednisone. Seven months ago, the patient developed malar rash and hemo-proteinuria prompting immunological studies and kidney allograft biopsy. Anti-nuclear, double stranded DNA, smith and histone antibodies were all strongly positive with low serum complement levels. Serum creatinine increased by 0.5 mg/dL from baseline; urine protein to creatinine ratio revealed nephrotic range proteinuria peaking at 9.6grams. Immunofluorescence revealed granular “full house” pattern, C4d negative; Electron microscopy revealed intramembranous deposits. The patient was treated with high dose prednisone, continued cyclosporine and addition of mycophenolate mofetil.

Discussion: Although rare, de novo auto-immune disease should be considered for transplant patients despite maintenance immunosuppression.

FR-PO048

Atypical Hemolytic Uremic Syndrome Allograft Outcome in the Post Eculizumab Era Laura Panarey, Karthik M. Ranganna, Alden Michael Doyle. Division of Nephrology & Hypertension, Drexel Univ Hahnemann Hospital, Philadelphia, PA.

Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is an exceedingly rare etiology of renal failure; recurrent forms of HUS are often linked to underlying viral illness or particular classes of immunosuppression in transplant recipients. Exceedingly rare are genetic etiologies of aHUS for which transplantation is undesirable due to very high recurrence rates of disease.

Case Description: Herein we describe a case of misdiagnosis; 78 year old man initially diagnosed with rapidly progressive glomerulonephritis (RPGN) by kidney biopsy developed anuria necessitating hemodialysis. The patient had no family history of kidney disease. Immunological work-up negative for Anti-nuclear or cytoplasmic antibodies; complement deemed within normal limits. Pt received a living-unrelated kidney transplant from a 40 year old healthy donor. Standard induction solumedrol and thymoglobulin. Initiation of maintenance calcineurin inhibitor (CNI), steroid, antimetabolite. Favorable outcomes were observed, creatinine 1.77 mg/dL and urine output upon discharge. One week post-transplant, patient was observed to have increased creatinine, peak 4mg/dL, not amenable to discontinuation of CNI or typical offending agents; prompting renal biopsy. Histologically Thrombotic Microangiopathy (TMA), C4d (-) observed and deemed comparable to native biopsy slides. Laboratory studies confirmed aHUS: (-)ADAMSTS13; low lactate dehydrogenase, elevated haptoglobin; peripheral smear schistocytes. Negative viral studies including Shiga toxin. Pt was treated with high dose solumedrol, plasma exchange and eculizumab; resolution of kidney function, creatinine 1.88 mg/dL, month post-transplant period. Interim six month follow-up, with twice monthly eculizumab reveal no recurrent TMA on biopsy; despite bouts of acute kidney injury related to CNI levels or volume fluctuations.

Discussion: aHUS, as presented above, may be misdiagnosed and therefore present at the time of post-transplant recurrence. With the advent of treatment, alternative pathway complement inhibitor eculizumab; a high degree of suspicion must be maintained when managing post-transplant dysfunction.

FR-PO049

An Unusual Manifestation of Disseminated Histoplasmosis in a Renal Transplant Patient Kana N. Miyata, Lilly M. Barba. Nephrology, Harbor-UCLA Medical Center, Torrance, CA.

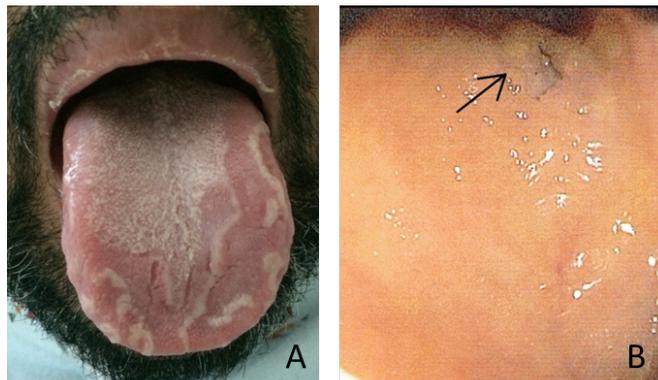
Introduction: Disseminated histoplasmosis is rare but can develop in immunocompromised patients. We present a case of histoplasmosis presenting as fever of unknown origin with oral and gastrointestinal (GI) manifestations.

Case Description: The patient is a 42 year-old man with ESRD secondary to unclear etiology, who had a living related renal transplant from his cousin 4 years ago in Mexico. He was born in El Salvador, moved to California at age 7, and had traveled to Mexico and Cuba (last travel 1 year ago). His post-transplant course was complicated by antibody mediated rejection and borderline acute cell mediated rejection 2 years ago, for which he was successfully treated with IVIG, plasma exchange, and rituximab. His medication included tacrolimus, MMF, and prednisone. He presented with 2-3 weeks of fever and mild abdominal pain after unsuccessful treatment with ciprofloxacin. He had fever of 38.7

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

°C, painless tongue ulcers (Fig.A), and mild periumbilical tenderness. CT chest/abdomen showed multiple lung nodules, mild mediastinal lymphadenopathy, and a severe wall thickening of the distal loop of ileum. Colonoscopy revealed an 8 mm ulcer at terminal ileum (Fig.B), whose pathology was positive for intracellular *Histoplasma capsulatum*. Urine histoplasma antigen was positive. He improved soon after oral itraconazole was started.



Discussion: This is an unusual case of disseminated histoplasmosis. Histoplasmosis is most commonly diagnosed in the first year after transplant. Fever, fatigue, and dry cough are the most common presenting symptoms, and GI manifestations are recognized clinically in less than 10% of cases. Post-transplant histoplasmosis remains a rare event with only 1 case per 1000 person-years but the mortality is as high as 10%. We should maintain a high index of clinical suspicion to diagnose and treat it properly.

FR-PO050

Successful Strategy for Management of Anuric Acute Kidney Injury Complicated by Severe Hyponatremia Using Continuous Venovenous Hemodialysis Rahul N. Pawar, Rajat Lamba, Amy R. Patel, Venkata Buddharaju, Michael D. Klein. *Nephrology, Westchester Medical Center, Valhalla, NY.*

Introduction: Anuric acute kidney injury (AKI) with hyponatremia presents a therapeutic challenge. Hemodialysis (HD) using a standard Na⁺ bath can cause excessive correction of [Na⁺], and a risk of osmotic demyelinosis. We report the controlled correction of hyponatremia via continuous venovenous HD (CVVHD) against a standard bath using an infusion of dextrose 5% in water (D5W) to blunt the [Na⁺] shift.

An 83 year old man with respiratory failure developed altered mentation and oliguria. Labs demonstrated severe hyponatremia with [Na⁺] 119 mEq/L, [K⁺] 6.8 mEq/L, and AKI with BUN 46 mg/dL, creatinine 3.08 mg/dL. Emergent renal replacement therapy (RRT) was required, but HD would have risked overly rapid correction of [Na⁺]. Instead, we started CVVHD with a [Na⁺] 140 mEq/L bath. The dialysate rate was 2 L/hr and blood flow rate was 200 cc/min. Net target was zero, with all drips included in the calculation. We simultaneously infused D5W at 100 cc/hour. [Na⁺] was monitored every 4 hrs. The D5W was held if the CVVHD was stopped for any reason. The D5W was to be increased if the [Na⁺] rise was > 0.5 mEq/hr or 6 mEq in 24 hrs. It was to be reduced if the correction was suboptimal. The patient's [Na⁺] rose from 118 mEq/L to 125 mEq/L on day 1, 125 mEq/L to 131 mEq/L on day 2, and reached 137 mEq/L by day 3. The patient was then safely converted to HD.

Discussion: CVVHD is a safer option for RRT than HD in the setting of severe hyponatremia, but low Na⁺ CVVHD dialysate is not available. Some have suggested adjusting the dialysate [Na⁺] using sterile water to achieve the desired [Na⁺] prior to treatment. This may produce a predictable response in [Na⁺], but there are concerns for infection and/or dosing error which makes this strategy problematic. Reducing dialysate or effluent flow, though effective, often results in unacceptable clearances. We demonstrated, that CVVHD with a standard Na⁺ bath, a separate D5W drip, and strict monitoring of [Na⁺], can yield a predictable response in [Na⁺], obviating the cumbersome and risky point of care manipulations of the dialysate formula.

FR-PO051

Case Report: Renal Squamous Cell Carcinoma of a Native Kidney After Renal Transplant Adam Daniel Jakes,¹ Poonam Jani,² Mini Menon,³ Kate Adams,⁴ Matthew Edey,³ Stewart Fleming,⁵ Sunil Bhandari.³ ¹Dept of Renal Medicine, Hammersmith Hospital, London, United Kingdom; ²Hull York Medical School, Hull, United Kingdom; ³Dept of Renal Medicine, Hull Royal Infirmary, Hull, United Kingdom; ⁴Dept of Infection & Tropical Medicine, Castle Hill Hospital, Hull, United Kingdom; ⁵St. James's Univ Hospital, Leeds, United Kingdom; ⁶Cellular and Molecular Pathology, Ninewells Hospital, Dundee, United Kingdom.

Introduction: Renal squamous cell carcinoma is a rare primary tumour of the kidney, which rapidly invades local structures and has a poor prognosis. Presentation is usually non-specific and is associated with renal stone disease and chronic infection. We present a case of squamous cell carcinoma of a native kidney in a renal transplant recipient, which has not previously been described in the literature.

Case Description: A 46-year-old white male with previous renal stones and recurrent urinary infections underwent a right nephrectomy and subsequent renal transplantation due to failure of the remaining kidney. Five years post-transplant, an abdominal ultrasound scan was performed due to recurrent urinary infections and ongoing pyuria. This was reported as normal, but he later developed a discharging sinus in his left flank. A CT scan revealed a tracking peri-nephric abscess with an associated cystic lesion of the left kidney. A left nephrectomy was performed and histological examination suggested an invasive squamous cell carcinoma of the renal pelvis. The patient later required major surgery for chronic infection, and further imaging revealed metastatic disease, resulting in the decision to manage palliatively.

Discussion: Renal transplant recipients are three-four times more likely to develop a malignancy than the general population. The patient also had renal stone disease and recurrent urinary infections; further increasing his risk of developing this condition. Abdominal ultrasound was unhelpful and only a later CT scan revealed the underlying malignancy. Given the non-specific nature of the symptoms and the poor prognosis, healthcare professionals should have a lower threshold for diagnostic imaging in these patients. This should be expedited if there is a persistent abnormality on urinalysis.

FR-PO052

A Case of Hydronephrosis due to Adenovirus Hemorrhagic Cystitis following Peripheral Blood Stem Cell Transplantation for Malignant Lymphoma Rio Noto,¹ Hideki Yokoi,² Akihiro Yoshimoto,¹ Motoko Yanagita.² ¹Clinical Nephrology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan; ²Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Introduction: In patients receiving stem cell transplantation (SCT), adenoviral infections are associated with mortality and morbidity. Cystitis is the most common clinical presentation of adenoviral urinary tract infection, which unusually causes inflammation of the upper urinary tract. We report a rare case of adenoviral ureteritis accompanied by hydronephrosis after autologous peripheral blood SCT.

Case Description: A 50-year-old male, who had undergone SCT 4 months ago for the treatment of nasal-type extranodal NK/T cell lymphoma and received tacrolimus as prophylaxis for graft-versus-host disease, developed fever, right back pain and dysuria. Computed tomography (CT) showed perirenal and periureteral fat heterogeneity and dilation of the right ureter. He was diagnosed as pyelonephritis caused by ureteral stones (already dropped), but antibiotics did not relieve symptoms. In addition, he exhibited a left solitary pulmonary mass, which was diagnosed as *Mycobacterium avium* complex (MAC) infection by lung needle biopsy. Cystoscopy and retrograde pyelography revealed hemorrhagic cystitis and right ureteral stenosis, where a catheter was placed. Viral PCR test was performed for differentiating hemorrhagic cystitis, and adenovirus was detected both in urine and in blood. Symptoms and abnormal findings on CT were improved by the placement of a catheter and the decrease of tacrolimus dosage.

Discussion: Differential diagnoses were urothelial carcinoma, recurrence of malignant lymphoma, retroperitoneal fibrosis and disseminated MAC disease. Urine cytology result was negative for malignancy. Gallium scintigraphy excluded recurrence of malignant lymphoma. Fat heterogeneity disappeared after catheter placement, suggesting that malignant lymphoma and retroperitoneal fibrosis were unlikely. MAC was not detected from blood and urine cultures. Clinical course and laboratory data indicated that inflammation of adenoviral hemorrhagic cystitis spread to the right ureter, leading to ureteral stenosis and hydronephrosis in an immunocompromised patient after SCT.

FR-PO053

Unusual Cause of Thrombocytopenia in a Dialysis Patient Rahul N. Pawar, Savneek S. Chugh, Amy R. Patel, Rudrick V. Ledesma, Rajat Lamba. *Nephrology, Westchester Medical Center, NY.*

Introduction: Hemodialysis (HD) is an invasive treatment with many adverse effects, thrombocytopenia being one of them. Most of the cases of thrombocytopenia on dialysis are related to the use of heparin creating auto-antibodies leading to heparin induced thrombocytopenia (HIT). Here we report a case of severe thrombocytopenia, which was initially thought to be due to HIT, but later revealed to be secondary to a specific dialyzer membrane.

An 81 year old female started on HD 2 months prior for progressive CKD was sent to the ED for excessive bleeding around the tunneled catheter site and a platelet (PLT) count of 27 K/uL. When she was first started on inpatient HD, she was found to be thrombocytopenic and heparin autoantibodies were weakly positive so she was started on argatroban. At the 1st outpatient HD unit, her PLT count increased to 200 K/uL. After transferring to a 2nd outpatient HD center, her PLT count, once again, dropped to 27 K/uL along with recurrent bleeding at the catheter site. This prompted investigation of heparin exposure as a cause, but it was revealed that the patient never received heparin during any of her treatments. Despite being restarted on argatroban, her PLT count remained in the 20 K/uL range. The serotonin release assay was negative. It was noted that the hospital and the 2nd outpatient unit both used a F160NR dialyzer, different from the dialyzer used in the first outpatient unit. With the suspicion of a possible dialyzer reaction, the membrane was switched from F160NR to Gambro Revaclear. Her PLTs increased to 125 K/uL in 4 days. Discharge instructions indicated that the patient must use a Revaclear dialyzer. A week later, repeat PLT count was noted to be 200 K/uL.

Discussion: This case demonstrates a rare dialyzer reaction, in which a specific dialyzer membrane leads to severe thrombocytopenia and bleeding. It has been postulated that complement activation might have a role, but this patient had normal complement levels

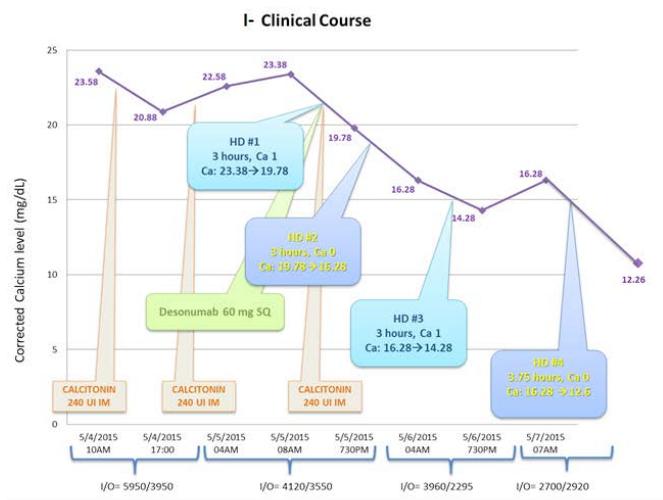
and a negative coombs test. Heparin induced reactions are still the most common etiology of thrombocytopenia in HD patients, but other causes, such as a dialyzer reaction should be considered as part of the initial differential.

FR-PO054

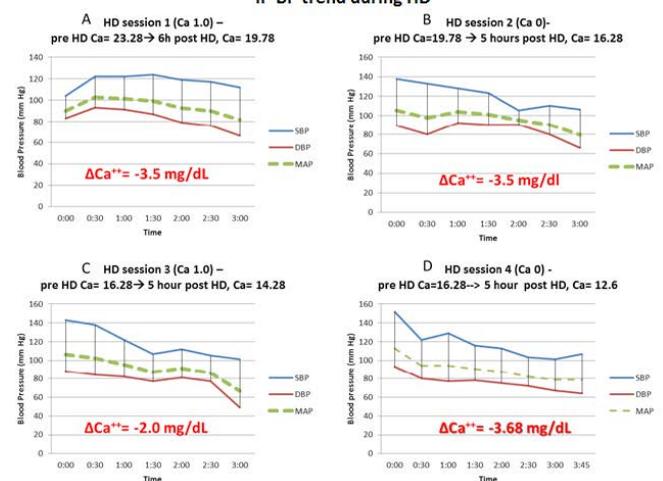
Calcium Free Dialysis for Hypercalcemic Crisis Karim El Hachem, Eduardo J. Zouain, Isha Gupta, Anip Bansal. *Nephrology, Mt Sinai- St Luke's Hospital, New York, NY.*

Introduction: Hypercalcemic crisis, a potentially life-threatening condition, has been defined as a calcium of 14 mg/dl or more with evidence of multi-organ dysfunction including cardiovascular, renal or CNS involvement. We describe a case of hypercalcemic crisis due to primary hyperparathyroidism treated with low calcium/calcium free dialysis.

Case Description: A 62 year old healthy man was brought by his wife to the ED for lethargy, worsening confusion over 3 days, weight loss and constipation. On exam, he was hemodynamically stable, had flat jugular veins and dry mucous membranes. His corrected calcium was 23.58 mg/dL with a creatinine of 3.60 mg/dL. He was aggressively hydrated with normal saline and received a total of 2 doses of Calcitonin 240 IU IM with no improvement in his mental status or in his calcium levels. He was then given Denosumab 60 mg SQ and underwent a 3 hour session of low calcium dialysis (Ca bath 1.0 mEq/L). During the treatment, he was given NS boluses in addition to his maintenance NS 250 cc/hr to avoid hypotension. He subsequently underwent 3 additional treatments (Treatments 2 and 4- using calcium free dialysate and Treatment 3- using Ca 1.0 mEq/L) that were well tolerated. Following his 2nd treatment, his mental status improved significantly. After his 4th treatment, his calcium was 12.26 mg/dL. His intact PTH was 1324 pg/mL. A Sestamibi thyroid scan showed a large left parathyroid mass. The patient underwent surgical resection of a 13 gm parathyroid adenoma after which his calcium normalized to 9.8 mg/dL. His clinical course and a blood pressure trend during hemodialysis is reported below.



II- BP trend during HD



Discussion: Calcium free dialysis and the use of low calcium dialysate was tolerated with no hemodynamic instability. Aggressive hydration is important to maintain tolerability. It can be safely used as a bridge to definitive surgical treatment in the setting of primary hyperparathyroidism.

FR-PO055

Antineutrophil Cytoplasmic Antibody Crescentic Allograft Glomerulonephritis following Sofosbuvir Therapy Shilpa Gadde. *Nephrology, Tulane Univ, New Orleans, LA.*

Introduction: Sofosbuvir is used for the treatment of hepatitis C virus infection. We report first case of ANCA/RPGN following Sofosbuvir in a kidney transplant recipient.

Case Description: 51 yo male had a living unrelated donor kidney transplant, received alemtuzumab induction, and tacrolimus and mycophenolate maintenance. sCr was 1.4, 1 week after transplant. 12 weeks post-transplant, sCr was 2.0; renal biopsy showed ATN and tubular isometric vacuolization. Tacrolimus was replaced with cyclosporine. His sCr stabilized at 1.6. He had HCV genotype 1a and high viral load. At week 40 after transplant, he was started on ribavirin and sofosbuvir. At 12 weeks of HCV treatment, sCr was 3.7. UA with 30 protein and 131 RBCs, and PCR was 0.6. Allograft biopsy showed TMA. Therefore, sofosbuvir, ribavirin and cyclosporine were stopped. He was started on prednisone and continued on mycophenolate. His sCr was at 2.4. 70 weeks after transplant (30 weeks after initiation of sofosbuvir and ribavirin treatment), he had a sCr of 4.3 and PCR of 5. Urinalysis showed >500 of protein, 70 RBCs. Biopsy showed cellular crescents in glomeruli with pauci-immune IF. EM had normal GBM with subendothelial "fluff". p-ANCA titer was 1:320 and MPO ab >100. He was diagnosed with p-ANCA associated crescentic GN in the allograft. The patient was treated with solumedrol, cyclophosphamide and a course of plasmapheresis. He later started HD and Rituximab was added. He remains dialysis-dependent despite of our efforts in treating his RPGN.

Discussion: Renal biopsy showed 3 different pathologies. Initially tubular toxicity of tacrolimus. After sofosbuvir and ribavirin, he had TMA, we stopped his HCV treatment, although the concurrent cyclosporine use was implicated. 30 weeks after the initiation of sofosbuvir and ribavirin therapy he had ANCA-associated crescentic GN. Ribavirin had no reported cases of ANCA vasculitis. Sofosbuvir was approved in 2013 and we suspect it as likely cause of ANCA vasculitis. Therefore, our case represents the first case of drug-associated ANCA vasculitis in an allograft kidney. Further drug monitoring is necessary to elucidate the degree of association and possible causal effect of sofosbuvir and p-ANCA vasculitis.

FR-PO056

Malignant PEComa Post Combined Kidney and Pancreas Transplantation Rapeepat Lekham, Mauricio Alexander Pedroza, Gitana Bradauskaitė, Daranee Chewaproug. *Medicine, Nephrology, Albert Einstein Medical Center, Philadelphia, PA.*

Introduction: Perivascular epithelioid cell tumors or clear cell "sugar" tumor or PEComas is a very rare mesenchymal neoplasm. The biological behavior of such tumors can range from benign to malignant. We report the first case of primary renal malignant PEComas with lung metastasis after combined kidney and pancreas transplantation.

Case Description: The patient was a 44-year-old Hispanic female with a history of DM type I with living related kidney transplant back in 1998 and followed by a pancreas transplant in 1999 with transplant pancreatectomy and retransplant of the second pancreas in 2010. Her immunosuppressive agents were mycophenolic acid, prednisone and tacrolimus. Fifteen years post-kidney-transplant, she developed fever with chronic cough for a month. CT of the chest revealed multiple, bilateral, solid, non-cavitating pulmonary masses with mediastinal lymphadenopathy. CT of the abdomen showed right native kidney mass measured 5.8x5.8x8 cm. Right lower lobe lung biopsy showed perivascular epithelioid cell neoplasm. The PEComas of the lung are traditionally considered benign. To investigate the nature of the renal mass, the patient underwent right open radical nephrectomy. Again, the right nephrectomy pathology showed malignant PEComa, 10 cm with pure epithelioid with carcinoma-like growth pattern, involving the entire kidney. The tumor is histologically identical to the patient's lung mass and confirms that the kidney mass is the primary tumor and the lung tumor is a metastasis. The patient also found metastatic osteolytic lesions involved pelvis, proximal femurs, cervical and thoracic spines. After confirmed the diagnosis of malignant PEComas, mycophenolic acid was stopped. She was started on Temsirolimus 25 mg intravenous weekly, tacrolimus was changed to rapamycin and continue with oral prednisone. Unfortunately 3 weeks later patient became unresponsive, cardiac arrest and passed away.

Discussion: Although the majority of PEComas is recognized as benign, but in the immunocompromised patient, especially with a history of multiple solid organ transplants like in our patient, the tumor could be presented in advance and aggressive way with fatal outcomes.

FR-PO057

A Case of Post-Transplant Kaposi Sarcoma Treated with Combination Chemotherapy and mTOR Inhibitor Nadeen J. Khoury, Dina Abdelwahab, William S. Asch. *Internal Medicine/Nephrology, Yale Univ School of Medicine, New Haven, CT.*

Introduction: Kaposi sarcoma is a viral-induced malignancy caused by human herpes virus 8. Clinical presentation varies from minimal mucocutaneous disease to extensive organ involvement. We present a case of transplant-associated visceral Kaposi sarcoma without cutaneous manifestations treated with sirolimus and liposomal doxorubicin.

Case Description: A 43 y old African American male with history of ESRD s/p deceased donor kidney transplant in 2013 induced with alemtuzumab, maintained on tacrolimus, mycophenolate and prednisone was admitted with worsening shortness of breath and productive cough. His course was complicated by hypoxemic respiratory failure requiring intubation. He received broad-spectrum antibiotics initially and his anti-

proliferative was held. His exam was unremarkable except for an exophytic gingival lesion on his right mandible. His kidney function was at baseline. Imaging revealed diffuse lung and liver nodularities with bulky lymphadenopathy. An axillary lymph node biopsy was performed and was consistent with Kaposi sarcoma (HHV8+). Tacrolimus was stopped and the patient was transitioned to the mTOR inhibitor: sirolimus. He was initiated on liposomal doxorubicin after extubation with significant improvement in metastatic disease after four cycles. His renal function remained stable on sirolimus and prednisone.

Discussion: Post-transplant malignancies are common and constitute a major burden. Adjustment of immunosuppression is the mainstay of therapy in these cases. It is standard of care to switch from calcineurin inhibitors to sirolimus upon the diagnosis of Kaposi sarcoma. However, there's no literature regarding chemotherapy in transplant-associated Kaposi sarcoma. Most of the available data is from the AIDS population that we extrapolated to our patient. His bulky disease triggered us to explore aggressive therapy. Combination chemotherapy and sirolimus seem to be a good therapeutic strategy that should be considered in cases of disseminated post-transplant Kaposi sarcoma.

FR-PO058

Warfarin-Related Nephropathy in a Kidney Transplant Patient Nadeen J. Khoury,¹ Gilbert W. Moeckel,² Mark A. Perazella.¹ ¹*Nephrology, Yale Univ, New Haven, CT;* ²*Dept of Pathology, Yale Univ, New Haven, CT.*

Introduction: Anticoagulant-related nephropathy is a new entity manifesting as AKI in the setting of excessive anticoagulation. Initial cases were related to warfarin use; however, more recently AKI is reported with direct thrombin inhibitors. We present biopsy-proven warfarin-related nephropathy (WRN) in a transplant patient on anticoagulation for atrial fibrillation with INR<2.

Case Description: A 69 y old man with hypertension, atrial fibrillation (on warfarin), T2DM and ESRD s/p living unrelated kidney transplant with baseline sCr 2.0 mg/dl (on cyclosporine, mycophenolate and prednisone) presented with nausea, vomiting and abdominal pain. Acute cholecystitis was diagnosed and percutaneous cholecystostomy drainage performed. Initial labs revealed leukocytosis and AKI on CKD with sCr: 2.7 mg/dl. INR was 1.8. Urinalysis revealed 3+ blood, 2+ protein with 179 RBCs/HPF, urine sediment 1-2 RBC casts/LPF. Transplant kidney ultrasound was unremarkable. Complements were normal. Urine microscopy demonstrated persistent RBC casts and kidney biopsy was performed. Acute tubular injury with numerous occlusive RBC casts suggestive of WRN was observed. Kidney function slowly improved but sCr remained above baseline upon discharge. Warfarin was resumed due to high stroke risk.

Discussion: Our patient's presentation with AKI in the setting of acute cholecystitis raised the possibility of sepsis-induced AKI. However, the presence of microscopic hematuria and numerous RBC casts suggested a glomerular process. Biopsy suggested WRN developing in the setting of CKD and anticoagulation. Our case is somewhat unusual given the INR<2. Most cases of WRN have an INR>3. However, the patient had risk factors that have been linked to WRN including CKD, diabetes mellitus and hypertension. Interestingly, INR levels several months prior were all consistently below 2 yet the patient had 2 bleeding episodes requiring hospitalizations (GI bleed and thigh hematoma) suggesting an underlying bleeding predisposition. It is reasonable to consider WRN in cases of unexplained AKI with RBC casts in a patient with INR<3 in the presence of other risk factors and bleeding tendency.

FR-PO059

Successful Preemptive Kidney Transplantation Using Rituximab Induction in a Patient with Focal Segmental Glomerulosclerosis and Nephrotic Syndrome – Case Report Aureliusz Kolonko, Grzegorz Piecha, Andrzej Wiecek. *Dept of Nephrology, Transplantation and Internal Diseases, Medical Univ of Silesia, Katowice, Poland.*

Introduction: Focal segmental glomerulosclerosis (FSGS) recurs in 30% of patients receiving their first kidney transplant and often leads to graft loss. In the past, patients with FSGS and overt nephrotic syndrome were rarely transplanted, mostly due to the worries about its relapse. Rituximab (RTX), an anti-CD20-specific monoclonal antibody, was previously reported to be valuable option in resistant nephrotic syndrome and in relapsing FSGS after second kidney transplantation. Hereby, we present a successful first kidney transplantation of a young patient with FSGS and full-blown nephrotic syndrome, treated with RTX induction.

Case Description: The patient is a 24-year-old woman, who developed nephrotic syndrome at the age of 4. FSGS was confirmed early by renal biopsy, she was treated with cyclosporine A, mycophenolate mofetil (MMF), and steroids, with no remission. She was referred to preemptive, deceased donor kidney transplantation despite of 10 g/day proteinuria. She received induction therapy with two doses of RTX (375 mg/m²) at day 0 and 7, followed by tacrolimus 5 mg BID, MMF 500 mg BID, and steroids therapy after transplantation. We observed immediate kidney graft function and protein-absent diuresis since 6th day post-transplant. Pre-transplant soluble urokinase plasminogen-type activator receptor (suPAR) serum concentration was 4550 pg/mL, it decreased to 2191 pg/mL at day 13th and was 2073 pg/mL at 6 months posttransplant. Steroids were tapered and discontinued at 10 months post-transplant. Twenty months after transplantation serum creatinine is 0.8 mg/dL and no proteinuria is observed.

Discussion: Successful kidney transplantation in a patient with pretransplant overt nephrotic syndrome secondary to FSGS, using rituximab as an induction therapy strongly suggest the need for larger clinical trials in such patients.

FR-PO060

Black Appearing Peritoneal Effluent Manjunath Ramaiah, Carol Motes Headley, Geeta G. Gyamlani, Adnan Naseer, Barry M. Wall. *Nephrology, Veterans Affairs Medical Center, Memphis, TN.*

Introduction: Endoscopic tattooing with India ink is a useful and safe tool for localizing small colorectal lesions.

Case Description: 60 year old man with End Stage Renal Disease due to Lupus Nephritis on Continuous Ambulatory Peritoneal Dialysis (CAPD), developed black effluent from the peritoneal dialysis drain bag following screening colonoscopy. Findings included an ulcerated tumor occupying 25% to 49% of the colon circumference. There was no evidence of bleeding and multiple forceps biopsies were taken. The tumor area was marked with tattoos using 3 injections (5 ml each) of India ink. He resumed CAPD and noticed his dialysate effluent was "black". He presented to the ER with nausea, vomiting and black colored peritoneal fluid. Examination revealed a mildly tender abdomen without rebound or guarding. Vitals were stable and he was afebrile. CT scan of abdomen revealed small amount of free intraperitoneal air consistent with his peritoneal dialysis. Peritoneal effluent cell count was elevated at 0.619 K/ul and WBC count of 5.5 K/ul. His presentation was consistent with peritonitis (cloudy dark gray/black peritoneal effluent and elevated cell count)and empiric antibiotics were initiated with vancomycin, cefepime and metronidazole. Within 48 hours the peritoneal effluent was clear (cell count down to 0.105 K/uL). The effluent culture grew *Escherichia coli* and *Providencia Sturtii*. Dialysate remained normal. At the time of partial colectomy performed one month later, dark dye was still visible on mesenteric transverse colon, but no abscess was identified.

Discussion: Complications associated with India ink tattooing include abscesses, inflammatory pseudotumor, focal peritonitis and peritoneal staining, most of which have been attributed to inadequate dilution or sterilization of the India ink. Dye spillage into the peritoneal cavity has been reported to occur at a rate between 2.4% and 13%. This occurrence has been attributed to injection technique (deep), and the possibility of transmural movement of the dye. In our patient the development of black appearing dialysate and bacterial peritonitis with gram-negative organisms is consistent with microperforation of the colon during the tattooing procedure.

FR-PO061

Sevelamer-Induced Colonic Injury – A Unique Case of Gastrointestinal Bleeding in End Stage Renal Disease Patient Nivin Haroon,¹ Unnikrishnan Ponnamma Kunjan Pillai,² Zeenat Yousuf Bhat.¹ ¹*Internal Medicine/ Nephrology, Wayne State Univ, Detroit, MI;* ²*Internal Medicine/ Nephrology, Indiana Univ Ball Memorial Hospital, IN.*

Introduction: End stage kidney disease patients experience significant morbidity and mortality. One common complication in this population is Gastro-intestinal bleeding(GIB) and common causes of GIB are platelet-dysfunction, anticoagulation use, Angiodysplasias and malignancies. Also medications like Sodium-polystyrene-sulfonate can cause direct mucosa damage. We report a case of GIB in Hemodialysis-patient attributed to Sevelamer-induced colonic-ulceration.

Case Description: 56Y/O ESRD-Hemodialysis patient with multiple comorbidities including hypertension, systolic cardiac-dysfunction, Atrial-fibrillation, H/o Breast Cancer s/p mastectomy/chemo(2005),presented to the hospital with passage of bright red blood per rectum,accompanied with syncope and shortness of breath. Her medications included Amiodarone, Aromasin, baby-Aspirin, Carvedilol, Diltiazem, Pantoprazole, Sevelamer, Cincalcet. Her clinical examination was unremarkable(including neurologic exam)except for palor. Orthostatic vital signs not checked due to dizziness, Significant labs findings were-hemoglobin-5.7mg/dl, Serum Potassium-5.5meq/L,BUN and Serum-Creatinine 46mg/dl and 8.5mg/dl respectively and INR-1.1. CT head- no acute abnormalities, Mesenteric angiogram-no source identified, Endoscopic-Gastro-duodenoscopy- normal, colonoscopy-no active bleeder, multiple diverticulosis+. Bleeding scan showed activity near the hepatic flexure. She underwent emergent right-hemicolectomy for the continued bleeding. Pathology report showed metastatic Carcinoma involving proximal Colon, Colonic-Mucosa inflamed and ulcerated,cluster of organophilic Fish scale like crystals suggestive of Sevelamer crystals were noted in colonic mucosa. Patient improved post surgery.

Discussion: There is only handful of literature on the Sevelamer colonic toxicity. This case highlight the fact that with widespread use of sevelamer in dialysis patient, physicians should be aware of this entity. Our understanding of Sevelamer-associated mucosal injury is limited and there are no known prevention strategies available.

FR-PO062

Successful Eculizumab Therapy in De Novo Atypical Hemolytic Uremic Syndrome in a Renal Transplant Recipient Adil Mohammad Hazara, Matthew Edey, Martin Chanayireh, Sunil Bhandari. *Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom.*

Introduction: The use of terminal complement inhibitor eculizumab has not been well described in the treatment of de novo atypical hemolytic uremic syndrome (aHUS) post renal transplantation.

Case Description: We present a 47 years old female with end-stage renal disease due to reflux nephropathy who had received a living-donor renal transplant from her sister 18 months previously. Her maintenance immunosuppression medications included tacrolimus 6mg twice daily, mycophenolate sodium 720mg (AM) and 360mg (PM), and prednisolone 5mg on alternate days. She presented with 2 day history of diarrhea, vomiting and dehydration. Admission biochemistry revealed stage III acute kidney injury with a serum creatinine of 640 µmol/l (baseline 90 µmol/l). She was anemic (Hb 90 g/l) and

required multiple blood transfusions. Her trough tacrolimus level was raised at 22 ng/l. Stool microscopy and culture was negative for shiga-toxin producing bacteria. Blood film showed red cell fragments; serum lactate dehydrogenase was raised at 752 u/l. ADAMTS-13 activity was normal. Renal biopsy was consistent with thrombotic microangiopathy. Complement genetic analyses (factors H, I, B and MCP tested) did not reveal any pathogenic mutations. Anti-factor H antibodies were negative. She was treated, first with four cycles of plasma exchange and then commenced on eculizumab at 900mg infusion weekly for first four doses and then 1200mg fortnightly. Her renal and anemia parameters rapidly normalised.



Fig 1. Changes in serum creatinine at the time of diagnosis (arrow), with plasma exchange (PEX) and following eculizumab treatment.

Discussion: Eculizumab has been used successfully in treatment of aHUS in our patient who had developed this condition de novo. Uncertainties still remain regarding the duration of treatment and long-term efficacy.

FR-PO063

Lowering of Dialysate Conductivity Stopped a Painful Sickle Cell Crisis in an ESRD Patient Amit N. Shah, Jacques A. Durr. *Div of Nephrology, Univ of South Florida, Tampa, FL.*

Introduction: Deoxy Hg-S gelation in sickle cell disease (SCD) is highly temperature-sensitive, and causes RBC sickling that impairs capillary flow and cause painful crises (Embury SH, PMID 15280086). On O₂ loss, the rate of gelation has a lag inversely related to the 30th power of its concentration (Hofrichter J, 4531026), and is in the range of capillary transit and circulatory times. Within limits, RBCs behave like perfect osmometers (Ponder E, 16994612). This led to claim that as RBC shrink during medullary transit Hg-S concentrates and sickling leads to papillary necrosis and hypostenuria in SCD (Perillie PR, 13942410). Similarly, some claimed that induced hyponatremia treats SCD crisis (Rosa RE, 6999348), others did not (Charache S, 7296001).

Case Description: A 42 yo SCD ESRD patient is admitted ~ once a month for severe pain crisis that last for several days and are not relieved by oxycodone, dilaudid, nasal O₂, or IV fluids, and not due to low dry weight. Her baseline HgB is 5-6 g/dl, and P₅₀ is stable at ~ 140 mmol/l. One of us was in the dialysis unit as she had a severe crisis, and had exhausted all resources. We asked for permission to lower her dialysate Na by 5-8 mmol/l.

This abolished her pain within ~10 min. She says that this was the first time something helped.

Discussion: We wish to call our colleagues' attention to this case, as SCD patients with ESRD and painful crises are not uncommon, and since an ingenious method (Du E, Proc Natl Acad Sci USA. 2015 Feb 3; 112(5): 1422-1427) is now available that allows to study RBC sickling kinetics during a mimicked capillary transit, under controlled conditions of temperature, tonicity, O₂ tension, pH, etc. There was a strong correlation between sickling and MCHC-S concentration, and MCV. However, the slope was negative between cell velocity and cell volume (R = -0.89, P < 0.001). This method should help resolve which factor predominates during RBC swelling induced by acute hyponatremia: the desired decrease in Hg-S concentration, or undesired decrease in RBC velocity in the capillaries (low O₂ tension). Our observation should trigger controlled studies. Would decreasing the dialysate temperature also have a positive effect?

FR-PO064

Hemophagocytic Lymphohistocytosis Associated Nephrotic Syndrome Caused by Cytomegalovirus Infection in a Renal Transplant Recipient Gaurav Agarwal,¹ Abolfazl Zarjou,¹ Todd M. Stevens,² Shikha Mehta.¹ *¹Div of Nephrology, Univ of Alabama at Birmingham; ²Dept of Pathology, Univ of Alabama at Birmingham, Birmingham, AL.*

Introduction: Hemophagocytic lymphohistocytosis (HLH) is a life threatening syndrome representing severe uncontrolled inflammatory reaction caused by hypercytokinemia and excessive immune activation. It is rare in solid organ transplantation and carries a mortality of 47%.

Case Description: 31 year old black man with end stage kidney disease who was status post deceased donor kidney transplant, received induction with alemtuzumab and was maintained on prednisone, mycophenolate mofetil and tacrolimus. He presented 4 months post-transplant with diarrhea and fever and was diagnosed with CMV disease with a viral load of 2.7 million copies/ml. He had acute kidney injury with serum creatinine (Cr) of 3.3 mg/dl. Despite 2 weeks of adequate antiviral therapy with IV ganciclovir and reduction of immunosuppression, patient continued to have high grade fever, worsening pancytopenia, AKI and developed new onset nephrotic range proteinuria of 15.5 gms/24 hrs. Kidney allograft biopsy revealed characteristic CMV inclusion bodies within glomerular endothelial cells and diffuse foot process effacement consistent with acute CMV glomerulopathy. There was no evidence of focal segmental glomerulosclerosis, thrombotic microangiopathy or rejection. He had pancytopenia, elevated ferritin level (15,605 ng/ml), transaminitis,

hypertriglyceridemia, elevated LDH and D-dimer. Patient met the clinical criterion for HLH. His nephrotic syndrome was attributed to HLH associated with CMV infection. Treatment was started with anakinra 100 mcg subcutaneously daily. Patient responded to the therapy with initial decline in serum Cr to 2.4 mg/dl. At 2 months follow up, proteinuria has improved to 2.1 g/g, ferritin to 1875 ng/ml, but Cr remains elevated at 3.6 mg/dl.

Discussion: Most cases of HLH in kidney transplant recipients are triggered by CMV infection or other herpesviruses. This is a unique case of HLH and nephrotic syndrome caused by CMV infection which is likely secondary to cytokine storm and histiocytic proliferation. Treatment with anakinra could be beneficial in these patients.

FR-PO065

BK Nephropathy in Allogeneic Stem Cell Transplant Recipient without Thrombotic Microangiopathy and Graft-Versus-Host Disease: A Unique Observation Rima N. Pai,¹ Maria del Pilar Fernandez,² Jai Prakash Babu Thippaiah Jaggedanahalli,² William F. Glass,³ Sairah Ahmed,⁴ Ala Abudayyeh.¹ *¹Section of Nephrology, UT MD Anderson Cancer Center; ²Nephrology and Hypertension, UT-Houston Medical School; ³Pathology, UT-Houston Medical School; ⁴Dept of Stem Cell Transplantation, UT MD Anderson Cancer Center.*

Introduction: BK virus is emerging as an important pathogen in allogeneic stem cell transplant (SCT) recipients and more prevalent in patients of Graft versus Host Disease (GVHD) and Thrombotic microangiopathy (TMA). Due to immunosuppression, different drugs and/or drug combinations have been associated with BK nephropathy such as tacrolimus. BK virus causes chronic kidney disease, ureteral stenosis and hemorrhagic cystitis in stem cell transplant patients leading to increase mortality and long hospital stay. We present a unique case of BK nephropathy that has occurred in patient who was asymptomatic and without any co-infections, TMA, or GVHD. The patient was tapered off tacrolimus which showed improvement in the BK viral urine and serum load.

Case Description: A 31-year-old female with history of Acute Myeloid Leukemia (AML) underwent an allogeneic stem cell transplant a year ago. Patient was treated with 4 cycles of Fludarabine, IDArubicin, CYTarabine (FIA) and sorafenib regimen. Post-transplant course was complicated by GVHD of gastrointestinal tract and skin (Grade I). Patient was maintained on tacrolimus and later tapered off. She remained asymptomatic; however, kidney function worsened with elevated creatinine at 1.8. BK Serum viral Load of 10,800 was seen. Therefore, renal biopsy was done which was consistent with BK nephritis. With limited effective therapeutic options, immunosuppression by tacrolimus was tapered off and Lefflumide was started showing a decrease in viral load and creatinine stabilizing to 1.37.

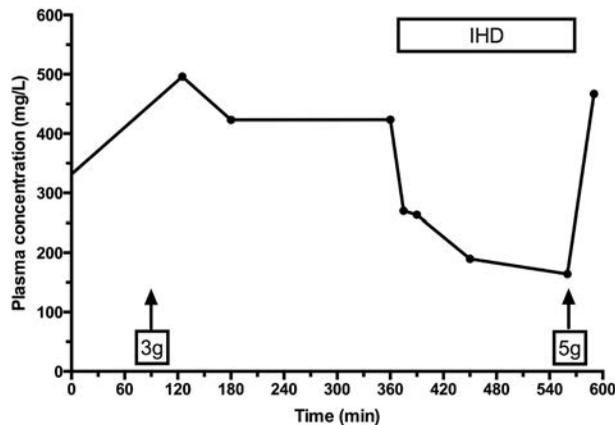
Discussion: A definitive diagnosis of BK nephritis is confirmed with a kidney biopsy. BK nephropathy is an important and often overlooked cause of chronic kidney disease in allogeneic stem cell transplant patients. This case report helps to recognize the much needed development of guidelines in detection and treatment of BKV for early intervention.

FR-PO066

Pharmacokinetics and Total Removal of Fosfomycin in a Patient with Chronic Kidney Failure Undergoing Haemodialysis Julius Schmidt, Jan T. Kielstein. *Nephrology, Medical School Hannover, Hannover, Germany.*

Introduction: Fosfomycin shows bactericidal activity against various gram-positive, gram-negative and anaerobic pathogens, including antibiotic resistant *S. aureus*. However, dosing of fosfomycin in critically ill patients undergoing renal replacement is based on scarce data.

Case Description: A female chronic dialysis patient (76 years, BMI 20) was admitted to our hospital due to distinct dorsalgia. Computed tomography of the lumbar spine unveiled spondylodiscitis of the thoracic vertebrae 11/12. A punch biopsy of the affected bone region showed focal osteomyelitis. As the patient was allergic to penicillin, antibiotic therapy with clindamycin and fosfomycin sodium (8 g per day, 3 g before, 5 g after IHD session) was initiated. Maximum plasma concentration after the 3 g infusion was 496 mg/L. IHD led to a distinct reduction of fosfomycin plasma levels of 61%, with a dialyzer clearance of 75 ml/min. The total amount of fosfomycin in the total collected dialysate was 2430 mg. C_{max} after the additional administration of 5 g of fosfomycin after IHD treatment was 467 mg/L.



Discussion: Fosfomycin dosing guidelines in dialysis patients are based on publications from the 1970s and 1980s. These publications indicate a high elimination of fosfomycin during hemodialysis with a dialyzer clearance of 60 ml/min. Modern dialysis even exceeds these clearance rates, as seen in this case report (75 ml/min). The large amount of fosfomycin in the total spent dialysate indicates the need for an additional dose after dialysis therapy. About 81% of the admitted dose of fosfomycin was found in the dialysate. This suggests, that intermittent hemodialysis can decrease fosfomycin serum levels beyond ranges, where minimal inhibitory concentrations in bone spongiosa can be achieved. Therefore, fosfomycin dosage after hemodialysis seems crucial to provide sufficient drug concentrations.

FR-PO067

Tumoral Calcinosis – A Rarely Seen Complication in Dialysis Patients
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Introduction: Tumoral calcinosis is characterized by solitary or multiple painless, periarticular soft-tissue calcium deposits. Tumoral calcinosis was first described by Giard and Duret in 1898 and 1899. There are two categories, a familial variant also called Teutschlaender disease and Secondary tumoral calcinosis also called Uremic tumoral calcinosis.

Case Description: Case : 50 year old female with end stage renal disease secondary to hypertension presented for evaluation of painful left shoulder mass. She has been on dialysis for 12 yrs. Has multiple painful swellings on her hands, elbow and feet. States that her shoulder mass appeared 2 years ago and has progressively increased in size. Also complained excruciating pain causing trouble carrying out her daily activities. Her surgical history significant for a right neck dissection for a neck mass, parathyroidectomy and a remote history of partial thyroidectomy. Physical examination significant for multiple soft immobile nodular swellings on the left shoulder, dorsum of left foot, right elbow and index finger. Mass on the left shoulder about 12 X 10 cm in size, immobile, tender and firm to palpation. The swelling on the right elbow non tender to palpation and the one on the right index finger involved the distal and proximal interphalangeal joints. Imaging studies showed nodular swellings with significant calcification. Excision of the left shoulder mass showed exudation of a chalky white material. Pathology results were consistent with tumoral calcinosis.

Discussion: Secondary tumoral calcinosis is associated with high serum Ca X P in dilaysis patients, secondary or tertiary hyperparathyroidism, aluminium intoxication and vitamin D overload. These lesions are painless but massive swellings can cause mechanical limitation, pain and neurovascular symptoms due to compression of adjacent structures. Management includes dietary phosphate restriction, noncalcemic phosphate binders, intense dialysis with a low-calcium dialysate and calcimimetics. Surgical excision is indicated in symptomatic lesions. Parathyroidectomy recommended in patients with persistently elevated PTH levels. Tumoral calcinosis resolves after successful renal transplantation.

FR-PO068

Palate Nodule in a Hemodialysis Patient: A Long and Winding Road Until Diagnosis
Precil Diego Miranda de Menezes Neves,¹ Ramaiana Aparecida Bridi,¹ Rosilene M. Elias,¹ Fábio Luiz de Menezes Montenegro,¹ Rosa M.A. Moyses,^{1,2} *Nephrology, Univ of São Paulo, Sao Paulo, Brazil;* ²*Univ Nove de Julho-UNINOVE, Sao Paulo, Brazil.*

Introduction: Secondary hyperparathyroidism (SHPT) is a common condition in end-stage renal disease patients. We highlighted a complication that usually affects long bones, a brown tumor (BT). We report a case of a patient with SHPT, with a palate nodule, which diagnosis investigation led to a BT of maxilla.

Case Description: A 25 years-old female, previously hypertensive, who returned to hemodialysis after her kidney transplant fails. She was referred to our CKD-MBD service with a 3-month history of a progressively enlarging submucosal nodule with hard consistency on her posterior left palate. The mass was painful since the beginning, and presented progressive growth. She had no fever, neither consumptive symptoms nor palpable lymph nodes. Before coming to our service, she was referred to a maxillofacial surgery service, where a computed tomography (CT) and a biopsy were requested, as no initial suspected diagnosis was done. CT disclosed a lytic bone lesion located in alveolar process

of maxilla, measuring 3.0 X 2.5cm, and damaging the superior molar roots, producing a bulging in the left maxillary sinus, nasal cavity and palate. Microscopy view evidenced the presence of multinucleated giant cells among ovoid and fusiform mesenchymal cells, large amount of hemorrhage and trabecular of lamellar bone tissue, being compatible with Brown Tumor. On review of her case, she confirmed that Sevelamer 1,6g thrice a day, but the administration of Vitamin D analogs was not possible due to hyperphosphatemia. Her serum intact Parathormone levels were 1,500pg/ml, Vitamin D 36ng/ml, ionized calcium: 4,8mg/dl, phosphorus: 6,1mg/dl. Technetium sestamibi parathyroid scan revealed hyperactive glands at both superior thyroid lobes and at the low cervical region. The patient was submitted to total parathyroidectomy, and the lesion is progressively decreasing despite of other modalities of treatment.

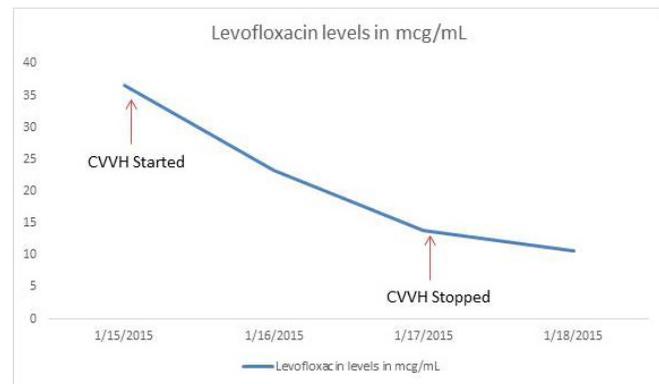
Discussion: Brown Tumors must be kept in mind as a differential diagnosis in patients with SHPT even when these lesions are located in unusual sites such as the maxilla.

FR-PO069

A Case of Levofloxacin Toxicity Treated with Continuous Veno-Venous Hemofiltration
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Introduction: Levofloxacin is a commonly prescribed antibiotic. Multiple adverse events such as central nervous system and cardiovascular toxicity have been described. Cardiovascular toxicity, namely QT prolongation when present can be particularly dangerous and requires urgent management. Aside from stopping the drug there is paucity of data regarding other urgent treatment modalities such as CRRT when potential toxicity is suspected.

Case Description: A 53 year-old African American female with a history of ESRD on peritoneal dialysis (PD) for 2 years was admitted for concern of levofloxacin toxicity. She had been admitted to an outside hospital and discharged approximately 1 week prior to presentation with a levofloxacin prescription for presumed bronchitis. During initial evaluation, she admitted to taking levofloxacin 500 mg every 8H for the preceding 5 days. She admitted she had been performing PD every other day as she was concerned she was volume depleted. After 3 days she developed nausea, vomiting, left heel pain, left hand tremor, and palpitations. She had not performed peritoneal dialysis since the onset of her symptoms. Her initial physical exam was consistent for left hand tremor and Achilles tendon tenderness. Her QTc upon initial evaluation was 534. Serum levofloxacin level was ordered and a decision was made to start continuous veno-venous hemofiltration (CVVH) to increase clearance of levofloxacin. CVVH was stopped after clinical recovery of her symptoms and normalization of QTc. Her initial levofloxacin level was 36.65 mcg/mL (normal therapeutic range 8-12 mcg/mL) and serum levels were followed for the duration of treatment every 12 hours. Below is a graphical trend of her levofloxacin levels.



Discussion: Levofloxacin toxicity represents a unique and dangerous clinical challenge. This case report shows successful and effective treatment of critical toxicity with the use of CVVH.

FR-PO070

Utility of Cystatin C in the Setting of Urinoma
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Introduction: Urinomas (i.e. presence of urine outside of the urinary tract) are common in the setting of urologic/pelvic surgery. Due to the resorption of extravasated urinary constituents such as urea nitrogen and creatinine, determination of renal function is typically confusing and often leads to the false impression of acute renal failure, a situation referred to as pseudo-renal failure. We describe the superior precision of cystatin C (CysC) vs serum creatinine (SCr) in estimating renal function in a patient with urinoma.

Case Description: 79 yo M with a history of urinary retention requiring a chronic indwelling Foley catheter presented with catheter obstruction leading to bladder rupture and apparent acute renal failure. Presenting SCr was 5.8mg/dl (baseline 1.5mg/dl). A cystogram was consistent with urinoma. Treatment of the bladder leak consisted of urinary catheter replacement and he maintained urine output of > 2L/24h for several days. SCr decreased to 2.9mg/dL. A second episode of catheter obstruction subsequently occurred resulting in a significant increase of the extraperitoneal bladder leak and acute rise of creatinine to 4.6mg/dL. After placement of a larger catheter, his SCr decreased to 1.7mg/dL. During the second episode of urine leakage, simultaneous CysC levels were obtained. In contrast to

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

the marked variation of SCr during the onset and resolution of the urinoma, CysC levels demonstrated greater stability, increasing modestly from 1.6mg/L to 2.0mg/L during onset, followed by return to near baseline level of 1.7mg/L upon catheter replacement. CysC based eGFR values using CKD-EPI demonstrated similar relative stability, decreasing from 39 to 29mL/min during the recurrent bladder rupture, followed by an increase to 36 mL/min after recatheterization. In contrast, the eGFR decline based upon SCr-based CKD-EPI equation was notably labile declining from 20 to 11mL/min during episode then increased to 38mL/min with treatment.

Discussion: These findings imply superiority of CysC over SCr in estimating renal function in patients with urinoma and pseudo-renal failure. Discordant estimates of eGFR between CysC and SCr may be indicative of urinoma.

FR-PO071

Two Cases of Nonocclusive Mesenteric Ischemia Triggered by Intradialytic Hypotension in Patients on Maintenance Hemodialysis Norihiko Morisawa, Izumi Yamamoto, Yasuyuki Nakada, Yusuke Okabayashi, Yudo Tanno, Ichiro Ohkido, Takashi Yokoo. *Dept of Internal Medicine, Div of Nephrology and Hypertension Jikei Univ School of Medicine, Tokyo, Japan.*

Introduction: Among dialysis patients, non-occlusive mesenteric ischemia (NOMI), defined as diffuse intestinal ischemia without any organic blood vessels occlusion, is rare (1%patient-year) but has a very high mortality (56-90%). The factors associated with mortality from this disease include age, diabetes, hypertension, intradialytic hypotension, atherosclerosis, medications, etc. Early diagnosis and treatment are important for improving survival in patients with this disease.

Case Description: We here report two cases of NOMI, who were triggered by hypotension during hemodialysis. Case 1: A 52-year-old man who had a low left ventricular ejection fraction after myocardial infarction showed intradialytic prolonged hypotension. On physical examination, he was hypotensive with diffuse abrupt abdominal tenderness. The laboratory investigation showed a high white blood count of 20,000. Case 2: A 88-year-old woman on maintenance hemodialysis for 5 years had hemorrhagic shock. On physical examination, she was also hypotensive with mild abdominal tenderness. The laboratory investigation showed a high white blood count of 16,000. We performed multiple detector computed tomography (MDCT) and found patent mesenteric vessels in both cases. Subsequent surgical procedure revealed the necrosis of terminal ileum in case 1 and autopsy revealed necrosis of cecum in Case 2. Finally, we diagnosed them as having NOMI. The former underwent surgical procedure and was discharged alive from the hospital but the latter was dead.

Discussion: Considering the fact that NOMI is very high mortality disease, early diagnosis must be important. However, a diagnosis of this disease is very difficult because clinical manifestations are nonspecific. We speculated that the profile of hemodialysis is very similar to that of risk factors, therefore, we should evaluate patients who showed intradialytic hypotension with abdominal pain using multiple detector computed tomography.

FR-PO072

Aggressive Renal Cell Carcinoma in a Renal Allograft Hafiz Ali Sroya, Antonia Harford. *Nephrology, UNM, Albuquerque, NM.*

Introduction: Kidney cancers arising in renal allografts are very rare and most publications focus on cancers in native kidneys of transplant recipients. We are reporting a case of a renal cell carcinoma (RCC) arising 14 years post-transplant.

Case Description: A 46-years old man with a history of ESRD due to diabetic nephropathy underwent hemodialysis for one year prior to receiving a Living Un-Related Renal Transplant from his brother –in law, a 36 yo healthy male in 2001. The patient had immediate graft function post-transplant and was maintained on MMF, Cyclosporine and Prednisone. He underwent renal allograft biopsy in 2004 for a gradual decline in renal allograft function; this biopsy showed chronic transplant glomerulopathy. The patient had very gradual decline in renal allograft (CKD G3bA1) until Jan 2015, when he developed mild lower abdominal pain over several weeks. Imaging including abdominal US and CT revealed a 14 X 12 X 12 cm mass arising from the transplant kidney with extensive regional adenopathy involving the right common iliac vein and IVC with evidence of lung metastasis. Biopsy showed RCC, clear cell type with extensive necrosis. The venous involvement precluded surgical excision. The patient was treated with sunitinib. Several weeks later, he developed extensive bilateral pulmonary embolism treated with heparin infusion and IVC filter. Soon after the initiation of the heparin infusion he developed severe hematuria. Alcoholic embolization of the tumor was then performed. Immunosuppressive medications were tapered and the patient returned to hemodialysis.

Discussion: Characteristics of *de novo* kidney allograft RCCs are currently unknown. These tumors can be *de novo* or transmitted by the donor and differentiation between these 2 modes of transmission may be difficult. The most common reported histologic type of graft tumor is papillary carcinoma; clear cell type as in our case is less usual. Tumors occurring in renal transplants are usually incidental, asymptomatic, low grade and small but may be symptomatic or with vague clinical picture, high grade, aggressive and very large size as in our case. Frequent and continued surveillance imaging of both the renal allograft and native kidneys is paramount.

FR-PO073

A Case of Acute Allograft Rejection Combined with BK Virus-Associated Nephropathy Bernice Kim, Soo Ryeong Ryoo, Kyung Soo Kim. *Div of Nephrology, Dept of Internal Medicine, Dongguk Univ Ilsan Hospital, Goyang, Republic of Korea.*

Introduction: Rejection and BK virus-associated nephropathy (BKVAN) are major causes of renal allograft dysfunction. Treatment can be difficult when both conditions coexist, because potent immunosuppression is required in acute rejection and reduction of immunosuppressive agents is essential in BKVAN. We present a case of acute allograft rejection combined with BKVAN.

Case Description: A 41-year-old male with end stage renal disease because of hypertensive nephrosclerosis received a deceased donor renal transplantation. Immunosuppressive therapy was started with mycophenolate mofetil, tacrolimus, methylprednisolone, and anti-thymocyte globulin. On post-operative day (POD) 19, serum creatinine (sCr) level was 1.89 mg/dl but was elevated to 2.4 mg/dL on POD 25. Diffuse C4d staining in peritubular capillaries was noted on kidney biopsy and acute antibody-mediated rejection was diagnosed. Plasmapheresis was initiated and intravenous immunoglobulin (IVIG) and rituximab were administered. After 10 days of treatment, sCr was decreased to 1.5 mg/dL. Additional episodes of sCr elevation occurred and more sessions of plasmapheresis and IVIG administration were done, but sCr was elevated to 2.48 mg/dL on POD 67. Decoy cells were detected on urine cytology and high levels of viremia and viremia were found on polymerase chain reaction for BK virus DNA. On second kidney biopsy, findings of acute cellular rejection were noted and viral inclusion bodies in tubular epithelium were seen, suggestive of BKVAN. For treatment of BKVAN, reduction of immunosuppressive agents and administration of IVIG and leflunomide were performed. Steroid pulse therapy was done in regard of acute cellular rejection. Despite therapy, his renal function did not recover completely and sCr was elevated to 3.2mg/dL on POD 138.

Discussion: It is difficult to treat when BKVAN and acute rejection coexist. In our patient, IVIG and leflunomide was administered and immunosuppression was reduced for BKVAN while steroid pulse therapy was performed for acute rejection, but his allograft function deteriorated. Studies are required to optimize the management of these difficult cases.

FR-PO074

Decreased Ultrafiltration in an End-Stage Renal Disease Patient with Sickle Cell Anemia: A Potential Strategy to Facilitate Kidney Transplantation Ekamol Tantisattamo,¹ Siwadon Pitukweerakul,² Praveen Ratanasrimetha.³ *¹Nephrology, Northwestern Univ; ²Presence St. Francis Hospital, Evanston; ³Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.*

Introduction: Sickle cell crisis (SC) leads to mortality and morbidity in sickle cell anemia(SCA) patients. Volume depletion is a common precipitating cause. Volume overload may require increasing ultrafiltration(UF). We report a case of SCA woman with acute kidney injury (AKI) who suffered from recurrent episodes of SC and acute hemolytic anemia requiring blood transfusions after hemodialysis(HD) was initiated. She became more sensitized from blood transfusions. Decreased UF reduced episodes of SC and blood transfusions.

Case Description: A 39-year-old African American woman with a longstanding history of SCA presented with a severe episode of SC complicated by AKI requiring chronic HD 5 years ago. Since starting HD, she had more episodes of SC from once a year up to every other month and required more blood transfusions. She presented for a pre-kidney transplant evaluation. Her panel reactive antibody(PRA) increased from 28 and 0 to 44 and 10, for class I and II, respectively. Upon interview, she has HD 3 times/week. Her estimated dry weight was 62 kg and intradialytic weight gain was 2-2.3 kg. She sometimes had intradialytic hypotension with BP of 90s/50s. As concern for over UF being a potential cause of volume depletion and subsequently precipitating SC, the UF was decreased. She had fewer episodes of SC and blood transfusions. She remained on the kidney transplant waiting list with this HD prescription and stable hemoglobin.

Discussion: Our patient presented with more frequent episodes of SC after HD initiation. Intradialytic hypotension indicates intravascular volume depletion which subsequently precipitating SC and hemolytic anemia. Volume management in SCA patients with ESRD is challenging and critical to avoid intravascular volume depletion. SC and acute hemolysis may be surrogate markers of over UF. Avoiding over fluid removal can prevent SC, acute hemolysis, and blood transfusion which potentially increases immunological barrier for kidney transplantation from sensitization.

FR-PO075

Recurrent Catastrophic Antiphospholipid Syndrome Treated with Eculizumab in a Peritoneal Dialysis Patient Karl W. Schoenholzer,¹ Marianna De Francesco,¹ Giulia Bedino,¹ Josua Van den Berg,² Silvio Pianca.¹ *¹Nephrology and Dialysis Div, Ospedale Regionale di Lugano, Lugano, Switzerland; ²Interventional Radiology Div, Ospedale Regionale di Lugano, Lugano, Switzerland.*

Introduction: Catastrophic Antiphospholipid Syndrome (CAPS) is a severe variant of Antiphospholipid Syndrome (APS), a systemic autoimmune disease characterized by multiple arterial and/or venous thromboses in presence of elevated titers of antiphospholipid antibodies (aPL). These autoantibodies, promote thrombosis by activating endothelial cells and platelets. We describe a case of a clinical remission in recurrent CAPS via inhibition of terminal complement with Eculizumab in a Peritoneal Dialysis (PD) patient.

Case Description: A 48-year-old man has shown recurrent CAPS characterized by diffuse arterial thromboses in the heart, kidneys, liver and lungs, confirmed by positivity of aPL. Angiography revealed a bilateral subclavian arterial thrombosis, a right iliac arterial stenosis that was treated with a stent and a left renal arterial occlusion. The patient's renal function was decreased until End Stage Renal Disease, secondary to chronic thrombotic microangiopathy, and PD therapy was started. During 14 months, our patient presented 8 recurrent episodes of disease with pulmonary involvement characterized by multiple alveolar hemorrhages in concomitance with liver necrosis (biopsy proven) and myocardial ischemia. The patient was treated with high-dose pulse corticosteroids (methylprednisolone 500 mg/day for 3 days) followed by prednisone (1 mg/Kg/day), plasma exchange (5 series with a total of 74 sessions), IV immunoglobulin (400 mg/Kg/day for 5 days), IV Rituximab (initial therapy and maintenance after 6 months), clopidogrel, aspirin and anticoagulation. Despite this standard therapy, we did not observe a sustained remission.

Discussion: After a review of the literature, we decided to administer Eculizumab, a monoclonal antibody against complement C5, that blocks and prevents the generation of the prothrombotic and proinflammatory molecules C5₅ and membrane attack complex C5₅-9. The patient has been in remission with long-term Eculizumab treatment and anticoagulation therapy, without further thrombotic events during 1 year of follow-up.

Funding: Private Foundation Support

FR-PO076

A Case Report of Post-Transplant Lymphoproliferative Disorder in Kidney Allograft Dina Abdelwahab, Nadeen J. Houry, William S. Asch. *Div of Nephrology, Yale Univ, New Haven, CT.*

Introduction: Renal tumors are rare in transplanted kidneys. Nephrectomy is the traditional approach for renal masses. We are reporting a renal mass that was found to be post-transplant lymphoproliferative disorder in the renal allograft which we chose to biopsy instead of using traditional surgical resection.

Case Description: A 63 year old female with past medical history of renal cell carcinoma in native kidney treated by right nephrectomy, ESRD secondary to MPGN status post living donor kidney transplant presented with abdominal pain, fever and diarrhea. Ultrasound of renal allograft showed a solid appearing 4.8x5.6x4.3 cm mass in the upper pole of the transplanted kidney which was predominantly homogenous with internal vascularity; MRI revealed a 6.2x 4.9 x4.5 cm mass with solid enhancing and non-enhancing components within the transplanted kidney concerning for renal cell carcinoma. Given her previous history of RCC there was an increased concern for recurrence. Nephrectomy would have been the traditional approach but that would have meant sacrificing her allograft and initiating hemodialysis. The mass was biopsied and pathology revealed post-transplant lymphoproliferative disorder. Microscopic description showed a small kidney portion with tubules and glomeruli overrun by a dense lymphoid infiltrate. Immunohistochemical stains revealed that the large atypical cells were positive for CD20, Bcl-2, Mum-1 and CD30 but negative for BCL-6, CD10 and CD138. C-myc stained approximately 10-20% of cells and Ki-67 30-40%. In situ hybridization for Epstein Barr virus encoded RNA (EBER) was positive. Patient received 6 cycles of R-CHOP, follow-up MRI showed decrease in mass size.

Discussion: The biopsy of renal tumors for the diagnosis of small masses has not been widely adopted despite recent safety reports with advanced techniques and physicians' expertise. It has been shown to be safe and reliable and should be considered in all patients with small masses especially in transplanted kidneys to decrease the risk of unnecessary surgical intervention.

FR-PO077

Renal Replacement Therapy for Severe Hyponatremia (PNa 99mEq/L), Using 5% Dextrose Solution Infusion Method Masataka Hasegawa, Takuya Fujimaru, Yuki Heath, Fumika Taki, Miyuki Futatsuyama, Masahiko Nagahama, Yasuhiro Komatsu. *Nephrology, St. Luke's International Hospital, Tokyo, Japan.*

Introduction: Dialysis therapy for patients with severe hyponatremia poses risk of osmotic demyelination syndrome due to rapid correction of serum sodium concentration. To prevent rapid correction, low sodium dialysate or filtration fluid can be used; however, dialysate sodium concentration needs to be changed frequently as patient's serum sodium concentration rises. Instead of using low sodium dialysate, infusion of 5% dextrose solution (D5W) to the dialysis circuit after dialyser/hemofilter can adjust the serum sodium concentration of returning blood to the desired level (D5W infusion method). We successfully treated a patient with severe hyponatremia, who required dialysis therapy for severe hyperkalemia and acute kidney injury (AKI), using continuous venovenous hemofiltration (CVVH) with D5W infusion method.

Case Description: A 46 year-old woman presented to the emergency department with confusion and dysarthria, due to severe hyponatremia (PNa 99mEq/L). She also had anuric AKI (creatinine 10mg/dL), hyperkalemia (K 7.7mEq/L) with ECG changes (widened QRS complex), and metabolic acidosis (pH 7.0, pCO₂ 7.7, HCO₃- 1.9mEq/L). After admission, supportive therapy including fluid resuscitation, insulin with glucose and sodium bicarbonate failed to improve hyperkalemia and AKI. Decision of dialysis therapy was made, but to avoid rapid correction of serum sodium concentration, we started CVVH using D5W infusion method. CVVH using standard filtration fluid (Na conc. 140 mEq/L) was started (QB 100mL/min, Qf 1000mL/hr), with continuous infusion of D5W (rate: 400mL/hr) to the CVVH circuit after hemofilter. By adjusting the infusion volume of D5W, sodium concentration of returning blood can be adjusted to the desired level; if the correction rate is faster than expected, D5W infusion rate can be increased. After 24 hours of CVVH, her serum sodium level increased to 108mEq/L. She recovered completely from hyponatremia and AKI without any sequelae.

Discussion: CVVH using D5W infusion method is safe and effective treatment modality for patients with severe hyponatremia requiring dialysis.

FR-PO078

Performing Chronic Hemodialysis Therapy in a Patient with Total Artificial Heart Simona Pozzoli, Marco Simonini, Federico Pappalardo, Chiara Lanzani, Teresa Arcidiacono, Maria Teresa Sciarrone Alibrandi, Donatella Spotti, Paolo Manunta, Stefano Tentori, Giorgio Slaviero. *San Raffaele Scientific Inst, Italy.*

Introduction: Total Artificial Heart (TAH) is an implantable artificial heart usually used as a temporary bridge till heart transplantation. Recently a review showed that bleeding (47%), AKI requiring hemodialysis (40%) and infection (33%) are the most common complications following implantation of a TAH. Currently there are no data in the literature on long term renal function outcome and on management of ESRD related complications. We present our experience on a patient with TAH in chronic hemodialysis therapy.

Case Description: A 55 years old Caucasian man was admitted on 1st March 2012 at our Hospital ER with cardiogenic shock for AMI with rupture of the papillary muscle. His medical history included hypertension and dyslipidemia in good pharmacological control. On 9th March TAH has been implanted in order to replace the lost heart function. From the day of admission to ICU, the patient developed oliguric AKI and CRRT was started. Subsequently, the patient was switched to four times a week haemodialysis. To maintain an appropriate circulating volume for the operation of cardiac device, atrial filling pressures were maintained between 5-5.5 mmHg and 6.0-6.5 mmHg in the right and left atrium respectively. At the same time it was decided to record the change of hematocrit which the patient was subjected during the dialysis sessions (via Blood Volume Monitor (BVM)) in order to identify the critical BVM value for the functioning of the cardiac device. In this way we were able to manage the patient's dialysis sessions even once he was discharged from the hospital with the portable version of TAH.

Discussion: This patient received dialysis therapy four times a week in order to maintain a more content and constant weight till March 2015, when he underwent to combined heart and kidney transplantation. To the best of our knowledge this is the longer case of continuous dialysis therapy in a patient with total artificial heart. Total Artificial Heart is confirmed to be a valid therapeutic option for those patients waiting for heart transplantation even for long periods of time.

FR-PO079

Severe Varicella Zoster Virus Encephalitis and Retinal Necrosis in a Renal Allograft Recipient Jean Luc Franck, Srijita Mukherjee, Tina Thomas, Sharon M. Graves. *Nephrology, Emory Univ, Atlanta, GA.*

Introduction: Varicella zoster virus infection (VZV) has devastating potential complications and should be considered more often for testing by clinicians. Our case reflects the need to maintain a higher degree of suspicion for VZV by clinicians treating the immunosuppressed population.

Case Description: A 31-year-old man underwent living related renal transplantation in 2008 for chronic glomerulosclerosis. The clinical course was uneventful until January 2015, when he was diagnosed with grade IA rejection after admitting to four months of nonadherence to his prescribed immunosuppression regimen, consisting of tacrolimus, mycophenolate mofetil, and prednisone. The rejection was addressed with pulse IV steroids and resumption of his oral immunosuppressant regimen. Over the next four months, the patient sought medical attention for worsening and persistent occipital headache. Lumbar puncture was performed and suggested a viral etiology. MRI imaging was performed and revealed a large cerebellar infarct and diffuse vasculitis. Upon transfer to our institution, the patient underwent emergent neurosurgical correction of acute obstructive hydrocephalus with decompressive craniotomy. Polymerase chain reaction (PCR) testing in the cerebrospinal fluid was positive for VZV. The patient was started on acyclovir and steroids for treatment of VZV encephalitis and diffuse vasculitis. Ophthalmologic evaluation revealed retinal necrosis of the left eye, with PCR testing of the anterior chamber fluid also positive for VZV. After four weeks of acute care, the patient is currently in rehabilitation.

Discussion: Varicella Zoster Virus infection requires timely diagnosis and treatment for positive outcomes in the immunosuppressed patient. Clinical presentation can vary dramatically, from subtle rash to encephalitis. Therefore, clinicians caring for immunosuppressed patients should more routinely consider VZV as part of the differential diagnosis. Our case raises several questions including consideration for lengthening duration of VZV prophylaxis in allograft recipients and consideration for resuming VZV prophylaxis when resuming immunosuppression after extended periods of nonadherence.

FR-PO080

Hemodialysis Related Acute Thrombocytopenia During Pregnancy Nikulkumar Chaudhari, Belinda Bun Jim, Anjali Acharya. *Dept of Nephrology, Jacobi Medical Center, Bronx, NY.*

Introduction: Thrombocytopenia is not uncommon during pregnancy. It could be multifactorial and range from a mild asymptomatic condition to severe thrombocytopenia with fetal effects.

Case Description: A 29 year old woman with hypertension, CKD-IV from primary FSGS, presented at 10th week of gestation. Intermittent hemodialysis had to be initiated at 20th gestation week. Thrombocytopenia developed as described in the table below.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Relation of Hemodialysis	Platelet Count
Pre-dialysis	215,000-239,000
After 1st HD with Fresenius Optiflux Dialyzer	152,000
After 2nd HD	119,000
After 3rd HD	75,000
After 4th HD	82,000
Prior to 5th HD	48,000
Holding HD for next 3 days without any intervention	Gradually increased to 121,000
Re-started and continued HD with Exeltra Dialyzer	150,000-220,000

Patient was not on antiplatelet agents and panel for HIT antibodies was negative. Patient remained asymptomatic throughout hospitalization. Hematological evaluation ruled out all routine causes of thrombocytopenia during pregnancy such as gestational thrombocytopenia, preeclampsia, HELLP, TTP/ITP and autoimmune causes. Given the chronological correlation of platelet decrease and hemodialysis it was concluded that thrombocytopenia was likely hemodialysis related. Patient was switched from a Fresenius dialyzer optiflux to Exeltra 210 high flux dialyzer.

Discussion: Complement activation, anti-coagulation use, exposure of blood to the roller pump, dialysis tubing, micro-bubbles, and use of cellulose membrane are potential causes of dialysis related thrombocytopenia. In addition, sterilization techniques have shown to have a differential impact. A major difference between the two dialyzers used was the technique of sterilization. Electron beam radiation used in the Fresenius dialyzer might affect membrane integrity or physical properties that could lead to platelet activation, aggregation, or adsorption causing thrombocytopenia, which is not seen with gamma sterilization. Thrombocytopenia is an important, if rare, complication of hemodialysis that should be considered in the differential diagnosis of thrombocytopenia in pregnancy. Dialysis associated thrombocytopenia may occur despite the use of biocompatible membranes.

FR-PO081

A Rare Case of Nephrocalcinosis Caused by Hereditary Renal Hypouricemia Three Months After Kidney Transplantation Yo Komatsuzaki,¹ Izumi Yamamoto,¹ Yasuyuki Nakada,¹ Yusuke Okabayashi,¹ Takafumi Yamakawa,¹ Akimitsu Kobayashi,^{1,2} Takahito Niikura,^{1,2} Yudo Tanno,¹ Ichiro Ohkido,¹ Hiroyasu Yamamoto,^{1,2} Keitaro Yokoyama,¹ Takashi Yokoo.¹ ¹Dept of Internal Medicine, Div of Nephrology and Hypertension Jikei Univ School of Medicine, Tokyo, Japan; ²Dept of Internal Medicine, Div or Nephrology and Hypertension Atsugi City Hospital, Kanagawa, Japan.

Introduction: Renal hypouricaemia (MIM: 220150) is a syndrome that involves a defect in urate transporter1 (URAT1) for urate reabsorption at the brush border of the proximal tubule. Nephrocalcinosis and exercise-induced acute renal failure are two major complications affecting renal function. A C889T mutation in SLC22A12 encoding URAT1 is the rare mutation in Japanese. Here we report a rare case of nephrocalcinosis caused by hereditary renal hypouricaemia three month after kidney transplantation.

Case Description: A 41-year-old man had undergone living-related kidney transplantation because of Henoch-Schönlein purpura nephritis. Three month protocol biopsy showed several localized nephrocalcinosis determined by either von kossa or de Galantha's stain (staining for urate crystals). The evaluation for nephrocalcinosis showed hypouricaemia at 1.9 mg/ dl with a high fractional excretion of uric acid at 26.8% (normal range, 6-10%). DNA direct sequencing followed by restriction fragment length polymorphism showed that both the recipient and donor were heterozygous for C889T. This mutation induce stop codon, therefore subsequent immunostaining were performed using antibody to C terminals of URAT1 and found that of immunoreactivities were partially deleted. We finally diagnosed him as having hereditary renal hypouricemia. We directed them to avoid hard exercise, drink plenty of water, and alkalinize their urine for the long term renal survival.

Discussion: Renal hypouricemia is a rare but have the possibilities to affect renal function. The patient did not show hypouricemia during hemodialysis because an anuric dialyzed patient with hereditary renal hypouricemia does not eliminate uric acid. Nephrocalcinosis could be a characteristic feature suspicious of renal hypouricemia. DNA direct sequencing and immunostaining help to diagnose renal hypouricemia.

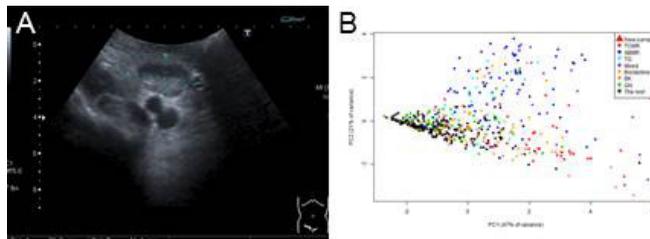
FR-PO082

An Unusual Cause of Lymphadenopathy in a Renal Transplant Patient Anna Bertram,¹ Marcus Hiss,¹ Jan H. Braesen,² Philip F. Halloran,³ Gunilla Einecke.¹ ¹Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany; ²Pathology, Hannover Medical School, Hannover, Germany; ³Alberta Transplant Applied Genomics Centre, Univ of Alberta, Edmonton, Canada.

Introduction: We report an uncommon cause of lymphadenopathy in a kidney transplant patient.

Case Description: The 28y old male patient presented 10y after living donor kidney transplantation with painful inguinal swelling. He had returned to dialysis 8 months ago after graft failure due to antibody-mediated rejection (AMR), which had been unsuccessfully treated with plasmapheresis, intravenous immunoglobulins, and rituximab between 10/2013-03/2014. To sustain diuresis, immunosuppression was continued with tacrolimus (trough

level 7ng/mL) and 5mg prednisolone. At presentation, no local injury was detectable, and the patient denied systemic symptoms. Work-up including MRI revealed enlargement of inguinal and iliac lymph nodes on his right side. Laboratory results showed elevated inflammatory parameters (CRP 120 mg/L; PCT 1.0 µg/L; leukocytes 13.2/nL). Tacrolimus trough level was 3.7 ng/mL, EBV-DNA in plasma was detectable at low values (3200 IU/mL). To rule out PTLD, biopsy of a 3 cm inguinal lymph node (fig.1B) was performed. However, histology showed lymphangitis and no sign of malignancy. Because the allograft in his right Fossa iliaca was tender, we performed a biopsy, as well, although ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy confirmed an unusually severe form of AMR with intense inflammation (fig.1B). Due to the clinical symptoms, we performed transplant nephrectomy. Inguinal lymphadenopathy regressed rapidly, and the patient made a full recovery.



Discussion: This case illustrates that severe allograft rejection, confirmed on histopathological and molecular level, can in rare cases present with pronounced lymphadenopathy.

FR-PO083

Prevnar 13 Associated Immune Thrombocytopenic Purpura in a Renal Transplant Recipient Sagar Gupta, Daniel C. Brennan. *Renal, WashU, St. Louis, MO.*

Introduction: ACIP recommends all adults with immunocompromising conditions should receive PCV13 to prevent invasive disease caused by 13 serotypes of *S.pneumoniae*. We describe here a case of ITP associated with Pevnar13 administration in a renal allograft recipient, which is the first reported case of its kind.

Case Description: A 77 year old Caucasian male presented with chief complaint of increased bruising at insulin injection sites for one week. There was no history of fever, abdominal pain, diarrhea, bleeding episodes, neurological deficits, new medications or insect bites. He had ESRD secondary to hypertension and DM2. He received a living unrelated kidney allograft 22mo ago. He was on tacrolimus, MMF, prednisone, MMF later discontinued indefinitely due to BK viremia. Family history was non-contributory. Medications included allopurinol, ASA, statin, bactrim, carvedilol, insulin glargine and aspart, prednisone and tacrolimus. He received Pevnar13 1 month ago. Exam showed normal vital signs and petechial rash in the areas of insulin injections. Lab testing resulted in Hb 11.7 & WBC 7.7 (baseline) and platelet 3000 (baseline 140). BUN 31 and Cr1.50 (baseline). PT, PTT, LDH and haptoglobin were normal. No schistocytes seen. Infectious workup was negative and ADAMTS-13 activity resulted at 102%. The isolated thrombocytopenia was diagnosed as ITP and was attributed to the Pevnar 13 vaccine. He was started on pulse dose steroids and IVIG. He received 6 units platelets with counts increasing to 94000, later discharged on a prednisone taper. Weekly blood counts showed improvement to his baseline of 140,000 in 3 weeks.

Discussion: PCV13 contains the *S.pneumoniae* serotypes' capsular polysaccharide covalently linked to an immunogenic carrier protein resulting in a T cell- dependent antigen, causing a T helper-cell response. The pathogenesis of ITP involves antibody production driven by CD4-positive helper T cells reacting to platelet surface glycoproteins. Antibodies formed during viral or bacterial infections may also cross-react with normal platelet antigens (a form of molecular mimicry). Isolated cases of ITP have been reported but are relatively rare. Our case is further unique to occur in a pt on immunosuppression with a calcineurin inhibitor and corticosteroids.

FR-PO084

Placement of a Tunneled Hemodialysis Catheter in the Superior Vena Cava for Multiple Central Venous Occlusions Qinghua Yin, Tianlei Cui, Li Zhou, Ping Fu, Fang Liu. *Div of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.*

Introduction: A tunneled hemodialysis catheter is essential for dialysis access when the use of a functioning arteriovenous fistula is not possible. In extreme situations of multiple central venous occlusions, it remains a challenge to establish durable vascular access. Unconventional routes to the central veins are typically used. We successfully performed placement of a tunneled hemodialysis catheter in the superior vena cava (SVC) with fluoroscopic guidance in a hemodialysis patient with multiple central venous occlusions due to repeated catheterization. We report on a feasible option for hemodialysis patients with multiple central venous occlusions.

Case Description: A 49-year-old diabetic male who had been diagnosed with ESRD one year prior came to our medical center because of temporary catheter occlusion. CT venography revealed occlusion of the bilateral brachiocephalic, internal jugular and the common femoral veins, and central venography showed occlusion of the bilateral jugular and innominate veins. Guided by ultrasound, a percutaneous transhepatic route, as described by Duncan et al[9], was developed, which was applied to SVC venography and provided access for a 5F indwelling catheter, which was used to locate the distal end of

the SVC (Figure 2A). The puncture point of the skin was beneath and 0.5-1.0 cm outside of the junction of the right clavicle and head of the sternocleidomastoid, and the direction of the subcutaneous tunnel was along the distal end of the SVC, which was marked by a 5F indwelling catheter. Under fluoroscopic guidance, a micro-21G needle (Cook) was used to puncture the stump occlusion of the SVC; dark red blood was drawn when the micro-21G needle (depth approaching 15 cm) met the 5F indwelling catheter. Additionally, under anteroposterior and lateral fluoroscopic guidance, a 21G needle was punctured into the SVC (Figure 2B-C), and the tunneled hemodialysis catheter (cuff to tip 23 cm, Bard) was then exchanged with a 0.035-inch guide wire in the SVC. Chest radiography showed positioning of the hemodialysis catheter tip into the right atrium (Figure 2D). CT showed that the needle did not enter the chest.

Funding: Clinical Revenue Support

FR-PO085

Crystal Nephropathy in a Kidney Transplant Recipient due to Excessive Consumption of Oxalate Rich Diet and Vitamin C Sudheer Muduganti,¹ Padmavathi Mali,² Sandesh Parajuli,¹ Maha A. Mohamed.¹ ¹*Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI;* ²*Internal Medicine, Marshfield Clinic, Marshfield, WI.*

Introduction: Acute kidney injury due to crystal nephropathy has been reported mainly in patients with gastrointestinal (GI) malabsorption or GI surgery. We present a rare case of crystal nephropathy in the kidney transplant recipient (KTR) without obvious GI risk factors.

Case Description: 68 year old obese female, who is living-unrelated KTR for five years, with a stable post-transplant course and a baseline serum creatinine (scr) of 1.1 mg/dl, presents to our hospital with tiredness and diarrhoea for one week. She had extensive work up in the past for chronic diarrhoea which is described as "soft stool". 24 hour fecal fat, serum amylase and serum lipase were normal. Upon presentation, scr was 7.1 mg/dl, which prompted us to perform an allograft kidney biopsy demonstrating multiple oxalate crystals deposited in the renal tubules. Reviewing her history further revealed that she was consuming 3 gm vitamin C (over the counter) daily for the last one month. Her preferred diet always consisted of oxalate rich foods (spinach). Renal functions improved in one month (scr 2mg/dl) with hydration, discontinuation of vitamin C, and changes in dietary habits. Urine studies obtained after one week of treatment showed normal urine calcium, low urine oxalate and citrate.

Discussion: Oxalate nephropathy can occur from hyperoxaluria due to ingestion of oxalate rich diet or substances which metabolize to oxalate like vitamin C or from enteric causes like malabsorption. In our patient, we ruled out enteric causes and determined oxalate nephropathy was secondary to ingestion of oxalate rich diet and excess vitamin C. Renal functions improved with modification of diet, hydration and discontinuation of offending agents. Although vitamin C and high oxalate diet are rare causes of oxalate nephropathy in patients with normal renal function, it may cause significant nephropathies in KTR. KTR patients therefore, should follow low oxalate diet and avoid excessive vitamin C even with normal renal functions to avoid development of crystal nephropathy.

FR-PO086

The Conundrum of Dry Weight in a Pregnant Dialysis Patient Sweta Carpenter, Akshatha Rao, Sandeep Aggarwal. *Nephrology, Drexel Univ.*

Introduction: The frequency of pregnancy in women of child bearing age who are on dialysis ranges from 0.3-1.5% per year. When a dialysis patient does become pregnant, nephrologists become extra vigilant to ensure a successful outcome for both mother and child. An important question that often arises is how to adjust a patient's dry weight as pregnancy progresses.

Case Description: We present a case of a 23 year old pregnant dialysis patient who was admitted to the hospital with shortness of breath at 26 weeks gestation. She had a past medical history of a miscarriage, hypertension, and a failed deceased donor renal transplant. At her outpatient dialysis unit, she was being dialyzed 6 times per week. Her dry weight was increased by 1.5 kg during the first trimester and during the second trimester by 1 pound a week to account for normal pregnancy weight gain. On this admission, her weight was 113.5 kg and her estimated dry weight was 114 kg. Her vital signs on admission revealed that she was mildly hypertensive with a blood pressure of 150/94 and her oxygen saturation was 90% on room air. After other etiologies were excluded, it was determined that the patient's hypertension and hypoxia were due to volume overload despite the patient being below her expected dry weight. A fetal monitor was placed on the patient and she was dialyzed for three consecutive days with a net ultrafiltration of 7 liters. There were no signs of fetal distress during volume removal on the monitor. A uterine artery doppler was also performed and showed no signs of hypoperfusion to the fetus during dialysis. Subsequently, the patient's shortness of breath and hypertension resolved. Upon discharge, her new dry weight was 108 kg, which was 6 kg below her expected dry weight. The patient delivered a baby weighing 5.4 lbs at 37 weeks with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively.

Discussion: In a pregnant dialysis patient, it is difficult to distinguish between normal pregnancy weight gain and extra fluid. A fetal monitor and uterine artery doppler during dialysis are useful tools that nephrologists can employ to titrate ultrafiltration goals. Better volume management in turn could avoid pre-term delivery.

FR-PO087

A Rare Cause of AKI in a Renal Transplant Recipient Ronald Brian Vigo,¹ Sandra Barrow,¹ Lillian W. Gaber,² Wadi N. Suki.¹ ¹*Nephrology, Houston Methodist Hospital, Houston, TX;* ²*Pathology, Houston Methodist Hospital, Houston, TX.*

Case Description: We present a 66 year-old African American woman who underwent pre-emptive living related donor kidney transplant for ESRD secondary to DMII and hypertension. She had immediate graft function and was discharged on the fourth post-operative day with Na 136 mEq/L, K 3.5 mEq/L, Cl 102 mEq/L, total CO₂ 19 mEq/L, creatinine 1.3mg/dL and urine pH 7.0. Baseline renal biopsy was normal. Her medications on discharge included Prograf, Cellcept, Prednisone, Bactrim, Valcyte and sodium bicarbonate. She presented 10 days later with complaints of nausea, and vomiting as many as 10 times. Serum chemistries revealed the following: Na 136 mEq/L, K 5.0 mEq/L, Cl 95 mEq/L, and total CO₂ 20 mEq/L, consistent with a high-anion gap metabolic acidosis (AG 21). Serum creatinine was 1.3 mg/dL and urinalysis revealed a urine pH of 7.5, pyuria and bacteriuria. Urine culture grew E. Faecalis and renal transplant ultrasound was normal. She was started on IV antibiotics and IV fluids, including sodium bicarbonate. The following day, her chemistries revealed her anion gap metabolic acidosis had resolved, with total CO₂ rising to 27 mEq/L. However, serum creatinine increased to 1.8 mg/dL, and continued to rise further despite treatment. A renal allograft biopsy was performed. Microscopic examination of the biopsy revealed widespread nephrocalcinosis with calcium-phosphate deposition. PTH at the time was 255 pg/mL, Ca 8.5 mg/dL, iP 4.1 mg/dL and fractional excretion (FE) of Ca 0.15%, FEiP 29%, and urine anion gap was 29.

Discussion: We propose that our patient had developed post-transplant RTA, given the presence of non-anion gap metabolic acidosis, low K, and urine pH of 7.0 in the immediate post-transplant period. Positive urine anion gap is suggestive of decreased ammonium excretion (although it should be confirmed with measurement of the urine osmolal gap and urinary P_{CO2}). The combination of high urine pH, as a consequence of bicarbonate administration and decreased bicarbonate reabsorption, in conjunction with hyperparathyroidism and consequent increase phosphate excretion, provided the perfect medium for calcium phosphate precipitation.

FR-PO088

A Rare Case of Rabbit Anti-Thymocyte Globulin Induced Disseminated Intravascular Coagulation Vasanthi Balaraman,^{1,2} Anup Patel.¹ ¹*Dept of Renal Transplant, Saint Barnabas Medical Center, Livingston, NJ;* ²*Dept of Nephrology, Newark Beth Israel Medical Center, Newark, NJ.*

Introduction: Rabbit anti-thymocyte globulin (RATG) is a purified polyclonal immunoglobulin used for induction therapy in renal transplantation. Adverse effects include cytokine release syndrome, leukopenia, thrombocytopenia and serum sickness. We report a rare case of renal transplant recipient who developed severe coagulopathy and post-operative bleeding in whom RATG was used for induction.

Case Description: A 61 year old female with end stage renal disease received a deceased donor renal transplant. RATG (2 mg/kg) was initiated intraoperatively. Over the ensuing 2 hours, the patient became hemodynamically unstable with excessive bloody output from the surgical site drain. Exploration of the renal transplant revealed diffuse oozing from surrounding tissues but no bleeding from the arterial or venous anastomosis. Labs revealed an elevated prothrombin time of 27.0 sec, thrombin time of 36.4 sec, INR of 2.5 and d-dimer greater than 5250 ng/ml, reduced fibrinogen level of 135 mg/dl and platelet count of 66000/cmm. The RATG infusion was stopped. Multiple units of packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate were transfused. There was persistent bloody output. A reexploration revealed persistent diffuse oozing which required packing of the transplant bed. On postoperative day 4, the patient's condition improved.

Discussion: We suspect Disseminated Intravascular Coagulation(DIC) may be secondary to RATG in our case. The donor biopsy showed no evidence of DIC. Other causes including calcineurin inhibitors, hyperacute rejection and sepsis were ruled out. Only a few case reports of RATG induced coagulopathy exist in the literature. Weber et al reported 12 hematopoietic stem cell transplant patients having coagulopathy after using RATG therapy. These cases had elevated D-dimer, tissue factor, thrombin-antithrombin III complex, and thrombomodulin, but had no bleeding, thromboembolic or vaso-occlusive complications. We contemplate that DIC is a rare but potential life threatening complication of RATG induction and awareness of this potential complication is important.

FR-PO089

A Page Transplant Kidney Supreet Sethi, Shalini Bumb, Scott Leonard Sanoff. *Div of Nephrology, Dept of Internal Medicine, Duke Univ Health System, Durham, NC.*

Introduction: Page kidney occurs by extrinsic compression of the renal parenchyma from a hematoma or a mass, leading to activation of the renin-angiotensin-aldosterone system and resulting in systemic hypertension.

Case Description: A young-adult male, with ESRD of uncertain etiology underwent living related kidney transplantation 3-months prior to presentation. His post-transplant serum creatinine (SCr) stabilized around 1.3-1.5mg/dl. He was maintained on a 3 drug immunosuppressive regimen including tacrolimus, prednisone and myfortic. The patient presented to the hospital with pain over allograft site and low grade fever. He reported an altercation with a family member without clear direct trauma to his right lower quadrant graft, but admitted to blunt trauma to his right flank region in a shoving match. Patient was hypertensive with blood pressures in the 170-180/100-110 mm Hg range. Labs revealed a SCr of 4.1mg/dl, potassium of 5.7mmol/L, hemoglobin of 10.8g/dl from a baseline of 12g/

dl, and WBC of 15,000/uL. Urinalysis was bland. The patient was given a dose of solumedrol 500mg due to concerns for rejection. US of the transplant kidney showed a 2.2 x 10.5 x 4.1 cm subcapsular fluid collection exerting a mass effect on the transplanted kidney, concerning for sub-capsular hematoma. The main renal artery and vein were patent, but the resistive indices were elevated within the arcuate renal arteries. Cross-sectional imaging of the abdomen confirmed a moderate sized renal transplant subcapsular/perinephric hematoma. The patient was managed conservatively and by hospital day 3, the renal function started improving. The patient was discharged with a SCr of 2.1mg/dl on hospital day 4 on his home regimen of amlodipine and labetalol. Most recently his SCr was 1.4mg/dl.

Discussion: The clinical syndrome of Page kidney in a kidney allograft due to subcapsular/perinephric hematoma following trauma or biopsy is characterized by acute hypertension with a concomitant acute decrease in kidney function. Our cases illustrates that this syndrome may occur without a history of direct trauma to the kidney, and that despite severe acute kidney injury, can be managed conservatively in some cases, with a good long term outcome.

FR-PO090

Black Colored Dialysate: A Rare Complication of Peritoneal Dialysis due to Cholecystitis Yi Li,¹ Basmah A. Abdalla,² Pang-Yen Fan.² ¹Dept of Internal Medicine, Univ of Massachusetts Medical School; ²Dept of Nephrology, Univ of Massachusetts Medical School.

Introduction: We report a rare complication of black colored dialysate in a patient with ESRD on peritoneal dialysis (PD) with acute cholecystitis.

Case Description: A 73 year old man was undergoing peritoneal dialysis for ESRD secondary to obstructive uropathy. He presented with black discoloration of his PD effluent, preceded by persistent abdominal pain and fever. Exam was notable for abdominal tenderness and a clean PD catheter exit site. Peritoneal fluid analysis was consistent with peritonitis. Contrast CT showed a distended indistinct gallbladder with punctate stones and an ill-defined wall. No biliary obstruction or dilatation identified. There was no evidence of pancreatitis and serum lipase level was 12. Subsequent HIDA scan was consistent with acute cholecystitis. A total bilirubin from PD effluent was 14.6mg/dL and serum bilirubin was only 0.8mg/dL. Both blood cultures and PD fluid cultures were negative. He received empiric antibiotics and a percutaneous cholecystostomy tube was placed and similar turbid dark fluid was aspirated from his gallbladder.

Discussion: Dark colored dialysate has been reported in hemorrhagic and non-hemorrhagic pancreatitis. Acute bile leak or choleperitoneum is a recognized complication of cholecystectomy due to extrahepatic bile duct rupture or due to gall bladder rupture in patients without ESRD. There are few reports of biliary peritonitis due to intrahepatic bile duct rupture spontaneously and in the setting of cholelithiasis. An ascitic fluid bilirubin level of > 6mg/dL with an ascitic fluid/serum bilirubin ratio of >1.0 has been shown to correlate with choleperitoneum. The black colored PD effluent in our patient represented a biliary leak likely from increased permeability of the gallbladder wall or microperforation in the setting of non-perforated cholecystitis or from an unidentified intrahepatic bile duct rupture. In conclusion black colored PD effluent should prompt investigation for gall bladder disease and/or pancreatitis. Peritoneal fluid and serum bilirubin levels and lipase levels can aid in making a diagnosis.

FR-PO091

NK Cell Lymphoproliferative Disorder (PTLD) Associated with Pure Red Cell Aplasia in a Renal Transplant Recipient Treated with ATG – A Case Report and Literature Review Daniel Taiwo Adeneye, Amarपाल Brar, Fasika M. Tedla, Nabil Sumrani, Devon John. *Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.*

Introduction: PRCA can be idiopathic or secondary to parvovirus infection, SLE, thymoma or lymphoma. PTLD are lymphoid proliferations that develop following immunosuppression for solid organ transplantation. While they are predominantly B cell PTLD, few NK/T cell PTLD have been published. Secondary PRCA may resolve with treatment of the underlying disorder while PRCA occurring in the setting of NK/T cell PTLD (due to T cell inhibition of marrow erythroid cells) are treated like idiopathic PRCA as immunologically mediated disease. This is the first published report of PRCA associated with NK cell PTLD in a 41yr old renal transplant recipient.

Case Description: This is the first published report of PRCA associated with NK cell PTLD in a 41 year old renal transplant recipient.

A 41 year old woman with ESRD from lupus nephritis, received living related renal transplant 9 years ago; admitted with hemoglobin of 5.6 g/dl with normal WBC count and platelet count. Patient had well-functioning allograft with serum Cr of 1.5. There was no evidence of joint swelling, rash, or alopecia. No proteinuria, RBC, WBC or cast on urine analysis. Serum Protein was 4.9 g/dl, Albumin 2.7 g/dl. LDH, haptoglobin, DS DNA, ANA, C3, C4, hepatitis B, C, HIV, Parvo virus PCR, EB PCR, free kappa/Lambda were normal. MCV was 95.9 fL. Peripheral smear showed many normal lymphocytes with normal count. Bone marrow biopsy showed normal lymphocyte population, many macrophages but absence of erythroid precursors. Flow cytometry revealed increased NK 56(-), CD3 -, CD8+ cells. Renal allograft Ultrasound, CT Chest and CT abdomen were normal. This patient had her last epogen in 2003 and anti-EPO antibody induced PRCA though possible is very unlikely. Patient received 2 units of packed red cells and Anti-Thymocyte globulin (ATG) daily for 5 days. She was continued on tacrolimus with stable hemoglobin with no further need for transfusion.

Discussion: We present a case of PRCA in a renal transplant recipient due to NK cell lympho proliferative disorder which was successfully treated with ATG.

FR-PO092

New-Onset Diabetes After Transplantation in a Pediatric Patient with Congenital Anomalies of the Kidney and Urinary Tract: The Role of Hepatocyte Nuclear Factor 1 β Naoto Kaneko,¹ Naoya Morisada,² Keiichi Takizawa,¹ Tomoo Yabuuchi,¹ Hirotaka Hama,¹ Norimasa Tada,¹ Eiji Nakano,¹ Shoichiro Kanda,¹ Kiyonobu Ishizuka,¹ Hiroko Chikamoto,¹ Yuko Akioka,¹ Kazumoto Iijima,² Motoshi Hattori.¹ ¹Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan; ²Dept of Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Japan.

Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most frequent cause of end-stage renal disease (ESRD) in children. New-onset diabetes after transplantation (NODAT) is one of the major complications following kidney transplantation (KTx). Mutations of hepatocyte nuclear factor 1 β (HNF1B), a transcriptional factor involved in the development and maintenance of several organs, cause a multi-system disorder, including CAKUT, diabetes, liver dysfunction. We report a pediatric patient with renal hypodysplasia carrying a novel mutation of HNF1B who developed NODAT and liver dysfunction.

Case Description: The patient was a 14-year-old girl. She was diagnosed with bilateral hypodysplastic kidney in the newborn period. At the age of 3 years, she received living-related KTx from her mother preemptively. At the age of 4 years, a steroid pulse for acute rejection resulted in development of diabetes mellitus (NODAT). At the age of 13 years, she complained of acute right flank pain and fever. Laboratory data showed elevated transaminase levels and computed tomography showed malformation of the bile duct. The causes of NODAT were initially thought to be steroid and tacrolimus. However, based on her clinical features, including CAKUT, NODAT, and liver dysfunction, screening for a mutation of HNF1B (approved by the central ethics board of Tokyo Women's Medical University and Kobe University) was performed. Direct sequencing identified a novel splicing mutation of HNF1B, c.344+2T>C.

Discussion: CAKUT is the leading cause of ESRD in children and HNF1B is the most frequently mutated gene of CAKUT. Therefore, the contribution of HNF1B mutations to development of NODAT appears to be large in the field of pediatric KTx. An oral glucose tolerance test and screening for HNF1B mutations may be advisable before KTx in pediatric CAKUT patients.

FR-PO093

Acute Kidney Injury from Biopsy Proven Oxalate Nephropathy in a Combined Kidney and Lung Transplant Recipient Minesh Rajpal, Reejis Stephen, Brian R. Stephany. *Cleveland Clinic, Cleveland.*

Introduction: Acute oxalate nephropathy (AON) is a rare, but well reported cause of acute kidney injury (AKI) in patients with cystic fibrosis (CF) after lung transplant. We report the only known case of late AON of a transplanted kidney in a combined kidney and lung transplant patient without CF after undergoing medical and surgical management of infective endocarditis.

Case Description: A 62 year old Caucasian male with a remote history of Hodgkin's disease complicated by radiation-induced pulmonary fibrosis and aortic stenosis underwent a simultaneous double lung transplant and bioprosthetic aortic valve replacement (AVR) in February 2013. His post operative course was complicated by recurrent bronchopneumonias secondary to MSSA requiring prolonged oxacillin as well as ESRD secondary to presumed unrecovered acute tubular necrosis (ATN). The patient subsequently underwent a successful living unrelated kidney transplant from his wife in October 2014 with baseline creatinine of 1.4mg/dl. Unfortunately, he developed E. faecalis bacteremia secondary to urosepsis and subsequent finding of multivalvular endocarditis with superior vena cava involvement. This was treated with a prolonged antibiotic course, but recurrent admissions thereafter for CHF and cardiorenal AKI necessitated a redo AVR along with mitral valve replacement and tricuspid valve repair, "Commando Procedure" on 3-9-2015. Immediate post-operative AKI occurred and was thought due to ATN given the presence of muddy brown casts on sediment exam along with hemodynamic instability requiring temporary intra- and post-operative vasopressor support. Anuric AKI persisted for four weeks leading to a surveillance kidney biopsy to investigate for superimposed rejection. Notable histologic findings were tubular injury consistent with ATN, but more prominent was that of extensive calcium oxalate deposits consistent with AON.

Discussion: In summary we report the first known case of AKI due to AON in a lung and renal transplant recipient after infective endocarditis requiring prolonged antibiotics and the Commando heart procedure. Though the clinical presentation mimics ATN it is important for clinicians to include AON in the differential diagnosis.

FR-PO094

Pax2 and PTIP Regulate AVPR2 Expression in the Inner Medulla Sanjeevkumar R. Patel, Saji Abraham. *Internal Medicine, Univ of Michigan, Ann Arbor, MI.*

Background: In mammals, Pax genes encode developmental regulatory proteins that specify cell lineages and tissues in metazoans and Pax2 is essential for kidney development. Upon binding to DNA through the conserved paired-domain, Pax proteins can recruit both activating and repressing complexes that imprint distinct patterns of histone methylation associated with either gene activation or silencing. Expression of Pax2 persists in the medulla of the adult kidney, where it is proposed to prevent apoptosis in response to increased osmolality. Deletion of the Pax2 interacting protein PTIP in the inner medulla of

mice results in a concentrating defect in part related to a reduction of AVPR2 expression. As Pax proteins interact with PTIP, and Pax2 expression persists in the inner medulla, we hypothesized that Pax2 and PTIP are required for AVPR2 expression.

Methods: In IMCD-3 cells with control, Pax2 or PTIP deletion, we determined Pax2 and AVPR2 expression at the mRNA and protein level in response to normal and elevated osmolality. By ChIP analysis, we identified sites of Pax2 and PTIP enrichment on the AVPR2 promoter and determined changes in histone modifications, PolII occupancy in both IMCD cells and in murine medullary tissue.

Results: Pax2 mRNA peaks 8 hours after an increase in osmolality, Pax2 protein peaks at 12 hours, and AVPR2 mRNA after 20 hours. Pax2, PTIP and the HMT activation complex localize to a 100 bp fragment of the AVPR2 promoter, resulting in increases in activation marks, recruitment of PolII to this locus and an increase in gene expression in both cell lines and murine tissue. We identify the minimal promoter that Pax2 binds to and drives expression of the AVPR2 locus. Deletion of this 100 bp region of DNA results in lack of gene expression in the absence and presence of Pax2. Deletion of PTIP results in loss of gene expression even though Pax2 localizes to the promoter region, as histone activation marks are not increased and PolII is not recruited to this locus.

Conclusions: Thus, Pax2 and PTIP both regulate the expression of AVPR2 in the murine inner medulla and in cells derived from this tissue. Pax2 provides the locus specificity for PTIP recruitment of the HMT activating complex and gene expression.

Funding: NIDDK Support

FR-PO095

Adenine Downregulates NKCC2 and AQP2 in the Rat Kidney and Causes Early Nephrogenic Diabetes Insipidus Hassane Amlal, Rose P. Webster, Ingrid Fernandes dos Santos. *Internal Medicine, Univ of Cincinnati, Cincinnati, OH.*

Background: Long-term feeding of adenine is extensively used to develop animal models of chronic renal failure with metabolic features resembling those observed in humans. However, the mechanisms by which adenine induces renal failure are poorly understood.

Methods: In this study, we examined the early effects of adenine (ADN) feeding on water metabolism and renal function in rats placed in metabolic cages. Rats were fed control diet or diet supplemented with 0.25% or 0.50% ADN, or 0.50% adenosine ad libitum with free access to dH₂O, and monitored daily for food intake, water balance and urine osmolality, and euthanized for blood and kidney collections after 7 days.

Results: ADN-treated rats exhibited a sharp polyuria and polydipsia and decreased urine osmolality as early as 3 days, and the magnitude of these effects is dose-dependent. Further, ADN caused a significant reduction in food intake and body weight at 0.50% but not at 0.25%. None of these physiologic parameters was altered by adenosine treatment. dDAVP treatment induced a significant increase in urine osmolality in control but not in ADN-treated rats. Immunoblotting experiments demonstrated a sharp reduction in AQP2/actin proteins ratio in the cortex (-75%), Outer medulla (-65%) and inner medulla (-80%) of kidneys of ADN-treated vs. control animals. The results also demonstrated that the abundance of NKCC2/actin proteins ratio was reduced to zero in the kidney outer medulla of ADN-treated vs. control rats. Blood chemistry of ADN-treated rats was normal except for a significant 3.8-fold increase in BUN, as compared to control rats. When rats were fed adenine diet supplemented with 7% NaCl, their BUN was corrected to normal level, but still exhibited a significant reduction in urine osmolality.

Conclusions: In conclusion, adenine acts on renal tubules as a signaling molecule and causes nephrogenic diabetes insipidus, likely by directly downregulating NKCC2 and AQP2 in the kidney. The combination of renal fluid loss and decreased food intake likely plays an important role in the development of early acute renal injury that progresses to chronic kidney disease in long-term periods of adenine treatment.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO096

AMPK Activation Increases Urine Concentrating Ability in a Rat Model of Congenital Nephrogenic Diabetes Insipidus Orhan Efe, Huiwen Ren, Lauren M. Larocque, Janet D. Klein, Jeff M. Sands. *Medicine, Renal Div, Emory Univ School of Medicine, Atlanta, GA.*

Background: The urine concentration mechanism is primarily regulated by vasopressin which activates NKCC2 and urea transporters to generate a hypertonic interstitium that promotes water reabsorption through AQP2. Congenital nephrogenic diabetes insipidus (NDI) is caused by vasopressin V2 receptor (V2R) mutations. Present treatment options are limited. We studied AMPK as an alternate pathway to stimulate transporters involved in urine concentration.

Methods: Tolvaptan (10 mg/kg/day), a selective V2R antagonist, was given by oral gavage to rats for 4 days, +/- metformin (800 mg/kg/day). Urine volume and osmolality were measured daily. Following sacrifice, kidneys were dissected into inner medullary tip, base and outer medulla, and UT-A1, AQP2, and NKCC2 were analyzed by Western blot. Immunohistology was used to localize AQP2, pAQP2, pAMPK, and NKCC2.

Results: Tolvaptan was used to produce a rat model of NDI. Urine volumes of tolvaptan-treated rats increased 105% within 24 h. Metformin was used to stimulate AMPK as a candidate NDI treatment. Metformin decreased urine volume by 110% back to control levels in 3 days. Urine osmolality in control rats (mean: 2107 mOsm) was significantly decreased by tolvaptan (mean: 1303 mOsm, p<0.05) and restored to near control levels by metformin (mean: 2335 mOsm, p<0.05). Metformin increased protein abundance of IM tip UT-A1 by 61% in tolvaptan treated rats (p<0.05). IM tip AQP2 was also increased 44% but failed to reach statistical significance (p=0.057). In contrast, IM base UT-A1 and AQP2 protein levels were not changed with AMPK stimulation. Outer medullary NKCC2 abundance was increased 117% with AMPK stimulation in control rats (p=0.004) but not in

V2R-blocked rats. Immunohistochemistry showed that AQP2 and p-AQP2-Ser256 appear to be localized on the cell membrane with acute and chronic AMPK stimulation, both in control and V2R-blocked rats.

Conclusions: AMPK stimulation in V2R-blocked rats is able to reduce the urine concentrating defect by increasing UT-A1 and AQP2. These results indicate that specific AMPK pathway activators might provide a promising treatment for congenital NDI.

Funding: NIDDK Support

FR-PO097

HYAL2 Disruption Leads to Impaired Urinary Dilution Capacity in Mice Vanessa Colombaro,¹ Inès Jadot,¹ Anne-Emilie Declèves,^{1,2} Isabelle Habsch,¹ Bruno Flamion,¹ Nathalie Caron.¹ ¹*Molecular Physiology Research Unit-URPHYM, Univ of Namur, Namur, Belgium;* ²*Laboratory of Experimental Nephrology, Univ Libre de Bruxelles, Bruxelles, Belgium.*

Background: Hyaluronan (HA) is a glycosaminoglycan present in high amount in the inner medulla of the kidney but almost absent in the cortex. Hyaluronidase 2 (HYAL2) is one of the two major hyaluronidases acting synergistically to degrade HA. Recently, it has been shown that *Hyal2*^{-/-} mice display HA accumulation in the kidney. Renal HA content is known to vary with hydration status. Therefore, our study was set up to characterize the renal excretory capacities and renal water handling in response to water deprivation and acute water loading in *Hyal2*^{-/-} mice.

Methods: Experiments were performed in *Hyal2*^{-/-} mice and in their wild-type controls. After appropriate acclimation, water deprivation was performed during 24 hours. The capacity to excrete a water load was tested on an hourly basis for the next 6h after i.p. injection of 2 ml of sterile water. Diuresis and urinary osmolality were measured. HA concentration was measured in the kidney tissue and its distribution through the different kidney zones was examined using immunohistochemistry. Expressions of aquaporin 2 (AQP2) and p-Ser 256 AQP2 were also assessed using immunohistochemistry and immunoblotting.

Results: After water deprivation, *Hyal2*^{-/-} mice showed the same ability to concentrate urine as the *Hyal2*^{+/+} mice. On the other hand, *Hyal2*^{-/-} mice had a significant delay in the diuretic response induced by an acute water loading. As for renal HA content, *Hyal2*^{-/-} mice maintained higher HA concentration than *Hyal2*^{+/+} mice after both water deprivation and acute water loading. HA was present around tubules in all kidney zones including cortex. Plasma AVP levels, kidney AQP2 and kidney p-Ser AQP2 expressions were increased after water deprivation and decreased after acute water loading to the same extent in KO and WT mice.

Conclusions: HYAL2 deficiency and/or increased renal interstitial HA delays the diuretic response to acute water loading without any increase in plasma AVP or collecting duct AQP2 expression.

FR-PO098

Phosphorylated AQP2 and NR3a Reduce NSAID-Induced Urine Concentration Defect Huiwen Ren,^{1,2} Baoxue Yang,² Patrick A. Molina,¹ Jeff M. Sands,¹ Janet D. Klein.¹ ¹*Medicine, Renal Div, Emory Univ School of Medicine, Atlanta, GA;* ²*Pharmacology, School of Basic Medical Sciences, Peking Univ, Beijing, China.*

Background: Vasopressin increases urine concentration through activation of aquaporin-2 (AQP2) in the collecting duct. Nonsteroidal anti-inflammatory drugs (NSAIDs) block PGE2 synthesis, and may suppress AQP2, producing a urine concentrating defect. NR3a can regulate cellular Ca²⁺ entry and may influence AQP2 trafficking.

Methods: We treated rats with a nonselective NSAID, ibuprofen, and a COX-2-selective NSAID, meloxicam, daily for 2 weeks. We assessed urine osmolality and volume, and monitored p-AQPs by Western blotting. NR3a^{-/-} mice were used to examine if NR3a has a protective role.

Results: Both NSAIDs significantly increased urine output and decreased urine osmolality by days 7 - 14. Meloxicam significantly reduced total AQP2 in inner medulla (IM) tip to 64% and base to 63% of control. Ibuprofen decreased total AQP2 in IM tip to 70% of control, with no change in base. Meloxicam significantly increased the ratios of p²⁵⁶-AQP2 and p²⁶¹-AQP2 to total AQP2 in IM tip (to 44% and 40%, respectively). Ibuprofen increased the ratio of p²⁵⁶-AQP2 to total AQP2 in IM tip but did not affect p²⁶¹-AQP2/total AQP2. Both NSAIDs increased p²⁶⁴-AQP2 and p²⁶⁹-AQP2 ratios in tip and base. Ibuprofen increased UT-A1 levels in IM tip, but not base. NR3a, present in rat IM tip and base, was significantly increased in the meloxicam and ibuprofen treated IM bases (37% and 20%, respectively), but unchanged in IM tip. AQP2 and UT-A1 abundances were decreased both in wild type (AQP2: to 76%, UT-A1: to 62%) and NR3a^{-/-} mice (AQP2: to 52%, UT-A1: to 33%) by ibuprofen treatment. Meloxicam did not show any changes either in wild type or in NR3a^{-/-} mice. Notably, ibuprofen treatment caused AQP2 and UT-A1 to decrease more in NR3a^{-/-} mice than in wild type mice.

Conclusions: We conclude that NSAIDs reduce AQP2 abundance contributing to decreased urine concentrating ability. In compensation, p-AQP2 increases, resulting in increased AQP2 membrane insertion. The beneficial effects of NR3a may reflect the altered Ca²⁺ entry that could be limiting dephosphorylation of AQP2 and promoting improved water homeostasis.

Funding: NIDDK Support, Government Support - Non-U.S.

FR-PO099

The Role of Klotho in Renal Sodium and Water Transport Talita R. Sanches,¹ Fernanda O. Coelho,¹ Leticia Jorge,¹ Leticia U. De Castro,¹ Makoto Kuro-o,² Lucia Andrade.¹ ¹Div of Nephrology, Univ of Sao Paulo, Brazil; ²Jichi Medical Univ, Japan.

Background: Klotho (Kl), a transmembrane protein hormone, counteracts aging. Aging is often paralleled by dehydration, which could promote age-related disorders, because it decreases renal Kl protein abundance, as well as increasing plasma osmolality, antidiuretic hormone (ADH), aldosterone, and 1,25 vitamin D. ADH and aldosterone decrease Kl transcription in HEK293 cells and are elevated in the sera of Kl knockout mice. We explored the effects of Kl deficiency on renal transporters.

Methods: 8-12 week old male Kl^{+/+}, Kl^{+/-} and Kl^{-/-} mice (n=6/group) were fed standard mouse chow and given ad libitum access to tap water. We evaluated serum levels of Na, K, Cl, Mg, creatinine and urea. We immunoblotted for sodium/hydrogen exchanger isoform 3 (NHE3), renal outer medullary potassium channel (ROMK), the Na-K-2Cl cotransporter (NKCC2), alpha subunit of the epithelial sodium channel (α ENaC) and aquaporin 2 (AQP2) in kidney membrane fractions; and for phosphorylated glycogen synthase kinase 3 beta (pGSK3 β) in cytoplasmic fractions.

Results: Data are mean \pm SEM.

	Kl +/+	Kl +/-	Kl -/-
Body weight (g)	25.1 \pm 3.4	24.5 \pm 3.0	9.5 \pm 2.2 ^a
Na (mEq/L)	148 \pm 0.6	144 \pm 0.6	157 \pm 2.3 ^a
K (mEq/L)	4.6 \pm 0.2	4.2 \pm 0.1	4.2 \pm 0.4
Cl (mEq/L)	114 \pm 1.4	111 \pm 1.5	121 \pm 4.0 ^a
Mg (mg/dl)	1.6 \pm 0.1	1.7 \pm 0.0	2.5 \pm 0.1 ^a
Urea (mg/dl)	50.5 \pm 3.3	52.0 \pm 2.1	101.6 \pm 7.8 ^a
Creatinine (mg/dl)	0.1 \pm 0.0	0.1 \pm 0.0	0.12 \pm 0.02
NHE3*	99.1 \pm 1.1	92.5 \pm 2.2	58.2 \pm 4.5 ^a
ROMK*	99.3 \pm 2.4	92.5 \pm 4.7	20.5 \pm 4.8 ^a
NKCC2*	97.5 \pm 1.1	97.8 \pm 1.4	130.6 \pm 10.7 ^a
α ENaC*	99 \pm 0.4	98 \pm 0.9	48 \pm 4.9 ^a
AQP2*	98.5 \pm 0.8	98.3 \pm 0.4	133.5 \pm 2.2 ^a
pGSK3 β *	100 \pm 0.7	98.3 \pm 0.7	60.3 \pm 1.3 ^a

^ap<0.05 vs. Kl^{+/+} and Kl^{+/-}; *% Kl^{+/+} protein expression

Conclusions: In Kl knockout mice, there seems to be normal regulation of NKCC2 and trafficking of AQP2 to the apical plasma membrane in response to ADH. However, Kl knockout mice present reduced sensitivity to elevated plasma aldosterone levels with no increase in α ENaC or ROMK protein expression. A lack of Kl can deregulate the adaptive response. (FAPESP).

FR-PO100

Urine Aquaporin-2: Improvement in ELISA Measurements by Alkali Pre-Treatment and Mechanisms of the Secretion Sei Sasaki,^{1,3} Yoko Saijo,² Yasukazu Ohmoto,² Fusako Iwata,² Daisuke Koga,² Takayuki Shimada,³ Masaki Sakai,³ Yasuko Tanaka,³ Kenichi Ishibashi,³ Kiyonori Katsuragi.² ¹Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan; ²Research and Development and Inst of Biomedical Innovation, Otsuka Pharmaceutical Co Ltd, Tokushima, Japan; ³Medical Physiology, Meiji Pharmaceutical Univ, Tokyo, Japan.

Background: Vasopressin-regulated water channel, aquaporin-2 (AQP2) is excreted in urine in the form of extracellular vesicles (mostly exosomes). Urine AQP2 has been measured in many clinical water-balance disorders as a potential biomarker for diagnosis and prognosis. However, despite such a clinical application, fluctuations of the measured values in ELISA were sometimes observed depending on storage conditions, and basic mechanisms of urinary AQP2 excretion are still largely unknown. We characterized urinary excretion of AQP2 by using a highly sensitive and specific ELISA system for human AQP2, which has been developed by us.

Methods: Human urine samples from healthy subjects were measured by a sandwich ELISA. Effects of maneuvers to disrupt the exosome membranes mechanically (freezing and thawing at different temperatures) and chemically (treating with alkali and detergents) prior to ELISA were examined. Stably AQP2-transfected MDCK cells were grown on permeable support and excretion of AQP2 to the medium was measured.

Results: 1. Urine samples stored at 4°C or -80°C did not show significant AQP2 values in ELISA, whereas those stored at -25°C for more than 2 weeks provided the values. Urine samples treated with 0.4N NaOH/0.5% Triton X-305 showed the consistent and comparable values to those stored at -25°C, indicating the need of disruption of the exosome membranes. 2. Supernatants of 200,000g ultracentrifugation contained less than 0.5% of AQP2 of original urine samples. 3. In the culture, AQP2 concentration was more than 10 times higher in apical medium compared to basolateral, and apical AQP2 excretion was stimulated with 3h-incubation of 10⁻⁵M forskolin and 100mM NaCl.

Conclusions: Almost all urine AQP2 is enclosed in exosomes, and pre-treatment of alkali (0.4N NaOH) allows consistent ELISA measurements. Mechanisms of urinary excretion of AQP2 can be examined in culture system.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical, Government Support - Non-U.S.

FR-PO101

Inhibition of EGFR Activity Induces Aquaporin 2 Phosphorylation and Increases Water Reabsorption in Lithium Treated Mice Pui Cheung, Naohiro Nomura, Anil V. Nair, Hua Ann Jenny Lu, Richard Bouley, Dennis Brown. *Medicine, Massachusetts General Hospital, Boston, MA.*

Background: Impairment of vasopressin (VP) receptor type 2 signaling in the kidney is detrimental to water homeostasis. However, strategies targeting cAMP signaling to treat diseases associated with water balance have so far been unsuccessful in humans, prompting a search for alternative pathways that modulate AQP2 trafficking.

Methods: The effect of erlotinib (Erl) oral gavage in a lithium induced nephrogenic diabetes insipidus mouse model was analyzed by measuring urine volume and osmolality. The effect of Erl on aquaporin 2 trafficking and expression in kidneys was studied by immunostaining and western blot analyses. EGF and Erl regulation of AQP2 trafficking and phosphorylation were studied using selective kinase inhibitors and phospho-specific antibodies on AQP2-expressing LLC-PK1 cells.

Results: EGF alone had only a subtle effect on AQP2 trafficking, but it exerted a significant antagonizing effect on VP-induced AQP2 phosphorylation and membrane accumulation. Conversely, erlotinib (Erl), an EGFR inhibitor, led to a VP-independent increase of apical AQP2 accumulation in collecting ducts, and significantly reduced urine volume by more than 40% after 4 days of treatment in lithium-induced NDI mice. Erl enhanced AQP2 plasma membrane localization in cells by increasing AQP2 exocytosis and decreasing endocytosis. This effect was cAMP, cGMP, and PKA independent. Despite apparently bypassing cAMP pathways, Erl resulted in AQP2 phosphorylation in a dose dependent manner at serine 256, an essential step in VP-induced AQP2 membrane accumulation. We propose that EGF has a tonic inhibitory effect on VP action, and that relief of such inhibition enhances AQP2 phosphorylation and results in membrane accumulation.

Conclusions: We showed a crosstalk between EGF and VP in the modulation of AQP2 trafficking. EGFR inhibition increases AQP2 membrane expression bypassing the canonical VP/cAMP/PKA pathway and ameliorates lithium-induced NDI in mice. This study improves our understanding of the diversity of mechanisms that regulate water reabsorption in the body, and uncovers a novel pathway for potential therapeutic targets for NDI.

Funding: NIDDK Support

FR-PO102

ChIP-seq Analysis of Genomic Binding Sites for the Transcription Factor E1f1 in mpkCCD Cells Hyun Jun Jung, Viswanathan Raghuram, Jae Wook Lee, Mark A. Knepper. *Systems Biology Center, NHLBI, NIH.*

Background: Collecting duct cells selectively express a number of transport proteins (aquaporins and ion channels) vital to water and electrolyte balance. Previous studies of tissue-specific gene expression in collecting duct cells have implicated Ets family transcription factors (TFs) (Yu et al. PNAS 2009;106:2441). We integrated data from prior proteomics and transcriptomics studies of mouse mpkCCD cells using Bayes' Rule to create a probability-based ranking of all known TFs with regard to likelihood of a role in collecting duct-specific gene expression. Among the top-ranked TFs were several Ets family TFs including E1f1.

Methods: To identify genomic binding sites for E1f1 in mpkCCD cells, we carried out ChIP-seq analysis using an antibody successfully employed in the *Mouse ENCODE Project*. The mpkCCD cells were treated with the vasopressin analog dDAVP (100pM) for 24 hr prior to crosslinking and chromatin immunoprecipitation (ChIP) (n=3). DNA libraries were prepared from immunoprecipitated DNA and sequenced using an Illumina HiSeq 2000 sequencer to identify TF-enriched genomic regions. Control ChIP was carried out with nonspecific IgG.

Results: The analysis (MACS peak-calling software) identified >2000 binding sites seen in all three replicates and not seen in IgG-only controls. The identified sites mapped to within 2000 bp of annotated transcription start sites (TSSs) of several genes whose transcript abundances were previously demonstrated to be regulated by vasopressin including *Id3*, *Txnip*, *Jun*, *Sat1* and *Spag1* (Khositseth et al. Mol Cell Proteomics 2011;10:M110). There was no E1f1 binding in the vicinity of any aquaporin or any ENaC subunit, indicating that any role of E1f1 in regulating these targets is likely to be indirect. However, E1f1 binding was mapped to additional TFs that are predicted to bind within 1000 bp upstream of TSSs for aquaporin-2, β -ENaC or γ -ENaC (Genomatix motif analysis). These TFs were *Creb1*, *Gata3*, *Sox4*, *Junb*, *Sp1*, *Sp3*, *Gabpa*, *Nfkb1*, *Hmbox1*, *Rreb1* and *Rxra*.

Conclusions: These data provide an initial step in identification of the transcriptional network that determines cell-type-specific expression in renal collecting duct cells.

Funding: Other NIH Support - NHLBI Intramural Research Program

FR-PO103

Deletion of Aquaporin 11 in Transgenic Mice prior to Post-Natal Day 12 Results in Proximal Tubule Injury and Cyst Formation Søren Nielsen,¹ Mads Vammen Damgaard,^{1,2} Michael R. Rutzler,¹ Robert A. Fenton,² Aleksandra M. Rojek,² ¹Dept of Health Science and Technology, Aalborg Univ, Aalborg, Denmark; ²Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark.

Background: AQP11 is expressed in the proximal tubule (PT). Neonate AQP11 KO mice show PT vacuolization and cysts, resulting in renal failure and death. This study examined; 1) whether AQP11 deficiency at specific stages of kidney development is important for PT injury and cyst formation; 2) if cysts are closed structures or dilations of PT; 3) the role of metabolic challenges on PT injury and cyst formation.

Methods: Tamoxifen-inducible AQP11 KO mice were generated.

Results: Deletion of Aqp11 at post-natal (PN) day 2, 4, 6, 8, 10, 12 or 21 was investigated alongside neonate total Aqp11 KO mice. PT cell vacuolization and tubular cysts developed only in mice where Aqp11 gene disruption was instigated before PN day 12. Aqp11 gene deletion after PN week 3 did not result in PT injury or cyst formation. Similarly, 3 weeks of metabolic stress induced by repeated fasting (16hrs) / re-feeding (2hrs) of PN day 21 induced Aqp11 KO mice or total neonate AQP11 KO mice resulted in PT cytoplasmic vacuoles but not PT cysts. IP injection of biotinylated-dextran (10kDa) in adult, neonatally induced Aqp11 KO mice revealed endocytotic uptake in both cystic and PT epithelium. Thus apparent cysts were continuous with PT hence representing PT dilations. This was confirmed by serial sectioning and digital 3-D tracing of PT cysts in adult, neonatally induced Aqp11 KO mice. Electron microscopy of PT in kidneys from adult neonatally induced Aqp11 KO mice revealed dilated RER and extensive autophagosomes.

Conclusions: 1) AQP11 deficiency prior to PN day 12 leads to PT cell injury and severe PT tubular dilatation. 2) Aqp11 gene deletion after full kidney development results in normal PT morphology, and only present with PT injury in response to metabolic challenge. 3) Apparent cysts represent PT dilations and are not closed cysts. Conclusion: AQP11 deficiency prior to PN day 12 sensitizes PT cells of the developing kidney to cellular injury and causes severe PT dilations thus revealing a novel mechanism for PT cyst formation.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO104

Involvement of NADPH Oxidase 2 in the Kidney Injury of Aquaporin-11 KO Mouse Yuya Hoshino,¹ Hiroko Sonoda,¹ Kenichi Ishibashi,² Masahiro Ikeda,¹ ¹Veterinary Pharmacology, Univ of Miyazaki, Miyazaki, Japan; ²Medical Physiology, Meiji Pharmaceutical Univ, Tokyo, Japan.

Background: Aquaporin-11 (AQP11), the latest member of the AQP protein family to be described, is an intracellular AQP. Several in vivo studies have shown that AQP11 deficiency causes kidney injury characterized by the formation of multiple cysts. Recently, this kidney injury was reported to be related to the production of reactive oxygen species (ROS). However, the underlying molecular mechanism is largely unknown.

Methods: In this study, we examined the mechanism by which AQP11 deficiency induces ROS production using PCR array, real-time PCR, immunoblotting, and immunohistochemistry techniques. Also, a pathway analysis was performed with the results from the gene expression analysis.

Results: Immunohistochemistry studies showed that the number of 8-hydroxy-2'-deoxyguanosine-positive cells in renal interstitium was increased in AQP11 KO mice in comparison with wild-type mice. In parallel, immunoblotting analysis showed the increased levels of renal protein carbonylation in the KO mice. The NADPH oxidase (NOX) enzyme family is important sources of ROS and so far, six members (NOX1, NOX2, NOX3, NOX4, DUOX1, DUOX2) have been identified in mouse. Among them, real-time PCR analysis showed that renal NOX2 mRNA level was markedly increased in the KO mice. Furthermore, mRNAs for the assembly factors (p40phox, p47phox, p67phox) for NOX2 in the kidney were dramatically up-regulated in the KO mice. Immunoblotting analysis revealed that renal NOX2 protein expression was significantly increased in the KO mice. Immunohistochemistry showed that NOX2-positive cells were observed in renal interstitium.

Conclusions: These data strongly suggested that increased ROS production in AQP11 KO mice was mediated by NOX2, leading to the kidney injury.

FR-PO105

Intracellular Vacuoles in the Kidney of AQP11 Null Mice May Simulate the Cisplatin Nephrotoxicity Kenichi Ishibashi, Ichiru Akinaga, Takashi Kusano, Sei Sasaki, Yasuko Tanaka. *Medical Physiology, Meiji Pharmaceutical Univ, Kiyose, Tokyo, Japan.*

Background: Nephrotoxicity is a major side effect of cisplatin in chemotherapy. Despite years of research, the mechanism underlying cisplatin nephrotoxicity remains unclear and effective renal protective approaches during chemotherapy are still unavailable. Pathologically, cisplatin nephrotoxicity is characterized by cell injury with multiple intracellular vacuoles in the proximal tubule which are very similar to the kidney phenotype of AQP11 null mice before the polycyst development. We speculated that cisplatin may inhibit the function of AQP11 to induce intracellular vacuoles.

Results: The importance of caspase (Casp) 12 in cisplatin nephrotoxicity has been reported in the literature (J Am Soc Nephrol. 16: 1985, 2005), the expression of Casps was examined by real-time PCR in the kidney of AQP11 null mice with intracellular vacuoles, i.e. two weeks after birth. Casp3/Casp8 for apoptosis were not induced, while Casp12 for ER stress were strongly induced by 9 folds and Casp1/Casp4 for inflammation by 6/7.5 folds. We next examined the effect of cisplatin on AQP11 expression in the kidney. The

real-time PCR showed the decrease of AQP11 expression by half in mice kidney at three days after 20 mg/g BW i.p. cisplatin with almost normal renal function. When AQP11 hetero-mice were challenged with the same cisplatin treatment, the renal parameters were increased: (hetero/wild) BUN 159.1/53.4 mg/dl, Cr 0.33/0.17 mg/dl, UA 3.13/2.0 mg/dl. We next searched for the interventions which enhance AQP11 expression in the kidney. Two-day dehydration decreased the AQP11 mRNA expression while three-day glucose 5g/kg BW i.p. or 1g/kg BW D-cysteine p.o. increased the AQP11 mRNA expression. We then treated AQP11 hetero-mice with the D-cysteine p.o. daily for three days after the cisplatin i.p. The increase of BUN by cisplatin was attenuated.

Conclusions: The results suggests that AQP11 may play an important role in the development of cisplatin nephrotoxicity. The enhancing the AQP11 expression in the kidney will be a renoprotective strategy in cisplatin nephrotoxicity.

Funding: Government Support - Non-U.S.

FR-PO106

Development of a Model on Chronic SIADH: Effect of Water Challenge and Treatment on Behavior, Learning, Memory and Brain Edema Marta Tejedor, Ana Durán Vila, Carmen Grande, Margarita Fernández, Teba González, Maria Melendo, Ana Morales, Cristina Vila, Juan Carlos Jado, Ignacio Lizasoain, Alberto Tejedor Jorge. *Nephrology, Hospital Gregorio Marañón, Madrid, Spain.*

Background: AIM: to develop a model on chronic SIADH and study the effects of acute water overload on behavior, brain edema and response to treatment.

Methods: We induced chronic SIADH by daily injection of ddAVP and water over a 3-5 day period to balb-c mice. We induced acute on chronic SIADH by giving an acute i.p. water challenge of 5% of body weight. We assessed behavioral changes by filming spontaneous activity in cages and under controlled conditions in a Morris water maze. We studied brain edema by means of continuous Percoll gradients to fraction grey and white brain substance. We administered tolvaptan to evaluate their effects in the abovementioned conditions.

Results: ddAVP administration alone was able to induce significant changes in spontaneous behavior despite minimal changes in natremia (3mEq/l). These changes were earlier and more severe if a chronic water overload was given. Overall, learning and memory improved over time with training, measured by times of resolution (p=0.004) and trajectory (p=0.002) in a water maze. This was more evident in the control group than in the SIADH group (learning (p=0.06), memory (p=0.08)). The mean trajectory length to resolve the maze was 185±55 cm in the control group, 360±44 cm in SIADH with no acute water overload (p<0.05) and 808±94 cm in SIADH with an acute water challenge of 5% (p<0.05). Treatment with tolvaptan significantly shortens the length of the trajectory to nearly baseline values. The SIADH group who received a 5% water challenge developed significant brain edema which was reversed by tolvaptan. No significant changes were seen in animals who did not receive the water challenge. An acute water overload of 5% in SIADH was equivalent to a 10% one in controls, as shown by similar worsening in the water maze.

Conclusions: ddAVP injection alone is enough to induce subtle behavioral changes, even in the absence of significant hyponatremia. Acute on chronic SIADH significantly worsens brain edema and resolution of a water maze, and such changes can be reverted by tolvaptan.

FR-PO107

Warburg-Like Proliferation Underlies Lithium-Induced Nephrogenic Diabetes Insipidus Theun de Groot, Peter M.T. Deen, Mohammad Alsady. *Dept of Physiology, Radboud Univ Medical Center, Netherlands.*

Background: Lithium is the first-choice medication for treatment of bipolar disorders and is used by 0.1% of the western population. Unfortunately, lithium treatment is associated with development of severe renal side effects. In approximately 50% of treated patients, lithium causes a urinary concentrating defect, which develops in ~20% of patients into symptomatic Nephrogenic Diabetes Insipidus (NDI). This disorder is characterized by polyuria and polydipsia and is caused by downregulation of AQP2 water channels in principal cells of the renal collecting duct. Furthermore, lithium induces proliferation of these cells *in vitro* and *in vivo*. Cell proliferation is often characterized by aerobic glycolysis (Warburg effect). Here, we investigated whether lithium may induce Warburg-like aerobic glycolysis and whether inhibition of this Warburg effect may rescue lithium-induced-NDI (Li-NDI).

Methods: Polarized mouse cortical collecting duct (mpkCCD) cells were cultured as a 2D transwell model and exposed to lithium chloride on the apical side (10 mM) and basolateral side (1 mM) to mimic clinical conditions in patients. C57BL/6J mice were fed a normal rodent diet or a diet with lithium chloride in a concentration of 40 mmol/kg of chow. During the last 48 hours of the experiment, mice were housed in metabolic cages in order to determine water intake and urine output/osmolality during the last 24 hours.

Results: Lithium induced proliferation of mpkCCD cells as shown by increased levels of the proliferation markers PCNA and cyclin D1. In addition, lactate and succinate, main products of the Warburg effect, were both increased in lithium-treated mpkCCD cells and mice. This was accompanied by a decrease in the ratio of phospho-pyruvate dehydrogenase PPDH/PDH, confirming the induction of aerobic glycolysis by lithium in mice. Interestingly, inhibition of lithium-induced glycolysis with 2-deoxyglucose (2DG) attenuated lithium-induced AQP2 downregulation in mpkCCD cells.

Conclusions: Our results reveal that lithium induces aerobic glycolysis in mpkCCD cells and mice. Targeting of aerobic glycolysis with 2-deoxyglucose rescued lithium-induced AQP2 downregulation and may represent a potential therapy for Li-NDI.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

FR-PO108

RNA-seq Profiling of the Cortical Collecting Duct in Vasopressin Escape
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Background: Vasopressin escape is a protective mechanism that limits hyponatremia in the syndrome of inappropriate antidiuresis (SIADH). Using RNA-seq, we investigated transcriptomic changes in microdissected cortical collecting duct (CCD) of rats undergoing vasopressin escape.

Methods: Male Sprague-Dawley rats (120-160 g) were placed on continuous dDAVP (5 ng/hr) infusion for 5 days, and received either a high water load (50 mL/d, "escape") or a normal water load matching insensible losses plus urine output (25 mL/d, "control"). Rats were sacrificed at day 1, 2, and 4, and 4 mm of CCDs were collected by manual microdissection. RNAs were processed into cDNA libraries and 50-bp paired-end reads were obtained using an Illumina platform. Reads mapping to Ensembl genes were counted for differential-expression analysis.

Results: Sequence depths were 40-65 million reads, with 80% of reads mapping to Ensembl genes. At day 2, 180 transcripts were downregulated and 339 transcripts were upregulated at a false discovery rate < 0.1. Consistent with increased water excretion in vasopressin escape, transcripts of aquaporin-2 and aquaporin-3 were significantly downregulated at day 1, 2 and 4. Among downregulated transcripts were transcription factors (*Hes1*, *Hmx2*, *Hoxb5*, *Hoxb6*, *Hoxb7*, *Jun*, and *Tox3*) and a cyclin-dependent kinase inhibitor (*Cdkn1b*). Among upregulated transcripts were proteins involved in cell division, such as centromere proteins (*Cenpa*, *Cenpf*, *Cenpl*, and *Cenpt*); cyclins (*Ccna2*, *Ccnb2* and *Ccdn1*); a cyclin-dependent kinase (*Cdk1*); components of DNA replication machinery (*Pold3* in DNA polymerase complex; *Mcm2*, *Mcm3*, *Mcm4*, *Mcm6*, and *Mcm7* in MCM replicative helicase complex; *Orc5* in origin recognition complex); polo-like kinase 1 (*Plik1*); and forkhead box protein M1 (*Foxm1*). GO terms related to cell division were enriched in upregulated transcripts ("cell cycle phase", adjusted $p=8 \times 10^{-23}$; "mitosis", 2×10^{-13}). Immunohistochemistry showed PCNA-positive cells in CCD of escape rats but none in control rats.

Conclusions: RNA-seq revealed that increased rate of cell division may be an activated mechanism involved in remodeling of the CCD to restore water homeostasis as a part of the renal adaptation to SIADH.

Funding: Other NIH Support - Division of Intramural Research, NHLBI Projects ZIA-HL001285 and ZIA-HL006129

FR-PO109

Silencing of the Kinome Identifies a Novel Modulator of Aquaporin-2 Trafficking
Hana Cernecka,¹ Dorte Faust,¹ Kerstin Zuehlke,¹ Marc Wippich,² Katina Lazarow,² Martin Neuenschwander,² Jens Peter von Kries,² Enno Klussmann.¹ ¹Anchored Signalling, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, (MDC), Berlin, Germany; ²Leibniz-Inst für Molekulare Pharmakologie (FMP), Campus Berlin-Buch, Berlin, Germany.

Background: Arginine vasopressin (AVP)-dependent water reabsorption requires the redistribution of aquaporin-2 (AQP2) from intracellular vesicles into the plasma membrane of renal principal cells. Despite identification of several proteins participating in the control of AVP-dependent AQP2 trafficking, the molecular mechanisms underlying the AQP2 redistribution are largely unknown. The aim of this study was to identify proteins controlling the localization of AQP2 and thereby to elucidate molecular mechanisms underlying the AQP2 translocation.

Methods: We established a large-scale siRNA screening using mouse collecting duct cells, stably expressing human AQP2. The expression of 719 kinases was knocked down and the AQP2 localisation was analysed by automated immunofluorescence microscopy. Generated images were analysed automatically to quantitatively evaluate cellular phenotypes in an unbiased approach by utilizing CellProfiler. Machine learning in combination with advanced statistical and computational techniques were applied.

Results: The screening revealed 13 genes whose expression was relevant for the AQP2 redistribution. One of them is a recently identified member of the cyclin-dependent kinase family. Its knockdown blocks the AQP2 translocation and simultaneously increases the AQP2 protein abundance.

Conclusions: Our approach contributes to understanding the molecular mechanisms underlying the control of AQP2 trafficking and to identify potential therapeutic targets for the treatment of diseases caused by or associated with aberrant AVP-mediated water reabsorption such as diabetes insipidus or heart failure.

Funding: Government Support - Non-U.S.

FR-PO110

The Circadian Clock in the Kidney Controls Several Essential Metabolic Pathways
Svetlana Nikolaeva,^{1,2} Camille Ansermet,¹ Gabriel Centeno,¹ Robert Koesters,³ Sylvain Pradervand,⁴ Olivier Bonny,^{1,5} Dmitri Firsov.¹ ¹Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; ²Sechenov Inst of Evolutionary Physiology and Biochemistry, St. Petersburg, Russian Federation; ³Univ Pierre et Marie Curie, Paris, France; ⁴Genomic Technologies Facility, Univ of Lausanne, Lausanne, Switzerland; ⁵Service of Nephrology, CHUV, Lausanne, Switzerland.

Background: The circadian clock is the central mechanism for regulating body metabolism and energy homeostasis. However, the role of the intrinsic renal circadian system in the control of renal and/or systemic metabolic pathways remains elusive.

Methods: A combined metabolomic/transcriptomic approach was performed on plasma or kidney tissue samples obtained from mice devoid of the molecular clock in renal tubular cells (Bmal1^{lox/lox}/Pax8-rtTA:LC1Cre mice/cKO mice).

Results: We found that cKO mice exhibit significant changes in several essential metabolic pathways, including (i) increased renal arginine production resulting in the increased plasma arginine and asymmetric dimethylarginine levels; (ii) significantly increased arginase activity in the PST resulting in the increased renal polyamines production and increased plasma urea levels; (iii) increased plasma levels of several phosphatidylcholine and sphingomyelin species; and (iv) a significant reduction in plasma carnitine levels, paralleled by a significant decrease in the expression levels of Slc22a5 (OCTN2) transporter involved in the apical carnitine reabsorption in the proximal tubule. Transcriptome analysis revealed a significant reduction in expression levels of all transcripts encoded by the mitochondrial genome as well as of a great number of nuclear transcripts encoding proteins involved in the mitochondrial oxidative phosphorylation. In parallel kidneys from cKO mice exhibited a significant decrease in the NAD/NADH ratio suggesting an increased glycolysis and/or decreased mitochondrial function.

Conclusions: These results suggest that the local renal circadian clock control a variety of metabolic processes both on the intra-renal and systemic levels.

Funding: Government Support - Non-U.S.

FR-PO111

Mouse Monocarboxylate Transporter 9 Functions as a Urate Transporter
Promsuk Jutabha, Naoyuki Otani, Motoshi Ouchi, Naohiko Anzai. *Dept of Pharmacology and Toxicology, Dokkyo Medical Univ School of Medicine, Mibu, Tochigi, Japan.*

Background: Monocarboxylate transporter 9 (MCT9/SLC16A9) has been suggested to be involved in the onset of hyperuricemia or gout by genome-wide association studies (GWAS). Since no experimental data about MCT9 function has been reported, we tried to clarify its physiological roles.

Methods: The expression of SLC16A9 was investigated by quantitative RT-PCR (qRT-PCR) against human tissue cDNAs. Using oocyte expression system, we injected mouse MCT9 (mMCT9) cRNA to perform the functional characterization of mMCT9.

Results: qRT-PCR showed that the mRNA expression of MCT9 is quite higher in kidney than other tissues. Its expression is also found in spleen, ovary, pancreas, prostate and testis. *Xenopus* oocytes expressing mMCT9 mediated the transport of [¹⁴C]urate in Na⁺, Cl⁻ and voltage-independent manner. Radiolabelled urate uptake via mMCT9 was not inhibited by 2.5 mM unlabelled urate and was not *trans*-stimulated by intracellularly-injected monocarboxylates (counterions for URAT1) nor dicarboxylates (counterions for OATs).

Conclusions: Here, we suggested, for the first time, that MCT9 functions as a low affinity urate facilitatory transporter in kidneys.

Funding: Government Support - Non-U.S.

FR-PO112

Mutation in the Creatine Transporter MCT12 Causes Low Plasma Level and Increased Fractional Excretion of Guanidinoacetate but Not Glucosuria
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Background: A heterozygous mutation (c.643C>A; p.Q215X) in the creatine transporter gene MCT12 (also known SLC16A12) was recently identified as the cause of a syndrome with juvenile cataracts, microcornea and glucosuria in a single family. While the MCT12 mutation co-segregated with the eye phenotype, poor correlation with the glucosuria phenotype questioned a pathogenic role of the mutation in the kidney.

Methods: We undertook a detailed phenotypic investigation of the index family and performed complementary *in vitro* studies.

Results: Here we show that MCT12 resides on basolateral membranes of proximal tubules. Patients with MCT12 mutation exhibit reduced plasma levels and increased fractional excretion of guanidinoacetate, but normal creatine levels, suggesting that MCT12 may function as a guanidinoacetate transporter *in vivo*. However, functional studies in *Xenopus* oocytes revealed that MCT12 transports creatine but not its precursor guanidinoacetate. This indicates that impaired MCT12-mediated cellular creatine efflux affects guanidinoacetate homeostasis indirectly, e.g. by an increase of the cellular creatine concentration, which is known to inhibit guanidinoacetate synthesis. Genetic analysis revealed a separate, hitherto undescribed heterozygous mutation in SGLT2 (c.265G>A; p.A89T) in the family that segregated with the renal glucosuria phenotype. When overexpressed in HEK293 cells, the mutant SGLT2 transporter is not efficiently translocated to the plasma membrane and displays greatly reduced transport activity.

Conclusions: Our data indicate that MCT12 functions as basolateral exit pathway for creatine in the proximal tubule. Heterozygous mutation of MCT12 affects systemic levels and renal handling of guanidinoacetate. Furthermore, our data reveal the presence of a digenic syndrome in the index family with simultaneous MCT12 and SGLT2 mutation. Thus, glucosuria is not part of the MCT12 mutation syndrome.

Funding: Government Support - Non-U.S.

FR-PO113

NaDC1 Knockout: Effects on Blood Pressure and Urine pH
 Federico Jose Teran,¹ Weitao Huang,¹ L. Lee Hamm,^{1,2} Kathleen S. Hering-Smith,¹ ¹Nephrology, Tulane Univ School of Medicine, New Orleans, LA; ²Research, SLVHCS, New Orleans, LA.

Background: NaDC1 reabsorbs filtered citrate (Cit); thus its regulation is important in preventing calcium nephrolithiasis. Importantly NaDC1 reabsorbs other Krebs cycle intermediates such as succinate (Suc) and αKG. Recently Suc and αKG have been found to be important in paracrine signaling as their luminal presence stimulates distal nephron G-protein coupled receptors GPCR91 and GPCR99 respectively. Luminal Suc via GPCR91 has been found to stimulate renin release; while αKG via GPCR99 stimulates bicarbonate secretion by type B intercalated cells. The purpose was to determine whether knockout of NaDC1 produces hemodynamic or urine pH changes that might be anticipated by activation of these receptors.

Methods: Adult NaDC1 KO, heterozygous (Het), and wild-type mice (WT), under normal or acid diet for 72 hr, were studied using standard clearance techniques. After anesthesia direct measurements of hemodynamic parameters were determined in real time. Urine, blood and tissue were collected for measurement of Suc, Cit, αKG, and pH.

Results: NaDC1 KO produced 2, 4, and 10-fold increases in urinary Suc, Cit, and αKG, respectively. There was substantial residual reabsorption of Cit and Suc in KO mice, indicating other transporters involved in reabsorption of these substrates. Despite the increase in urinary αKG there was no significant increase in urine pH (normal or acid diet); in fact on normal diet urine pH was lower in KO mice (5.41 ± 0.04 vs 5.90 ± 0.13 WT; p < 0.001). The lower urine pH in KO mice on normal diet may be a response to loss of potential bicarbonate in the form of increased Krebs cycle intermediate excretion. There was no change in the ability of KO animals to excrete ammonia. In regard to potential hemodynamic effects mediated by NaDC1 KO and increased urinary Suc, no change in MAP was determined comparing WT, Het or KO either on normal or acid diet.

Conclusions: In sum, NaDC1 is responsible for significant reabsorption of filtered αKG and Suc, but knockout of NaDC1 does not impair acid-base homeostasis or BP changes on normal or acid diets.

Funding: NIDDK Support

FR-PO114

The Ablation of Dendritic Cells Prevents the Upregulation of the Intrarenal Renin-Angiotensin System and Renal Sodium Transporters in Response to Angiotensin II and High Salt Diet
 Patricio A. Araos,¹ Daniel E. Hevia,¹ Carolina E. Prado,² Eugenia L. Fuentes,¹ Rodrigo Pacheco,² Luis F. Michea.¹ ¹Univ de Chile, Chile; ²Fundación Ciencia y Vida, Chile.

Background: Blood pressure depends on the renal sodium reabsorption mediated by the tubular transporters that are modulated by the intrarenal renin-angiotensin system (iRAS). Angiotensin II (AngII) and a high salt diet (HS) cause hypertension (HT) and the upregulation of the iRAS and sodium transporters. Our previous studies showed that the ablation of Dendritic Cells (DC) in mice prevented the development of HT in response to AngII+HS. In the present study, we evaluated if the ablation of DCs alters the modulation of the iRAS and tubular sodium transporters by AngII+HS.

Methods: CD11c.DOG mice, for selective loss of DCs (CD11c^{fl/fl}) cells after Diptheria Toxin (DT) injection, received vehicle, AngII+HS (AngII, 450 mg Kg/day+1% NaCl in drinking water) or AngII+HS+DT (DT, 8ng/g) during 14 days; Paired WT mice received vehicle, AngII+HS or AngII+HS+DT. We measured blood pressure (days 0, 4, 8, 14), and at day 14 we harvested tissues to measure the abundance of renal DCs (MHC-II⁺ and CD11c⁺) by immunofluorescence, the iRAS, the sodium-proton exchanger 3 (NHE3), the sodium-chloride cotransporter (NCC) and the Epithelial Sodium Channel (αENaC) by qRT-PCR and Western blot.

Results: The injection of DT prevented the development of HT in response to AngII+HS only in CD11c.DOG mice. CD11c.DOG and WT mice showed increased abundance of DCs in the cortex (peritubular); Only the CD11c.DOG mice showed a sharp reduction of renal DCs after DT injection. Both, in WT as in CD11c.DOG mice the administration of AngII+HS increased the iRAS (in fold of induction: Angiotensinogen, 1.5; Angiotensin converting enzyme, 1.9; and Angiotensin II receptor type I, 5), NHE3, NCC and αENaC (in fold of induction: 4.2; 6; 2), respectively vs vehicle-treated mice (p<0.05; n=5-9). The injection of DT concomitant to AngII+HS prevented the changes in sodium transporters and iRAS in CD11c.DOG mice (p<0.05 compared to AngII+HS; n=5-9).

Conclusions: We conclude that DCs are required for the modulation of iRAS and tubular sodium transporters by AngII+HS.

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FR-PO115

Splenectomy Differentially Affects Angiotensin-II and L-NAME Murine Models of Hypertension
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Background: The immune system plays a major role in animal models of hypertension (HTN) and end-organ damage. However, few studies have assessed the role of lymphoid organs in the pathogenesis of HTN. We have shown previously that prior splenectomy (SPLX) significantly alters tissue inflammation; however the effect of SPLX on HTN remains unclear. Therefore, the objective of the current study is to determine whether prior SPLX influences the development of HTN in 2 different mouse models.

Methods: Mice underwent SPLX or sham surgery 7 days prior to the induction of HTN using angiotensin-II (AngII, 400ng/kg*d) or nitric oxide synthase inhibition using L-NAME

(30mg/kg*d). Systolic blood pressure (SBP) was measured by tail-cuff manometer daily and mice were euthanized 14 days after induction of HTN. Heart weight/body weight (H/BW) ratios were calculated and kidney leukocyte infiltration was analyzed by flow cytometry.

Results: Mice with prior SPLX+AngII had significantly lower (P=0.03) SBP at both week 1 (148±7) and week 2 (135±7) as compared to Sham+AngII (174 and 173±7mmHg). Similarly, SPLX+AngII mice had significantly smaller (P=0.007) H/BW (4.3±0.3) as compared to Sham+AngII treated mice (5.2±0.4mg/g BW). Interestingly, no difference was observed in renal CD45⁺ (9.8±3 vs 10.6±3x10⁶ cells/g, P=0.64) or CD3⁺ T-cell infiltration (8.8±0.2 vs 9.6±0.1x10⁶ cells/g, P=0.64) between the Sham+AngII and SPLX+AngII treated mice, respectively. Furthermore, SPLX did not appear to influence the development of L-NAME HTN. SPLX+L-NAME mice had similar P=0.84) SBP (145±4mmHg) as the Sham+L-NAME group (146±4mmHg, n=6) after 2 weeks. Relative heart weights were also similar (P=0.45) between SPLX+L-NAME (4.9±0.2) and Sham+L-NAME treated mice (4.8±0.3mg/g BW).

Conclusions: Our data suggests that the full pressor response to AngII is dependent on the spleen. However, the effect of the spleen appears to be independent of renal inflammation. Moreover, the protective effect of the spleen is specific to AngII-dependent HTN and does not appear to be generalizable to all mouse models of hypertension. Further studies are needed to understand the physiological link between lymphoid organs (such as the spleen), renal inflammation, and the development of chronic HTN.

FR-PO116

Salt Overload Promotes Severe Renal Injury and Activates AngII, Renal NF-κB and Other Components of Innate Immunity in a Model of Arterial Hypertension
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Background: Hypertension (HTN) develops in rats that received the NF-κB inhibitor pyrrolidinedithiocarbamate (PDTC) during lactation. High salt (HS) and uninephrectomy (UNx) aggravate HTN, increase renal AngII and lead to severe renal injury. Here, we further investigated the mechanisms of renal injury and the effect of Losartan (L) in this model.

Methods: Munich-Wistar pups received PDTC (PDTC_{lact}) or no treatment (C) during lactation. At 10 wks of age, all rats underwent UNx and were divided in: C, given normal salt diet (NS); PDTC_{lact} given NS; PDTC_{lact}+HS, given HS; PDTC_{lact}+HS+L, given HS and L, 50 mg/kg/d. After 3 mo, we assessed: tail-cuff pressure (TCP, mmHg), glomerulosclerosis (GS), interstitial collagen 1 (COL), arterial lesions (AL), interstitial AngII+, macrophages (Mφ) and lymphocytes (Ly), cells/mm², TLR4 and nuclear NF-KB (x C), and serum IL-6 (pg/mL).

Results:

	C	PDTC _{lact}	PDTC _{lact} +HS	PDTC _{lact} +HS+L
TCP	144±2	167±3 ^a	195±4 ^{ab}	163±5 ^{ac}
GS%	2±1	1±1	12±2 ^{ab}	7±2 ^{abc}
AL%	0±0	1±1	17±5 ^{ab}	10±4 ^{ab}
AngII+	2±1	2±1	7±1 ^{ab}	4±1 ^{abc}
Mφ	33±3	34±4	140±21 ^{ab}	42±7 ^c
Ly	37±3	43±4	141±25 ^{ab}	65±8 ^{abc}
COL%	2.8±0.2	2.8±0.4	7.3±1.2 ^{ab}	3.5±0.5 ^c
NF-κB	1.0±0.2	1.7±0.4	2.6±0.5 ^a	0.9±0.3 ^c
IL-6	23±3	32±3	40±4 ^a	28±1 ^c
TLR4	1.0±0.1	1.5±0.4	2.9±0.7 ^{ab}	0.9±0.2 ^c

Mean±SE, ^ap<0.05 vs C, ^bp<0.05 vs PDTC_{lact}, ^cp<0.05 vs PDTC_{lact}+HS

HS+UNx led to severe HTN and renal/vascular injury, intense Mφ/Ly infiltration, increased AngII+ and TLR4, and NF-κB activation, with increased plasma IL-6, all correlating positively with TCP. L strongly attenuated renal damage, normalizing renal TLR4, renal NF-κB and plasma IL-6.

Conclusions: In PDTC_{lact} renal injury caused by HS+UNx involves activation of renal AngII and innate immunity, including the NF-κB system. FAPESP/CNPq.

FR-PO117

Interleukin-6 Inhibition Attenuates Hypertension and Proteinuria in Dahl Salt-Sensitive (SS) Rats
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Background: The infiltration of T lymphocytes in the kidney accompanies hypertension and renal damage in Dahl SS rats. Pharmacological or genetic reduction of T cells attenuates hypertension and renal damage in SS rats fed high salt. An examination of the infiltrating T cells in the kidney demonstrated that interleukin 6 (IL-6) mRNA levels are >50-fold higher in T cells isolated from the kidney in comparison to circulating T cells. IL-6 is a pro-inflammatory cytokine which positively correlates with hypertension in humans.

Methods: Experiments were performed to assess the potential role of IL-6 in Dahl SS hypertension by administering goat anti-rat IL-6 neutralizing antibody (anti-rIL-6; 4 µg/day, IP; R&D Systems, Minneapolis, MN) or normal goat IgG control (4 µg/day, IP) for 11 days.

Results: The MAP and urine protein excretion rates (Upro) were similar between the groups of SS rats (n=13-16/group) when fed low salt (0.4% NaCl) chow. Following 11 days of high salt (4.0% NaCl), the rats receiving anti-rIL-6 demonstrated a significant reduction in immunoreactive IL-6 in the renal medulla compared to control group (954±133 pg/ml vs 1802±336 pg/ml). Moreover, the increase in MAP following 11 days of 4.0% NaCl intake was significantly attenuated in treated (MAP=138±3 mmHg) vs the control group (MAP=149±3 mmHg). The Upro as a marker of renal damage was also significantly attenuated in treated (193±17 mg/day) vs control group (252±20 mg/day). To investigate mechanisms of action, a flow cytometry analysis of infiltrating immune cells in the kidney (n=4-5/group) was performed. The total number of leukocytes (CD45+) was significantly lower in the treated vs the control group averaging 4.8±0.5x10⁶ vs 6.8±0.5x10⁶ cells/kidney. The total number of monocytes and macrophages (CD11b/c+) was significantly lower in the treated vs the control group by 31%. The total number of T cells and T regulatory cells were not different among the groups.

Conclusions: The present studies indicate that IL-6 may participate in the development of SS hypertension and end-organ damage by mediating the infiltration of leukocytes into the kidney.

FR-PO118

High Salt Affects Toll-Like Receptor-Induced Gene Expression in Macrophages David Severs, Martin Hoogduijn, Alexander H. Danser, Robert Zietse, Ewout J. Hoorn. *Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands.*

Background: High dietary salt intake is a major risk factor for cardiovascular disease. A high-salt (NaCl) diet increases NaCl concentrations in the skin. In the skin, macrophages respond to high NaCl by the osmosensitive transcription factor NFAT5 and promote NaCl efflux via lymph vessels. Other effects of NaCl on local macrophages have remained largely elusive. Recent evidence suggests that NFAT5 also regulates multiple Toll-like receptor (TLR)-induced genes such as NOS2, TNF and IL6 in macrophages, independently of osmotic stress. We aimed to investigate the effects of NaCl-generated hypertonicity on the expression of these genes in TLR-activated macrophages.

Methods: We simulated the hypertonic skin microenvironment by culturing macrophage-like RAW 264.7 cells in NaCl-induced hypertonic media (340-480 mOsm/kg) and compared this with normotonic media (320 mOsm/kg). After 1 to 24 hours of stimulation with lipopolysaccharide (LPS) or Zymosan A, a TLR2 ligand, we measured nitrite production, and analyzed TLR response genes by quantitative RT-PCR, and p38-MAPK, NFAT5, and NOS2 by immunoblot.

Results: NaCl significantly and dose-dependently increased nitric oxide (NO) production (2-fold), NOS2 mRNA (3-fold) and NOS2 protein expression (2.25-fold) in LPS- and Zymosan A-stimulated cells. In contrast, equimolar mannitol or urea did not affect expression levels. NaCl also increased LPS-induced p38 phosphorylation and total NFAT5 protein expression. Similarly, NaCl increased TNF mRNA expression 1.25-fold. Remarkably, NaCl significantly downregulated LPS-induced expression of CCL5 (4-fold), IL6 (2.4-fold) and IL12b mRNA (3.5-fold).

Conclusions: Elevated concentrations of NaCl, comparable with those found in the skin after high dietary salt intake, amplify expression of NOS2 and TNF in TLR-stimulated macrophages. This effect is likely mediated via p38 and NFAT5. Increases in NOS2 and TNF expression were paralleled by a sharp decline in mRNA expression of other proinflammatory genes. Modulation of TLR-mediated macrophage activation by NaCl may be relevant both for the physiological response to high dietary salt and salt-sensitive hypertension.

FR-PO119

Indoxyl Sulfate Upregulates Aortic Expression of (Pro)renin Receptor by Reactive Oxygen Species and Activation of AhR/NF-κB Pathway in Vascular Smooth Muscle Cells Maimaiti Yisireyili,¹ Toshimitsu Niwa.² *Cardiology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan;* *Faculty of Health and Nutrition, Shubun Univ, Ichinomiya, Aichi, Japan.*

Background: Chronic kidney disease (CKD) is considered major causes of death in cardiovascular disease (CVD) patients. (Pro)renin receptor (PRR) is significantly expressed in the kidney of CKD and vascular system. In this study we aimed to clarify the role of indoxyl sulfate (IS), a uremic toxin, in PRR activation in rat aorta and human aortic smooth muscle cells (HASMCs).

Methods: CKD rats and IS-administrated rats were subjected for in vivo experiments. Human aortic smooth muscle cells (HASMCs) was treated with or without indoxyl sulfate.

Results: Immunohistochemistry showed increased expression of PRR and renin/prorenin in aorta of CKD rats and IS-administrated rats compared with normal rats. IS elevated the expression of PRR and prorenin in HASMCs. N-acetylcysteine, an antioxidant, and diphenyleioidonium, an inhibitor of nicotinamide adenine dinucleotide phosphate oxidase, suppressed IS-induced expression of PRR and prorenin in HASMCs. Knock down of organic anion transporter 3 (OAT3), aryl hydrocarbon receptor (AhR) and nuclear factor-κB p65 (NF-κB p65) with small interfering RNAs inhibited IS-induced expression of PRR and prorenin in HASMCs. Knock down of PRR inhibited cell proliferation and tissue factor expression induced by not only prorenin but also IS in HASMCs.

Conclusions: IS promotes aortic expression of PRR and renin/prorenin through OAT3-mediated uptake, production of reactive oxygen species, and activation of AhR and NF-κB p65 in vascular smooth muscle cells.

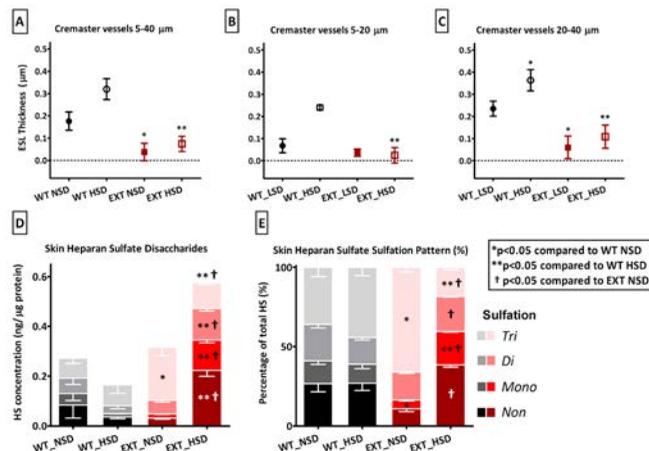
FR-PO120

Role of Skin and Endothelial Surface Layer Heparan Sulfates in Blood Pressure Regulation Rik Hg Olde Engberink,¹ Naomi Van Vlies,² Bert-Jan Van den Born,³ Ed van Bavel,⁴ Liffert Vogt.¹ *¹Nephrology, AMC, Amsterdam, Netherlands;* *²Laboratory of Genetic Metabolic Disease, AMC, Amsterdam, Netherlands;* *³Vascular Medicine, AMC, Amsterdam, Netherlands;* *⁴Biomedical Engineering and Physics, AMC, Amsterdam, Netherlands.*

Background: Besides the skin, the endothelial surface layer (ESL) contains many glycosaminoglycans (GAGs) that can osmotically inactivate Na⁺ and may affect blood pressure (BP). EXT genes regulate heparan sulfate (HS) polymerization, the predominant ESL GAG. In mice with heterozygous loss of EXT1 and EXT2 (EXT), and wildtype (WT) mice, we investigated the role of HS in the skin and ESL in BP regulation after an acute and chronic NaCl load.

Methods: We investigated BP effects of a 7-d normal (0.3%, NSD) and high (8.0%, HSD) NaCl diet, with tail cuff measurements, and an acute 1.8% NaCl load (8 µl/g) with intracarotid measurements. We used intravital microscopy to estimate ESL thickness in <40 µm cremaster vessels on both diets. We used high performance liquid chromatograph-mass spectrometry to measure skin HS disaccharide concentration.

Results: Baseline BP was equal in WT and EXT mice (p=0.9), with no difference between NSD and HSD. Relative to WT, acute NaCl infusion increased BP in EXT mice (p=0.02), while heart rate remained equal (p=0.5). After a NSD and HSD, EXT mice had a 78% reduction of ESL thickness compared to WT mice (Fig A). HSD increased ESL thickness in WT, especially in 20-40 µm vessels, but not in EXT mice (Fig BC). Skin HS concentration and sulfation patterns were equal between diets in WT mice (Fig DE). On NSD, EXT mice had more highly sulfated HS compared to WT (Fig DE). EXT mice on a HSD had the highest skin HS concentration, of which most were low-sulfated.



Conclusions: An intact ESL is pivotal to prevent a BP increase during acute NaCl excess. Skin GAGs may be particularly important to prevent detrimental NaCl effects on the long-term, especially when the ESL is damaged.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO121

Functional and Dynamic Microcompartmentation of Cav-1/TRPV4/K_{Ca} in Caveolae of Endothelial Cells Andreas Hofmeister, Sybille Goedicke-Fritz, Anuradha Kaistha, Ivica Grgic, Joachim Hoyer. *Dept of Internal Medicine and Nephrology, Philipps-Univ Marburg, Marburg, Germany.*

Background: Ca²⁺-activated K⁺ channels (K_{Ca}) play an important role in the endothelium-dependent hyperpolarization and regulation of vascular tone and blood pressure. For activation, K_{Ca} depend on an increase of intracellular calcium which is largely mediated by Ca²⁺-permeable cation channels including the transient receptor potential V4 (TRPV4). It has been proposed that K_{Ca} and Ca²⁺-permeable cation channels may be clustered in localized positions within the cell membrane to form functional units and that caveolae may constitute the scaffolding for such microcompartmental organization.

Methods: Here, we sought to elucidate the composition and functional relevance of these microcompartments in vitro and in vivo.

Results: We show that TRPV4 and small-conductance K_{Ca}2.3 are enriched in caveolae of human microvascular endothelial cells. Using immunoprecipitation, immunocytology and superresolution microscopy, we found a caveolae-dependent association between caveolin-1, TRPV4 and small conductance K_{Ca}2.3, but not intermediate conductance K_{Ca}3.1, in endothelial cells under static condition. Mechanical stimulation of cells via exposure to shear stress led to a partial de-novo colocalization of K_{Ca}3.1 with Cav-1 and TRPV4. In a mouse model of genetic Cav-1 deficiency, we found significantly reduced K_{Ca}-mediated currents as determined by patch-clamping in carotid artery endothelial cells (CAEC) from Cav-1^{-/-} mice compared to wildtype. Functionally, Cav-1 deficiency was associated with impaired endothelium-derived hyperpolarizing factor (EDHF)-mediated vasodilation in response to shear stress and acetylcholine.

Conclusions: In summary, our findings provide evidence for a dynamic microcompartmentation of TRPV4/K_{Ca} in caveolae of endothelial cells and highlight the importance of Cav-1 for endothelial K_{Ca} functions and flow-induced vasodilation.

Funding: Government Support - Non-U.S.

FR-PO122

Adenosine A1 Receptor Exacerbates Water-Sodium Retention in Deoxycorticosterone Acetate-Salt Hypertensive Mice Janet Yanqing Mei,¹ Xiaoxiao Shi,¹ Dongli Tian,¹ Xiaoyan Peng,¹ Wei Chen,² Limeng Chen.¹
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Background: Water-sodium retention is the key change in salt sensitive hypertension. Adenosine A1 receptor (A1AR) engages in tubuloglomerular feedbacks; its activation is followed by increased secretion of atrial natriuretic peptides (ANP) in the heart. We aim to study the function of A1AR in water-sodium retention.

Methods: DOCA-salt hypertensive model was established by removal of left kidney, implantation of a DOCA pellet (200mg, 60-day release), and feeding with high salt diet (8%NaCl). Arterial blood pressure and heart rate were measured by tail-cuff method. Urine samples were collected using metabolic cage. The CD73 (an adenosine synthetase), A1AR, ANP and Corin (a protease cleaves pro-ANP, producing ANP) mRNA expression were measured by real-time PCR.

Results: Wildtype DOCA-salt mice showed higher blood pressure (124.7±20.3 vs. 105.8±14.1 mmHg, *P*<0.01), slower heart rate (562.0±90.8 vs. 681.5±90.1, *P*<0.01), and increase in 24h urine output (3606±2359 vs. 1399±752 ml, *P*<0.01). The adenosine pathway was activated in DOCA-salt mice evidenced by increased CD73 (2.22 and 17.7 times increased expression in kidney and heart, *P*=0.034 and 0.001) and A1AR expression (2.54 and 11.12 times increased expression in kidney and heart, *P*=0.032 and 0.009). The cardiac mRNA expression of ANP and Corin were also significantly higher in DOCA-salt mice (176.67 and 30.93 times increased expression, *P*=0.030 and 0.005). The A1AR^{-/-} mice showed no significant changes in blood pressure or heart rate between DOCA-salt and sham group. The elevation in 24h urine output (7003±3742 vs. 3606±2359 ml, *P*=0.031) and 24h urine sodium excretion (1246.5±860.0 vs. 149.7±48.9 mmol/d, *P*=0.028) was more prominent compared to wildtype DOCA-salt mice. There was no change in either ANP or Corin mRNA expression.

Conclusions: A1AR may exacerbate water-sodium retention in salt sensitive hypertension. The reduction in glomerular hyperperfusion and hyperfiltration through tubuloglomerular feedback possibly outweighs the up-regulation of Corin and subsequent ANP expression.

FR-PO123

Dietary Fructose Increases Renal Sympathetic Nerve Activity in Response to High Salt Diet in Awake Freely Moving Rats Noreen F. Rossi,^{1,2} Kevin L. Gordish,^{1,3} Pablo A. Ortiz,^{1,3} William H. Beierwaltes.^{1,3} ¹*Physiology, Wayne State Univ School of Medicine, Detroit, MI;* ²*Nephrology, John D. Dingell VA Medical Center, Detroit, MI;* ³*Hypertension Research, Henry Ford Health Systems, Detroit, MI.*

Background: High consumption of fructose containing foods is increasingly prevalent. Fructose intake is associated with metabolic syndrome including hypertension. Fructose upregulates renal Na and Cl transport and induces neuroexcitation, both of which may increase blood pressure. Here we tested the hypothesis that fructose-fed rats fed a high salt diet will have higher plasma renin activity (PRA), renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) than glucose-fed rats on similar diet.

Methods: Male Sprague Dawley rats were instrumented for telemetric MAP and RSNA measurements. They were placed on 20% glucose (GF) or 20% fructose (FF) in their drinking water and 0.4% NaCl diet for 10 days then switched to 4% NaCl diet with further monitoring. RSNA recordings were obtained using LabChart 7 Pro. Rats were also subjected to air jet stress and nasopharyngeal reflex testing.

Results: Baseline MAP was similar in both groups, but was 20 mmHg higher in FF vs GF rats after high salt diet (*P* < 0.05). Baseline integrated RSNA did not differ between GF and FF rats. RSNA decreased in GF rats to 0.961 ± 0.182 mV.s after high salt diet. In contrast, integrated RSNA increased from 1.199 ± 0.245 to 1.600 ± 0.231 mV.s after high salt intake in FF rats (*P* < 0.05 vs high salt GF rats). Air jet stress and nasopharyngeal reflex responses in MAP and RSNA in GF rats were as expected and brief but in FF rats both responses were significantly greater and sustained for a longer period of time. High salt suppressed PRA by only 40% in FF rats: 2.05 ± 0.27ng Ang I/ml/hr (high salt) vs 3.48 ± 0.45 ng Ang I/ml/hr (baseline; *P* < 0.05).

Conclusions: We found that the expected suppression of RSNA by high salt diet is completely reversed into stimulation with high fructose diet. The suppression of PRA by high salt diet is blunted and the response to acute stressors enhanced, thus suggesting increased RSNA is a critical component of fructose-induced salt-sensitive hypertension.

Funding: NIDDK Support, Veterans Administration Support

FR-PO124

A 20% Fructose Diet Enables Low Concentrations of Angiotensin II to Activate Sodium Transport in the PT via Protein Kinase C (PKC) Pablo D. Cabral, Jeffrey L. Garvin. *Physiology & Biophysics, Case Western Reserve Univ, Cleveland, OH.*

Background: Consumption of high-fructose corn syrup is implicated in the development of hypertension but the mechanisms are poorly understood. The proximal tubule (PT) reabsorbs ~70% of the filtered fluid, Na and most of the bicarbonate via Na/H exchanger 3. Enhanced PT transport is implicated in many forms of hypertension. Angiotensin II (Ang II), atrial natriuretic peptide (ANP) and dopamine regulate Na transport. Enhanced effects of Ang II and decreased actions of ANP and dopamine in the PT may cause salt-sensitive hypertension. Hypothesis: A 20% fructose diet enables low concentrations of Ang II to activate Na transport in the PT via protein kinase C (PKC).

Methods: We isolated and perfused PTs from Sprague Dawley rats that were fed either a control or a 20% fructose diet for 1 week. NHE activity was measured as the recovery of intracellular pH after an NH₄Cl acid pulse using the pH-sensitive dye BCECF. The rate of pH recovery was measured in Fluorescent Units per second (FU/sec).

Results: Ang II (10⁻¹²M) did not stimulate NHE under normal conditions. When rats were fed a 20% fructose diet, this concentration stimulated NHE activity from 0.6±0.1 to 1.3±0.1 FU/sec (*p*<0.002; *n*=5). In the presence of the PKC inhibitor G66976 (10⁻⁷M), Ang II was unable to stimulate NHE activity (from 1.9±0.6 to 1.2±0.2 FU/sec; *n*=12). The dopamine 1 receptor agonist fenoldopam (10⁻⁶M), decreased NHE activity to the same extent in PTs from rats fed either a control or a 20% fructose diet (-0.6±0.2 vs -1.1±0.4 FU/sec; *n*=5). ANP (10⁻⁸M) also decreased NHE activity to the same extent in PTs from rats fed either a 4% NaCl diet or a 4% NaCl plus 20% fructose diet (-0.9±0.4 vs -1.1±0.5 FU/sec; *n*=12).

Conclusions: A 20% fructose diet enables low concentrations of Ang II to activate Na transport in the PT via PKC without affecting the inhibitory effects of dopamine and ANP on NHE activity in the PT. These results may partially explain the mechanism by which a fructose diet induces hypertension.

Funding: NIDDK Support

FR-PO125

Megalin-Dependent Intrarenal Generation of Angiotensin II Induced by Podocyte Injury Taiji Matsusaka,¹ Fumio Niimura,¹ Akira Nishiyama,² Akihiko Saito,³ Motoko Yanagita,⁴ Iekuni Ichikawa.^{1,5} ¹*Tokai Univ School of Medicine, Japan;* ²*Kagawa Univ School of Medicine, Japan;* ³*Niigata Univ School of Medicine, Japan;* ⁴*Kyoto Univ School of Medicine, Japan;* ⁵*Shinsyu Univ, Japan.*

Background: We previously demonstrated that podocyte injury enhances glomerular filtration of liver-derived angiotensinogen (Agt) and renal angiotensin(A)II generation and that filtered Agt is reabsorbed by proximal tubular cells dependently on megalin. In the present study, we tested whether megalin is involved in intrarenal AII generation.

Methods: For this purpose, we generated proximal tubule specific megalin knockout (KO) mice by crossing megalin-loxP, Ndr1g1-Cre, and Kap-Cre mice. Renal AII contents were measured by radioimmunoassay.

Results: In megalin KO mice (*n*=12), renal megalin mRNA was decreased to 2.5% of that in control mice (*n*=16). Renal Agt staining was markedly diminished, with increase in urinary Agt in KO mice. However, renal AII levels were similar between KO and control mice (108±11 vs. 101±17 fmol/g). We next tested the effect of megalin KO on AII generation in the kidney with abnormally increased filtered load of Agt in mice with podocyte-specific injury, by crossing with NRP25 mice. Control NRP25 mice (*n*=10) showed markedly intense renal Agt staining and enhanced renal AII level (450±61). Megalin KO/NRP25 mice (*n*=12) showed diminished renal Agt staining and significantly attenuated renal AII level (119±23, *p*<0.01). KO/NRP25 mice showed similar renin and Agt mRNA, and more preserved Ace mRNA in the kidney.

Conclusions: These indicate that, in podocyte injury, abnormally increased filtered load of Agt is reabsorbed via megalin by proximal tubular cells and induces the inappropriate activation of intrarenal renin-angiotensin system, which may be involved in the progression of tubulointerstitial damage secondary to podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO126

Ciliary Neurotrophic Factor Deficiency Protects from Cardiovascular Death in Angiotensin II-Induced Hypertension Ivo Quack,¹ Yuriko Mori,² Sebastian Alexander Potthoff,¹ Magdalena Woznowski,¹ Eva Koenigshausen,¹ Lorenz Sellin,¹ Lars C. Rump,¹ Johannes Stegbauer.¹ ¹*Nephrology, Univ Hospital Duesseldorf, Duesseldorf, Germany;* ²*Nuclear Medicine, Univ Hospital Duesseldorf, Duesseldorf, Germany.*

Background: It has been shown that the JAK2 / STAT3 signaling cascade modulates Ang II (Ang II)-dependent hypertension. The ciliary neurotrophic factor (CNTF) is an interleukin-6-like cytokine so far known for mediation of survival and differentiation of neuronal cells via JAK2 / STAT3. This study focuses on the role of CNTF in Ang II-dependent hypertension.

Methods: Two weeks after uninephrectomy, Ang II osmotic minipumps (1000 ng/min/kg BW) were implanted in CNTF-KO and age-matched C57/B16J male mice (WT). Blood pressure (BP) were measured for 3 weeks by radiotelemetry, starting one week before implantation. Histological and mRNA analysis were performed at the end of the observation period. Renal vascular function was evaluated in the isolated perfused kidney.

Results: At baseline systolic BPs were similar in CNTF-KO and WT mice (119±2 vs. 124±1 mmHg). CNTF deficiency significantly attenuated BP increase under Ang II infusion (week 1: 139±3 vs. 153±3 mmHg; week 2: 151±5 vs. 168±4 mmHg; n=19; $P<0.01$). Strikingly, in the CNTF-KO group significantly less animals died of cardiovascular causes (4.2% (KO) vs. 29.2% (WT) $P<0.05$). In accordance, end organ damage (cardiac hypertrophy, renal vascular fibrosis and tubulo-interstitial damage) was attenuated in the CNTF-KO group. In the isolated perfused kidney, pressor response to Ang II was significantly attenuated in CNTF-KO mice. Administration of CNTF (0.5nM) nearly restored the Ang II dependent pressor response. This effect was mediated through a JAK2/STAT3 dependent pathway as static (0.1µM), a selective STAT3 inhibitor abolished the CNTF induced increase in pressor response in kidneys of CNTF-KO. On cellular basis, CNTF induced phosphorylation of STAT3 and MYPT in VSMCs.

Conclusions: Better survival and less end organ damage strongly suggest that CNTF has a major impact on blood pressure regulation. CNTF seems to modulate the Ang II induced vasoreactivity via a JAK2 / STAT3 dependent mechanism. Thus, CNTF might qualify as therapeutic target in hypertension.

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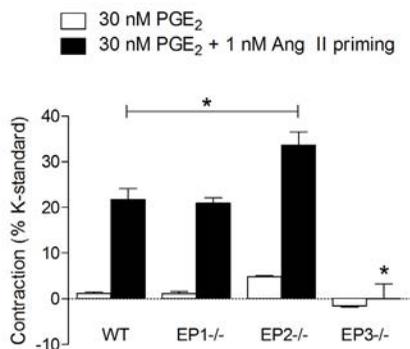
FR-PO127

Angiotensin II AT1 Receptor Potentiates Prostaglandin E2 Vasoconstrictor Effects Maria Palazzo Kraemer,² Fred S. Lamb,³ Richard M. Breyer.¹ ¹Div of Nephrology and Hypertension, Dept of Veterans Affairs and Vanderbilt Univ, Nashville, TN; ²Dept of Biochemistry, Vanderbilt Univ, Nashville, TN; ³Dept of Pediatrics, Vanderbilt Univ, Nashville, TN.

Background: Prostaglandin E₂ (PGE₂) is a key modulator of blood pressure and arterial tone. It usually has vasodepressor effects however under certain circumstances can act as a vasopressor. Recent reports demonstrated that sub-threshold concentrations of KCl and phenylephrine augment PGE₂-mediated constriction in rat femoral arteries, however the effects of angiotensin II (Ang II) on PGE₂-mediated constriction are unknown.

Methods: Wire myography was performed on femoral arteries isolated from WT or EP deficient mice.

Results: PGE₂ had no effect on mouse femoral arteries at doses up to 1 µM. Pretreatment of arterial rings with 1 nM Ang II potentiated PGE₂-evoked constriction in a dose dependent manner (AUC_{untreated} 1.784±0.353, AUC_{Ang II} 23.27±9.820, $P<0.05$). To identify the relevant E-Prostanoid (EP) receptor, femoral arteries from EP1, EP2, and EP3 receptor null mice were tested. Arteries isolated from EP1^{-/-} or EP2^{-/-} but not EP3^{-/-} mice responded to PGE₂ after Ang II priming. Pretreatment of arterial rings with 1 µM losartan, an AT1 angiotensin receptor antagonist, blocked PGE₂-induced constrictor effects primed with Ang II (% KCl, Ang II 21.72 ± 5.296, Ang II + losartan 3.025 ± 1.046, n=3). No constriction was observed in Ca²⁺-free buffer; re-addition of extracellular Ca²⁺ to the arterial bath restored PGE₂-induced contractions (n=5). The Rho-kinase inhibitor Y-27632 blocked contraction (n=3).



Conclusions: Taken together these data are consistent with angiotensin AT1 and prostaglandin EP3 receptors mediating a synergistic Ca²⁺/Rho-kinase-dependent contractile response. The synergistic interaction of Ang II and PGE₂ may have physiological relevance in the context of hypertension.

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FR-PO128

Angiotensin II Increases Uromodulin Expression and Excretion in Rats Independent of Blood Pressure and Alterations in Tubular Reabsorption Magali Araujo, William J. Welch, Gabriel A. Cordeiro dos Santos, Daurea M. Vieira Paiva, Christopher S. Wilcox. *Medicine, Georgetown Univ, Washington, DC.*

Background: Increased uromodulin (UMOD) has been associated with salt-sensitive hypertension and chronic kidney disease. Evidence suggests that UMOD regulates the trafficking and activity of the Na-K-2Cl cotransporter (NKCC2) and the inward-rectifier type potassium channel (ROMK), the two main transporters involved in Na⁺ reabsorption by the TAL. Angiotensin II (AngII) increases net TAL Na⁺ transport and Na⁺ apical entry; however its interaction with UMOD remains elusive. We hypothesized that ANG II interacts with UMOD to modulate Na⁺ transport.

Methods: Sprague-Dawley rats (n=5) were infused with a subpressor dose of AngII (100ng/kg/min) or vehicle for 3 days. Blood pressure (BP) was measured by telemetry. On day 2, rats were placed in metabolic cages for 24 h and urine was collected for UMOD

and Na/K measurements. On day 3, proximal and distal reabsorption were measured by renal micropuncture and the renal medulla was harvested for determination of UMOD expression by western blot.

Results: Blood pressure was unchanged after 3 days of AngII (veh: 89±3, AII: 81±1mmHg). AngII treated rats had significantly increased UMOD excretion compared with control rats (Veh: 17.63±2.19, AII: 28.09±3.6, mg/24h, $p<0.05$). Sodium excretion was unchanged (veh: 3.46±0.6 AII: 3.38±0.6 mmol/24h). There were no changes in proximal fractional reabsorption (Veh: 57±2%, AII: 59±0.6%) and distal fractional reabsorption (Veh: 83±3%, AII: 87±2%). UMOD expression in the renal medulla was 3 fold higher in AngII treated rats compared to vehicle rats.

Conclusions: Our data demonstrate that AngII increases UMOD expression and excretion independent of blood pressure and alterations in tubular reabsorption. These results suggest that the interaction of AngII with UMOD precedes Na⁺ transport alterations and therefore can be an important mechanism involved in the development of hypertension.

FR-PO129

Effects of Systemic Deletion of Angiotensin Receptor-Binding Molecule on the Aging Kidney Kazushi Uneda, Kouichi Tamura, Hiromichi Wakui, Akinobu Maeda, Kengo Azushima, Sona Haku, Ryu Kobayashi, Masato Ohswawa, Yoshiyuki Toya, Satoshi Umemura. *Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.*

Background: The renin-angiotensin system plays a key role in the maintenance of cardiovascular and renal homeostasis, principally via appropriate activation of the angiotensin II type 1 receptor (AT1R). On the other hand, exaggerated activation of AT1R signaling would exert detrimental effects, such as various aging-related diseases including renal dysfunction. We previously identified an AT1R-associated protein (ATRAP/*Atrap*), which is a molecule directly interacting with the AT1R. Accumulating results indicate that ATRAP exerts functionally selective inhibition on exacerbated AT1R activation in response to pathological stimuli. The present study was performed to investigate pathophysiological significance of ATRAP in aging-related phenotypes by employing systemic ATRAP-knockout mice (ATRAP-KO mice).

Methods: ATRAP-KO mice and their wild-type control mice (WT mice) were fed the standard diet and maintained until death to estimate their life spans. Their growth (body weight change and appearance) and physiological parameters (blood pressure, caloric intake and glucose and lipid metabolism) were also analyzed. Furthermore, aging-related organ damages in the hearts, aortas and kidneys were examined in young (3 to 4 months old) and aged (22 to 25 months old) mice in both groups.

Results: There was no difference in the growth between two groups. In addition, ATRAP-KO mice did not show any evident alteration of physiological parameters. However, the life span of ATRAP-KO mice was significantly shorter than that of WT mice (KO vs WT; median life span, 100.4 weeks vs 123.1 weeks, log-rank test, $P<0.001$). By further analysis we found no significant difference in cardiovascular aging-related phenotype between two groups. On the other hand, renal fibrosis was exacerbated in aged ATRAP-KO mice compared to aged WT mice.

Conclusions: In the present study, ATRAP-KO mice showed accelerated renal fibrosis with shortened life span. Therefore, ATRAP deficiency seems to exacerbate the aging-related renal fibrosis and to inhibit the longevity.

FR-PO130

Effects of Deficiency of Angiotensin Receptor-Binding Molecule on Blood Pressure Regulation in Chronic Kidney Disease Ryu Kobayashi, Kouichi Tamura, Hiromichi Wakui, Kengo Azushima, Sona Haku, Kazushi Uneda, Kotaro Haruhara, Kohji Ohki, Sho Kinguchi, Masato Ohswawa, Yoshiyuki Toya, Satoshi Umemura. *Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.*

Background: The renin-angiotensin system plays a key role in the maintenance of cardiovascular and renal homeostasis, principally via appropriate activation of Ang II type 1 receptor (AT1R). On the other hand, exaggerated activation of AT1R signaling would exert detrimental effects, such as promoting various aging-related diseases including chronic kidney disease (CKD). We previously identified an AT1R-associated protein (ATRAP/*Atrap*), which is a molecule directly interacting with the AT1R. Accumulating results indicate that ATRAP exerts functionally selective inhibition on exacerbated AT1R activation in response to pathological stimuli. The present study was performed to investigate pathophysiological significance of ATRAP in mice model of CKD by employing systemic ATRAP-knockout mice (ATRAP-KO mice).

Methods: ATRAP-KO mice and their wild type control mice (WT mice) were subjected to 5/6 nephrectomy (Nx) as CKD model. To examine the effects of ATRAP deficiency, blood pressure and other parameters were measured in ATRAP-KO mice and WT mice after 5/6 Nx.

Results: At baseline, blood pressure was similar in ATRAP-KO and WT mice. In ATRAP-KO mice, blood pressure increased from 2 to 8 weeks after 5/6 Nx and was significantly higher than that in WT mice (ATRAP-KO vs WT; systolic blood pressure at 4 weeks after 5/6 Nx, 124±2 mmHg vs 107±1mmHg, $P<0.01$). With respect to the mechanism of elevated blood pressure in ATRAP-KO mice after 5/6 Nx, plasma volume was significantly higher in ATRAP-KO mice than in WT mice after 5/6 Nx, in spite of no significant difference in creatinine clearance between two groups after 5/6 Nx.

Conclusions: Although ATRAP-KO mice show similar blood pressure and renal function with WT mice in normal condition, ATRAP-KO mice exhibited significantly

increased blood pressure and plasma volume after 5/6 Nx compared with WT mice. Therefore, endogenous ATRAP may exert a protective function against pathological blood pressure elevation in CKD.

FR-PO131

In Vivo Action of Angiotensin II Type 1a Receptor in Renal Injury Induced by Deoxycorticosterone Acetate-Salt Hypertension Mikako Hisamichi,¹ Atsuko Ikemori,^{1,2} Takeshi Sugaya,¹ Daisuke Ichikawa,¹ Kenjiro Kimura,³ Yugo Shibagaki.¹ ¹Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; ²Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; ³Dept of Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: The AT1a receptor plays a major role in the renal action of Ang II and is expressed in vascular smooth muscle cells of the afferent arterioles. In this study, we investigated the morphological change in deoxycorticosterone acetate (DOCA)-salt hypertensive pathology in order to confirm the in vivo function of the AT1a receptor against renal damage due to hypertension.

Methods: To examine urinary L-type fatty acid binding protein (L-FABP) as an indicator of tubulointerstitial damage, we used human L-FABP chromosomal transgenic mice (L-FABP^{+/+} AT1a^{+/+}) and L-FABP transgenic mice in addition to disrupting the AT1a receptor gene (L-FABP^{+/+} AT1a^{-/-}), L-FABP^{-/-} AT1a^{+/+} and L-FABP^{-/-} AT1a^{-/-} mice were administered DOCA tablets plus 1% NaCl water for 28 days.

Results: In the DOCA salt hypertensive model with L-FABP^{+/+} AT1a^{+/+} (L-FABP^{+/+} AT1a^{+/+}-DOCA), slight expansion of the glomerular area and tubulointerstitial damage were observed, but not glomerular sclerosis. In the AT1a knockout mice administered DOCA-salt (L-FABP^{+/+} AT1a^{-/-}-DOCA mice), glomerular sclerosis with expansion of the mesangial area was found, and the degree of tubulointerstitial damage was more severe compared to L-FABP^{+/+} AT1a^{+/+}-DOCA mice. Both urinary albumin and L-FABP levels were significantly higher in the L-FABP^{+/+} AT1a^{-/-}-DOCA mice than in the L-FABP^{+/+} AT1a^{+/+}-DOCA mice. This renal damage induced in the L-FABP^{+/+} AT1a^{-/-}-DOCA mice was significantly attenuated by reduction of blood pressure using Hydralazine. Activation of the AT1a receptor may contribute to myogenic response of the afferent arteriole involved in the renal autoregulatory mechanism.

Conclusions: In conclusion, kidneys without AT1a receptors exhibited an increased vulnerability to hypertension, and therefore activation of the AT1a receptor inhibited the transmission of the elevated systemic pressures to the glomeruli.

FR-PO132

Renal Blood Flow and Oxygenation During Renin-Angiotensin-Aldosterone System Activation – Two Sides of the Same Coin? René van der Bel,¹ Aart J. Nederveen,² Bram F. Coolen,² Wouter V. Potters,² Hein J. Verberne,³ Liffert Vogt,¹ Erik Stroes,¹ C.T.P. (Paul) Krediet.¹ ¹Internal Medicine, AMC, Univ of Amsterdam, Netherlands; ²Radiology, AMC, Univ of Amsterdam, Netherlands; ³Nuclear Medicine, AMC, Univ of Amsterdam, Netherlands.

Background: In chronic kidney disease, renal hypoxia and renin-angiotensin-aldosterone system (RAAS) activation may augment each other. Although renal oxygenation (RO) measured by Blood Oxygen Level Dependent (BOLD) MRI is not correlated to Glomerular Filtration Rate (GFR), recent data suggest that RO relates to inter-individual variation in RAAS activity. To further explore this we measured the effects of Angiotensin II (Ang-II) on renal blood flow (RBF) and RO in healthy humans.

Methods: After a 30 min baseline phase, 8 healthy volunteers (age 19-22 years) were subjected to continuous Ang-II infusion at 0.3, 0.9 and 3.0 ng/kg/min for 12 minutes per dose. RO and RBF were assessed by BOLD and phase contrast MRI, respectively (Ingenia 3.0T, Philips Healthcare). Off-line, R2* values were calculated for cortex and medulla, via mono-exponential fitting to multi-echo 2-dimensional fast field-echo data (TR 140 ms; FA 70°; min TE 2 ms; DTE 5 ms; 16 echoes; voxel 1.2 mm² by 4 mm). RBF was calculated in the proximal renal artery after manual vessel segmentation. During a second visit (n=6), GFR and Effective Renal Plasma Flow (ERPF) were measured by ¹²⁵I-thalamate and ¹³¹I-hippuran clearing test during equal Ang-II infusion.

Results: Mean arterial blood pressure increased from 83.0±2.85 at baseline to 91.3±3.76 mmHg (p=0.002). RBF decreased dose dependently from 11.1±2.08 to 8.05±1.02 (p=0.02) ml/s. GFR and ERPF both decreased (10±7.1%, p=0.016; 24±4.5%, p<0.001). RBF and ERPF measurements strongly correlated (R = 0.75 p<0.001). There was a trend towards a cortical R2* increase by 7.2±3.76% (p=0.014); medullary R2* did not change. Cortical DR2* and DRBF inversely correlated (R=0.42, p=0.044). Cortical DR2* and ΔGFR correlated (R=0.48, p=0.017).

Conclusions: Ang-II causes a dose dependent DRBF. The observed DRO seem to differ between cortex and medulla. Only for the cortex BOLD may provide an index of tissue perfusion.

FR-PO133

Chloride Contributes to Hypertension and Renal Injury in Aldosterone-Salt Treated Rats Takahiro Yamauchi, Shigehiro Doi, Toshiki Doi, Kensuke Sasaki, Toshinori Ueno, Ayumu Nakashima, Takao Masaki. Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Aldosterone-salt treatment is known to induce renal inflammation and plays an important role in the development of renal fibrosis as well as elevation in blood pressure. In addition to sodium, chloride has recently been reportedly to be involved in renal

damage, raising the possibility that sodium-bicarbonate may ameliorate renal injury and hypertension in rats treated with aldosterone. This study investigated the role of chloride on renal damage and hypertension by comparing rats treated with aldosterone in combination with either sodium chloride or sodium carbonate.

Methods: Following a left nephrectomy, 8-week-old male Sprague-Dawley rats were implanted with an osmotic infusion mini-pump and then allocated to the following 3 groups; 1) drinking a 1% NaCl solution with aldosterone infusion (NaCl-aldosterone treated group), 2) drinking a 1% NaHCO₃ solution with aldosterone infusion (NaHCO₃-aldosterone treated group), and 3) drinking water with vehicle infusion. Blood pressure levels were measured weekly by the tail cuff method. After 6 weeks, the rats were sacrificed and their renal tissues examined by immunoblotting and immunohistochemistry.

Results: The NaCl-aldosterone group had higher blood pressure levels than the NaHCO₃-aldosterone group. Protein expression of αENaC and Pendrin in the membrane fraction was also increased in the NaCl-aldosterone group compared with the NaHCO₃-aldosterone group. In addition, the NaCl-aldosterone group had high protein levels of NCC and phosphorylated NCC in the whole protein and membrane fractions. On the other hand, the expression of inflammatory (CD3, CD68, IL17A, IL-23 receptor) and fibrotic markers (α-smooth muscle actin, collagen1) were greater in the NaCl-aldosterone group.

Conclusions: These findings suggest that chloride plays an important role in the development of NaCl-aldosterone-induced hypertension and renal injury.

FR-PO134

RAGE-DNA Aptamer Improves Aldosterone-Induced Renal Injury Possibly via Inhibition of Rac1-MR Axis in Mice with Hypertensive Nephropathy Kensei Taguchi,¹ Sho-ichi Yamagishi,² Yuichiro Higashimoto,³ Yosuke Nakayama,¹ Katsuhiko Asanuma,⁴ Seiji Ueda,¹ Kei Fukami.¹ ¹Div of Nephrology, Dept of Medicine; ²Dept of Pathophysiology and Therapeutics of Diabetic Vascular Complications; ³Dept of Chemistry, Kurume Univ School of Medicine, Kurume, Japan; ⁴Div of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: Advanced glycation endproducts (AGEs) stimulate the generation of reactive oxygen species (ROS) and subsequently enhance various intracellular pathways through the interaction with receptor for AGEs (RAGE). Although AGEs-RAGE axis has been mainly investigated in diabetic nephropathy, its pathophysiological role in hypertensive nephropathy (HN) is unknown. In addition, recent evidence has suggested that aldosterone (aldo)-mineralocorticoid receptor (MR) system plays a crucial role for the pathogenesis of HN. In this study, we examined whether AGEs-RAGE system could interact with aldo-MR axis in deoxycorticosterone acetate (DOCA)-induced HN in mice. Further, we explored the inhibitory effects of DNA-aptamer directed against RAGE (RAGE-aptamer) on the progression of HN.

Methods: Uninephrectomized 8-week-old C57Bl/6J male mice were divided into three groups; 4% salt diet (control), 4% salt diet with DOCA (50mg), and DOCA with hydralazine (Hyd). RAGE-aptamer constructed by SELEX method was continuously administered with osmotic mini pump.

Results: DOCA elicited-UAE was independent of blood pressure. Renal ROS generation, RAGE protein expression and plasma carboxymethyl lysine (CML) levels were elevated in DOCA/salt mice. RAGE was colocalized MR in podocytes by immunohistological analysis. Further, GTP-bound Rac1 activation and MR overexpression were observed in DOCA/salt mice. DOCA-elicited increase in UAE, renal ROS generation and RAGE expression, plasma CML levels were improved by RAGE-aptamer independent of blood pressure. Interestingly, RAGE-aptamer suppressed GTP-bound Rac1 activity and MR overexpression in DOCA/salt mice.

Conclusions: AGEs-RAGE axis and Rac1-MR pathway could be correlated with each other, which could lead to podocyte injury in HN. RAGE-aptamer may be a novel therapeutic strategy for the progression of HN.

FR-PO135

Dipeptidyl Peptidase-4 Inhibitor Ameliorates the Aldosterone-Induced Renal Fibrosis Kang-Yung Peng, Vincent Wu. Dept of Internal Medicine, National Taiwan Univ, Taipei, Taiwan.

Background: Renal fibrosis is considered a common outcome of a wide variety of chronic kidney diseases with diverse causes. However, no antifibrotic agent has been approved in clinical practice yet. In this study, we examined the effect of dipeptidyl peptidase-4 (DPP-4) inhibitor against renal fibrosis induced by aldosterone.

Methods: Human proximal tubular epithelial cells (HK2) were used to examine the inhibitory effect of DPP-4 inhibitor on aldosterone induced epithelial-mesenchymal transition (EMT). Besides, aldosterone infusion mice were used to evaluate the effect of DPP-4 inhibitor, linagliptin, on aldosterone induced renal fibrosis. Expression of TGF-β, OPN and molecules involved in EMT were examined using western blot and immunohistochemistry. Renal fibrosis was determined by Masson's trichrome staining.

Results: *In vitro* studies showed that aldosterone significantly increases the expression of TGF-β, OPN and markers of EMT in HK2 cells, while these effects were abolished in that treated with DPP-4 inhibitor. Similarly, the aldosterone-infused mice exhibited severe kidney fibrosis. The expression of TGF-β, OPN, vimentin and α-SMA were induced by aldosterone, and oral DPP-4 inhibitor ameliorated the kidney fibrosis and lessened the increase in fibrotic proteins without significant changes in blood pressures.

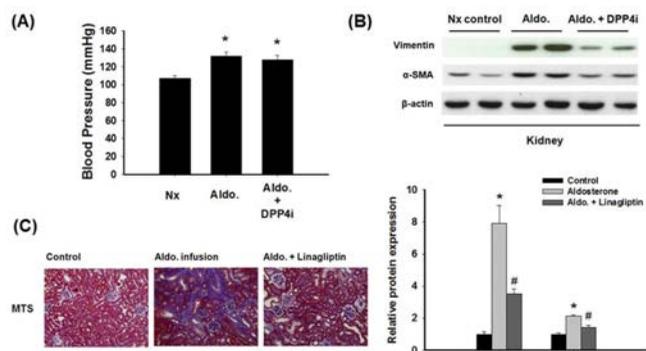


Figure. Effect of DPP4 inhibitor on aldosterone induced renal fibrosis

Conclusions: In this study, our results suggest that DPP-4 inhibitor possesses anti-EMT effect to ameliorate the aldosterone-induced renal fibrosis, which may partly attribute to regulating TGF-β/OPN pathways. These findings may guide us in therapeutic strategies for aldosterone-induced renal fibrosis.

FR-PO136

G-Protein-Coupled Receptor 40 Mediates the Regulation of Epithelial Sodium Channel by Epoxyeicosatrienoic Acid Signaling Seong Kwon Ma, Ha Yeon Kim, Chang Seong Kim, Eun Hui Bae, Soo Wan Kim. *Internal Medicine, Chonnam National Univ Medical School, Gwangju, Republic of Korea.*

Background: Epoxyeicosatrienoic acid (EET) plays diverse functions including cellular proliferation, anti-inflammation and vasorelaxation. Although it has been demonstrated that EET also regulate epithelial sodium channel (ENaC), the potential functional receptor mediating the biological effect of EET has remained elusive. In the present study, we investigated the role of GPR40 mediating ENaC regulation of EET in mouse cortical collecting duct (M1-CCD) cell line.

Methods: M1-CCD cells were cultured with aldosterone in the absence or presence of 14,15-EET. In addition, M1-CCD cells treated with aldosterone were cultured in the absence or presence of GW9110, a GPR40 antagonist.

Results: The mRNA and protein of ENaC-α and GPR40 were endogenously expressed in the M1-CCD cells as well as the cortical collecting ducts of murine kidney. Treatment with aldosterone increased the protein expression of ENaC-α and mineralocorticoid receptor (MR). These changes were abolished by 14,15-EET treatment, and treatment with 14,15-EET increased the phosphorylation of ERK1/2. Inhibition of GPR40 by treatment with GW9110 enhanced the aldosterone-induced upregulation of ENaC-α and MR, while decreased ERK1/2 phosphorylation.

Conclusions: In conclusion, EET inhibits aldosterone-induced ENaC activation by the inhibition of MR and activation of ERK1/2. GPR40 inhibition augmented the aldosterone-induced ENaC activation by the activation of MR and inhibition of ERK1/2. These findings suggest that GPR40 mediated the ENaC regulation by EET signaling.

FR-PO137

The Extra Renal Effect of Hydrochlorothiazide on Systemic Blood Pressure: Role of Vasodilation in Volume Depleted States Saeed Alshahrani,¹ Jack Rubinstein,² Min Jiang,² Sharon L. Barone,²³ Jie Xu,² Kamyar A. Zahedi,²³ Manoocher Soleimani.^{1,2,3} ¹Pharmacology, Univ of Cincinnati, Cincinnati, OH; ²Internal Medicine, Univ of Cincinnati, Cincinnati, OH; ³Research Services at VA Hospital, Cincinnati, OH.

Background: Thiazides are specific inhibitors of the Na⁺-Cl⁻ Co-transporter (NCC) in the distal nephron, and the most commonly used diuretics for the treatment of mild hypertension. The mechanism of hypotensive action of thiazides is not clear. The accepted belief is that the primary effect of thiazides is through the enhancement of salt excretion; however, several studies point out the extra renal effects of thiazides. The blood pressure response to thiazides requires an initial volume loss of about 1.5 kg, which it is not observed in individuals who are ingesting a high-salt diet.

Methods: Balance studies were performed in age/sex-matched wild type and NCC deficient mice. The blood pressure was measured using computerized tail cuff method. Cardiac functions were analyzed by echocardiography.

Results: Hydrochlorothiazide (HCTZ) significantly reduces systemic blood pressure when NCC KO mice are volume-depleted and their renin-angiotensin system (RAS) is activated, however, it had no effect on blood pressure of salt replete NCC KO mice. The reduction in blood pressure in salt depleted animals was dramatic, happened within hours after HCTZ and occurred in the absence of any increase in salt excretion, indicating its extra-renal origin. Echocardiography showed no significant changes in cardiac output in response to HCTZ. The antihypertensive effects of HCTZ were abrogated in the presence of a blocker of large conductance Ca²⁺ activated K⁺ (BK) channels, Paxilline. Western blots demonstrated significant enhancement of BK expression in vascular system of salt depleted, NCC-deficient mice.

Conclusions: Our results indicate that vasoconstriction secondary to RAS activation amplifies the extra-renal hypotensive action of HCTZ through vasodilation irrespective of

the status of its renal target. Patients on a combination diuretic regimen such as furosemide and HCTZ are at increased risk of hypotension and kidney hypoperfusion subsequent to systemic vasodilation by HCTZ.

Funding: Veterans Administration Support, Government Support - Non-U.S.

FR-PO138

Mitochondrial Oxidative Stress-Activated Renal Local RAS Promotes the Expression and Function of NCC in Proteinuric Kidney Disease Songming Huang,^{1,2} Yibo Zhuang,¹ Guixia Ding,¹ Zhanjun Jia,^{1,2} Aihua Zhang.^{1,2} ¹Nephrology Dept, Nanjing Children Hospital, Nanjing Medical Univ, Nanjing, China; ²Nanjing Key Laboratory of Pediatrics.

Background: The fluid retention and hypertension are common complications of kidney diseases, whose pathogenic mechanisms remain elusive.

Methods: Kidney tissues from mice subjected to albumin overload via i.p injection for 12 days and renal biopsy specimens were analyzed.

Results: Following albumin overload, we found a striking increase of Na⁺-Cl⁻ cotransporter (NCC) expression by 2.3-fold in mouse kidneys determined by Western blotting and qRT-PCR. To evaluate NCC function in these mice, NCC inhibitor hydrochlorothiazide (10mg/kg) was administered via a single i.p injection. In agreement with NCC upregulation, the response to hydrochlorothiazide was significantly enhanced in albumin overloaded mice. Considering the established role of renin-angiotensin system (RAS) in regulating sodium transporters, we examined key components of RAS and found a striking elevation of angiotensinogen (AGT) and angiotensin converting enzyme (ACE) by 2-3 folds in line with enhanced urinary AngII excretion. In proteinuric patients, we also observed 4-fold upregulation of NCC and remarkable stimulation of ACE detected by immunohistochemistry in accord with significantly increased urinary Ang II output. To further investigate the role of RAS in NCC upregulation, we did primary culture of renal tubular cells and observed that albumin directly increased NCC paralleled with significant induction of AGT, ACE, and Ang II. Strikingly, administration of specific ACE inhibitor captopril to the cells remarkably abolished albumin-induced enhancement of NCC and RAS components. Additionally, albumin overload significantly reduced mitochondrial superoxide dismutase (SOD2) by 60%, and administration of a SOD2 mimic (MnTBAP) entirely abolished the stimulation of NCC, AGT, and ACE in mice with albumin overload.

Conclusions: The findings demonstrated an important role of albuminuria in upregulating NCC expression via a mitochondrial oxidative stress-initiated stimulation of renal local AGT/ACE/Ang II, which may contribute to the fluid retention and hypertension in proteinuric kidney disease to some extent.

Funding: Government Support - Non-U.S.

FR-PO139

Prophylactic and Therapeutic Tenapanor Are Vascular Protective in a Rat Model of CKD Ann-Cathrine Jönsson-Rylander,¹ Margareta Behrendt,¹ Craig F. Plato,² Denise L. Schwabauer,² Peter J. Greasley.¹ ¹AstraZeneca R&D, Mölndal, Sweden; ²Plato Biopharma Inc., Denver, CO.

Background: Tenapanor (AZD1722), an inhibitor of the Na⁺/H⁺ exchanger NHE3, reduces absorption of gut sodium and phosphate. It is being developed for renal and constipation-related indications.

Methods: 5/6 nephrectomized Sprague Dawley rats were fed 4% NaCl chow to induce salt-sensitive arterial hypertension. Oral tenapanor (1 mg/kg/day) was initiated either at the start of NaCl intake (prophylactic; Px) or 2 weeks later (therapeutic; Tx), and was administered for up to 6 weeks. Disease controls (DCs; vehicle-treated) and healthy controls (HCs; sham operated, normal chow) were included to enable assessment of disease progression. Systemic hemodynamics and urinary and plasma biomarkers were assessed every 2 weeks. *Ex vivo* vascular function (isometric tension recording) or arterial stiffness (pulse wave velocity) was evaluated at 2 and 6 weeks.

Results: Compared with DCs, rats in the Px and Tx groups had reduced urinary albumin, protein, sodium and phosphorus excretion (*p*<0.05), and looser stools. Systolic, diastolic and mean BP increased in DCs but were normalized in the Tx group. Arterial stiffness was reduced by Px and Tx tenapanor (*p*<0.05). Compared with HCs, DCs had impaired aortic vasoconstrictor and vasodilator function at 2 weeks (*p*<0.05) and significant endothelial dysfunction at 6 weeks. Px tenapanor normalized, and Tx tenapanor attenuated arterial hypertension, vascular stiffness, vasoconstrictor and endothelium-dependent and independent vasodilator function (Table).

	ΔEC ₅₀ (denuded vs intact endothelium) ^a		EC ₅₀ (intact endothelium) ^b	Pulse wave velocity change
	Phenylephrine (nM)	Nitroprusside (nM)	Acetylcholine (nM)	
HCs	187.5±49.3	0.5±0.2	11.9±1.21	—
DCs	12.7±3.2*	15.4±2.7*	80.3±8.7*	75.4%*
Tx tenapanor	102.7±28.6†	2.8±0.9†	10.3±1.38†	-60.7%†
Px tenapanor	120.5±25.3†	1.06±0.3†	8.15±0.71†	-81.9%†

**p*<0.05 vs HCs; †*p*<0.05 vs DCs; ^aMean±SEM; ^bMean±SD. DCs, disease controls; HCs, healthy controls; Px, prophylactic; Tx, therapeutic; EC₅₀, half maximal effective concentration.

Conclusions: Tenapanor prevented most of the maladaptive consequences in a rat model of renal insufficiency-induced salt-sensitive arterial hypertension and CKD. The benefit of Tx treatment was similar to that elicited by Px use, suggesting disease modification.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO140

Urinary Exosome Profiling in Thiazide Induced Hyponatremia Sarath Kiran Channavajihala,¹ Theresa Peltz,³ Wenjing Jia,¹ Ian Hall,¹ Kevin O'Shaughnessy,² Matthew A. Bailey,³ James W. Dear,³ Mark Glover.¹ ¹*Div of Therapeutics and Molecular Medicine, Univ of Nottingham, United Kingdom;* ²*Clinical Pharmacology Unit, Univ of Cambridge, United Kingdom;* ³*Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom.*

Background: Thiazides are one of the most widely used and cost-effective class of anti-hypertensive medication. Thiazide-Induced Hyponatremia (TIH) is one of their major adverse effects and the leading cause of drug-induced hyponatremia requiring hospitalization. *A priori* TIH must result from excessive saluresis and/or water reabsorption. The water and electrolyte transporter composition of urinary exosomes (UE) reflects their cellular origin and are a promising way to study renal dysfunction. This study assessed the expression of AQP2 and NCC in the UE of TIH patients.

Methods: 100 patients admitted to hospital with severe TIH donated urine samples during acute TIH and at two months post thiazide cessation. Matched normonatremic controls were recruited both on and off thiazides (groups 1 & 2 respectively). UE from a representative sample of each patient group were isolated and AQP2 and NCC were evaluated by Western blotting and Nanoparticle Tracking Analysis (NTA). AQP2 and NCC expression was normalized by urinary creatinine. Immunoblots were also corrected for total protein and results expressed as units of optical density/Ucr.

Results: Westerns showed that UE expression of AQP2 was higher in cases during acute TIH compared to convalescent (32.93 vs 28.71, $P < 0.01$) and compared to control groups 1 & 2 (15.61 and 15.09 respectively, $P < 0.001$). NCC expression was lower in TIH patients acutely compared to convalescent (17.72 vs 31.86, $P < 0.05$) and compared to both control groups (30.32 and 31.17, $P < 0.05$). NTA also demonstrated increased AQP2 expression in acute & convalescent TIH.

Conclusions: This study highlights the utility of UE analysis to probe the molecular pathophysiology of TIH. Increased AQP2 and reduced NCC expression suggests that TIH results from increased water reabsorption and sodium wasting in the distal nephron. TIH studies may further understanding of renal physiology and inform the design of new thiazide medicines less prone to cause hyponatremia.

Funding: Government Support - Non-U.S.

FR-PO141

Epigenetic Modulation of Renal Arterioles Induced by DOCA-Salt Loading in Mice Hiroyuki Inoue, Kazutoshi Miyashita, Masaaki Sato, Kentaro Fujii, Aika Hagiwara, Masanori Tamaki, Hiroshi Itoh. *Internal Medicine, School of Medicine, Keio Univ, Tokyo, Japan.*

Background: The relationship between salt intake and development of hypertension is familiar; however, the mechanism for the onset has not been fully revealed. Our previous report showed that the medial hypertrophy of renal arterioles after transient salt loading in spontaneous hypertensive rat caused lasting elevation in blood pressure. The present study investigated the significance of epigenetic modulation of the gene expressions which are relevant to the medial hypertrophy after transient salt loading.

Methods: Male 6 week old C57bl6 mice were implanted deoxycorticosterone acetate (DOCA) pellets and given drinking water containing 1% NaCl for 2 weeks for generation of salt-induced hypertension. The blood pressure was measured by a tail-cuff method during and after the transient salt loading. Histological examinations of the kidney were performed during and after the salt loading. Gene expressions in the kidney such as matrix metalloproteinases (MMPs), which promote the medial hypertrophy, were quantified. Epigenetic modulation of the genes were analyzed.

Results: Transient salt loading caused elevation in blood pressure during the loading period. Blood pressure after stopping salt-loading was also significantly higher than that before salt loading. Salt loading caused medial hypertrophy of renal arterioles, and it remained after stopping salt loading, as to cause lasting renin elevation. Real time PCR revealed that MMP2 and MMP9 were increased during the salt loading. CGN5, CBP and p300, which are histone acetyltransferases, were elevated. Sirt1, Sirt3, HDAC1 and HDAC5, which are histone deacetylases, were decreased. Histone H3K9 and H4K16 acetylations in the MMP2 gene were enhanced by the salt loading.

Conclusions: The lasting medial hypertrophy and renin elevation after transient salt loading were suggested to be caused by the increased expression of MMPs along with augmented histone acetylations by the salt loading. Increased expressions of acetyltransferases along with decreased expressions of Sirts and HDACs by transient salt loading would be involved in the enhancement of the histone acetylations.

FR-PO142

Radio-Frequency Catheter-Based Renal Denervation in Hypertensive Sheep with Chronic Kidney Disease Impairs Responses to Hemorrhage Reetu R. Singh,¹ Karen M. Moritz,² Kate M. Denton.¹ ¹*Physiology, Monash Univ, Clayton, VIC, Australia;* ²*School of Biomedical Sciences, The Univ of Queensland, St. Lucia, QLD, Australia.*

Background: Renal sympathetic nerves modulate kidney function and blood pressure (BP). Trials using catheter-based renal denervation (cDNX) in hypertensive patients yielded results both in support of and, against its efficacy in lowering BP. A critical question is whether cDNX has adverse consequences, in situations of clinical challenge, such as hemorrhage in denervated patients where intact nerves would be required. This study examined consequences of cDNX 1) on BP and renal function and 2) on reflex activation of sympathetic nerve activity (SNA) in hypertensive sheep with chronic kidney disease (CKD).

Methods: Sheep with established hypertension and renal dysfunction (CKD group) with an appropriate control group were used. At 10 months of age, some animals underwent cDNX (CKD-cDNX; control-cDNX) while the remaining underwent sham procedure (CKD-intact; control-intact). At 2 months post-cDNX, BP, renal function, and plasma renin activity (PRA) were assessed before, during and after hemorrhage (20% blood volume withdrawn over 15 minutes).

Results: CKD sheep had higher BP compared to all groups but CKD-cDNX sheep had similar BP to control sheep. Basal renal function was not further reduced. In response to hemorrhage, BP fell in all groups but the greatest decrease occurred in CKD-cDNX. In Control-intact sheep this fall in BP gradually recovered, associated with increase in PRA reflecting an increase in reflex SNA. In contrast, in Control-cDNX and CKD-cDNX groups, PRA did not increase and BP did not recover reflecting an absence of increase in reflex SNA.

Conclusions: cDNX effectively reduced BP at 2 months post-cDNX in previously hypertensive sheep but had no effect on renal function. However, the lack of reflex activation of neural mechanisms observed during hemorrhage suggest, that cDNX may impair a patient's ability to adequately respond to physiological challenges.

Funding: Government Support - Non-U.S.

FR-PO143

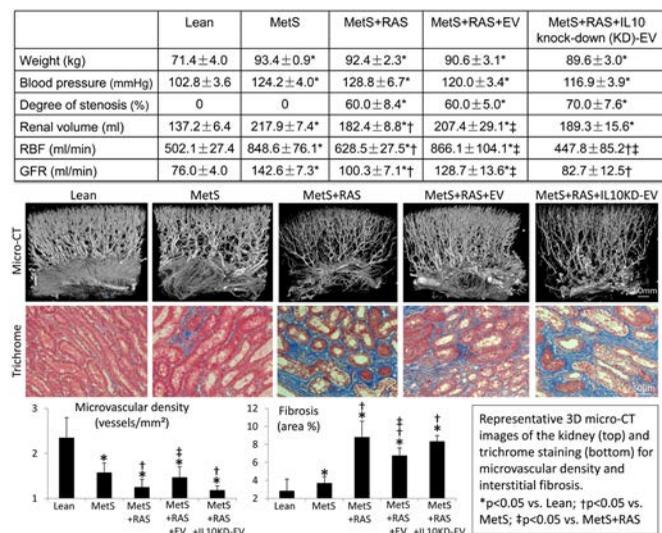
Interleukin-10 Mediates the Renoprotective Properties of Mesenchymal Stem Cells-Derived Extracellular Vesicles in Porcine Metabolic Syndrome and Renal Artery Stenosis Alfonso Eirin,¹ Xiang-yang Zhu,¹ Christopher M. Ferguson,¹ Scott Riester,² Andre J. Van Wijnen,² Amir Lerman,³ Lilach O. Lerman.^{1,3} ¹*Divs of Nephrology and Hypertension, Mayo Clinic;* ²*Orthopedic Surgery, Mayo Clinic;* ³*Cardiovascular Diseases, Mayo Clinic, Rochester, MN.*

Background: Mesenchymal stem/stromal cells (MSCs) are immunomodulatory and have unique potential to restore the renal microvasculature, but may generate safety concerns. MSC-derived extracellular vesicles (EVs) emerged as a novel non-cellular alternative. Using a swine model of metabolic syndrome (MetS) superimposed on renal artery stenosis (RAS) we tested whether intrarenal injection of EVs attenuates renal injury and if this capacity is mediated by their cargo of the anti-inflammatory cytokine IL-10.

Methods: MetS pigs were studied after 16 weeks of RAS untreated or treated 4 weeks earlier with a single intrarenal delivery of labeled EVs harvested from autologous MSCs (2.5x10⁵/Kg) with or without pre-silenced IL-10 (IL-10 knock-down). Lean and MetS Sham served as controls (n=7 each). Single-kidney renal blood flow (RBF) and glomerular filtration rate (GFR) were studied in-vivo, and microvascular architecture (micro-CT) and fibrosis ex-vivo.

Results: EVs were detected in the stenotic-kidney 4 weeks after injection. RBF and GFR, which increased in MetS compared to Lean, fell in MetS+RAS, but improved in EV-treated pigs (Table). EVs also improved cortical microvascular density and renal fibrosis (Figure). Yet, these renoprotective effects were blunted in pigs treated with IL-10 depleted EVs.

Conclusions: Intrarenal delivery of MSC-EVs improves renal structure and function in chronic experimental MetS+RAS, partly mediated by their cargo of IL-10. These observations suggest that EV-based regenerative strategies might be useful for patients with MetS+RAS.



Funding: NIDDK Support, Other NIH Support - DK102325-01 & DK100081

FR-PO144

Role of Mitochondrial Dysfunction and ROS Production in Ang II-Induced NLRP3 Inflammasome Activation Wen Yi, Liu Yiran, Tang Taotao, Bi-Cheng Liu. *Inst of Nephrology, Southeast Univ, Nanjing, Jiangsu Province, China.*

Background: The type 1 angiotensin (AT1) receptor plays an important role in maintaining blood pressure. Previous studies suggested that the activation of immune responses by angiotensin (Ang) II during hypertension may aggravate renal damage. NLRP3 inflammasome activation promotes renal inflammation and contributes to chronic kidney damage. Further investigation should be performed to explore the correlation between the RAS and NLRP3 inflammasome activation, and possible mechanisms.

Methods: C57BL/6 AT1R-/- and NLRP3-/- mice underwent left nephrectomy followed 1 week for recovery. Blood pressure measurements were recorded at baseline and following 4 weeks of chronic Ang II or saline infusion. At the end of the experiment, the kidney were harvested and fixed. AT1R siRNA and mitoTEMPO treatment were performed before the Ang II stimulation in HK2 cells. The expression levels of NLRP3 inflammasome and mitochondrial dysfunction were measured.

Results: Ang II significantly induced kidney injury and NLRP3 inflammasome activation. Mitochondria swelling and fragmentation were observed by transmission electron microscope. AT1R-/- blocked Ang II-induced hypertension, inhibiting the mitochondrial dysfunction and NLRP3 expression. Deficiency of NLRP3 attenuated kidney injury in hypertension with no significant influence to blood pressure. In vitro studies showed that Ang II stimulation increase the mitochondrial damage and NLRP3 activation in dose- and time- dependent manner. AT1R silence effectively blocked Ang II-induced damage. MitoTEMPO attenuated the activation of NLRP3 inflammasome through clearance of reactive oxygen species (ROS). Moreover, Ang II-induced mitochondrial dysfunction was markedly inhibited by silence of NLRP3.

Conclusions: Ang II stimulation induces NLRP3 inflammasome activation through AT1R receptor. Ang II-induced NLRP3 activation is mediated by mitochondrial dysfunction, with overproduction and accumulation of ROS. NLRP3 inflammasome activation plays an important role in kidney injury, and blocking it can be a potential therapeutic target for hypertension-associated kidney damage.

Funding: Other NIH Support - National Nature Science Foundation of China

FR-PO145

The Endoplasmic Reticulum Stress Inhibitor 4-Phenylbutyric Acid Prevents the Development of Essential Hypertension in Young Spontaneously Hypertensive Rats Safaa Naeel,¹ Chao Lu,² Jeffrey G. Dickhout.^{1,2} *Medicine, McMaster Univ, Hamilton, ON, Canada; ²St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.*

Background: Essential Hypertension is the leading global risk factor for premature death. This complex multifactorial disease has no known cause and has been shown to contribute to the progression of chronic kidney disease (CKD). Mechanistically both Endoplasmic Reticulum (ER) stress and the Unfolded Protein Response (UPR) have been implicated in the pathobiology of this disease. A small molecular chaperone, 4-phenylbutyric acid (4-PBA), is known to inhibit ER stress. In our previous studies, we found that 4-PBA is able to lower blood pressure in animal models of hypertension. It remains unclear however if ER stress is a cause of hypertension or a consequence.

Methods: Young spontaneously hypertensive rats (SHR) were used in this study and Wistar Kyoto (WKY) rats were used as its normotensive control. High blood pressure begins to develop in the young SHR at 4-weeks of age. Radio-telemetry transmitters (HD-X11 transmitter, Data Sciences International) were implanted to monitor blood pressure development, heart rate and ECG activity in both SHR and WKY. SHR and WKY were both randomized into 4-PBA (1 g/kg/day) or vehicle groups at 4-weeks of age to determine

if ER stress inhibition would prevent the development of hypertension. Resistance vessels, such as mesenteric arteries and renal arteries were collected after 8 weeks and analyzed for specific ER stress markers using real-time polymerase chain reaction (RT-PCR).

Results: 4-PBA treatment significantly lowered systolic, diastolic and mean arterial pressures in the SHR rats, but not in the WKY rats. 4-PBA treatment also significantly abolished pre-hypertensive tachycardia in the SHR. Additionally, 4-PBA significantly prevented the expression of UPR markers CHOP and GRP78 in SHR resistance blood vessels.

Conclusions: ER stress appears to play a causative role in the development of hypertension. Novel pharmacological strategies aimed at ER stress inhibition might represent useful therapeutic tools for people with a high risk of developing hypertension and progressive CKD. **Funding:** Government Support - MOP-133484.

Funding: Government Support - Non-U.S.

FR-PO146

Macrophage Endothelin-B Receptors Clear Endothelin-1 and Regulate Blood Pressure Neeraj Dhaun. *Queen's Medical Research Inst, University of Edinburgh.*

Background: Hypertension is common. Its cause remains unclear in the majority of those affected. Recent data suggest that macrophages (MΦ) contribute to, and protect from, hypertension. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor with additional pro-inflammatory properties. The effects of ET-1 on MΦ biology are not well studied.

Methods: To examine the interactions between the ET and MΦ systems we administered incremental doses of intravenous ET-1 to CD11b-diphtheria toxin receptor (DTR) mice given diphtheria toxin (DT) and to mice lacking ET_B receptors solely on myeloid cells (*LysMET_B^{-/-}*). We also cultured bone marrow derived MΦ (BMDM) from both these mice and human monocytes *in vitro*. Finally, we examined BP and the ET system in patients receiving MΦ depleting and non-depleting therapy.

Results: MΦ depletion or loss of function - Cdl1b-DTR mice given DT and *LysMET_B^{-/-}* mice - were not associated with a difference in baseline BP or endothelial dysfunction. In both, administration of ET-1 resulted in an exaggerated hypertensive response compared to controls. At a dose of ET-1 1nmol/kg the maximal change in BP was ~2-fold greater in MΦ deficient mice compared to control groups. *In vitro*, mouse BMDM and human MΦ possess both ET_A and ET_B receptors. Whereas stimulation of mouse and human MΦ with exogenous ET-1 did not polarize MΦ to a classical or alternative phenotype, both displayed chemokinesis to ET-1. This was reduced by selective ET_A and completely blocked by ET_B receptor antagonism. BMDM stimulation with LPS/INFγ led to an increase in the concentration of ET-1, an effect that was blocked by phosphoramidon, an inhibitor of endothelin converting enzyme. Importantly, using pharmacological and gene targeting studies we show a novel clearance mechanism for ET-1 through ET_B receptor mediated dynamin-dependent endocytosis present in both murine and human MΦ. Finally, patients receiving MΦ depleting therapy we show that BP is higher and the ET system more activated than in those receiving non-depleting therapies.

Conclusions: Overall, these data suggest that MΦ and ET-1 may play an important role in BP control and potentially have a critical role as a therapeutic target in hypertension.

FR-PO147

Role of the Myeloid Endothelin-B Receptor in Angiotensin II Mediated End-Organ Damage Neeraj Dhaun. *Inst de Recherche, PARCC, Inserm, Paris.*

Background: Hypertension is common and in the majority of cases its cause remains unknown. Recent interest has focused on the role of macrophages (MΦ) in blood pressure (BP) regulation. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor mediating its effects through two receptors - the endothelin-A receptor (ET_A) and endothelin-B (ET_B) receptor. The ET_B receptor has a specific role in ET-1 clearance. We investigated the role of the MΦ ET_B receptor in a model of angiotensin II (Ang II)-mediated end-organ damage.

Methods: MΦ ET_B receptor deficient mice (*LysMET_B^{-/-}*) and controls were exposed to Ang II infusion for 6 weeks under a high salt diet. We assessed BP *via* telemetry, cardiac structure and function and endothelial function by Doppler ultrasound, end-organ injury and plasma and urine ET-1.

Results: At baseline, components of BP did not differ between groups and increased similarly with Ang II. Whereas after 6 weeks of Ang II *LysMET_B^{-/-}* and controls had similar left ventricular hypertrophy and cardiac insufficiency, endothelial function was better in *LysMET_B^{-/-}* at both baseline and after Ang II (% dilation of basilar artery in response to CO₂, *LysMET_B^{-/-}* vs. controls: baseline: 20 vs. 11%, p<0.01; at 6 weeks: 11 vs. 0%, p<0.01). Baseline renal function and proteinuria did not differ between groups. After Ang II, *LysMET_B^{-/-}* showed similar renal function compared to controls but less proteinuria (urine albumin:creat, mg/mmol: 208±10 vs. 530±25, p<0.01), glomerulosclerosis (34±2 vs. 61±4%, p<0.001), and fewer renal MΦ compared to controls (F4/80 staining per high power field, *LysMET_B^{-/-}* vs. controls: 1.1±0.7 vs. 3.2±0.5%, p=0.02), although similar levels of CD3⁺ T cells. Plasma ET-1 was no different at baseline but increased more in *LysMET_B^{-/-}* with Ang II vs. controls after 6 weeks Ang II: 3.7±0.7 vs. 1.4±0.2pg/ml, p=0.03). Urine ET-1 was similar baseline and 6 weeks.

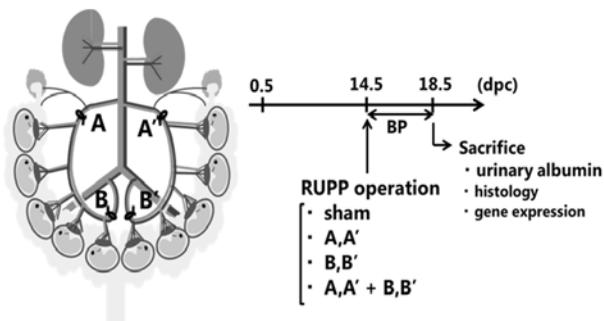
Conclusions: Deletion of the MΦ ET_BR is associated with a blunting of the effects of systemic Ang II infusion as reflected by less endothelial dysfunction, reduced inflammation and end-organ damage. The mechanisms for these effects are the focus of ongoing research.

FR-PO148

A Novel Reduced Uterine Perfusion Pressure (RUPP) Model of Preeclampsia in Mice Tomofumi Fushima,¹ Yuji Oe,² Emiko Sato,^{1,2} Sadayoshi Ito,² Hiroshi Sato,^{1,2} Nobuyuki Takahashi.^{1,2} ¹Graduate School of Pharmaceutical Sciences, Tohoku Univ, Sendai, Miyagi, Japan; ²Div of Nephrology, Endocrinology, and Vascular Medicine, Tohoku Univ, Sendai, Miyagi, Japan.

Background: Preeclampsia (PE) is a pregnancy-related hypertension with proteinuria that typically develops after 20 weeks of gestation. PE is caused by a reduction in uterine blood flow due to abnormal trophoblast invasion of the spiral arteries. The ischemic placenta releases anti-angiogenesis factors such as sFlt-1, leading to maternal hypertension and proteinuria. The reduced uterine perfusion pressure (RUPP) model is widely used in rats, but not in mice, hindering the clarification of genetics of PE. The aim of the present study is to establish a novel PE model using an improved RUPP method in mice.

Methods: As shown in the Figure. 1, uterine vessels of pregnant ICR mice were ligated at 14.5 dpc, and BP, renal phenotype and pregnancy outcome were analyzed.



Results: RUPP in mice increased blood pressure. B,B' ligation mice showed increased urinary albumin excretion, mesangial expansion and endotheliosis as shown by the reduction of glomerular open capillary area. RUPP increased the risk of miscarriages and premature deliveries, and significantly reduced fetal weights at 18.5 dpc compared to those of sham mice.

Conclusions: We developed a novel RUPP mouse model that recapitulates the phenotype of PE. This model is expected to be useful for investigating pathogenesis of PE and evaluating its new therapies.

FR-PO149

Sildenafil Treatment Is Protective against Progression of Renal Injury in the Preeclamptic Dahl Salt Sensitive Rat Ellen Elizabeth Gillis, Jennifer N. Mooney, Michael R. Garrett, Jennifer M. Sasser. *Pharmacology and Toxicology, Univ of Mississippi Medical Center, Jackson, MS.*

Background: Preeclampsia, a hypertensive disorder of pregnancy, is characterized by transient glomerular damage and increased risk for kidney disease later in life. Recent studies in our lab have identified the Dahl salt sensitive (Dahl S) rat on a 0.3% NaCl diet as a spontaneous model of superimposed preeclampsia. We hypothesized that sildenafil treatment would result in an improvement in renal function during the preeclamptic pregnancy exhibited by the Dahl S rat.

Methods: Female Dahl S rats (n=4-9) were mated, and rats were randomly divided into control and sildenafil treated groups. Sildenafil was administered to the treated group via food on gestational days 10-20 at a dose of 50 mg/kg/d. Rats were placed in metabolic cages on gestational day 19 for 24-hr urine collection, and blood and tissues were harvested on gestational day 20. Urinary protein excretion, nephrin excretion, and plasma and urinary creatinine concentrations were measured by Bradford assay, Exocell ELISA, and the picric acid method, respectively. Kidney sections were stained with Masson's trichrome, and glomeruli were measured (n=20 per rat) and analyzed using Nikon software.

Results: Sildenafil treatment significantly improved renal function, as observed in the increase in creatinine clearance and corresponding decrease in plasma creatinine (Table, *p<0.05 vs control). Treated rats exhibited less renal injury, with a significant decrease in proteinuria and nephrinuria during late pregnancy (Table). Histological analysis showed that the treated rats did not exhibit glomerulomegaly during pregnancy compared to the untreated controls (Table).

Conclusions: This study provides preclinical evidence that sildenafil prevents the progression of renal injury during preeclampsia.

	Creatinine Clearance (ml/min)	Plasma Creatinine (mg/ml)	Proteinuria (mg/day)	Nephrinuria (µg/day)	Glomerular Area (relative units)	Glomerular Diameter (relative units)
Control	0.31± 0.05	2.03± 0.04	209± 42	1433± 245	8217± 404	108± 12
Sildenafil	0.51± 0.06 *	1.52± 0.19 *	105± 14 *	675± 132 *	6675± 258 *	96± 2 *

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

FR-PO150

Recessive Mutations of the Interaction Partners, TENC1, DLC1 or MAGI2, Cause Nephrotic Syndrome in Humans Shazia Ashraf,¹ Jia Rao,¹ Merlin Airik,¹ Svyetlana Lovric,¹ Jennifer A. Lawson,¹ Weizhen Tan,¹ Carolin Sadowski,¹ Werner Lukas Pabst,¹ Daniela A. Braun,¹ Heon Yung Gee,¹ Richard P. Lifton,² Martin Zenker,³ Friedhelm Hildebrandt.^{1,4} ¹Div of Nephrology, Boston Children's Hospital, Boston, MA; ²Dept of Genetics, Yale Univ School of Medicine, New Haven, CT; ³Inst of Human Genetics, Univ Hospital Magdeburg, Magdeburg, Germany; ⁴HHMI.

Background: Identification of monogenic causes of nephrotic syndrome (NS) has furthered the understanding of its pathogenesis. However, many genes and disease mechanisms remain unknown.

Methods: We performed homozygosity mapping (HM) and whole exome sequencing (WES) in individuals of consanguineous families with NS to identify the underlying mutations. To identify additional families, we performed microfluidic PCR (Fluidigm Access Array™) and next generation sequencing (NGS) to screen worldwide cohort of ~2000 individuals with severe NS.

Results: By WES in consanguineous family A1358, we identified a homozygous missense mutation (p.R292Q) in the TENC1 (Tensin-2) gene in an amino acid residue conserved since *Ciona intestinalis*. By microfluidic PCR and NGS, we detected additional mutations in TENC1 in three unrelated families with NS. Later, we also discovered mutations in 2 different families with NS in DLC1 gene, a known binding partner of TENC1. Interestingly, most of the individuals with TENC1 or DLC1 mutations had steroid sensitive NS or histologically showed biopsy of MCNS. Furthermore, in 2 families with NS and neurological impairment, we identified 2 different homozygous truncating mutations in MAGI2 gene. Deficiency of Tenc1 or Magi2 has been previously shown to cause NS in mice. By Co-IP, we now show that TENC1 and DLC1 interact with MAGI2 in HEK293T cells and these interactions are abrogated in one of the MAGI2 mutant. Knockdown of TENC1, DLC1 or MAGI2 in cultured podocytes exhibited an altered podocyte migration rate. Immunofluorescence microscopy showed that TENC1 and DLC1 colocalize with phosphotyrosine at the focal adhesions in cultured human podocytes.

Conclusions: We, thus, identified mutations of TENC1, DLC1 and MAGI2 as three novel single-gene causes of NS revealing a potential new pathogenic pathway for NS.

Funding: Other NIH Support - DK076683

FR-PO151

Mutation of DHTKD1 Can Cause Nephrotic Syndrome with Neurological Impairment and Ketoacidic Aciduria Weizhen Tan,¹ Shazia Ashraf,¹ Svyetlana Lovric,¹ Jia Rao,¹ Merlin Airik,¹ David Schapiro,¹ Daniela A. Braun,¹ Heon Yung Gee,¹ Martin Zenker,² Friedhelm Hildebrandt.^{1,3} ¹Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; ²Inst of Human Genetics, Univ Hospital Magdeburg, Magdeburg, Germany; ³Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid-resistant nephrotic syndrome (SRNS) is the second most frequent cause of end-stage kidney disease in children. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain obscure. To identify a new causative gene for SRNS with neurological impairment, we combined homozygosity mapping (HM) and whole human exome sequencing (WES).

Methods: In two siblings (of consanguineous parents) with SRNS, neurological impairment, and ketoacidic aciduria, HM yielded 8 segments of homozygosity by descent with a cumulative genomic length of ~485 Mb. We performed WES in both siblings to identify the underlying single-gene disease-causing mutation.

Results: WES in this consanguineous family detected a homozygous missense mutation (p.Val296Met) in the DHTKD1 (dehydrogenase E1 and transketolase domain containing 1) gene in an amino acid residue that is evolutionary conserved to prokaryotes (*Saccharomyces cerevisiae*). The mutation segregated with the affected status in this family and was absent from the 1,000 genomes project and Exome Aggregation Consortium (ExAC) databases. DHTKD1 functions as a 2-oxoglutarate-dehydrogenase E1 component and plays an important role in energy production in mitochondria through the tricarboxylic-acid cycle. Mutations in DHTKD1 have previously been identified as cause of 2-aminoacidic and 2-oxoacidic aciduria via impaired turnover of decarboxylation 2-oxoadipate to glutaryl-CoA¹. [1] Danhauser K. et al., *Am J Hum Genet*, 91:1082-1087, 2012.

Conclusions: We identified a recessive mutation of DHTKD1 as a novel single-gene cause of SRNS with neurological impairment and ketoacidic aciduria. Further genetic and functional studies will shed light on the involvement of this protein in the pathogenesis of NS and will provide a further step in understanding the disease mechanism.

Funding: Other NIH Support - R01-DK076683, Private Foundation Support

FR-PO152

Genes Encoding Nuclear Pore Outer Ring Components *NUP85*, *NUP107*, and *NUP133* Are Mutated in Patients with Nephrotic Syndrome Svetlana Lovric,¹ Weizhen Tan,¹ David Schapiro,¹ Shazia Ashraf,¹ Daniela A. Braun,¹ Jia Rao,¹ Richard P. Lifton,² Heon Yung Gee,¹ Friedhelm Hildebrandt.^{1,3}
¹Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; ²Dept of Genetics, Yale Univ School of Medicine, New Haven, CT; ³Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid resistant nephrotic syndrome (SRNS) almost invariably progresses to end-stage kidney disease. Although more than 30 single-gene causes of SRNS are known, a large proportion of SRNS remains unexplained. Recently, mutations in genes encoding proteins of the nuclear complex (NPC), *NUP93* and *NUP205* were identified as novel causes of nephrotic syndrome. Study of these proteins has implicated SMAD signaling in the pathogenesis of nephrosis.

Methods: To identify additional novel causes of nephrotic syndrome, we performed a candidate screen of 17 nuclear pore complex (NPC) genes in an international cohort of >900 individuals with SRNS via microfluidic multiplex PCR (Fluidigm Access Array™) and next generation sequencing (Illumina MiSeq™).

Results: In two families we identified two homozygous missense mutations, p.A477V and p.R645W, (conserved to *S. cerevisiae*) in the NPC outer ring protein *NUP85*. We then sequenced the exons of 1,000 additional families in genes encoding other outer ring proteins and found mutations in *NUP107* (1 family, p. Y889C, conserved to *C. elegans*) and *NUP133* (2 families, p.S974R and p.R231G, p.L1055S, conserved to *D. rerio*). Although the structure resolution of the NPC 3D complex is incomplete, we modeled the interacting portions of the Y-subcomplex proteins *NUP107* and *NUP133*. Two of the mutations, p.S974R in *NUP133* and p.Y889C in *NUP107*, are located in the interacting alpha helix between the two proteins. 5 of 6 families demonstrated FSGS on biopsy.

Conclusions: As a novel cause of SRNS we identified mutations in 3 different NPC outer ring proteins *NUP85*, *NUP107*, and *NUP133* that form an integral part of the Y-subcomplex. Further functional studies are needed to illuminate how the defect of NPC contributes to the pathogenesis of nephrotic syndrome.

Funding: Other NIH Support - DK076683

FR-PO153

Defining the Genetic Epidemiology of a Phenotypically Well-Characterized Adult-Onset Focal and Segmental Glomerulosclerosis Cohort Moumita Barua,¹ Daniel C. Cattran,¹ Heather N. Reich,¹ Michelle A. Hladunewich,⁶ Mark Leung,² Weili Li,^{3,4} Andrew D. Paterson,⁵ York P. Pei.¹
¹Nephrology, Toronto General Hospital, UHN, Toronto, ON, Canada; ²Biology, Univ of Waterloo, Waterloo, ON, Canada; ³The Centre for Applied Genomics, Hospital for Sick Children, Toronto, ON, Canada; ⁴Dalla Lana School of Public Health, Univ of Toronto, Toronto, ON, Canada; ⁵Genetics and Genome Biology, Hospital for Sick Children, Toronto, ON, Canada; ⁶Nephrology, Univ of Toronto, Toronto, ON, Canada.

Background: The genetic epidemiology underlying adult-onset sporadic FSGS has not been well characterized and rigorous correlation of rare genetic forms of disease with clinical outcomes is also lacking. We defined the genetic epidemiology of the phenotypically well characterized sporadic and familial Toronto GN FSGS cohort using next-generation sequencing.

Methods: We have ascertained the clinical information and performed whole exome sequencing in adult-onset disease of 90 sporadic FSGS cases, 41 steroid-sensitive nephrotic syndrome (SSNS) cases and 22 families with FSGS. A variant in a known FSGS gene was called disease-causing if it was novel or had a MAF $\leq 1\%$ for dominant and recessive genes, respectively, in 1000 genomes project, NHLBI exome sequencing project and ExAC; compound heterozygosity was consistent with reported inheritance pattern for that gene; segregated in affected family members; and called damaging by at least two *in silico* prediction programs or affected highly conserved residues.

Results: In 7 of 90 sporadic FSGS cases, a disease-causing mutation was found in the following genes: *WT1*, *TRPC6*, *PAX2* and *COL4A5*. No mutations in the known FSGS genes were identified in 41 SSNS cases. In contrast, in 4 of 23 autosomal dominant and recessive families with FSGS, a disease-causing mutation was identified in the following genes: *INF2*, *TRPC6*, *LMX1B* and *ADCK4*. Mutations in the known FSGS genes were found in 7.8 and 17.4% of sporadic and familial cases of adult-onset disease, respectively, but none were discovered in patients with SSNS.

Conclusions: Our results are consistent with extensive genetic heterogeneity in FSGS. We will test the association of rare variants with phenotype. Clinical outcomes will be described.

Funding: Private Foundation Support

FR-PO154

A Novel Mouse Mutant with a Point Mutation in Laminin $\alpha 5$ Exhibits Chronic Nephrotic Syndrome Sara Falcone,¹ Thomas Nicol,¹ Cheryl Scudamore,² Frederick W.K. Tam,³ Charles D. Pusey,³ Jeffrey H. Miner,⁴ Steve Dm Brown,¹ Paul K. Potter.¹ ¹Mammalian Genetics Unit, MRC Harwell, Harwell, Oxfordshire, United Kingdom; ²Mary Lyon Centre, MRC Harwell, Harwell, Oxfordshire, United Kingdom; ³Renal Section, Imperial College, London, United Kingdom; ⁴Renal Div, Washington Univ, St. Louis, MO.

Background: Diseases associated with ageing pose an increasing social and financial burden on society and represent an imperative for research in the biomedical sciences. We are undertaking the first large-scale project to investigate the interaction between genetic variation and the pleiotropic effects of ageing, employing random mutagenesis and phenotyping to generate new models of late onset or age-related disease.

Methods: Mutant mice are being aged to 18 months and undergo comprehensive phenotyping across a wide range of disease areas at several time points throughout the life of the mice. To date we have identified lines with a variety of late onset phenotypes which are being characterised in detail.

Results: Mutant mice were identified at 6 months of age with elevated creatinine and urea levels, which reached end stage renal failure at approximately 10 months of age. Mapping and whole genome sequencing identified a *Lama5*^{EB84G} mutation in the L4a domain of *Lama5*. Time course studies of *Lama5*^{EB84G} homozygotes showed reduced serum albumin (18.0 ± 1.2 vs 24.9 ± 3.1 , g/l, mean SD) and proteinuria from 12 weeks of age with a gradual loss of renal function over time. Affected mice also have significantly elevated cholesterol levels and a progressive nephropathy leading to diffuse glomerular fibrosis, dilated protein filled tubules and pigment deposition suggesting this is a model of nephrotic syndrome. The mutation does not affect expression of the LAMA5 protein within the glomerular basement membrane.

Conclusions: We have identified a novel mouse mutant with a missense mutation *Lama5* resulting in nephrotic syndrome. Recent patient sequencing data suggests LAMA5 mutations are associated with focal segmental glomerulosclerosis (Chatterjee et al, PLOS One, 8:e76360) and we are investigating this in our model. Other models of late-onset renal disease are also being investigated.

Funding: Government Support - Non-U.S.

FR-PO155

Exome Sequencing Suggests a Role for Nephron Number in FSGS Adele Mitrotti,¹ David Fasel,¹ Yifu Li,¹ Monica Bodria,¹ Landino Allegri,³ Gerald B. Appel,¹ Jai Radhakrishnan,¹ Loreto Gesualdo,⁴ Gian Marco Ghiggeri,⁵ Richard P. Lifton,² Ali G. Gharavi,¹ Simone Sanna-Cherchi.¹ ¹Medicine, Columbia Univ Medical Center, New York, NY; ²Genetics, Yale, New Haven, CT; ³Medicine, Univ of Parma, Parma, Italy; ⁴Medicine, Univ of Bari, Bari, Italy; ⁵Medicine, Gaslini Children Hospital, Genova, Italy.

Background: Exome sequencing is a powerful tool to identify disease-causing mutations. Identification of novel genes for dominant FSGS has proven difficult.

Methods: We performed exome sequencing in 41 patients from 31 families affected by FSGS. Exome sequencing was conducted on Illumina HiSeq2500. Annotations were conducted with semi-automated scripts developed in the lab.

Results: We detected diagnostic variants for FSGS in 4 genes in 5/31 families (16%): *TRPC6*, *INF2*, *LMX1B*, and *LAMB2*. We detected two variants of unknown significance in FSGS-associated genes (*EMP2*, *INF2*). We detected 7 variants in additional 6 patients (19%) in genes that predispose to different kidney diseases when mutated (*FN1*, *SIX5*, *COL4A4*, *FRAS1*, *FREM1*, *FREM2*, *UMOD*). While these conditions can represent phenocopies of FSGS, it is possible that genes involved in renal development predispose to proteinuria and adaptive FSGS.

Diagnosis	Gene	Type of mutation	Kidney disorder	cDNApos	Exac Freq
Familial FSGS	TRPC6	nonsynonymous	Nephrotic syndrome	p.H145R	novel
FSGS (resistant)	INF2	nonsynonymous	Nephrotic syndrome	p.R1045Q	novel
Small kidney and FSGS	INF2	frameshift	Nephrotic syndrome	p.A457fs	novel
FSGS	INF2	nonsynonymous	Nephrotic syndrome	p.G220L	novel
Familial FSGS (uncle and nephew)	EMP2	nonsynonymous	Idiopathic steroid-sensitive nephrotic syndrome with focal segmental hyaline	p.G157S	0.00006713
IgAN/MCD	LAMB2	nonsynonymous	Nephrotic syndrome, with or without ocular abnormalities	p.H1295Q	0.000008240
	LAMB2	nonsynonymous	Nephrotic syndrome, with or without ocular abnormalities	p.T890I	0.00008843
Nail-patella syndrome with FSGS	LMX1B	Frameshift insertion	Nail-Patella syndrome	p.S259fs	novel
proteinuria, familial FSGS/CKD	FN1	nonsynonymous	MPGN (Glomerulopathy with fibronectin deposits)	p.S2131T	novel
Familial FSGS: 2 brother affected by FSGS	SIX5	nonsynonymous	CAKUT (Branchio-oto-renal syndrome)	p.P80S	novel
	COL4A4	nonsynonymous	Autosomal recessive Alport syndrome	p.P1291A	0.001687
FSGS, tx (no recurrence)	FRAS1	nonsynonymous	CAKUT (Fraser Syndrome)	p.F3316L	novel
Prot + small kidneys	FREM1	nonsynonymous	CAKUT (Fraser syndrome related)	p.A1173S	0.0008949
FSGS	UMOD	nonsynonymous	Medullary cystic kidney disease	p.T614N	novel
FSGS	FREM2	missense	Unilateral renal agenesis, and Frem2 related Fraser syndrome	p.G2144A	0.000008284

Analysis of the remaining 20 families (65%) did not reveal any gene with rare segregating mutations present in multiple independent families.

Conclusions: Mutations in genes known to be associated to FSGS are identified in a small proportion of cases. Mutations in genes involved in GBM assembly or kidney development can result in defects that present as FSGS. These findings can point to a correct genetic diagnosis and the identification of mutations in genes involved in CAKUT suggests that glomerular sclerosis could be the manifestation of a maladaptive reaction to reduced nephron mass from birth.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

FR-PO156

Role of CD2AP Mutations in Steroid Resistant Nephrotic Syndrome Revisited – New Insights from Next Generation Sequencing Ania B. Koziell,³ Katrina Soderquest,³ Andrey S. Shaw,¹ Michael A. Simpson.² ¹Immunology and Pathology, Washington Univ School of Medicine, St. Louis, MI; ²Genomics Medicine Group, King's College London, London, United Kingdom; ³Experimental Immunobiology, King's College London, London, United Kingdom.

Background: Steroid Resistant Nephrotic Syndrome (SRNS) is a rare disease characterized by glomerular filter malfunction. Analysis of inherited cases has identified mutations in >50 genes. However, clinical data can be limited and the true pattern of inheritance difficult to verify. In light of recent advances in next generation sequencing (NGS) and rare disease genetics, we re-examined CD2AP, a gene considered to cause autosomal dominant SRNS in early life.

Methods: In-house whole exome sequencing (WES) data on 200 deeply phenotyped SRNS patients was tested to assess the ability of CD2AP mutations to act as autosomal dominant. All protein altering CD2AP variants detected with a MAF < 0.05 were selected for further examination in the Exome Aggregation Consortium (ExAC) database. Samples with likely pertinent variants in CD2AP were also analysed for causal mutations in other SRNS genes.

Results: Variants with a frequency of > 1 in 1000 in the ExAC database were considered unlikely to cause autosomal dominant SRNS based on frequency of SRNS in populations. Two rare CD2AP variants remained after filtering but one case also demonstrated a rare heterozygous non-synonymous disease causing variant in SYNPO (allele frequency 0.0002179 in ExAc, non-homozygous) and the other a variant in NPHS2 (not seen in ExAc). SYNPO interacts with CD2AP and combined, these genes causes FSGS in mice. The NPHS2 variant neighbored a mutation linked previously to bigenic heterozygosity with CD2AP in SRNS.

Conclusions: Some heterozygous CD2AP variants occurred in normal controls or were detected co-incident disease causing variants. This indicates that mutations behaving as a dominant negative in a small number of cases may in fact demonstrate more complex inheritance on interrogation of a larger cohort. Computational analysis of WES provides a useful adjunct to rapidly examine and ascertain actual heritability in rare disease populations, especially in seemingly sporadic cases.

FR-PO157

Chemical Chaperone 4-PBA Is Not Nephroprotective in Experimental Podocin Nephropathy Tanja Tamara Wlodkowski,¹ Mansoureh Tabatabaieifar,¹ Geraldine Mollet,² Corinne Antignac,² Franz S. Schaefer.¹ ¹Pediatric Nephrology Div, Heidelberg Univ Hospital, Germany; ²Inserm U983, Hopital Necker, France.

Background: 4-PBA has been demonstrated to improve protein trafficking from ER to plasma membrane and function of mutant ΔF508-CFTR protein in cystic fibrosis. In hereditary nephrotic syndrome the most common NPHS2 (podocin) mutation, R138Q, leads to retention of podocin in the ER and therefore to defective intracellular protein trafficking. In order to investigate beneficial effect of chemical chaperone in podocin nephropathy, we administered 4-PBA to knock-in mice carrying this mutation. Analogous to human disease, these mice develop heavy proteinuria, podocyte loss, focal segmental glomerulosclerosis and progressive renal failure.

Methods: In C57BL/6 mice with Nphs2^{Fllox/R140Q}Cre⁺, hemizyosity for mutant podocin was induced by tamoxifen injection. From the time of induction the animals (n=5) received 4-PBA added to the chow (200 mg/kg/d) or remained untreated (Co). Weight, blood pressure and proteinuria were monitored weekly. Biochemical and histopathological changes were examined after 4 weeks of treatment.

Results: All animals developed massive proteinuria (116% of untreated controls). Hypoalbuminemia at 4 weeks was slightly ameliorated (21.1 (Co) vs. 24.7 g/dl; n.s.). Serum urea, cholesterol and creatinine levels were deteriorated by 4-PBA treatment. Podocyte loss (podocytes per glom: (53% (Co), 69% (4-PBA) of healthy animals, n.s) and glomerular sclerosis index (1.75 (Co), 1.82 (4-PBA) were unchanged, whereas an increase in tubulointerstitial fibrosis was noted in 4-PBA treated animals (1.36 (Co) vs. 3.82 (4-PBA).

Conclusions: In an in vivo model of hereditary podocin nephropathy, prophylactic 4-PBA treatment showed no beneficial effect on proteinuria and podocyte loss but aggravated tubulointerstitial fibrosis and renal failure. Our findings argue against a nephroprotective action of 4-PBA in this hereditary podocinopathy.

FR-PO158

Prominent Renal Complications in the c.80A>G in MMACHC Gene Fang Wang, Xiaoyu Liu, Huijie Xiao, Yong Yao, Jie Ding, Yanqin Zhang. Dept of Pediatrics, Peking Univ First Hospital, China.

Background: Cobalamin C defect is a clinically heterogeneous disease caused by mutations in the MMACHC gene. The aim of the present study was to delineate renal phenotype in Chinese children with Cobalamin C defect.

Methods: Detailed clinical data were collected and analyzed, and all coding exons of MMACHC gene were PCR-amplified and sequenced from genomic DNA.

Results: Four unrelated Chinese children (1 female, 3 male) with unexplained microscopic hematuria and proteinuria were included. The onset age of renal symptoms ranged from 9 months to 4 years. Two patients had nephrotic-level proteinuria in their initial visit, and renal dysfunction was detected in 2 patients in 3 months and 6 years after

onset, respectively. Only 1 patient had hypertension in 6 years after onset. All patients had moderate anemia, and megaloblastic anemia was detected in 2 patients. None of 4 patients had thrombocytopenia or pancytopenia. One of 4 patients had mild development backward. Four patients had hyperhomocysteinemia, and 2 of 4 patients presented with remarkable elevated urinary methylmalonic acid. Renal biopsy in 3 patients showed thrombotic microangiopathy. Mutations in MMACHC gene was found in four patients. Two patients were a compound heterozygote for c. 658_660delAAG and c.80A>G, one patient was a compound heterozygote for c.609G>A and c.80A>G, and one patient was a homozygote for c.80A>G. Three patients were in follow up. After vitamin B12 [in the form of hydroxycobalamin (OHChl), i.m.], folic acid and L-carnitine betaine supplementation, urine protein became negative in 2 patients and reduced in 1 patient, and renal function in 1 patient was improved. In all 3 patients, hemoglobin increased to normal, plasma homocysteine decreased and still was abnormal. In 2 patients with remarkable elevated urinary methylmalonic acid, the level of urinary methylmalonic acid was normal in 1 patient and decreased in another patient. Blood pressure of the patient with hypertension was well-controlled using calcium channel blocker.

Conclusions: Prominent renal complications can be found in c.80A>G in MMACHC gene, and treatment resulted in improvement of renal and hematological signs.

Funding: Government Support - Non-U.S.

FR-PO159

The Susceptible Human Leukocyte Antigen Class II Genes and the Encoding Amino Acid Residues on Major Histocompatibility Complex Molecules to Primary Membranous Nephropathy Li-jun Xie,^{1,2} Zhen Qu,¹ Zhao Cui,¹ Gang Liu,¹ Yun-hua Liao,² Ming-hui Zhao.¹ ¹Renal Division, Peking Univ First Hospital, Beijing, China; ²Div of Nephrology, the First Affiliated Hospital, Guangxi Medical Univ, Nanning, China.

Background: Primary membranous nephropathy (MN) is an organ-specific autoimmune disease. M-type phospholipase A2 receptor (PLA2R) appears to be the specific target antigen, which needs to be presented by major histocompatibility complex (MHC) class II molecule. In genome wide association studies, risk alleles at PLA2R1 loci and single nucleotide polymorphism (SNP) (rs2187668) within HLA-DQA1 closely associate with the disease. However, the full association of HLA class II genes and MHC molecule amino acids has not been investigated in MN.

Methods: We genotyped 860 Chinese individuals, including 261 primary MN patients and 599 healthy controls, for DRB1, DQA1, DQB1 and DPB1, 4 digits resolution HLA alleles, and extracted the encoding amino acid sequences from IMGT/HLA database. Circulating anti-PLA2R antibody was detected in all patients.

Results: We found that DRB1*1501 (OR=3.49, P=1.77×10⁻²¹) and DRB1*0301 (OR=3.44, P=3.46×10⁻¹⁰) were two independent risk alleles for MN. In patients with positive anti-PLA2R antibodies, DRB1*1501 (OR=6.06) and DRB1*0301 (OR=4.92) showed even higher risk for the disease. The SNP (rs2187668) is the tag SNP of DRB1*0301. After conditioning on DRB1*1501 and DRB1*0301, no other HLA allele showed significant association with MN. At amino acid level, the most significant and independent associations were mapped to amino acid position 13 (P=5.78×10⁻²⁵) and position 71 (P=7.99×10⁻²⁵) on MHC DRβ1 chain. After conditioning on these positions, no other amino acid position showed significant association with MN. Alanine on position 71 and Arginine on position 13 were encoded by DRB1*1501; lysine on position 71 was encoded by DRB1*0301. These amino acids were susceptible to MN and showed positive association with the presence of anti-PLA2R antibodies (P=0.001).

Conclusions: We concluded that two alleles of HLA class II genes, and the encoding three amino acid residues on two positions at the epitope-binding pockets of MHC DRβ1 chain, were responsible for higher risk to MN.

Funding: Government Support - Non-U.S.

FR-PO160

Somatic Mosaicism and Variant Frequency Detected by Next Generation Sequencing in X Linked Alport Syndrome Naohiro Kamiyoshi,¹ Kandai Nozu,¹ Tomohiko Yamamura,¹ Takeshi Ninchoji,¹ Yuko Shima,² Koichi Nakanishi,² Norishige Yoshikawa,³ Kazumoto Iijima.¹ ¹Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan; ²Pediatrics, Wakayama Medical Univ, Wakayama, Japan; ³Pediatrics, National Center for Child Health and Development, Tokyo, Japan.

Background: Alport syndrome is a hereditary disorder of type IV collagen, characterized by chronic kidney disease progressing to end-stage renal disease, sensorineural hearing loss, and ocular abnormalities. Approximately 85% of Alport syndrome patients show X-linked inheritance (XLAS) and variants in the type VI collagen, α5 gene (COL4A5), which encodes the type IV collagen α5 chain. Although male patients with XLAS usually develop end-stage renal disease before 30 years of age, some male patients show a milder phenotype and develop end-stage renal disease later in life. However, the molecular mechanisms associated with this milder phenotype have not been fully identified.

Methods: We genetically diagnosed 186 male patients with suspected XLAS between January 2006 and August 2014. Genetic examination involved: (1) extraction and analysis of genomic DNA using polymerase chain reaction and direct sequencing using Sanger's method for all patients; and (2) next-generation sequencing to detect variant allele frequencies for four patients who suspected somatic mosaic variants.

Results: We identified somatic mosaic variants in the COL4A5 in four patients. Interestingly, two of these four patients with variant frequencies in kidney biopsies or urinary sediment cells of ≥50% showed hematuria and moderate proteinuria, while the other two with variant frequencies of <50% were asymptomatic or only had hematuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: *De novo* variants can occur even in asymptomatic male cases of XLAS resulting in mosaicism, with important implications for genetic counseling. This is the first study to show a tendency between the variant allele frequency and disease severity in male XLAS patients with somatic mosaic variants in *COL4A5*. Although this is a very rare status of somatic mosaicism, further analysis is needed to show this correlation in a larger population.

FR-PO161

A New Non-Invasive Method to Examine Collagen $\alpha 5$ (IV) Expression Using Plucked Hair Follicles: Analysis of an X-Linked Alport Family with a Novel COL4A5 Splice Region Variant Andrew F. Malone, Steven Daniel Funk, Jeffrey H. Miner. *Renal Div, Dept of Medicine, Washington Univ, St. Louis, MO.*

Background: Alport syndrome is a hereditary disease caused by mutations in *COL4A5* in 85% of cases. Many different mutation types in this gene have been described. Levels and patterns of type IV collagen deposition are variable in the glomerular basement membranes of Alport kidneys. As *COL4A5* is also expressed in the skin, we sought to characterize *COL4A5* deposition in the basement membrane of plucked hair follicles from a family with a novel *COL4A5* variant as a way of confirming the functional significance.

Methods: Whole-exome sequencing was done on the proband of a family with biopsy (renal and skin)-confirmed Alport syndrome. Sanger sequencing was performed on all affected family members and a married-in unaffected individual. Immunofluorescence microscopy was performed on whole mount and sectioned hair follicles co-stained with monoclonal antibodies to collagen $\alpha 2$ and $\alpha 5$ (IV). Staining intensity between males and females, affecteds and unaffecteds, was analyzed.

Results: Family WU1 is a 3 generational family with chronic kidney disease secondary to Alport syndrome. Affecteds are in each generation, and both males and females are symptomatic. Whole-exome sequencing of affected individual 3227 revealed a novel splice region variant c.1780-6T>G in *COL4A5*. There were no other potentially pathogenic variants found in *COL4* or other podocyte genes. This variant was confirmed by Sanger sequencing and segregated with disease. Reduced and abnormal expression of *COL4A5* protein was confirmed in affected family members by immunofluorescence microscopy of hair follicles.

Conclusions: We confirmed linkage of a novel splice region variant in *COL4A5* to Alport syndrome in a family with a typical X-linked inheritance pattern; this variant may be pathogenic. We developed and validated a new approach to characterize the expression of *COL4A5* protein using immunofluorescence microscopy of plucked hair follicles. Furthermore, we demonstrated variability of *COL4A5* expression between patients in this family, suggesting intermittent failure of splicing and/or variable lyonization in females.

Funding: NIDDK Support

FR-PO162

X-Linked Alport Dogs Demonstrate Mesangial Filopodial Invasion of the Capillary Tuft as an Early Event in Glomerular Damage Sabrina D. Clark,¹ Mary B. Nabity,¹ Rachel Cianciolo,² Brianna M. Dufek,³ Dominic E. Cosgrove.³ ¹Veterinary Pathobiology, Texas A&M Univ, College Station, TX; ²Veterinary Biosciences, The Ohio State Univ, Columbus, OH; ³Genetics, Boys Town National Research Hospital, Omaha, NE.

Background: X-linked Alport syndrome (XLAS), caused by a mutation in the type IV collagen *COL4A5* gene, accounts for approximately 80% of the cases of human Alport syndrome. Dogs with XLAS have a similar clinical progression. Prior studies in autosomal Alport mice demonstrated early mesangial cell invasion as the source of laminin 211 in the glomerular basement membrane (GBM), leading to proinflammatory signaling. Thus far, these findings have not been confirmed in a large animal model.

Methods: XLAS dogs and unaffected littermates were monitored with serial clinicopathologic data and renal biopsies. Biopsies were obtained at the onset of microalbuminuria (MA), overt proteinuria (urine protein:creatinine (UPC) > 2), onset of azotemia, moderate azotemia, and at euthanasia. Glomeruli were analyzed by immunohistochemistry.

Results: With disease progression, XLAS dogs showed a progressive decrease in renal function (based on serum creatinine, symmetric dimethylarginine (SDMA), UPC, and iohexol clearance) and increase in interstitial fibrosis and glomerulosclerosis (based on light microscopy and/or immunostaining for α SMA and fibronectin). The only identifiable structural abnormality at the time of MA was segmental multilamination of the GBM observed on transmission electron microscopy (TEM), which was more extensive when overt proteinuria developed. Co-localization studies showed that mesangial laminin 211 and integrin $\alpha 8\beta 1$ accumulate in the GBM, which was identified with laminin $\beta 2$. This was first observed when overt proteinuria developed and coincided with evidence of mild cellular interpositioning on TEM, consistent with invasion of the capillary loops by mesangial cell processes.

Conclusions: These findings confirm, in a large animal model, the induction of mesangial filopodial invasion of the glomerular capillary tuft leading to the irregular deposition of mesangial laminin 211 as an early initiating event in Alport glomerular pathology.

Funding: Pharmaceutical Company Support - IDEXX Laboratories, Inc

FR-PO163

Drug Repurposing for the Treatment of Experimental Alport Syndrome Vanessa R. Williams,¹ Ana Konvalinka,² Xuewen Song,² Eun Hui Bae,³ Fei Fang,¹ Rohan John,⁴ York P. Pei,² James W. Scholey.^{1,2} ¹Inst of Medical Science, Univ of Toronto, Canada; ²Div of Nephrology, Univ of Toronto, Canada; ³Internal Medicine, Chonnam National Univ Medical School, Korea; ⁴Pathology, Univ of Toronto, Canada.

Background: Alport Syndrome (AS) is a hereditary nephropathy caused by mutations in genes that encode type IV collagen, leading to progressive injury and eventually end-stage renal disease. Currently there are few effective therapies for AS. Therefore we applied a drug repurposing strategy, utilizing data on drugs currently approved for use in humans, to identify a novel AS treatment.

Methods: 129/SvJ *Col4a3*^{-/-} (KO) and wild-type (WT) mice were studied at 4 and 7 weeks (*N* = 8/group). Histological analyses of formalin-fixed mouse kidney sections were performed. Plasma and 24-hour urine samples were collected. Global gene expression profiling of RNA from renal cortex was performed with the Affymetrix Mouse Gene 2.0 ST Array. Significance Analysis of Microarrays (SAM) was used to identify differentially expressed genes. *In silico* drug repurposing with the Connectivity Map (CMAP) was used to identify drugs expected to effectively treat murine AS.

Results: Mice with AS developed a progressive rise in albuminuria and serum creatinine. These changes were associated with glomerulosclerosis and tubulointerstitial fibrosis. SAM was used to generate a disease signature of differentially expressed genes, comparing 7-week-old KO versus WT mice. The disease signature was used to query the CMAP. Vorinostat, a lysine deacetylase inhibitor, was the top drug predicted to reverse the signature. KO mice were treated with vehicle or vorinostat daily from 4 to 7 weeks of age. Vorinostat treatment induced hyperacetylation of kidney lysine residues. This was associated with reduced albuminuria, decreased α SMA protein expression, and reduced gene expression of inflammatory cytokines.

Conclusions: *In silico* drug repurposing identified a novel therapeutic approach to AS. *In vivo* testing of the putative therapy showed that vorinostat exerts a renoprotective effect. Further studies will better define the mechanisms underlying the protective effect of this novel therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO164

KCTD1 Mutations in Scalp-Ear-Nipple ('Finlay-Marks') Syndrome: A Further Cause of Thin Basement Membrane Nephropathy Dongmao Wang,¹ Peter Diakumis,² Melanie Bahl,² Deb J. Colville,¹ Judith A. Savage.¹ ¹Medicine, The Univ of Melbourne (Melbourne Health), Melbourne, VIC, Australia; ²Bioinformatics, WEHI, Melbourne, VIC, Australia.

Background: Scalp-Ear-Nipple syndrome is an ectodermal dysplasia, with a scalp defect, prominent ears and absent breasts. It results from mutations in *KCTD1*, an inhibitor of the transcription factor, AP2. AP2 regulates the expression of the collagen IV $\alpha 3$ and $\alpha 4$ chains, which are major components of the glomerular, corneal and retinal basement membranes. This study characterised the clinical phenotype in Scalp-Ear-Nipple syndrome and how mutations caused disease.

Methods: Two unrelated families with Scalp-Ear-Nipple syndrome were examined by a renal physician and an ophthalmologist. One family member provided a skin biopsy that was used to derive a fibroblast cell line. Urine specimens from two family members were used to study the expression of the collagen IV $\alpha 3$ and $\alpha 4$, and laminin $\alpha 5$ and $\beta 1$ transcripts. The ER size was measured using immunohistochemistry before and after treatment with PBA, a chemical chaperone.

Results: Seven family members had developed renal cysts and impaired renal function by late adulthood, and all 14 who were examined had astigmatism. A renal biopsy demonstrated a thinned glomerular membrane. One individual had a thinned cornea and the two who were examined with optical coherence tomography had a small optic disc, and thinned retinal nerve fibre layer.

There was reduced transcription of the collagen IV $\alpha 3$ and $\alpha 4$ chains in the urine. The fibroblast cell cultures confirmed reduced laminin transcripts. ER size was increased in the fibroblast cells *in vitro* but 4PBA chaperone treatment reduced ER size. However no *KCTD1* mutations were identified in 20 individuals with Thin membrane nephropathy and no *COL4A3*/*COL4A4* mutations nor in 20 individuals with familial astigmatism.

Conclusions: The clinical features of Scalp-Ear-Nipple syndrome are due to *KCTD1* mutations that affect basement membrane collagen IV and laminin expression. Chemical chaperones represent a potential treatment to delay renal failure.

FR-PO165

Podocyte Globotriaosylceramide (GL3) Accumulation in Fabry Disease Is Influenced by Age and Genotype Behzad Najafian,¹ Camilla Tøndel,² Einar Svarstad,² Michael L. West,³ Michael Mauer.⁵ ¹Univ of Washington; ²Univ of Bergen; ³Dalhousie Univ; ⁴Univ of Washington.

Background: Podocyte injury plays a key role in Fabry nephropathy, a major complication of Fabry disease. Identification of factors affecting podocyte injury may help to understand the pathophysiology of Fabry nephropathy. We studied effects of age and genotype on podocyte GL3 accumulation in Fabry patients.

Methods: Kidney biopsies from 55 male Fabry disease patients, age 25 [4-65] (median [range]) years were studied using electron microscopic stereology. Podocyte GL3 volume

density [Vv(GL3/Podo)] was estimated and correlated with age and GLA mutation. The latter, known in 38 of these patients, included 35 classical, 2 cardiac variant (N215S) and one late onset (R363H) GLA mutation.

Results: There was a wide range of Vv(GL3/Podo) among the patients, 0.41 [0.003-0.58]. Vv(GL3/Podo) increased linearly with age in younger patients up to age 30 years ($r=0.56$, $p=0.001$), but plateaued thereafter, varying within the narrow range of 0.35-0.58. There were 4 outliers, ages 37-50 with low Vv(GL3/Podo) (range 0.003-0.22), including patients with N215S ($n=2$) and R363H mutations and one patient whose GLA mutation was unavailable. Vv(GL3/Podo) directly correlated with urine albumin creatinine ratio ($r=0.67$, $p=0.02$) and foot process width ($r=0.49$, $p=0.05$) in males younger than 30 years. Volume density of podocytes per glomerulus was inversely correlated with age ($r=-0.69$, $p=0.0001$) across the age range with no plateauing, suggestive of continuous podocyte loss.

Conclusions: The fraction of podocyte cytoplasm filled with GL3 inclusions increase with age up to about age of 30 in Fabry males with classical GLA mutations and is associated with podocyte injury and albuminuria. Plateauing of podocyte GL3 volume density after age of 30 is suggestive of a threshold beyond which GL3 accumulation may not be compatible with podocyte survival. The clinical progression of Fabry nephropathy beyond age 30 in FD males with classical mutations could be reflected in other podocyte parameters such as podocyte hypertrophy and/or loss. Thus further studies are underway to explore these possibilities.

Funding: NIDDK Support, Pharmaceutical Company Support - Sanofi

FR-PO166

Outcomes of Patients Over 65 in the Canadian Fabry Disease Initiative Study Michael L. West,¹ Daniel G. Bichet,² Aneal Khan,³ Joe T. Clarke,⁴ Sandra Sirrs,⁵ Steve Doucette,⁶ Christiane Auray-Blais,⁷ Kaye Lemoine.⁸ ¹Medicine, Dalhousie Univ, Halifax, NS, Canada; ²Medicine, Univ of Montreal, Montreal, QC, Canada; ³Genetics, Univ of Calgary, Calgary, AB, Canada; ⁴Emeritus, Univ of Toronto, Toronto, ON, Canada; ⁵Medicine, Univ of British Columbia, Vancouver, BC, Canada; ⁶Dept of Community Health and Epidemiology, Dalhousie Univ, Halifax, NS, Canada; ⁷Pediatrics, Univ of Sherbrooke, Sherbrooke, QC, Canada; ⁸Nursing, Nova Scotia Health Authority, Halifax, NS, Canada.

Background: The Canadian Fabry Disease Initiative (CFDI) is a multicentre prospective study of outcomes with enzyme replacement therapy (ERT) in Fabry disease. ERT has been shown to be of benefit in reducing Fabry cardiac and renal disease. There is uncertainty as to the benefits of ERT in older patients. We compared outcomes of ERT in patients over 65 years of age with the overall CFDI population.

Methods: Patients are reviewed every 6-12 months as to clinical status. ERT is provided every 2 weeks according to national guidelines with intravenous dose agalsidase alfa (0.2 mg/kg) or agalsidase beta (1.0 mg/kg). Cardiovascular risk factor modification is promoted with use of ASA, statins and ACEi/ARB. Clinical outcomes are defined as stage 5 CKD, stroke/TIA, acute deafness, cardiac arrest, CHF, arrhythmia, unstable angina, MI, PTCA, pacemaker/ICD, AVR/CABG and death.

Results: As of Jan 2015, 429 subjects were enrolled. There were 51 patients over 65 y, 68.6% female, and 60.8% on ERT with mean age 71.8 y. There were no differences in mean age, cardiac variant genotype, or time in the CFDI between those on ERT and those not. Compared with patients not on ERT, those on ERT had lower eGFR, greater proteinuria and higher LVMI at both baseline and 6 y later. Three patients not on ERT had 5 clinical events, prevalence 15%, no deaths with clinical event rate of 1/34.5 patient years. Twenty patients on ERT had 5 deaths, 38 clinical events, prevalence 64.5% and clinical event rate of 1/9.3 patient years. Death was more likely in females 21% vs. males 8.3%. Patients over 65 y had greater prevalence of cardiac indications for ERT than the overall CFDI population. Time to first clinical event was earlier in those on ERT ($p=0.003$).

Conclusions: Older patients with Fabry disease continue to have clinical events, mainly cardiac, despite ERT but appear to be living longer. Use of the Canadian Fabry Disease guidelines appears to successfully target high-risk older patients. ERT use in this subgroup appears to be of benefit.

Funding: Pharmaceutical Company Support - Genzyme, a Sanofi Company Shire Inc, Government Support - Non-U.S.

FR-PO167

A Founder Haplotype of APOE-Kyoto Mutation Associated with Lipoprotein Glomerulopathy Zhangxue Hu. Dept of Nephrology, West China Hospital, Chengdu, Sichuan, China.

Background: Lipoprotein glomerulopathy (LPG) is a rare dominant inherited kidney disease with incomplete penetrance, histological characterized by the formation of intraglomerular lipoprotein thrombi. Their main clinical manifestation includes proteinuria, the elevated level of serum triglyceride and apolipoprotein E (apoE). Approximately 15 APOE mutations associated with LPG have been reported so far, the most common being APOE-Kyoto mutation. Our previous study revealed the largest population of LPG from a county 200 kilometer near Chengdu city, in Sichuan province, China. All these patients shared APOE Kyoto mutation in e3 allele, which suggests that the APOE-Kyoto mutation spread from one founder.

Methods: we enrolled 26 patients with LPG from twenty-six unrelated Chinese families who were diagnosed by renal biopsy. After informed consents were obtained from them and their families, APOE mutation was detected by PCR-RFLP with Aor51HI, and a haplotype analysis of APOE was carried out by DNA sequencing using the method of TA cloning.

Results: We investigated the haplotype of APOE allele from twenty-six unrelated LPG families, and found the haplotype of APOE-Kyoto mutant allele was identical, and

was likely derived from haplotype 1 of APOE3; as for the counterpart APOE allele, the haplotype of counterpart APOE allele was not identical. Also, we identified a new haplotype of APOE4 named 32.

Conclusions: The haplotype of APOE-Kyoto mutation allele associated with LPG in the narrow country was identical, suggesting that mutation is common in Chinese patients through a founder effect. And patients didn't have a common haplotype of counterpart APOE allele as the asymptomatic carriers, which association with the onset of LPG isn't known. To the new haplotype 32 of APOE4, its clinical value isn't clear now.

Funding: Government Support - Non-U.S.

FR-PO168

Eleven Pregnancies in Four Women with Atypical Hemolytic Uremic Syndrome Martina M. Gaggl,¹ Christof Aigner,¹ Zoltan Prohaszka,² Gere Sunder-Plassmann,¹ Alice Schmidt.¹ ¹Dept of Medicine III, Div of Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria; ²IIIrd Dept of Internal Medicine, Research Laboratory, Semmelweis Univ, Budapest, Hungary.

Background: Pregnancy activates the maternal alternative pathway of the complement system due to presentation of paternal antigens. In females with atypical Hemolytic Uremic Syndrome (aHUS) – a disease of the complement regulatory proteins and C3 – each pregnancy can trigger life-threatening disease episodes.

Methods: Data were collected from patients with aHUS, enrolled in the Viennese TMA Cohort. Pregnancies occurred between 2002 and 2015.

Results: We report 11 pregnancies in 4 women (table 1). Two had an established diagnosis of aHUS prior to the first pregnancy (case 2 and 3). Case 1 presented with end-stage renal disease due to TMA (biopsy-proven) 12 months after her first delivery and case 4 presented postpartum after her uncomplicated first delivery. In 8 pregnancies females received preventive plasma infusions (PI, 200-1600 mL) 2 to 4 weeks apart. After kidney transplantation case 1 received a maintenance therapy (PIs once a month), which was intensified during the II. pregnancy to every other week. Two pregnancies (case 1 III., case 4 III.) are currently ongoing without evidence of a disease flare so far. Nine pregnancies went without any complication and the offspring are healthy. One pregnancy (case 3, III., without PIs) resulted in an intrauterine fetal death at gestation week 36, but without signs of TMA in the mother.

	Case 1	Case 2	Case 3	Case 4
Ethnicity	Caucasian	Caucasian	African	African
Genetics: Disease-causing mutation	CFH	CFI, MCP	CFH	C3
Risk-haplotype/polymorphism	CFH-H3	C3	CFH, CFI, C3, CFB	CFH-H3, CFI, MCP _{ggac}
Maintenance treatment	PI	none	none	none
Age of diagnosis of aHUS (yrs)	19	3	24	20
Age at renal transplant (yrs)	25	-	26	-
Number of pregnancies	3	2	3	3
Age at I. pregnancy	18	19	29	20

Conclusions: Our case series underscores the fact that the recommendation to avoid pregnancies in aHUS is questionable. The strategy to prevent disease episodes with plasma infusions might be superior to primary monitoring and initiation of treatment in acute disease episodes.

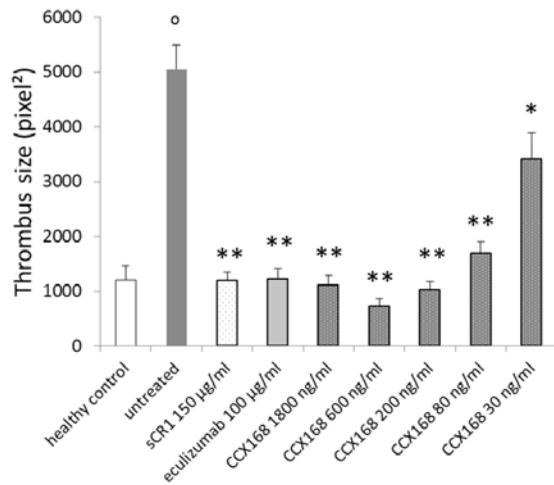
FR-PO169

Orally Administered Complement 5a Receptor Inhibitor CCX168 Development in Atypical Hemolytic Uremic Syndrome Miriam Galbusera,¹ Sara Gastoldi,¹ Valentina Portalupi,¹ Elena Mondo,¹ Pirow Bekker,² Thomas J. Schall,² Marina Noris,¹ Giuseppe Remuzzi.¹ ¹Mario Negri Inst; ²ChemoCentryx.

Background: The orally administered complement 5a receptor (C5aR) inhibitor CCX168 is in Phase 2 development for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, atypical hemolytic uremic syndrome (aHUS), and IgA nephropathy. The anaphylatoxin C5a is a potent neutrophil attractant involved in neutrophil priming and activation as well as inducing endothelial cell injury. The latter causes increased neutrophil and platelet adhesiveness, leading to thrombosis, one of the hallmarks of aHUS. We report here progress in the aHUS program.

Methods: In an ex vivo thrombus formation system, serum from aHUS patients induces thrombus formation on microvascular endothelial cells. CCX168 was compared with the anti-C5 antibody eculizumab and soluble complement receptor 1 (sCR1) in this assay.

Results: CCX168 resulted in a dose-dependent inhibition of thrombus size.



o P<0.001 vs control, * P<0.05, ** P<0.0001 vs untreated. 200 ng/mL CCX168, equal to trough plasma levels achieved with 30 mg CCX168 twice daily (b.i.d) in patients, showed maximal inhibition of aHUS serum-induced thrombus formation, comparable to sCR1 and eculizumab at 100 mg/mL, the trough level observed in aHUS.

Conclusions: CCX168 was effective in reducing aHUS-induced thrombus formation, similarly to eculizumab and sCR1. A Phase 2 study was launched. Ten patients with aHUS who are on dialysis are treated with CCX168 30 mg b.i.d. for 15 days. The primary aim is to evaluate whether in vivo CCX168 treatment dampens the ex vivo prothrombotic properties of serum from these patients. Secondary outcome measures include the effect of CCX168 on biomarkers of complement, soluble thrombomodulin and VCAM-1, platelet count, hemoglobin, LDH, neutrophil count, and the pharmacokinetic profile of CCX168.

FR-PO170

Whole Exome Sequencing Reveals Mutation of *PAPLN* as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT) Jing Chen,^{1,6} Asaf Vivante,^{1,6} Julian Jakob Schulz,¹ Shirlee Shril,¹ Stefan Kohl,¹ Daw-yang Hwang,¹ Richard P. Lifton,^{2,3} Elijah O. Kehinde,³ Velibor Tasic,⁵ Friedhelm Hildebrandt.^{1,3} ¹Dept of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA; ²Dept of Human Genetics, Yale Univ School of Medicine, New Haven, CT; ³Howard Hughes Medical Inst, Chevy Chase, MD; ⁴Dept of Surgery, Kuwait Univ, Safat, Kuwait; ⁵Dept of Pediatric Nephrology, Univ Children's Hospital, Skopje, Macedonia, The Former Yugoslav Republic of; ⁶These authors contributed equally to this work.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in children. Knowledge from animal models suggests that single gene mutations in genes governing kidney and urinary tract development may lead to CAKUT in humans. However, the genetic pathogenesis of human CAKUT remains mostly elusive.

Methods: To identify novel monogenic causes of CAKUT we applied homozygosity mapping with whole exome sequencing (WES) to 36 families with CAKUT. Then we investigated a worldwide cohort of ~1,600 families with CAKUT with a barcoded array based multiplex exon PCR (48x48 Fluidigm Access Array™) and next generation sequencing (Illumina MiSeq™).

Results: In a consanguineous family with isolated CAKUT we detected a homozygous protein truncating mutation (p.Arg480*) in the *PAPLN* gene by WES. *PAPLN* encodes papilin, a component of the extracellular matrix (ECM) that plays a role in ECM development and interacts with ADAMTS metalloproteases. Papilin contains several thrombospondin type I domains homologous to ADAMTS-1, in which mutations leads to very distinct CAKUT phenotype in mice.

Conclusions: We identified a recessive truncating mutation in *PAPLN* as a novel monogenic cause of CAKUT, suggesting that CAKUT in humans may result from disruption of ECM degradation and turn over.

FR-PO171

Whole Exome Sequencing Identifies Mutations in *TUBAL3* as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT) Shirlee Shril,^{1,6} Asaf Vivante,^{1,6} Jan Halbritter,¹ Jing Chen,¹ Julian Jakob Schulz,¹ Stefan Kohl,¹ Daw-yang Hwang,¹ Elijah O. Kehinde,² Richard P. Lifton,³ Martin Zenker,⁴ Friedhelm Hildebrandt.^{1,5} ¹Dept of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA; ²Dept of Surgery, Kuwait Univ, Safat, Kuwait; ³Dept of Genetics, Yale Univ School of Medicine, New Haven, CT; ⁴Dept of Human Genetics, Otto von Guericke Univ, Magdeburg, Germany; ⁵Howard Hughes Medical Inst, Chevy Chase, MD; ⁶These authors contributed equally to this work.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of end-stage kidney disease in children. The morphogenesis of kidney and urinary tract is modified by genetic mutations that lead to CAKUT. Identifying these mutations will not only provide a deeper insight on disease mechanisms but also aids in improving diagnosis. *TUBAL3* was identified as a potential candidate gene for causing CAKUT.

Methods: Homozygosity mapping with whole exome sequencing (WES) was performed in 20 consanguineous families with CAKUT from India. Homozygous recessive mutations within the homozygous region were further evaluated as the strongest candidates. Furthermore, we screened an additional cohort of 900 patients with CAKUT for additional mutations with a barcoded array based multiplex exon PCR (48x48 Fluidigm Access Array™) followed by next generation sequencing (Illumina MiSeq™) All identified mutations were confirmed by Sanger sequencing.

Results: A homozygous truncating mutation (p.Tyr179*) in the gene *TUBAL3* was identified in the consanguineous Indian family A3838 using WES. We then independently detected another mutation homozygously (p.Gly10Ser) in the gene *TUBAL3* in a family A1347 of Kurdish descent. *TUBAL3* (Tubulin, alpha-like 3) is a protein coding gene and is very conserved across species. Tubulin is the major constituent of microtubules.

Conclusions: We identified recessive mutations in *TUBAL3* as a novel single-gene cause of CAKUT. Further genetic information and functional studies will help understand disease mechanisms and the role of *TUBAL3* in the pathogenesis of CAKUT.

FR-PO172

Association of *PAX2* and Other Gene Mutations with the Clinical Manifestations of Renal Coloboma Syndrome Kengo Furuichi,¹ Toshiya Okumura,² Yasuyuki Shinozaki,² Yasunori Iwata,² Norihiko Sakai,¹ Takashi Wada.² ¹Div of Blood Purification, Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; ²Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.

Background: Renal coloboma syndrome (RCS) is characterized by kidney hypoplasia or dysplasia and abnormality of the optic nerve. Diagnosis of RCS is based on the morphological examination of the kidney, ophthalmologic findings, and family history. Approximately 170 cases with *PAX2* gene mutations have been reported in cases with RCS worldwide. However, around 50% cases of RCS have no mutation in *PAX2* gene.

Methods: To investigate the incidence and effects of mutations of *PAX2* and 25 related genes, 26 patients with RCS were screened using next-generation sequence analysis, and candidate mutations were confirmed using Sanger sequencing. The correlation between mutations and clinical manifestation was evaluated.

Results: Thirty patients, including two family cohorts (n = 5 and 2), 19 patients with sporadic RCS, and 4 coloboma only control cases were evaluated in the present study. Screening the sequences of *PAX2* and 25 other genes identified 46 nonsynonymous single nuclear changes and 9 indels. Among these candidate gene abnormalities, eleven *PAX2* mutations, including four novel mutations, were confirmed using Sanger sequencing, as were mutations in *CHD7*, *SALL4*, *KIF26B*, and *SIX4*. A *SALL4* mutation was detected in one patient, and *CHD7*, *KIF26B*, and *SIX4* mutations were detected in another patient, of which *KIF26B* mutation is novel. Kidney function and proteinuria were more severe in patients with *PAX2* mutations than in those without the mutation. Moreover, the coloboma score was significantly higher in patients with *PAX2* gene mutations. Three out of five patients with *PAX2* mutations had focal segmental glomerulosclerosis diagnosed from kidney biopsies.

Conclusions: Our data indicate that *PAX2* mutation is a key mutation in RCS and may make a major contribution to the pathogenesis of kidney and eye abnormalities. However, other factors and gene mutations may play a role, and further human and animal studies will be required to define the mechanism of pathogenesis of RCS.

Funding: Government Support - Non-U.S.

FR-PO173

Whole Exome Sequencing Identifies a Mutation in *TTC25* as a Novel Monogenic Cause of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) Julian Jakob Schulz,¹ Asaf Vivante,¹ Jing Chen,¹ Shirlee Shril,¹ Elijah O. Kehinde,² Friedhelm Hildebrandt.^{1,3} ¹Dept of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA; ²Dept of Surgery, Kuwait Univ, Safat, Kuwait; ³Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) cover a wide range of renal malformations which account for most cases of pediatric CKD. So far more than 30 monogenic CAKUT-causing genes have been identified. However, for most cases the underline genetic cause is still unknown.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: To identify causative genes for CAKUT we investigated consanguineous families with CAKUT by applying whole exome sequencing (WES) combined with homozygosity mapping.

Results: In one family we detected a homozygous loss-of-start mutation in the gene *TTC25* (tetra-tricopeptide repeat-containing 25). This mutation (p.Met1Thr; c.2T>C) was present in an affected child that had a posterior urethral valve, vesicourethral reflux and bilateral hydronephrosis. *TTC25* plays a role in ciliogenesis, pronephric cilia function and signal transduction in the sonic hedgehog pathway (Hayes, J. M. *et al.*, 2007. *Dev. Biol.* 312: 115; Xu Y *et al.*, 2015. *PLOS ONE* 10(4): e0124378). The latter has been shown to coordinate bladder as well as urethra formation in mice (Haraguchi R *et al.*, 2007. *Development* 134(3):525; Haraguchi R *et al.*, 2012. *PLOS ONE* 7(7): e42245).

Conclusions: By WES and homozygosity mapping we identified *TTC25* as a novel monogenic CAKUT-causing gene if mutated.

Funding: NIDDK Support

FR-PO174

Phenotypic Analysis of a Cohort of Patients with Hepatocyte Nuclear Factor 1 Beta (HNF1 β) Mutations and Correlation with Established Scoring Systems Emma Kaye Montgomery,¹ John Andrew Sayer.^{1,2} ¹Renal Scoring Centre, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, Tyne and Wear, United Kingdom; ²Inst of Genetic Medicine, International Centre for Life, Newcastle Univ, Newcastle upon Tyne, Tyne and Wear, United Kingdom.

Background: Hepatocyte nuclear factor 1 beta (HNF1 β) mutations may lead to a wide spectrum of clinical phenotypes including developmental defects of the kidney, pancreas, liver, and Mullerian duct. HNF1 β mutations account for Renal Cysts and Diabetes (RCAD) syndrome. We reviewed patients with known HNF1 β mutations to determine the range of phenotypes and identified if these patients would have been detected based on established scoring systems.

Methods: We selected patients who had been screened for HNF1 β mutations from 2009 to 2014 within our hospital. Serum magnesium, potassium, urate and creatinine levels were noted as well as renal morphology based on imaging. All positive and negative patients for HNF1 β mutations had their phenotypes quantified and correlated with published HNF1 β scoring systems and screening criteria.

Results: 135 patients were screened over 5 years. The cohort included 17 patients from 10 families with confirmed HNF1 β mutations. The majority of these patients had CKD stage 3, with a mean creatinine of 144 μ mol/L. Only 35% of mutation positive patients had both renal cysts and diabetes. 57% of patients had hypomagnesaemia, 50% of the patients had hyperuricaemia and 4 patients had clinical symptoms of gout with 75% of these patients presenting with gouty symptoms before the age of 30. Using a published HNF1 β scoring system, 16 patients reached a threshold score of >8, sufficient for a presumed diagnosis, validating the sensitivity of the scoring system in our cohort. Based on alternative screening criteria, all 17 patients would have been identified for screening.

Conclusions: The majority of patients with HNF1 β mutations demonstrated hypomagnesaemia (50%), hyperuricaemia (53%) and deranged liver function tests (59%). RCAD remains a misnomer and patients with HNF1 β mutations have a wide phenotypic spectrum, with only one third having renal cysts and diabetes. The use of a HNF1 β scoring/ screening system will help to improve detection rates.

FR-PO175

CTNS Gene Mutations and Variants in Adult Hemodialysis Patients Craig B. Langman,¹ Paul C. Grimm,² Elena N. Levchenko,³ Krishna R. Polu.⁴ ¹Feinberg Sch Med, Northwestern U; ²Stanford U. Sch. of Med; ³Univ of Leuven; ⁴Raptor Pharmaceuticals, Novato, CA.

Background: Nephropathic Cystinosis (NC), a rare, systemic, autosomal recessive disease due to *CTNS* gene mutations causes end-stage renal disease (ESRD). While most cases of NC are recognized in infancy (95%), late-onset NC with ESRD is rare but might be under-diagnosed. NC is rarely diagnosed in African-Americans (AA). **Objective:** To identify *CTNS* mutations and possible pathogenic variants (Δ) in a representative sample of ESRD patients (pts) in the US.

Methods: Genomic DNA was extracted from whole blood from 4007 adult hemodialysis pts from the Davita biorepository. Fluidigm's Access Array IFC was used for the *CTNS* target enrichment. Enriched DNA was sequenced on the HiSeq 2500 using 2 x 100bp read length. Reads were mapped to the human genome version hg19 using the BWA aligner. Mutations and Δ were called using both GATK and Samtools and confirmed by Sanger sequencing.

Results: 16 pts had homozygous (HoZ) and 52 pts had compound heterozygous (HTZ) *CTNS* sequence Δ . 1/68 pts had a known diagnosis of NC (W138X). In HoZ pts, 6 had known mutations in *CTNS* (V42I; 5/6 were AA) consistent with NC. 9 had upstream promoter mutations (UPM) (7 with -294C>T and 2 with -295G>C, a mutation locus with known disease association), and 3 of these pts were AA. In 52 HTZ *CTNS* sequence Δ , 2 AA pts had UPM. The other 50 had combinations of changes in the *CTNS* coding sequence & promoter region.

Conclusions: The unexpected frequency of *CTNS* gene mutations & Δ suggest that late-onset NC may be underrecognized in ESRD. These *CTNS* alterations need further study to determine pathogenicity and association with NC. In addition, *CTNS* mutations & Δ in AA sub population signals a need for evaluation for a diagnosis of late onset nephropathic cystinosis in ESRD.

Funding: Pharmaceutical Company Support - Raptor Pharmaceuticals

FR-PO176

Sixteen Monogenic Genes Cause 20% of Early-Onset Urinary Stone Disease Jennifer A. Lawson,¹ Daniela A. Braun,¹ Heon Yung Gee,¹ Jan Halbritter,¹ Shirlee Shril,¹ Weizhen Tan,¹ John Andrew Sayer,² Danko Milosevic,³ Michelle Baum,¹ Velibor Tasic,⁴ Friedhelm Hildebrandt.^{1,5} ¹Nephrology, Boston Children's Hospital, Boston, MA; ²Inst of Genetic Medicine, Newcastle Univ, Newcastle upon Tyne, United Kingdom; ³Dept of Pediatric Nephrology, Univ of Zagreb Medical School, Zagreb, Croatia; ⁴Medical Faculty Skopje, Univ Children's Hospital, Skopje, Macedonia, The Former Yugoslav Republic of; ⁵Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Urinary stone disease (USD) is a prevalent condition that affects 10-15% of adults in their lifetime. It is associated with high morbidity due to colicky pain, the necessity for surgical intervention, and sometimes progression to chronic kidney disease. In recent years, multiple monogenic causes of USD have been identified. However, the prevalence of each monogenic gene has yet to be systematically studied in a pediatric urinary stone cohort.

Methods: To determine the percentage of cases that can be explained molecularly by mutations in 1 of 30 known urinary stone genes, we conducted a high throughput exon sequencing analysis in an international cohort of consecutively recruited individuals from three renal stone clinics. The cohort consisted of 143 individuals under 18 year of age, with nephrolithiasis (n=123) or isolated nephrocalcinosis (n=20).

Results: We detected likely causative mutations in 16 of 30 analyzed genes, leading to a molecular diagnosis in 20% (29 of 143) of affected individuals; 14 of the 32 detected mutations were not previously described as disease causing (43.8%). We show that mutations in recessive genes are more likely to cause infantile onset disease, whereas mutations in dominant genes are more likely to manifest later.

Conclusions: We present the first exclusively pediatric cohort examined for monogenic causes of urinary stone disease, and our data demonstrates that important therapeutic and preventative measures may result from mutational analysis in individuals with early-onset USD.

Funding: Other NIH Support - DK1069274, DK1068306, and DK064614

FR-PO177

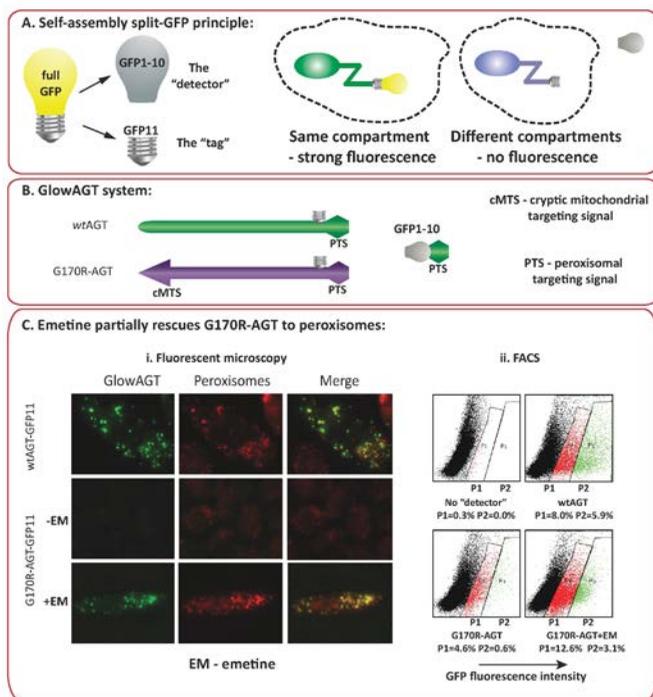
Mild Inhibition of Alanine-Glyoxylate Aminotransferase Translation as a Possible Treatment of Primary Hyperoxaluria Type I Roman Lyakhovetsky,¹ Yaacov Frishberg,¹ Bodo B. Beck,² Ruth Belostotsky.¹ ¹Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel; ²Inst of Human Genetics, Cologne, Germany.

Background: Primary hyperoxaluria type 1 (PH1) is a kidney stone disease, often leading to ESRD, caused by absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT), encoded by *AGXT*. The most frequent mutation G170R, responsible for 30% of PH1 cases in Caucasians, results in aberrant mitochondrial localization rather than catalytic inactivity. Modulating AGT maturation and folding has long been perceived as a therapeutic approach. Yet, numerous attempts over the years failed to rescue AGT mutants. We propose mild translational inhibition as a novel approach to improve folding and localization of AGT mutants.

Methods: The antihelminthic FDA-approved drug emetine, was used as a translation inhibitor. To ensure selective and specific discrimination between the mitochondrial (major) and the peroxisomal (minor) subpopulations of mutated AGT we developed the *GlowAGT* assay based on the recently described self-assembly split GFP approach.

Results: Using *GlowAGT*, WT-AGT but not G170R-AGT was detectable by GFP fluorescence, although both variants were visible by indirect immunofluorescence. Long-term treatment with low concentrations of emetine showed statistically significant increase of fluorescent subpopulation of G170R-AGT. GFP fluorescence was exclusively co-distributed with the peroxisomal staining in all cases.

Conclusions: We have developed and applied successfully *GlowAGT* as a unique self-assembly split-GFP-based assay for detecting peroxisomal subpopulation of AGT. Using *GlowAGT* we show that mild translation inhibition by emetine is a novel therapeutic approach for PH1 caused by AGT misfolding/mislocalization



Funding: Government Support - Non-U.S.

FR-PO178

Functional Analysis of CLCNKB Mutations Causing Bartter Syndrome Type III Yohan Bignon,¹ Mathilde Keck,¹ Stéphane Lourdel,¹ Rosa Vargas-Poussou,² Jacques Teulon,¹ Olga Andrini,¹ ¹Metabolisme et Physiologie Renales, Centre de Recherche des Cordeliers, UPMC, Paris, France; ²Dept of Human Genetics, Hôpital Européen Georges Pompidou, Univ Paris 5, Paris, France.

Background: Bartter Syndrome type III is a human autosomal recessive disease characterized by salt wasting, hypokalemic metabolic alkalosis and secondary hyperaldosteronism. Therefore, patients affected by Bartter syndrome type III display polyuria, polydipsia, dehydration, nephrocalcinosis and failure to thrive. The disease is caused by inactivating mutations in the CLCNKB gene encoding for the ClC-Kb Cl⁻ channel that is present in the distal nephron, where it mediates the basolateral step of Cl⁻ absorption [2]. In this study, we have investigated the functional consequences of five previously reported pathogenic ClC-Kb missense mutations (A204T, A210V, P216L, G424R, G437R [3]).

Methods: We characterized the electrical activity, total protein expression, surface expression and subcellular localization of mutated forms of ClC-Kb in *X. laevis* oocytes and mammalian cell lines.

Results: Currents produced by G424R and G437R ClC-Kb channels were reduced by 50%, in proportion to membrane targeting without any change in total protein abundance. A210V and P216L mutants did not produce any current but their membrane insertion was only partially reduced (50-80%). Protein abundance of A210V was decreased by half. Conversely, that of P216L was comparable to WT ClC-Kb, suggesting that the P216L mutation might alter channel gating. Finally, A204T seems to be electrically functional, rather well inserted into the plasma membrane and protein level is comparable to that of wild-type ClC-Kb.

Conclusions: In conclusion, the loss-of-function of ClC-Kb mutants is the result of different molecular defects including lower stability of the mutant protein, impaired membrane targeting and altered channel gating. References: [1] Simon D.B. et al, Nature Genetics 17, 171-178 (1997) [2] Andrini O. et al, American Journal of Physiology Renal Physiology, in press (2015).

Funding: Government Support - Non-U.S.

FR-PO179

Changes in Urologic and Medical Treatment of Cystinuric Patients Over Time Caroline Prot-Bertoye,¹ Said Lebbah,² Michel Daudon,³ Isabelle Tostivint,⁴ Olivier Traxer,⁵ Bertrand Knebelmann,⁶ Marie Courbebaisse.¹ ¹Physiology, APHP, Georges Pompidou European Hospital, Paris, France; ²Biostatistics, AP-HP, Necker Hospital for Sick Children, Paris, France; ³Physiology, AP-HP, Tenon Hospital, Paris, France; ⁴Nephrology, AP-HP, Pitié-Salpêtrière Hospital, Paris, France; ⁵Urology, APHP, Tenon Hospital, Paris, France; ⁶Nephrology, AP-HP, Necker Hospital for Sick Children, Paris, France.

Background: Cystinuria is the most common monogenic nephrolithiasis disorder, but few studies have described its urological and medical treatment in a large cohort.

Methods: We retrospectively collected data from 442 French cystinuric patients. Clinical and laboratory data, urological and medical treatments were described. A mixed-effects logistic regression model was used to estimate the effects of urinary pH, urinary specific gravity, and cysteine-binding thiol agents (CBT) on the risk of cystine crystalluria.

Results: The median follow-up [min-max] was 15.8 years [0.1-65.6]. The average annual rate of surgical procedures increased with time (P<0.001). During the period 2000-2004, 7.3 % of patients had at least one flexible ureteroscopy, versus 23.2 % after 2005 (P<0.001). CBT were prescribed for 55.3% of patients. Prescription of tiopronin increased with time in newly symptomatic patients (P<0.001). At least one side effect was recorded in 23.7% of patients treated with tiopronin, and 30.2% of patients treated with D-penicillamine (P=0.23). Increasing urinary pH and decreasing urinary specific gravity significantly reduced the risk for a patient to have a cystine crystalluria whereas D-penicillamine and tiopronin did not reduce this risk. The estimated probability of cystine crystalluria was 45%, 38%, 31% and 25% for an urinary pH of 6.5, 7.0, 7.5 and 8 and was 52%, 31% and 16% for an urinary specific gravity of 1015, 1010 and 1005.

Conclusions: The number of urological interventions and the prescription of tiopronin has increased over time. We show for the first time that D-penicillamine and tiopronin don't impact cystine crystalluria although inducing frequent adverse effects in the same proportions. Urinary pH above 7.5 and morning urinary specific gravity below 1005 should be the goals of medical therapy.

FR-PO180

Defect of Interdependent Membrane Targeting and Endocytosis of Cubilin and Amnionless Leads to Imerslund-Gräsbeck Syndrome Tomohiro Udagawa,¹ Ken-ichiro Miura,¹ Akihiko Saito,² Yutaka Harita,¹ ¹Pediatrics, Graduate School of Medicine, The Univ of Tokyo, Bunkyo-ku, Tokyo, Japan; ²Applied Molecular Medicine, Niigata Univ Graduate School of Medical and Dental Sciences, Chuo-ku, Niigata, Japan.

Background: Imerslund-Gräsbeck syndrome (IGS) is an autosomal recessive disorder characterized by low-molecular-weight proteinuria and megaloblastic anemia. IGS is caused by mutations of either cubilin (*CUBN*) or amnionless gene (*AMN*). Cubilin forms protein complex with amnionless (cubam complex) and functions as the receptor-mediated endocytotic machinery.

Methods: A six year-old boy with history of megaloblastic anemia was diagnosed with IGS because of low-molecular weight proteinuria. Whole-exome sequencing identified novel heterozygous missense mutations, one each in *CUBN* and *AMN*. The *CUBN* mutation was de novo and the *AMN* mutation was inherited from a healthy parent.

Results: Renal biopsy showed translocation of amnionless from the apical membrane to the cytoplasm of proximal tubular cells. Using cultured cells, the mechanism of membrane trafficking of cubam and the effect of the mutations were analyzed. Although wild-type cubilin and amnionless were interdependently targeted to the cell membrane, the *CUBN* or *AMN* mutation abrogated membrane expression and endocytosis without affecting the interaction between cubilin and amnionless. Coexpression of amnionless induced maturation of cubilin protein, and the modification were identified by stable isotope labeling using amino acids in cell culture (SILAC)-based quantitative mass spectrometry. Notably, the *CUBN* mutation completely abrogated the amnionless-dependent glycosylation of cubilin. Tunicamycin or substitution of several Asn residues to Asp abrogated membrane targeting of cubam without affecting cubilin and amnionless interaction, further supporting a role of cubilin glycosylation.

Conclusions: Our results demonstrate that digenic heterozygosity can lead to IGS and suggest that interdependent membrane trafficking of cubam complex mediated by posttranslational modification is crucial for the renal and intestinal absorption.

FR-PO181

Metabolic Control of Nephron Progenitor Cell Renewal and Differentiation Anna Abrams, Jiao Liu, Zubaida R. Saifudeen. *Pediatrics, Tulane Univ, New Orleans, LA.*

Background: Nephron progenitor cells (NPC) availability and differentiation potential determine nephron endowment. Emerging data from embryonic stem cells and other developing systems emphasizes the significance of energy metabolism in cell fate determination. Systemic metabolic dysfunction such as hyperglycemia alters neural and adipocyte stem cell fate. Nephron deficit in kidneys of infants of diabetic mothers (idm) is known; however the effect on NPC and nephrogenesis under maternal hyperglycemia are unknown. Metabolic parameters of renewing NPCs are also unknown. Based on published stem cell data, we hypothesized that NPC self-renewal and differentiation are balanced by energy metabolism.

Methods: a. Fetal kidneys were exposed to maternal hyperglycemia using Streptozotocin (STZ). P0 kidney sections were immunostained to detect apoptosis (active caspase3) in the CM (Six2 and NCAM) and nascent nephrons (Lef1 and NCAM). b. Glycolysis was inhibited *ex vivo* in E12.5 kidneys by pharmacological inhibition of PFKFB3 (YN1 5-25nM). c. Glycolysis and oxidative phosphorylation were measured in NPC of Six2CreGFP+;p53fl/fl, a genetic model of impaired cap mesenchyme renewal.

Results: a. CM of P0 kidneys of STZ-treated females showed increased apoptosis and reduction in nascent nephron number (Lef1+ and NCAM+). b. Glycolysis inhibition resulted in a smaller dispersed CM, accelerated but not ectopic differentiation of the NPC with up to a 50% increase in Lhx1+ nascent nephrons 24-48h post-treatment, and decreased Cited1 expression by QPCR in isolated NPC. UB tip and branch numbers were unchanged. Thus, increased nephrogenesis was independent of UB branching. Expression of Wnt4 was unchanged. c. Conditional deletion of p53 in NPC also resulted in dispersed CM, depletion of the Cited1+/Six2+ NPC independent of apoptosis, and hypoplastic kidneys with fewer nascent nephrons. Isolated mutant cells show reduced basal oxygen consumption rate and decreased maximal respiratory capacity. Accordingly, the mutant cells exhibit a significant, nearly two-fold decrease in ATP ($p < 0.005$, $n = 3$).

Conclusions: Our data are consistent with the idea that the metabolic status of the NPC is a critical determinant of NPC renewal and differentiation.

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FR-PO182

Prorenin Receptor Signaling Promotes Nephron Induction During Mouse Kidney Development Renfang Song,¹ Graeme James Preston,¹ Laura R. Kidd,² Ihor V. Yosypiv,¹ ¹*Pediatrics, Tulane Univ, New Orleans, LA;* ²*Pathology, Tulane Univ, New Orleans, LA.*

Background: Deficient nephrogenesis is the major factor contributing to congenital renal hypodysplasia (RHD), one of the leading causes of childhood end-stage kidney disease. Nephron induction is driven by reciprocal interactions between progenitor cells of the cap mesenchyme and the ureteric bud (UB).

Methods: To determine the potential role of the prorenin receptor (PRR) in nephrogenesis, we generated mice with a conditional deletion of the PRR in Six2-positive nephron progenitors of the cap mesenchyme and their epithelial derivatives (Six2^{PRR-/-}).

Results: Inactivation of PRR in nephron progenitors caused a marked decrease in the number of developing nephrons, severe congenital RHD with collapsed glomeruli and an enlarged Bowman's space (such as those seen with a collapsing FSGS), podocyte foot process effacement and early postnatal death within 48 hours from birth. UB branching was greatly reduced, likely secondary to decreased nephrogenesis. Reduced congenital nephron endowment resulted from premature depletion of nephron progenitor cell population due to impaired progenitor cell proliferation and loss of normal molecular inductive response to canonical Wnt/ β -catenin signaling within the metanephric mesenchyme. At 2 months of age, heterozygous Six2^{PRR+/-} mice exhibited focal glomerulosclerosis, decreased kidney function and massive proteinuria.

Conclusions: Collectively, these results are consistent with a cell-autonomous requirement for the PRR within nephron progenitors for progenitor maintenance, induction of nephrogenesis, normal kidney development and function. Thus, PRR is a potential candidate for future genetic screening studies in patients with congenital RHD and proteinuric kidney disease.

FR-PO183

Functional Dissection of Enhancers for Bmp7 in Kidney Development Taro Tsujimura,^{1,2,3} Osamu Takase,^{1,2,3} Masaomi Nangaku,² Keiichi Hishikawa.^{1,2,3} ¹*Advanced Nephrology and Regenerative Medicine, The Univ of Tokyo Hospital, Tokyo, Japan;* ²*Div of Nephrology and Endocrinology, The Univ of Tokyo Hospital, Tokyo, Japan;* ³*Div of Tissue Engineering, The Univ of Tokyo Hospital, Tokyo, Japan.*

Background: Bmp7 is a critical player in the kidney development, as shown by its severe retardation in the KO mice of the gene and their subsequent perinatal lethality due to the malfunction. Previous studies identified two potential enhancers for the Bmp7 expression in the developing kidney around the locus: one residing inside the 1st intron of Bmp7 for expression in the developing ureteric bud; the other located downstream of the 3' end of Bmp7, which is rather active in the metanephric mesenchymal cells. Consistently, Bmp7 is also expressed in these two distinct domains. However, neither the requirement of these elements nor the precise roles of Bmp7 secreted from these different cell types for the kidney development has been uncovered so far. In this study, we aimed to characterize the roles of the two enhancers to better understand the cis-regulation of Bmp7 and the kidney development.

Methods: We established and analyzed homozygous mice carrying a large genomic deletion of the downstream region of Bmp7 including the mesenchymal enhancer.

Results: We found that they have significantly smaller body size than their wild type littermates, although they are viable unlike the KO mice of Bmp7. We previously showed that the same deletion also disrupts the topological partition of the chromatin conformation between the Bmp7 domain and the neighboring one of another developmental gene, Tjap2c, resulting in a merger between them (Tsujimura *et al.* PLoS Genetics 2015). Interestingly, upon this deletion, we scored significant up-regulation of Tjap2c in the kidney probably by the action of the intron enhancer.

Conclusions: These results suggest that the endogenous genomic context guarantees robustness in the regulation of the kidney development by linking the more important

ureteric bud enhancer to Bmp7 tightly. The differential roles of the two enhancers will be further discussed based on the histological and functional analysis of the kidney in the homozygous deletion mice.

Funding: Government Support - Non-U.S.

FR-PO184

BMP7 Regulates Expansion of the Postnatal Nephron Mary E. Taglienti,¹ Seymour Rosen,² Jordan A. Kreidberg.^{1,3,4} ¹*Dept of Medicine, Boston Children's Hospital, Boston, MA;* ²*Dept of Pathology, Beth Israel Deaconess Medical Center, Boston, MA;* ³*Dept of Pediatrics, Harvard Medical School, Boston, MA;* ⁴*Harvard Stem Cell Inst, Cambridge, MA.*

Background: The factors that regulate the expansion of nephrons after their initial induction and differentiation are largely unknown. Bone morphogenic protein 7 (BMP7) is a crucial factor driving proliferation and self-renewal of nephron progenitor cells during the development of the embryonic kidney. In this study we investigated a potential role for BMP7 as a regulator of post-induction nephron growth and differentiation.

Methods: The Bmp7 gene was conditionally mutated in progenitor cells using Six2-GFP/Cre. Kidneys from mutant and control mice were analyzed using a novel approach to quantify proximal tubule expansion as an indicator of nephron growth in the postnatal mouse.

Results: Kidneys of Bmp7 conditional mutant mice were smaller with reduced numbers of nephrons. Bmp7 was expressed in developing nephron tubules of control kidneys and was absent from mutant kidneys. Proximal tubule growth, as determined by computationally measuring the area of lectin-stained proximal tubules in postnatal kidneys, was reduced in mutant kidneys. However, the proximal tubule area per glomerulus was increased in mutant kidneys, indicating that those nephrons that were induced underwent hypertrophy. Proliferation, as defined by Ki67+ nuclei per LTL lectin+ cells within the proximal tubule compartment, was initially greater in mutants but declined by P10.

Conclusions: Loss of Bmp7 in progenitors leads to low nephron number. Bmp7 appears to be an important driver of postnatal nephron expansion. This phenotype is similar to oligomeganephronia and may be used to understand the basis for nephron hypertrophy in low nephron number situations.

Funding: NIDDK Support

FR-PO185

Grainyhead-Like 2 (Grhl2) Regulates Collecting Duct Barrier Function, Aquaporin 2 Expression and Urinary Concentration Christian Hinze,^{1,2} Janet Ruffert,^{2,5} Katharina Walentin,² Max Werth,³ Jonathan M. Barasch,³ Andong Qiu,³ Kerim Mutig,⁴ Sebastian Bachmann,⁴ Kai M. Schmidt-Ott.^{1,2} ¹*Dept of Nephrology, Charité-Universitätsmedizin, Berlin, Germany;* ²*Max Delbrueck Center for Molecular Medicine, Berlin, Germany;* ³*Div of Nephrology, Columbia Univ, New York;* ⁴*Dept of Anatomy, Charité-Universitätsmedizin, Berlin, Germany;* ⁵*Urological Research Laboratory, Charité-Universitätsmedizin, Berlin, Germany.*

Background: Osmotic homeostasis is tightly regulated by the kidney and its collecting ducts which form tight barriers, thereby maintaining steep concentration gradients and allowing transcellular reabsorption of water via aquaporins. The transcription factor grainyhead-like 2 (Grhl2) is highly expressed in renal collecting ducts. Using cultured collecting duct cells, we recently showed that Grhl2 regulates epithelial barrier formation and lumen expansion via a target gene set comprising the transcription factor Ovo-like 2 (OvoL2), the small GTPase Rab 25 (Rab25) and the tight junction component claudin 4 (Cldn4). The role of Grhl2 in the collecting duct *in vivo* is unknown.

Methods: To investigate the role of Grhl2 in the renal collecting duct, we generated a collecting duct-specific knockout with Hoxb7/Cre; Grhl2^{Hoxb7} mice, which exhibit a deletion of Grhl2 protein in most cells of the collecting duct. The molecular and cellular alterations in their kidneys and their response to water deprivation were analyzed.

Results: Transcriptional profiling of Hoxb7/Cre; Grhl2^{Hoxb7} mice kidneys and control littermates showed deregulation of OvoL2, Rab25 and Cldn4, but also differential expression of Aquaporin 2 (Aqp2). Following water deprivation, Grhl2-deficient mice displayed significantly lower urinary osmolality at 6 hours ($P = 0.001$) and 24 hours ($P = 0.04$) when compared to control mice. Moreover, Grhl2-deficient mice had more than 35% more urine volume during the first 24 hours in response to water deprivation when compared to controls ($P = 0.005$).

Conclusions: Our data indicate that Grhl2 critically participates in water homeostasis, epithelial barrier function and Aqp2 expression. This might be of relevance to diseases involving defective renal responses to water deprivation.

FR-PO186

Loss of the Transcription Factor Tcf21 in the Renal Stroma Leads to Polyuria and Defects in Tubular Development Shintaro Ide,¹ Yoshiro Maezawa,¹ Rizaldy P. Scott,² Tuncer Onay,² Kana Ide,¹ Minoru Takemoto,¹ Koutaro Yokote,¹ Susan E. Quaggin.² ¹*Clinical Cell Biology and Medicine, Chiba Univ Graduate School of Medicine, Chiba, Japan;* ²*Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.*

Background: Renal stromal cells serve as a supportive framework for nephrons and the collecting duct network, produce erythropoietin, and contribute to renal fibrosis when they undergo myofibroblast-like transformation. Tcf21/Pod1 is a bHLH transcription factor

strongly but not restrictively expressed in the developing renal stroma. Conventional Tcf21 knockout mice die perinatally and have maldevelopment of nephrons and mispatterning of the renal interstitium. However, the precise function of Tcf21 within renal stromal cells has yet to be clarified as Tcf21 is also expressed within the condensing metanephric mesenchyme during development.

Methods: In order to characterize the role of Tcf21 in stromal development and function, we bred floxed Tcf21 mice with Foxd1-Cre mice allowing specific inactivation of Tcf21 within the developing renal stroma and its derivatives.

Results: Mice lacking Tcf21 in the renal stroma (Tcf21^{stflox}) do not have an overt phenotype at birth and exhibit normal ureteric bud branching in embryonic kidney explant cultures. However, by 4 weeks postnatal, Tcf21^{stflox} mutant mice develop polyuria similar to diabetes insipidus. Polyuric mutant mice produce urine with significantly reduced osmolarity and creatinine levels but with higher levels of sodium and chloride relative to control littermates. Mutant kidneys are smaller, have a disorganized interstitium, and shriveling of the medullary rays due to a reduction in the loops of Henle and collecting ducts, whereas proximal tubule densities appear undisturbed.

Conclusions: Specific inactivation of Tcf21 in the stroma causes polyuria underscoring an important role of the renal interstitium in regulating postnatal development of tubules critical for urine concentration. Identification of direct targets of Tcf21 will provide novel insights regarding interactions between stromal cells, renal tubules and the collecting ducts.

Funding: Government Support - Non-U.S.

FR-PO187

Genetic Deletion of Cyclooxygenase-2 Impairs Glomerular Slit Diaphragm Formation During Late Stages of Kidney Development Kirsten Madsen,^{1,2} Niels Marcussen,² Boye Jensen.¹ *¹Dept of Cardiovascular and Renal Research, Univ of Southern Denmark, Odense, Denmark; ²Dept of Pathology, Odense Univ Hospital, Odense, Denmark.*

Background: Renal cyclooxygenase-2 (COX-2) expression is necessary for normal glomerular development. Impaired COX-2 activity has been associated with decreased expression of VEGF, a vascular growth factor of significant importance for glomerular capillary development. Therefore experiments were designed to test the hypothesis that COX-2 expression supports glomerular development through stimulation of capillary loop formation.

Methods: Kidney tissue was collected from a developmental series of COX-2 knockout (KO) mice and wild-type littermates (WT).

Results: Renal COX-2 expression showed developmental regulation with significantly higher COX-2 expression at postnatal (P) days 1 and P7 than at any later time points (P14, P21 and P40). Quantitative unbiased stereology at P28 showed significantly reduced glomerular number in COX-2 KO mice compared to WT littermates (8188 ± 781 and 12251 ± 454 glomeruli/kidney respectively, P=0.0001). Subcapsular accumulation of small and immature glomeruli was seen in COX-2 KO mice whereas glomeruli deeper in the cortex towards the medullary junction appeared normal. Tissue abundance of VEGF, angiopoietin-1 and -2 mRNAs was significantly reduced in COX-2 KO mice compared to WT at P7. By electron microscopy at P28, immature subcapsular glomeruli showed normal appearance of fenestrated endothelial cells but severe podocyte foot process effacement and absence of mesangial cells. Normal morphology was confirmed in glomeruli deeper in the cortex. At P7, COX-2 KO mice showed reduced expression of slit diaphragm proteins nephrin and podocin but not synaptopodin compared to WT.

Conclusions: In summary, deletion of COX-2 leads to decreased renal expression of vascular growth factors without changes to glomerular endothelial cell ultrastructure and severe podocyte foot process effacement and impaired expression of slit diaphragm proteins. In conclusion, COX-2 activity is necessary for normal podocyte function and slit diaphragm formation during late stages of kidney development.

Funding: Private Foundation Support

FR-PO188

Functional Cross Talk Between Tyrosine Phosphorylation of Crumbs Homolog 2 and Mechanistic Target of Rapamycin Complex1 in Developing Podocyte Sho Hamano, Yukino Nishibori, Kunimasa Yan. *Dept of Pediatrics, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan.*

Background: Mutation of crumbs homolog 2 (CRB2) is a novel cause of congenital nephrotic syndrome. CRB2 is suggested to function in apical polarity and epithelial integrity; however, how CRB2 functions in podocyte development is unknown. Other isoform: CRB3 is known to be involved in deactivation of mechanistic target of rapamycin complex1 (mTORC1): a master regulator for cell growth. The objective of the present study is to determine functional cross talk between CRB2 tyrosine phosphorylation and mTORC1 pathway and the relevance of CRB2-mTORC1 interaction to podocyte development.

Methods: MDCK cells expressing mouse full-length CRB2 or mutated-CRB2 lacking tyrosine phosphorylation site were established. Specific antibodies against CRB2 intracellular domain (int-CRB2Ab) or tyrosine phosphorylation site (pY-CRB2Ab) were generated. The samples from cultured cells and rat kidneys were subjected to Western blot study and immunofluorescence microscopy.

Results: Int-CRB2Ab determined CRB2 to locate at the apicobasolateral membrane in wild-CRB2 cells. Specificity of pY-CRB2Ab was confirmed by using samples from mutated-CRB2 cells and wild-CRB2 cells treated with protein tyrosine phosphatases inhibitor. Int-CRB2Ab identified that CRB2 expression commenced at the comma-shaped body stage, observed in the apical side of glomerular epithelium. CRB2 in the S-shaped body was still visible at the apical side of immature podocytes, then translocated along the lateral side to basal side during capillary stage. At the mature stage, CRB2 was observed in the podocyte foot processes. In contrast, phosphorylation of CRB2 was determined faintly

in immature podocyte at the S-shaped body stage, intensely at the capillary stage and then disappeared at the mature stage. mTORC1 pathway was strongly activated in the podocyte at the mature stage, but was not in immature podocyte. Finally, mTORC1 in mutated-CRB2 cells was activated more than that in wild-CRB2 cells.

Conclusions: CRB2 tyrosine phosphorylation may regulate energy system of developing podocytes through suppressing excessive mTORC1 activation.

FR-PO189

Specific Deletion of Early B Cell Factor 1 within the Kidney Mesangium Recapitulates the Abrogated Renal Development Present in the Global Knockout Jackie A. Fretz, Tracy Nelson, Li Li. *Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT.*

Background: Globally deficient mice lacking the transcription factor Ebf1 (Ebf1 KO) are extremely sick owing to the multiple functions of Ebf1 across the body. We recently described a novel function of Ebf1 as an essential component of the latest stages of metanephric development. Within the kidney Ebf1 is present within multiple cell types including distinct tubular epithelium, interstitial pericytes, glomerular mesangium, and podocytes. This investigation aimed to identify if the actions of Ebf1 in the mesangium and pericytes was driving the developmental defects present in the global knockout.

Methods: In this study we made a specific deletion of Ebf1 within the Foxd1+ lineage using a cre-driver that targets the progenitors of the kidney glomerular mesangium and interstitial pericytes and mating these with mice where the 3rd exon of Ebf1 (encoding part of the DNA-binding domain) is flanked by flox sites. This is the same genetic region that is excised in the global deletion model.

Results: Restricted deletion of Ebf1 from Foxd1-lineage cells resulted in development of hypoplastic kidneys, poorly differentiated peripheral glomeruli, and decreased proximal tubular mass. Renal insufficiency was apparent at P21 (one week later than Ebf1 KO mice), with the appearance of proteinuria and 2+ leukocytes in urine. Growth of the animals is normal until P25, and approximately a third of the Foxd1+Ebf1^{fl/fl} mice die before they are 3 months old. This phenotype is similar to that seen in the Ptg2/Cox-2 insufficient models (chemical inhibition and genetic deletion), and mechanistic investigation revealed impaired Ptg2 expression in both the global KO and Foxd1-specific Ebf1 deletion models.

Conclusions: Taken together these results suggest that Ebf1 regulates metanephric development mainly through its actions in the mesangial lineage where it participates in proper regulation of prostaglandin biosynthesis.

Funding: NIDDK Support

FR-PO190

Epithelial Cell Fate in the Nephron Tubule Is Mediated by the Ets5a Transcription Factor During Zebrafish Kidney Development Amanda N. Marra, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: Kidney development requires the differentiation and organization of discrete nephron epithelial lineages, however the genetic and molecular pathways involved in these events remain poorly understood. The embryonic zebrafish kidney, or pronephros, provides a simple and useful model to study nephrogenesis.

Methods: The pronephros is comprised of two types of epithelial cells: transportive and multi-ciliated cells (MCCs). Transportive cells occupy distinct tubule segments and are characterized by expression of solute transporters, while MCCs function in fluid propulsion and are dispersed in a "salt-and-pepper" pattern in the tubule. Epithelial cell identity is reliant on interplay between the Notch signaling pathway and retinoic acid (RA) signaling, where RA promotes MCC fate by inhibiting Notch signaling in renal progenitors, while Notch activity acts downstream to trigger transportive cell formation and restrict MCC identity. Previous research has shown that *ets5a* and its ETS family members are required for ciliogenesis in other zebrafish tissues.

Results: Here, we mapped *ets5a* expression to renal progenitors that occupy domains where MCCs later emerge. Thus, we hypothesized that *ets5a* is required for ciliogenesis of MCCs in the nephron. *ets5a* loss of function produced a decline of MCC number and reduced expression of the MCC markers *odf3b* and *centrin*, where rescue experiments partially restored wild-type MCC number. In epistatic studies, exogenous RA treatment expanded the *ets5a* domain, indicating that *ets5a* acts downstream of RA. Additionally, treatment with exogenous RA partially rescues the reduced MCC phenotype after loss of *ets5a*. Further, abrogation of Notch with the small molecule inhibitor DAPT increased *ets5a* expression, while overexpression of Notch using a transgenic line reduced the *ets5a* domain, suggesting Notch acts upstream to inhibit *ets5a*.

Conclusions: Taken together, these findings provide novel insights about the mechanisms of epithelial cell development during nephrogenesis.

Funding: NIDDK Support, Other NIH Support - Office of the Director

FR-PO191

Emx1 Is Essential for Distal Segment Development During Nephrogenesis Elvin E. Morales, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: Vertebrate kidneys are comprised of functional subunits called nephrons that typically have three basic parts: a renal corpuscle, a tubule with proximal and distal segments, and a duct. The developmental pathways that establish nephron segment identities from renal progenitors remain poorly understood.

Methods: The zebrafish embryo forms a simple two-nephron pronephric kidney that possesses a conserved segment anatomy with higher vertebrates. *emx1* is a homeobox gene that, along with its paralog *emx2*, is known for playing essential roles in brain development. While both genes are expressed in the pronephros, their roles in nephrogenesis have not been established. Using whole mount *in situ* hybridization, we found that *emx1* and *emx2* were dynamically expressed in renal progenitors, and became localized to the distal and proximal segments, respectively.

Results: In knockdown studies, *emx1* morphants formed a normal distal domain, marked by *clenk*, but within it formed an expanded distal early (DE) segment, marked by *slc12a1*, and a reduced distal late (DL) segment, marked by *slc12a3*. These data suggest that *emx1* is essential to promote the DL, and may restrict the DE and/or negotiate the site of the DE/DL boundary. Furthermore, *emx1/2* expression is responsive to changes in retinoic acid (RA), which is essential to induce proximal segments and repress distal segments during nephrogenesis. RA treated embryos had a restricted *emx1* domain and expanded *emx2* domain, while exposure to the RA biosynthesis inhibitor DEAB conversely expanded *emx1* and restricted *emx2* expression. These data suggest that RA signaling acts upstream of both genes in renal progenitors, positively regulating *emx2* and negatively regulating *emx1*.

Conclusions: Future studies will define the role of *emx2*, independently explore *emx1/2* nephron patterning functions with CRISPR-Cas lines, and assess the relationship of these *emx* genes to other factors, such as *irx3b*, that have been shown recently identified to be components of the gene regulatory networks that direct nephron segmentation. Preliminary data looking at factor interactions suggest that *emx* genes may be located downstream of them or work independently.

Funding: NIDDK Support, Other NIH Support - Office of the Director

FR-PO192

Prostaglandins as Regulators of Nephron Proximo-Distal Cell Fate Decisions Shahram Jevin Poureteezadi, Christina N. Cheng, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: To date, there have been a number of important discoveries furthering our understanding of nephron segmentation. Despite this, the factors that direct nephron cell-fate decisions remain largely unknown. *Danio rerio*, the zebrafish, possess an embryonic kidney composed of two nephrons and a blood filter that share a remarkable degree of genetic, structural, and functional homology with the human nephron and when coupled with genetic tractability, *ex utero* development, and optically transparent embryos make it a cutting-edge model to study nephrogenesis.

Methods: The zebrafish embryonic kidney, the pronephros, is organized in a proximal-distal pattern of contiguous segments much like the human nephron. The proximal segments, the proximal convoluted tubule (PCT) and the proximal straight tubule, share a name with their mammalian counter parts; the distal segments, the distal early (DE) and the distal late (DL) – are homologous to the mammalian thick ascending limb (TAL) and distal convoluted tubule (DCT) respectively. We performed a chemical genetic screen using zebrafish embryos during nephrogenesis and analyzed the effects on segmental patterning.

Results: Interestingly, a large number of prostaglandin (Pg) pathway components were identified among our hits. Prostaglandins (PGs) are fast-acting lipids necessary for an array of physiological functions. We discovered that treatment with bioactive Pg agonists restrict the PCT and DL, while inducing an expansion of the PST. Genetic knockdown and small molecule inhibition of the Pg producing Cox1/2 enzymes or the Pg Ep G-protein receptors triggered an expansion of the DE segment at the expense of the DL. Further, we saw that modifying levels of Pg pathway components significantly altered renal progenitor expression domains, including *sim1a* and *mecom*, which are required for normal proximal and distal tubule patterning, respectively.

Conclusions: Thus, we show here for the first time that Pg signaling has an impactful role in nephron cell-fate decisions, suggesting that PGs may have considerable implications for therapeutic treatment of congenital kidney diseases as well as end-stage renal disease.

Funding: NIDDK Support, Other NIH Support - Office of the Director

FR-PO193

Cloning of the Zebrafish Kidney Mutant Zeppelin Reveals That Brca2/Fancd1 Is Essential for Renal Development Paul T. Kroeger, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: Zebrafish kidneys are conserved with other vertebrates, making them an excellent genetic model to study renal development. The kidney collects metabolic waste using a blood filter with specialized epithelial cells known as podocytes. Podocyte formation is poorly understood but relevant to many kidney diseases, as podocyte injury leads to progressive scarring and organ failure.

Methods: *zeppelin* (*zep*) was isolated in a forward screen for kidney mutants and identified as a homozygous recessive lethal allele, which has a loss of podocyte numbers, deficient filtration, and fluid imbalance. Addition of retinoic acid did not rescue the *zep* mutant phenotype. Although mutants had normal proliferation and cell death, the interrenal gland was increased in size, suggesting a possible cell fate switch between these related lineages. This data was corroborated by interrenal gland volume identified by FISH analysis. 3 β -HSD staining indicated the interrenal gland produced more hormones in the *zep* mutants, possibly suggesting an alternative mechanism of an endocrine feedback loop leading to overproliferation of interrenal cells.

Results: Meiotic mapping and whole genome sequencing of *zep* identified a splicing mutation in *breast cancer 2, early onset (brca2)/fancd1*, which was confirmed by sequencing of individual fish. Several independent *brca2* morpholinos phenocopied *zep*, causing edema and podocyte reductions, as well as an increase in the size of the interrenal gland. Additionally, 3 β -HSD staining suggests that morphants have an increased number of cells that generate hormones, similar to *zep*. Histological analyses of the adult kidney in *zep*

heterozygotes, *brca2^{2M_00075660}* juveniles and adults showed renal pathologies associated with glomerular defects. Taken together, these data suggest for the first time that *brca2/fancd1* is essential for kidney development and homeostasis.

Conclusions: These findings impart novel insights into genetic components that impact kidney biology, and as *Brca2/Fancd1* mutations cause Fanconi anemia and several common cancers, specifically breast and ovarian cancer in humans, this work has identified a new model to understand the role of *Brca2/Fancd1* in disease.

Funding: NIDDK Support

FR-PO194

Development of the Vasculature in the Bladder Julia K. Schaffer,¹ Kenneth A. Walker,² Caitlin M. Schaefer,² Daniel S. Bushnell,² Elina Mukherjee,² Sunder Sims-Lucas,² Carlton M. Bates.² ¹*Div of Newborn Medicine, Univ of Pittsburgh;* ²*Div of Nephrology, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Developing bladder consists of differentiating outer muscle, middle stromal, and inner epithelial layers. To date, formation of the bladder vascular network has not been determined. Aim: To determine vascular patterning through bladder development.

Methods: We examined developing bladder vasculature from embryonic day (E) 11.5 through postnatal day (P) 30 by general histology and immunohistochemistry (including morphometry with GSL1 lectin staining). We performed quantitative realtime PCR (qPCR) for genes associated with vascular formation (e.g. Angiopoietin 1 and Vegfa ligands and Tie2 and Vegfr2 receptors) and hypoxia inducible factors (Hifs).

Results: In early bladder development (E11.5-13.5) vascular branches from the umbilical arteries grow towards a network of developing vessels within the primitive bladder mesenchyme. However, by E15.5, connections between the umbilical arteries and the maturing vascular network in the bladder are diminished, suggesting major vascular remodeling. Perfusion (presence of red blood cells) of most bladder vessels was identified even at early developmental time points. Morphometric assessment revealed a peak in relative vascular tissue content in the bladder at E15.5, which regressed with further maturation. This reduction in vascular content after E15.5 suggests vascular pruning and further remodeling. qPCR revealed that *Angpt1* and *Vegfr2* expression peaked during early embryonic development, whereas expression of the *Angpt1* receptor, *Tie2*, peaked in early postnatal mice. The *Vegfr2* ligand *Vegfa* displayed consistent expression at all ages. Interestingly, *Hif1a* and *Hif2a* demonstrate inverse mRNA expression profiles with *Hif1a* highest in embryonic bladders and *Hif2a* expression peaking in adult bladders.

Conclusions: Unexpectedly, bladder vasculature appears to arise from angiogenic vessels that arise from the umbilical artery. Subsequently, early bladder vessels undergo pruning with age. Key molecules that regulate vascular development, including hypoxia inducible factors, have differential expression patterns.

Funding: Private Foundation Support

FR-PO195

Exploring the Relation Between Cells and Extracellular Matrix in the Developing Human Fetal Kidney Astgik Petrosyan,¹ Estefanie Rodriguez,¹ Ruby Kim,¹ Hasmik Soloyan,¹ Brendan Grubbs,² Matthew Edward Thornton,² Roger E. De Filippo,¹ Laura Perin,¹ Stefano Da Sacco.¹ ¹*Urology, Children's Hospital Los Angeles, Los Angeles, CA;* ²*Univ of Southern California.*

Background: It is widely accepted that, during development, the renal compartment undergoes dramatic changes in regards to cell specification and differentiation, matrix deposition and spatial organization. However, despite the growing number of studies focusing on kidney mouse development, very little is known of changes, including cell differentiation and extracellular matrix (ECM) deposition, occurring during human development. To fill this gap, we have characterized human embryonic kidneys (hEK) at different weeks of gestation to better understand renal progenitor biology and cell-matrix interactions.

Methods: Histological analysis were carried out on hEK between 11-22 weeks of gestation for ECM components (such as collagen IV a1-6 chains, collagen I, fibronectin) and progenitor/mature renal cells markers such as WT1, Pax-2, Six-2, Cited1, VE-Cadherin, a-SMA.

Results: We observed dynamic changes in the hEK throughout the progression of the gestational ages. In particular, decrease in nephrogenic zone size along with a higher presence of C- and S-shaped structures and fully developed glomeruli and tubules was confirmed in 19-22 week samples. Identification of progenitors or mature renal cells and fibrous proteins confirmed that ECM composition varies depending on the differentiation state of the surrounding cells. Collagen IV and fibronectin were absent in nephrogenic zone and condensing mesenchyme but found in C- and S-shaped bodies. In addition, *Pdgfra* (marker of cortical interstitial cells) was strongly expressed in the stromogenic zone and later restricted to the interstitium, co-localized with collagen I, suggesting a strong link between cell specification and matrix environment.

Conclusions: Our data suggest that, during hEK development, cell specification is accompanied by marked changes in ECM composition. This characterization might increase our knowledge of reparative processes enabling investigations focused on matrix remodeling and progenitor cell activation, thus ultimately enhancing the chances to treat renal damage.

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Underline represents presenting author.

FR-PO196

Enalapril Treatment Modulates Lymphangiogenesis and Fibrogenic Machinery in the Developing Rat Kidney Kee Hwan Yoo, Hyung Eun Yim, In Sun Bae, Byungkwan Kim, Young Sook Hong, Joo Won Lee. *Dept of Pediatrics, Korea Univ Medical Center, Seoul, Republic of Korea.*

Background: The renin angiotensin system plays a pivotal role in both renal development and progressive renal disease. Lymphangiogenesis occurs during normal organ development and pathological processes. In this study, we aimed to investigate the effect of angiotensin II inhibition on the expression of fibrogenesis-related molecules and lymphatic vessels in the developing rat kidney.

Methods: Newborn rat pups were treated with enalapril (30 mg/kg) or vehicle for 7 days after birth. We investigated the intrarenal expression of fibroblast growth factor (FGF)-1, FGF-2, FGF receptor (R)-1, fibroblast-specific protein (FSP)-1, intercellular adhesion molecule-1, toll-like receptor (TLR)-2, and TLR-4 with Western blotting and immunohistochemistry at postnatal day 8. For the determination of lymphatics, the lymphatic vessel markers of vascular endothelial growth factor (VEGF)-C, VEGFR-3, and podoplanin were assessed. For the detection of cell proliferation and collagen fibers, Ki-67 and Sirius red stainings were performed.

Results: In the enalapril-treated group, intrarenal FGF-1, FGF-2, FGFR-1 and VEGF-C protein expression were decreased, compared to the controls ($P < 0.05$). Immunohistochemistry for the lymphatic vessel markers of VEGF-C, VEGFR-3, and podoplanin showed reduced lymphatic immunostainings in the enalapril-treated kidneys. However, FSP-1 expression was prominent in the interstitium and glomeruli in enalapril-treated kidneys. While cell proliferation was reduced in the enalapril-treated group, collagen deposition was enhanced in the enalapril-treated kidneys ($P < 0.05$). Intercellular adhesion molecule-1, TLR-2, and TLR-4 protein expression showed no differences between the two groups.

Conclusions: Enalapril treatment during postnatal 7 days may induce perturbations in FGF/FGFR signals, cell proliferation, and lymphangiogenesis required for renal development and maturation and activate in part the fibrogenic machinery in the developing rat kidney.

FR-PO197

The Effect of Prenatal Hypoxia and a Postnatal High Salt Diet on Renal Structure in the Aged Mouse Sarah L. Walton,¹ Reetu R. Singh,² Joan Li,³ Helle Bielefeldt-Ohmann,⁴ Tamara Paravicini,¹ Melissa H. Little,³ Karen M. Moritz.¹ ¹School of Biomedical Sciences, Univ of Queensland, Brisbane, Queensland, Australia; ²Dept of Physiology, Monash Univ, Melbourne, Victoria, Australia; ³Inst for Molecular Bioscience, Univ of Queensland, Brisbane, Queensland, Australia; ⁴School of Veterinary Science, Univ of Queensland, Gatton, Queensland, Australia.

Background: Chronic fetal hypoxia leads to growth restriction and increased risk of adulthood disease. This study examined the long-term renal outcomes of offspring prenatally exposed to hypoxia, and whether a postnatal high salt diet could exacerbate impairments.

Methods: Pregnant CD1 mice were housed in a hypoxic chamber (12.0% O₂; N=8, HYP) or control (21% O₂; N=8, CON) environment from embryonic day (E) 14.5 to birth (E19.5). A subset of male offspring was randomly allocated to a control diet (0.2% NaCl; NS) or high-salt diet (5% NaCl; HS) from 10 weeks of age. Blood pressure was measured at 12 months of age and kidneys were collected. Kidney sections were examined for nephron number, glomerulosclerosis, interstitial fibrosis, renal vascular remodeling, and alpha-smooth muscle actin (α -SMA) expression by a researcher blinded to treatment groups.

Results: Prenatal hypoxia led to a decrease in nephron number and elevated blood pressure. Kidneys of HYP offspring showed expansion of the mesangial matrix, thickening of glomerular basement membranes and increased glomerulosclerosis compared to CON. These changes were exacerbated by the HS diet. Interstitial fibrosis and renal vascular remodeling scores were increased in CON and HYP offspring fed the HS diet, with the effect greatest in HYP offspring. α -SMA staining of CON kidneys was confined to vascular smooth muscle cells; however, aberrant glomerular and interstitial α -SMA staining was observed in CON offspring fed the HS diet and HYP offspring fed NS and HS diets.

Conclusions: Prenatal hypoxia led to reduced nephron number and pathological renal abnormalities, likely contributing to elevated blood pressure. The combination of prenatal hypoxia and a postnatal high salt diet significantly exacerbated renal abnormalities and signs of injury.

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FR-PO198

Folic Acid Alleviates Reduced Ureteric Branching and Nephrogenesis Induced by Maternal Undernutrition in Rat Embryonic Kidney Midori Awazu, Mariko Hida. *Dept of Pediatrics, Keio Univ School of Medicine, Tokyo, Japan.*

Background: We reported that maternal undernutrition reduces nephron number, ureteric branching, and global DNA methylation. Also, blockade of DNA methyltransferase 1, which maintains DNA methylation, inhibited ureteric branching in organ culture. Since the supplementation of folic acid (FA), a methyl-group donor, ameliorates hypertension due to maternal low protein diet, we examined whether FA rescues the kidney developmental defects induced by maternal undernutrition.

Methods: The kidneys of embryonic day 14 and 18 (E14 and E18) fetuses from dams given food ad libitum (CON), those subjected to 50% food restriction throughout pregnancy

(NR), and NR supplemented with FA 5 mg/kg (NRFA) were examined (n=3-7 litters). Ureteric buds were visualized by pancytokeratin staining. DNA methylation was assessed by methylated DNA quantification kit. E13 metanephroi from normal rats were subjected to organ culture in DMEM with or without FA 8 μ g/ml for 3 days.

Results: Maternal undernutrition significantly reduced fetal body weight (0.143 \pm 0.004 vs 0.173 \pm 0.003 g), kidney surface area (2.4 \pm 0.3 vs 3.8 \pm 0.5), and ureteric tip number (4.0 \pm 0.4 vs 8.5 \pm 0.8) at E14. FA supplementation did not affect body weight (0.147 \pm 0.003 g) or kidney surface area (2.2 \pm 0.4), but restored ureteric tip number (7.0 \pm 0.7, $P < 0.05$ vs NR). At E18, FA supplementation again did not affect body weight (1.28 \pm 0.02 vs NR: 1.24 \pm 0.05 g) or kidney weight (6.1 \pm 0.8 vs NR: 5.5 \pm 0.4 mg). FA, however, partially restored the glomerular density (15.6 \pm 2.7/mm², $P < 0.05$ vs NR) that was significantly lower in NR (10.3 \pm 0.9) than CON (20.2 \pm 3.7). DNA methylation of NR was significantly reduced in NR (8.7 \pm 1.1%) vs CON (29.8 \pm 5.6%) at E18. IN NRFA, DNA methylation was partially restored to 20%. In the metanephroi cultured under FA deficiency, the ureteric tip number was significantly reduced (6.6 \pm 0.3, n=10) vs controls (9.9 \pm 0.9, n=7). The kidney surface area was also significantly reduced by FA deficiency (3.0 \pm 0.2 vs 3.8 \pm 0.2).

Conclusions: FA is needed for the metanephric development, and its supplementation alleviates the reduced ureteric branching and nephrogenesis in the offspring of nutrient restricted rats probably by restoring DNA methylation.

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FR-PO199

A Perinatal Switch in Iron Utilization Determines Postnatal Chronic Kidney Disease Rongjia Deng,¹ Rosemary V. Sampogna,¹ Andong Qiu,^{1,2} Jonathan M. Barasch.¹ ¹Columbia Univ; ²Tongji Univ, China.

Background: Iron deficiency affects 2 billion people world-wide and is a threat to embryonic and early postnatal development. Periconceptual maternal iron deficiency (PM-ID) results in hypoplastic postnatal kidneys but it is not clear whether PM-ID causes cell-lineage or cell-stage specific hypoplasia, nor which species of iron is involved.

Methods: We investigated a mouse model of dietary iron deficiency and a series of deletions of the transferrin receptor, TfR1 (cell autonomous transferrin iron deficiency, ATF-ID) in different cellular lineages using a novel TfR1-floxed construct.

Results: Severe PM-ID depleted both Tf iron and NTBI (non-transferrin bound iron) resulting in severely hypoplastic proximal tubules and even anephria during gestation, whereas the overall structure of ureteric bud was maintained. Milder PM-ID resulted in surviving but severe postnatal kidney hypoplasia, disruption of the growth of the proximal tubule and TALH and increased mortality before weaning. To determine the mechanism of hypoplasia we examined mesenchymal, ureteric and stromal ATF-ID with different Cre drivers. Mesenchymal ATF-ID (Six2Cre or KspCre) demonstrated increasing demand for transferrin by the time of birth, resulting in worsening proximal tubule hypoplasia, remarkable cystic transformation and interstitial fibrosis, and even anephria (ProPax3Cre) after birth, the timing of which coincided with accelerated segment-specific growth. The combination of ATF-ID and PM-ID further worsened nephron development. In contrast, the collecting ducts (HoxB7Cre) and stroma (Foxd1Cre) did not depend on transferrin.

Conclusions: In sum, NTBI supported prenatal and postnatal stromal and ureteric development and the initial stages of metanephric development, whereas Tf iron was required for perinatal maturation of the nephron. Tf-iron depletion resulted in hypoplasia, cysts, and fibrosis, the timing and specificity of which was the result of a sequence of utilization of NTBI followed by Tf-iron. We propose that a peri-natal switch in the mechanisms of iron utilization accompanies the compartmentalization of the kidney and reflects changing cellular control of iron delivery. Iron deficiency is a cause of CKD.

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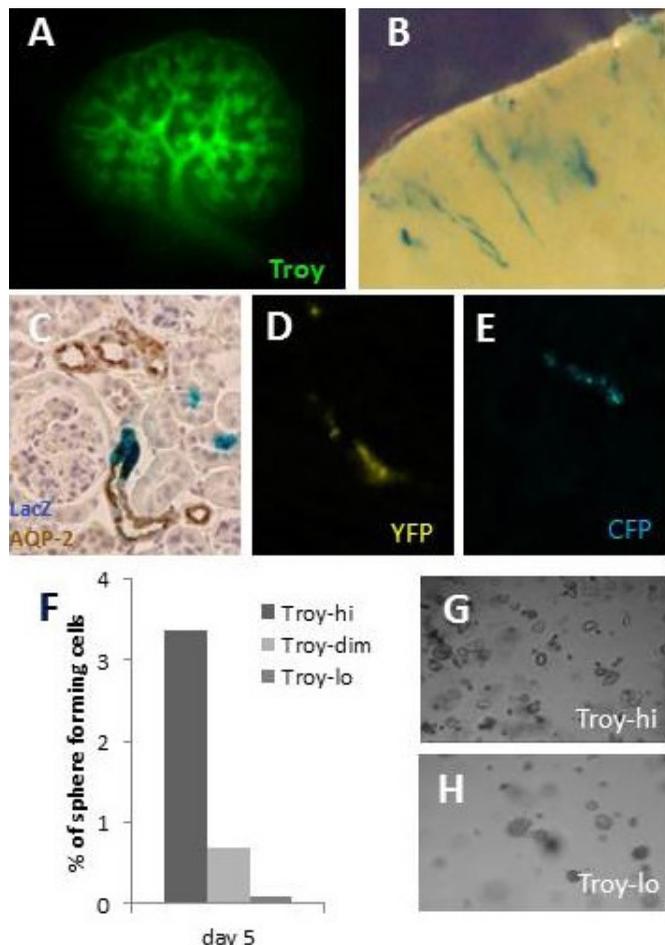
FR-PO200

Troy/TNFRSF19 Marks a Progenitor/Stem Cell Population in the Kidney Frans Schutgens,^{1,2} Maarten B. Rookmaaker,¹ Robert Vries,² Marianne C. Verhaar,¹ Hans Clevers.² ¹Nephrology and Hypertension, UMC Utrecht, Utrecht, Netherlands; ²Hubrecht Inst, Utrecht, Netherlands.

Background: Segment committed stem cells play a crucial role in renal development and regeneration. Identification of these stem cells is an important step towards the development of new diagnostic and therapeutic strategies for renal diseases. In this study, we evaluated Troy, an adult stem cell marker in other organs, as a marker for segment committed stem cells in the developing and adult kidney.

Methods: Renal Troy expression was assessed during embryonic development and adult turnover using Troy-GFP mice. The contribution of Troy⁺ cells to renal development and turnover was investigated using *in vivo* lineage tracing in Troy-GFP-CreERT2;Rosa-LacZ mice and the clonality of this contribution in Troy-GFP-CreERT2;Rosa-4color mice. Tracing was induced during or after cessation of nephrogenesis (p1 or p35) by tamoxifen injection. Daughter cells were identified using immunohistochemistry for tubular segment-specific markers. In addition, *in vitro* stem cell capacity was assessed by a sphere-forming assay.

Results: During embryonic development Troy⁺ cells were present in the ureteric bud [1A], whereas in adult kidney Troy⁺ cells were present in the papilla. After p1 induction, Troy⁺ cells gave rise to tubular structures by clonal expansion that persisted up to 2 years after induction [1B-1E]. Immunohistochemistry revealed predominant co-staining with collecting duct marker AQP2 [1C]. Troy⁺ cells continued to contribute to collecting duct formation after cessation of nephrogenesis. Finally, Troy^{hi} cells had a higher *in vitro* sphere forming capacity than Troy^{dim} and Troy^{lo} cells [1F-1H].



Conclusions: These data show that Troy marks a stem/progenitor population for the collecting duct in the developing kidney. Moreover, our data also suggest a role for Troy+ progenitor cells in the adult kidney.

FR-PO201

Preserved Nephrogenesis following Partial Nephrectomy in Early Neonates Yuhei Kirita,¹ Daisuke Kami,² Ryo Ishida,¹ Tetsuro Kusaba,¹ Takaomi Adachi,¹ Satoshi Gojo,² ¹Nephrology, Graduate School of Medical Science, Kyoto Prefectural Univ of Medicine, Kyoto, Japan; ²Regenerative Medicine, Graduate School of Medical Science, Kyoto Prefectural Univ of Medicine, Kyoto, Japan.

Background: For a long time, although the appendage regeneration has been limited to non-mammalian vertebrates, the rodent neonates demonstrated the capability to regenerate the resected cardiac apex. In this study, we hypothesized that neonatal kidney could maintain the capability of nephrogenesis.

Methods: One sixth-partial resection at the inferior pole of right kidney was performed on neonatal rats at postnatal day 1 (P1) and day 4 (P4) under the hypothermic anesthesia. The animals were sacrificed with time to examine by pathology and quantitative PCR, including key transcription factors, cytokines, and signaling molecules related to nephrogenesis, whether the resected portions were regenerated, or not.

Results: The pathological findings in nephrectomized kidney on P1 (P1X-kidney) seemed to bulge the newly formed cortex from the edge of the wound with the minimum inflammations, on the contrary, the inflammations was prominent in nephrectomized kidney on P4 (P4X-kidney). Immunohistochemistry in P1X-kidney demonstrated the preservation of the nephron number and the cortex area 28 days post-resection. On the other hand, P4X-kidney showed that those significantly decreased. Numerous apoptosis and sparse cell proliferation were significantly recognized in P4X-kidney, and P1X-kidney expressed the opposite findings. An array of quantitative PCR postulated the implication of Six2 expression to those differences between P1 and P4 kidney following the partial nephrectomy. The Six2 expression was reinforced in P1X-kidney more than age matched control kidney, whereas it had already gone in P4X-kidney.

Conclusions: Our results indicate that rat kidney maintains the capability to generate new nephrons in early neonates. Neonatal period could offer the unique model to study the regenerative or reparative phenomena.

FR-PO202

BrdU Labeling Adult Renal Stem Cells in Development Kidney Li Ni, Jing Chen. *Nephrology, Huashan Hospital, Shanghai Medical College, Fudan Univ, Shanghai, China.*

Background: The labeling-retaining cell (LRC) approach is a reliable way to identify adult stem cells. To identify the best labeling time for adult renal stem cells, we administered BrdU in different periods of the kidney development.

Methods: A pulse of BrdU was administered at different periods during E11.5-20.5, respectively, covering the whole process of the kidney development. The adult kidney were examined the distribution of BrdU-positive cells. A subtotal nephrectomy (Nx) was induced in adult mice to observe the response of BrdU-retaining cells to injury.

Results: In adult kidneys, the distribution of BrdU-retaining cells was heterogeneous with different BrdU-labeling time. With BrdU labeled at E11.5-13.5, lots of BrdU-positive cells were located in the papilla and inner medulla, only few scattered in the proximal tubules. With BrdU labeled at P0.5-2.5, lots of cells in the inner medulla and outer medulla could retain the immunoreactivity of BrdU. With BrdU labeled at P3.5-5.5, P6.5-8.5, or P9.5-11.5, the distribution of BrdU-positive cells was mainly in the outer medulla, few in the cortex inner medulla, no longer in the papilla. With BrdU labeled at P12.5-14.5 and P15.5-17.5, lots of BrdU-positive cells were in the outer medulla, but no longer in the papilla or inner medulla. With BrdU labeled at P18.5-21.5, BrdU-positive cells were only found in the cortex. The proximal tubules were the only nephron segments stably containing few BrdU-retaining cells after a chase period of six months. After Nx in adult mice, BrdU-positive cells were more significantly increased in the cortex near the incision edge. BrdU-positive cells mainly distributed in the proximal tubules at the site of injury. Some BrdU-positive cells did not express PCNA, even though numerous PCNA-positive cells were found near the incision edge of kidney. In contrast, originally retained abundant BrdU-positive cells in the outer medulla and inner medulla significantly reduced and disappeared rapidly in the vicinity of incision.

Conclusions: The locations of LRCs were different if BrdU was administered in different periods of kidney development. Most of BrdU-retaining cells were quiescent, few of them in the proximal tubule and papilla may be the renal progenitor cells.

FR-PO203

Tissue-Specific Transport and Injury Response in Kidney Tubules Derived from Human Pluripotent Stem Cells Benjamin S. Freedman,^{1,2,3} Craig R. Brooks,^{1,2} Albert Q. Lam,^{1,2} Ryuji Morizane,^{1,2} Joseph V. Bonventre,^{1,2} ¹Brigham and Women's Hospital; ²Harvard Medical School; ³Univ of Washington School of Medicine.

Background: Human pluripotent stem cells (hPSCs) can differentiate into cells expressing markers of kidney proximal tubules, but the functional capacity of these structures remains poorly understood. We developed a new, adherent, 3D culture system to evaluate transport and injury characteristics in hPSC-derived kidney tubules, compared to undifferentiated hPSCs.

Methods: hPSCs sandwiched in extracellular matrix were maintained in pluripotency-sustaining media to form undifferentiated cavitated spheroids (SOX2⁺OCT4⁺), or differentiated with growth factors into nephron progenitor cells (PAX2⁺SIX2⁺) and subsequently proximal tubules (LTL⁺LRP2⁺). hPSC spheroids or differentiated tubules were incubated with small molecule fluorescent probes to monitor transport into lumens, or with nephrotoxic chemicals to assess upregulation of kidney injury molecule-1 (KIM-1).

Results: Kidney tubule lumens selectively accumulated rhodamine-dextran (RD) and fluorescein methotrexate (MTX) transport cargoes. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA, significantly reduced cargo accumulation. When treated with the nephrotoxic compounds gentamicin or cisplatin, ~70% of hPSC-derived proximal tubules expressed KIM-1 at the apical/luminal surface. In contrast, the lumens of undifferentiated hPSC spheroids did not accumulate RD and MTX, nor express KIM-1 after toxic injury with cisplatin or gentamicin.

Conclusions: hPSC-derived kidney tubules are capable of transport and injury responses, which are characteristic of kidney proximal tubules and distinct from undifferentiated hPSC epithelia. The accessibility of this system to small molecules and live-cell microscopy enables rapid and real-time visualization of transport processes and testing of molecular pathways. KIM-1 expression in hPSC-derived kidney tubules may provide a quantifiable standard with which to predict human nephrotoxicity. Our findings introduce a framework in which to evaluate the functionality of hPSC-derived kidney epithelia, prior to transplantation into ESRD patients.

Funding: NIDDK Support, Private Foundation Support

FR-PO204

Progress in the Development of Human iPSC Derived Proximal Tubule-Like Cells for Drug Toxicity Screening Anja Wilmes, Georg Kern, Caroline Rauch, Gerhard Gstraunthaler, Paul Jennings. *Dept of Physiology, Medical Univ of Innsbruck, Innsbruck, Tirol, Austria.*

Background: Nephrotoxin exposure can initiate acute kidney disease and accelerate the progression of chronic kidney disease. The proximal tubule is a frequent target as it transports a wide variety of chemical entities, some of which can cause tubular injury. Primary cell culture and cell lines have been used successfully to investigate molecular mechanisms of chemical toxicity. However, there are several disadvantages of traditional cell culture, including limited tissue availability, phenotypic alterations due to immortalisation and a lack of genetic diversity. With the dawn of induced pluripotent stem cell (iPSC) technology,

many of these disadvantages could potentially be overcome. To this end we have been attempting to develop a protocol to produce proximal tubule-like cells from human iPSCs with xenobiotic transport capabilities.

Methods: Human iPSCs were differentiated into the intermediate mesoderm (IM) using Wnt and retinoic acid activation (CHIR99021 and TTNBP). Cells were further differentiated using combinations of different growth factors.

Results: The derived cells exhibit cobble stone morphology and express certain proximal tubule proteins such as claudin-2. Additionally, the cells can be maintained for up to 4 weeks in culture. Preliminary results demonstrate the ability of the differentiated cells to take up organic cations (4-Di-10-ASP) and organic anions (6-CF) and to extrude p-glycoprotein substrates (calcein-AM).

Conclusions: While further characterization will be needed, the initial results are promising, indicating that proximal tubule-like cells derived from iPSCs could be a new tool for screening the nephrotoxic potential of compounds.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO205

The Direct Differentiation Method of Renal Tubular Cells by Synthetic mRNAs of Transcription Factors Identified from TF-Inducible Human ES Bank Ken Hiratsuka,¹ Toshiaki Monkawa,¹ Shintaro Yamaguchi,¹ Ryuji Morizane,¹ Shigeru B.h. Ko,² Minoru S.h. Ko,² Hiroshi Itoh.¹ ¹Dept of Internal Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan; ²Dept of System Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.

Background: To find transcription factors which promote differentiation towards renal tubular cells, we utilize the human ES lines with doxycycline-controllable transcription factors (TF-inducible hES bank). To establish the differentiation method of renal tubular cells, we transfect the synthetic human mRNA of the target transcriptional factors into human ES cells.

Methods: We performed exhaustive search for DNA microarray data after TF induction in the hES bank, and analyzed them in silico to find the specific transcription factors, which expressed in kidney epithelial cells. We synthesized the synthetic human mRNA of the target transcription factors. By using the lipofection method, we transfected the synthetic mRNA of target transcription factors to human ES cells, and cultured them. The morphological changes, mRNA expressions, and protein expressions were analyzed.

Results: Some candidate transcription factors, which expressed in human kidney epithelial cells, were identified by in silico analysis. We successfully made synthetic mRNA of candidates of transcription factors. Five days after the transfection of the synthetic mRNA to human ES cells, we were able to observe characteristic morphological changes in the differentiated cells. The mRNA expression of OSR1, ITGA8, AQP1, and MEGALIN were increased. Moreover, the protein expression of AQP1 and LTL were also detected in the differentiated cells.

Conclusions: We identified specific transcription factors for differentiation toward kidney (especially, proximal tubular cells), and demonstrated that the differentiation of proximal tubular cell phenotype from human ES cells by a novel method using synthetic mRNA.

FR-PO206

Differentiation of Human iPSC into Functional Podocytes Caroline Rauch,¹ Anja Wilmes,¹ Elisabeth Feifel,¹ Georg Kern,¹ Paul Jennings,¹ Gerhard Gstraunthaler.¹ ¹Innsbruck Medical Univ; ²Innsbruck Medical Univ; ³Innsbruck Medical Univ; ⁴Innsbruck Medical Univ.

Background: Podocyte injury and subsequent loss of glomerular integrity is a major cause for chronic kidney disease (CKD). Two-thirds of patients with CKD suffer from disorders that arise from the glomerulus, mainly due to podocyte injury. Podocytes are highly specialized cells with a complex cytoarchitecture composed of foot processes that form the glomerular filtration barrier. The study of the molecular processes of glomerular injury is hampered by the fact that cultured primary podocytes have a limited capacity to divide and are difficult to maintain. However, generation of pluripotent stem cells (induced PSCs) from somatic cells allows the possibility of a new source of human cells. The high differentiation capacity of iPSCs would potentially enable the establishment of differentiation protocols for iPSC-derived podocytes which can overcome the burden of primary podocytes in culture.

Methods: To this end we applied and optimized a previously published protocol for podocyte differentiation (Song et al., 2012; PMID: 23029522). Human iPSCs are grown in differentiation media for ten days, containing growth factors known to be important for *in vivo* podocyte differentiation, BMP-7, activin A, and retinoic acid. Conditionally immortalized human podocyte cultures served as controls.

Results: After three days in differentiation media, iPSCs showed a clear podocyte morphology with podocyte foot processes. To further prove the state of podocyte differentiation, expression of specific podocyte markers was examined via immunofluorescence. Marked expression of the podocyte specific markers podocin and synaptopodin could be successfully verified on differentiated iPSCs. In addition, iPSC-derived podocytes showed significant release of VEGF into the culture medium. Finally, doxorubicin, a podocyte specific toxin, was highly toxic to these cells with an IC50 of 1 μM after 48h.

Conclusions: Podocytes generated from iPSCs have far reaching applications in disease modelling, tissue engineering, drug screening and discovery, and toxicity testing.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO207

Sourcing of Renal Tubular Epithelial Cells from Human Stem Cell-Derived Kidney Organoids Elijah Weber,¹ Benjamin S. Freedman,² Jonathan Himmelfarb,³ Edward J. Kelly.¹ ¹Pharmaceutics, Univ of Washington, Seattle, WA; ²Nephrology, Univ of Washington, Seattle, WA; ³Kidney Research Inst, Univ of Washington, Seattle, WA.

Background: Human pluripotent stem cells (hPSCs) provide a self-renewing, reproducible source of kidney cells for laboratory investigation and regenerative medicine approaches. We tested the potential of hPSC-derived renal tubular epithelial cells (RTECs) to grow and maintain differentiation in 2D and 3D cultures, compared to primary RTECs from adult kidneys.

Methods: hPSCs were treated with growth factors to promote differentiation into nephron progenitor cells (PAX2⁺SIX2⁻) and subsequently proximal tubules (LTL⁺ZO1⁺LRP2⁻). RTECs purified from tubular organoids were re-plated on tissue culture plates with or without extracellular matrix. RTECs were analyzed for proliferation, kidney-specific marker expression, and their capacity to seed a 'kidney on a chip' 3D microphysiological system (MPS).

Results: RTECs purified from hPSC organoids grew to confluent monolayers in minimal RTEC growth media on extracellular matrix. hPSC-derived RTECs resembled primary RTECs morphologically. Marker immunofluorescence analysis revealed that purified hPSC-RTECs possessed ZO1⁺ tight junctions and reacted with LTL. Sub-cultivation was limited to 2-3 passages, after which hPSC-RTECs underwent epithelial-to-mesenchymal transition and senesced. In a 3D MPS, hPSC-derived RTECs formed tubular structures comparable to primary RTECs. Immunofluorescence staining demonstrated positive signals for the tubule transporters SGLT2 and OAT3 as well as the epithelial markers CD13 and E-cadherin.

Conclusions: We have shown that hPSC-RTECs can propagate *in vitro* and maintain their differentiated characteristics, with morphology and markers similar to primary RTECs. When hPSC-RTECs are grown in a 3D MPS, they maintain an epithelial phenotype and express membrane transporters essential for functions including glucose reabsorption and organic anion secretion. This system establishes a platform in which to optimize hPSC-RTEC expansion and function in a 3D, microfluidic context, with relevance for human disease modeling *in vitro* and bioengineering of regenerative therapeutics.

Funding: Other NIH Support - UH3TR000504, Other U.S. Government Support

FR-PO208

Genome-Wide Methylation Analysis of Epigenetic Memory in Human Kidney Derived iPSC Cells Osamu Takase, Taro Tsujimura, Masaomi Nangaku, Keiichi Hishikawa. Dept of Advanced Nephrology and Regenerative Medicine, The Univ of Tokyo, Tokyo, Japan.

Background: Epigenetic memory such as DNA methylation signature of iPSC cells derived from parental cells was reported to determine the differentiation fate of the iPSC cells (Nature 2012). Last year, we reported the result of kidney specific induction protocol (Nature Commun, 2013) by using two different kinds of human iPSC cells established from human fibroblast (F-iPSC) and human kidney epithelial cells (K-iPSC), and demonstrated more efficient induction of markers of kidney development (WT-1, Pax-1, Sall-1) and differentiation (AQP-1, Nephron) in K-iPSC as compared with F-iPSC cells.

Methods: In this study, we performed a genome-wide methylation analysis of K-iPSC and F-iPSC cells, and tried to clarify the mechanism of kidney lineage specific induction of human iPSC cells.

Results: Among 27,578 sites, we focused on high CpG promoter lesion (GC>0.55, CpG>0.75). 56 genes such as Kid1 and SOD2 were strongly methylated in F-iPSC than in K-iPSC. 17 genes such as KCN12 and GATA4 were strongly methylated in R-iPSC than in F-iPSC. The markers of kidney development were strongly methylated in F-iPSC than in K-iPSC cells (Pax-2; 23.6 vs 2.1, Sall-1; 28.7 vs 4.3). However, the marker of differentiation was strongly methylated in K-iPSC (AQP-1; 1.7 vs 1.1).

Conclusions: These results demonstrate that epigenetic memory in parental cell determine the induction of human iPSC cells toward kidney lineages, and the role of key genes in kidney lineage specific induction will be discussed.

Funding: Government Support - Non-U.S.

FR-PO209

Mechanism of Kidney Repair in the Omentum-Kidney Model – Tubulogenesis and Differentiation of Free-Lying WT-1 Cells to Podocytes Occurring in the Fusion Zone Ignacio Garcia-Gomez,^{1,3} Krishnamurthy P. Gudehithlu,² Peter D. Hart,^{1,2,4} Jose A.L. Arruda,^{1,3} Ashok K. Singh.^{1,2,3} ¹Hektoen Inst of Medicine, Chicago, IL; ²Div of Nephrology, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL; ³Section of Nephrology, Univ of Illinois at Chicago, Chicago, IL; ⁴Internal Medicine, Rush Univ Medical College, Chicago, IL.

Background: When activated omentum was fused to the injured kidney it induced glomerular repair and ameliorated chronic kidney disease (Garcia-Gomez et al JASN 2014). The fusion zone between the omentum and the injured kidney was highly proliferative (high BrdU uptake), with abundant free-lying nephron progenitor WT-1 cells. In this study, we examined the fusion area to further understand the mechanisms of repair in this model.

Methods: In 5/6 surgically nephrectomized rats polydextran gel was introduced intraperitoneally to activate the omentum and fuse to the injured kidney. Nephrectomized rats with complete omentectomy were used as control. Kidney tissues were examined 1-3 weeks after injury by histology and immunofluorescence (Pax-2, WT-1 and podocalyxin).

E15 embryonic rat kidney served as control for immune-staining. Two-week fusion zone tissue and tissue far from fusion zone, control and normal was quantified for mRNA for selected developmental genes (WT-1, Wnt-4, Pod1, Lim1, HNF-6, BMP-7) by RT-PCR.

Results: We found that the fusion zone tissue showed proliferation and expansion of collecting ducts, as evidenced by intense staining for Pax2, in a pattern similar to that seen in E15 embryonic rat kidney. Further, several islands of WT-1 cells in the fusion zone differentiated to podocytes, as judged by co-expression of podocalyxin. mRNA for Wnt-4 and WT-1 increased by 10-20 folds and mRNAs for other developmental genes increased by 2-5 folds in the fusion zone. Control tissue did not show the above changes.

Conclusions: The fusion zone tissue between the injured kidney and omentum appears to be a highly active tissue with proliferation and differentiation of kidney progenitor cells (WT-1, Pax-2, podocalyxin) taking place, and thus providing a healing environment to the injured kidney.

Funding: Private Foundation Support

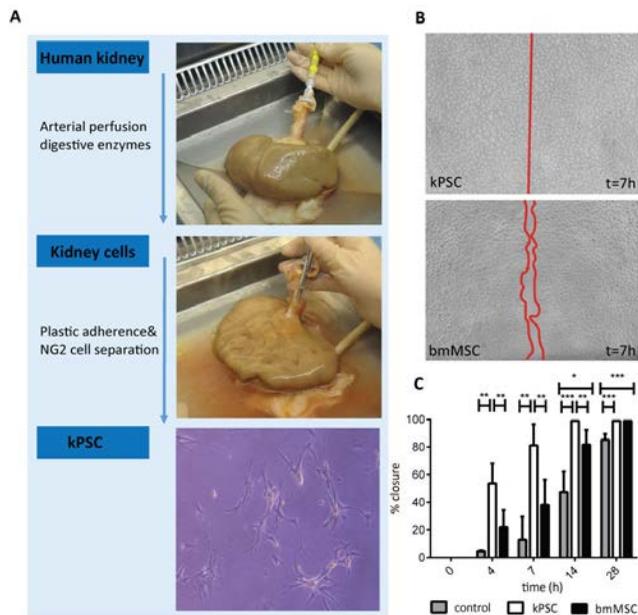
FR-PO210

Transcriptional and Functional Characterization of Clinical Grade Isolated Human Kidney Derived Perivascular Stromal Cells Danielle Leuning, Marlies Reinders, Ellen Lievers, Cees van Kooten, Marten A. Engelse, Ton J. Rabelink. *Nephrology, LUMC, Netherlands.*

Background: Mesenchymal stromal cells (MSCs) are immunomodulatory cells and have shown beneficial effects in kidney disease. It has previously been shown that human perivascular stromal cells (PSCs) from several different organs share characteristics of bone marrow derived MSCs (bmMSC), however, at the same time there are tissue specific properties. We hypothesized that human kidney derived PSCs (hkPSCs) are, due to tissue specific imprinting, more potent in kidney repair compared to bmMSCs and sought to find a novel clinical grade isolation method.

Methods: Human transplantation grade kidneys (n=3) were digested with continuously circulating proteolytic enzymes. The resulting crude cell suspension was cultured in α MEM 5% platelet lysates and cells were selected for plastic attachment and NG2 cell enrichment (fig A). Culture was continued until spindle shaped cells appeared (kPSCs) and were compared to bmMSCs between passages 5-10.

Results: hkPSCs have comparable marker expression, cytokine excretion patterns, vascular stabilization and immunosuppressive capacity compared to bmMSCs. hkPSCs showed a distinct gene expression profile including an increased expression of HoxD11, a homeobox factor important in nephrogenesis. In a wound scratch assay, kidney epithelial wound healing with conditioned medium of hkPSCs was significantly faster and after 7 hours approx. 80% closure was seen with hkPSC conditioned medium, which was only 40% with bmMSC supernatant ($p < 0.01$) (fig B, C).



Conclusions: Here we show a novel, clinical grade isolation method of hkPSCs and compared these cells to bmMSCs. hkPSCs showed a distinct expression profile and are able to enhance kidney tubular epithelial wound healing to a greater extent than bmMSCs. Therefore hkPSCs are a promising new cell therapeutic candidate to explore for treatment of kidney disease.

Funding: Government Support - Non-U.S.

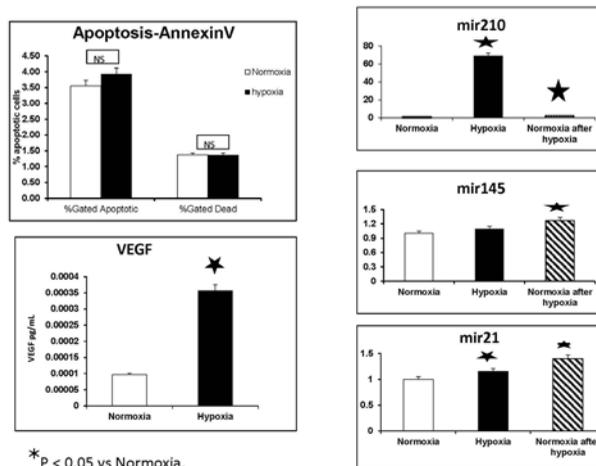
FR-PO211

Functional Alterations of Adipose-Derived Mesenchymal Stem Cells from Human with Atherosclerotic Renovascular Disease Under Hypoxic Conditions Ahmed Saad, Allan B. Dietz, Sandra Herrmann, Alfonso Eirin, Abdelrahman Abdallah Abohashem Aly, Hui Tang, Soon Hyo Kwon, Kyra L. Jordan, John R. Woollard, Joseph P. Grande, Lilach O. Lerman, Stephen C. Textor. *Mayo Clinic.*

Background: Atherosclerotic renal vascular disease (ARVD) induces microvascular loss and interstitial inflammation, ultimately leading to ischemic injury. Mesenchymal stem cells (MSCs) can induce angiogenesis, decrease inflammation, and limit apoptosis in experimental animals. Aging and co-morbid conditions may blunt these properties in older human subjects. This study tested the hypothesis that hypoxic preconditioning of adipose tissue-derived MSCs would modify expression of MicroRNAs (miR) associated with MSCs survival, angiogenic, and anti-inflammatory properties.

Methods: MSCs obtained from subcutaneous tissue of 7 patients with ARVD (Age 75.3±4) were cultured under normoxic or hypoxic conditions (1% O₂) for 4 days. Hypoxic MSCs were returned to normoxia thereafter. Levels of the pro-survival and pro-angiogenic factors vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) were measured in the supernatant by ELISA. Expression of MiRs- 210, 21 and 145 in MSCs was measured by quantitative rt-PCR and apoptosis by flow cytometry for Annexin V.

Results: Hypoxic conditions increased VEGF and IGF ($p < 0.05$) in MSC supernatant, but had no effect on apoptosis.



MiR-210 rose more than 68 fold in hypoxic MSCs over control conditions ($p < 0.0001$), and reversed when returned to normoxia. Levels of miR-21 and 145 rose in hypoxic MSCs ($p < 0.05$) and remained so after restoring normoxic conditions.

Conclusions: Hypoxia augmented angiogenic cytokine secretion and both reversible (miR-210) and irreversible (miR-21 and miR-145) micro-RNA expression in MSC from older human subjects with ARVD. These data support a potential role for hypoxic preconditioning to enhance the angiogenic potency of MSCs in humans with ARVD.

Funding: NIDDK Support

FR-PO212

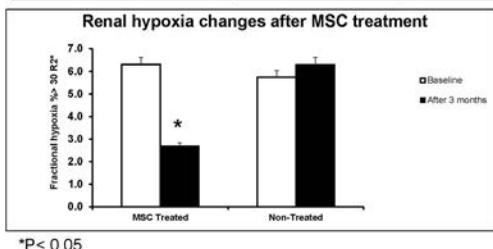
Safety of Intra-Arterial Autologous Adipose-Derived Mesenchymal Stem Cells in Human Atherosclerotic Renovascular Disease Ahmed Saad, Sandra Herrmann, Michael A. Mckusick, Sanjay Misra, James Glockner, Alfonso Eirin, Joseph P. Grande, Allan B. Dietz, Lilach O. Lerman, Stephen C. Textor. *Mayo Clinic.*

Background: Atherosclerotic Renovascular disease (ARVD) reduces blood flow (RBF) and GFR, and amplifies kidney hypoxia and inflammation. Adipose-derived mesenchymal stem cells (aMSCs) improve renal function in swine ARVD, in part by improving cortical micro-vascularization, but their safety and efficacy in humans are unknown. We report initial results from a pilot study of unilateral intra-arterial administration of low dose of autologous aMSCs in human subjects with ARVD under an FDA-approved IND.

Methods: Seven patients (Age 75.3±4) with severe ARVD were studied during fixed Na⁺ diet and ACE/ARB Rx before and 3 months after unilateral arterial injection of 2x10⁵ autologous aMSCs/kg. Stenotic-kidney (SK) cortical and medullary perfusion, volume and RBF were measured using multidetector CT and GFR by iohalamate clearance. SK deoxyhemoglobin levels (R2*) and fractional hypoxia were measured by 3T BOLD-MRI. Renal vein levels of neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor (TNF- α) were also measured.

Results: All patients tolerated aMSC without adverse effects. SK cortical volume and whole kidney RBF increased after three months (Figure 1), as did measures of tissue oxygenation, whereas no changes observed in the contralateral untreated kidneys (CLK) (data not shown). SK GFR did not change, nor did renal vein levels of TNF- α , MCP-1, or NGAL.

SK N=7	Baseline	After 3 months	P-value
Cortical Kidney volume (CT) mL	49.9 ± 22.4	54.7 ± 25.4	0.03
RBF(ml/min)	115.1 ± 74.4	135.2 ± 96.5	0.05
TNF-α (pg/mL)	8.5 ± 2.1	10.3 ± 2.8	0.2
MCP-1 (pg/mL)	577.5 ± 169.7	573.3 ± 103.04	0.5
NGAL (ng/mL)	226.4 ± 32.9	247.3 ± 28.1	0.18
Cortical R2* (1/Sec)	18.7 ± 2.1	16.9 ± 2.5	0.01
Kidney hypoxia (% R2* > 20/sec)	41.8 ± 18.02	35.8 ± 15.3	0.05
GFR(ml/min/1.73m ²)	14.6 ± 8.1	14 ± 7.2	0.2



Conclusions: Intra-arterial autologous aMSCs were tolerated with no adverse effects. This low dose, delivered without renal revascularization, was associated with increased tissue oxygenation and cortical RBF, consistent with improved renal microcirculation. Our results provide first-in-humans evidence to support a role for aMSC to restore local blood flow and oxygenation in ARVD.

Funding: NIDDK Support

FR-PO213

Cell Therapy with Serelaxin Promotes Angiogenesis and Anastomosis which Is Critical for the Preservation of Vascular Integrity After Kidney Injury Brooke M. Huuskens,¹ Alexander Ruvantha Pinto,² Chrishan S. Samuel,³ Sharon D. Ricardo.¹ ¹Dept of Anatomy and Developmental Biology, Monash Univ, Clayton, Victoria, Australia; ²Australian Regenerative Medicine Inst, Monash Univ, Clayton, Victoria, Australia; ³Dept of Pharmacology, Monash Univ, Clayton, Victoria, Australia.

Background: We previously reported that the combination of mesenchymal stem cells (MSCs) and serelaxin (Rln) attenuates ureteral obstruction (UUO)-induced fibrosis. However the affect on endothelial cell regeneration is yet to be elucidated. Here we tested the hypothesis that a mechanism of repair after fibrosis is induced via endothelial anastomosis and sprouting in the presence of MSCs and Rln.

Methods: Live cell imaging of human bladder endothelial cells (HBECs) and human umbilical vein endothelial cells (HUVECs) in tube forming assays were conducted with MSC-conditioned media and Rln (1-100mg/mL) to observe their affects on anastomosis. Spheroid assays determined the effects of MSC and Rln on HBECs and HUVECs sprouting *in vivo*. Proliferation of HBECs and HUVECs in the presence of MSCs and Rln was investigated. A qPCR for angiogenic genes was performed on MSCs cultured with or without Rln (100ng/mL). Endothelial integrity was visualized using CD31 protein localization in kidneys from mice 3, 5 and 7days post-UUO, with or without MSCs Rln (n=4-6/group).

Results: Anastomosis of HBECs was modulated in the presence of MSC-conditioned media and Rln with tube number and branch length increased compared to control. HUVECs readily formed sprouts in culture, which was enhanced when both Rln and MSCs were present. The migration capacity of MSCs towards injured HBECs was significantly increased when Rln was added. Rln induced the expression of angiogenic genes from the MSCs. Immunofluorescent microscopy of CD31 determined a decrease of endothelial integrity in a time-dependent manner *in vivo*. However the administration of MSCs and Rln preserved the vasculature.

Conclusions: These results suggest that both anastomosis and sprouting is enhanced only when both MSCs and Rln are used in combination. This may be in part due to Rln-induced release of angiogenic factors from MSCs which may aid in revascularization of the fibrotic kidney.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO214

Effects of Adipose Derived Stem Cells in a Model of Chronic Renal Hypoxia Crysthiane Saveriano Rubiao, Jose Tarcisio Giffoni, Rosemara Silva Ribeiro, Milene Subtil Ormanji, Vanessa A. Varela, Mirian A. Boim. *Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: Chronic renal artery stenosis causing chronic hypoxia may lead to irreversible damage of the kidney with progressive deterioration of renal function. Due to reduced regenerative abilities of the kidney, mesenchymal stem cells (MSC) emerge as an alternative therapy. The aim of this study was to investigate the effects of MSC, isolated from adipose tissue (ASC) on renal fibrogenesis induced by chronic renal artery stenosis.

Methods: Left renal artery of male Wistar rats was partially occluded and ASC were injected through caudal vein. ASC were characterized by their immunophenotype/multipotentiality. To analyze the migration and retention time, labeled ASC were injected 6 weeks after renal occlusion (RO) and analyzed 24, 48, 72 hours or 15 days after injection by

flow cytometry. Caudal systolic blood pressure (SBP) was weekly estimated. Renal function and the mRNA expression levels of collagen 1 (Col I), Fibronectin (FN) and TGF-β were determined by qPCR, 6 weeks after renal artery occlusion in the following groups: Sham; Stenotic control (StC, receiving PBS i.v.); Stenotic + ASC (S+ASC). ASC were injected 3 and 5 weeks after RO i.v.

Results: After 48 hours cells were retained in both kidneys, stenotic and contralateral followed by heart and lung. After 15 days the presence of ASC decreased significantly in the lungs and heart but they were still present in the kidneys. StC animals showed progressive increase in SBP while the S+ASC rats had a stabilization of SBP with no further increases after 5 weeks. Plasma creatinine was similar among groups however, StC animals developed proteinuria which was reduced by ASC treatment. There was an increase in the expression of Coll, FN and TGFβ in the stenotic kidney (cortex and medulla) which was reversed by ASC treatment.

Conclusions: In conclusion ASC prevented further increase in SBP and reduced the expression of molecules induced-fibrosis. ASC migration and retention in the clipped and contralateral kidneys can be potentially beneficial to restore damaged tissue and to preserve the function of the contralateral kidney.

Funding: Government Support - Non-U.S.

FR-PO215

Therapeutic Effects of Erythropoietin Producing Kidney Mesenchymal Stem Cell Derived Microparticles on Anemia in Chronic Kidney Disease Mice Hoon Young Choi, Mirae Lee, Yuri Kang, Ah Ran Choi, Sung-Kyu Ha, Hyeon Cheon Park. *Dept of Internal Medicine, Gangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Progression of chronic kidney disease (CKD) results in aggravation of erythropoietin (EPO)-dependent anemia. Microparticles (MPs) shed from kidney mesenchymal stem cells (KMSC) have been demonstrated to confer protective effects against acute kidney injury and kidney fibrosis via transfer of messenger RNA. Previous studies have demonstrated improvement of renal anemia by EPO transfected MSC. We investigated whether MPs derived from EPO producing KMSC can exert therapeutic effects on anemia in CKD mice.

Methods: Mouse model of CKD and renal anemia was induced by the electrocoagulation of right renal cortex and sequential left nephrectomy. Six weeks post-nephrectomy, CKD and anemia was confirmed via blood urea nitrogen (BUN) and hemoglobin measurements as well as renal histology. Stable human EPO-producing KMSC (EPO-KMSC) and their MPs isolated by differential ultracentrifugation were injected intraperitoneally into established CKD mice and followed for 2 weeks (EPO-KMSC: 1×10^6 per mice, MP: 2×10^7 per mice). BUN and hemoglobin were evaluated and degree of renal tubulointerstitial damage was examined for 2 weeks after CKD.

Results: EPO secretion from EPO-KMSC was confirmed to sustain over 4 weeks in vitro and RT PCR revealed the presence of EPO mRNA within MPs. Injected EPO KMSC-derived MPs were demonstrated within tubulointerstitial area. Animals that received EPO-KMSC and MPs demonstrated significantly lower BUN levels compared to CKD control mice (60 ± 2 , 62 ± 7 vs 83 ± 7 mg/dL, $P < 0.05$, respectively). Importantly, hemoglobin levels were significantly higher in CKD mice treated with EPO-KMSC and MPs compared to CKD control mice (11.7 ± 0.1 , 11.3 ± 0.5 vs 9.7 ± 0.5 g/dL, $P < 0.05$, respectively).

Conclusions: The use of EPO secreting MSC is a viable strategy for cell therapy in renal anemia. Our results suggest that EPO-KMSC derived MPs as well as EPO-KMSC can improve renal function and renal anemia in CKD mice.

FR-PO216

Transplantation of Human Embryonic Mesenchymal Stem Alleviates Lupus Nephritis in MRL/lpr Mice Yuan Li,¹ Yaping Fan,² Shi Hui,³ Chen Xiao Lan.⁴ ¹Affiliated Hospital of Nantong Univ, Nantong, China; ²Affiliated Hospital of Nantong Univ, Nantong, China; ³Affiliated Hospital of Nantong Univ, Nantong, China; ⁴Affiliated Hospital of Nantong Univ, Nantong, China; ⁵Affiliated Hospital of Nantong Univ, Nantong, China.

Background: Compared with bone marrow derived MSC, embryo-derived MSC have greater expansion and differentiation potentials. T helper cell 17(Th17) and interleukin 17(IL-17) is closely related to the occurrence and development of Lupus. The glial cell-derived neurotrophic factor (GDNF) which is closely related to the kidney development is found to be a kidney protection factor and can increase the renal protective effects of stem cells as well. Persephin (PSP) is a member of the family of GDNF and also involves in the kidney development. We investigated the effects of human embryonic MSC (hMSC) in lupus nephritis in MRL/lpr mice.

Methods: The MRL/lpr mice were divided into 2 groups: Control, hMSC group. hMSC were injected at one dose of $1 \times 10^6/200\mu$ l twice (at the 16th, 19th weeks of age) through tail vein. Mice were sacrificed at 24th weeks of age.

Results: Multi-treatment of hMSC was able to increase the survival, decrease the levels of 24-h proteinuria, and anti-double-stranded DNA (dsDNA) antibody. hMSC treatment Alleviated the extent of renal injury such as crescent formation and Interstitial inflammatory cell infiltration in MRL/lpr mice. hMSC treatment also inhibited Th17 cell differentiation in spleen and decrease the serum level of IL-17. The level of GDNF and PSP was increased in renal of hMSC treatment MRL/lpr mice.

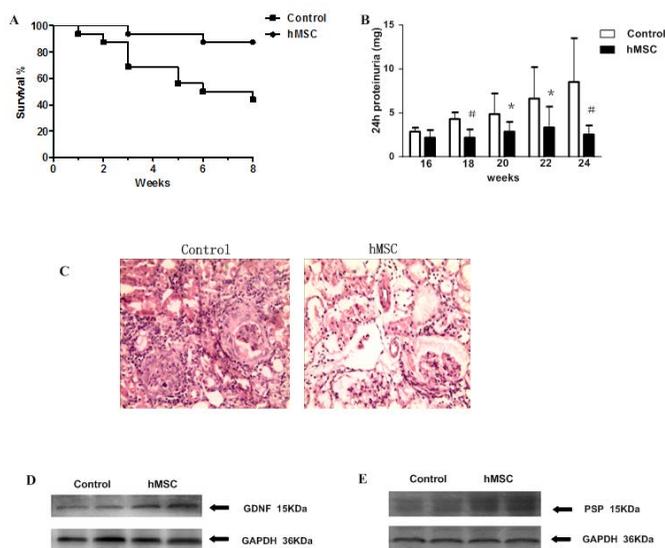


Figure 1. hMSC transplantation alleviates lupus nephritis in MRL/lpr mice. (A) hMSC treatment prolongs survival ($p < 0.01$ vs Control). (B) hMSC significantly reduced urine protein ($*p < 0.05$ vs Control). (C) Representative hematoxylin and eosin staining of renal sections from each group. Original magnification, $\times 400$. (D) Western blot analyses showed that hMSC treatment MRL/lpr mice has increased expression of GDNF and PSP ($*p < 0.05$ vs Control).

Conclusions: These findings indicated that hMSCs transplantation might be a potentially promising approach in the treatment of lupus nephritis, possibly by inhibiting Th17 cell differentiation and increasing GDNF and PSP level in renal.

Funding: Government Support - Non-U.S.

FR-PO217

Microarray Analysis of Gene Expression to Compare Low Serum Cultured Adipose Derived Stromal Cell with High Serum *Yutaka Kamimura, Naotake Tsuboi, Takayuki Katsuno, Shoichi Maruyama. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan.*

Background: We established human adipose tissue-derived stromal cells (hASCs) cultured in low (2%) serum (hLASCs), which demonstrated great therapeutic potential for inflammatory diseases. We have already reported that hLASCs significantly attenuated rat folic acid-induced acute kidney injury than did hASCs cultured in high (20%) serum (hHASCs). However, the mechanism for hLASCs to exert greater anti-inflammatory function than hHASCs was partly evaluated. In the current study, we compared gene expression profiles and functional difference between hLASCs and hHASCs.

Methods: Human abdominal subcutaneous adipose tissue was obtained from patients underwent liposuction. Cells were cultured under the two conditions; a low serum culture medium containing 2% fetal bovine serum (FBS) and a high serum culture medium containing 20% FBS. Total RNA was isolated from hLASCs and hHASCs. We performed cDNA microarray analysis in total RNA from hLASCs and hHASCs and confirmed microarray data by real-time PCR. Moreover, we performed in vitro functional analysis in some identified molecules.

Results: 312 genes were significantly (False Discovery Rate: FDR < 0.01) up-regulated (Fold Change > 5.0) and 211 genes were down-regulated in hLASCs. Microarray analysis revealed several differentially expressed genes including C-X-C chemokine receptor type 7 (CXCR7), superoxide dismutase (SOD) 3, Toll-like receptor (TLR) 3. Data were validated by real-time PCR, confirming the differential expression profiles of CXCR7 (Fold change 26.54), SOD3 (Fold change 4.79) and TLR3 (Fold Change 2.22) in hLASCs. Related to CXCR7 function, hLASCs demonstrated accelerated cell migration depending on SDF-1 α , a CXCR4/7 agonist, compared to hHASCs. For TLR activation, hLASCs secreted more IL-6 and MCP-1 in response to poly:IC for TLR3 stimulation than hHASCs, but not to LPS for TLR4 ligand.

Conclusions: Our data suggest hLASCs can be characterized by cell migration, intense oxidative stress and immune response through toll-like receptor activation, which determine therapeutic potential of hASC.

FR-PO218

Renoprotective Effects of Tonsil-Derived Mesenchymal Stem Cells in Gentamicin-Induced Acute Kidney Injury (AKI) *Duk-Hee Kang, Eun Sun Ryu, Hyun-soo Shin, Jiyeon Ko. Ewha Womans Univ School of Medicine.*

Background: Gentamicin (GM)-induced AKI occurs in 10-20% of treated patients. GM is accumulated in renal epithelial cells, which causes the loss of the brush border, apoptosis and overt necrosis of renal tubules. Recent developments in stem cell research have shown a promise for the treatment of AKI, however the mechanisms underlying the improvement in kidney function provided by stem cell therapy remain unclear. Tonsil-derived mesenchymal

stem cells (T-MSCs) can be isolated from tonsils of the patient undergoing tonsillectomy, and are reported to be effective in treatment of various diseases. The aim of this study is to investigate the therapeutic potential of T-MSCs in the treatment of AKI induced by GM.

Methods: Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, ip for 10 days), GM+T-MSCs (1×10^7 cells, intravenous injection at 1 day after the 1st GM injection) and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a transwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H₂O₂ generation, NOX mRNA expressions with DCF-DA staining.

Results: PKH-26-labeled T-MSCs were observed in renal tubular cells in GM+T-MSCs group. The infusion of T-MSCs preserved renal function with a decrease in proteinuria. T-MSCs also ameliorated renal tubular dilatation and reduced apoptosis of renal tubular cells in the rats with GM-induced AKI. The infusion of T-MSCs downregulated the expression of Bax, Cytochrome c, Cleaved caspase-9 and -3 and upregulated Bcl-2 of renal cortical tissue. In-vitro study revealed an amelioration of GM-induced oxidative stress and apoptosis of NRK cells by T-MSC.

Conclusions: Our results suggest that T-MSCs protect the kidney from GM-induced AKI, possibly via the mechanism of modulation of oxidative stress and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO219

Exosomes Secreted by Human Urine-Derived Stem Cells Could Prevent Kidney Complications from Type I Diabetes in Rats *Zhenzhen Jiang, Yumei Liu, Ying Fan, Jing Zhang, Yang Fei, Niansong Wang. Dept of Nephrology and Rheumatology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Stem cells are currently the main candidates for the development of new treatments for diabetic nephropathy, as they may exert their therapeutic effects mainly through paracrine mechanisms. Exosomes derived from stem cells have been reported to play an important role in kidney injury.

Methods: Exosomes from conditioned medium of human urine-derived stem cells (USCs-Exo) were isolated using ultra-filtration and purification methods. USCs-Exo was then verified by morphology characteristics and specific biomarkers. After the establishment of the streptozotocin (STZ) induced Sprague - Dawley (SD) rats' model, the effects of USCs-Exo on kidney injury were observed via tail intravenous injection of USCs-Exo or control weekly until 12 weeks. In vitro, podocytes cultured in high glucose medium were treated with USCs-Exo to test the protective effect of USCs-Exo on podocyte apoptosis.

Results: USCs were cultured and were verified by positive markers of CD29, CD73, CD90 and CD44 antigens, and negative markers of CD34 and HLA-DR. USCs-Exo were 100 nm spherical vesicles under transmission electron microscopy and the specific markers including CD9, CD63 and CD81. Intravenous injections of USCs-Exo could potentially reduce the urine volume and urinary microalbumin excretion, prevent podocytes and tubular epithelial cells apoptosis, suppress the caspase-3 overexpression and increase glomerular endothelial cells proliferation in diabetic rats. In addition, USCs-Exo could reduce podocyte apoptosis induced by high glucose in vitro.

Conclusions: USCs-Exo may have the potential effect to prevent kidney injury from diabetes by inhibiting podocytes apoptosis and promoting vascular regeneration.

FR-PO220

Characterization of a Nanotube-Based Mechanism for Hematopoietic Stem Cell-Mediated Kidney Repair in Cystinosis *Spencer M. Goodman,¹ Swati Naphade,¹ Jay Sharma,¹ Heloise P. Gaide Chevronnay,² Pierre J. Courtoy,² Stephanie Chergui.¹ ¹Dept of Pediatrics, Div of Genetics, Univ of California, San Diego, La Jolla, CA; ²Cell Biology Unit, de Duve Inst, Univ Catholique de Louvain, Brussels, Belgium.*

Background: Cystinosis is a lysosomal storage disorder caused by mutations in the CTNS gene, encoding the lysosomal transmembrane transporter cystinosin. As a consequence, cystine builds up in all tissues and eventually causes multi-organ degeneration. Patients develop renal Faconi syndrome before the age of one, and ultimately, end-stage renal failure. We previously showed in *Ctns*^{-/-} mice that transplantation of hematopoietic stem cells (HSCs) resulted in abundant integration of bone marrow-derived cells into all tissues and long-term kidney preservation. To address the cellular mechanism of kidney rescue, we observed that HSCs differentiated into macrophages that extended intercellular bridges called tunneling nanotubes (TNTs). TNTs were seen transporting cystinosin-GFP lysosomes into diseased proximal tubular cells (PTCs) across the tubular basement membrane.

Methods: In vitro co-culture of primary DsRed *Ctns*^{-/-} fibroblasts with IC21 macrophages expressing CTNS-GFP allowed visualization of bidirectional lysosome transfer. We designed an application using ImagePro to automatically quantify TNTs via morphological filters. In vivo, we further evidenced glomerular rescue by HSCs in DsRed *Ctns*^{-/-} mice transplanted with GFP-expressing HSCs. Cells and glomeruli are currently analyzed by confocal and electron microscopy.

Results: We thus showed that HSC-derived cells result in morphological and functional preservation of both PTCs and glomeruli in grafted *Ctns*^{-/-} mice. However, while PTC rescue implied differentiation of donor cells into F4/80+ macrophages, glomeruli-engrafted HSCs were apparently not macrophages. Work is ongoing to characterize the cellular mediators of glomeruli repair.

Conclusions: In conclusion, HSC transplantation can repair and preserve near-normal kidney architecture in cystinosis. Understanding mechanisms underlying kidney repair could spur the development of novel stem cell-based therapies for degenerative renal disorders.

Funding: NIDDK Support, Other NIH Support - NINDS, Private Foundation Support

FR-PO221

Towards the Clinical Application of Gene-Modified Hematopoietic Stem Cell Transplantation for Cystinosis *Tatiana Vm Lobry*, Jay Sharma, Sarah Ur, Celine Rocca, Betty Cabrera, Stephanie Cherqui. *Pediatrics, Univ of California San Diego, San Diego, CA.*

Background: Cystinosis is an autosomal metabolic disease caused by mutations in the *CTNS* gene, encoding a lysosomal cystine transporter, leading to cystine accumulation and multi-organ failure. Affected individuals present before 2 years of age with a Fanconi syndrome and eventually progress to end-stage renal failure. Treatment with cysteamine does not prevent these complications. We showed previously that wild-type HSC transplantation could treat cystinosis in the *Ctns*^{-/-} mice. Thus, we developed an autologous transplantation strategy of HSCs genetically modified *ex vivo* to express a functional *CTNS* gene. Preclinical studies using a SIN-lentivirus vector containing *CTNS* to transduce *Ctns*^{-/-} HSCs and transplanted in *Ctns*^{-/-} mice led to cystine reduction in all tissues and kidney function improvement.

Methods: Pharmacological and toxicological studies are in progress. We established the optimal conditions to transduce human CD34⁺ HSCs with our lentiviral vector to obtain a Vector Copy Number (VCN) included between 1 and 3. We performed Colony Forming Unit (CFU) assays to ensure normal proliferation and differentiation of transduced human CD34⁺ HSCs from healthy donors and cystinotic patients and the In Vitro Immortalization (IVIM) assay, a genotoxicity test. Serial transplantations in the *Ctns*^{-/-} mice will assess the safety of our vector *in vivo*.

Results: While we obtained VCN within the range for healthy donors CD34⁺ HSCs, the VCN for the *CTNS*^{-/-} CD34⁺ HSCs is below 1, requiring further optimization. CFU assays did not show aberrant differentiation of the transduced CD34⁺ cells from the healthy donors and cystinotic patients. Finally, no immortalized clones were observed with the IVIM assays suggesting a good safety profile of our vector. These results will be included in our IND for a phase I clinical trial for cystinosis. The *in vivo* serial transplantations are in progress.

Conclusions: This work represents the first stem cell and gene therapy treatment strategy for cystinosis and should lead to a phase I clinical trial.

Funding: NIDDK Support, Private Foundation Support

FR-PO222

Mesenchymal Precursor Cell Therapy for Diabetic Nephropathy: 24 Week Results from a Phase 2A Randomized Controlled Trial *David K. Packham*,¹ Ian R. Fraser,² Peter G. Kerr,³ Silviu Itescu,⁴ Karen R. Segal.⁴ ¹*MRRG, Melbourne, VIC, Australia;* ²*Eppworth H, Melbourne, VIC, Australia;* ³*Dept Neph, Monash M C, Melbourne, VIC, Australia;* ⁴*Mesoblast PLC, NY, NY.*

Background: Renal inflammation and endothelial dysfunction contribute to the etiology of diabetic nephropathy (DN). Bone marrow derived mesenchymal precursor cells (MPC) can modulate both inflammatory cells and microvasculature. We conducted a randomized, placebo (PBO) controlled, dose-escalating trial of allogeneic MPC in 30 subjects with type 2 DN.

Methods: Patients (24 men, 6 women) with an estimated glomerular filtration rate (eGFR) of 20-50 ml/min/1.73m² and on a stable regimen of renin-angiotensin inhibition were randomized to a single IV infusion of PBO (saline) or 150 million (M) or 300M MPCs (N=10 per group). Patients have been followed-up for 24 w. Baseline mean age was 70 years mean eGFR was 34.6, 35.7 and 34.6 ml/min/1.73m² for PBO, 150M and 300M, and 19/30 patients had eGFR>30.

Results: There were no treatment-related adverse events. For eGFR change from baseline at 24 w, the least square mean (LSM) differences from PBO were 3.2±2.5 (8.1%) in both 150M and 300M groups. PBO-adjusted treatment differences were greater in pooled MPC with baseline eGFR>30: 4.9±2.3 (+12%) at 24w. The LSM differences from PBO for mean individual annualized slopes of eGFR change over 24w was 6.8±4.8 in both treatment groups. Baseline IL6 levels correlated with Scr and eGFR improvement at 12 w in the MPC groups (r=0.57 and 0.50; both p<0.05) but not in PBO. The LSM differences from PBO for mean individual annualized slopes of eGFR change over 24w was 7.8±4.8 ml/min/1.73 m²/y in pooled MPC patients with baseline IL-6 >3.5 pg/dl and 5.6±5.0 in MPC patients with baseline IL-6 <3.5 pg/dl, suggesting greater preservation or improvement in eGFR relative to PBO in the presence of elevated IL-6.

Conclusions: In this first in humans study, a single MPC infusion improved or stabilized GFR over 24w. Baseline eGFR>30 and high IL-6 levels suggest two biomarkers that may predict efficacy with MPC treatment. Positive response to MPC therapy may be enhanced by the presence of non-fibrotic, but at-risk, renal tissue and aberrant pro-inflammatory milieu.

Funding: Pharmaceutical Company Support - Mesoblast PLC

FR-PO223

Long-Term Effect of Methylprednisolone Pulse and Autologous SVF (Stromal Vascular Fraction) Therapy in Severe IgA Nephropathy with CKD Stage III *Byoung-Soo Cho*,¹ Yumi Choi,² Jin-Soon Suh.³ ¹*The All Medical Hub Kidney Center; MIRAE ING Research Inst, Seoul, Republic of Korea;* ²*Dept of Pediatrics, Gwangmyeong Sung-Ae Hospital, Gwangmyeong-si, Gyeonggi-do, Republic of Korea;* ³*Dept of Pediatrics, College of Medicine, The Catholic Univ of Korea, Bucheon-si, Gyeonggi-do, Republic of Korea.*

Background: Up to date there is no specific method of treatment in severe IgA nephropathy with CKD, but giving ACE inhibitor, angiotensin II receptor blocker (ARB), omega-3 etc. and eventually almost all cases fall into CKD V and need KTP or dialysis. Cell-based therapy is an emerging field in nephrology field especially adipose derived stem cells (ASCs). The beneficial effects of mesenchymal stem cell occur through differentiation-independent pathways include increased cell survival and proliferation, decreased inflammation, immune modulation, tissue regeneration etc.

Methods: We tried methylprednisolone (MP) pulse therapy followed by autologous SVF (stromal vascular fraction), which contained ASCs in severe IgA nephropathy with CKD stage III. This case was 44 years old female patient, Renal biopsy finding showed Grade IV (Lee's classification) with CKD stage 3. MP pulse was tried 6 cycles followed by autologous SVF were injected through intravenously 4 times at 3 weeks interval.

Results: Initial renal biopsy findings before treatment (Tx) showed 61% sclerotic glomeruli, however follow up renal biopsy 18 months after Tx showed 41% sclerotic glomeruli and disappeared immune deposits, The serum creatinine level before Tx was 1.77mg/dl with GFR 35ml/min, however 18 months after Tx serum creatinine was 1.03mg/dl with GFR 61ml/min.

Conclusions: In conclusion MP pulse therapy with autologous SVF treatment in intractable IgA nephropathy might be a promising therapeutic means without any notable side-effect or complications especially in early stage CKD, although the efficacy and safety, of SVF infusion therapy needs long term studies.

FR-PO224

Extracellular Vesicles in Glomerular VEGF Homeostasis *Sargis Sedrakyan*,¹ Stefano Porta,² Hasmik Soloyan,¹ Nikita Tripuraneni,¹ Roger E. De Filippo,¹ Benedetta Bussolati,² Laura Perin.¹ ¹*Children's Hospital Los Angeles;* ²*Univ of Turin.*

Background: Strict regulation of VEGF signaling between podocytes and glomerular endothelial cells (GEC) is critical for GEC survival and function, therefore, loss of glomerular VEGF homeostasis during disease progression can impact GEC integrity leading to decline in glomerular function. Importantly, recent studies have described extracellular vesicles (EVs) to play important role in stem cell mediated paracrine modulation, including in kidney. We have already established that amniotic fluid stem cells (AFSC) are renoprotective, and we hypothesize that EVs released within damaged glomeruli are involved in VEGF regulation. Herein, we investigate the impact of AFSC derived EVs in the maintenance of glomerular VEGF homeostasis.

Methods: Using qPCR and ELISA we measured VEGF expression along the course of disease progression in isolated glomeruli of mice affected by Alport Syndrome (AS). Endothelium morphology was evaluated by IHC and TEM. GEC were FACS sorted from a GEC specific Tek reporter mice and studied by gene and protein arrays for VEGF/VEGF-R, oxidative stress, and apoptotic pathways. Co-cultured GEC and AFSC overstimulated with VEGF were used to study the direct role of EVs in VEGF regulation. EVs were characterized and injected into AS mice for *in vivo* evaluation.

Results: Mice at advanced stages of Alport disease presented with aberrant VEGF activity within glomeruli, significant GEC apoptosis, oxidative stress and loss of GEC fenestrations. Delivery of AFSC derived EVs normalized VEGF expression and ameliorated endothelial damage. Importantly, the soluble receptor of VEGF, sFlt1—involvement in regulating VEGF signaling—was also modulated upon treatment, indicating a VEGF/sFlt1 mechanism of regulation by EVs. In vitro experiments further confirmed the direct role of EVs in VEGF/sFlt1 regulatory mechanism.

Conclusions: In conclusion, our data demonstrate for the first time the aberration of VEGF signaling within AS glomeruli. We further showed that AFSC derived EVs play an important role in maintaining glomerular homeostasis of VEGF signaling, so critical to normal GEC integrity and function, presenting with a potential for new targeted therapies in CKD.

Funding: Other U.S. Government Support

FR-PO225

Renal Exosomes Store and Transfer the Ischemia Preconditioning State and Protect Rats with Severe Renal Ischemia *Katherine J. Kelly*,¹ Jesus H. Dominguez,^{1,2} ¹*Medicine, Indiana Univ Medical School, Indianapolis, IN;* ²*Medicine, Veterans Administration, Indianapolis, IN.*

Background: Acute Kidney Injury (AKI) is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD). We have reported that intravenous renal cell transplants (IRCT) improve outcomes in rats with AKI (AJP 303:F357, 2012). IRCT action was mediated by relatively small number of anchored and retained cells, and we hypothesized that cells amplified renal protection by releasing exosomes (EX) acting at a distance.

Methods: We tested if renal EX from cultured cells used for IRCT improved AKI. Normal Sprague Dawley rats (SD, n = 4-7) were subjected to 45 minutes of bilateral ischemia (IR). Renal exosomes (600 ug/protein/rat) were then given intravenously.

Results: There were 5 groups of rats: 1, sham, no IR; 2, renal ischemia (IR) untreated (NO-EX); IR treated with heat inactivated EX (HI-EX); 3, IR treated with normal EX (NL-EX); 4, IR treated with EX released by kidney cells subjected to ischemia preconditioning (IPC-EX). In sham, serum creatinine was 0.3 ± 0.03 at 24 hrs and 0.3 ± 0.02 at 48 post-surgery. In NO-EX it was 2.1 ± 0.6 and 1.7 , post IR, respectively. In HI it was 2.2 ± 0.1 and 1.6 ± 0.3 . However, in NL-EX it was 2.4 ± 0.4 and 0.78 ± 0.1 . The most striking effect was from IPC-EX: 2.0 ± 0.2 , and 0.54 ± 0.1 , $p < 0.05$ vs. all including NL-EX. Kidney weight (mg/gm body weight) 6 days post IR was also improved by EX: 3.8 ± 0.1 in sham; 6.7 ± 0.6 in NO-EX; 6.7 ± 0.6 in HI; 5.2 ± 0.2 in NL-EX 5.2 ± 0.2 , and 4.4 ± 0.2 in IPC-EX, which was significantly lower than all IR groups, including NL-EX. Neutrophils (PMN) in IPC-EX were also reduced by 65% ($p < 0.05$) when compared to NL-EX. IPC-EX reduced renal C3 expression in glomeruli and tubules by 73% and 82% respectively ($p < 0.05$ for both). IPC-EX also protected 76% of renal tubules when compared to NO-EX.

Conclusions: IPC is effective but impractical. However, EX given IV can communicate the IPC state, reach the kidneys, modulate inflammation and protect function and structure following severe IR.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

FR-PO226

The Impact of Preexisting Chronic Kidney Disease on the Severity and Recovery of Acute Kidney Injury Sung Yoon Lim,¹ Young Ju Na,¹ Myung-gyu Kim,¹ So-young Lee,² Sang-Kyung Jo,¹ Won-Yong Cho.¹ ¹Dept of Nephrology, Korea Univ Hospital, Seoul, Korea; ²Dept of Nephrology, Eulji Univ Hospital.

Background: Recent observational studies have shown that a substantial proportion of patients with acute kidney injury (AKI) have often progression to chronic kidney disease (CKD). Among several risk factors for the development of CKD after AKI, decreased baseline glomerular filtration rate (GFR) represents an important risk factor. However, precise mechanisms involved in the development of fibrosis after AKI with preexisting CKD have not been completely ascertained. Here in this study, we assessed the impact of preexisting CKD on the severity and recovery of AKI in mouse model of 5/6 nephrectomy.

Methods: Male CD-1 mice underwent 5/6 nephrectomy or sham operation, and 6 weeks later ischemia reperfusion injury (IRI) was performed. On day 1, 7 and 28 after IRI, functional, histological, and molecular parameters were compared between them.

Results: Twenty five minutes clamping of renal pedicle in 5/6 nephrectomized mice did not provoke more severe functional, histological deterioration compared to normal mice on day 1 and 7. Similar elevations in SCr were observed in both groups until day 7 after IRI; however, SCr remained higher on day 28 in 5/6 nephrectomized mice compared to normal mice, suggesting that preexisting CKD does not modify severity of AKI but adversely affect the recovery process. From day 7 to 28, mRNA expression of p21, and protein level of p3, both representing cell cycle arrest were significantly increased in 5/6 nephrectomized mice (CKD+AKI) compared to sham (sham+AKI). Treatment with p53 inhibitor after IRI resulted in not only decreased p21 and p3 protein level, but also fibrosis in CKD+AKI mice, suggesting that epithelial cell cycle arrest is partially responsible for impaired recovery from AKI in 5/6 nephrectomized mice.

Conclusions: Taken together, reduced nephron mass do not seem to increase severity of AKI, but have negative effect on repair process, leading to development of fibrosis.

FR-PO227

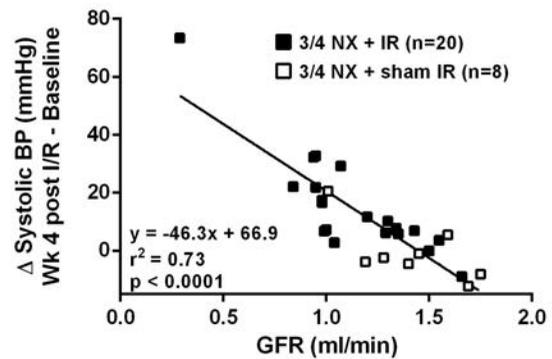
Impaired Functional Recovery from Acute Kidney Injury in Rats with Preexisting Chronic Kidney Disease Predicts the Severity of De Novo Hypertension Aaron J. Polichnowski,^{1,2} Karen A. Griffin,^{1,2} Mana Dissadee,^{1,2} Anil K. Bidani.^{1,2} ¹Edward Hines Jr. VA Hospital, Hines, IL; ²Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: The mechanisms by which AKI accelerates the progression of CKD remain poorly understood. We have recently demonstrated that preexisting CKD predisposes to impaired recovery from AKI as evidenced by exaggerated levels of tubulointerstitial fibrosis and modest elevations in blood pressure at 4 weeks post injury. However, a rigorous examination of the relationship between impaired functional recovery from AKI and the development of hypertension has not been examined.

Methods: Male SD rats underwent normotensive 3/4 nephrectomy (3/4 NX) and were chronically instrumented with a BP radiotelemeter. Two weeks later, rats were subjected to 40 min IR (n=20) or sham IR (n=8). BP was assessed every 10 min, 24 hr/day for 4 weeks and glomerular filtration rate (GFR) was then assessed in the conscious state (FITC-inulin).

Results: As compared to baseline values, systolic BP was significantly elevated ($P < 0.05$) in rats at 4 weeks post IR (134 ± 2 vs. 149 ± 5 mmHg, respectively) but not sham IR (139 ± 4 vs. 140 ± 2 mmHg, respectively). GFR was significantly less ($P < 0.05$) in rats subjected to IR vs. sham IR (1.1 ± 1 vs. 1.4 ± 1 ml/min, respectively). As shown in Figure 1, a very strong negative correlation was observed between GFR and the increase in systolic BP over the 4 week protocol. S_{cr} values 48 hours post AKI did not correlate with either GFR or the change in systolic BP at 4 weeks post AKI, indicating that the development of hypertension following IR was due to impaired recovery from AKI as opposed to a greater severity of AKI.

Figure 1



Conclusions: The development of hypertension following AKI in the presence of pre-existing CKD is likely to significantly contribute to the subsequent progression of CKD.

Funding: NIDDK Support, Veterans Administration Support

FR-PO228

Exocytosis of Endothelial Lysosome-Related Organelles Hair-Triggers a Patchy Loss of Glycocalyx at the Onset of Sepsis Joseph A. Zullo,¹ Jie Fan,² Tala F. Azar,¹ Wan-yi Yen,² Min Zeng,² Jun Chen,¹ Brian B. Ratliff,¹ Jungol Song,³ John Tarbell,² Bingmei M. Fu,² Michael S. Goligorsky.¹ ¹New York Medical College; ²The City College of The City Univ of New York; ³Ulsan Medical College, Seoul, Republic of Korea.

Background: Endothelial surface glycocalyx (ESG) is a well-known regulator of leukocyte surveillance, vascular permeability, and a sensor of shear stress. ESG is degraded during sepsis, thus contributing to systemic multiorgan involvement. Our previous demonstration of a very early post-stress exocytosis of lysosome-related organelles (LRO) with their lytic enzymes led us to hypothesize that exocytosis of LRO may catapult a synchronized degradation of ESG.

Methods: To test this hypothesis we first analyzed the time-course of exocytosis of Weibel-Palade bodies and secretory lysosomes after application of lipopolysaccharides (LPS) to endothelial cells.

Results: Time-lapse video microscopy revealed that LROs undergo agitation and vectorial movement with a time course of a few minutes after LPS. In addition, spectrophotometry measurements illustrated an increase of lysosomal cargo, cathepsin B, within the media after 10min of LPS exposure. Two therapeutic maneuvers, a nitric oxide intermediate, NG-hydroxy-L-arginine (NOHA), and culture media conditioned by endothelial progenitor cells (EPC-CM) reduced the directionality and motility of LRO. The patchy loss of ESG occurring with the similar fast kinetics was confirmed using confocal fluorescence microscopy and Stochastic Optical Reconstruction Microscopy. The loss of ESG was blunted by pretreatment with NOHA or EPC-CM. Moreover, these treatments resulted in a significant reduction of mortality of septic mice.

Conclusions: In summary, above studies provide the first demonstration of the very early patchy disintegration of ESG which can be prevented by pretreatment with NOHA and EPC-CM, maneuvers that reduced exocytosis of LRO. Data support the hypothesis assigning to stress-induced exocytosis of these organelles the role of a hair-trigger for local degradation of ESG that in turn initiates leukocyte infiltration, increase in vascular permeability, and partially accounts for the later morbidity and mortality.

Funding: NIDDK Support

FR-PO229

Vitamin D Deficiency Contributes to Vascular Damage in Sustained Ischemic Acute Kidney Injury Ana C. de Bragança,¹ Rildo A. Volpini,¹ Purvi Mehrotra,² Charlie M. Ivancic,² Lucia Andrade,¹ David P. Basile.² ¹Nephrology, Univ of Sao Paulo School of Medicine, Sao Paulo, SP, Brazil; ²Cellular and Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN.

Background: It has been shown that injury to the renal vasculature may play an important role in the pathogenesis of ischemic acute kidney injury (AKI). Reductions in microvascular density may play a critical part in the progression of chronic kidney disease (CKD) following AKI-induced ischemia/reperfusion injury (IRI). Vitamin D deficiency (VDD) is associated to tubulointerstitial damage and fibrosis progression following IRI-AKI. We evaluated the effect of VDD in sustained IRI-AKI, hypothesizing that VDD contributes to vascular damage.

Methods: Wistar rats were fed 25(OH)D-free or standard diets for 35 days. On day 28, rats were randomized into four groups: control (sham), VDD, bilateral IRI and VDD IRI. Rats were analyzed 7 days after the surgeries.

Results: VDD rats showed impaired capillary density (by cablin staining) and reduced VEGF expression, even in the absence of injury. In addition, VDD IRI rats manifested a remarkable capillary rarefaction and also had increased RW/BW, tissue injury scores, FSP-1,

α -SMA when compared to either VDD or IRI rats. VDD IRI also had increased levels of infiltrating activated CD4+ and CD8+ cells secreting higher levels IFN- γ and IL-17 while the number of regulatory T cells was reduced, relative to IRI rats.

	Control n=6	VDD n=5	IRI n=7	VDD IRI n=7
RW/BW ratio	0.34 \pm 0.009	0.33 \pm 0.005	0.50 \pm 0.031 ^{ad}	0.58 \pm 0.030 ^{ad}
Vessel density %	100.0 \pm 14.08	77.45 \pm 3.33	75.50 \pm 6.91	53.42 \pm 8.58 ^b
FSP1 +cells/field	5.99 \pm 1.28	7.35 \pm 0.79	18.31 \pm 1.72 ^{b,c}	27.0 \pm 3.11 ^{ad}
α -SMA %	0.15 \pm 0.04	0.16 \pm 0.01	2.89 \pm 0.43	7.74 \pm 1.56 ^{ab}
VEGF %	30.56 \pm 3.05	20.51 \pm 5.49	16.56 \pm 2.08	13.42 \pm 4.49 ^c

^ap<0.001, ^bp<0.01 and ^cp<0.05 vs Control; ^dp<0.001 and ^ep<0.01 vs VDD; ^fp<0.01 and ^gp<0.05 vs IRI

Conclusions: VDD impairs renal capillary density and exacerbates fibrotic damage and pro-inflammatory milieu following AKI, which may contribute to the transition of CKD following AKI. *Funding:* CAPES/CNPq/FAPESP, NIH DK63114 (DPB).

Funding: NIDDK Support

FR-PO230

Exosome-Mediated Delivery of Pro-Survival MicroRNA-486-5p in Acute Kidney Injury Jose L. Vinas, Dylan Burger, Alex Gutsol, William A. Knoll, David Allan, Kevin D. Burns. *Nephrology, Dept of Medicine, Ottawa Hospital Research Inst, Univ of Ottawa, Ottawa, ON, Canada.*

Background: We recently showed that administration of human endothelial colony forming cells (ECFCs) and their exosomes to mice with ischemic acute kidney injury (AKI) attenuated renal damage. Our data also indicate that ECFCs release exosomes that are highly enriched in micro-RNA (miR)-486-5p and protect against hypoxia-induced endothelial cell apoptosis. MiR-486-5p targets phosphatase and tensin homologue (PTEN), which may enhance the pro-survival Akt pathway. In this study, we further examined the role of exosomes and miR-486-5p on the Akt pathway *in vivo*, and tested the hypothesis that exosomes transfer miR-486-5p to endothelial cells *in vitro*.

Methods: Mice with ischemic AKI were injected (i.v.) with exosomes at reperfusion. Kidneys were subjected to immunoblots and RT-PCR for miR-486-5p. Transfer of ECFC exosomes and miR-486-5p was studied in human umbilical vein endothelial cells (HUVECs).

Results: Bioinformatic analysis of the 10 most abundant miRs in ECFC exosomes revealed that they were all involved in the Akt pro-survival pathway. In mice with AKI, exosome treatment significantly increased renal miR-486-5p levels (P<0.01 vs ischemia alone, n=6-7), associated with decreased PTEN expression, and increased Akt phosphorylation. In cultured HUVECs, ECFC exosomes labeled with the fluorescent dye PKH-26 localized to the perinuclear compartment. Treatment of HUVECs with ECFC-derived exosomes or co-culture of ECFCs with HUVECs caused a 40-fold increase in levels of miR-486-5p. Transfection of ECFCs with pre-miR-486-5p, followed by co-culture with HUVECs was associated with a further marked increase (~20-fold) in miR-486-5p levels in HUVECs (P<0.001 vs control, n=3). This effect was blocked by pre-incubation of HUVECs with ethylisopropyl amiloride (an inhibitor of exosome uptake).

Conclusions: These data suggest ECFC-derived exosomes exert renoprotective effects in AKI, possibly via the transfer of miR-486-5p to endothelial cells. Exosome-mediated transfer of miRs could represent a strategy to target pro-survival pathways in the injured kidney.

Funding: Private Foundation Support

FR-PO231

The Role of Vascular Endothelial Cells in the Protective Effect of Delayed Ischemic Preconditioning in Renal Ischemia/Reperfusion Injury Xiaolan Xu, Xiaoyan Jiao, Nana Song, Xiaoqiang Ding. *Div of Nephrology, Zhongshan Hospital, Shanghai, China.*

Background: We have previously reported that up-regulation of miR-21 contributed to the protective effect of delayed ischemia preconditioning (IPC) in renal ischemia/reperfusion injury (IRI). The role of vascular endothelial cells in renal IRI is not well-understood. In the present study, we examined the role of vascular endothelial cells in the protective effect of miR-21 in renal delayed IPC.

Methods: For the delayed IPC and IR model, 4 d after IPC (15min ischemia) or sham surgeries, preconditioned mice were subjected to 35 min occlusion of bilateral renal pedicles, followed by 24 h reperfusion. Human umbilical vein endothelial cells (HUVEC) were treated with cobalt chloride for hypoxia model *in vitro*. Locked nucleic acid (LNA) modified anti-miR-21 or anti-scrambled was transfected into cells or delivered into the mice via tail vein injection less than 1 hour prior to IPC. Vascular permeability was determined by the Evans Blue dye. Cell apoptosis was estimated by Annexin V-FITC apoptosis detection. Expression of programmed cell death 4 (PDCD4) protein and miR-21 was examined by western blot and real-time PCR, respectively.

Results: Compared with the Sham+IR group, mice in the IPC+IR group showed significant improvement of renal function and histology injury (P<0.01). MiR-21 was up-regulated in the IPC+IR group with concomitant decline of PDCD4 (P<0.05) and improvement of vascular permeability (P<0.05). *In vitro*, miR-21 in HUVEC was increased in hypoxia, while PDCD4 expression was decreased. Knockdown of miR-21 by LNA anti-miR-21 attenuated the protection conferred by delayed IPC, with concomitant up-regulation of PDCD4 (P<0.05) and exacerbated renal vascular permeability (P<0.05). Cell apoptosis significantly decreased after knockdown of miR-21 *in vitro*.

Conclusions: Up-regulation of miR-21 in renal delayed IPC improved the apoptosis of vascular endothelial cell by inhibiting its target PDCD4. This may be another mechanism underlying the protective effect of the delayed IPC.

Funding: Government Support - Non-U.S.

FR-PO232

Role of Vascular Mineralocorticoid Receptor in Renal Ischemia/Reperfusion Jonatan Barrera-Chimal,¹ Alan Le Mercier,¹ Sonia Prince,¹ Soumaya El Moghrabi,¹ Norma Bobadilla,² Frederic Jaisser.¹ *¹INSERM U1138, Centre de Recherche des Cordeliers, Paris, France; ²Inst de Investigaciones Biomédicas UNAM and INNSZ, Mexico City, Mexico.*

Background: Renal ischemia/reperfusion (IR) is a major cause of acute kidney injury and is associated with chronic kidney disease (CKD) development. Mineralocorticoid receptor (MR) antagonism prevents the acute and chronic consequences of renal IR. Whether the benefit of the MR antagonists is due to the blockade of the MR in the vessels is unclear.

Therefore we want to study the specific contribution of endothelial and smooth muscle cells (SMC) MR in acute and chronic consequences of renal IR.

Methods: To inactivate MR in endothelial cells (MR^{endoKO} mice), floxed MR mice (MR^{fl}) were crossed with mice expressing the inducible Cre recombinase under the VEcadherin promoter. To allow inactivate MR in smooth muscle cells (MR^{SMCKO} mice), MR^{fl} mice were crossed with mice expressing the inducible Cre recombinase under the SMA promoter. Sham surgery or bilateral renal IR for 20 min was performed in MR^{fl} and KO mice and the animals were studied at short term (24 h) and long term (30 days) after reperfusion.

Results: In MR^{fl} mice, IR induced renal dysfunction (plasma creatinine from 8.9 \pm 0.3 in sham to 33.8 \pm 4.8 μ mol/L in IR), tubular injury and increased mRNA levels of kim-1 (400-fold) and NGAL (220-fold). The MR^{endoKO} mice displayed similar alterations induced by IR as MR^{fl} mice. In contrast, after 24 h of IR, the MR^{SMCKO} mice presented normal renal function (plasma creatinine was 9.6 \pm 0.7 and 14.0 \pm 1.9 μ mol/L in sham and IR, respectively), absence of histological alterations and reduced kim-1 and NGAL levels.

After 30 days, the MR^{fl} mice developed CKD characterized by renal dysfunction (plasma creatinine from 10.5 \pm 0.1 in sham to 15 \pm 0.8 μ mol/L in IR), tubule-interstitial fibrosis and increased mRNA levels of fibronectin and Galectin-3 (2-fold). The MR^{SMCKO} mice developed similar alterations.

Conclusions: We provide evidence that the deficiency of MR in the SMC protects against the development of acute kidney lesions induced by IR, however MR deficiency in SMC did not impact the appearance of CKD induced by IR, suggesting that MR in other cell types is involved.

Funding: Government Support - Non-U.S.

FR-PO233

Renal Vein Hydrodynamic Fluid Delivery Ameliorates Established Renal Injury following Ischemia/Reperfusion Injury Jason Andrieu Collett,¹ Purvi Mehrotra,¹ David P. Basile,¹ Robert L. Bacallao.^{2,3} *¹Cellular and Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN; ²Div of Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; ³Richard L. Roudebush VA Medical Center, Indianapolis, IN.*

Background: Past and current treatment for Acute Kidney Injury (AKI) is mainly supportive in nature; no therapeutic modalities to date have shown efficacy in treating the condition. While numerous experimental approaches can prevent AKI, there are few potentially translatable studies which may influence the course of established AKI. The goal of this study was to target vascular congestion and inflammation, which contribute to impaired renal perfusion and renal damage, following the established injury. We hypothesized that high-pressure retrograde hydrodynamic delivery (HD) of saline will improve established AKI, in part, by improving vascular congestion.

Methods: Male Sprague Dawley rats underwent left unilateral ischemia (35 min) and right unilateral nephrectomy or bilateral IRI (35min) and reperfusion for 24 hours to induce AKI. 0.5ml of isotonic saline was then injected into either the vena cava (VC) or retrograde to left kidney via the renal vein (RV) under high pressure (~60mmHg). Recovery was evaluated via serum creatinine and accumulation of immune cells were evaluated using FACS.

Results: Average serum creatinine at 24hrs was similar between groups (sCr=3.3mg/dl), however, RV-HD treated rats showed a rapid improvement in serum creatinine over the following 24 hours vs VC HD rats (24 to 48 hr Δ serum creatinine -0.544 mg/dl vs. +0.6375 mg/dl; p=0.0237). To evaluate effects on inflammation, bilateral IRI rats subjected to left-RV HD resulted in a significant reduction in CD4+ (54% \pm 18; p<0.05), CD8+ (60% \pm 8; p<0.05), B cells (56% \pm 3.5; p<0.05) and DC/Macs (71% \pm 13; p<0.05) compared with VC rats.

Conclusions: These results indicate that high pressure retrograde HD may provide a novel and effective therapeutic strategy for the treatment of AKI and transition of AKI to CKD.

Funding: NIDDK Support, Veterans Administration Support

FR-PO234

Human Adipose Stromal Cells Ameliorate Renal Injury and Attenuate Capillary Rarefaction following Ischemia-Reperfusion

Jason Andrieu Collett, Purvi Mehrotra, Dmitry O. Traktuev, Stephanie Merfeld-Clauss, Keith March, David P. Basile. *Indiana Univ School of Medicine, Indianapolis, IN.*

Background: Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of the kidney's excretory function, resulting in excess of 17 million hospital admissions a year. Although the tubular epithelium is the primary target of ischemic injury, early damage to endothelial cells contribute to AKI by resulting in impaired perfusion. Moreover, renal capillary density is permanently compromised in rats following AKI induced by ischemia reperfusion (IRI), which is hypothesized to promote CKD. Therefore, strategies to preserve capillaries may impact both short-term recovery and long-term function post-AKI. Adipose stromal cells (ASCs) have pro-angiogenic and anti-inflammatory properties. It is hypothesized that ASCs facilitate repair by capillary preservation, revascularization of damaged endothelium and decreased inflammation.

Methods: Male Sprague Dawley rats were subject to bilateral IRI (40 min). At the time of reperfusion, $\sim 2 \times 10^6$ human ASCs (hASCs; n=15) or vehicle (n=14) were injected into the suprarenal abdominal aorta. Recovery was evaluated via serum creatinine and capillary specific staining. Accumulation of immune cells in the kidney were evaluated using FACS.

Results: hASC-treated rats had a 90% survival by day 7, compared with 70% for vehicle. Serum creatinine showed a significant reduction in hASC-treated rats vs vehicle at 48 hrs, (35%; p=0.0008). By day seven, vehicle-treated rats showed a reduction in renal capillary density relative to sham (43%), which was significantly attenuated in hASC-treated rats (28%). Additionally, hASCs-treated rats exhibited a significant decrease in CD4+ (62%±16.8) and CD8+ (72%±3.5) T-cell infiltration (p<0.05). Further, IL-17 cytokine secreted by CD4+T cells was also reduced by $\sim 40\%$ in hASC-treated rats (185±66) as compared to vehicle (299±83.9). Conversely, the number of regulatory T cells was increased in hASC-treated rats compared with vehicle (35%; p<0.05).

Conclusions: These results suggest that ASCs may ameliorate injury, at least in part, by preserving capillary density, decreasing inflammation and restoring renal function.

Funding: NIDDK Support

FR-PO235

Studying the Effect of Induced Expandable Human Kidney Progenitor Cells on Renal Function Using Transcutaneous Assessment

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Background: The use of induced stem cells from adult tissues is a promising therapeutic approach for the treatment of kidney diseases. However, traditional techniques to monitor recovery from damage or a delay in chronic renal disease development after cell therapy are cumbersome and time-consuming, as well as inaccurate to detect early changes in function. A recent method allows the evaluation of renal function transcutaneously, using an optical device and the exogenous renal marker FITC-sinistrin, with no need for plasma or urine samples. For the first time, we have studied the effect of human adult kidney epithelial cells (hKEpCs) induced to stably overexpress the SIX2 or OSR1&SIX2 genes in a cisplatin (CP)-induced injury model using the transcutaneous assessment of renal function.

Methods: Three different animal groups were established: induced SIX2-hKEpCs, SIX2&OSR1&mCherry-hKEpCs and CP control group. On days 2 and 7 following a single dose of CP (7mg/kg b.w.), rats received intravenously either vehicle or 1×10^6 of the corresponding cell type. Kidney function was assessed over 14 days transcutaneously. In addition, urinary and plasma parameters, as well as histological changes were evaluated.

Results: Before cell treatment, all the groups experienced a comparable decrease in renal function with respect to baseline. Transcutaneous measurement showed that both cell types improve renal function compared to control group, with a substantial amelioration on day 7 after CP administration. The rise of creatinine and urea serum levels was also ameliorated in the cell treated groups and the histological analysis supported the beneficial of hKEpCs administration shown in renal function.

Conclusions: SIX2- and SIX2&OSR1mCherry-hKEpCs display therapeutic potential in CP-induced injury, preventing loss of kidney function and diminishing renal tissue damage. The transcutaneous assessment of renal function is a suitable method to detect changes due to disease progression or therapeutic interventions.

FR-PO236

Indole Analogs Have Novel Therapeutic Effects on Mitochondrial Diseases and Kidney Injury

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Background: Mitochondrial dysfunction causes various mitochondrial diseases and kidney injuries. Anti-oxidant quinones have been used clinically to prevent the disease progression but the effectiveness is yet to be established. We recently found that an indole-derivative increased ATP levels in Hep3B cells and analyzed 41 newly synthesized indole derivatives. Among those compounds, we focused on the most potent derivative #5(MA-5). The aim of this study was to clarify the effects of MA-5 in mitochondrial diseases and kidney injury.

Methods: Fibroblasts from patients with mitochondrial diseases (Leigh syndrome, MELAS, Leber disease, and Kearns-Sayres syndrome) were cultured in ROS generating condition with BSO(L-buthionine-(S,R)-sulfoximine) and cell viabilities, cellular ROS and glutathione levels were measured. The redox property of MA-5 was examined by cyclic voltammetry. The site of MA-5 distribution was visualized by fluorescence-labeled MA-5(MA-5 FL). MA-5 was administrated, at 50mg/kg body weight by gavage, to mice 3 hr before they were exposed to kidney ischemia (26 min) reperfusion injury (IRI) or cisplatin (20 mg/kg body weight). Plasma creatinine (Cr), blood urea nitrogen (BUN) and renal pathology were assessed.

Results: MA-5 improved cell viabilities in a dose dependent manner in mitochondrial disease fibroblasts. MA-5 exhibited irreversible oxidation peaks by cyclic voltammetry, suggesting that MA-5 did not have antioxidant property like anti-oxidant quinones. MA-5 did not affect the cellular ROS or GSH levels. MA-5 FL co-localized with the mitochondrial marker, mitotracker. In IRI, Cr at 48 hr after ischemia (0.88 ± 0.38 mg/dl vs 1.60 ± 0.66 , control) and tubular cell injury were significantly reduced in MA-5-treated group. BUN (70.9 ± 10.1 vs 101 ± 13.0 mg/dl) and tubular injuries, at 96 hr after cisplatin injection, were significantly reduced in Indole #5 treated groups.

Conclusions: MA-5 exhibited therapeutic effects in fibroblasts from mitochondrial disease patients as well as renoprotective effects in both IRI and cisplatin nephrotoxicity.

FR-PO237

Mechanism of 5-Hydroxytryptamine 1F Receptor Stimulation of Mitochondrial Biogenesis in the Kidney

Whitney Sharee Gibbs, Craig Cano Beeson, Rick G. Schnellmann. *Dept of Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: Pharmacological induction of mitochondrial biogenesis (MB), the process of creating new mitochondria to replace damaged mitochondria, is a potential therapeutic target for AKI. Our laboratory has demonstrated that LY344864, a selective 5-HT_{1F} receptor agonist, promotes recovery from AKI as demonstrated by an increase in MB and decreased BUN and Kim-1 in a mouse model of ischemia/reperfusion AKI. While the 5-HT_{1F} receptor is a G_i-coupled GPCR, the mechanism of 5-HT_{1F} receptor mediated MB is unknown.

Methods: Mitochondrial respiration was measured in renal proximal tubule cells (RPTC) using a Seahorse XF Extracellular Flux Analyzer. Signaling pathways were explored using pharmacological inhibitors and immunoblot analysis.

Results: LY344864 (10 nM) increased FCCP-uncoupled respiration in RPTC, a marker of MB. LY344864 induced FCCP-uncoupled respiration was attenuated by pretreatment with gallein, L-NAME, and ODQ, pharmacological inhibitors of G_{βγ}, nitric oxide synthase, and soluble guanylyl cyclase, respectively. LY344864 upregulated p-Akt and p-eNOS protein expression after 15 min and 1 hr exposures, respectively. Gallein blocked increases in both p-Akt and p-eNOS following LY366864 treatment. Following pretreatment with MK2206, an Akt inhibitor, the increase in p-eNOS protein expression was attenuated.

Conclusions: This study reports the novel finding that G_{βγ} heterodimer initiates MB and does so through a new pathway. Specifically, 5-HT_{1F} stimulation of G_{βγ} activates Akt and eNOS, leading to the induction of MB. The identification of this pathway provides additional therapeutic targets for a drug intervention which could treat AKI.

Funding: NIDDK Support, Other NIH Support - NIGMS Support, Veterans Administration Support

FR-PO238

Formoterol Induces Renal Mitochondrial Biogenesis Through Gβγ-Dependent Signaling

Robert Bruce Cameron, Craig Cano Beeson, Rick G. Schnellmann. *Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: Acute kidney injury (AKI) carries a high morbidity and mortality with no effective treatments beyond renal replacement therapy. AKI is characterized by mitochondrial dysfunction, particularly in the renal proximal tubule cells (RPTC). The induction of mitochondrial biogenesis (MB) is a therapeutic target for AKI. Our group has shown that formoterol, a β₂ adrenoceptor agonist, can induce MB in vitro and in vivo, and stimulate recovery of mitochondrial and renal function following AKI in mice. However, the signaling events leading to formoterol-induced MB remain unknown.

Methods: RPTC were pretreated with DMSO, 100 nM gallein, 10 μM L-NAME, or 100 nM MK2206 for 30 min and then treated with formoterol (30 nM). FCCP-uncoupled oxygen consumption rates (FCCP-OCR) were measured using the Seahorse XF-96 analyzer and protein phosphorylation was determined by immunoblot analysis.

Results: Formoterol increased Akt phosphorylation in RPTC at 30 min, and this increase was attenuated by the G_{βγ} inhibitor gallein. Gallein also attenuated formoterol-induced increases in FCCP-OCR, a biomarker of MB. Formoterol increased the phosphorylation of eNOS, a downstream target of Akt, at 1 hr, and pretreatment with the Akt inhibitor MK2206 blocked Akt and eNOS phosphorylation. Additionally, treatment with the NOS-inhibitor L-NAME attenuated formoterol-induced increases in FCCP-OCR.

Conclusions: This study demonstrates that formoterol-induced MB occurs via β₂-adrenoceptor coupling to G_{βγ}. G_{βγ} leads to the activation of Akt and eNOS, promoting MB. Stimulation of these signaling pathways represents an attractive therapeutic target for AKI.

Funding: NIDDK Support, Other NIH Support - 5T32HL007260-38, 5T32GM008716-14, Veterans Administration Support

FR-PO239

Identification of Slow-Cycling Cells in the Kidney Using TetOP-H2B-GFP Mice Shunsuke Takahashi, Akito Maeshima, Masao Nakasatomi, Hidekazu Ikeuchi, Toru Sakairi, Yoriaki Kaneko, Keiju Hiromura, Yoshihisa Nojima. *Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Maebashi, Gunma, Japan.*

Background: Renal tubular epithelium can regenerate after a variety of insults. During tubular regeneration, survived tubular cells proliferate, migrate and differentiate into mature tubular epithelium. Using BrdU pulse/chase method, we previously reported that slow-cycling cells (label-retaining cells: LRCs) are present in renal tubules and act as the source of regenerating cells after renal ischemia (JASN 14:3138-46, 2003). However, it is difficult to isolate and characterize LRCs in vitro, because there is no LRCs specific markers identified. In this study, we utilized the transgenic mice with doxycycline-inducible expression of an H2B-GFP fusion protein (TetOP-H2B-GFP mice), in which dividing cells can be labeled with GFP under doxycycline control.

Methods: TetOP-H2B-GFP mice were treated with doxycycline for the indicated periods (pulse). After several chase periods, kidneys were removed for analysis. Localization of GFP-positive cells was examined by immunostaining with several nephron markers and their cell number was quantitatively assessed.

Results: 1) After a pulse of doxycycline, GFP-positive cells were found in the kidney of TetOP-H2B-GFP mice. Most GFP-positive cells were AQP-1-positive tubular cells. 2) As pulse periods become longer, the number of GFP-positive tubular cells increased (pulse 8h-0.5%, pulse 24h-10%, pulse 72h-18%, pulse 1 week-40%, pulse 3 weeks-50%). 3) After a short pulse (8h) of doxycycline with no chase, all GFP-positive cells were present as a single cell, but after 2 weeks or 4 weeks chase periods, GFP-positive cells were found in clusters of two cells or three cells. 4) In TetOP-H2B-GFP mice treated with a long pulse (3 week) of doxycycline, the number of GFP-positive cells decreased according to chase periods (Chase 0w-50%, Chase 4w-40%, Chase 8w-5%).

Conclusions: These data suggest that slow-cycling cells can be detected as GFP-positive cells using TetOP-H2B-GFP mice under doxycycline control. This model will be applicable for selective isolation and in vitro characterization of slow-cycling tubular cells.

FR-PO240

Renal ERK1/2 Regulates PGC-1 α and Mitochondrial Biogenic Homeostasis Physiologically and During Renal Injury Justin B. Collier, Ryan Whitaker, Rick G. Schnellmann. *Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: Acute kidney injury (AKI) is defined as a sudden decline in kidney function and the outcomes of AKI have not changed in the past few decades. Previous studies demonstrated that persistent disruption of mitochondrial homeostasis (e.g. peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α), a master regulator of mitochondrial biogenesis (MB)), is an important contributor to renal ischemia reperfusion (IR) injury and repair. While the MAPK extracellular-regulated kinases 1/2 (ERK1/2) regulates numerous cell signaling pathways, the role of ERK1/2 activation in MB physiologically and as a consequence of renal IR injury remains limited.

Methods: Renal proximal tubule cells (RPTC) were treated with the specific MEK1/2 inhibitor trametinib (10nM) for various time points. Control mice were treated with trametinib (1mg/kg). Trametinib was administered 1 hour before 18 min of bilateral IR. Signaling pathways were explored using qRT-PCR and immunoblot analysis.

Results: Trametinib blocked ERK1/2 phosphorylation in RPTC within 10 min that continued for 24 hr. Trametinib also inhibited ERK1/2 phosphorylation *in vivo* at 4 and 24 hr. Trametinib increased PGC-1 α mRNA at 1, 4, and 24 h in RPTC. The mRNA levels of PGC-1 α target genes NDUFS1, NRF1, and TFAM increased at 1, 4, and/or 24 h after ERK1/2 inhibition in RPTC. Trametinib administered to control mice increased PGC-1 α , NRF1, and TFAM mRNA at 4 h in the renal cortex and increased PGC-1 α and TFAM protein. In the IR AKI model, pERK1/2 increased 4-fold at 1 and 3 h post IR. Increased pERK1/2 was linked to decreased mRNA levels of PGC-1 α , NRF1, TFAM, and NDUFS1. Trametinib treatment attenuated suppression of mRNA PGC-1 α and NRF1 at 3 h, increased TFAM protein 2.5-fold, and attenuated renal dysfunction as measured by BUN and KIM-1.

Conclusions: ERK1/2 downregulates renal mitochondrial homeostasis under physiological conditions and ERK1/2 inhibition during renal IR promotes recovery of PGC-1 α and MB, and contributes to both mitochondrial and renal recovery. These results reveal a novel target for pharmacological intervention in AKI.

Funding: Other NIH Support - NIGMS, Veterans Administration Support

FR-PO241

The Guanylyl Cyclase Activator BAY 58-2667 Stimulates Mitochondrial Biogenesis and Promotes Recovery from Ischemia-Reperfusion Induced AKI Ryan Whitaker, Rick G. Schnellmann. *Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: Mitochondrial dysfunction is an important pathophysiological component of acute kidney injury (AKI). As reduced mitochondrial function can impair energy-dependent renal repair processes following AKI, stimulation of mitochondrial biogenesis (MB), the generation of new, functional mitochondria, could promote renal recovery. We explored the efficacy of the guanylyl cyclase activator, BAY 58-2667, to induce MB and promote renal recovery following ischemia-reperfusion (I/R)-induced AKI.

Methods: Mitochondrial respiration was measured in primary renal proximal tubules cells (RPTC) using the Seahorse XF96 Extracellular Flux Analyzer. I/R injury was induced

in male C57BL/6 mice aged 8-10 weeks by bilateral clamping of the renal pedicle for 19 minutes. Mice received daily treatment with saline vehicle or BAY 58-2667 (0.1 mg/kg) beginning at 24 h after I/R.

Results: Treatment of RPTCs with BAY 58-2667 increased FCCP-uncoupled respiration, a marker of MB. BAY 58-2667 also increased mitochondrial gene and protein expression, and mtDNA content in the renal cortex of naive mice. Beginning 24 h after I/R injury, daily treatment with BAY 58-2667 accelerated recovery of renal function evidenced by reduced BUN and renal expression of NGAL and Kim-1 at 6 d. Histological examination demonstrated reduced renal tubular necrosis in BAY 58-2667 treated mice at 6 d. Furthermore, BAY 58-2667 decreased renal expression of the inflammatory cytokines TNF- α and IL-1 β , and reduced oxidative DNA damage. These changes were associated with the recovery of renal MB signaling evidenced by increased mRNA expression of PGC-1 α , NRF1, ND1, COX1 and ATP5 β , as well as mtDNA content and protein expression of PGC-1 α and COX1. In addition, mitochondrial function was recovered as renal ATP returned to sham control levels. Finally, BAY 58-2667 blunted the progression of renal fibrosis evidenced by reduced COL1A2 and α SMA expression.

Conclusions: These data demonstrate that activation of guanylyl cyclase by BAY 58-2667 promotes recovery from AKI by stimulation of MB, reduction of inflammatory and oxidative damage, and inhibition of renal fibrosis.

Funding: NIDDK Support

FR-PO242

Adult Human Renal Papilla CD133⁺ Cells Improve Erythropoietin Production, Show Long Term Engraftment and Repair Glycerol-Induced Kidney Injury in SCID Mice Shikhar Aggarwal,¹ Cristina Grange,² Benedetta Bussolati.¹ ¹Dept of Biotechnology and Health Sciences, Univ of Turin, Turin, Italy; ²Dept of Medical Sciences, Univ of Turin, Turin, Italy.

Background: Acute kidney injury (AKI) often involved deregulation of erythropoietin (EPO) production in the kidney. Novel treatment foresees introduction of cell therapies or strategies involving pharmacological modulations of intrinsic populations to produce EPO and repair of renal injury. CD133⁺ adult human renal cells have been identified by our group as a promising adult renal progenitor cell. Of note, papillary CD133⁺ cells show activation of hypoxia-inducible genes and are specifically involved in EPO production. However, their role in EPO production and fate to repair renal injury for long time has not yet been deconstructed in mice.

Methods: AKI is induced in immunodeficient mice using glycerol (8mg/gbw, i.m.) and adult human CD133⁺ papillary cells (0.5 million cells per mice) are injected (*i.v.*) 1 day after the injury. Mice are euthanized at different time intervals (day 15/day 30) and blood and other tissues (kidneys, lungs, liver) are collected for EPO, creatinine/urea, histological/morphological analysis and molecular analysis (RNA, DNA and protein) respectively.

Results: Data showed that adult human CD133⁺ papillary cells improve EPO production (of both human and mice origin) in the injured mice and protect against AKI in mice at day 15 and day 30 as compared to control group. The group of injured mice that received cells showed higher level of human and mice specific EPO, lower level of creatinine and urea in serum, lower level of kidney injury marker, KIM-1 and improved histology. CD133⁺ papillary cells also reduced development of fibrosis in the injured tissues during repair (as shown by lower expression of alpha-SMA, profibrotic gene TGF- β and trichromic stain). In addition, immunohistochemical and fluorescence studies show localization of CD133⁺ papillary cells within interstitium and tubules of the injured renal tissues.

Conclusions: Thus, our data supports that these CD133⁺ papillary cells may provide an important source of EPO stimulation *in situ* and repair.

Funding: Government Support - Non-U.S.

FR-PO243

Early Mesenchymal Stem Cell Administration Prevents Acute Kidney Injury Superimposed on Chronic Kidney Disease in Rats and High Risk Patients Anna Gooch,¹ Nicole Molin,¹ Ping Zhang,¹ Zhuma Hu,¹ Christof Westenfelder.^{1,2} ¹Medicine, U of Utah and VAMC, Salt Lake City, UT; ²Physiology, U of Utah, Salt Lake City, UT.

Background: We showed that ischemic-reperfusion injury (I/R) causes renal and urine levels of the chemokine SDF-1 (CXCL12) to rise significantly within ~ 2 hrs. This rise mediates the homing of infused, CXCR4 (SDF-1 receptor)-expressing Mesenchymal Stem Cells (MSCs) to the sites of injury, where they act renoprotectively. CKD is a major risk factor for AKI. We tested here whether MSC administration is effective both in preventing I/R AKI superimposed on CKD and in arresting the AKI-induced further deterioration of CKD.

Methods: Rats: Groups of 6 rats underwent 5/6th Nephrectomy. Once CKD was established (~8 weeks), I/R AKI of the kidney remnant was induced and rats were treated either with vehicle or 2x10⁶ MSC/kg bw, i.a. SCR and urine SDF-1/creatinine levels were assessed at pre- and post-operatively. **Patients:** 12 subjects with established CKD and at high risk for cardiac surgery associated AKI were treated i.a. with 2x10⁶ MSCs per kg bw immediately post on-pump CABG or valve surgery. SCR and urinary SDF-1/creatinine levels were determined pre- and post-op. RIFLE criteria defined post-op AKI. Study subject data were compared to well-matched historical controls.

Results: Rats: MSCs significantly hastened improvement in AKI vs. controls. Urine SDF-1 levels remained low by 24 hrs in MSC vs. vehicle treated animals. **Patients:** No study subject had AKI at discharge, but 2 met post-op AKI Risk criteria. Urinary SDF-1/Cr ratios were significantly elevated at 2 and 6 hrs in subjects who developed AKI Risk, but remained stable in those who did not. In contrast to historical controls, 6 months post-op, no treated subject's CKD had worsened.

Conclusions: MSC administration offers renoprotection from AKI on CKD when given immediately post insult. Early, specific biomarker-guided diagnosis of AKI identifies the optimal time for MSC-based therapy. Another clinical trial in high-risk cardiac surgery patients showed that giving MSCs 24-48 hrs post insult, based on the late and non-specific rise in SCr, abolished their protective effects.

Funding: Veterans Administration Support

FR-PO244

Improved Survival of Graft Bone Marrow-Derived Mesenchymal Stem Cells in the Ischemia-Reperfusion-Induced Injured Kidney with Overexpression of Heme Oxygenase-1 Nanmei Liu, Jimin Hospital of Shanghai.

Background: one marrow-derived mesenchymal stem cells (BMSCs) transplantation offers therapeutic potential for acute kidney injury (AKI), but with limited efficacy. This study investigated the effect of HO-1 overexpression on the donor BMSCs' survival, and its impact on the repair of AKI was also observed.

Methods: Ischemia/reperfusion (I/R)-AKI kidney homogenate supernatant (KHS) was prepared. SD BMSCs, eGFP-BMSCs and HO-1-BMSCs were harvested and treated by the AKI-KHS. Cell viability, apoptosis and cell cycle were evaluated. Activities of oxidant stress-related enzymes, expression of p65 and the protein levels of Caspase-3 and Bcl-2 in BMSCs were tested. Survivals of the implanting BMSCs in the AKI rat model as well as the renal function were also assessed.

Results: HO-1-BMSCs showed a high expression of HO-1 and AKI-KHS treatment further enhanced this level. This increased HO-1 expression promoted BMSCs survival under the AKI microenvironment with decreased apoptotic cells as well as less proportion of G0/G1 cells. AKI-KHS induced reduction of SOD activity and GSH-Px in BMSCs with increased MDA and XOD levels, however, HO-1 overexpression changed this phenomenon. Activation of NF- κ B p65 was inhibited in HO-1-BMSCs. Western blot showed decreased Caspase-3 expression and increased Bcl-2 expression in HO-1-BMSCs. The in vivo study showed increased survival of HO-1-BMSCs in the AKI kidneys, which was associated with improved renal function.

Conclusions: HO-1 overexpression could enhance survival of BMSCs under the I/R-AKI microenvironment both in vitro and in vivo as the result of ROS elimination. Activity of NF- κ B p65 and Caspase-3/Bcl-2 signal transduction pathways were involved in this process.

Funding: Government Support - Non-U.S.

FR-PO245

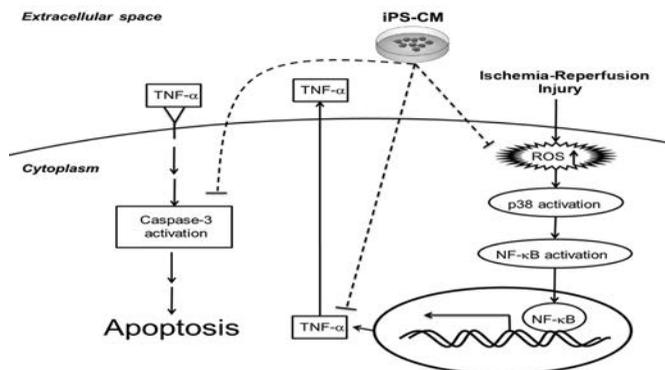
Induced Pluripotent Stem Cell-Conditioned Medium Mitigates Renal Ischemia-Reperfusion Injury by Suppressing Oxidative Stress Wei-Cheng Tseng,¹ Der-Cherng Tarn,² ¹Div of Nephrology, Dept of Medicine, Taipei City Hospital Heping-Fuyou Branch, Taipei, Taiwan; ²Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Ischemic acute kidney injury (AKI) carries high mortality and current treatment remains unsatisfying. Induced pluripotent stem cell (iPS) is a promising therapeutic option for AKI; nonetheless, teratoma formation addresses critical safety concerns for iPS cell transplantation. iPS-derived conditioned medium (iPS-CM) is comparable with iPS cells on ameliorating acute lung injury but the beneficial role of iPS-CM on AKI remains unclear.

Methods: Rat model of renal ischemia-reperfusion injury (IRI) and NRK52E cells subjected to hypoxia-reoxygenation (H/R) were used to explore the role of iPS-CM on AKI. BUN, creatinine, tubular cell apoptosis, level of reactive oxygen species (ROS), expressions of proinflammatory cytokines and animal survival were investigated.

Results: Administration of iPS-CM intraperitoneally significantly improved renal function and decreased tubular cell apoptosis after renal IRI. Moreover, elevated ROS level in IRI-rat kidneys was markedly attenuated by iPS-CM. Co-culture of NRK52E cells with iPS-CM also significantly diminished H/R-induced apoptosis and ROS production. Furthermore, iPS-CM downregulated both H/R- and IRI-stimulated expressions of p38 MAPK, TNF- α , NF- κ B and caspase 3. Additionally, the IRI-related IL-6 and MCP-1 expressions were also suppressed by iPS-CM. Finally, after being subjected to renal IRI, the rats treated with iPS-CM demonstrated better survival as compared those treated with phosphate-buffered saline or normal control medium.

Conclusions: iPS-CM decreases renal IRI-related lethality by suppressing ROS, inflammation, and tubular cell apoptosis. iPS-CM may be a potential therapeutic option for kidney repair in ischemic AKI.



FR-PO246

Vascular Adhesion Protein-1 (VAP-1) Inhibition Ameliorate Cisplatin Induced Acute Kidney Diseases and Disorders (AKD) Daisuke Katagiri,^{1,2} Yoshifumi Hamasaki,¹ Kent Doi,^{1,3} Kousuke Negishi,¹ Takeshi Sugaya,⁴ Masaomi Nangaku,^{1,2} Eisei Noiri.¹ ¹Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; ²Apheresis and Dialysis, The Univ of Tokyo, Tokyo, Japan; ³Emergency and Critical Care Medicine, The Univ of Tokyo, Tokyo, Japan; ⁴CMIC Ltd, Tokyo, Japan.

Background: Cisplatin (CP) is a platinum compound that is used as an effective chemotherapeutic agent for many malignancies. Its nephrotoxicity is dose dependent, which often limits its administration. Research in the field of acute kidney diseases and disorders (AKD), including acute kidney injury (AKI), is important to prevent their progression to chronic kidney disease (CKD).

Methods: A new clinically relevant animal model using multiple low doses of CP was used to evaluate AKD. Human liver fatty acid-binding protein (L-FABP) transgenic (Tg) mice were administered 10 mg/kg of CP (three times, at 0, 1, 3 weeks) for four weeks. Vascular adhesion protein-1 (VAP-1) inhibitor that was recently reported to prevent fibrosis in organs was studied in this model. For treating group, mice received 2 mg/kg/day of PXS-4728A, a selective VAP-1 inhibitor, starting 3 weeks after the first CP administration.

Results: Moderate renal interstitial fibrosis occurred with multiple CP administration. Urinary L-FABP, one of the promising AKI biomarkers, increased about 10-fold one week after every CP injection. Although no further elevation of L-FABP was observed at 3W, following the omission of CP at 2W, L-FABP did not revert to baseline levels. Treatment of PXS-4728A for one week attenuated interstitial fibrosis in this model. VAP-1 inhibitor treatment remarkably reduced 4-HHE- and 8-OHdG-positive areas. The mRNA expressions of TGF- β , α -SMA, VEGF, and MCP-1 in the kidney were increased significantly by multiple CP treatments and attenuated by VAP-1 inhibitor treatment. Further, the inhibition of lipid accumulation in the S3 segments, together with L-FABP suppression was confirmed.

Conclusions: Multiple treatments with CP lead to moderate kidney dysfunction with increased biomarkers and renal fibrosis. As a standing point of onco-nephrology, VAP-1 inhibitors are promising candidates for the prevention of CKD in patients using CP for the treatment of malignancy.

Funding: Government Support - Non-U.S.

FR-PO247

Pulsed Focused Ultrasound Improves Mesenchymal Stem Cell Therapy for Acute Kidney Injury by Upregulating Renal Interferon-Gamma to Stimulate Stem Cell Production of Interleukin-10 Scott R. Burks, Matthew Nagle, Michele Bresler, Saejeong Kim, Blerta Milo, Joseph A. Frank. *Frank Lab, NIH Clinical Center, Bethesda, MD.*

Background: Pulsed focused ultrasound (pFUS) to kidneys enhances mesenchymal stem cell (MSC) homing to kidneys and improves outcomes when treating early or established acute kidney injury (AKI) compared to MSC infusions alone. However, mechanisms of improved combination therapy are unclear.

Methods: AKI was induced in C3H or interferon- γ (IFN γ)-deficient mice with cisplatin (15 mg/kg). pFUS (40W, 5%dc) was delivered to kidneys ~3hr before infusion of 10⁶ human MSC. MSCs were observed by immunostaining for human mitochondria. For some experiments, MSCs were treated in culture with recombinant IFN γ or siRNA against IL-10. Cytokines were analyzed by mouse- and human-specific ELISAs. Serum creatinine and blood urea nitrogen values were measured spectrophotometrically.

Results: Proteomic profiling of AKI kidneys revealed that pFUS upregulated renal IFN γ and after MSC homed to pFUS-treated kidneys, they produced more human IL-10 compared to MSC in kidneys without pFUS. pFUS+MSC in IFN γ -ko mice led to greater MSC homing to pFUS-treated kidneys, but MSCs failed to produce greater IL-10 and pFUS+MSC yielded identical outcomes as MSC alone (ie, no improvement from pFUS+MSC). Supplementing MSC with IFN γ improved AKI outcomes in C3H mice in the absence of pFUS, while the improved outcomes seen pFUS+MSC were abrogated by knocking down IL10 in MSC.

Conclusions: pFUS pretreatment of kidneys during AKI alters the renal molecular environment to increase MSC homing to treated kidneys. However, improved disease outcomes from combination therapy are the result of pFUS upregulating IFN γ in the kidney so that MSCs homing to pFUS-treated kidneys are subsequently conditioned to produce more IL10, which has been shown to improve AKI.

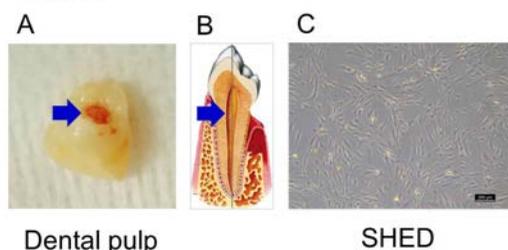
Funding: Other NIH Support - NIH Intramural Research Program

FR-PO248

Stem Cells from Human Exfoliated Deciduous Teeth Ameliorate Acute Kidney Injury in Mice Yuka Hattori,¹ Hangsoo Kim,² Naotake Tsuboi,² Akihito Yamamoto,¹ Seiichi Matsuo,² Shoichi Maruyama.² ¹Oral and Maxillofacial Surgery, Nagoya Univ Graduate School of Medicine, Japan; ²Nephrology, Nagoya Univ Graduate School of Medicine, Japan.

Background: Preclinical studies have indicated that administered mesenchymal stem cells (MSCs) ameliorated various types of renal injury and promoted the subsequent kidney repair. Recently, stem cells from human exfoliated deciduous teeth (SHED), which has been discarded as a medical waste, has received attention as a novel kind of MSCs.

Figure 1



The purpose of this study is to clarify the therapeutic effects of SHED on AKI induced by IRI.

Methods: Seven days after heminephrectomy, the renal artery and vein were clamped for 20 min to induce ischemia in male C57BL/6 mice. SHED or PBS as a control was administered into subrenal capsule right after the reperfusion. Blood, urine and tissue samples were collected. In order to confirm renoprotective potential of conditional media of SHED (SHED-CM) *in vitro*, H₂O₂ stimulation assay and scratch wound assay using mouse tubular epithelial cells (TECs) were also performed.

Results: Serum creatinine and BUN levels and urinary Kim-1 excretion were significantly decreased in SHED-treated group. Inflammatory cell infiltrations and inflammatory cytokine/chemokine concentrations of kidneys were significantly reduced in SHED-treated group. In *in vitro* assay, MCP-1 secreted from TEC was reduced and TEC proliferation and migration were significantly promoted by SHED-CM treatment.

Conclusions: In the present study, SHED administration successfully attenuated mouse IRI-induced AKI. Our results indicate that SHED exerted anti-inflammatory activity in early stage of inflammation and promote cell proliferation by paracrine effect, thereby renoprotective effect in a mouse model of ischemic kidney injury. These results suggest that SHED might offer novel stem cell resource, which can be applied for the treatment of ischemic kidney injury.

FR-PO249

Endothelial Autophagy and Endothelial-to-Mesenchymal Transition (EndoMT) in eEPC Treatment of Ischemic AKI Daniel Patschan, Susann Patschan, Gerhard A. Mueller. *Clinic of Nephrology and Rheumatology, Dept of Internal Medicine, Göttingen, Niedersachsen, Germany.*

Background: Autophagy potentially prolongs the cellular lifespan. Early Endothelial Progenitor Cells (eEPCs) protect mice from ischemic AKI. The mid-term prognosis in AKI critically depends on vascular rarefaction and interstitial fibrosis with the latter partly being induced by mesenchymal transdifferentiation of endothelial cells (EndoMT). Aim of the study was to determine the impact of eEPC preconditioning with different autophagy inducing agents (SAHA / Temsirolimus - Teme) in ischemic AKI.

Methods: Male C57/Bl6N mice were subjected to bilateral renal ischemia (40 minutes). Animals were injected with either untreated SAHA- or Temsirolimus-pretreated syngeneic murine eEPCs at the time of reperfusion. Mice were analyzed 48 hours and 4 weeks later. In addition, cultured eEPCs were treated with TGF- β +/- SAHA, autophagy (perinuclear LC3-II) and Stress Induced Premature Senescence (SIPS - SA-b-Gal) were evaluated 96 hours later.

Results: Cultured eEPCs showed reduced perinuclear density of LC3-II+ vesicles and elevated levels of SA-b-Gal after treatment with TGF- β alone, indicating impaired autophagy and aggravated SIPS. These effects were completely abrogated by SAHA. Systemic administration of either SAHA or Teme pretreated eEPCs resulted in elevated intrarenal endothelial p62 at 48 h and 4 weeks. This effect was most pronounced after injection of SAHA treated eEPCs. At 4 weeks endothelial expression of mesenchymal α SMA was reduced in animals receiving untreated and SAHA pretreated cells. In addition, SAHA treated cells reduced fibrosis at week 4. Teme in contrast aggravated EndoMT. Postschismic renal function declined after renal ischemia and remained unaffected in all experimental cell treatment groups.

Conclusions: In ischemic AKI, intrarenal endothelial autophagy may be stabilized by systemic administration of pharmacologically preconditioned eEPCs. Early EPCs can reduce postschismic EndoMT and fibrosis in the mid-term. Autophagy induction in eEPCs may either increase or decrease the mesenchymal properties of intrarenal endothelial cells. Thus, endothelial autophagy induction in ischemic AKI is not a renoprotective event per se.

FR-PO250

Impact of Timing Administration of Mesenchymal Stromal Cells on Serum Creatinine following Renal Ischemia/Reperfusion in Rats Pauline Erpicum,^{1,2} Pascal Rowart,² Laurence Poma,² Jean-Marie H. Krzesinski,^{1,2} Oliveir Detry,³ Francois Jouret.^{1,2} ¹Nephrology, Univ of Liege Hospital (ULG CHU), Liege, Belgium; ²GIGA Cardiovascular Sciences, Univ of Liege, Liege, Belgium; ³Abdominal Surgery and Transplantation, Univ of Liege Hospital (ULG CHU), Liege, Belgium.

Background: Experimental models of renal ischemia/reperfusion (I/R) have suggested protective effects of mesenchymal stromal cells (MSC) therapy. Still, parameters of MSC injection, including volume, route and timing of cell administration, remain largely debated. Particularly, MSC infusion in mouse has been shown to be beneficial "a priori" but deleterious "a posteriori" of renal I/R injury.

Methods: In order to further investigate the influence of the timing of MSC administration, we used 10-week-old Lewis rats categorized in 4 groups. Groups 1 (MSC D-7, n=10) and 2 (MSC D+1, n=7) received caudal i.v. injection of MSC (1.5x10⁶ in 1 mL of saline) 7 days before or 1 day after renal I/R, respectively. Control groups 3 (saline D-7, n=6) and 4 (saline D+1, n=6) received equal volume of saline at similar time points. Left renal ischemia (by clamping of the renal pedicle) lasted 45 minutes. Right nephrectomy was simultaneously performed. Blood sample was collected from inferior vena cava at 48 hours post reperfusion. MSC phenotype was confirmed by FACS analysis.

Results: In groups 1 and 3, serum creatinine (Scr) reached 1.4 \pm 0.7 versus 2.4 \pm 0.8 mg/dL, respectively (p<0.05). In groups 2 and 4, Scr was 4.9 \pm 0.7 versus 3.3 \pm 0.9 mg/dL, respectively (p<0.001). Furthermore, Scr levels were statistically worse when MSC were administered after renal I/R in comparison to a priori infusion (p<0.0001).

Conclusions: MSC administration 7 days prior to renal I/R may attenuate kidney injury in comparison to (i) saline infusion or (ii) MSC infusion 1 day after renal I/R. Conversely, on the basis of Scr levels, MSC therapy performed after renal I/R worsens kidney injury in rats.

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FR-PO251

Cytosolic Phospholipase A2 Regulates the G2 to M Transition by Modulating the Activity of Tumor Suppressor Sirtuin 2 Said Movahedi naini, Joseph V. Bonventre. *Brigham and Women Hospital, Renal Division, Boston, MA.*

Background: SIRT2, a tumor suppressor gene, contributes to the control of the G2 to M transition checkpoint of the cell cycle under cellular stress. However, the mechanisms underlying both SIRT2 activation and the regulation of the G2 to M transition remain largely unknown. Here, we describe the regulatory function of cPLA₂ α on SIRT2 activity and the G2/M transition.

Methods: G2 to M transition *in vitro* was evaluated in LLC-PK1 cells overexpressing SIRT2 or cPLA₂ α and in mouse embryonic fibroblasts (MEFs) derived from *cpla2 α* ^{-/-} mice. G2 to M transition *in vivo* was assessed in *cpla2 α* -deficient mice during moderate IRI and under mitotic stress induced by colchicine. G2 and mitotic cells were identified by staining with pH3 and MPM-2 antibodies, respectively. Analysis of the phosphorylation state of SIRT2 was carried out in the presence or absence of cPLA₂ α *in vitro* by kinase assay and *in vivo* using a SIRT2 ser331 phosphospecific antibody.

Results: cPLA₂ α , SIRT2, and cyclin A-Cdk2 form a multiprotein complex at the G2/M transition *in vivo* and *in vitro*. cPLA₂ α acts as a bridge in this complex to promote binding of SIRT2 to cyclin A-Cdk2. Cyclin A-Cdk2 then phosphorylates SIRT2 at ser331. Phosphorylation of SIRT2 at ser331 diminishes its catalytic activity and reduces its binding affinity to centrosomes and mitotic spindles. This detachment of SIRT2 from mitotic spindles in the presence of cPLA₂ α promotes G2 to M transition. In *cpla2 α* ^{-/-} MEFs and kidney tubular cells SIRT2 was hypophosphorylated at the G2/M transition. Lack of cPLA₂ α in these cells resulted in a reduction in the number of mitotic cells in response to mitotic stress.

Conclusions: cPLA₂ α is a regulator of the G2 to M transition *in vitro* and during ischemia/reperfusion injury in kidney epithelial cells. This function of cPLA₂ α may be further exploited to better understand the important link between cPLA₂ α and tumorigenesis and between inflammation and the age-related disorders such as Alzheimer's disease, in which SIRT2 has been implicated.

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FR-PO252

The Cytohesin Guanosine Exchange Factors Are Required to Promote HGF-Mediated Renal Recovery After Acute Kidney Injury in Mice Lorraine C. Santy, Marta Reviriego-Mendoza. *Dept of Biochemistry and Molecular Biology, Pennsylvania State Univ, Univ Park, PA.*

Background: The lack of current treatment and preventable measures for acute kidney injury (AKI) in hospitalized patients results in an increased mortality rate of up to 80% and elevated health costs. The molecular aspects of kidney injury and repair are still uncertain. Hepatocyte growth factor (HGF) promotes recovery of the injured kidney by inducing survival and migration of tubular epithelial cells to repopulate bare tubule areas. HGF-stimulated kidney epithelial cell migration requires the activation of ADP-ribosylation factor 6 (Arf6) and Rac1 via the cytohesin family of Arf-guanine-nucleotide-exchange-factors (GEFs), *in vitro*.

Methods: We used an ischemia and reperfusion injury (IRI) mouse model to analyze the effects of modulating this signaling pathway on kidney recovery. We treated IRI mice with either HGF, the cytohesin inhibitor SecinH3, or a combination of both. Kidney function was assessed by measuring creatinine (Cre) and blood urea nitrogen (BUN) levels. Standard H&E staining was used to assess kidney structures and immunohistochemistry was performed to detect active-Rac1 and active-Arf6.

Results: Simultaneous treatment with SecinH3 and HGF blocks the ability of HGF to promote kidney recovery as evidenced by Cre and BUN levels. Immunohistochemistry showed that HGF treatment promoted recovery of tubule structure, and had enhanced levels of active, GTP-bound Arf6 and GTP-Rac1. SecinH3 treatment, however, caused a dramatic decrease in GTP-Arf6 and GTP-Rac1 levels when compared to kidney sections from HGF treated IRI mice. Additionally, SecinH3 counteracted the renal reparative effects of HGF.

Conclusions: We show that HGF-dependent damaged kidney recovery requires the function of a cytohesin-dependent signaling module, and that inhibiting cytohesins counteracts HGF-stimulated recovery. In addition, we demonstrate that HGF treatment of ischemic mice promotes the activation of Arf6 and Rac1 in the recovering kidneys in a cytohesin-dependent manner, and that cytohesin activity is required to promote epithelial repopulation of kidney tubules and thus kidney recovery.

Funding: NIDDK Support

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Underline represents presenting author.

FR-PO253

Regulation of Kidney Injury Molecule-1-Mediated Efferocytosis by Rho GTPases Ola Ismail,¹ Xizhong Zhang,² Lakshman Gunaratnam.^{1,2} ¹*Dept of Medicine, Western Univ, London, ON, Canada;* ²*Matthew Mailing Centre and Lawson Research Inst, London Health Sciences Centre, London, ON, Canada.*

Background: Kidney injury molecule 1 (KIM-1) is a phagocytic receptor for apoptotic cells that is specifically upregulated on the apical membrane of proximal tubule cells (PTECs) after acute kidney injury. KIM-1-mediated clearance of apoptotic cells (efferocytosis) has been shown to protect from tissue damage during acute kidney injury by down-regulating innate immunity and inflammation. As cytoskeletal remodeling is essential for phagocytosis, we examined the relative importance of Rac1 and RhoA, two key Rho GTPases that mediate actin remodeling, in KIM-1-dependent efferocytosis. We also investigated a possible link between Gal2, which we previously identified as a KIM-1-interacting protein, and these Rho GTPases.

Methods: To study the role of Rac1 and RhoA in KIM-1-mediated uptake of apoptotic cells, we utilized chemical inhibitors or plasmids encoding dominant negative forms of Rac1 and RhoA proteins, and measured the uptake of apoptotic cells by flow cytometry. Using commercially available GTPase pull-down assays, we measured the endogenous Rac1 and RhoA activity in KIM-1-expressing cells after apoptotic cell-stimulation. To decipher whether these Rho GTPases are down-stream mediators of Gal2-KIM-1 signaling, we silenced Gal2 using siRNA and measured Rac1 and Rho GTPase activity.

Results: Inhibition of Rac1 resulted in a significant decrease in KIM-1-mediated phagocytosis, whereas inhibition of and RhoA increased it. RhoA activity gradually increased during phagocytosis and peaked during the later stages of phagocytosis, whereas Rac1 activity remained constant over the entire course of phagocytosis. Furthermore, silencing a key KIM-1-interacting protein, Gal2, caused a significant decrease in RhoA activity.

Conclusions: We conclude that Rac1 and RhoA play opposing roles during KIM-1-mediated efferocytosis, where RhoA serves to mediate signaling by KIM-1 and its interacting partner, Gal2.

Funding: Government Support - Non-U.S.

FR-PO254

Periostin Induces Kidney Fibrosis After Ischemia-Reperfusion Injury via p38 MAPK Pathway Jung Nam An,^{1,2} Seung Hee Yang,³ Jin Ho Hwang,⁴ Chun Soo Lim,^{1,2} Yun Kyu Oh,^{1,2} Yon Su Kim,² Jung Pyo Lee.^{1,2} ¹*Seoul National Univ Boramae Medical Center;* ²*Seoul National Univ Hospital;* ³*Seoul National Univ Kidney Research Inst;* ⁴*Chung-Ang Univ Hospital, Republic of Korea.*

Background: Periostin, a matricellular protein, has been reported to play a crucial role in inflammatory and fibrotic mechanism. We hypothesized that periostin involves in the progression of acute kidney injury to kidney fibrosis.

Methods: To establish a kidney progression model, we induced unilateral ischemia-reperfusion injury of left kidney pedicle for 30minutes in wild type (WT) C57BL/6 mice and *Postn null* mice (*Postn*^{-/-}), and observed during 4 to 6 weeks. In addition, inner medulla collecting duct cell line was subjected to put in the hypoxic incubator (1% O₂, 5% CO₂, and 94% N₂) for 24 and 72 hours.

Results: After 4 to 6 weeks, the left kidneys in *Postn null* mice were significantly less atrophied and less small in weight compared to those of WT mice. Apparent tubular atrophic changes and collagen fiber deposition, and expressions of collagen I, S100A4, and periostin were also remarkably alleviated in *Postn null* mice compared within WT mice. Furthermore, the expressions of phosphorylated p38 mitogen-activated protein kinase (p-p38 MAPK) and cleaved caspase-3 were significantly decreased in *Postn null* mice compared to in WT mice. *Postn null* mice also attenuated intra-kidney mRNA expression of fibrosis markers, p53, caspase 9, and p-p38 MAPK. *In vitro*, hypoxic injury during 72 hours resulted in cellular morphologic changes and increased the expressions of several fibrosis markers, periostin, and p-p38 MAPK. Treatment of recombinant periostin in hypoxic condition magnified the cellular changes and the expression of p-p38 MAPK, which were comparable to treatment with transforming growth factor- β 1. In contrast, inhibition of p38 MAPK attenuated the periostin induced inflammation and fibrosis.

Conclusions: In conclusion, periostin is related to the progression via p38 MAPK pathway to kidney fibrosis following acute kidney injury triggered by hypoxic or ischemic insult. Periostin ablation could have protective effects in kidney progression.

FR-PO255

Tim-3/Gal-9 Pathway Activation Ameliorates Renal Ischemia Reperfusion Injury by Shifting the Balance of Activated CD4⁺ T Cell Immune Response in Mice Yamei Wang, Yuhong Tao. *Dept of Pediatrics, West China Second Univ Hospital, Sichuan Univ, Chengdu, Sichuan, China.*

Background: Renal ischemia reperfusion injury (IRI) is characterized by kidney inflammation. Galectin-9 (Gal-9) is identified as a T-cell immunoglobulin domain and T mucin domain protein-3 (Tim-3) ligand, and Tim-3/Gal-9 interaction acts as a specific inhibitor of immune response. The purpose of this study was to study whether activation of Tim-3/Gal-9 pathway can ameliorate renal IRI by shifting the balance of activated CD4⁺ T cell immune response in mice.

Methods: Expression of renal Gal-9 and Tim-3 were detected in mice with left renal IRI at baseline, day 3,10. The percentage of Th1, Th17 and Foxp3⁺ Tregs and their mRNA expression in kidney were measured. rAAV9 carrying Gal-9 was injected to mice two weeks before kidney IRI to overexpress Gal-9 and activate Tim-3/Gal-9 pathway. Then, CD4⁺ T cell subsets and cytokines in kidney were evaluated at day 3 and 10.

Results: The expression of Gal-9 and Tim-3 in IR kidney at day3 and 10 increased (P<0.05). The percentage of Foxp3⁺ Treg in CD4⁺ T cells and Foxp3 mRNA was up-regulated with time. Compared with normal control kidney, the mRNA levels of Foxp3, Gal-9 and Tim-3 of kidney at day 3, 10 after renal IRI were increased in IRI kidney. Compared with empty virus group at 3 days and 10 days after IRI, over-expression of Gal-9 can reduce tubular damage in the healing phase of renal IRI. Protein plex results showed that the expression levels of inflammatory cytokines including TNF- α , IFN- γ , IL-17 and IL-6 was decreased, while the expression level of IL-10 was increased. The mRNA level of Foxp3 in kidney, the percentage of Foxp3⁺ Treg cells in IRI kidneys was increased. However, the proportions of Th1, Th17 cells and the gene levels of T-bet and ROR γ t were decreased. In the bilateral renal IRI model, the mice mortality was decreased after rAAV-Gal-9 intervention.

Conclusions: Tim-3/Gal-9 pathway activation can ameliorate kidney damage and increase survival rate of mice after renal IRI, inhibit Th1 and Th17 cell-mediated immune responses, and promote the proliferation of Foxp3⁺ Treg after renal IRI, which may be an important mechanism for renal protection of Gal-9 /Tim-3 pathway.

Funding: Government Support - Non-U.S.

FR-PO256

Administration of an Inhibitor of I κ B Kinase Inhibitor at 24 Hours After Acute Kidney Injury Improves Functional Recovery and Prevents Renal Fibrosis Florence Lilian Johnson,¹ Nimesh Patel,¹ Massimo Collino,² Christoph Thiemermann.¹ ¹*Translational Medicine and Therapeutics, The William Harvey Research Inst, Queen Mary Univ of London, London, United Kingdom;* ²*Dept of Drug Science and Technology, Univ of Turin, Turin, Italy.*

Background: Acute kidney injury (AKI) is a major risk factor for the development of chronic kidney disease (CKD). Renal ischemia may cause post-inflammatory scarring leading to the loss of nephrons and the development of fibrosis. Nuclear factor kappa-B (NF- κ B) is a family of transcription factors activated post-ischemia, but its role in the progression of AKI to CKD is unknown.

Methods: Male Wistar rats were subject to a RH nephrectomy and LH unilateral renal ischemia for 30 min, or nephrectomy only (sham) (n=8). Animals subject to ischemia (control animals) were allowed to recover and culled at 1 (n=4), 2 (n=4), 7 (n=4), 14 (n=4) or 28 (n=7) days (d) post reperfusion. A separate group of animals subjected to ischemia were administered IKK16, an inhibitor of I κ B kinase (IKK), at 24h post AKI (1mg/kg i.v in 10% DMSO), and culled at 2 (n=4), 7 (n=8) or 28d (n=7).

Results: Compared to sham-operated rats, rats subjected to unilateral renal ischemia developed AKI (increases in serum creatinine and decreases in the estimated creatinine clearance). The delayed administration of IKK16 at 24h post AKI (at peak creatinine values) significantly improved renal functional recovery and structural injury at 48h post AKI. Compared to sham-operated rats, rats culled at 7d post AKI demonstrated significant increases in α smooth muscle actin (α -SMA) and CD68⁺ staining for myofibroblasts and macrophages, respectively. IKK16 administration significantly decreased α -SMA and CD68⁺ staining at 7d post AKI. Rats culled at 28d post AKI demonstrated a significant increase in Sirius red staining compared to sham rats, indicating the development of fibrosis. Administration of IKK16 at 24h significantly attenuated Sirius red staining, and therefore the level of fibrosis at 28d.

Conclusions: Inhibition of IKK at 24h post AKI (at peak creatinine values) improves renal functional recovery at 48h post AKI, and reduces the degree of fibrosis observed at 28d.

FR-PO257

The Peroxisome Proliferator-Activated Receptor γ (PPAR- γ) Agonist Pioglitazone Prevents NF- κ B Activation in Cisplatin Nephrotoxicity by Reducing p65 Acetylation Through AMPK-SIRT1/p300 Pathway Junhua Li, Ying Zhang, Jiong Zhang, Ying Yao, Gang Xu. *Dept of Nephrology, Tongji Hospital, Huazhong Univ of Science and Technology, Wuhan, China.*

Background: NF- κ B is a ubiquitously expressed transcription factor controlling the expression of numerous genes involved in inflammation. The aim of this study was to evaluate whether the activation of peroxisome proliferator-activated receptor- γ (PPAR- γ) could attenuate cisplatin-induced NF- κ B activation in cisplatin nephrotoxicity.

Methods: Acute kidney injury model was established of by intraperitoneal injection of cisplatin. C57BL/6 mice were divided into three groups: normal group; model group; and treatment group, with pioglitazone gavage of three days. Respectively after injection in 24, 48 and 72 hours, the mice serum were collected for renal function and kidney specimen for pathological, Western blot, immunohistochemistry and real time PCR detection.

Results: Our results showed PPAR- γ agonist Pioglitazone could decrease the expression of NF- κ B p65 transcription target genes such as pro-inflammatory cytokines interleukin 6 (IL-6), interleukin-1 b(IL-1b), and tumor necrosis factor- α (TNF- α) and inhibit cell apoptosis and MPO infiltration in cisplatin nephrotoxicity. Suppressing NF- κ B activity following Pioglitazone treatment was involved in inhibiting I κ B- α degradation, phosphorylation modification and NF- κ B p65 subunit translocation induced by cisplatin injection. The NF- κ B p65 subunit translocation is dependent on p65 acetylation, which is mainly regulated by SIRT1 or p300. Of note, The subsequent AMP kinase (AMPK) activation not only decreases the p300 phosphorylation, activation and its interaction with p65, but also increases the SIRT1 expression, activation and binding to p65, leading to a significant reduction p65 acetylation. Interestingly, the reduction in expressions of IL-6, TNF- α and IL-1 β , inhibition of cell apoptosis and MPO infiltration following Pioglitazone treatment in cisplatin nephrotoxicity were attenuated by the PPAR-gantagonist GW9662.

Conclusions: Our results suggest that PPAR- γ agonist Pioglitazone prevents NF- κ B activation in cisplatin nephrotoxicity by reducing p65 acetylation through AMPK-SIRT1/p300 pathway.

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FR-PO258

Competitive Inhibition of CD95L Reduces Inflammation, but Only Modestly Improves Outcomes in Experimental Ischemia-Reperfusion Injury Luis Eduardo Becker, Clara Daschner, Martin G. Zeier, Christian Morath. *Nephrology, Univ of Heidelberg, Heidelberg, Germany.*

Background: After previous encouraging results in CD95L (FasL) mutant mice in ischemia-reperfusion injury (I/R) models, we sought to investigate the effect of the competitive pharmacologic inhibition of CD95 (FAS) in kidney I/R using APG101, an orphan drug developed for the treatment of recurrent glioma, which has shown a good patient tolerability in phase I and II clinical studies.

Methods: C57BL/6 mice treated with different dosages of APG 101 (10, 30 or 100 µg/kg-body weight, single-dose, 12h before I/R) or vehicle (PBS) alone were submitted to a 30min bilateral renal I/R. Sham-op animals were either treated with the highest APG101 dose or PBS. The experiment was further divided into two observation periods: day 2 (injury phase) and day 7 (recovery phase). Serum and kidney tissue analysis were performed focusing on function recovery, cell proliferation, macrophage infiltration and relevant markers of the target pathway. Results are given as mean±SD.

Results: Optimal serum CD95L saturation was only achieved in the APG 100µg/kg group (98.4±0.35% and 96.9±1.3% at day 2 and 7, respectively), so that experiments were further conducted with this dosage. At day 2, serum creatinine was significantly higher in the I/R PBS group, but not in the I/R APG group compared to sham-op (0.26±0.12 and 0.20±0.07 vs. 0.09±0.03 mg/dl P<0.05), a similar pattern was seen in macrophage infiltration and MCL-1 mRNA expression in the kidney, both persisting until day 7. Apoptosis, however, was similar between the I/R groups in both observation periods. APG treatment markedly reduced cell proliferation in both sham and I/R animals compared to PBS (0.5±0.9 vs. 8.4±5.7 Ki67 positive cells/hpf, p=0.0004), which was observed at day 2, but didn't persist until day 7.

Conclusions: Despite an anti-inflammatory effect, the APG101-induced impairment of the tubular cell proliferation may have hampered the early recovery phase after I/R leading to the modest results.

FR-PO259

Oral Treatment with PBI-4050 Reduces Ischemia-Reperfusion-Induced Fibrosis Jean-François Thibodeau, Mikael Tremblay, Brigitte Grouix, Liliane Geerts, Alexandra Felton, François Sarra-Bournet, Pierre Laurin, Lyne Gagnon. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in CKD patients, displays antifibrotic activities via a novel mechanism of action. In a double-blind ascending dose (400 to 2400 mg) clinical phase I trial, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant side effects. Clinically, ischemia is a leading cause of acute kidney injury (AKI), which may result from a variety of conditions, such as decreased cardiac output, renal vascular occlusion or obstruction, and kidney transplantation. The aim of this study was to investigate the anti-fibrotic activity of PBI-4050 in a mouse model of acute ischemic kidney injury.

Methods: Renal ischemia-reperfusion (IR) injury was induced by the clamping of the left renal pedicle for 60 minutes in C57BL/6 mice (6-8 week old). Mice were treated with oral administration of vehicle or PBI-4050 (200 mg/kg) from day -3 to day 13 and sacrificed at day 14.

Results: Renal IR-injury induced a rise in serum creatinine at day 2 that was prevented by oral treatment with PBI-4050. At day 14, mice suffering from renal IR demonstrated a loss in hematocrit which was also prevented by PBI-4050 treatment. Furthermore, histomorphometric analysis demonstrated a significant increase in renal fibrosis, determined by medullary collagen accumulation in mice with IR-injury, which was significantly reduced by PBI-4050 treatment. In addition, PBI-4050-treatment reduced kidney type-III collagen mRNA expression.

Conclusions: Taken together, these pre-clinical results suggest that PBI-4050 offers the potential as a novel therapy for the treatment of AKI and may delay or prevent the onset of fibrosis in renal transplant recipients.

FR-PO260

Cisplatin Acute Kidney Injury and Conversion to Chronic Kidney Disease Robert L. Safirstein,^{1,2} Heino Velazquez,^{1,2} Richard Torres,² Gilbert W. Moeckel,² Gary V. Desir.^{1,2} ¹*Nephrology, VACT HealthCare System, West Haven, CT;* ²*Nephrology, Yale Univ, New Haven, CT.*

Background: Chronic Kidney Disease (CKD) develops in humans after repeated doses of cisplatin (CP). We report on a new model to investigate the mechanism of this form of CKD.

Methods: 8-week old C57BL6 mice were given either a single or double dose (2 weeks apart) of CP (15 mg/kg) and studied 2,4,6,9 and 16-25 weeks after the first dose. GFR was measured by inulin clearance followed by intravascular perfusion-fixation. Immunohistochemistry and Multiphoton Microscopy (MPM) were applied to the fixed tissue.

Results: GFR fell precipitously to below 50% of controls 2 weeks after the second dose and progressed without hypertension, loss of glomerular number, or glomerulosclerosis. Kidney weight fell as a result of loss of cortical tissue. Collagen deposition increased but was mainly restricted to peritubular locations along the cortico-medullary region. Influx of macrophages, increased cell cycle activity (Ki67) and apoptosis (TUNEL) were followed by vascular rarefaction. Ki67 failed to increase after the second dose as it did after a single dose. The cyclin-dependent kinase inhibitor protein p21 increased and paralleled the lack

of cell cycle activity. Abnormal glomerulotubular junctions (GTJ) developed only after the second dose, which included loss of megalin positive parietal epithelial cells and the formation of atubular glomeruli. These changes correlated well with the development of progressive renal insufficiency.

Conclusions: MPM uncovered abnormalities of the GTJ that marked the transition from AKI to CKD in CP-induced CKD. Coupled with the failure of the proximal tubule (PT) to re-enter the cell cycle suggests a causal relationship between failed repair of this segment and the conversion of AKI to CKD. The increased expression of the p21 gene seen here and its demonstrated role in progression in the renal ablation model of CKD suggests its sustained activation may cause the conversion of AKI to CKD. Understanding why injured PT cells fail to re-enter the cell cycle following the second dose of CP is likely to yield new means to prevent CP-induced CKD, which may be applicable to other forms of AKI to CKD conversion.

Funding: NIDDK Support, Veterans Administration Support

FR-PO261

The MEK1/2 Inhibitor, U0126, Decreases Cisplatin-Induced AKI and Slows Cancer Growth in Mice Kameswaran Ravichandran, Abdullah Ozkok, Qian Wang, Alkesh Jani, Charles L. Edelstein. *Univ of Colorado Denver.*

Background: Nephrotoxicity is cisplatin's major dose-limiting side effect as a chemotherapeutic agent. We have developed a model of 4 week, low dose cisplatin (Cis)-induced AKI in mice with cancer. In the 4 week model of AKI, there is an increased ERK expression in kidneys.

Methods: Wild type C57BL/6 mice were injected subcutaneously with murine lung cancer cells derived from C57BL/6 mice. Ten days later, Cis (10 mg/kg/week) was given for 4 weeks. Mice were treated with the ERK inhibitor U0126 (5 mg/kg 2 times a week for 4 weeks).

Results: There was a significant decrease in BUN, SCr and serum NGAL in mice treated with Cis+U0126 vs. Cis only. Tumor weight and volume was decreased in mice treated with vehicle+U0126 vs vehicle alone demonstrating that U0126 decreases tumor growth. Tumor weight and volume was decreased in mice treated with Cisplatin+U0126 vs. Cisplatin alone demonstrating that U0126 significantly increased the therapeutic effect of cisplatin.

	Vehicle	Vehicle+U0126	Cis	Cis+ U0126
BUN (mg/dL)	26.7	27.1	58.9*	40.1**
Scr (mg/dL)	0.1	0.1	0.3*	0.18***
sNGAL (ng/mL)	90 ± 13	185±34	569*	313**
Tumor weight (g)	1.8	1+	0.9+	0.5**
Tumor volume week 1 (mm ³)	19	1	8	1.8
Tumor volume week 4 (mm ³)	789	235+	341+	70++

N=11-15 per group. *P<0.01 vs. Vehicle. **P<0.05 vs. Cis. ***P<0.05 vs. Cis, NS vs. vehicle. +P<0.01 vs Vehicle. ++P<0.01 vs. Vehicle and Cis

Conclusions: U0126 decreased cisplatin-induced AKI. In addition, U0126 decreased tumor growth and improved the therapeutic effect of cisplatin. Discovery of a drug that decreases cisplatin-induced AKI and improves the therapeutic effect of cisplatin would be a significant finding for patients with cancer.

Funding: Veterans Administration Support

FR-PO262

Glycogen Synthase Kinase-3 Regulates Fibroblast Activation and Development of Fibrosis following Renal Ischemia/Reperfusion in Mice Shailendra Pratap Singh,¹ Shixin Tao,¹ Timothy A. Fields,¹ Raymond C. Harris,² Reena Rao.¹ ¹*The Kidney Inst, Dept of Medicine, Univ of Kansas Medical Center, Kansas City, KS;* ²*Dept of Medicine, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Glycogen synthase kinase-3β (GSK3β) is a serine /threonine protein kinase that plays an important role in renal tubular injury and regeneration in acute kidney injury. However its role in the development of renal fibrosis, often a long-term consequence of acute kidney injury is unknown. Using a mouse model of renal fibrosis induced by ischemia/reperfusion (I/R) injury, we demonstrate increased GSK3β expression and activity in fibrotic kidneys.

Methods: Bilateral I/R was carried out on male C57/BL6J mice; both renal pedicles were exposed by flank incision and clamped for 30 minutes at 37°C. GSK3inhibitor (TDZD-8) was administered by daily IP injection at 1mg/Kg BWt. dose starting 1h before (TDZD-pre) or 48h after I/R (TDZD-post). Studies were also carried out in rat fibroblast NRK-49F cells.

Results: GSK3β expression and activity increased significantly starting 48h after I/R and remained high in the fibrotic kidneys 12 days after I/R. GSK3β was detected in renal myofibroblasts and tubules. GSK3 inhibition suppressed fibrosis, with significantly reduced myofibroblast population, extracellular matrix deposition, inflammatory mediators and TGF-β signaling in TDZD-pre and TDZD-post treatment groups compared to vehicle treated group. *In vitro*, TGF-β1 treatment increased GSK3β expression in NRK-49F cells and GSK3 inhibition abolished TGF-β1 induced SMAD-3 activation and α-SMA expression. Importantly, overexpression of constitutively active GSK3β stimulated α-SMA expression

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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even in the absence of TGF- β 1 treatment. These results suggest that TGF- β regulates GSK3 β expression, which in turn is important for TGF- β / SMAD-3 signaling and fibroblast-to-myofibroblast differentiation.

Conclusions: The study thus demonstrates that GSK3 could promote renal fibrosis by activation of TGF- β signaling and the use of GSK3 inhibitors might represent a novel therapeutic approach for progressive renal fibrosis that develops as a consequence of AKI.

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FR-PO263

Regulating Cx43 and TRPC6 Expression Protects Renal Epithelial Damage in a Rat AKI Model Zilong Li, Wei Wang, Juan Wang, Lining Wang. *Dept of Nephrology, First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning, China.*

Background: Intracellular Ca²⁺ homeostasis plays an essential role in maintaining normal cell function. Connexin43 (Cx43) and transient receptor potential channel (TRPC6) has been reported to regulate Ca²⁺ entry in some pathologic conditions. The aim of this study was to elucidate whether the modifier protein of glyceraldehyde-3-phosphate dehydrogenase (MP) and ATP-MgCl₂ could regulate Cx43 and TRPC6 in a rat model of acute kidney injury (AKI).

Methods: Male Sprague-Dawley rats were divided into the following groups: normal control, gentamicin-treated, MP plus gentamicin-treated, ATP-MgCl₂ plus gentamicin-treated (n=15 for each), as well as control group for MP and ATP-MgCl₂ alone (n=5 for each). Levels of serum creatinine (sCr) for each group were measured on the 14th days of treatment. The "in vivo cryotechnique" was used for preparing kidney specimen as before. Immunohistochemistry staining for Cx43 and TRPC6 was performed.

Results: The gentamicin-treated group showed a significant increase in sCr compared to the normal control group. Co-treatment of gentamicin with MP and/or ATP-MgCl₂ produced marked decreases preventing the increase of sCr. Under light microscope, the gentamicin-treated group showed tubular epithelium damage indicating AKI. This was attenuated by MP and/or ATP-MgCl₂ co-treatment. Immunohistochemistry staining indicated that MP and/or ATP-MgCl₂ co-treatment prevented gentamicin-induced down-regulation of Cx43 and TRPC6 in renal epithelium cells using the "in vivo cryotechnique". Furthermore, the expressions of Cx43 and TRPC6 in gentamicin-treated group showed much weaker intensity using conditional fixation method compared to that using "in vivo cryotechnique" suggesting there might be artificial damage during the conditional fixation procedure.

Conclusions: Using a rat model of AKI, MP and ATP-MgCl₂ were able to prevent the down-regulation of Cx43 and TRPC6, which might reduce Ca²⁺ entry and its downstream signaling, thus minimizing the damage in the renal epithelium cells.

FR-PO264

S-Glutathionylation of TAZ Might Contribute to Acute Kidney Injury and Repair Rajesh kumar Gandhirajan,¹ Benedikt Bernd Walla,¹ Manaswita Jain,¹ Malte P. Bartram,¹ Markus M. Rinschen,¹ Thomas Benzing,^{1,2} Bernhard Schermer,^{1,2} ¹Dept II of Medicine and Center for Molecular Medicine, Univ of Cologne, Cologne, NRW, Germany; ²Cluster of Excellence on Cellular Stress Responses in Ageing-Associated Diseases (CECAD), Univ of Cologne, Cologne, NRW, Germany.

Background: The clinical syndrome of acute kidney injury (AKI) is one of the most important diseases in nephrology and associated with increased morbidity and mortality. Kidney displays a remarkable potential for repair even after severe acute injury. Recent studies identified the Hippo pathway as a master regulator of organ growth and proliferation and uncovered the importance of the two mammalian Hippo-signaling effector molecules YAP and TAZ as regulators of proliferation and apoptosis during kidney development. The objective of the current study is to demonstrate that TAZ undergoes redox regulation via s-glutathionylation.

Methods: Immunoprecipitation, reporter gene assay, XTT assay, cycloheximide assay.

Results: Our findings indicate that exposure to hydrogen peroxide (H₂O₂) increased TAZ/TEAD transcriptional activity without affecting YAP/TEAD. Consistently, TAZ/TEAD interaction was slightly enhanced upon H₂O₂ exposure. Furthermore, H₂O₂ exposure increased nuclear localization of TAZ in a stable NIH3T3/Flp-in cell line expressing TAZ-GFP. We confirmed s-glutathionylation using recombinant TAZ protein in vitro and biotinylated glutathione ester in cell culture. To identify cysteine residues undergoing s-glutathionylation we generated TAZ C>A mutants. Reporter assays revealed that TAZ C358A showed increased transactivation of TEAD, the effect on cell proliferation and migration was also enhanced in TAZ C358A mutant. Finally, cycloheximide chase assay revealed that all of the TAZ mutants exhibited increased stability following 6h incubation.

Conclusions: Our data indicate a novel mechanism how pro-proliferative TAZ activity is regulated by ROS via s-glutathionylation, which could play an important role in tissue injury and repair. Currently, we are following the hypothesis that ROS derived from constitutively active NOX4 could modulate TAZ activity in the kidneys and we are investigating the importance of s-glutathionylation of TAZ *in vivo*.

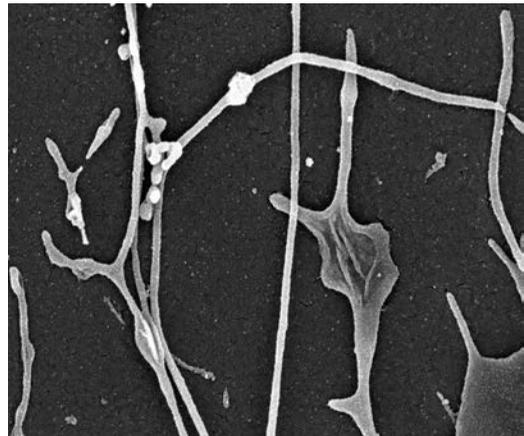
FR-PO265

Bud-Like Structure Capable of Developing to Lamellipodia in Wound Healing of Tubular Epithelium – A Scanning Electron Microscopic Approach Kiyoko Inui,¹ Hiroyuki Morita,² Yoshihiko Inoue,¹ Shinya Omiya,¹ Tomoaki Miyazaki,¹ Ashio Yoshimura.¹ ¹Div. of Nephrology, Showa Univ Fujigaoka Hosp., Yokohama, Kanagawa, Japan; ²Div. of Endocrinology and Metabolism, Aichi Medical Univ School of Medicine, Nagakute, Aichi, Japan.

Background: Cell migration is essential in wound healing during which filamentous (F)-actin assembly plays a pivotal role. Cell biological approaches, using confocal microscopy, succeeded in identifying molecules regulating the assembly, such as the Arp2/3 complex, N-WASP, cofilin, and profilin. Although cells form filopodia (microspike) and lamellipodia (membrane), and move forward, much remains to be seen in the ultrastructure of these processes.

Methods: Rat tubular epithelium (NRK-52E) was cultured, grown to confluency, and scratched. The cells were subjected to scanning electron microscopy (SEM) at various time points. In separate experiments, immunoelectron microscopy was performed using an antibody against Arp3. Lastly, 60% confluent NRK-52E cells were cultured in the presence or absence of si-RNA for Arp3, grown to confluency, and scratched. The cells were observed periodically at the SEM levels, and, the length of time for complete recovery was compared.

Results: As shown in the figure, SEM elucidated elaborated network of filopodia containing "bud-like structure" (bud) that may develop to lamellipodia. Arp3 was expressed in filopodia and lamellipodia but not in a bud. The Si-RNA knockdown significantly prolong the length of time for the recovery. It at least partially inhibited the formation of filopodia network and lamellipodia but not the formation of a bud.



Conclusions: This is the first SEM analysis of scratch wound healing in cultured tubular epithelium, and that the bud was previously undescribed. Although the Arp2/3 complex does not apparently induce lamellipodia formation of a bud, further molecular analysis may shed a new light into cell motility in wound healing.

FR-PO266

Inhibition of Microtubule Dynamics Delays Kidney Recovery After Ischemia/Reperfusion Injury in Mice Sang Jun Han,¹ Jee in Kim,² Kwon Moo Park.¹ ¹Dept of Anatomy and BK21 Plus, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; ²Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Republic of Korea.

Background: Ischemia/reperfusion (I/R) is a major cause of acute kidney injury (AKI). If recovery from AKI is delayed, kidney progresses toward chronic renal failure. Microtubules, a component of the cytoskeleton, contribute to cell damages, cell shape, cell motility, and cell division. Here, we investigate that the role of microtubule network on the kidney injury, recovery and progression of fibrosis after I/R injury.

Methods: Mice were subjected to 30 minutes of bilateral renal ischemia, and mice were sacrificed 16 days after ischemia. Some mice were administered either saline (vehicle) or paclitaxel (taxol), a microtubule stabilization agent; 1 day before ischemia (pretreatment) or from 1 day after ischemia until sacrifice every 2 days (post-treatment).

Results: Pretreatment of taxol did not affect post-I/R renal function compared with vehicle-treated I/R group. Post-treatment of taxol delayed renal functional and histological recovery with retardation of tubular regeneration, and accelerated proliferation of interstitial cells after ischemia. Post-treatment of taxol from 24 hours after ischemia enhanced cell cycle arrest, progression of fibrosis, and macrophage infiltration into the kidney. Furthermore, post-treatment of taxol suppressed repolarization of primary cilia in tubular epithelial cells.

Conclusions: In conclusion, our results demonstrate that microtubule stabilization or inhibition of cell proliferation delays kidney tubule cell restoration after ischemic injury, whereas interstitial cell proliferation is accelerated, leading to kidney fibrosis. It suggests that regulation of microtubule dynamics is critical to repair from AKI and progression of AKI to chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO267

Tubulin Acetylation in the Kidney Tubular Cells After Ischemia/Reperfusion Injury Jihyeon Kim, Sang Jun Han, Kwon Moo Park. *Dept of Anatomy and BK21, Kyungpook National Univ, Daegu, Korea.*

Background: Acetylation of tubulin is known to play an important role in the stabilization of microtubules. Kidney ischemia/reperfusion (I/R) is a major cause of acute renal failure. I/R causes damage to the cytoskeleton in the tubular epithelial cells.

Methods: We investigated the tubulin acetylation in kidney tubular epithelial cells after I/R injury using western blotting and immunohistochemical staining. Mice were subjected to either 30 min of ischemia or sham-operation. Kidneys were harvested at various times after ischemia.

Results: Acetylated- α -tubulin expression dramatically decreased 24 hours after ischemia and then gradually increased over time. However, total α -tubulin expression was not significantly changed after I/R. In normal kidney, immune-reactivities of kidney epithelial cell to acetylated α -tubulin antibody were different in tubules; the orders were the collecting duct, the distal tubules and the proximal tubule. Twenty-four hours after ischemia, acetylated α -tubulin expression increased in the proximal tubule and the distal tubule with strong expression in the nuclei of the tubular cells. In the glomerulus, acetylated α -tubulin was also observed and the expression was very strong in the podocyte and Bowman's capsule. Twenty-four hours after ischemia, acetylated α -tubulin expression in the podocyte was lower than that of normal cells. Nine days after ischemia, acetylated α -tubulin expression in the podocyte and interstitial cell increased. Expression of α -tubulin acetyltransferase-1 (α TAT1), an enzyme involved in acetylation of α -tubulin, continuously decreased after ischemia. Histone deacetylase 6 (HDAC6), an enzyme involved in deacetylation of tubulin, also significantly decreased after ischemia.

Conclusions: Ischemia/reperfusion reduced tubulin acetylation in renal tubular cells, suggesting that I/R-induced decrease of tubulin acetylation is associated with reduction of stability of microtubule in cells.

Funding: Government Support - Non-U.S.

FR-PO268

Hypertension Aggravates Acute Kidney Injury (AKI) and Accelerates Progression to Chronic Kidney Disease (CKD) in CD1 Mice Robert Greite,¹ Anja Thorenz,¹ Faikah Gueler,¹ Katja Huetper,² Song Rong,³ Hermann G. Haller,¹ Jan H. Braesen,⁴ ¹Nephrology, Hannover Medical School, Hannover, Germany; ²Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Germany; ³Central Animal Facility, Hannover Medical School, Hannover, Germany; ⁴Pathology, Hannover Medical School, Hannover, Germany.

Background: AKI can be complicated by hypertension due to activation of the RAAS system. However, the most frequently used laboratory mouse strain (C57Bl/6) lacks blood pressure elevation after renal injury. In this study we provide evidence that hypertension aggravates post-ischemic AKI and accelerates progression to chronic kidney disease (CKD) in CD1 mice.

Methods: IRI was induced by transient clamping of the renal pedicles for 35 minutes in CD1 compared to C57Bl/6 mice. Survival, renal function (creatinine, BUN), glomerular filtration rate (GFR) and renal blood flow (RBF) were measured by inulin/PAH-clearance and renal perfusion impairment was assessed by functional magnetic resonance imaging (MRI). Systemic blood pressure was measured by a tail cuff method at different time points after IRI. Morphological changes were investigated by Masson Goldner staining and immunohistochemistry for inflammation (myeloid cell infiltration) and fibrosis (collagen and fibronectin expression). In addition, silver stain was done to quantify mesangial matrix expansion.

Results: Renal function impairment after IRI was similar in CD1 and C57Bl/6 mice but only the CD1 mice developed severe blood pressure elevation (+20 mmHg) within 2 weeks. Functional MRI revealed long lasting impairment of renal perfusion in CD1 mice and markedly better recovery in C57Bl/6 mice. Similar results were obtained by PAH clearance measurements. Histologically, AKI score and inflammation was similar at day 1 after IRI in both mouse strains. Within 14 days after IRI CD1 mice developed severe tubulo interstitial fibrosis. In contrast, C57Bl/6 recovered and had only mild focal cortical scarring after 14 days. Silver stain revealed significant mesangial matrix expansion only in CD1 mice correlating with accelerated glomerulosclerosis.

Conclusions: CD1 mice show severe blood pressure elevation in ischemia induced AKI which accelerates the progression to CKD.

Funding: Government Support - Non-U.S.

FR-PO269

Pericyte MyD88 Controls Inflammatory and Fibrotic Responses to Kidney Injury Irina Alexandra Leaf,¹ Ivan G. Gomez,¹ Bryce Gordon Johnson,¹ William A. Altemeier,² Jeremy Stuart Duffield.¹ ¹Research & Development, Biogen, Cambridge, MA; ²Medicine, Univ of Washington, Seattle, WA.

Background: Sterile inflammation is increasingly recognized as a central problem in many acute and chronic diseases but the mechanisms controlling responses to sterile inflammation are poorly understood. Injured or dying cells release products, or Danger Associated Molecular Patterns (DAMPs), recognized by immune receptors contributing to disease progression. Here we show that DAMPs isolated from injured kidney activate TLR2/4 and MyD88 dependent transcription of immune genes in non-immune kidney resident cells, pericytes. When treated with extracellular DAMPs pericytes form an active NLRP3 inflammasome, process pro-IL1 and pro-IL18 to their active secreted forms and undergo pyroptosis, thereby contributing to inflammation and leukocyte trafficking.

Results: Recent studies have indicated that kidney pericytes represent a major source of interstitial myofibroblasts in renal fibrogenesis. We show that treatment with DAMPs *in vitro* activate pericyte to myofibroblast transition indicated by upregulation of transcription of fibrotic genes *Coll1a1* and *Acta2* and production of SMA. MyD88^{-/-} pericytes showed significant reduction in fibrogenesis markers. In wound healing assays DAMPs caused pericyte migration, which was significantly reduced in the absence of MyD88. Cell-specific ablation of MyD88 in perivascular and stromal cells in models of ischemic acute kidney injury in mice significantly attenuates innate immune activation, injury and fibrogenic responses. In addition, we show that human pericytes respond to DAMPs in a similar manner by activating immune genes, secreting pro-inflammatory cytokines and inducing pyroptotic cell death.

Conclusions: In conclusion, pericytes respond to sterile inflammation via two divergent mechanisms both of which are controlled by MyD88: activation of immune signaling which enables detection and amplification of the inflammatory signal; and activation of fibrogenesis contributing to pathology. Therefore, this regulation could be an important new therapeutic target for tissue injury.

Funding: Pharmaceutical Company Support - Biogen

FR-PO270

Gadd45-Gamma Protects against Acute Kidney Injury Gyu Tae Shin, Inwhhee Park, Heungsoo Kim. *Dept of Nephrology, Ajou Univ School of Medicine, Suwon, Kyunggi, Korea.*

Background: Growth arrest and DNA-damage-inducible protein-gamma (Gadd45-gamma) is a protein which plays a role in the G2/M cell cycle checkpoint. We previously suggested that Gadd45-gamma may be involved in chronic kidney damage. In the present study, we investigated the function of Gadd45-gamma in acute septic and toxic kidney injury.

Methods: Acute kidney injury (AKI) was induced *in vivo* by intraperitoneal injection of lipopolysaccharide (LPS, 10mg/kg) and cisplatin (20mg/kg) in wild-type (WT) and Gadd45-gamma KO mice. Proteome array kits were used to detect differentially regulated proteins in serum (40 pro-inflammatory proteins) and kidney cortex (111 proteins). Stable Gadd45-gamma knockdown cell lines were established in primary human renal epithelial (HRE) cells using shRNA expression vectors. Gadd45-gamma was over-expressed using the recombinant adenovirus harboring the Gadd45-gamma open reading frame. Differentially regulated genes in cisplatin treated HRE cells were determined using the microarray analysis.

Results: Gadd45-gamma was significantly induced as early as 2 h after LPS injection in the kidney of WT mice. At 24 h after LPS injection, both WT and KO mice showed AKI evidenced by high urinary NGAL and elevated serum creatinine levels, where KO mice showed significantly higher serum creatinine levels with lower creatinine clearance than WT mice. Pro-inflammatory cytokines in serum were not different, however, the expression of several chemokines in kidneys were significantly higher in KO mice. In contrast, the expression of pro-fibrotic cytokines was significantly lower in KO mice. At 48 h after cisplatin injection, only KO mice showed significantly elevated serum creatinine levels with heightened NGAL expression. In cisplatin treated HRE cells, pro-inflammatory cytokines were significantly up-regulated by Gadd45-gamma knockdown, and down-regulated by Gadd45-gamma overexpression, whereas pro-fibrotic cytokines were significantly down-regulated by Gadd45-gamma knockdown.

Conclusions: The up-regulation of Gadd45-gamma protects against acute kidney injury, however, maladaptively increases the expression of pro-fibrotic molecules.

FR-PO271

Pyridorin® Reduces Renal Injury and Post Injury Fibrosis After Ischemia Reperfusion Induced Acute Kidney Injury Nataliya Skrypnik,¹ Paul A. Vozyian,¹ Haichun Yang,¹ Carrie Turich Taylor,² Raymond C. Harris,¹ Billy G. Hudson,¹ Mark P. de Caestecker.¹ ¹Div of Nephrology, Vanderbilt Univ, Nashville, TN; ²NephroGenex, Inc., Raleigh, NC.

Background: Pyridorin (PYR), an inhibitor of pathogenic oxidative chemistries, has a favorable safety profile in clinical trials and has been shown to scavenge reactive oxygen species (ROS) and reactive carbonyl species (RCS) *in vitro* and *in vivo* animal studies. ROS and RCS are highly up regulated during kidney injury. In this study we propose that PYR treatment will reduce injury and ameliorate long-term fibrosis after ischemia-reperfusion acute kidney injury (IR-AKI).

Methods: Ischemia-reperfusion mouse models: 1) unilateral ischemia reperfusion (UIR) (31min), injury evaluation on day 3 after injury (UIR D3); and 2) UIR with delayed contralateral nephrectomy (DCN) on day 9, fibrosis and injury evaluation on day 28 (UIR DCN D28).

Results: Preventive treatment with PYR at 500 mg/kg/day (PYR500) and 1000 mg/kg/day (PYR1000) via drinking water in the UIR D3 model demonstrated dose dependent reduction in mRNA levels of kidney injury markers Kim1 and NGAL, tubular injury score, and an oxidative stress marker, isofuran-to-isoprostanate ratio. Plasma PYR levels were proportional to PYR dose. There was a dose dependent reduction in fibrosis after PYR pre-treatment in the UIR DCN D28 model. PYR1000 reduced mRNA levels of Col1a1, Col3a1 and α SMA. PYR pre-treatment was more effective at inhibiting expression of these pro-fibrotic markers compared with post-injury treatment, which only reduced expression of α SMA mRNA in the UIR DCN D28 model.

Conclusions: PYR pre-treatment ameliorates I/R-AKI in dose dependent manner. Pre-treatment with PYR is more effective than post injury treatment and can inhibit progression to chronic kidney disease. These studies suggest PYR as a prospective drug for treatment of patients at risk of AKI. Funded by research grant from NephroGenex, Inc.

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FR-PO272

Canonical BMP Signaling via BMPRIA and Smad1/5/8 Mediates the Transition to Fibrosis After Renal Ischemia Reperfusion Injury Emilia Vigolo,¹ Lajos Marko,² Christian Hinze,¹ Dominik N. Müller,^{1,2} Ruth Schmidt-Ullrich,¹ Kai M. Schmidt-Ott.^{1,2,3} ¹Max Delbrueck Center for Molecular Medicine, Berlin, Germany; ²Experimental and Clinical Research Center, Charité, Berlin, Germany; ³Dept of Nephrology, Charité - Universitaetsmedizin, Berlin, Germany.

Background: Ischemia reperfusion injury (IRI) of the kidney leads to acute kidney injury (AKI) and frequently precipitates the development of tubulointerstitial fibrosis. Bone morphogenetic protein (BMP) signaling has been implicated in the pathogenesis and progression of the disease, but its tubular-specific role is unclear.

Methods: We induced IRI in mice by clamping the left renal pedicle for 25 minutes. The severity of the damage was confirmed by histology scoring, elevated mRNA expression of renal injury markers NGAL and KIM-1 and increased urinary NGAL (uNGAL) excretion 24h post-ischemia. Activation of canonical BMP signaling was detected by nuclear pSmad1/5/8 immunostaining and Western blotting. To achieve a doxycycline-dependent Cre-mediated inactivation of BMP receptor 1a (Bmpr1a) in renal tubules, we generated *Pax8rtTa;LCL1;Bmpr1a*^{fl/fl} mice (Bmpr1a cKO).

Results: Canonical BMP activity, as revealed by pSmad1/5/8, was widely detected in healthy wild-type (wt) mouse kidney tubules. IRI caused a sustained injury in wt kidneys as shown by elevated NGAL and KIM-1 expression and increased uNGAL excretion. In parallel, we observed a transient decrease of pSmad1/5/8 with minimal activity at 48 hours and a subsequent re-activation at 7 days post-ischemia. Bmpr1a cKO mice displayed normal renal tissue morphology and renal functions at baseline. Following IRI, Bmpr1a cKO mice exhibited an initial injury similar to controls, but at 7 days post-ischemia, the expression of collagen IV and TGF- β 1 were significantly up-regulated in Bmpr1a cKO kidneys compared to controls. Unlike controls, Bmpr1a cKO mice failed to reactivate tubular pSmad1/5/8 activity at 7 days after injury. 21 days following IRI, Bmpr1a cKO kidneys displayed an increased percentage of tubulointerstitial fibrosis compared to controls.

Conclusions: Tubular Bmpr1a-dependent Smad1/5/8 signaling is transiently decreased after renal IRI and its reactivation limits the progression of tubulointerstitial fibrosis.

FR-PO273

PNUTS (Phosphatase 1 Nuclear-Targeting Subunit) Is Down-Regulated in Acute Kidney Injury and by Aging, and Regulates Cell Cycle, Fibrosis, DNA Damage of Renal Tubular Cells Yuki Osakabe, Tatsuki Matsumoto, Kazu Hamada-Ode, Yoshiko Shimamura, Koji Ogata, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Shimpei Fujimoto, Yoshio Terada. *Kochi Univ, Japan.*

Background: PNUTS (phosphatase 1 nuclear-targeting subunit, also known as PPP1R10) has recently reported to be regulated in cardiac aging and play roles in DNA damage. Aging and fibrosis play crucial roles in AKI to CKD transition, however the precise mechanism are not known. Because the biological role of PNUTS in aged kidney, fibrosis, and cell cycle in AKI is poorly understood, we studied the regulation and the functional roles of PNUTS in AKI and aging.

Methods: We used an in vivo mice aristolochic acid(AA)-induced AKI model and cultured renal tubular cells (NRK-52E cells). To assess aging effects, we evaluated PNUTS expression, renal function, and renal fibrosis in AA-induced AKI model in different aged mice (20-, 50- and 90-week-old). To elucidate the function of PNUTS, cell cycle regulation (by FACS), DNA damage (by gammaH2AX expression), and fibrosis (by CTGF expression) were examined in NRK-52E cells transfected with siRNA for PNUTS or PNUTS expression vector.

Results: In mice with AA-induced AKI, protein and mRNA expression of PNUTS were reduced compared with control mice. Moreover, PNUTS expression were decreased in accordance to aging. Reduction of renal function and renal fibrosis were more apparent in aged AKI mice. Immunohistological examination revealed the reduced expression of PNUTS in the proximal tubular cells in AA-induced AKI. PNUTS mRNA and protein expression showed a dose-dependent reduction by H₂O₂ in NRK-52E cells. Overexpression of PNUTS reduced H₂O₂-induced caspase3 activity and apoptotic (TUNEL positive) cell number. Transfection of siPNUTS significantly increased G2/M phase cells, CTGF expression, and DNA damage.

Conclusions: These results indicate that PNUTS expression was reduced in AA-induced AKI and in aged mice. Expression of PNUTS was partially regulated by oxidative stress. PNUTS regulates cell cycle, CTGF expression, DNA damage, and apoptosis in NRK-52E cells. These results suggest that regulation of PNUTS may play a key role in the pathophysiology of AKI and age-related renal damage.

FR-PO274

Class Ia HDAC Inhibitors Restore BMP-7 Expression and Inhibit the Pathogenesis of Renal Fibrosis following Chronic Renal Injury Qiusha Guo, Scott R. Manson, Katelynn H. Moore, Paul F. Austin. *Dept of Surgery, Div of Urology, Washington Univ, St. Louis, MO.*

Background: BMP-7 is a potent anti-fibrotic cytokine that is also required for the repair of renal injuries. However, chronic renal injury leads to the loss of BMP-7 and fibrosis. Here, we delineate the molecular mechanisms that lead to the loss of BMP-7 expression and examine potential therapeutic strategies for stimulating the innate repair mechanisms of the kidney.

Methods: BMP-7 expression was studied *in vitro* in inner medullary collecting duct (IMCD) cells and *in vivo* in a murine model of unilateral ureteral obstruction (UUO). The therapeutic effects of broad spectrum histone deacetylase (HDAC) inhibition with Trichostatin A (TSA) and Class Ia HDAC inhibition with MS-275 were evaluated by assessing renal pathology.

Results: UUO results in an 83.1% decrease in BMP-7 mRNA expression that is paralleled by a 63.0% decrease in the acetylation of histone proteins in the proximal *Bmp7* promoter, a process that results in gene repression. These changes are HDAC-dependent and blocked by treatment with TSA. An *in vitro* pharmacologic screen in IMCD cells revealed that MS-275 stimulates BMP-7 expression, while inhibitors of other HDAC isoforms have no effects. These results were confirmed by using siRNA-mediated genetic ablation to demonstrate specificity and chromatin immunoprecipitation to show binding of the Class Ia HDAC proteins HDAC1 and HDAC2 to the *Bmp7* promoter. MS-275 also stimulates the anti-fibrotic functions of BMP-7 *in vitro* by suppressing the expression of the TGF- β -dependent pro-fibrotic genes *COL1A1* and *aSMA* by 68.2% and 97.6%, respectively. Finally, these effects extend to the obstructed kidney *in vivo* where HDAC inhibition results in a 2.7-fold increase in BMP-7 expression, 42.7% decrease in fibroblast activation, and 63.7% decrease in renal fibrosis.

Conclusions: These findings demonstrate that HDAC1 and HDAC2 are responsible for the loss of BMP-7 expression and its renal protective functions in the injured kidney. Furthermore, our study suggests that Class I HDAC inhibitors have a tremendous therapeutic potential for stimulating kidney repair and inhibiting disease progression following chronic renal injury.

Funding: NIDDK Support, Private Foundation Support

FR-PO275

Gli2 in Perivascular MSC Is Required for Kidney Fibrosis and Can Be Targeted Pharmacologically Rafael Kramann, Susanne V. Fleig, Steven L. Fabian, Omar H. Maarouf, Janewit Wongboonsin, Yoichiro Ikeda, Benjamin D. Humphreys. *Renal Div, Brigham and Women's Hospital, Boston, MA.*

Background: We recently demonstrated that perivascular mesenchymal stem cell (MSC)-like cells are defined by expression of Gli1 and are critical myofibroblast precursors. We now investigate the role of Gli transcriptional activators in myofibroblast progenitors during kidney fibrosis and value as therapeutic targets.

Methods: We utilized mouse genetics, drug binding, RNAi and retroviral overexpression to dissect the roles of Gli1 vs. Gli2 in myofibroblast activation and fibrosis. We pharmacologically targeted Gli proteins with Darinapsin, an arsenical, and GANT61, a small molecule Gli inhibitor. We evaluated them in two separate mouse CKD models. We measured hedgehog pathway activity and expression of Gli in human kidney fibrosis specimen.

Results: In vitro knockdown of Gli1 had no appreciable effect whereas knockdown of Gli2 induced a G0/G1 cell cycle arrest of mouse fibroblasts. Conversely, Gli2 overexpression rescued this cell-cycle effect and drove proliferation. In vivo, knockout of Gli1 showed no effect on fibrosis severity after UUO whereas either conditional knockout of Gli2 or overexpression of the Gli3 repressor in Gli1⁺ pericytes ameliorated fibrosis and induced a G0/G1 cell cycle arrest specifically in myofibroblasts, consistent with our in vitro results. We show that darinapsin directly binds to Gli2, lowers Gli2 protein levels and induces a G0/G1 cell cycle arrest. This effect of darinapsin absolutely requires Gli2, and Gli2 overexpression rescued the cell cycle defect. When administered in a therapeutic dosing strategy after UUO or IRI, darinapsin potently reduced Gli1 and Gli2 expression, induced myofibroblast specific G0/G1 cell-cycle arrest and ameliorated fibrosis. GANT61, structurally unrelated to darinapsin, showed the exact same effects. In human kidneys with fibrosis there is strong upregulation of Gli1 and Gli2 mRNA, suggesting this pathway is conserved in humans.

Conclusions: Gli2 is a critical driver of myofibroblast proliferation and a novel therapeutic target in kidney fibrosis.

Funding: NIDDK Support

FR-PO276

Klotho Influences the Fate of Fibrosis in Cardio-Renal Protection Steven M. Weldon,¹ Hu Sheng Qian,¹ Nestor X. Barrezaeta,¹ Jorge L. Villalona,¹ R. Paul Fracasso,¹ Glenn A. Reinhart,¹ Jian Xie,² Chou-Long Huang,² Noelynn Oliver.¹ ¹Cardiometabolic Disease Research, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; ²Univ of Texas SW Medical Center, Dallas, TX.

Background: Soluble Klotho is an endogenous hormone produced predominantly by extracellular domain shedding of membrane Klotho in the kidney. Although Klotho is thought to provide cardio-renal protection through its regulation of ion transport and growth factor signaling, specific cellular localization and function of Klotho in the normal and diseased kidney are not clearly defined.

Methods: We evaluated Klotho expression and localization in human and mouse kidney via in situ hybridization (ISH), immunohistochemistry (IHC) or RNAseq. Cardio-renal protective effects of soluble human Klotho administration were studied in mouse unilateral ureteral obstruction (UUO; 5 day) and isoproterenol-induced cardiac hypertrophy (ISO, 5 mg/kg/d x 10d) models.

Results: In normal adult human kidney (fresh nephrectomy and autopsy, n=9), Klotho was highly expressed in distal tubules (DT) and in both cortical and outer medulla collecting ducts (CD). Proximal tubule and podocyte expression was low but detectable. Following UUO, renal Klotho RNA was decreased 61% and protein content was reduced greatly in the distal nephron vs Sham kidney. Klotho treatment (10 ug/kg, Q2D, IP) attenuated UUO-induced tubulointerstitial fibrosis (picosirius red stain, n=10) by 67%* (*p<.05) and

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biomarker mRNA (40%*:FN1; 25%:aSMA; 16%:TGF β) vs Vehicle control. In the ISO model, Klotho (10 ug/kg QD, IP) inhibited cardiac hypertrophy (HW:BW, n=6); 5.4 \pm 0.08 (p<.01) in Klotho- vs 5.8 \pm 0.08 in Vehicle control.

Conclusions: Klotho is highly expressed in normal human and mouse distal nephron. Klotho mRNA and protein are reduced in preclinical models of cardiac and renal disease. Delivery of recombinant Klotho attenuates severity of pathology and biomarker expression in the UUU model of renal fibrosis and ISO-induced cardiac hypertrophy. Klotho pharmacotherapy has the potential to prevent CKD progression as well as the progression of extra-renal Klotho-dependent diseases.

FR-PO277

Kidney Interstitial Cell Derived Tenascin C Plays an Important Role in Promoting Injury-Repairing of the Kidney by Stimulating Cell Proliferation Min Zhang, Qionghong Xie, Xiaoyi Mao, Da Shang, Chuanning Hao. *Div of Nephrology, Huashan Hospital, Shanghai, China.*

Background: Tenascin-C (TNC) is a glycoprotein expressed in extracellular matrix during development and injury repairing. This study explored the role of TNC in acute kidney injury (AKI).

Methods: A TNC promoter driven inducible CreER2 knock-in mouse line with EGFP reporter (IRES-EGFP) as generated (TNC-CreER-eGFP). AKI was induced by 40 minutes of ischemia followed by reperfusion in unilateral nephrectomized mice (UN+UIR). Cell lineage tracing was conducted in TNC-CreER;R26-tdTomato mice to examine the origin of TNC expressing cells. The effect of TNC on cell proliferation was examined using a cell count kit in cultured HK2 cells. TNC expression was also examined in human biopsies with IRB approval.

Results: In normal kidney, TNC was restricted in renal papilla in both mice and human. Following IR, TNC was markedly induced in renal cortex, particularly in injured areas. TNC reporter showed that induced TNC expression is localized in interstitial cells, but not tubular epithelial cells. TNC induction was also shown in human renal biopsies with AKI. Co-staining IF showed that TNC was expressed by the PDGFR β (+) renal interstitial cells, but not NG2(+) pericyte, F4/80(+) macrophage and FSP-1(+) cells. Lineage tracing revealed that TNC expressing cells following IR were not derived from the renal medullary interstitial cells that constitutive express TNC, suggesting new TNC induction. To examine the role of TNC induction following AKI, TNC^{-/-} mice were generated. TNC deletion significantly increased mortality (0% vs 50% on day 7, n=14, P=0.002), with significantly higher BUN levels (108 vs 22 mmol/L on day 2, P<0.05) compared with wide type mice. More severe kidney damage in TNC knockouts was also supported by histology study. To examine the mechanism by which TNC protected the kidney from injury, HK2 cells were cultured. Exogenous TNC significantly increased cell proliferation by 50%.

Conclusions: TNC is induced in renal interstitial cells after IR-induced AKI, protecting the kidney from injury. The protective effect of TNC on AKI may be associated with promoting renal recovery by stimulating epithelial cell proliferation.

Funding: Government Support - Non-U.S.

FR-PO278

TAZ and YAP Are Mechanoregulators of TGF- β -Smad Signaling and Renal Fibrogenesis Darren A. Yuen, Stephen G. Szeto, Masahiro Narimatsu, Ahmad Mohammad Omar Sidiqi, Mingliang Lu, Jeffrey Wrana, Andras Kapus. *Univ of Toronto, Canada.*

Background: Fibrosis is a final common injury pathway responsible for the progression of most forms of CKD, for which no specific treatments exist. Driven largely by TGF- β signalling, fibroblast-myofibroblast transition is crucial for fibrogenesis. While it is known that fibroblast activation is mechanosensitive, with soft matrix akin to a healthy kidney impairing TGF- β responsiveness, the underlying mechanisms remain poorly understood. TAZ and YAP are homologous transcription co-factors with TGF- β regulatory activity, whose nuclear localization and activity are regulated by matrix stiffness. Here, our aim was to examine how stiffness regulates TGF- β signalling via TAZ/YAP, and to test if TAZ/YAP inhibition can attenuate renal fibrosis.

Methods: The effects of matrix stiffness on TAZ/YAP localization and TGF- β /Smad signalling were examined in rat renal fibroblasts (NRK49Fs) cultured on soft (2 kPa) and stiff (100 kPa) gels. To test the effect of TAZ/YAP inhibition, NRK49F cells and mice were treated with verteporfin (VP), a drug used as a macular degeneration treatment with recently described TAZ/YAP inhibitory properties.

Results: In NRK49F cells, stiff matrix resulted in nuclear TAZ/YAP localization and enhanced TGF- β signalling. Growth on soft matrix, in contrast, lead to reduced TAZ/YAP nuclear localization, and impaired TGF- β -induced Smad2/3 nuclear accumulation and transcriptional activity. VP treatment of NRK49F cells grown on stiff plastic surfaces resulted in a dramatic loss of TAZ/YAP, leading to a similar inhibition of TGF- β /Smad signalling. VP-induced TAZ/YAP loss also enhanced proteasomal Smad2/3 degradation following TGF- β stimulation. *In vivo*, VP similarly reduced renal TAZ/YAP and Smad2/3 levels in UUU mice, leading to diminished myofibroblast accumulation and interstitial collagen deposition.

Conclusions: Our data suggest that renal fibrogenesis is regulated by a novel mechanical stimulus (stiffness) that, through control of the mechanosensory proteins TAZ and YAP, modulates TGF- β /Smad signalling. Furthermore, we identify verteporfin as a potential anti-fibrotic treatment that interferes with this pro-fibrotic mechano-chemical synergy.

Funding: Government Support - Non-U.S.

FR-PO279

Targeted Deletion of Numb from Proximal Tubules Attenuates Interstitial Fibrosis by Mitigating G2/M Arrest Fengxin Zhu, Jing Nie. *Div of Nephrology, Nanfang Hospital, Guangzhou, Guangdong, China.*

Background: Progressive tubulointerstitial fibrosis (TIF) is the final common pathway leading to end stage renal disease. Tubular epithelial cells (TECs) have a crucial role in the pathogenesis of TIF. Numb is a multifunctional protein involved in diverse cellular processes. However, little is known about the physiologic and pathologic role of Numb in kidney.

Methods: We examined the expression and distribution of Numb in normal adult mouse kidney as well as in mouse model of renal fibrosis induced by unilateral ureteral obstruction (UUO). To explore Numb's role in renal fibrosis, we generated a conditional knockout mouse model in which Numb is selectively ablated from proximal tubules (PEPCK-Numb-KO). To confirm the role of Numb in regulating cell cycle, Numb was overexpressed in NRK52E cells by infecting with a Numb adenovirus (Ad-Numb) and endogenous Numb was knocked down by siRNA in HK-2 cells before aristolochic acid (AA) treatment. To examine the role of p53 in Numb-induced G2/M arrest, Ad-Numb infected HK-2 cells were incubated with pifithrin- α , a p53 inhibitor.

Results: Numb is expressed in renal tubules and glomeruli. The expression of Numb in renal tubules was significantly increased after UUO. After UUO, PEPCK-Numb-KO mice exhibited significantly attenuated TIF. Ectopic expression of Numb increased the fraction of cells in G2/M stage and upregulated the expression of TGF- β 1 and CTGF in NRK52E cells. Knocking down endogenous Numb attenuated AA-induced G2/M arrest and profibrotic cytokines production. Furthermore, G2/M arrest and expression of profibrotic cytokines were significantly reduced in PEPCK-Numb-KO mice after UUO. Inhibiting p53 activity dramatically mitigated Numb-induced G2/M arrest and profibrotic cytokines production.

Conclusions: In summary, our studies demonstrate that Numb has a profound effect on promoting G2/M arrest of TECs through stabilizing p53 protein. Depletion of Numb markedly attenuates G2/M arrest of proximal tubules which in turn reduces TIF. Collectively, these data indicate that targeting Numb might be a novel therapeutic approach for the treatment of fibrotic kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO280

Identification of a New Aldosterone Synthase Inhibitor with Anti-Fibrotic Activity in Animal Models Bert Oehlen, Siobhan McCormack, Ping Zhou, Liming Zhang, Xingxi Peng, Jingsong Li, Xiaokang Zhu, Bijoy Panicker, Itzhak D. Goldberg. *Angion Biomedica Corp., Uniondale, NY.*

Background: The renin-angiotensin-aldosterone system (RAAS) plays a critical role in renal physiology. Inhibitors of ACE and ARBs are currently the mainstay in the clinical management of chronic kidney disease (CKD). Despite initial success in reducing aldosterone, concentrations return to pretreatment levels in 30-40% of patients. This "aldosterone escape" significantly limits the therapeutic effectiveness. Through mineralocorticoid receptor dependent and independent processes, aldosterone is thought to directly accelerate renal damage by sustaining inflammation and fibrosis. An attractive approach to deal with aldosterone escape is to inhibit aldosterone synthase (AS), the enzyme responsible for aldosterone production (encoded by the CYP11B2 gene).

Methods: We have identified a promising series of potent and selective small molecule inhibitors of AS. Lead compound ANG3586 has 7 nM potency against AS and excellent selectivity against other P450 enzymes. It is orally bioavailable in rodents and appears to be well tolerated. ANG3586 was tested in the rat remnant kidney model (25 mg/kg, po, bid) and the mouse unilateral ureteral obstruction (UUO) model (25 mg/kg, po, bid, ten days).

Results: In the rat remnant kidney model, animals with overt renal dysfunction were treated with vehicle or ANG3586. The elevated blood pressure in 5/6 nephrectomized animals was reduced to normal by compound treatment. ANG3586 also markedly reduced kidney collagen content and improved renal histology. Renal function, as determined by serum BUN and creatinine levels, urine albumin to creatinine ratio and urine NGAL, was found to be markedly improved. In the mouse UUO model, ANG3586 reduced the increase in kidney weight, kidney collagen and alpha-smooth muscle actin staining. Since UUO does not result in distinctly increased blood pressure, the anti-fibrotic activity appears independent of blood pressure lowering activity of ANG3586.

Conclusions: Taken together, ANG3586 shows promise as a potential novel anti-fibrotic agent.

Funding: NIDDK Support

FR-PO281

Tubulointerstitial Fibrosis Increases Peritubular Capillary Permeability and Induces Subsequent Hypoxia Jun Zou,^{1,2} Jae Won Yang,¹ Haichun Yang,¹ Agnes B. Fogo,¹ ¹Dept of Pathology, Microbiology, and Immunology, Vanderbilt Univ, Nashville, TN; ²Div of Nephrology, Xinhua Hospital, Shanghai Jiao Tong Univ, Shanghai, China.

Background: We previously showed that folic acid-induced tubulointerstitial injury sensitizes to subsequent glomerular injury. In this study, we evaluated whether the function of peritubular capillaries and oxygen supply changes contribute to this cross-talk of tubular to glomerular injury.

Methods: Col I-luciferase mice, which have luciferase inserted in the collagen I promoter, were mated with Nep25 mice, which express human CD25 receptor on podocytes, and develop glomerulosclerosis when immunotoxin is administered. Mice were treated with folic acid (FA, 240mg/kg BW, i.p.) or vehicle (VEH). At day 42,

mice were sacrificed to assess interstitial fibrosis, peritubular capillary number (CD31 immunostaining), endothelial function (in vivo injection of Evans blue dye), and tissue hypoxia (hypoxyprobe, pimonidazole).

Results: Folic acid induced acute tubular injury over two weeks, evidenced by increased urinary NGAL and Kim-1 levels. Six weeks later, tubular epithelial cells had regenerated and urinary NGAL and Kim-1 returned to baseline level. However, bioluminescence imaging, an indicator of collagen I mRNA transcription, showed higher density in folic acid vs vehicle (FA $31.6 \pm 5.1 \times 10^4$ vs. VEH $3.2 \pm 0.6 \times 10^4$ p/sec/cm²/sr, $P < 0.05$). Interstitial fibrosis and collagen I were increased in FA compared to VEH (picrosirius red area, FA 14.5 ± 1.6 vs. VEH $7.4 \pm 0.7\%$, $P < 0.05$; collagen I IHC, FA 16.7 ± 1.2 vs. VEH $10.6 \pm 1.3\%$, $P < 0.05$), with a patchy distribution. Folic acid did not reduce peritubular capillary density (FA 5.5 ± 0.7 vs. VEH $6.0 \pm 0.8\%$, pNS). However, peritubular capillary permeability, measured by extravasated Evans blue dye in the kidney, significantly increased in folic acid-treated group (FA 50.4 ± 5.3 vs. VEH 28.6 ± 3.2 mg/g, $P < 0.05$). Pimonidazole staining intensity was increased, suggesting tubulointerstitial hypoxia.

Conclusions: We conclude that tubulointerstitial fibrosis may lead to increased peritubular capillary permeability and subsequent hypoxia, which may contribute to crosstalk of interstitial fibrosis promoting glomerular injury.

Funding: NIDDK Support

FR-PO282

Homocysteine Induces Collagen I Expression by Downregulating Histone Methyltransferase G9a Wenjing Lei, Jing Nie. *State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, China.*

Background: Hyperhomocysteinemia (HHcy) leads to several clinical manifestations including renal fibrosis. Excess deposition of extracellular matrix (ECM) components including collagen is the eponymous lesion of renal fibrosis.

Methods: Wild-type C57BL/6 mice, at the age of 6-9 weeks, were fed with either standard rodent chow or HM diet. After 2 weeks on the diet, mice were sacrificed. Kidney tissues were removed. HK-2 cells were cultured in DMEM containing DL-Hcy. The expression of G9a and Collagen I were examined by Western blot and qPCR. Renal pathological changes were assessed in tissue sections stained with Collagen I and Masson staining. HK-2 cells were transfected with pCol-Gl3 reporter plasmid, pRL null together with siG9a or Flag-tagged G9a to examine the promoter activity of *COL1A1*. The level on G9a and H3K9me2 on the promoter of *COL1A1* was assessed by CHIP assay.

Results: We demonstrated that elevated concentration of Hcy induced the expression of collagen type I in cultured HK-2 cells as well as in kidney tissue of HHcy mice. Meanwhile, Hcy inhibited the expression of histone methyltransferase G9a. Mechanistically, silencing endogenous G9a by siRNA enhanced the promoter activity of *COL1A1* in HK-2 cells. Conversely, overexpressing G9a inhibited the promoter activity of *COL1A1*. CHIP assay demonstrated that G9a binds to the neuron-restrictive silencer element (NRSE) on the promoter of *COL1A1*. Hcy treatment decreased the binding of G9a on NRSE, which in turn decreased the level of H3K9me2 on the promoter of *COL1A1*, led to upregulation of *COL1A1*.

Conclusions: These results show that homocysteine induces collagen I expression by downregulating histone methyltransferase G9a and provide a novel mechanism on explaining how HHcy promotes ECM production.

Funding: Government Support - Non-U.S.

FR-PO283

The Podocyte Adhesome Exhibits Matrix Ligand Specificity with Implications for Glomerular Disease Michael J. Randles,^{1,2} Roy Zent,³ Martin J. Humphries,¹ Rachel Lennon.^{1,2} ¹Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, Univ of Manchester, Manchester, United Kingdom; ²Inst of Human Development, Faculty of Medical & Human Sciences, Univ of Manchester, Manchester, United Kingdom; ³Dept of Medicine, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Adhesion at both the podocyte slit diaphragm and podocyte-extracellular matrix (ECM) interface is essential glomerular filtration barrier integrity. These structures converge onto many of the same signalling pathways, including those controlling the actin cytoskeleton. Podocytes adhere to laminin-521 in the glomerular basement membrane via integrin $\alpha 3 \beta 1$ and evidence suggests that attachment to collagen IV is upregulated in disease states. Whether changes in ECM ligand alter podocyte adhesion signalling remains unclear.

Methods: We analysed podocyte morphology following engagement of either laminin-521 or type IV collagen ($\alpha 1 \alpha 2$) and isolated basolateral adhesion complexes for analysis by mass spectrometry (MS). To isolate nephrin-nephrin complexes for analysis by MS we generated nephrin-FLAG podocyte and recombinant nephrin.

Results: Human podocytes cultured on type IV collagen spread rapidly in an unpolished manner forming radial actin stress fibres. By comparison, elongated cells with multiple lamellipodia and filopodia-like projections were formed on laminin 521. These cell phenotypes were enhanced with overexpression of the key slit diaphragm protein nephrin. The composition of isolated adhesion complexes was determined by ECM ligand and nephrin expression status. MS and protein interaction network mapping highlighted PKC α as a key signalling node in laminin adhesion complexes. Analysis of nephrin-nephrin complexes highlighted significant overlap with ECM adhesion signalling suggesting crosstalk mechanisms.

Conclusions: In human podocytes we discovered that both ECM ligand and overexpression of nephrin influences morphology, adhesion complex composition and

intracellular signalling. Enhanced understanding about the pathways that control podocyte adhesion may ultimately inform therapeutic strategies to correct or repair glomerular barrier function.

Funding: Private Foundation Support

FR-PO284

Low-Density Lipoprotein Receptor-Related Protein 5 Drives Tubulointerstitial Fibrosis via Regulation of TGF- β Signaling Xuemin He, Rui Cheng, Jian-xing Ma. *Dept of Physiology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: Low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of the canonical Wnt/ β -catenin pathway, was recently reported to drive idiopathic pulmonary fibrosis through activating β -catenin. In this study, we examined the potential role of LRP5 in the regulation of TGF- β signaling in tubulointerstitial fibrosis.

Methods: LRP5-deficient (*Lrp5*^{-/-}) mice and age-matched wild-type (WT) mice were subjected to unilateral ureteral obstruction (UUO). Renal expression of fibrotic factors, including α -SMA, CTGF, collagens and fibronectin, was quantified by picro-sirius red staining, western blot analysis and immunostaining. Primary tubular epithelial cells (PTECs) were cultured from *Lrp5*^{-/-} mice and WT mice. Co-immunoprecipitation was performed in a human proximal tubular epithelial cell line (HKC-8) over-expressing LRP5 and TGF- β receptors.

Results: *Lrp5*^{-/-} mice with UUO showed ameliorated renal fibrosis and alleviated TGF- β signaling compared with WT mice with UUO. However, activation of the Wnt/ β -catenin signaling was not different between *Lrp5*^{-/-} mice and WT mice, indicating that attenuated tubulointerstitial fibrosis in *Lrp5*^{-/-} mice was not due to mitigated activation of the fibrotic Wnt/ β -catenin pathway. Instead, LRP5^{-/-} UUO kidneys displayed alleviated TGF- β signaling in comparison to that in WT/UUO kidneys. Overexpression of LRP5 in HKC-8 resulted in enhanced TGF- β signaling including enhanced TGF- β -driven transcriptional activity and elevated expression of fibrosis markers regulated by TGF- β signaling. Knock-down of LRP5 in HKC-8 cells diminished the activation of the TGF- β signaling pathway. Meanwhile, LRP5^{-/-} PTECs also displayed attenuated activation of the TGF- β signaling, compared to WT PTECs. In addition, immunoprecipitation assay demonstrated physical association between LRP5 and TGF- β receptor I, suggesting that LRP5 might act as a co-receptor of the TGF- β signaling pathway in the regulation of tubulointerstitial fibrogenic process.

Conclusions: LRP5 promotes tubulointerstitial fibrosis via regulation of the TGF- β signaling. This activity is independent of its role in the Wnt/ β -catenin pathway.

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FR-PO285

Loss of Endothelial Nitric Oxide Augments Smad3 Linker Phosphorylation and Precedes Insulin Resistance in High-Fat Diet Induced Obesity Yu bo yang Sun, Xinli Qu, Jinhua Li. *Anatomy and Developmental Biology, Monash Univ, Melbourne, Victoria, Australia.*

Background: Deficiency of endothelial nitric oxide synthase (NOS3/eNOS) confers susceptibility to diet-induced obesity and its complications. eNOS-derived nitric oxide (NO) acts as a potent vasodilator, enhances insulin sensitivity and also inhibits inflammation. TGF- β /Smad signaling plays an important role in regulating glucose and energy homeostasis. Smad3 deficient mice are protected from diet-induced obesity and obesity-related kidney injury. This study investigated whether the loss of endothelial-derived NO promotes Smad3 activation, which precedes insulin resistance in high-fat diet (HFD) induced obesity.

Methods: C57B6L/J wild type, eNOS deficient (eNOS^{-/-}) with C57B6L/J background mice were given HFD or normal diet (ND) treatment for 1, 3, 7 days and 4, 8 or 16 weeks.

Results: Within 7 days of HFD treatment in WT mice, Western blotting showed a marked decrease in total eNOS level. Phosphorylation of Smad3 linker region was only seen 4 weeks after HFD treatment, indicating endothelial injury precedes phosphorylation of Smad3 linker region. Compared to WT mice, eNOS^{-/-} mice on HFD showed early onset of peripheral and renal insulin resistance, increased microalbuminuria, elevated blood pressure, which suggested that endothelial injury drives renal metabolic disorders induced by HFD. Confocal microscopy demonstrated that fibronectin and collagen IV significantly increased in glomeruli in the HFD-treated eNOS^{-/-} group compared to that in HFD-treated WT group. An *in vitro* model, palmitate acid addition to culture endothelial cells induced rapid C-terminal phosphorylation of Smad3, subsequent loss of eNOS, phosphorylation of Smad3 linker region and insulin resistance. L-NAME, a specific NOS inhibitor, significantly increased phosphorylation of Smad3 linker region and insulin resistance. Finally, endothelial cell overexpressing eNOS significantly inhibited Smad3 linker region phosphorylation and protected insulin sensitivity.

Conclusions: In summary, our studies showed that eNOS and Smad3 signaling pathway play essential roles in HFD-induced renal injury. eNOS/Smad3 pathway may be a novel therapeutic target in obesity-related kidney disease.

Funding: Government Support - Non-U.S.

FR-PO286

HIF1 α and HIF2 α Both Mediate Glomerulosclerosis but Differentially Regulate the COL1A2 Promoter Bethany Baumann, Tomoko Hayashida, Xiaoyan Liang, H. William Schnaper. *Northwestern Univ, Chicago, IL.*

Background: TGF β increases HIF1 α and HIF2 α levels in normoxia and both HIFs contribute to TGF β induction of type I collagen *in vitro*, suggesting a potential role for HIFs in renal disease regardless of oxygen tension. Here, we studied the role of HIFs in mouse glomerulosclerosis (GS).

Methods: HIF1 $\alpha^{fl/fl}$ or β^+ , bactin-Cre-ERT2, NRP25 mice express human Tac on podocytes. LMB2, a toxin/anti-Tac chimera, binds to Tac, ablating podocytes to cause GS. Systemic Cre recombination was induced by tamoxifen at 4 weeks of age and LMB2 injected at 9 weeks. Mice were sacrificed 4 weeks later. HIF2 $\alpha^{fl/fl}$ or β^+ mice were generated on a 129 background and bred with PDGFR β -Cre mice to delete HIF2 α from pericytes and mesangial cells. GS was induced by Adriamycin injection at 8 weeks of age. Mice were sacrificed 2 weeks later. Disease progression was analyzed by histology, scoring 50-100 glomeruli/animal on a fibrosis scale of 0-4, and by qPCR for COL1A2 mRNA with laser-captured glomeruli. *In vitro* studies investigating a mechanism by which HIFs regulate COL1A2 promoter were also performed.

Results: HIF1 α : Histologically, control mice scored 0.46 (+/- 0.12), diseased WT mice 3.13 (+/- 0.19), and diseased HIF1 α KO mice 1.42 (+/- 0.28). Glomerular COL1A2 mRNA with LMB2 injection was increased 3.4x over the healthy controls in WT, but only 1.9x with HIF1 α KO. *In vitro*, TGF β induced COL1A2 promoter activity by 2.4x, which was abrogated when a hypoxia response element (HRE) 335 bp 5' to the transcription start site was mutated. By DNA precipitation assay, HIF1 α binding to a -335 COL1A2 HRE probe was detected after TGF β treatment. Interestingly, Smad3 also bound the -335 COL1A2 HRE probe in both TGF β -treated cell lysate and whole kidney lysate from WT HIF1 α NRP25 mice with GS. HIF2 α : HIF2 $\alpha^{fl/fl}$ PDGFR β -Cre mice showed less GS than HIF2 $\alpha^{+/+}$ mice by histology. *In vitro*, HIF2 α enhanced COL1A2 promoter activity independently of the -335 HRE. Instead, HIF2 α increased the transcriptional activity of Smad3.

Conclusions: Both HIF1 α and -2 α contribute to the development of GS in mice. Our *in vitro* studies strongly suggest that HIF1 α and -2 α each enhance TGF β -mediated fibrogenesis, but through distinct mechanisms.

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FR-PO287

Mir302a-3p Modulates Renal Epithelial-Mesenchymal Transition in DKD by Targeting ZEB1 Wenbin Tang, Linfeng Zheng, Renheng Yan, Jiayi Yang, Linlin Peng, Qiaoling Zhou, Liping Chen. *Dept of Nephrology, Xiangya Hospital, Central South Univ, Kidney Inst, Changsha, Hunan, China.*

Background: Recent study found that miRNAs are involved in diabetic kidney disease (DKD). The objective of this study is to determine the role of miR302a-3p in the process of renal epithelial-mesenchymal transition (EMT) in DKD.

Methods: The levels of miR302a-3p in the plasma of DKD patients were detected by realtime PCR and the relationship of miR302a-3p and UAE or eGFR were analyzed. Secondly, miR302a-3p expression was determined in HK-2 cells treated with high glucose for different time. And then miR302a-3p mimics and inhibitor were transfected to HK-2 cells following exposure to high glucose and low glucose respectively. The expressions of ZO-1, vimentin and ZEB-1 were determined by realtime PCR and western blot.

Results: The expression of circulating miR-302a-3p was significantly increased in the diabetes mellitus group (DM, n=22) compared with control (healthy persons, n=30) and then decreased in the early stage of diabetic nephropathy group (DNE, n=20). Furthermore, its expression in clinical diabetic nephropathy group (DNC, n=18) was decreased significantly compared with DM group. Circulating miR-302a-3p had negative relevance with UAE in DNE group (r=-0.649, P=0.002) and DNC group (r=-0.681, P=0.006); It had positive relevance with eGFR in DNC group (r=0.486, P=0.041). *In vitro*, miR-302a-3p expression in HG group increased at 6h and ascended to the highest level at 12h and then gradually decreased at 48h and 72h. More interesting, ZEB1 protein expression had an opposite change which gradually decreased from 6h to 24h and then gradually increased from 48h to 72h. Moreover, overexpression of miR-302a-3p suppressed expression of ZEB1 in the post-transcriptional level and reversed high glucose-mediated downregulation of E-cadherin and upregulation of vimentin. Meanwhile, loss of miR-302a-3p expression can lead to EMT of HK-2 cells just as high glucose stimulation.

Conclusions: miR-302a-3p may play a protective role by targeting ZEB1 in renal epithelial- mesenchymal transition in DKD. It may serve as a potential novel target in pre-EMT states for the amelioration renal fibrosis seen in DKD.

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FR-PO288

Kruppel-Like Factor 15 Works as an Early Anti-Fibrotic Transcriptional Regulator in Angiotensin II-Induced Renal Fibrosis via Down-Regulation of Connective Tissue Growth Factor Xiangchen Gu,¹ Xiang Gao,¹ Changlin Mei,¹ ¹Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China; ²Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China; ³Kidney Inst of PLA, Dept of Medicine, Changzheng Hospital, Second Military Medical Univ, Shanghai, China.

Background: Angiotensin II (Ang II) has been regarded as an important profibrogenic cytokine in renal fibrosis. One of the main targets of Ang II in renal fibrosis is CTGF. Kruppel-like factor 15 (KLF15) is recognized as an important negative transcription factor in renal fibrosis. This study is aimed to detect the possible role and mechanism of KLF15 in renal fibrosis induced by Ang II.

Methods: Firstly, mice were randomized into control group, Ang II group, Ang II+losartan group, the renal fibrosis levels and KLF15 were measured by Real-Time PCR and IMF methods respectively at 4 weeks or 6 weeks. Then NRK-49F were stimulated with Ang II and (or) infected with Ad-GFP-KLF15, and the expressions of KLF15, CTGF and extracellular matrix were detected by Real-Time PCR and Western Blot. CoIP and ChIP assay were also performed to investigate the relationship among coactivator P/CAF, transcription regulator KLF15, and CTGF promoter.

Results: The murine model of Ang II-induced renal fibrosis demonstrated a significant decrease in renal KLF15 expression at 4 weeks and progressive renal fibrosis at 6 weeks. Losartan effectively prevented the decrease in KLF15 expressions induced by Angiotensin II. Stimulated with Ang II, NRK-49F exhibited significant decreases in KLF15, accompanied by a marked increase in CTGF and extracellular matrix. Losartan prevented the decrease in Ang II induced KLF15. Furthermore, overexpression of KLF15 inhibited Ang II induced CTGF in NRK-49F. CoIP and ChIP demonstrated KLF15, could directly bind to P/CAF, and repressed its recruitment to CTGF promoter.

Conclusions: These results unveiled that Ang II could downregulate KLF15 via AT1 receptor. Transcription repressor KLF15 is likely to inhibit Ang II induced CTGF by repressing coactivator P/CAF's recruitment to CTGF promoter.

Funding: Government Support - Non-U.S.

FR-PO289

Biomarkers of Collagen Type III and VI Turnover Can Identify Renal Allograft Failure in Kidney Transplant Recipients Federica Genovese,¹ Signe Holm Nielsen,^{1,2} Daniel Guldager Kring Rasmussen,^{1,3} Morten Asser Karsdal,¹ Stephan J.L. Bakker,⁴ Peter Olinga,⁴ Elisabeth G.D. Stribos,⁴ Henricus A.M. Mutsaers,⁴ ¹Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; ²System Biology, Denmark Technology Univ, Kgs. Lyngby, Denmark; ³Southern Denmark Univ, Odense, Denmark; ⁴Univ of Groningen, Groningen, Netherlands.

Background: Chronic allograft loss poses a major problem in improving long-term survival in renal transplant recipients (RTR). Interstitial fibrosis and tubular atrophy are already present in 40% of kidney allografts 3-6 months after transplantation. Extracellular matrix (ECM) turnover levels, reflecting the onset of fibrosis, can be early and superior prognostic markers for renal allograft function. We evaluated a non-invasive tool measuring the plasma and urinary biomarker profile related to ECM turnover.

Methods: 78 patients attending the University Medical Center Groningen during one week for a routine check-up after kidney transplantation were enrolled in the study. Plasma and/or 24h-urine samples were collected from 75 and 42 RTR, respectively. Afterwards, markers of collagen remodeling were determined by competitive ELISAs.

Results: There was no correlation between age or time after transplant and glomerular filtration rate (eGFR) in this population. Urinary levels of C3M, a marker for collagen type III degradation, were strongly correlated with eGFR (p<0.0001), with lower levels in advanced disease stages compared to early and mild stages. Plasma levels of Pro-C6, a marker for collagen type VI formation, significantly increased with disease progression and strongly correlated with eGFR (p<0.0001). In contrast, plasma C3M and urinary Pro-C6 levels showed no correlation with renal function.

Conclusions: We identified two biomarkers of tissue turnover associated with ECM remodeling and subsequent fibrosis in the transplanted kidney leading to loss of renal function. As such they have great potential as early diagnostic markers for kidney allograft failure.

FR-PO290

Hyaluronidase-2 Dependent Regulation of CD44 Variant Expression in Anti-fibrotic versus Pro-Fibrotic Cells Soma Meran, Adam Midgley, Robert Steadman, Aled O. Phillips. *Nephrology, Cardiff Univ, Cardiff, United Kingdom.*

Background: Hyaluronan (HA) is a GAG with increased expression in progressive renal disease, and its expression correlates with poor renal outcomes. The HA receptor (CD44) is a transmembrane protein that can undergo alternative exon splicing to produce over 20 CD44 variant isoforms. We identified that the standard isoform (CD44s) is critical for myofibroblast formation, whereas the variant isoform (CD44v7/8) promotes reversal of myofibroblast phenotype. Hyaluronidase-(Hyal)2 is a weak HA degrading enzyme and is a key mediator in reversal of myofibroblast phenotype, but its mechanism is unknown. Here we investigate whether Hyal2 plays a regulatory role in alternative splicing of CD44v7/8 variant isoform expression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: Fibroblasts & renal epithelial cells were incubated with TGF β 1 to induce myofibroblast formation, and compared to cells incubated with TGF β 1 & BMP7 to induce myofibroblast reversal. QPCR, confocal microscopy, ChIP, siRNA & plasmid overexpression were used to assess Hyal2 effects.

Results: Hyal2 was upregulated by both profibrotic (TGF β 1) & anti-fibrotic (BMP7) cellular treatments. However in profibrotic cells, Hyal2 was cytoplasmic, whereas in antifibrotic cells Hyal2 translocated to the nucleus. In profibrotic cells Hyal2 did not associate with CD44. In contrast in antifibrotic cells Hyal2 associated with CD44s at the nucleus, whilst CD44v7/8 located to the cell surface. In antifibrotic cells Hyal2 nuclear translocation was crucial for increased CD44v7/8 mRNA & protein expression. CD44v7/8 was subsequently necessary for HA internalization and consequent reversal of myofibroblast phenotype. ChIP demonstrated association between Hyal2 and introns flanking the CD44v7/8 exon nucleotide sequence similar to Ago2 splice facilitator. Moreover, Hyal2 inhibition attenuated BMP7 driven upregulation of splice regulators SLM2 & SRSF6.

Conclusions: Hyal2 displays nonenzymatic activity & translocates to the nucleus regulating expression of CD44v7/8 splice variant, which is crucial for reversing myofibroblast phenotype. Hence Hyal2 is a novel splice regulator and a critical regulator in reversal of myofibroblast phenotype & fibrosis prevention.

FR-PO291

FGF Signaling Contributes to Podocyte Injury in Murine HIV-Associated Nephropathy Koji Okamoto,¹ Eisei Noiri,² Jeffrey B. Kopp.¹ ¹Kidney Section, NIDDK, NIH, Bethesda, MD; ²Dept of Nephrology, Endocrinology, Hemodialysis & Apheresis, Univ Hospital, The Univ of Tokyo, Tokyo, Japan.

Background: We reported that fibroblast growth factor receptor (FGFR), its ligand fibroblast growth factor 2 (FGF2), and their amplifying co-factor glypican 5 (GPC5) play important roles in idiopathic nephrotic syndrome and diabetic nephropathy (Okamoto, Nature Genetics, 2011). We have investigated the role of the FGF2 signal pathway in HIV-associated nephropathy (HIVAN).

Methods: FGF2 ligands and FGFR expression were studied in a mouse podocyte cell line and a HIVAN transgenic mouse, both of which express the HIV accessory protein Vpr in the presence of doxycycline. To study FGF2 trapping in glomeruli, biotinylated FGF2 was administered intravenously and detected with fluorescent streptavidin. Vpr mice and control mice received FGF2 (5 mg/animal/weekly for 4 weeks) or FGF antagonist (PD173074, 50mg/animal/ bi-weekly for 4 weeks).

Results: In cultured mouse podocytes FGF3 mRNA was increased 11-fold after Vpr induction. In Vpr mice compared with control mice, renal cortex FGF2 content was increased 3-fold, as assessed by ELISA. Intra-glomerular protein expression of FGFR3 and GPC5 were increased, as detected by immunofluorescent staining. These results suggest that Vpr mouse glomeruli might have increased FGF2 binding capacity and so we tested the binding capacity of FGF2 in vivo. One hour after intravenous administration of biotinylated FGF2, more biotin signal remained in glomeruli of Vpr mice compared with control mice (60% increase). Urine albumin/creatinine ratios (g/g) were significantly increased in FGF2-treated Vpr mice compared to untreated Vpr mice on day 14 (0.55±0.19 vs 2.3±0.6), day 21 (1.17±0.16 vs 18.7±5.1) and day 28 (1.87±0.44 vs 21.8±9.9). Further, the FGF antagonist decreased albuminuria in Vpr mice at day 21 (0.47±0.16 vs 1.1.7±0.16 g/g) and at day 28 (0.36±0.41 vs 1.87±0.44 g/g).

Conclusions: In a HIVAN mouse model, podocyte Vpr expression increased protein expression of FGF2, FGF receptors and GPC5. Administration of FGF2 increased albuminuria, and treatment with an FGF antagonist reduced albuminuria, suggesting a pathogenic role for FGF2 in this murine HIVAN model.

FR-PO292

Role of AMP-Activated Protein Kinase Signaling in Fibroblast Activation and Renal Fibrosis Yuguo Wang, Yanlin Wang. *Medicine, Baylor College of Medicine, Houston, TX.*

Background: Renal fibrosis is a common manifestation of chronic kidney disease resulting in progressive loss of kidney function. Although activated fibroblasts are responsible for the production and deposition of the extracellular matrix, the molecular mechanisms underlying fibroblast activation are not fully understood. In this study, we examined the functional role of AMP-activated protein kinase α 1 (AMPK α 1) in the activated of fibroblasts and the development of renal fibrosis.

Methods: To examine the functional role of AMPK α 1, we generated mice with fibroblast-specific deletion of AMPK α 1 using Cre-LoxP strategy. Unilateral ureteral obstruction (UUO) and ischemia-reperfusion injury (IRI) models were used to induce renal fibrosis. Cultured cells were used to examine AMPK α 1 signaling in fibroblast activation.

Results: AMPK α 1 is induced in the kidney during the development of renal fibrosis. Mice with mesenchymal-specific deletion of AMPK α 1 were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed AMPK α 1 mice, mice with fibroblast-specific deletion of AMPK α 1 exhibited fewer α -smooth muscle actin (α -SMA) positive myofibroblasts and expressed less α -SMA protein in the kidney following UUO or IRI. Furthermore, mesenchymal-specific deletion of AMPK α 1 significantly reduced total collagen deposition and suppressed expression of extracellular matrix proteins (collagen I and fibronectin) in the kidney in response to UUO or IRI. In cultured fibroblasts, activation of AMPK α 1 caused cofillin phosphorylation, cytoskeleton remodeling, and myocardin-related transcription factor A (MRTF-A) nuclear translocation leading to fibroblast activation and extracellular matrix protein production.

Conclusions: Our results have shown that AMPK α 1 is critically involved in fibroblast activation through regulation of cytoskeleton dynamics and MRTF-A nuclear translocation. Therefore, AMPK α 1 may represent a novel therapeutic target for chronic kidney disease.

Funding: NIDDK Support

FR-PO293

Increased Expression of Complement C1 from Pericyte/Myofibroblasts Contributes to Renal Fibrosis via Activation of Wnt/ β Catenin Signaling Sandhya Xavier,¹ Susan G. Landes,¹ Amandeep Bajwa,¹ Jing Yu,² Jeremy Stuart Duffield,³ Didier Portilla.¹ ¹Dept of Medicine and Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia, VA; ²Univ of Virginia; ³Biogen Idec.

Background: Pericytes/fibroblasts are progenitors of scar-forming cells known as myofibroblasts. We have characterized the inflammatory nature of pericytes/fibroblasts isolated from UUO mice. We have also shown that Wnt/ β -catenin signaling is activated during kidney fibrosis. Role of complement C1 on pericyte function or in Wnt activation remains unknown.

Methods: We used the unilateral ureteral obstruction (UUO) and folic acid nephropathy models. Pericytes were isolated using magnetic beads containing anti-PDGFR β Receptor ab. Expression of C1 complex was examined by western blotting, immunofluorescence, and realtime-PCR in tissue and in cell lysates and supernatants obtained from pericytes cultured from sham, day3 and day10 UUO mice kidneys. Topflash reporter assays were used to study Wnt signaling.

Results: Expression of C1q chains a,b,c, as well as subunits C1r and C1s were increased during fibrosis along with increased expression of TGF- β , α -SMA and Wnt target genes wisp1 and 2. Immunostain showed C1q localization in the interstitial compartment of UUO but not in sham mice consistent with PCR and western blot data. In cultured pericytes, C1 complex component C1q protein was increased in culture supernatants of Day3 and Day 10 but not in shams. Expression of C1q proteins was absent in supernatants of UUO pericytes isolated from C1qKO mice. Topflash reporter assays for Wnt signaling showed that pericytes from UUO kidneys had pronounced activation of the reporter following Wnt3a treatment as compared to shams, and this effect was blunted in pericytes isolated from C1qKO mice.

Conclusions: We demonstrate both in vivo and in vitro that increased expression of the C1 complex occurs in response to kidney injury along with activation of Wnt signaling. Given previous data, showing that inhibition of C1 complex using C1INH prevents renal fibrosis, we conclude that its inhibition in pericytes/myofibroblasts leads to inhibition of Wnt activation and reduced renal fibrosis.

Funding: NIDDK Support, Veterans Administration Support

FR-PO294

The Role and Association of Inflammatory and Apoptotic Caspases in Tubulointerstitial Fibrosis Chun Zhang, You Ke, Hua Su. *Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: Caspases are a family of cysteine proteases with pivotal functions in apoptotic and inflammatory signaling. According to their difference of structures and functions, 14 mammalian Caspases are classified into three categories, which are apoptosis activator, apoptosis executioner and inflammatory mediator. Caspase-1 is an inflammatory caspase, and Caspase-7 belongs to apoptosis executioner. The roles and association of these two distinct types of Caspases protein in tubulointerstitial fibrosis (TIF) are not well recognized.

Methods: Unilateral Ureteral Obstruction (UUO) animal model was constructed on wild-type(WT) and caspase-1 knock out (KO) mice. In vitro study, the cultured tubular epithelial cell line NRK-52E (TECs) was employed and the expression of caspase-1 and caspase-7 was modulated by transfection of Lentiviral shRNA.

Results: In current study, we found both Caspase-1 and Caspase-7 protein levels were elevated in UUO WT mice. While in UUO mice with Caspase-1 KO background the increased Caspase-7 was suppressed significantly along with the minimized extracellular matrix accumulation which was demonstrated by western blot, immunohistochemistry and Masson trichrome staining. In vitro TGF- β 1 stimulation promoted the expression of Caspase-1 and Caspase-7 simultaneously in TECs. Notably, genetic deletion of either Caspase-1 or Caspase-7 could abrogate TGF- β 1 driven TECs' transdifferentiation and apoptosis. In addition, knocking down Caspase-1 dampened Caspase-7 upregulation in TGF- β 1 treated TECs which was consistent with in vivo study. However genetic deletion of Caspase-7 did not influence Caspase-1's abundance.

Conclusions: Our observation firstly links inflammatory and apoptotic Caspases together in TIF and further elucidates Caspase-1 activation is an upstream event of apoptotic Caspase-7 induction during TIF and TECs' transdifferentiation and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO295

MAD2B-SnoN-Smad3 Signaling Pathway Is Implicated in Fibroblast Activation and Tubulointerstitial Fibrosis Chun Zhang, Hui Tang, Hua Su. *Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: Mitotic arrest deficient protein MAD2B, an anaphase-promoting complex (APC)/cyclosome inhibitor, is indispensable for mitotic checkpoint control. Previously we found MAD2B was expressed in glomerular and tubulointerstitial compartment. In addition our data indicated MAD2B was involved in podocyte injury triggered by high glucose. But its role in renal fibrosis remains elusive.

Methods: The object of this study included patients with renal tubulointerstitial fibrosis (TIF) (secondary glomerulonephritis and interstitial nephritis were excluded), Unilateral Ureteral Obstruction(UUO) mice and in vitro cultured tubular epithelial cell line (NRK-52E) and renal fibroblast cell line (NRK-49F). In vivo gene silencing of MAD2B was carried out by intrarenal Lentiviral gene delivery.

Results: By immunohistochemistry and western blot, it showed the expression of MAD2B was increased obviously in TIF patients and UUO mice. Next we assessed the types of cells attributing to the elevated MAD2B abundance. It is well-known that TECs and fibroblast are the main culprits in TIF. Our data suggested under TGF- β 1 exposure the level of MAD2B in NRK-52E was not altered, whereas in NRK-49F MAD2B was upregulated in a time dependent manner significantly. Furthermore TGF- β 1 induced fibroblast activation can be abrogated by MAD2B genetic deletion. Intriguingly, SnoN, a repressor of Smad3, was decreased in NRK-49F cells treated with TGF- β 1 which could be alleviated by MAD2B knocking down. Consistently, in UUO mice the expression of SnoN was significantly reduced in renal cortex accompanying with enhanced p-Smad3. And locally genetic deletion of MAD2B by Lentiviral transfection preserved SnoN abundance and consequently suppressed Smad3 signaling which finally dampened the fibroblast activation and ECM accumulation in UUO mice.

Conclusions: Our observation proposes that MAD2B participates in fibroblast activation and tubulointerstitial fibrosis by repressing SnoN and subsequent activating Smad3 signaling pathway. Regulation of MAD2B-SnoN pathway may be a promising therapy for tubulointerstitial fibrosis. However, the regulatory mechanisms between MAD2B and SnoN still need further investigation.

Funding: Government Support - Non-U.S.

FR-PO296

Losartan Reduces Renal Fibrogenesis by Up-Regulating Klotho in Uremic Rats Edgar Maquigussa, Josne Carla Paterno, Gabriel H. Pokorny, Mariana S. Perez, Nestor Schor, Mirian A. Boim. *Nephrology, UNIFESP, Sao Paulo, Brazil.*

Background: Klotho is a transmembrane protein expresses mainly in the kidney. Soluble klotho acts as an endocrine factor with diverse functions through mechanisms involving Wnt and TGF β 1 signaling. Renal fibrosis is the end stage of the progressive chronic kidney disease (CKD) and renal klotho is markedly decreased in CKD patients. Renin angiotensin system (RAS) blockade is a relevant therapy to reduce CKD progression and the beneficial effects go further to the antihypertensive effect. The aim of this study was to investigate a possible link between RAS and Klotho by evaluating the effects of losartan on Klotho/Wnt signaling in 5/6 nephrectomy model of CKD in rats.

Methods: Adult male Wistar rats were underwent 5/6 nephrectomy (Nx). The Nx animals were separated into three groups: control, with no treatment (Nx), treated with losartan (LOS; 25 mg/kg/day, p.o.) or propranolol (PROP; 25mg/kg/day, p.o.). Results were compared with SHAM group. Blood pressure was measured by tail-cuff plethysmography. After 8 weeks, animals were sacrificed and the remnant kidney was removed to determine the renal expression of collagen, fibronectin, epithelial-to-mesenchymal transition (EMT) markers (FSP1 and α -SMA) and Klotho signaling (Klotho, Wnts and GSK3 β) by real time PCR.

Results: Nx rats presented hypertension that was blunted by both losartan and propranolol. The expression levels of collagen and fibronectin were increased in Nx group which was reverted only in LOS group. The presence of the EMT markers, FSP1 and α -SMA, was observed in Nx group which was decreased with losartan treatment. Klotho was reduced in Nx animals and LOS but not propranolol significantly increased klotho expression. Nx animals showed upregulation of GSK3 β , Wnt 7a and Wnt 3. LOS treatment prevented the increase in Wnt 7a and GSK3 β but not Wnt 3.

Conclusions: These data suggest that the beneficial effect of losartan on renal fibrosis is independent of blood pressure reduction and may be, at least in part, due to upregulation of klotho. Since, the antihypertensive agent, propranolol induced no change in klotho expression. The interaction between the RAS and Klotho can inactivate the Wnt pathway.

Funding: Government Support - Non-U.S.

FR-PO297

PBI-4050 Inhibits the Development of Renal Fibrosis in a Model of Tubulointerstitial Fibrosis Ming-Zhi Zhang,¹ Lyne Gagnon,² Raymond C. Harris.¹ ¹Medicine, Vanderbilt Univ, Nashville, TN; ²ProMetic Biosciences, Laval, QC, Canada.

Background: Kidney fibrosis occurs in chronic kidney diseases and leads to gradual loss of kidney function. Although the etiology of kidney fibrosis is multifactorial, there is increasing evidence linking chronic inflammation to kidney fibrosis. PBI-4050, a novel first-in-class orally active low molecular weight compound currently in phase II clinical trials, has anti-fibrotic and anti-inflammatory properties in different *in vivo* models. Activation of epidermal growth factor receptor (EGFR) contributes to the development of renal fibrosis, and homozygous transgenic mice with overexpression of an EGFR ligand, human heparin-binding EGF (HB-EGF), in renal proximal tubule develop spontaneous tubulointerstitial fibrosis by 3-4 weeks of age. We examined whether PBI-4050 affected the development of renal fibrosis in homozygous HB-EGF mice.

Methods: Homozygous HB-EGF mice on a C57/BL6 background were treated with PBI-4050 (200 mg/kg/day) by daily gastric gavage from 4 to 14 weeks of age.

Results: Immunohistochemical analysis showed that in untreated homozygous HB-EGF mouse kidney, ERK was activated in both proximal tubule epithelial cells (PTEC) and their surrounding interstitial cells. PBI-4050 treatment led to marked decreases in ERK activity in proximal tubule epithelial cells and interstitial cells, suggesting that PBI-4050 inhibits not only HB-EGF/EGFR-mediated p-ERK activation in PTEC, but also subsequent ERK activation in the interstitial cells, leading to inhibition of the development of renal fibrosis. PBI-4050 treatment significantly reduced the development of renal interstitial fibrosis. PBI-4050 caused marked decreases in renal macrophage infiltration (F4/80 staining) as well as oxidative stress (nitrotyrosine staining). In addition, PBI-4050 treatment reduced the expression levels of the pro-fibrotic and fibrotic components including CTGF and TGF- β , α -SMA (a marker of myofibroblasts), fibronectin, collagen I and collagen IV.

Conclusions: These studies suggest that PBI-4050 significantly inhibits the development of renal fibrosis in homozygous HB-EGF mice through multiple mechanisms, including through anti-inflammatory effects.

Funding: NIDDK Support, Pharmaceutical Company Support - ProMetic Biosciences

FR-PO298

FHL2 Promotes Tubular Epithelial-to-Mesenchymal Transition by Regulating β -Catenin Activity Ting Cai, Danqin Sun, Chunsun Dai, Junwei Yang, Weichun He. *Center for Kidney Disease, 2nd Affiliated Hospital of Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Fibrotic kidneys exhibit aberrant activation of β -catenin signaling, one of the main pathways that play a critical role in mediating tubular epithelial-to-mesenchymal transition (EMT). FHL2 (four-and-a-half-LIM-only protein 2), an adapter protein, is an endogenous regulator of β -catenin.

Methods: To determine whether FHL2 is also involved in the EMT process, we investigated its regulation and function during TGF- β 1-stimulated EMT.

Results: TGF- β 1 induced FHL2 mRNA and protein expression in rat proximal tubular epithelial cells (NRK-52E) in a time- or dose- dependent fashion, an effect that was largely dependent on intracellular Smad signaling. Overexpression of FHL2 suppressed E-cadherin, increased α -smooth muscle actin (α -SMA), vimentin and fibronectin expression, whereas knockdown of FHL2 via small interfering RNA partially reduced TGF- β 1-mediated α -SMA, vimentin and fibronectin expression, and restored E-cadherin. TGF- β 1 induced FHL2 physically interact with β -catenin in the nuclei in NRK-52E cells. Ectopic expression of FHL2 promoted β -catenin nuclear translocation, induced β -catenin-mediated gene transcription, and upregulated the expression of β -catenin target genes such as plasminogen activator inhibitor-1 (PAI-1) and Twist. Conversely, downregulation of FHL2 expression reduced β -catenin nuclear translocation, abolished β -catenin-mediated gene transcription, and inhibited PAI-1 and Twist expression in the basal and TGF- β 1-stimulated conditions. In a mouse model of obstructive nephropathy, FHL2 expression increased in a time-dependent manner, suggesting that it may play a role in tubular EMT and renal fibrosis *in vivo*.

Conclusions: We conclude that FHL2, through manipulating β -catenin activity, plays an important role in regulating TGF- β 1-mediated EMT and could be a potential future therapeutic target to prevent progression of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO299

Depletion of Endothelial Sirtuin 1 Aggravates Capillary Rarefaction and Tissue Fibrosis following Kidney Injury Yujiro Kida, Michael S. Goligorsky. *New York Medical College.*

Background: Capillary rarefaction and tissue fibrosis are hallmarks of chronic kidney diseases. Although recent studies point to sirtuin 1 (SIRT1) in endothelial cells as being protective against tissue injury, mechanisms of this effect are incompletely understood.

Methods: We deleted SIRT1 catalytic domain in endothelial cells in mice (Sirt1 mutant mice). Both wild type control and Sirt1 mutant mice were subjected to kidney injury by unilateral ureteral obstruction (UUO). In *in vitro* studies, we used human umbilical vein endothelial cells (HUVECs).

Results: After UUO kidney injury, compared to control kidneys, Sirt1 mutant kidneys demonstrated significantly exaggerated (1) capillary rarefaction (2) expansion of myofibroblast population, and (3) tissue fibrosis compared to wild type kidneys. In HUVECs, siRNA knockdown or chemical inhibition of SIRT1 significantly suppressed transcriptional expression of platelet derived growth factor- β (PDGF-B) and vascular endothelial growth factor receptor-2 (VEGFR2). Both effects were partially abrogated by Notch inhibition. This indicates that SIRT1 enhances PDGF-B and VEGFR2 expression via Notch inhibition in endothelial cells. In scratch wound healing assay, SIRT1 inhibition impaired migration of HUVECs under oxidative stress by hydrogen peroxide, indicating SIRT1 dysfunction decreases migratory phenotype of endothelial cells. In transwell co-culture assay, endothelial SIRT1 inhibition impaired recruitment of PDGFR β + cells to HUVECs. Consistent with this finding, detachment of PDGFR β + pericytes was increased in Sirt1 mutant kidneys compared to control kidneys, suggesting that pericyte detachment and subsequent pericyte-myofibroblast transition are augmented in Sirt1 mutant kidneys, resulting in excessive fibrosis.

Conclusions: Functional depletion of SIRT1 in endothelial cells aggravates capillary rarefaction and fibrosis at least in part due to impaired endothelial expression of VEGFR2 and PDGF-B, respectively.

Funding: NIDDK Support

FR-PO300

In Vivo Reprogramming of Myofibroblasts with Endothelial Progenitor Cell Extract Ameliorates Fibrosis Kei Matsumoto,^{1,2} Sandhya Xavier,¹ Jun Chen,¹ Yujiro Kida,¹ Brian B. Ratliff,¹ Stefan Rose-john,³ Michael S. Goligorsky,¹ ¹New York Medical College; ²Showa Univ, Tokyo, Japan; ³Christian-Albrechts Univ, Kiel, Germany.

Background: Accumulation of myofibroblasts is a hallmark of renal fibrosis. We hypothesized that exposing myofibroblasts to the extract of endothelial progenitor cells (EPC extract) could reverse endothelial-mesenchymal transition.

Methods: We used α -SMA-GFP mice to visualize fibroblast-to-myofibroblast conversion and embryonic mouse EPC to prepare extract. Cell phenotype was assessed using standard biochemical and molecular biology techniques.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Results: In vitro treatment of TGF- β 1-activated fibroblasts with EPC extract prevented expression of α -SMA, but did not enhance expression of endothelial markers. In two distinct models of renal fibrosis, unilateral ureteral obstruction (UUO) and chronic phase of folic acid-induced nephropathy (FAN), subcapsular injection of EPC extract to the kidney prevented and reversed accumulation of α -SMA-positive myofibroblasts and reduced fibrosis. Screening the composition of EPC extract for cytokines revealed that it is enriched in LIF and VEGF. Only LIF was capable of reducing fibroblast-to-myofibroblast transition of TGF- β 1-activated fibroblasts. In vivo subcapsular administration of LIF reduced the number of myofibroblasts, improved the density of peritubular capillaries, but did not reduce the degree of fibrosis. Effects of LIF, as well as Hyper-IL-6, in the presence of TGF- β 1 were mediated via gp130/STAT3 pathway resulting in induction of pluripotency transcription factors KLF4, c-Myc, OCT4, and Nanog in association with the open chromatin conformation.

Conclusions: EPC extract does not reverse endothelial-mesenchymal transition, but it prevents and reverses fibroblast-to-myofibroblast transition and renal fibrosis. The component of EPC extract, LIF, is capable of preventing development of the contractile phenotype of activated fibroblasts, but does not eliminate TGF- β 1-induced collagen synthesis in cultured fibroblasts and models of renal fibrosis. LIF component of EPC extract is a participant of its antifibrotic effect, but not the sole one, as other yet undisclosed factors contribute to the antifibrotic effect of the extract.

Funding: NIDDK Support

FR-PO301

Mitochondrial Metabolic Switch to Glycolysis in Proximal Tubular Epithelial Cell in Fibrotic Kidneys Lei Jiang, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Renal proximal tubule is susceptible to hypoxic injury since its reliance on aerobic oxidative metabolism. Mitochondrial dysfunction contributes to progression of chronic renal disease. However, the profile of the energy metabolism of renal tubule in progression of fibrosis is uncertain, and the relationship between the change of energy metabolism and tubular epithelial cell damage is unclear.

Methods: Gene expression profiles related to energy metabolism of the proximal tubule in fibrotic kidneys were analyzed. 2-Deoxyglucose (2-DG) was given to CD-1 mice under UUO intraperitoneally. Primary tubular epithelial cells (PTC) cultured from normal CD-1 mice renal cortex was used. 2-DG (inhibitor of glycolysis), bromopyruvic acid (inhibitor of hexokinase), dichloroacetic acid (inhibitor of glycolysis), oligomycin (inhibitor of oxidative phosphorylation), etomoxir (inhibitor of fatty acid oxidation), DON (inhibitor of glutamine metabolism), PKM2 siRNA or HIF-1 α siRNA was used in PTC with or without TGF- β 1 stimulation. The oxygen consumption rate (OCR) and extracellular acidification rate (ECR) were detected by Seahorse Metabolic Analyzer.

Results: 1. Glycolysis was upregulated in the proximal tubule in fibrotic kidney. 2. Genes related to glycolysis were upregulated, however, genes related to oxidative phosphorylation, fatty acid metabolism and glutamine metabolism were downregulated. The key limiting-rate enzymes for glycolysis were upregulated in the fibrotic kidney. 3. 2-DG could block the renal fibrosis under UUO. 4. OCR was decreased under TGF- β 1 stimulation in PTC, however, ECAR was increased after TGF- β 1 stimulation. 5. Inhibiting oxidative phosphorylation, fatty acid oxidation or glutamine metabolism could increase the lactate production in PTC. Lactate could directly induce PTC damage. 6. Inhibiting glycolysis could ameliorate the damage of PTC under TGF- β 1 incubation.

Conclusions: The mitochondrial metabolism including oxidative phosphorylation, fatty acid oxidation and glutamine metabolism is defective in proximal tubular epithelial cell in fibrotic kidney. The metabolism is switch to glycolysis, and the glycolytic product lactate further aggravates the injury.

Funding: Government Support - Non-U.S.

FR-PO302

The Effects of CCN3/NOV on the Formation of Extracellular Matrix in Human Mesangial Cells Haifei Liu, Long Chen, Hong Liu, Bi-Cheng Liu. *Dept of Nephrology, Zhong Da Hospital, Southeast Univ, Nanjing, Jiangsu, China.*

Background: Glomerulosclerosis is characterized by mesangial cells proliferation and progressive extracellular matrix (ECM) accumulation. Mesangial cells are activated in a variety of damage factors, leading to ECM deposition. ECM accumulation is the net result of the balance between synthesis and degradation. CCN3, a matricellular protein of the CYR61-CTGF-NOV (CCN) family, associates specifically with ECM. A recent study found that treatment with the matricellular protein CCN3 can block and/or reverse fibrosis development in obesity with diabetic nephropathy. However, whether CCN3 can alleviate the formation of glomerulosclerosis by inhibiting the production of ECM and/or promoting the degradation of ECM is still unknown. This study aims to explore the potential role of CCN3 in ECM accumulation of mesangial cells induced by TGF- β 1.

Methods: Human mesangial cells lines were stimulated with TGF- β 1 (2ng/ml) and CCN3 for different concentration (5 to 500 ng/ml) after 24 hours of serum starvation. The expressions of fibronectin (FN), type I collagen (COL1), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) were evaluated with RT-PCR and Western blot.

Results: In human mesangial cells lines, TGF- β 1 significantly upregulated FN, COL1 and TIMP-1 at mRNA and protein levels ($P < 0.05$). However, a 1-hour pretreatment of the cells with CCN3 for different concentration (5, 50, 500 ng/ml) virtually blocked this TGF- β 1 induced effect on them ($P < 0.05$). On the other hands, TGF- β 1 downregulated

MMP-2 and MMP-9 at mRNA and protein levels, whereas a 1-hour pretreatment of the cells with CCN3 for different concentration (5, 50, 500 ng/ml) enhanced the expression of MMP-2 and MMP-9 ($P < 0.05$).

Conclusions: This study identifies that CCN3 as a new actor alleviates the formation of glomerulosclerosis by inhibiting the production of ECM and promoting the degradation of ECM.

Funding: Government Support - Non-U.S.

FR-PO303

Spleen Tyrosine Kinase (Syk) Inhibition Suppresses Renal Fibrosis Through Anti-Inflammatory Effects and Down-Regulation MAPK-p38 Pathway Kuan-hsing Chen, Hsiang-Hao Hsu, Cheng-chieh Hung. *Nephrology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.*

Background: Spleen tyrosine kinase (Syk) is a 72-kDa, a member of the Src family of non-receptor tyrosine. The central role of Syk in signaling processes is known to be involved in adaptive immunity, but also in autoinflammatory and allergic disease. However, the possible role of the anti-fibrogenic properties in renal interstitial fibrosis had not been established.

Methods: In vitro study: Cultured rat renal interstitial fibroblasts (NRK-49F) were stimulated with recombinant human TGF- β 1 1ng/ml for different periods before harvesting. Alternatively, NRK-49F cells were pre-incubated with Syk inhibitor for 30 mins before TGF- β 1 treatment. Total RNA was extracted for RT-PCR and total cell lysates were extracted for Western Blot analysis. In vivo study: Urinary unilateral obstruction model was induced in adult male B6 mice (3-5 months, 20-25 g). Mice with UUO were given with intra-peritoneal Syk inhibitor (20 and 40 mg/kg, bid) or saline daily, one day prior the UUO surgery. Both obstructed and contralateral kidneys were harvested 7 days after surgery. Kidney tissues were prepared for further pathological and molecular biological analysis.

Results: Our results demonstrated that the inhibition of Syk in NRK49F cells inhibited the stimulation effect of TGF- β leading to fibroblast transition to the myofibroblast phenotype (upregulation of α -SMA) and extracellular matrix proteins accumulation, collagen type I, type IV. In addition, in UUO model, Syk inhibitor attenuated the tubule-interstitial fibrosis and expression of α -SMA, collagen I and fibronectin in UUO kidney. The anti-fibrosis of Syk inhibitor in UUO model may be related to anti-inflammatory effects (down-regulate inflammatory cytokines and reduce macrophage infiltration). Moreover, the effects of Syk inhibitor in inhibition of kidney myofibroblast activation by TGF- β 1 were associated with down-regulation of MAPK-p38 pathways.

Conclusions: In conclusion, we demonstrated that Syk inhibitor ameliorates TGF- β 1 induced kidney myofibroblast activation and also reduces the tubulointerstitial fibrosis in UUO mice. The mechanisms may be related to anti-inflammatory effects and down-regulate MAPK-p38 pathway.

Funding: Government Support - Non-U.S.

FR-PO304

Optimization of Identification of the Glomerular Extracellular Matrix Proteome Liliane Hobeika,¹ Michelle T. Barati,¹ Jon B. Klein,^{1,2} Kenneth R. McLeish,^{1,2} Michael Merchant.¹ ¹Medicine, Univ of Louisville; ²Dept of Veterans Affairs, Louisville, KY.

Background: Increased glomerular extracellular matrix (ECM) is present in many glomerular diseases, eg. diabetic nephropathy and FSGS. Defining the ECM proteome by mass spectrometry (MS) offers the opportunity to determine the mechanism for increased ECM and identify disease specific markers. The optimal conditions for ECM isolation and MS analysis have not been determined. This study compared three extraction techniques in glomeruli isolated by laser capture microdissection (LCMD) from two types of tissue preparation.

Methods: Frozen (FR) and formalin-fixed paraffin embedded (FFPE) tissue from the same human kidney were cut into 10mm sections, stained with hematoxylin, glomeruli isolated by LCMD. Glomerular proteins were extracted by a) Protease MAX surfactant + boiling (MAX) or sequential decellularized with b) SDS or c) NH4OH/TritonX-100 (TX) followed by extraction of residual ECM by MAX. Proteins were trypsinized, peptides identified by MS, and data analyzed with Mascot/Sequest search strategy. ANOVA was used to determine differences in protein abundances.

Results: The total protein yield and number of proteins identified were determined in various numbers of glomeruli slices ranging 50 to 150. There was no significant increase in yield above 75 glomeruli slices. Compared to MAX (2032), extraction with SDS or TX increased the total number of proteins identified (2207 and 2246). The total number of proteins identified from FR and FFPE tissue did not differ for any of the extraction methods. More proteins were identified in residual ECM from FFPE than FR with TX (1863 vs 1713) and SDS (1826 vs 1385). By GO annotation, sequential extraction improved the abundance of ECM, as shown by identification of an increased number of, and increased total sequence coverage of, collagen isoforms. More proteins were identified in the cellular fraction from FR compared to FFPE with TX (1646 vs 1294) and SDS (1804 vs 1115).

Conclusions: Using LCMD, sequential extraction with SDS or TX, and peptide identification by MS, the glomerular ECM proteome of patients can be identified from a number of glomeruli compatible with a typical renal biopsy embedded in paraffin.

FR-PO305

BMP-7 Inhibits Renal Akt Signaling Debra F. Higgins, Catherine Godson. School of Medicine, Conway Inst, Univ College Dublin, Dublin, Ireland.

Background: Bone morphogenetic protein-7 (BMP-7), a member of the TGF β -superfamily, counteracts pro-fibrotic TGF β , and protects from fibrosis in acute and chronic renal injury models.

Methods: Using the chronic renal fibrosis model, unilateral ureteral obstruction (UUO), we investigated the effect of exogenous-rhBMP-7 on signaling pathways involved in hypoxia and TGF β -induced fibrosis. Mice undergoing UUO were treated with either vehicle or rhBMP-7 (300mg/kg i.p.), kidneys were harvested on day 8 post-obstruction and analysed for markers of renal fibrosis and activation of SMAD, MAPK, and PI3K signaling.

Results: In response to UUO, SMAD1/5/8 activity was lost in vehicle-treated kidneys yet maintained in BMP-7-treated kidneys. Collagen accumulation was significantly increased in obstructed kidneys of vehicle-treated animals compared with contralateral and this response was not observed in BMP-7-treated obstructed kidneys. Immunohistochemical analysis of type I, III, and IV collagen revealed that accumulation of type I collagen was significantly impaired in BMP-7-treated obstructed kidneys. Activation of SMAD2, SMAD3, ERK, p38 and Akt signaling pathways occurred during fibrogenesis and BMP-7 significantly attenuated SMAD3 and Akt signaling in vivo. In the kidney, inner medullary collecting duct and tubular epithelial cells are responsive to BMP-7. Analysis in mouse inner medullary collecting duct (mIMCD) and human tubular epithelial (HK-2) cell lines stimulated with either TGF β , or hypoxia (1% oxygen) to induce Akt activation provided further evidence that BMP-7 could specifically inhibit PI3K / Akt signaling.

Conclusions: These data demonstrate an important mechanism by which BMP-7 orchestrates renal protection through Akt inhibition and strengthens the argument for use of Akt inhibitors as anti-fibrotic therapeutics.

Funding: Pharmaceutical Company Support - Hoffmann La Roche, Government Support - Non-U.S.

FR-PO306

Prevention of Renal Interstitial Fibrosis by Simultaneous Deletion of Bax and Bak Hee-Seong Jang,¹ Babu J. Padanilam.^{1,2} ¹Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE; ²Internal Medicine, Section of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Proximal tubular injury and apoptosis are key mediators of development of kidney fibrosis, a hallmark of chronic kidney disease. However, the molecular mechanism by which tubular apoptotic cell death leads to kidney fibrosis is poorly understood.

Methods: Here we tested the roles of Bax and Bak, two crucial proteins involved in intrinsic apoptotic cell death, in progression of kidney fibrosis. Mice with proximal tubule-specific Bax deletion, systemic deletion of Bak and dual deletion of Bax and Bak were subjected to unilateral ureteral obstruction (UUO).

Results: Dual deficiency of Bax and Bak inhibited tubular apoptosis and atrophy. Consistent with decreased tubular injury, dual ablation of Bax and Bak suppressed UUO-induced inflammation and kidney fibrosis with decreased tubular cell cycle arrest, expression of fibrogenic and inflammatory cytokines, and oxidative stress in the kidney. Bax or Bak deficiency was insufficient to prevent apoptosis and all other aforementioned malevolent effects, suggesting compensatory mediation by each other in the respective signaling pathways.

Conclusions: These data suggest that dual ablation of Bax and Bak in the kidney is required to prevent UUO-induced tubular apoptosis and the consequent kidney inflammation and fibrosis.

Funding: NIDDK Support

FR-PO307

Investigating the Role of Cilia in Regulating Fibrosis in the Kidney and Liver Using PKD Mouse Models Kurt Zimmerman, Cheng 'Jack' Song, Bradley K. Yoder. Cell, Developmental, and Integrative Biology, UAB, Birmingham, AL.

Background: Cystic kidney disorders are frequently caused by mutations in cilia associated proteins (intraflagellar transport, IFT) or ciliary signaling proteins (polycystin-1 or polycystin-2). Comorbidities commonly associated with renal cysts include biliary duct abnormalities with associated fibrosis in both tissues. In the kidney of cilia mutants, ischemia reperfusion (IR) injury greatly exacerbates the rate of cyst development; however, it is not known whether injury will similarly affect the liver and how loss of cilia affects injury induced fibrosis.

Methods: To address these questions, we are utilizing Oak Ridge Polycystic Kidney (ORPK) mice that have a congenital hypomorphic IFT88 mutation and conditional mutant mice where cilia are disrupted in the kidney (CaggCreER). The conditional mutant mice undergo IR injury and are analyzed to evaluate disease progression, inflammatory responses, and production of extracellular matrix (ECM) and pro-fibrotic growth factors.

Results: Our preliminary studies in the kidney indicate that IFT88 mutant mice receiving IR injury have increased ECM transcripts for *Coll1a2*, *Col3a1*, and *fibronectin* compared to the sham operated kidney. Despite the increased ECM production, the pro-fibrotic growth factor TGF- β , which is frequently associated with fibrosis, was not significantly elevated in mutant mice. However, another TGF- β family member, inhibin β_x , was increased in the injured kidney of mutant mice suggesting a possible mechanism for ECM production. ORPK mutant mice have a noticeable liver phenotype characterized by biliary hyperplasia and, similar to the kidney, an increase in *Col3a1* and *Coll1a2* transcripts. ORPK mutant mice also have increased transcript levels of the monocyte chemoattractant

protein, *MCP1*, and the pro-inflammatory cytokine, *IL-1 β* . Furthermore, in both mutant kidney and liver there is an increase in the number of infiltrating macrophages, which may drive fibrosis.

Conclusions: Together, our preliminary data suggest that defects in cilia formation promote fibrotic disease progression possibly through altered cytokine production and enhanced recruitment of infiltrating monocytes.

Funding: NIDDK Support, Other NIH Support - MERIT fellow grant number: 2K12GM088010-06 to Kurt Zimmerman

FR-PO308

Klotho Suppresses Epithelial-Mesenchymal Transition /or Transformation in Adriamycin Nephropathy Tsuneo Takenaka,¹ Tsutomu Inoue,² Matsuhiko Hayashi.³ ¹International Univ of Health and Welfare; ²Saitama Medical Univ; ³Keio Univ.

Background: Klotho interacts with various proteins to alter their function. Klotho may bind to the receptor for WNT and TGF β , inhibiting their signals.

Methods: Experiments were performed to assess how klotho protects kidney from its injury. Adriamycin (5 mg/Kg) was injected into rats to induce nephropathy. Human recombinant klotho (K, 30 micro-g/kg/day), 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (GSK3beta blocker, 0.2mg/kg/day, T) or vehicle (A) was administered. Rats which were untreated with Adriamycin were used as control (U). Animals were killed 8 weeks later. Renal expressions of Wnt1, GSK3beta, TGF β 1, Twist and collagen I were assessed with RT-PCR against GAPDH. Western blot was used for p-GSK3beta and beta-actin.

Results: Adriamycin increased albuminuria, renal expression of Wnt1, p-GSK3beta, TGF, Twist and collagen I in comparison to the control. Klotho and T suppressed adriamycin-induced albuminuria and the phosphorylation of GSK3beta with sustained elevations of Wnt1, supporting that klotho inhibit Wnt signaling without changes in Wnt level. While klotho and T reduced TGF β , klotho preferentially ameliorated Twist and collagen I in comparison to T.

	U	A	K	T
Alb/Cr	8±2	316±39*	152±21*#	163±29*#
CCr	1.1±0.1	0.9±0.1	1.0±0.1	1.0±0.1
Wnt1	0.2±0.1	3.6±0.3*	3.3±0.3*	3.5±0.3*
p-GSK3beta	0.2±0.1	0.9±0.1*	0.5±0.1*#	0.5±0.1*#
TGFbeta	0.1±0.1	1.2±0.2*	0.7±0.1*#	0.7±0.1*#
Twist	0.2±0.1	1.8±0.2*	0.6±0.1*#	1.0±0.2*#
Collagen I	0.3±0.2	2.3±0.4*	0.7±0.2*#	1.4±0.3*#

Alb/Cr: Albuminuria(mg)/Creatinine(g), CCr: creatinine clearance (ml/min/g.kidney.wt) *: p<0.05 vs U, #: P<0.05 vs A, S: p<0.05 vs K.

Conclusions: Our data indicate that WNT is involved in pathogenesis of Adriamycin nephropathy. Furthermore, the present findings demonstrated that the inhibition of WNT contributed to glomerular protective actions of klotho. Finally, our results suggest that klotho suppresses Epithelial-Mesenchymal Transition /or Transformation by inhibiting TGF β as well as WNT signaling.

Funding: Government Support - Non-U.S.

FR-PO309

The Molecular Mechanism of miR-382 in the Pathogenesis of Renal Tubulointerstitial Fibrosis Yi Fang,^{1,2} Ting Xie,¹ Hui Zhang,¹ Sheng Wu.¹ ¹Nephrology, Zhongshan Hospital Fudan Univ, China; ²Shanghai Key Laboratory of Kidney Diseases and Blood Purification.

Background: To investigate the roles of microRNA-382 (miR-382) in the pathogenesis of renal tubulointerstitial fibrosis.

Methods: Human kidney epithelial (HK2) cells that transfected with a miR-382 inhibitor (antagomiR-382) was used to exam the effect of miR-382 abundance on cell polarity, as well as to test the complementary relationship between miR-382 and its predicted target gene, heat shock 60kDa protein 1 (HSPD1), which was further verified by site-directed mutagenesis. We also examined the in vivo role of miR-382 in the development of renal interstitial fibrosis, in a mouse unilateral ureteral obstruction (UUO) model. Locked nucleic acid-modified anti-miR-382 was intravenously delivered via tail vein less than 30mins prior to UUO, and repeated the dosage 24 hours after the surgery. For clinical verification, renal biopsy specimens from 12 IgA nephropathy (IgAN) patients were collected, 6 with moderate to severe tubulointerstitial fibrosis (TIF) and 6 with no TIF. The relative abundance of miR-382 and HSPD1 protein was analyzed using in situ hybridization and immunohistochemistry.

Results: HSPD1 was confirmed to be a new, direct target gene of miR-382 by in vitro transfect technique and mutation experiments. The development of epithelial transition or renal interstitial fibrosis was accompanied with up-regulated abundance of miR-382. Down-regulation of miR-382 was associated with significant attenuation of interstitial fibrosis, but increase protein expression of HSPD1 and thioredoxin, both in the obstructed mouse kidneys and renal biopsy specimen from IgAN patients.

Conclusions: MiR-382, a profibrotic microRNA, is up-regulated with the development of renal interstitial fibrosis in humans and in mice. The down-regulation of HSPD1 and the decreased ability of anti-oxidative stress are secondary to the increased abundance of miR-382.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

FR-PO310

Assessing the Role of Gremlin-1 on Renal Fibrosis In Vitro Marcela Herrera, Lihuan Liang, Asha Seth, Carol Patricia Moreno Quinn. *Cardiovascular & Metabolic Diseases, Medimmune, Cambridge, United Kingdom.*

Background: Bone Morphogenic Proteins (BMPs) signal through SMAD1/5/7 to upregulate genes that antagonize fibrosis. The endogenous antagonist gremlin-1 binds and antagonizes extracellular BMPs, inhibiting their anti-fibrotic effects. Gremlin-1 is up-regulated in the proximal tubule (PT) of DN patients. We hypothesized that Gremlin-1 participates in the development of renal fibrosis by inducing a pro-fibrotic phenotype in proximal tubules and renal interstitial fibroblasts.

Methods: To test this hypothesis we used HK-2 (human PT cell line) and NRK49F (rat renal fibroblasts) cell lines where the pro-fibrotic phenotype was induced by Transforming Growth Factor β 1 (TGF β : 2.5 ng/mL, 72 hrs). Gremlin-1 secretion and protein expression was measured by Western blotting and gene expression by qPCR.

Results: In PT cells, TGF β stimulated gremlin-1 protein secretion by 2.3 fold (from 57 ± 5 to 134 ± 2 arbitrary units; $p < 0.05$), increased fibronectin-1 (FN1, an extracellular matrix component) by 50% ($p < 0.05$) and reduced expression of e-cadherin (e-CAD, an epithelial marker) by 95% ($p < 0.05$). All changes also occurred at the mRNA level. Gremlin-1 siRNA significantly reduced gremlin-1 mRNA expression and efficiently blocked the TGF β -induced Gremlin-1 release by 100%. However, Gremlin-1 knockdown did not prevent the pro-fibrotic changes of TGF β . In contrast to PT cells, TGF β did not induce gremlin-1 secretion in renal fibroblasts. TGF β increased FN1 and α -smooth muscle actin (α SMA, marker of fibroblast activation) in a dose-dependent manner. Addition of gremlin-1 (mimicking the in vivo setting) did not exacerbate fibrosis at any dose of TGF β . Addition of recombinant BMP2 was not sufficient to prevent TGF β -induced fibrosis in either cell type. Recombinant BMP2 alone (1 nM) increased SMAD5 phosphorylation and the expression of ID1 (a marker of BMP signalling) at 1 and 24 hrs post treatment. The stimulatory effect of BMP2 was blocked by pre-treatment with recombinant Gremlin-1 (2 nM). These data confirm intact BMP2/gremlin-1 signalling in both cell types.

Conclusions: Our data does not support the participation of gremlin-1 in TGF β -dependent renal fibrosis in vitro.

Funding: Pharmaceutical Company Support - Medimmune

FR-PO311

Vitamin (Vit) D Repletion Ameliorates Muscle Wasting and Muscle Fibrosis in Mice with Chronic Kidney Disease Wei Ding, Wai W. Cheung, Mary Christine Esparza, Ping Zhou, Richard L. Lieber, Robert H. Mak. *Pediatric Nephrology, Univ of California, San Diego, La Jolla, CA.*

Background: Cachexia presenting as muscle wasting and weakness is prevalent in CKD patients and may impact their quality of life. We investigated the effects of vitamin D repletion in a mouse model of CKD-associated cachexia and vitamin D deficiency.

Methods: CKD in c57BL/6 mice were induced by 5/6 nephrectomy. CKD and sham mice were treated with 25VitD (25 mg/kg/day), 1,25VitD (40 ng/kg/day) or vehicle (V) for 6 weeks via a subcutaneous osmotic pump. CKD+V mice were fed *ad libitum* while other groups of mice were pair-fed to CKD+V mice. Parameters of energy homeostasis, skeletal muscle histomorphometry and *in vivo* muscle function were measured. The expression of key molecules implicated in myogenesis and fibrosis pathway was assessed using a focused PCR array.

Results: Serum 25VitD and 1,25VitD levels were significantly lower in CKD than sham mice ($p < 0.01$) and was increased, within the physiological range, by 25VitD and 1,25VitD repletion in CKD mice. CKD mice exhibited reduced weight gain, increased energy expenditure, loss of lean mass and decreased muscle function (measured by grip strength and rotarod tests) than sham mice ($p < 0.01$). Increased energy expenditure in CKD mice was associated with upregulation of uncoupling proteins (UCPs) in skeletal muscle and adipose tissues. Soleus muscle fiber area and *in vivo* muscle function was significantly reduced in CKD mice than sham controls ($p < 0.05$). Skeletal muscle fibrosis, a major pathological hallmark of myopathies, is evident in CKD mice. Soleus collagen content was significantly increased in CKD than sham mice ($p < 0.01$). Gene expression of myogenesis and fibrotic pathways were increased in CKD than sham mice ($p < 0.01$). Perturbations in weight gain, energy expenditure, UCPs, loss of lean mass, muscle function tests, soleus muscle fiber area, soleus collagen content as well as aberrant gene expression involved in myogenesis and muscle fibrotic pathway in CKD mice were normalized by 25VitD but only partially attenuated by 1,25VitD repletion.

Conclusions: 25VitD and 1,25VitD repletion have differential effects on muscle wasting and muscle fibrosis in CKD mice.

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FR-PO312

The Effect of Cell Culture Surface Coating on Glomerular Endothelial Cell Phenotype Kamilla Pajacka,^{1,2} Troels Krarup Hansen,¹ Julie Williams,² ¹*Endocrinology and Internal Medicine, Aarhus Univ Hospital, Aarhus, Denmark;* ²*Diabetes Complications Biology and Pharmacology, Novo Nordisk A/S, Maaloev, Denmark.*

Background: Glomerular endothelial cells (GEnCs), podocytes and the glomerular basement membrane are the major constituents of the glomerular filtration barrier (GFB), which is fundamentally impaired in diabetic nephropathy (DN). The DN drug-candidate screening process involves in vitro use of the GFB components either singly or in combination. The aim of this study was to determine the effect of commercially available extracellular matrix (ECM) components on GEnC characteristics.

Methods: Primary human GEnCs were from Cell Systems. Cell culture surface coating included: collagen IV (COLIV), laminin521 (hLN521), laminin111 (hLN111) or Attachment Factor (AF; Cell System's proprietary GEnC coating). Cell adhesion was monitored by the xCELLigence system. The mRNA expression was assessed by qPCR. The localization of zonula occludens (ZO)-1 protein was studied by fluorescent immunolabeling.

Results: Coating with AF or COLIV increased the cell index (CI) of GEnCs in the cell adhesion phase (0-6h) but not in the spreading and proliferation phase (6-72h). Coating with hLN521 displayed a continuous increase in CI over 72h. On the contrary, hLN111 caused a significant decrease in CI over 72h. Cells grown on AF or COLIV showed similar mRNA expression pattern of chosen genes as cells grown on uncoated surfaces. By contrast, coating with hLN521 decreased the expression of COL4A1, COL4A2, MMP2 [all 2-fold] and TGFB1 [1.5-fold] as compared to no coating. Likewise, ITGA1, ITGA2, ITGAV, ICAM1, NOX4 were decreased with hLN521 in a dose-dependent manner. Expression of LAMA5, COL4A5, ITGA3 and NOS3 were unchanged in all groups. Tight junction formation was assessed by ZO-1 immunostaining. Laminin521, contrary to other ECM coatings, stimulated tight junction formation in GEnCs.

Conclusions: Usage of AF or COLIV in GEnC culture shows little advantage. DN-associated hLN111 is a poor attachment substrate resulting in GEnC loss. This is in contrast to the more physiologically relevant hLN521 which promotes cell adhesion, spreading, proliferation and tight junction formation.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S, Government Support - Non-U.S.

FR-PO313

Development of an Ex Vivo Model to Elucidate the Matrix Turnover Profile in Renal Interstitial Fibrosis Signe Holm Nielsen,^{1,2} Zsolt Soma Karpati,¹ Daniel Guldager Kring Rasmussen,^{1,3} Morten Asser Karsdal,¹ Federica Genovese,¹ ¹*Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark;* ²*System Biology, Denmark Technology Univ, Kgs. Lyngby, Denmark;* ³*Southern Denmark Univ, Odense, Denmark.*

Background: Renal interstitial fibrosis is characterized by dysregulated extracellular matrix (ECM) turnover and protease activity. ECM protein fragments generated by protease cleavage can be measured by specific ELISAs, providing a protein fingerprint of the disease. The aim of this study was to set up an *ex-vivo* model for renal interstitial fibrosis in order to investigate the ECM turnover profile in the fibrotic kidney.

Methods: 14 male 12 weeks old Sprague-Dawley rats underwent Unilateral Ureteral Obstruction (UUO) surgery by ligation of the right ureter. The left kidney (contralateral) was used as internal control. 6 rats were sham-operated and used as control group. Rats were terminated 2 weeks after the surgery, when advanced fibrosis is known to be present. The kidneys were excised and precision-cut tissue slices (PCTS) were cultured for 5 days in serum free medium. Markers of collagen type I formation (P1NP), collagen type III degradation (C3M) and α -smooth muscle actin (α -SMA) were measured in the PCTS supernatants. The extent of tubulointerstitial fibrosis was evaluated by histology.

Results: P1NP, C3M and α -SMA were significantly increased in supernatants of tissue slices from the UUO ligated kidneys compared to the contralateral kidneys ($p < 0.001$) and to sham operated animals ($p < 0.0001$). However the markers had a high inter-individual variability in the UUO group. When comparing the levels of the markers from the UUO kidney to those from the corresponding contralateral kidney, animals with pronounced differences were those presenting advanced fibrosis in histology.

Conclusions: The UUO PCTS *ex vivo* model provides a valuable translational tool for investigating the ECM remodeling associated with renal interstitial fibrosis. Since the protein fingerprint technology allows the measurement of the markers measured in the supernatants also in circulation and in urine, these markers have the potential to accurately and non-invasively describe the tissue remodeling during fibrosis.

FR-PO314

Collagen Degradation Profile in a Nephrotoxic Nephritis Model Signe Holm Nielsen,^{1,2} Daniel Guldager Kring Rasmussen,^{1,3} Gabriela Campanholle,⁴ Robert V. Martinez,⁴ Morten Asser Karsdal,¹ Federica Genovese,¹ ¹*Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark;* ²*System Biology, Denmark Technology Univ, Kgs. Lyngby, Denmark;* ³*Southern Denmark Univ, Herlev, Denmark;* ⁴*Inflammation and Immunology, WRD, Pfizer Inc., Cambridge, MA.*

Background: The nephrotoxic nephritis (NTN) mouse model is characterized by a rapid onset of nephritis, followed by tissue destruction and progression to renal scarring. We aimed at identifying markers for early disease onset that were directly linked to the events of scar formation in the kidney.

Methods: Neo-epitope degradation fragments of collagen type I, III and IV generated by MMP cleavage were measured by specific ELISAs (namely C1M, C3M and C4M) in urine of NTN and healthy mice terminated at 7 and 21 days after injury (NTN: n=21, Controls: n=6). Urinary albumin/creatinine (ACR), urinary proteinuria, plasma creatinine and blood urea nitrogen (BUN) were measured as markers of renal function. Interstitial fibrosis and glomerulosclerosis were evaluated by histology and quantification of α -SMA and collagen type I in immunohistochemistry.

Results: While C1M levels in urine were not different between NTN mice and controls, C3M levels were elevated in NTN rats at 7 days ($p < 0.05$) and decreased to levels close to the controls at 21 days. This elevation was also reflected in proteinuria, peaking at 7 days, but not in BUN and plasma creatinine. C4M levels were elevated at 21 days and not at 7 days ($p < 0.01$), and correlated with the extent of interstitial fibrosis.

Conclusions: Different degradation markers of the most abundant proteins in the renal interstitial matrix (collagen type I and III) and in the tubular basement membrane and mesangium (collagen type IV - a1 chain) presented a different longitudinal release in urine. While degradation of collagen type III is an early event in this model, maybe reflecting the early inflammatory state, degradation of collagen type IV appears later, when the formation of the scar is evident in histology. These markers could potentially be used to non-invasively describe the fibrotic events in the kidney in experimental models and, since the targeted epitopes are conserved in human, they could be applied in clinical settings.

FR-PO315

Evidence of Podocyte Protrusions into the Basement Membrane in Glomerular Disease Sophie C. Collinson,¹ Michael J. Randles,^{1,2} Mira Krendel,³ Eva Koenigshausen,⁴ Lorenz Sellin,⁴ Ian Roberts,⁵ Jeffrey H. Miner,⁶ Rachel Lennon,^{1,2} ¹*Inst of Human Development, Faculty of Medical & Human Sciences, Univ of Manchester, United Kingdom*; ²*Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, Univ of Manchester, United Kingdom*; ³*Dept of Cell and Developmental Biology, SUNY Upstate Medical Univ, Syracuse, NY*; ⁴*Dept of Nephrology, Heinrich Heine Univ, Duesseldorf, Germany*; ⁵*Dept of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom*; ⁶*Renal Div, Washington Univ School of Medicine, St. Louis, MO*.

Background: Glomerular disease is a leading cause of kidney failure. Podocyte foot process effacement and glomerular basement membrane (GBM) disruption are frequent abnormalities regardless of the underlying molecular etiology. Standard electron microscopy techniques provide 2D information and 3D ultrastructural relationships are poorly understood. We hypothesized that creation of detailed 3D models of the glomerulus would identify novel pathological features.

Methods: Serial block face-scanning electron microscopy was performed on a series of genetic mouse models of glomerular disease with established albuminuria. 3D reconstructions of glomeruli were created using IMOD 4.7.11.

Results: Sub-podocyte expansions of the GBM were dominant features in *Glepp1*^{-/-}, *Myo1e*^{-/-} and *Col4a3*^{-/-} mice and overall GBM thickness was significantly different to matched wild-type (WT) controls ($p < 0.0001$). There was a corresponding reduction in podocyte foot process number in each of the models ($p < 0.0001$). Furthermore we identified novel podocyte protrusions into the GBM in all mutant mice and these were not present in WT controls. There was no evidence of endothelial or mesangial cell protrusions into the GBM and no correlation between GBM thickness and the site of podocyte protrusions.

Conclusions: 3D ultrastructural imaging revealed expected GBM abnormalities in addition to podocyte protrusions, resembling invadosomes, in the GBM. This novel finding provides new insight into disease mechanisms and suggests that a common matrix-adhesion pathway is activated regardless of the primary molecular insult.

Funding: Private Foundation Support

FR-PO316

Multi-Clonal Population of Cells of Renin Lineage (CoRL) Transdifferentiate into Podocytes and PECs in Experimental FSGS Natalya V. Kaverina,¹ Diana G. Eng,¹ Jeffrey W. Pippin,¹ Michael E. Rusiniak,² Kenneth W. Gross,² Stuart J. Shankland,¹ ¹*Division of Nephrology, Univ of Washington, Seattle, WA*; ²*Dept of Molecular and Cellular Biology, Roswell Park Cancer Inst, Buffalo, NY*.

Background: Focal segmental glomerulosclerosis (FSGS) is secondary to podocyte injury and loss. Because adult podocytes cannot proliferate, their replacement by progenitors is critical for their repair and regeneration in disease. Here we explored whether single or multiple clones of cells of renin lineage (CoRL) serve as a local progenitor source to replace reduced podocytes in experimental FSGS.

Methods: Experimental FSGS was induced following abrupt podocyte depletion by administration of a cytotoxic anti-podocyte antibody in two confetti mouse reporters. First, to confirm adult podocyte regeneration following abrupt depletion, podocytes were genetically fate-mapped in adult NPHSP2^{Cre}/Confetti^{TR} reporter mice with experimental FSGS. Second, to prove that adult podocyte regeneration by CoRL was multi-clonal, CoRL were fate mapped in RenCre / Confetti^{TR} reporter mice with experimental FSGS.

Results: FSGS in NPHSP2^{Cre}/Confetti^{TR} mice was characterized by marked podocyte depletion (45% decrease) on d7. A multi-clonal repopulation of podocytes resulted in an increase in their overall number to 77% of normal by d28. No podocyte proliferation was detected by BrdU staining. In RenCre/Confetti^{TR} mice, a multi-clonal expansion of 4 color-labeled CoRL (GFP, RFP, CFP, YFP) was detected in glomeruli at FSGS d28. A subset of all clonal reporters co-expressed 5 podocyte markers (podocin, synaptopodin, p57, WT-1, nephrin). CoRL were also observed along Bowman's capsule and co-expressed PEC markers (PAX2, claudin-1). BrdU staining did not co-localize with CoRL reporters.

Conclusions: Following an abrupt depletion of adult podocytes in experimental FSGS, their number was increased in the absence of podocyte proliferation. Regeneration of adult podocytes was likely in part due to multiple clones of CoRL serving as local progenitors.

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FR-PO317

Macula Densa-Derived Factors Control Glomerular Cell Remodeling Anne Riquier-brison, Donna Ralph, Jasmine Ann Arevalo Castillejos, Janos Peti-Peterdi. *Physiology and Biophysics, Univ of Southern California, Los Angeles, CA*.

Background: Macula densa (MD) cells are strategically positioned at the vascular entrance of the glomerulus and control renal hemodynamics and renin. In this study, we addressed a novel, non-traditional role of MD cells regulating glomerular cell plasticity/remodeling by mesenchymal progenitor cells.

Methods: For genetic cell fate tracking, tamoxifen-induced NG2CreERT2-Tomato mice were fed either a control or salt-deficient + ACE inhibition (SD+ACEi) diet, for 2 weeks to achieve strong MD stimulation.

Results: We observed a 5-fold increase in renal interstitial density of NG2-derived (NG2+) cells (5.9±1.1 cells per field in control, 30.2±4.5 in SD+ACEi), and the homing of NG2+ cells to the mesangium under the MD and into the glomerulus. This effect was blunted by the selective COX-2 inhibitor SC58236 (COX-2i) or the nNOS inhibitor 7-NI (13±2.2 cells per field with COX-2i and 11.6±1.7 with 7-NI). Immunofluorescence (IF) of Claudin-1 showed a 4-fold increase in the number of NG2+ cells in the glomerular parietal layer (0.5±0.2 cells per glomerulus in control, 2.0±0.4 in SD+ACEi). Podocin IF identified a few NG2+ podocytes. NG2+ cell homing was blunted by COX-2i and 7-NI (1.2±0.3 cells per glom with COX-2i, 0.8±0.3 with 7-NI). Co-localization of endogenous NG2-Tomato fluorescence with IF of renin revealed an increase in the proportion of NG2+ renin-expressing cells from 22.0%±6.6 to 70.6%±7.4 after SD+ACEi, inhibited by COX-2i. Similarly, the density of proliferating cells expressing Ki67 increased after treatment (2.0±0.5 Ki67+ cells per field in control, 11.3±2.8 in SD+ACEi, $p < 0.05$), in particular in the vicinity of the juxtaglomerular area, inhibited by COX-2i (5.6±1.0) and 7-NI (2.7±0.3).

Conclusions: Our results suggest that NG2+ pericytes may be an important progenitor cell population in the kidney. In response to MD-derived (from COX-2 and nNOS) paracrine factors, NG2+ cells from the renal interstitium proliferate and migrate towards the MD along the afferent arteriole and via the vascular pole into the glomerular epithelium and mesangium. In conclusion, MD cells play new important roles in the maintenance and remodeling of the glomerulus.

Funding: NIDDK Support

FR-PO318

A Novel Method for Assessing Podocyte Depletion in Whole Glomeruli Victor G. Puelles,¹ James William Van der Wolde,¹ Luise A. Cullen-McEwen,¹ Keith E. Schulze,² Jonathan Guy Bensley,¹ Kieran M. Short,¹ Georgina Caruana,¹ Stacey Hokke,¹ Stephen D. Firth,² Ian S. Harper,² David J. Nikolic-Paterson,³ John F. Bertram,¹ ¹*Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Victoria, Australia*; ²*Monash Micro Imaging, Monash Univ, Melbourne, Victoria, Australia*; ³*Dept of Nephrology, Monash Medical Centre, Melbourne, Victoria, Australia*.

Background: Podocyte depletion plays a major role in the development and progression of glomerulosclerosis. Given that glomerulosclerosis is often focal, affecting some but not all glomeruli, our aim was to develop a rapid, accurate and precise method for quantifying podocyte depletion in whole glomeruli.

Methods: Pod^{Cre}iDTR mice, in which expression of the human diphtheria toxin (DT) receptor is driven by the podocin promoter, and iDTR mice (controls) were injected with DT (100ng/kg). Tissue was collected at day 35 for podocyte analysis (n=3 mice per group). 800mg thick kidney slices were immunostained with antibodies against p57 and synaptopodin. Slices were cleared with benzyl alcohol, benzyl benzoate (BABB). An SP8 confocal microscope (Leica, Germany) fitted with a BABB objective (NA: 0.95; working distance: 2mm) was used. Total podocyte number was obtained by manual counting and using a semi-automated system (Imaris, Bitplane) in 88 whole glomeruli - 38 from iDTR mice and 50 from Pod^{Cre}iDTR mice.

Results: In iDTR mice (controls), total podocyte number per glomerulus was almost identical between manual counts (66.61±11.92) and Imaris (65.47±9.26; $P = 0.65$). In Pod^{Cre}iDTR mice, total podocyte number was also similar between manual counts (52.96±11.74) and Imaris (53.51±11.35; $P = 0.81$). With both methods, podocyte counts were obtained in less than 2 minutes per glomerulus, a significant time reduction compared to existing methods. Imaris also facilitates the estimation of podocyte and glomerular volumes for a complete assessment of podocyte morphology.

Conclusions: This is the first method to combine immunofluorescence, BABB-clearing and confocal microscopy to count podocytes in whole glomeruli. The method is accurate, precise and rapid, and provides a novel approach for podocyte morphometrics in settings where sufficient tissue is available for analysis.

FR-PO319

Characterization of Heterogeneous Podocyte Biomechanics Using Atomic Force Microscopy Evren U. Azeloglu,¹ Jia-Jye Lee,² Kevin D. Costa,² ¹*Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY*; ²*Cardiology (Medicine), Icahn School of Medicine at Mount Sinai, New York, NY*.

Background: Biomechanical signals play a key role in glomerular physiology, where pathological changes in blood pressure can significantly affect podocyte morphology and function. While there has been a great focus on mechanobiological signaling in podocytes, their spatial biomechanical properties have been largely overlooked due to a lack of *in*

vitro systems that can spatially segment subcellular components. We have developed a novel microengineered culture system that mechanically induces arborization of podocytes such that they form functional peripheral shape-induced processes that locally express slit diaphragm markers and bundled actin fibers *in vitro*. We then used atomic force microscope elastography to quantitatively characterize the subcellular biomechanical properties of isolated human podocytes.

Methods: Glass coverslips were micropatterned with interconnected channels using standard photolithography techniques. Immortalized human podocytes were plated on micropatterned slides, and cultured at 37°C for five days. They were then transferred to an Asylum Bioscope AFM and probed with 2 mm deep indentations at a rate of 1 mm/sec. Depth-dependent pointwise apparent elastic modulus was computed at each indentation point to create a 3-D elastography map of cellular biomechanics.

Results: Live-cell imaging showed dynamic cycling of F-actin in peripheral shape-induced processes of micropatterned podocytes. These cells exhibited heterogeneous depth-dependent biomechanical properties where processes were significantly stiffer than the central cell body. Increase in stiffness correlated with presence of crosslinked actin bundles.

Conclusions: We saw significant increase in stiffness of peripheral processes in podocytes, which reaffirm the key structural role of the interdigitating foot processes in maintenance of the glomerular filtration barrier. Our microengineered culture system provides a new means to rapidly test the micromechanics of podocytes with high spatial resolution in a physiologically relevant *in vitro* setting.

Funding: Private Foundation Support

FR-PO320

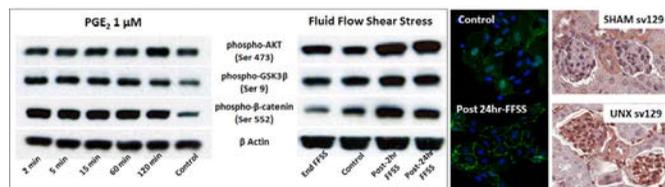
Identification and Validation of Fluid Flow Shear Stress (FFSS)-Induced Changes in Podocyte Signaling Pathways Using Bioinformatic Tools

Tarak Srivastava,¹ Hongying Dai,¹ Ashraf El-Meanawy,² Ellen T. McCarthy,³ Virginia J. Savin,⁴ Ram Sharma,⁴ Mukut Sharma.⁴ ¹Nephrology, The Children's Mercy Hospital, Kansas City, MO; ²Nephrology, Medical College of Wisconsin, Milwaukee, WI; ³Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; ⁴Renal Research Laboratory, Kansas City VA Medical Center, Kansas City, MO.

Background: The flow of filtrate through Bowman's space generates FFSS over podocytes. Adaptive hyperfiltration is characterized by increased single nephron GFR (SNGFR), capillary pressure (P_{GC}) and glomerular hypertrophy. The mechanism of podocyte injury from hyperfiltration-induced FFSS is not known.

Methods: We performed microarray analysis (Affymetrix GeneChip Mouse Exon 1.0 ST Array) on immortalized podocytes without FFSS (Control), immediately after FFSS (End-FFSS), 2 hours (post-2hr FFSS), and at 24 hours (post-24hr FFSS) after cessation of FFSS at 2 dynes/cm² for 2 hr. Mouse exon 1.0 ST Array has ~4 probes/ exon and ~40 probes/ gene. Data from the microarray were log transformed, normalized and filtered to generate a set of 17,494 genes. Genes that were significant at $p < 0.01$ were analyzed using Ingenuity Pathway Analysis (IPA) and Enrichr Program to identify key pathways.

Results: IPA showed Akt, COX-2, and AMPK (at End-FFSS); TGF- β (at post-2hr FFSS); and p38MAPK, ERK1/2 (at post-24hr FFSS) in the main network. Enrichr Kinase Enrichment Analysis showed GSK3 β , ERK1/2 in all three treatment groups compared with the control group. ChIP-x Enrichment Analysis identified transcription factor β -catenin. Western blotting, fluorescence microscopy and immunocytochemistry were used to validate changes in these signaling molecules.



Conclusions: Increased FFSS affects pathways that mediate podocyte survival and inflammation, and provide targets to address the mechanism of hyperfiltration-mediated glomerular injury.

FR-PO321

A Podocyte-Based Screening Assay Identifies Paullone-Derivatives as Novel Podocyte Protective Agents

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Background: Podocyte injury and loss is an early hallmark in the pathogenesis of a variety of glomerular diseases. Therefore, podocytes are an excellent cellular target for the development of kidney directed therapeutics. We recently described a novel cell-based high content screening (HCS) assay for quantifying podocyte damage *in vitro*. Here, we describe utilization of this HCS assay to identify a family of novel small molecules that significantly protect podocytes from injury.

Methods: We utilized cultured murine podocytes in an HCS assay using 96-well imaging plates. Phenotypic changes with podocyte damaging agent puromycin aminoglycoside (PAN) were analyzed and quantified using automated methods using thousands of podocytes per condition. Identified hits were confirmed and a number of biochemical and cell biological assays were used to validate the findings.

Results: We identified a family of small molecules, paullones, as highly potent agents that protected podocytes from damage. Kenpaullone and three other paullones (paullone, 1-azakenpaullone, and alsterpaullone) showed dose-dependent protection of podocytes

from PAN-damage induced loss in F-actin fibers. Among the four paullones identified, alsterpaullone showed the highest level of protection. At a molecular level, alsterpaullone reduced the elevation in the expression of *Desmin*, a podocyte damage marker, and inhibited PAN-induced podocyte migration. While PAN treatment reduced AKT phosphorylation in podocytes, alsterpaullone maintained the levels of phosphorylated AKT in podocytes.

Conclusions: Employment of our newly described podocyte-based screening assay results in the discovery of podocyte-directed therapeutics for treating a number of glomerular diseases. Paullones represent a family of small molecules that show podocyte protection from damage. We also describe a proposed molecular mechanism for the efficacy of these novel agents. We hope that these methodologies will lead to the development of novel types of specific kidney protective drugs.

FR-PO322

Novel Podocyte Quantification Assay to Ascertain Patient Serum Toxicity

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Background: Focal segmental glomerulosclerosis (FSGS) is a glomerular kidney disease that affects the podocytes and progresses to renal failure within 5-7 years, requiring dialysis or renal transplantation. In > 50% of patients, the disease is idiopathic and may recur post-transplant suggesting the presence of a pathogenic toxic factor/s circulating in the blood. The identity of this factor and the pathogenic mechanisms remain enigmatic. Recent *in vitro* studies from our lab showed that plasma from recurrent FSGS patients disturbs the human podocyte cytoskeleton and focal adhesion complexes (FACs). We developed a novel unbiased assay to quantify the toxic effects of patient plasma and nephrotoxic drugs on cultured human podocytes and to identify strategies that block serum toxicity.

Methods: Cultured human differentiated podocytes are exposed to adriamycin, recombinant TNF α or human sera from patients with various forms of FSGS. FACs are visualized with anti-vinculin antibody, and cell images are analyzed to define the number of FACs/1000mm² cell area. We analyzed sera from 12 patients: 2 with idiopathic, 4 recurrent FSGS, 4 non-recurrent FSGS and 2 de novo FSGS.

Results: Both adriamycin and recombinant TNF α disrupt podocyte actin cytoskeleton and FACs in a dose-dependent manner. Comparing to healthy control, sera from patients with idFSGS (no known mutations identified), rFSGS and de novo FSGS post-transplant drastically reduces FACs number, yet sera from nrFSGS post-transplant does not statistically affect FACs. In ~ 60% of the patients with serum toxicity, these effects on podocytes can be averted by TNF α pathway blockade.

Conclusions: Our *in vitro* podocyte assay provides, for the first time, means to reliably identify those patients with idiopathic FSGS who are at high risk of recurrence post-transplant. It may also identify FSGS patients who may be candidates for anti-TNF α therapy that could prevent progressive glomerular injury.

Funding: Government Support - Non-U.S.

FR-PO323

Agalsidase Treatment Clears Gb3 from a Podocyte Model of Fabry Disease

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Background: In Fabry disease the deficiency of the enzyme α -galactosidase A leads to an accumulation of globotriaosylceramide (Gb3). An enzyme replacement therapy with agalsidase alfa (Replagal®) or beta (Fabrazyme®) is licensed since 2001. The establishment of an α -galactosidase A-deficient human podocyte cell line has already been published by our group. These podocytes accumulate Gb3, exhibit dysregulated AKT and mTOR signaling and dysregulated autophagy. We analyzed changes in cellular signal transduction in α -galactosidase A-deficient podocytes treated with agalsidase alfa to further investigate the molecular mechanisms underlying podocyte damage.

Methods: For seven days, α -galactosidase A-deficient podocytes were treated with 250 nM agalsidase alfa. Cells were grown on collagen-coated coverslips, fixed with PFA and processed according to standard protocols for immunofluorescence. For mass spectrometry and immunoblot detection, cell lysates were used.

Results: Compared to control cells, α -galactosidase A-deficient podocytes showed massive Gb3 accumulation in immunofluorescence and mass spectrometry analysis. The Gb3 content in Fabry podocytes was significantly reduced after treatment with agalsidase alfa. Interestingly, the strong Gb3 clearance dysregulation of the AKT and mTOR signaling pathways remained unchanged upon treatment with 250 nM agalsidase alfa for 7 days. In both treated and untreated Fabry podocytes autophagic activity was elevated.

Conclusions: A significant reduction of accumulated Gb3 in Fabry podocytes was shown with enzyme replacement therapy. Surprisingly, no significant changes in agalsidase-treated podocytes were detected for key enzymes of autophagy regulation under these conditions. In ongoing studies we will use mass spectrometry and different treatment conditions to focus on identifying additional proteins modified by Gb3 accumulation.

Funding: Pharmaceutical Company Support - Shire, Government Support - Non-U.S.

FR-PO324

Loss of Robo2 in Podocytes Protects Adult Mice from Acute Glomerular Injury Anna Pisarek-Horowitz, Xueping Fan, Hila Milo Rasouly, Stefanie Chan, Hui Chen, Ramon G. Bonegio, Joel M. Henderson, David J. Salant, Weining Lu. *Renal, Boston Univ Medical Center, Boston, MA.*

Background: SLIT2 and its receptor ROBO2 play an important role during kidney development. We have recently found that ROBO2 is expressed in developing glomerular podocytes. However, the role of ROBO2 in the adult mouse kidney, particularly under acute glomerular injury conditions, is not clear.

Methods: To test the hypothesis that loss of *Robo2* in glomerular podocytes affects the outcome of acute glomerular injury, we applied two *in vivo* acute glomerular injury models induced by nephrotoxic serum (NTS) injection and protamine sulfate (PS) perfusion, in *Robo2* podocyte specific knockout mice (*Robo2* cKO) and wild type controls. Kidney glomerular ultrastructure was analyzed by scanning and transmission electron microscopy before and after injury. Podocyte foot process width and slit diaphragm density were measured to quantify the severity of the glomerular injury. Urine albumin to creatinine ratio was measured in the NTS model. Podocyte specific gene expression was analyzed using TaqMan real time PCR for mRNA and Western blot for protein levels.

Results: *Robo2* podocyte specific knockout mice developed less proteinuria after the NTS injury with lower urine albumin/creatinine ratio as compared to the wild type controls. Electron microscopy showed that *Robo2* cKO mice have milder foot process effacement and less defects in the slit diaphragm induced by either NTS or PS injury. TaqMan and Western blot analyses revealed that nephrin, a crucial transmembrane component of the podocyte slit-diaphragm, was significantly up-regulated at both mRNA and protein levels in the *Robo2* cKO mice before NTS injury and at the late stage of heterologous phase after the NTS injury. In addition, the mRNA levels of *Robo2* and *Slit2* in the wild type kidneys were also upregulated after the NTS injury.

Conclusions: SLIT2-ROBO2 signaling pathway plays an important role in the adult mouse kidney podocytes and loss of *Robo2* protects mice from acute glomerular injury. Our findings suggest that SLIT2-ROBO2 signaling might also have a negative impact on nephrin expression during podocyte injury and be a potential therapeutic target.

Funding: NIDDK Support, Private Foundation Support

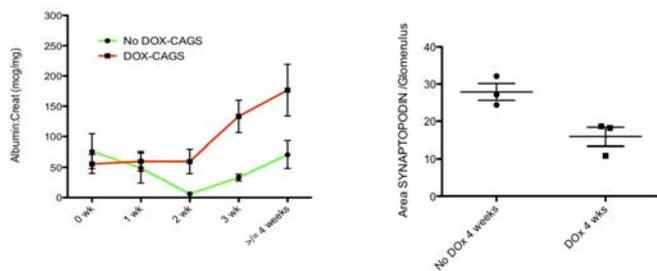
FR-PO325

Inducible Knockdown of Shroom3 Induces Proteinuria with Podocyte Dedifferentiation Madhav C. Menon, Chengguo Wei, Karen Lok Yee Keung, Ilana Greene, Weijia Zhang, John C. He, Barbara T. Murphy. *Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Intronic loci in *Shroom3* have been associated with CKD and CAN. A role for *Shroom3* in the podocyte cytoskeleton has been shown. However *Shroom3* knockout mice die neonatally with neural tube defects and detailed renal phenotypes are unknown. Here we report our findings from Doxycycline (DOX) inducible, shRNA-mediated *shroom3* knockdown mice.

Methods: In these mice *Shroom3*-specific shRNA expression was induced upon DOX-feeding, with RTTA expression in all cells driven by CAGS-promoter. Six-wk old mice were fed DOX-feed/water. Non-DOX fed littermates were controls (n=6 each). At 4- and 8-weeks, renal tissue was obtained for histology. Twenty-five glomeruli were analyzed per mouse and quantification was using imageJ.

Results: DOX-mice developed significantly increased Albumin-to-creatinine ratios starting at 2 weeks compared to controls.



Proteinuria persisted at 8 weeks of DOX-feeding. No light microscopic changes were detectable on PAS-stained sections in DOX- or control-mice in glomerular mesangial matrix expansion or intratubular protein casts upto 8-weeks of DOX feeding. Assessment of WT-1 stained nuclei/ glomeruli by immunofluorescence (IF) showed no reduction in podocyte number at 4- or 8-weeks in DOX-mice compared to controls (p=ns; n=3 each). However, by IF, significant reduction in area and intensity of glomerular synaptopodin staining was observed by 4 weeks in DOX-mice compared to controls (p<0.01; n=3 each at 4-wks, Fig 2). Electron microscopic studies are ongoing.

Conclusions: Our preliminary findings suggest that inducible and global knockdown of *Shroom3* induces proteinuria with features of podocyte dedifferentiation without evidence of podocyte loss. Further studies are needed to elucidate the precise role of *Shroom3* in proteinuria and its function in the glomerular filtration barrier.

FR-PO326

Protective Role of Cyclodextrin in Focal Segmental Glomerulosclerosis (FSGS) Alla Mitrofanova,^{1,2} Patricia R. Wahl Pristau, Ximena A. Morales,¹ Mayrin Correa-Medina,¹ Christopher E. Pedigo,¹ Gloria Michelle Ducasa,¹ George William Burke,² Sebastian Martini,³ Matthias Kretzler,^{3,4} Sandra M. Merscher,¹ Alessia Fornoni.¹ ¹Katz Family Drug Discovery Center, Nephrology & Hypertension, Univ of Miami, FL; ²Surgery, Univ of Miami, FL; ³Internal Medicine, Nephrology, Univ of Michigan, MI; ⁴Computational Medicine & Bioinformatics, Univ of Michigan, MI.

Background: We recently demonstrated that cholesterol accumulation contributes to podocyte injury in diabetic kidney disease (DKD), where 2-hydroxypropyl-β-cyclodextrin (CD) protects podocytes from cholesterol-dependent damage *in vitro* and *in vivo*. We hypothesize that lipid related genes are affected in glomeruli of patients with primary FSGS and treatment with CD protects podocytes in experimental FSGS.

Methods: Microarray analysis on glomerular transcripts of lipid-related genes from patients with FSGS (n=54) and from normal living donors (n=6) were obtained from patients enrolled in NEPTUNE, a longitudinal observational cohort looking at individuals with proteinuria. 5-week-old BALB/c female mice were injected with a single intravenous dose of adriamycin (ADR, 11 mg/kg) to develop FSGS-like lesions. 24-hours after ADR injection, osmotic pumps with CD in 0.9% saline solution (40 mg/kg/day) were implanted under the skin for 10 weeks. Measurements of body weight and urine collections for ACR (Albumin/creatinine ratios) were performed weekly. At time of sacrifice, serum creatinine and Blood Urea Nitrogen (BUN) were determined and kidneys collected for histological analysis.

Results: Microarray analysis of the glomerular transcripts in the NEPTUNE cohort demonstrated that cholesterol efflux related genes, such as PLIN3, S1PR2, S1PR4, S1PR1, and lipid dysmetabolism related genes, such as SCD, LDLR, ABCG1, were increased in FSGS. CD administration reduced mesangial expansion as well as ACR and BUN observed at 10 weeks in the ADR+CD group compared to the ADR group (p<0.05). No changes in body weight were found.

Conclusions: We concluded that glomerular lipids are altered in FSGS and that 2-hydroxypropyl-β-cyclodextrin protected podocytes in an experimental model of FSGS. Our data suggest that CD could be used as a safe and effective drug therapy in FSGS patients.

Funding: NIDDK Support

FR-PO327

Podocyte-Derived CXCL12 Has a Dual Role in Glomerular Injury and Regeneration Simone Romoli, Santhosh Kumar Vr, Shrikant R. Mulay, Hans J. Anders. *Nephrologisches Zentrum, Klinikum der Univ Muenchen, Munich, Bavaria, Germany.*

Background: Stromal-derived factor (SDF)-1/CXCL12 is a homeostatic chemokine facilitating homing and activation of stem cells. Podocytes constitutively produce CXCL12, hence, we speculated on a role of CXCL12 in glomerular regeneration upon injury.

Methods: Glomerular injury was induced by a single *i.v.* injection of 13mg/kg adriamycin (ADR) in male Balb/c mice, which received either the CXCL12 inhibitor NOX-A12 or the inactive control s.c. at 13.4mg/kg thrice a week. Human renal progenitor cell properties (RPC) were used for *in-vitro* studies.

Results: ADR-induced proteinuria peaked at day 7 (injury phase), which subsequently declined without returning back to baseline and being associated within FSGS lesions after 14 days (repair phase). CXCL12 blockade aggravated ADR-induced A/C and podocyte loss at day 7, which implies an autocrine role of CXCL12 for podocyte survival. In contrast, CXCL12 blockade reduced A/C levels and the glomerular sclerosis scores as well as increased podocyte numbers at 14 days indicating a beneficial effect of CXCL12 blockade during the repair phase. The pro-survival effect of CXCL12 on podocytes was further confirmed in a model of diphtheria toxin-induced podocyte depletion using CXCL12 blockade. To investigate the dual effect of CXCL12, we focused on the Notch signaling pathway. ADR injection reduced renal Notch expression, which was reversed following CXCL12 blockade. *In-vitro* studies with RPC revealed that CXCL12 suppressed RPC proliferation, which was reversed with CXCL12inhibitor. Similar results were obtained when RPC were exposed to supernatants from necrotic podocytes. CXCL12 blockade also increased the capacity of RPC to differentiate into podocytes.

Conclusions: Podocyte-derived CXCL12 has a dual role in glomerular injury. CXCL12 protects podocytes during the injury phase in an autocrine manner by suppressing Notch signaling, which otherwise triggers mitotic catastrophe and podocyte loss. Podocyte-derived CXCL12 assures Notch-mediated quiescence of RPC. Our data also demonstrate that therapeutic CXCL12 inhibition in glomerular injury can improve long term outcomes possibly by enforcing the intrinsic regenerative capacity of RPC.

FR-PO328

Shank2 Modulates Glutamatergic Signaling in Podocytes Evgenia Dobrinskikh,¹ Linda Lewis,¹ R. Brian Doctor,² Judith Blaine.¹ ¹Medicine, Univ of Colorado, Aurora, CO; ²Biology, Univ of Mississippi, Oxford, MS.

Background: Shank2 is a large scaffolding protein that is a master regulator of glutamate receptors at the neuronal postsynaptic density. Knockout (KO) of Shank2 in mice leads to autistic behaviours and abnormal glutamatergic signaling in neurons. Podocytes have also been shown to express functional N-methyl D aspartate (NMDA) and metabotropic glutamate receptor 1 (mGluR1) receptors which are both members of the glutamate receptor family.

Results: We have found that podocytes express Shank2 *in vivo* and *in vitro*. Since Shank2 plays an important role in regulating glutamate receptor function, we examined the effect of Shank2 knockout on NMDA and mGluR1 expression and function in podocytes. Shank2 KO resulted in decreased expression of NMDA and mGluR1 receptors in glomeruli. We isolated podocytes from wild type and Shank2 knockout mice and created conditionally immortalized podocyte lines. Conditionally immortalized Shank2 KO podocytes also demonstrated decreased expression and altered localization of glutamate receptors. In neurons, activation of glutamate receptors modulates intracellular calcium levels by allowing calcium influx into the cell (NMDA receptors) or release of calcium from intracellular stores (mGluR1). Using Fluo-4, a cell permeant calcium sensing dye, we examined intracellular calcium levels in wild type and Shank2 KO podocytes. At baseline, Shank2 knockout podocytes had significantly fewer calcium spikes than wild type podocytes. Treatment with NMDA and glutamate increased the number of calcium spikes in both wild type and Shank2 KO podocytes but the number of spikes in the KO podocytes was significantly reduced compared to wild type. Podocytes have been shown to communicate with each other via calcium waves. To examine podocyte to podocyte communication after injury, we "burned" a podocyte using high intensity laser power and then examined calcium wave propagation from the site of injury. After burning, wild type podocytes exhibited calcium waves emanating from the injured podocyte whereas no waves were seen in the knockouts.

Conclusions: Taken together these data indicate that Shank2 regulates glutamate receptor function in podocytes.

Funding: NIDDK Support

FR-PO329

Podocytes Transcytose Albumin and IgG Using the Neonatal Fc Receptor (FcRn) In Vitro and In Vivo Evgenia Dobrinskikh,¹ Linda Lewis,¹ Jeffrey B. Kopp,² Judith Blaine.¹ ¹Medicine, Univ of Colorado, Denver, CO; ²Kidney Disease Section, NIDDK, NIH, Bethesda, MD.

Background: Proteinuria is strongly associated with kidney disease progression. Podocytes are key constituents of the glomerular filtration barrier (GFB), which determines the selectivity of protein filtration. By even the most conservative estimates between 2 and 9 g of serum proteins a day normally pass through the GFB. The molecular mechanisms whereby podocytes handle albumin and IgG remain to be fully determined.

Results: We have found that transcytosis is the major pathway whereby cultured podocytes handle albumin and IgG. In other epithelial cell types, the neonatal Fc receptor (FcRn) is required to transcytose endocytosed albumin and IgG, thereby salvaging these proteins from degradative pathways. To examine the role of FcRn in albumin and IgG transcytosis in podocytes, we knocked down FcRn in cultured podocytes using lentiviral shRNA. FcRn knockdown (KD) resulted in a 71±3% decrease in FcRn expression compared to control. In an *in vitro* transcytosis assay, FcRn KD increased intracellular accumulation and decreased appearance of albumin and IgG in the supernatant, suggesting impaired transcytosis, but the differences were not statistically significant, possibly due to residual FcRn. We therefore isolated podocytes from wild type (WT) and FcRn knockout (KO) mice and created conditionally immortalized WT and KO podocyte lines. Knockout of FcRn resulted in significantly increased intracellular accumulation, assessed by immunostaining and Western blot (densitometric analysis of intracellular protein 1 hr after loading showed 0.37 ± 0.1 (WT) vs 0.97 ± 0.2 (KO), p<0.05 for albumin and 0.52 ± 0.04 (WT) versus 1.03 ± 0.19 (KO), p<0.05 for IgG), and decreased appearance of supernatant albumin or IgG, indicating defective transcytosis. We extended our studies to an *in vivo* model by creating a podocyte-specific FcRn KO mouse. Podocyte-specific FcRn KO mice demonstrated intraglomerular accumulation of IgG by 8 weeks of age, assessed by immunostaining. Studies of albuminuria are in progress.

Conclusions: Taken together, these studies indicate that podocytes *in vitro* and *in vivo* transcytose albumin and IgG using FcRn.

Funding: NIDDK Support, Private Foundation Support

FR-PO330

Transcriptional Reprogramming by Wilms' Tumor 1 and FoxC2 in Glomerular Disease Sandrine S. Ettou,¹ Lucy Jung,³ Martin Kann,^{1,2} Mary E. Taglienti,¹ Peter Park,³ Jordan A. Kreidberg.¹ ¹Nephrology, Boston Children's Hospital, Boston, MA; ²Internal Medicine and Center for Molecular Medicine, Univ of Cologne, Cologne, Germany; ³Center for Biomedical Informatics, Harvard Medical School, Boston, MA.

Background: Foot process effacement and proteinuria, representing a breakdown of the glomerular filtration barrier (GFB) are typically accompanied by decreased expression of key podocyte proteins. We sought to determine whether decreased expression of key podocyte proteins was caused by transcriptional reprogramming in the injured podocyte. We reported a Wilms' tumor-1 (WT1) ChIP-Seq study that identified components of the GFB and many other important podocyte genes as WT1 bound genes. Many WT1 target genes in podocytes also appear to be bound by FoxC2, including Podocin (*Nphs2*), Sulfatase 1 (*Sulf1*) and Synaptopodin (*Synpo*).

Methods: We now use ChIP-Seq to study the DNA binding of WT1 to target genes in the context of Adriamycin-induced podocyte injury that is considered a model for human FSGS. WT1 ChIP-Seq was performed using isolated glomeruli from 6 days post-injection or control Balb/C mice. FoxC2 binding was determined by direct ChIP-qPCR.

Results: Following injury, expression of WT1 and FoxC2 decreased in podocytes, as did binding of WT1 and FoxC2 to their common targets. WT1/FoxC2 target gene expression was also reduced. In contrast to these WT1/FoxC2 target genes that represent a set of genes required for normal podocyte function, we identified a second set of WT1-bound genes,

not bound by FoxC2, including *Hdac5* and 7, whose expression increased after podocyte injury and for which WT1 binding decreased, suggesting that WT1 acts as a repressor for a distinct set of target genes.

WT1 binding at known target genes showed both decreased and increased peak intensity after treatment suggesting that WT1 regulation of gene expression is complex and may involve activating and repressive functions.

Conclusions: These results suggest a model whereby WT1 and FoxC2 activate gene expression in normal podocytes, WT1 represses other genes in normal podocytes independently of FoxC2.

Funding: Other NIH Support - R01

FR-PO331

A Basophilic Kinase Site at the N-Terminus of TRPC6 Controls Channel Activity Henning Hagmann,¹ Markus M. Rinschen,¹ Alexander Kuczkowski,¹ Stuart E. Dryer,² Bernhard Schermer,¹ Thomas Benzing,¹ Paul T. Brinkkoetter.¹ ¹Nephrology, Univ Hospital Cologne, Cologne, Germany; ²Biochemistry, Univ of Houston, Houston, TX.

Background: The non-selective cation channel TRPC6 plays a pivotal role in the development of proteinuric kidney disease. Hyperactivity of TRPC6 either through gain of function mutations, increased total protein levels or membrane abundance of the channel protein has been associated with glomerular disease.

Results: To investigate regulation of the TRPC6 channel activity we conducted mass spectrometry experiments to screen for phosphorylation sites in the TRPC6 protein. We identified several new as well as previously known phospho-peptides. The serine residues in position 13 and 14 of the human TRPC6 protein are phosphorylated and embedded in a basophilic kinase motif. Substitution of the serine residue in position 14 with alanine (S14A) leads to reduced TRPC6 conductance in voltage clamp experiments in *Xenopus* oocytes. The atypical cyclin-dependent kinase (Cdk5), a serine- threonine-kinase expressed in the podocyte, is directed to basophilic motifs. In the podocyte, Cdk5 is activated by the specific activators p35, p25, and Cyclin I. In cell culture experiments a direct phosphorylation of TRPC6 by Cdk5/p35 at position S14 could be confirmed with mass spectrometry and radioactive *in-vitro* kinase assays. Co-expression of Cdk5/p35 and TRPC6 enhanced channel conductivity of TRPC6 in voltage clamp experiments. This effect was abrogated by the amino acid substitution S14A.

Conclusions: A basophilic kinase site at the N-terminus of TRPC6 was identified which controls channel activity. As exemplarily shown for Cdk5/p35, basophilic kinases phosphorylate TRPC6 at serine 14 and affect channel function. This site may serve as a molecular switch for TRPC6 activity and as a potential future drug target.

Funding: Private Foundation Support

FR-PO332

Hantaviruses Associate with Actin Fibers and Cause Podocyte Damage Stefan Hägele,¹ Alexandra Kowalski,¹ Jochen Reiser,² Martin G. Zeier,¹ Ellen Krautkrämer.¹ ¹Nephrology, Univ Hospital Heidelberg, Heidelberg, Germany; ²Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL.

Background: Characteristic for the clinical picture of Old World hantaviruses is an acute renal failure with often massive non-selective proteinuria. Previously, we showed that cell-to-cell contact proteins were disrupted and levels were decreased in infected human renal cells, correlating with the clinical picture. However, the exact mechanisms driving hantaviral pathogenesis are not well characterized.

Methods: Renal biopsies of patients with acute hantavirus infection were analyzed by electron microscopy. A human podocyte cell line was used for infection with Hantaan virus (HTNV). Cell-to-cell contact proteins were analyzed by immunoblotting, qRT-PCR and immunofluorescence. The cytoskeleton was examined by confocal microscopy and by depolymerising drugs. Cell motility was measured by migration assays.

Results: Analysis of renal biopsies revealed podocyte foot process effacement with loss of cell-to-cell contacts. To examine the underlying mechanism of hantavirus-induced alterations, we performed *in vitro* infection studies. We showed that HTNV had no influence on transcription levels of cell-to-cell contact proteins, indicating another mechanism of cell-to-cell contact disruption. Next, we focused on an impact on the cytoskeleton which is important for barrier function. We detected a filamentous pattern of the hantaviral nucleocapsid (N) protein which was associated with actin fibers. This N protein localization depends on the integrity of the actin cytoskeleton, because the filamentous pattern disappeared after actin depolymerization. Correspondingly, we measured decreased viral release levels after loss of N protein filaments. During infection, we revealed impaired podocyte motility as a functional consequence due to hantavirus-induced effects on actin dynamics.

Conclusions: These results demonstrate that hantavirus infection leads to podocyte injury by morphological changes. Disruption of cell-to-cell contacts may be caused by the association of N protein and actin leading to changes in podocyte motility. These findings provide useful insights into the mechanism inducing renal failure.

FR-PO333

ARF6: A New Player in Injury-Induced Podocyte Effacement Jamie Lin,¹ Jin Seok Jeon,² Qingfeng Fan,¹ Lawrence B. Holzman.¹ ¹*Renal-Electrolyte and Hypertension Div, Univ of Pennsylvania Perelman School of Medicine, Philadelphia, PA;* ²*Dept of Nephrology, Soon Chun Hyang Univ Hospital, Seoul, Korea.*

Background: The transmembrane slit-diaphragm protein nephrin is tyrosine-phosphorylated and endocytosed during acute podocyte injury, resulting in cell spreading and effacement *in vivo*. We hypothesize that these events are facilitated by ARF6, a small GTPase that regulates endocytosis, endosomal trafficking, and actin dynamics possibly through regulation of Rac1, a Rho GTPase.

Methods: Using human podocyte cultures transfected with chimeric nephrin intracellular domain, we investigated the molecular mechanisms underlying its role in nephrin signaling. Using wild-type, constitutively-active, dominant-negative, and siRNA-knock-down of ARF6, we assessed lamellipodia activity (a marker of cell spreading) and podocyte motility.

Results: Results of co-immunoprecipitation suggested that activated nephrin formed a signaling complex with ARF6. Furthermore, nephrin tyrosine phosphorylation increased ARF6 activity in cultured podocytes. A constitutively active ARF6 mutant resulted in increased lamellipodia formation compared to wild-type ARF6, while dominant-negative ARF6 mutant resulted in decreased lamellipodia formation. A scratch assay of ARF6 knock-down cultured podocytes revealed slowed cell migration.

Conclusions: Together, our results suggest that ARF6 is an important protein involved in the regulation of injury-induced podocyte cytoskeletal rearrangement. Inhibition of ARF6 might prevent podocyte effacement and confer a protective phenotype *in vivo*, making it an attractive target for the amelioration of glomerular disease.

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FR-PO334

Albumin Sieving Coefficient in Isolated Perfused Kidney: Effects of EDTA Turgay Saritas, Ralf Hausmann, Thiago Strieder, Jürgen Floege, Marcus J. Moeller. *Nephrology and Immunology, Univ Hospital RWH Aachen, Aachen, NRW, Germany.*

Background: It is still controversial how the glomerular filter works. The widely accepted pore model is limited by multiple unresolved and incomplete issues. Previously, we have proposed that an electrical field is generated across the glomerular filter by forced filtration of the small solutes in plasma (i.e. water, Na⁺, K⁺, Cl⁻, HCO₃⁻, and divalent ions). The electrophoretic force of this electrical field retains plasma proteins within the circulation. If validated, this novel 'electro-kinetic model' could explain most of the remaining issues about the glomerular filter. The model predicts a crucial role of the divalent cations in the perfusate (Ca²⁺ and Mg²⁺) for the generation of the electrical field ('streaming potential'). The aim of the present study was to test this.

Methods: According to the current physical model for the generation of streaming potentials with a reversed polarity, a physical phenomenon termed 'over-charging' is predicted to occur which requires the presence of divalent cations. Thus, to verify the 'electrokinetic model', divalent cations are predicted to be required for generation of the electrical field and a physiological low albumin sieving coefficient. Isolated perfused rat kidneys (IPK) were perfused-fixed with glutaraldehyde to exclude any cellular effects. Subsequently, the absolute concentrations of the major divalent cations (Ca²⁺, Mg²⁺) were manipulated in our IPK model. Albumin solutions containing 0.9 mM Ca²⁺ and 0.5 mM Mg²⁺ or 0.52 mM ethylenediaminetetraacetic acid (EDTA) were used to perfuse the IPK to achieve normal or very low Ca²⁺ and Mg²⁺ concentrations within the perfusate.

Results: Decreased polycation concentrations resulted in a significant increase of the albumin-sieving coefficient from a baseline value of 0.0031±0.00024 to 0.0068±0.0014 (+120%, n=5, p<0.05). Changes in albumin sieving coefficient were partially reversible. The glomerular filtration rate was stable.

Conclusions: The results indicate that Ca²⁺ and Mg²⁺ are required for the integrity of the glomerular filter. Cellular artifacts or active transport processes were excluded by fixation. The results support the electrokinetic model of glomerular filtration.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO335

γ Isoform of Phosphoinositide 3 Kinase Plays a Role for Podocyte Damage and Is a Potential Marker for Glomerular Sclerosis Tomoko Hayashida, Xiaoyan Liang, H. William Schnaper. *Pediatrics, Northwestern Univ, Chicago, IL.*

Background: We recently reported that, in the Adriamycin (ADR)-induced mouse glomerular sclerosis (GS) model, the γ isoform of the p110 catalytic subunit (p110γ) of phosphoinositide 3 kinase is selectively upregulated in podocytes of the sclerosing glomeruli, and that a specific inhibitor to p110γ (AS605240) prevented proteinuria and GS. Here, we evaluated the molecular mechanisms by which p110γ mediates podocyte damage *in vitro* and a possible role for p110γ in a mouse genetic model of GS *in vivo*.

Methods: CD2AP^{-/-}, synaptopodin^{-/-} mice develop FSGS-like lesion to a variable degree at age 8-9 months. Mice were sacrificed at 8 months old and glomerular COL1A2 mRNA content was evaluated by qPCR of laser-captured glomeruli. Fixed kidney sections were stained for p110γ, and positive staining was counted in manually identified glomeruli (~100 gloms per section) using the TissueGnostics system. *In vitro*, podocytes were isolated from wild type (WT) or p110γ kinase-dead knock-in (KD) mouse mated with the Immortomouse, and cellular signaling was evaluated in cells overexpressing GFP-actin with or without ADR treatment by live-cell imaging with an Andor spinning confocal microscope.

Results: The mice showed variable levels of proteinuria and GS. p110γ-positive cells per total nuclei in glomeruli correlated significantly with glomerular COL1A2 mRNA content. In culture, p110γ KD podocytes, but not WT cells, demonstrated increased membrane ruffling along with distinct Rac1 staining at the membrane, and KD podocytes were resistant to *in vitro* ADR treatment. WT cells expressing constitutively active p110γ showed decreased cytoskeletal assembly and cytoDEATH early apoptosis marker staining was detected, suggesting that p110γ activity directly mediates podocyte dysfunction.

Conclusions: p110γ expression in podocyte correlates with degree of GS, and therefore, a potential marker for GS. p110γ activity mediates podocyte damage by affecting signals that is critical for cytoskeletal structure.

Funding: NIDDK Support

FR-PO336

Effects of FSGS-Associated Mutations on the Stability and Function of Myosin-1 Mira Krendel, Jing Bi, Robert T. Carroll, Michael L. James, Jessica L. Ouderkerk, Vladimir Sirotkin. *Cell and Developmental Biology, SUNY Upstate Medical Univ, Syracuse, NY.*

Background: Myo1e is expressed in podocytes and plays a key role in regulating the integrity of their cell-cell junctions, however, the effects of FSGS mutations on Myo1e motor activity and stability have not been directly tested. In this study, we used a simple model organism, fission yeast *Schizosaccharomyces pombe*, to test the effects of FSGS-associated mutations on myosin activity. Fission yeast has only one class I myosin, Myo1, which is involved in actin patch assembly at the sites of endocytosis.

Methods: The amino acid residues mutated in the FSGS patients are conserved between human Myo1e and yeast Myo1, which allowed us to introduce equivalent mutations into yeast myosin and use the resulting mutant strains for functional analysis. Myo1-mGFP localization and stability was analyzed using fluorescence imaging and Western blotting, while Myo1 functional activity was tested using growth and endocytosis assays.

Results: Yeast strains expressing mutant Myo1 exhibited defects in growth and endocytosis similar to those observed in the myo1 deletion strain. These mutations also disrupted Myo1 localization to endocytic actin patches and resulted in mis-localization of Myo1 to eisosomes, linear membrane microdomains found in yeast cells. While both mutants examined in this study exhibited loss of function, one of these mutants was also characterized by the decreased protein stability.

Conclusions: Using the yeast model system we were able to determine that the kidney disease-associated mutations impair myosin functional activity and have differential effects on protein stability. This study provides the first example of using fission yeast as a model system to test the effects of FSGS mutations on Myo1e function. This novel system allowed us to definitively establish for the first time the connection between the myosin motor activity and its ability to support normal glomerular filtration.

Funding: NIDDK Support

FR-PO337

Vinculin Binds Zonula Occludens-1 (ZO-1) and Is Required for Podocyte Stabilization of the Slit Diaphragm following Injury Xuefei Tian, Kazunori Inoue, Shuta Ishibe. *Dept of Internal Medicine, Yale Univ School of Medicine, New Haven, CT.*

Background: Cell-matrix interactions and intercellular junctions in podocytes are important factors to prevent protein leakage through the glomerular filtration barrier. Vinculin, a cytoplasmic protein, links the actin filaments to integrin-based cell-matrix proteins and cadherin-based intercellular junctions. We have observed that vinculin is highly expressed in podocytes, and appears to be critical in maintaining slit diaphragm integrity following injury through its interaction with ZO-1.

Methods: Wild type and Vinculin (*Vcl*) podocyte knock out (KO) mice were analyzed to determine the role of vinculin *in vivo*, and primary podocytes were isolated for *in vitro* studies.

Results: Podocyte specific ablation of *Vcl* resulted in no significant difference in body weight, albuminuria, and kidney histology up to 18 months when compared to littermate controls. However, Pod-*Vcl* KO mice had significantly increased albumin/creatinine ratios following lipopolysaccharide (LPS) or rabbit anti-mouse glomerular basal membrane (NTS) induced podocyte damage respectively (284±40 vs 411±31 μg/mg, and 205±28 vs 314±38 μg/mg, P<0.05). In addition, loss of *Vcl* in podocytes resulted in worsened foot process effacement. Co-immunoprecipitation assays demonstrated that vinculin associates with ZO-1 in the primary podocytes and isolated glomeruli respectively. Cell fractionation of control and Pod-*Vcl* KO podocytes treated with either LPS or protamine sulfate (PS) revealed a mislocalization of ZO-1 and nephrin to the cytoplasm in the mutant podocytes when compared to the control. These findings were further validated by immunofluorescence imaging of the primary podocytes following LPS or PS stimulation and from isolated glomeruli following LPS or NTS stimulation. No changes in cell adhesion or focal adhesion number were observed between the control and Pod-*Vcl* KO podocytes following LPS or PS stimulation on various substrates.

Conclusions: Our results reveal an association between vinculin and ZO-1 in podocytes. Loss of *Vcl* in podocytes results in the mislocalization of slit diaphragm proteins ZO-1 and nephrin following injury, thus exacerbating proteinuria.

Funding: NIDDK Support

FR-PO338

AT₁ Receptors in Podocytes Control GFR and Susceptibility to Kidney Injury Stacy Alana Johnson,¹ Tiffani N. White,¹ Susan B. Gurley,^{1,2} Thomas M. Coffman.^{1,2,3} ¹Duke Univ; ²Durham VA; ³Duke-NUS.

Background: Angiotensin II, acting via AT₁ receptors, plays a critical role in CKD progression. Pharmacologic blockade of AT₁ receptors reduces albuminuria and is linked to its efficacy in CKD. Within the kidney, the density of AT₁ receptor expression is highest in the glomerulus, where AT₁ receptors are expressed in multiple cell lineages and are involved in regulating glomerular pressures and GFR. However, the key cellular sites of action in the glomerulus involved in physiological regulation and in promoting proteinuria have not been directly defined. Since podocyte dysfunction and injury have been implicated in the pathogenesis of many glomerulopathies, we investigated the role of AT₁ receptors in podocytes using cell-specific gene targeting.

Methods: Because the minor AT₁ receptor isoform (AT_{1b}) is expressed at significant levels in podocytes, we generated mice lacking all AT₁ receptors in the podocyte (PodKOs) by carrying out podocyte-specific, Cre-mediated excision of a conditional allele of the major AT₁ receptor isoform (AT_{1a}) on an AT_{1b}-null background.

Results: PodKO mice develop normally with kidney weights similar to controls (6.9±0.5 vs 7.0 ± 0.3 mg/g BW) and their glomerular morphology appears normal. GFR was significantly reduced in 24-week old PodKOs (8.9±3.5 μl min⁻¹g⁻¹) compared to controls (29.5±4.5 μl min⁻¹g⁻¹; p=0.04), but there was no significant difference in the low levels of albumin excretion between the groups. To determine whether the elimination of AT₁ receptors from podocytes impacts albuminuria and kidney injury in a model with high levels of Ang II, a transgene (*RenTg*) driving constitutive expression of renin was crossed onto the PodKO background. At 24 weeks of age, levels of albuminuria were increased in RenTg mice (210±71 μg/24 hr) compared to controls (29±9 μg/24 hr; p=0.02), but this increase in albuminuria was unaffected in RenTg-PodKOs (229±38 μg/24hr). Despite similar levels of albumin excretion, kidneys from RenTg-PodKO mice had exaggerated kidney injury with more glomerulosclerosis, mesangial expansion and tubular casts.

Conclusions: Our results suggest that AT₁ receptors in podocytes do not promote albuminuria and may protect against glomerular injury.

Funding: Private Foundation Support

FR-PO339

H₂O₂ Production by Nox4 Drives Ang II – Dependent Calcium Influx Through TRPC6 Channels in the Podocytes Daria Ilatovskaya, Oleg Palygin, Leonid S. Shuyskiy, Alexander Staruschenko. *Physiology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Improper Ca²⁺ handling by the podocyte can result in cell damage and loss of function. Podocyte depletion and associated glomerulosclerosis are typical for progressive chronic nephropathies, which have been associated with elevated levels of ROS, including H₂O₂. One of the key mediators of Ca²⁺ flux in the podocytes is a TRPC6 channel. The goal of this study was to provide a mechanistic insight into the Ang II-dependent regulation of TRPC6 channel.

Methods: Changes in intracellular Ca²⁺ levels were measured with live confocal microscopy in podocytes of isolated glomeruli. Patch clamp analysis was performed to assess the activity of TRPC channels in this preparation. Enzymatic biosensors technique was applied to determine H₂O₂ release in the kidney cortex and isolated glomeruli.

Results: NADPH oxidase 4 (Nox4) is one of the main renal sources of H₂O₂. Here we demonstrated substantial attenuation of Ang II-evoked H₂O₂ release in the kidney and glomeruli suspension of the Nox4^{-/-} rats, generated on the Dahl salt-sensitive (SS) background. Furthermore, basal Ca²⁺ levels and Ca²⁺ influx in response to Ang II were decreased in the podocytes of Nox4^{-/-} rats compared to SS rats. Basal Ca²⁺ level increase was also attenuated in Nox4^{-/-} podocytes when rats were fed a high salt diet. To further test effects of H₂O₂, we employed patch clamp analysis. The data revealed an acute increase in TRPC6 channel open probability in response to H₂O₂. A dose-dependent increase in intracellular Ca²⁺ was observed when H₂O₂ was applied (2.5 μM to 300 μM; EC₅₀=56 μM). Lower concentrations of H₂O₂ caused a transient Ca²⁺ peak, whereas doses of 50 μM and higher evoked a long-term Ca²⁺ elevation attributed to apoptotic effects. Experiments with TRPC6^{-/-} and TRPC5/6 double KO mice showed a diminished Ca²⁺ response to H₂O₂.

Conclusions: Our data indicate that in the podocytes Ang II stimulates generation of H₂O₂ by the Nox4, which evokes a dose-dependent Ca²⁺ influx through TRPC6 channels. This mechanism might be an important determinant of podocyte loss in kidney diseases associated with oxidative stress and elevated interstitial Ang II levels.

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FR-PO340

Role of Unliganded Vitamin D Receptor (VDR) in Providing Podocyte Protection During AT1R Blockade (BLK) in Adverse Milieus Tejinder Singh,¹ Kamesh R. Ayasolla,¹ Shabirul Haque,¹ Nirupama Chandel,¹ Himanshu Vashistha,² Ashwani Malhotra,¹ Leonard G. Meggs,² Pravin C. Singhal.¹ ¹Medicine, Hofstra North Shore LLI Medical School, Great Neck, NY; ²Medicine, Ochsner Health System, New Orleans, LA.

Background: AT1R-BLK is used extensively to slow down the progression of kidney diseases. We hypothesized that AT1R-BLK provides podocyte protection through regulation of VDR and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) expression under adverse milieus (AMs).

Methods: Human podocytes (HPs) were treated with losartan (AT1RB) or VDR agonist (EB1089;VDA) with or without AMs (HIV/high glucose/Ang II; 48h) and evaluated for

mRNA and protein expressions of Cytochrome P450 Family 24 (CYP24)A1, VDR and molecular markers of co-repressor and co-activator complexes. Protein interactions in these complexes were evaluated by immunoprecipitation (IP) studies followed by Western blot analysis. Role of proteasomal degradation of VDR in AMs was determined.

Results: Both AT1R-BLK and VDA stimulated VDR complexes formation that differed in their composition and in their functionality. AT1R-BLK- induced VDR complexes contained unliganded VDR, SMRT, and phospho-histone deacetylase (HDAC)3, whereas, VDA-VDR complexes were constituted by liganded VDR and CBP/p300. AT1R-BLK-induced complexes attenuated podocyte acetyl- histone (Ac-H)3 levels and CYP24A1 expression, thus indicating their de-acetylating and repressive properties. On the other hand, VD-VDR complexes not only increased podocyte Ac-H3 levels but also enhanced CYP24A1 expression, thus suggesting their acetylating and gene activation properties. AT1R-BLK- induced podocyte SMRT inhibited expression of the pro-apoptotic gene BAX through down regulation of Wip1 and phosphorylation of Chk2 in high glucose milieu. Since SMRT-depleted podocytes lacked AT1R-BLK-mediated protection against DNA damage, it appears that SMRT is necessary for DNA repairs during AT1R-BLK.

Conclusions: AT1R-BLK provides podocyte protection in AMs predominantly through SMRT expression and partly through unliganded VDR expression in 1, 25(OH)₂D deficient states, on the other hand, ATR1-BLK contributes to liganded VDR expression in 1, 25(OH)₂D sufficient states.

Funding: NIDDK Support

FR-PO341

Enhanced S-Nitrosylation and N-Glycosylation of Podocin-R138Q May Contribute to Its Defective Trafficking and Rapid Degradation Maria Carmen Serrano-Perez,¹ Fabien Nevo,¹ Christelle Arrondel,¹ Alda Tufro,² Corinne Antignac,¹ Geraldine Mollet.¹ ¹Inserm U1163 - Imagine Inst - Paris Descartes Univ-Sorbonne Paris Cité, France; ²Yale Univ School of Medicine-Dept of Pediatrics.

Background: Missense mutations in the *NPHS2* gene, encoding podocin, are a major cause of inherited and sporadic cases of steroid-resistant nephrotic syndrome (SRNS). Among them, those encoding endoplasmic reticulum (ER)-retained mutant proteins, e.g. R138Q, correlate with the most severe cases of SRNS.

Methods: We generated two human podocyte cell lines stably expressing 2HA-podocin^{wt} or 2HA-podocin^{R138Q} to perform comparative studies on podocin post-translational modifications and podocin degradation.

Results: We detected increased podocin S-nitrosylation and N-glycosylation in 2HA-podocin^{R138Q} vs. 2HA-podocin^{wt} podocytes, which may modify podocin topology, degradation and trafficking. We also suggest that a further interaction of podocin^{R138Q} with the ER-chaperone calnexin may contribute to its ER-retention. In line with the higher degradation rate of podocin^{R138Q} previously found in R140Q knock-in mice, we found that non-glycosylated (ng) podocin^{R138Q} has a dramatically shorter half-life than podocin^{wt}. Moreover, the N-glycosylated forms of podocin^{R138Q} are more stable than its non-glycosylated fraction. We also show that ng-podocin^{R138Q} is mainly degraded by the proteasome, whereas ng-podocin^{wt} can be degraded by both the proteasomal and the lysosomal proteolytic machineries. Furthermore, preventing ng-podocin^{R138Q} degradation allows its partial localization to the podocyte filopodia, improves the ratio between its non-glycosylated and glycosylated forms and reduces its interaction with calnexin.

Conclusions: These findings show podocin S-nitrosylation for the first time and suggest that increased S-nitrosylation and N-glycosylation may contribute to the defective trafficking and degradation of podocin^{R138Q}, the product of the most frequent human podocin missense mutation, and possibly of other ER-retained podocin missense mutants.

Funding: Government Support - Non-U.S.

FR-PO342

RAS Inhibition Enhances Proliferation and Migration of Cells of Renin Lineage (CoRL) as Progenitors in Experimental FSGS Julia Lichtnekert,¹ Diana G. Eng,¹ Jeffrey W. Pippin,¹ Kenneth W. Gross,² Stuart J. Shankland.¹ ¹Div of Nephrology, Univ of Washington, Seattle, WA; ²Dept of Molecular and Cellular Biology, Roswell Park Cancer Inst, Buffalo, NY.

Background: RAS inhibitors are used therapeutically in proteinuric glomerular diseases. In focal segmental glomerulosclerosis (FSGS) where podocyte number is depleted, recent data showed that ACE-Inhibitors could improve podocyte number. Because adult podocytes cannot proliferate, their replacement by renal progenitors is critical for their regeneration in disease. The impact of RAS blockade on adult podocyte progenitors is not well understood.

Methods: Experimental FSGS characterized by podocyte depletion was induced by an anti-podocyte antibody in two strains of Cells of Renin Lineage (CoRL) reporter mice (RenCre and RenCreER) where CoRL are fate mapped. Diseased mice were randomized at day 3, when podocyte number was depleted by 40%, to receive Enalapril or Losartan, or the controls Hydralazine or water. BrdU was injected to monitor proliferation.

Results: Following initial podocyte depletion in all groups, podocyte number (measured by p57 staining) was higher in both Enalapril and Losartan groups on d14 and d28. This was accompanied by significantly lower proteinuria and glomerulosclerosis. The number of CoRL increased in the intra-glomerular compartment in FSGS mice given water or hydralazine. However, the number of labeled CoRL further increased significantly in FSGS mice given Enalapril or Losartan. A subset of CoRL detected in the glomerular compartment co-expressed several markers for podocytes and PEC's. RAS inhibition increased BrdU staining in CoRL in the juxta- and intraglomerular compartments, but was not seen in podocytes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Following the abrupt depletion of adult podocytes in experimental FSGS, RAS blockade significantly increased their number despite the absence of their proliferation. This regeneration of adult podocytes is likely in part due to proliferation and migration of CoRL progenitor cells into the glomerular compartment. We show the first time that RAS inhibition has the potential to stimulate progenitor cells necessary for kidney repair and regeneration following podocyte depletion.

FR-PO343

ShcA Influences Nephrin Endocytosis and Protects from Glomerular Injury Claire E. Martin,¹ Kelly A. Petersen,¹ Lamine Aoudjit,² Tomoko Takano,² Nina Jones,¹ ¹Molecular and Cellular Biology, Univ of Guelph, Guelph, ON, Canada; ²Dept of Medicine, McGill Univ, Montreal, QC, Canada.

Background: The transmembrane protein nephrin is a key component of the slit diaphragm (SD). It has recently been postulated that nephrin turnover plays a key role in maintaining a healthy SD, and multiple theories regarding the role of nephrin phosphorylation in endocytosis are emerging. Tyrosine phosphorylation of the cytoplasmic tail of nephrin facilitates recruitment of several signaling proteins that regulate podocyte shape and thereby permselectivity of the SD. Previous work from our lab has identified and mapped the interaction between nephrin and the ShcA adaptor protein and demonstrated an early requirement for ShcA in maintenance of the filtration barrier in mice. Given ShcA's established role in endocytosis, we now hypothesize that ShcA may regulate nephrin endocytosis to ultimately maintain filtration barrier integrity.

Methods: Multiple approaches were used to measure the influence of ShcA and ShcA domain mutants on the levels of surface nephrin and signaling downstream of nephrin. Puromycin aminonucleoside (PAN) nephrosis was induced in Sprague-Dawley rats for 0, 4, 7, or 14 days and nephrin endocytosis was monitored via biotinylation and immunofluorescence experiments.

Results: We demonstrate that ShcA expression is increased in podocytes in response to PAN injury, which is accompanied by activation of the stress-activated p38 and JNK MAP kinases. Interestingly, we found that transactivation of AP-1, which occurs downstream of nephrin as well as p38 and JNK, is attenuated by ShcA, and this effect is reversed by mutation of the ShcA SH2 domain, which mediates nephrin binding. Further investigation revealed that ShcA promotes nephrin endocytosis in a phospho-dependent manner by enhancing Src-mediated nephrin phosphorylation, its own binding to nephrin and endocytosis into EEA1-positive endosomes both *in vitro* and in PAN-treated rats.

Conclusions: Together these findings suggest a protective effect of ShcA in podocytes by influencing phospho-dependent nephrin endocytosis and possibly attenuating nephrin-mediated p38/JNK signaling in response to injury.

Funding: Government Support - Non-U.S.

FR-PO344

Podocyte Specific Response to Complement Challenge Anne Katrin Dettmar,^{1,2} Magdalena Riedl,² Fred G. Pluthero,² Moin Saleem,³ Jun Oh,¹ Christoph Licht,² ¹Dept of Pediatrics, Univ Medical Center Hamburg-Eppendorf; ²Dept of Pediatric Nephrology, Hospital for Sick Children; ³Academic Renal Unit, Univ of Bristol.

Background: There is a multilayered system of fluid phase and surface bound complement regulatory proteins, which ensure that complement activation occurs only site specific and spares the body's own cells. Unrestricted complement activation is a main cause for damage in complement-mediated glomerulopathies such as C3G or membranous nephropathy (MN). In MN, podocytes, key components of the glomerular filtration barrier, are target of overshooting complement activation. The aim of this study was to characterize the complement defense mechanisms in podocytes and their response to complement challenge (CC).

Methods: We analyzed complement regulators by immunofluorescence, flow cytometry and qRT-PCR in immortalized human podocytes and compared them to blood grown endothelial cells (BOECs). Functionality of secreted complement factor H (CFH) was tested via a cofactor assay. In a model for CC (sensitization with antibodies against membrane-anchored complement regulators CD46, CD55 and CD59 and normal human serum (NHS)) we analyzed C3c deposition, LDH-release, and cell morphology.

Results: Podocytes showed similar levels of CD46, CD55 and CD59 as BOECs. Expression of CFH-mRNA was higher in podocytes (1.03 +/-0.27 vs. 0.25 +/-0.09 fold change, p=0.03). Podocyte secreted CFH served as active cofactor to CFI in splitting C3b. CC led to increased C3c deposition (NHS vs CC: 660+/-189 vs 5290+/-2231 MFI, p=0.05), which was complement dependent (heat inactivated serum: 211+/-25, p=0.04). There was a significant increase in LDH release (NHS vs. complement 1.92 +/-0.98 vs. 2.30 +/-0.86 fold increase, p=0.02), and podocytes showed a reduction of stress fibres and cell size after CC.

Conclusions: In summary, podocytes expressed complement regulators in response to complement activation similar to the response found in BOECs. CFH, less abundant in BOECs, may play an important role in a complement specific stress response of podocytes. These findings might help to understand the role of podocytes in local complement activation and will help to identify new therapeutic strategies in future.

Funding: Private Foundation Support

FR-PO345

Ephrin-B1 Is Essential for the Formation and the Maintenance of the Integrity of the Slit Diaphragm Component: Inducible Podocyte-Specific Ephrin-B1 Deletion Causes Irregular Localization of Nephrin, NEPH1, CD2AP and ZO-1 Yoshiyasu Fukusumi, Hiroshi Kawachi. *Dept of Cell Biology, Inst of Nephrology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: Ephrin and eph function as receptor-ligand pairs, and are reported to play multiple functions in several tissues. We have reported ephrin-B1 was expressed at the podocyte slit diaphragm (SD) and had an interaction with nephrin, a critical component of the SD (Kidney Int 72: 954, 2007). However, the function of ephrin-B at the SD is remained uncertain. In this study, the role of ephrin-B at the SD and the functional association of ephrin-B and nephrin were elucidated.

Methods: (i) The expressions of the SD components (nephrin, NEPH1, podocin, CD2AP and ZO-1) were analyzed in tamoxifen-inducible podocyte-specific Ephrin-B1 knockout (KO) mice (Podocin-CreERT2; Ephrin-B1 flox/flox). (ii) The effect of the nephrin stimulation on the molecular conformation of ephrin-B were analyzed.

Results: (i) Tamoxifen-induced inactivation of the ephrin-B1 gene at E18.5 resulted in the dislocalization of nephrin, NEPH1, CD2AP and ZO-1, although podocin dislocalization was not detected. These alterations of the molecular arrangement of the SD components were also detected in the mice of which ephrin-B1 was deleted at 3 month-old with tamoxifen (KO vs. cont, n=5: nephrin, score 3.11 vs 3.40, p<0.01; NEPH1: 2.97 vs 3.36, p<0.05; CD2AP, 3.01 vs 3.24, p<0.05; ZO-1: 3.28 vs 3.66, p<0.05). (ii) Not only nephrin but also ephrin-B was phosphorylated in the rat nephrotic model caused by the injection with the antibody against nephrin, although phosphorylation of these molecules was not detected in normal rats. The phosphorylation of these molecules were detected already at 1 h after the antibody injection. The ephrin-B phosphorylation was also induced by the treatment with the anti-nephrin antibody in HEK293 cells co-transfected with ephrin-B and nephrin.

Conclusions: Ephrin-B1 is essential for the formation and the maintenance of the proper arrangement of the SD molecules. The stimulation to nephrin with the antibody phosphorylated not only nephrin but also ephrin-B, indicating ephrin-B is functionally associated with nephrin.

Funding: Government Support - Non-U.S.

FR-PO346

Ubiquitin C-Terminal Hydrolase-L1 Deficiency in Podocytes Protects from Immune Complex Nephritis in Mice Julia M. Fehlert,¹ Marlies Sachs,¹ Thorsten Wiech,² Rolf A. Stahl,¹ Catherine Meyer-Schwesinger.¹ ¹Nephrology, III. Medical Clinic, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; ²Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) is a central deubiquitinating enzyme of the neuronal ubiquitin proteasomal system. UCH-L1 is thought to regulate the intracellular pool of monoubiquitin in neurons. Recently we identified a *de novo* expression of UCH-L1 in podocytes of patients with membranous nephropathy. Upregulation of UCH-L1 correlated with disease progression, accumulation of ubiquitinated proteins and altered expression of podocyte-specific proteins in human and rodent podocytes. Inhibition of UCH-L1 enzymatic function in a rat model of membranous nephropathy decreased the abnormal protein accumulation and ameliorated the clinical course of disease. We generated mice with podocyte-specific UCH-L1-deficiency to investigate the role of UCH-L1 *de novo* expression in injured podocytes.

Methods: Mice with podocyte-specific UCH-L1-deficiency were generated by Cre-Lox technology and back-crossed into the C57/BL6 background. Podocyte phenotype was evaluated by morphological (immunohistochemistry, electron microscopy) and biochemical techniques (Western blotting, proteasomal activity assays, real-time PCR) in unchallenged and anti-podocyte antibody challenged wildtype and knock-out mice.

Results: Unchallenged podocyte-specific UCH-L1-deficient mice exhibited normal podocyte morphology throughout life and delayed age-related proteinuria accompanied by a decreased accumulation of poly-ubiquitinated proteins. Following induction of anti-podocyte nephritis, podocyte-specific UCH-L1-deficient mice showed decreased signs of podocyte injury and decreased proteinuria despite a comparable immunologic reaction to the injected anti-podocyte antibodies. Podocyte-specific proteins such as nephrin and podocin were stabilized and protein accumulation was decreased. UCH-L1-deficiency resulted in increased proteasomal capacity and activity in injured podocytes.

Conclusions: Podocyte-specific UCH-L1-deficiency protects podocytes from age-related degenerative changes and from immune complex nephritis through increased proteasomal capacity.

Funding: Government Support - Non-U.S.

FR-PO347

Adhesion and Repulsion of Podocytes: Role of EphB-Receptors Eva Koenigshausen, Julius Hoffacker, Lukas Ludwig Peter Heimann, Nils Tim Haep, Magdalena Woznowski, Ivo Quack, Lars C. Rump, Lorenz Sellin. *Univ Hospital Duesseldorf.*

Background: Eph-receptor kinases mediate cell adhesion and repulsion at specialized cell contacts. Eph-receptor kinases bind to their cell-membrane bound ligands, the ephrines. EphrinB1 and EphB4 have been localized at the slit diaphragm. The molecular function of the EphB1,2,3 receptors in podocytes is unknown so far. Proteinuria is a hallmark for

glomerular disease and results from disruption of the glomerular filter. The slit diaphragm is a specialized cell-cell contact between adjacent podocytes. Maintenance of the correct positioned, adjacent podocytes has not been well understood.

Methods: RNA was isolated from differentiated human podocytes and isolated murine glomeruli and PCR performed. Human podocytes were retrovirally transduced with EphB2-YFP or ephrinb1-CFP. EphB2-YFP and ephrinb1-CFP podocytes were differentiated in co-cultures and time lapse video imaging was performed. In addition, a co-culture of differentiated EphB2-YFP and ephrinb1-CFP cells was examined. To investigate the role of the intracellular domains of the EphB2 receptor and ephrinb1 ligand, truncated mutants of EphB2 (EphB2.DC-YFP) and ephrinb1 (ephrinb1.DC-CFP) were analyzed.

Results: Human podocytes as well as murine glomeruli express EphB1, 2 and 3 receptors. Co-cultures of differentiating EphB2-YFP and ephrinb1-CFP podocytes show repulsion between the two cell types. Transendocytosis (YFP particles in CFP cells and vice versa) occurs in both cell types during repulsion. The repulsion is dependent on the intracellular domain of EphB2 as EphB2.DC-YFP cells adhere to ephrinb1-CFP and ephrinb1.DC-CFP cells. However, repulsion is maintained in co-cultures of EphB2-YFP with ephrinb1.DC-CFP cells. Co-culture experiments of differentiated, confluent podocytes confirm the results presented above.

Conclusions: EphB2 receptors mediate podocyte repulsion upon binding to their ligand ephrinb1. The EphB2 receptor cytoplasmic domain seems to be crucial for repulsion. Maintaining the correct podocyte distance within the highly organized glomerular architecture is not been well understood. These cell culture data provide a promising concept of potential regulation of podocyte distance in vivo.

FR-PO348

Overexpression of the Splice Isoform VEGF165b Is Sufficient for Kidney Function when All VEGF Isoforms Are Depleted Megan Stevens, Chris R. Neal, Andy Salmon, David O. Bates, Steven J. Harper, Sebastian Oltean. *Univ of Bristol, United Kingdom.*

Background: Chronic kidney disease is associated with reduced VEGF-A expression. However, the role VEGF-A splice isoforms play in kidney physiology and pathology is unclear. Use of an alternative 3' splice site in the terminal exon of VEGF-A results in the expression of anti-angiogenic VEGF_{165b}. Previous studies suggest that VEGF_{165b} is protective in renal function in diabetic rodent models. This study aimed to investigate whether constitutive podocyte over-expression of VEGF_{165b} is able to rescue the injury phenotype seen in the inducible podocyte-specific VEGF-A KO mouse. The mechanism of action of VEGF_{165b} within the glomeruli was also investigated.

Methods: Podocyte-specific VEGF-A KO was induced via doxycycline for 10-14 weeks in WT, VEGF-A KO and VEGF-A KO x neph-VEGF_{165b} mice. In situ hybridization confirmed a knock-down of VEGF-A. The kidney functional phenotype was determined through the urinary albumin creatinine ratio (uACR) and measurement of glomerular water permeability. Electron microscopy was used to examine the ultra structure of the glomeruli, and immunofluorescence to determine the expression levels of podocyte and endothelial-specific proteins. Glomerular endothelial cells (GenCs) in culture were used to determine the mechanism of action of VEGF_{165b} through VEGFR-2.

Results: The VEGF_{165b} isoform alone is sufficient to rescue the increase in albuminuria and glomerular water permeability in the context of progressive depletion of all VEGF-A isoforms. Ultra structural studies show glomerular basement membrane thickening and increased podocyte slit width in the VEGF-A KO mouse, with both being rescued in the VEGF_{165b} over-expressors. VEGF_{165b} also restores PECAM expression in GenCs, and glomerular capillary circumference. Mechanistically, VEGF_{165b} increases VEGFR-2 expression and phosphorylation both in vivo and in vitro. Furthermore, it down regulates genes involved in the migration and proliferation of GenCs, which are otherwise up regulated by VEGF₁₆₅.

Conclusions: Our study indicates that VEGF-A splice isoform manipulation could be a novel therapeutic avenue in chronic glomerular disease.

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FR-PO349

Rituximab Prevents TNF α Induced Podocyte α 3 Integrin Activation Farah Leclercq, Christopher E. Pedigo, Alessia Fornoni, Sandra M. Merscher. *Katz Family Drug Discovery Center, Nephrology, Univ of Miami, FL.*

Background: Focal Segmental Glomerulosclerosis (FSGS) is a disease characterized by podocyte damage and scarring of the glomeruli. FSGS accounts for up to 20% of end stage renal disease (ESRD) cases in the United States. Podocyte urokinase-receptor (uPAR) dependent α V β 3 integrin activation and decreased glomerular sphingomyelin phosphodiesterase acid-like-3b (SMPDL3b) expression were described in glomerular biopsies from patients with FSGS. Circulating TNF α is increased in a fraction of patients with FSGS and anti-TNF α therapy has shown efficacy in a subset of patients with recurrent FSGS. We hypothesized that TNF α reduces SMPDL3b expression resulting in α n3 Integrin activation.

Methods: Differentiated human podocytes were cultured in the presence of TNF α (100ng/ml). Caspase 3 activity was determined in human podocytes. Protein and mRNA was isolated and the expression of key genes was investigated by Western blot analysis and quantitative real time PCR. Rituximab was used at the dose of 100 μ g/ml.

Results: TNF α treatment of human podocytes significantly reduced SMPDL3b expression (p<0.05), increased uPAR expression (p<0.05) and β 3 integrin activation (p<0.05). TNF α treatment induced caspase 3 activity, which was prevented by preserving SMPDL3b expression with Rituximab (p<0.05) or by inhibiting β 3 integrin activation with cycloRGD (p<0.05). Likewise, SMPDL3b overexpressing podocytes were protected

from TNF α induced β 3 integrin activation. Injection of recombinant TNF α in mice led to increased glomerular uPAR mRNA expression (p<0.05) and caused albuminuria (p<0.05), which was significantly attenuated with Rituximab (p<0.05).

Conclusions: TNF α decreases SMPDL3b expression, increases uPAR expression and activates β 3 integrin signaling leading to podocyte injury and apoptosis. Our data suggest that treatments targeting the TNF α -SMPDL3b- β 3 integrin axis may prevent podocyte injury in FSGS.

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffman La Roche

FR-PO350

Deletion of the Major Soluble Flt1 Isoform from Mice Reveals New Vegf Decoy Variants Biao Li,² Tuncer Onay,¹ Chengjin Li,² Vera Eremina,² Susan E. Quaggin.^{1,2} ¹Feinberg Cardiovascular Research Inst; ²Lunenfeld-Tanenbaum Research Inst.

Background: sVEGFR1 (sflt1) is an alternative splicing product of VEGFR1 (flt1) gene. Both flt1 and sflt1 can function as "decoy receptors" for VEGF. sflt1 plays a key role in maintaining avascularity of the cornea, and increased circulating levels of sflt1 are linked to preeclampsia. Moreover, deletion of flt1 from mouse podocytes results in proteinuria at 6 weeks of age, while deletion of the kinase signaling domain of this receptor alone results in no renal phenotype. *In vitro* studies showed that sflt1 can induce formation of foot process-like structures in human podocytes. We hypothesize that sflt1 regulates podocyte cytoskeletal dynamics and glomerular barrier function by titrating local glomerular Vegf levels.

Methods: To determine function of the soluble variant of Flt1 in the glomerulus, we generated a conditional KO model for the single sFlt1 (sFlt1 cKO) isoform reported in mice (removal of intron 13). Renal phenotype was examined by evaluating kidney function and histology. qPCR and Northern blot were used to identify splice variants of flt1; 3'RACE was used to clone the spliced genes. Proteins of splice variants were generated by BacMam system.

Results: We generated sflt1 cKO mice, and confirmed the deletion of Flt1 intron 13 using Southern blot. Surprisingly, it did not result in any overt kidney phenotype by 6 months of age. Northern blot and Western blot analyses revealed the existence of a major compensatory isoform, previously reported as human-specific. We also confirmed the existence of 17 new sFlt1 isoforms in RNA isolated from mice and 12 from human preeclamptic placentas.

Conclusions: We report a large number of novel, soluble flt1 isoforms in both mouse and human placenta samples. We posit that the presence of these isoforms compensates for the loss of sflt1 in our transgenic model. The functions of these isoforms warrant further investigation and may provide insight into regulation of Vegf levels, podocyte function and preeclampsia.

Funding: Government Support - Non-U.S.

FR-PO351

Polarity Signaling at the Kidney Filtration Barrier: Questioning the Function of Par3A Sybille Köhler,^{1,2} Markus M. Rinschen,^{1,2} Carlen M. Niessen,⁴ Wilhelm Bloch,³ Bernhard Schermer,^{1,2} Thomas Benzing,^{1,2} Paul T. Brinkkoetter.^{1,2} ¹Dept II of Internal Medicine and Center for Molecular Medicine, Univ Hospital Cologne, Germany; ²Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Germany; ³Dept of Molecular and Cellular Sport Medicine, German Sport Univ Cologne, Germany; ⁴Dept of Dermatology and CECAD Cologne, Univ of Cologne, Germany.

Background: The slit diaphragm (SD) represents the only cell-cell contact in-between neighbouring podocytes. Classical adherence as well as tight junction proteins are part of this protein-protein supercomplex including ZO-1, occludin, catenins and cadherins. Polarity signaling is critical to maintain the SD complex as the Par3/Par6/aPKC complex clusters at the SD via direct interaction of Par3 with neph/nephrin via its PDZ-domains.

Methods: To understand the role of the Par3 proteins at the slit diaphragm, we generated a novel podocyte specific Par3A knockout mouse model where exon 6 is flanked by loxP sites. Following podocin:cre mediated recombination expression of all known Par3A isoforms should be abrogated. We validated cre recombination efficiency, lack of Par3A mRNA and protein expression by qPCR from isolated primary podocytes as well as by immunofluorescence stainings on renal sections.

Results: Mice were born in predicted Mendelian frequency. Par3A^{flx/flx} mutants appeared as healthy as wt Par3A^{flx/flx} mice at birth and did not show any signs of disease in their later life. Even challenging Par3A^{flx/flx} mice with the albumin overload model did not result in an overt glomerular phenotype. Therefore, we performed additional immunoprecipitation experiments for aPKC α out of immortalized mouse podocytes and carried out nLC-MS/MS analysis to identify the aPKC α podocyte interactome. Interestingly, the most abundant aPKC α interacting proteins were Par6 and Lgl1/2.

Conclusions: Our results challenge the current view of the aPKC/Par3/Par6 complex and its role at the slit diaphragm. In contrast to tight junctions where aPKC-signaling depends on clustering by Par3A, its role at the SD is independent of Par3A. Here Lgl1/2 seem to be the predominant interactors clustering aPKC/Par6 at the SD.

Funding: Government Support - Non-U.S.

FR-PO352

Focal Segmental Glomerulosclerosis (FSGS) Permeability Factor (FSPF) Interacts with Glomerular Filtration Barrier Through Glycoconjugates Ram Sharma,¹ Ellen T. McCarthy,² Tarak Srivastava,³ Virginia J. Savin,¹ Mukut Sharma.¹ ¹Renal Research, KC VA Medical Center- MBRF, Kansas City, MO; ²Kidney Inst, KU Medical Center, Kansas City, KS; ³Renal Div, UMKC Children's Mercy Hospital, Kansas City, MO.

Background: Galactose (Gal) blocks the FSGS serum-induced increase in *in vitro* glomerular albumin permeability (P_{alb}) (*Trans Res* 2008, 151:288-292) and decreases proteinuria in some patients with recurrent FSGS (*NDT* 2009, 24:2938-2940). Thus, the interaction of FSPF with glomerular cell surface glycoconjugates may play an essential role in its effect on the filtration barrier.

Methods: We selected sugars and lectins to model the interaction between glomerular glycoconjugates and FSPF. We used, (i) affinity techniques to evaluate the binding of FSPF with immobilized sugars (ii) immobilized neuraminidase to remove sialic acid to assess its significance in FSPF-induced increase in P_{alb} and (iii) Gal/N-acetyl Gal (GalNac)-specific lectins to determine their effect on P_{alb} as FSPF mimetics.

Results: Plasma FSPF activity was retained by immobilized Gal, GalNac or galactosamine. Gal dose-dependently blocked FSPF-induced increase in P_{alb} (10^{-9} - 10^{-6} M) and partially reversed the effect of FSPF on P_{alb} ($p < 0.01$). In contrast, glucose, glucosamine or mannose did not interact with FSPF. Removal of sialic acid by neuraminidase diminished the FSPF-induced increase in P_{alb} . We screened twenty Gal/GalNac-specific lectins as potential mimetics of FSPF. Only *Dolichos biflorus* agglutinin (DBA, 10 mg/mL) and *Helix pomatia* lectin (10 mg/mL) increased P_{alb} to 0.65 and 0.55, respectively ($p < 0.001$). The increases in P_{alb} , like that induced by FSPF were blocked by Gal (100 μ M) ($p < 0.001$).

Conclusions: One or more carbohydrate-recognizing domains of FSPF participate in its interaction with specific sugar(s) of glomerular cells resulting in altered filtration barrier function. Our novel findings regarding the affinity of FSPF for select sugars, the loss of activity after removal of sialic acid and the direct effect of certain lectins on barrier function provide new information regarding the molecular composition of FSPF and its interaction with glomerular proteins/glycolipids.

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FR-PO353

EPB4115 Is a Critical Regulator of the Kidney Filtration Barrier Christoph Schell,¹ Martina Suhm,¹ Manuel Rogg,¹ Martin Helmstaedter,¹ Mariko Hirano-Kobayashi,² Tobias B. Huber.¹ ¹Dept of Nephrology, Univ Medical Center Freiburg, Freiburg, Baden-Württemberg, Germany; ²Laboratory for Vertebrate Body Plan, Center for Developmental Biology - RIKEN, Kobe, Japan.

Background: Podocyte loss represents the final common pathway of various glomerular pathologies. Hence, tightly regulated adhesion towards the glomerular basement membrane is a fundamental biological process of glomerular podocytes.

Methods: Based on podocyte single cell isolation and a mass-spec candidate approach the composition of podocyte focal adhesions was resolved. Combining a drosophila nephrocyte model with a newly generated conditional mouse model and various high resolution microscopy techniques (TEM, STORM) the candidate protein EPB4115 was analyzed.

Results: Knockdown of the Epb4115 homolog Yurt in drosophila nephrocytes resulted in mis-localization of slit membranes and defective endocytic capacity. Evaluation of a conditional knockout model revealed a rapid loss of podocytes implicating deregulated adhesion of podocytes. Employing immunogold electron microscopy and STORM super resolution microscopy EPB4115 was clearly localized towards the basal compartment of podocytes, in close proximity to INTEGRIN-beta1. Further functional experiments revealed that loss of EPB4115 resulted in decreased activation of INTEGRIN-beta 1, reflected by altered migratory behavior of primary podocytes.

Conclusions: Our findings indicate that EPB4115 is a highly conserved, specific regulator of podocyte adhesion by modulating focal adhesion composition and function. Future studies will need to clarify its potential implications in genetic and acquired glomerular pathologies.

FR-PO354

The Effect of Anti-PLA2R Autoantibodies on Human Podocytes In Vitro Maryline Fresquet,¹ Rachel Lennon,¹ Paul E. Brenchley,² ¹Wellcome Trust Centre for Cell-Matrix Research, Univ of Manchester, Manchester, United Kingdom; ²Inst of Cardiovascular Sciences, Manchester Royal Infirmary, Manchester, United Kingdom.

Background: PLA₂R was identified as a major target antigen in idiopathic membranous nephropathy. 70% of patients have circulating autoantibodies which bind this receptor on the podocyte leading to immune complex deposition in the glomerular basement membrane. We recently identified the major epitope on PLA₂R recognised by anti-PLA₂R autoantibodies, produced the first 3D model of PLA₂R domains and demonstrated that autoantibodies are of high affinity. We seek to understand if affinity-pure anti-PLA₂R alone in the absence of complement can modulate podocyte function.

Methods: We prepared affinity purified human anti-PLA₂R (91% IgG4, 9% IgG2) and assessed podocyte morphology following autoantibody treatment using immunofluorescence staining of actin and measurement of cell surface area and circularity. Integrity of the filtration barrier was assessed by Electric Cell-substrate Impedance Sensing and the

response of a confluent monolayer of differentiated podocytes to 10mg/ml purified human anti-PLA₂R and purified human IgG was measured. Cell apoptosis was determined by cleaved caspase-3 staining in podocytes and oxidative stress was measured with CellROX reagent in differentiated podocytes challenged with the autoantibody.

Results: We have developed an *in vitro* podocyte model to define mechanisms of anti-PLA₂R effects on cell morphology and function. Purified anti-PLA₂R altered podocyte shape, with rounding and loss of actin stress fibres within 24 hours. Integrity of a confluent podocyte monolayer was significantly reduced at 72 hours by anti-PLA₂R but not by the IgG control. Within 30 minutes of anti-PLA₂R treatment, there was evidence of caspase-3 cleavage in podocytes peaking at 6 hours promoting apoptosis. In the same time frame anti-PLA₂R induced free radical generation ($P < 0.0001$, treated v. untreated), triggering oxidative stress which could be neutralised using a scavenger.

Conclusions: Anti-PLA₂R in the absence of complement activation modulates podocyte cell biology by inducing changes in cell shape and monolayer permeability, activation of free radical production and apoptosis.

Funding: Private Foundation Support

FR-PO355

Deletion of the Ste20-Like Kinase, SLK, in Podocytes Induces Injury Andrew V. Cybulsky,¹ Elena Torban,¹ Joan Papillon,¹ Julie Guillemette,¹ Natalya Belkina.² ¹Medicine, McGill Univ, Montreal, QC, Canada; ²NIH, Bethesda, MD.

Background: SLK is essential for embryonic development, and may play a key role in wound healing, tumor growth and metastasis. Expression and activation of SLK is increased during recovery from ischemic acute kidney injury. Overexpression of SLK in glomerular epithelial cells/podocytes *in vivo* induces injury and proteinuria. Conversely, insufficient SLK expression leads to abnormalities in cell adhesion, spreading, and motility. Tight regulation of SLK expression thus appears to be critical for normal renal structure and function. We address the functional role of SLK in podocytes.

Methods: Podocyte-specific SLK knockout (KO) mice were produced by breeding mice with loxP sites surrounding exons 4-7 with podocin (NPHS2)-Cre mice. LoxP-mediated excision results in deletion of the kinase domain. Deletion of SLK exons 4-7 in glomeruli was confirmed with PCR.

Results: Podocyte-specific deletion of SLK resulted in albuminuria at 4-5 months of age in male mice, and 8-9 months in female mice, which persisted for up to 13 months (albumin/creatinine in KO was 2-3-fold above control). At 11-12 months, KO mice did not show renal histologic abnormalities by light microscopy, and glomerular area of KO was comparable to control. However, by electron microscopy, KO mice showed focal foot process effacement and microvillous transformation of podocyte plasma membranes. Mean foot process width was ~2-fold greater in KO, compared to control. By immunofluorescence microscopy, WT1-positive cells were reduced by 35% in KO mice compared to control, and staining for nephrin and podocalyxin was reduced in KO mice by 20-30%. SLK is reported to phosphorylate ezrin. Staining for phospho-ezrin/radixin/moesin (ERM) was reduced by 20% in KO glomeruli, in keeping with reduced SLK catalytic activity in glomeruli; however, tubular phospho-ERM staining was comparable in KO and control.

Conclusions: Podocyte-specific deletion of SLK leads to albuminuria, loss of podocytes and morphologic evidence of podocyte injury. Thus, SLK is essential to the maintenance of podocyte integrity as mice age. The mechanism may, at least in part, relate to ezrin phosphorylation and cytoskeletal integrity.

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FR-PO356

A Podocyte-Specific Knockout of the DNA Repair Gene Ercc1 Leads to Proteinuria and Focal Segmental Glomerulosclerosis Fabian Braun,¹ Roman Aaron Akbar,¹ Björn Schumacher,² Wilhelm Bloch,³ Bernhard Schermer,^{1,2} Thomas Benzing,^{1,2} Christine E. Kurschat.^{1,2} ¹Nephrology, Univ Hospital Cologne, Cologne, Germany; ²CECAD, Univ Hospital Cologne, Cologne, Germany; ³German Sport Univ Cologne, Cologne, Germany.

Background: The prevention and therapy of aging-related diseases will become a major health problem. Among elderly patients mild to severe impairment of kidney function is common. Models to study renal aging have not been established yet. In a previous study, we identified a progeria mouse model of Ercc1-deficiency to exhibit expression profiles similar to those of glomerular aging in wt mice. Ercc1 is involved in nucleotide excision repair, facilitating 5' incision around bulky DNA lesions. In humans, the lack of Ercc1 leads to a progeria phenotype. Thus, a podocyte-specific knockout of Ercc1 may help us gain new insights into glomerular and podocyte aging processes.

Methods: Ercc1^{flx/flx} mice were bred in a mixed CD1/FVB background with CD1 mice expressing Cre recombinase under the podocin promoter. We analyzed weight, urine and serum of animals at 7, 9, 11 and 13 weeks of age. Kidneys were fresh-frozen in OCT, fixed in paraformaldehyde and embedded in paraffin or prepared for electron microscopy.

Results: Ercc1^{flx/flx} mice are born in normal mendelian ratios and show no developmental abnormalities. We detected an onset of proteinuria at week 8 to 10. Animals maintain a normal weight curve compared to controls until week 11 to 18. 7 week old kidneys show no morphological changes in light or electron microscopy. Male and female mice develop foot process effacement and focal segmental glomerular sclerosis at 9 weeks of age. This phenotype is aggravated by week 11. PAS staining of end-stage kidneys reveals sclerosed glomeruli, interstitial fibrosis with tubular atrophy and tubular protein casts. We observed an increase in DNA damage shown by positive pH2A.X staining in glomerular nuclei at week 11.

Conclusions: Our study reveals a critical role for nucleotide excision repair in murine podocytes. This severe and early phenotype underlines the importance of podocyte DNA maintenance in these postmitotic cells. In ongoing studies we will characterize the role of Ercc1 in a podocyte cell culture model.

Funding: Government Support - Non-U.S.

FR-PO357

Mice Heterozygous for Rac1 in the Podocyte Are Protected against Nephrotic Serum Nephritis-induced Albuminuria, but Knockout Mice Are Not Stephanie Wylie,¹ Jinghui Luo,¹ Yingbao Yang,¹ David J. Salant,² Jeffrey B. Hodgins,¹ ¹Pathology, Univ of Michigan, Ann Arbor, MI; ²Renal Section, Boston Univ Medical Center, Boston, MA.

Background: Podocyte injury, either by genetic or acquired abnormalities, can lead to progressive proteinuria and glomerulosclerosis. Current treatments are not designed to specifically target the podocyte but are used for broader immunotherapeutic or anti-inflammatory properties, thus podocyte-targeted therapies are needed. Rac1, a member of the Rho GTPase family, has been suggested as a therapeutic target for podocyte injury. However we previously demonstrated that podocyte-specific Rac1 knockout mice have exacerbated albuminuria with a hypertensive injury model. We hypothesize that partial reduction of podocyte Rac1 is protective.

Methods: We employed the nephrotoxic serum (NTS) nephritis model, which causes predominant podocyte injury and high-grade proteinuria without appreciable inflammation, in wild-type (WT), podRac1-KO (podRac1-KO), and podocyte-specific Rac1 heterozygous mice (podRac1-HET). A separate group of NTS treated WT mice were given EHT1864 (40mg/kg), a Rac inhibitor. Mice were injected with NTS (1.5 mg/kg body weight) (n=8-10 mice per group) and placed in metabolic cages for 1 or 2 days for daily urine collection. Urine albumin was measured by SDS-PAGE gel with standard curve, normalized by urine creatinine.

Results: NTS treatment resulted in robust albuminuria in wild-type mice on days 1 and 2 with albumin-to-creatinine ratios (ACR) of 400-500 ug/mg. However, podRac1-KO mice showed an equally robust albuminuric response on day 1, but less on day 2 compared to wild-type, suggesting accelerated recovery. In contrast, NTS treated podRac1-HET mice demonstrated nearly 70% reduction in ACR compared to wild-type (130 versus 390 ug/mg, P<0.01). The Rac inhibitor EHT1864 was equally effective.

Conclusions: These results demonstrate that a partial reduction in Rac1 activity, through genetic or pharmacologic inhibition, provides a protective effect against NTS-mediated podocyte injury, whereas Rac1 deletion is not beneficial. Our findings should help guide the development and assessment of Rac1 inhibitors to target podocyte injury.

Funding: NIDDK Support, Private Foundation Support

FR-PO358

The Ectodomain of Syndecan-4 Increases Surface Expression of Podocyte TRPC6 Channels: An Essential Role for Integrin Signaling Eunyoung Kim, Hila Roshanravan, Stuart E. Dryer. *Biology and Biochemistry, Univ of Houston, Houston, TX.*

Background: Excessive activation of podocyte TRPC6 channels has been implicated in glomerular diseases. Syndecan-4 (Sdc-4) is a type-1 single-pass proteoglycan that can be cleaved to produce a soluble product capable of paracrine and autocrine signaling. A previous study (1) showed that the Sdc-4 core protein increases the surface expression of TRPC6 in podocytes. Here we show that the Sdc-4 ectodomain can also modulate TRPC6 channels and we describe some of the pathways that surround this effect.

Methods: Cell surface expression of TRPC6 was monitored using surface biotinylation assays and whole-cell patch clamp recordings from cultured mouse podocytes. Signaling pathways were examined using assays for activated components and selective inhibitors. Protein interactions were examined by co-immunoprecipitation and confocal microscopy.

Results: We have confirmed previous studies showing effects of over-expression and knockdown of Sdc-4 core protein on podocyte TRPC6 (1). In addition, exposing podocytes to Sdc-4 ectodomain caused an increase in the surface abundance of TRPC6, accompanied by an increase in cationic currents evoked by diacylglycerol (OAG). Sdc-4 ectodomain increased the generation of reactive oxygen species (ROS) and effects of Sdc-4 on TRPC6 were blocked by the ROS quencher TEMPOL. Exposure to Sdc-4 ectodomain caused activation of NFATc1 and Rac1, inhibition of RhoA, and increased the total abundance of b3-integrin. However, Sdc-4 ectodomain effects on surface expression of TRPC6 persisted after inhibition of calcineurin or NFAT. The Sdc-4 core protein immunoprecipitated and co-localized with b3-integrin in podocytes. Moreover, effects of Sdc-4 ectodomain were inhibited by cilengitide, an inhibitor of outside-in signaling through av-containing integrins. Exposure to TNF caused a marked increase in shedding of Sdc-4 ectodomain from podocytes into the surrounding medium. This also occurred after over-expression of Sdc-4 core protein.

Conclusions: Locally produced Sdc-4 ectodomain may play a role in regulating podocyte TRPC6 channels and may contribute to glomerular pathology. (1) Liu et al. (2012). *Atheroscler Thromb Vasc Biol* 32: 378-385.

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FR-PO359

Regulation of Fascin-1 by Mechanical Stress in Podocytes Felix Kliewe,¹ Christian Scharf,² Sandra Schordan,¹ Elisabeth Rumpel,¹ Katrin Darm,² Silke Vogelgesang,³ Kerstin U. Amann,⁴ Henny Wegner,¹ Jürgen Giebel,¹ Karlhans Endlich,¹ Nicole Endlich.¹ ¹Anatomy and Cell Biology, Univ Medicine of Greifswald, Greifswald, Germany; ²ENT, Univ Medicine of Greifswald, Germany; ³Pathology, Univ Medicine of Greifswald, Germany; ⁴Nephropathology, Univ Hospital of Erlangen, Germany.

Background: Glomerular hypertension causes glomerulosclerosis via the loss of podocytes, which are challenged by an increased mechanical load. We and others have demonstrated that podocytes are mechanosensitive cells. However, the response of podocytes to stretch remains incompletely understood.

Methods: Using 2D fluorescence difference gel electrophoresis (2D DIGE), we analyzed the proteome of cells of our mouse podocyte cell line that were cultured on flexible membranes with or without cyclic biaxial mechanical stress (0.5 Hz, 5% linear strain, 3 d).

Results: Mechanical stress profoundly altered the podocyte proteome. Several spots containing the actin-bundling protein fascin-1 were differentially regulated by mechanical stress. By immunofluorescence, fascin-1 was found to colocalize with nephrin in mouse kidney sections. The presence of fascin-1 in foot processes was confirmed by immunoelectron microscopy. Knockdown of fascin-1 in cultured podocytes increased the cell loss in response to mechanical stress. The mRNA levels of fascin-1 were not affected by mechanical stress. However, mechanical stress resulted in an almost complete dephosphorylation of fascin-1. It is known that phosphorylation at Ser-39 regulates the bundling activity of fascin-1, e.g. required for filopodia formation. Podocytes expressing wild type GFP-fascin-1 and non-phosphorylatable GFP-fascin-1-S39A showed marked filopodia formation, being absent in podocytes expressing phosphomimetic GFP-fascin-1-S39D. Finally, the immunofluorescence signal of phosphorylated fascin-1 was strongly reduced in glomeruli of patients with diabetic nephropathy as compared to glomeruli of healthy controls.

Conclusions: In summary, mechanical stress dephosphorylates fascin-1 in podocytes thereby increasing the actin-bundling activity of fascin-1. Fascin-1 may play an important role in the adaptation of podocytes to mechanical stress.

Funding: Government Support - Non-U.S.

FR-PO360

Deletion of the Vps34 Downstream Effector PIKfyve Establishes Milder Endocytic Dysfunction in Healthy Glomerular Podocytes Compared to Proximal Tubular Cells Madhusudan Venkatareddy, Rakesh Verma, Sanjeevkumar R. Patel, Puneet Garg. *Internal Medicine/ Nephrology, Univ of Michigan, Ann Arbor, MI.*

Background: The mechanisms by which the glomerular filtration barrier prevents the loss of large macromolecules and at the same time maintain the filter remain poorly understood. Recent studies have proposed that podocytes play an active role in both endocytosis of filtered macromolecules and maintaining the filtration barrier.

Methods: We generated podocyte and proximal tubular specific deletion of PIKfyve using the cre-loxP system. Indirect IF and immune EM was used to assess the endocytic pathways.

Results: Deletion of a key endosomal trafficking regulator, the class III phosphoinositol 3-kinase or Vps34 in podocytes results in aberrant endosomal membrane morphology and podocyte dysfunction. We recently demonstrated that the vacuolation phenotype in cultured Vps34-deleted podocytes is due to the absence of a substrate for the Vps34 downstream effector PIKfyve. PIKfyve is a Fyve finger domain containing phosphoinositide 5-kinase that phosphorylates Vps34-generated phosphatidylinositol (PtdIns)3P to produce PtdIns(3,5)P2. PIKfyve perturbation and PtdIns(3,5)P2 reduction have been shown to result in massive membrane vacuolation along the endosomal system. We show here that deletion of PIKfyve in endocytically active proximal tubular cells resulted in the development of large cytoplasmic vacuoles that appear as a result of arrested endocytic traffic progression at a late-endosome stage. In contrast, deletion of PIKfyve in podocytes did not alter significantly the endosomal morphology even in aged, 18-month-old mice. However upon culturing, the PIKfyve-deleted podocytes obtained from the knockout mouse developed massive cytoplasmic vacuoles. Measurement of phosphoinositides using HPLC shows reduction of both PtdIns(3,5)P2 and PtdIns(5)P in PIKfyve deleted podocytes *in vitro* confirming reduced PIKfyve enzymatic activity following deletion. Using double fluorescent mtmG mouse we were able to confirm Cre-mediated gene deletion in both podocytes and proximal tubular cells *in vivo*.

Conclusions: In summary, these data suggest that healthy podocytes have a low level of endocytic flux *in vivo*.

Funding: NIDDK Support

FR-PO361

Albumin-Induced Podocyte Injury Can Be Endocytosis-Independent Shipra Agrawal,¹ Xiaojing Nie,¹ Tetsuya Kitao,¹ Melinda A. Chanley,¹ William E. Smoyer.^{1,2} ¹Clinical and Translational Research, Research Inst at Nationwide Childrens Hospital, Columbus, OH; ²Pediatrics, Ohio State Univ, Columbus, OH.

Background: Endocytosis plays a crucial role in podocytes in nephrotic syndrome, wherein podocytes are exposed to serum levels of albumin. We have previously reported an association between podocyte exposure to albumin (and its associated factors) and proteinuria, cell injury and induction of pro-inflammatory genes. We thus hypothesized that albumin-induced podocyte injury can also be partially endocytosis independent.

Methods: Endocytosis was analyzed by fluorescence microscopy and fluorometry in cultured differentiated podocytes at varying temperatures and times and in the absence and presence of inhibitors of clathrin- and caveolae-mediated endocytosis. Cells were analyzed for viability, activation of major kinases (p38, ERK1/2, JNK, MK2), and expression of pro-inflammatory, heat shock, and glucocorticoid-regulated genes.

Results: Endocytosis was detected in podocytes at 37°C, but not at 4°C, and was attenuated by inhibitors for both clathrin- and caveolae-mediated endocytosis. Inhibition of endocytosis, however, did not correlate with reductions in kinase activation or pro-inflammatory gene induction. While albumin exposure resulted in lower endocytosis in murine vs. human podocytes, murine cells activated kinases, induced pro-inflammatory genes and exhibited cell death more than human podocytes.

Conclusions: Inhibition of both clathrin- and caveolae-mediated albumin endocytosis did not correlate with activation of kinases and induction of pro-inflammatory genes in podocytes. Moreover, disparate responses were identified in human vs. mouse podocytes with regard to albumin endocytosis, cell injury, kinase activation, and pro-inflammatory gene induction. Taken together, our data suggest that although podocytes endocytose albumin in both clathrin- and caveolae-mediated manners, albumin-induced podocyte injury can occur in an endocytosis-independent manner.

Funding: NIDDK Support

FR-PO362

Genome-Modified Pluripotent Stem Cells Reveal a Critical Role for Podocalyxin in Human Podocyte Morphogenesis Benjamin S. Freedman,^{1,2,3} Craig R. Brooks,^{1,2} Jing Zhou,^{1,2} Joseph V. Bonventre.^{1,2} ¹Brigham and Women's Hospital; ²Harvard Medical School; ³Univ of Washington School of Medicine.

Background: Human pluripotent stem cells (hPSCs) can self-renew extensively and differentiate into diverse tissues. We investigated the potential of hPSCs to differentiate into kidney podocytes, and used CRISPR/Cas9 gene editing to explore the function of podocalyxin, an apical sialomucin altered in glomerular disease states.

Methods: Cas9 nuclease and guide RNAs targeting *PODXL* were transfected into hPSCs. *PODXL*^{-/-} clones were identified by chromatogram and immunoblot analysis. hPSCs were differentiated stepwise with growth factors into kidney progenitor cells (SIX2⁺PAX2⁺) and subsequently kidney tubular organoids. Podocyte marker expression was investigated by confocal microscopy in unmodified or *PODXL*^{-/-} organoids of otherwise identical genetic background.

Results: In kidney organoids, podocyte markers including podocalyxin, WT1, and synaptopodin were strongly expressed in tight clusters of spherical cells, which resembled capillary loop stage podocytes by electron microscopy. These cells did not react with LTL, but arose in capsule-like termini in LTL⁻LRP⁺ proximal tubules. Podocalyxin coated the plasma membrane, whereas ZO-1, synaptopodin, and β -catenin co-localized in linear tracks between adjacent cells. *PODXL*^{-/-} hPSCs differentiated into similar clusters, which did not express podocalyxin. In *PODXL*^{-/-} clusters, ZO-1, synaptopodin, and β -catenin failed to organize into linear tracks, instead migrating laterally in a diffuse expression pattern. This correlated with a ~40% decrease in intercellular distance between nuclei, compared to unmodified isogenic controls.

Conclusions: hPSCs can differentiate into cells resembling immature podocytes. Podocalyxin is dispensable for podocyte specification, but is required for proper organization of junctional complexes and podocyte spacing. Our findings suggest a functional role for podocalyxin in the establishment of human podocyte architecture. Genome-modified hPSC-podocytes present a new tool for investigating human podocytes, with potential for 'disease in a dish' models and therapeutic screens.

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FR-PO363

Molecular Targeting of Neph1 Signaling: A Therapeutic Approach to Protect Podocyte Injury Deepak Nihalani,¹ Ehtesham Arif,³ Fnu Ashish,² Lawrence B. Holzman.¹ ¹Medicine, Univ of Pennsylvania, Philadelphia, PA; ²Proteomics, Inst of Microbial Technology, Chandigarh, India; ³Medicine, Temple Univ, Philadelphia, PA.

Background: Glomerular injuries that induce podocyte dysfunction are the leading causes of renal malfunction. Podocyte proteins Neph1 and Neph1 are essential components of the glomerular filtration barrier and signaling from these proteins is involved in maintaining podocytes structure and function. Thus understanding the mechanisms that regulate signaling and organization of these proteins are therapeutically valuable.

Methods: This study presents a novel hypothesis that attenuating Neph1 and Neph1 signaling is therapeutically significant in protecting podocytes from injury. Consistent with this hypothesis, using a unique protein transduction approach, we recently demonstrated

that inhibiting Neph1 signaling protected podocytes from injury. Since we first reported the solution structures of Neph1CD and ZO-1-PDZ1, we used them to identify novel molecules or compounds that can specifically bind Neph1 and target its interactions.

Results: Using a novel approach of targeting protein-protein interaction, we identified many potential molecules and to test the proof of principle and the validity of this approach, one of the compounds ID (isodesmosine) was commercially procured and investigated. Biochemical experiments suggested that addition of ID under *in vitro* and *in vivo* conditions significantly increased and stabilized the interaction between Neph1 and ZO-1. As a consequence, induction of glomerular injury by PAN (puromycinaminonucleoside) did not alter the distribution of Neph1 at the podocyte cell membrane; in addition, these cells resisted injury induced changes in their actin cytoskeleton. Furthermore, using an *in vivo* zebrafish model system, we demonstrated that pre-treatment with ID rescued zebrafish from adriamycin induced toxicity and preserved their renal filtration system.

Conclusions: Collectively, this is the first study that provides compelling initial evidence that molecular approaches can be used to directly target slit diaphragm proteins to prevent podocyte damage.

Funding: NIDDK Support

FR-PO364

Extracorporeal Mesenchymal Stromal Cell Therapy for Critical Care Biju Parekkadan. *Surgery (Bioengineering), Harvard Medical School, Massachusetts General Hospital, Boston, MA.*

Background: Human mesenchymal stromal cells (MSCs) metabolize and secrete anti-inflammatory and regenerative factors that can be of systemic benefit to acute, critical injury. When transplanted MSCs are limited in dose and rapidly cleared by the body, therefore prohibiting controlled exposure to this cell therapy. We have developed a bioreactor technology to maintain MSC viability at high fidelity and continuously deliver secreted factors into the blood stream in a clinical setting.

Methods: MSCs were integrated into hollow-fiber bioreactor devices whereby the cells, separated by a permeable membrane, can directly and dynamically provide systemic therapy without entering the body. We present a human scale prototype of the technology that has shown sustained cell viability and function throughout cGMP manufacturing in preparation for a Phase I human trial set to begin in 2015.

Results: The presentation will also report encouraging *in vivo* therapeutic trials in a large animal (canine) model of ischemic acute kidney injury (AKI) where 91% of animals survived compared to 50-60% in control arms. Pharmacological analysis of this bioreactor technology *in vivo* allowed for an unprecedented look at MSC function during product use and verified potency that is unattainable by conventional intravascular delivery of MSCs.

Conclusions: A combined approach to optimize MSC therapy that employs pharmacology principles and cell delivery strategies will be essential to translating this cell therapy product to humans for AKI and other critical organ dysfunction syndromes.

Funding: NIDDK Support, Pharmaceutical Company Support - Sentient Biotechnologies, Inc.

FR-PO365

Extracorporeal Diffusive Clearance of Silicon Nanopore Membranes in a Pumpless Porcine Blood Circuit Steven Kim,¹ Willieford Moses,² Jaehyun Park,³ Clarence Chow,³ Charles Blaha,^{3,4} Zohora Iqbal,³ Rishi Kant,³ Benjamin Chui,⁵ Ken Goldman,⁶ William Henry Fissell,^{7,4} Shuvo Roy.^{3,4} ¹Nephrology, UCSF; ²Surgery, UCSF; ³Bioengineering, UCSF; ⁴Silicon Kidney, LLC; ⁵Ben Chui Consulting; ⁶H-Cubed; ⁷Nephrology & Hypertension, Vanderbilt Univ.

Background: Silicon nanopore membranes designed for hemofiltration (HF-SNM) have demonstrated increased permeability compared to polymer membranes. Previously, we reported *in-vitro* data showing a 3-fold improvement in diffusive clearance using SNM optimized for diffusion (HD-SNM). Here we test the diffusive clearance of HD-SNM vs HF-SNM in an extracorporeal porcine model without a blood pump.

Methods: A microelectromechanical systems fabrication technique was used to decrease the SNM thickness (HD-SNM 100 μ m vs HF-SNM 400 μ m). Polyethylene glycol coated HD-SNM (n=3) and HF-SNM (n=3) with sub-10nm pore sizes were tested in a single channel flow circuit (h=1mm). Vascular access was obtained by placing tunneled catheters within the carotid artery and jugular vein of healthy ~50kg pigs. Blood flow was achieved via the arterial-venous pressure differential (35-120ml/min). Dialysate was recirculated in a counter-current fashion (30ml) and flow rates were adjusted to ensure 0 transmembrane pressure. Dialysate creatinine concentration was measured hourly and serum creatinine was measured at time 0 and 6 hours. The pore size of each SNM was measured before and after blood exposure using hydraulic permeability.

Results: Blood flow was achieved using only the arterial-venous pressures differential with <5mmHg pressure drop. The average plasma creatinine concentration was 1.38 \pm 0.1mg/dL. The creatinine clearance was 37.2 \pm 3.9ml/min/m² (HF-SNM) vs 126.0 \pm 27.1ml/min/m² (HD-SNM) at 92.5 \pm 36.6ml/min. There was no detectable albumin transport into the dialysate. The HD-SNM maintained mechanical integrity at over 250mmHg *in-vitro*. The pore size change following blood exposure was 1.4 \pm 2.3nm vs 1.9 \pm 1.2nm for HF-SNM and HD-SNM, respectively.

Conclusions: This study demonstrates the successful transport of creatinine in an extracorporeal circuit without a blood pump. We also showed a ~3-fold improvement in diffusive clearance of creatinine using HD-SNM in a blood circuit.

Funding: NIDDK Support, Private Foundation Support

FR-PO366

Hemofilter Design Based on Computational Simulations of Pulsatile Flow Amanda Buck,¹ Joseph J. Groszek,² Clark David Kensing,³ Daniel Colvin,¹ Shuvo Roy,⁴ William Henry Fissell.² ¹Dept of Radiology and Radiological Sciences, Vanderbilt Univ; ²Div of Nephrology and Hypertension, Vanderbilt Univ; ³Dept of Surgery, Vanderbilt Univ; ⁴Dept of Bioengineering and Therapeutic Sciences, Univ of California San Francisco.

Background: In the US, the ratio of patients with end stage renal disease (ESRD) on dialysis to annual kidney transplants for ESRD is 20:1 (USRDS 2014 Annual Data Report), underscoring the grave need for an artificial kidney alternative. Hypothesis: For the development of a hemofiltration device, computational fluid dynamics (CFD) simulations can predict potentially thrombogenic zones [e.g. low and high wall shear stress (WSS) areas, associated with stasis and shear induced cell damage, respectively] and can be used to refine device design to minimize such areas.

Methods: CFD simulations of pulsatile blood flow through a prototype hemofilter were validated *in vitro* using MR velocimetry. Hemofilters were implanted in large animals (n=4) for 30 days or until thrombosis and then explanted. Based on the CFD results, a subsequent flow path was devised to minimize predicted thrombogenic regions, and simulations were conducted on the second design.

Results: The *in vitro* and *in silico* models showed strong agreement. Pulsatile CFD simulations of the prototype device demonstrated zones of low WSS, and clot formation occurred in two of the four implants at the CFD-predicted sites. Flow simulations of the second-generation design showed reduced areas of low WSS.

Conclusions: Thrombogenic low WSS regions predicted *in silico* correspond with clot formation *in vivo*. In addition to predicting areas of thrombogenicity, CFD can be used to guide hemofilter device design to minimize these sites.

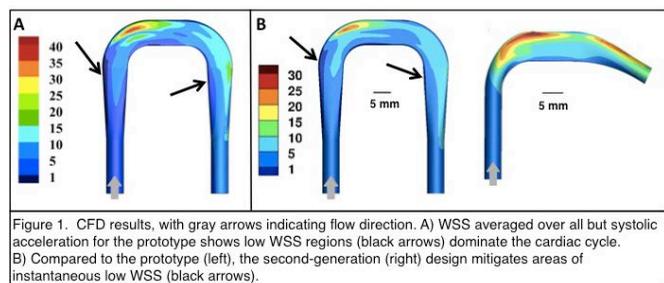


Figure 1. CFD results, with gray arrows indicating flow direction. A) WSS averaged over all but systolic acceleration for the prototype shows low WSS regions (black arrows) dominate the cardiac cycle. B) Compared to the prototype (left), the second-generation (right) design mitigates areas of instantaneous low WSS (black arrows).

Funding: NIDDK Support, Private Foundation Support

FR-PO367

Characterization of Dialyzer Membranes by MALDI-Mass-Spectrometric Imaging Techniques Joachim Jankowski, Vera Jankowski. *Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, Germany.*

Background: Dialyzer polymer membranes are grossly classified as cellulose-based and synthetically produced membranes. Although cellulose membrane's clearance and mechanical properties qualify it for use in dialyzer membranes, hydroxyl groups of these membranes lead to strong activation of the complement system. Therefore, recent membranes are manufactured from synthetic polymers.

Methods: For physical and chemical characterization of these materials of dialyzer a wide range of analytical methods is available. Over the last few years, MALDI mass-spectrometry has been developed as a powerful tool for space-resolved analysis, not least because of its mass accuracy and high sensitivity. MALDI imaging techniques combine the potential of mass-spectrometric analysis with imaging as additional spatial information with relevance for biocompatibility of the dialyzer membranes. MALDI imaging enables the visualization of localization and distribution of biomolecules, chemical compounds and other molecules on different surfaces.

Results: In this study, surfaces of polymeric dialyzer membranes, consisting of polysulfone (PS) and polyvinylpyrrolidone (PVP) were investigated, regarding to chemical structure and compound's distribution. According to the manufacturing process luminal and abluminal membrane surfaces are characterized by differences in chemical composition and physical characteristics. The MALDI imaging demonstrated that the abluminal membrane surface is more consisting of polysulfone than polyvinylpyrrolidone, the luminal membrane surface displayed more PVP than PS. The addition of PVP as hydrophilic modifier to polysulfone-based membranes increases the biocompatibility of the dialysis membranes. The analysis of polymer distribution is a relevant feature for characterization of dialysis membranes.

Conclusions: In conclusion, MALDI imaging is a powerful technique for polymer membrane analysis, regarding not only detection and identification of polymers but also localization and distribution in membrane surfaces, which has strong impact on the biocompatibility of the dialyzer membranes.

FR-PO368

Effect of Peristalsis with Pediatric Catheters Anna Lorenzin, Francesco Garzotto, Claudio Ronco. *Nephrology and International Renal Research Inst Vicenza, St. Bortolo Hospital, Vicenza, Italy.*

Background: Thanks to the technological advances of the last years, Continuous Renal Replacement Therapy (CRRT) machines have been upgraded and equipped with circuits specific for pediatric patients. To date, to treat these patients the most used catheter is the bilumen 7Fr, however with a neonate it is inadequate for the dimensions. It is not clear if it is possible to use a smaller catheter with adult CRRT machine or a specific pediatric machine is needed. We set up a dedicated circuit to assess the usability of a peristaltic blood pump designed for adults and compare it with a pediatric pump in terms of access pressure.

Methods: We performed *in vitro* test with milk as medium. The circuit was composed of a bilumen catheter (4Fr-5cm, 5Fr-7cm, 7Fr-13cm), an arterial pressure sensor, a blood pump and a venous pressure sensor (Fig 1). We compared two different blood pumps: an adult one with 10,5cm diameter and a pump line with inner and external diameter of 3.9 and 7.8mm; a pediatric pump of CARPEDEMI machine with 4cm diameter and a pump line with inner and external diameter of 3.5 and 5.5mm. We set the pumps to have flow rates of 7, 10, 15, 20ml/min and we recorded the pressure values.

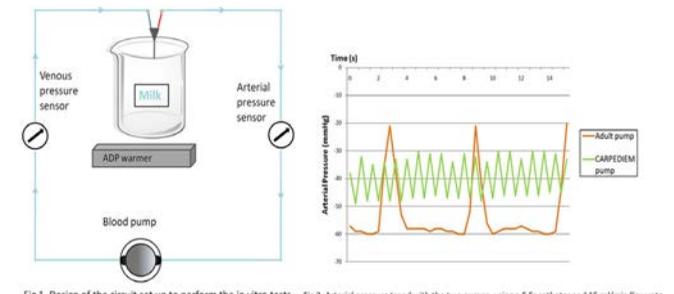


Fig 1. Design of the circuit set up to perform the *in vitro* tests. Fig 2. Arterial pressure trend with the two pumps, using a 5 Fr catheter and 15 ml/min flow rate

Results: We are presenting the data of the two pumps with 5Fr catheter and 15ml/min flow rate. Analyzing the arterial pressure values, we found that the spikes are more frequent with the CARPEDEMI pump than with the adult one. The min and max value are respectively (-5, -28mmHg) and a mean Dp=18mmHg with CARPEDEMI pump, (-61, -20mmHg) and a mean Dp=40mmHg with adult pump (Fig 2).

Conclusions: We can notice that there is a high discrepancy in terms of Dp between the two pumps: high values of Dp lead to a high shear stress. As the shear stress in one of the main causes of hemolysis, it seems that a specific pediatric machine is advisable for neonates that need small catheter. Further investigation have to be performed with blood to confirm our results.

FR-PO369

Hemodialysis with CARPEDEMI Machine: An In Vitro Test Anna Lorenzin, Dario Galeano, Stefania Aresu, Francesco Garzotto, Claudio Ronco. *Nephrology and International Renal Research Inst Vicenza, St. Bortolo Hospital, Vicenza, Italy.*

Background: Despite the development of continuous renal replacement therapies machines, their employment still remain unsuitable in newborn and infants. This gap has been filled thanks to the coming of a specific pediatric dialysis machine, CARPEDEMI. To date it is set up only for continuous hemofiltration (CVVH), to provide a wider range of applications, specific filters have been conceived to implement a continuous hemodialysis (CVVHD). We tested a prototype kit to evaluate its performance in terms of clearance K.

Methods: We performed *in vitro* test with plasma for the 3 filters HD010 HD020 HD035 (surface 0.1, 0.2, 0.35m²). Fibers were put manually into the housing of CVVH filters. CVVHD in concurrent configuration (otherwise a longer circuit is required) is carried out using infusion pump as dialysate pump and ultrafiltration as effluent pump. All the combinations of plasma and dialysate flow rate are set (Q_p=5, 10, 15ml/min, Q_d=5, 10, 15ml/min), net ultrafiltration is 0ml. Plasma samples are collected every Q_p, Q_d change (time interval 8min) to evaluate K of urea and creatinine using the standard formula.

Results: Among all filters, our tests estimated a common trend of urea K (min 3.0, max 10.5ml/min) and creatinine K (min 3.4, max 11.8ml/min). Filters efficiency increases with the increase of both the flow rates Q_p, Q_d (fig 1), moving towards a plateau at the higher flows configuration.

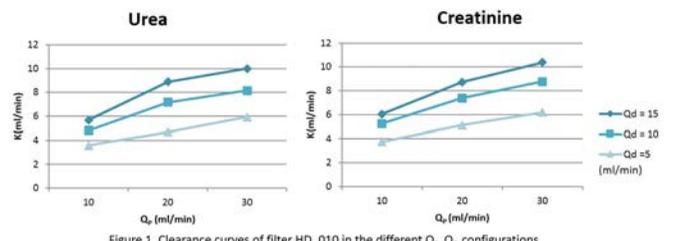


Figure 1. Clearance curves of filter HD_010 in the different Q_p, Q_d configurations

Conclusions: CVVHD with CARPEDIEM seems to be effective for diffusion transport of small molecular weight solutes, according to specific clinical needs. In the light of these findings CARPEDIEM can be a promising alternative to peritoneal dialysis, i.e. in treating electrolyte imbalance with accurate fluid removal. Limitation: handmade filters could induce variability in the results due to disposition and variable number of fibers.

FR-PO370

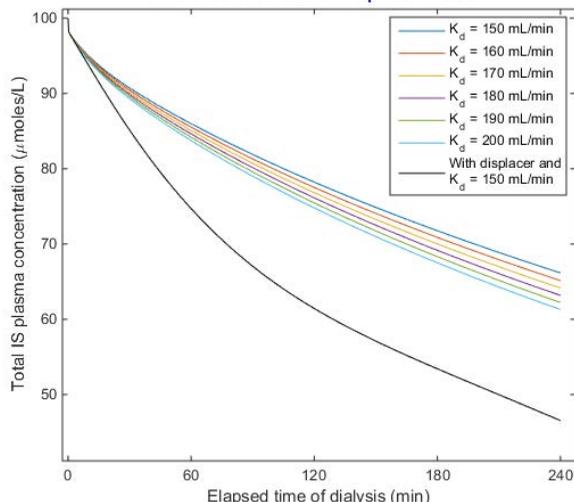
Removal of Protein-Bound Uremic Toxins: Simulating the Effect of Toxin Displacement versus Increase in Dialyzer Clearance Vaibhav Maheshwari,¹ Stephan Thijssen,¹ Doris H. Fuerstinger,¹ Franz Kappel,² Peter Kotanko.¹ ¹Renal Research Inst, NY; ²Univ of Graz, Austria.

Background: Protein-bound uremic toxins (PBUT) exert numerous deleterious effects. Their removal with standard hemodialysis (HD) is poor. Meyer *et al.* have modeled the impact of increasing dialysate flow rate and dialyzer mass transfer area coefficient on PBUT removal [JASN, 2004]. Here, we compare those results to a novel approach based on PBUT displacement by infusion of binding competitors [Tao, Blood Purif, 2015].

Methods: We developed a multi-compartment patient model and a dialyzer model depicting spatiotemporal dynamics based on law-of-mass-action kinetics. We chose indoxyl sulfate (IS) as a prototypical PBUT and ibuprofen as the binding competitor. We modeled IS removal during a 4-hr HD ($Q_D=250$ mL/min, $Q_{UF}=750$ mL/h, initial total IS 100 μ mol/L, initial free fraction of IS 8%), with IS dialyzer clearances from 150 to 200 mL/min. This was compared to IS removal achieved by ibuprofen infusion (800 mg/200 mL) into the arterial line at 50 mL/hr (IS clearance 150 mL/min).

Results: IS removal during HD with a clearance of 150 mL/min was 438 μ moles (plasma reduction ratio 34%), which conforms to literature data [Niwa, Blood Purif, 2012]. With IS clearance of 200 mL/min, removal improved by 8.7% to 476 μ moles. With ibuprofen infusion (IS clearance back at 150 mL/min), removal improved by 11.2% to 487 μ moles.

Time course of total IS concentration with different clearances vs. displacer infusion



Conclusions: Our model yields predictions of IS kinetics that agree with empirical and modeled data [Niwa *et al.*; Meyer *et al.*]. Of note, a mere 8.7% improvement in IS removal would require an increase in dialysate flow rate from 800 to 1350 mL/min plus a 70% increase in membrane surface area. The modeled ibuprofen infusion alone yields an 11.7% improvement even absent an increase in dialyzer clearance. The use of binding competitors holds great promise. These results require validation *in vivo*.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO371

Membrane Driving Blood Flow for Extracorporeal Therapies Francesco Garzotto, Sean M. Bagshaw, Anna Lorenzin, Mauro Neri, Claudio Ronco. *Nephrology, St. Bortolo H.*

Background: From the first application of ContinuousVenoVenousHemofiltration CVVH, the blood flow has been driven by a peristaltic pump. Several attractive alternatives, with both advantages and disadvantages, have been proposed for many years. SAM (Spectral Medical Inc.; Toronto, Canada) is a novel instrument, in which the pumping of whole blood and fluids is performed through the use of pistons, chambers and valves. A plastic cartridge blood circuit system fig 1b incorporates all of the pumps, air trap system, pressure monitors and clamps. This circuit is covered on one side by a plastic membrane adhered to the pumping pistons via a drawn vacuum. Aim of the present is to evaluate the new pumping system.

Methods: We set up the machine for CVVH. An 11.5 Fr 20 cm catheter was connected to the lines. We ran the machine for 6 hours in order to characterize the performance of the system.

During the first cycle, suction generated by the drawing back of the piston, moves the blood into the arterial-chamber AC. Positive pressure generated by the piston then

drives the blood through the circuit. The camshaft design can allow different profiles for Withdrawal and infusion flows. The largest Priming volume measured (both the ACs full), is 98 ml with a stroke volume for each AC of 14ml.



Results: We did not observe a reduction of blood flow due to a loss of membrane elasticity. The use of an "all integrated" cassette reduces the number of manual operations, avoiding operator related errors and favoring an easy and time saving set up.

Conclusions: S.A.M could represent a valid alternative to the classic peristaltic pumping system driven machines. Analyzing the pumping-system/cassette equipment, we identified potential advantages, in addition to usability, such as: accurate balancing system, blood flow ideally designed to avoid a membrane protein layer, constant blood flow over time, accurate volumetric balancing system, less clotting activations, and an optimal withdrawal flow profile. More tests should be performed in order to validate the device in various aspects and conditions.

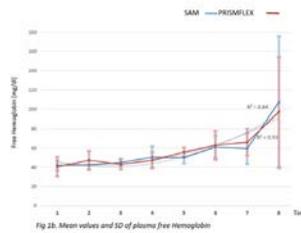
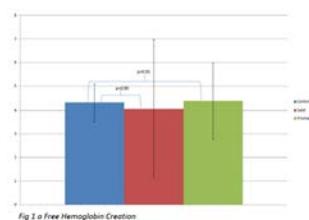
FR-PO372

Membrane versus Peristaltic Blood Pumps for Extracorporeal Therapies: Comparison on Index of Hemolysis Francesco Garzotto,¹ Sean M. Bagshaw,² Claudio Ronco.¹ ¹Nephrology and IRRIV, St. Bortolo H., Italy; ²Critical Care Medicine, Univ of Alberta Hospital.

Background: Hemolysis during extracorporeal treatments mainly occurs as a consequence of mechanical stress on the blood. Red blood cell deterioration is undetected because it is far from any acute hemolytic threshold but represents a potential harm for patients. A new membrane-piston driven pump has been recently proposed on the S.A.M. (©Spectral Medical Inc, Toronto) device designed for continuous renal replacement therapies (CRRT). Aim of this investigation is to compare the membrane with peristaltic pumps by measuring the Normalized Index of Hemolysis NIH during *in vitro* testing.

Methods: Three sessions of hemoperfusion with a line inserted in place of a hemofilter were performed both with SAM and Prismaflex (©Baxter International). A single pool of fresh heparinized bovine blood (Heparin 500 u/L, Hb 12±1 g/dl, Base Excess 0+/-5 mmol/L) were split into three aliquots containing 900 mL (Control, SAM, Prismaflex) and circulated for 6 hours/session. Blood samples were drawn at baseline, 30 min and every 1 hour. NIH were calculated as median hourly variation of free hemoglobin and used for comparison. Data was compared with two tailed Student's t-test based on F-Test results.

Results: NIH values of 0.12±0.03 and 0.13±0.09 mg/100L for SAM and Prismaflex respectively are lower than those reported in literature due to the simplified circuit used (no vascular access and filter). Creation of hemoglobin between sam and control, and prisma and control are non-significant fig 1a. Slope of the curves that describe the creation of hemolysis are nearly identical with a slow rate of production of free hemoglobin.



The r^2 close to 1 demonstrate a good linearity of the damage.

Conclusions: Device compatibility in terms of lethal damage to blood cells, is an important aspect of the development of artificial organs. Since a validation based on dangerous level of free hemoglobin do not exist, an empirical evaluation using comparative test suggest that piston driven membrane is safe from a hemolysis point of view.

FR-PO373

Enhanced Middle Molecule Clearance by a Biomimetic Dialyzer Membrane

Joseph J. Groszek,¹ Jin Cheng,¹ Charles Blaha,² Rishi Kant,² Jaehyun Park,² Benjamin Chui,³ Ken Goldman,⁴ Shuvo Roy,² William Henry Fissell,¹
¹Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; ²Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA; ³Ben Chui Consulting, Sunnyvale, CA; ⁴H-Cubed, Inc, Olmstead Falls, OH.

Background: Although polymer dialyzers attain very high small solute clearance rates, polydisperse pore sizes limit middle molecule clearance by conventional polymer dialyzers. We hypothesized that a biomimetic membrane with uniform slit pores would enhance middle molecule clearance.

Methods: thin film silicon membrane samples (surface area 1.4 x 10⁻⁵ m²) with monodisperse slit-shaped 5-8 nanometer pores ("SNM-HD") were manufactured as previously described, surface-modified with polyethylene glycol and mounted in a custom designed cartridge. Membrane pore size was estimated from hydraulic permeability measurements. Human blood was spiked with PABA and fluorescent-labelled Ficoll, a polydisperse globular polysaccharide. Blood flow was set at 100 ml/min and dialysate flow varied between 70 and 140 ul/min. Blood and dialysate concentrations of PABA and Ficoll were measured by size-exclusion chromatography. Clearance as a function of dialysate flow rate was extrapolated to estimate KoA as a function of molecular weight.

Results: B2M clearance in high-flux dialyzers is typically 5-8% of the value of urea clearance. PABA clearance was 139 ml/min/m². 15.7Angstrom Ficoll (same radius as B2M) clearance in the SNM dialyzers was 16.9 ml/min/m², 3-5 fold higher than reported B2M clearance in polymer dialyzers.

Conclusions: A biomimetic membrane of uniform slit pores potentially offers much higher middle molecule clearance than conventional polymer dialyzers.

Funding: Other U.S. Government Support

FR-PO374

Anti-Fouling of Silicon Nanopore Membranes Using SLIPS Bas Meusen,^{1,2}

Steven Kim,¹ Zohora Iqbal,¹ Charles Blaha,¹ William Henry Fissell,^{3,4} Shuvo Roy.^{1,3} ¹UCSF; ²Univ of Eindhoven; ³Silicon Kidney; ⁴Vanderbilt Univ.

Background: Silicon Nanopore Membranes (SNM) have been developed for application in an implantable bioartificial kidney. However, SNM are subject to fouling and thrombosis with continuous blood exposure. Thin polymer coatings have been applied to SNM as a strategy to limit cell adhesion and protein adsorption. Slippery Liquid Infused Porous Surface (SLIPS) is a bioinspired "omniphobic" surface coating that has been reported to prevent thrombosis and fouling on arteriovenous shunts. Here we present the application of SLIPS coating to SNM and evaluate protein adsorption in vitro.

Methods: SNM with ~10 nm pores were coated with SLIPS and incubated with BSA-FITC (2 mg/ml in PBS) for 24 hours at 37°C. Uncoated (bare) silicon substrates served as controls. Fluorescence microscopy and ellipsometry were used to evaluate the surfaces and water transport through the SNM was tested using established hydraulic permeability assays.

Results: SLIPS strongly reduced BSA-FITC adsorption on SNM compared to bare silicon. Ellipsometry confirmed the presence of SLIPS coating with a thickness of 0.5±0.2nm, which is theoretically thin enough to keep open the pores in the membrane. However, hydraulic permeability testing revealed no ultrafiltration through the SNM for at least 24 hours and transmembrane pressures of up to 5 psi.

Conclusions: SLIPS is a promising and easy-to-apply protein repellent coating, but its highly omniphobic characteristic prevents ultrafiltration even through pores that are over 5x the coating thickness. For use in the bioartificial kidney, SLIPS has relevant implications as an anti-fouling coating where an ultra-thin blood compatible, but non-filtering surface is desired.

Funding: Other NIH Support - NIBIB

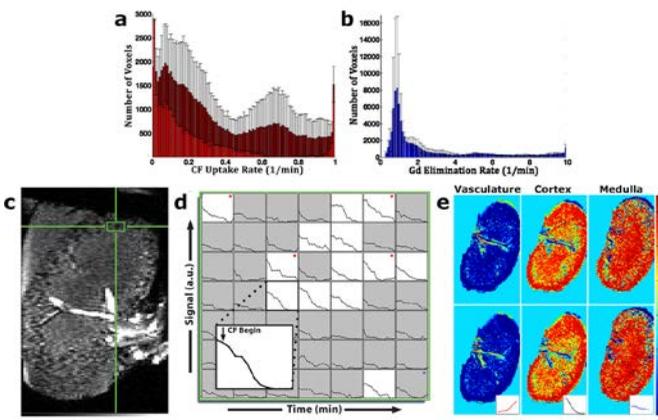
FR-PO375

Measuring Spatial Trends of Single Nephron Filtration with Molecular MRI Edwin Baldelomar,¹ Jennifer R. Charlton,² Kevin M. Bennett,¹ ¹U. of Hawaii, Honolulu, HI; ²U. of Virginia, Charlottesville, VA; ³U. of Hawaii at Manoa, Honolulu, HI.

Background: To better develop drugs to treat kidney disease their physiological mechanisms during development, noninvasive techniques to measure whole kidney function at the level of the single nephron are needed. We investigated the combined use of two MRI contrast agents, cationic ferritin (CF) and Gd-DTPA, to measure local (voxel) macromolecular uptake and glomerular filtration rates of single nephrons over the whole rat kidney with 3D MRI using the isolated, perfused rat kidneys under physiological conditions.

Methods: Krebs-Ringer (KR) bicarbonate solution with 7.5 mg/100mL of Fraction-V BSA and a bubbling infusion of carbogen was perfused into isolated rat kidney. Temp was maintained at 37°C. CF in KR solution (0.071 mg/mL of CF), was infused into the system first. After CF, KR solution was re-infused to wash. Next, a bolus of 0.25 mmol Gd-DTPA in 10mL of KR solution was re-infused into the perfusion system. (All rates = 5ml/min) Kidneys were imaged during the perfusion with MRI. Voxel time courses were then fitted to a bi-exponential model.

Results: Glomeruli were distinguished by uptake of CF and a distribution of CF accumulation rates and gd-DTPA elimination rates was visible. (Fig 1a-b) We used the location of the glomeruli in 3D and the time course of CF labeling (Fig 1c-d) to discern spatial trends in uptake rate of CF. Time course structures also mapped well with the different morphological structures in the kidney (Fig 1e).



Conclusions: CF and gd-DTPA were used in conjunction to map glomerular filtration in the isolated, perfused rat kidney in 3D. To our knowledge this is the first report to assess spatial trends with macromolecular and free filtration dynamics in the whole kidney.

Funding: NIDDK Support, Other NIH Support - NIH DK-091722

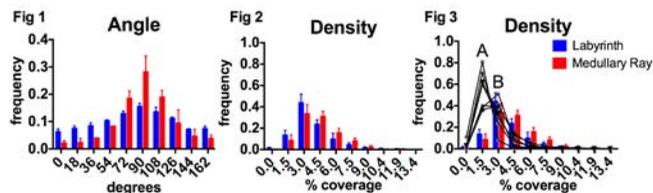
FR-PO376

Automated Quantification of Renal Microvascular Abnormalities: A Novel Computational Mapping Approach Kyle I. Harrington, Beverly Elizabeth Faulkner-Jones, Katie Bentley, Seymour Rosen. Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Alteration of the microvasculature is considered to be crucial to the understanding of chronic kidney disease, yet few studies have quantified the microvasculature in normal and diseased kidneys.

Methods: We created customized software for automatically quantifying morphology of renal microvasculature. 10 kidneys (2 nephrectomies, 8 biopsies) were studied; 3 cases of relatively normal tissue, others chosen because of a significant degree of tubulointerstitial injury and included a variety of diseases (diabetes, amyloidosis, end-stage glomerulonephritis, and renal artery stenosis). Images of CD34 stains were segmented, high-pass filtered based on size, and glomeruli were manually segmented. Morphological signatures were calculated using 3 parameters: roundness, angulation, and density.

Results: The normal cortex, as a whole, presented heterogeneity in histogram analysis. However, color density mapping and histogram studies revealed 3 distinct regions: glomeruli (GM), labyrinth (LB), and medullary ray (MR). MR was characterized by correlated angulation (Fig 1). Microvascular density varied in LB but peaked at 3% coverage within a 200um circular radius (Fig 2). Density in MR was approximately the same. As expected, GM density was far greater, sometimes exceeding 11% coverage. With disease, capillary shape did not shift, roundness factor remaining in 0.2-0.3 range (circular profile 1.0). However, diminishment in capillary density was overt (Fig 3), and distribution shifts were marked (peak A) or more moderate (peak B).



Conclusions: Our results demonstrate that automated quantification is capable of not only distinguishing between anatomical features of kidneys, but also characterizing the degree of abnormality in diseased tissue.

FR-PO377

Angio-μCT: New Polymer-Based Contrast Agent Makes Kidney Morphometry Look Attractive Ruslan Hlushchuk, Sebastien Barre, Carlos Correa Shokiche, Valentin Djonov. Inst of Anatomy, Univ of Bern, Bern, Switzerland.

Background: The fundamental features of the morphological substrate of the renal function are nephron number and glomerular volume. The accurate estimation of these parameters has become increasingly important. The present golden-standard method of kidney morphometry is the exhaustive physical fractionator/dissector method. It is extremely time-consuming and laborious, let alone disturbing preceding artefacts. **Purpose:** to develop a contrast agent appropriate for high-resolution μCT *ex vivo* with superior perfusion features in order to visualize the vasculature and glomeruli of rodent kidney. The elucidated approach should allow **fast and reliable** estimation of such parameters as nephron number, glomerular volume, glomerular size distribution and kidney volume.

Results: the developed contrast agent (μ Angiofil) turned out appropriate for μ CT *ex vivo* with superior perfusion and contrast-to-noise features. The obtained μ CT datasets were of superior quality and allowed clear visualization of the microvasculature and glomeruli.

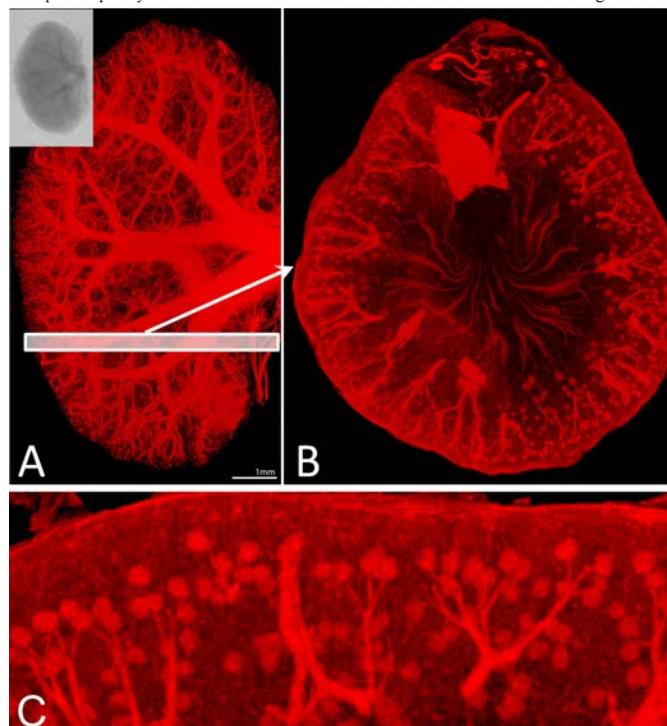


Figure 1: MicroCT visualization of the murine kidney using the developed contrast agent. **A - Overview of the vascular network. B - virtual cut of the obtained 3D volume. C - visualization of the glomeruli (sphere-like structures)**

In kidney, modern high-resolution microCT (SkyScan-1172) provided the whole mouse kidney vasculature in 3D with the spatial resolution of approx. 2 μ m. The sample is fixed prior the microCT-scan and therefore can be processed for the histological evaluation after the scan. This circumstance brings multiple advantages, including much easier localization of the μ CT-findings in the post-scan histological sections.

Conclusions: using μ Angiofil we obtained 3D- μ CT datasets of superior quality, which are sufficient for estimation of relevant kidney morphometry parameters. **The developed angio- μ CT-based approach will substitute the existing golden-standard.** Besides classical kidney morphometry, it provides the data on the vasculature through the whole kidney in 3D what makes the technique even more beneficial.

Funding: Government Support - Non-U.S.

FR-PO378

Rising Accuracy of Transcutaneous GFR Measurement Jochen Friedemann,^{1,2} Ralf Heinrich,³ Yury Shulhevich,^{1,2} Johannes Pill,² Daniel Schock-Kusch.^{1,2} ¹Mannheim Univ of Applied Sciences, Inst for Process Control and Innovative Energy Conversion, Germany; ²Mannheim Pharma & Diagnostics GmbH, Germany; ³Freudenberg New Technologies SE & Co. KG, Weinheim, Germany.

Background: Transcutaneous measurement of GFR (tGFR) is now getting used frequently in animal studies. tGFR allows consecutive GFR measurements in the same animal even on a daily basis as no blood sampling is required. Here we describe and validate a novel three compartment model (tGFR_{new}) for tGFR assessment by FITC-Sinistrin clearance, automatically correcting influences like bleaching of skin fluorescence.

Methods: Bolus clearance tGFR was measured in awake Sprague Dawley (SD) rats using the commercially available NIC-Kidney system, immediately followed by a blood sampling based constant infusion clearance (cGFR). GFR was calculated by a one compartment model (tGFR_{std}), tGFR_{new} and cGFR. Also 46 tGFR measurements in SD rats were reevaluated by tGFR_{new} .

Results: Results are given in table 1. Mean values of the three methods are comparable with no significant difference. The accuracy (larger STD) of tGFR_{std} is lower compared to tGFR_{new} and cGFR. This finding was verified by the 46 measurements in SD rats (tGFR_{std} : 0.97 ± 0.18 ml/min/100g b.w.; tGFR_{new} : 0.95 ± 0.14 ml/min/100g b.w.).

n=11 SD rats	cGFR	tGFR_{std}	tGFR_{new}
		ml/min/100g b.w.	
mean \pm STD	0.94 \pm 0.13	1.00 \pm 0.18	0.88 \pm 0.12
effect size_{10%}	0.73	0.55	0.73

Conclusions: The results indicate that tGFR_{new} yields data in comparable accuracy as cGFR. For an a priori estimation of the sample size to detect a change in GFR of 10%

in the SD rats investigated, the effect size rises from 0.55 (tGFR_{std}) to 0.73 (tGFR_{new}). The required sample sizes in fig. 1 illustrate the strong contribution of tGFR_{new} to the concepts of refining and reduction of animal studies.

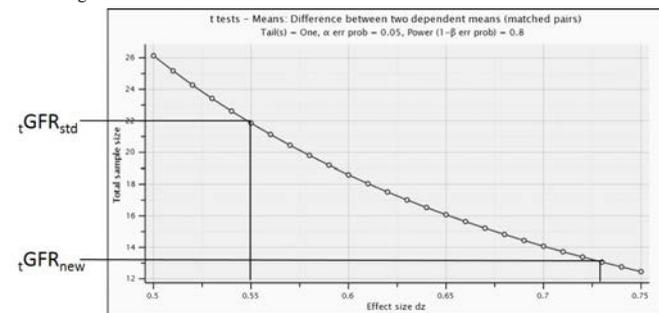


Figure 1: Impact of the increased effect size yield with tGFR_{new} compared to tGFR_{std} .

FR-PO379

Quantification of the Progressive Fibrosis Development in Mouse Kidney Unilateral Ureteral Obstruction Model Using Fluorescence Lifetime and Second Harmonic Generation Imaging Microscopy Evgenia Dobrinskikh,¹ Suman Ranjit,² John Ross Montford,¹ Alexander Dvornikov,² David J. Orlicky,¹ Allison M.b. Lehman,¹ Raphael A. Nemenoff,¹ Enrico Gratton,² Seth B. Furgeson,¹ Moshe Levi.¹ ¹Univ of Colorado Denver; ²Univ of California Irvine.

Background: Renal fibrosis is considered to be the final common pathway for most forms of chronic kidney disease (CKD) and involves glomerular sclerosis and/or tubulointerstitial fibrosis. There is great interest in identifying renal fibrosis in the early stages of CKD to prevent progression. Unilateral ureteral fibrosis (UUO) is a well-characterized model of CKD and renal fibrosis. Kidney injury and fibrosis usually are assessed by Picrosirius Red staining or immunohistochemistry for collagen isoforms.

Methods: The goal of this study is to compare histologic measures of renal fibrosis to Fluorescence Lifetime Imaging (FLIM) and Second Harmonic Generation (SHG) techniques in our deep imaging microscope DIVER. FLIM and SHG allow quantification of collagen in unstained tissue and can be adapted for live animal imaging. Male C57BL/6 mice were subjected to UUO of right kidney. At 7, 14 and 21 days, both kidneys were harvested. The uninjured left kidney was used as a control. Serial sections of both kidneys were analyzed by Picrosirius Red staining or FLIM with SHG.

Results: We performed quantification of Picrosirius Red stained-kidneys using polarized light. This showed progressive increase for the number of positive pixels for fibrosis in the left kidney $9631.9 \pm 0.1626.2$, 16167.8 ± 6647.7 and 20511.5 ± 5727.6 compared to 5625.3 ± 770.6 , 3909.33 ± 2395.9 and 4493.8 ± 2018.4 in the control kidney respectively. Using the Phasor approach to FLIM, comparisons between the two kidneys show that the auto fluorescence lifetime signature give rise to two well separate phasor clusters. Quantification of ten different fields of view for each kidney at the above time-points for SHG signal confirms Picro-Sirius Red scoring.

Conclusions: Finally, the combined FLIM and SHG images let us establish a criterion for quantitative determination of fibrosis directly from the microscope images.

Funding: NIDDK Support

FR-PO380

Chemical Imaging: A Novel Approach to Obtaining Label-Free Biochemical Information in Renal Transplant Patients with Recurrent Diabetic Nephropathy Michael J. Walsh,¹ Vishal K. Varma,¹ Andre Kajdacsy-Balla,¹ Sanjeev Akkina,² Suman Setty.¹ ¹Dept of Pathology, Univ of Illinois at Chicago, Chicago, IL; ²Dept of Nephrology, Univ of Illinois at Chicago, Chicago, IL.

Background: The main treatment for end-stage renal disease is kidney transplantation, which over time undergo chronic rejection including changes in the glomerular, tubulointerstitial and vascular compartments. Also, recurrence of disease in diabetics can mimic transplant glomerulopathy. We have identified biochemical markers using Chemical Imaging that were associated with recurrent diabetic nephropathy. Chemical Imaging is an emerging approach to obtain images of the biochemical composition of tissue biopsies in a label-free fashion.

Methods: An initial study focused on identifying patients with no evidence of diabetic nephropathy and patients with advanced diabetic nephropathy in native kidneys. Serial sections were acquired and stained with PAS or imaged using chemical imaging. IR spectra were extracted to identify biomarkers associated with diabetic nephropathy progression. A second study identified transplant patients who underwent very rapid recurrent diabetic nephropathy and patients with no evidence of diabetic nephropathy.

Results: Biomarkers were identified that were changed in renal structures associated with the progression of diabetic nephropathy, including increased levels of glycation. These biomarkers were found to be increased in the cohort of transplant patients that underwent rapid diabetic nephropathy recurrence. In addition, the early biopsies from the patients that underwent later diabetic nephropathy progression were biochemically different from the non-progressive patients, suggesting that chemical imaging may identify pre-histological biomarkers that will predict outcome.

Conclusions: We have identified a number of biomarkers that are associated with the advancement of diabetic nephropathy and that we can track the early recurrence of diabetic nephropathy in surveillance biopsies. In addition, we have highlight a 'biochemical-signature' that may be predictive of the later progression of diabetic nephropathy recurrence.

Funding: NIDDK Support

FR-PO381

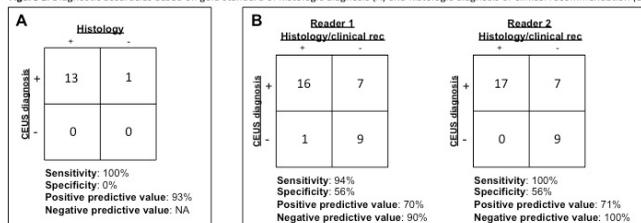
Contrast-Enhanced Ultrasound Characterizes Kidney Lesions with Accuracy Comparable to Contrast-Enhanced CT or MR Emily H. Chang,¹ Sandeep Kasoji,^{1,2} Paul Dayton,^{1,2} Wui K. Chong,¹ Kimryn Rathmell.¹ ¹Univ of North Carolina, Chapel Hill, NC; ²North Carolina State Univ, Raleigh, NC.

Background: Incidental kidney lesions are often detected on imaging performed for other reasons. Indeterminate lesions are further characterized with a contrast-enhanced computed tomography(CT) or magnetic resonance imaging(MRI). These tests have many limitations and are contraindicated in patients with allergies to contrast, metallic hardware and chronic kidney disease(CKD). An accurate alternative study is needed. Contrast-enhanced ultrasound (CEUS) is one potential alternative. CEUS uses microbubbles, non-nephrotoxic, gas filled bubbles with lipid or albumin shells, as the contrast agent. We investigated the accuracy of CEUS for malignancy in patients with incidental kidney lesions.

Methods: CEUS was performed on 33 patients. Results were independently interpreted by 2 blinded readers and risk-stratified by the Bosniak classification system. Sensitivity, specificity and predictive values were calculated for lesions with histologic diagnosis as the gold standard. As histology was available for resected lesions only, we performed secondary analyses using an expanded gold standard definition that included clinical recommendation.

Results: Of the 33 patients, 12 had CKD and 14 had histologic diagnoses. There was 100% inter-reader agreement in the primary analysis (Figure 1A) and 97% agreement in the secondary analysis (Figure 1B). Sensitivities (94-100%), positive (70-93%) and negative predictive (90-100%) values for CEUS were comparable to CT (83-100, 50-67 and 77-100%, respectively) and MRI (81-100, 60-78 and 80-96%, respectively). CEUS specificity (0-56%) was lower than MRI (71-100%).

Figure 1. Diagnostic accuracies based on gold standard of histologic diagnosis (A) and histologic diagnosis or clinical recommendation (B).



Conclusions: CEUS has excellent potential as an alternative diagnostic tool for kidney lesions among patients with CT/MRI contraindications. Further evaluation is needed.

Funding: Other NIH Support - CTSA (Clinical and Translational Science Awards) funding, University of North Carolina at Chapel Hill (UL1TR001111)

FR-PO382

Lead-Free Drape Applied to Xray Detector Significantly Decreased Radiation Scatter During Access Intervention Jie Cui,¹ Fengyong Liu,² Zubin Irani.³ ¹Nephrology Dept, Massachusetts General Hospital, Boston, MA, China; ²Interventional Radiology Dept, Chinese People's Liberation Army General Hospital, Beijing, China; ³Div of Vascular Imaging and Intervention, Massachusetts General Hospital, Boston, MA, China.

Background: Exposure from scattered radiation can be very high during access interventional procedures because of the relatively closer operative position. The purpose of this study is to evaluate whether applying a lead-free, sterile, disposable drape can decrease scatter radiation exposure during access intervention.

Methods: An upper extremity phantom was placed on the angiography table to mimic real-time patient's upper extremity access. Using this model, measurement of scatter radiation was made every one foot away from the phantom before and after applying the drape using a collimated and low-output condition. The scattered radiation dose was measured three times in each spot. And the measurement was taken at 0.9m (waist level) as well as neck level (1.5m). Statistical significance was compared using t-test.

Results: Scatter radiation was attenuated throughout the measurement field when the drape was applied. The degree of scatter radiation reduction was distance and height dependent. Scatter radiation decreased 61.6% at the waist level and 81% at the neck level (P<0.05).

Conclusions: The application of this sterile, lead-free drape can significantly reduce scatter radiation in the procedure room. This novel technique can be used to reduce exposure radiation dose to the operators.

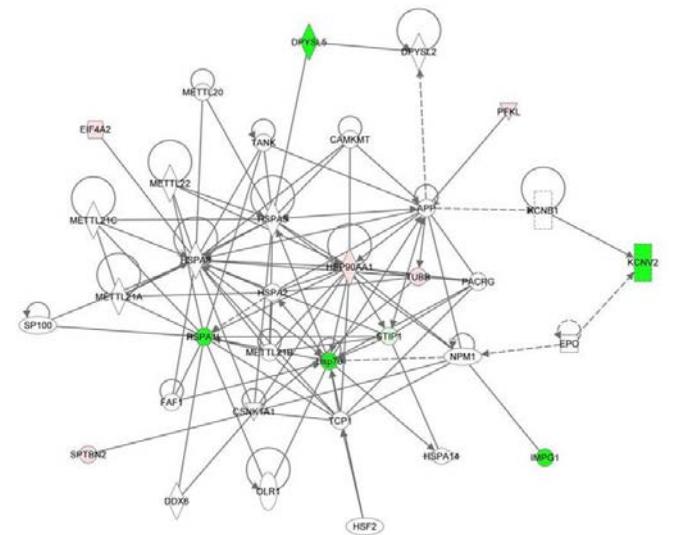
FR-PO383

Pathogenesis of Brain Damages in Chronic Kidney Disease and Clues for Early Diagnosis Yao-ping Lin,^{1,2} Der-Cherng Tarn,^{1,2} ¹Medicine, National Yang-Ming Univ, Taipei, Taiwan; ²Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: There is globally increased prevalence of chronic kidney disease (CKD). Vigorous efforts have been devoted to ameliorate renal deterioration and prevent cardiovascular morbidity/mortality. However, patients also have enough incubation time to develop deranged cognition that severely disturbs quality of life. Neurological pathology/damages may occur in CKD patients long before any overt clinical symptoms can be noticed. Given the similar embryological development as brain, the eyes can be the windows to pinpoint the internal brain pathology. Herein we employed proteomics, animal model and behavior analysis to investigate the possible overlapping biological signatures in the eyes and brain of CKD.

Methods: Subtotal nephrectomized rats were established as CKD model. Open field and object recognition tests were adopted as neurological screen. Brain and eyes were harvested for proteomic analysis. Western blotting and immunohistochemistry were used to confirm and localize the identified proteins. To elucidate the global protein changes in the brain and eye of SNX rats, the data was analyzed by Ingenuity Pathways Analysis (Ingenuity Systems, http://www.ingenuity.com/).

Results: The eye pathology appeared in parallel with the brain damages. The significantly dysregulated proteins in the SNX rat eyes were spectrin beta 3, 26S proteasome non-ATPase regulatory subunit 2, 6-phosphofructokinase, dihydropyrimidinase-related protein, and the heat shock 70, 90α, and chaperonin containing Tcp1, subunit 6A (Zeta 1).



All these proteins have been linked to the neuro-degeneration in humans. **Conclusions:** There were overlapping eye and brain biological networks. Our results might pave the way for early diagnosis of CKD-neurological pathology via eye examinations, and targeted interventions towards the neurological diseases.

Funding: Government Support - Non-U.S.

FR-PO384

Metabolomic Profiling of Chronic Kidney Disease Using a Local Exhaustive Exploration Approach Margaux Luck,² Eric Thervet,¹ Cécilia Damon,² Nicolas Pallet.¹ ¹Nephrology, Georges Pompidou European Hospital, Paris, France; ²Hypercube Inst, Paris, France.

Background: ¹H Nuclear Magnetic Resonance (NMR)-based metabolomic profiling is useful for the diagnosis of CKD stages. Due to the high dimension of NMR spectra datasets and the complex mixture of metabolites in biological samples, the identification of discriminant biomarkers of a disease is challenging. None of the widely used chemometric methods in NMR metabolomics performs local exhaustive exploration of the data.

Methods: We developed a descriptive and easily understandable approach searching for discriminant local phenomena. We selected the most discriminant features from the dataset based on both the normalized mutual information and the chi-2 test. We studied the local distribution of the patient subgroups with identical degree of CKD severity on each feature, using the proprietary algorithm HyperCube, which searches for local overdensities of an explanatory variable modality, and identifies a combination of variables as well as their value ranges that give the optimal prediction of the outcome of interest. Further, logistic regression on these discriminant features was used to build a predictive model of the CKD severity stage.

Results: We explored a complex dataset that includes ¹H-NMR urinary metabolomics, clinical, demographic, clinical chemistry and histo-pathological variables, in a cohort of 110 individuals with a CKD. The HyperCube algorithm combined with logistic regression supports the discriminant metabolites obtained with standard Orthogonal Projection to Latent Structure Discriminant Analysis (O-PLS-DA) model. Unlike the O-PLS-DA model, HyperCube algorithm provided clues into the distribution of the CKD severity subgroups

with respect to spectral data. The built predictive model identifies metabolomics profiles composed of metabolites such as citrate, dimethylsulfone, trigonelline and glycine. The majority of the predictive variables were urinary metabolites identified by ¹H-NMR, indicating that CKD significantly impacts the urinary metabolome.

Conclusions: Our findings indicate that HyperCube is a valuable analytical method for the description of CKD severity phenotypes.

FR-PO385

RNA-seq Profiling in Uninephrectomized Rats Jae Wook Lee, Mark A. Knepper. *NHLBI, NIH, Bethesda, MD.*

Background: Renal hypertrophy occurs as a compensatory response to reduction in nephron mass. To identify early gene expression changes in renal hypertrophy, we profiled whole-kidney transcriptome in the contralateral kidney of uninephrectomized rats using RNA-seq.

Methods: 5-week-old male Sprague-Dawley rats received right uninephrectomy (UNx, n=4 at each time point) or sham surgery (S, n=4 at each time point). Rats were sacrificed at 24, 48, and 72 hours after surgery. 1.5 µg of total RNAs from the left kidney was used to make cDNA libraries for Illumina sequencing. Reads were mapped to Ensembl genes and Wald test for a negative binomial model was used to call differentially expressed genes.

Results: Total RNA yields did not differ significantly between UNx and sham kidneys. Each library had 35-42 million reads and more than 80% of reads were uniquely aligned. At 24 h, 45 transcripts were upregulated and 72 downregulated in UNx. Upregulated transcripts included connective tissue growth factor (*Ctgf*), regulator of cell cycle (*Rgcc*), serum/glucocorticoid-regulated kinase (*Sgkl*), glucocorticoid-induced leucine zipper protein (*Tsc22d3*), a zinc finger transcription factor (*Zbtb16*), and genes related to steroid biosynthesis (e.g. *Insig1*). At 48 h, 183 transcripts were upregulated and 103 downregulated in UNx. Among upregulated transcripts were cell-cycle genes including centromere proteins (*Cenpa*, *Cenpf*, and *Cenpi*); MMC helicase subunits (*Mcm3*, *Mcm5*, and *Mcm8*); cyclins (*Cena*, *Cend1*, *Cene*, and *Cenf*); cyclin-dependent kinase (*Cdk1*); and polo-like kinase (*Plkl1*). Among downregulated transcripts at 48 h were transcription factors (*Jun*, *Hmx2*, *Klf9*, *Klf15*, *Foxo3*, *Zfp36*, *Zfp354a*, *Zbtb16*, and *Zlx3*). At 72 h, 769 transcripts were upregulated and 704 downregulated in UNx. Upregulated transcripts included *Ctgf*, *Sgkl*, *Zbtb16*, and cyclins (*Ccnb1*, *Cena2*, *Ccnb1*). Interestingly, *Ctgf*, *Sgkl*, *Zbtb16*, and *Tsc22d3* showed a triphasic response, upregulated at 24 h and 72 h and downregulated at 48 h, consistent with an underdamped control system.

Conclusions: RNA-seq revealed upregulation of multiple transcripts involved in cell division as a central mechanism of compensatory response in the contralateral kidney after uninephrectomy. Genes upregulated at 24 h such as *Ctgf*, *Rgcc*, *Sgkl* and *Tsc22d3* may trigger this response.

Funding: Other NIH Support - Division of Intramural Research, NHLBI Projects ZIA-HL001285 and ZIA-HL006129

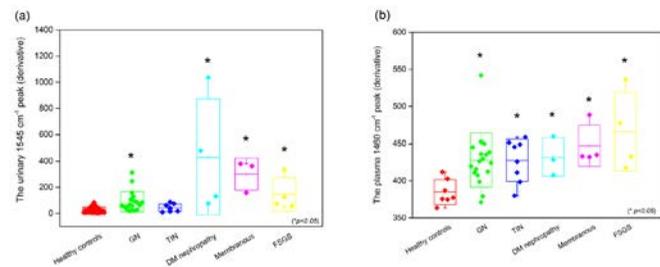
FR-PO386

The Application of Potential Label-Free Mid-Infrared Biomarkers in Patients with Biopsy-Proven Kidney Diseases Mei-Ching Yu,^{1,2} Peter R. Rich,³ Vinod Sathyanarayana Dibbur,² Jennifer Smith,² Robert J. Unwin,⁴ Frederick W.K. Tam,² ¹Paediatric Nephrology, LinKou Chang Gung Medical Centre, Taiwan; ²Imperial College Kidney & Transplant Centre, Hammersmith Hospital, United Kingdom; ³Structural and Molecular Biology, Univ College London; ⁴UCL Centre for Nephrology, Univ College London, Royal Free Hospital.

Background: We have previously discovered novel spectral markers, the urinary 1545 cm⁻¹ & plasma 1460 cm⁻¹ peaks, indicating progression of experimental GN using Fourier transform infrared spectroscopy (FTIR) (2013 & 2014 ASN). In this study, the aims were to investigate these spectral markers in patients with different biopsy-proved kidney diseases, and the correlations between the spectral markers with clinical features.

Methods: The urine and plasma samples were collected at the time of renal biopsy from 50 patients at Imperial College Renal & Transplant Centre, London, UK and compared with healthy volunteers. All samples were measured by FTIR spectrometer and analysed by the established method. The biochemistry results such as urine protein/creatinine ratio (uPCR), Scr and renal histopathology were collected.

Results: In comparison with healthy volunteers, patients with GN, diabetic nephropathy (DN), membranous nephropathy and FSGS exhibited significantly higher levels of the urine 1545 cm⁻¹ marker. Furthermore, this urine spectral marker correlated with uPCR in both GN and DN (*p*<0.05). There was significant elevation of the plasma 1460 cm⁻¹ marker in all the disease groups compared with healthy volunteers.



Interestingly, for DN, this plasma spectral marker correlated positively with the degree of interstitial fibrosis, tubular atrophy and Scr (*p*<0.05).

Conclusions: Our results show the use of the specific urine and plasma FTIR biomarkers will be a novel approach to investigate progressive kidney diseases, including GN and DN, without chemical manipulation of samples.

Funding: Private Foundation Support

FR-PO387

Omics Investigation of Urine Samples with and without Addition of a Protease Inhibitor Claire Boulange,¹ Ilse M. Rood,² Petra Zürgbig,³ Manuja Kaluarachchi,¹ Elaine Holmes,^{1,4} Franz S. Schaefer,⁵ John C. Lindon,^{1,4} Jack F. Wetzels,² Jeroen Deegens.² ¹Metabotrix Ltd, London, United Kingdom; ²Dep of Nephrology, RadboudUMC, Nijmegen, Netherlands; ³Mosaiques Diagnostics GmbH, Hannover, Germany; ⁴CSM, Dep of Surgery & Cancer, Imperial College London, London, United Kingdom; ⁵Dep of Nephrology, Univ of Heidelberg, Heidelberg, Germany.

Background: Urine is an ideal biofluid for biomarker discovery. To conserve the protein profile integrity, samples are stored with a protease inhibitor (PI). It is unknown whether the PI alters the metabolomic and proteome profiles. This study aimed to test the influence of the PI on metabolomic and proteomic analysis of urine samples.

Methods: We collected 10 urines from normal controls (NC; n=4) and membranous nephropathy patients (MN; n=6) and the samples were aliquoted. A PI (mini complete, Roche) was added to an aliquot of each sample. Urine samples were stored at -80°C. For metabolomics, samples were analyzed by ¹H NMR spectroscopy and HILIC-UPLC-MS. Multivariate analysis (MVA) was used to elucidate any PI effect in normal urine and proteinuria. For peptidomics, capillary electrophoresis-coupled mass spectrometry was used to profile the low molecular weight proteome in urine.

Results: Unsupervised MVA of urine NMR metabolic profiles showed clear discrimination between NC-PI, NC+PI, MN-PI and MN+PI. Supervised MVA of PI+ and PI- samples revealed subtle changes in metabolite levels and the presence of intense signals between 3.63 to 3.91 ppm in the PI+ samples, obscuring endogenous metabolite peaks. Unsupervised MVA of HILIC-UPLC-MS data showed discrimination between MN-PI and NC-PI. Supervised MVA of PI+ and PI- samples showed no detectable difference between these two sample types. For peptidomics, MVA between PI+ and PI- resulted in no statistically significant peptide differences. Further validation with a proteome classifier for CKD (CKD273) showed no statistical significant difference between samples with and without PI.

Conclusions: The PI addition did not affect the distinction between MN and NC in the metabolome and proteome analysis. However, PI may affect the analysis of metabolic subclasses using NMR. Therefore, samples with PI can be used, but with caution.

Funding: Other NIH Support - The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 305608 (EURenOmics).

FR-PO388

CNVkit – Software Tools for Analyzing Genomic Structural Variants David Fasel, Miguel Verbitsky, Simone Sanna-Cherchi. *Medicine, Columbia Univ Medical Center, New York, NY.*

Background: Copy number variations (CNVs) are increasingly recognized as genetic susceptibility factors for kidney disease. Determining whether CNVs are pathogenic or associated with a specific phenotype is challenging and few tools exist to aid in this process. Here we describe new software tools that provide semiautomated and flexible annotation and case-control analyses.

Methods: Copy number variations can be detected by multiple technologies, including DNA microarrays and next-generation sequencing (NGS). They span a few hundred base pairs to several million, often disrupting multiple genes. Our first software tool allows for customizable annotation of CNVs, and is flexible to keep up with changing annotation databases. The second tool compares the genomic coordinates of CNVs in case and control populations, and finds matching CNVs based on the percentage of mutual overlap. The tool then performs a Fisher's Exact tests on each pair of matching CNVs. The tool can also be used to compare CNVs with known pathogenic or benign variants. The software runs using command-line inputs and is able to handle data from tens of thousands of individuals in a timely fashion.

Results: CNVkit was recently used as a key component of a study (Verbitsky, JCI 2015), which compared CNVs in 419 children with chronic kidney disease against those found in 21,575 controls, and against predefined coordinates of known genomic imbalances. The software was used to homogenize results and output from different detection platforms, including array CGH, DNA SNP microarrays, and NGS, and to perform joint analyses. It was also used to identify copy number variable regions by using a sliding window approach to detect regions or genes that are enriched for deletions or duplications.

Conclusions: Structural variants are major susceptibility factors to congenital kidney malformations and pediatric kidney disease, and should be considered when investigating the cause of genetic disorders. CNVkit provides freely available and easy-to-use tools to help CNV annotation and interpretation.

Funding: NIDDK Support, Private Foundation Support

FR-PO389

Quantifying Uropathogenic Bacteria Infection in 3D Neal A. Paragas,¹ Alexander Klose,² ¹Medicine, Univ of Washington, Seattle, WA; ²In Vivo Analytics, Inc, New York, NY.

Background: Urogenital tract infection is a disease that annually afflicts more than 250 million people worldwide; however, the number of antibiotic resistant strains have been increasing while newly validated antibiotics have been lagging behind. We have developed a method to monitor and quantify a uropathogenic bacterial infection with the multispectral bioluminescence tomography (BLT) of a novel bioluminescent uropathogenic E. coli (UPEC-lux).

Methods: We modeled pyelonephritis by transurethral injection of UPEC-lux. First, we acquired bioluminescence images with a bioluminescent optical imager at four different spectral windows centered at 575, 615, 655, 695 nm and with bandwidth of 50 nm. The multi-orientation images were acquired using a mirror gantry for simultaneous imaging of the dorsal and ventral view. The animal was placed in a fixed position into a novel body shape conforming animal mold, placed onto the mirror gantry and spectral images were acquired. For in vivo bacterial quantification, a novel calibration device using tissue mimetic material was used. The light intensity imaging data became input to a novel BLT reconstruction algorithm based on an expectation-maximization (EM) method and the simplified spherical harmonics (SP3) equations for modeling in vivo light propagation. Post reconstruction, we calculated the total photon emission density of a volume of interest (VOI). We then calculated the in vivo organ bacterial load by co-registering it to a novel organ probability map.

Results: The EM method reconstructed the 3D photon emission density of the UPEC-lux and mapped the signal to a novel organ probability map. We analyzed these UPEC-lux in a model of pyelonephritis and we were able to determine the bacterial load in the kidney by BLT which correlated to CFUs from serial dilution of kidney homogenate (Pearson correlation coefficient R2=0.92). For the first time, we could demonstrate the feasibility of determining the bacterial burden in the kidneys.

Conclusions: The ability to monitor bioluminescent signal non-invasively will be a powerful tool to understand the pathophysiology of urinary tract infections and a new method to test novel antibiotics.

Funding: NIDDK Support

FR-PO390

Public Engagement of Kidney Related Health Information on the Internet Samir Sulaiman, Joseph A. Vassalotti, Vijay Lapsia. *Medicine, Icahn School of Medicine, New York, NY.*

Background: The National Kidney Disease Education Program (NKDEP), a part of the National Institutes of Health (NIH) provides an authoritative, up-to-date and trusted consumer health information resource for patients with kidney disease. We hypothesized that the US government (GOV) supported websites would have the highest consumer engagement of kidney related health information on the internet.

Methods: We used traffic rank based on publicly available data obtained from alexa.com and semrush.com, as a marker of website consumer engagement and popularity. We identified the top websites in the health category and disease sub-categories. The websites were classified based on ownership and data collected on unique US visitors, rank, page views per visitor and daily time spent.

Results: In the general health category, the NIH website ranked at the top; however, the consumer focused NLM website ranked 9th, behind webmed.com (2nd) and mayoclinic.org (5th). Among the top 25 websites across all disease categories, Davita.org, a for-profit business, was the only kidney related website. Cancer was the only disease condition with more than 1 website in the top 25 (7 total). The NKDEP ranked 8th in the genitourinary disorders group. The NKDEP had fewer unique US visitors (59,408) compared to Davita.com (307,729) and Kidney.org (241,550).

Rank	Website	Unique US Visitors *	Global Rank	US Rank	Daily Pageviews per Visitor	Daily Time
1	Davita.com	307,729	41,440	8,699	3.98	5:36
2	Kidney.org	241,550	59,136	17,450	1.94	3:02
3	Depend.com	107,230	199,782	40,617	2.5	3:16
4	Kidneyfund.org	81,945	197,479	53,036	1.73	3:02
5	Auanet.org	37,892	229,408	68,797	2.2	2:34
6	ic-network.com	44,773	270,113	58,424	2.5	3:45
7	Urologyhealth.org	68,523	184,328	86,788	1.24	2:06
8	Nkdep.nih.gov	59,408	subdomain data NA			
9	Renalinfo.com	NA	738,600	401,828	2.1	1:55
10	Kidneyurology.org	NA	929,030	415,571	1	1:43

*Estimates as of 05/15/2015
NA: Not available

Conclusions: In terms of consumer engagement, the kidney specific NIH website - NKDEP, as well as the non-profit kidney.org supported by the National Kidney Foundation were out performed by Davita.com, a publicly listed for-profit company by an unexpectedly wide margin.

FR-PO391

Media Awareness and Reporting of Dialysis Disruptions and Death from Natural Disasters in the United States Samir Sulaiman, Lindsay E. Jubelt, Vijay Lapsia. *Medicine, Icahn School of Medicine, New York, NY.*

Background: Patients receiving in-center hemodialysis are particularly vulnerable during and after disasters. Evidence of morbidity/mortality from disruption to dialysis in a disaster is limited and is so far based on statistical inference. We investigated media awareness and reporting of dialysis disruptions and death during natural disasters in the US.

Methods: We identified all major disaster declarations by the US Federal Emergency Management Agency. Disasters since 2000, excluding man-made and wildfires, with at least 1 known death were included. We then conducted a systematic Google News search to identify articles within 30 days of each disaster in the electronic mass media (media). Articles were screened for dialysis related key words and classified into 3 categories according to reported potential for missing dialysis, missed dialysis or death.

Results: Of 887 natural disasters from 2000-2015, 120 had at least 1 reported death (total 4,383 deaths). Hurricanes and winter storms had the highest impact on dialysis patients with 5 reported deaths. Of 19 hurricanes incidents, 13 articles referred to dialysis, reporting 7 dialysis disruptions, 4 dialysis deaths and 12 instances of potential disruptions to dialysis. Only 1 of the 61 deaths reported during 3 winter storms was dialysis related, with 2 instances of dialysis disruptions and 3 instances with potential for dialysis disruption. Tornadoes, which occurred most often and resulted in the second highest mortality had no coverage in the media during its aftermath.

Variable	Number	Deaths	Articles with dialysis disruptions	Instances of Dialysis Death	Instances of Dialysis Disruptions	Potential For Dialysis Disruptions
Hurricanes	19	2,702	13	4	7	12
Tornadoes	84	1,454	0	0	0	0
Earthquakes	2	3	0	0	0	0
Floods	11	162	0	0	0	0
Tsunami	1	1	0	0	0	0
Wildfires	0	0	0	0	0	0
Winter Storms	3	61	5	1	2	3
Total	120	4,383	18	5	9	15

*Dialysis Death: Death due to disaster related disruption to dialysis

Conclusions: Based on media reports, hurricanes and winter storms are major contributors of treatment disruption and mortality in patients on dialysis. Media reports can help identify the magnitude of disruption to dialysis operations as well as deaths.

FR-PO392

A Comparison of Physician Reporting versus Computer Algorithms for CMS Data Reporting on Form CMS-2728 Mohammed Said Malas,^{1,2} Ranjani N. Moorthi,¹ Jon D. Duke,² Sharon M. Moe.¹ ¹IU, Indianapolis, IN; ²RI, Indianapolis, IN.

Background: The CMS-2728 form (ESRD Medical Evidence Report) assesses 23 comorbidities chosen to reflect poor outcomes and increased mortality risk. Previous studies have questioned the validity of physician data entry on forms CMS-2728 and the relationship to hard outcomes. We hypothesize that reporting of comorbidities by a computer algorithm identifies more comorbidities and therefore is superior to physicians' completion of the forms.

Methods: We collected data from CMS-2728 forms for all 296 patients who had incident ESRD diagnosis and received chronic dialysis between 2005 and 2014 at Indiana University outpatient dialysis centers. We analyzed patients' data from electronic records systems that collated information from multiple sources. Previously utilized computer algorithms or natural language processing was used to extract data on 10 comorbidities (Table) for a period of up to 10 years prior to ESRD incidence. These algorithms incorporate billing codes, prescriptions, and other elements that are relevant to each comorbidity. We compared the presence of these comorbidities on the forms to the determined presence according to the algorithms.

Results: The computer algorithms had higher reporting of comorbidities compared to physician completion of the forms (Table). This remained true when decreasing the data span to one year and using only single health center data sources.

Comorbidity	Computer algorithms		Physician completed forms		p-value
	% Present	% Absent	% Checked	% Unchecked	
CHF	44.3	55.7	16.9	83.1	<0.01
DM	57.4	42.6	36.8	63.2	<0.01
HTN	95.3	4.7	88.9	11.1	<0.01
CAD	28	72	9.8	90.2	<0.01
COPD	14.5	85.5	5.4	94.6	<0.01
Alcohol abuse	12.8	87.2	3.7	96.3	<0.01
Cancer	15.9	84.1	6.1	93.9	<0.01
Substance abuse	27.7	72.3	4.4	95.6	<0.01
CVA	11.1	88.9	6.1	93.9	<0.01
Inability to ambulate	6.8	93.2	3	97	<0.05

Conclusions: Data reporting using computer algorithms may increase the capture of comorbidities for form CMS-2728 which may result in more accurate standardized mortality ratio for dialysis units and improve quality reporting.

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FR-PO393

Kidney Dashboard: An Integrated Support Tool for Clinical Care and Research Involving Kidney Patients Jamie S. Hirsch,^{1,2} Hojjat Salmasian,² Amy Y. Chan,³ David Vawdrey,^{3,2} Matthew Fred,³ Krzysztof Kiryluk,¹ ¹Div of Nephrology, Dept of Medicine, Columbia Univ, New York, NY; ²Dept of Biomedical Informatics, Columbia Univ, New York, NY; ³NewYork-Presbyterian Hospital, New York, NY.

Background: Large amounts of data are contained in electronic health records (EHR), and retrieval of relevant information for nephrology patients is cognitively complex and time-consuming. This results in inefficiencies, missed opportunities to improve care, and difficulty adhering to complex clinical guidelines. We developed a Kidney Dashboard, an integrated tool that gathers and analyzes information to facilitate the care and research of kidney patients.

Methods: Relevant clinical data were catalogued and categorized, including visit history, billing data, vital signs, labs, imaging, pathology, and medications. We automated generation of derived data, such as estimation and trending of eGFR, proteinuria, and automated CKD staging. We implemented a comprehensive rule-based alert system based on KDIGO guidelines to provide real-time clinical decision support.

Results: The Dashboard was created within the clinical information system at NewYork-Presbyterian Hospital, incorporating inpatient and outpatient data from multiple sources. It uses a tile layout, where each tile represents a relevant section of data that matches clinician workflow, e.g., renal function, anemia, bone and mineral metabolism, glomerulonephritis, etc. Repeat eGFR and proteinuria data are presented as interactive longitudinal graphs. The Dashboard integrates delivery of comprehensive stage-specific decision support and creates a portable phenotypic patient profile for genetic and epidemiologic research in kidney disease.

Conclusions: The Kidney Dashboard aims to improve care and facilitate research by consolidating all relevant EHR data at the point-of-care and generating phenotypic profiles of kidney patients. This project promotes precision nephrology, exemplifying the next generation of “smart” EHR tools. Following its public release, effectiveness of the Dashboard will be studied in focus groups and by time-motion studies and audit log analyses. The improvement in adherence to KDIGO guidelines will be tested prospectively.

FR-PO394

Forecasting a Renal Prognosis of IgA Nephropathy Using Machine Learning: Validation Study Hajeong Lee,¹ Junhyug Noh,² Hyosang Kim,³ Won Seok Yang,³ Yon Su Kim,¹ Dong Ki Kim,¹ ¹Internal Medicine, Seoul National Univ Hospital; ²Computer Science and Engineering, Seoul National Univ College of Engineering; ³Internal Medicine, Asan Medical Center.

Background: We aimed to develop and validate individual outcome prediction models in IgAN patients using machine learning.

Methods: We included adult IgAN patients from Seoul National University Hospital (SNUH, n = 1,540) and Asan Medical Center (AMC, n = 1,044) at the time of renal biopsy. They were divided into development (followed up ³10 years) and prediction (follow up <10 years) sets, respectively. The outcome was 10-year renal survival (10YRS) probability. We developed prediction models from SNUH test set by using logistic regression (LR) with Lasso method, a classification and regression tree (CART), and neural network (NN) using 16 clinico-pathologic variables. We also used bagging, random forest (RF) and boosting for ensemble learning. Finally, those models were validated internally in SNUH prediction set and externally in AMC development and prediction sets.

Results: Considering missing data, 1,514 and 847 patients were included from SNUH and AMC cohorts. In the LR model, eGFR, hemoglobin, proportions of GS and SS, interstitial fibrosis (IF) were selected as predictors for ESRD. In the CART model, eGFR 53.3 ml/min/1.73m² was proved to be a watershed for 10YRS, followed by, proportion of

GS and SS, IF, hemoglobin and proteinuria, sequentially. In addition, the ensemble learners showed good performance (accuracies of bagging, 0.868; RF, 0.874; boosting, 0.862). Those individual learners were validated internally with good performance (sensitivities of LR, 0.855; CART, 0.921; NN, 0.952; bagging, 0.857; RF, 0.921; boosting, 0.921). And finally, we proved the robustness of those models from external validation. Good performances of both development (sensitivities of LR, 0.847; CART, 0.867; NN, 0.855; bagging, 0.852; RF, 0.872; boosting, 0.851) and prediction sets (sensitivities of LR, 0.980; CART, 0.902; NN, 0.941; bagging, 0.882; RF, 0.902; boosting, 0.922) were showed.

Conclusions: We developed robustness of prediction models using machine learning for the individual’s likelihood of 10YRS in IgAN with both internal and external validation.

FR-PO395

Quantifying the Gender Reimbursement Gap in Nephrology Sadeem Ali, Xiangming Fang, Pankaj Jawa, Tejas P. Desai. *Nephrology, East Carolina Univ, Greenville, NC.*

Background: 2015 Medscape Compensation Report suggests that female providers earn less than male providers but the sample size was 19657; only 1% Nephrologists. To analyze the financial disparities, we compared total Medicare reimbursements paid to males & females.

Methods: We obtained reimbursement data from 2014 Medicare Provider Utilization & Payment Data Physician Public Use File. We consolidated all reimbursements by NPI number & categorized them by specialty & sex. We adjusted reimbursement differentials against number of Medicare beneficiaries seen & services provided. Linear regression models were used to compare reimbursements.

Results: We analyzed 246,996 providers in 13 specialties; 3% were Nephrologists. Female Nephrologists were reimbursed less \$41,776.96 (unadjusted); the 6th worst female-to-male reimbursement differential. In the adjusted analysis, female Nephrologists had the worst reimbursement differential: less \$17,971.66.

	Unadjusted	Lower	Upper	Adjusted	Lower	Upper
All	34125.68	34991.61	33259.79	19980.23	20599.45	19361.00
Cardiology	49532.75	54955.76	44109.75	8455.53	11946.07	4964.98
Endocrinology	21583.72	24379.99	18787.44	6217.03	7598.03	4836.03
Critical Care	21161.13	28712.74	13609.52	4532.58	8341.91	723.24
Family Practice	15029.77	15627.83	14431.70	8505.32	8957.32	8053.33
Gastroenterology	26556.29	28968.12	24144.45	4931.95	6055.77	3808.14
Hematology/Oncology	94350.55	109996.00	78705.13	7824.90	13788.98	1860.82
Infectious Disease	19176.82	23177.82	15175.83	6849.35	9562.13	4136.56
Internal Medicine	24158.97	25003.32	23314.62	11202.12	11792.19	10612.05
Nephrology	41776.96	47751.56	35802.36	17971.66	22675.94	13267.37
Hematology	52257.03	86317.14	18196.91	10160.85	21535.90	+1214.21
Medical oncology	81433.39	106482.80	56383.97	6330.41	16167.31	+3506.49
Rheumatology	85356.80	98925.86	71787.74	17127.52	23448.97	10806.07
Pulmonary	32543.52	36514.82	28572.21	11461.55	13870.45	9052.66

Female Reimbursement Deficits (\$). Lower & Upper Refer To 95% Confidence Interval Bounds.

Conclusions: When adjusted for the number of beneficiaries seen & services provided, female Nephrologists endure the largest reimbursement gap by sex in any specialty. Steps should be considered to close his gap.

FR-PO396

Protein Engineering for Renal Delivery of Molecular Therapies Pan Liu, Jing Jin. *Dept of Medicine-Nephrology/Hypertension, The Feinberg School of Medicine, Chicago, IL.*

Background: Targeted delivery of therapeutic enzymes to the kidney is desirable for treatment of renal diseases and beyond. Previously, approaches that exploit the renal excretion of low-molecular weight proteins (LMWP) have been attempted. However, these carriers can only deliver chemical compounds, and their efficiency is further hampered by fast renal clearance. In order to deliver enzyme cargos, we designed carrier proteins for specific and long-lasting renal delivery. We engineered a fusion protein comprised of a kidney-targeting polybasic tag (PBT) and an Fc segment for extended stability.

Methods: PBT-Fc and Fc-only control were produced as recombinant proteins. We used Duramycin as a LWMP control for alternative means of renal targeting through excretion. The probes were then separately labeled with a radionuclide ^{99m}Tcnetetium (^{99m}Tc) tracer. Following i.v. injection of the probes to rats, we performed SPECT in whole body scanning. Radiographs were obtained in a time series for up to 1 hour. In parallel, we performed histology studies of kidney sections to determine the sub-anatomical patterns of the injected probes.

Results: Prominent and sustained kidney localization of ^{99m}Tc-PBT-Fc (>95%) was observed by SPECT, a pattern in contrast to that of the ^{99m}Tc-Fc control that was mainly in blood circulation during the course of observation (only <5% in the kidney). ^{99m}Tc-

Duramycin reached the kidney quickly and then followed through urinary excretion to the bladder. By 20 minutes less than 5% remained in the kidney. The imaging results were consistent with IHC findings from mouse kidney following probe injections, which shows the PBT-Fc, but not Fc-alone, binding the glomeruli and tubule basement membrane shortly after injection. PBT-Fc sustained in the kidney for at least 10 days.

Conclusions: Our engineered PBT-Fc carrier exclusively targets kidney through binding to the glomeruli and tubule basement membrane. This recombinant probe also achieves long-lasting kidney retention (days as compared to minutes for LMWP), yet another desirable property for targeted therapeutic delivery. This vehicle will potentially be useful for delivery of molecular therapies, particularly enzyme proteins, to the kidney.

FR-PO397

Dynamic Culture on an Orbital Shaker Alters the Phenotype of Primary Human Renal Tubular Epithelial Cells *Nicholas J. Ferrell,¹ Jin Cheng,¹ Simeng Miao,² William Henry Fissell,¹* ¹*Nephrology, Vanderbilt Univ Medical Center, Nashville, TN;* ²*Biomedical Engineering, Vanderbilt Univ, Nashville, TN.*

Background: Primary cells cultured *in vitro* gradually lose features characteristic to the *in vivo* cell type, variously termed “senescence” or “culture stress.” Culture conditions that help maintain cell-specific phenotype are advantageous for cell biology and tissue engineering. Here we evaluated the phenotype of primary renal tubular epithelial cells after applying apical fluid shear stress using an orbital shaker.

Methods: Human renal tubular epithelial cells were isolated from donor kidneys not suitable for transplant. Cells were cultured on Transwell inserts under static conditions or on an orbital shaker at a frequency producing fluid shear stresses of 2 dyn/cm². Transepithelial resistance was measured daily. After 2 weeks in culture, cell density was analyzed by counting DAPI stained nuclei, and expression of tubule-specific markers was measured by PCR and western blotting.

Results: Dynamic culture significantly increased steady state transepithelial resistance from 344±31 to 544±32 Ω·cm² (p<0.001) and resulted in a 21.5±2.1% (p<0.001) increase in cell density. Gene expression of tubule epithelial cell markers (GGT1, COL4A1, COL4A2, NHE3, and NAPP2) increased with fold changes in expression of 4.3±0.3, 4.1±0.3, 3.1±0.2, 2.1±0.4, and 1.9±0.2, respectively. Cells grown under shear also showed increased protein expression of gamma-glutamyl transpeptidase.

Conclusions: Primary renal tubular epithelial cells grown on an orbital shaker with physiological levels of fluid shear stress appear to express proximal tubule markers more than cells grown in static conditions. This may be due to increased nutrient delivery and waste removal with improved mixing at the apical brush border, or due to specific gene regulation related to mechanotransduction. Further mechanistic insight may allow investigators to develop improved *in vitro* culture systems for cell biology and tissue engineering and more accurate *in vitro* models of disease.

Funding: NIDDK Support

FR-PO398

CRISPR/Cas9-Mediated Site-Specific Mutation in Rat Angiotensin Gene via Direct Injection of One-Cell Embryos *Yaochun Zhang,¹ Zakir Hossain,² Bo Lan,¹ Chang-Yien Chan,¹ Hui Kim Yap,¹ Kar Hui Ng,¹* ¹*Dept of Paediatrics, National Univ of Singapore, Singapore;* ²*Cancer Science Inst of Singapore, National Univ of Singapore, Singapore.*

Background: Genetically modified animals represent a crucial tool for understanding gene function in development and disease. The recently developed CRISPR/Cas9 system is an efficient gene-targeting technology to generate genetically modified animals. We have performed exome sequencing in a Singapore Chinese family with X-linked recessive membranous nephropathy associated with Fanconi syndrome and anti-tubular basement antibodies, and identified AMOT, coding for angiotensin, as a novel candidate gene with a putative disease-causing mutation p.S50G in the N-terminal of the p130-AMOT isoform. Preliminary work confirmed the expression of angiotensin in renal tubular cells. This study aimed to introduce the mutation into rat genome via direct injection of CRISPR/Cas9 into one-cell embryos, establishing rat models for downstream pathological studies.

Methods: The tracrRNA:crRNA fused single guide RNA (sgRNA, 20ng/μl), together with Cas9 protein (40ng/μl) and a single-stranded oligonucleotide (ssODN, 3ng/μl), which encodes the p.S50G mutation of angiotensin and serves as template for HR-mediated repair, were introduced into the rat pronucleus via microinjection. Pups produced from the injected embryos were first detected by mismatch-sensitive T7 endonuclease I digestion. Animals carrying mutations were sequenced to determine the precise sequence.

Results: In the 32 survived pups, one (3.1%) founder rat was identified to carry the heterozygous mutation. After crossing F0 with a wild-type rat, ten F1 rats were delivered, of which four males (40%) were carrying the mutation on their X chromosomes, while 2 (20%) were heterozygous females. No phenotype data is available currently as the animals are only three weeks old. Homozygous female rats are expected to be produced by crossing between the F1 animals.

Conclusions: In conclusion, a heritable site-specific mutation was successfully introduced into the rat genome with the CRISPR/Cas9 system. This one-step method of generating site-specific mutations in rats will greatly accelerate the *in vivo* study of gene functions.

Funding: Government Support - Non-U.S.

FR-PO399

Double Transduction of a Cre/LoxP Lentiviral Vector: A Simple Way to Generate Cell-Specific Knockdown Mice *Shin-Wook Kang, Bo Young Nam, Meiyan Wu, Tae-Hyun Yoo.* *Brain Korea 21 PLUS, Severance Biomedical Science Inst, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Genetically engineered mice have been used to elucidate the function of specific genes. Transgenic mice generated by conventional knockout techniques using oocytes or embryonic stem cells are most commonly used to downregulate genes, but this method has certain limitations. Therefore, a novel method to knock down specific genes in a cell specific manner in adult mice was devised by lentivirus (LV)-assisted transfer of short hairpin RNA.

Methods: *In vitro*, the LV suspension containing LV-Hoxb7 Cre and/or LV-Aquaporin 3 shRNA (shAQP3) was added to cultured mouse renal collecting duct cells (CDs) and mouse mesangial cells (MMCs). *In vivo*, first, LV-Hoxb7 Cre was injected into the loxP-EGFP mice to check the Hoxb7 promoter efficiency. Second, LV-loxP shAQP3 was injected into the Hoxb7 Cre transgenic mice to check shAQP3 function. Third, consecutive injections of LV-Hoxb7 Cre and LV-loxP shAQP3 were made to C57BL6/J mice.

Results: *In vitro*, LV-Hoxb7 Cre worked only in CDs due to the presence of Hoxb7 in CDs but not in MMCs. Furthermore, combined infection of CDs with LV-Hoxb7 Cre and LV-loxP shAQP3 significantly inhibited the protein expression of AQP3 along with the disappearance of EGFP protein expression, suggesting that LV-Hoxb7 Cre and LV-loxP shAQP3 used in this study worked together effectively. *In vivo*, kidney CD-specific AQP3-knockdown mice were generated by consecutive injection of LV-Hoxb7 Cre and LV-loxP shAQP3 in adult C57BL6/J mice. In mice treated with LV-Hoxb7 Cre alone, mCherry protein expression occurred only in CDs, while LV-loxP shAQP3 injection alone led to an increase in EGFP expression in all cells. In the kidney, AQP3 expression in mice injected with LV-Hoxb7 Cre or LV-loxP shAQP3 alone did not differ, but consecutive injection of LV-Hoxb7 Cre and LV-loxP shAQP3 significantly reduced AQP3 expression. However, the expressions of AQP3 in other organs did not differ between the groups.

Conclusions: Double transduction of Cre- and loxP-based LV can be a simple way to generate cell-specific knockdown mice, and this method may also be applicable to other species.

FR-PO400

Local Delivery of Interleukin-10 via Injectable Hyaluronic Acid Hydrogels to Prevent Local and Systemic Injury in Ischemic Acute Kidney Injury *Danielle Soranno,¹ Chris Altmann,² Sarah Faubel,² Ana Andres-hernando,²* ¹*Pediatrics & Bioengineering, Nephrology, Univ of Colorado, Aurora, CO;* ²*Medicine, Nephrology, Univ of Colorado, Aurora, CO.*

Background: AKI is pro-inflammatory and causes systemic complications via IL-6. Here, we use injectable hyaluronic acid (HA) hydrogels to deliver IL-10, an anti-inflammatory cytokine, to improve local and systemic outcomes of AKI.

Methods: Four treatment groups were followed for 28 days following AKI (15 μL of therapy delivered 3 days status-post AKI), and compared to healthy and untreated AKI controls (n=5): IL-10 in saline delivered under the left kidney capsule (LK IL-10); IL-10 suspended in HA delivered subcutaneously (SQ gel/IL-10); HA with or without IL-10 injected under the left kidney capsule (LK gel, LK gel/IL-10); HA hydrogels were developed as previously reported. Serial measurements of blood urea nitrogen and creatinine were followed at 1, 4, and 28 days. Serum IL-6 was measured at sacrifice. Immunohistochemistry (IHC) was performed to identify collagen type III deposition. Positive cells were quantified (20 images/section, in cortex). ANOVA with Dunnett’s posthoc was used to determine significance.

Results: All treatment groups normalized BUN, Cr and serum IL-6 by day 28 while the untreated AKI cohort had a persistent increase in BUN, Cr and IL-6. All treatment groups showed a significant reduction in collagen deposition in both left and right kidneys compared to untreated AKI, with variable effect depending on the mode of HA/IL-10 delivery.

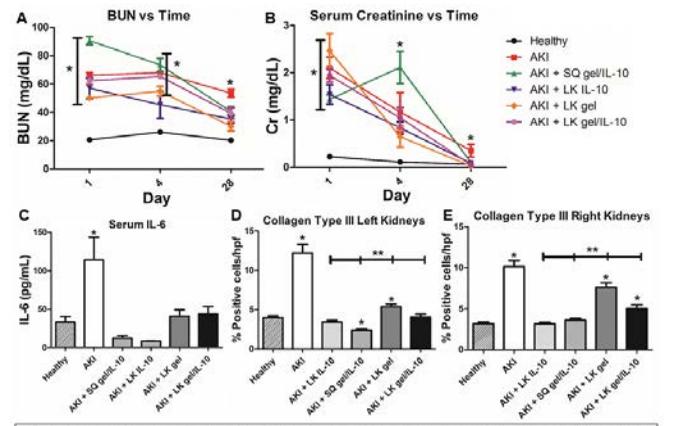


Figure 1: Serial sera (A) blood urea nitrogen (BUN) and (B) creatinine (Cr) to assess kidney function over time. (C) Serum IL-6 to assess systemic inflammation 28 days following AKI. IHC for Collagen type III in (D) left and (E) right kidneys. * indicates statistical significance compared to healthy or AKI control, respectively. n = 5, p < 0.01.

Conclusions: Injectable HA hydrogels can be used to deliver IL-10 and improve local and systemic outcomes of ischemic AKI. Therapy improved renal function, reduced collagen deposition, and reduced systemic IL-6 28 days following AKI. HA alone improved outcomes; the addition of IL-10 to the HA resulted in further histological improvement.

Funding: Private Foundation Support

FR-PO401

Substrate Stiffness Regulates Renal Epithelial Cell Cilia Formation via Autocrine TGF β Signaling Mingfang Ao,¹ Jin Cheng,¹ Nicholas J. Ferrell,¹ H. David Humes,³ Shuvo Roy,² William Henry Fissell.¹ ¹*Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN;* ²*Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA;* ³*Nephrology, Univ of Michigan, Ann Arbor, MI.*

Background: The primary cilium senses the extracellular environment. Malformation of primary cilia has been shown to result in kidney disease. Although much is known regarding ciliogenesis, the role of mechanical features of the microenvironment in cilia formation is poorly understood.

Methods: Human primary proximal tubule epithelial cells (HRECs) and LLC-PK1 cells were plated on collagen-coated polyacrylamide gels with different stiffness (0.5 KPa, 1 KPa, 10 KPa and 40 KPa) and grown for 5 to 7 days. Cilia formation was analyzed by immunofluorescence staining of AC-tubulin followed with microscopy imaging. Protein expression was measured by immunoblotting. Recombinant TGF β 1 and an inhibitor of TGF β RII SB431542 were used for TGF β signaling modulation. LiCl was utilized to stimulate P-GSK3 β .

Results: Stiff hydrogels (10 KPa and 40 KPa) gave rise to higher ciliary density than compliant gels (0.5 KPa and 1KPa) did (60% vs 20%). Furthermore, this phenotype could be altered by manipulation of transformation growth factor beta (TGF β) signaling: addition of TGF β 1 could increase the cilia frequency even when the cells were on compliant gels; similarly, inhibition of TGF β receptor II impairs cilia formation in the context of stiff substrates. Further supporting a role for TGF β , substrate stiffness was associated with increased SMAD2 and GSK3 β phosphorylation. Incubation with LiCl also increased GSK3 β phosphorylation and cilia formation independent of TGF β .

Conclusions: Substrate stiffness determines cilia formation through TGF β signaling via downstream GSK3 β phosphorylation. This work highlights that substrate mechanical properties have a strong influence on markers of differentiation. This has relevance for tissue engineering efforts and also suggests a mechanism of disease progression in the scarred kidney. This may broaden researches on kidney disease and contribute to disease therapy.

Funding: Other U.S. Government Support

FR-PO402

An Additive Role of Microfluidics on KLF 15-Induced Differentiation of Human Primary Podocyte Seung Hee Yang,¹ Eunjin Bae,² Sejoong Kim,² Kwon Wook Joo,^{1,2} Chun Soo Lim,^{1,2} Yon Su Kim,^{1,2} Dong Ki Kim.^{1,2} ¹*Kidney Research Inst;* ²*Internal Medicine, Seoul National Univ College of Medicine, Seoul.*

Background: Podocyte de-differentiation is one of major problems during the process of primary podocyte culture. Recently, much interest has been focused on the topic; yet lengthy podocyte differentiation process hinders a progress. Kruppel-like factor 15 (KLF 15) was reported to be a novel transcriptional regulator of podocyte differentiation and its expression was increased by retinoic acid (RA) which promotes the differentiation of podocytes. But, the duration of podocyte differentiation process remains long. Here, we present a novel in vitro protocol to induce podocyte differentiation.

Methods: To mimic in vivo biological environment of glomerulus, a polydimethyl siloxane (PDMS) microfluidic device was used. The human primary podocytes were cultured in the 500 μ m by 130 μ m microfluidic channel and were stimulated with a laminar fluidic shear stress of 0.5 dyn/cm² for 5 days. Various dose of RA was used to promote podocyte differentiation.

Results: In this research, we were able to reduce the time required for podocyte differentiation with higher shear stress and higher dose of RA. A couple of tests were conducted to verify the podocyte differentiation through the protocol. First, the phenotype of podocytes changed from cobblestone like shape to arborized cells. Through immunofluorescence staining, the increased expression of cytoplasmic synaptopodin and intercellular junction ZO-1 was confirmed. Moreover, KLF 15 expression was also increased. These molecules were also quantified with mRNA expression through real-time PCR. The size of podocytes became larger and the height of podocytes increased by a factor of 2.3 fold. Lastly, the podocytes aligned with the direction of flow.

Conclusions: In conclusion, we were able to promote podocyte differentiation in the shorter processing time with microfluidics and RA. Yet, more effort to mimic biological aspects of kidney such as complex structure with multiple cell layers and round surface is necessary.

FR-PO403

CCL18 Correlates with Disease Activity in ANCA-Associated Necrotizing Glomerulonephritis Silke R. Brix,¹ Christian F. Krebs,¹ Martin Busch,² Thorsten Wiech,³ Ulf Panzer,¹ Rolf A. Stahl.¹ ¹*III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Germany;* ²*Klinik für Innere Medizin III, Universitätsklinikum Jena, Germany;* ³*Inst für Pathologie, Universitätsklinikum Hamburg-Eppendorf, Germany.*

Background: Microarray analysis of renal tissue from patients with antineutrophil cytoplasmic antibody (ANCA)-associated necrotizing glomerulonephritis (GN) revealed the CC chemokine ligand 18 (CCL18) as the highest up-regulated chemokine. The renal production of CCL18 was associated with fresh glomerular lesions and impairment of renal function. The cellular sources of CCL18 were identified as macrophages and dendritic cells. CCL18 serum levels were elevated in patients with newly diagnosed ANCA GN as well. In order to test whether CCL18 might serve as a biomarker of relapsing renal ANCA disease, we prospectively analyzed CCL18 serum levels.

Methods: Hundred thirty-five patients with biopsy proven ANCA GN were prospectively analyzed for CCL18 serum levels. Patients included in the study were in remission on maintenance therapy (n=117) or without immunosuppressive treatment (prednisolone 5mg or less was accepted) (n=18). Serum levels of CCL18 were measured by ELISA every three months. Renal relapse was defined as either rising serum creatinine with urinary red cell casts or biopsy-confirmed active ANCA-associated glomerular lesions (i.e. fibrinoid necrosis and/or cellular crescents) accompanied by an intensification in immunosuppressive treatment.

Results: During a mean follow up time of 11.6 \pm 8.3 months, 16 patients developed a renal relapse. CCL18 levels were higher in relapsing patients when compared with patients who remained in remission (p<0.0001; 167.50 \pm 85.04 ng/ml vs. 83.17 \pm 46.38 ng/ml). CCL18 serum levels increased at the time of relapse and decreased after immunosuppressive therapy was restarted or intensified (n=16; ANOVA; p<0.001).

Conclusions: CCL18 serum levels are associated with disease activity in patients with ANCA GN and might serve as a marker of renal relapses in the surveillance of these patients.

Funding: Government Support - Non-U.S.

FR-PO404

Prognostic Value of Persistent Hematuria and Proteinuria in ANCA-Associated Vasculitis: Data from the European Vasculitis Study Group (EUVAS) Therapeutic Trials Alexandre Karras,^{1,3} Thomas F. Hiemstra,^{2,3} Rachel B. Jones,^{2,3} David R.W. Jayne.^{2,3} ¹*Nephrology, HEGP Hospital, Paris, France;* ²*Nephrology, Addenbrooke's Hospital, Cambridge, United Kingdom;* ³*On behalf of the EUVAS Study Group.*

Background: Renal involvement is frequent ANCA-associated vasculitis (AAV), due to crescentic glomerulonephritis (CGN). Hematuria (Hu) and proteinuria (Pu) are detected during the initial and active phase of CGN but the prognostic value of the persistence of these urinary abnormalities during the remission phase of AAV is still controversial.

Methods: Data were combined from three EUVAS trials (IMPROVE, RITUXVAS, MYCYC), providing data for Hu and Pu at month 6 (M6) following initiation of immunosuppression and patient follow-up until month 18 (M18). Hu was defined as the presence of >10 RBC/mm³. Proteinuria was evaluated by protein-to-creatinine ratio (PCR, g/mmol).

Results: Data concerning 337 patients were available for analysis. ANCA specificity (PR3/MPO) was 58/37%, renal involvement was present in 73% of cases and initial mean eGFR was 46 \pm 32 ml/min/1.73m². Hu was still positive at M6 in 27% of cases, although 96% of patients were in AAV remission. Positivity of Hu at M6 was associated with more severe initial nephropathy but was not predictive of renal dysfunction at last FU (mean eGFR at M18 was respectively of 55 \pm 24 and 60 \pm 24 ml/min for Hu+ and Hu- patients, p=NS). Proteinuria at M6 was <0.03 g/mmol in 53% of cases, between 0.03 and 0.1 g/mmol in 25%, >0.1 g/mmol in 22%. Among patients with M6 Pu >0.1 g/mmol, 29% had CKD stage 4 or 5 at M18, vs 3.5% and 11.5% respectively for patients with M6 PCR <0.03 and 0.03-0.1 g/mmol. Multivariate analysis using a mixed effects model demonstrated that decrease of eGFR during follow-up was independently associated with age (p<0.001), baseline eGFR (p<0.001) and M6 proteinuria (p=0.002), but not with M6 haematuria (p=0.284) nor ANCA specificity (p=0.82).

Conclusions: Persistence of micro-hematuria during the remission phase of AAV is associated with more severe initial renal involvement but does not predict poor renal outcome. Degree of proteinuria at M6 reflects more severe kidney damage and is an independent predictor of CKD progression in AAV nephropathy.

FR-PO405

ANCA Associated Vasculitis: Safe and Effective Induction of Remission with Low Dose Cyclophosphamide, Rituximab, and Reduced Exposure to Glucocorticoids Frank B. Cortazar, Karen A. Laliberte, Andrew P. Murphy, Katherine M. Cosgrove, William Franklin Pendergraft, John Niles. *Renal Associates, Massachusetts General Hospital, Boston, MA; Kidney Center, Univ of North Carolina (UNC), Chapel Hill, NC.*

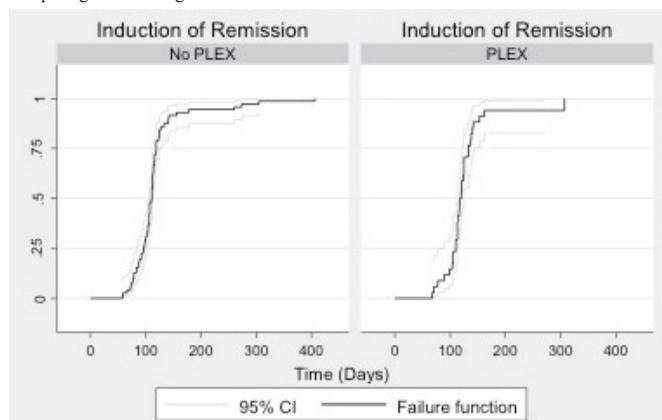
Background: Rapid induction of remission in ANCA-associated vasculitis(AAV) is essential to prevent irreversible organ damage. Current regimens use glucocorticoids(GC) combined with either cyclophosphamide(CYC) or rituximab(RTX). To effectively induce remission while minimizing GC exposure, we devised a standard induction(SI) protocol that combines RTX, low-dose bridging oral CYC, and a rapid GC taper.

Methods: Retrospective analysis of AAV pts treated w/ new SI regimen: RTX 1gm Q2wk x 2 doses, oral CYC 3mg/Kg/d x 1 wk and 1.5mg/Kg/d x 2 mths (adj for eGFR), and pulse solumedrol followed by a rapid prednisone(pred) taper to 15mg/d by 5wks. Remission defined as BVAS-WG 0 and pred dose \leq 7.5mg/d. Pts received SI alone or SI+ plasma exchange (PE).

Results: 74 pts treated with SI and 35 pts w/SI+PE (table1). Time to remission in the SI and SI+PE was 117 \pm 53 and 122 \pm 39 days, respectively (p=0.67). Cumulative incidence plots (Figure 1). Among survivors, 100% of SI and 97% of SI+PE achieved remission. 3 pts (4%) in SI and 1 (3%) in SI+PE died during induction. There were 0.04 treatment-related serious adverse events/pt month in both groups.

Baseline	SI	SI+ PE	p value
Age	61 \pm 16	65 \pm 17	0.24
% Women	62	49	0.17
% MPO	67	60	0.35
Baseline Cr (mg/dL)	1.8 \pm 1.1	4.9 \pm 1.9	<0.01
% Dialysis Dependence	1	11	<0.01
Initial BVAS-WG	6.3 \pm 2.8	8.7 \pm 3.3	<0.01

Conclusions: RTX with low-dose bridging CYC allows for successful induction of remission in essentially all AAV pts while attenuating exposure to high dose GC. Treatment-related adverse events were minimal. Our data provide an impetus for a randomized trial comparing this new regimen with the standard of care.



Funding: Clinical Revenue Support

FR-PO406

Reduced Risk of Cancer with Substitution of Cyclophosphamide with Azathioprine for Maintenance Treatment of ANCA Associated Glomerulonephritis Sanjeevan Srikandarajah,¹ Knut Aasrod,² Tor Aage Myklebust,³ Anna Reisaeter,⁴ Rune Bjoerneklett.^{1,5} ¹Renal Research Group, Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; ²Dept of Nephrology, St. Olav Univ Hospital, Trondheim, Norway; ³Cancer Registry of Norway, Oslo, Norway; ⁴Norwegian Renal Registry, Oslo Univ Hospital Rikshospitalet, Oslo, Norway; ⁵Dept of Medicine, Haukeland Univ Hospital, Bergen, Norway.

Background: ANCA associated vasculitis (AAV) is associated with an increased risk of cancer and a dose-dependent oncogenic effect of cyclophosphamide (CYC) appears to be a major explanatory mechanism. The concept that Azathioprine (AZA) can safely substitute for CYC in maintenance treatment of AAV was demonstrated in the CYCAZAREM study (2003) and has been adopted by all hospitals treating ANCA associated glomerulonephritis (AAGN) in Norway. In the present study, risk of cancer in patients with AAGN using CYC versus AZA for maintenance treatment has been compared.

Methods: Patients diagnosed with AAGN registered in the Norwegian Kidney Biopsy Registry 1988-2012 were included. The study cohort was linked to the Cancer Registry of Norway. Standardized incidence ratios of cancer were calculated. A competing risk regression model, using death as a competing risk, and with adjustment for; age, gender, ANCA category and kidney transplantation were used to compare the CYC and AZA groups regarding risk of cancer. The observation period was time from diagnostic kidney biopsy to death, first-time cancer or end of year 2013.

Results: We identified 485 patients with AAGN for analysis. Mean age was 58 years (SD 17 years) and 267 (55%) were males. Mean duration of follow-up was 7.2 years (SD 6 years and range 0.0-24.3 years). During follow-up 53 cancers (first cancer, all-sites) appeared, SIR 1.26 (0.97-1.67). In the CYC maintenance group 49 cancers appeared, SIR 1.40 (1.06-1.87) and in the AZA maintenance group 4 cancers, SIR 0.57 (0.22-1.98). Risk of cancer was significantly lower in the AZA as compared to the CYC maintenance group (p<0.05), estimated risk reduction being approximately 60%.

Conclusions: Substitution of CYC with AZA for maintenance treatment of AAGN is associated with significantly reduced risk of cancer.

FR-PO407

Double Positivity for ANCA and Anti-GBM Antibodies: Clinical Characteristics and Long-Term Outcomes of a Multi-Centre Cohort Stephen Paul McAdoo,¹ Anisha Tanna,¹ Sophie Ohlsson,² Zdenka Hruskova,³ Maria Weiner,⁴ Jeremy B. Levy,¹ Vladimir Tesar,³ Marten Segelmark,⁴ Charles D. Pusey.¹ ¹Imperial College London; ²Lund Univ; ³Charles Univ Prague; ⁴Linköping Univ.

Background: Co-presentation with both ANCA and anti-GBM disease is a rare phenomenon. Current studies of such cases include small numbers and report variable outcomes. We aim to describe the clinical features and outcomes of a large cohort of contemporary patients identified from three large European centres.

Methods: This is a retrospective cohort study, which included patients with both ANCA and anti-GBM antibodies ('double-positive', DP) from three centres, who presented after 2000, and for whom at least 1 year follow-up data was available. We have compared parameters to patients presenting with 'single-positive' (SP) anti-GBM disease.

Results: We have identified 78 anti-GBM+ patients, of whom 37 (47%) were DP for ANCA (70% MPO, 27% PR3, 3% MPO+PR3). DP patients were older (mean age 63 vs 54 yrs, p=0.048) and had longer symptom duration before diagnosis (6 vs 2.5 wks, p=0.049). There were no differences in renal function, dialysis-requirement, or frequency of lung haemorrhage between groups, although DP patients had more chronic injury on renal biopsy (33% vs 7% tubular atrophy, p=0.001). SP and DP groups were treated similarly. There were no differences in early (3 month) or late (5 year) patient or renal survival (5 year survival 78% vs 81%, p=0.49), although DP patients had a significant risk of relapse (8 vs 0 relapses over median follow-up of 3.9 years, p=0.01) that in all cases was associated with recurrence or rising titre of ANCA.

Conclusions: This is the largest reported series of European patients with double seropositivity for ANCA and anti-GBM antibodies. Patient and renal-survival was comparable to SP anti-GBM disease, although DP patients have greater risk of relapse related to their ANCA status, and so require long-term follow-up and consideration of maintenance immunosuppression. DP cases had a longer prodrome of symptoms and evidence of chronic damage of renal biopsy, suggesting that ANCA-induced glomerular inflammation may precede and contribute to the development of anti-GBM disease.

Funding: Government Support - Non-U.S.

FR-PO408

Pulse Methylprednisolone for Induction of Remission in Severe ANCA Associated Vasculitis Is Associated with an Increase in Adverse Events but No Improvement in Outcome Dimitrios Chanouzas,¹ Julie Anne G. McGregor,² Alan D. Salama,³ Wladimir M. Szpirt,⁴ Neil Basu,⁵ Matthew David Morgan,¹ Caroline J. Poulton,² Juliana Bordignon Draibe,³ Elizabeth Krarup,⁴ Paula I. Dospinescu,⁵ Jessica Anne Dale,¹ William Franklin Pendergraft,² Keegan Lee,³ Martin Egfjord,⁴ Susan L. Hogan,² Lorraine Harper.¹ ¹Univ of Birmingham, United Kingdom; ²Univ of North Carolina Kidney Center; ³Univ College London, United Kingdom; ⁴Copenhagen Univ Hospital, Denmark; ⁵Univ of Aberdeen, United Kingdom.

Background: Intravenous pulse methylprednisolone (MP) is frequently used as part of remission induction in severe ANCA associated vasculitis (AAV). However, there are no studies assessing its efficacy in the setting of AAV, while treatment related complications remain the main source of morbidity.

Methods: We retrospectively analysed outcomes of 114 patients that presented with severe AAV at 5 large centers in the United Kingdom, United States and Denmark between 2000-2013. All patients received high dose oral corticosteroids, cyclophosphamide and plasma exchange. Rituximab treated patients were excluded. The chi square and Mann Whitney U tests were used for statistical analysis.

Results: Fifty-two patients received MP (median dose 1.5g over 3 days) in addition to standard therapy while 62 did not. Patient characteristics and disease severity were comparable between the two groups. There was no difference in survival at 3 months (MP: 94.2 vs non MP: 91.9%, p=0.633) or 12 months (84.6 vs 80.6%, p=0.579). Renal recovery amongst survivors (63.5 vs 72.6%, p=0.297) and relapse rates at 12 months (11.6 vs 8.6%, p=0.617) were similar. MP therapy was associated with more infections per patient at 3 months (0.7 vs 0.3, p=0.005) and more new onset diabetes (28.6 vs 6.6%, p=0.002).

Conclusions: Within the limitations of this study we found that the addition of MP to standard therapy for remission induction in severe AAV led to a significant increase in adverse events with no improvement in survival, renal recovery or relapse rates. Our results question the currently widespread use of MP in severe AAV and suggest that a randomised controlled trial is urgently needed in order to definitively address this issue.

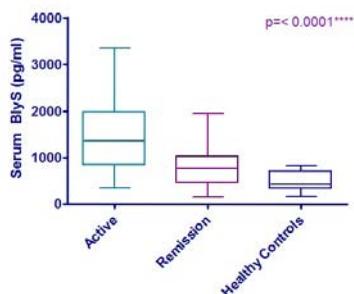
FR-PO409

Serum B Lymphocyte Stimulator (BlyS) Levels as Markers of Disease Activity in Anti-Neutrophil Cytoplasm Antibody (ANCA) Associated Vasculitis (AAV) Anisha Tanna, Stephen Paul McAdoo, Frederick W.K. Tam, Charles D. Pusey. Imperial College, London.

Background: B lymphocyte stimulator (BlyS) has been implicated in the pathogenesis of AAV. Previous studies have shown elevated levels in active disease, and following anti-CD20 therapy. Antineutrophil cytoplasm antibodies (ANCA) are not reliable predictors of disease activity and relapse and alternative markers are needed in order to tailor immunosuppressive therapy. The aim of this study was to determine the clinical significance of serum BlyS levels in our patients with AAV.

Methods: Serum samples were obtained from patients with AAV at our centre, and BlyS levels detected using sandwich ELISA. Clinical data were obtained by review of patient records.

Results: Samples were collected from 68 patients with AAV and 13 healthy controls. Thirty one patients were male, 44 Caucasian and 21 Indoasian. Fifty patients had granulomatosis with polyangiitis, 13 patients had microscopic polyangiitis and 5 had eosinophilic granulomatosis with polyangiitis. Significantly higher BlyS levels were found in patients with active disease than those in remission and healthy controls.



Thirty seven patients who had been treated with Rituximab had significantly higher BlyS levels ($p < 0.0001$). Eighteen patients had relapsed at 1 year following recruitment. These relapsing patients had significantly higher BlyS levels than those patients who did not relapse ($p = 0.0016$).

Conclusions: This study supports the role of BlyS in the pathogenesis of AAV. BlyS levels could be used as markers of disease activity and predictors of relapse. With increased use of rituximab in AAV, further studies are needed to assess the impact of B cell depletion on B cell survival factors. These findings highlight the potential role for BlyS antagonists in the maintenance of remission of AAV.

Funding: Government Support - Non-U.S.

FR-PO410

Predictors of Renal Histopathology in Antineutrophil Cytoplasmic Antibody Associated Glomerulonephritis Sophia Lionaki,¹ Clio Mavragani,² George Liapis,³ George Somarakis,⁴ John N. Boletis,¹ Alexandros Drosos,⁴ Athanasios Tzioufas,² Haralampos Moutsopoulos.² ¹Nephrology, Laiko Hospital, Athens, Greece; ²Pathophysiology, Univ of Athens, Greece; ³Pathology, Laiko Hospital; ⁴Rheumatology, Univ of Ioannina.

Background: Prompt, aggressive therapy is vital for anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN). In this regard, we aimed to identify predictors of distinct renal histopathological classes at the time of clinical diagnosis.

Methods: An inception cohort of patients with biopsy proven ANCA-associated GN was studied retrospectively. Demographics, clinical, laboratory, serological and radiological parameters were analyzed. Patients were classified on the basis of renal histopathology, according to the report by Berden et al (JASN 2010) for ANCA-associated GN by a renal pathologist into: focal class, crescentic class, mixed class and sclerotic class. A risk score was developed for each histopathological class using univariate and logistic regression analyses.

Results: Variables independently associated with focal class included disease duration up to diagnosis < 8 weeks, absence of red blood cell (RBC) casts by urine microscopy and eGFR > 49ml/min/1.73m²; with crescentic class > 40 erythrocytes/hpf, identification of RBC casts in urine, ear nose and throat (ENT) involvement and eGFR < 49ml/min/1.73m²; with mixed class age > 54 years, male gender, and absence of ENT involvement. In the presence of 2 or 3 risk factors a predictive risk score of each histopathological class was calculated: odds ratio (OR), 95% confidence intervals (CI), for focal class (2 risk factors) 17.5 (95% CI) [4.9-62.9], 38.0 [6.8-213.7] for crescentic class (3 risk factors), and 8.3 [1.0-67.5] (2 risk factors) for mixed class.

Conclusions: We propose a predictive algorithm of specific histopathological classes of ANCA-associated GN, which might provide a crude estimation of the disease activity in the glomeruli at presentation. This tool might assist the clinician in making decisions regarding the level of intensity of inductive immunosuppressive therapy at clinical diagnosis.

FR-PO411

Rituximab as a Cyclophosphimide Sparing Agent for Patients with Multi-Relapsing ANCA-Associated Small Vessel Vasculitis Sophia Lionaki,¹ George E. Fragoulis,² Alice Venetsanopoulou,² John N. Boletis,¹ Panagiotis Vlachogiannopoulos,² Haralampos Moutsopoulos,² Athanasios Tzioufas.² ¹Nephrology, Laiko Hospital, Greece; ²Pathophysiology, Univ of Athens, Greece.

Background: To evaluate the clinical efficacy and outcomes, of patients with multi-relapsing ANCA-associated Vasculitis (AAV), who received induction therapy with rituximab for a new disease relapse.

Methods: We retrospectively studied all patients with biopsy proven AAV, who were treated with rituximab upon a new relapse. A control group consisted of patients from the era prior to the initiation of rituximab in the treatment of AAV, was selected using the following criteria; i/history of relapse, ii/organ involvement at relapse, iii/ treatment with the standard regimen. Patients and controls were matched for age, gender, and disease

duration. Comparisons of disease outcomes along with the frequency and severity of adverse events were performed between groups. Rituximab was used with high dose glucocorticoids and depending on the organ involvement a short course of cyclophosphamide was added.

Results: Of 147 patients with AAV and a mean total follow up time of 78.2 months, 18 patients (12.2%) received induction treatment with rituximab for disease relapse. Time to 1st relapse from the 1st diagnosis of AAV was shorter in the rituximab group and the mean number of relapses per patient was significantly higher in this group. The mean BVAS score was similar between groups at study entry while 13/18 patients received a 3-month course of cyclophosphamide in addition to rituximab.

Characteristic	Rituximab group, N=18	Control group, N=18	p-value
Number of relapses per patient up to study entry (median) (range)	2 (1-4)	1(1-2)	0.009
Subsequent relapse, N(%)	3(11.1)	4(22.2)	1.00
Cyclophosphimide exposure post study entry (mean±sd) (grams)	24.39 (±32.5)	3.25(±3.09)	0.02
Follow up time post study entry (months)(range)	37(6-68)	53(8-228)	0.07

Conclusions: Rituximab was shown efficacious in patients with multiple relapsing AAV including cases with renal and pulmonary involvement. It allowed us to minimize the ultimate exposure to cyclophosphamide in these patients, which is crucial, as they accumulate remarkable toxicity in long-term.

FR-PO412

Differences Between Patients with Definite and Suspected ANCA-Associated Vasculitis in a Secondary Care Hospital Eline Houben,¹ Willem A. Bax,¹ Valentina A. Slieker,² Bastiaan Van Dam,¹ Fenneke C.P. Frerichs,¹ Gideon Verhave,¹ Erik Lars Penne.¹ ¹Dept of Nephrology, MCA-Gemini Group, Alkmaar, Netherlands; ²Laboratory of Clinical Chemistry, Hematology and Immunology, MCA-Gemini Group, Alkmaar, Netherlands.

Background: ANCA-associated vasculitis (AAV) is a rare disease with a broad spectrum of symptoms. Therefore, diagnosing AAV is often challenging. In an effort to provide guidance for clinicians, we aimed to identify differences between ANCA positive patients with a definite and suspected diagnosis of AAV.

Methods: In this retrospective study, all patients that tested positive for MPO and/or PR3 ANCA between 2005 and 2015 in a secondary care hospital in the Netherlands were analyzed. Patients were divided into subgroups according to clinical diagnosis and the Birmingham Vasculitis Activity Score (BVAS). Possible predictors for AAV, such as patient characteristics, clinical symptoms and ANCA titers were identified. Patients were also screened for commonly used exclusion criteria in trials.

Results: We included 240 patients with a positive MPO and/or PR3 ANCA, of which 120 patients were clinically diagnosed with AAV (group 1); all had a BVAS ≥ 3. Of the patients without the diagnosis AAV, 50 had a BVAS ≥ 3 (group 2) and 70 had a BVAS < 3 (group 3). In group 2, 39 patients had an alternative diagnosis, including other rheumatic diseases and infection. In a multivariable linear regression model, higher ANCA titers, higher BVAS and Ear Nose Throat (ENT) symptoms were predictive for AAV (all $p < 0.001$). Of the patients diagnosed with AAV, 21 (18%) would have been excluded from most trials, based on a malignancy (n=13) or drug use associated with vasculitis (n=8). Notably, characteristics of these patients did not differ significantly from the other AAV patients.

	age	male%	Median PR3	MPO	BVAS	renal symptoms %	ENT symptoms %
Group 1	62±14	63	94 (45-179)	38 (18-101)	6 (4-8)	68	67
Group 2	56±21	50	20 (10-32)*	9 (6-15)*	4 (4-5)*	56	20*
Group 3	50±21	53	24 (11-51)*	9 (7-18)*	2 (0-2)*	23	7*

* $p < 0.001$ as compared to Group 1

Conclusions: MPO and PR3 ANCA can be positive in a variety of diseases that may mimic AAV. Higher ANCA titers, BVAS and ENT symptoms were predictive for AAV in ANCA positive patients.

FR-PO413

Rituximab and Low-Dose Cyclophosphamide Therapy for Renal ANCA-Associated Vasculitis: Long-Term Follow-Up Nicholas R. Medjeral-Thomas,^{1,2} Nicholas D. Mansfield,¹ Stephen Paul McAdoo,^{1,2} Anisha Tanna,^{1,2} Megan Griffith,^{1,2} Jeremy B. Levy,¹ Tom Cairns,¹ H. Terence Cook,^{1,2} Alan D. Salama,¹ Ruth M. Tarzi,² Charles D. Pusey.^{1,2} ¹Imperial College Renal and Transplant Centre, Imperial College Healthcare NHS Trust, London, United Kingdom; ²Imperial College London, London, United Kingdom.

Background: The previously reported study of rituximab (RTX) and low-dose cyclophosphamide (CYP) followed by azathioprine maintenance for ANCA-associated renal vasculitis (AAV), suggested it was efficacious in inducing remission and has an acceptable side-effect profile (N Mansfield et al 2011). We have followed the cohort for over seven years and report the regimen's efficacy and safety profile.

Methods: Long-term outcomes were retrospectively ascertained from all 23 previously treated patients.

Results: Mean time since starting the treatment regimen was 83 months; twenty-one patients started the regimen more than five years ago. All patients achieved clinical remission within six weeks, with depletion of circulating CD19-positive B cells and significant reduction in median anti-PR3/MPO ANCA titre. After 84 months follow-up, five renal and four non-renal relapses were observed and treated in five patients. Median eGFR improved from 28 ml/min (range 11-63) at presentation to 49 ml/min (range 13-87) after one year and was maintained at 50 ml/min (8-90) at five years (n=21) and 46ml/min (22-76) at seven years follow-up (n=9). To date, three infections requiring hospital admission and four malignancies have been recorded.

Conclusions: This rituximab-based low-dose cyclophosphamide regimen followed by maintenance therapy provides safe and effective long-term treatment at more than five years follow-up.

FR-PO414

The Histopathologic and Clinical Determinants of the Change in GFR During the 1st year of Treatment in ANCA-Associated Vasculitis Pierre-Luc Lavoie,¹ Remi Goupil,¹ Michelle Goulet,² Maxime Rheume,² Soumeya Brachemi,³ Stephan Troyanov.¹ ¹Nephrology, Hôpital du Sacré-Coeur, Univ de Montréal, Montréal, QC, Canada; ²Internal Medicine, Hôpital du Sacré-Coeur, Univ de Montréal, Montréal, QC, Canada; ³Nephrology, CHUM, Montréal, QC, Canada.

Background: Identifying the predictors of the change in GFR in ANCA-associated vasculitis (AAV) is helpful to avoid prolonged immunosuppression in those where no benefits exist and to consider modifying therapy in those who should improve but fail to do so.

Methods: We retrospectively reviewed cases of AAV with a renal biopsy in 3 hospitals to determine predictors of the change in GFR (Δ GFR) during the 1st year of treatment. We considered demographics, pathology findings, treatments and complications incurred. In particular, we addressed the histopathologic classification (Berdin JASN 2010) proposing focal, crescentic, mixed and sclerotic subsets.

Results: Of 120 patients with AAV, 71 had a renal biopsy and received immunosuppression. They presented at an age of 59±13 with 48% female, 49% anti-MPO+ and a GFR of 32±30 mL/min including 22 patients on dialysis. Induction consisted of cyclophosphamide (93%), rituximab (6%), plasma exchange (27%) and pulse methylprednisolone (69%) in addition to oral corticosteroids. During the 1st year, patients recovered 15±20 mL/min/1.73m² with 11 no longer requiring dialysis. The Δ GFR increased up until 6 months, although it varied greatly individually. Age, hypertension, MPO positive serology, the extent of crescentic and sclerotic glomeruli, tubular atrophy and the histopathological classification were associated with a lower GFR at diagnosis. However, at one year only the histopathologic classification and the number of admissions for treatment-related complications predicted a lower Δ GFR. The focal, crescentic, mixed and sclerotic subsets experienced a 19±23, 17±15, 11±12 and -1±26 mL/min Δ GFR, respectively (p=0.026, trend test).

Conclusions: The change in GFR during the 1st year of treatment in AAV increased 15±20 mL/min. It appeared maximal at 6 months into therapy. The histopathologic classification helped predict the Δ GFR at 12 months, with a reduced benefit of therapy in the sclerotic subset.

FR-PO415

Analysis of Clinical Features in ANCA-Associated Vasculitis: 30 Years Single Center Experience – Relationship Between RPGN and Renal Prognosis Soko Kawashima, Shinya Kaname, Yoshinori Komagata, Yoshihiro Arimura. *First Dept, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan.*

Background: The clinical features of AAV, with respect to rapidly progressive glomerulonephritis (RPGN), have been changing, but were not well examined in Japan, where MPO-ANCA-associated vasculitis (MPO-AAV) are dominant in contrast to the Western countries. Thus, we retrospectively analyzed the clinical database of the 179 patients with AAV who were admitted to our hospital for the last 30 years.

Methods: At the onset, all patients fulfilled the Chapel Hill Consensus Conference (CHCC) classification criteria for MPA, GPA and EGPA. We divided the AAV patients into the 4 groups based on the presence or the absence of RPGN and hemodialysis, and compared the clinical features and renal prognosis. Among 179 AAV patients, 166 cases (92.7%) were MPO-ANCA positive and 14 cases (7.8%) were PR3-ANCA positive.

Results: RPGN was observed in 100 (55.9%) of the 179 patients, including 49 cases of maintenance hemodialysis group (A), 2 cases of temporary dialysis group (B) and 49 cases of non-dialysis group (C), in addition to 79 cases without RPGN and dialysis (D). Significant differences were observed in BVAS, CRP, eGFR and serum Cr concentration. There were no differences for treatment choice, rate of kidney biopsy and frequency of relapses among the groups. Comparison among the different periods for every 10 years show the tendency of an increase in age of onset and the downward trend of serum Cr concentration, rate of RPGN and maintenance hemodialysis, BVAS scores, and frequency of relapses and mortality.

Conclusions: These results have clearly shown the changing features of AAV in Japan, with an earlier detection and the improvement of renal and patient survival during the periods.

FR-PO416

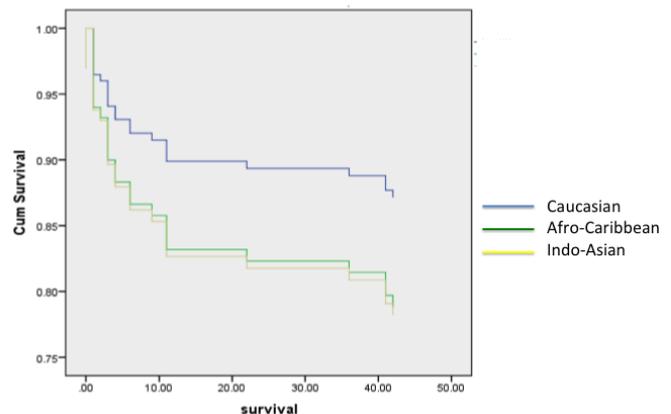
The Effect of Race on 5-Year Survival Outcomes in ANCA-Associated Renal Vasculitis Luxme Nadarajah, Vasantha M. Muthuppalaniappan, Ravindra Rajakariar. *Nephrology, Barts and The London NHS Trust, United Kingdom.*

Background: Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is a multi-systemic autoimmune disease characterized by inflammation of microscopic vessels. Renal involvement occurs in 70% of patients, with 1 year mortality rates exceeding 15%. With a prevalence of two cases per 100,000 populations there is a significant preponderance to Caucasians (C). Little is known about the outcomes in patients from Indo-Asian (IA) and Afro-Caribbean (AC) race despite an increasing number of cases seen with the disease.

Methods: We performed a single center, retrospective study, observing 5-year survival outcomes and relapse rates between C, IA and AC in ANCA-associated renal vasculitis. Electronic case notes over a 10-year period (2004-2014) were used collect data to include age at time of diagnosis, Birmingham vasculitis activity score (BVAS) at presentation, race, presence of diabetes and renal function. 5-year survival outcomes were analyzed using a cox proportional hazard model.

Results: In total 121 patients were included in the study, there were 84 (70%) C's, 31 (25%) IA's and 6 (5%) were of AC background. Median age was 66 years, 56% were men, 20% were diabetic and average BVAS score at presentation was 5. One-year relapse rates were low with 8 (6%) relapses seen. No significant difference in 5-year survival outcome was found between the races. Age at presentation significantly affected survival outcomes (p=0.007).

5 year survival outcomes dependent on race



Conclusions: We conclude that survival outcomes for IA and AC are not worse compared to those of C origin. Age remains to be a significant predictor in determining mortality outcomes. This study provides valuable clinical information in an area that has not been well studied.

FR-PO417

Prevalence of Increasing Prevalence of Otitis Media with ANCA Associated Vasculitis in Japan Takeshi Nakatsue,¹ Yukiko Nozawa,¹ Hiroe Sato,¹ Yoko Wada,¹ Takeshi Kuroda,² Masaaki Nakano,³ Ichie Narita.¹ ¹Div of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata Univ, Niigata, Japan; ²Health Administration Center, Niigata Univ, Niigata, Japan; ³Dept of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata Univ, Niigata, Japan.

Background: A new disease concept, otitis media with ANCA associated vasculitis (AAV), has been advocated.

Methods: One hundred and fifty seven patients (74 males and 83 females) with AAV (81 microscopic polyangiitis, 54 granulomatosis with polyangiitis (GPA), and 22 eosinophilic GPA) were admitted to Niigata University Hospital from 1989 through 2014. Twenty seven patients (17%, 13 males and 14 females) with otitis media were recruited. Their clinical features and laboratory data were analyzed.

Results: Fifteen patients were diagnosed as having definite GPA. Five were probable GPA. Lung or kidney lesions were not detected in other seven patients (Ears (E) only group). The initial symptoms in 22 patients (81%) were ears' one, such as impaired hearing (91

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%, congested feeling (32%), otalgia (14%), or tinnitus (14%). No evidence of vasculitis was proved in E only group. MPO- and PR3-ANCA were positive in 19 (70%) and six cases (22%), respectively. PR3-ANCA was observed only in definite GPA. MPO-ANCA titer in definite or probable GPA and in E only group were 103 ± 73.4 U/ml and 41.8 ± 26.4 U/ml, respectively ($p < 0.05$). From 1989 through 2009, 10 cases of otitis media with AAV (OMAAV) (0.48/year) out of 84 cases of AAV (4.0/year) were observed, whereas 17 cases of OMAAV (3.4/year) out of 73 cases of AAV (14.6/year) were observed from 2010 through 2014 ($p < 0.05$). All of E only group was seen in this period. Hypertrophic pachymeningitis was seen in seven cases (26%). Otitis media was involved in bilateral ears in 19 cases (70%). Lung and kidney lesions were in 20 and 11 cases, respectively. Necrotizing crescentic glomerulonephritis were observed in six cases. Some renal biopsies were avoided because of patients' impaired hearing.

Conclusions: OMAAV is increasing. Chest X ray, urinary test, and measuring ANCA should be considered in refractory otitis media.

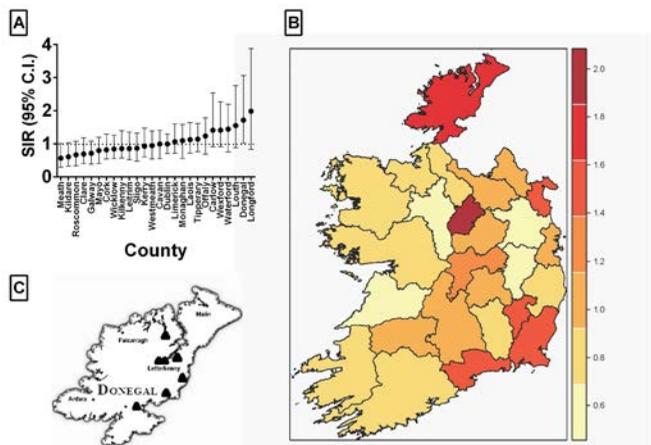
FR-PO418

Temporal and Spatial Clustering of Anti-Glomerular Basement Membrane Disease Mark N. Canney,^{1,2} Paul O'Hara,¹ Caitriona M. McEvoy,¹ Aileen C. Niland,¹ Mark Alan Little.² ¹*Irish Anti-GBM Study Group;* ²*Trinity Health Kidney Centre, Trinity College Dublin.*

Background: An environmental trigger has been proposed as an inciting factor in anti-glomerular basement membrane (anti-GBM) disease. We aimed to define country-wide incidence of anti-GBM disease, investigate clustering of cases in time and space and to assess the impact of spatial variability in incidence on outcomes.

Methods: National multicentre observational study of anti-GBM disease cases diagnosed in Ireland 1.6.2003-31.5.2014. We ascertained cases by screening immunology laboratories for instances of positive anti-GBM antibody and the national renal histopathology registry for biopsy-proven cases. We defined the population at risk using census figures. A variable-window scan statistic was used to detect temporal clustering. A Bayesian autoregressive spatial model was used to provide standardised incidence ratio (SIR) estimates for each county. Patient and renal survival were assessed using Kaplan-Meier and log-rank test.

Results: Seventy-nine cases were included. National incidence was 1.64 (95% CI 0.82-3.35) pmp/year. A temporal cluster was identified (n=10) in a 3 month period in early 2013; 6 (60%) were resident in the southeast. Spatial analysis revealed wide regional variation in SIR (fig 1A) and a cluster (B,C) in the northwest (n=7, SIR 1.71, 95% CI 1.02-3.06).



However, being in a cluster or distance from diagnosis site to treating center did not significantly impact on patient (HR 1.8, 95% CI 0.9-3.8) or renal survival (HR 0.7, 95% CI 0.4-1.1).

Conclusions: Country-wide incidence of anti-GBM disease is higher than reported by single centre studies. We detected clustering of cases in time and space supporting the hypothesis of an environmental trigger. Wide regional variation in incidence highlights the need for country-wide epidemiological studies of anti-GBM disease to further our understanding of its aetiology.

Funding: Government Support - Non-U.S.

FR-PO419

Venous Thromboembolism in ANCA Vasculitis Is Associated with Elevated Microparticle Tissue Factor Activity Elizabeth J. Brant, Carmen E. Mendoza, Yichun Hu, Susan L. Hogan, Ronald J. Falk, Patrick H. Nachman, Vimal K. Derebail, Donna O. Bunch. *UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Venous thromboembolism (VTE) is a severe complication of ANCA vasculitis (AAV). Mechanisms of VTE are not known, but tissue factor (TF)-bearing microparticles (MPs) from activated or apoptotic cells may play a role. We hypothesized that elevated microparticle tissue factor activity (MPTFa) is associated with VTE in AAV.

Methods: Patients without VTE (VTE^{neg}) were enrolled prospectively during active disease. Patients with VTE (VTE^{pos}) were included whether active or in remission at the time of VTE. Longitudinal platelet-free plasma (PFP) samples from 28 patients and 16 healthy

controls (HC) were assayed for MPTFa. All patients had ³3 samples spanning ³12 months. MPs isolated by centrifugation were incubated with Factor VIIa and Factor X. Absorbance was measured after addition of Factor Xa chromogenic substrate. Recombinant relipidated human TF was used as a standard. Values were expressed as a percent of MPTFa from a positive control (PFP from LPS-stimulated HC blood). Fisher's exact tests and Wilcoxon tests were used to compare categorical and continuous variables, respectively.

Results: Demographics were similar among patients and HC. VTE^{pos} and VTE^{neg} patients did not differ in ANCA serotype or titer, BVAS, D-dimer, other laboratory data, or organ involvement. VTE^{pos} patients had significantly higher peak MPTFa than VTE^{neg} patients (median 10.5 (IQR 9.7, 31.3) vs 2.8 (IQR 0.8, 5.2), $p < 0.0001$) and tended to have recurrently elevated levels. MPTFa of VTE^{pos} patients was similar to HC (median 2.0 (IQR 1.1, 3.3), $p = 0.4$). All VTE^{pos} patients had peak MPTFa above normal (mean + 2SD of HC = 6.5) versus 2/20 VTE^{neg} patients ($p < 0.0001$).

Conclusions: Patients with AAV who develop VTE have a notable propensity for increased MPTFa at times both near and remote from VTE. Conversely, those without VTE rarely exhibit MPTFa significantly higher than healthy controls during their disease course. Further study is needed to determine if elevated MPTFa can identify AAV patients at high risk for VTE and whether MPTFa contributes to thrombogenesis.

Funding: NIDDK Support, Private Foundation Support

FR-PO420

CD80 and Angiopoietin-Like 4 in Glomerulopathies Gabriel M. Cara-Fuentes,¹ Alfonso Segarra,² Eduardo H. Garin.¹ ¹*Pediatrics- Div of Nephrology, Univ of Florida, Gainesville, FL;* ²*Nephrology, Vall D'Hebron, Barcelona, Catalonia, Spain.*

Background: Proteinuria in MCD is thought to be due to an increased CD80 podocyte expression. Recently, podocyte angiopoietin-like 4 (Angptl4), has been suggested to induce proteinuria in MCD. **Objective:** To determine the pattern of CD80 and Angptl4 in MCD and other glomerulopathies.

Methods: 34, 30 and 32 patients with biopsy-proven MCD, FSGS and MN respectively, were included. Urinary and serum CD80 and Angptl4 were measured by Elisa. Differentiated human podocytes were incubated for 6 h with 15% of serum from MCD patients in relapse or in remission. Podocyte expression of CD80 and Angptl4 were measured by Western-Blot analysis. Urinary Angptl4 pl was measured by 2D electrophoresis. Statistical analysis: Mann-Whitney U test, Wilcoxon matched-pairs signed rank test for comparison of paired groups, and Spearman correlation.

Results: Urinary CD80 was increased in MCD patients during relapse, but not in patients with FSGS or MN, or normal controls. Serum CD80 was lower in patients with glomerulopathies during relapse compared to normal controls. Urinary Angptl4 was increased in patients with glomerulopathies compared to normal controls, whereas serum Angptl4 was higher in normal controls compared to patients with glomerulopathies. Both urinary CD80 and Angptl4 correlated with proteinuria in MCD, FSGS and MN. Podocytes exposed to sera from MCD patients in relapse showed a significant increase in CD80 expression but not Angptl4 when compared to MCD patients in remission. Urinary Angptl4 pl was 5.4.

Conclusions: 1) Decreased serum CD80 and Angptl4 in nephrotic syndrome is likely due to increased urinary losses. 2) Increased urinary CD80 was only observed in MCD patients in relapse while increased urinary Angptl4 was seen in all the glomerulopathies. 3) Podocyte CD80 but not Angptl4 expression was increased by serum from MCD patients in relapse. 4) Urine Angptl4 in MCD has a pl of 5.4, suggesting no role on Glomerular Basement Membrane charge. 5) While CD80 seems to play a role in proteinuria in MCD, Angptl4 detected in urine in MCD and other glomerulopathies is likely the result of an increased glomerular permeability.

FR-PO421

APOL1 Polymorphism Determines HIV Boarding in Human Podocytes Pravin C. Singhal,¹ Xiqian Lan,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,² Joanna Mikulak.³ ¹*Dept of Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY;* ²*Medicine, Rambam Health Care Campus, Haifa, Israel;* ³*Clinical and Experimental Immunology, Humanitas Clinical and Research Center, Milan, Italy.*

Background: Patients of African ancestry with untreated HIV infection, carrying the G1 or G2 kidney disease risk variants (Vs) at the *APOL1* gene are at a >10-fold greater risk for developing HIV-associated nephropathy (HIVAN) compared to those without these risk variants. Although podocytopathy in HIVAN has been attributed to the direct effect of HIV infection, the mechanistic contribution to kidney injury of the *APOL1* allelic state remains to be elucidated.

Methods: We evaluated the priming effect of IL-1 β on human podocyte (HP) *APOL1* expression. To evaluate the effect of IL-1 β on HIV-1 processing in podocytes, HPs were pre-stimulated with human recombinant IL-1 β for 6h and then incubated with HIV-1 followed by analysis for the HIV-1 strong stop DNA by qPCR analysis. HPs treated under similar conditions were evaluated for Dc-sign (a receptor known to contribute for podocyte HIV entry) expression. To determine the effect of over expression of *APOL1* (G0) and *APOL1* variants (G1/G2) HPs were either transfected with *APOL1*G0/G1/G2 plasmids, or HPs were pre-stimulated with 10 ng/mL of IFN- γ and then incubated with HIV-1 and analyzed for HIV-1 strong stop DNA concentration at various time points and also measured for their lysosomal bioactivity.

Results: *APOL1* expression increased after incubation of podocytes with the HIV. In turn, *APOL1* expression was further enhanced in response to augmented entry of virus consequent to enhanced expression of Dc-sign and IL-1 β treatment, consistent with viral load dependency. Podocytes over-expressing the non-risk *APOL1* gene (G0), either through

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pre-treatment with IFN- γ or through transfection with the specific APOL1-expressing plasmid displayed diminished HIV accumulation. In contrast, comparably increased expression of the APOL1 variants was not only permissive for HIV entry but also facilitated HIV accumulation through down regulation of lysosomal bioactivity.

Conclusions: These findings indicate that ApoL1 polymorphism may determine HIV boarding in human podocytes.

Funding: NIDDK Support

FR-PO422

Podocyte Depletion in Alport Syndrome Complex *Larysa T. Wickman, Jeffrey B. Hodgin, Su Qing Wang, Farsad Afshinnia, David B. Kershaw, Roger C. Wiggins. Univ of Michigan.*

Background: Increasing evidence suggests that podocytes may play a role in Alport Syndrome Complex (ASC) progression of renal disease. We previously reported that podocyte detachment rate measured in urine is increased in ASC, suggesting that podocyte depletion could play a role in causing progressive loss of kidney function. This result therefore raised the question as to whether progression in ASC could be due to progressive podocyte depletion from glomeruli.

Methods: To address this question we measured podocyte nuclear number, density and cell area (Glepp1 positive) density in the same 3 μ m thick formalin-fixed paraffin-embedded histologic section. Twenty six kidney biopsies from 21 patients were collectively designated as ASC including both classic Alport Syndrome (with thin and thick GBM segments and lamellated lamina densa [n=20]) and Thin GBM [n=6]. Twenty protocol kidney biopsies from deceased kidney transplant donors were used as age-matched controls.

Results: When compared to controls, podocyte number per glomerulus, % podocyte depletion, nuclear density and cell area density were all decreased in the ASC cohort (P<0.01). The mean podocyte volume (MPV) was correspondingly larger for ASC than control (P<0.05) representing podocyte hypertrophy to compensate for reduced podocyte number and density. Podocyte depletion was present in ASC biopsies prior to detectable histologic abnormalities. No abnormality was detected by light microscopy at <30% podocyte depletion, minor pathologic changes (mesangial expansion and adhesions to Bowman's capsule) were present at 30-50% podocyte depletion, and FSGS was progressively present above 50% podocyte depletion. Estimated GFR did not change measurably until >70% podocyte depletion. Low level proteinuria was an early event at about 25% podocyte depletion and increased in proportion to podocyte depletion.

Conclusions: These data support the concept that progressive podocyte depletion occurs from an early stage in ASC leading to FSGS-like pathologic changes and eventually to End Stage Kidney Disease. Early intervention to reduce podocyte depletion is projected to prolong kidney survival in ASC.

FR-PO423

Actinin-4, Synaptopodin, Nephrin, and Nep-1 Expression in Proteinuric Patients *Ashwani Kumar,¹ Ritambhara Nada,¹ Charan Singh Rayat,¹ Krishan L. Gupta,² ¹Dept of Histopathology, Post Graduate Inst of Medical and Research, Chandigarh, India; ²Dept of Nephrology, Post Graduate Inst of Medical and Research, Chandigarh, India.*

Background: Podocytes have an important role in glomerular filtration barrier. Primary podocytopathies and secondary podocyte injuries in presence of immune deposits at different locations results in proteinuria. We compared expression of podocyte structural proteins; alpha actinin-4 (α Act-4), synaptopodin (Syn), and slit diaphragm proteins; nephrin (Nep), and nep-1 by immunofluorescence (IF) in minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous glomerulonephritis (MGN), and IgA nephropathy (IgAN).

Methods: Two hundred cases (n=50 each) along with controls were stained with FITC tagged α Act-4, Nep, Syn, and Nep-1 antibodies. Immunofluorescence was graded as mild, moderate, and intense. Immunogold staining with α Act-4, and Syn antibodies was done to see localization electronmicroscopically (EM).

Results: The α Act-4 showed mild to moderate intensity (40% & 60%) in controls and most of the cases in all proteinuric groups. Up-regulation was noted in 52% cases of MGN and only 14-19% of other groups. Loss of α Act-4 was seen in about 15-25% in all groups except MGN where it was rare. Syn showed mostly mild staining (70%) in controls. Marked up-regulation (61%) was seen in the majority of MGN cases whereas moderate intensity was seen in other groups (MCD>IgAN>FSGS). Loss of staining was less but equally present in all groups. Nep showed mild intensity in controls; however moderate to intense staining was seen in MGN (46% & 14%), whereas loss of staining was noted in all other groups (FSGS-54%, MCD-43, IgAN-59%). Nep-1 also showed mild staining in controls. However, up-regulation was seen in only MGN (47%). Similar to Nep, complete loss of Nep-1 was seen in FSGS-74%, MCD-53%, and IgAN-54%. These differences in staining of MGN were statistically significant when compared with controls and with other groups. EM showed α Act-4 and Syn in podocyte body and processes.

Conclusions: Structural proteins and slit diaphragm proteins are up-regulated in MGN whereas the variable degree of loss is commonly seen in FSGS, MCD, and IgAN.

Funding: Government Support - Non-U.S.

FR-PO424

Use of Spot Urine Protein Creatinine Ratio to Predict Proteinuria in Nephrotic Syndrome in NEPTUNE *Marie C. Hogan,¹ Jonathan P. Troost,² Peter J. Nelson,³ Heather N. Reich,⁴ Sharon G. Adler,⁵ Daniel C. Catran,⁴ Gerald B. Appel,⁶ Debbie S. Gipson,² Wenjun Ju,² Matthias Kretzler,² John C. Lieske.¹ ¹Mayo; ²UMich; ³UWash; ⁴UT; ⁵UCLA; ⁶ColumbiaU.*

Background: Random urine protein creatinine ratio (UPC) is used to estimate 24 hr urine protein excretion (24P) yet little data are available wrt sensitivity & specificity, especially in pts with glomerular proteinuria.

Methods: The Nephrotic Syndrome Study Network (NEPTUNE) studies newly diagnosed patients with MCD, FSGS, & MN. Total protein, alb & creat are measured in random & 24 hr urine collections at a central biobank at postbiopsy baseline & subsequent visits within 2 yrs of dx.

Results: Of 603 participants, 302 have same day spot & 24 hr ur samples with a total of 827 samples across all visits eligible for this analysis. Urine protein excretion (g; median; 25, 75%) was higher in adults (1.0; 0.3, 2.3) than peds (0.2; 0, 0.7). Spot UPC correlated better with 24 hr UPC than 24P in both adults ($r=0.79$ vs 0.60) & peds ($r=0.84$ vs 0.67). Using these data we derived equations to predict 24P from spot UPCs: for adults $24P = [10]^{(0.88 * (\log_{10} [\text{Spot UPC}]))}$ & for peds $24P = [10]^{(1.06 * (\log_{10} [\text{Spot UPC}]))}$. The efficiency (AUC) of spot UPC to accurately predict 24P values above thresholds of 0.5g, 1.0g, 2.0g, 3.0g, 6.0g and 10.g ranged from 0.83-0.97 in adults & peds. In subgroup analysis the correlation between log-transformed UPC and log-transformed 24P was similar in all age ranges & diseases, but stronger in obese vs. normal wt subjects ($b_{\text{Normal wt}} = -0.78$ (0.69, 0.88); $b_{\text{Overwt}} = 0.85$ (0.78, 0.93); $b_{\text{Obese}} = -0.93$ (0.85, 1.0) $p=0.03$).

Conclusions: Among MCD, FSGS, & MN pts UPC correlates only moderately with 24P. 24P is best derived from spot UPC using a non-linear estimating equation. Wt influences reliability of spot UPC. Our data also suggest UPC can be used with caution to identify those pts with 24P above clinically relevant cut points. As 24P is susceptible to collection errors & implications of threshold values may be dependent on patient size, additional studies to evaluate spot UPC vs 24P and clinical outcomes are warranted.

Funding: NIDDK Support, Other NIH Support - The Nephrotic Syndrome Study Network Consortium (NEPTUNE); U54-DK-083912, is a part of NCATS Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, and the National Institute of Diabetes, Digestive, and Kidney Diseases. RDCRN is an initiative of ORDR, NCATS. Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, NephCure Kidney International and the Halpin Foundation., Private Foundation Support

FR-PO425

Rituximab in Steroid Dependent and Calcineurin Inhibitor (CNI) Dependent/Intolerant Adult Idiopathic Minimal Change Disease and Focal Segmental Glomerulosclerosis *Harbir Singh Kohli, Raja Ramachandran, Vivekanand Jha, Krishan L. Gupta. Nephrology, PGIMER, Chandigarh, UT, India.*

Background: Steroid dependent (SD) nephrotic syndrome (NS) is managed with CNIs but the long-term results are limited by CNI nephrotoxicity and dependence. This prospective study was done to evaluate the effect of rituximab in those SD-NS who were either CNI dependent or had CNI induced nephrotoxicity.

Methods: This prospective study was undertaken in patients of SD MCD/FSGS patients were given initially CNI (tacrolimus). Of these, who were either tacrolimus (TAC) dependent (relapse NS on tapering or stopping after 1 year at least) or had TAC induced nephrotoxicity (rise in serum creatinine >2 times the baseline) were enrolled for rituximab administration during Oct 2013 to Oct 2014. Patient with at least 6 months follow-up were analysed. After achieving remission with oral prednisolone the steroids were tapered to stop and single dose of Rituximab (375 mg/m²) was administered. CD-19 count was performed at Day 2 and at 3 months. Outcome studied was remission complete or partial at the end of 6 months. Complete remission (CR): 24-hour urine protein < 500 mg/day with normal serum albumin (≥ 3.5 gm/dl). Partial remission (PR): 24 hour urine protein ≥ 500 mg/day but <2 gm/day or <50% of baseline with normal serum albumin (≥ 3.5 gm/dl).

Results: A total of 12 cases, 10 Tac dependent (duration of TAC-35 \pm 12.6 months) and 2 with nephrotoxicity were studied. Basic disease was MCD in 4 (33.3%) and FSGS in 8 (66.7%). Mean age was 21.8 \pm 8.4 yrs. Mean proteinuria, serum albumin and serum creatinine prior to enrollment in the study were 3.24 \pm 1.57 gm/day, 2.52 \pm 0.78 gm/dl and 0.79 \pm 0.15 mg/dl respectively. All achieved target CD-19 (<1%) with single infusion and 4 (25%) cases had risen in their CD 19 at 3 months and were given second dose. At 6 months, CR and PR was achieved in 9(75%) and 1(8.3%) respectively. There were 2 non-responders (16.6%). Of the 10 responders, 3 have completed 1 yr of follow-up and are in remission. Adverse event (pneumonia) was noted in 1 patient (8.3%).

Conclusions: Rituximab appears to be a promising agent in the management of adult CNI dependent or intolerant NS due to MCD/FSGS with minimal short-term adverse events.

FR-PO426

Treatment and Outcomes in Minimal Change Disease: Experience of a Single UK Centre Anthony Fenton, Stuart W. Smith, Peter Hewins. *Dept of Renal Medicine, Univ Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.*

Background: Minimal change disease (MCD) accounts for 10-25% of nephrotic syndrome in adults. We retrospectively reviewed the treatment and outcomes of MCD patients in our centre.

Methods: We identified adults who had undergone renal biopsy between June 1996 and March 2012 which was reported as being consistent with MCD, and who had at least 12 months of follow-up. Electronic hospital records were used for data collection.

Results: There were 78 cases, with median follow-up of 72 months. Baseline and treatment data are shown in the table (averages are mean, or median where distribution is skewed). 27% had a history of nephrotic syndrome in childhood. All but one patient (who entered remission spontaneously) were treated with prednisolone, and 97% achieved complete remission at a median time of 33 days (6-309), although 12% needed a second-line agent to do so. Mean number of relapses during the first 24 months was 1.0. 68% experienced at least one relapse, and 45% patients required second-line agents at some point. Regarding complications: 12% developed thromboembolic disease, 14% had an admission-requiring infection, and 41% had at least one episode of AKI. Mean follow-up creatinine was 91 µmol/L, but significantly higher in those who had had AKI (104 vs 85 p=0.04) and those who had received an ACEi (99 vs 78 p=0.01). Of 16 patients who underwent subsequent biopsy (all of whom had received a CNI), 8 showed evidence of CNI damage, and 5 were consistent with FSGS. Diabetes mellitus developed in 12% cases, and 8% patients died during follow-up.

Conclusions: Almost all treated adult MCD patients enter remission, although second-line agents are frequently required. Despite therapy, complications remain common, including AKI which is associated with residual reduced excretory function.

Demographics, clinical features, and therapies	
Age (years)	36
Sex (% male)	60
Ethnicity (%)	
White	72
South Asian	18
Black	8
Other	3
Baseline clinical findings	
Creatinine (µmol/L)	91
eGFR (ml/min/1.73m ²)	80
Urine ACR (mg/mmol)	645
Serum albumin (g/L)	22
Serum cholesterol (mmol/L)	9.6
Haematuria (%)	15
AKI (%)	28
Treatment (%)	
Prednisolone	99
CNI	32
Cyclophosphamide	13
Levamisole	9
MMF	8
Rituximab	5
ACEi/ARB	63

FR-PO427

Predictors for Relapse in Adult Minimal Change Disease Hajeong Lee, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim, Chun Soo Lim. *Internal Medicine, Seoul National Univ Hospital.*

Background: Minimal change disease (MCD) is well-known benign primary glomerulonephritis in adults because of their distinct rare renal progression to end-stage. However, their relapse-associated morbidity has been underestimated. In this study, we aimed to explore the predictors of relapse in adult MCD patients.

Methods: We reviewed clinical and pathologic characteristics of adult primary MCD patients from Seoul National University Hospital from 1979 to 2013. Patients who were presented by nephrotic syndrome and followed up more than 12 months were included. Patients suspicious for secondary MCD were excluded. Initial treatment regimens, their response, and complication were also reviewed. The number of relapse were classified as follows, no relapse, 1-2 relapses (relapse group 1), and ≥ 3 relapses (relapse group 2).

Results: A total of 195 patients were included in the final analysis. Among them, median age at the time of diagnosis was 38 (23-53) years and 113 (57.9%) were men. During median follow up of 81 (44-153) months, more than 90% of patients reached to remission after initial treatment. However, only 64 (32.8%) patients did not experience any relapse. Remaining 131 patients, 69 (35.4%) relapsed once or twice and 62 (31.8%) relapsed more than three-times. The younger, the more relapse was found. In addition, severity of nephrotic syndrome including was proportional to the relapse. Interestingly, proportion of mesangial proliferation was higher in no-relapse group compared with relapse group 1 and 2 (P = 0.033). Initial treatment regimen did not affect relapse, however, patients who received shorter treatment duration tended to relapse more. Considering complications, relapse group

2 showed significantly higher proportion of thromboembolic event than other two groups. Multivariate analyses found that younger age, lower serum albumin, mesangial proliferation and treatment duration remained as independent risk factor for relapse.

Conclusions: We proved that patients with younger age, severe nephrotic syndrome, lower mesangial proliferation and shorter treatment duration were prone to relapses. Moreover, relapse is morbid due to higher thromboembolic events in adult MCD patients.

FR-PO428

Rituximab in Relapsing Minimal Change Glomerulonephritis: Clinical Outcomes and Financial Analysis Kevin William Loudon, Clare Morlidge, Suresh Mathavakkannan, Ken Farrington, Barbara Thompson, Paul Warwicker. *Dept of Renal Medicine, Lister Hospital, United Kingdom.*

Background: Minimal change disease (MCD) accounts for 10-15% of adult nephrotic syndrome, with frequent relapses or steroid-dependency occurring in 25-30%. Glucocorticoids and calcineurin inhibitors are the mainstay of treatment, but can be associated with significant toxicity. Rituximab holds potential to induce long term remission in these patients, but in the United Kingdom is currently not funded based on perceived excessive cost.

Methods: Nine patients with frequently relapsing MCD (histologically confirmed) were given total dose Rituximab 1g - 2.4g divided into two - four doses from 2012 - 2014. Time from diagnosis to first Rituximab dose was 140 months (10 - 336). Cost effectiveness of Rituximab was assessed based on comparing annual relapse rates; inpatient/outpatient attendances and immunosuppressant medication in the two years prior, and one year post Rituximab. Data was obtained retrospectively using hospital finance records, NHS standard tariff and the British National Formulary (2015) respectively.

Results: In all nine patients Rituximab induced complete remission. All steroid-sparing agents were discontinued. Four patients remain on low dose prednisolone (less than 4mg). Mean follow-up was 15 months (6 - 30) with only one relapse at 19 months. Annual relapse rates fell from 1.83/year (0.5 - 6.0) to 0.12/year (0-0.57). Inpatient days fell from a mean of 4.2 days/year (0-39.6) to 1.7 days/year (0-4.5). Outpatient consultations fell from 12.5/year (5-26.4) to 7.3/year (4.5-25). Mean annualised pre-Rituximab costs were £6172 and post Rituximab, £5046, in 6/9 patients with sufficient length of follow up for comparison. No major complications were noted following treatment.

Conclusions: In patients with relapsing MCD, Rituximab proved to be cost effective and well tolerated. Burden of medication with attendant side effects, as well as inpatient and outpatient attendance were significantly reduced. Annualised costings showed a modest saving post Rituximab. Further randomised studies are required to confirm and extend these findings.

FR-PO429

Long-Term Outcomes of Nephrotic Syndrome, from Childhood into Adulthood Rebecca C. Hjorten, Frederick J. Kaskel, Kimberly J. Reidy. *Pediatrics, Div of Nephrology, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY.*

Background: Steroid Resistant Nephrotic Syndrome (SRNS) is known to have several long term sequelae including chronic and End Stage Kidney Disease (CKD and ESKD). However there are few studies on the long-term outcomes of steroid sensitive nephrotic syndrome. Presented here is a single center, retrospective case series from an urban, ethnically diverse population in the Bronx.

Methods: We utilized a medical record data mining tool to identify patients by ICD-9 code (1) with a diagnosis of nephrotic syndrome prior to age 18 (2) with a documented albumin <3.5 g/dL or random urine protein > 1 g/dL and (3) with at least one hospital encounter after age 18. Patients with a history of renal biopsy or who received immunosuppressant medication other than steroids were termed complicated nephrotic syndrome (CNS). All others were termed simple nephrotic syndrome (SNS). Patients with a diagnosis of asthma prior to age 18 with at least one hospital encounter after the age of 18 were used as controls. Each cohort was evaluated for diagnosis of hypertension, osteoporosis, cataracts, infertility and malignancy. Their last height, weight and creatinine were used to evaluate their height and weight percentile, BMI and estimated GFR by the MDRD equation.

Results: All three groups - SNS (n=173), CNS (n=169) and control (n=18225) had similar age at diagnosis, length of follow-up. Both the SNS and CNS groups had a greater proportion of short stature, cataracts, infertility and malignancy (Chi square statistic p < 0.05) [table 1]. In addition they had a greater percentage of patients with CKD by eGFR which is most notable at CKD stages 4 and 5 (Chi square statistic p < 0.05).

Conclusions: Our results show that even patients with uncomplicated nephrotic syndrome are at risk for significant outcomes, including chronic kidney disease. Further study is needed, however it implies that all patients with a diagnosis of nephrotic syndrome will need to be counseled regarding the risks associated with their diagnosis and should have long term monitoring for these outcomes, including worsening renal function, hypertension and malignancy.

Funding: Other NIH Support - NIH T32 Training Grant

FR-PO430

Apolipoprotein CI Levels Are Associated with the Urinary Protein/Urinary Creatinine Levels in Pediatric Idiopathic Steroid-Sensitive Nephrotic Syndrome Jun Odaka, Takahiro Kanai, Takane Ito, Jun Aoyagi, Takanori Yamagata. *Pediatrics, Jichi Medical Univ, Shimotsuke, Tochigi, Japan.*

Background: Various humoral factors have been proposed as causal agents of idiopathic steroid-sensitive nephrotic syndrome (ISSNS). In the present study, we analyzed serum proteins using mass spectrometry (MS) in a search for proteins that might be related to ISSNS pathophysiology.

Methods: We collected serial serum samples from 33 children with ISSNS. The serum samples were collected in each phase as follows: Phase A1 [the acute phase prior to steroid treatment (STx)], Phase A2 [remission with STx], and Phase A3 [remission without any medication]. We also included two control groups comprised of children with normal urinalysis (Group B) and children with a nephrotic syndrome other than ISSNS (Group C). The urinary protein/urinary creatinine (UP/UCr) ratios were not statistically different between Phase A1 and Group C. We used surface-enhanced laser desorption/ionization time of flight MS to analyzed samples.

Results: A total of 207 peptide ion peaks were detected in the range of m/z 2000–10000. Four peptide ions (m/z 6444, 6626, 8695, and 8915) were significant elevated during Phase A1 compared with Phase A2, Phase A3, and Group C. The intensities of m/z 6626, 8695, and 8915 were significantly correlated with UP/UCr levels. The m/z 6626 was identified as apolipoprotein CI (Apo CI).

Conclusions: Apo CI was detected as a protein associated with the UP/UCr levels in pediatric ISSNS. Our findings provide new insight into elucidating the pathophysiology of ISSNS.

Funding: Government Support - Non-U.S.

FR-PO431

Ofatumumab in Two Nephrotic Syndrome Children Marina Vivarelli,¹ Manuela Colucci,¹ Alice Bonanni,² Francesco Emma,¹ Gian Marco Ghiglieri.² ¹*Nephrology and Dialysis, IRCCS Bambino Gesù Pediatric Hospital, Rome, Italy;* ²*Nephrology and Dialysis, Gaslini Pediatric Hospital, Genova, Italy.*

Background: Rituximab (RTX), an anti-CD20 monoclonal antibody, is an effective treatment in patients with frequently-relapsing or steroid-dependent nephrotic syndrome (Ravani, JASN 2015). However, some patients develop adverse reactions. We describe the use of a humanized anti-CD20 monoclonal antibody, ofatumumab (OFA), as a viable alternative.

Methods: Patient 1 is a 3-yr-old boy who presented at 18 months with NS initially resistant to treatment with oral prednisone. He was then treated with 3 iv boluses of methylprednisolone followed by cyclosporinA, with remission. Upon steroid discontinuation, NS relapsed. Prednisone was restarted and a single dose of RTX was planned, but was never completed as at start of infusion a severe allergic reaction (urticaria, dyspnea) occurred. Patient 2 is a 14-yr-old boy with SDNS since the age of 2 years treated with oral prednisone, cyclosporinA and micophenolate mofetil (MMF), with the development of severe obesity. A first infusion of RTX at age 12 was well tolerated and allowed prednisone discontinuation for over 2 years. Then a prolonged (>30 days) relapse occurred under treatment with oral prednisone, MMF and cyclosporinA. Therefore, a second RTX infusion was attempted, but the child presented severe dyspnea and it was interrupted. The use of OFA at 1,5 g/1.73 m², described in steroid-resistant NS children (Basu, NEJM 2014), was attempted. In patient 2 OFA was preceded by three boluses of iv methylprednisolone to induce remission.

Results: In pt 1, OFA infusion was uneventful. In pt 2, a mild allergic reaction was observed and treated. Remission was maintained during the follow-up period (9 months for pt 1, 5 months for pt 2), despite the interruption of prednisone treatment in both patients, and in pt 1 of cyclosporinA, while in pt 2 of MMF with ongoing cyclosporinA at last follow-up. After OFA infusion, CD19+ B cells reappeared at 7 months in pt 1, while remained depleted (0%) at 5 months in pt 2.

Conclusions: OFA could be a therapeutic option in managing severe forms of drug-resistant nephrotic syndrome in patients who have developed intolerance to RTX.

Funding: Private Foundation Support

FR-PO432

Population-Based Identification of Children with Primary Nephrotic Syndrome: Kaiser Permanente Nephrotic Syndrome Study Alan S. Go,¹ Dongjie Fan,¹ Thida Tan,¹ Janet M. Wojcicki,² Jingrong Yang,¹ Juan Daniel Ordonez,¹ Glenn Matthew Chertow,³ Sijie Zheng,¹ David Law.¹ ¹*Kaiser Permanente Northern California;* ²*Univ of California, San Francisco;* ³*Stanford Univ.*

Background: Few population-based data exist about children with primary nephrotic syndrome (NS) in the US. We identified a cohort of children with primary NS in a large integrated healthcare system.

Methods: Kaiser Permanente Northern California cares for >750,000 children. We identified members age<18 yrs between 1996-2012 who had nephrotic range proteinuria (UACR>3500 mcg/mg, PCR>3.5 mg/mg, 24-hr protein>3500 mg, dipstick>300 mg/dL) or diagnosed NS (ICD-9 581.x) in electronic records and lab databases. Nephrologists reviewed records for clinical presentation, lab and biopsy results to confirm primary NS.

Results: We identified 179 children with NS due to minimal change disease (72%), focal segmental glomerulosclerosis (23%) or membranous nephropathy (5%); incidence was 1.47 per 100,000 (95% CI:1.27-1.70). Biopsies were available in 40% of cases. Baseline features at diagnosis are shown by cause of NS:

	Overall (N=179)	Minimal Change Disease (N=129)	FSGS (N=42)	Membranous Nephropathy (n=8)
Median (IQR) age, yr	6.9 (3.7-12.9)	5.9 (3.6-9.9)	11.4 (6.3-16.2)	14.5 (3.3-16.5)
Female, N(%)	77 (43)	58 (45)	16 (38)	3 (38)
Race, N(%)				
White	46 (26)	31 (24)	12 (29)	3 (38)
Black	23 (13)	15 (12)	7 (17)	1 (13)
Asian/Pacific Islander	31 (17)	29 (23)	2 (5)	0
Other/unl	79 (44)	44 (41)	21 (49)	4 (49)
Hispanic ethnicity, N(%)	57 (32)	37 (29)	17 (41)	3 (38)
Baseline lab results				
Median (IQR) serum creatinine, mg/dL	0.4 (0.3-0.7)	0.4 (0.3-0.6)	0.7 (0.4-1.3)	0.4 (0.4-0.9)
Missing, N(%)	67 (37)	46 (36)	20 (48)	1 (13)
Median (IQR) serum albumin, mg/dL	1.7 (1.5-2.2)	1.6 (1.5-2.1)	2.0 (1.6-2.7)	2.1 (1.7-3.8)
Missing, N(%)	86 (48)	56 (43)	26 (62)	4 (50)
Total cholesterol, mg/dL, N(%)				
<=240	10 (5)	8 (6)	2 (5)	0
>240	56 (31)	43 (33)	10 (24)	3 (38)
Missing	113 (63)	78 (61)	30 (71)	5 (62)

Conclusions: Leveraging electronic health records and linked data sources, we identified a population-based cohort of children with primary NS that will provide a unique platform for describing the natural history of NS and identifying predictors of adverse outcomes.

Funding: Private Foundation Support

FR-PO433

Abatacept Treatment and B7-1 Immunostaining in Patients with Primary and Post-Transplant FSGS Rutger J. Maas,¹ Brigith Willemsen,² Henry Dijkman,² Catharina M. Haring,³ Jeroen Deegens,¹ Jack F. Wetzels.¹ ¹*Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands;* ²*Pathology, Radboud Univ Medical Center, Nijmegen, Netherlands;* ³*Nephrology, Deventer Hospital, Deventer, Netherlands.*

Background: Podocyte B7-1 expression has been implicated in the pathogenesis of idiopathic nephrotic syndrome for many years. Recently, podocyte B7-1 was described as a potential therapeutic target by demonstrating efficacy of B7-1 blocking agent abatacept in five patients with primary and post-transplant FSGS (Yu et al. New Engl J Med 2013). The authors speculated that patients who will respond to abatacept can be identified by positive B7-1 immunostaining on kidney biopsy. Here, we report our experience with abatacept and B7-1 staining in patients with FSGS.

Methods: Patients with no or partial proteinuria remission after plasmapheresis for treatment of FSGS received abatacept (2 or 3 doses of 10 mg/kg). After several trials of unsuccessful immunofluorescence staining, we performed B7-1 immunohistochemistry on paraffin embedded tissue with a primary antibody mouse anti CD80 (R&D systems).

Results: Three patients with post-transplant FSGS, and one patient with FSGS in the native kidney (Table, Patient 4) were treated with abatacept. All transplant patients had developed nephrotic proteinuria immediately after transplantation. Patient 1 had been treated with plasmapheresis for many years, and was previously unresponsive to B7-1 blocking agent belatacept. None of the patients had proteinuria remissions after abatacept, nor did we observe positive podocyte B7-1 immunostaining.

Conclusions: In our hands B7-1 staining was absent in patients with FSGS. Our data caution against too much optimism regarding the efficacy of abatacept.

Clinical Characteristics of FSGS patients treated with abatacept

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Male	Male	Male
Age	39	27	20	19
Previous treatment for FSGS	PP	PP	PP	Steroid; MMF; rituximab; PP
Time between proteinuria onset and abatacept	4 years	17 days	17 days	4 years
Urinary PCR before / after treatment (g/10 mmol)	16 / 15	7.2 / anuric	20.1 / 8.7	4.5 / 5.7
Screat before / after treatment (μmol/L)	115 / 100	dialysis	218 / 204	81 / 86

PP = plasmapheresis

Funding: Private Foundation Support

FR-PO434

Steroid Resistant Nephrotic Syndrome: A Prospective, Open Label Study of the Safety and Efficacy of Combination Tacrolimus and ACTHar Gel Therapy James A. Tumlin,¹ Claude Mabry Galphin,¹ Brad H. Rovin,² ¹Univ of Tennessee College of Medicine, Chattanooga, TN; ²The Ohio State Univ, Columbus, OH.

Background: Steroid resistant nephrotic syndrome (SRNS) in adults is associated with increased risk for progression to ESRD. Tacrolimus is a calcineurin inhibitor (CNI) that is an alternative to steroids, but is associated with progressive fibrosis and loss of GFR. ACTHar gel has shown benefit in the treatment of SRNS. To investigate additive effects, we followed 23 SRNS patients receiving combination therapy with Tacrolimus and ACTHar Gel.

Methods: 23 patients with SRNS (IMGN 8, 11 FSGS and 4 other) receiving ACE/ARB and 8 weeks of oral steroids prior to combination therapy of ACTH and Tacrolimus. Eleven patients received 2 or more drug therapies. Of the 23, 17 (71%) initially received ACTH followed by Tacrolimus. Duration of ACTH/TAC therapy averaged 6.2 months [range 1-12 months]. Complete or partial responses were defined as UP/Cr ratio of < 0.30 or > 50% reduction in pre-ACTH/TAC proteinuria, respectively.

Results:

Table-1	Number	Age	Baseline	Peak	ACTH	ACTH+ TAC
Responder	17	Yrs	6.2±1.4	11.0±1.4	3.3±1.0	1.4±0.4
IMN	6	58±3	6.6±2.3	13.1±2.7	4.9±1.2	1.2±0.5
FSGS	9	67±5	4.3±2.3	10.4±1.4	2.6±0.5	1.7±0.9
Other	2	58±1	9.9±5.6	12.4±3.0	0.3±0.2	0.63±0.7
Non-Responder	6	52±5	5.7±1.6	11.6±1.5	7.5±1.5	7.8±1.5
IMN	3	46±7	6.3±2.2	11.6±2.9	7.6±2.5	9.2±4.3
FSGS	3	52±8	6.0±2.3	11.8±0.5	7.4±1.6	7.3±1.6

Of the 23 patients, 6 (26%) achieved a complete response; a partial responses were observed in 11 (48%) for an overall response of 74%. Proteinuria levels (expressed as a UP/Cr ratio) before and after treatment are listed in the Table. There was no difference in the rate or time to complete or partial remission between IMGN and FSGS (IMGN: 75%;7.0+1.5mths; FSGS: 82%;6.1+0.8 mths).

Conclusions: Combination therapy with ACTHar Gel and Tacrolimus achieved a 75% and 82% complete or partial response rate in patients with steroid resistant IMGN and FSGS patients respectively. The mean time to partial response was 6.2 months, but could range up 12 months. Combination therapy ACTH and Calcineurin inhibitors may offer an effective alternative therapy to SRNS.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals; Dialysis Corporation Inc., Genzyme Pharmaceuticals, Private Foundation Support

FR-PO435

Treatment of Nephrotic Syndrome Secondary to Primary FSGS – Prednisolone or Tacrolimus? A Two Centre Experience Hannah R. Wilson,¹ Thomas M. Connor,² Tom Cairns,² Mona Saleh Wahba,¹ Marie B. Condon,¹ Megan Griffith.² ¹St. Helier Hospital, London, United Kingdom; ²Hammersmith Hospital, London, United Kingdom.

Background: Focal segmental glomerulosclerosis (FSGS) is a significant cause of end-stage renal failure. Patients with nephrotic syndrome have a worse prognosis. Current guidelines advise prolonged prednisolone (pred) at 1mg/kg. Tacrolimus (Tac) is an alternative for patients, but long-term therapy is often necessary, and there are concerns about toxicity.

Methods: Retrospective review of all patients with nephrotic syndrome secondary to primary FSGS treated with a minimum of 12 mths follow-up at 2 centres. All patients

received standard therapy with max tolerated ACEi +/- ARB. Complete remission (CR) was defined as normal serum albumin with PCR <50; partial remission (PR) as proteinuria ≤50% baseline. Results described as Median (Range). p value <0.05 significant.

Results:

Demographics	Pred n=15	Tac n=23	p value
Age	50 (19-75)	45 (19-78)	ns
Gender	8M, 7F	12M, 11F	ns
Ethnicity			ns
Caucasian	12	9	
Afro-carib	1	5	
Asian	2	9	
Follow up (mths)	43 (12-257)	45 (12-86)	
Baseline parameters			
Creatinine umol/L	167 (61-480)	101 (52-312)	<0.05
%creat>125	67%	26%	ns
UPCR	906 (478-1910)	1035 (602-3626)	<0.001
Albumin	23 (10-30)	16 (9-27)	
Results	Pred	Tac	p value
Duration (mths)	13 (2-56)	32 (5-74)	
Dose	60mg (40-60) 3 mths 16mg (2-60) 6 mths	6.4mg/L 3 mths 6.3mg/L 12 mths	
2nd Agent	9 (6 Non-response; 1 Relapse; 2 Pred sparing)	2 (Relapse)	
Response to primary agent (pts)			
Remission	60% (9)	91% (21)	<0.05
PR	60% (9)	91% (21)	<0.05
CR	33% (5)	87% (20)	<0.005
Time to remission (wks)	PR 8 (3-40) CR 10 (5-44)	PR 9 (2-52) CR 25 (3-117)	ns ns
Relapse	22% (2)	25% (5)	ns
ESRF	26% at 1,13,19,69 mths	0	<0.05
Creat latest f/u	92 (61-390)	92 (54-234)	ns
Adverse events			
Deaths	1 (lung ca)	1 (colon ca)	<0.01
Diabetes/Insulin	3	0	
Severe Infection	4	1	

Conclusions: In the Tac cohort a higher remission rate was demonstrated and a suggestion of fewer adverse events although numbers are small. However the baseline parameters show the GFR was significantly lower in the prednisolone group. Patients treated with Tac had a longer duration of treatment but appeared to have a better adverse event profile overall. A randomised controlled trial is required to investigate this further.

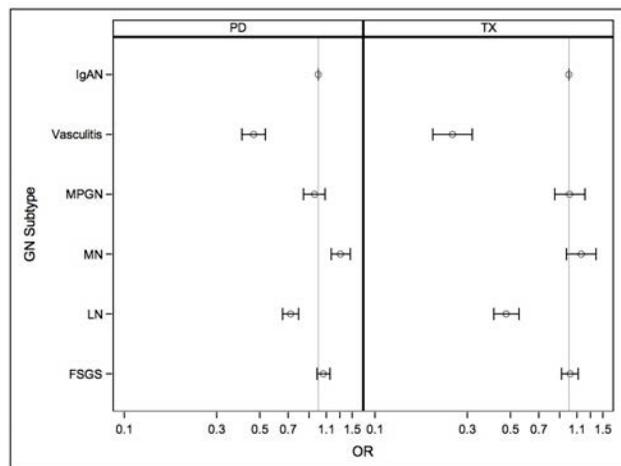
FR-PO436

Differences in Initial End Stage Renal Disease (ESRD) Treatment Modality Across Glomerulonephritis Subtypes Michelle M. O’Shaughnessy,¹ Maria E. Montez-Rath,¹ Richard A. Lafayette,¹ Wolfgang C. Winkelmayer.² ¹Div of Nephrology, Stanford Univ School of Medicine; ²Section of Nephrology, Baylor College of Medicine.

Background: Kidney transplantation (Tx) is the treatment of choice for end-stage renal disease (ESRD). Hemodialysis (HD) and peritoneal dialysis (PD) outcomes are largely equivalent. Whether access to these modalities is equal across glomerulonephritis (GN) subtypes has not been established.

Methods: We identified all patients in the US Renal Data System 18-75 years who initiated ESRD therapy with Tx, HD, or PD (1996-2011) and had ESRD attributed to 6 GN subtypes [focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN), membranoproliferative GN (MPGN), lupus nephritis (LN), vasculitis]. Odds ratios (ORs) for PD vs HD and for Tx vs HD were computed using multinomial logistic regression (IgAN as reference group), with multivariate adjustment for demographic, socioeconomic, and comorbidity differences.

Results: Among 75,278 patients studied, demographic, socioeconomic, and comorbidity characteristics differed considerably across GN subtypes. In unadjusted analyses, patients with FSGS, MN, MPGN, LN, and vasculitis were significantly less likely to receive Tx or PD as a first ESRD treatment modality than patients with IgAN: OR for Tx 0.52, 0.35, 0.48, 0.23, and 0.13, respectively; OR for PD 0.77, 0.66, 0.59, 0.48, and 0.30, respectively (all p<0.0001). After adjustment, differences were attenuated but patients with secondary GN subtypes (LN, vasculitis) remained significantly less likely to receive Tx or PD as compared to patients with IgAN (figure).



Conclusions: Patients with ESRD attributed to secondary GN subtypes (LN, vasculitis) are significantly less likely to receive Tx or PD as an initial ESRD treatment than patients with primary GN subtypes. The clinical appropriateness and sequelae of this apparent inequity must be determined.

Funding: Private Foundation Support

FR-PO437

Non Collapsing Focal and Segmental Glomerulosclerosis in Patients with HIV Julien Hogan,^{1,2} Claire Cartery,² Emmanuelle M. Plaisier.² ¹*Pediatric Nephrology, Robert Debré Hospital, Paris, France;* ²*Nephrology and Dialysis, Tenon Hospital, Paris, France.*

Background: With the improvement of the treatments against HIV, non collapsing focal and segmental glomerulosclerosis (FSGS) has become more frequent than HIV associated nephropathy (HIVAN). However, the physiopathology of non-collapsing FSGS among HIV patients remains poorly understood. We thus aimed to compare patients with HIV and non collapsing FSGS with patients with HIVAN and with non HIV patients with FSGS.

Methods: HIV patients with a kidney biopsy in our center between 2000 and 2012 (24 non collapsing FSGS and 13 HIVAN) and two control groups (10 primary and 12 secondary FSGS) were included. Clinical and biological data were collected; viral load in serum and urine was assessed by PCR and histological exam was performed together with immunohistochemical staining for PCNA to study epithelial cells proliferation.

Results: Clinical and biological features of HIV patients with non-collapsing FSGS were close to those of controls with secondary FSGS. Among HIV patients, the prevalence of cardiovascular risk factors was greater in those with non collapsing FSGS than in those with HIVAN (79% vs. 38%, p=0.01) but was comparable to the one in controls with secondary FSGS (100% vs. 79%, NS). HIV patients with non collapsing FSGS and controls with secondary FSGS had more frequently arteriosclerosis on the biopsy than patients with HIVAN (75% and 82% vs 36%, p<0.01). Visceral epithelial cells expression of PCNA showed that, despite a stronger staining in collapsing lesions, it can be found among all patients groups and in any FSGS lesion type. The majority of HIV patients with non collapsing FSGS had undetectable viral load in serum and urine.

Conclusions: Major clinical, biological and histological differences between HIV patients with non collapsing FSGS and HIVAN support the hypothesis of two distinct physiopathological entities. They are striking similarities between non collapsing FSGS in HIV patients and secondary FSGS found in patients with polyvascular disease. Non collapsing FSGS in HIV patients might be due to nephronic reduction secondary to vascular lesions in an ageing population with major metabolic abnormalities associated with antiviral drugs.

FR-PO438

Diabetic Glomerulosclerosis or Idiopathic Nodular Glomerulosclerosis – Role for Insulin Resistance Manish Anand, Mehri Mollae, Ravi Sunderkrishnan, Andres Rodrigo Caero, Mehrdad Hamrahian. *Nephrology, Thomas Jefferson Univ Hospital.*

Background: Diabetic nephropathy (DN) is characterized histologically by nodular mesangial sclerosis, a thickened glomerular basement membrane, and hyalinized arterioles. Differential diagnoses by light microscopy (LM) include membranoproliferative glomerulonephritis, amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary or immunotactoid glomerulopathy. These can readily be excluded by special stains, immunofluorescence (IF) and electron microscopy (EM). Idiopathic nodular glomerulosclerosis (ING) is the term used to denote classic DN confirmed by LM, IF, and EM, but in the absence of diabetes mellitus (DM). Case reports suggest insulin resistance (IR) as a possible cause.

Methods: Data was collected retrospectively on 21 cases of diabetic glomerulosclerosis or ING biopsied due to proteinuria (1+ on urinalysis to 12.3 grams/day), with or without renal insufficiency (creatinine 0.6-4.4mg/dL).

Results: 13 patients were male with majority of patients being African American (10) and non-Hispanic white (7). 1 patient was post-renal transplant and another post-

liver transplant. None of these patients were diagnosed with DM, although some had intermittently elevated blood glucose and borderline HbA1c. All patients had hypertension, but only 5 were active tobacco users and 8 were former smokers. BMI range was 21-43kg/m². Hemoglobin A1c range was 4.6-6.1% in 10 patients and 6 patients denied DM by telephone survey. The remaining 5 patients had no history of DM per records with few elevated random plasma glucose levels noticed on steroids. None of them fulfilled current diagnostic criteria for DM. Metabolic syndrome (MS) defined by Adult Panel III criteria was evident in 11 patients.

Conclusions: The pathogenesis of ING remains unclear. It involves the interplay of hypertension, obesity, and heavy smoking. We feel that IR is critically important, whether evident as subtle, prediabetic elevations of blood glucose, MS, or elevated HOMA-IR score being the only manifestation. Insulin sensitivity assessed by HOMA-IR score is possibly an important predictive factor in pathophysiology of ING and needs to be tested routinely.

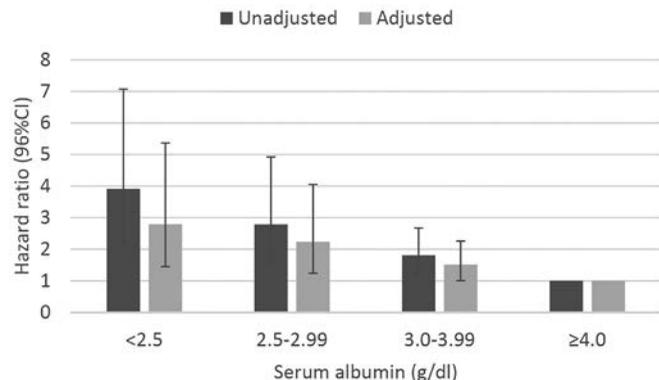
FR-PO439

Association of Serum Albumin Level and Venous Thromboembolic Events in Seven-Thousand Patients with Nephrotic Syndrome Geeta G. Gyamiani,¹ Miklos Zsolt Molnar,² Jun Ling Lu,² Keiichi Sumida,² Kamyar Kalantar-Zadeh,³ Csaba P. Kovacs,^{1,2} ¹*VA Medical Center, Memphis, TN;* ²*Univ of Tennessee Health Science Center, Memphis, TN;* ³*Univ of California, Irvine, CA.*

Background: Prior studies have shown that low serum albumin in patients with nephrotic syndrome (NS) is associated with an increased risk of venous thromboembolic (VTE) events. This is based on small studies with a low number of thromboembolic events and short term follow-up.

Methods: From a nationally representative cohort of over 3 million US veterans with baseline estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m², we identified 7037 patients with NS based on ICD9 codes. Association between serum albumin and risk of incident VTE events (based on ICD9 codes) was assessed using Cox regression analysis with adjustments for age, gender, race, comorbidities, eGFR, BMI and anticoagulant treatment.

Results: Mean age was 57±11 years, and patients were 96% male, 32% African-American and 60% diabetic. There were a total of 158 VTE events over a median follow-up was 8.1 years; 16 events (4.1%, event rate (ER): 8.5/1000 patient-years(PY)) in patients with albumin <2.5 g/dl, 18 events (3.4%, ER: 5.7/1000 PY) in patients with albumin 2.5-2.99 g/dl, 89 events (2.5%, ER: 3.4/1000 PY) in patients with albumin 3-3.99 g/dl and 35 events (1.4%, ER: 1.9/1000 PY) in patients with albumin ≥4 g/dl. Compared to patients with albumin ≥4 g/dl, those with albumin levels of 3-3.99 g/dl (adjusted HR: 1.51; 95%CI: 1.01-2.26), 2.5-2.99 g/dl (2.24, 1.24-4.05) and <2.5 g/dl (2.79, 1.45-5.37) experienced a linearly higher risk of VTE events.



Conclusions: Lower serum albumin is a strong incremental risk factor for VTE events in NS. The risk increases proportionately with declining albumin levels. Our finding may have important clinical implications regarding initiation and duration of prophylactic anticoagulation.

Funding: NIDDK Support, Veterans Administration Support

FR-PO440

Hypercoagulopathy Is Directly Correlated with Disease Severity in Nephrotic Syndrome Amanda P. Waller,¹ Samir Parikh,² Brad H. Rovin,² William E. Smoyer,¹ Marvin T. Nieman,³ Matthias Kretzler,⁴ Bryce A. Kerlin.¹ ¹*Clin/Trans Research, Nationwide Children's, Columbus, OH;* ²*Nephrology, Ohio State Univ, Columbus, OH;* ³*Pharmacology, Case Western Reserve Univ, Cleveland, OH;* ⁴*Nephrology, Univ of Michigan, Ann Arbor, MI.*

Background: Nephrotic syndrome (NS), a leading cause of end stage kidney disease, is characterized by massive proteinuria, hypoalbuminemia, and an increased risk for venous thromboembolism (VTE). We recently reported that hypercoagulopathy is proportional to the severity of both proteinuria and hypoalbuminemia in two animal models of NS. This study was designed to determine if this relationship translates to human NS.

Methods: Aliquots of plasma anticoagulated with 0.32% (final concentration) sodium citrate were obtained from the NEPTUNE biorepository (n=147 patients), along with corresponding clinical lab data (e.g. urine protein:creatinine (uP:C), serum albumin (sAlb)). Samples collected from a local patient cohort (n=21) were used to validate biorepository

specimen integrity. Endogenous thrombin potential (ETP) was determined using the Technothrombin TGA kit and RC Low reagent after 2:1 dilution with buffer. Plasma antithrombin (pAT) activity was measured by the amidolytic method.

Results: As expected, NEPTUNE patients exhibited a wide range of proteinuria values (median (range) uP:C: 1.85 mg/mg (0-17.6)). Hypoalbuminemia and proteinuria severity in these patients were proportional to ETP ($R^2=0.252$ & 0.128 , respectively, $P<0.001$). These correlations were stronger in the subset of patients with uP:C>2 ($R^2=0.331$ & 0.157 , respectively, $P<0.001$). Plasma AT activity was also significantly correlated to hypoalbuminemia and proteinuria severity ($R^2=0.125$ & 0.031 , $P<0.001$ & 0.03 , respectively). There was no correlation between AT activity and ETP. Results were similar in the validation cohort.

Conclusions: Both hypoalbuminemia and proteinuria severity in humans with NS is significantly, albeit weakly, correlated to ETP (an established marker of thrombotic risk). Adjusting these data for confounding clinical variables (e.g. smoking status, BMI, etc.) may aid in the modeling and development of evidence-based cut-offs to guide indications for prophylactic anticoagulation.

Funding: NIDDK Support

FR-PO441

Successful Social Media Recruitment into the NephCure Kidney Network, a Rare Disease Patient Registry Laura H. Mariani,¹ Joanna Dauber,² Chelsey Fix,² Alyssa Fisher,² Jane Shen,² Lalita Subramanian,¹ Marilyn Hailperin,² Elizabeth L. Cope.¹ ¹Arbor Research Collaborative for Health; ²NephCure Kidney International.

Background: Participation in clinical research for primary Nephrotic Syndrome (NS) has been limited by the rarity of the disease. There is growing interest in leveraging social media to expand demographic and geographic reach for recruitment. Because of the isolating nature of rare diseases, patients turn to social media for support, creating online communities that, if accessible, could potentially serve as a resource for recruitment.

Methods: The NephCure Kidney Network (NKN) is a web-based patient opt-in registry for primary NS. Participants provide data, including kidney disease history, demographics, and research participation preferences. Recruitment efforts launched in March 2014 relied on email campaigns to contacts of the patient advocacy group, NephCure Kidney International (NKI), but then expanded in September 2014 to include social media. Weekly posts were made to NKI's Facebook page, with analysis of performance based on impressions (# of people reached) and engagements (likes, clicks, shares, comments). Relationships with other closed Facebook kidney disease groups were established and posts made to their sites.

Results: 45,151 impressions and 2,927 engagements were made from 9/2014-6/2015. Relationships were made with 54 kidney disease groups (>15,000 members) from which to find NS patients. Engagements were highest on posts focusing on patient-centeredness in research and lifestyle. 414 patients (51% female, 47% <18 yo, 22% racial/ethnic minority) from 27 countries enrolled between 3/2014 and 6/2015, with 27% of enrollees having no previous engagement with NKI. 94% reported a willingness to be contacted about research, including 77% willing to donate a biospecimen. However, only 16% currently or previously participated in a clinical trial. 78% were willing to travel >50mi to participate in a study and 34% were willing to travel >500mi.

Conclusions: A recruitment strategy which includes social media is an efficient, cost-effective opportunity to engage rare disease patients across a wide geography, including those who have not previously participated in research.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO442

The Expression of Podocyte Protein PREX2 in Glomerular Diseases Anna Levin,¹ Julia Wijkstrom,¹ Jenny Hulkko,¹ Jenny C. Nystrom,² Kerstin Ebefors,³ Annette Bruchfeld,¹ Jaakko Patrakka,⁴ Kjell Hulten,⁵ Annika Wernerson.¹ ¹CLINTEC, Karolinska Inst (KI), Stockholm, Sweden; ²Dept of Physiology, Sahlgrenska Academy, Gothenburg, Sweden; ³Dept of Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg, Sweden; ⁴Dept of Medicine, KI, Stockholm, Sweden; ⁵LabMed, KI, Stockholm, Sweden.

Background: Phosphatidylinositol-3,4,5-triphosphate-dependent Rac exchange factor 2 (PREX2) is a 183 kDa protein that functions as a RAC guanine nucleotide exchange factor (GEF), activating Rac proteins. It has been discovered in several tissues, e.g. brain, lung, liver and kidney. The specific function of PREX2 in the kidney is unknown. The aim of the present study was to investigate the localization of PREX2 in the kidney and the possible role in renal disease.

Methods: RT-PCR, Western Blot and immunohistochemistry (IHC) was used to identify the localization of PREX2 in renal tissue. The mRNA expression in diseased kidney was analyzed by microarrays on isolated glomeruli from patients with IgA Nephropathy (IgAN), Membranous Nephropathy (MN) and normal tissue. Immuno electron microscopy (iEM) was used to semiquantify PREX2 in renal biopsies from patients with IgAN (n=6), Minimal Change Nephropathy (MCN, n=5) and control tissue from healthy kidney donors (n=5). The morphology was correlated to proteinuria at time of biopsy.

Results: RT-PCR and Western Blot showed the presence of PREX2 in glomerulus. IHC and iEM revealed that PREX2 was localized to podocyte foot processes. In disease samples, mRNA levels were not changed in IgAN and MN. Semi-quantitative iEM showed a significantly lower expression of PREX2 in IgAN and MCN compared to controls. A tendency towards a negative association between PREX2 and proteinuria was seen, although this was not significant.

Conclusions: We found that PREX2 is a new podocyte-associated protein. Although no difference in mRNA levels were found, the expression of PREX2 was significantly

lower in IgAN and MCN compared to controls. The function of PREX2 in the glomerular filtration barrier will now be further investigated in an extended patient cohort and in genetically modified animals.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO443

Urinary and Serum Soluble Urokinase Receptor Levels Predicts the Therapeutic Response of Nephrotic Syndrome Keiji Fujimoto, Yuki Matsui, Norifumi Hayashi, Junko Imura, Hiroki Adachi, Hideki Yamaya, Hitoshi Yokoyama. *Div of Nephrology, Kanazawa Medical Univ, Uchinada, Ishikawa, Japan.*

Background: It is necessary to develop noninvasive biomarkers to predict the treatment response for nephrotic syndrome (NS), and to differentiate their histological types in the initial phase.

Methods: The subjects were 32 patients with primary NS [8 with focal segmental glomerulosclerosis (FSGS), 12 with minimal change nephrotic syndrome (MCNS), 10 with membranous nephropathy (MN), and 2 with membranous proliferative glomerulonephritis]. Using ROC analysis, we examined whether or not it is possible to differentiate refractory NS from non-refractory NS, and MCNS from FSGS based on the pretreatment values of clinical markers [urinary protein (UP), serum/urinary soluble urokinase receptor (s-u-suPAR), urinary L-FABP, and eGFR], and values and changes (Δ) after 2 months (2M). We also examined the renal expression of activated b3 integrin (AP-5) by immuno-staining in primary NS and normal tissues.

Results: The following parameters were useful for differentiating refractory NS from non-refractory NS: 2MUP (AUC=0.968, p=0.001), 2Ms-suPAR (AUC=0.913, p=0.002), D2Mu-suPAR (AUC=0.906, p=0.007), D2Ms-suPAR (AUC=0.881, p=0.005), and D2MUP (AUC=0.833, p=0.014). On the other hand, D2Ms-suPAR (AUC=0.905, p=0.007) and D2Mu-suPAR (AUC=0.816, p=0.048) were useful for differentiating MCNS from FSGS. In addition, u-suPAR before treatment was positively correlated with UP (p=0.501, p=0.003) and urinary L-FABP (p=0.427, p=0.017). The expression of activated b3 integrin was primarily strong in the proximal tubular epithelial cells in FSGS or MN, but, weak in MCNS and normal tissues. Otherwise, there was no expression of activated b3 integrin on podocytes in both normal and diseased tissues.

Conclusions: It may be possible to evaluate the treatment response of NS and to differentiate MCNS from FSGS based on changes in s/u-suPAR within 2 months after the start of treatment. As a mechanism involved in proteinuria in NS patients, u-suPAR may inhibit protein reabsorption in the proximal tubules through the activation of b3 integrin.

FR-PO444

Turkish Atypical Hemolytic Uremic Syndrome Registry: Initial Pediatric Results Nesrin Besbas,¹ Oguz Soylemezoglu,² Bora Gülhan,¹ Z.birsin Özçakar,³ Emine Korkmaz,⁴ Fatih Ozaltin.^{1,4} ¹Pediatric Nephrology, Faculty of Medicine Hacettepe Univ, Ankara, Turkey; ²Pediatric Nephrology, Faculty of Medicine Gazi Univ, Ankara, Turkey; ³Pediatric Nephrology, Ankara Univ Faculty of Medicine, Ankara, Turkey; ⁴Nephrogenetics Laboratory Dept of Pediatric Nephrology, Hacettepe Univ, Ankara, Turkey.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, genetic, life-threatening disease of chronic complement activation leading to systemic thrombotic microangiopathy and end-organ damage. The national aHUS registry was initiated in November 2013 and collects information on the progression and treatment of disease.

Methods: A clinical diagnosis of aHUS is required for inclusion. Demographic, medical histories, treatments, efficacy and safety outcomes data are collected initially and every 3 months.

Results: By May 15, 2015, 122 pediatric patients (55.8% female and 44.2% male) were enrolled from 22 centers covering all the country. Mean age at diagnosis was 4.38±4.23 years. A total of 90 patients (74.6%) had oliguria or anuria at the time of diagnosis. Serum complement 3 was low in 49 patients (40.2%). Neurologic system involvement was present in 34 patients (27.2%). Renal biopsy was performed in 37 patients (30.7%). Renal replacement therapies (RRT) were initiated in 61.5% of the patients at administration where only 10% of the patients were discharged with RRT. Genetic studies including the complement pathway, DGKE and factor H antibodies were studied in 73% of patients. Plasma infusion or plasma exchange was the initial treatment in 82% of patients and 59% of patients (n=72) had eculizumab treatment. At the time of discharge after initial management, 78 patients (63.9%) and 92 patients (75.4%) achieved renal and hematological remission, respectively. Four patients died at the acute stage of the disease. Mean duration of follow-up was 2.28±2.30 years. During follow-up, eculizumab was stopped in 18 patients and re-started in four of them due to relapse.

Conclusions: The pediatric aHUS Registry will provide data to help increase our knowledge of the aHUS patient with different genetic background and also evaluate the long-term safety and efficacy of treatment options including the eculizumab.

FR-PO445

Long-Term Outcomes of Thrombotic Microangiopathy Treated with Plasma Exchange – A Systematic Review Bashir Thejeel,^{1,2} Amit X. Garg,^{2,3,4} Aiden Liu,² Arthur Iansavichus,² Ainslie M. Hildebrand.^{2,4} ¹Schulich School of Medicine; ²Kidney Clinical Research Unit, London Health Sciences Centre; ³Epidemiology and Biostatistics, Western Univ; ⁴Nephrology, Western Univ.

Background: With the adoption of plasma exchange as standard treatment for thrombotic microangiopathy, more patients are surviving and longer-term outcomes have greater relevance.

Methods: We conducted a systematic review of observational studies between 1980 and 2013 that reported outcomes of adults with thrombotic microangiopathy at least 6 months after initiating plasma exchange. We searched several databases from 1980 to 2013 for eligible articles published in any language. We abstracted data in duplicate and assessed the methodological quality of each study using an assessment tool developed based on recommended validity criteria.

Results: We screened 6672 articles, reviewed 213, and included 34 studies totaling 1182 patients (study median [range], 24 [10-118]). The mean (or median) follow-up ranged from 6 months to 13 years. The cumulative incidence of relapse and mortality was highly variable and ranged from 3 to 84% and 0 to 61%, respectively. The incidence of other outcomes across 10 studies also varied (outcomes included hypertension, kidney disease, preeclampsia, stroke, seizure, severe cognitive impairment, and depression); in 3 other studies long-term neurocognitive function and health-related quality of life were significantly lower than the general population.

Conclusions: In summary, patients who survive an episode of thrombotic microangiopathy may be susceptible to long-term vascular complications including chronic kidney disease, but the magnitude of this risk and how to mitigate it remains unclear from prior studies.

FR-PO446

Eculizumab Prevents Thrombotic Microangiopathy in Atypical Hemolytic Uremic Syndrome Patients: Long-Term Follow-Up Jan Menne,¹ Yahsou Delmas,² Eric Rondeau,² Christoph Licht,⁴ Jimmy Wang,⁵ Chris Mix,⁵ John F. Kincaid,⁵ Francois Provot,⁶ Larry A. Greenbaum,⁷ Fadi Fakhouri.⁸ ¹Klinik für Nieren- und Hochdruckerkrankungen, Hannover, Germany; ²CHU de Bordeaux, France; ³Hôpital Tenon & Univ Paris VI, Paris, France; ⁴Hospital for Sick Children, ON, Canada; ⁵Alexion Pharmaceuticals, Inc., Cheshire, CT; ⁶CHU de Lille, France; ⁷Emory Univ, Atlanta, GA; ⁸CHU de Nantes, France.

Background: In 5 previous studies of patients (pts) with aHUS, ECU effectively treated and prevented thrombotic microangiopathy (TMA) and improved renal function and hematological parameters for up to 2 yrs.

Methods: An observational, multicenter, long-term follow-up study of aHUS pts treated with ECU in 5 prior clinical studies. The primary endpoint was exposure/follow-up TMA event rate post-parent study on-(ON) and off-treatment (OFF; among pts who discontinued ECU).

Results: 85 pts enrolled (Table); of these, 74 pts had ON and 37 pts had OFF treatment periods with median follow-up of 24.6 and 16.6 months, respectively. The TMA event rate was 6.7 per 100 pt-yrs for ON pts, and 23.5 per 100 pt-yrs for OFF pts. The rate of TMA in ON pts was greater in those not receiving on-label dosing (Table). OFF pts had higher eGFR at time of discontinuation than ON pts. Age, frequencies of higher-risk complement factor mutations and kidney transplant status were not different between ON and OFF pts. Treatment status and higher-risk mutations independently predicted TMA.

Conclusions: The TMA event rate was 3.5-fold higher after ECU discontinuation vs. on ECU. TMA event rates were lowest during on-label dosing, higher during off-label dosing, and highest off-treatment. Pts with aHUS have a progressive increase in the risk of TMA events during periods of reduced dosing and after discontinuation of ECU compared with on-label ECU dosing. Medical writing support – Kenyon Ogburn PhD, of Alexion.

Table. Baseline Demographics and Efficacy Outcomes

Baseline Demographics and Disease Characteristics		N=85*			
Age at first ECU infusion, median (range), years		22.0 (0–80.0)			
<12 years, n (%)		24 (28.2)			
12–18 years, n (%)		10 (11.8)			
≥18 years, n (%)		51 (60.0)			
Age at entering current study, median (range), years		26.0 (1.6–81.6)			
<12 years, n (%)		21 (24.7)			
12–18 years, n (%)		3 (3.5)			
≥18 years, n (%)		61 (71.8)			
Female sex, n (%)		52 (61.2)			
Identified complement regulatory protein mutation or autoantibody, n (%)		52 (61.2)			
Time from aHUS diagnosis to first dose (months), median (range)		5.21 (0–313.3)			
Time from current aHUS manifestation to first dose (months), median (range)		0.92 (0.0–47.4)			
Number of aHUS events, n (%)		54 (63.5)			
Single		31 (36.5)			
Multiple					
Total number of PE/PI sessions per pt, median (range)		11 (0.0–230.0)			
Dialysis at baseline, n (%)		29 (34.1)			
Prior renal transplant, n (%)		21 (24.7)			
Efficacy Outcomes	OFF Treatment ^{abc} (n=37)	ON Treatment ^{ab}			
		Reduced Dose and/or Frequency (n=30)	On-label Dosing (n=62)	All ON Treatment (n=74)	
TMA event rate ^{de}	23.5	12.3	4.1	6.7	

Results as of February 10, 2015.
 *Pts could be included in both the ON and OFF groups.
 †One pt had TMA events while on both on-label and reduced dose and/or frequency of treatment.
 ‡Includes 11 pts who did not receive ECU post-parent study.
 ††A TMA event was defined as the new occurrence of increased creatinine and/or LDH, and/or decreased platelet count, and/or the occurrence of signs or symptoms of TMA, and/or receipt of plasma therapy, blood transfusion, dialysis or kidney transplant secondary to TMA.
 ‡‡The TMA event rate refers to the number of events per 100 pt-yrs.
 aHUS, atypical hemolytic uremic syndrome; ECU, eculizumab; pt, patient; TMA, thrombotic microangiopathy.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

FR-PO447

An Update on Tailored Eculizumab Maintenance Treatment in Patients with Atypical Haemolytic Uremic Syndrome Gianluigi Ardisino,¹ Francesca Tel,¹ Sara Testa,¹ Ilaria Possenti,¹ Donata Cresseri,¹ Samantha Griffini,¹ Elena Grovotto,¹ Stefania Salardi,¹ Silvana Tedeschi,¹ Nicolò Borsa,² Massimo Cugno.¹ ¹Center for HUS Management, Fondazione IRCCS Ca' Granda Policlinico, Milan, Italy; ²Molecular Otolaryngology & Renal Research Laboratory, The Univ of Iowa.

Background: Atypical hemolytic uremic syndrome (aHUS) is a severe, systemic thrombotic microangiopathy often related to mutations in the genes encoding complement regulatory proteins. Since 2009, Eculizumab (ECU) has been successfully used in patients (pts) with aHUS. The standard maintenance treatment suggests ECU administration every two weeks (wks), life-long but the best treatment schedule is not yet defined. To update on our experience on individualized ECU treatment schedule for preventing relapses based on drug biological activity, with the rational of improving the patient's quality of life, reducing the risk of adverse reactions and reducing the heavy costs of the treatment.

Methods: Pts undergoing ECU treatment for aHUS at our Center were addressed to a progressive extension of the interval between ECU doses from the standard 2 wks to 3 or 4 wks with a strict monitor of global complement activity. AP50 was routinely determined before each ECU administration and the interval between doses was adjusted with the target of maintaining AP50<25%. Strict monitoring of indicators of disease reactivation, namely blood in the urine with home dipstick, was regularly performed.

Results: The interval between doses was extended in 33 pts (13 ≤ 18 yrs) with a median age of 28.1 yrs (5-62), 17 F; 21 with native kidney and 12 with graft. Identified mutations were: CFH:15; CFI:2; CD46:1; MCP:1; CFHR3-CFHR1 homoz. deletion with (3) or w/o (1) anti-FHAb:4; multiple mutations:3; Idiopathic:7. In 19 pts the optimal interval between ECU doses was 4 wks while in 14 pts it was 3 wks. No relapses was observed over a cumulative observation period of 748 mos (mean 23 mos/pt).

Conclusions: In patients with aHUS, our experience supports the possibility of tailoring ECU maintenance treatment schedule based on global complement activity. In a cohort of 10 adult pts the described novel approach leads to an average estimated saving >2 million USD/yr.

FR-PO448

Chemokines as Potential Biomarkers of Renal Involvement in Scleroderma Edward Stern,^{1,2} Voon Ong,¹ Aine Burns,² Robert J. Unwin,² Christopher Paul Denton.¹ ¹Centre for Rheumatology, UCL, London, United Kingdom; ²Centre for Nephrology, UCL, London, United Kingdom.

Background: Renal disease in scleroderma (SSc) remains a major clinical challenge. Previous studies showed up to 50% of SSc patients have CKD. We sought to gain insight into the pathogenesis of SSc-CKD by examining markers of disease in serum and urine.

Methods: We collected urine and serum from 80 SSc patients, with or without renal disease, for comparison with patients with CKD of other causes (n=10) and healthy controls (n=12). We performed multiplex analysis of candidate markers of disease activity or severity in SSc and renal injury: MCP-1, MCP-3, IL-6, IL-18, TNFa, and VEGF.

Results: 40 SSc patients had CKD defined by eGFR and urinalysis. Serum MCP-1 was increased in SSc compared with controls, with SSc-CKD significantly lower than SSc without CKD. Mean serum MCP-1 was 132 pg/ml (95% CI 105-162) for SSc with normal renal function compared with 65 pg/ml in SSc-CKD (49-81, p<0.001 for this comparison). MCP-1 was not increased in CKD of other causes (mean 47 pg/ml, 23-85) compared with

controls (mean 53 pg/ml, 25-85, p=0.848). Conversely, urine MCP-1:creatinine ratio was higher in SSc-CKD (mean 64, 32-111) than in SSc with normal renal function (mean 23, 18-28, p=0.046). MCP-3 was upregulated in the urine of patients with SSc with or without CKD (mean MCP-3:creatinine ratio 3.6, 2.5-4.6) compared with healthy controls (mean 0.9, 0.5-1.4, p=0.016). There was no difference between groups in serum MCP-3.

Conclusions: This is the first study to measure MCP-1 and MCP-3 in the urine of SSc patients. Elevated urine MCP-1 in SSc-CKD suggests increased expression in the renal tract and may help define organ-specific effects of this potential pathogenic mediator that has previously been reported to be increased in serum in association with pulmonary complications. In contrast to MCP-1, other markers of SSc severity (e.g. IL-6) or renal injury (e.g. IL-18) did not differentiate between groups. Our findings support further investigation of urine concentrations of chemokines MCP-1 and MCP-3 as markers or mediators of CKD in SSc.

Funding: Government Support - Non-U.S.

FR-PO449

Towards a Deeper Understanding of Fibrillary Glomerulonephritis: Clinicopathologic Analysis of Patients in a Long-Term Inception Cohort Fernanda Pavan Schober,¹ Caroline J. Poulton,¹ Yichun Hu,¹ Harsharan Kaur Singh,² Volker Nickleleit,² William Franklin Pendergraft.¹ ¹UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC; ²UNC Pathology, UNC Chapel Hill, Chapel Hill, NC.

Background: Fibrillary glomerulonephritis is an uncommon primary glomerular disease. Accordingly, there are no clinical trials to guide treatment making this a challenging disease to manage. Here, we report clinical characteristics and treatment outcomes of patients with fibrillary glomerulonephritis diagnosed and/or treated at UNC or through the Glomerular Disease Collaborative Network and compare them to a previously published cohort from Mayo clinic†.

Methods: Patients were identified through the UNC Division of Nephropathology database. Clinical data were extracted from the electronic medical records starting at the time of diagnosis.

Results: There were 31 patients with fibrillary glomerulonephritis who were treated at UNC and another 245 patients who were diagnosed by the UNC Division of Nephropathology. Demographic and clinical data from the date of biopsy are displayed in the table.

	UNC (n=31)	UNC Path (n=245)	Mayo (n=66)	p-value
Sex				
Female (%)	19 (61%)	153 (62%)	36 (55%)	0.487
Male (%)	12 (39%)	92 (38%)	30 (45%)	
Race				
white	18 (60%)	167 (68%)	68 (95%)	< 0.0001
black	8 (27%)	38 (16%)	2 (3%)	
other	4 (13%)	40 (16%)	1 (2%)	
Age mean (%)	49.6 ± 10.4	56.7 ± 11.5	53 ± 12	0.0011
15-34	4 (13%)	8 (3%)	1 (8%)	0.0049
35-54	18 (58%)	91 (37%)	9 (39%)	
>54	9 (29%)	146 (60%)	12 (53%)	
Serum creatinine (mg/dl)	2.1 ± 1.2	3.3 ± 3.4	2.1 ± 1.6	0.0041
24hr urine protein (gm)	6.5 ± 4.0	7.5 ± 28.2	5.6 ± 4.2	0.8454
Serum albumin (g/dl)	3.0 ± 0.9	3.1 ± 0.8	3.2 ± 0.7	0.4751

Conclusions: This clinicopathologic analysis of patients with fibrillary glomerulonephritis is the largest study of its kind in the literature to date. The patients in our cohort were more ethnically diverse than the Mayo clinic group but presented with similar degree of kidney impairment and nephrotic range proteinuria. Fibrillary glomerulonephritis is an understudied glomerular disease that portends a poor prognosis warranting the need for prospective multi-center treatment studies to determine durable therapeutic avenues. †Nasr, S. et al. *CJASN*. 6:775-784; 2011.

Funding: NIDDK Support

FR-PO450

Clinical, Histologic, and Genetic Predictors of Response to MMF in C3 Glomerulopathy Rupali Surendra Avasare,¹ Pietro A. Canetta,¹ Andrew S. Bomback,¹ Yasar Caliskan,² Yasemin Ozluk,² Gerald B. Appel.¹ ¹Div. of Nephrology, Columbia Univ Medical Center, New York, NY; ²Div. of Nephrology, Istanbul Faculty of Medicine, Istanbul; ³Dept of Pathology, Istanbul Faculty of Medicine, Istanbul.

Background: Treatment of C3 Glomerulopathy (C3G) with anti-complement therapy has yielded mixed results and there is no consensus on optimal treatment. We reviewed the experience of our C3G patients who received a course of mycophenolate mofetil (MMF) to determine predictors of treatment response.

Methods: In a retrospective chart review of patients with biopsy-diagnosed C3G, we identified 24 patients treated with a course of MMF (> 6 months) with >1 year follow-up. The primary outcome was either complete remission (stable GFR with decline in proteinuria to < 0.5 g/gCr) or partial remission (stable GFR with >50% decline in proteinuria to

between 0.5 – 3.5 g/gCr) at last follow-up. Responders and nonresponders were compared by two-tailed T test or Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables.

Results: There were 15 men and 9 women with 21 White and 3 Black patients. Median age was 27 years (IQR 21 – 37). Median creatinine was 1.17 (IQR 0.87 – 1.74) mg/dl, eGFR 59 (IQR 34 – 89) ml/min/1.73m². Median proteinuria was 3.6 g/gCr (IQR 1.6 – 7.7). Of 24 patients treated with MMF, 14 (58%) were responders (8 CR, 6 PR). 22 of 24 patients received steroids. The only variable associated with remission was elevated soluble membrane attack complex (sMAC) level (responders 100%, nonresponders 25%, p < 0.05). Age, eGFR, proteinuria, hypocomplementemia, complement factor mutations or autoantibodies, interstitial fibrosis/tubular atrophy, location of deposits on electron microscopy, and presence/absence of immunoglobulin staining on IF were no different between responders and nonresponders.

Conclusions: 14 of 24 C3G patients treated with a course of MMF experienced remission. Elevated sMAC level was associated with response to MMF. While not a specific anti-complement therapy, MMF may be an effective treatment for some patients with C3G. This and other series suggest elevated sMAC may indicate treatment-susceptible disease.

FR-PO451

Genetic Sequences May Influence Clinical Progression or Clinical Presentations of C3 Glomerulopathy Hostensia M. Beng, Basema I. Dibas, Hsiao Ling Lai, Guillermo Hidalgo. *Pediatrics, ECU, Greenville, NC.*

Background: We describe clinical course of 2 girls with C3 Glomerulopathy (C3 GN) with different genetic sequences and clinical courses.

Methods: **Case 1 (A).** 12 yrs old AAF who presented with stage 2 HTN and nephrotic range proteinuria (u. p/cr 4.6). A renal biopsy showed C3 GN. She received steroids. (HD) was initiated (s. cr 2.24 mg/dL, BUN 127mg/dL). She received 5 anti-hypertensive medications & 3 PE sessions. She had no improvement, D#29 she received Eculizumab 900 mg q wk & after 2 doses of Eculizumab, GFR improved and no longer required HD or PE. **Case 2 (B).** 15 yrs old WF who presented at 7 yrs of age with hematuria, stage 2 HTN & nephrotic range proteinuria (u. p/cr 13). Kidney biopsy showed C3 GN. She received only Lisinopril and had maintained normal GFR without RRT/steroids. Though she continued to have nephrotic range proteinuria.

Results: Both presented with hematuria, HTN and nephrotic range proteinuria and their biopsies showed C3 GN, persistent nephrotic range proteinuria despite improvement in GFR and normal levels of FH, properdin, C5b9. Gene analysis for A showed deletion of CFHR3, CFHR1 and carry a variant of unknown significance in CFH and CFI. B in contrast had abnormal high complement plasma Bb antibody and 0% complement alternative pathway.

Conclusions: CFH competes with CFB for C3b binding, it impedes the formation of APC3 convertase. CFH accelerates AP C3 convertase decay & is a cofactor for complement factor I (CFI) - mediated proteolysis of C3b. Complement regulatory protein with CFI cofactor activity. CFI is a serine protease encoded by the *CFI* gene on chromosome 4q25. Looking closely at the genetic difference in our two patients, we hypothesized that the genetic variants defects in CFH could have led to a more severe clinical presentation of A and mild disease presentation in B with AP alternative pathway abnormality. Genetic sequences may influence clinical manifestation/ progression of the C3GN.

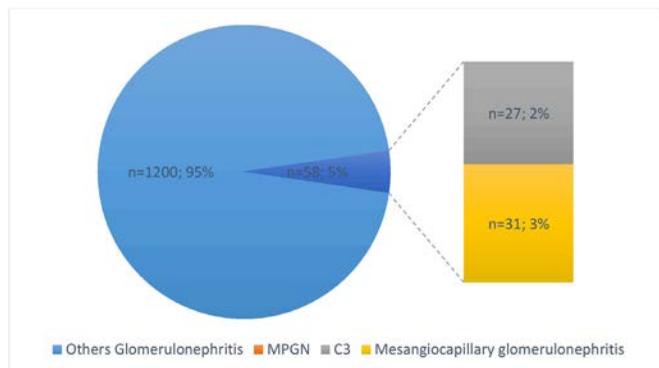
FR-PO452

Membranoproliferative Glomerulonephritis C3 Deposits: Clinicopathological Study Luis A. Castillo,¹ Eduardo I. Navarro,² Ismael Lopez,² Kelly Camacho,² Mayra Olivero,² Ismael Lopez,² Gustavo Aroca Martinez,^{1,2} Henry J. Gonzalez Torres,² Raul Garcia.^{1,2} ¹Nephrology, Clinica de la Costa, Barranquilla, Atlántico, Colombia; ²Medicine, Univ Simón Bolívar, Barranquilla, Atlántico, Colombia.

Background: Membranoproliferative glomerulonephritis (MPGN) is a pattern of damage characterized in the light microscopy by mesangial hypercellularity, thickening of the glomerular basement membrane and mesangial interposition in the capillary wall. Recent advances in the understanding of its underlying pathogenesis led to a classification scheme based on the findings in the immunofluorescence. Alteration complement regulation has proven to be a risk factor for the development of MPGN.

Methods: Cross-sectional study. The data were extracted from NefroRed®, a software platform that contains the socio-demographic, anthropometric, clinical and laboratory data of 1200 patients with kidney biopsies from 2008 to 2014. It was selected for the study those patients that showed the pattern of glomerulonephritis and membranoproliferative and C3 deposits only or predominant. Each biopsy was studied by light microscopy and immunofluorescence, light microscopy included hematoxylin-eosin, PAS, and Jones y Tricromico. Immunofluorescence was performed using antibodies directed against IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, Lightweight Kappa and Lambda chains.

Results: Mean age of men was 42.3 years and women was 36.7 years. The minimum age was 18 years. The maximum age was 69 years; 51.8% (n = 14) of patients were women. The 1200 biopsies showed 58 injuries MPGN (5%) of these 58 cases only 27 (32%) lesions showed C3 deposits only or predominant.



Conclusions: 30% of patients with GMP have as pathogenic mechanism the complement activation with complement C3 deposition in the glomerulus. Our research group has found C3 deposition causally related to GMP. The most common clinical presentation is nephrotic syndrome.

FR-PO453

Steroids Alone for the Treatment of C3 Glomerulonephritis with Monoclonal Gammopathy *In Sara Jaffer Sathick,¹ Ladan Zand,¹ Samih H. Nasr,² Sanjeev Sethi,² Fernando C. Fervenza,¹ Nelson Leung.^{1,3}* ¹*Div of Nephrology and Hypertension, Mayo Clinic;* ²*Div of Anatomic Pathology, Mayo Clinic;* ³*Div of Hematology, Mayo Clinic.*

Background: C3 glomerulonephritis (C3GN) is a rare disease with no trial data to guide treatment. In patients with C3GN with monoclonal gammopathy, steroids alone may be a viable treatment option.

Methods: We present our experience in managing C3GN with monoclonal gammopathy with prednisone.

Results: 5 patients presented to our institution from 2011 to 2014 with biopsy proven C3GN and underlying monoclonal gammopathy. Median age of this cohort was 63 years. Median estimated GFR by MDRD equation was 35.4 ml/min/1.73m² and median proteinuria was 2 g/day at presentation. All patients had IgG kappa monoclonal gammopathy. Patient 5 required renal replacement therapy but recovered renal function. All patients were treated with Prednisone 60mg/day tapering to zero in all except one. Patient 2 and 4 continue on 2.5-5mg/day. Median duration of follow up was 26.9 months. Median estimated GFR at follow up was 40.16 ml/min/1.73m². All patients showed improvement in proteinuria. 3/5 patients showed improvement in kidney function.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	69	63	47	69	23
Gender	M	M	F	M	M
eGFR at presentation (MDRD) ml/min/1.73m ²	24.6	26.2	48.2	37.6	35.4
Proteinuria (g/day)	1.87	2	2.8	2.6	1
Serum M spike (g/dl)	0.6	0.5	0.5	1	0.8
Bone Marrow Biopsy	<5% kappa restricted cells	10% kappa restricted cells	Normocellular	<5% kappa restricted cells	Hypercellular
Presenting features	CKD, hematuria	CKD, hematuria	AKI, nephritic syndrome	CKD, hematuria	AKI with flu like symptoms
Alternative complement pathway evaluation	C3 nephritic factor negative	Elevated soluble membrane attack complex (sMAC)	No abnormality	C3 nephritic factor positive, elevated sMAC	Heterozygous for CFH/DDD/C3GN associated allele. C3 nephritic factor positive
Proteinuria on follow up (g/day)	0.14	0.55	0.82	0.62	0.01
eGFR on follow up	24.6	30	40	40	58

Conclusions: Our experience suggests that prednisone alone may be a treatment option in some patients with C3GN associated with a monoclonal gammopathy. Work up should be done to exclude a plasma cell neoplasm and inherited complement abnormalities.

FR-PO454

The National Study of Membranoproliferative Glomerulonephritis and C3 Glomerulopathy: Characterisation of the Initial United Kingdom Paediatric Cohort *Edwin KS Wong,¹ Claire L. Harris,² Kevin J. Marchbank,¹ Isabel Y. Pappworth,¹ Rebecca Walters,¹ Hannah J. Lomax-Browne,³ Daniel P. Gale,⁴ Tim Goodship,¹ David Kavanagh,¹ Roger D. Malcomson,⁵ Paul Morgan,² Matthew C. Pickering,³ H. Terence Cook,³ Sally A. Johnson.¹* ¹*Newcastle Univ;* ²*Cardiff Univ;* ³*Imperial College London;* ⁴*Univ College London;* ⁵*Leicester Royal Infirmary.*

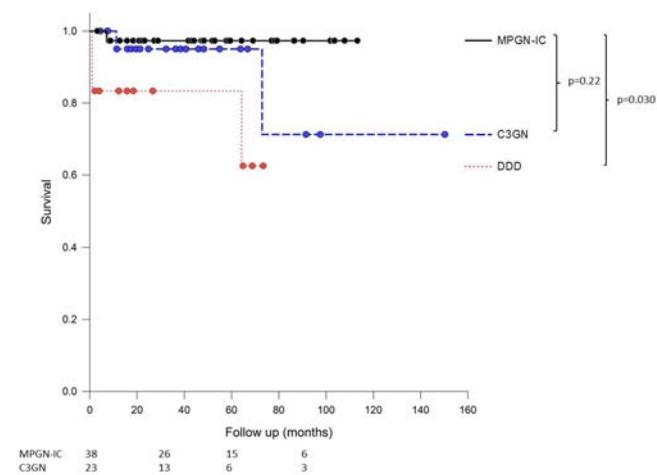
Background: The National Registry of Rare Kidney Diseases (RaDaR) in the United Kingdom allows recruitment, research and longitudinal follow-up of patients with membranoproliferative glomerulonephritis (MPGN) and C3 glomerulopathy (C3G). The aim of the MPGN/C3G Rare Disease Group (RDG) is to deep phenotype and analyse complement abnormalities in a paediatric cohort of MPGN/C3G.

Methods: The MPGN/C3G RDG recruited patients with MPGN/C3G for central review of biopsies and clinical data, and studied complement abnormalities previously described in MPGN/C3G.

Results: 83 prevalent patients with MPGN/C3G were identified and centrally reviewed. 79 could be classified: 40 had immune-complex MPGN, 25 had C3GN and 14 had DDD. Complement abnormalities are shown in Table 1. Follow-up data on 73 patients is shown in Figure 1.

	MPGN-IC	C3GN	DDD
Low C3 at presentation	22/28 (79)	16/18 (89)	10/11 (91)
C3 nephritic factor	9/21 (43)	6/18 (33)	6/7 (86)
Anti-FH autoantibodies	7/39 (18)	3/24 (13)	3/14 (21)
Rare variant (C3, FB, FH, FI)	4/35 (11)	1/22 (5)	1/12 (8)
	Positive/number tested (%)		

Renal Survival to ESRD



Conclusions: RaDaR has facilitated the development of a large nationwide cohort of paediatric patients with MPGN/C3G who have now undergone deep phenotyping and genotyping centrally. Acquired complement abnormalities were common; rare genetic abnormalities were infrequent. Patients with DDD had the worst renal outcome. Ongoing recruitment and longitudinal follow up will clarify prognosis according to phenotype/genotype and allow stratification into future treatment studies.

FR-PO455

Plasma Neutrophil Gelatinase-Associated Lipocalin, Procalcitonin and C-Reactive Protein as the Predictor of Acute Pyelonephritis in Children with Febrile Urinary Tract Infections *Byungkwan Kim, Hyung Eun Yim, Kee Hwan Yoo.* *Dept of Pediatrics, Korea Univ Medical Center, Seoul, Republic of Korea.*

Background: We have recently reported that plasma and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels are useful for the prediction of acute pyelonephritis (APN) in pediatric urinary tract infection (UTI). This study was aimed to determine the accuracy of NGAL measurements, compared with serum measurements of procalcitonin, C-reactive protein (CRP), and white blood cells (WBCs) in predicting APN and associated renal problems in children with febrile UTIs.

Methods: Total 138 children with febrile UTIs (59 APN, 79 lower UTI) were enrolled. Patients with renal failure, congenital urologic anomaly except vesicoureteral reflux

(VUR), and recurrent UTIs were excluded. Serum levels of NGAL, procalcitonin, CRP and WBC counts were measured at admittance. Laboratory, clinical, and imaging results were reviewed.

Results: Receiver operating curve analyses showed NGAL (area under the curve (AUC) 0.893), procalcitonin (AUC 0.855), CRP (AUC 0.879), and WBCs (AUC 0.654) had good diagnostic profiles for identifying APN (all $P < 0.05$). Using the best cut-off values (NGAL 117 ng/mL, procalcitonin 0.173 ng/mL, CRP 2.78 mg/dL, WBC 15,870/mm³), odds ratios for APN were all highly increased after adjusting for age and gender (NGAL 41.2, procalcitonin 22.8, CRP 25.3, WBC 4.2). The sensitivity and specificity of plasma NGAL for diagnosing APN was the highest among all examined biomarkers (sensitivity 88.1%, specificity 84.8%). Univariate analysis showed that female gender, NGAL, procalcitonin, CRP, and WBCs were associated with APN (all $P < 0.05$). However, multivariate analysis revealed that only plasma NGAL was an independent predictor of APN ($P < 0.001$). NGAL, procalcitonin, and CRP levels also showed good predictive values for the presence of VUR (AUCs of NGAL, procalcitonin, and CRP 0.798, 0.756, 0.845).

Conclusions: Plasma NGAL, procalcitonin and CRP are sensitive predictors for identifying APN and VUR. Plasma NGAL can be more reliable than serum procalcitonin, CRP, and WBCs in predicting APN in children with febrile UTIs.

FR-PO456

A Prospective Evaluation of Renal Contrast-enhanced Ultrasound (CEUS) in the Detection of Pyelonephritis Florian Buchkremer,¹ Daniel Drozdov,² Werner C. Albrich,³ Andreas H. Bock.¹ ¹Div of Nephrology, Kantonsspital Aarau, Aarau, Switzerland; ²Medical Univ Dept, Kantonsspital Aarau, Aarau, Switzerland; ³Div of Infectious Diseases, Kantonsspital St. Gallen, St. Gallen, Switzerland.

Background: Contrast-enhanced ultrasound (CEUS) has been described as a promising method for detecting acute pyelonephritis (PN) and its complications. We evaluated its value in diagnosis and risk stratification in the setting of a randomized controlled trial (RCT).

Methods: Immunocompetent adults with community-acquired urinary tract infection (UTI) presenting in the emergency department of Kantonsspital Aarau were enrolled in a RCT designed to evaluate the performance of a PCT/pyuria guided algorithm versus standard guidelines (Drozdov et al. BMC Medicine 2015). Outcomes included antibiotic exposure, duration of therapy, persistent infections and recurrences/re-hospitalizations. As part of the protocol, all hospitalized UTI patients with fever and/or flank pain were to undergo renal CEUS in addition to standard greyscale and Doppler examination within the first 72h of admission. Findings suggestive of PN such as triangular, hypoechogenic, hyperperfused areas were recorded.

Results: Of 70 UTI study patients hospitalized with fever and/or flank pain, 41 (59%) underwent the ultrasound study. Dropout reasons included missing consent (5), early discharge (6) or technical (18). Examined and non-examined patients did not differ significantly in baseline characteristics or outcome. Findings suggestive of PN were found in 5/41 (12%). In 3 patients, this was evident in greyscale/Doppler already, in 2 additional patients, critical findings were only present in CEUS. The presence of PN-suggestive findings was not predictable from any baseline clinical characteristic. Patients with and without PN-suggestive findings did not appear to differ in outcome.

Conclusions: Ultrasound evidence of pyelonephritis is rare in patients hospitalized for UTI with fever or flank pain. Adding CEUS to basic greyscale and Doppler ultrasound may substantially increase the number of positive findings.

Funding: Government Support - Non-U.S.

FR-PO457

ISN 0by25 AKI Global Snapshot Project: AKI Disposition Michael V. Rocco,¹ Ravindra L. Mehta,² Giuseppe Remuzzi,³ Jing Zhang,² Melanie Godin,⁴ Emmanuel A. Burdmann,⁵ John Feehally,⁶ Fredric O. Finkelstein,⁷ Guillermo Garcia-Garcia,⁸ Raul Lombardi,⁹ Etienne Macedo.³ ¹Wake Forest U; ²U California San Diego; ³Mario Negri Inst; ⁴Sherbrooke U; ⁵U Sao Paulo; ⁶U Leicester; ⁷Yale U; ⁸Hosp Civil de Guadalajara; ⁹Servicio Medico Integral.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians about pts with AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Nephrology management of AKI was more common in LLMIC (85.1%) versus HIC (58.4%) or UMIC (58.1%). Location of pts 7 days after AKI diagnosis varied by GNI category ($p < 0.0001$).

Location 7 days after AKI confirmation	Frequency	Percent	HIC	UMIC	LLMIC
ICU	567	16.5	23.5	17.2	7.2
Hospital ward	1980	57.5	57.1	58.2	56.8
Transfer to another hospital	51	1.5	0.7	1.5	2.3
Outpatient clinic	127	3.7	3.1	2.2	6.6
Other health facility			14 0.4 0.3	0.5	0.4
Home	612	17.8	13.8	17.2	23.3
Rehab/Nursing home	10	0.3	0.8	0.1	0
Unknown	84	2.4	0.8	3.2	3.3

AKI recovery was more often complete in LLMIC (34.5%) than in HIC (29.9%) or UMIC (25.9%). Patients were discharged home in 83.4% in HIC, 86.1% in UMIC and 92.0% in LLMIC ($p < 0.0001$). Data from 3861 pts showed that 88.8% were alive at the time of the last observation; this rate did not vary by GNI category ($p = 0.922$). Scheduled follow-up for AKI was arranged in only 14% of pts, with non-significant differences among GNI categories ($p = 0.5$).

Conclusions: Pts with AKI had hospital stays that typically exceeded 7 days, although this was less likely in LLMIC. Survival rates did not vary by GNI category. Pts were more likely to be sent home in LLMIC compared to HIC and UMIC; this observation may at least be partially due to the greater prevalence of patients in ICUs 7 days after AKI diagnosis in HIC vs. LLMIC countries. Scheduled follow-up for AKI was infrequent and did not vary by GNI category.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belco (Mirandola, Italy), Private Foundation Support

FR-PO458

ISN 0by25 AKI Global Snapshot Project: Indications for Initiating and Withholding Dialysis in AKI Worldwide Etienne Macedo,¹ Ravindra L. Mehta,² Giuseppe Remuzzi,³ Jing Zhang,² Melanie Godin,⁴ Michael V. Rocco.⁵ ¹U Sao Paulo; ²U California San Diego; ³Mario Negri Inst; ⁴Sherbrooke U; ⁵Wake Forest U.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians on pts who had a confirmed diagnosis of AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC). We analyzed the frequency of AKI requiring dialysis and the reasons for starting or withholding dialysis.

Results: Of 3855 pts, 768 (20%) were dialyzed. Mortality rate was significantly different in dialyzed (17%) vs. non-dialyzed (9%) pts ($p < 0.0001$). Among dialyzed pts, the mortality rate was similar in countries of different GNI categories. The main reason to start dialysis was solute control, with a similar distribution among country categories.

Reasons for dialysis	Frequency	Percent	HIC (n=236)	UMIC (n=230)	LLMIC (n=323)	p value
Fluid overload	406	51.5	55.1	50.4	49.5	0.4
Solute control	610	77.3	72.5	73.9	83.3	0.004
Electrolyte or acid/base disturbance	450	57.0	53.8	58.7	58.2	0.49
Intoxication/poisoning	31	3.9	3.4	8.7	0.9	<0.0001
Other	28	3.5	1.3	5.7	3.7	0.037

Of the non-dialyzed pts (3087), 244 (8%) had a clinical indication but were not dialyzed. Reason for withholding dialysis was different across country levels. In HIC, the main reason to withhold dialysis was futile treatment (79%). In UMIC, main reason was patient cultural beliefs (25%) and in LLMIC financial restriction was as frequent as futile perception (30 and 32%).

Conclusions: Solute control is the most common indication for AKI dialysis around the globe. Lack of resources is a frequent cause of withholding dialysis in LLMIC, while physician perception of futile treatment is the main reason in HIC. Knowledge of local deficits will be important to guide future interventions and to develop strategies to improve outcomes.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belco (Mirandola, Italy), Private Foundation Support

FR-PO459

ISN 0by25 AKI Global Snapshot Project: Differences in Location and Process of Care Among AKI Patients Around the Globe Etienne Macedo,¹ Ravindra L. Mehta,² Giuseppe Remuzzi,³ Jing Zhang,² Melanie Godin,⁴ Michael V. Rocco,⁵ ¹*U Sao Paulo*; ²*U California San Diego*; ³*Mario Negri Inst; ⁴Sherbrooke U*; ⁵*Wake Forest U*.

Background: The Global Snapshot (GSP) was a prospective cross-sectional study designed to capture standardized information on incidence, causes and treatment of AKI in all health care settings throughout countries of diverse economic status.

Methods: A web based survey tool was used to obtain data from pts with a confirmed diagnosis of AKI based on KDIGO criteria in 72 countries. Detailed methodology is found in the ISN GSP abstract on provider characteristics. We analyzed the characteristics of pt location and process of care by gross national income per capita (GNI) country levels. Countries were defined as: Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Based on GNI, 23 countries were classified as LLMIC, 20 as UMIC and 29 as HIC.

	HIC	UMIC	LLMIC
N of patients	1241	1594	1118
Age (adult, yrs)*	67 (55,78)	65 (52,77)	53 (38,65)
% Pediatric (n=343)	13	4	9
Age (peds, yrs)	0.4 (0.03,6.0)	8 (2,16.5)	4 (0.3,13.5)
Location where pts develop AKI **			
Community acquired	51.0	51.1	79.5
Location where patient seen **			
Emergency department	19.5	17.8	16.0
ICU	38.8	26.8	29.5
Ward or stepdown unit	39.1	50.6	47.2
Outpatient clinic	2.7	4.8	7.3
Outcomes			
Dialysis (%)*	63.3	58.3	71.8
Mortality in adults (%)	13.1	13.7	11.9
Mortality in pediatric (%)*	1.2	12.5	19.6
* p < 0.05 ***p<0.0001			

Urinalysis was more often performed in LLMIC (86%). More pts in LLMIC were dialyzed (71%). The mortality rate of dialyzed pts and the number of non-renal organ failures present was similar by GNI level. Mortality in community acquired AKI was higher in LLMIC (11%) vs 7% in HIC. LLMIC had higher mortality among ICU pts (21%) vs 13% in HIC (p=0.014). In pediatric pts, mortality was 19.6% in LLMIC compared to 1.2% in HIC (p<0.001).

Conclusions: Community acquired and pediatric AKI had a significantly higher mortality in LLMIC. Although mortality rates of dialyzed and non-dialyzed pts was similar, pts from HIC countries were significantly older. Improvement in risk assessment and early treatment of AKI in areas with fewer resources could lead to improvement in AKI outcomes.

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FR-PO460

ISN 0by25 AKI Global Snapshot Project: KDIGO Classification and AKI Diagnosis Around the Globe Etienne Macedo,¹ Ravindra L. Mehta,² Giuseppe Remuzzi,³ Jing Zhang,² Melanie Godin,⁴ Michael V. Rocco,⁵ ¹*U Sao Paulo*; ²*U California San Diego*; ³*Mario Negri Inst*; ⁴*Sherbrooke U*; ⁵*Wake Forest U*.

Background: The Global Snapshot (GSP) was a prospective cross-sectional study designed to capture standardized information on incidence, causes and treatment of AKI in all health care settings throughout countries of diverse economic status.

Methods: A web based survey tool was used to obtain data from pts with a confirmed diagnosis of AKI based on serum creatinine (sCr) and urine output (UO) KDIGO criteria in 72 countries. Detailed methodology is found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Of 4024 pts, 2891 (71%) had an available baseline sCr (BsCr), absence was greater in LLMIC (45% vs 18% in HIC, 21% in UMIC). AKI on CKD was seen in 40%. At AKI confirmation day, only 50% of pts had UO volume assessed.

Studies available at AKI diagnosis	HIC (n=1260)	UMIC (n=1605)	LLMIC (n=1153)
Baseline sCr (mg/dl)*	1.04 (0.71,1.60)	1.10 (0.86,1.71)	1.30 (1.00,2.24)
CKD (%)*	26.4	23.4	13.5
sCr at AKI diagnosis (mg/dl)*	2.43 (1.62,4.10)	2.30 (1.53,3.80)	3.26 (2.00,5.80)
UO past 24 hours of AKI diagnosis (ml)*	648 (275,1200)	900(400,1500)	500(200,1000)
sCr (alone) (%)	67.5	79.5	63.9
Oliguria (alone) (%)**	10.5	2.3	7.9
sCr + UO (%)	89.6	97.7	92.1
AKI stage at diagnosis			
1	424(36.7)	644(43.6%)	308(29.5%)
2	192(16.6%)	22(15.4%)	133(12.7%)
3	540(46.7%)	606(41.0%)	605(57.8%)
* p<0.001. **UO criteria by modified KDIGO: Oliguria defined as UO <400 ml or <0.5 ml/kg/hr last 24 h			

In LLMIC, 58% of pts were classified as AKIN stage 3 at AKI diagnosis. sCr was significantly higher in these pts (3.26 mg/dL) compared to 2.43 in pts from HIC and 2.3 in pts from UMIC.

Conclusions: BsCr was often present in pts from HIC and UMIC, where 1/3 of AKI cases occurred in CKD pts. Absence of BsCr was a common issue in LLMIC, associated with higher levels of sCr and KDIGO stage at AKI diagnosis. UO is often not computed in pts who develop AKI. Systematic assessment of urine output in high-risk pts could help identify AKI earlier.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belco (Mirandola, Italy), Private Foundation Support

FR-PO461

ISN 0by25 AKI Global Snapshot Project: Risk Factors for AKI Ravindra L. Mehta,¹ Giuseppe Remuzzi,² Jing Zhang,¹ Melanie Godin,³ Michael V. Rocco,⁴ Jorge Cerda,⁵ John Feehally,⁶ Fredric O. Finkelstein,⁷ Nathan W. Levin,⁸ Marcello Tonelli.⁹ ¹*U California San Diego*; ²*Mario Negri Inst*; ³*Sherbrooke U*; ⁴*Wake Forest U*; ⁵*Albany Med Coll*; ⁶*U Leicester*; ⁷*Yale U*; ⁸*Renal Research Inst*; ⁹*U Calgary*.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Detailed methodology is found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Participants were distributed from North/East Asia 26.4%, South Asia 18.9%, Latin America/Caribbean 14%, Africa 13.4%, North America 7.3%, Western Europe 6.2%, Oceania/Southeast Asia 4.3%, Russia/Commonwealth Independent States 3.9%, Middle East 3.4%, Eastern/Central Europe 2.2%. Ethnic groups included 53% Asian, 19% Caucasian, 9% Hispanic, 8% African, 7% Middle Eastern and 1.5% Native/Aboriginal. Causes of AKI varied by GNI and were compared by Kruskal-Wallis test.

Risk factors for AKI	Frequency	Percent	HIC	UMIC	LLMIC	p value
Dehydration	1536	38.2	39.1	32.3	45.6	<0.0001
Hypotension/shock	1615	40.2	44.8	38.2	38.2	0.0003
Cardiac	905	22.5	24.3	27.9	13.1	<0.0001
Liver	331	8.2	7.7	9.2	7.5	0.18
Acute kidney disease	488	12.2	11.1	9.4	17.2	<0.0001
Urinary obstruction	320	8.0	7.9	6.9	9.5	0.0421
Infection	1291	32.1	28.8	32.2	35.7	0.0013
Pregnancy related	56	1.4	0.4	0.9	3.1	<0.0001
Systemic diseases	322	8.0	9.4	9.4	4.6	<0.0001
Nephrotoxic agents	980	24.4	29.0	21.7	23.1	<0.0001
Poisoning	73	1.8	2.1	1.4	2.0	0.32
Envenomation			35 0.9 0.3	0.7	1.7	0.0005
Post-surgical	269	6.7	9.2	6.8	3.8	<0.0001

Other organ failures present were pulmonary 16.4% (more common in HIC), cardiovascular 23.1% (less common in LLMIC), neurologic 8.3%, hepatic 10.4%, hematologic 9.5% (more common in LLMIC) and none 53.9%

Conclusions: Hypertension was the most common cause of AKI in HIC and UMIC; dehydration was most common in LLMIC. Acute kidney disease, pregnancy and envenomation were more common in LLMIC.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO462

ISN 0by25 AKI Global Snapshot Project: Evaluation and Treatment Jorge Cerda,¹ Ravindra L. Mehta,² Giuseppe Remuzzi,³ Jing Zhang,² Melanie Godin,⁴ Michael V. Rocco,⁵ Emmanuel A. Burdman,⁶ Guillermo Garcia-Garcia,⁷ Vivekanand Jha,⁸ Andrew J.P. Lewington,⁹ Raul Lombardi.¹⁰ ¹Albany Med Coll; ²U California San Diego; ³Mario Negri Inst; ⁴Sherbrooke U; ⁵Wake Forest U; ⁶U Sao Paulo; ⁷Hosp Civil de Guadalajara; ⁸George Inst Global Health; ⁹Leeds Teaching Hosp; ¹⁰Servicio Medico Integral.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Initial evaluation of AKI included urinalysis in 73.6%, ultrasound in 55% and renal biopsy in 4.1%, with all three more commonly being performed in LLMIC. Initial treatment of AKI included fluids in 74.3%, vasopressors in 23.8%, diuretics in 41.4%, antibiotics in 63.8% and urinary diversion in 19.5%. The receipt of dialytic therapy occurred in 790 of 4018 pts (19.7%), with use in 18.8% in HIC, 14.3% in UMIC and 28.0% in LLMIC. In 244 instances where dialysis was recommended but not performed, futility was cited in 58.6% and cultural beliefs were cited in 25.4%. Unavailability of staff or material resources to perform dialysis was reported in 1.4% of HIC, 3.8% of UMIC and 16.4% of LLMIC. Inability to afford therapy was 1.4% in HIC, 1.9% in UMIC and 16.4% in LLMIC (p<0.0001). The ratio of pts not able to receive dialysis by those that did receive dialysis was 0.21 in HIC, 0.25 in UMIC and 0.18 in LLMIC. There were significant differences in the renal modality used.

Treatment (n=790)	Frequency	Percent	HIC	UMIC	LLMIC
IHD	516	65.3	63.3	58.3	71.8
PD	41	5.2	4.6	3.0	7.1
CRRT	157	19.9	31.7	29.1	4.6
UF	10	1.3	2.5	1.7	0
SLED	103	13.0	3.4	10.9	21.7
Other	8	1.0	0.6	1.4	0
Unknown	1	0.1	0	0.2	0

Conclusions: Lack of resources, staff or finances to perform dialysis was most prevalent in LLMIC. When dialysis was provided, it was less likely to be CRRT and more likely to be SLED in LLMIC.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO463

ISN 0by25 AKI Global Snapshot Project: Provider Characteristics Melanie Godin,¹ Ravindra L. Mehta,² Giuseppe Remuzzi,³ Jing Zhang,² Michael V. Rocco,⁴ Jorge Cerda,⁵ Vivekanand Jha,⁶ Nathan W. Levin,⁷ Andrew J.P. Lewington,⁸ Etienne Macedo,⁹ Marcello Tonelli.¹⁰ ¹Sherbrooke U; ²U California San Diego; ³Mario Negri Inst; ⁴Wake Forest U; ⁵Albany Med Coll; ⁶George Inst Global Health; ⁷Renal Research Inst; ⁸Leeds Teaching Hosp; ⁹U Sao Paulo; ¹⁰U Calgary.

Background: The ISN 0by25 AKI Global Snapshot Project (GSP) was designed to determine the spectrum of AKI pts seen in health care facilities throughout the world.

Methods: Health care providers joined the GSP after gaining approval from their local IRB. Providers chose one "index" day between 9/29/2014 and 12/7/2014 to provide data on AKI pts under their care. De-identified data on pts who met criteria for AKI by modified KDIGO criteria were entered through a secure website using a standard questionnaire developed by the 0by25 AKI workgroup. Data collected included pt demographics, initial clinical data, diagnostic, treatment and outcome information. Countries were grouped into three categories based on gross national income per capita (GNI); high income with GNI >US\$12476, low and lower middle income with GNI <US\$4035, and upper middle income with GNI between levels 1 & 3.

Results: 324 surveys from 72 countries were received describing 4024 pts with AKI. Providers included 248 nephrologists, 20 nephrology fellows, 14 intensivists, 26 pediatric nephrologists. Location of facilities by region included 52 from Africa, 47 from

Latin America & Caribbean, 45 from North America, 45 from South Asia, 40 from North and East Asia, 34 from Western Europe, 19 from Russia/Commonwealth of Independent States, 17 from Oceania & South East Asia, 14 from Middle East and 11 from Eastern & Central Europe. Size of catchment population for each facility was: >5 million in 28%, 0.5-1.5 million in 26%, 0.1-0.5 million in 19% and 1.5-3 million in 11%. Type of facility was institute in 47%, public hospital or health care concern in 37%, private multispecialty group in 14%. Dialysis was available in 97% of facilities.

Conclusions: This project is the first worldwide point prevalent survey of AKI. It demonstrates the feasibility of obtaining data on AKI using a secure website from practitioners in varied health care settings from six continents.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO464

Postoperative Acute Kidney Injury in Non-Cardiac Surgery Seokwoo Park, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Hajeong Lee. *Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.*

Background: Prevention of acute kidney injury (AKI) and amelioration of its severity remain important issues of improving surgical patient outcomes. Therefore, preoperative renal risk evaluation and patient optimization is crucial for nephrologists. Although there are several studies dealing with postoperative AKI in cardiac surgery, they have been seldom studied in non-cardiac surgery.

Methods: We included adult (age ≥ 18 years) patients who received major non-cardiac surgery in Seoul National University Hospital from 2004 to 2013. We extracted their clinical data from our electronic medical record system. Acute Kidney Injury Network criteria (AKIN) was used to define and classify AKI.

Results: Among a total of 95,266 operations, 1,560 cases (1.64%) developed AKI. Patients with AKIN stage I were 964 (1.01%), stage II, 117 (0.12%), and stage III, 479 (0.50%). AKI was most prevalent in urologic surgery, followed by general surgery, orthopedic surgery, and neurologic surgery. Patients who developed AKI tended to be older (53.7 vs. 58.9 years), and male (45.6% vs. 65.6%). Patients with AKI had higher prevalence of underlying diseases such as liver/heart/hematologic/vascular and neurologic disease than those without. Moreover, they showed higher baseline systolic blood pressure and lower baseline diastolic blood pressure than those without. Baseline renal function was lower in AKI-developed patients than the others (0.90 vs. 1.13 mg/dL, P <0.001). Multivariate logistic regression analyses found that older age, male sex, lower baseline renal function, presence of hypertension, longer duration of surgical time and orthopedic or urologic surgery were significant risk factors for postoperative AKI in noncardiac surgery.

Conclusions: In this study, we demonstrated the incidence of postoperative AKI in non-cardiac major operations. Moreover, we found clinical risk factors for postoperative AKI development. Further investigation of prediction models for postoperative AKI in major non-cardiac surgery should be warranted for development of preoperative renal optimization strategy.

FR-PO465

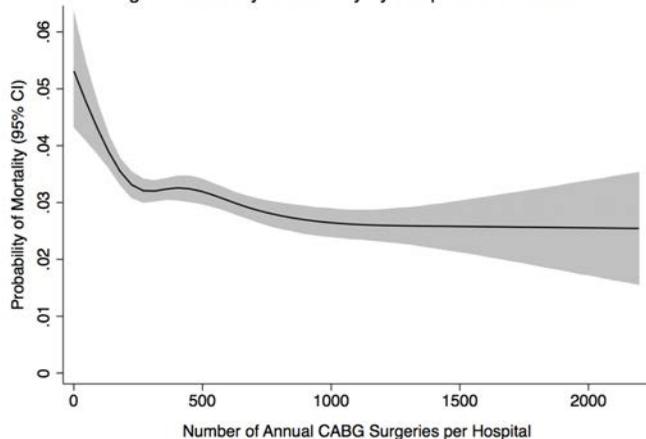
Impact of Hospital CABG Volume and AKI Needing Dialysis on CABG Hospitalizations Ankit Sakhuja,¹ Jesse D. Schold,² Edward G. Soltesz,³ Sevag Demirjian.² ¹Div of Nephrology, Univ of Michigan; ²Nephrology and Hypertension, Cleveland Clinic; ³Thoracic and Cardiovascular Surgery, Cleveland Clinic.

Background: Acute Kidney Injury (AKI) is common after Coronary Artery Bypass Grafting (CABG) and associated with poor outcome. Increased hospital procedure volume has been associated with better outcomes. We examined (1) impact of number of annual CABG procedures per hospital (CABG-vol) on AKI needing dialysis (AKI-D) and mortality, and (2) if it modifies the relationship between AKI-D and mortality.

Methods: Using Nationwide Inpatient Sample database from 2000-2010 we identified admissions with CABG using ICD-9-CM codes. Those with AKI-D were identified and those with kidney transplant or on maintenance dialysis were excluded. Multivariable logistic regressions were used to assess impact of CABG-vol on AKI-D and mortality. We used restricted cubic splines to account for non-linear relationship between CABG-vol and mortality. A priori interaction term between CABG-vol & AKI-D was assessed in model for mortality.

Results: Of estimated 3,337,292 (95% CI: 3,103,610-3,570,973) hospitalizations for CABG, 0.7% (24,126) had AKI-D. Those with AKI-D were older, more females (37.5% vs 29.1%; p<0.001) and blacks (7.4% vs 5.5%; p<0.001). On adjusted analysis, CABG-vol was not correlated with odds of developing AKI-D (0.99; 95% CI 0.99-1.00) but was associated with mortality (Fig 1).

Fig 1: Probability of Mortality by Hospital CABG volume



AKI-D was a significant predictor of mortality with OR 13.75 (95% CI: 11.37-16.64). Interaction term between CABG-vol & AKI-D was not significant (p=0.8).

Conclusions: Lower annual CABG hospital procedure volume is significantly associated with higher mortality but not with higher incidence of AKI-D. AKI-D is associated with higher mortality in those undergoing CABG, however, there is no differential effect of hospital volume on adjusted odds of mortality due to AKI-D.

FR-PO466

Five-Year Risk of Renal Outcomes After Pediatric Cardiac Surgery

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Background: Pediatric cardiac surgery is associated with a high risk of acute kidney injury (AKI) and other short-term adverse outcomes. However, the risk for long-term renal outcomes after cardiac surgery is unknown.

Methods: We performed 5 year follow-up on the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) cohort. TRIBE-AKI is a three-center prospective cohort study of children 1 month to 18 years old who underwent cardiopulmonary bypass.

Results: Out of 305 children who survived their index hospitalization, 4 (1.3%) died after discharge and 128 (42%) participated in the 5 year follow-up. Mean age of the cohort at follow-up was 9.2 years and 53% were male. 56 out of 128 patients had perioperative AKI defined as a post-operative serum creatinine rise by 50% or 0.3mg/dL from pre-operative baseline. At a median of 5.4 years of follow-up, hypertension, microalbuminuria, eGFR<90, and eGFR<60 were identified in 13%, 6.3%, 7.0%, and 0.8% of patients, respectively. CKD, defined as eGFR<90 or microalbuminuria, was present in 13% of children. There were no significant differences in renal outcomes between patients with and without perioperative AKI. 5 (4.0%) patients had been seen by a pediatric nephrologist. The 5-year post-operative prevalence of hypertension in our cohort was >8 fold higher than found in the general pediatric population (Table).

Conclusions: Overall, there is a high prevalence of CKD and hypertension in children 5 years after cardiac surgery. Despite this high prevalence of CKD, very few children were seeing a pediatric nephrologist. These findings may have implications for renal care and late cardiovascular disease in children after cardiac surgery.

	Definition	TRIBE-AKI 5 Year Follow-up	General pediatric population
Hypertension	BP>95 th percentile	13%(CI 7.8-19%)	1.6%(CI 1.0-2.4%)
Microalbuminuria	Albumin/Creatinine>30mg/g	6.3%(CI 3.2-12%)	9.9%
eGFR<90	Bedside CKID formula	7.0%(CI 3.7-13%)	Not available
CKD	eGFR<90 or albuminuria	13.3%(CI 8.5-20%)	Not available

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FR-PO467

Changes of Epidemiology and Influencing Factors of Acute Kidney Injury After Cardiac Surgery – A Five-Year Study from 2009 to 2013

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Background: Cardiac Surgery is a common cause of acute kidney injury (AKI). We collected the epidemiological data of patients with AKI from 2009 to 2013 in order to explore the influencing factors of changes of epidemiology after cardiac surgery.

Methods: Clinical data of patients undergoing cardiac surgery, which included demographic data of preoperative, intraoperative, postoperative were prospectively collected in our hospital from January 2009 to December 2013. The main endpoint was poor prognosis which included overall mortality and abandon of treatment. The second point was renal outcome.

Results: A total of 11693 patients enrolled, including 6637 males and 5056 females. The overall AKI incidence was 34.5% (n=4030). The AKI incidence increased during the five years from 34.2% to 36.5% (P<0.05). There was no significantly statistical differences in AKI-RRT incidences during the five years (p=0.360); The hospital mortality of AKI decreased from 6.3% in 2009 to 3.8% in 2013. The incidence of poor prognosis in AKI were 8.3%, 7.5%, 6.8%, 5.1%, 8.0% (P=0.196). The mortality of AKI-RRT decreased from 47.1% to 29.5%, but there was no statistical difference (P = 0.230). The incidence of poor prognosis in RRT decreased from 66.7% to 57.4%, also no significantly statistical difference (P=0.825). Multivariate logistic regression analysis showed that male, age (every additional 10 years), body mass index (every additional 5kg/m²), hypertension, chronic heart failure, pre-operative serum creatinine >115mmol/L, CPB (every additional 30min) were the risk factors of AKI after cardiac surgery.

Conclusions: The incidence of AKI after cardiac surgery increased from 2009 to 2013 and the rate of poor prognosis did not change. The incidence of AKI-RRT and the rate of poor prognosis remained high. The prevention and treatment of AKI still need improvement.

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FR-PO468

The Very Long-Term Co-Morbidity Adjusted Impact of AKI following Cardiac Surgery: A 15-Year Follow-Up Study

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Background: AKI is a frequent complication of cardiac surgery (CS) associated to high mortality. The co-morbidity adjusted residual impact on very long-term mortality (> 12 year) of AKI, excluding the initial catastrophic impact on early mortality has never been addressed before. **Objectives:** to evaluate the net attributable impact of AKI after CS on long-term mortality.

Methods: All adult patients submitted to CS between 1/1/2000 and 31/12/2013 (n=7755) were enrolled. The INCC prospective-collected database with more than 750 variables (demographics, comorbidities, type of CS, intraoperative and postoperative variables, peri-operative support and short time outcomes) was used. Long-term survival (up to 15 year by December 2014) was obtained by systematic telephone survey (minimum 1-year follow-up) and the National Population Registry. AKI stages were defined according to KDIGO definition. Demographics, logistic EuroSCORE (and their single components), type of CS, baseline renal function (Cockcroft-Gault formula) were used for comorbidity risk-adjustment. Statistical analysis: "t" test, c² test, Kruskal-Wallis test, Kaplan-Meier curves with long-rank test and Cox regression for multivariate survival analysis. Only patients alive after the first 1 year follow-up entered in the long-term survival analysis (n= 6956).

Results: AKI incidence: 38.4%. RRT: 1.7%. Long-term (15 years) actuarial survival after 1 year follow-up: no AKI 0.58; AKI (I): 0.47; AKI (II): 0.39; AKI (III): 0.27 (p<0.001). In multivariate Cox regression analysis, AKI stages I, II and III (OR 1.17; 1.24; 1.62 respectively) were independently associated with mortality between 1 year after CS and 15 year follow-up, even after adjustment with logistic EuroSCORE (OR 1.02), age (OR 1.038), diabetes (OR 1.58), pre operative eGFR (OR 0.996) and no-isolated coronary bypass surgery (OR 1.24).

Conclusions: AKI and its severity are independently associated with very long-term mortality, even after discarding short term events (1 year), in cardiac surgery. Should AKI be causative or a surrogate marker of late events in the long term follow up is a matter of concern to be evaluated.

FR-PO469

Incidence and Influencing Factors of Cardiac Surgery-Associated Acute Kidney Injury Based on the KDIGO Criteria: A Retrospective Cohort Study

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Background: The incidence and influencing factors of cardiac surgery-associated acute kidney injury (CSA-AKI) based on the KDIGO criteria have not been well studied. This study was aimed to evaluate the incidence, risk or protective factors of acute kidney injury (AKI) in patients after cardiac surgery.

Methods: A retrospective analysis of 2575 patients undergoing first documented cardiac surgery with cardiopulmonary bypass (CPB) between January 2008 and December 2012 in our hospital was conducted. Perioperative variables were collected and analyzed. Univariate and multiple logistic regression models were used for determining the association between the development of AKI and risk factors.

Results: Of 2575 patients, 931 (36%) developed AKI. A total of 30(1.2%) patients required renal replacement therapy. The overall in-hospital mortality rate was 1.5% (38 of 2575). CSA-AKI was significantly associated with in-hospital mortality (adjusted HR: 2.22, 95% CI 1.16-4.24, P = 0.016), especially in patients needing RRT (adjusted HR: 18.68, 95% CI 8.58-40.68, P < 0.001). The independent risk factors identified by multivariate analysis were shown in [table 1].

Variable	Odds ratio	95 % CI	P
Male	1.14	1.17-1.71	<0.001
BMI	1.29	1.11-1.49	0.001
History of hypertension	1.49	1.21-1.84	<0.001
Insulin-controlled diabetes	1.56	1.06-2.30	0.025
Creatinine (>88.4µmol/L)	1.88	0.94-3.72	0.074
Red blood cells transfused(U)	1.08	1.05-1.11	<0.001
CPB duration ≥110min	1.31	1.07-1.61	0.009
Mechanical ventilation ≥9h	1.45	1.20-1.75	<0.001
Ulinastatin administration	0.69	0.56-0.88	0.006
Body temperature (>38°C) after surgery within 3 days	1.23	1.02-1.50	0.032

Conclusions: This study demonstrates that mechanical ventilation duration, erythrocytes transfusion and postoperative body temperature above 38°C within 3 days were considered independent risk factors for CSA-AKI. Use of ulinastatin was associated with lower incidence of CSA-AKI.

Funding: Government Support - Non-U.S.

FR-PO470

Acute Kidney Injury Post-Major Orthopaedic Surgery: A Single Centre Experience Tracey Ying,¹ Samantha Chan,¹ Stephen E. Lane,^{2,3} Christine A. Somerville.¹ ¹Dept of Renal Medicine, Univ Hospital Geelong, Geelong, Victoria, Australia; ²Barwon Health Biostatistics Unit, Univ Hospital Geelong, Geelong, Victoria, Australia; ³School of Medicine, Deakin Univ, Geelong, Victoria, Australia.

Background: Given the increasing incidence of AKI and the burden this places on the medical system, there is a clear need to expand the practise of 'preventative nephrology' – the optimisation of renal function through minimisation of potential insults. Renoprotection is particularly critical in the perioperative setting, a period of high renal vulnerability. However, there is currently little evidence regarding numerous theoretical risk factors for postoperative AKI.

Methods: All patients undergoing MOS at our centre between 2008 and 2014 were included. Out of 2227 surgeries audited for AKI using comparisons of preoperative and postoperative creatinine, 164 cases were identified (per RIFLE criteria) and matched to controls 2:1 for age, sex, procedure and chronic kidney disease stage. Their records were reviewed for established and proposed risk factors for postoperative AKI: diuretic, non-steroidal anti-inflammatory (NSAID) and angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use. Associations of proven and hypothetical risk factors were estimated using conditional logistic regression.

Results: Controlling for known risk factors, both diuretic and ACEi or ARB use were found to be associated with an approximately twofold increased risk of AKI (diuretic – OR 2.06 95%CI:1.30-3.26, p<0.005, ACEi/ARB – OR 2.09 95%CI:1.31-3.32, p<0.005). A dose-effect model accounting for preoperative, intraoperative and postoperative NSAID administration demonstrated a linear relationship between the number of times NSAIDs were given and postoperative AKI risk (OR 1.35 95%CI:1.05-1.73, p<0.05).

Conclusions: Perioperative diuretic, NSAID and ACEi or ARB use were shown to be significantly associated with postoperative AKI, indicating that these medications should be used with caution in MOS. Further prospective studies are required to confirm this.

FR-PO471

Incidence of In-Hospital Acute Kidney Injury by Surgery and Invasive Surgical Procedures Among Non-Emergency Hospital Admissions Joshua Taylor Swan,^{1,2} Beverly A. Shirkey,¹ Linda W. Moore,¹ Wadi N. Suki,¹ A. Osama Gaber.^{1,3} ¹Houston Methodist Hospital; ²Texas Southern Univ; ³Weil Cornell Medical College.

Background: This study aimed to identify non-emergency invasive surgical procedures that are associated with the highest burden of in-hospital AKI.

Methods: Urgent and elective admissions to a quaternary teaching hospital in 2012-2013 with a principal procedure within 1 day of admission were included. Principal procedures were categorized using AHRQ's Clinical Classifications Software (CCS).

Patients <18 years, nephrectomy, and those with preexisting AKI or stage 5 CKD were excluded. AKI was defined as an increase in SCr by ≥0.3 mg/dL or ≥50% over a 72-hour interval, staged per KDIGO.

Results: AKI occurred during 18% (2,244) of 12,237 admissions. Of AKI cases, 82% (1,828) were stage 1, 12% (273) stage 2, and 6% (143) stage 3. Patients were 69% white, 51% female, aged 61±16, and 9% with CKD. Ten CCS groups with the largest number of AKI cases are presented.

CCS Category, CCS code	Admissions, n	Any AKI, n (%)	Stage 1 AKI, n (%)	Stage 2 AKI, n (%)	Stage 3 AKI, n (%)
Organ transplantation (other than bone marrow, corneal or kidney), 176	234	161 (69)	92 (39)	42 (18)	27 (12)
Heart valve procedures, 43	713	323 (45)	263 (37)	47 (7)	13 (2)
Coronary artery bypass graft (CABG), 44	403	176 (44)	152 (38)	19 (5)	5 (1)
Diagnostic bronchoscopy and biopsy of bronchus, 37	248	73 (29)	65 (26)	5 (2)	3 (1)
Other OR heart procedures, 49	251	59 (24)	46 (18)	10 (4)	3 (1)
Other OR procedures on vessels other than head and neck, 61	286	64 (22)	54 (19)	3 (1)	7 (2)
Diagnostic cardiac catheterization; coronary arteriography, 47	300	52 (17)	46 (15)	4 (1)	2 (1)
Colorectal resection, 78	439	57 (13)	44 (10)	7 (2)	6 (1)
Arthroplasty knee, 152	1100	126 (11)	113 (10)	7 (1)	6 (1)
Hip replacement; total and partial, 153	873	99 (11)	89 (10)	7 (1)	3 (0)

Conclusions: This study presents the incidence of AKI after invasive surgical principal procedures, and this data will help prioritize research to prevent in-hospital AKI. Non-kidney transplant, heart valve, and CABG surgical procedures were associated with the largest number of AKI cases at this single center, and non-kidney organ transplants were associated with a high severity of AKI.

FR-PO472

Acute Kidney Injury following Gastrointestinal Surgery Þórir E. Long,^{1,4} Dadi Helgason,¹ Sólveig Helgadóttir,^{2,4} Tomas Gudbjartsson,^{3,4} Gisli H. Sigurdsson,^{2,4} Martin I. Sigurdsson,^{2,5} Olafur S. Indridason.⁶ ¹Dept of Medicine; ²Dept of Anesthesia; ³Dept of Cardiothoracic Surgery, Landspítali; ⁴Faculty of Medicine, Univ of Iceland; ⁵Dept of Anesthesia, Brigham and Women's Hospital, Boston, MA; ⁶Div of Nephrology, Landspítali - The National Univ Hospital, Reykjavik, Iceland.

Background: Acute kidney injury (AKI) is a serious postsurgical complication but AKI after nonvascular abdominal surgery has not been thoroughly studied. The aim of this study was to examine the incidence of AKI after such operations, its risk factors and survival of patients.

Methods: We studied all nonvascular abdominal operations performed on adults 2007-2014 at Landspítali, the major hospital in Iceland. AKI was diagnosed according to the creatinine based KDIGO criteria. Risk factors for AKI were evaluated using logistic regression analysis. Survival was compared between AKI and non-AKI patients using Kaplan-Meier method after propensity score matching (1:1, nearest neighbor matching).

Results: A total of 10,022 patients underwent 11,552 operations during the study period, 38.0% were acute operations. Median age at operation was 52 yrs (IQR 32-66) and 59.5% of patients were female. AKI occurred after 246 operations (2.1%), with 157 (1.4%), 57 (0.5%) and 32 (0.3%) of stage 1, 2 and 3, respectively. Incidence of AKI was higher after major (5.3%), open (4.9%) and acute operations (3.0%) compared to minor (1.1%), laparoscopic (0.5%) and non-acute operations (1.8%). In multivariable analysis, postoperative AKI associated with age (OR 1.03 (95%CI 1.04-1.04)), male sex 1.5 (1.1 - 2.0), open operation 3.0 (2.2-4.2), re-operation 4.8 (3.7-8.6), hypertension 1.7 (1.2-2.4), eGFR <60ml/min/1.73 m² 2.0 (1.4-2.7) and ASA score 6.1 (4.2-8.8). Survival was worse for AKI patients compared to the propensity score matched controls, both at 30 days (82.4% vs. 94.7%, p=0.03) and at 1-year (69.9% vs. 82.6%, p=0.03).

Conclusions: The incidence of AKI is relatively low after gastrointestinal surgery compared to cardiac and vascular surgery. The rate of AKI is substantially higher after major and open operations and in patients with preexisting kidney disease. AKI is associated with increased short- and long-term mortality.

Funding: Private Foundation Support

FR-PO473

Risk Factors Associated with Post-Operative AKI After General Surgery Pradeep Arora,¹ Leili Pourafkari,² James W. Lohr,¹ Hasan H. Dosluoglu,³ Nader Nader.¹ ¹Div of Nephrology, VAMC, Buffalo, NY; ²Anesthesiology, VAMC, Buffalo, NY; ³Surgery, VAMC, Buffalo, NY.

Background: AKI after cardiac and vascular surgery has been extensively studied. However there is no study which has evaluated the factors associated with development of stage 1 AKI by AKIN criteria in general surgery patients.

Methods: We conducted a cohort study using a prospective database of patients undergoing surgical procedures since 2000 in the VA Western New York Healthcare System which are in part reported to the National Surgical Quality Improvement Program (NSQIP). Demographic, social history, co-morbid diseases, including coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive lung disease (COPD), peripheral vascular disease (PVD), cerebrovascular accidents (CVA), hypertension, and diabetes, were prospectively entered into the Veterans Affairs Surgical Quality Improvement Program (VASQIP) database at the time of surgery. Preoperative laboratory data were also entered for each participant. Univariate and multivariate logistic regression were performed to estimate the odds of AKI after surgery.

Results: A total of 13300 patients who underwent non-cardiac and non-vascular surgery whose data was available to define AKI between 2000-2014 were included in this analysis. A total of 1621 patients developed AKI stage 1. In univariate analysis, increasing age, male gender, ASA class, poor functional status, presence of COPD, Ascites, CVA, CVD, DM, CHF, HTN, preop coronary intervention or MI, HCT <24, Low serum albumin, increased operating room (OR) time and blood transfusions were associated with increased odds of AKI. Results of multivariate analysis are shown in table 1.

Variable	Odds ratio with 95% CI
Age	1.02 (1.02-1.03)
CHF	1.22 (1.03-1.47)
COPD	1.11 (1.02-1.21)
DM	1.21 (1.12-1.32)
OR time	1.15 (1.10-1.20)
Pre creatinine	1.21(1.08- 1.36)
HCT <24	1.75(1.59-1.92)
Transfusion during surgery	1.34 (1.07-1.69)
Serum albumin	0.72 (0.62-0.81)

Conclusions: AKI is associated with increased length of hospital stay and mortality. Efforts to recognize and intervene in preoperative modifiable factors to prevent AKI will improve outcomes in general surgical patients.

FR-PO474

The Comparison of the Incidence of Acute Kidney Injury Post Coronary Artery Bypass Graft versus Percutaneous Coronary Intervention: National Inpatient Sample Experience Wen Shen, Fernando Rodrigo Aguilar, Alex Montero. *Division of Nephrology & Hypertension, Georgetown Univ, Washington, DC.*

Background: AKI, a common complication after coronary revascularization, is associated with increased risk of short-term and long-term mortality, and renal loss. Although survival benefit of CABG over PCI was shown in patients with diabetes and congestive heart failure, the incidence of AKI post coronary revascularization needs to be considered when comparing the risks and benefits of CABG vs PCI.

Methods: We extracted total 485742 cases from National Inpatient Sample (NIS) to create a propensity-score matched cohort of patients who had multivessel coronary disease and underwent first-time CABG or PCI between 2004-2012. Patients received concomitant valvular repair or both CABG and PCI on same admission, history of organ transplant, CKD stage IV or ESRD on dialysis were excluded. Both groups were matched for age, gender, race, payer, prior MI, unstable angina, heart failure, CVA, stroke or TIA, peripheral arterial disease, mitral or aortic valve disease, atrial flutter/fibrillation, ventricular fibrillation or tachycardia, CKD, diabetes, HTN, dyslipidemia, smoking, cirrhosis, obesity, anemia and in-hospital GI bleeding. The odds ratios were estimated by logistic regression analysis.

Results: The incidence of AKI in CABG group was higher than PCI group (8.41% vs 4.00%, OR 2.20, 95% CI 2.15-2.25, P< 0.001). The incidences of severe AKI requiring RRT were similar in both groups (0.95% vs 0.91%, P=0.147). Compared with PCI group, CABG group had higher total in-hospital mortality (1.99% vs 1.48%, OR 1.34, 95% CI 1.24-1.40, P<0.0001).The in-hospital mortality in patients with AKI was higher in CABG (0.92% vs 0.59%, P<0.0001).

Conclusions: Patients received CABG were at higher risk of developing AKI and associated with higher total in-hospital mortality. The in-hospital mortality in patients with AKI was higher in CABG.

FR-PO475

Dialysis-Requiring Acute Kidney Injury Among Hospitalized Adults with Documented Hepatitis C Virus Infection: A Nationwide Inpatient Sample Analysis Girish N. Nadkarni,¹ Achint Patel,¹ Priya Simoes,¹ Rabi Yacoub,¹ Narender Annappureddy,² Sunil Kamat,³ Ioannis Konstantinidis,¹ Ponn Perumalswami,¹ Andrea D. Branch,¹ Steven G. Coca,¹ Christina M. Wyatt.¹ *¹Mount Sinai Medicine; ²Vanderbilt Univ; ³Kokilaben Dhirubhai Ambani Hospital and Medical Research Inst.*

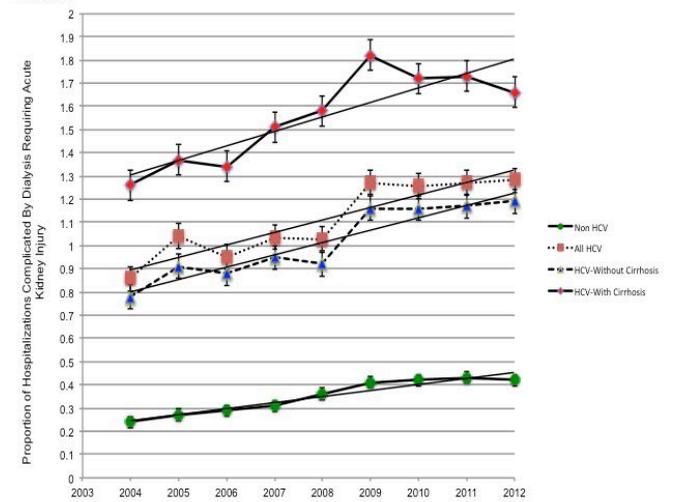
Background: Chronic Hepatitis C virus (HCV) infection causes kidney injury; data on acute kidney injury (AKI) epidemiology in HCV are limited. We aimed to describe national temporal trends of severe AKI requiring dialysis (“AKI-D”) in hospitalized adults with HCV.

Methods: We extracted our study cohort from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project using data from 2004-2012. We defined HCV

and AKI-D based on previously validated ICD-9-CM codes. We analyzed temporal changes in proportion of hospitalizations complicated by AKI-D and utilized survey multivariable logistic regression models to estimate its impact on in-hospital mortality.

Results: We identified a total of 4,603,718 adult hospitalizations with associated HCV from 2004-2012, of which 51,434 (1.12%) were complicated by AKI-D. The proportion complicated by AKI-D increased significantly from 0.86% in 2004 to 1.28% in 2012. Trend was similar when stratified by cirrhosis and paralleled that in HCV negative hospitalizations.

Figure 1. Temporal Trends in the Incidence of Acute Kidney Injury (AKI) Requiring Renal Replacement Therapy among Hospitalized Adults with and without Documented Hepatitis C Virus Infection



In-hospital mortality was significantly higher in hospitalizations complicated by AKI-D vs. those without (27.38% vs. 2.95%; adjusted odds ratio 2.09, 95% Confidence Interval 1.74-2.51) which remained stable over the study period.

Conclusions: The proportion of HCV hospitalizations complicated by AKI-D increased significantly between 2004-2012. Similar to observations in the general population, AKI-D was associated with two-fold increase in odds of in-hospital mortality. These results highlight the burden of severe AKI in hospitalized adults with HCV infection.

Funding: NIDDK Support

FR-PO476

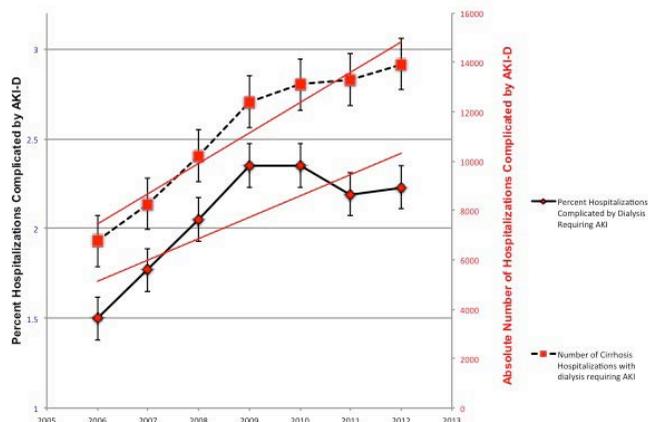
The Burden of Dialysis Requiring Acute Kidney Injury in Decompensated Cirrhosis: A Nationwide Inpatient Sample Analysis Girish N. Nadkarni,¹ Achint Patel,¹ Priya Simoes,¹ Rabi Yacoub,¹ Ioannis Konstantinidis,¹ Sunil Kamat,³ Narender Annappureddy,² Chirag R. Parikh,⁴ Steven G. Coca.¹ *¹Mount Sinai Medicine; ²Vanderbilt Univ; ³Kokilaben Dhirubhai Ambani Hospital; ⁴Yale Univ.*

Background: Cirrhosis affects nearly 5.5 million patients with an estimated cost of 4 billion. Previous studies about dialysis requiring acute kidney injury (AKI-D) in decompensated cirrhosis (DC) are from a single center or year. We aimed to describe national trends of incidence & impact of AKI-D in DC hospitalizations.

Methods: We extracted our cohort from Nationwide Inpatient Sample (NIS) from 2006-2012. We identified hospitalizations with DC & AKI-D by validated ICD9 codes. We analyzed temporal changes in proportion of DC hospitalizations complicated by AKI-D & utilized multivariable logistic regression models to estimate AKI-D impact on in-hospital mortality.

Results: We identified a total of 36,55,700 adult DC hospitalizations from 2006-2012 of which 78,015 (2.1%) had AKI-D. Proportion with AKI-D increased from 1.5% in 2006 to 2.23% in 2012; this was stable between 2009-12 despite increase in absolute number from 6773 to 13930.

Figure 1: Temporal Trends of Proportion and Absolute Number of Decompensated Cirrhosis Hospitalizations Complicated by Dialysis Requiring Acute Kidney Injury



The overall hospital mortality was significantly higher in hospitalizations with AKI-D vs. those without (40.87% vs. 6.96%; $p < 0.001$). After adjusting for demographics, mortality risk, acute/chronic comorbidities & hospital level factors, the adjusted odds ratio for mortality was 2.17 (95% CI 2.06-2.28; $p < 0.01$) with AKI-D, which was stable from 2006-2012.

Conclusions: The proportion of DC hospitalizations with AKI-D increased from 2006-09 & although, this was stable from 2009-12, there was an increase in absolute case number. These results elucidate burden of AKI-D on DC hospitalizations & excess associated mortality as well as highlight the importance of prevention, early diagnosis & testing of novel interventions in this vulnerable population.

Funding: NIDDK Support

FR-PO477

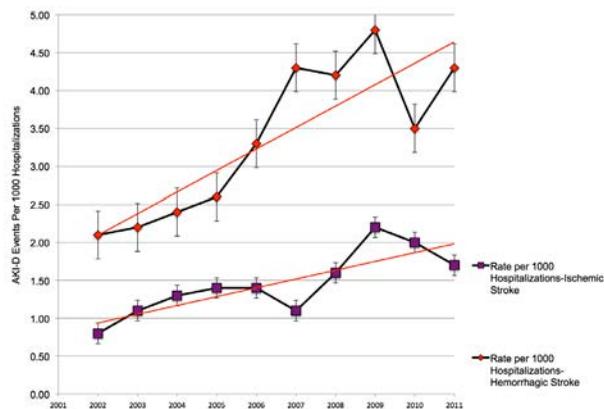
Temporal Trends of Burden of Dialysis Requiring Acute Kidney Injury in Cerebrovascular Accident Hospitalizations Girish N. Nadkarni,¹ Achint Patel,¹ Abhimanyu Mahajan,² Ioannis Konstantinidis,¹ Yuri Ahuja,³ Rabi Yacoub,¹ Charuhas V. Thakar.⁴ ¹Icahn School of Medicine at Mount Sinai; ²Henry Ford Hospital; ³Yale Univ; ⁴Univ of Cincinnati & Cincinnati VA Medical Center.

Background: The epidemiology of dialysis requiring acute kidney injury (AKI-D) in acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) admissions is poorly understood with previous studies being from a single center and/or year.

Methods: We used the Nationwide Inpatient Sample to evaluate the yearly incidence trends of AKI-D in AIS and ICH admissions from 2002 to 2011. We also evaluated the trend of impact of AKI-D on in-hospital mortality and adverse discharge utilizing adjusted odds ratios (aOR) after adjusting for demographics and comorbidity indices.

Results: We extracted a total of 3927267 AIS and 704648 ICH admissions, AKI-D occurred in 1.5 and 3.5 per 1000 in AIS and ICH admissions respectively. Incidence of admissions complicated by AKI-D doubled from 0.9/1000 to 0.1.7/1000 in AIS and from 2.1/1000 to 4.3/1000 in ICH admissions.

Figure 1: Temporal Trends of Proportion of AIS/ICH hospitalizations complicated by AKI-D



In AIS admissions, AKI-D was associated with 30% higher odds of mortality (aOR 1.30; 95% CI 1.12-1.48; $p < 0.001$) and 18% higher odds of adverse discharge (aOR 1.18; 95% CI 1.02-1.37; $p < 0.001$). Similarly, in ICH admissions, dAKI was associated with twice the odds of mortality (aOR 1.95; 95% CI 1.61-2.36; $p < 0.01$) and 74% higher odds of adverse discharge (aOR 1.74; 95% CI 1.34-2.24; $p < 0.01$).

Conclusions: Incidence of dAKI complicating CVA hospitalizations continues to grow and is associated with increased mortality and adverse discharge. This highlights the need for early diagnosis and better risk stratification in this vulnerable population.

FR-PO478

Long-Term Healthcare Utilization and Mortality After Acute Kidney Injury in Critically Ill Children Erin Hessey,¹ Genevieve Morissette,² Rami Ali,² Marc Dorais,³ Philippe Juvet,² Ana Palijan,¹ Veronique Phan,² Michael Pizzi,¹ Michael Zappitelli.¹ ¹McGill U, Montreal; ²U de Montreal, Montreal; ³StatScience, NDIP, Canada.

Background: Acute kidney injury (AKI) is common in the pediatric intensive care unit (PICU). The late illness burden of child AKI is unknown. We will evaluate if AKI in the PICU is associated with increased mortality and health care service use 5 years after discharge.

Methods: Retrospective cohort study of children admitted to two Montreal, Canada PICUs, 2003-2005 (N=2500). Exclusions: no health number, deceased in PICU. Clinical chart data was merged with provincial administrative health data. AKI (main exposure): by Kidney Disease Improving Global Outcomes serum creatinine (Scr) definition (if no PICU-Scr drawn, non-AKI was assumed). 5-year outcomes: all-cause mortality; healthcare utilization (HCU), defined as the number of hospitalizations, emergency room (ER) and physician visits per 100 person years. AKI-outcome relation was evaluated with multivariate logistic (mortality) and linear regression (HCU), adjusting for gender, age, cardiac surgery, PRISM (mortality) score, vasopressors and infection.

Results: Of 2407 children (mean±SD age=6.0±5.7yrs; PRISM = 8.2±5.9); 56% male; 448 (18.6%) developed AKI. AKI (yes/no) was associated with mortality in univariate ($p < 0.05$) but not multivariate analysis. Stage 2 AKI or worse was associated with 5-year mortality (adjusted[adj]OR=1.9, 95% CI= 1.1-3.2). AKI (yes/no) was associated with increased 5-year hospitalizations (adj $p < 0.05$) and physician visits (adj $p < 0.001$), but not ER visits (adj $p = 0.8$). There was a graded increase in 5-year HCU with higher AKI severity.

Figure 1: Association of increasing AKI severity with number of hospitalizations, ER visits and physician visits in the long-term. Box plots. Middle line = median; Upper and lower edges = 75% and 25%, respectively; Bars = 1.5 x IQR (Interquartile range).

Figure 1A Hospitalizations and ER visits.

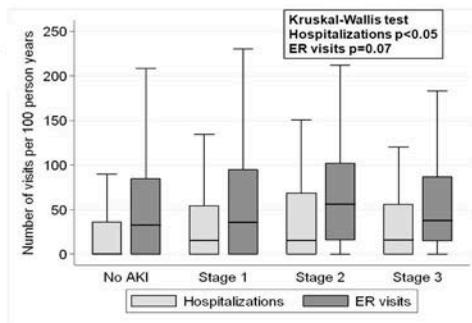
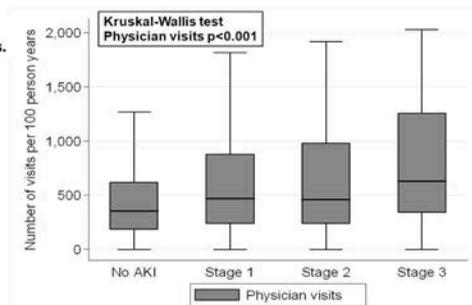


Figure 1B Physician visits.



Conclusions: PICU-AKI is associated with long-term increased mortality risk and HCU. Research should evaluate cost-effective interventions to improve child AKI treatment and evaluate effects on late outcomes.

Funding: Government Support - Non-U.S.

FR-PO479

Acute Kidney Injury: A 12 Month Follow, the Incidence and Mortality Hsu pheon Chong, Paul R. Cannon, Caroline J. Whyte, Kottarathil Abraham Abraham. *Nephrology, Aintree Univ Hospital, United Kingdom.*

Background: Acute Kidney Injury (AKI) affects nearly 1 in 5 hospital admission. It carries a poor prognosis with mortality ranging from 10-80% dependent on the population studied. Aintree University Hospital caters to about a population of 506,000 in North Liverpool. An observational study was carried out in this catchment area to ascertain the incidence of AKI, the length of stay and its effect on 12 months mortality.

Methods: Patients who were admitted between the time periods of August 2012 until January 2013 were included in this study. Liaising with the biochemistry department, all patients who had a rise in their creatinine based on the Acute Kidney Injury Network Criteria received an e-alert sign on the computer system. Clinical outcomes were obtained from each patient record.

Results: There were a total of 36,957 patients admitted during that 6 month time period of which a total of 358 cases of AKI were identified. There was total of 183 male patients and 171 female patients. Four of the male patients had a further AKI alert during the same hospital admission. The mean age was 72.18 years. Pre-renal causes were identified as the main contributors to the cases. Majority of the AKI alerts were Stage 1 AKI which was 70%, Stage 2 AKI was 25% and Stage 3 AKI was 5 % of the total cases. The data also revealed that the average length of stay (ALOS) did not differ in each of the stage. A patient ALOS for Stage 1 AKI 23.3 days, Stage 2 AKI 24 days and Stage 1 AKI 21 days. Of the total number of cases of patients with AKI, 50.6% (179/354) of the patients had died within the 12 months period. Looking into the mortality rate of each individual stages of AKI; the mortality rate at 12 months for Stage 1 AKI is 46.5%. For Stage 2 AKI, 62.7% and for Stage 3 AKI, 47.6%.

Conclusions: From the data collected, it shows that the degree of AKI does not affect the length of stay of patients. Despite the different stages of AKI indicating the severity of the injury, mortality rate for Stage 1 and Stage 3 did not differ. This indicates that AKI carries a high mortality rate regardless of the severity of the injury. Early recognition leads to early intervention in the prevention of AKI.

FR-PO480

Acute Kidney Injury: Adding Informatics to Injury – (Electronic Injury Alerts) Conor Patrick Moran,¹ Ying C. Kuan,¹ Patrick Lm Lynch,² Francis Mccarroll.¹ ¹Dept of Nephrology, Altnagelvin Hospital, Londonderry, United Kingdom; ²Dept of Clinical Chemistry, Altnagelvin Hospital, Londonderry, United Kingdom.

Background: Acute Kidney Injury, (AKI), is common with a variably reported mortality, (15-60%). UK national audit reported that up to 30% of cases were avoidable and that as much as 43-61% of post-admission AKI experienced an unacceptable delay in recognition of insult. There has been a paucity of work with regards to AKI recognition and prevention. National guidelines have recommended the use of electronic alerts (e-alerts) for AKI detection.

Methods: We introduced AKI e-alerts with accompanying electronic guidance in late October 2014 and prospectively collected data on the patients identified with severe AKI. Data collection was carried out for 3 months, (n=110). The demographics of this cohort were compared with a historical cohort of severe AKI (n=89).

Results: Mean age, (72 years vs. 73 years), gender distribution, (M:F: 46% / 54% vs. 47% / 53%), and median time to death, (10 days vs. 9 days), were comparable. Thirty day mortality was similar with regards to hospital acquired AKI, (27.3 % vs. 26.1%). 30 day mortality was significantly lower for community-acquired AKI: (10.7%). Mean and median age was demonstrated to be higher in the group of patient who died, (Mean: 80.1 years vs. 75.7 years), (Median: 82 years vs. 82 years) – negative skew due to outliers.

Conclusions: Although our initial data suggests an electronic AKI alert has no discernable effect on 30 day mortality rate and time to death. We feel that e-alerts with the addition of further Quality Improvement work will eventually result in a steady reduction in AKI mortality.

FR-PO481

Tenofovir Nephrotoxicity Is an Important Cause of Acute Kidney Injury in HIV Infected Inpatients Teg Marcos Veiga, Adriana Belo Prazeres, Daiane Silva, Gisele Vajgel Fernandes, Geraldo Jose de Amorim, Luis H.B.C. Sette, Lucila Maria Valente. *Nephrology, Univ Federal de Pernambuco, Recife, Pernambuco, Brazil.*

Background: Tenofovir disoproxil fumarate (TFD) is widely prescribed as a first choice therapy for HIV infection, because of its convenient dosing schedule, efficacy and relatively low side effects. However, renal toxicity may lead to acute kidney injury (AKI), chronic kidney disease (CKD), and proximal tubular injury. Here we describe clinical characteristics and outcomes of AKI associated to TDF.

Methods: In a retrospective cohort (between Mar/2011 to Feb/2015), we have described data of HIV-infected inpatients, in a single center infectious disease ward, referred to the Nephrology group due to AKI. AKI was defined according to AKIN criteria.

Results: During the study period, 72 patients were evaluated; the baseline characteristics are showed in table1. Nephrotoxic AKI was present in 36 cases, of which 19 cases (52%) were associated with TFD and the drug was withdrawn in all cases. Seven patients had TFD nephrotoxicity without other associated factors and only three patients achieved renal function recovery, but no one needed dialysis or died during follow up.

Parameters	N=19
Age	41.3 ± 11.3
Male	11 (58%)
Charlson Comorbidity Index	8
SCr baseline (mg/dL)	0.89
SCr at referral (mg/dL)	3.35
AKIN	
1	4 (21.0%)
2	3 (15.8%)
3	11 (58%)
Use of other nephrotoxic drug	6 (31.6%)
UCI admission	5 (26.3%)
Follow up (days)	19.3
Hemodialysis	7 (36.8%)
Renal function recovery*	8 (42%)
Mortality	4 (21.0%)
Hemorrhagic shock	1 (25.0%)
Sepsis	3 (75.0%)

* Defined as recovery to baseline SCr ± 25%

Conclusions: AKI associated to TFD nephrotoxicity was very prevalent in the HIV infected inpatients and showed high morbidity, including almost a third of patients requiring dialysis and more than a half not recovering renal function after withdrawing the drug.

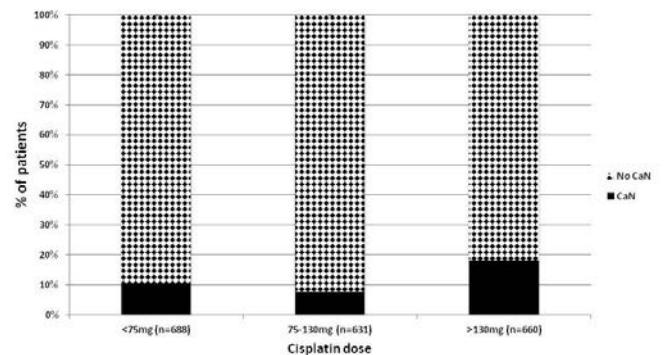
FR-PO482

Cisplatin-Associated Nephrotoxicity: Not as Frequent as Previously Reported Shveta S. Motwani, Sushrut S. Waikar, Benjamin D. Humphreys, Gary C. Curhan. *Nephrology, Brigham and Women's Hospital, Boston, MA.*

Background: Cisplatin-associated nephrotoxicity (CaN) is a frequent problem amongst patients with various cancers. Most older studies have reported 25-30% of patients who receive cisplatin experience acute kidney injury. However, these data have not been re-evaluated systematically recently despite rapid advances in oncologic care. Therefore, we examined the proportion of patients who develop acute kidney injury after exposure to the first cycle of cisplatin in a large patient database. We also examined the frequency of kidney injury stratified by sex and cisplatin dose regardless of cancer type.

Methods: We collected data on patients ≥ 18 years of age who had received cisplatin as a primary, secondary or adjuvant or neo-adjuvant therapy at a tertiary-care medical center (Massachusetts General Hospital) between 2006 and 2014. Detailed data regarding cisplatin dose, demographic characteristics, concurrent medical history and laboratory data including serum creatinine (Cr) and electrolytes were collected. CaN was defined as an elevation of Cr by ≥ 0.3 mg/dl during a 14 day period after administration of cisplatin (peak Cr) compared with baseline (bl Cr). Patients with bl Cr of >1.5 were excluded.

Results: Of the 1979 patients in our study, 55% were male with a mean ± SD of age of 61.6 ± 12.8. A bl Cr was 0.9 ± 0.2. 241 of 1979 (12.2%) patients developed CaN. However, it ranged from 7.8% in the medium dose group (cisplatin dose 75-130 mg) to 18.2% in the high dose group (>130mg) without a clear dose response relation.



In addition, a significantly lower frequency of CaN was noted amongst females compared with males (9.3% vs 14.5%, p<0.001).

Conclusions: Cisplatin-associated nephrotoxicity occurs less frequently than previously reported. This may reflect changes in preventive care such as more aggressive hydration with electrolyte-rich solutions.

Funding: Other NIH Support - T32 training grant

FR-PO483

Characteristics of 681 Patients with Atypical Hemolytic Uremic Syndrome in the Global aHUS Registry Christoph Licht,¹ Gianluigi Ardissino,² Gema Ariceta,³ David J. Cohen,⁴ Christoph Gasteiger,⁵ Larry A. Greenbaum,⁶ Sally A. Johnson,⁷ Masayo Ogawa,⁸ Varant Kupelian,⁸ Franz S. Schaefer,⁹ Johan Vande Walle,¹⁰ Veronique Fremeaux-bacchi,¹¹ *1The Hospital for Sick Children, ON, Canada; 2Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; 3Hospital Univ Vall d'Hebron, Barcelona, Spain; 4Columbia Univ Medical Center, NY, NY; 5Alexion Pharma International Sarl, Lausanne, Switzerland; 6Emory Univ, Atlanta, GA; 7Great North Children's Hospital, Newcastle, United Kingdom; 8Alexion Pharmaceuticals, Inc., Cheshire, CT; 9Heidelberg Univ Hospital, Heidelberg, Germany; 10Univ Hospital Ghent, Ghent, Belgium; 11Assistance Publique, Paris, France.*

Background: The observational atypical hemolytic uremic syndrome (aHUS) Registry collects patient (pt) information and facilitates availability of follow-up data for eculizumab (ECU).

Methods: Pts with clinical diagnoses of aHUS (irrespective of identified complement abnormality or treatment) are eligible. Demographic, medical/disease history, and treatment outcomes data are collected at enrollment and prospectively.

Results: By January 30, 2015, 681 pts enrolled (Table); 62.7% of adults were women. Thrombosis occurred more frequently in adults than pediatric pts. Nonrenal comorbid conditions occurred in both age groups. ECU was administered to 56.2% (87.7% prior to enrollment).

Conclusions: Registry baseline characteristics show differences between pediatric and adult aHUS pts, notably different frequencies of thrombosis. Ongoing and future analyses will further enhance understanding of aHUS history and progression. Medical writing support - Kristen W. Quinn, PhD, of Peloton Advantage, funded by Alexion

Table. Characteristics of Patients Enrolled in the Global aHUS Registry by January 30, 2015.

Characteristics	<18 Years of Age ^a (n=257)	≥18 Years of Age ^a (n=405)	Total (N=681)
Demographic			
Mean age at enrollment, years (SD)	8.3 (4.9)	40.0 (15.1)	27.7 (19.7)
Female, n (%)	116 (45.1)	254 (62.7)	370 (54.3)
Clinical			
Mean age at diagnosis of aHUS, years (SD)	n=250 4.5 (4.3)	n=381 34.8 (17.8)	n=631 22.8 (20.5)
Mean time from aHUS diagnosis to enrollment, years (SD)	n=250 3.8 (4.0)	n=381 5.2 (7.9)	n=631 4.7 (6.7)
Family history of aHUS, n (%)	42 (16.3)	67 (16.5)	109 (16.0)
Number of TMAs before enrollment, n (%) ^b	n=189	n=299	n=488
0	41 (21.6)	28 (8.7)	67 (13.7)
1	87 (46.0)	167 (55.9)	254 (52.0)
2	18 (9.5)	50 (16.7)	68 (13.9)
≥3	43 (22.8)	56 (18.7)	99 (20.3)
Kidney transplant prior to enrollment, n (%)	27 (10.5)	93 (23.0)	121 (17.8)
Thrombotic events prior to enrollment, n (%)	16 (6.2)	57 (14.1)	73 (10.7)
Comorbid conditions 6 months prior to enrollment, n (%)			
Renal	130 (50.6)	206 (50.9)	336 (49.3)
Gastrointestinal	59 (23.0)	75 (18.5)	134 (19.7)
Cardiovascular	50 (19.5)	81 (20.0)	131 (19.2)
Central nervous system	31 (12.1)	78 (19.3)	109 (16.0)
Pulmonary	22 (8.6)	56 (13.8)	78 (11.5)
Management			
PE/PI			
PE/PI prior to enrollment, n (%)	123 (47.9)	241 (59.5)	366 (53.7)
Duration of PE/PI, months	n=118	n=239	n=359
Mean (SD)	10.5 (23.7)	2.9 (11.9)	5.4 (17.1)
Median (range)	1.0 (0.0-143.1)	0.5 (0.0-125.6)	0.6 (0.0-143.1)
Dialysis			
Dialysis prior to enrollment, n (%)	117 (45.5)	234 (57.9)	353 (51.6)
Duration of dialysis, months	n=110	n=187	n=299
Mean (SD)	16.2 (27.6)	28.7 (48.3)	24.0 (42.1)
Median (range)	1.0 (0.0-133.3)	5.3 (0.0-278.1)	2.6 (0.0-278.1)
ECU			
Ever treated with ECU, n (%)	151 (58.8)	231 (57.0)	383 (56.2)
ECU initiation before enrollment, n (%)	133 (88.1)	203 (87.9)	336 (87.7)
Time from aHUS diagnosis to initiation of ECU, months	n=140	n=219	n=359
Mean (SD)	26.1 (43.6)	39.9 (76.9)	34.5 (66.2)
Median (range)	2.2 (-0.5-203.9)	0.7 (-0.5-235.6)	0.9 (-0.5-235.6)
Time from ECU treatment initiation to enrollment, months	n=124	n=197	n=321
Mean (SD)	14.2 (11.5)	10.9 (11.7)	12.2 (11.7)
Median (range)	12.9 (0.2-50.9)	6.8 (0.0-72.7)	9.1 (0.0-72.7)

Note: Demographic subgroups may not total to N=681 due to missing data.
^aPatients were categorized by age at time of enrollment.
^bThe n and percentage of patients with positive genetic screening tests for each mutation are shown.
^cExcludes the TMA event associated with diagnosis.
^dn patients with eculizumab initiation prior to enrollment.
 aHUS, atypical hemolytic uremic syndrome; CF8, complement factor B; CFH, complement factor H; CFHR, CFH receptor; CFI, complement factor I; DGKE, diacylglycerol kinase ε; ECU, eculizumab; PE/PI, plasma exchange/plasma infusion; SD, standard deviation; THBD, thrombomodulin; TMA, thrombotic microangiopathy.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

FR-PO484

Long-Term Renal Function After Recovery from Dialysis-Requiring Acute Kidney Injury Sokratis Stoumpos, Colin C. Geddes. *Renal and Transplant Unit, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom.*

Background: Current guidelines suggest that people should be monitored for the development of chronic kidney disease (CKD) for at least 2-3 years after acute kidney injury (AKI), even if serum creatinine has returned to baseline. The aim of this study was to determine the long-term renal outcome of patients experiencing AKI secondary to hypoperfusion injury and/or sepsis who recovered to apparently normal renal function.

Methods: We conducted a population-based cohort study of all adult patients in our catchment area (serving a population of approximately 1.5 million), with AKI who required in-hospital dialysis in the nephrology unit, survived for at least 12 months after discharge and had estimated glomerular filtration rates (eGFR) greater than 60mL/min 1 year after the episode of AKI between September 1, 1989, and March 5, 2015. Patients with underlying nephropathy and AKI due to causes other than hypoperfusion injury and/or sepsis were excluded. Follow up was censored to the date of the last serum creatinine recorded.

Results: From the 770 patients identified with dialysis-requiring AKI, 310 patients met the study inclusion criteria. Mean age at time of AKI was 49.0 (SD 16.4) years, 58.7% were male and the median duration of haemodialysis was 6 (IQR 3-11) days. After a median follow-up of 7.3 (IQR 4.6-12.6) years from first dialysis for AKI, eGFR was >60mL/min in 285 (91.9%) patients, 45-59mL/min in 18 (5.8%), 30-44mL/min in 6 (1.9%) and 15-29mL/min in 1 (0.3%) patient. None of the patients developed CKD stage 5 or end stage renal disease. 86 (27.7%) patients died during the duration of follow-up.

Conclusions: The excellent outcome for patients with normal renal function 1 year after an episode of dialysis-requiring AKI suggests that these patients are unlikely to derive benefit from life-long follow up of kidney function after AKI.

FR-PO485

Use of ACEIs and ARBs in Patients with Chronic Kidney Disease and Superimposed Community-Acquired Acute Kidney Injury Patrick Saudan,¹ Cyrielle Alves,² Fabien Stucker,³ Belen Ponte,¹ Pierre-Yves F. Martin,¹ Thomas Perneger,⁴ Sebastian Carballo,² *1Nephrology Unit, Department of Medical Specialties, Geneva Univ Hospitals, Geneva, Switzerland; 2Dept of General Internal Medicine, Geneva Univ Hospitals, Geneva, Switzerland; 3Nephrology Unit, Hôpital de la Providence, Neuchâtel, Switzerland; 4Clinical Epidemiology Unit, Geneva Univ Hospitals, Geneva, Switzerland.*

Background: Due to their long-term nephroprotective effect, ARBs and ACEIs are often used in patients with CKD despite their association with an increased risk of superimposed AKI. We aimed to better define its occurrence in relation to their use.

Methods: We undertook a prospective observational study within the Emergency Department, screening for any patient > 16 years admitted with an eGFR < 60 ml/min. Patients with CKD (previously known for an eGFR < 60 ml/min) were included and superimposed AKI was defined as a decline in eGFR compared to previous values according to KDIGO AKI criteria.

Results: From May 1st up to June 21st 2013, there were 8464 admissions of whom 361 (4%) had a eGFR < 60 ml/min and were known to have CKD. Use of ACEIs, ARBs, diuretics, NSAIDs was respectively found in 19, 23, 37 and 4 % of patients. AKI was superimposed in 102 (28%) CKD patients. Etiology was prerenal (73%), renal (17%) and postrenal (9%). Stage I/II/III AKI were 87, 5 and 8% respectively. One year survival rates were 81 and 78 % (p=0.62) in patients with stable CKD and those with superimposed community-acquired AKI. Multiple logistic analysis showed that its occurrence was associated with male gender (OR 2.03; 95%CI:1.23-3.35, p=0.005), diuretic use (OR 1.61; 95%CI:1-2.60, p=0.05) and ARBs use (OR 1.61; 95%CI:1-2.60, p=0.05). ACEIs use was found to be slightly nephroprotective (OR 0.49; 95%CI:0.25-0.96, p=0.04).

Conclusions: Mild community-acquired superimposed AKI in CKD patients does not seem to increase one year-mortality and is more frequently encountered in male patients and those treated with diuretics and ARBs, but not ACEIs. Although their impact on renal hemodynamics is supposed to be similar, further studies should be implemented in CKD patients to examine whether ARBs are more detrimental than ACEIs in terms of risk of superimposed AKI.

FR-PO486

Renal and Patient Outcomes of Dialysis Dependent Patients with ATN Who Survive Hospitalization Mohammad Alhaji, Rabeeh I. El-refadi, Jerry Yee, Bronwyn Larissa Small, Javier Rodriguez Sanchez, Jian Li, Lenar T. Yessayan. *Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI.*

Background: Acute tubular necrosis (ATN) accounts for the majority cases of acute kidney injury (AKI) in critical care units. The in-hospital mortality rate of dialysis requiring ATN in critically ill patients exceeds 50%. However, renal and patient outcomes among dialysis dependent patients with ATN who survive the hospitalization are lacking.

Objective: To determine 90 day renal recovery and mortality rates, 1 year cardiovascular and hospital readmission rates of patients with ATN discharged on hemodialysis.

Methods: We prospectively enrolled 38 Medicare beneficiaries who developed hemodialysis-dependent ATN and survived to discharge at a single center from January 1, 2013 to June 30, 2014. The ATN was identified by urine microscopy and clinical judgment. ATN causes, patients' comorbid conditions, potential contributors to ATN and indications for RRT were recorded. Cumulative hazard estimates of events and survival curves were generated using the Kaplan-Meier method.

Results: Twenty six patients (38%) had CKD, 18 had diabetes (47%), 29 had hypertension (76%), 10 had history of liver disease (26%). The 90 day renal recovery and mortality rates were 42% and 11% respectively. Of those who recovered kidney function, Only 1 patient recovered kidney function beyond 60 days. The 1 year cardiovascular event rates and readmission rates were 22% and 62% respectively.

Conclusions: Patient with dialysis dependent ATN following a hospitalization are unlikely to get off dialysis support beyond 60 days after discharge. In the first year post discharge, they experience a significant number of cardiovascular events and hospital readmissions. Identifying modifiable risk factors for readmission in this cohort may reduce health care costs.

FR-PO487

Long-Term Follow-Up of Children with STEC-HUS Caused by *E. coli* O104:H4 (German HUS Outbreak 2011): A GPN Registry
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Background: In 2011 *E. coli* O104:H4 caused the largest outbreak of HUS in adults and children. A total of 90 children were affected, of whom 64 (71%) required dialysis for a median of 11 days.

Methods: Currently follow-up data are available from 60 of 90 children (67%, 31 girls) from 11 pediatric centers in Germany. Median follow-up is 2.7 (range 1.2-3.6) years, median current age of patients is 14.7 (3.4-18.7) years.

Results: Median current serum-creatinine is 0.7 (0.3-8.9) mg/dl. In two patients (2.2%) with CKD stage 3 and 4 at discharge GFR improved and they are now in CKD Stage 2. One patient remained dialysis dependent initially and one reached ESRD after 3.5 years; both underwent successful living-related kidney transplantation. All these 4 patients were treated with eculizumab in the initial phase of STEC-HUS including 2 who also received plasmapheresis. Proteinuria is currently present in 17 (19%) patients and 9 (10%) require treatment for hypertension. Three patients have neurologic symptoms (headache, performance deficit, spastic movement disorder) and 3 patients have EEG abnormalities without symptoms.

Conclusions: Long-term follow-up is important after O104:H4 associated STEC-HUS. CKD stage 3-5 at discharge is a risk factor for ESRD, however some children show a significant improvement over time. Patients with proteinuria and hypertension need long-term follow-up. Follow-up studies after STEC HUS should include neurological investigations.

FR-PO488

SOFA Scores as Predictors of Mortality and Dialysis Dependency in Acute Kidney Injury
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Background: The Sequential Organ Failure Assessment (SOFA) score measures the severity of organ failure, and baseline SOFA scores have been used to predict mortality in patients with Acute Kidney Injury (AKI). We evaluated whether SOFA scores, either upon initiation of dialysis or clinically updated, predict mortality and dialysis dependency following AKI.

Methods: Data from patients enrolled in the Acute Renal Failure Trial Network (ATN) study, a randomized multicenter trial of the intensity of renal support in AKI, were used in Cox proportional hazards regression and multinomial logistic models to assess the degree to which SOFA scores predict mortality and dialysis dependency.

Endpoint	Odds Ratio(95% Confidence Interval)		
	Day 28	Day 60	1-year
Death	1.23(1.18-1.28)	1.20(1.15-1.24)	1.17(1.13-1.21)
Dialysis Dependency	0.92(0.89-0.96)	0.91(0.87-0.96)	0.87(0.79-0.95)

Results: SOFA scores were associated with increased mortality risk following AKI among the 1,124 ATN participants, but the concordance statistic was low, at 0.651 (standard error [se]=0.014). When time-dependent analyses were used to take advantage of prospectively updated SOFA scores, the concordance statistic increased to 0.753 (se=0.013). In analyses that examined mortality and dialysis dependency as competing outcomes at three fixed time points, increased SOFA scores were associated with higher mortality risk, and lower risk of dialysis dependency.

Conclusions: Similar to the general ICU population, updated SOFA scores better prognosticate the risk of death in patients with AKI. Higher SOFA scores are associated with increased mortality risk, but decreased dialysis dependency risk, when the two outcomes are evaluated as competing risks. Future studies should focus on prognostic tools that simultaneously prognosticate survival and need for dialysis in AKI patients.

Funding: Private Foundation Support

FR-PO489

Risk Factors of Acute Kidney Injury and In-Hospital Mortality in Adult Patients Receiving Extracorporeal Membrane Oxygenation (ECMO)
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Background: Although acute kidney injury (AKI) is the most frequent complication in patients receiving extracorporeal membrane oxygenation (ECMO), little has been studied about the risk factors of AKI and in-hospital mortality. Thus we performed the study to identify factors associated with AKI and in-hospital mortality.

Methods: We analyzed 322 adult patients receiving ECMO from January 2005 to November 2014 in two tertiary care hospitals. AKI and its stages were defined by Kidney Disease Improving Global Outcomes classifications. Variables within 24 h before ECMO initiation were collected and analyzed for the association with AKI and in-hospital mortality.

Results: Stage 3 AKI was associated with in-hospital mortality with HR (95% CI) of 2.690 (1.410-5.132), compared to no AKI (p=0.003). Simplified acute physiology score 2 was also significantly associated with in-hospital mortality with HR (95% CI) of 1.022 (1.004-1.040) with every 1 score increase (p=0.014). Initial pump speed of ECMO was significantly related to in-hospital mortality with HR (95% CI) of 1.397 (1.024-1.904) with every 1000 rpm increase (p=0.035). The pump speed was also significantly associated with total AKI (p=0.035) and stage 3 AKI (p=0.044) with ORs (95% CI) of 2.219 (1.059-44.652) and 1.676 (1.015-2.770), respectively. We also found that red cell distribution width (RDW), serum level of total bilirubin, and the duration of ECMO were significantly related to AKI and/or stage 3 AKI.

Conclusions: Initial pump speed was significant risk factor of in-hospital mortality and AKI in patients receiving ECMO. RDW, serum level of total bilirubin and the duration of ECMO were risk factors of AKI.

FR-PO490

Comparison of Clinical Characteristics of Patients with Acute Kidney Injury After Intravenous versus Inhaled Colistin Therapy
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Background: The aim of this study is to investigate the incidence and clinical characteristics of intravenous or inhaled colistin associated acute kidney injury (AKI) using the RIFLE criteria.

Methods: From 2010 to 2014, 160 patients were treated with intravenous or inhaled colistin. Of these, we included 139 patients who received colistin for >72 h, and compared the incidence and clinical characteristics of patients in the intravenous (n=120) and inhaled (n=19) groups.

Results: The patients included 116 men and 23 women, with a mean age of 68 years (range, 20-91). Patients were infected with either *A. baumannii* (54%) or *P. aeruginosa* 46 (%), and pneumonia (91%) was the most common type of infection. The mortality rate was 43.9%, and AKI occurred in 83 (60%) patients. At the end of therapy, bacteriologic cure rate was 64%. There were no differences in the clinical characteristics between the intravenous and inhaled groups except for age. In comparison with patients in the intravenous group, the patients in the inhaled group were older (74 ± 8 vs 67 ± 14 years, p=0.03). The incidence of AKI was not different between the two groups (62% vs 47%, p=NS), and there was no difference in the severity of AKI according to the RIFLE criteria. Of the 83 patients with AKI, 8 and 1 patients underwent renal replacement therapy.

Conclusions: In our study, the incidence of AKI in patients undergoing colistin therapy was 60%, and there was no difference in safety between the intravenous and inhaled colistin groups. Therefore, it is also important to monitor renal function during colistin therapy regardless of the route of administration.

FR-PO491

Acute Kidney Injury following Coronary Angiography
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Background: Acute kidney injury (AKI) is a known complication of coronary angiography (CA). The aim was to study the incidence, risk factors and outcome of AKI following CA in a whole nation.

Methods: This was a retrospective analysis of data from all CA in Iceland during a 9 year period. AKI was diagnosed according to the creatinine based KDIGO criteria and survival status for all patients was verified at Statistics Iceland. The epidemiology and clinical outcomes were compared between three 3-year periods using Chi-squared and Kaplan Meier method, and multivariate logistic regression was performed to find predictors of AKI.

Results: From Jan 1st 2005 to Dec 31st 2013 10713 patients underwent 13890 CA of whom 40% entailed an intervention. Median (range) age was 65 (19-96) years and 70.7% were men. AKI was diagnosed in 214 patients (1.5%); 168 (1.2%), 27(0.2%) and 19 (0.1%) of stage 1, 2 and 3, respectively. There was a trend towards a decreasing incidence of AKI: 1.8% in the first 3 year period, 1.3% in the second and 1.4% in the last (p=0.05). AKI was more common in the intervention group, 2.2% vs. 1.1% (p<0.0001). Patients with AKI were older, had more often prior history of AKI, more co-morbid diseases and lower baseline eGFR compared to non-AKI patients. In multivariate analyses age over 70 years (OR=1.01, 95% CI= 1.007-1.016), angiography with intervention (OR=1.01, 95% CI=1.008-1.016) COPD (OR=1.01, 95% CI =1.003-1.025), liver disease (OR=1.03, 95% CI=1.014-1.058) baseline eGFR<60 (OR=1.03 95% CI 1.027-1.039) and a prior history of AKI (OR=1.07, 95% CI= 1.051-1.080) were independent predictors of AKI after CA. One year survival of AKI patients did not differ between time periods: 67.0%, 63.1% and 69.0% in the first, second and third, respectively, p=0.3).

Conclusions: There is a trend towards a decrease in AKI incidence following CA in recent years. Aged patients with multiple co-morbidities and prior history of AKI need special attention in connection with this procedure.

Funding: Private Foundation Support

FR-PO492

Acute Kidney Injury in the First Hundred Days After Hematopoietic Stem Cell Transplantation: Experience with 222 Transplanted Patients in a Single Center Miguel A. Solis, Sandra Tejedor, Isidro Torregrosa, Carmen Ramos, Isabel Juan, Patricia Tomas, Patricia Zambrano Esteves, Juan José Guzmán Herrera, María Jesús Puchades, Alfonso M. Carrasco. *Nephrology, Univ Clinic Hospital, Valencia, Spain.*

Background: Hematopoietic stem cell transplantation recipients are at an increased risk of Acute Kidney Injury (AKI) or Chronic Kidney Disease (CKD). An earlier diagnosis could dramatically improve the patients' prognosis. **Objective.** To analyze the incidence of AKI in the first 100 days of Hematopoietic stem cell transplantation recipients and the relationship with mortality.

Methods: We carried out a retrospective study including 222 adult patients who underwent Hematopoietic stem cell transplantation between 2006 and 2010 at our institution. AKI was defined using the RIFLE criteria in the first 100 days after transplantation.

Results: 222 patients were included in the study, 137 males and 85 females. Median follow-up was 30 months, range 1-60 months. In the first 100 days after transplantation AKI developed in 78 patients according to the RIFLE criteria (35.1%). A total of 85 patients died during follow-up vs 47 who had developed AKI (38.2% versus 61%, p<0.05). Detailed patients' characteristics are summarized in table 1.

Sex	Male: 137. Female: 85
Median Age, years.	48.9,SD 13.43.
Type of transplantation.	Autologus: 117 (52.7%) Allogeneic: 105 (47.3%) ablativ: 57 (25.7%) non ablativ (miniAlo): 48 (21.6%)
Previous transplantation.	37(16.7%)
Follow-up, months.	30, range 1 to 60.
AKI. RIFLE criteria. 78 (35.1%)	R 36 (16.2%) I 30 (13.5%) F 9 (4.1%)
AKI in Type of Transplantation.	Autologus: 11.1% Allogeneic: 59.6% miniAlo: 66.7%
Overall Mortality	85 (38.2%)
Mortality in AKI.	47 (61%)

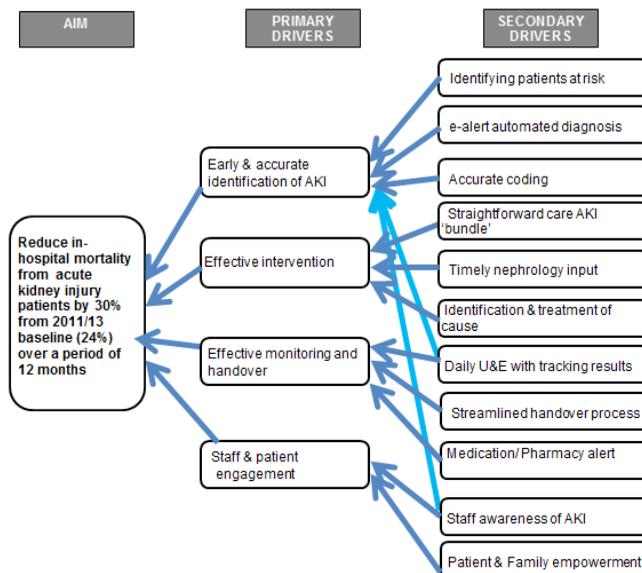
Conclusions: AKI incidence in hematopoietic stem cell transplantation recipients is very high. There is a statistically significant relationship between AKI and death in these patients. Earlier AKI identification could prevent kidney damage progression and improve patient outcome over time.

FR-PO493

STOP-Acute Kidney Injury (AKI): A Streamline Approach to the Management AKI Leads to Reduction of Mortality Rates Hsu pheen Chong, Thangavelu Chandrasekar. *Nephrology, Aintree Univ Hospital, United Kingdom.*

Background: Acute Kidney Injury (AKI) has a mortality rate of 30%, greater than common conditions such as myocardial infarction (8%) and stroke (9%). It is estimated that 15% of all inpatients at University Hospital Aintree (UHA), Liverpool, UK, suffer an AKI making it a condition of considerable importance in everyday practice. Through clinical audit, it was found that mortality rate of AKI in UHA was 33% on wards other than renal ward (9%).

Methods: To reduce AKI mortality by 30% and length of stay by 20% over a 12 month period from Oct 2013 using standardised, evidence based approach. Using plan, do, study act (PDSA) methodology, we developed and tested an automated e-alert diagnostics system, an AKI treatment bundle and a patient information leaflet. The STOP-AKI project was launched. Our Primary drivers were early and accurate identification of AKI, effective intervention and monitoring, staff and patient engagement. Initially, trialled at ward level, the project was scaled up to admission areas (Accident and Emergency Department and the Medical Assessment Unit) becoming part of routine management for all admitted patients.



Results: Fall in mortality rates from a baseline of 24% to 18.5 %, representing an overall reduction in mortality of 23%. Length of stay fell by 11% equating in a 2.0 day reduction in length of stay.

Conclusions: The STOP-AKI project led to the development of an AKI bundle in Oct 2013. This has achieved not only a significant reduction in patient mortality and length of stay but in addition a more structured and stream lined way of approaching the patients with AKI in our hospital. With the bundle being rolled out to primary care and the rest of our inpatient wards, we anticipate a further reduction in mortality.

FR-PO494

Race and Risk of Acute Kidney Injury (AKI) in VA Patients Michael Heung,¹ Diane Steffick,¹ Deidra C. Crews,² Neil R. Powe,³ Sharon Saydah,⁴ Meda E. Pavkov,⁴ Kara Zivin,^{1,5} Rajiv Saran.¹ ¹Univ of Michigan; ²Johns Hopkins Univ; ³Univ of California San Francisco; ⁴Centers for Disease Control and Prevention; ⁵VA Ann Arbor Health System.

Background: African Americans (AA) are at increased risk for AKI compared to Caucasians (C); potential explanations include differences in risk factors, genetic susceptibility and socioeconomic factors. We explored the influence of race on AKI risk in the Veterans Administration (VA), an integrated healthcare system.

Methods: Retrospective cohort analysis of all hospitalizations for VA patients with known AA or C race in 2011. AKI was defined by KDIGO criteria (≥ 0.3 mg/dL increase in serum creatinine from pre-admission baseline). Modified Poisson regression models estimated the effect of AA race on risk of AKI, adjusting for age, sex, baseline eGFR, comorbidities (DM, HTN, coronary heart disease,CHD; CHF), geographic region and severity of illness during hospitalization. Additional models including albuminuria were run for those with available data.

Results: We identified 180,429 VA hospitalizations. Compared to C, AA had higher prevalence of DM (43.1% v. 41.1%, P<.001), lower prevalence of CHD (45.7% v. 58.8%, p<.001), lower Charlson comorbidity scores (1.4 v. 1.6, p<.001) and higher baseline eGFR (89.2 v. 81.7, p<.001). AKI occurred in 19.5% of admissions (35,134) involving 23.2% of AA and 18.5% of C. In adjusted models, AA race remained an independent risk factor for AKI (RR 1.26, 95% CI 1.24-1.28). In the subgroup with albuminuria data (40,668), the risk was slightly attenuated (RR 1.20, 95% CI 1.16-1.24). A similar increased risk of hospital-acquired AKI in AA compared to C (RR 1.19, 95% CI 1.15-1.23) was found.

Conclusions: Although AA Veterans had higher baseline eGFR and lower comorbidity scores compared to C, AA had an increased risk of developing AKI, even after accounting for differences in risk factors & geographic region. This increased risk for AKI in AA persisted when examining AKI that developed during hospitalization. Given that VA patients have similar healthcare access and benefits, our results suggest that the increased AKI risk seen in AA is unlikely to be fully accounted for by disparities in access to care.

Funding: Other NIH Support - Centers for Disease Control and Prevention, Veterans Administration Support

FR-PO495

Mortality Risk Factors in Mexican Patients with Acute Kidney Injury Luis Alberto Evangelista-Carrillo,¹ Enrique Rojas-Campos,² Salvador Mendoza Cabrera,¹ Benjamin Gomez-Navarro.¹ ¹Nefrologia y Trasplantes, IMSS, Guadalajara, Jalisco, Mexico; ²Unidad Médica de Investigación en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico.

Background: Acute Kidney injury (AKI) data in Latin American is scarce. **Methods:** Aim: To determine patient survival, mortality risk factors and treatment in AKI patients from a tertiary hospital. **Methods:** Prospective cohort Dic 2010-2012 of 275 patients with AKI whom need Nephrology consultation. Recollected data at admission,

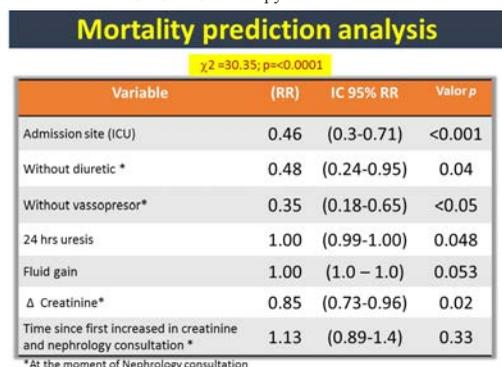
Nephrologists consultation and 30 days follow up included demographics and biochemical variables, time between AKI onset and Nephrology consultation, fluid balance, mortality scale, treatment and date of death or patient discharge.

Results: The overall mortality was 49%. Mean age 58 years. The principal diagnosis at admission was coronary syndrome. The AKI at the moment of consultation was 3 in the 64%.

VARIABLE	CONSERVATIVE	HEMODIALYSIS	CRRT
Age (mean)	60.8± 17.7 [‡]	53.1± 19.1	58.3± 16.7
Nephrology consultation (time since first creatinine increase hours)	50.5± 48.9	71.7± 69.8	61.3± 83.5
Mortality (%)	38	52.9	72
24 hrs uresis (L)	2.1±1.4 [‡]	1.2±1.4	1.4±1.2
Fluid gain	3.1±4.4 [‡]	4.5±4.8	6.6±6.2
Base creatinine (mg/dl)	0.96±0.26	1.01±0.35	1.02±0.30
Creatinine at nephrology consultation	2.98±2.04 [‡]	4.97±3.21	2.92±1.72
APACHE II	19±6 [‡]	20±5	24±5

[‡]p<0.05

Difference in characteristics accord therapy.



Mortality predicted analysis.

Conclusions: This is the first report of epidemiology of AKI in Mexico. The conservative treatment is associated with mortality. The consultation with nephrology was late. Use of diuretic, vasopressor and uresis less than 1 liter per day at the nephrology consultation time were associated with mortality.

FR-PO496

Cast Nephropathy versus Acute Tubular Necrosis in Newly Diagnosed Multiple Myeloma: A Comparative Study *Insara Jaffer Sathick,¹ Samih H. Nasr,² Nelson Leung.^{1,3}* ¹Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Div of Anatomic Pathology, Mayo Clinic; ³Div of Hematology, Mayo Clinic, Rochester, MN.

Background: Myeloma cast nephropathy (MCN) and acute tubular necrosis (ATN) are recognized causes of acute kidney injury (AKI) in newly diagnosed multiple myeloma patients. However it is currently not known if there is a difference in outcomes between these two groups. We conducted a retrospective study to compare the clinical characteristics and renal response rates in patients presenting with acute kidney injury at the time of myeloma diagnosis.

Methods: We included all patients with AKI at the time of multiple myeloma diagnosis with biopsy-confirmed diagnosis of MCN or ATN between 1998 and 2013. Patients with chronic kidney disease (estimated GFR by MDRD equation<45ml/min/1.73m2) and relapsed multiple myeloma were excluded. We assessed survival and renal outcomes. Six month landmark survival analysis was done with Kaplan Meier estimates. Renal response was classified according to IKMG consensus criteria.

Results: Out of a total of 51 patients who were included in the study, 42 had MCN and 9 had ATN. Baseline characteristics were not significantly different between the groups except urine albumin percentage of >6% was predictive of ATN.

	MCN (n=42)	ATN (n=9)	p value
Median Age, years	63	64	0.19
Gender, M:F %	60:40	56:44	0.4
eGFR at presentation by MDRDml/min/1.73m2	9.8	11.6	0.3
Serum M spike(g/dl)	0.6	1.4	0.2
Proteinura(g/day)	3.1	2.7	0.2
Urine albumin >6%	37%	77%	0.03
Serum free light chain level(mg/dl)	680	596	0.3
Myeloma ISS stage 3	78%	81%	0.7
Calcium(mg/dl)	9.4	9.8	0.2
Dialysis requirement	51%	33%	0.3
Median duration of dialysis, days	95	21	0.4
Dialysis independence	42%	100%	0.02
Stem cell transplant for myeloma	60%	45%	0.3
Time to Renal Response, months	3.6	1.86	0.04
Time to Myeloma Response, months	7.3	8.4	0.7
Median Survival, months	49.7	57.1	0.4

Conclusions: Our data suggests that AKI due to ATN at the time of myeloma diagnosis is more likely to recover compared to MCN with a faster time to response. However this does not seem to affect overall survival.

FR-PO497

Hospital Manifesting AKI Presents Worst Outcome Than Community Acquired AKI *Xose luis L. Perez-Fernandez,¹ Florentina E. Sileanu,² Joan Sabater Riera,¹ Kathleen D. Liu,³ John A. Kellum.²* ¹Servei de Medicina Intensiva, Hospital Univ de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain; ²Critical Care, Univ Pittsburgh Medical Center, Pittsburgh, PA; ³Nephrology & Critical Care, Univ California San Francisco Parnassus MC, San Francisco, CA.

Background: The objective of this study was to evaluate outcomes in critically ill patients with severe community-acquired AKI (CA-AKI) and hospital-manifesting AKI (HM-AKI). Secondary objectives were to identify characteristics that differ between patients with CA-AKI and HM-AKI to design future preventive strategies.

Methods: Observational retrospective study conducted at two tertiary care hospitals between 2000-2008 (UPMC, Pittsburgh, USA) and 2006-2012 (HUB Barcelona, Spain). Those with CA-AKI met criteria for KDIGO Stage 3 AKI at hospital admission whereas those with HM-AKI did not have AKI at hospital admission. HM-AKI subjects met KDIGO Stage 3 AKI criteria within 24 hours of ICU admission, with at least 72 hours elapsing between hospital admission and ICU admission. The relationship of type of AKI (CA-AKI, HM-AKI) with 90-day survival was analysed using Cox regression models controlling for differences between survivors and non-survivors.

Results: 534 patients met inclusion criteria. 92.5% of these patients required RRT at some point during ICU admission. 189 (35.4%) patients had AKI manifest while in-hospital, and these patients had a significantly higher 90-day mortality compared to 345 (64.6%) patients presenting with CA-AKI (68.3% vs 58.6%; p=0.03). Age, SOFA score, time from hospital admission to ICU, HM-AKI (compared to CA-AKI), and medical (vs surgical) admission, were all associated with lower 90 day survival. In the multivariate analysis, HM-AKI remained an independent risk factor for death compared to CA-AKI (HR 1.5; 95%CI (1.1 - 2)).

Conclusions: AKI manifesting after hospital admission has significantly worse outcomes compared to AKI present at hospital admission even among patients progressing to stage 3 by ICU admission. Future interventions should be directed to prevent AKI in patients admitted to hospital, especially those who present with the risk factors identified in this study.

Funding: Government Support - Non-U.S.

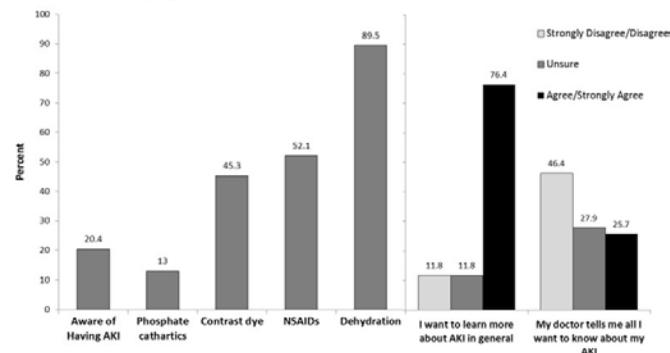
FR-PO498

Assessing Patient Awareness in Moderate to Severe Acute Kidney Injury *Sharidan Parr, Marcus G. Wild, Swee-Ling Levea, Talat Alp Ikizler, Edward D. Siew, Kerri L. Cavanaugh.* *Vanderbilt Center for Kidney Disease, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: We aimed to evaluate awareness and knowledge of kidney disease in patients experiencing moderate to severe AKI, which is important for implementing targeted patient self-care risk-reduction strategies.

Methods: We surveyed 150 hospitalized patients in one academic medical center who experienced KDIGO Stage II or III AKI. We characterized patients' awareness that AKI had occurred, and specific AKI knowledge and perceptions about kidney communication from their health providers. Laboratory data, disease severity, nephrology consultation, and need for dialysis were abstracted from the medical record.

Results: Median participant age was 54 years; 53% were male; 81% were white; 90% had high school education or higher; 30% had health literacy scores ≤ 6 ; baseline serum creatinine (SCr) was 0.9 mg/dL; peak SCr was 2.9 mg/dL; 50% had Stage 2 AKI and 50% had Stage 3 AKI. In total, 80% of patients were unaware that they experienced AKI, including 7 patients requiring dialysis. Predictors of awareness included female gender (71% vs 41%), peak serum creatinine (4.5 vs 2.7), Stage III AKI (82% vs 42%), nephrology consultation (68% vs 31%), dialysis (29% vs 6%), duration of injury (6 vs 3 days), discharge SCr (2.2mg/dL vs 1.5mg/dL), and reporting a discussion of AKI with a provider during the hospitalization (43% vs 21%) (p values <0.05 for all comparisons). We found poor patient recognition of preventable causes of AKI and most patients desired more information [Figure 1].



Conclusions: Most patients with moderate to severe AKI are unaware of their condition, lack understanding of risk factors for future AKI, and desire more information about AKI. Optimizing AKI awareness and understanding to promote patient-centered communication and care will require targeted educational strategies during and after hospitalization.

Funding: NIDDK Support

FR-PO499

Acute Kidney Injury Correlates with Remote Organ Injury and Predicts Outcome in Primary Acute Liver Failure Alexander Lukasz,¹ Michael P. Manns,³ Johannes Hadem,³ Philipp Kumpers.¹ ¹Dept of Nephrology and Rheumatology, Univ Hospital Muenster, Muenster, Germany; ²Dept of Nephrology & Hypertension, Hannover Medical School, Hannover, Germany; ³Dept of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany.

Background: In patients with acute liver failure (ALF) acute kidney injury (AKI) is not well defined. In this study, we examine whether the occurrence of AKI predicts the combined endpoint of death or liver transplantation in a cohort of patients with primary ALF admitted to intensive care unit (ICU).

Methods: 130 patients with primary ALF of different entities (drug-induced, viral, indeterminate or others) were included. Patients without hepatic encephalopathy were excluded. According to the acute Acute Kidney Injury Network (AKIN) definition AKI severity (stage 1, 2 or 3) was classified. The primary outcome studied was event-free 28-day survival (death or transplantation).

Results: 76 patients (58%) had normal renal function, while AKIN I/II and III was present in 15 (12%) and 39 patients (30%) on ICU admission, respectively. Between different ALF entities, AKI prevalence and severity was similar (Chi-Square; $p=0.28$). AKI severity correlated closely with the extent of remote-organ damage as assessed by Simplified Acute Physiology Score (SAPS) III ($r=0.56$, $p=0.0061$) and Sequential Organ Failure Assessment (SOFA) score ($r=0.57$, $p<0.0001$), respectively. Kaplan-Meier analysis demonstrated that 37 of 39 ALF patients with AKIN III reached the composite endpoint of death or transplantation during 28-day follow-up compared to 59 of 76 no-AKI and 10 of 15 AKIN I-II, respectively (Log-rank test: $p<0.0001$). Adjusted Cox's proportional hazards analyses identified AKI on ICU admission as an independent predictor of the composite end point of death or transplantation [HR 3.1 (95% CI 1.9-4.9) for no AKI vs. AKIN III].

Conclusions: Our data indicate that AKI is a frequent complication in primary ALF. AKI correlates with several features of remote-organ damage and independently predicts outcome in this cohort.

FR-PO500

Reduction of Nephrotoxic Medication Associated Acute Kidney Injury: Results from a Three Year Sustained Harm Reduction Program Stuart Goldstein, Eric S. Kirkendall, Theresa A. Mottes, Kendria Nicole Simpson, Stephen E. Muething. *Pediatrics, Cincinnati Children's Hospital, Cincinnati, OH.*

Background: Acute kidney injury (AKI) represents one of the most common comorbidities in hospitalized children. Our previously reported nephrotoxic medication (NTMx) exposure and AKI screening project (Nephrotoxic Injury Negative by Just-in-time Action [NINJA]) showed a 25% NTM-AKI rate and a 42% reduction in AKI days/100 days of NTMx-exposure in Year 1 of the program. This occurred due to rapid recognition of AKI and NTMx-exposure reduction. We now report on the 3-year NINJA results to assess for sustained harm reduction.

Methods: A daily serum creatinine (SCr) was recommended for all children admitted to a non-critical care unit who received >3 NTMx simultaneously or an IV aminoglycoside for >3 days (high NTMx-exposure) to assess for AKI development. We tracked biweekly outcomes from Sep 2011 through Mar 2015: 1) High NTMx-exposures per 1000 pt-days 2) AKI episodes per 1000 pt-days 3) AKI rates per exposure case (%) and 4) AKI days per 100 high NTMx-exposure days (intensity). AKI was defined by KDIGO SCr criteria. We used statistical process control charts to assess for changes from baseline rates.

Results: 1,783 patients accounted for 2,358 separate admissions and 3,243 individual episodes of high NTMx exposure. 170 patients (9.7%) had 2+ exposures. We observed two decreases in NTMx-exposure and AKI rates. Overall, the high-NTMx exposure rate decreased by 38% (11.63 to 7.24 admissions/1000 pt-days), and the AKI rate decreased by 64% (2.96 to 1.06 admissions with AKI/1000 pt-days). The NINJA project saved pts from 633 exposure and 398 AKI episodes (when compared to baseline rates). Medications/medication classes or admitting services for exposed or AKI pts did not differ between the 3 months preceding and following either time point improvement. AKI rates per exposure (23.3% to 15.4%) and AKI intensity (27.7 to 19.1 AKI days/100 exposure days) also decreased in Year 1; both improvements persisted for the entire period.

Conclusions: Implementation of systematic surveillance for NTMx-AKI can lead to sustained reductions in avoidable harm.

Funding: Private Foundation Support

FR-PO501

Early and Late Acute Kidney Injury in Severely Burned Patients Stanislaw Niemczyk,¹ Wojciech Witkowski,² Wojciech Klimm,¹ Agnieszka Surowiecka- Pastewka,² Marek Kawecki,^{3,5} Katarzyna Szamotulska.⁴ ¹Dept of Internal Medicine, Nephrology and Dialysisotherapy, Military Inst of Medicine, Warsaw, Poland; ²Dept of Burns, Plastic and Reconstructive Surgery, Military Inst of Medicine, Warsaw, Poland; ³Dept of Treatment of Burns, Centre for the Treatment of Burns, Siemianowice Slaskie, Poland; ⁴Dept of Epidemiology and Biostatistics, Inst of Mother and Child, Warsaw, Poland; ⁵Dept of Emergency Medicine, Faculty of Health Sciences, Academy of Technology and Humanities, Bielsko-Biala, Poland.

Background: Evaluation of factors influencing early and late acute kidney injury (AKI) in severely burned patients and assessment of the relationship between time of occurrence of AKI and mortality.

Methods: Retrospective analysis of severely burned patients with >30% total body surface area (TBSA), admitted to two centers for the treatment of burns. We selected and analysed 239 severely burned patients. Renal function was evaluated at three points: admission, critical or middle point of hospitalization and the endpoint death or discharge from the center. AKI criteria: decrease in glomerular filtration rate (GFR)>60 ml/min at admission, decrease in GFR>75% compared to baseline, decrease in the daily diuresis<500 ml.

Results: At admission 15.1% of the patients had GFR <60 ml/min. AKI occurred in 38.5%. The occurrence of AKI was associated with: elderly age ($p<0,001$), female gender ($p=0,017$), overweight and obesity ($p=0,055$); extent and depth of burns, respiratory failure, low protein concentration (for all $p<0,001$), low blood pressure ($p=0,014$) and high white blood cells count (WBC) ($p=0,010$). Early AKI was detected in 28%. Mortality was 100% with the initial GFR>60ml/min, 100% with the initial GFR <60 ml/min and early deterioration of renal function, 80% with the initial GFR <60 ml/min and late worsening, and 60% with the initial GFR <60 ml/min and no worsening. Late AKI was observed in 10% of patients and mortality was 79.2%. Mortality in the group with AKI was 88.0% versus 24.5% without AKI.

Conclusions: The frequent occurrence of AKI, especially early, worsens the prognosis for survival. The assessment of renal function should be included in the prognostic scales for burned patients.

FR-PO502

Acute Kidney Injury and Risk of Incident Heart Failure Among U.S. Veterans Nisha Bansal,¹ Michael Edwin Matheny,² Svetlana Eden,² Robert Greevy,² Sharidan Parr,² James Fly,² Khaled Abdel-Kader,² Jonathan Himmelfarb,¹ Ian H. De Boer,¹ Talat Alp Ikizler,² Edward D. Siew.² ¹UW; ²Vanderbilt.

Background: Acute kidney injury (AKI) is common and associated with poor long-term outcomes. Heart failure (HF) is a leading cause of cardiovascular disease among patients with chronic kidney disease (CKD). The relationship between AKI and HF remains unknown and may identify a novel mechanistic link between kidney and cardiovascular disease.

Methods: We studied a national retrospective cohort of 111,488 U.S. Veterans hospitalized between 2003-2012 without history of HF. AKI was defined as a 0.3 mg/dl or 50% increase in serum creatinine using the difference between peak hospitalization and baseline creatinine (as determined by mean outpatient creatinine over previous year) and staged according to Kidney Disease Improving Global Outcomes (KDIGO) criteria using change in serum creatinine. Incident HF was defined as > 1 hospitalization or >2 visits with a diagnosis of HF, as determined from validated ICD9 codes, through 2012. Propensity scores using 37 relevant inpatient and outpatient covariates were generated and patients with and without AKI were matched 1:1. Cox proportional hazards were used to determine the association of AKI with risk of incident HF, adjusting for baseline age, eGFR, coronary heart disease and hypertension. Patients who died or had an outcome after the end of the study were censored.

Results: There were 17,272 matched pairs with and without AKI in the study. Patients with and without AKI during the index hospitalization were well matched with median

age of 66 years and 22% were African-American. Median pre-admission eGFR was 65.6 ml/min/1.73 m², 37% had diabetes and 72% had hypertension prior to admission. Over a median follow-up time of 41 months, 11% of those without AKI vs. 14% in those with AKI had incident HF. AKI was associated with increased risk of incident HF (adjusted HR=1.3 [95% CI: 1.2, 1.4]).

Conclusions: AKI is an independent risk factor for incident HF adding further evidence to the long-term cardiovascular consequences of AKI. Future studies to identify underlying mechanisms, modifiable risk factors, and patients at highest risk for AKI are needed.

FR-PO503

Incidence of Acute Kidney Injury Among Patients with Chronic Kidney Disease: A Single-Center Retrospective Database Analysis Taro Horino,¹ Yutaka Hatakeyama,² Hiromi Kataoka,² Tatsuki Matsumoto,¹ Kazu Hamada-Ode,¹ Yoshiko Shimamura,¹ Koji Ogata,¹ Kosuke Inoue,¹ Yoshinori Taniguchi,¹ Yoshio Terada,¹ Yoshiyasu Okuhara.² ¹Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Japan; ²Center of Medical Information Science, Kochi Medical School, Kochi Univ, Nankoku, Japan.

Background: Acute kidney injury (AKI) is a serious complication among hospitalized individuals and is closely associated with chronic kidney disease (CKD). This study investigated the incidences of AKI in the various CKD stages.

Methods: This retrospective cohort study evaluated 125,059 individuals who visited Kochi Medical School hospital between October 19, 1981 and December 31, 2013. AKI was defined and staged according to the Kidney Disease Improving Global Outcomes criteria, using measured serum creatinine levels.

Results: We analyzed data from 122,653 Japanese patients, including 57,105 (46.6%) men. The incidence of AKI in this cohort was 7.8% (95% confidence interval: 7.7–8.0%). Compared to non-AKI patients, patients with stage 1–2 AKI were more likely to be men. Patients with stage 1–2 AKI were significantly older than non-AKI or stage 3 AKI patients. The incidences of AKI were 6.7%, 5.9%, 10.4%, 18.4%, 30.0%, and 48.8% in individuals with estimated glomerular filtration rates of ≥ 90 , 60–90, 45–60, 30–45, 15–30, and ≤ 15 mL/min/1.73 m², respectively. These incidences of AKI were significantly different, compared to the incidence for the baseline eGFR.

Conclusions: We found that CKD was a risk factor for AKI, and that the incidence of AKI was positively associated with pre-existing reduced kidney function (stage of CKD). We suggest that outpatients should be monitored for AKI, given its unexpected incidence in that population.

FR-PO504

Acute Kidney Injury in Patients without Atherosclerotic Cardiovascular Disease and Long-Term Risk of Myocardial Infarction, Revascularization, and Death Martin Holzmann,¹ Linda C. Ryden,¹ Ulrik Sartipy.¹ ¹Karolinska Inst; ²Karolinska Inst; ³Karolinska Inst.

Background: Acute kidney injury (AKI) is associated with death and cardiovascular disease (CVD). Prior studies on AKI have been conducted in populations with established CVD, or in mixed populations. We sought to investigate the association between AKI and risk of coronary artery disease (CAD), and death in patients with no prior history of any atherosclerotic disease.

Methods: All patients who underwent an isolated surgical aortic valve replacement in Sweden 1999–2011 were eligible. Patients with any history of atherosclerotic disease, i.e. myocardial infarction, angina, prior revascularization (PCI/CABG), ischemic stroke, peripheral vascular disease, and aortic aneurysm were excluded (n=4230). The primary outcome was myocardial infarction, and/or revascularization, and the secondary outcome all-cause mortality. AKI was defined according to AKIN criteria.

Results: We included 4823 patients (44% women), with a mean age of 67 (13) years. 489 (10%), 73 (1.5%), and 32 (0.7%) patients developed AKI stage 1, 2 and 3, respectively. During a mean of 6.4 (SD 3.5) years (31 009 person-years) in total 151 (3.1%) patients had a myocardial infarction/revascularization, and in total 850 (18%) patients died. Number of CVD events were: 130 (3.1%), 16 (3.3%), and 5 (4.8%); and number of deaths: 694 (16%), 122 (25%), and 34 (32%) in AKI stage 0, 1 and 2–3, respectively. There was no significant association between AKI stage 1 or 2–3 and CVD events: crude HR: 1.13 (95% CI 0.68–1.90), and 1.66 (95% CI 0.68–4.09); adjusted HR: 1.11 (95% CI 0.64–1.91), and 1.59 (95% CI 0.58–4.32) compared with no AKI. There was a significant association between AKI stage 1 or AKI stage 2–3 and all-cause mortality: crude HR: 1.81 (95% CI 1.49–2.20), and 2.60 (95% CI 1.84–3.67); adjusted HR: 1.12 (95% CI 0.92–1.37), and 1.86 (95% CI 1.31–2.65) compared with no AKI.

Conclusions: In a cohort of patients without any established atherosclerotic disease we found no association between AKI and subsequent coronary artery disease. However, patient with AKI stage 2–3 had an almost doubled risk of death during follow-up.

FR-PO505

Acute Kidney Injury Increases Medical Costs Even in the Pre-AKI Stage Jeonghwan Lee,¹ Seon Ha Baek,² Shin-Young Ahn,² Ho Jun Chin,² Ki Young Na,² Dong-Wan Chae,² Sejoong Kim.² ¹Internal Medicine, Hallym Univ Hangang Sacred Heart Hospital, Seoul, Republic of Korea; ²Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Gyeonggi-do, Republic of Korea.

Background: Early detection of acute kidney injury (AKI) is important to prevent the progression of AKI and to improve clinical outcomes. However the significance of mild increase in serum creatinine below AKI stage is not well established. In this study, we defined pre-AKI as the 25–50% increase of serum creatinine levels from the baseline levels. We aimed to investigate the influence of AKI stage including pre-AKI on clinical outcomes.

Methods: All clinical and laboratory data were retrieved from electronic medical record database. We enrolled a total of 20819 patients who admitted Seoul National University Bundang Hospital from January 1, 2013 to December 31, 2013. We excluded patients who had not checked serum creatinine levels during admission or who were on dialysis due to end-stage renal disease.

Results: The proportion of patients who had AKI during admission were 21.6% (pre-AKI), 15.8% (AKI stage 1), 5.9% (AKI stage 2), and 3.2% (AKI stage 3). In-hospital mortality increased according to the stage of AKI [log-rank $P < 0.001$; HRs 1.878 (1.189–2.966) AKI stage 1; 6.039 (3.948–9.239) AKI stage 2; 12.064 (7.992–18.210) AKI stage 3]. Patients with pre-AKI showed no differences in mortality compared to patients without AKI [HRs 1.180 (0.708–1.966), $P = 0.527$]. However, patients with pre-AKI were characterized with increased length of stay (no AKI 7.4 ± 9.0 days, pre-AKI 13.0 ± 13.3 days, $P < 0.001$) and increased medical costs (no AKI: 2806 \pm 3286 USD, pre-AKI: 4701 \pm 3476 USD, $P < 0.001$) during admission. Patients with Pre-AKI were more on surgical condition (51.1% vs 34.0%, $P < 0.001$) compared to patients without AKI.

Conclusions: Patients with pre-AKI stage are associated with longer length of hospital stay and increased medical costs during admission. Clinical significance of pre-AKI should be paid attention.

FR-PO506

Impact of Fluid Overload on Acute Kidney Injury Diagnosis and Associated Outcomes in Critically Ill Patients: A Retrospective Cohort Study Luis Ignacio Bonilla,^{1,2} Sara Samoni,² Maria Fernanda Golzarri,¹ Salvador Roberto Lopez,^{2,3} Jordana S. Lemus,⁴ Guillermo Cardenas,⁴ Claudio Ronco.² ¹Internal Medicine, Hospital General Dr. Manuel Gea Gonzalez, Mexico City, Mexico; ²IRRI, International Renal Research Inst Vicenza, Vicenza, Italy; ³Nephrology, National Inst of Cardiology, Mexico City, Mexico; ⁴ICU, Hospital General Dr. Manuel Gea Gonzalez, Mexico City, Mexico.

Background: Fluid overload (FO) changes the volume of distribution of creatinine, which is equivalent to total body water (TBW), this can alter the serum creatinine (sCr) concentrations; higher TBW result in lower sCr leading to underestimation of AKI. Adjustment of sCr is done by applying a formula (Adjusted Cr = $\text{Cr} \times [1 + (\text{cumulative fluid balance} / \text{TBW})]$). We hypothesized that in pts with $>5\%$ of FO the adjustment of sCr for TBW would diagnose more pts with AKI and diagnose AKI earlier than in pts with $<2.5\%$ of FO.

Methods: We made a retrospective analysis of 120 records of pts from 2 centers. We calculated daily fluid balance and divided it by the body weight to obtain a percentage of FO. Pts were divided into 2 groups, A and B, with $<2.5\%$ and $>5\%$ of FO, respectively. Measured daily sCr was corrected using the TBW formula and presence of AKI was evaluated daily according to KDIGO guidelines. We compared the prevalence, day of diagnosis and associated outcomes between the 2 groups.

Results: Mean age in the cohort was 54.4 yrs, 56.3% were male. In group A 24 (34.8%) of pts were diagnosed with AKI before adjustment and 25 (36.2%) after adjustment ($p=0.167$). In group B 21 (48.8%) and 25 (58.1%) were diagnosed with AKI before and after adjustment, respectively ($p=0.023$). Mean detection day of AKI without and with adjustment in group A was 3.22 ± 2.4 and 2.84 ± 2.1 , respectively ($p < 0.001$) and in group B 3.4 ± 2.3 and 3 ± 2.2 ($p > 0.001$). Mortality in group A was 10.14% and in group B 32.56% ($p=0.005$).

Conclusions: Correction of measured sCr for TBW in patients with $>5\%$ of FO is useful to diagnose more patients with AKI. Usage of the formula demonstrated usefulness for early diagnosis in patients with $<2.5\%$ and $>5\%$ of FO and we recommend its application in order to improve AKI prevention and treatment. FO of $>5\%$ is associated with increased mortality and worse outcomes in critically ill pts.

FR-PO507

Placental Growth Factor (PLGF) Is the Novel Predictor of CKD Progression: The Results from NARA-CKD Study Masaru Matsui, Katsuhiko Morimoto, Miho Tagawa, Ken-ichi Samejima, Yasuhiro Akai, Yoshihiko Saito. *First Dept of Internal Medicine, Nara Medical Univ, Kashihara, Japan.*

Background: PIGF plays a critical role in atherogenesis through vascular inflammation. We have already reported an independent association of PIGF with survival and cardiovascular risk in the patients with chronic kidney disease (CKD) in the Novel Assessment of Risk management for Atherosclerotic diseases in CKD (NARA-CKD) study; however, the relations between circulating levels of PIGF and the progression of CKD remains unknown.

Methods: A prospective cohort study of 402 participants undergoing renal biopsy was conducted to elucidate the predictive value of PIGF on renal prognosis in the patients with CKD.

Results: Histologically, elevated PIGF was significantly associated with the severity of tubulointerstitial damage and the intimal thickening of small renal arteries. During a median follow-up of 2.7 years, 82 patients reached primary end-points which were defined as the requirement of renal replacement therapy (38 patients) and the decline of eGFR by more than 25% from baseline (44 patients). Although baseline eGFR was not statistically different among patients in all PIGF quartiles, the rate of eGFR decline in the patients with the highest PIGF quartile was significantly faster than those with other quartiles. After adjustment of known confounding factors, PIGF was significantly associated with the risk of deterioration of renal function with the adjusted hazard ratio of 1.75 [1.38-2.26] for each quartile increment of PIGF. The combined use of eGFR and PIGF significantly improved the predictive accuracy for CKD progression compared with eGFR alone (c statistics from 0.689 to 0.772, $p < 0.001$).

Conclusions: Elevated PIGF is a novel and independent predictor of renal prognosis in the patients with CKD.

FR-PO508

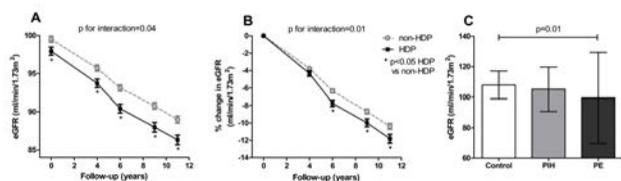
Steeper Decline in Renal Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study Nina Paauw,¹ Anne Marijn van der Graaf,² Rita Bozoglan,² David P. van der Ham,³ Gerjan Navis,² Ron T. Gansevoort,² Henk Groen,⁴ Titia Lely.¹ ¹Obstetrics, UMC Utrecht, Netherlands; ²Nephrology, UMC Groningen, Netherlands; ³Obstetrics, Martini Hospital, Netherlands; ⁴Epidemiology, UMC Groningen, Netherlands.

Background: Hypertensive disorders of pregnancy (HDP) occur in 10% of pregnancies. Population based studies report increased risk for ESRD after HDP. Longitudinal renal function after HDP has not been studied. Our aim was to longitudinally assess renal function and occurrence of CKD in women after HDP compared to controls.

Methods: Data from the PREVEND study, a population based prospective cohort with median follow-up of 11 years, were used to identify women without and with self-reported HDP (non-HDP, n=1805 and HDP, n=977). A case cohort, 10 years post-partum was created by record linkage, with subgroups: normal pregnancy (control, n=202), pregnancy-induced hypertension (PIH, n=56) and preeclampsia (PE, n=29). Renal function and the prevalence of CKD were compared.

Results: eGFR was lower at baseline and during follow-up in HDP vs non-HDP (A). In addition, the decline in eGFR was steeper in HDP vs non-HDP (B). At baseline and during follow-up there was more anti-hypertensive-drug use, including ACEi in the HDP group. 24-h albuminuria at baseline was higher in HDP vs non-HDP and remained steadily higher in HDP during follow-up. A trend towards increased risk of CKD was observed in HDP; HR 1.13 (0.92-1.38). In the case cohort, eGFR was significantly lower (C) and 24-h albuminuria significantly higher ($p=0.03$) in the PE vs controls. 7.8% of the controls, 10.9% of the PIH and 19.2% of the PE group met the criteria for CKD.

Conclusions: We report a lower renal function and a steeper renal function decline over time after HDP. Women with severe hypertensive disorders of pregnancy (PE) have the highest risk for renal function loss.



Funding: Private Foundation Support

FR-PO509

Pregnancy Outcomes in Women with Chronic Kidney Disease in South Australia Shilpa Jesudason,^{1,3} Alyssa Kate Fitzpatrick,⁴ Britt Melinda Catchside,² Wendy Katharine Scheil,² Stephen P. McDonald.^{1,3} ¹Central and Northern Adelaide Renal and Transplantation Services, Adelaide, Australia; ²South Australian Pregnancy Outcomes Unit, Adelaide, Australia; ³School of Medicine, Univ of Adelaide, Adelaide, Australia; ⁴Univ of Oxford, Oxford, United Kingdom.

Background: Chronic kidney disease (CKD) affects an estimated 3% of women in their childbearing years. CKD in pregnancy is associated with adverse maternal and neonatal outcomes. This study represents the first attempt to capture the distribution of CKD among pregnant women in the Australian context.

Methods: Data was obtained from the South Australian Pregnancy Outcomes Unit Supplementary Birth Record for singleton pregnancies from 1990-2012. Women with CKD were identified by renal ICD-9 codes for immunological renal conditions, cystic/genetic renal disease, vesicoureteral reflux, hypertensive CKD, urological conditions, pyelonephritis, and unspecified renal disease. Uncomplicated urinary tract infections were excluded. Data was obtained on maternal demographics, obstetric care and infant outcomes. Chi-squared or Fisher's exact tests were used to examine the crude association between renal disease and adverse outcomes.

Results: 1392 births to women with renal disease codes were identified from 407,580 recorded births. Women with renal disease were significantly more likely to be Aboriginal (5.2% vs 2.6%, $p < 0.001$), to have the lowest socioeconomic status (31.4% vs 26.2%, $p < 0.001$) and to smoke (24.1% vs 18.4%, $p < 0.001$). Higher unadjusted risks of adverse outcomes were noted in the renal group, including gestational hypertension (10.6% vs 5.0%,

$p < 0.001$) and emergency caesarean section (20.0% vs 15.0%, $p < 0.001$). Women with renal disease were more likely to have a preterm birth <34 weeks (6.7% vs 2.1%, $p < 0.001$), or a late preterm birth 34-36 weeks (10.8% vs 4.5%, $p < 0.001$). They were also more likely to be diagnosed with intrauterine growth restriction (11.2% vs 9.5%, $p = 0.03$) and to deliver a low birth weight baby <2500g (13.4% vs 5.5%, $p < 0.001$).

Conclusions: Indigenous Australian women and women with low socioeconomic status are disproportionately burdened by CKD in pregnancy. The data showed increased adverse maternal and neonatal outcomes among women with CKD.

FR-PO510

Identification of Renal Disease in Women with Hypertensive Pregnancies Kate Bramham, Katherine R. Clark, Daniel Stott, Daniela Paraschiv, Nicholas Kametas. Antenatal Hypertension Clinic, King's College Hospital, London, United Kingdom.

Background: Hypertension in pregnancy can be associated with renal injury which may be masked by gestational change. Postpartum assessment is an opportunity to detect persistent renal abnormalities. However previous studies are small and often exclude those with pre-existing hypertension, a risk factor for CKD. Aim: To determine the postpartum prevalence of renal abnormalities in women with chronic hypertension, pregnancy induced hypertension (PIH) or pre-eclampsia (PE) in a previous or current pregnancy.

Methods: Women with singleton pregnancies referred to a hypertension pregnancy clinic (Feb 2011-Nov 2014) attending postpartum review (offered to all) were included. Those with previously diagnosed CKD were excluded. Demographics, 24 hour urine protein, estimated GFR (CKD-EPI) and blood pressure after six weeks postpartum were recorded.

Results: Overall 120 (29.7%) of women were found to have features of renal disease postpartum. Subgroup analysis according to hypertensive groups is shown in Table 1.

	Chronic Hypertensive (N=115)	History of PE/PIH (N=102)	PE/PIH in current pregnancy (N=187)
Body mass index, Kg/m ²	31.7 (7.4)	28.7 (6.9) †	27.2 (5.3) †
Maternal age, years	35.8 (5.1)	34.1 (4.9)	32.3 (5.6) † §
Postnatal visit – weeks from delivery	7.2 (1.7)	7.6 (2.5)	7.2 (1.6)
Systolic blood pressure mmHg	137.4 (14.2)	128.2 (18.0) †	126.7 (14.2) †
Diastolic blood pressure mmHg	87.2 (9.2)	81.1 (11.7) †	80.2 (10.0) †
Normal renal function n (%)	72 (62.6)	131 (70.0)	81 (79.4)
Proteinuria ≥150mg/24h & eGFR <90ml/min n (%)	22 (19.1)	30 (29.4)	11 (5.8)
Proteinuria <150mg/24h & eGFR <90 ml/min n (%)	17 (14.7)	22 (11.7)	9 (8.8)
Proteinuria >150mg/24h & eGFR <90ml/min n (%)	4 (3.5)	4 (4.0)	1 (0.5)

PE:Pre-eclampsia; PIH: Pregnancy induced hypertension † $P < 0.001$ Compared with chronic hypertension. § $P < 0.001$ Compared with history of PE/PIH.

Conclusions: A substantial proportion of women with hypertension in pregnancy have renal abnormalities after six weeks postpartum. Identification of risk factors for progression of CKD in this population through longitudinal studies is needed.

FR-PO511

Changes of Markers of Prothrombotic State in Membranous Nephropathy Complicated with Type 2 Diabetes Yuanmeng Jin. Nephrology, Ruijin Hospital, Shanghai Jiao Tong Univ School of Medicine, Shanghai, China.

Background: Membranous nephropathy (MN) complicated with type 2 diabetes showed high incidence of thrombosis, which was related to abnormality of prothrombotic state. This investigation was designed to explore changes of prothrombotic state and mechanism of thrombosis in MN complicated with type 2 diabetes.

Methods: We enrolled total 30 patients with nephrotic syndrome (NS), 12 patients were pure MN, 6 patients were diabetic kidney disease (DKD), 12 patients were MN complicated with type 2 diabetes (MN+DM). All patients were diagnosed by renal biopsy. 14 healthy people were enrolled for normal control. The markers for prothrombotic state, including endothelial function (vWF, AngiotensinII), coagulation function (Protein C, Protein S, Antithrombin III, Thromboelastogram index), fibrinolytic function (Fibrinogen, Fibrinogen degradation product, D-D dimer) were tested.

Results: Compared to CKD group, vWF levels in MN and DKD group were higher, but was significantly higher in MN+DM group. Protein C and thromboelastogram index in MN+DM group were higher than control, which were not significantly changed in MN and DKD group. Fibrinogen levels in both MN+DM and MN group were higher than others, and D-D dimer levels were especially higher in MN+DM group, even compared to MN group. There were no changes of other marks in four groups.

Conclusions: Under NS state, MN+DM patients existed more serious prothrombotic state, compared to pure MN and DKD. The mechanism is related to disorders of endothelial function, coagulation function, as well as fibrinolytic function. More attention should be paid to treatment of prothrombotic state in MN+DM patients.

Funding: Government Support - Non-U.S.

FR-PO512

Serum C3 and Renal Outcome in Patients with Primary Focal Segmental Glomerulosclerosis Jian Liu, Jingyuan Xie, Jun Tong, Hong Ren, Weiming Wang, Nan Chen. *Dept of Nephrology, Rui Jin Hospital, Shanghai Jiao Tong Univ, School of Medicine, Shanghai, China.*

Background: The role of complement in the pathogenesis or progression of FSGS is uncertain. The aim of this observational cohort study was to identify the clinical implications of serum C3 levels and to investigate their utility as predictor of renal outcomes in patients with FSGS.

Methods: 591 biopsy-proven primary FSGS patients were recruited. Clinical, histological and progression data were recorded. Decreased serum C3 level was defined as C3 <85 mg/dl. The study endpoint was end-stage renal disease (ESRD).

Results: Of the patients, there were 117 patients (25.1%) with low serum C3. At the time-point of renal biopsy, compared to patients with C3 ≥85 mg/dl, those with C3 <85 mg/dl had higher level of serum creatinine, lower levels of eGFR, proteinuria, hemoglobin, triglyceride, cholesterol, IgA, more severe segmental sclerosis, tubular atrophy and interstitial fibrosis. Multivariate linear regression analysis showed low C3 level was an independent risk factor for eGFR (HR=42.56, 95%CI 11.21- 73.91, p<0.01) after adjusted by sex, age and clinical indicators. The follow-up was assessed in 221 patients. During a mean follow-up of 53.3 months, ESRD occurred in 32 patients (37.2%) with low serum C3 compared with 22 patients (16.3%) with normal C3 levels (P<0.001). Serum C3 level had a significant predictive value for renal outcome (AUC = 0.650, P = 0.001). The risk of reaching ESRD was significantly higher in patients with low serum C3 level (HR 4.044; 95% CI= 2.238 to 7.309; P < 0.0001).

Conclusions: Complement activation may occur in patients with FSGS. It is associated with clinical and histological severities. Low serum C3 is an independent risk factor for the decline of eGFR, and is associated with poor renal outcome in patients with FSGS.

FR-PO513

Role of Proteolytic Fragment suPAR D2-D3 in Prediction and Cause of FSGS Sanja Sever,¹ Marina V. Kasaikina,¹ Eileen Kapples,¹ Jian Cai,² Jon B. Klein,² Nada Alachkar,³ Changli Wei,⁴ Changkyu Gu,¹ Jochen Reiser.⁴ ¹Nephrology, Massachusetts General Hospital, Charlestown, MA; ²Univ of Louisville School of Medicine, Louisville, KY; ³Nephrology, Johns Hopkins Univ School of Medicine, Baltimore, MD; ⁴Medicine, Rush Univ Medical Center, Chicago, IL.

Background: Primary FSGS is a kidney disorder that leads to end stage renal disease and affects tens of thousands people annually. Several studies suggest the soluble urokinase-type plasminogen activating receptor (suPAR) to be a predisposing circulating factor and prognostic marker of FSGS through its interaction with avb3 integrin.

Methods: We collected serum samples from kidney transplant recipients with FSGS. We also analyzed sera from healthy controls and patients with sepsis and on peritoneal dialysis. These sera were used to assess integrin activation in podocytes. Western blot was utilized to identify full length and D2-D3 fragment of suPAR. Transgenic mice were created to drive mouse suPAR D1-D2-D3 and suPAR D2-D3 expression from adipocytes and consequent release into circulation.

Results: We found that multiple disorders, including FSGS, sepsis, and peritoneal dialysis, are associated with an increase in bulk serum suPAR levels; however, only a subset of sera from FSGS patients induced integrin activation in podocytes. Western blot identified a fragment of suPAR (containing the D2-D3) only in the subset of sera from patients with recurrent FSGS. In vitro, the EC50 response of D2-D3 for activating integrin avb3 was approximately ten fold than for D1-D2-D3. Exposure of podocytes to physiological concentrations of the D2-D3 increased the amount of surface uPAR and facilitated podocyte motility. Injections of the D2-D3, but not full-length suPAR, induced transient proteinuria in mice. Transgenic mice for D2-D3 developed rising serum suPAR levels and a variable degree of proteinuria. A composite risk analysis score was developed that included presence of the D2-D3 in patient serum, podocyte integrin activation capacity, and total suPAR serum level for the prediction of recurrent FSGS.

Conclusions: suPAR D2-D3 fragment is a prognostic marker and risk factor for recurrent FSGS.

Funding: NIDDK Support

FR-PO514

Prognosis, Survival and Renal Function in Patients with Lupus Nephritis Gustavo Aroca Martinez,^{1,2} Andres A. Cadena,² Eduardo Egea Bermejo,⁴ Jossie E. Fontalvo,¹ Yeneris Gaviria,¹ Henry J. Gonzalez Torres,¹ Moises A. Arquez Mendoza,¹ José Rafael Consuegra,¹ Santos Depine.¹ ¹Medicine, Univ Simon Bolivar, Barranquilla, Atlantico, Colombia; ²Nephrology, Clinica de la Costa, Barranquilla, Atlantico, Colombia; ³Medicine, Univ Nacional de Colombia, Colombia, Atlantico, Colombia; ⁴Medicine, Univ del Norte, Colombia, Atlantico, Colombia.

Background: Lupus nephritis is the most common glomerulonephritis in the Colombian Caribbean region, despite there is less published information about its evolution and clinico-pathological aspects. **Objective:** To evaluate prognosis, survival and renal function of patients with LN residing in the Colombian Caribbean region controlled between 2008 - 2014.

Methods: 229 patient study with LN corroborated by histology according to the International Society of Nephrology Classification /Renal Pathology Society (ISN/ RPS. 2003) treated with induction and maintenance therapy and with a systematized following of at least 2 years. The pharmacological treatments included prednisolone, azathioprine, and Cyclophosphamide mycophenolate mofetil in isolation or combined and the clinical laboratory and histopathology variables were correlated as predictive value of therapeutic response. To achieve this as methodology a non-parametric descriptive statistics ANOVA (k-w) was used and canonical correspondence analysis.

Results: 229 patients in total of 34±12 of age, which 88% women, whose evolution were controlled during 24±6 months. The most common form of clinical presentation was nephrotic syndrome and asymptomatic hematuria-proteinuria (68.07%) the type III and IV of LN (84.23%) were associated with patients under 25 of age and a negative response to treatment. The estimated glomerular filtration rate measured by MDRD4 showed a significant improvement at 24 weeks with regard the baseline figure of 74.36.

Conclusions: The early detection and reference of NL patients allows an early approach and therapy. Which will prevent chronic kidney disease.

FR-PO515

Association of ABO Blood Group with Progression of IgA Nephropathy Meng Yang, Jingyuan Xie, Yan Ouyang, Xiaoyan Zhang, Xiao Li, Wen Zhang, Weiming Wang, Nan Chen. *Dept of Nephrology, Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China.*

Background: ABO blood group antigens are major histocompatibility antigens and little is known about its association with progression of IgA nephropathy (IgAN).

Methods: Biopsy-proven primary IgAN patients were retrospectively recruited. Clinical, histological and progression data were recorded. Patients with eGFR<15ml·min⁻¹·(1.73m²)⁻¹ at time of biopsy were excluded. Renal tissue was semi-quantitative scored according to the Oxford scoring system. ABO blood group was determined by standard erythrocyte antiserum agglutination method. All patients were divided into B antigen group (type B and AB) and non-B antigen group (type A and O) based on their ABO types.

Results: Among the 752 IgAN patients recruited in this study, 210 patients were type A (27.9%), 221 were type B (29.4%), 72 were type AB (9.6%) and 249 were type O (33.1%). When renal biopsy was performed, patients in B antigen group had higher eGFR (82.44 vs. 65.68 ml/min), lower systolic blood pressure (sbp) (125.36 vs. 129.29 mmHg) and uric acid (373.59 vs. 393.93 mmol/l) than patients in non-B antigen group. No significant difference was detected between histological lesions and these two groups. Totally, 100 patients progressed to end-stage renal disease (ESRD) after a median follow-up period of 51.05 months, including 32 (15.2%) type A, 18 (8.1%) type B, 2 (2.8%) type AB and 48 (19.3%) type O patients. Kaplan-Meier analysis showed that median ESRD-free survival time of patients in B antigen group was significantly longer than patients in no-B antigen group [148.2±5.5 months vs. 138.8±7.5 months, p<0.001]. Furthermore, patients in B antigen group were associated with a decreased risk of ESRD (HR=0.56, 95%CI 0.33-0.94) after adjusted by age, sex and clinical variables including eGFR, sbp, serum albumin, urine protein and hemoglobin by Cox proportional hazards model.

Conclusions: Our data suggested that B antigen had an independent protective effect against the progression of IgAN.

FR-PO516

The Analysis of the Long-Term Outcomes of Patients with Primary IgA Nephropathy Hao Li, Jian Liu, Wei Huang, Pingyan Shen, Zhaohui Wang, Ya Li, Xiaoxia Pan, Jingyuan Xie, Weiming Wang, Nan Chen. *Dept of Nephrology, Shanghai Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China.*

Background: Primary IgA nephropathy (IgAN) is one of the most common glomerular diseases in China. In this study we try to investigate the clinical characteristics and the relationship between CKD stages and long-term outcomes of patients with primary IgAN through the retrospective analysis of their clinical data.

Methods: Patients with biopsy-proved primary IgAN from 2002 to 2013 were included in the retrospective analysis. They were older than 18 years old and their follow-up time was more than 12 months. We collected their medical history, laboratory test reports and other clinical data. Then we enrolled 297 patients who were followed up for 5 years for further research. Kaplan-Meier method was used to calculate the renal survival rate of the patients.

Results: A total of 1052 cases were included. There is an equal proportion of male and female (50.4% vs 49.6%). The mean age was 36.86±11.58 years old. Five-year renal survival rate of these cases was 92%, and ten-year renal survival rate was 88%. We enrolled 297 cases who were followed up for 5 years. These patients were divided into rapid progression and stable progression, we found that cases in rapid progression group had more proteinuria, higher blood pressure, poorer renal function, lower serum albumin and lower hemoglobin, compared with other groups. When cases were divided according to CKD stages, the results showed no significant difference of outcomes among patients in CKD1-3a stage ($P > 0.05$). Their five-year renal survival rate was more than 95%. But patients in CKD3b-4 stage had worse outcomes. The five-year renal survival rate of patients in CKD3b stage was 85.3%, while it is only 65.3% for patients in CKD4 stage.

Conclusions: Five-year and ten-year renal survival rate of patients with IgAN was 92% and 88%, respectively. Patients in CKD3b or CKD4 stage at biopsy may have a lower renal survival rate and a worse outcome. At the time of renal biopsy, patients with impaired renal function, mass proteinuria, hypertension, anemia and low serum albumin may have a greater risk of progressing to end-stage renal disease.

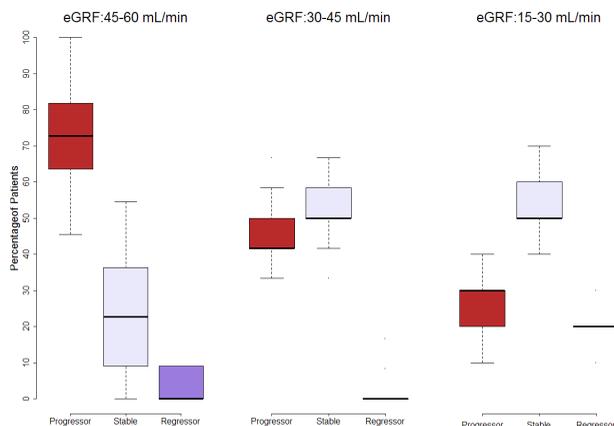
FR-PO517

Variability of GFR Decline in Alport Syndrome: Insights from a Provincial Database David Langsford,¹ Mila Tang,² Ognjenka Djurdjev,³ Lee Er,³ Adeera Levin.^{1,3} ¹UBC; ²BC Renal Agency.

Background: Alport syndrome (AS) is one of the inherited causes of CKD due to mutations in the collagen genes making up the glomerular basement membrane collagen. Design of clinical trials for intervention in AS proves challenging without a clear understanding of renal progression over time as observational data is lacking due to small sample size. We present here the utilization of population based data in a simulation to mimic clinical trial recruitment and endpoints to provide insights in trials design for AS.

Methods: AS patients were identified within a provincial CKD clinical database (PROMIS) in British Columbia, Canada for this observational simulation study. Patients were excluded if they have fewer than 4 eGFR-MDRD measurements or 2 as a study entry point to generate 100 random samples. Primary outcome was annual rate of eGFR change over 2 years categorized into: > -5 mL/min per year (progressor), -5 and 2 mL/min per year (stable), >2 mL/min year (regressor).

Results: 37 pts met inclusion criteria; median follow-up was 48.2 months, and median age of 36. The sample sizes for each random sample at the 3 enrolment eGFR levels were: 11, 12 and 10 respectively. Of those that 'enrolled' at eGFR 45-60 mL/min, 72.7% (IQR:63.6%,81.8%) progressed, and 22.7% (IQR:9.1%, 36.4%) remained in stable state.



For those recruited at eGFR 30-45 mL/min, 41.7% (IQR:41.7%,50%) had disease progression and 50% (IQR:50%, 58.3%) remained in stable state. Of those enrolled at eGFR 15-30 mL/min, 50% (IQR:50%,60%) were in stable state, 30.0% (IQR:20%, 30%) had disease progression, and 20% (IQR:20%,20%) had an improvement in eGFR.

Conclusions: Heterogeneity and non-linearity of AS renal progression ought to be taken into account when designing trials of interventions aimed at improving renal outcomes.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

FR-PO518

Discovery of Urine MicroRNA Biomarkers in a Pre-Clinical Model of Alport Nephropathy Martin Beaulieu,¹ Shirley Phillips,¹ Vivek Kaimal,² Shweta Pandya,² Nelson Chau,² Adam Pavlicek,² Steven Lockton,¹ Deidre Mackenna,² Neil W. Gibson.² ¹microMarkers, Regulus Therapeutics, San Diego, CA; ²R&D, Regulus Therapeutics, San Diego, CA.

Background: MicroRNAs (miRs) are a class of short (~23 nucleotide), highly conserved non-coding RNA that inhibit translation and facilitate degradation of messenger RNA (mRNA). MiRs are stable in biological samples and their levels can be deregulated in cells undergoing pathophysiological stress. We developed a miR profiling platform to discover novel biomarkers in bio-fluids. In this study, we aimed to profile miRs in urine, serum and kidney tissue from a pre-clinical model of Alport nephropathy in order to identify microRNA biomarkers with the ability to reflect disease progression.

Methods: Urine from 19 Col4a3^{-/-} mice (SV129 background) and 21 wild type litter mates was collected in metabolic cages over 22 hrs at 4, 6 and 8 weeks of age. The animals were sacrificed at week 8 to obtain kidney tissue and serum samples. Traditional markers of disease progression including blood urea nitrogen (BUN) and urinary microalbuminuria were measured using an Alera Clinical Chemistry analyzer. Following miR extraction, miR profiling was executed on a high-throughput, RT qPCR based system that reproducibly quantifies over 750 miRNAs.

Results: We identified miRs differentially expressed in the kidney (213), serum (60) and urine (67) of the Col4a3^{-/-} mice (FDR adjusted p-value < 0.05). Changes in miR expression in kidney were similar to other renal fibrosis models (e.g. increases in miR-21) reflecting the similarity in pathogenesis across disease models. A urine miR classifier was able to detect the Col4a3^{-/-} mice with 100% accuracy as early as 4 weeks of age.

Conclusions: We have developed a high-throughput, multiplex miR profiling platform with the capacity to profile tissues and bio-fluids. We discovered several urine microRNAs with highly significant differential expression in the Col4a3^{-/-} mouse model when compared to wild type mice. Our data suggest that urine is a favorable bio-fluid for the development of non-invasive microRNA based tests.

FR-PO519

Micronas as Predictive Biomarkers of Chronic Kidney Disease (CKD) in Patients (Pts) Undergoing Radical Nephrectomy (RN) for Kidney Cancer Francesco Trevisani,¹ Michele Ghidini,¹ Jens C. Hahne,¹ Andrea Lampis,¹ Paolo Manunta,² Maria Teresa Sciarone Alibrandi,² Giacomo Dell'Antonio,² Lorena Citterio,² Laura Zagato,² Francesco Montorsi,² Fabio Benigni,² Alberto Briganti,² Roberto Bertini,² Andrea Salonia,² Cristina Carenzi,² Matteo Fassan,³ Massimo Rugge,³ Paolo Rigotti,³ Giovambattista Capasso,⁴ Luciano Cascione,⁵ Chiara Braconi,¹ Nicola Valeri.¹ ¹ICR, London, United Kingdom; ²San Raffaele Inst, Milan, Italy; ³Univ of Padua, Padua, Italy; ⁴Univ of Naples, Naples, Italy; ⁵JOR, Bellinzona, Switzerland.

Background: MicroRNAs(miRs) are small non-coding RNAs involved in cell homeostasis and disease. Our study identified clinical and molecular markers associated with increased risk of developing CKD after RN for renal clear cell carcinoma(RCC).

Methods: 80 pts who underwent RN for RCC at a single institution between 2008-2013 were included. Inclusion criteria: normal renal function at surgery time(eGFR > 60 mL/min CKD-EPI formula 2009, serum creatinine < 1.1 mg/dL, no proteinuria). No pre-existing glomerulopathy. No evidence of metastatic disease. Minimum follow-up:12 months post-surgery. FFPE normal adjacent tissue to RCC(>3 cm) was micro-dissected to isolate cortex(10 glomeruli) and medulla and was subject to RNA extraction. miRs analysis was performed using Nanostring nCounter and validated by Real-Time, digital droplet PCR and in situ hybridization (ISH). Cox regression analyses were used to define variables associated with increased risk of CKD.

Results: 47.4% of pts developed CKD(stage 3a-3b-4 KDIGO) 12 months after RN. At multivariable Cox Regression, type II diabetes(pvalue:0.009),basal serum creatinine(pvalue:0.002) and miR-193b over-expression(pvalue:0.017) were independently associated with increased risk of CKD. ISH showed miR-193b over-expression in the tubular-interstitial compartment associated with abnormalities in keeping with early inflammatory and fibrotic changes. MiR-193b detection in matched urine samples is ongoing.

Conclusions: Tissue and urinary miRs deregulation may represent an early marker of kidney dysfunction and may anticipate clinical and laboratory evidence of CKD providing an important tool for personalized follow-up and prevention in pts undergoing RN for RCC.

Funding: Other NIH Support - Institute of Cancer Research Societa' Italiana di Nefrologia

FR-PO520

Urinary Angiotensinogen to Creatinine Ratio Is a Specific Biomarker for Renal Progression in Autosomal Dominant Polycystic Kidney Disease Hayne C. Park,¹ Hyunjin Ryu,² Miyeun Han,² Hyun Suk Kim,² Kook-Hwan Oh,² Young-Hwan Hwang,³ Curie Ahn.² ¹Internal Medicine, Armed Forces Capital Hospital, Seongnam-Si, Gyeonggi-Do, Korea; ²Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; ³Internal Medicine, Eulji General Hospital, Seoul, Korea.

Background: Urinary angiotensinogen to creatinine ratio (AGT/Cr) is elevated in autosomal dominant polycystic kidney disease (ADPKD), but whether AGT/Cr is a specific biomarker of ADPKD progression is not known. This study was performed to measure urinary AGT/Cr in subcohorts according to primary renal disease (glomerulonephritis (GN), diabetic nephropathy (DN), hypertensive nephropathy (HTN), ADPKD) and to demonstrate its usefulness as a specific biomarker in ADPKD.

Methods: Nine nephrology centers recruited adult subjects with chronic kidney disease (CKD) and classified into subgroups according to primary renal disease. First-voided morning urine was collected from all patients upon enrollment and stored at -80°C until measurement. Urinary AGT was measured by commercial sandwich enzyme-linked immunosorbent assay (ELISA). Urinary AGT/Cr levels and associated factors were compared among CKD subgroups.

Results: A total of 1528 patients were enrolled in KNOW-CKD cohort study (NCT 01630486)from Apr 2011 to Dec 2013. Among them, 153 patients were excluded (73 unclassified subgroups, 71 without urinary AGT measurement, 9 without available eGFR) and a total of 1375 (519 GN, 310 DN, 292 HTN, 254 ADPKD) patients were included in the final analysis. The mean age was 53 years and baseline serum creatinine was 1.9 ± 1.2 mg/dL. The GN and ADPKD subgroups showed younger age and earlier elevation

of urinary AGT/Cr levels according to CKD stages. When we performed the risk factor analysis separately in GN and ADPKD subgroups, the highest quartile of urinary AGT/Cr was associated with GN subcohort, female gender, hypertension, decreased eGFR, decreased plasma Hb, and higher degree of albuminuria. However, in multivariate logistic regression analysis, ADPKD subcohort demonstrated higher urinary AGT/Cr compared to GN subcohort after adjusting other co-factors.

Conclusions: Urinary AGT/Cr is greatly increased in ADPKD independent of albuminuria and renal function.

Funding: Government Support - Non-U.S.

FR-PO521

Using Biomarkers to Predict Progression to End-Stage Renal Disease within 6 Months of Liver Transplant Joseph T. Bahng,¹ Kimberly Autumn Forde,¹ Peter Abt,¹ Michael R. Bennett,² Anirban Ganguli,¹ Mary Ann C. Lim,¹ Debra J. Mccorriston,¹ Mary C. Shaw,¹ Deirdre L. Sawinski.¹ ¹Perelman School of Medicine at the U. of Pennsylvania; ²Cincinnati Children's Hospital.

Background: Liver transplant (LT) recipients are at increased risk for CKD and progression to ESRD. Creatinine, the standard for assessing renal function, provides limited prognostic information for recovery from AKI. Our aim is to create a predictive model for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers.

Methods: We enrolled 202 patients, of whom 138 have 6mos follow up. 13 patients progressed to ESRD, defined as GFR<20 ml/min, dialysis, or transplant evaluation. Logistic regression models evaluated neutrophil gelatinase-associated lipocalin, IL-18, Cystatin-C, Kidney Injury Molecule-1, & liver fatty acid binding protein for inclusion. Receiver operating characteristic curves and concordance statistics were used to assess the models.

Results: In one model, MELD score at LT, pre-LT AKI, pre-LT renal replacement therapy, & highest creatinine 3mos pre-LT were associated with ESRD at 6mos (p<.05). In another model with biomarkers, only urinary IL-18 was included for its association with ESRD (p=.2). The C-statistics for both models were similar (C=0.80 and 0.82, respectively).

Recipient Characteristics	COHORT n = 138	ESRD n = 13	NO ESRD n = 125	p-value
Age Median (IQR)	59 (54, 64)	60 (46, 64)	59 (54, 64)	.94
Male Sex n (%)	92 (69.2)	6 (54.6)	86 (70.5)	.31
Race n (%)				.39
Caucasian	99 (71.7)	8 (61.5)	91 (72.8)	
African American	25 (18.1)	4 (30.8)	21 (16.8)	
Other	14 (10.1)	1 (7.7)	13 (10.4)	
Hepatitis C n (%)	71 (51.8)	8 (61.5)	63 (50.8)	.80
Diabetes Mellitus n (%)	46 (33.6)	2 (16.7)	44 (35.0)	.34
Hypertension n (%)	53 (40.2)	4 (33.3)	49 (39.2)	.77
Highest Creatinine 3Mos Pre-transplant median (IQR)	1.49 (1.03, 2.95)	4.37 (2.34, 5.45)	1.4 (1.01, 2.71)	.001
MELD at LT median (IQR)	28 (22, 35)	36.5 (31, 44)	28 (22, 34)	.01
AKI Pre-LT n (%)	64 (49.2)	10 (83.3)	54 (45.8)	.02
Renal Replacement Therapy Pre-LT n (%)	15 (11.0)	6 (50.0)	9 (7.2)	<.01

Conclusions: Biomarkers did not significantly improve ESRD prediction over clinical characteristics. The overall event rate was low and longer follow up may be needed.

FR-PO522

Detection of Inflammatory BioMarkers in Urine Using a Dried, Shelf Stable Transport Device, ViveST™ Daniel R. Mcclernon,¹ Timothy W. Murray,² Anita M. Mcclernon.¹ ¹bioMONTR Labs, Research Triangle Park, NC; ²Vivebio LLC, Alpharetta, GA.

Background: Current medical practice assesses health of implanted kidney by monitoring non-specific signals (serum creatinine) after rejection has started and gold standard diagnostic method is invasive kidney biopsy. Studies of non-invasive biomarkers (CXCL9) have shown utility (CTOT-01) in identifying subsets of patients at risk for acute rejection. A urine based test for post surgical evaluations to pinpoint rejection and expedite therapeutic intervention is needed. Here we describe detection of CXCL9/MIG and CXCL10/IP-10 in urine in combination with a novel collection device ViveST, eliminating need for cold chain transport and storage.

Methods: Urine collected and centrifuged (4°C)@2,000xg (30 min). Supernatant decanted into clean tubes and diluted 1:1 with proprietary diluent buffer. Recombinant Human CXCL9/MIG and CXCL10/IP-10 (R&D Systems) was reconstituted using molecular grade water to concentrations of 10,000pg/uL and serially diluted. Urine was spiked with diluted recombinant human MIG or IP-10. 1mL aliquots were loaded onto ViveST and dried. ViveST samples were reconstituted with 1mL of molecular grade water and analyzed concurrently with frozen aliquots using quantitative sandwich enzyme immunoassay techniques specific for MIG or IP-10. Linear regression analysis from seven levels of calibration standard used to calculate MIG and IP-10 concentration.

Results: ViveST samples yielded MIG or IP-10 concentrations similar to corresponding frozen aliquots (see table). Replicate aliquots gave similar results.

Level	MIG (pg/uL)		IP-10 (pg/ul)			
	ViveST (n=3)	Frozen (n=1)	Male Urine		Female Urine	
			ViveST (n=2)	Frozen (n=2)	ViveST (n=2)	Frozen (n=2)
1	117	98	>1572	>1572	>1572	>1572
2	67	53	>1572	>15772	>1572	>1572
3	34	27	1534	1472	1541	1501
4	14	11	1096	1029	1157	1042
5	5	2	Not included in Experiment			
6	0	2				
7	0	0				

Conclusions: MIG and IP-10 can be detected in urine as inflammatory biomarker to assess risk of transplant rejection. ViveST can be used as ambient storage and transport device eliminating need for cold chain storage. Additional studies warranted assessing detection of biomarkers at therapeutically relevant concentrations.

Funding: Pharmaceutical Company Support - Vivebio LLC

FR-PO523

Albuminuria-Induced Apoptosis in Children with Nephrotic Syndrome Is a Result of the Dysbalance in Apoptosis Controlling System Ievgeniia Burlaka, Dept of Pediatrics No.4, National O.O. Bogomolets Medical Univ, Kyiv, Ukraine.

Background: Albuminuria promotes cell death, and is associated with faster progression of chronic kidney disease (CKD). However, the molecular mechanisms regulating cell death in response to albuminuria are not fully understood.

Methods: 53 patients aged 10-15 years with active stage of nephrotic syndrome were included to the study. Immunohistochemical examination of pro-apoptotic factor Bax, anti-apoptotic factor Bcl-xL, number of apoptotic cells in kidney biopsy specimens were done. Comparison of the level of these parameters between the different segments of nephron at different stages of glomerulosclerosis has been performed.

Results: Measurement of the pro-apoptotic factor Bax in kidney slices obtained from children with morphological form of nephrotic syndrome focal segmental glomerulosclerosis (FSGS) showed the presence of high level of Bax in both glomerular and tubule-interstitial segments. Higher immunosignal of Bax was evaluated in glomeruli with FSGS I-II st. as compared to tubular segment. When FSGS III-IV st. observed higher expression of Bax was detected in surrounding tubule-interstitial segment. Expression of the anti-apoptotic factor Bcl-xL was studied. Higher expression of Bcl-xL was recorded in tubule-interstitial segment as compared to glomeruli when FSGS I-II st. occurs. When FSGS III-IV st. occurs higher immunosignal of Bcl-xL is localized in surrounding tubule-interstitial segment with almost complete absence in glomeruli. The number of apoptotic cells was analysed. Quantitative analysis of apoptosis in kidney sections of patients with FSGS I-II st. revealed higher apoptotic index (AI) in glomeruli as compared to tubule-interstitial component. In kidney sections with FSGS III-IV st. higher AI was found in tubule-interstitial compartment.

Conclusions: Thus, progression of kidney injuries in nephrotic syndrome is associated with increased activity of pro-apoptotic factor Bax and simultaneous reduction of anti-apoptotic factor Bcl-xL. The level of the expression of Bax and Bcl-xL depends on the stage of FSGS and indicates the step-dependent manner of glomerular and interstitial injuries development upon the chronic influence of albuminuria.

Funding: Government Support - Non-U.S.

FR-PO524

eGFR, Renal, and Cardiovascular Risk and Nucleoside/Nucleotide Backbones of Human Immunodeficiency Virus Patients in the USA Jonathan A. Winston,¹ Grace Mccomsey.² ¹Icahn School of Medicine at Mount Sinai; ²Case School of Medicine.

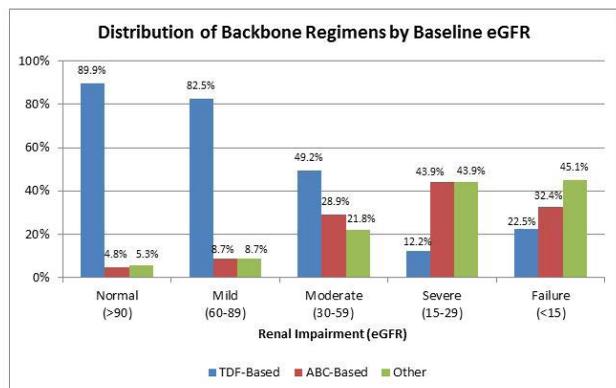
Background: HIV treatment involves choices in complex environments, and must balance disease management and potential safety issues (kidney and Cardiovascular diseases (CVD)) in an aging population. This study examined renal, CVD and comorbid conditions, and treatment of HIV patients.

Methods: Patients diagnosed with HIV using ICD-9 codes were selected from the Quintiles database (33M patients). Patients enrolled for ≥ 1 year during 2012-14, maintaining a single antiretroviral therapy, and for whom baseline eGFR could be computed were stratified based on backbone: regimens including tenofovir disoproxil fumarate (TDF), abacavir (ABC), or other (OTH). eGFR and rate of CV comorbidities at baseline were assessed.

Results: 14,942 HIV patients (mean age: 43; 76% male) were included; 85% TDF, 7% ABC, 7% OTH. Mean baseline eGFR was 99 mmol/l, with differences observed among regimens (102 TDF, 82 ABC, 87 OTH). Classified by degree of kidney impairment at baseline, regimen was highly correlated with level of impairment, with normal or mild impairment (eGFR≥60) more likely to be treated with TDF, and patients with moderate to

severe impairment (eGFR<60) more likely to be on ABC. Several CVD risk factors were more prevalent in ABC patients compared to TDF, hypertension (25% v 13%), dyslipidaemia (30% v 16%), and diabetes (12% v 5%) (p<0.001 in all) being the most common.

Conclusions: HIV patients often present with prevalent CVD risk and reduction in kidney function. Physicians make treatment choices that reflect concern for kidney function, consistent with labeling. This choice may come with cost, with more CVD risk factors correlated with alternative choices of NRTIs. As some antiviral regimens may be associated with CVD while others with kidney disease, understanding CVD risk profile versus kidney function protection may help optimize care of patients.



Funding: Private Foundation Support

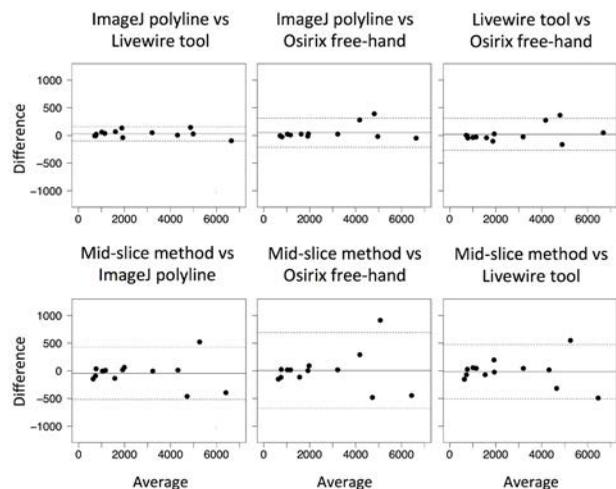
FR-PO525

Total Kidney Volume Computation in ADPKD: Different Methods in Comparison Kanishka Sharma,¹ Anna Caroli,¹ Katja Petzold,⁴ Andreas L. Serra,⁴ Giuseppe Remuzzi,^{1,3} Andrea Remuzzi.² ¹Bioengineering, Mario Negri Inst, Bergamo, Italy; ²Biomedical Engineering, Univ of Bergamo, Bergamo, Italy; ³Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; ⁴Univ of Zurich, Zurich, Swaziland.

Background: In ADPKD, kidney enlargement is associated with renal function decline, and total kidney volume (TKV) is gaining acceptance as surrogate marker of disease progression. In view of its effective use, TKV assessment should be as quick and accurate as possible. Aim of this study was to compare different TKV quantification methods.

Methods: TKV was computed on 13 MRIs from ADPKD patients enrolled in the EuroCYST Initiative (TKV=[707-6605] ml) by two tracers twice, using 4 methods: 1) polyline manual tracing with ImageJ software; 2) free-hand manual tracing with Osirix software; 3) semi-automatic tracing with customised ImageJ Livewire Plugin; 4) TKV estimation using mid-slice (Bae KT, Am J Nephrol 2013). Reproducibility, reliability, and agreement between methods were assessed.

Results: All of the methods were comparable in terms of intra- and inter-rater reliability (CCC=1, p>0.95). ImageJ polyline and Livewire tool showed highest agreement (30±65 ml difference), while mid-slice method showed largest discrepancies.



Mid-slice method required significantly less time than all other methods (~5 min), followed by Osirix free-hand (20±9 min), Livewire tool (24±9 min), and finally ImageJ polyline (35±12 min).

Conclusions: Mid-slice is much faster than whole kidney contouring for TKV quantification, but can provide only a clinical estimate of TKV. Whole kidney contouring must be used to monitor ADPKD progression and assess the efficacy of novel therapies.

Livewire tool provides the best compromise between accuracy and time required. **Acknowledgments.** This study was funded in part by the European Community (FP7-PEOPLE-MCA-ITN-317246, TranCYST project).

Funding: Private Foundation Support

FR-PO526

Renal Reserve: Development of a Kidney Stress Test Kyle Rodenbach,¹ Dana F. Fuhrman,² Paula S. Maier,¹ Katherine D. Shaw,¹ George J. Schwartz.¹ ¹Peds, Univ of Rochester, Rochester, NY; ²Peds, Univ of Pittsburgh, Pittsburgh, PA.

Background: Renal reserve (RR) is the difference in stimulated versus baseline glomerular filtration rate (GFR); it might predict future kidney health. The purpose of this study was to compare a meat versus liquid protein load in a cystatin-C-based (Cys-C) RR test using cimetidine-inhibited creatinine clearance (Cr Cl) and iohexol infusion clearance (Io Cl) for validation.

Methods: Participants (N=18) were screened for health status, blood pressure, and proteinuria. They followed a low protein diet and took cimetidine (20 mg/kg) for two days prior to the study. Water loading was used to maintain urine flow, and two hours were allotted for iohexol steady state equilibration. Participants 1-10 received a burger (1 g/kg protein); 11-15 received a ProCel® shake (1 g/kg protein); and 16-18 received a high dose ProCel® shake (1.5 g/kg protein). Data were analyzed for significance of RR. Cystatin-C estimated GFR (Cys-C eGFR) was calculated using the CKD-EPI Cys-C formula (Inker NEJM 2012) following IFCC calibration (ERM-DA471).

Results: Participants (N=18) had a mean (SD) age of 22 (2) years and were 39% male and 72% white. Baseline GFR (SD) in mL/min/1.73m² averaged 103.4 (14.7) for Cr Cl; 108.9 (9.0) for Io Cl (N=8); and 117.4 (6.1) for Cys-C eGFR. For the burger group (N=10), mean RR (SD) in mL/min/1.73m² was 17.1 (11.6) for Cr Cl (P=0.001); 8.4 (4.3) for Io Cl (P<0.001); and 4.7 (2.4) for Cys-C eGFR (P<0.001). For 1.0-1.5 g/kg shakes (N=8), mean RR (SD) in mL/min/1.73m² was 15.8 (5.8) for Cr Cl (P<0.001), 11.7 (9.0) for Io Cl (P=0.008), and 2.4 (2.9) for Cys-C eGFR (P=0.05). The burger and shake groups did not differ significantly in RR determined by Cr Cl, Io Cl, or Cys-C but Cys-C based RR was significantly less than Io-based RR for both groups. There were no differences in post-load versus pre-load Cr/Io clearance ratios.

Conclusions: Cys-C based RR following a burger provides a simple stress test of kidney function which was validated by classical renal clearances and can be applied to those who recover from acute kidney injury. Why Cys-C based RR was smaller than Io RR, the reference standard, is a topic for future investigation.

Funding: Other NIH Support - CTSI, University of Rochester, Private Foundation Support

FR-PO527

AT1 Receptor Antagonism Before Ischemia Prevents Acute Kidney Injury Transition to Chronic Kidney Disease Roxana Rodriguez Romo, Kenia Benitez, Rosalba Perez-villalva, Jonatan Barrera, Arturo Gómez, Gerardo Gamba, Norma O. Uribe-uribe, Norma Bobadilla. *Molecular Physiology Unit, Unidad de Fisiología Molecular, Inst de Investigaciones Biomédicas, UNAM e Inst Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico.*

Background: Despite the clinical recovery of an acute kidney injury (AKI) episode, progression to chronic kidney disease (CKD) could be observed on long time follow-up. The mechanisms are poorly understood. To analyzed if angiotensin II receptor blockade (ARB) before the ischemic insult is effective in abrogating the severity of the AKI episode and/or the progression to CKD.

Methods: Male Wistar rats were divided into 4-groups of rats: sham; sham plus losartan 3-d before surgery; bilateral renal ischemia for 45-min (UTxI); and losartan administration (3-d) before ischemia (Los-Pre). Animals were studied after 1, 3, 5, 15 days or 9-months. At the end of each experimental period, physiological, histopathological, immunohistochemistry, biochemical and molecular studies were performed.

Results: UTxI group developed CKD characterized by renal dysfunction, proteinuria, renal hypertrophy, glomerulosclerosis, tubular atrophy and tubulointerstitial fibrosis. At the ultra-structural glomerular level, foot process effacement was observed, which was associated a reduction in immune-gold staining for nephrin. Renal injury was mediated by increased oxidative stress, inflammation and up-regulation of TGFβ, αSMA, and Collagen I protein levels. TGFβ overexpression was mainly observed in epithelial cells. Interestingly, in spite of, ARB did not prevent or reduced AKI severity; it was enough effective to prevent CKD. The renoprotection conferred by ARB was associated with the early recovery of renal blood flow, lesser inflammation and greater nuclear hypoxic inducible factor 1α (HIF1α) staining.

Conclusions: Our data shows that in spite of, losartan pre-treatment did not protect the rats against AKI, it was effective to prevent the transition to CKD. The mechanisms by which losartan prevented CKD were in part due to the early renal blood flow recovery, lesser inflammation and greater HIF1α nuclear translocation within the 15 days post-ischemia.

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FR-PO528

Specific Endothelial Heparin-Binding EGF-Like Growth Factor Deletion Ameliorates Renal Injury Induced by Chronic Angiotensin II Infusion
 Fenghua Zeng, Lance A. Kloepfer, Raymond C. Harris. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Transactivation of EGFR by angiotensin II (Ang II) plays important roles in the initiation and progression of chronic kidney diseases (CKD). In vitro studies suggested that HB-EGF may be a critical mediator in this process, whereas its role in vivo has not been reported.

Methods: Age-matched male littermates of HB-EGF^{lox/lox} mice with endothelial-SCL-cre-ER (T) (+) or (-) were used. Tamoxifen injections produced control (HB^{lox/lox}) and mice with specific deletion of HB-EGF from endothelium (HB^{endo-/-}), which underwent uninephrectomy and osmotic minipump-mediated infusion with saline or Ang II for 8 weeks. Systolic blood pressures (SBP) were measured by tail-cuff. Renal injury was evaluated by albuminuria using urinary albumin/creatinine ratios and by morphology with periodic acid-Schiff (PAS) staining. Renal EGFR activation was determined by immunoblotting and immunostaining. Endothelium/podocyte injury, inflammation and renal fibrosis were evaluated by immunostaining.

Results: Compared to control, kidneys from HB^{endo-/-} mice with Ang II-infusion had significantly reduced EGFR activation. Endothelial HB-EGF deletion did not significantly prevent the hypertension induced by Ang II infusion, albeit lower SBP was detected in HB^{endo-/-} mice compared to HB^{lox/lox} mice. However, it decreased Ang II-infusion related renal injury, as demonstrated by 1) less albuminuria; 2) less glomerulosclerosis with glomerular score of 0.793 versus 1.652 in the control; 3) preserved endothelial integrity and decreased podocyte injury, as shown by more glomerular tufts area and WT1 positive cells, and less apoptotic cells measured by cleaved caspase 3 and TUNEL staining; 4) reduced inflammation in perivascular area and interstitium measured by F4/80 and CD3 immunostaining; and 5), reduced renal fibrosis, as shown by α -SMA immunostaining.

Conclusions: Shedding of HB-EGF from endothelium plays an important role in Ang II induced renal injury by linking Ang II-AT1R with EGFR transactivation. Inhibition of HB-EGF shedding could be a potential therapeutic strategy for CKD.

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FR-PO529

Effects of Acute Kidney Injury (AKI) Severity and Co-Morbidities on Chronic Kidney Disease (CKD) Progression
 Gregory John Wilson,^{1,2} Adrian Lawrence Kark,^{1,2} Andrew John Mallett,^{1,2,3,4} Anne Salisbury,^{1,2,4} Zaimin Wang,^{2,4} Helen G. Healy,^{1,2,4} Wendy E. Hoy,^{2,4} ¹Kidney Health Service, Royal Brisbane and Women's Hospital, Australia; ²CKD.QLD and NHMRC CKD.CRE, The Univ of Queensland, Australia; ³Inst for Molecular Bioscience and School of Medicine, UQ, Australia; ⁴Centre for Chronic Disease, UQ, Australia.

Background: AKI is a common and important cause of CKD. It remains unknown how AKI severity influences CKD progression. Which co-morbidities influence the progression of CKD also remains undetermined.

Methods: We aimed to explore whether AKI severity and patient comorbidities influence CKD progression. Patients with CKD associated with a clinical diagnosis of AKI were identified in the Royal Brisbane & Women's Hospital cohort (n=1150) of the CKD.QLD registry. AKI events were confirmed through historical creatinine values (2005 onward), and severity determined using AKIN criteria. CKD progression was assessed by change in glomerular filtration rate per year (DeGFR/yr) based on initial and final eGFR(CKD-EPI) values. All co-morbidities identified at the time of enrolment into the registry were explored.

Results: 384 patients were recorded as having a primary or secondary AKI diagnosis; 157 of these (99 male, mean age 67yrs) were biochemically confirmed. 133 patients (84.7%) were identified as Stage 1 AKI, 16 (10.2%) as Stage 2 and 8 (5.1%) as Stage 3. A one-way ANOVA revealed that AKI severity did not modulate CKD progression. However, numerically DeGFR/yr was largest for Stage 3 patients (5.1mL/min/1.72m²), and smallest for Stage 1 patients (1.6mL/min/1.72m²). The only two co-morbidities found to influence CKD progression were diabetes mellitus (DM; 35.6% of patients) and peripheral vascular disease (PVD; 12.1% of patients). CKD progression was significantly increased in patients with DM compared with patients without (DeGFR/yr 3.7mL/min/1.72m², p<0.001), and patients with PVD compared with those without (DeGFR/yr 4.4mL/min/1.72m², p<0.05).

Conclusions: Surprisingly, AKI severity did not alter CKD progression. Both DM and PVD influenced CKD progression in patients with AKI suggesting an increased vulnerability to AKI in these patients.

FR-PO530

Association Between Gut Microbiome and Cardiovascular Risk in Chronic Kidney Disease Patients with Type 2 Diabetes Mellitus
 Ruchi Singh, Tetyana L. Vasylyeva. *Pediatrics, Texas Tech Health Sciences Center, Amarillo, TX.*

Background: Diabetes is one of the leading causes of CKD. It is well established that patients with T2DM often experience persistent low-grade inflammation leading to microvascular deterioration and progression of vascular complications along with impaired gut motility, which impacts their microbiomes. The aim of the study is the assessment of gut microbiota, plasma zonulin, and inflammatory cytokines (TNF- α , IL-6) in conjunction with FGF-23, ET and levels of LPS in CKD (stage 4 and 5) patients with Diabetic Nephropathy (DN).

Methods: Healthy controls were matched by age and gender. Their dietary habits have been reviewed. Total of 40 subjects participated in the study. TNF- α , IL-6, FGF 23, LPS, ET-1 and zonulin, levels were measured by ELISA and quantitative analysis of gut microbiota composition (454 pyro sequencing).

Results: Higher circulation serum zonulin, TNF- α , and IL-6, FGF 23 LPS, ET-1 levels were found in the CKD (stage 4 and 5) with T2DM. Gut microbiota in T2DM patients with advanced CKD was substantially different from healthy population with increased in percentage of LPS producing bacteria. Significant diversity was observed in gut microbiota in study subjects compared to control group. CKD patients had high serum concentration of zonulin, a marker of leaky gut syndrome. Zonulin concentration was found positively correlated with LPS, inflammatory markers and FGF-23.

Conclusions: Gut microbiota is a modifiable factor and zonulin could be a potential future target to control chronic inflammatory responses. Gut microbiota and increased gut permeability in patients with advanced CKD secondary to DN results in high level of circulation LPS that mediates chronic inflammation which was implicated in deterioration of cardiovascular health.

FR-PO531

Metabolomics of Chronic Kidney Disease in Cohort of Patients Given Probiotics
 Subodh J. Saggi,¹ Eli A. Friedman,¹ Natarajan Ranganathan,³ Kelly Mercier,² Susan Mcritchie,² Susan Sumner.² ¹Nephrology/Medicine, SUNY Downstate Medical Center, New York, NY; ²Metabolomics, Research Triangle Inst, Research Triangle Park, NC; ³Kibow Biotechnology Inc., Kibow Biotechnology Inc., Newtown Square, PA.

Background: Persistent reduction in Glomerular Filtration Rate (GFR) below 60 ml/min/1.73 m² BSA over 3 months are hall marks of Chronic Kidney Disease (CKD). Urea is still considered a major uremic toxin clinically despite the description of middle molecules as being toxic. Persistent elevation of BUN may accompany reductions in GFR in some patients. We were specifically interested in obtaining pilot data identifying metabolites that differentiated patients with CKD whose BUN decreased after 4 months of probiotics treatment and its possible mechanisms.

Methods: Broad spectrum ¹H-NMR metabolomics was used to analyze baseline and 6 month plasma samples frozen from a phenotypically characterized cohort of patients with CKD Stage 3 and below from a prior Probiotic Renadyl™ study. NMR spectral data of baseline and 6 month plasma samples were analyzed after identical treatment of all samples. A total of 24 baseline samples were differentiated by a change in their BUN. Principal components analysis and orthogonal partial least squares discriminant analysis was used to analyze the data and determine the metabolites that best differentiated the phenotypic groups.

Results: Characteristics of the cohort population were age 57.7 \pm 14 yrs, mean BMI 31.3 \pm 6.1 Kg/m², 10 males and 14 females, 20 with HTN, 8 with DM, 11 Caucasian and 9 AA, 3 other, 1 unknown. 16 patients who had a decrease in BUN after 4 months of probiotics treatment could be differentiated based on baseline samples from those whose BUN increased or did not change. The majority of the metabolites that differentiated the groups were microbiome related metabolites.

Conclusions: Metabolomics analysis revealed a signature of metabolites that were associated with a decrease in BUN, and holds promise for use in predicting individuals with CKD that would most benefit from use of probiotics. The majority of the metabolites important to the differentiation of groups map to pathways involved in microbial metabolism.

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FR-PO532

Potential Uremic Toxin Precursors in the Gut Identified by Metabonomics and Proteomics
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Background: Many factors, e.g., the intestinal bacterial disorder, result in the species and amounts of harmful substances in the gut increasing, which leads to the increase of uremic retention molecules (URMs) in blood. These URMs may be classified according to their site of origin, that is, endogenous metabolism, microbial metabolism, or exogenous intake. The latter two are known as gut-derived uremic toxins, i.e., gut is a significant origin of URMs; but, it is currently unclear of the profile of these uremic toxins.

Methods: Excluding special factors which affected the intestinal environment, the subjects were divided into two groups: hemodialysis patients with end-stage renal disease (HD group, n = 20) and healthy controls (CT group, n = 20). Fecal metabonomics based on the ultra-performance liquid chromatography-tandem mass spectrometry was undertaken to explore the low molecular weight metabolites, and fecal proteomics based on the two-dimensional gel electrophoresis was employed to investigate the high molecular weight proteins. The data was analyzed with statistic and bioinformatic methods.

Results: Thirty-three metabolites and 31 proteins were identified. Among them, 17 metabolites and 13 proteins were significant higher in HD group than those in CT group, including phenols, which are well-known uremic toxins originating from the gut; reactive carbonyl compounds (RCC), which are well-known URMs in serum but first identified in the gut; other harmful metabolites (e.g., fenthion, halosulfuron-methyl and diethylpropion), and two inflammation-associated proteins. However, the levels of 16 metabolites and 18 proteins were lower in HD group comparing to CT group, including ajoene, which has been shown to exhibit anti-microbial and anti-cancer functions, and three proteins, which have indicated anti-inflammatory and anti-cancer activities.

Conclusions: This study not only demonstrated RCC URMs originated from the gut, but also identified numerous potential uremic toxin precursors and deficient beneficial substances in the gut of uremic patients.

Funding: Government Support - Non-U.S.

FR-PO533

AST-120 Affects the Level of Circulating TNF-Alpha Receptors That Predict Both Renal and Cardiovascular Outcomes in Patients with Advanced Renal Dysfunction Ran-hui Cha,¹ Dong Ki Kim,² Yon Su Kim,² ¹Internal Medicine, National Medical Center, Seoul, Republic of Korea; ²Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea.

Background: Tumor necrosis factor alpha and its two receptors have a critical role in kidney diseases. We aimed to establish the role of circulating TNF-alpha receptors (cTNFRs) as a new biomarker of renal disease and to identify the impact of AST-120 on the level.

Methods: 579 patients from 11 medical centers in Korea were prospectively recruited and followed up for 36 months after randomization into AST-120 and control arms. A total of 6 gram of AST-120 was given to participants in AST-120 arm as well as conventional treatment. cTNFRs were measured by ELISA method at the time of randomization and 1 year after. The renal outcome was composite of serum creatinine (SCR) doubling, 50% reduction of estimated glomerular filtration rate (eGFR), or initiation of renal replacement therapy. Major adverse cardiovascular events (MACE) were also evaluated.

Results: A total of 465 patients were analyzed. Mean SCR and eGFR level was 2.8 ± 0.67 mg/dl and 26.79 ± 7.263 ml/min/1.73m², respectively. The levels of cTNFRs throughout the study period were not different between two treatment arms. But the higher AST-120 compliance patients had, the lower cTNFRs they showed in the AST-120 arm. The highest tertile of cTNFRs showed the highest cumulative rate of composite renal outcomes followed by the intermediate tertile of cTNFRs after the adjustment for traditional risk factors. More change of cTNFRs was also independently associated to the more occurrence of composite renal outcomes. MACEs occurred more frequently in patients with higher baseline cTNFRs and more change of cTNFRs (log-rank P = 0.01, 0.002 and 0.021 for cTNFR1, cTNFR2, and change of cTNFR2, respectively) and the significance of cTNFR2 remained after adjustment for diabetes, CKD stage, and proteinuria.

Conclusions: Baseline and change of cTNFRs did not improve the predictability of composite renal outcomes in comparison with classic biomarkers. But cTNFRs predicted both renal and cardiovascular outcomes in patients with advanced renal dysfunction. And AST-120 was effective to lessen the increase of cTNFRs.

FR-PO534

Swimming Exercise Training (EXE) Normalize Blood Urea Nitrogen (BUN), Decrease Glomerulosclerosis, and Attenuates the Loss of Myokine IL6 in Rats with Chronic Kidney Disease (CKD) by 5/6 Nephrectomy (5/6Nx) Rafael Luiz, Rodolfo Rosseto Rampaso, Kleiton Augusto Santos Silva, Luciana Jorge, Edson Andrade Pessoa, Maria A. Gloria, Mario Luis Ribeiro Cesaretti, Nestor Schor. *Nephrology, Federal Univ of São Paulo, São Paulo, Brazil.*

Background: The aim of this study was to evaluate the EXE effects on renal function, glomerulosclerosis and myokine IL6 (has been associated with stimulation of hypertrophic muscle growth and myogenesis through regulation of the proliferative capacity of muscle stem cells) in rats with 5/6Nx.

Methods: Adult Wistar rats were divided in groups (n=8): Control (CS), Control+EXE (CE), Sedentary 5/6Nx (NS) and 5/6Nx+EXE (NE). The protocol was employed in 5/6Nx rats after 7 days from the surgical procedures. EXE periods were 60min/day/5 days a week during 8 weeks. It was evaluated arterial pressure (AP), maximal exercise test (METest), creatinine clearance (CrCl), BUN, proteinuria (uProt), glomerulosclerosis, myokine IL6 (by Luminex) as well mortality rate.

Results: EXE did not modify the increment in MAP but prevent, at least in part, a lower decline in the METest caused by 5/6Nx (29±1 vs 16±2 m/min, p<0.05). A higher CrCl in NE was observed compared with NS, 2.27±0.33 vs 0.96±0.20 ml/min, respectively (p<0.05). BUN was normalized in NE (43.62±7.30 mg/dL). Proteinuria was not significantly different in NE vs NS group (36.87±3.53 vs 40.13±2.35 mg/24h). Glomerulosclerosis was 48% higher in NS vs NE. Myokine IL6 (pg/ml) was decreased in NS (286.40±14) and attenuated the loss in NE (384.00±20.82). A higher mortality rate was observed in NS (70%) vs NE group (39%, p<0.05).

Conclusions: Results suggested that the EXE minimize the impact of 5/6Nx, by decreasing glomerulosclerosis and reducing the impact on CrCl (42%). Finally, attenuating myokine IL6 in NE, the decreasing mortality rate in NE vs NS and by minimizing the impact of 5/6Nx on CrCl indicate that EXE in this protocol, induced protection on renal function. Thus, it is reasonable to suggest that EXE could be an additional strategy to be employed in CKD.

FR-PO535

Does Autophagosome-Proteolysis Contribute to CKD-Induced Muscle Atrophy? Zhen Su,¹ Haidong Wang,³ Janet D. Klein,³ William E. Mitch,² Xiaonan H. Wang,³ ¹Dept of Nephrology, The First Affiliated Hospital of Wenzhou Medical Univ, Wenzhou, Zhejiang, China; ²Nephrology, Baylor College of Medicine, Houston, TX; ³Renal Medicine, Emory Univ, Atlanta, GA.

Background: CKD-induced muscle wasting results from activation of the ubiquitin proteasome system (UPS). Since FOXO simulates the UPS but also activates autophagosomes, we hypothesized that autophagosome-induced proteolysis may contribute to CKD-induced muscle wasting.

Methods: CKD model in mice: subtotal nephrectomy for one month. Muscle overloading model: removal of gastrocnemius and soleus to overload the plantaris muscle (mimics resistant exercise) in normal and CKD mice. Acupuncture with low frequency electric stimulation (Acu/LFES) was applied 15 minutes daily for 2 weeks (Hu, JASN, 26:626 2015). Electrical stimulation used a consistent pulse, electric frequency 20HZ, current 1mA.

Results: Both exercise and Acu/LFES reduced CKD muscle loss. In muscles of CKD mice, mRNAs related to autophagy-lysosomal function, Bnip3, Atg12, Atg8, LC3II and Beclin-1, were upregulated and Bnip3, Beclin-1 and LC3II proteins were increased. Acu/LFES treatment reversed these changes. Exercise in control mice also increased autophagy-lysosomal related protein LC3-II, Beclin-1, P62 and Vps34. The levels of these mediators were not additive to changes observed in mice with CKD. We cultured C2C12 myotubes in uremic serum and found increased autophagy markers, indicating activation of autophagosomes. Acidification alone did not stimulate autophagy markers. Based on the C2C12 results, the UPS, but not autophagosomes, is responsible for degradation of structural proteins (myosin and actin).

Conclusions: 1) Autophagosome-mediated proteolysis occurs in CKD-induced muscle atrophy. In mice with CKD, the UPS was principally involved in muscle proteolysis; the role of autophagosomes was convoluted. 2) Prevention of muscle atrophy by exercise is not due to inhibition of the autophagy-lysosomal proteolysis pathway in CKD. 3) Muscle atrophy cannot be equated with increased autophagy markers. 4) Acu/LFES and exercise promote different autophagy consequences.

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FR-PO536

Indoxyl Sulfate, a Uremic Toxin, Accelerates Skeletal Muscle Atrophy in CKD Condition Yuki Enoki,¹ Hiroshi Watanabe,¹ Masafumi Fukagawa,² Toru Maruyama,¹ ¹Dept of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto Univ, Kumamoto-shi, Japan; ²Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara-shi, Japan.

Background: Skeletal muscle atrophy is often observed in chronic kidney disease (CKD) patients, especially in patients underlying hemodialysis. Uremic toxins have been known to link to CKD complications. However there has been no report on the relationship between uremic toxins and skeletal muscle atrophy. The purpose of this study is to investigate the involvement of uremic toxins on skeletal muscle atrophy observed in CKD condition.

Methods: *In vitro* cytotoxicity of uremic toxins on cell proliferation and differentiation was evaluated by using a mouse myoblast cell line (C2C12). The effect of uremic toxin on proteolysis and protein synthesis system in C2C12 was also evaluated. In the animal study, we examined the contribution of uremic toxin on muscle atrophy using uremic toxin overloaded half- or 5/6-nephrectomized mice.

Results: We focused on six protein bound solutes including indoxyl sulfate (IS), indole acetic acid, *p*-cresyl sulfate, hippuric acid, kynurenic acid and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid. Among these uremic toxins, IS significantly inhibited proliferation and differentiation of C2C12 myoblast cell, and decreased phosphorylation of Akt. Moreover, IS significantly increased atrophy-related genes expression but it did not affect differentiation-related genes expression. In the animal experiments, IS-overload reduced body weights and skeletal muscle weights of half- or 5/6-nephrectomized mice, and consequently weakened its muscular endurance. IS-overload mice showed increased skeletal muscle atrophy-related genes expression. In the same experimental condition, IS also induced the expression of inflammatory cytokine and transforming growth factor-β in skeletal muscle cells.

Conclusions: IS is the potent uremic toxin inducing skeletal muscle atrophy associated with CKD by increasing muscle atrophy-related genes.

FR-PO537

Myostatin Stimulates Progenitor Cells to Differentiate into Fibrocytes Leading to Muscle Fibrosis in Chronic Kidney Disease Liping Zhang,¹ Jiangling Dong,^{1,2} William E. Mitch,¹ ¹Medicine/Nephrology, Baylor College of Medicine, Houston, TX; ²Life Science & Engineering College, Northwest Univ for Nationalities, Lanzhou, Gansu, China.

Background: In chronic kidney disease (CKD), fibrosis develops in damaged kidneys leading to loss of functions. Fibrosis in muscle also complicates CKD but the identity of cells developing into fibrocytes and mechanisms causing fibrosis are not defined. The potential precursors of muscle fibrosis are mesenchymal progenitor cells (fibrotic and adipogenic progenitors (FAPs)) while mechanisms causing fibrosis include myostatin as

CKD raises its expression and muscle injury can stimulate injured muscles to develop fibrocytes. Our hypothesis is that CKD stimulates myostatin expression causing FAPs to differentiate into fibrocytes.

Methods: 1) we isolated and cultured FAPs, adding recombinant myostatin to determine if it causes FAPs to proliferate and differentiate into fibrocytes. 2) We isolated GFP-labeled FAPs from transgenic, GFP-expressing mice and transplanted them into tibialis anterior (TA) muscles of CKD mice. We assessed conversion of FAPs into GFP-fibrocytes using α -SMA expression. 3) CKD mice were injected with an anti-myostatin peptibody to determine if myostatin stimulates muscle fibrosis. 4) Interactions between myostatin signaling and FAP conversion to fibrocytes were tested by knocking down Smad3 with a lentivirus expressing Smad3 SiRNA.

Results: In cultured FAPs, myostatin stimulated their proliferation and conversion into fibrocytes and there is proliferation of FAPs in injured muscles of CKD mice. GFP-labeled FAPs transplanted into TA muscles of CKD mice differentiate into fibrocytes identified as expressing the fibrosis marker, α -SMA. FAP proliferation and muscle fibrosis were prevented in CKD mice injected with the anti-myostatin peptibody. Finally, Smad3 knock-down blocked FAP differentiation into fibrocytes indicating that a myostatin to Smad3 pathway is responsible for the conversion of FAPs to fibrocytes.

Conclusions: CKD stimulates myostatin production to activate FAPs which differentiate into fibrocytes. The process is blocked by an anti-myostatin peptibody, providing a new target for preventing muscle fibrosis as a complication of CKD.

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FR-PO538

Effect of Methoxy Polyethylene Glycol – Epoetin Beta on Plasma Levels of IL-1 β , TNF-RI, TNF-RII, sFAS, sFASL, TGF β , MMP-9 in Patients with CKD Piotr Bartnicki,¹ Ewa Majewska,² Zbigniew Baj,² Jacek Rysz.¹ ¹Dept of Nephrology, Hypertension and Family Medicine, Medical Univ of Lodz, Poland; ²Dept of Pathophysiology and Immunology, Medical Univ of Lodz, Poland.

Background: In patients with CKD are observed disturbances of immune cells function and endothelium dysfunction with high tissues fibrosis. ESAs using in these patients, beyond anemia correction seem to have renoprotective effect and slow progression of CKD. In this study we aimed to determine effect of methoxy polyethylene glycol – epoetin beta (Mircera) on plasma levels of selected parameters in predialysis patients with CKD.

Methods: 28 patients with CKD and anemia, treated with Mircera, were enrolled to the study. The healthy control group included 15 volunteers. Plasma levels of evaluated parameters were measured with available enzyme – linked immune-sorbent assay (ELISA) kits.

Results: The results of our study are shown in the table.

	CKD before treatment	CKD after treatment	Control group
Hb [g/dl]	9.6 (9.1 – 10.1) *	11.6 (11.1 – 12.1) **	14.4 (13.3 – 14.9)
eGFR [ml/min]	16.4 (13.9 – 21.8) *	16.6 (14.0 – 23.3) *	65 (63 – 74)
IL-1 β [pg/ml]	2.72 (1.63 – 3.81) *	2.97 (2.24 – 3.7) *	1.29 (1.25 – 1.33)
TNF-RI [pg/ml]	5268 (3741 – 6795) *	5430 (3906 – 6954) *	1136 (912 – 1360)
TNF-RII [pg/ml]	8092 (7183 – 9001) *	9308 (7912 – 10703) **	2360 (1899 – 2821)
sFAS [pg/ml]	3325 (2444 – 4207) *	3174 (2666 – 3682) *	507 (333 – 580)
sFASL [pg/ml]	90.3 (61 – 119.6) *	87.5 (66.1 – 108.9) *	60.1 (20.4 – 100.8)
TGF β [pg/ml]	25.2 (16.3 – 34.1) *	25.3 (12.1 – 38.5) *	12.3 (8.7 – 15.9)
MMP-9 [ng/ml]	1125 (659 – 1591) *	687 (330 – 1044) **	273 (157 – 389)

*p < 0.05 to control group, **p < 0.05 to CKD before treatment

Conclusions: Plasma concentrations of evaluated parameters are significantly higher in CKD patients in comparison to control group. After ESA treatment plasma level of TNFII was significantly higher and MMP-9 was significantly lower in CKD patients. These data suggest that Mircera used in correction of anemia in CKD might influence on immune cells function, apoptosis and tissue fibrosis.

FR-PO539

Qualitative Changes in Erythrocytes in Chronic Kidney Disease Ken Aizawa, Ryohei Kawasaki, Yoshihito Tashiro, Michinori Hirata, Koichi Endo, Ken-ichi Serizawa, Yasushi Shimonaka. *Product Research Dept, Chugai Pharmaceutical Co., Ltd., Kamakura, Japan.*

Background: Therapeutic control of anemia in chronic kidney disease (CKD) is assessed by monitoring hemoglobin (Hb) levels. However, monitoring Hb alone could potentially fail to reveal pathological changes in erythrocytes, because erythrocyte lifespans are shorter in CKD. Shortening of erythrocyte lifespans may attenuate erythropoietin responsiveness, resulting in poor prognosis of CKD. Erythrocyte lifespans are thought to be shortened by qualitative changes such as deterioration of deformability and stability, but it is not yet clear whether these aspects are changed in CKD.

Methods: To assess qualitative changes in erythrocytes were first confirmed in a rat model of iron-deficiency anemia. Deformability was quantified by laser diffraction ektacytometry and stability was quantified by hemolysis test. We next produced CKD model rats by anti-Thy1.1 antibody injection plus uninephrectomy. Epoetin beta pegol (C.E.R.A., 25 mg/kg) was intravenously injected the day after surgery. At 11 wks, Hb levels, erythrocyte deformability and stability, plasma urea nitrogen (UN) and creatinine (pCre) were assessed.

Results: Iron-deficiency rats showed significant anemia and had impaired erythrocyte deformability and stability. These changes in erythrocytes were almost normalized by administration of iron sucrose. In the CKD model, Hb level was significantly decreased and deformability and stability of erythrocytes were significantly impaired. Stability significantly recovered and deformability tended to recover in the C.E.R.A. group, although there was no significant difference in Hb levels between the disease group and C.E.R.A. group. Kidney function (UN and pCre) correlated significantly with stability, but not with deformability. Morphologic parameters (mean corpuscular volume and red cell distribution width - standard deviation) did not reflect changes in deformability and stability.

Conclusions: Deformability and stability of erythrocytes were impaired in CKD rats, and may be linked with kidney dysfunction. Focusing on qualitative aspects of erythrocytes may provide a better understanding of pathological conditions and therapeutic benefit in anemia.

FR-PO540

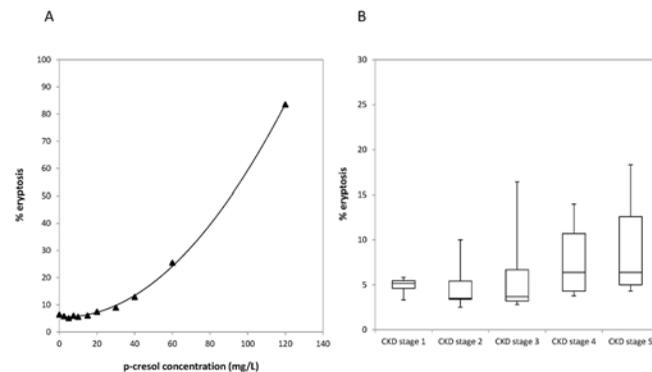
Eryptosis in Chronic Kidney Disease Grazia Maria Virzi, Anna Clementi, Alessandra Brocca, Massimo de Cal, Claudio Ronco. *Nephrology-IRRIV.*

Background: Even though anemia in CKD results mainly from the lack of erythropoietin, accelerated erythrocyte death (eryptosis) seems to be a contributor factor. Eryptosis is characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine (PS)-exposure at the erythrocyte (RBC) surface. Eryptosis may be triggered by some uremic toxins. P-cresol is an uremic toxin which has negative cardiovascular and cytopathic effects. This study explored if eryptosis is triggered by p-cresol and if different stages of CKD may influence erythrocyte death.

Methods: RBCs from healthy subjects were incubated in vitro at a hematocrit of 0.4% in RPMI with different concentrations of p-cresol (0-2.5-5-10-20-40mg/l) and with plasma from CKD patients (5 for each stage) for 24hours. PS exposure was estimated from AnnexinV binding in flow cytometer.

Results: Increasing concentrations of p-cresol modified significantly the percentage of PS exposure on RBC surface, thus suggesting that increasing concentrations of p-cresol may stimulate eryptosis in vitro. Moreover, there was no significant difference in terms of median values of eryptosis between CKD stages, but a positive trend was evident: eryptosis increase with CKD progression.

	CKD1	CKD2	CKD3	CKD4	CKD5
ERYPTOSIS %	4.7 (4.2-5.0)	3.5 (3.4-5.4)	3.7 (3.2-6.7)	6.4 (4.3-10.3)	6.4 (5.0-12.6)



Conclusions: In addition to its known cardiovascular and cellular effects, p-cresol seems to stimulate eryptosis in vitro and increasing concentrations of this uremic toxin may be responsible for higher levels of eryptosis in vivo. Our data show that CKD plasma contains components able to trigger eryptosis and different stages of CKD may be responsible for different levels of RBC death, thus suggesting that progression of CKD may increase eryptosis in vivo. These results suggest a role of uremic toxicity in the genesis of eryptosis and renal anemia. It is necessary to increase the sample size to validate our hypothesis.

Funding: Private Foundation Support

FR-PO541

Palmitate Exacerbates Renal Anemia: Suppression of Renal Erythropoietin Production via Endoplasmic Reticulum Stress Reiko Inagi,¹ Thitunui Anusornvongchai,¹ Yu Ishimoto,² Akira Okada,² Norio Suzuki,³ Masayuki Yamamoto,³ Masaomi Nangaku.² ¹Div of CKD Pathophysiology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan; ²Div of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan; ³Tohoku Univ School of Medicine, Sendai, Japan.

Background: Derangement of erythropoietin (EPO) production in renal EPO-producing (REP) cells causes renal anemia. Palmitate induces endoplasmic reticulum (ER) stress that contributes to glomerular and tubular cell damages. Thus, we evaluated the effect of palmitate-ER stress axis on EPO production in REP cells.

Methods: C57/BL6 or the mice, in which the renal EPO gene was replaced with GFP or REP cells were lineage labeled with tdTomato, were daily injected with palmitate

(BSA-conjugated, PAL) or BSA for 11 days or fed with high palmitate (10%) diet for 4 months. The hypoxia-induced EPO production or ER stress status in kidney, especially in REP cells, were then assessed by real-time PCR, WB, and IF assay. *In vitro* study, we used HepG2 (hepatic EPO producing cells) treated with PAL.

Results: PAL (injection and diet) suppressed EPO production *in vivo* and *in vitro* under hypoxia (HIF activation with CoCl₂). It was associated with activation of ER stress signal (ATF4 and XBP-1, $p < 0.05$). ATF4 activated by PAL significantly bound to a novel ATF4 binding site (TGACCTCT) at the 3'-enhancer region of EPO gene and suppressed the enhancer activity and subsequent EPO mRNA expression. HepG2 overexpressing dominant negative ATF4 ameliorated the suppression of EPO production by PAL. Importantly, PAL did not change the REP cell number, while REP cells markedly declined EPO production by PAL. In contrast, the number of REP cells positive for ATF4 was increased by PAL, indicating that suppression of EPO production in REP cells by PAL was mediated by ATF4 activation, namely ER stress.

Conclusions: EPO production by REP cells was suppressed by palmitate, especially under hypoxic condition, via the ER stress pathway (ATF4 activation). The link between dyslipidemia (palmitate) and ER stress may contribute to development and progression of renal anemia, and subsequent CKD and highlight the impact of palmitate diet on CKD prevention.

Funding: Government Support - Non-U.S.

FR-PO542

The Function of Integrin β 4 in Epithelial-to-Mesenchymal Transition of HK2 Cells Qi Wang, Yan Wang, Xiaoyan Huang, Zibo Xiong, Zuying Xiong. *Dept of Nephrology, Peking Univ Shenzhen Hospital, Shenzhen, Guangdong, China.*

Background: To explore the function of integrin β 4 in epithelial-to-mesenchymal transition (EMT) of HK2 cells, and further study the role of integrin β 4 in renal fibrosis.

Methods: (1) Cultured HK2 cells were divided into 4 groups: 0ng/ml TGF β 1 treated group (negative control), 1ng/ml TGF β 1 group, 3ng/ml TGF β 1 group and 9ng/ml TGF β 1 group. (2) We constructed a stable shRNA mediated repression of integrin β 4 in HK2 cells and divided into 4 groups: control-shRNA HK2 cells without TGF β 1; control-shRNA HK2 cells with 5ng/ml TGF β 1; β 4-shRNA HK2 cells without TGF β 1; β 4-shRNA HK2 cells with 5ng/ml TGF β 1 (3) The *in vivo* experiment was performed in IgA nephropathy kidney tissues obtained from 45 patients that underwent a biopsy procedure during 2013-2014. According to the degree of tubulointerstitial lesion, kidney specimens were divided into 3 groups: mild lesion, moderate lesion, and severe lesion. We handle normal kidney portions as controls. The expressions of integrin β 4, E-cad, CTGF and α -SMA were assessed by qRT-PCR and western blot; immunofluorescence was used in different degrees of tubulointerstitial lesions.

Results: (1) Compared with negative control, integrin β 4 and E-cad were significantly lower, however, CTGF and α -SMA were increased (2) Integrin β 4 and E-cad in β 4-shRNA HK2 cells group were lower than control-shRNA HK2 cells, in contrast, CTGF and α -SMA were increased; integrin β 4 and E-cad with TGF β 1 treatment were significantly lower than without TGF β 1 groups. CTGF and α -SMA expressions were increased. (3) Compared with mild lesion group, E-cad staining in moderate lesion group and severe lesion group reduced, α -SMA staining and integrin β 4 staining increased. After being further analyzed, the most of integrin β 4 staining located in neonatal renal tubules.

Conclusions: Integrin β 4 was decreased in the process of EMT, and reduced integrin β 4 can exacerbate HK2 cells from epithelial cells transition to mesenchymal cells, therefore loss of integrin β 4 may be the marker of TIF. However, the results of *in vivo* experiment appeared to contradict *in vitro* experiments, the reason of this phenomenon may be that many neonatal renal tubules possess the ability of proliferation.

Funding: Government Support - Non-U.S.

FR-PO543

Signal Regulatory Protein- α Is Elevated in Uremic Cardiomyopathy and May Exacerbate Muscle Fibrosis Sandhya S. Thomas, Jiangling Dong, Liping Zhang, William E. Mitch. *Medicine, Baylor College of Medicine, Houston, TX.*

Background: Insulin resistance in chronic kidney disease (CKD) begins early in the disease, compromising anabolic responses to insulin/IGF-1 signaling. We have previously demonstrated that a novel protein, signal regulatory protein alpha (SIRP α) is involved in insulin signaling, exacerbating skeletal muscle metabolism. We now describe for the first time elevation of SIRP α in CKD cardiac muscle which not only adversely influences insulin signaling, but may exacerbate muscle fibrosis.

Methods: CKD was created via subtotal nephrectomy and mice with CKD greater than 2 months hearts were harvested and left ventricle muscle samples were examined for SIRP α , IRS-1, α -SMA, GAPDH. Additionally, C2C12 myoblasts were treated to overexpress SIRP α vs. GFP plasmid. Also, myoblasts were transfected with silencing RNA (siRNA) SIRP- α or scrambled siRNA (control). Western blots analysis was performed based on skeletal and cardiac muscle cell lysates.

Results: After ~2 months of CKD, the mice experience left ventricle hypertrophy with a heart weight to body weight that is significantly larger vs. control mice. SIRP α was significantly increased in cardiac muscles of mice with CKD, with reduction in tyrosine phosphorylation of IRS-1. This finding was previously reported in skeletal muscles of mice with CKD. Additionally, fibrosis marker α -SMA was increased in cardiac muscles of mice with CKD vs. control mice. In order to determine a cause and effect relationship, SIRP α was overexpressed utilizing a SIRP α plasmid vs. GFP plasmid for control. In myoblasts in which SIRP α was overexpressed, fibrosis marker α -SMA increased. Finally, when we silenced SIRP α in muscle cells treated with a cytokine mixture, containing cytokines present in CKD patients, fibrosis marker α -SMA was downregulated.

Conclusions: These results imply that SIRP α increases fibrosis, and suggesting that SIRP α may have influences on cardiac muscle fibrosis via a new pathway in chronic kidney disease. Ultimately blocking SIRP α in heart muscle may improve cardiac fibrosis associated with chronic kidney disease.

Funding: Veterans Administration Support

FR-PO544

Retinal Microvascular Abnormalities and Incidence and Progression of Chronic Kidney Disease Charumathi Sabanayagam,^{1,2} Peng Guan Ong,¹ Boon Wee Teo,³ Carol Y. Cheung,^{1,2} Ching-Yu Cheng,^{1,2} Ecosse L. Lamoureux,^{1,2} Tien yin Wong.^{1,2} ¹Singapore Eye Research Inst, Singapore; ²Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore; ³National Univ of Singapore, Singapore.

Background: To examine the longitudinal association of a panel of retinal vascular parameters, markers of microvascular damage, with the incidence and progression of chronic kidney disease (CKD) in middle-aged Asian adults.

Methods: The population consisted of a cohort of Malay adults aged 40-80 years examined from 2004-06 and again from 2010-2012 (n=1464; 1306 free of CKD and 158 with pre-existing CKD). The outcomes were incidence (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m²+25% decrease in eGFR) and progression of CKD (drop in eGFR category ≥ 60 , 30-59, 15-30, <15)+25% decrease in eGFR or an annualized eGFR rate >3 mL/min/1.73m²/year). Retinal vascular parameters (arteriolar and venular caliber, tortuosity, branching angle, and fractal dimension) were measured from baseline retinal photographs using a computer-assisted program (Singapore 1 Vessel Assessment, SIVA). Retinopathy was graded using a standard protocol. Associations were examined using Cox proportional hazards regression models adjusting for age, sex, blood glucose, systolic blood pressure and baseline eGFR.

Results: Over a median follow-up of 6.6 years, 6.4% (70% had diabetes) developed incident CKD and 26.6% (62% had diabetes) developed progressive CKD. In multivariable models, retinal arteriolar narrowing, retinal venular widening, and presence of retinopathy were significantly associated with incident CKD. The HR (95% CI) of incident CKD was 1.31 (1.01-1.72) per SD decrease in arteriolar caliber, 2.20 (1.10-4.41), for tertile 3 vs. tertile 1 of venular caliber; 2.06 (1.24-3.44) for retinopathy. Increased arteriolar tortuosity alone was associated with progressive CKD (1.57 [1.04-2.37] per SD decrease. All associations were consistently present among those with diabetes.

Conclusions: Retinal vascular abnormalities increased the risk of CKD by more than two times in Asian adults. Our findings provide evidence that retinal imaging may be a useful tool to improve risk stratification for CKD.

Funding: Government Support - Non-U.S.

FR-PO545

Relationship Between Serum Bilirubin and Hyalinization of Renal Arterioles Tsuyoshi Miyagi,¹ Kentaro Kohagura,² Yusuke Ohya,¹ Kunitoshi Iseki.² ¹Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Nishihara-cho, Okinawa, Japan; ²Dialysis Unit, Univ of the Ryukyus, Nishihara-cho, Okinawa, Japan.

Background: It has been suggested that there is a relationship between serum bilirubin and microangiopathy. In the present study, we examined the relationship between serum bilirubin levels and the hyalinization of renal arterioles in patients with chronic kidney disease (CKD).

Methods: We reviewed the clinical records of 138 patients with CKD (mean age: 44 years) who underwent renal biopsy at our department during a 3-year period starting in 2010. Patients who were receiving calcineurin inhibitors were excluded. The subjects were divided into three groups based on their total serum bilirubin levels: tertile group 1 (0.2-0.4 mg/dl; 40 patients), tertile group 2 (0.5-0.7 mg/dl; 61 patients), and tertile group 3 (0.8-1.4 mg/dl; 37 patients). Using the pathological specimens obtained from renal biopsies, the hyalinization of renal arterioles was semiquantitatively evaluated, and the mean score of renal arteriolar hyalinization grade was used for analysis.

Results: Tertile group 1 had markedly higher urinary protein levels and markedly lower serum hemoglobin (Hb) levels than tertile group 3. We defined total serum bilirubin levels under 0.5 mg/dl (tertile group 1) as low levels and divided them into two groups of values under and above 0.5 mg/dl. These were set as explanatory factors, and a multiple regression analysis was performed, with the degree of hyalinization of renal arterioles as the objective variable. A low serum bilirubin level was a significant risk factor for the hyalinization of renal arterioles ($R^2 = 0.45$, $\beta = 0.26$, $p = 0.003$), even when adjustments were made for age, sex, HbA1c levels, mean blood pressure, history of smoking, and LDL cholesterol levels. Furthermore, even when the explanatory factor of serum Hb level was added, the results of the analysis remained the same.

Conclusions: Low serum bilirubin levels may be a risk factor for the hyalinization of renal arterioles independent of classical risk factors of cardiovascular disease.

FR-PO546

Autonomic Nervous Dysfunction in Predialytic Chronic Kidney Disease: 3 Years Observational Follow-Up Study Su Min Park, Sang Heon Song, Eun Young Seong, Ihm Soo Kwak, Harin Rhee, Il Young Kim, Woo Jin Jung, Jong Man Park, Dong Won Lee, Soo Bong Lee, Min Jung Kim, Joo Hui Kim. *Internal Medicine, Pusan National Univ School of Medicine, Busan, Republic of Korea.*

Background: Generally, sympathetic overactivity and impairment of the parasympathetic system are often seen in patients with dialytic CKD, COPD, RA as well as elderly. Also, arterial stiffness and edema have been related with mortality in patients with cardiovascular disease. However, to date, few data regarding autonomic nervous system, vascular stiffness, edema in pre-dialytic CKD was proposed. This study was designed to explore the interrelationship of those parameter in pre-dialytic CKD (G3, 4) and uncover the risk factor related with renal functional deterioration.

Methods: Thirty-three patients were enrolled. Hydration status (extracellular water [ECW]/total body water [TBW]) was determined by bioimpedance analysis. Brachial-ankle pulse wave velocity (baPWV) and neck ultrasonography for carotid plaque and intima-media thickness were conducted for checking up of vascular status. CAN was scored using Ewing's method and we also expressed the standard deviation of normal-to-normal interval (SDNN), low frequency/high frequency ratio (LF/HF ratio). Serial serum creatinine change over a median follow-up of 3 years was used for assessment of renal function.

Results: Of the 33 patients, 14 (42%) have suffered with CAN. Patients with CAN have higher progressive declining rate of renal function, baPWV, systolic BP compared with patients without CAN. The group having declining renal function has higher CAN score, baPWV and lower SDNN compared with preserved renal function group. CAN score correlated positively with ECW/TBW ($r=0.405$, $p=0.019$), mean PWV ($r=0.623$, $p<0.001$) and SBP ($r=0.513$, $p=0.002$). CAN score correlated negatively with declining rate of renal function ($r=-0.471$, $p=0.006$), Hb ($r=-0.659$, $p<0.001$) and albumin ($r=-0.484$, $p=0.004$).

Conclusions: Autonomic nervous dysfunction including lower SDNN and increased arterial stiffness including high baPWV may be important risk factors for deterioration of renal function in pre-dialytic CKD patients. Also, autonomic nervous dysfunction was related with arterial stiffness and edema.

FR-PO547

Inhibition of EGFR Alleviates the Development and Progression of Hyperuricemic Nephropathy in Rats Na Liu,¹ Li Wang,¹ Andong Qiu,² Shougang Zhuang,³ ¹Nephrology, Shanghai East Hospital, Tongji Univ School of Medicine, Shanghai, China; ²School of Life Science and Technology, Advanced Inst of Translational Medicine, Tongji Univ, Shanghai, China; ³Dept of Medicine, Rhode Island Hospital and Brown Univ School of Medicine, Providence.

Background: Hyperuricemia is an independent risk factor for chronic kidney disease and contributes to kidney fibrosis. In this study, we investigated the effect of epidermal growth factor receptor (EGFR) inhibition on the development of hyperuricemic nephropathy (HN) and the mechanisms involved.

Methods: In this experiment, we did Cell Culture and Treatments, processed the establishment of Hyperuricemic nephropathy (HN) model, assessment of serum uric acid, renal Function and other biochemistry index, performed Immunoblot Analysis, Immunohistochemical Staining, as well as ELISA analysis.

Results: In a rat model of HN induced by feeding a mixture of adenine and potassium oxonate, increased EGFR phosphorylation and severe glomerular sclerosis and renal interstitial fibrosis were evident, accompanied by renal dysfunction and increased urine microalbumin excretion. Administration of gefitinib, a highly selective EGFR inhibitor, prevented renal dysfunction, reduced urine microalbumin and inhibited activation of renal interstitial fibroblasts and expression of extracellular proteins. Gefitinib treatment also inhibited hyperuricemia-induced activation of the transforming growth factor- β 1 (TGF- β 1) and nuclear factor- κ B (NF- κ B) signaling pathways and expression of multiple profibrogenic cytokines/chemokines in the kidney. Furthermore, gefitinib treatment suppressed xanthine oxidase activity, which mediates uric acid production, and preserved expression of organic anion transporters 1 and 3, which promotes uric acid excretion in the kidney of hyperuricemic rats.

Conclusions: Thus, blocking EGFR can attenuate development of HN via suppression of TGF- β 1 signaling and inflammation, and promotion of the molecular processes that reduce uric acid accumulation in the body.

FR-PO548

Probiotic and Yogurt Consumption Is Associated with a Lower Prevalence of Albuminuria: A Cross-Sectional Analysis of NHANES Rabi Yacoub, Girish N. Nadkarni, Deepak Kaji, Shanti N. Patel, John C. He, Steven G. Coca, Jaime Uribarri. *Medicine/Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Animal data suggest that probiotic supplements may retard CKD progression. Yogurt is the most widely available probiotic food in the United States. However, the relationship between frequent yogurt consumption or probiotic use, and kidney parameters has not yet been evaluated. We aimed to study this association in the National Health and Nutrition Examination Survey (NHANES) database.

Methods: We utilized NHANES data with reported one year yogurt consumption frequency and probiotic use (2003-2005). The "consumers group" was defined as either

yogurt consumption \geq thrice weekly or regular use of probiotic, and we analyzed its association with albuminuria and eGFR after adjustment for demographic and clinical parameters.

Results: We had complete data on 6853 participants (mean age 48.3 \pm 20.45.2% male), of which, 1559 (20.3%) were frequent consumers and 918 participants (12.2%) had detectable albuminuria (Median=67.1, IQR=41.6-157.1 mcg/mg). Frequent consumers had a trend towards lower mean UACR compared to non-consumers (mean difference [MD]: -12.3, 95% CI -29.8 to 5.2, $P=0.17$) that was attenuated after complete adjustment. On the other hand, frequent consumers had decreased odds of albuminuria (UACR > 30 mcg/mg) compared to non-consumers (adjusted Odds Ratio 0.79; 95% CI 0.63-0.97; $P=0.03$).

	Unadjusted			Adjusted †		
	OR	95% CI	P	OR	95% CI	P
Albuminuria	0.69	0.58-0.84	<0.001	0.79	0.63-0.97	0.03
CKD	0.79	0.65-0.96	0.02	0.89	0.69-1.14	0.34
	MD	95% CI	P	MD	95% CI	P
UACR	-12.3	-29.8 to 5.2	0.17	-0.5	-16.9 to 15.9	0.95
eGFR	1.1	-0.3 to 2.6	0.14	0.6	-0.3 to 1.6	0.21

† Gender, age, race, medical history of hypertension and diabetes, socioeconomic status (family income to poverty index), HgbA1c, BMI, insulin, statin, RAAS blockers use and probiotic use duration

Neither CKD III-V prevalence, nor continuous eGFR was significantly different between the consumers and non-consumers.

Conclusions: We observed an inverse association of probiotic/yogurt consumption and albuminuria in a large, nationally representative general population sample. Future studies evaluating the association between probiotic/yogurt use and kidney diseases are warranted.

FR-PO549

Assessment of Serum Levels of Heavy Metals in Patients with Chronic Kidney Disease of Unknown Etiology Om Prakash Kalra,¹ Akash Gupta,¹ Alpana Raizada,¹ Sunil Agarwal,¹ Basu Dev Banerjee,² ¹Medicine, UCMS and GTB Hospital, Delhi, India; ²Biochemistry, UCMS and GTB Hospital, Delhi, India.

Background: Chronic kidney disease (CKD) encompasses a wide spectrum of different etiological processes associated with abnormal kidney function and gradual progressive decline in glomerular filtration rate. CKD of unknown etiology (CKDu) has emerged as an important entity accounting for approximately 10% of CKD patients worldwide. Of the environmental toxins implicated in causation of CKDu, heavy metals form an important group. In the present study, we estimated the serum levels of lead, cadmium, arsenic and chromium in patients with CKDu and evaluated their role in the etiopathogenesis of CKDu.

Methods: The study was conducted in the Departments of Medicine and Biochemistry at University College of Medical Sciences and GTB Hospital, Delhi from December 2013 - April 2015. It was a case control, cross sectional study. Ninety subjects in the age group 18 - 60 years of either sex were divided into 3 groups: Group I: Healthy controls (n=30), Group II: Individuals satisfying case definition of CKDu (n=30) and Group III: Individuals having CKD of known etiology (CKDk) (n=30). Detailed history, complete physical examination, routine investigations, urine albumin excretion (UAE) estimation was done. Estimation of serum level of heavy metals was done using Atomic Absorption Spectrophotometry.

Results: The median levels of lead, cadmium and chromium were significantly higher in patients of group II and this difference was statistically significant as compared to subjects of group I and III. The median levels of arsenic in patients of group II and III were similar but significantly higher than patients of group I. The levels of arsenic, cadmium and chromium detected in healthy controls (group I) were negligible. UAE in patients of group II and III were similar but significantly higher than patients of group I.

Conclusions: As compared to healthy controls, the serum levels of lead, cadmium, arsenic and chromium were found to be significantly higher in patients of CKDu. The study indicates a possible role of heavy metals in causation of CKDu.

FR-PO550

High Prevalence of Elevated Molybdenum Levels in CKD Patients Guido Filler,^{1,2,3} Vladimir Belostotsky,⁴ Marta Caroline Kobrzynski,¹ Shih-Han S. Huang,^{1,2} Liju Yang,³ ¹Paediatrics, Univ of Western Ontario, London, ON, Canada; ²Medicine, Univ of Western Ontario, London, ON, Canada; ³Pathology and Laboratory Medicine, Univ of Western Ontario, London, ON, Canada; ⁴Paediatrics, McMaster Univ, Hamilton, ON, Canada.

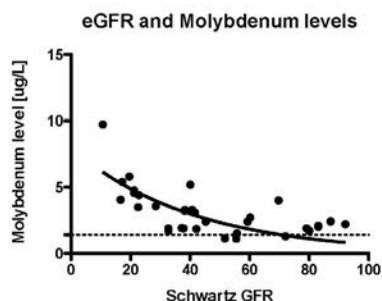
Background: Molybdenum (Mo, atomic number 42) is an essential trace element present in water and is crucial for human survival because four mammalian enzymes harbor a pterin-based Mo cofactor (Moco) at their active site and are Mo-dependent. Mo can be lethal in high doses, and chronic toxicity in animals leads to stunted growth, skeletal abnormalities, anemia, and histological changes in the kidney and liver. There is no information about Mo levels in patients with CKD.

Methods: After approval by the ethics board, and as part of a larger study on zinc supplementation in CKD, we studied 87 plasma Mo and copper (Cu) levels in 50 children with an eGFR < 90 and > 15 mL/min/1.73 m² using the Schwartz formula. Where available,

we also recorded the cystatin C eGFR using the Filler formula in 35 children. Mo and Cu levels were measured using High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS).

Results: The mean Schwartz eGFR was 46±23 and the Cystatin C eGFR was 48±20 mL/min/1.73 m². The median Mo level was 2.26 (interquartile range 1.7, 3.3 ug/L, mean 2.78±1.70 ug/L), significantly higher than the upper reference interval of 1.4 ug/L, and with an exponential increase with lower eGFR.

Figure: The relationship between Schwartz eGFR and plasma Mo levels in 39 patients (initial screening time point for zinc study).



The mean Cu level was 1124±378 ug/mL, not significantly different from the reference interval of 822 to 1201 ug/mL. eGFR was significantly negatively correlated with Mo levels (Spearman r = -0.57, p=0.0002).

Conclusions: With worsening kidney function, Mo levels accumulate, while Cu levels remain unaffected.

Funding: Clinical Revenue Support

FR-PO551

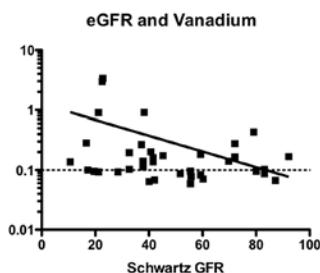
High Prevalence of Elevated Vanadium Levels in CKD Patients
 Guido Filler,^{1,2,4} Vladimir Belostotsky,³ Marta Caroline Kobrzynski,¹ Liju Yang,⁴
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Background: Vanadium (V, atomic number 23) is an essential trace element present in many industrial products, especially in steel, which can be very toxic if levels are too high. The excretion of vanadium by the kidneys is rapid with a biological half-life of 20-40 hours in the urine. Chronic poisoning is associated with respiratory symptoms, nervous disturbances, vegetative symptoms, tremors, palpitation of the heart, extrasystoles, anemia, leukopenia, and punctate basophilia of the erythrocytes. While adult data suggest that V is accumulating in dialysis patients, there is no information about V levels in patients with CKD.

Methods: After approval by the ethics board, and as part of a larger study on zinc supplementation in CKD, we studied 87 plasma V levels in 50 children with an eGFR < 90 and > 15 mL/min/1.73 m² using the Schwartz formula. Where available, we also recorded the cystatin C eGFR using the Filler formula in 35 children. V levels were measured using High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS).

Results: The mean Schwartz eGFR was 46±23 and the Cystatin C eGFR was 48±20 mL/min/1.73 m². The mean V level was 0.117 (interquartile range 0.082, 0.1840 ug/L, mean 0.1170±0.4899 ug/L), significantly higher than the upper reference interval of 0.1 ug/L (p=0.0057), and with a trend towards exponential increase with lower eGFR (r=0.3075, p=0.0604).

Figure 1: The relationship between Schwartz eGFR and plasma V levels in 50 patients (initial screening time point for zinc study).



Conclusions: We observed a high prevalence of elevated V levels in the CKD patients. With worsening kidney function, V levels accumulate.

Funding: Clinical Revenue Support

FR-PO552

Chronic Nicotine (Ch-Nic) Exacerbates Suppressor Angiotensin II (SP-AngII) Induced Renal Dysfunction in Part via the Renal Sympathetic Nervous System
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Background: Ch-Nic exacerbates SP-AngII-induced renal dysfunction and vascular remodeling while having minimal changes on blood pressure. However, the mechanisms are incompletely understood. Because Ch-Nic activates the renal sympathetic nervous system, we hypothesized that this activation contributes to nicotine's deleterious effects on SP-AngII-induced renal dysfunction and injury.

Methods: Sprague Dawley rats underwent either sham or renal denervation (RD) surgery and then subdivided to get nicotine (12 g/ml) or vehicle (saccharine 2%). These were randomized to get either SP-AngII (SQ, 200ng/kg/min) or vehicle (saline). Hemodynamics were measured in anesthetized animals and tissue collected for biochemical analysis.

Results:

	Systolic BP (mmHg)	RVR (ml/min/mmHg)	Pl. Creatinine (mg/dl)	NGAL UI/mg creat	TGF (ng/µg protein)
Ct+Sham	107± 6	15± 0.7	0.7± 0.02	0.26± 0.03	10± 1
CT+ RD	107± 5	14± 1	0.7± 0.02	0.3± 0.4	9.5± 1
Ch-Nic+ Sham	108± 5	14± 0.2	0.9± 0.03	0.5± 0.06	20± 0.6
Ch-Nic+RD	101± 3	15± 0.7	0.7± 0.04	0.4± 0.02	16± 1.6
SP-AngII+Sham	162± 4*†	23± 1.3*†	2.4± 0.1*†	4.3± 0.4*†	29± 1.3*†
SP-AngII+RD	123± 3*#	17± 0.8#	2± 0.07#†	2.7± 0.2*#†	25± 1.3*†
Sp-AngII+Ch-Nic+Sham	172± 4*#	31± 1.2*#†	3± 0.1*#†	8.3± 0.4*#†	40± 1.4*#†
SP-AngII+CH-NIC+RD	134± 2*†λ	18± 0.2λ	2.4± 0.04*†λ	3.7± 0.3*#†	27± 1.2*#†λ

Conclusions: Renal denervation ameliorated SP-AngII-induced HTN, renal dysfunction, inflammation and injury. While RD did not appear to provide additional benefit to blood pressure control in Ch-Nic+SP-AngII group, it provided protection against the renal effects of Ch-Nic in the SP-AngII rats. These results support a role for the sympathetic nervous system in SP-AngII-induced renal dysfunction, as well as in the exacerbating effect of Ch-Nic on SP-AngII mediated renal dysfunction.

FR-PO553

Elevated Plasma Chymase Is Associated with Risk of Chronic Kidney Disease
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Background: Chymase is the primary enzyme that mediates angiotensin II formation independent of angiotensin-converting enzyme and also play a role in activating transforming growth factor-beta and matrix metalloproteinase-9. Experimental studies suggest that it may cause renal and cardiac fibrosis. However, the association of circulating chymase with chronic kidney disease (CKD) is not well studied.

Methods: We investigated the association of chymase and the risk of CKD in 163 CKD patients and 186 controls without CKD. CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² or presence of albuminuria. Multivariable analyses were used to examine the relationship of plasma chymase and CKD.

Results: The multivariable-adjusted medians (interquartile ranges) were 1.6 (1.1, 2.2) in patients with CKD vs. 1.2 (0.7, 1.9) pg/mL in controls without CKD (p=0.002 for group difference) after adjusting for age, gender, race, physical activity, smoking, drinking, systolic blood pressure, glucose, low-density lipoprotein cholesterol, body mass index, and history of cardiovascular disease. After adjustment for the above risk factors, the odds ratio for CKD comparing the highest to the lowest tertile of chymase was 2.85 (95% confidence interval, 1.41-5.76).

Conclusions: These data indicate that elevated circulating chymase is associated with risk of CKD.

Funding: Other NIH Support - the National Center for Research Resources, National Institutes of Health, Bethesda, MD.

FR-PO554

Methionine Sulfoxide Reductase A (MsrA) Protects Progression of Kidney Fibrosis After Unilateral Ureteral Obstruction Mi Ra Noh,¹ Jee in Kim,² Kwon Moo Park.¹ ¹Dept of Anatomy and BK21 Plus, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; ²Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Republic of Korea.

Background: Methionine sulfoxide reductase A (MsrA) reduces oxidized methionine and protects cells against oxidative stress. Oxidative stress accelerates kidney fibrosis. Here, we investigated the role of MsrA in unilateral ureteral obstruction (UO)-induced kidney fibrosis using MsrA gene-deleted mice.

Methods: MsrA^{+/+} and MsrA^{-/-} male mice were subjected to UO. Kidneys were harvested 5 days after the UO surgery.

Results: UO reduced MsrA expression and activity in the kidney. UO resulted in expansion of interstitial area with increased collagen deposition. In addition, UO increased the levels of α -smooth muscle actin and collagen III expression. MsrA deficiency significantly enhanced collagen deposition and expression of those proteins. UO resulted in the increase of hydrogen peroxide (H₂O₂) formation and lipid peroxide in both MsrA^{+/+} mouse kidneys and MsrA^{-/-} mouse kidneys, and these increases were significantly higher in MsrA^{-/-} mouse kidneys than in MsrA^{+/+} mouse kidneys. Furthermore, post-UO increases in the oxidized glutathione ratio to total glutathione were significantly greater in MsrA^{-/-} mouse kidneys than in MsrA^{+/+} mouse kidneys. Number of F4/80 expressing cells increased in the kidney after UO. These increase of F4/80 expressing cells were greater in MsrA^{-/-} mouse kidneys than in MsrA^{+/+} mouse kidneys. Levels of Ly6G, a marker of granulocyte, were also higher in MsrA^{-/-} mouse kidneys than in MsrA^{+/+} mouse kidneys.

Conclusions: In conclusion, MsrA protects kidney against UO-induced fibrosis, suppressing oxidative stress and inflammatory responses.

Funding: Government Support - Non-U.S.

FR-PO555

The Soluble Urokinase-Type Plasminogen Activator Receptor Serum Levels in Adults with Nephrotic Syndrome Qiuling Fan. *Nephrology, The First Hospital of China Medical Univ.*

Background: The serum levels of soluble urokinase type fibrinolytic enzyme activators receptor (suPAR) in adults with nephrotic syndrome were analyzed.

Methods: The serum levels of soluble urokinase type fibrinolytic enzyme activators receptor (suPAR) in 70 nephrotic syndrome patients with membranous nephropathy, diabetic nephropathy group, lupus nephritis, minimal change kidney disease and focal segmental glomerular sclerosis group was detected by enzyme-linked immunosorbent assay. The relationship between the the clinical parameters and suPAR levels were analyzed.

Results: Serum soluble urokinase receptor levels of nephrotic syndrome patients are significantly higher than the normal control group (P < 0.01). The serum suPAR levels of FSGS and MN patients were significant higher than MCD patients (P < 0.05). Serum suPAR level was positively correlated with age, serum creatinine, blood urea nitrogen (rs=0.401 p=0.001;rs=0.286 p=0.016;rs=0.249 p=0.037;rs=0.245 p=0.041;rs=0.247 p=0.039), and negatively correlated with eGFR (rs=-0.265 p=0.026;rs=-0.237 p=0.048;rs=-0.309 p=0.009).

Conclusions: Serum suPAR level was positively correlated with age, serum creatinine, blood urea nitrogen, and negatively correlated with eGFR. The serum suPAR levels of FSGS and MN patients were significant higher than MCD patients and may be a potential marker to distinguish FSGS and MCD.

FR-PO556

Urinary Sodium: Impact on Blood Pressure and Progression of Chronic Kidney Disease Adriano Luiz Ammirati, Maria Eugenia F. Canziani. *Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: Chronic kidney disease (CKD) is characterized by chronicity and progression of renal damage. The presence of hypertension is relates to the progression of renal damage. Diets high in salt have been associated with an increased risk of hypertension. Sodium analysis in the urine of 24 h is considered the standard method to estimate the daily intake of this mineral. The aim of this study was to evaluate the impact of sodium intake estimated by urinary sodium in the urine of 24 hours (Nau24hs) on renal outcomes and their impact on hypertension.

Methods: Data were collected from medical records of 118 patients with CKD in conservative treatment, that had one Nau24hs dosage and a follow-up of at least five years. Information collected initially and after 5 years were: demographics, etiology of CKD; comorbidities, blood pressure; routine laboratory tests and estimated creatinine clearance (EPI-CKD). The Nau24hs values were classified into two groups by the median and also divided into tertiles and compared with the rate of progression of CKD (fall of the estimated clearance greater than 20% at 5 years) and the change in blood pressure.

Results: Patients had a mean of 186 ± 64 mEq/L of Nau24hs which represented a high sodium intake (10 grams; 96% of patients with sodium intake greater than 6 grams). Patients with Nau24hs > 170 mEq/L had higher systolic blood pressure and those with Nau24hs > 200 mEq/L had higher systolic and diastolic blood pressure when compared to other patients. In addition, patients with higher Nau24hs present significant decrease in systolic blood pressure over 5 years. The decrease in creatinine clearance over 5 years (29% of patients) were more frequent in diabetics and those who did not use converting enzyme inhibitors and are also associated with the presence of proteinuria. There was no association of Nau24hs with the progression of renal dysfunction.

Conclusions: In patients with stable and low rate of CKD progression urinary sodium was associated with high blood pressure, but was not associated with more pronounced worsening of long-term renal function, probably because these patients were treated more intensively over the pressure control.

FR-PO557

Risk of End-Stage Renal Disease with Longitudinal Change in Filtration Markers Casey Rebholz, Lesley Inker, Yuan Chen, Meredith C. Foster, John H. Eckfeldt, Paul L. Kimmel, Vasan S. Ramachandran, Harold I. Feldman, Chi-yuan Hsu, Andrew S. Levey, Josef Coresh. *Chronic Kidney Disease Biomarkers Consortium.*

Background: Change in estimated glomerular filtration rate (eGFR) based on creatinine has been proposed as a surrogate outcome in clinical trials of chronic kidney disease (CKD). Risk of end-stage renal disease (ESRD) associated with change in other kidney filtration markers has not been previously assessed in chronic kidney disease (CKD) populations.

Methods: We conducted prospective analyses of the Modification of Diet in Renal Disease (MDRD; N=840; mean age 52 years) and African-American Study of Kidney Disease and Hypertension (AASK; N=1,094; mean age 55 years) trials. Creatinine, cystatin C, b₂-microglobulin, and β -trace protein levels were measured in serum samples collected at baseline and at the 24-month follow-up visit and were expressed using CKD-EPI eGFR equations. Multivariable Poisson regression was used to estimate associations between continuous percent change in eGFR for each marker (alone and in combination) with subsequent risk of developing ESRD. Seemingly unrelated regression was used to compare the strength of risk estimates from different models.

Results: In MDRD and AASK, respectively, there were 310 and 161 incident ESRD cases during a median follow-up of 4.7 and 7.1 years. Percent change in eGFR from the four filtration markers was significantly associated with incident ESRD risk (Table). The average of percent change in eGFR based on all four filtration markers was more strongly associated with ESRD risk than percent change in eGFR-creatinine alone.

Table. Risk of Incident ESRD Associated with Percent Change in Filtration Markers in MDRD and AASK

Filtration Marker	MDRD		AASK	
	IRR† (95% CI) per 30% decline	P-value	IRR† (95% CI) per 30% decline	P-value
eGFR-Cr	2.09 (1.78, 2.45)	<0.001	3.40 (2.82, 4.10)	<0.001
eGFR-Cys	2.58** (2.11, 3.16)	<0.001	4.33* (3.40, 5.50)	<0.001
eGFR- β Tp	3.59*** (2.83, 4.56)	<0.001	6.87*** (5.08, 9.28)	<0.001
eGFR- β_2 M	2.55** (2.11, 3.08)	<0.001	3.96 (3.17, 4.94)	<0.001
Average of 4 Markers	2.89*** (2.35, 3.55)	<0.001	4.74*** (3.71, 6.05)	<0.001

AASK, African-American Study of Kidney Disease and Hypertension; β_2 M, β_2 -microglobulin; β Tp, β -trace protein; CI, confidence interval; Cr, creatinine; Cys, cystatin C; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IRR, incidence rate ratio; MDRD, Modification of Diet in Renal Disease

†Adjusted for age, sex, race, body mass index, systolic blood pressure, diabetes, total cholesterol, first eGFR for the respective filtration marker

* p<0.05 from seemingly unrelated regression comparing IRR for the respective marker vs. IRR for eGFR-Cr

** p<0.01 from seemingly unrelated regression comparing IRR for the respective marker vs. IRR for eGFR-Cr

*** p<0.001 from seemingly unrelated regression comparing IRR for the respective marker vs. IRR for eGFR-Cr

Conclusions: Decline in kidney function over two years, assessed using eGFR-creatinine as well as multiple other filtration markers, is associated with ESRD. Novel filtration markers (cystatin C, b₂-microglobulin, β -trace protein) may provide additional information about CKD progression beyond creatinine.

Funding: NIDDK Support

FR-PO558

Validation and Clinical Associations of a Predictive Model for Progression to Renal Replacement Therapy: A Retrospective Cohort Study James Ritchie,¹ Afshan Ahmed,¹ Olivier J. Wouters,² Darren Green,¹ Smeeta Sinha,¹ Donal J. O'Donoghue,¹ Philip A. Kalra.¹ ¹Salford Royal NHS Foundation Trust, United Kingdom; ²London School of Economics and Political Science, United Kingdom.

Background: Timely planning for initiation of renal replacement therapy (RRT) is vital. Despite existing, validated risk-prediction models, RRT preparation is often based upon clinical judgment. Here, we consider the benefits of applying an existing model (Tangri et al. JAMA, 2011) in a UK secondary care population.

Methods: Patients with ≥ 5 years of potential follow-up were identified from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). 5-year RRT risk was estimated using a logistic regression model incorporating age, gender, eGFR, albuminuria, PO₄, Ca²⁺, HCO₃⁻, and albumin.

Results: 728 patients were included in this analysis (median follow-up 4.4 [IQR 2.4-5.6] years), with 118 patients (16%) progressing to RRT. Mean baseline age was 64 \pm 14 years and eGFR 34 \pm 14 ml/min/1.73m².

Risk was right skewed, with 328 (45%) of patients having a 5-year risk of <5%. 80 patients (11%) had a 5-year RRT risk of >50%. The overall area under the curve was 0.89. This did not vary by primary disease: glomerulonephritis (0.87); pyelonephritis (0.95); polycystic kidney disease (0.91); and diabetic nephropathy (0.88).

In higher-risk groups, a greater proportion of patients commenced RRT using peritoneal dialysis, and a smaller proportion commenced RRT as an in-patient. The proportion of patients transplant listed at the time of starting RRT was greater in the lower risk group than the higher risk group.

Risk group and number of patients	Number starting RRT	Months to RRT	In-patient start	Transplant eligible / listed	Peritoneal dialysis
LOW: <20% n=538 (73%)	23 (4%)	48(12)	14%	81% / 60%	18%
MEDIUM: 20 - 40% n=91 (13%)	32 (35%)	37(15)	9.5%	77% / 54%	22%
HIGH: >40% n=98 (14%)	64 (64%)	20(14)	5.7%	72% / 49%	30%

Time to RRT presented as mean (standard deviation). Percentages represent the proportion of patients within that risk group.

Conclusions: The risk model performed well in our patient population and was disease agnostic. Further work will consider potential causes of the differences in modality and in-patient starts between risk groups.

FR-PO559

Do Electronic Health Records Contain Enough Information to Calculate End-Stage Renal Disease Risk Scores? C. Blake Cameron,¹ Benjamin Neely,² Mark Dakkak,¹ Uptal D. Patel,^{1,2} L. Ebony Boulware.¹ ¹Duke Univ School of Medicine; ²Duke Clinical Research Inst, Durham, NC.

Background: Physicians often can't predict which patients with CKD will progress to end-stage renal disease (ESRD) in the near future, contributing to poor outcomes and expensive care. It is unknown to what extent validated ESRD prediction models can be applied to real-world electronic health records (EHRs) for use by population health management programs to target those at greatest risk for renal progression.

Methods: We characterized EHR availability of laboratory results (urine albumin-to-creatinine ratio and serum albumin, bicarbonate, calcium, and phosphorous) required for use in a validated ESRD risk prediction model at Duke University. We identified outpatients with at least two eGFR results, and we defined CKD as the presence of at least two eGFR results <60 mL/min/1.73m² separated by ≥ 90 days.

Results: Among 151,097 eligible patients, the median age was 59.4 years, 85,533 (56.6%) were female, 45,425 (30.1%) were African-American, and 31,581 (20.9%) had evidence of CKD stages 3-5. Few CKD patients had results for urine albumin-to-creatinine ratio (n=3,487, 11.0%) or serum phosphorus (n=9,696, 30.7%), but more had serum albumin (n=28,192, 89.3%), bicarbonate (n=24,650, 78.1%), or calcium (n=31,463, 99.6%) results. Although more lab results were available among patients with worse CKD (p<0.001), the full set of results needed to calculate ESRD risk were available for only a few (n=1,407, 4.5%) patients.

Result Availability	GFR <15 (n=2,061)	GFR 15-29 (n=3,909)	GFR 30-44 (n=10,144)	GFR 45-59 (n=15,467)
Serum phosphorus	1,695 (82.2%)	2,048 (52.4%)	3,088 (30.4%)	2,865 (18.5%)
Urine ACR	157 (7.6%)	570 (14.6%)	1,302 (12.8%)	1,458 (9.4%)
All 5 results present	123 (6.0%)	393 (10.1%)	551 (5.4%)	340 (2.2%)

Conclusions: Few patients with CKD had the full set of laboratory results needed to employ a validated ESRD risk prediction model for population health management. Urine ACR and serum phosphorus results were often unavailable. To improve risk stratification, efforts are needed to more frequently obtain these laboratory tests during clinical care or to develop refined models that use more readily available information.

Funding: Other NIH Support - Duke Training Grant in Nephrology - 5T32DK007731

FR-PO560

Effect and Safety of Sofosbuvir (SOF) Containing Direct-Acting Antiviral (DAA) Hepatitis C Virus (HCV) Therapy in a Real-World Population with Chronic Kidney Disease (CKD) Guillermo Ortiz,¹ Gregory L. Hundemer,¹ Elke Backman,² Ravi I. Thadhani,¹ Raymond T. Chung,³ Meghan E. Sise.¹ ¹Nephrology Div, MGH, Boston, MA; ²Pharmacy, MGH, Boston, MA; ³Gastrointestinal, MGH, Boston, MA.

Background: Early trials of SOF-based regimens excluded patients with CKD, thus little is known about safety, efficacy, and effect on kidney function.

Methods: We retrospectively evaluated 72 patients with CKD starting DAA treatment (tx) between 11/2013-12/2014. CKD was defined by average eGFR <60mL/min or albuminuria >30mg/g 6 months prior to tx. Safety, tolerability and laboratory results were assessed by chart review. Models predicting sustained virological response (SVR) were performed.

BL Predictors	Univariate		Multivariable	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age, per 10 years	1.25 (0.58,2.67)	0.57	0.68 (0.16,2.85)	0.60
Female	3.10 (0.62,15.55)	0.17	4.20 (0.41,43.45)	0.23
Black	0.44 (0.11,1.79)	0.25	0.22 (0.03,1.62)	0.14
HCV Genotype 3	0.08 (0.01,0.84)	0.04*	0.07 (0.00,5.56)	0.23
Early discontinuation	0.11 (0.02,0.69)	0.02*	0.06 (0.00,0.90)	0.04*
Cirrhosis	1.85 (0.51,6.77)	0.35	1.00 (0.17,5.89)	1.00
Prior HCV tx	0.58 (0.17,1.99)	0.39	1.17 (0.20,6.88)	0.87
Liver or kidney transplant	1.02 (0.29,3.54)	0.98	0.34 (0.04,2.69)	0.31
Baseline eGFR, per 10 ml/min decrease	1.79 (1.27,,2.50)	<0.01*	2.10 (1.22,3.63)	0.01*

Results: Subjects were aged 61 \pm 8 years, 60% white, 22% black, 12% Hispanic, and 74% male. 50% were diabetic, 39% cirrhotic, 54% HCV tx naïve, 39% had prior liver or kidney transplant, and 7% were HIV/HCV coinfectd. DAA regimens were: SOF/simeprevir 50%, SOF/ledipasvir 13%, SOF/ribavirin 28%, other SOF regimens 10%. 8% had a transient creatinine rise ≥ 0.5 mg/dL during tx. Average eGFR on tx was similar to baseline [mean (95% CI): 57 (52-62) vs. 58 (53 - 63) mL/min, respectively P=0.26]. SVR was 77% (95% CI 66-88). 76% experienced at least 1 adverse effect (AE); only 5 (7%) discontinued tx due to an AE.

Conclusions: SOF-containing DAA regimens are effective and relatively safe in patients with CKD. Although AEs were common, serious AEs or significant nephrotoxicity were rare. Lower eGFR at baseline predicted an increase likelihood of HCV cure with SOF-based regimens.

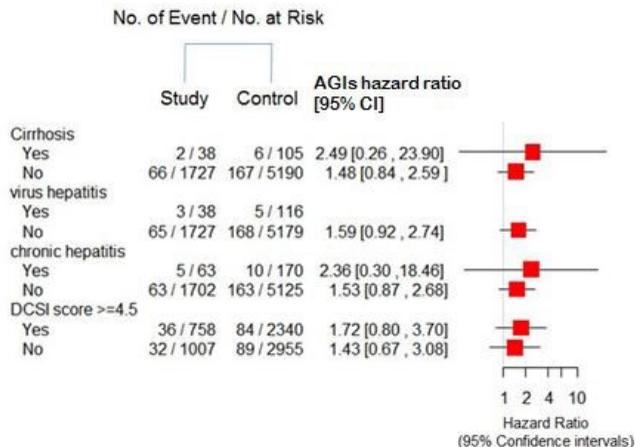
FR-PO561

Risk of Liver Injury After α -Glucosidase Inhibitors Therapy in Advanced Chronic Kidney Disease Patients: A Population-Based Study Vincent Wu,¹ Chih-chin Kao,² Taomin Huang.¹ ¹Internal Medicine, National Taiwan Univ Hospital, Taipei; ²Internal Medicine, Taipei Medical Univ Hospital.

Background: α -glucosidase inhibitors (AGIs) are commonly used to control postprandial blood glucose. However, AGIs-related liver injury has been reported, but whether the relationship of AGIs and liver injury applies to advanced chronic kidney disease (CKD) patients remains uncertain.

Methods: In the nationwide case-control study, we recruited advanced diabetic CKD patients, who has taken AGIs from January 1, 2000 through December 31, 2010 as cases and matched 5295 matched controls. Recent and former AGIs users were defined as patients who received the AGIs prescription 30-60 days and 30-210 days before the event of liver injury. The risk of AGIs-related liver injury was examined via time-dependent cox proportional hazards model and stratified analysis.

Results: The age of enrollee is 63 \pm 11 years and nearly 51% is men. Liver injury developed in 3.9% of cases and 3.3% of control patients. Patients who received insulin treatment (p=0.03), had chronic liver disease (p=0.01) were predictive to liver injury. AGIs use did not increase the risk of liver injury in advanced CKD patients (p= 0.22), both among recent users (P=0.28) or former users (P=0.22). The stratified analysis showed no increased risk of liver injury in virus hepatitis, liver cirrhosis, subsequent end stage renal disease or patients who has diabetic related comorbidities. (all p> 0.05) .



Conclusions: Available evidence supports expansion of AGIs use in patients with advanced CKD, without increased risk of liver injury. Neither accumulated dose-dependent effect of AGIs, or subsequent ESRD will aggravate AGIs-associated liver injury. Further randomized controlled trials are warranted to confirm our results.

Funding: Government Support - Non-U.S.

FR-PO562

Add-On Renoprotective Effect of Pentoxifylline in Pre-Dialysis Advanced Chronic Kidney Disease Treated with Renin-Angiotensin-Aldosterone System Blockade – A Nationwide Database Analysis Ko-Lin Kuo,¹ Szu-Chun Hung,¹ Jia-sin Liu,² Der-Cherng Tarn,³ ¹Taipei Tzu Chi Hospital, Taiwan; ²National Health Research Insts, Taiwan; ³Taipei Veterans General Hospital, Taiwan.

Background: Pentoxifylline decreases proteinuria in patients with glomerular disease due to its anti-inflammatory and anti-fibrotic properties. A combination therapy of pentoxifylline with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) decreased proteinuria and the glomerular filtration rate (GFR) decline in early chronic kidney disease (CKD). Whether adding pentoxifylline to ACEI/ARB provides additional benefits on renal outcome or survival is unclear in CKD stage 5 patients who have not yet received dialysis (CKD 5 ND).

Methods: A prospective cohort study was conducted based on the Taiwan National Health Insurance Research Database. From January 1, 2000 to June 30, 2009, we enrolled 14,117 CKD 5 ND patients with serum creatinine levels >6 mg/dL and hematocrit levels <28% and who have been treated with ACEI/ARB. All patients were further divided into two groups with or without pentoxifylline within 90 days after starting erythropoiesis-stimulating agent therapy (index date). Patient follow-up took place until dialysis, death before initiation of dialysis or December 31, 2009.

Results: With a mean follow-up of 12 months, 9,867 patients (69.9%) required long-term dialysis and 2,805 (19.9%) died before progression to end-stage renal disease requiring dialysis. After propensity score-matching, add-on use of pentoxifylline was associated with a lower risk for long-term dialysis or death in those treated with ACEI/ARB (HR, 0.94; 95% CI, 0.90-0.99) or ARB alone (HR, 0.91; 95% CI, 0.85-0.97).

Conclusions: Pentoxifylline exhibited an add-on renoprotective effect in reducing the risk for long-term dialysis in CKD 5 ND patients who received renin-angiotensin-aldosterone system blockade. Randomized studies are needed to validate this association.

FR-PO563

Novel Therapy Regimens Have Reduced the High Risks of Bladder and Haematological Malignancies in ANCA-Associated Vasculitis Chinar Rahmattulla,¹ Annelies Evaline Berden,¹ Sophie-charlotte Wakker,¹ Marlies Reinders,¹ Ernst C. Hagen,² Ron Wolterbeek,¹ Jan A. Brujin,¹ Ingeborg M. Bajema,¹ ¹Leiden Univ Medical Center; ²Meander Medical Center Amersfoort.

Background: The introduction of immunosuppressive therapy has dramatically improved the prognosis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). As a result, attention has shifted to long-term complications in patients. In this study, we investigate the incidence of malignancies in AAV patients. Additionally, we investigate the effect of therapy on malignancy incidence.

Methods: We included patients with histopathologically-proven AAV diagnosed at a large university hospital. Malignancy incidence was assessed with the Dutch National Pathology Database, which covers all the histologically confirmed malignancies diagnosed in The Netherlands. We used the Netherlands Cancer Registry incidence rates for comparing the malignancy incidence in our AAV cohort to that of the general Dutch population.

Results: Thirty-six of 138 patients with AAV developed a total of 85 malignancies during a mean follow-up of 9.7 years. We observed 61 non-melanoma skin cancers (NMSCs), three colon carcinomas, three breast carcinomas, three prostate carcinomas, two lung carcinomas, two soft tissue sarcomas, two unknown primary malignancies, and

a variety of malignancies that occurred only once. The gender-, age-, and calendar year-adjusted malignancy risk was 2.21-fold (95%CI: 1.64–2.92) higher than that of the general population. Only the incidence of NMSCs was significantly increased compared to the general population (standardized incidence ratio: 4.23, 95%CI: 2.76–6.19). Malignancy risk was associated with the duration of cyclophosphamide therapy, and was not increased in patients that received cyclophosphamide for less than 1 year.

Conclusions: AAV patients have a higher risk of malignancies than the general population, but this risk is accounted for solely by NMSCs. Throughout the years, the risk of other malignancies – specifically bladder and haematological malignancies – has decreased in patients with AAV. This finding reflects the beneficial results of ongoing efforts to reduce cyclophosphamide exposure by developing new therapy regimens.

FR-PO564

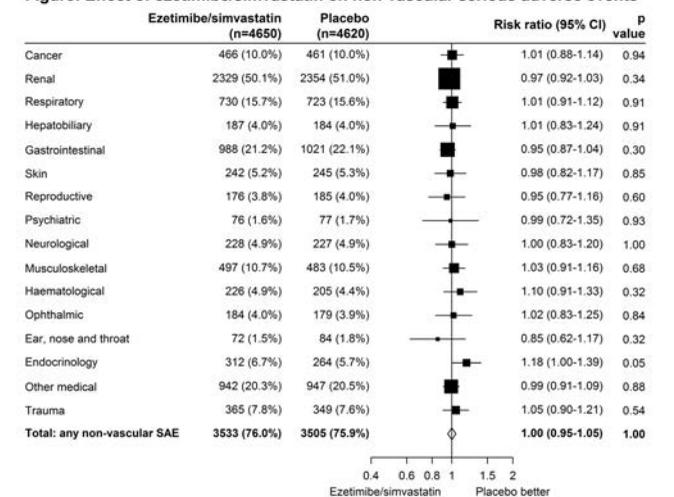
Effect of Lowering LDL-Cholesterol with Simvastatin plus Ezetimibe on Non-Vascular Outcomes in Patients with Chronic Kidney Disease (CKD): Results from the Study of Heart and Renal Protection (SHARP) Christina A. Reith, Natalie Staplin, William G. Herrington. *On behalf of the SHARP Collaborative Group. CTSU, Univ of Oxford.*

Background: The Study of Heart and Renal Protection (SHARP) was a randomized placebo-controlled trial of LDL cholesterol (LDL-C)-lowering among 9270 patients with CKD which showed that combination therapy with ezetimibe 10mg/ simvastatin 20mg (E/S) reduced vascular events with no significant adverse effects on muscle, hepatobiliary outcomes or cancer. However, assessment of the effects of lowering LDL-C on other non-vascular outcomes has not been extensively explored in patients with CKD.

Methods: All post-randomization serious adverse events (SAEs) were routinely recorded. Post-hoc intention-to-treat analyses were performed of the effect of allocation to treatment on time to first non-vascular SAE by system of disease with sub-categories.

Results: During 4.9 years' median follow-up, similar numbers of participants in the two groups experienced non-vascular SAEs overall (3533 [76.0%] E/S vs 3505 [75.9%] placebo; risk ratio [RR] 1.00, 95% CI 0.95-1.05). After due allowance for multiplicity, there was no evidence of any significant hazard of E/S on non-vascular SAEs by system of disease. Within the class of endocrinology SAEs, there were no significant effects of E/S on any particular individual category of SAE: new-onset diabetes (172 [4.8%] E/S vs 162 [4.5%] placebo; RR 1.06, 95% CI 0.86-1.32 among 3596 vs 3580 participants without diabetes at baseline), diabetes-related complications (136 [2.9%] E/S vs 126 [2.7%] placebo; RR 1.08, 95% CI 0.84-1.37), and other endocrine disorders (58 [1.2%] E/S vs 39 [0.8%] placebo; RR 1.47, 95% CI 0.99-2.19).

Figure: Effect of ezetimibe/simvastatin on non-vascular serious adverse events



Conclusions: In the SHARP trial, allocation to ezetimibe 10mg plus simvastatin 20mg reduced vascular events with no evidence of significant non-vascular hazards.

Funding: Pharmaceutical Company Support - Merck/Schering-Plough Pharmaceuticals (North Wales, PA, USA), Government Support - Non-U.S.

FR-PO565

Association of β-Blocker Therapy with Renal Outcomes in CKD Patients without prior Cardiovascular Disease Naohiko Fujii,¹ Takayuki Hamano,² Yoshitsugu Obi,³ Yoshitaka Isaka,² ¹Univ of Pennsylvania, Philadelphia, PA; ²Osaka Univ, Suita, Osaka, Japan; ³Univ of California, Irvine, Irvine, CA; ⁴Osaka General Hospital, Osaka, Japan.

Background: Sympathetic overactivity due to impaired kidney function can deteriorate hypertension, renal failure, and cardiovascular disease (CVD) among CKD patients. Mortality benefit of its antagonist, β-blocker (BB), has been shown in patients with prior CVD; however, such evidences are scarce in CKD patients without CVD. Our aim is to evaluate the association between BB and renal outcomes in such patients.

Methods: We extracted 340 predialysis CKD patients without prior CVD but with drug information at baseline from a Japanese CKD cohort (OVIDS-CKD, N=738). The primary

endpoint was a composite of Cr doubling, initiation of RRT, and death. We performed Cox proportional hazards analyses to estimate the hazards ratio (HR) of BB use at baseline adjusting for other parameters, such as age, sex, eGFR, proteinuria, diabetes, BMI, blood pressure, the number of anti-hypertensive drugs, ACEi/ARB use, Hb, Alb, corrected Ca, iP, and FGF23. We also employed 1:k (k = 1-6) propensity-score full matching, where one BB user matched to at most k non-users.

Results: BB users showed significantly-lower eGFR, more proteinuria, higher BMI, more anti-hypertensive drugs, lower Alb, higher 1-84 PTH, higher FGF23, and lower 25OHD levels, most of which suggested a poor risk for CVD at baseline. During a median follow-up of 4.4 years, 109 patients reached the outcome. Of those, 12 patients died before RRT, 71 reached a doubling of Cr, and 26 started dialysis. A multivariable Cox model with covariates that were significantly-different between BB users and non-users at baseline showed non-significant HR of 1.58 (C.I. 0.86 – 2.90). We also evaluated a fully-adjusted model and a parsimonious model with a stepwise backward-elimination method; however, the results remained non-significant. The 1:k (k=1-6) full matching using propensity score did not show significant results, either. (0.93 (0.52 – 1.68)).

Conclusions: The BB therapy was not associated with renal outcomes in CKD patients without prior CVD. Confirmation in a larger study is required.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin

FR-PO566

Lactobacillus plantarum 299v Reduces the Incidence of Clostridium difficile Infection in Patients Treated with Antibiotics in the Nephrological and Transplantation Department Marcin Adamczak, Agata Kujawa-Szewieczek, Katarzyna Kwieciec, Sylwia Malgorzata Dudzicz, Magdalena Gazda, Andrzej Wiecek. *Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.*

Background: Lactobacillus plantarum 299v (LP299v) has been introduced into the clinical practice in order to reduce gastrointestinal symptoms during antibiotic exposure. However it remains controversial whether or not probiotics are also effective in the prevention of Clostridium difficile infections (CDI) among patients receiving antibiotics. The aim of this clinical, retrospective, single-centre study was to analyze the C.difficile infections among patients receiving antibiotics and hospitalized in the period before and after initiation of LP299v routine use, as a prevention of CDI, in the nephrology and transplantation ward.

Methods: Among 3533 patients hospitalized in Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia in Katowice during two years (October 2012 – October 2013 and December 2013 – December 2014) 23 patients with CDI were diagnosed and enrolled in this study. Since November 2013 prevention of C. difficile infection with the oral use of LP299v was performed in all patients treated with antibiotics and who were at a high risk of developing CDI (patients after organ transplantation and receiving immunosuppressive drugs for any other reasons). For the further analysis the observation period was divided into two twelve-months intervals before (October 2012 to October 2013) and after initiation of LP299v use as the prophylactic manoeuvre against CDI (December 2013 to December 2014).

Results: It was found a significant (p=0.0001) reduction of the number of cases of C. difficile infection after beginning of LP299v routinely used (n=2; 0.11% of all hospitalized patients) compared with the previous twelve-months period of observation (n=21; 1.21% of all hospitalized patients).

Conclusions: Routine use of Lactobacillus plantarum 299v during treatment with antibiotics may prevent C. difficile infection, particularly in patients at high risk of CDI in the nephrology and transplantation ward.

Funding: Government Support - Non-U.S.

FR-PO567

In Patients with Chronic Kidney Disease, Comanagement by Nephrologists Is Associated with Lower Risk of Medication Errors Justin XG Zhu, Danielle Marie Nash, Eric Mearthur, Alexandra Farag, Amit X. Garg, Arsh Jain. *London Health Sciences Centre, London, ON, Canada.*

Background: Patients with chronic kidney disease (CKD) are commonly prescribed drug doses that are excessive for their kidney function. Many CKD patients are followed solely by a family physician. We wish to determine whether care by both a nephrologist and family physician (i.e. comanagement) versus family physician alone is associated with lower risks of inappropriate antibiotic dosing in patients with stage 4 or 5 CKD.

Methods: A retrospective case-control study was conducted, among individuals aged >66 years, with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² using linked healthcare databases from 2003-2014. Cases were antibiotic prescriptions dosed inappropriately, whereas controls were prescriptions dosed appropriately. Exposure was comanagement, defined as at least one outpatient visit with a nephrologist in the 1 year prior to antibiotic prescription. A multivariable logistic regression model was used to determine the independent association between comanagement and inappropriate dosing.

Results: Of 21,848 eligible prescriptions studied, 64% were inappropriately dosed. The patients were 82 (IQR 76-87) years of age with comorbidities including: hypertension (89%), diabetes (49%), coronary artery disease (49%), and congestive heart failure (38%). 77% of all prescriptions were prescribed by family physicians and 2% were prescribed by nephrologists. Multivariable analysis revealed that patients with appropriate prescriptions were more likely to have seen a nephrologist in the one year prior with an unadjusted odds ratio of 1.07 (95% CI 1.01-1.14, p=0.02), adjusted odds ratio 1.23 (95%CI 1.15-1.32, p<0.001).

Conclusions: In patients with stage 4 or 5 CKD prescribed an antibiotic, those with an appropriate dose were 23% more likely to have been cared for by a nephrologist in

the previous year. Although we cannot conclude what caused the improved prescribing practice, this improvement may, in part, explain the improved patient outcomes associated with seeing a nephrologist in observational studies.

FR-PO568

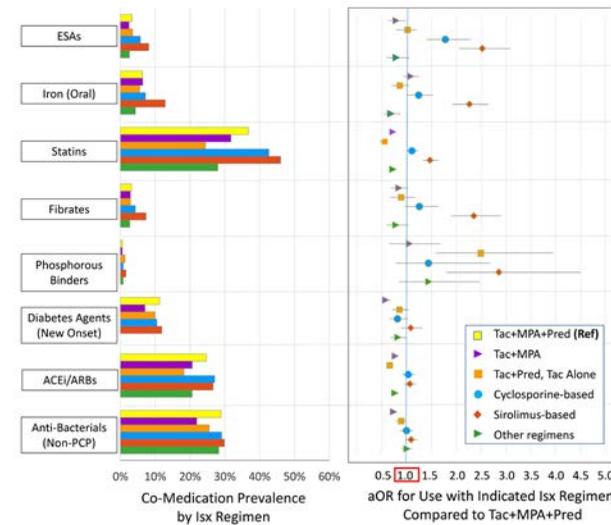
Variation in Co-Medication Use According to Kidney Transplant Immunosuppressive Regimen: Application of Integrated Registry and Pharmacy Claims Data Krista L. Lentine,¹ Abhijit S. Naik,² Mark Schnitzler,¹ David A. Axelrod,³ Jiajing Chen,¹ Daniel C. Brennan,⁴ Dorry L. Segev,⁵ Bertram L. Kasiske,⁶ Vikas R. Dharnidharka.⁴ ¹Saint Louis Univ; ²Univ Michigan; ³Dartmouth; ⁴Washington Univ; ⁵Johns Hopkins; ⁶Univ Minnesota.

Background: While modern immunosuppressive therapies (ISx) have substantially reduced acute rejection, ISx medications have many side effects, and transplant recipients must take an array of “co-medications” to help mitigate complications. Co-medication utilization patterns are not well described in large, representative samples due to lack of available data.

Methods: We integrated national U.S. transplant registry data with pharmacy records (2005-2010) from a large pharmaceutical claims clearinghouse to examine treatments for anemia, metabolic disorders and infections according to ISx regimen in mo 6-12 post-transplant (N=22,453). Associations of ISx with co-medication use (adjusted odds ratio, aOR) were examined with multivariate logistic regression including adjustment for recipient, donor and transplant factors.

Results: Compared to a reference regimen of tacrolimus (Tac), mycophenolate (MPA) and prednisone, rapamycin-based ISx was associated with significantly (P<0.05) higher use of ESAs (aOR 2.52), iron (aOR 2.26), statins (aOR 1.47), fibrates (aOR 2.35), and phosphorous binders (aOR 2.85) (Figure). Cyclosporine-based ISx was associated with more common use of anemia treatments. Compared to those taking triple ISx, recipients of tacrolimus-based dual and mono-therapies had lower use of statins, ACEi/ARBs, and anti-bacterial agents. Recipients of steroid-free ISx were less commonly treated for new onset diabetes.

CO-MEDICATION USE BY IMMUNOSUPPRESSION REGIMEN, 6-12 MO POST-TRANSPLANT



Conclusions: Alternate ISx regimens are associated with varying treatment requirements for hematologic, metabolic and infectious complications. Co-medication use should be considered in the cost-effectiveness and individualization of ISx regimens.

Funding: NIDDK Support

FR-PO569

Association of Urinary Biomarkers of Injury and Repair with Incident Chronic Kidney Disease in Type 2 Diabetes: An Ancillary Study of the ACCORD Trial Girish N. Nadkarni,¹ Veena Rao,² Faramarz Ismail-beigi,³ Vivian A. Fonseca,⁴ Sudhir V. Shah,⁵ Michael S. Simonson,³ Prasad Devarajan,⁶ Chirag R. Parikh,² Steven G. Coca.¹ ¹Mount Sinai; ²Yale Univ; ³Case Western Reserve Univ; ⁴Tulane Univ; ⁵UAMS; ⁶Univ of Cincinnati.

Background: Urinary kidney injury molecule (KIM)-1, monocyte chemoattractant protein (MCP)-1, interleukin (IL)-18, & YKL-40 are biomarkers representing renal injury, inflammation and fibrosis. We evaluated their association with incident CKD3b in the ACCORD trial.

Methods: We designed a case-cohort study of 721 participants & measured KIM-1, MCP-1, IL-18, and YKL-40 on baseline urine samples with Mesoscale platform. Biomarker associations with CKD3b were modeled continuously & by tertiles using Cox proportional hazards models.

Results: Mean age was 62, 51% were female & baseline eGFR was 88 ml/min. There were 159 incident CKD3b events over median(IQR) of 4.2(3.9-4.7) years. Top tertiles of all biomarkers had higher proportions of incident CKD3b. After adjusting for demographics,

clinical characteristics, baseline eGFR & UACR, highest tertiles of uMCP1 & uKIM1 had adjusted HRs of 1.82(95% CI 1.18-2.81) & 1.51(95% CI 1.01-2.27) respectively. Area under ROC improved from 0.70(with eGFR & UACR) to 0.72 with addition of uMCP1 & uKIM1(p<0.05). No association was seen for urinary IL-18 & YKL-40.

	Events	Adjusted HR(95% CI)
MCP1		
<=116	36	Ref
117-253	62	1.85(1.23-2.81)
>=254	61	1.90(1.26-2.88)
Per log increase	NA	1.23(1.06-1.44)
IL18		
<=26	49	Ref
27-60	62	1.22(0.82-1.80)
>=60	48	1.07(0.70-1.64)
Per log increase	NA	1.09(0.92-1.28)
KIM-1		
<=586	42	Ref
587-1549	54	1.38(0.91-2.10)
>=1550	63	1.51(1.01-2.27)
Per log increase	NA	1.14(0.98-1.32)
YKL40		
<=197	54	Ref
198-682	61	1.38(0.94-2.02)
>=673	44	0.95(0.62-1.44)
Per log increase	NA	0.97(0.89-1.06)
Baseline Covariates:Age; Sex; Ethnicity; eGFR, UACR, MAP, BMI; cardiac history; ACEI/ARB use; smoking; HbA1C; intensive diabetes control and duration		

Conclusions: Urinary levels of MCP1 and KIM1 are independently associated with incident CKD3b & marginally added to risk prediction after accounting for clinical variables including eGFR/albuminuria.

Funding: NIDDK Support

FR-PO570

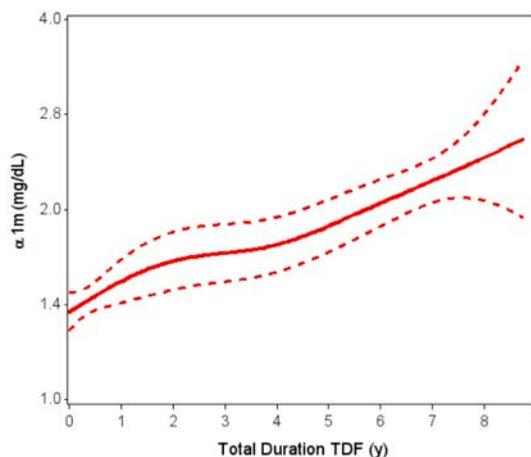
Association of Tenofovir Disoproxil Fumarate Exposure with Urine α 1-microglobulin, a Biomarker of Proximal Tubule Dysfunction
 Vasantha Jotwani,¹ Rebecca Scherzer,¹ Michelle M. Estrella,² Chirag R. Parikh,³ Joachim H. Ix,⁴ Michael Shlipak.¹ ¹UCSF; ²Johns Hopkins; ³Yale; ⁴UCSD.

Background: Tenofovir disoproxil fumarate (TDF) is a well-recognized contributor to HIV-related kidney disease, via proximal tubular injury. Urine α 1-microglobulin (α 1m), a low molecular weight protein indicative of proximal tubule dysfunction, may enable earlier detection of TDF-associated toxicity.

Methods: In this cross-sectional study of 883 HIV-infected men enrolled in the Multicenter AIDS Cohort Study, we evaluated associations of TDF exposure with urine α 1m levels, using multivariable generalized gamma regression models to adjust for traditional and HIV-related risk factors.

Results: Mean age was 52 and mean eGFR was 90 ml/min/1.73m². Median TDF exposure duration was 4.2 years (IQR:2.3,6.1) among the 573 (65%) current and 112 (13%) former TDF users. Cumulative TDF duration was linearly associated with higher urine α 1m levels (p<0.0001).

Figure: Association of cumulative TDF exposure with urine α 1m levels



In adjusted analyses, each year of TDF exposure was associated with 8% higher urine α 1m, a 4-fold effect size relative to age (2% per year). Compared with men who never received TDF, α 1m levels were 43-50% higher in former and current TDF users. Time since last TDF exposure was only modestly associated with lower α 1m.

Adjusted associations of TDF exposure with urine α 1m levels

TDF Exposure	% Estimate ¹ (95%CI)	P Value
Cumulative TDF exposure (per year)	8 (6,11)	<0.001
Current vs never TDF use	50 (25,80)	<0.001
Past vs never TDF use	43 (11,84)	0.006
Duration off TDF (per year)	-3 (-8,4)	0.41

¹Estimated % difference in α 1m attributable to each TDF exposure variable, adjusted for demographics, traditional kidney risk factors, and HIV-related factors

Conclusions: In HIV-infected men, TDF exposure was strongly associated with higher urine α 1m levels. α 1m is a promising biomarker for the detection and monitoring of TDF-associated tubular toxicity.

Funding: NIDDK Support

FR-PO571

Impact of Kidney Function and Urinary Protein Excretion on Pulmonary Function
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Background: Although the cardiorenal relationship in patients with chronic kidney disease (CKD) has been investigated, information about the lung-kidney relation is limited. Here, we investigated the impacts of kidney function and urinary protein excretion on pulmonary dysfunction.

Methods: The data of pulmonary function tests (PFTs) and kidney function tests from 1 April 2005 to 30 June 2010 were selected from our laboratory database. Data were classified into 4 categories according to eGFR and proteinuria. Category 1: eGFR \geq 60 ml/min/1.73 m² and urinary protein < 0.3 g/gCr; Category 2: eGFR < 60 ml/min/1.73 m² and urinary protein < 0.3 g/gCr; Category 3: eGFR \geq 60 ml/min/1.73 m² and urinary protein \geq 0.3 g/gCr; Category 4: eGFR < 60 ml/min/1.73 m² and urinary protein \geq 0.3 g/gCr. Pulmonary function data were evaluated according to these 4 categories.

Results: A total of 133 participants without major respiratory disease, abnormal computed tomography and smoking history were enrolled. Hb-adjusted %DL_{CO} in category 4 (46.2 \pm 7.5) and category 2 (63.6 \pm 17.8) were significantly lower than that in category 1 (75.8 \pm 18.9) (P < 0.05). Hb-adjusted %DL_{CO} was strongly correlated with eGFR in participants with urinary protein \geq 0.3 g/gCr (R = 0.81, P < 0.001). In addition, eGFR was associated with Hb-adjusted %DL_{CO} (P = 0.023) and urinary protein tended to be associated with Hb-adjusted %DL_{CO} (P = 0.095) after adjusting for physical features and the presence or absence of DM and Hypertension.

Conclusions: This study suggests that eGFR and urinary protein excretion were associated with pulmonary function (Hb-adjusted %DL_{CO}).

FR-PO572

Renal Biomarkers in Diabetes, Role Beyond Nephropathy, Relation to Retinopathy Mohamed E. Elraggal,¹ Ahmed Fathy Elkeriaie,² Ahmed M. Abdelhadi,³ Ashraf Nabil Abdalla.⁴ ¹Nephrology, Kidney and Urology Center, Alexandria, Egypt; ²Nephrology, Alexandria Univ, Alexandria, Egypt; ³Ophthalmology, Alexandria Univ, Alexandria, Egypt; ⁴Pharmacology, Umm Al-Qura Univ, Saudi Arabia.

Background: Diabetic nephropathy and retinopathy remain two of the most frequent complications of diabetes and is the leading cause of end-stage renal disease (ESRD) and blindness worldwide. The concordance rate between both complications is often present in diabetic patients.

Methods: We tried to study the relation between renal biomarkers including serum creatinine (SCR), urinary albumin/creatinine ratio (ACR), serum cystatin-C (cysC) and urinary NGAL (uNGAL) with diabetic retinopathy (DR) in 100 diabetic patients. Patients were classified according to severity into 3 stages: no diabetic retinopathy (No DR), Non-Proliferative DR (NPDR) and proliferative DR (PDR).

Results: Urinary ACR, serum cysC and uNGAL were higher significantly among patients with DR (NPDR & PDR) than patients without, while SCR showed a non significant rise with progression of retinopathy. All markers were higher among PDR than NPDR group.

	No DR	NPDR	PDR	P
SCr (mg/dl)				
Mean ± SD	0.86 ± 0.14	0.96 ± 0.31	1.13 ± 0.49	0.175
Urinary ACR (mg/g)				
Mean ± SD	34.54 ± 55.59	87.43 ± 93.27	118.48 ± 122.75	<0.001*
P between each stage	p1<0.001; p2= 0.003; p3= 0.184			
Serum cysC (mg/L)				
Mean ± SD	0.73 ± 0.19	0.89 ± 0.31	1.0 ± 0.43	0.043*
P between each stage	p1= 0.041; p2= 0.017; p3=0.358			
uNGAL (ng/ml)				
Mean ± SD	11.14 ± 9.1	22.6 ± 23.79	26.07 ± 23.96	0.016*
P between each stage	p1= 0.033; p2= 0.013; p3=0.622			

p₁: p value for comparing between No DR and NPDR
 p₂: p value for comparing between No DR and PDR
 p₃: p value for comparing between NPDR and PDR
 Statistically significant at p ≤ 0.05

Conclusions: Renal biomarkers namely urinary ACR, serum cysC and uNGAL may point to a more advanced stage of diabetic retinopathy, which might be an aid to identify the degree of retinopathy beside the traditional fundus examination in diabetic patients.

FR-PO573

Prognostic Importance of Urea and Urea: Creatinine Ratio for Mortality as Compared to Creatinine Concentrations Alone in the General Population Ronan Cusack,² Austin G. Stack,^{1,2,3} John P. Ferguson.² ¹Nephrology, Univ Hospital Limerick, Ireland; ²Graduate Entry Medical School, Univ of Limerick, Ireland; ³Health Research Inst, Univ of Limerick, Ireland.

Background: High Creatinine (Cr) concentrations reflect poor kidney function and are associated with a higher risk of death. It is unclear whether other measures of kidney function such as blood urea nitrogen (BUN) concentration and BUN/creatinine ratio, are better predictors of mortality in the general population.

Methods: A cohort of 15,773 non-pregnant subjects age >20, representative of the U.S. population, were identified from the Third National Health and Nutrition Examination Survey (1988-1994). Vital status was obtained through linkage with the National Death Index through to 2006. Subjects were classified into categories of Cr, BUN and BUN/Creatinine Ratio (B/Cr). Weighted multivariable Cox regression models, compared hazard ratios [HR] and 95% CI for death among the decile groups and the prognostic capacity of differing models was compared using Akaike Information Criterion (AIC).

Results: In multivariable analysis, BUN was found to be the most important single predictor of mortality with Cr being second best. A strong interaction (P< 0.001) between BUN and Cr with mortality was identified and explored by fitting stratified models, as shown below.

			Creatinine (µmol/L)				
	< 70.7	70.7-79.6	79.6-88.4	88.4-97.2	97.2-106.1	106.1-114.9	≥ 114.9
Urea (mmol/L)							
< 2.86	1.55 (0.75-3.18)	1.00	0.60 (0.28-1.26)	0.51 (0.16-1.67)	0.21 (0.06-0.69)	0.20 (0.06-0.62)	0.09 (0.02-0.45)
2.86-7.5	1.04 (0.81-1.34)	1.00	0.99 (0.82-1.20)	1.04 (0.87-1.25)	1.04 (0.83-1.29)	0.97 (0.77-1.23)	1.28 (1.00-1.64)
> 7.5	0.84 (0.31-2.25)	1.00	1.78 (0.72-4.40)	1.13 (0.55-2.34)	1.49 (0.70-3.19)	1.98 (0.96-4.09)	2.31 (1.15-4.63)

Conclusions: Both BUN and Cr independently predict death in the general population. Among patients with malnourished states (Low BUN); higher SC were associated with lower mortality. In contrast, among patients with normal-high BUN concentrations, higher Cr was associated with elevated death risk. Risk Prediction models should take BUN levels into consideration when estimating future death risk.

Funding: Government Support - Non-U.S.

FR-PO574

Serum Uric Acid and the Development of Chronic Kidney Disease in a General Japanese Population: The Hisayama Study Keita Takae,^{1,2} Masaharu Nagata,^{1,2} Kazuhiko Tsuruya,² Takanari Kitazono,^{2,3} Yutaka Kiyohara,^{1,3} Toshiharu Ninomiya.^{2,3} ¹Dept of Environmental Medicine, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ²Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ³Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Growing evidence suggests that high serum uric acid (SUA) levels are causally related to an increased risk of kidney dysfunction. However, the association remains inconclusive in general Asian populations. Additionally, there are limited studies investigating the influence of SUA levels on the development of albuminuria.

Methods: A total of 2,059 community-dwelling Japanese subjects aged ≥40 years without chronic kidney disease (CKD) were followed for 5 years. CKD were defined as eGFR <60 mL/min/1.73m² or urine albumin/creatinine ratio (UACR) ≥30 mg/g. The odds ratios (ORs) for the development of CKD and the rates of decline in eGFR were estimated according to quartile of SUA (≤4.0, 4.1-4.9, 5.0-5.8, and ≥5.9 mg/dL).

Results: During follow-up period, 396 subjects experienced CKD, of whom 125 had eGFR <60 mL/min/1.73m² and 312 had UACR ≥30 mg/g. The age- and sex-adjusted incidence rate of CKD increased significantly with higher SUA levels (p for trend <0.001). Compared with those with SUA of ≤4.0 mg/dL, the multivariable-adjusted ORs for the development of CKD were 1.21 (95% confidence intervals, 0.84-1.74), 1.47 (1.01-2.17), and 2.10 (1.37-3.23) in subjects with SUA of 4.1-4.9 mg/dL, 5.0-5.8 mg/dL, and ≥5.9 mg/dL, respectively. Likewise, there were positive associations of SUA levels with the adjusted risk of developing eGFR <60 mL/min/1.73m² (OR 1.00 [reference] in ≤4.0 mg/dL, 2.30 [1.10-4.82] in 4.1-4.9 mg/dL, 2.81 [1.34-5.88] in 5.0-5.8 mg/dL, and 3.73 [1.65-8.44], in ≥5.9 mg/dL) and UACR ≥30 mg/g (1.00 [reference], 1.12 [0.76-1.65], 1.35 [0.90-2.03], and 1.81 [1.14-2.87], respectively). Additionally, higher SUA was significantly associated with a greater decline in eGFR (p for trend = 0.002).

Conclusions: Higher SUA level is a significant risk factor for the development of both kidney dysfunction and albuminuria in a general Japanese population.

FR-PO575

Do Protein-Energy Wasting Criteria Reflect Protein/Energy Wasting? Xiaorui Chen,¹ G. Wei,¹ Robert E. Boucher,¹ Dominique Ferranti,³ Michel Chonchol,¹ Kalani L. Raphael,¹ Srini Beddhu.^{1,2} ¹U of Utah; ²VA SLC; ³UC Denver.

Background: The term protein-energy wasting (PEW) implies a state of depleted protein and/ or energy stores. An International Society of Renal Nutrition and Metabolism (ISRNM) panel proposed objective criteria for the definition of PEW syndrome. However, the extent to which these variables used in PEW syndrome definition are indicative of low protein or energy stores is unknown. Muscle is the largest protein store and fat mass is the largest energy store in the body. Therefore, we examined the associations of these variables with lean body mass (LBM) and fat mass (FM) measured by DXA scans in 11,834 participants in the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: Definitions of PEW variables are summarized in the table. The associations of each PEW variable with LBM and FM in the entire cohort and CKD (CKD-EPI eGFR < 60) sub-population were examined in linear regression models using svy suite in STATA 13.

Results: Mean age was 46.0 yrs, 50.3% were male, 9.5% were black. 6.7% had CKD. Unintentional weight loss and low levels of serum albumin, serum cholesterol, BMI and MAMC were associated with lower LBM and FM. On the other hand, low protein and energy intakes were associated with higher LBM and FM.

PEW variables	Lean body mass (kg)	Fat mass (kg)
	β (95% CI)	
Albumin<3.25 g/dl	-3.5 (-7.5, 0.4)	-3.6 (-7.2, -0.1)
Cholesterol<100 mg/dl	-2.5 (-6.8, 1.8)	-5.2 (-10.6, 0.1)
BMI<20 kg/m ²	-9.7 (-10.3, -9.1)	-14.6 (-14.9,-14.2)
Unintentional wt loss>10% over 1 yr	-2.2 (-3.3, -1.0)	-3.8 (-5.2, -2.4)
Body fat %<10%	NA	NA
Low MAMC*	-8.6 (-9.0, -8.3)	-8.4 (-8.9, -7.9)
Protein intake<0.6 g/kg/d	3.6 (3.0, 4.2)	6.4 (5.7, 7.0)
Energy intake<25 kcal/kg/day	4.3 (3.9, 4.7)	7.3 (6.9, 7.7)

* 10% or more lower than the 50th percentile of reference group

Results were similar in the CKD sub-population.

Conclusions: Serum chemistry, body weight and muscle mass PEW criteria appear to be indicative of both protein stores (as indicated by LBM) and energy stores (as indicated by FM). Dietary variables are not reflective of protein or energy wasting. A modified PEW syndrome definition without the dietary variables would be a better indicator of PEW syndrome.

Funding: NIDDK Support

FR-PO576

Low-Proteinuric CKD and Risk of ESRD in Nephrology Clinics: Emerging Role of Serum Phosphorus Luca De Nicola,¹ Michele Provenzano,¹ Paolo Chiodini,² Giuseppe Conte,¹ Roberto Minutolo.¹ ¹Nephrology, Second Univ, Naples, Italy; ²Med Stat, Second Univ, Naples, Italy.

Background: In low-proteinuric (LP) CKD, factors other than proteinuria (Uprot) likely act as predictors of ESRD. However, comprehensive assessment of epidemiologic features of LP versus high-proteinuric (HP) patients is still lacking. This information is critical in renal clinics where LP patients are common.

Methods: We pooled three prospective cohorts that in 2000-2010 enrolled 2,488 CKD patients stage III-V under stable care for ≥ 6 months in 40 Italian renal clinics. Patients were followed for ESRD (chronic dialysis-transplant) up to 12/2014. Patients were classified in two groups, LP (56%) and HP (44%), by Uprot ≤ 0.5 and >0.5 g/24h, respectively.

Results: Besides lower Uprot (median, IQR: 0.15, 0.06-0.28 vs 1.20, 0.78-2.05 g/24h), LP differed from HP because male gender (55 vs 62%), diabetes (28 vs 35%) and use of anti-RAS (73 vs 78%) were less frequent. In LP, moreover, age (70 \pm 12 vs 65 \pm 14 y), GFR-EPI (35.2 \pm 13.3 vs 26.6 \pm 13.2 mL/min/1.73m²) and Hb (12.7 \pm 1.7 vs 12.3 \pm 1.8 g/dL) were higher while systolic BP (137 \pm 18 vs 140 \pm 18 mmHg) was lower. Serum phosphorus (P) was lower in LP (3.68 \pm 0.73 vs 3.95 \pm 0.83 mg/dL, with P $>$ 4.5 mg/dL in 10 vs 20%) [P $<$ 0.001 for all comparisons]. History of cardiovascular disease (CVD), BMI and uric acid levels did not differ. Over a median follow-up of 38 months, ESRD occurred in 154 LP and 422 HP, (incidence rate 2.9 and 12.2/100 pts/y). At multivariable Cox analyses (HR, 95% CI), significant predictors of ESRD were male gender, younger age and lower eGFR in both LP and HP. Only in LP, however, higher P (1.28, 1.02-1.61) and lower BMI (0.96, 0.93-0.99) predicted renal risk while CVD (1.28, 1.03-1.60), Hb (0.90, 0.85-0.97) and anti-RAS (0.74, 0.60-0.91) had a prognostic role exclusively in HP. A negative interaction P*Uprot was detected in HP (beta= -0.046, P=0.004). Results were consistent across cohorts.

Conclusions: In renal clinics, LP patients are prevalent and characterized by nontrivial renal risk despite higher eGFR. Risk factors for ESRD are peculiar; in particular, results in LP and HP suggest that lower Uprot allows full expression of the negative role of P, the effect being evident for P levels mostly normal.

FR-PO577

Trends in CKD Awareness in the U.S. Population, 1999-2012, Overall and by KDIGO Risk Groups Yunnuo Zhu,¹ Tanushree Banerjee,¹ Delphine S. Tuot,¹ Jennifer L. Bragg-Gresham,² Mark Eberhardt,³ Sharon Saydah,³ Rajiv Saran,² Neil R. Powe.¹ ¹UCSF; ²UM; ³CDC.

Background: Despite medical knowledge of chronic kidney disease (CKD) as a risk factor of cardiovascular disease, hypertension, and progression to kidney failure, a majority of patients are not aware of their disease. Early identification and management of CKD can decrease its rate of progression.

Methods: We used cross-sectional National Health and Nutrition Examination Survey data (1999-2012) of non-pregnant adults aged ≥ 20 years with CKD who had complete urinary albumin and creatinine data (N=8,480-10,296). CKD stages 1-4 were classified using KDIGO's prognosis of CKD risk levels based on GFR and albuminuria. The risk categories range from low to very high risk and predict the risk of CKD progression, ESRD, and mortality. eGFR was estimated using the MDRD equation. CKD awareness was defined by answering "yes" to the question "Have you ever been told that you had weak or failing kidneys?" amongst those with CKD. We used weighted, age-adjusted regression analyses via SAS SURVEYREG to analyze prevalence and trends.

Results: Overall prevalence of CKD awareness across all risk groups in 2009-2012 was 4.7% and had not significantly changed compared to 4.4% in 1999-2004 or 4.7% in 2005-2008 (p trend=0.96). Awareness in the very high KDIGO risk group for progression was greatest and increased from 40.5% in 1999-2004 to 51.6% in 2009-2012 (p trend=0.007). The prevalence of self-report CKD awareness was 16.6% in the next highest risk group in 2009-2012 but did not exhibit a statistically significant trend (p trend=0.56). The moderately increased risk group showed a decrease in awareness from 6.3% in 1999-2004 to 4.1% in 2009-2012 that was not statistically significant (p trend=0.14). Awareness in the low-risk group was the lowest of all risk groups at 2.0% in 2009-2012 and showed no change over time (p trend=0.67).

Conclusions: Although overall awareness of CKD has not changed over time, awareness among those at highest risk for CKD progression has increased. Recent education efforts to increase awareness among providers and patients may be reaching those at greatest risk and acceleration might help mitigate CKD progression and associated comorbidities.

Funding: Other U.S. Government Support

FR-PO578

Intermittent Abnormal Kidney Function and Mortality in Community Dwelling Individuals Donal J. Sexton,¹ Scott Reule,² Robert N. Foley.² ¹Medicine, HRB Clinical Research Facility, NUI Galway, Galway, Ireland; ²Medicine, Univ of Minnesota, Minneapolis.

Background: The health implications of persistently abnormal kidney function as measured by estimated glomerular filtration rate and spot urinary albumin excretion has been well characterized to date. However little data is available regarding the implications of intermittent abnormalities in these tests as defined by established thresholds.

Methods: We evaluated the frequency of intermittent abnormal kidney function and its association with all-cause mortality in the US general population using the National Health and Nutrition Examination Survey III, 1988-1994. Mortality linkage data were available through December 2006. Estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI equation and urinary albumin-creatinine ratios (ACR) were measured twice, a mean of 17 days apart (N=1161).

Results: Proportions of abnormal tests included: for eGFR $<$ 60ml/min/1.73m² either test 7.32%, first test 5.94%, second test 5.68%, first test only 1.64%, second test only 1.38%, both tests 4.31%. Compared to participants with eGFR \geq 60 ml/min/1.73m² on both testing occasions, adjusted hazard ratios were 1.8 (95%CI 1.3, 2.4) for intermittent and 1.7 (95%CI 1.1, 2.5) for persistent abnormal eGFR. Proportions with ACR \geq 30 mg/g were as follows: either test 16.54%, first test 11.63%, second test 13.35%, first test only 3.19%, second test only 4.91%, both tests 8.44%. Compared to those with ACR $<$ 30 mg/g on both occasions' mortality hazard ratios for intermittent abnormal function was 2.1 (95%CI 1.6, 2.7), and persistent abnormal 2.0 (95%CI 1.5, 2.8). Models were adjusted for age, sex, race, diabetes mellitus, cardiovascular disease (congestive heart failure, previous myocardial infarction or stroke), current smoking, self reported hypertension, systolic and diastolic blood pressure, total cholesterol and body mass index.

Conclusions: CKD as defined by established thresholds may be persistent or intermittent in community dwelling individuals. Participants with intermittently abnormal kidney function as defined by current thresholds were at similar mortality risk to those with persistently abnormal function on both occasions.

FR-PO579

Renal Outcome of APRT Deficiency Presenting in Childhood Hrafnhildur L. Runolfsson,¹ Runolfur Palsson,^{1,2} Inger Maria Agustsdottir,³ Olafur S. Indridason,² Vidar O. Edvardsson.^{1,3} ¹Faculty of Medicine, Univ of Iceland; ²Div of Nephrology; ³Children's Medical Center, Landspítali – The National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Adenine phosphoribosyltransferase (APRT) deficiency is an inherited disorder of purine metabolism that leads to nephrolithiasis and chronic kidney disease (CKD). Scarce data are available on APRT deficiency presenting in childhood.

Methods: All patients in the APRT Deficiency Registry of the Rare Kidney Stone Consortium who presented with clinical manifestations of the disorder and/or were diagnosed with the disease before age 18 years were included in the study. Presenting features, time to diagnosis and disease course were examined. Glomerular filtration rate (eGFR) was estimated with the modified Schwartz equation in children and the MDRD equation in adults. CKD was defined as eGFR $<$ 60 ml/min/1.73 m² and acute kidney injury (AKI) according to the KDIGO criteria. Data are presented as median (range).

Results: Nineteen children presented at the age of 1.6 (0.2-16.5) years. Presenting features included reddish-brown diaper spots in 11 patients (58%), kidney stones in 8 (42%), lower urinary tract symptoms in 8 (42%) and AKI in 2. The diagnosis was promptly made in 7 patients, while it was delayed in 12 (63%) patients for 15.2 (0.8-39.2) years. One patient, who did not receive drug treatment, developed ESRD at age 11 years. Twelve patients were placed on allopurinol at the age of 2.1 (0.6-16.5) years. During follow-up of 18.9 (1.7-31.5) years, 3 of these patients developed 4 kidney stone events and AKI occurred in 2 patients during episodes of volume depletion; none had developed CKD. Six patients did not begin pharmacotherapy until age 29.8 (20.5-42.4) years. At last follow-up, at 43.9 (32.5-56.9) years of age, 3 had experienced a total of 9 kidney stone events, 2 had suffered AKI, 3 had stage 3 CKD and one had progressed to ESRD at the age of 44 years.

Conclusions: A substantial proportion of patients with APRT deficiency present in childhood. The commonly observed delay in diagnosis and treatment may have grave consequences. APRT deficiency must be excluded in all children with kidney stones, renal dysfunction and reddish-brown diaper spots.

Funding: Other NIH Support - This study was supported by the Rare Kidney Stone Consortium (U54KD083908), a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR). The Rare Kidney Stone Consortium is funded through collaboration between NCATS and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

FR-PO580

Association of Chronic Kidney Disease with Increased Risk of Recurrence of Upper Urinary Tract Urothelium Cancer – A Population-Based Study Shang-Jyh Hwang,^{1,3} Ming-Yen Lin,¹ Huei-Lan Lee,¹ Wei-Ming Li,¹ Chun-Nung Huang,¹ Wen-Jeng Wu,¹ Li-Tzong Chen,³ Sheng-wen Niu.¹ ¹Medical Univ Hospital, Kaohsiung, Taiwan; ²National Health Research Insts, Miaoli, Taiwan.

Background: Taiwan has significantly high incidence of upper urinary tract urothelial cancer (UTUC) and end-stage renal disease (ESRD). UTUC coexisted with chronic kidney disease (CKD) may deteriorate cancer progression and increase mortality risk. The aim of study was to explore the association of CKD with the risk of UTUC recurrence.

Methods: We conducted a population-based cohort study through Taiwan National Health Insurance Research Dataset. Incident UTUC patient was extracted from Taiwan Cancer Registry Dataset and linked to claim data. Status of CKD including non-dialysis CKD, dialysis ESRD, and renal transplant were identified before the index date of UTUC. Recurrence was defined as either new tumor lesion in bladder, or at the other site of urinary tract, or occurrence of distant metastasis within 3 months after first surgery. Differences of characteristics between CKD and non-CKD group was described as mean ± standard deviation or percentage and tested by independent t test and chi-square test. Competing risk approach was used for estimating cause-specific hazard ratio (CSHR) and 95% confidence interval (CI).

Results: Totally, 4,002 UTUC patients from 2001 to 2005 were included and traced until disease recurrence or end of 5 years after the index date of UTUC. Near half patients accompanied with various stages and status of CKD at index date. UTUC patients with CKD were younger, more female, and had more co-morbidities than patients without CKD. After adjusting factors of age, tumor grade, and co-morbidities, CKD significantly increased risk of UTUC recurrence in female (CSHR: 1.72, 95%CI: 1.13-2.61, p=0.01), but not in male (CSHR: 0.91, 95%CI: 0.44-1.86, p=0.79).

Conclusions: CKD increases risk of recurrence in female UTUC patient and is an important prognostic indicator. (This study was granted by the Ministry of Science and Technology (NSC 102-2314-B-037-012-MY3) and by the Ministry of Health and Welfare (MOHW103-TD-B-111-05, MOHW104-TDU-B-212-124-003, budget from health and welfare surcharge of tobacco product).)

Funding: Government Support - Non-U.S.

FR-PO581

Single Centre Experience of Late Referral and Achievement of Useable Dialysis Access Over a 9-Year Period Mohamed Salah Eldin Khogali. *Renal Dept, Dorset County Hospital, Dorchester, Dorset, United Kingdom; Renal Dept, Dorset County Hospital, Dorchester, Dorset, United Kingdom.*

Background: We describe a single centre, retrospective analysis of late (≤ 90 days) referral for dialysis over a 9 year period from April 2003 till March 2012. Factors that contributed to late referral and success in creating permanent dialysis access were determined.

Methods: Data on adult patients referred ≤ 90 days from dialysis were collected including patient demographics, source of referral, mortality, reason for late referral, creation of permanent dialysis access and use of permanent dialysis access at first dialysis.

Results: One hundred and twenty-seven patients were referred in ≤ 90 days over the 9 year period. Ninety-nine (78%) patients were referred within 30 days prior to dialysis and 28 (22%) patients within 30 – 90 days. Their median age was 63 years and 80 (63%) patients were male. Twenty-five (20%) patients were diabetic. Forty (33%) patients died within the first year after referral, 25 (21%) patients within the first 6 months and 15 (12%) patients between 6 months and 1 year. (figure1) Sixty-five patients (51 %) presented late due to acute renal failure (myeloma 24, vasculitis 14, irreversible acute kidney injury 10, renal cell carcinoma 5, glomerulonephritis 3 and others 9). Twenty-nine patients (23%) referred by physicians and surgeons, and 24 patients (19%) referred by GPs were late referrals of patients with known chronic renal failure. Nine patients (7%) presented late due to lack of understanding of their disease, denial, and fear of the unknown. One hundred and ten patients had permanent dialysis access created and 17 patients no permanent access procedures. The average time to create permanent dialysis access was 44 days post-dialysis commencement. Six permanent haemodialysis accesses were created pre-dialysis, 56 post-dialysis; 19 peritoneal dialysis accesses were created pre-dialysis, 29 post-dialysis.

Conclusions: Overall the number of patients presenting late for dialysis has decreased. Late referral has a poor 1 year survival and most patients require haemodialysis long-term. Only a minority of patients referred late have permanent dialysis access created and used at their first dialysis.

FR-PO582

Abnormal Global Glomerular Sclerosis Rate in Remnant Kidney of Ipsilateral Nephroureterectomy Is Associated with Higher Risk of End-Stage Renal Disease within Five Years in Patients of Upper Urinary Tract Urothelial Carcinoma Sheng-wen Niu,¹ Peir-In Liang,¹ Shih-Mong Yeh,¹ Ming-Yen Lin,¹ Shang-Jyh Hwang,^{1,2} Wen-Jeng Wu.¹ ¹Kaohsiung Medical Univ, Taiwan; ²National Health Research Insts.

Background: Aristolochic acid in Chinese herbs induce renal tubuleinterstitial disease and increase the risk of upper urinary tract urothelial carcinoma(UTUC). However, we are still not sure if UTUC itself has impact on renal outcome. We studied the pathological

changes of remnant kidney tissue from UTUC patients post ipsilateral nephroureterectomy to investigate the correlation between renal histopathology and outcome of end-stage renal disease.

Methods: This cohort study included 132 cases of non-dialysis UTUC patients post ipsilateral nephroureterectomy from 2002 to 2010. We collected clinical and laboratory data before surgery, tumor size, whether into dialysis after surgery, and followed up to dialysis or to December 31, 2014. Renal histopathology was read by 3 specialists: nephrologists or pathologist. We used logistic regression for studying tubuleinterstitial fibrosis score and global glomerular sclerosis (GGS) rates and Cox regression to investigate factors associated with renal survival.

Results: There was no significant factor associated with tubuleinterstitial fibrosis, but advanced CKD was significantly related to GGS rate adjusted with age and gender [OR(95%CI): 4.8(1.4-16.9), p=0.014]. Kaplan-Meier survival curve showed five-year renal survival rate was 86.3%. Factors affect five-year renal survival were hypertension [HR(95%CI): 4.0(1.1-15.2), p=0.043] and GGS rate [HR(95%CI): 17.4(2.4-124.1), p=0.004].

Conclusions: Our findings demonstrated that UTUC patients with hypertension before surgery or abnormal GGS rate in remnant kidney have higher risk of entering dialysis within five years post ipsilateral nephroureterectomy. (This study was granted by the Ministry of Science and Technology (NSC 102-2314-B-037-012-MY3) and by the Ministry of Health and Welfare (MOHW103-TD-B-111-05, MOHW104-TDU-B-212-124-003, budget from health and welfare surcharge of tobacco product).)

Funding: Government Support - Non-U.S.

FR-PO583

Renal Outcomes following Transjugular Intrahepatic Portosystemic Shunt Placement for Refractory Ascites: A Large Case Series Andrew S. Allegretti,¹ Guillermo Ortiz,¹ Jie Cui,¹ Ishir Bhan,¹ Raymond T. Chung,² Zubin Irani.³ ¹Div of Nephrology, MGH, Boston, MA; ²Div of Hepatology, MGH, Boston, MA; ³Dept of Radiology, MGH, Boston, MA.

Background: Patients with cirrhosis and refractory ascites have decreased effective circulating volume that contributes to impaired renal perfusion and diminished estimated glomerular filtration rate (GFR). Reversing these hemodynamic alterations via transjugular intrahepatic portosystemic shunt (TIPS) procedure may improve GFR.

Methods: Multicenter, retrospective review of patients who underwent first-time TIPS placement for refractory ascites from 1995 to 2014. Patients were analyzed at 90 days prior to TIPS, immediately pre- and post-TIPS, and 90 days after TIPS. Change in renal function 90 days after TIPS was analyzed by GFR tertiles (T1: > 60 mL/min, T2: 37-60 mL/min, T3: <37 mL/min) at the time of TIPS procedure.

Results: 153 TIPS cases were analyzed. Mean GFR was 62 (95% CI 58, 69) mL/min at 90 days prior to TIPS, 53 (48, 58) mL/min immediately pre-TIPS, 64 (59, 69) mL/min post-TIPS, and 74 (CI 68, 80) mL/min 90 days after TIPS.

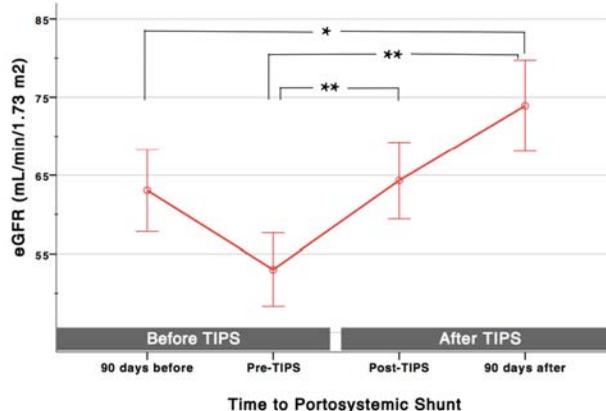


Figure. Longitudinal measures of mean eGFR around time of TIPS procedure. *p<0.001, **p<0.0001

GFR improved by 16 (11, 21) mL/min from pre-TIPS to 90 days after TIPS (p<0.0001). Comparison of Tertiles 1, 2, and 3 showed respectively: GFR increased by T1: 6 (-1, 14), T2: 22 (15, 30), and T3: 22 (12, 33) mL/min (p = 0.006); 90-day mortality was T1: 20%, T2: 17%, and T3: 49% (p = 0.0007); encephalopathy rate at 90 days was T1: 21%, T2: 42%, and T3: 65% (p = 0.0005).

Conclusions: There was a significant improvement in GFR from pre-TIPS to 90 days after TIPS. Those with the lowest GFRs at the time of TIPS had greater improvement in renal function but also had higher 90-day mortality and encephalopathy rates post-TIPS.

Funding: NIDDK Support

FR-PO584

The Epidemic of Chronic Kidney Disease in Rural and Remote Canadian First Nations: Results from Manitoba's FINISHED Screening Program
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Background: Chronic Kidney Disease (CKD) is a global epidemic affecting 10-15% of the general population. Canadian First Nations children and young adults are known to suffer from a high rate of proximate risk factors for CKD, in particular elevated rates of diabetes. The rates of CKD are not well defined in this population. We used data from The First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project, a 3-year initiative completed in 2015 that accomplished community wide screening in 11 rural and remote First Nations communities in Manitoba, Canada.

Methods: Detailed methods of the FINISHED study have been previously published (Lavallee et al. CJKHD, 2015). An interdisciplinary team screened for CKD in adults and children aged 10 + using both urine albumin-to-creatinine ratio (ACR) and eGFR in 11 communities across 2 tribal councils. We present here the data on demographic variables, risk factors for CKD, and the prevalence and severity of CKD in the adult (age 18+) screening cohort.

Results: 1346 adults were screened. 26.7% of those screened had CKD defined as elevated urine ACR (micro- or macroalbuminuria) or eGFR < 60 ml/min/1.73m². Road access communities had a lower prevalence of CKD (18.4%) than remote air access communities (36.0%). Macroalbuminuria (urine ACR > 300 mg/g) was present in 5% of those screened (2.8% in road access and 7.5% in air access communities).

Conclusions: Rural and remote Canadian First Nations suffer up to a 3-fold higher prevalence of CKD than the general population and a nearly 5-fold higher prevalence of macroalbuminuria. This prevalence is comparable to high-risk populations such as those with diabetes and/or hypertension. Given these risks, screening and treatment interventions may be cost-effective, as they have been shown to be in other high-risk populations.

Funding: Government Support - Non-U.S.

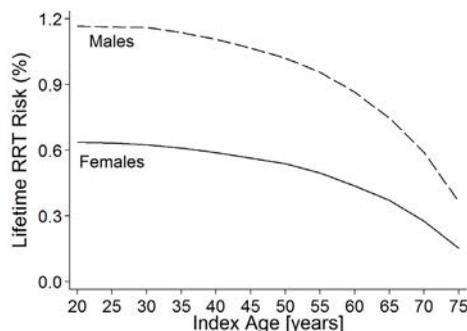
FR-PO585

Age and Gender Specific Lifetime Risk of Renal Replacement Therapy
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Background: Kidney transplantation is the preferred treatment of end stage renal disease (ESRD). Graft and patient survival are highest after transplantation with a graft from a living donor. However, persons who donate a kidney are themselves at risk of ESRD. Personalized risk prediction requires age and gender specific risk estimates. Here, we report lifetime risk of renal replacement therapy (RRT) for ESRD by age and gender across Europe.

Methods: We defined ESRD as chronic RRT and age 80 as the lifetime horizon. Death was considered a competing event. We obtained RRT incidence rates by age and gender from the ERA-EDTA Registry. Mortality rates were calculated from census data provided by EuroStat. We used these rates to estimate cumulative incidence of RRT by age and gender for countries providing individual patient data to the ERA-EDTA Registry. We pooled lifetime RRT risks using inverse variance weighted means.

Results: At index age 20, lifetime RRT risk for females ranged between 0.40% and 0.87% across countries, and for males between 0.77% and 1.59%. At age 60, lifetime RRT risk ranged between 0.26% and 0.68% for females and 0.56% and 1.32% for males. Pooled lifetime RRT risk in Europe was 0.62%, 0.58% and 0.43% in 20, 40 and 60 year old females. In males the respective risks were 1.16%, 1.10% and 0.87% for index ages 20, 40 and 60. The figure shows pooled lifetime RRT risk estimates by index age.



Conclusions: Lifetime RRT risk differs across Europe. Women are at lower risk compared to men. These data offer a basis to provide personalized prediction of lifetime ESRD risk when evaluating a potential kidney donor. The estimates presented here are population averages. We expect that lifetime risk is lower in persons with normal eGFR and no albuminuria.

FR-PO586

Characterizing Risk Among Type 2 Diabetics with Preserved EGFR and Abnormal Urine Albumin Excretion
 Robert M. Perkins,¹ Alex R. Chang,² H. Lester Kirchner,² ¹Bayer HealthCare, Whippany, NJ; ²Geisinger Medical Center, Danville, PA.

Background: Updated CKD risk stratification guidelines promote earlier identification of higher-risk patients. Two conditions are required to improve outcomes among such patients: robust risk characterization, and the presence of modifiable factors.

Methods: We investigated a retrospective cohort of all adult type 2 diabetic patients receiving care in an integrated health care system in central Pennsylvania during the period 1/1/2004-12/31/2014. Patients were risk stratified using the 2002 NKF and, separately, the 2012 KDIGO CKD classification systems. We compared the predictive performance of the two classification systems for death and ESRD using Akaike Information Criterion (AIC) obtained from multivariate, Cox proportional hazards models. Using only the KDIGO 2012 classification system, we then investigated patients categorized as stage G1 or G2 (with 'high' or 'very high' albuminuria) for the presence of modifiable risk factors.

Results: 17,385 type 2 diabetics comprised the study population (median follow-up 6.8 years). Median age and eGFR were 60 years and 95 ml/min/1.73m², respectively. 53% were male, 44% had a smoking history, and 16% and 5% had a history of coronary disease and CHF, respectively. Although both classification systems discriminated risk reasonably well, the KDIGO 2012 system—incorporating uACR—had lower AIC scores and was more likely to minimize information loss. Across all risk factors examined, less than half the population was receiving recommended care.

Risk Classification System	Adjusted HR (95% CI)
ESRD¹	
NKF 2002 (eGFR < 60 vs ≥ 60)	11.4 (9.2–14.0)
KDIGO 2012 (moderate vs. low risk)	2.2 (1.6–2.9)
KDIGO 2012 (high vs low risk)	10.1 (7.6–13.3)
Death²	
NKF 2002 (eGFR < 60 vs ≥ 60)	1.6 (1.5–1.8)
KDIGO 2012 (moderate vs. low risk)	1.5 (1.4–1.6)
KDIGO 2012 (high vs low risk)	2.3 (2.1–2.6)

KDIGO 2012 Risk Category	NSAID Prescription	Blood Pressure ≤ 130/80	LDL ordered (index +/- 12 months)	Status Prescription	ACE/ARB prescription
G1-A2	13%	39%	20%	6%	31%
G1-A3	9%	35%	15%	5%	35%
G2-A2	12%	37%	34%	8%	39%
G2-A3	9%	26%	23%	6%	41%

Conclusions: This investigation confirms the feasibility of early risk characterization among patients with preserved eGFR and abnormal urinary albumin excretion. Care gaps are highly prevalent among these individuals and may serve as targets to improve long term outcomes.

FR-PO587

Detecting Bowel Cancer in Chronic Kidney Disease (CKD): The Detect Study
 Germaine Wong. Univ of Sydney, Australia.

Background: CKD confers a 20% higher risk of colorectal cancer (CRC) than the general population, and has a very poor prognosis, with less than 50% of kidney transplant recipients surviving one year after diagnosis. The benefits and harms of screening for advanced colorectal neoplasms in CKD are unknown. We aim to determine the prevalence and spectrum of advanced colorectal neoplasms in CKD, and to evaluate the test performance characteristics of immunochemical faecal occult blood testing (iFOBT) for screening advanced colorectal neoplasms in CKD.

Methods: Participants with CKD stages III-V, on dialysis and with a kidney transplant, aged between 35 and 74 years were recruited from 10 centres in Spain, Canada, Australia and New Zealand. All received two screening iFOBTs, and those with at least one or more positive screens underwent colonoscopy, with test negatives verified by clinical follow up and data linkage.

Results: Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. The prevalence of advanced colorectal neoplasms (7 colorectal cancers and 101 advanced colorectal adenomas) among those with CKD stages III-V, on dialysis and with kidney transplants was 5.7% (95%CI: 4.3%-7.6%), 7.9% (95%CI: 5.6%-11.0%) and 5.9% (4.1%-8.4%) (p=0.10), respectively. The majority of the polyps were located in the sigmoid and transverse colon (n=63, 58%). The risk of serious complications including peritonitis and perforation was minimal (less than 1%). Overall, the positive predictive value (PPV) of iFOBT was 35.4% (95%CI: 29.9% - 41.3%).

Conclusions: Overall, the screening program appears acceptable to patients, appears safe, has reasonable predictive values and has detected a higher prevalence of advanced CRC neoplasms than in the general population.

Funding: Government Support - Non-U.S.

FR-PO588

Subclinical Pulmonary Congestion Is Pervasive in Nephrotic Syndrome Francesca Mallamaci,^{1,2} Francesco Marino,² Carmela Martorano,² Rocco Tripepi,¹ Marianna Bellantoni,¹ Giovanni Tripepi,¹ Carmine Zoccali.¹ ¹National Research Council of Italy, Inst of Clinical Physiology, Reggio Cal Unit, CNR-IFC, Reggio Calabria, Italy; ²Nephrology, Transplantation and Hypertension Unit United Hospitals, Reggio Calabria, Italy.

Background: In patients with Nephrotic Syndrome (NS) the lung is considered as an organ protected from the risk of edema. However information on objectively measured lung water in NS patients is lacking.

Methods: We measured lung water with an ultrasound technique (US) and with standard transthoracic impedance in an incident series of 42 asymptomatic patients with active NS. Eleven of these patients were re-studied during NS remission. Twenty-one healthy subjects formed the control group. US lung studies were performed after 5 and 60 minutes of supine resting and after 5 minutes of standing. Transthoracic impedance was measured after 30 min of supine resting only.

Results: In patients with active NS the median number of US-B lines (a metric of lung water) after 5 min in supine position was markedly higher [12; Interquartile range :7-25; p<0.001] than in healthy subjects [4; 2-9]. The difference between patients [16, 11-35] and controls [4; 2-9] amplified (p<0.001) after 60 min of supine resting and attenuated after 5 min of standing [9; 7-25 vs 4; 3-5, p=0.001]. After NS remission, the number of US B lines reduced to 5 (4-18) at 5 min and to 6 (5-22) at 60 min (P<0.001) approaching the normal range. Lung congestion in patients with active disease was fully confirmed by transthoracic impedance measurements (p<0.001 vs healthy controls).

Conclusions: Asymptomatic pulmonary congestion is pervasive in patients with NS. A clinical trial is needed to assess the usefulness of the application of this technique for the management of patients with NS.

FR-PO589

The Incidence of Malignancies prior to the Diagnosis of ANCA-Associated Vasculitis (AAV) Is Not Increased in Comparison to the Incidence in the General Population Emma Elisabeth Van Daalen,¹ Chinar Rahmattulla,¹ Ron Wolterbeek,² Jan A. Bruijn,¹ Ingeborg M. Bajema.¹ ¹Pathology, Leiden Univ Medical Center, Leiden, Netherlands; ²Medical Statistics and Bioinformatics, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Several studies have found an increased malignancy risk before the diagnosis of AAV, especially in granulomatosis with polyangiitis (GPA), whereas data on microscopic polyangiitis (MPA) are scarce. It has been hypothesized that malignancies and AAV have common pathways in their pathogenesis (Ann Rheum Dis 2004, Rheumatology 2009). We studied the malignancy risks in patients before their AAV diagnosis to further elucidate this hypothesis.

Methods: We retrospectively retrieved data on 138 patients with biopsy-proven AAV diagnosed in the Netherlands. Malignancies prior to AAV diagnosis were identified using the Dutch National Pathology Database. The malignancy incidence was compared to the incidence in the general population, as reported by the Netherlands Cancer Registry. The Standardized Incidence Ratios (SIRs) were calculated, matching for gender, age and calendar time period. Separate analyses were performed for GPA and MPA.

Results: Twelve patients were diagnosed with cancer before the AAV diagnosis (mean follow-up: 11.8 years). Overall malignancy risk was not increased (SIR: 0.92, 95%CI: 0.48-1.61). Malignancy risks were also not increased for malignancies of the skin, bladder, kidney, lung, stomach, rectum and uterus (SIRs ranging from 1.71 to 4.77, not significantly increased). There was no difference in malignancy risk between GPA (SIR: 1.23, 95%CI: 0.49-2.53) and MPA (SIR: 0.98, 95%CI: 0.27-2.50) patients (relative risk: 1.26, 95%CI: 0.32-5.86).

Conclusions: We did not find an increased incidence of malignancies prior to AAV diagnosis compared to the general population. This is in contrast with previous studies, in which GPA was associated with preceding renal cell carcinoma, bladder cancer and non-melanoma skin cancer. Most other studies have not included microscopic polyangiitis patients, for which malignancy risk was not increased in our study. Our findings do not support the hypothesis that malignancies and AAV have a shared pathogenic pathway.

FR-PO590

Gastrointestinal Symptoms and Hypoalbuminemia in Chronic Kidney Disease Patients Xuehan Zhang,^{1,2} Nisha Bansal,³ Alan S. Go,⁴ Chi-yuan Hsu.^{2,4} ¹Peking Union Medical College Hospital; ²Univ of California-San Francisco; ³Univ of Washington; ⁴Kaiser Permanente Northern California.

Background: Hypoalbuminemia is an important risk factor for adverse outcomes in patients with CKD. Little is known about the relationship between gastrointestinal (GI) symptoms and serum albumin level in CKD.

Methods: This is a cross-sectional study of participants (N=3599) in the Chronic Renal Insufficiency Cohort (CRIC) study which collected information regarding potential uremic symptoms. For each of the 4 following symptoms: "bad taste in mouth," "loss of appetite," "nausea," "vomiting," we created a severity score by multiplying the number of symptomatic days in the past month by a severity scale of 1 to 3 (mild, moderate and severe). We then summed up the individual severity scores for an overall "GI symptom score." Dietary protein intake was measured via 24-hour urine. The main outcome was serum albumin level.

Results: Mean eGFR was 42.9±13.4ml/min/1.73m², and serum albumin level was 3.95±0.46 g/dL. 1702 subjects had one or more symptoms. Patients with lower eGFR were more likely to have GI symptoms.

Symptom	Odds Ratio (95% CI)			
	eGFR≥60ml/min/1.73m ² (n = 370)	eGFR 45-60ml/min/1.73m ² (n = 1166)	eGFR 30-45ml/min/1.73m ² (n = 1375)	eGFR<30ml/min/1.73m ² (n = 688)
A bad taste in your mouth?	1.0 (reference)	0.99 (0.75-1.32) P=0.9	1.22 (0.92-1.62) P=0.2	1.34 (0.99-1.82) P=0.06
Loss of appetite?	1.0 (reference)	1.21 (0.88-1.68) P=0.2	1.83 (1.34-2.52) P<0.001	2.01 (1.43-2.82) P<0.001
Nausea or being sick to your stomach?	1.0 (reference)	0.95 (0.72-1.25) P=0.7	1.24 (0.95-1.63) P=0.1	1.32 (0.98-1.78) P=0.06
Vomiting?	1.0 (reference)	1.08 (0.70-1.67) P=0.7	1.67 (1.11-2.54) P=0.02	1.76 (1.13-2.75) P=0.01

Compare with those without symptoms, CKD patients with progressively higher tertiles of GI symptom score were more likely to have lower serum albumin levels (-0.07, -0.09 and -0.13 g/dL, respectively)(all p<0.01). Patients with more GI symptom also had lower dietary protein intake (r=-0.141, P<0.01).

Conclusions: Increased prevalence of GI symptoms become apparent among CKD patients at relatively high eGFR levels (45 ml/min/1.73m²). These symptoms correlated with important nutritional parameters.

FR-PO591

Obstructive Lung Function in CKD: NHANES 2007-2012 Sankar D. Navaneethan,¹ Susana Arrigain,¹ Mahboob Rahman,¹ Jesse D. Schold.² ¹Cleveland Clinic; ²CWRU.

Background: Lung diseases are one of the leading causes of death in the general population. We aimed to study the prevalence of obstructive lung function in those with CKD. In addition, factors associated with obstructive lung function were examined.

Methods: Participants aged 20-79 years from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 who underwent spirometry testing using similar protocols were included in this analysis. Global Initiative for Chronic Obstructive Lung Disease classification of COPD (FEV1/FVC <0.7) based on post-bronchodilator spirometric results was used to establish the prevalence of obstructive lung function with weights adjusted for non-response to spirometry. CKD was defined as presence of eGFR <60 ml/min/1.73 m² and/or UACR >30 mg/g. Factors associated with obstructive lung function were identified using logistic regression model for the entire cohort, CKD and non-CKD groups separately (using baseline spirometry).

Results: Out of 11,995 participants (CKD=1563; Non-CKD=10,432) who completed the baseline spirometry testing, 1,986 participants were eligible for but only 1049 complete post-bronchodilator spirometry. Prevalence of obstructive lung function using baseline spirometry data were 25% in CKD and 13% in non-CKD and GOLD criteria were 17% in CKD and 8% in non-CKD. Each 5 ml/min lower eGFR and proteinuria were associated with higher odds of having obstructive lung function in the entire cohort.

Table. Factors associated with obstructive lung function in the study cohort

Variable	Multivariable adjusted OR* (95% CI) for obstructive lung function N=10,876
Age per 1 yr increase	1.06(1.06,1.07)
Gender (Female vs. Male)	0.53(0.44,0.64)
Race	
White	Ref
Black	0.64(0.54,0.76)
Mexican American	0.37(0.31,0.45)
Other Hispanic	0.42(0.31,0.57)
Other race	0.88(0.55,1.41)
Smoking status	
Former	2.17(1.77,2.67)
Current	4.83(3.94,5.91)
Never	Ref
BMI, kg/m ² (per 1 unit increase)	0.96(0.95,0.98)
Diabetes	0.94(0.73,1.21)
Hypertension	1.07(0.92,1.24)
Self-reported COPD	2.49(1.92,3.24)
eGFR (each 5 ml/min decline)	1.03(1.01,1.05)
Proteinuria (yes/no)	1.31(1.02,1.68)

a-model adjusted for demographics, smoking, comorbidities and kidney function

Old age, white race, smoking and self-reported COPD were associated with obstructive lung function in both CKD and non-CKD groups.

Conclusions: In this representative cohort of US population, prevalence of obstructive lung function is higher in those CKD. Lower eGFR and proteinuria are associated with obstructive lung function. Further studies examining the impact of lung diseases in CKD are warranted.

FR-PO592

Association of Serum Osteoprotegerin with Bone Loss in Chronic Kidney Disease: From the KNOW-CKD Study Chang Seong Kim,¹ Eun Hui Bae,¹ Seong Kwon Ma,¹ Kook-Hwan Oh,² Curie Ahn,² Soo Wan Kim.¹ ¹Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Republic of Korea; ²Dept of Internal Medicine, Seoul National Univ, Seoul, Republic of Korea.

Background: Osteoprotegerin (OPG), a potent inhibitor of osteoclast activation, decreases bone resorption and has protective effects on bone mineral density (BMD). This study examined the association between serum OPG and bone loss in patients with chronic kidney disease (CKD), a condition associated with increased risk of bone fracture and mineral and bone disorder.

Methods: BMD at the lumbar spine, total hip and femur neck was assessed by dual energy X-ray absorptiometry; and serum OPG was measured at baseline in 1,423 CKD patients in the prospective Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease. Osteoporosis was defined to T score ≤ -2.5 in patients aged over 50.

Results: Increasing quartiles of serum OPG were significantly associated with lower BMD (lumbar spine, total hip and femur neck) compared with the lowest quartile of serum OPG. Multivariable linear regression model indicated that serum OPG was independently associated with decreased lumbar spine and total hip BMD (B, -0.489; 95% confidence interval [CI], -0.883,-0.095; $P = 0.015$, B, -0.349; 95% CI, -0.672,-0.027; $P = 0.027$, respectively); but femur neck BMD was not associated with serum OPG in women. No independent association was found between serum OPG and BMD in men after adjustments. In multivariable logistic regression analysis, serum OPG was associated with increased risk of osteoporosis in women, but was not in men (odds ratio [OR], 4.01; 95% CI, 1.27-12.67, $P = 0.018$; OR, 0.31; 95% CI, 0.06-1.52, $P = 0.311$, respectively).

Conclusions: Serum OPG was independently associated with lumbar spine and total hip BMD and increased risk of osteoporosis in female CKD patients. However, these associations were not found in male CKD patients.

Funding: Government Support - Non-U.S.

FR-PO593

Growth in Children with Chronic Kidney Disease: A Report from the KNOW-Ped CKD (Korean Cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease) Eujin Park,¹ Yo Han Ahn,¹ Kyoung Hee Han,² Seong heon Kim,³ Joo Heon Lee,⁴ Young seo Park,⁴ Hee Gyung Kang,¹ Hae Il Cheong,¹ Curie Ahn,⁵ IL-Soo Ha.¹ ¹Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Korea; ²Dept of Pediatrics, Jeju National Univ School of Medicine, Jeju, Korea; ³Dept of Pediatrics, Pusan National Univ Children's Hospital, Yangsan, Korea; ⁴Dept of Pediatrics, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Korea; ⁵Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.

Background: Growth impairment is common in children with chronic kidney disease (CKD) with profound and lifelong psychosocial impact. We investigated the characteristics of growth in Korean children with CKD.

Methods: Clinical characteristics along with anthropometric measurements were examined in subjects of KNOW-Ped CKD, Korean Cohort Study for Outcome in Patients With Pediatric Chronic Kidney Disease. Findings of 322 children (M:F 218:104), who were enrolled to the study from July 2010 to December 2013 in seven major pediatric nephrology centers of Korea, were analyzed to investigate the characteristics of growth in Korean pediatric CKD.

Results: Mean height- and weight- z scores of Korean pediatric CKD patients were -0.88 ± 1.43 and -0.91 ± 1.65 . Mean BMI- z score was -0.36 ± 1.25 . Height defect was observed from early stage of CKD with mean height z-score 0.42 in CKD stage I. Short stature (z score < -1.88 , 20% of the subjects) and underweight (z score < -1.65 , 28% of the subjects) were associated with female sex, age younger than 2-year-old at enrollment, co-morbidity, and advanced CKD stage. Low BMI was associated with high blood pressure, co-morbidity and younger age. The final height-z score was -0.86 ± 1.19 , which is shorter than predicted adult height-z score (-0.33 ± 0.7) calculated from their parental height.

Conclusions: Growth failure is one of the most important complications in pediatric CKD patient. More profound height, weight and BMI impairment were associated with younger age and co-morbidity. Children with these findings need close attention on their growth and may require earlier intervention to avoid severe growth impairment.

Funding: Government Support - Non-U.S.

FR-PO594

Risk of Early Preterm Delivery in Pregnant CKD Patients – A Model for Counseling – The TOCOS Cohort (Torino Cagliari Observational Study) Giorgina B. Piccoli,¹ Rossella Attini,² Gianfranca Cabiddu,³ Antonello Pani,³ Tullia Todros.² ¹ss Nefrologia Dept of Clinical and Biological Sciences, Univ of Torino, Italy; ²Dept of Surgery, Univ of Torino, Italy; ³Nephrology, Brotzu Hospital, Cagliari, Italy.

Background: Chronic kidney disease (CKD), whose prevalence almost equals preeclampsia in pregnancy, increases the risks of adverse pregnancy outcomes; the degree is only partially known.

Methods: Objective: Development and internal validation of a prediction model to quantify the risks of early preterm delivery (<34 gestational weeks) selected as most relevant pregnancy outcome, in pregnant women with CKD. We developed the model in CKD

women. A homogeneously followed-up, low-risk pregnant population served as controls. Setting: The two largest Italian Outpatient Units dedicated to the multidisciplinary follow-up of CKD in pregnancy. Patients: Pregnant women with CKD: 503 live-born singletons in CKD; 835 low-risk controls (2000-2013). Measurements: Outcome: early pre-term delivery. The candidate variables were readily measurable, available, inexpensive (hypertension, proteinuria, kidney disease and function). Bootstrapping was used for internal validation.

Results: Early preterm delivery was more frequent in CKD (12.5%) versus controls (1%) ($p < 0.0001$). The most parsimonious model (Likelihood ratio test $p < 0.0001$; McFadden's pseudo $R^2 = 0.2290$) summarized various combinations of CKD stages, hypertension and proteinuria and defined a scale of risk. First step included CKD stage 1, normotension and proteinuria $< 1g/24h$ (OR:2.8); second step included CKD stages 2-5 without hypertension and proteinuria, and CKD stage 1 with either hypertension or proteinuria (OR:19.5 and 20.9); third step included CKD stages 2-5 with either hypertension or proteinuria (OR:44.7); the combination of hypertension and proteinuria was associated with the highest risk, but the low number of cases prevented precise quantification. Limitations: the study was performed in two Centers only. The number of cases with severe CKD is small.

Conclusions: The model may support counselling and clinical management by grading the risk for adverse pregnancy outcomes. Further studies are needed to externally validate the model.

FR-PO595

Solitary Kidney Is Associated with a Higher Risk of Adverse Outcomes in Pregnancy Jessica B. Kendrick,^{1,2} John R. Holmen,³ Gerard John Smits,¹ Michel Chonchol.¹ ¹Univ of Colorado Denver, Aurora, CO; ²Denver Health Medical Center, Denver, CO; ³Intermountain Health Care, Salt Lake City, UT.

Background: Chronic kidney disease is associated with adverse outcomes in pregnancy. Data regarding the effect of decreased glomerular filtration rate on pregnancy in women with a single kidney primarily has come from studies of kidney transplant recipients and living kidney donors. We set out to determine the risk of adverse outcomes in women with a single kidney from etiologies other than donation.

Methods: Using data from an integrated health care delivery system from 2000 through 2014, we conducted a study of 1,556 pregnant women hospitalized for childbirth. A total of 333 women had a single kidney with normal kidney function and were matched 1:3 by age and race to women with two kidneys. Adverse pregnancy outcomes included preterm delivery, delivery via cesarean section, preeclampsia/eclampsia, length of stay at hospital and low birth weight ($< 2,500$ g). Multivariate logistic regression analysis was used to examine the association between a single kidney and adverse pregnancy outcomes.

Results: Of the women with a solitary kidney, the mean (SD) age and mean (SD) gestational age at delivery was 28 ± 6 years and 38 ± 2 weeks, respectively. Compared to women with two kidneys, those with a single kidney had an increased risk of preterm delivery (OR 2.33, 95% CI 1.61-3.38), delivery via cesarean section (OR 1.85, 95% CI 1.33-2.56), and preeclampsia/eclampsia (OR 1.87, 95% CI 1.23-2.85). Women with a single kidney also had an increased risk of a length of stay > 3 days in the hospital (OR 1.50, 95% CI 1.01-2.20) and low infant birth weight (OR 2.99, 95% CI 1.95-4.59).

Conclusions: Women with a solitary kidney from causes other than kidney donation have a higher risk of adverse outcomes in pregnancy.

Funding: NIDDK Support

FR-PO596

Thiamine Deficiency in Non-Dialysis CKD Patients Yukako Ohyama, Toshikazu Ozeki, Shun Minatoguchi, Hideaki Shimizu, Yoshiro Fujita. *Nephrology and Rheumatology, Chubu Rosai Hospital, Nagoya, Japan.*

Background: Thiamine deficiency is associated with malnutrition, alcoholism and chronic diseases such as cancer. Long use of diuretics also induces thiamine deficiency, which is due to an increased urinary loss of thiamine. Some papers report that thiamine tend to accumulate because of decreased urinary flow in chronic kidney disease (CKD) patients. Others report that a protein restricted diet causes thiamine deficiency in CKD patients. This study aimed to examine the prevalence and factors associated with thiamine deficiency in CKD patients.

Methods: This is a single center cross-sectional study in patients with non-dialysis CKD under regular follow-up in nephrology center of Chubu Rosai Hospital from July 1, 2014 to January 31, 2015. The patients who meet the CKD criteria of Japanese Society of Nephrology were selected. We use the data from medical records, questionnaires and nutrition surveys.

Results: The study population consisted of 149 patients aged 71.2 ± 10.9 years with estimated GFR of 33.2 ± 18.2 ml/min per $1.73m^2$. They were divided to low thiamine group (serum thiamine level $< 30ng/ml$) and high thiamine group (serum thiamine level $\geq 30ng/ml$). In univariate comparisons, patients with low thiamine group had significantly lower protein intake which is estimated by the nutrition survey. The use of loop diuretics was not associated with thiamine deficiency. In multivariate analyses, high age, low eGFR and low protein intake, especially less than $0.8g/kg$, were independently associated with thiamine deficiency.

	Odds Ratio(95% CI)	P Value
Age (years)	1.12(1.00-1.26)	0.047*
Sex (men)	0.89(0.12-6.45)	0.91
Malignancy (yes)	0.59(0.05-6.49)	0.67
Alcoholism (yes)	0.00(0.00-)	1.00
furosemide (yes)	0.04(0.00-1.22)	0.07
eGFR	0.86(0.75-0.98)	0.02*
protein intake <0.6 g/kg	46.21(1.77-1208.48)	0.02*
protein intake ≥0.6 and <0.8 g/kg	30.93(1.47-649.92)	0.03*
protein intake ≥0.8 and <1.0 g/kg	12.57(0.84-187.20)	0.07
protein intake ≥1.0 g/kg	1.00(reference)	

Conclusions: Protein intake is an important factor for thiamine levels of CKD patients. Protein restriction for CKD patients especially with high age and low eGFR have a high risk of thiamine deficiency.

FR-PO597

Controlled Attenuation Parameter Measured by FibroScan Is Closely Associated with Metabolic Syndrome in Patients with Chronic Kidney Disease Meiyuan Wu,¹ Sul A Lee,² Chang-Yun Yoon,² Tae ik Inst,³ Shin-Wook Kang,^{1,2} Tae-Hyun Yoo.^{1,2} ¹Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea; ²Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; ³Dept of Internal Medicine, NHIC Ilsan Hospital, Gyeonggi-do, Korea.

Background: Hepatic steatosis can be determined by the measurement of liver controlled attenuation parameter (CAP) using FibroScan. Although the practical methods predicting the risk of metabolic syndrome (MS) development are lacking, recent studies represent that this parameter is closely correlated with the presence of MS in the general population. Therefore, we investigated whether CAP measured by FibroScan could predict the presence of MS in chronic kidney disease (CKD) patients.

Methods: A total of 468 CKD patients were evaluated. MS was defined by using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Multivariate logistic regression analysis was used to identify the independent association between CAP and MS.

Results: The mean age of the patients was 57.5 years and 225 patients (48.1%) were male. The mean value of CAP was 241.7 dB/m. CAP was independently associated with body mass index ($\beta=7.818$, $P<0.001$), triglyceride ($\beta=0.246$, $P=0.002$) and estimated glomerular filtration rate (eGFR) ($\beta=0.581$, $P=0.005$). MS was diagnosed in 142 (30.3%) patients. In patients with MS, diabetes was more prevalent (59.9 vs. 25.8%, $P<0.001$), hemoglobin (13.1±2.4 vs. 12.6±2.1 g/dL, $P=0.026$) and CAP (262.0±60.6 vs. 232.9±49.0 dB/m, $P<0.001$) levels were significantly higher, while eGFR (82.9±27.5 vs. 91.6±26.0 mL/min/1.73m², $P=0.001$) was lower compared with patients without MS. Multivariate logistic regression analysis revealed that high CAP levels were independently correlated with the increased risk of MS (per 1 dB/m increase, odds ratio=1.010, 95% confidence interval=1.002-1.018, $P=0.014$) after adjustment for confounding factors.

Conclusions: High CAP levels measured by FibroScan were significantly associated with an increased risk of MS in CKD patients. These data suggests liver FibroScan could be a practical method for evaluating the risk of MS development in CKD patients.

FR-PO598

Outcomes in Women Switched from Mycophenolate to Azathioprine in Advance of Pregnancy Kate S. Wiles,¹ Adam D. Jakes,² Asra Alwandi,¹ Kate Bramham,¹ Paramit Chowdhury,¹ Lucy C. Chappell,¹ Catherine Nelson-piercy,¹ Liz Lightstone.² ¹Guy's and St. Thomas' NHS Foundation Trust; ²Imperial College London.

Background: Mycophenolate is teratogenic and should be replaced in advance of pregnancy. There is concern that this change may have adverse consequences including transplant rejection and disease flare. The aim of this study was to determine the risk of adverse outcome in women switched from mycophenolate to azathioprine.

Methods: Records of women attending regional renal pre-pregnancy counselling clinics 2011-2014 were examined. Women taking mycophenolate were included and the decision to switch to azathioprine reviewed. Outcomes were a decline in eGFR within a year, renal biopsy, disease flare or rejection, and conversion back to mycophenolate. Pregnancy outcomes were analysed.

Results: Data were available for 60 women (31 kidney transplant, 4 kidney-pancreas transplant and 25 glomerulonephritis, predominantly lupus). Most women were considered eligible for a switch to azathioprine and one woman chose to switch against advice.

Decision to switch	n	%
Yes	44	73
No: Unstable graft function	7	12
No: No immediate plans for pregnancy	5	8
No: Active lupus	2	3
No: Advanced renal dysfunction as a barrier to pregnancy	2	3

There was a mean fall in eGFR of 4.8mL/min/1.73m²/year in the women who did not conceive within 12 months of the switch (n=26). This decline included two flares of biopsy-confirmed lupus nephritis and one case of progressive antibody mediated rejection in the woman advised not to switch. 3/45 (7%) of women had a renal biopsy. There were no cases of acute rejection. 10/45 (22%) of women were converted back to mycophenolate, 3 empirically and 7 with a clinical indication. There were 14 pregnancies. 63% were complicated by pre-existing hypertension or pre-eclampsia. 67% of women had a Caesarean delivery and 33% of babies were preterm (<37 weeks).

Conclusions: Most women taking mycophenolate can be converted to azathioprine. Drug switch was not associated with acute rejection, but lupus flare did occur. Most women did not require conversion back to mycophenolate. Pre-eclampsia and pre-term delivery are associated with chronic kidney disease and are not thought to be due to medication use.

FR-PO599

Chronic Kidney Disease Linearly Predicts Outcomes After Elective Total Joint Arthroplasty Edward J. Filippone,¹ Timothy L. Tan,¹ Dean D. Tan,¹ Michael M. Kheir,¹ Antonia F. Chen.¹ ¹Medicine, Thomas Jefferson Univ, Philadelphia, PA; ²Orthopedics, Thomas Jefferson Univ.

Background: Kidney disease has been widely associated with increased complications in total joint arthroplasty (TJA). The purpose of this study is to determine the association of kidney disease severity as measured by the chronic kidney disease (CKD) staging system with complications and outcomes after TJA.

Methods: A retrospective review of an institutional database of 12,308 primary TJAs (6,361 hips and 5,947 knees) from 2008 to 2013 was performed. The following preoperative variables were obtained from medical records: chemistry 7 panel, Elixhauser comorbidities, and demographic factors. CKD stages were defined based on estimated glomerular filtration rate in mL/min/1.73m² (eGFR): (1) 90+, (2) 60-89, (3A) 45-59, (3B) 30-44, (4) 15-29, and (5) <15. Multivariate analysis was performed to assess the independent influence of CKD stage on the aforementioned endpoints.

Results: Patients with CKD stage greater than 2 demonstrated an increased risk of transfusions (CKD 3A odds ratio [OR]: 1.67, CKD 3B OR: 2.80, CKD 4 OR: 2.24), length of stay greater than 3 days (CKD 3A OR: 1.34, CKD 3B OR: 1.39, CKD 4 OR: 3.57), and in-hospital complications (CKD 3A OR: 1.21, CKD 3B OR: 1.80, CKD 4 OR: 3.36) compared to all patients with eGFR > 60. Additionally, the relationship between eGFR and the above complications were found to increase linearly rather than exponentially at a certain threshold. In contrast, CKD stage was not associated with septic or aseptic revisions.

Conclusions: Severe CKD is associated with an increased risk of transfusion, length of stay, and in hospital complications. Rather than finding a clear threshold, complications increased linearly with disease severity. Surgeons should be cognizant of this increase when evaluating TJA patients with renal disease.

FR-PO600

The Assessment of Incidental Risk for Microalbuminuria According to the Level of Depression Scale Dong-Young Lee,¹ Younjoo Jung,¹ Beom Kim,¹ Kyoung Hyoub Moon,¹ Sung Keun Park.² ¹Internal Medicine, VHS Medical Center, Seoul, Korea; ²Total Health Care, Kangbuk Samsung Hospital, Seoul, Korea.

Background: Depression is one of the most common psychiatric disorders. The burden of disease for depression goes beyond function and extends to somatic health. A growing body of evidence shows that depression is significantly associated with chronic kidney disease. Nonetheless, the incidental relationship between microalbuminuria and depression was not identified yet. Therefore, we conducted this study to investigate incidental relationship of microalbuminuria with depression scale.

Methods: This study was conducted for 45,293 Korean men and their spouses without microalbuminuria who got medical health check up in Kangbuk Samsung Total healthcare center in 2010. To assess the degree of their depression, Center for Epidemiology Studies-Depression Scale (CES-D) was used (CES-D ≤ 15: normal, CES-D 16-20: moderate risk group, CES-D > 21: high risk group). On the basis of CES-D score in 2010, they were classified into 3 groups (normal, moderate, high risk group) and monitored for the development of microalbuminuria from January, 2011 to April, 2015.

Results: While the general incidence was 1.7%, the incidence of microalbuminuria increased in proportion to the risk score of depression evaluated by CES-D (CES-D ≤ 15: 0.4%, CES-D 16-20: 1.8%, CES-D > 21: 3.6%). When the hazard ratio (HR) of normal group (CES-D ≤ 15) was set to reference value (HR: 1.00), the HRs for microalbuminuria also increased according to the score of CES-D scale. In addition, these associations were preserved even after adjusting for the various metabolic covariates such as age, physical activity, total cholesterol, LDL-cholesterol, triglyceride, body mass index, and obesity [CES-D 16-20: 1.98, CES-D > 21: 3.37].

Conclusions: Our study showed that the risks of microalbuminuria in proportion to the severity of depression. These findings imply the clinical role of the depression for

development of the microalbuminuria. Especially, considering the clinical significance of microalbuminuria as an early predictor of health outcomes related to chronic kidney disease, our study implications can be expanded to other diseases entity.

FR-PO601

Outcomes in CKD Patients with Hospital Acquired Complications Babak Bohlouli,¹ Terri Jurgens Jackson,² Marcello Tonelli,³ Scott Klarenbach.¹ ¹Medicine, Univ of Alberta, Edmonton, AB, Canada; ²Northern Clinical Research Centre, Univ of Melbourne, Epping, Vic, Australia; ³Medicine, Univ of Calgary, Calgary, AB, Canada.

Background: Patients with CKD are at increased risk of hospital acquired complications (HACs) including those considered preventable. The impact of HACs on patient and health system outcomes has not been well described.

Methods: Subjects hospitalized from April 1, 2003 to March 31, 2008 from a population based cohort (Alberta Kidney Disease Network) were studied. Outpatient eGFR and proteinuria (protein/creatinine ratio or dipstick) in the year prior to index hospitalization were used to define CKD status. Co-morbid conditions were identified using validated algorithms applied to administrative data. ICD 10 CA was used to classify reason for admission. A specific diagnostic indicator (type II) was used to identify hospital acquired complications (HACs) that were sub-classified as “potentially” and “always” preventable. We studied the following outcomes: re-admission within 90 days of discharge, all cause mortality at 90 days, and index hospitalization costs. Multivariable regression models examined the association of HACs with re-admission, mortality, and incremental health care costs, accounting for confounders.

Results: Of 536,549 subjects, 45,377 (8.5%) with CKD were hospitalized. In patients with HACs, the OR of re-admission and death at 90 days was 1.37 (95% CI: 1.32 – 1.43), and 3.31 (95% CI: 3.06 – 3.58) respectively compared with those without HAC. Hospitalizations with any HAC were associated with median incremental health costs of \$4028 (95% CI: \$3898 – \$4158). A graded association was observed for those outcomes with increasing number of HACs and severity of CKD. Similar results were noted when only potentially preventable HACs were considered.

Conclusions: Complications occurring during hospitalization in patients with CKD is independently associated with an increased risk of hospital re-admission, health care costs, and mortality. Targeted strategies to reduce HACs in this patient population may have a significant benefit.

FR-PO602

Plasma Proteins Associated with Declining Renal Function in Patients with Type 1 Diabetes: Results of a Global Proteomic Analysis Using SOMAscan Platform Andrew L. Schlaffly, Monika A. Niewczasz, Marcus G. Pezzolesi, Andrzej S. Krolewski. *Joslin Diabetes Center, Boston, MA.*

Background: Increases in serum creatinine and cystatin C are considered measures of declining renal function in patients with diabetes.

Methods: To search for other proteins correlated with declining renal function, we conducted a follow-up study, following 30 patients with T1D and proteinuria for 1-3 years. Mean eGFR was 67 ml/min at baseline, and was 59 ml/min at the end of follow-up. Plasma concentrations of circulating proteins were measured on the SOMAscan platform at baseline and at the end of follow-up. The platform measured 954 proteins for each of the 30 patients, with median limit of detection (LOD) of 1.6pg/mL, dynamic range of 8 logs, and median coefficient of variation (CV) of 5% for individual proteins measured repeatedly in replicate runs of plasma samples.

Results: Renal function change during follow-up in each patient was expressed as the difference between eGFR_{cre} at baseline and at follow-up and was referred to as ΔGFR (mean: -7.7 ml/min, range: -44 ml/min to 11 ml/min). For each protein, the Spearman rank correlation coefficient between ΔGFR and the percent change in the protein’s level (RFU) was used to measure the protein’s association with renal function decline. In 27 proteins, concentrations increased with decreasing renal function (r: -0.67 to -0.46, p<0.01). In 16 proteins, concentrations decreased with decreasing renal function (r: 0.46 to 0.57, p<0.01). The top 5 proteins in each category are shown below.

Negatively correlated proteins:			Positively correlated proteins:		
Name	r _{Spearman}	P	Name	r _{Spearman}	P
IL-17F	-0.67	5.5E-05	ATS1	0.57	1.0E-03
ARMEL	-0.62	2.2E-04	CDC2	0.54	2.2E-03
TNFRSF19L	-0.62	2.4E-04	FGF6	0.53	2.6E-03
TNFRSF1A	-0.57	1.1E-03	CA1	0.50	4.7E-03
Cystatin C	-0.56	1.1E-03	CDH12	0.50	4.8E-03

Conclusions: In conclusion, increasing or decreasing concentrations of plasma proteins with eGFR loss may reflect worsening renal function, as is the case with cystatin C. However, changes in plasma concentration of these proteins may represent the extent and intensity of the disease process underlying progressive renal decline, which is most likely the case with IL-17F and the TNFR’s.

Funding: NIDDK Support, Pharmaceutical Company Support - Bristol-Myers Squibb

FR-PO603

Mass Spectrometry Imaging Reveals Disease Specific Alterations in Protein Abundance in Human Diabetic Nephropathy Haichun Yang,¹ Audra M. Judd,² Michelle Reyzer,² Jeremy L. Norris,² Richard M. Caprioli,² Raymond C. Harris,³ Agnes B. Fogo.¹ ¹Pathology, Microbiology and Immunology, Vanderbilt Univ; ²Mass Spectrometry Research Center, Vanderbilt Univ; ³Nephrology, Vanderbilt Univ, Nashville, TN.

Background: Diabetic nephropathy (DN) is a major complication in diabetic patients. However, progression and albuminuria are variable among patients with DN. Matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI) is a technology that acquires molecular information from thin tissue sections in a spatially-defined manner. We examined MALDI mass spectra to discover alterations in protein expression in human DN glomeruli, and compared to the morphology and clinical features.

Methods: DN biopsies (n=36) and normal kidney (n=9) were assessed. DN cases were divided into mild, moderate and severe, based on biopsy findings. Follow-up was available in 23 patients, and patients were sub-grouped into stable DN (decreased eGFR ≤50%, n=13) vs. progressive DN (decreased eGFR >50%, n=10). Peptide mass spectra were acquired over the mass-to-charge range 600-4500 from at least 12 glomerular areas per case.

Results: DN patients had reduced eGFR and increased proteinuria, compared to normal. Mass spectrometry showed 168 peptide peaks, with 8 peaks increased and 21 peaks decreased in DN compared to normal. Moderate and severe DN showed more nodular glomerulosclerosis than mild DN by study design (moderate 2.13±0.10, severe 2.17±0.22 vs. mild 0.43±0.30, 0-4+ scale, p<0.05) and mesangial expansion (moderate 1.97±0.09, severe 2.28±0.15 vs. mild DN 1.21±0.15, p<0.05). Peptide maps were more similar in moderate vs severe DN groups, compared to mild DN. Thirteen of 168 peptide peaks were significantly different among three groups. In progressive DN, 10 peptide peaks were decreased and 1 was increased, compared to stable DN. Of note, these peaks differed from those associated with the morphologic phenotype.

Conclusions: We conclude that different peptide maps correlate with DN onset, severity and prognosis, and that clinical and morphological phenotypes have differing proteomic correlates. These peptides will now be further validated and identified by MS/MS fragmentation and database searching.

Funding: NIDDK Support

FR-PO604

Urine Metabolomic Profiling Reveals a Unique Signature for Type 2 Diabetes Jane J. Kim, Rintaro Saito, Satoshi Miyamoto, Minya Pu, Loki Natarajan, Kumar Sharma. *Univ of California, San Diego.*

Background: Increased circulating branched chain amino acids (BCAAs) are associated with type 2 diabetes (T2D) and insulin resistance. However, it is not clear whether increased plasma BCAA concentrations result from increased synthesis, or impaired degradation or excretion. Here, we employ a targeted metabolomics approach to evaluate diabetic patients without overt kidney disease to identify urine metabolites associated with T2D, presenting potential urine biomarkers for clinical prediction and further insight into disease pathogenesis.

Methods: We measured 105 urine metabolites by GC/MS in a screening T2D cohort (n=27), validation T2D cohort (n=14), and healthy control group (n=23). We also examined kidney cortex of *db/db* and control *db/m* mice to measure gene expression by Illumina microarray and protein expression by western blot.

Results: Following FDR correction, 57 metabolites were found to be different in the screening cohort compared to controls. When these 57 metabolites were carried forward for analysis in a validation T2D cohort, 24 of these urine metabolites were confirmed to be different from controls using Bonferroni adjustment for multiple comparisons. 16 of the 24 significant metabolites were amino acids, and 8 of these represented BCAA degradation products. To further investigate BCAA metabolism, we examined kidney tissue from *db/db* mice and found that the gene expression of key enzymes related to BCAA catabolism was decreased. Western blot studies confirmed that renal expression of branched-chain ketoacid dehydrogenase, a mitochondrial enzyme complex that catalyzes an irreversible step in BCAA catabolism, was reduced in *db/db* mice compared with controls.

Conclusions: Prior studies have reported impaired mitochondrial BCAA metabolism in adipose, muscle and liver. However, our results show a robust pattern of increased BCAA metabolites, likely reflecting increased BCAA catabolism and/or increased metabolic flux. The reduced renal expression of BCAA enzymes supports a role for dysregulated BCAA metabolism by the kidney. The elevated BCAA metabolites may have an affect on regulating insulin resistance and the development of kidney disease with T2D.

Funding: NIDDK Support

FR-PO605

Urinary Matrix Metalloproteinase Activities Are Associated with Renal Hyperfiltration in Adolescents With Type 2 Diabetes Petter Bjornstad,¹ Laura Pyle,¹ Janet Snell-bergeon,¹ Karen S. Moulton,² Kristen Nadeau.³ ¹Barbara Davis Center for Diabetes; ²Univ of Colorado Denver; ³Children’s Hospital Colorado.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. Matrix metalloproteinases (MMP) modify extracellular matrix during vascular remodeling and are known to be elevated in diabetes, and associated with DN in type 1 diabetes. We hypothesized that activities of latent MMP and neutrophil gelatinase-associated lipocalin (NGAL) proteins in urine would be associated with microalbuminuria and hyperfiltration in adolescents with type 2 diabetes (T2D).

Methods: 295 adolescents with T2D (14.0±1.8 years, <2 years duration, BMI ≥85%, and HbA1c ≤8%) in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study had urine and blood evaluated at baseline and annually for 5-years. MMP2, MMP9 and NGAL activities were measured by gelatin zymography and normalized to urine creatinine. Microalbuminuria was defined as albumin-to-creatinine ratio (ACR) ≥30mg/g. Estimated GFR was calculated by Schwartz (eGFR=36.5*height/creatinine) and hyperfiltration defined as ≥135mL/min/1.73m². Mixed models evaluated the longitudinal relationships between MMP-2, MMP9 and NGAL with eGFR, ACR, hyperfiltration and microalbuminuria respectively. MMP2, MMP9 and NGAL-MMP9 activities were natural log-transformed (ln) due to skewed distribution.

Results: MMP2, MMP9 and NGAL-MMP9 were associated with eGFR, but not ACR over time after adjusting for age, sex, HbA1c, SBP and treatment group. One standard deviation increase in ln MMP2, ln MMP9 and ln NGAL-MMP9 were each associated with a greater odds of having microalbuminuria and hyperfiltration over time, respectively.

Table Mixed-logistic regression models

	Hyperfiltration		Microalbuminuria	
	OR [*] , 95% CI, P-value			
MMP2	1.3 (1.1-1.5)	0.001	1.6 (1.3-1.9)	<0.0001
MMP9	1.2 (1.0-1.4)	0.046	1.4 (1.2-1.7)	0.001
NGAL-MMP9	1.2 (1.0-1.5)	0.03	1.4 (1.1-1.7)	0.004

*Odds ratio of hyperfiltration or microalbuminuria per 1 SD increase in natural log transformed variable adjusted for age, sex, SBP, HbA1c and treatment group

Conclusions: In conclusion, urinary MMP and NGAL activities were associated with early DN in adolescents with T2D over time.

Funding: Other NIH Support - Juvenile Diabetes Research Foundation Grants 1-2007-622 (K. S. Moulton) and 5-2008-291 (K. Nadeau); National Institutes of Health Grants RC4 DK090852 (K. S. Moulton) and K23 RR020038 (K. Nadeau)

FR-PO606

A Serum Metabolite Classifier Predicts Response to ARBs in Diabetes Michelle Pena,¹ Bernd Mayer,² Andreas Heinzl,² Peter Rossing,³ Hiddo Jan Lambers Heerspink,¹ ¹UMC Groningen; ²Emergentec Biodevelopment; ³Steno Diabetes Center.

Background: Individual patients show a large variability in albuminuria response to Angiotensin Receptor Blockers (ARB). Identifying novel biomarkers that predict ARB response may help optimize treatment. We aimed to discover and validate a novel serum metabolite classifier that predicts response in urinary albumin excretion (UAE) to ARBs in diabetes.

Methods: Flow injection analysis/liquid chromatography-tandem mass spectrometry based targeted metabolomics was performed on serum samples from type 2 diabetes patients (n=49) enrolled in a clinical study assessing the effect of irbesartan 300mg/day. Individual serum metabolites were selected with LASSO regression to predict UAE response to irbesartan. The classifier was developed with ridge regression. Improvement in risk prediction was tested on top of a control model (age, sex, HbA1c, SBP, GFR, UAE) by assessing differences in explained variation (R²) between the control model and the classifier model. The classifier was externally validated in a clinical study in type 1 diabetes patients (n=50) testing the effect of losartan 100mg/day. Metabolite mapping was performed on a molecular model of diabetic kidney disease to identify underlying molecular processes contributing to ARB response.

Results: The classifier included 21 metabolites. Median reduction in UAE was -42% [-69,-8] in type 2 diabetes. The classifier was significantly associated with UAE response to irbesartan (p<.001) and significantly improved prediction of UAE response on top of the control model (R² increase from 0.10 to 0.69; p<.001). In the external validation cohort, median reduction in UAE was -43% [-62,-23]. The classifier significantly improved prediction of UAE response to losartan (R² increase from 0.17 to 0.52; p<.001). Metabolites included in the classifier were assigned to stress/inflammation pathways and downstream consequences of fibrosis and extra cellular matrix remodeling. Moreover, ADMA, impacting eNOS activity, appears to be a specific factor relevant in ARB response.

Conclusions: A classifier of 21 serum metabolites was identified and externally validated to significantly improve prediction of albuminuria response to ARBs in diabetes.

FR-PO607

Is Urinary Proteomics Useful to Predict Retinopathy in Type 2 Diabetic Patients in the DIRECT 2 Study Mie K. Eickhoff,¹ Marie Fridmodt-Moller,¹ Morten Lindhardt,¹ Mohammed Dakna,² Harald Mischak,^{2,3} Direct Steering Group,⁵ Peter Rossing,^{1,4} ¹Steno Diabetes Center, Gentofte, Denmark; ²Mosaiques Diagnostics GmbH, Hannover, Germany; ³BHF Glasgow Cardiovascular Research Centre, Univ of Glasgow, Glasgow, United Kingdom; ⁴HEALTH, Univ of Aarhus, Denmark; ⁵Univ College London, London, United Kingdom.

Background: Diabetic microvascular complications affect the kidney and the eyes, being a leading cause of renal failure and blindness. Urinary proteomics has shown promise as an early indicator of future development of diabetic nephropathy. Here we investigate if this could also predict progression of diabetic retinopathy.

Methods: In a post-hoc study of the DIRECT 2 study, a randomized, controlled clinical trial of candesartan for prevention of retinopathy, we studied patients with type 2 diabetes

and normoalbuminuria (n=792), followed for a mean of 4.7 years. We address the predictive ability of a previously defined CKD risk score based on proteomic measurement of 273 urinary peptides (CE-MS). We also assessed the possibility of a new EYEscore based on discriminative features chosen out of 1161 peptides in a training set of 528 patients. Progression were either 2 step (E2) (primary) or 3 step (E3) change in retinopathy on the concatenated Early Treatment Diabetic Retinopathy Study severity scale.

Results: Progression of retinopathy was seen in 37% of E2 and 19% of E3 patients. None of the peptides were significantly differentially expressed in cases vs control. In Cox models five peptides were associated with E3 but not E2 in the training set but were not validated. The CKD risk score was able to predict E3 (HR 1.54 95% CI 1.02 to 21.34, p=0.042) but not E2 (HR 1.14 p=0.34) during follow-up, independent of treatment (candesartan/placebo), age, gender, systolic BP, baseline UAER, baseline eGFR, HbA_{1c} and diabetes duration.

Conclusions: In this cohort of patients with type 2 diabetes and normoalbuminuria from a large intervention study, the CKD classifier was an independent predictor of severe but not mild progression in retinopathy. It was not possible to develop a retinopathy specific marker panel with clinically relevant accuracy.

Funding: Pharmaceutical Company Support - The DIRECT study was jointly funded by AstraZeneca and Takeda.

FR-PO608

Urine Exosomal Analysis Reflects Underlying Kidney Pathology Better Than Whole Urine Analysis Krishnamurthy P. Gudehithlu,¹ Ignacio Garcia-Gomez,² Jane Vernik,^{1,2} Carolyn S. Brecklin,^{1,3} Mark A. Kraus,^{1,2} David J. Cimbaluk,² Peter D. Hart,^{1,2} George Dunea,^{1,3,4} Jose A.L. Arruda,^{1,3,4} Ashok K. Singh,^{1,3,4} ¹Div of Nephrology, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL; ²Dept of Internal Medicine, Rush Univ Medical College, Chicago, IL; ³Section of Nephrology, Univ of Illinois at Chicago, Chicago, IL; ⁴The Hektoen Inst of Medicine, Chicago, IL.

Background: Predicting or diagnosing underlying kidney pathology by analyzing whole urine has remained unrealized. This is because whole urine mostly represents proteins from the plasma and little from the kidney. Urinary exosomes, on the other hand, being kidney-derived, contain proteins of the kidney. We experimentally tested the hypothesis, 'urine exosomal proteome more truly represents the underlying pathology of kidney disease than a whole urine based analysis.' Comparison between whole urine and urine exosomal gelatinase and ceruloplasmin, two kidney disease markers, was performed on normal and diabetic kidney disease patients.

Methods: Urinary exosomes were separated from urine by ultra-centrifugation. Gelatinase, an enzyme which measures matrix degrading activity collectively from several matrix metalloproteinases (mainly MMP-2, 9), was measured by an activity assay using fluoresceinated gelatin as the substrate, and ceruloplasmin, an oxido-reductase enzyme involved in iron metabolism, was measured by sandwich ELISA. Biopsies were immunostained for MMP-9 and ceruloplasmin.

Results: We found that changes in both, gelatinase (decreased activity; 20-50%; p<0.05) and ceruloplasmin (increased levels; 300%; p<0.05), in the urinary exosomes of diabetic kidney patients were in agreement with the alterations of these two proteins in the kidney tissue as judged by immune-staining. In contrast, the levels of these two proteins in the whole urine were highly variable (p=NS) and in disagreement with the results of immune-staining.

Conclusions: In conclusion, our findings support our hypothesis that protein markers found in urinary exosomes better reflect the changes in the kidney than protein measurements carried out in whole urine samples.

Funding: Private Foundation Support

FR-PO609

Neutrophil Gelatinase Associated Lipocalin as an Early Biomarkers of Nephropathy in Diabetic Patients and Effect of RAAS Blockade on NGAL as Marker of Tubular Damage in Diabetic Nephropathy Anupama Kaul, Dharmendra Bhaduria, Narayan Prasad, Amit Gupta, Raj K. Sharma. *Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, India.*

Background: T2DM is the primary cause leading to kidney disease. Novel, more sensitive biomarkers that may be used to detect diabetic nephropathy at an early stage, and possibly also detect disease progression or regression after drug therapy.

Methods: • 150 Diabetic patients were enrolled in the study from nephrology and endocrinology OPD at Sanjay Gandhi Post Graduate Institute Of Medical Sciences, Lucknow India from 2012-14, 50 each of normo-,micro- and macroalbuminuric with 50 normal healthy control. Serum NGAL and cystatin C were measured at enrollment and after 12-15 months. ACEI as intervention was given in all normo hypertensive ,microalbuminuric and macroalbuminuric Diabetics and after follow up period 1 year repeat NGAL levels assessment. Normoalbuminuric ,normotensive individuals with raised NGAL at the baseline and follow up after 1 year were assessed.

Results: • As compared to control population the normoalbuminuric Diabetics had higher serum as well as urinary NGAL levels but lesser than microalbuminuria. Mean NGAL levels were not significantly different between Normoalbuminuric diabetics and controls. At re-evaluation, mean NGAL value and mean eGFR value in patients with diabetes had increased (p=0.078 and p=0.006 respectively). At both baseline and reevaluation, NGAL positively correlated with cystatin C (p<0.001) and creatinine (p=0.010). NGAL correlated negatively with eGFR (r=-0.26, p=0.049). Among micro,macroalbuminuric diabetics the baseline urine albumin excretion rate was significantly correlated with the rate of eGFR

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

decline ($P < 0.004$). The baseline serum NGAL levels were also correlated with the rate of eGFR decline ($P = 0.066$). During ACE inhibitor treatment ie Ramipril 5mg daily , urine-NGAL was reduced (95% CI) 11% (not significant).

Conclusions: Urine-NGAL are elevated in Type 2 diabetic patients, with or without albuminuria, indicating tubular damage at an early stage. ACE inhibitor Ramipril reduced urine-NGAL predominantly in Micro/macroatbuminuric diabetic patients .

FR-PO610

Mechanism of Increased Urinary Full-Length Megalin Excretion in Type 2 Diabetes Mellitus Patients with Nephropathy Shankhajit De,¹ Shoji Kuwahara,² Michihiro Hosojima,³ Tomomi Ishikawa,¹ Ryohei Kaseda,³ Yusuke Yoshioka,⁴ Yoshiki Suzuki,⁵ Ichiei Narita,¹ Takahiro Ochiya,⁴ Akihiko Saito.² ¹*Clin Nephrol & Rheumatol, Niigata Univ, Niigata, Japan;* ²*Applied Mol Med, Niigata Univ, Niigata, Japan;* ³*Clin Nutr Sci, Niigata Univ, Niigata, Japan;* ⁴*Mol & Cell Med, NCCRI, Tokyo, Japan;* ⁵*Health Admn Center, Niigata Univ, Niigata, Japan.*

Background: Megalin, an endocytic receptor of proximal tubule cells (PTCs), is excreted into urine in both of the extracellular domain and the full-length forms. Previously we developed urinary ELISA systems to measure the two forms of megalin and found that the excretion of the full-length form, mainly present in the insoluble urinary fraction, may be a candidate biomarker for the progression of diabetic nephropathy (DN). We thus aimed to investigate the molecular mechanism of urinary excretion of the full-length form of megalin.

Methods: Megalin content of urinary extracellular vesicles (EVs) from normal control and type 2 diabetes mellitus (T2DM) patients with different albuminuria stages were measured by western blotting. By immunoelectron microscopy and Nanoparticle Tracking Analysis using NanoSight®, we characterized the size and number of the EVs. To study increased EVs excretion *in vitro*, we cultured immortalized rat proximal tubule cells (IRPTCs) and treated with advanced glycation end products-modified bovine serum albumin (AGEs).

Results: The number of urinary EVs excretion is increased in T2DM patients in comparison with the normal control subjects in a correlation with the progression of DN. The megalin content of the EVs are also increased in those patients, indicating increased excretion of PTC-derived EVs in DN condition. However, other tubular segment markers in EVs are not well correlated with the disease progression. By immunoelectron microscopy we found that megalin is excreted through the smaller vesicles which are likely to be exosomes in nature. Treatment on IRPTCs with AGEs for 24h causes lysosomal dysfunction which subsequently increases multivesicular body formation as well as release of megalin-containing exosomes.

Conclusions: Exocytosis-mediated urinary excretion of full-length megalin via exosomes might be a useful biomarker for early detection and progression of DN.

Funding: Government Support - Non-U.S.

FR-PO611

Urinary Excretion of Kidney Aquaporins as Possible Biomarker of Diabetic Nephropathy Luigi Rossi,¹ Maria Celeste Nicoletti,² Monica Carmosino,² Antonella Di Franco,¹ Francesca Indrio,¹ Rosa Lella,¹ Luigi Laviola,¹ Maria Svelto,² Loreto Gesualdo,¹ Giuseppe Procino.² ¹*DETO, Univ of Bari, Bari, Italy;* ²*Dept of Biosciences, Biotechnologies and Biopharmaceutic, Univ of Bari, Bari, Italy.*

Background: Diabetic nephropathy (DN) is is classified into four hierarchical glomerular lesions on the basis of histological analysis of kidney biopsies. This is clearly a highly invasive diagnostic approach numerous studies have been conducted to identify a non-invasive biomarker of the disease, but none of these is considered to be sufficiently specific and sensitive Experimental evidences showed that the water channel aquaporins (AQP), expressed at the plasma membrane of epithelial cells lining in the kidney tubule, are often dysregulated during DN. Interestingly, apical membrane protein are excreted in the urinary space as nano-scale exosome vesicles, to an extent proportional to their amount expressed at the plasma membrane, thus allowing their quantitation in urine samples.

Methods: In this work we compared excretion of AQP5 and AQP2 (uAQP5 and uAQP2) in the urine of 35 diabetic patients: 12 with histological diagnosis of DN, 12 with with normal renal function and normoalbuminuric DM (D) and 11 with non-diabetic nephropathy (NDN). Both proteins were quantified by ELISA method on urine samples and the results were validated by Western blotting analysis on the exosome fraction isolated by ultracentrifugation.

Results: BothELISA and Western blotting analysis independently showed that uAQP5 was three- to fourfold higher in DN patients (7458 ± 2576, $p < 0.05$) compared to the other two groups (D 847,2 ± 70,51; NDRD1882 ± 215). uAQP5 was not statistically different between D and NDN patients. Strikingly, uAQP5 dramatically increased in parallel with the clinical severity of DN. The same analysis showed comparable results for uAQP2.

Conclusions: Our data showed, for the first time, that uAQP5 and uAQP2 dramatically and specifically increase in patients with DN and positively correlate with the histological class of DN. Taken together these data suggest a possible role of AQP5 and AQP2 as novel non-invasive biomarkers to help diagnosing DN and classifying its histological stage.

FR-PO612

Urinary Neutrophil Gelatinase-Associated Lipocalin as Complementary to Albuminuria Biomarker of Early Stage Diabetic Kidney Disease in Type 2 Diabetes Agnieszka Gala-Bladzinska,¹ Paulina Dumnicka,² Agnieszka Zylka,¹ Beata Kusnierz-cabala,³ Marek Kuzniewski.⁴ ¹*St' Queen Jadwiga District Hospital No 2, Rzeszów, Poland;* ²*Dept of Medical Diagnostics, Jagiellonian Univ Medical College, Kraków, Poland;* ³*Dept of Diagnostics, Chair of Clinical Biochemistry, Jagiellonian Univ Medical College, Kraków, Poland;* ⁴*Dept of Nephrology, Jagiellonian Univ Medical College, Kraków, Poland.*

Background: Two clinical phenotypes of diabetic kidney disease (DKD) have been reported, i.e. with or without increased albuminuria. The aim of this study was to assess the usefulness of uNGAL for the preclinical diagnosis of DKD in the course of diabetes mellitus type 2 (DMT2).

Methods: The study group consisted of 115 DMt2 patients (63F, 58M) aged 18 and over (62±14), with normal to moderately increased albuminuria (i.e. urine albumin/creatinine ratio (UACR) <300 mg/g) and eGFR (CKD-EPI) ≥60ml/min/1.73m². Control group included 22 non-diabetic persons with comparable age (57±14; $p=0.1$) and sex (9F, 13M; $p=0.5$), and with similar comorbidities. Urine concentrations of NGAL, albumin and creatinine (uCr) were measured in the first morning urine sample. Urine albumin/creatinine ratio (UACR), and analogically, uNGAL/uCr were calculated.

Results: In control group, maximum uNGAL/uCr was 39.64 µg/g. In DMt2 group, 24 patients (21%) had higher results, with the maximum value of 378.6 µg/g. Twenty three (20%) of DMt2 patients had UACR >30 mg/g; of those, 11 had uNGAL/uCr >39.64 µg/g. Among patients with uNGAL/uCr >39.64 µg/g, 13 did not have markedly increased albuminuria (UACR in those patients ranged from 2.35 to 16.10 mg/g). Women with DMt2 had significantly higher uNGAL/uCr than men (median 28.06; IQR 9.05-65.60 versus 11.40; 3.36-18.02 µg/g; $p<0.001$), without significant difference in UACR ($p=0.09$). uNGAL/uCr in DMt2 patients correlated significantly with HbA1c ($R=0.28$; $p=0.013$), however, it did not correlate with eGFR ($R=-0.54$; $p=0.1$), age ($R=0.14$; $p=0.1$), or time from DMt2 diagnosis ($R=0.13$; $p=0.1$).

Conclusions: Increase in urine NGAL and uNGAL/uCr may indicate early tubular damage particularly worse diabetes control patients, especially female with DMt2.

Funding: Private Foundation Support, Clinical Revenue Support

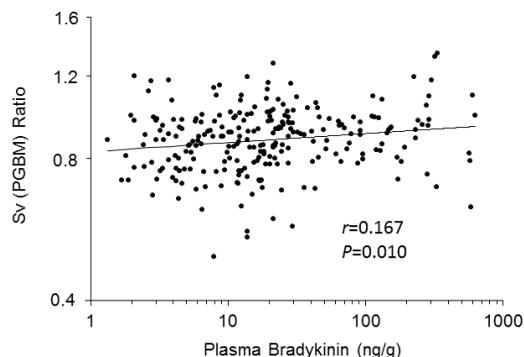
FR-PO613

Plasma Bradykinin and Early Diabetic Nephropathy in Type 1 Diabetes Mellitus E. Jennifer Weil,¹ Gudeta D. Fufaa,¹ Robert G. Nelson,^{1,6} Michael Merchant,^{4,6} Brad H. Rovin,^{2,6} Michael Mauer,^{3,6} Jon B. Klein.^{4,5,6} ¹*NIDDK;* ²*Ohio State Univ;* ³*Univ of Minnesota;* ⁴*Univ of Louisville;* ⁵*Robley Rex VAMC;* ⁶*for the CKD Biomarkers Consortium.*

Background: Bradykinin (BK) and its modified forms are potential biomarkers of diabetic nephropathy (DN). We examined their association with development of DN lesions in normoalbuminuric normotensive subjects with normal or increased glomerular filtration rate (GFR) and type 1 diabetes (T1D) from the Renin-Angiotensin System Study (N Engl J Med 2009;361:40-50).

Methods: Plasma concentrations of BK and modified BKs were measured at baseline by a quantitative mass spectrometry-based multiple reaction monitoring assay in samples from 246 subjects who underwent kidney biopsies at baseline and after 5 years. Relationships of BK and modified BKs with morphometric variables were assessed using multiple linear regression after adjustment for age, sex, T1D duration, HbA1c, mean arterial pressure, albumin excretion rate (AER) and GFR (iohexol).

Results: Baseline mean age was 29.8 years, mean duration of T1D 11.3 years, median AER 5.1 mg/min, and mean GFR 128 mL/min/1.73 m². After multivariable adjustment, higher BK concentration was associated with the peripheral glomerular basement membrane surface density 5-year/baseline ratio (partial $r=0.167$, $P=0.010$; figure) and with the 5-year measurement alone (partial $r=0.179$, $P=0.006$). BK was not associated with other morphometric variables and modified BKs were not associated with any of these variables.



Conclusions: Elevated plasma BK concentration measured before clinical findings of DN in people with T1D was associated with increased peripheral glomerular basement membrane surface density, suggesting that it may reflect an adaptive response to early glomerular changes in DN.

Funding: NIDDK Support

FR-PO614

Serum Omentin and Progression of Diabetic Nephropathy Tetsuharu Oku, Fumihiko Furuya, Takeyuki Takamura, Kenichiro Kitamura. *Third Dept of Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.*

Background: A novel adipokine, omentin, preferentially produced by visceral adipose tissue compared with subcutaneous adipose tissue. Animal experiments indicated that treatment with recombinant omentin enhanced insulin-stimulated glucose uptake in subcutaneous and omental adipocytes. Furthermore, serum omentin levels are decreased in obesity and diabetics. The purpose of this study was to elucidate whether serum omentin is associated with progression of diabetic nephropathy in diabetic patients.

Methods: The prospective follow-up study; 114 diabetes patients were followed for 5.0 ± 1.1 years. Patients were divided at baseline into three groups according to their urinary albumin-to-creatinine ratio (UACR): 68 patients with normoalbuminuria (UACR < 30 mg/gCr), 31 patients with microalbuminuria ($30 \text{ mg/gCr} \leq \text{UACR} < 300 \text{ mg/gCr}$), and 17 patients with macroalbuminuria (UACR $\geq 300 \text{ mg/gCr}$). Progression of albuminuria was the main outcome. Omentin was measured by ELISA, and the values were adjusted for age, BMI, and sex before analysis.

Results: Progression either to the next albuminuria level in 16 patients or to end-stage renal disease (ESRD) occurred in 5 patients. No difference in adiponectin concentrations was observed between progressors and nonprogressors in patients with normoalbuminuria. In the patients with microalbuminuria and macroalbuminuria, progression of albuminuria was associated with higher omentin. Progression to ESRD was also associated with estimated glomerular filtration rate (eGFR). When these covariates were inserted in a Cox regression analysis, eGFR and omentin were significantly associated with progression of albuminuria.

Conclusions: Increased serum omentin levels predict the progression from microalbuminuria to macroalbuminuria and macroalbuminuria to ESRD in diabetic patients.

FR-PO615

The Expressions of Vitamin D and Its Receptor in Patients with Diabetes Associated with Proteinuria and Diabetic Nephropathy Yang Yang, Jia Guo, Zhangsuo Liu. *The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China.*

Background: Vitamin D receptor (VDR) is a member of the nuclear receptor superfamily, and there was no report about the expression of Vitamin D and its receptor in patients with diabetes associated with proteinuria and diabetic nephropathy. So, this study aimed to test the expression trends of VDR in blood, urine specimens and renal tissues of diabetic nephropathy, and the relationship with urinary protein, to explore the role of VDR in diabetic nephropathy.

Methods: 1. 65 patients who had been diagnosed with T2DM (with or without albuminuria) were enrolled in this study and 25 healthy control subjects were enrolled (NC group). The patients were classified according to the ratio of urinary excretion of albumin/creatinine (ACR). Diabetic patients without proteinuria (DM group, ACR: less than 30 mg/g , $n = 25$), with microalbuminuria (DN1 group, ACR: 30 to 300 mg/g , $n = 24$) and clinical proteinuria (DN2 group, ACR: more than 300 mg/g , $n = 18$). 25 diabetic nephropathy patients who were diagnosed by renal biopsy (DN3 group). 2. The expressions of VD and VDR in the plasma and urine supernatant were measured by ELISA, and the VDR in blood cells was measured by qRT-PCR. The expressions of VDR in kidney tissue were measured by immunohistochemical staining.

Results: Plasma VD and VDR levels were significantly lower in DN2 and DN3 groups as compared with NC group (plasma VD 0.78 ± 0.24 and 0.88 ± 0.29 vs. $2.32 \pm 1.33 \text{ ng/ml}$, $P < 0.05$, VDR 157.52 ± 98.36 and 164.20 ± 64.50 vs. $325.33 \pm 194.68 \text{ ng/ml}$, $P < 0.05$). [circ2] Urinary VD and VDR levels were significantly elevated in DN2 and DN3 groups as compared with NC group (urinary VD 1.34 ± 0.58 and 1.42 ± 0.44 vs. $1.18 \pm 0.65 \text{ ng/ml}$, $P < 0.05$, VDR 83.60 ± 31.78 and 88.40 ± 28.10 vs. $60.93 \pm 12.03 \text{ ng/ml}$, $P < 0.05$). The expressions of VDR in kidney tissue in DN groups were obviously lower than those in control groups, differences were statistically significant ($P < 0.05$).

Conclusions: These results verify that VDR declined with the increase of the amount of urine protein. Based on these results, VDR may play a role of renal protection in diabetic nephropathy.

FR-PO616

Mitochondrial DNA in the Plasma and Urine: A Potential Biomarker to Predict the Progression of Nephropathy in Type 2 Diabetes Mellitus Li Fang, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Mitochondrial dysfunction and chronic sterile inflammation are the most common features of type 2 diabetes mellitus. Thus, our objective was to investigate whether extracellular mitochondrial DNA (mtDNA) in the plasma and urine could be used as a biomarker predicating the progression of type 2 diabetes and nephropathy.

Methods: A total of 42 people with type 2 diabetes and 35 ages-, sex- matched people without diabetes were enrolled in this study. The absolute quantification of mtDNA content was measured by real-time polymerase chain reaction. Relationships among different variables were analyzed by general linear model correlation.

Results: The plasma mtDNA contents were significantly lower in the people with type 2 diabetes, particularly in those participants with clinically significant proteinuria. The plasma mtDNA content was negatively correlated with diastolic blood pressure, urine microalbumin and 24-hour urine protein; while positively correlated with platelets count, serum albumin and alkaline phosphatase. The urinary mtDNA contents did not change

obviously; however, the creatinine-adjusted values were significantly higher in the group with diabetes. Besides, the urinary mtDNA-to-creatinine ratio was negatively correlated with the duration of diabetes, fasting glucose and glycosylated hemoglobin.

Conclusions: Our results indicated that lower plasma mtDNA content and higher urinary mtDNA-to-creatinine ratio might be the potential biomarkers predicting the progression of nephropathy in type 2 diabetes.

Funding: Government Support - Non-U.S.

FR-PO617

Involvement of Fractalkine and Its Receptor CX3CR1 in Disease Progression of Patients with Diabetic Nephropathy Takahiro Uchida,¹ Takashi Oda,² Hidehito Matsubara,¹ Atsushi Watanabe,¹ Hanako Takechi,¹ Toshihiko Imakiire,¹ Naoki Oshima,¹ Hiroo Kumagai.¹ *¹Dept of Nephrology and Endocrinology, National Defense Medical College, Tokorozawa, Japan; ²Dept of Nephrology, Tokyo Medical Univ Hachioji Medical Center, Hachioji, Japan.*

Background: Upregulated expression of fractalkine (CX3CL1) and its receptor CX3CR1 has been reported in some renal diseases. However, whether they are involved in human diabetic nephropathy (DN) is unclear. We therefore examined expression of these molecules in human DN.

Methods: Twelve patients with DN who were diagnosed by renal biopsy were studied. Expression of CX3CL1 and CX3CR1⁺ cells and degree of inflammatory cells were evaluated. Glomerular endothelial cell (GEC) was assessed by measuring the immunofluorescence (IF) intensity of CD34 staining.

Results: Expression of CX3CL1 or CX3CR1 was not observed in normal control tissues. CX3CL1 was expressed on GECs, tubular epithelial cells, and endothelial cells of peritubular capillaries in renal tissues with DN. Expression of CX3CL1 on GECs was found in 9 patients, and its expression was seen with an increase tendency in patients with early stage of DN; CX3CL1 expression was found in all patients with the early stage of DN, whereas its expression was found only in 5 out of 8 patients with the advanced stage. CX3CR1 expression was also upregulated in renal tissues with DN. The majority of the CX3CR1⁺ cells in glomeruli were GECs; CX3CR1⁺ inflammatory (CD45⁺) cells composed only a small number of CX3CR1⁺ cells in glomeruli, most of which were CD68⁺ macrophages. Double stainings for CX3CL1 and CD34, and for CX3CR1 and CD34 revealed that both CX3CL1 and CX3CR1 were expressed on GECs with decreased expression for CD34.

Conclusions: These data demonstrate that CX3CL1 and CX3CR1 were upregulated in human DN from early stage. Interestingly, not only CX3CL1 but also CX3CR1 were expressed on GECs, and their expression on GECs may be involved in GEC injury. Targeting CX3CL1 and CX3CR1 may be promising therapeutic approaches for DN.

FR-PO618

Klotho Association with Markers of Mineral Metabolism and Insulin Resistance in Diabetic Patients with Chronic Kidney Disease Ana Paula Silva, Filipa Brito Mendes, Pedro L. Neves. *Nephrology, Centro Hospitalar do Algarve, Faro, Portugal.*

Background: Klotho is a protein implicated in multiple organic processes, being able to regulate growth factors signaling pathways, ion channels and transporters. Several animal and clinical demonstrated that Chronic Kidney Disease (CKD) is associated with Klotho deficiency. Moreover, Klotho seems to play a renoprotective role through its anti-oxidation properties, protection of vasculature, and promotion of vascularization and inhibition of fibrinogenesis. In this study we investigated potential associations between serum Klotho levels and known markers of mineral metabolism and insulin resistance, in order to better understand how Klotho affects/is affected by these variables in diabetic patients with CKD.

Methods: In this study we included 107 type 2 diabetic patients (67 males, 62.6%) with CKD stage 2-3, a mean age of 66.6 ± 9.7 years. Several laboratory parameters were assessed: eGFR, phosphorus, vitamin D, PTH, urine albumin/creatinine ratio (UACR), IL-6, FGF-23, OxLDL and the homeostasis model assessment (HOMA). Simple linear and multiple regressions model were used to investigate possible correlations between these variables and Klotho.

Results: In the simple linear model, Klotho levels were correlated with age ($r = -0.232$, $p = 0.016$), phosphorus ($r = -0.381$, $p < 0.001$), PTH ($r = -0.606$, $p < 0.001$), UACR ($r = -0.336$, $p < 0.001$), HOMA ($r = -0.482$, $p < 0.001$), IL-6 ($r = -0.571$, $p < 0.001$), FGF-23 ($r = -0.695$, $p < 0.001$), OxLDL ($r = -0.598$, $p < 0.001$), eGFR ($r = 0.228$, $p = 0.018$) and vitamin D ($r = 0.661$, $p < 0.001$) levels. Applying the multivariate linear regression, only the UACR ($r = -0.636$, $p = 0.036$), HOMA ($r = -0.322$, $p = 0.018$), FGF-23 ($r = -0.668$, $p < 0.001$) and Vitamin D ($r = 0.465$, $p = 0.010$) independently influenced the Klotho levels.

Conclusions: In our study, Klotho levels are influenced by FGF-23, vitamin D and insulin resistance, variables that are affected by the renal function. However, in the multiple regression model the eGFR lost its relationship with Klotho, and Klotho was associated mainly with the UACR and insulin resistance. More studies are needed to clarify the relationship with UACR and confirm if proteinuria is more critical in the definition of the Klotho levels.

Funding: NIDDK Support

FR-PO619

Macrophage Accumulation and Phenotype in Human Diabetic Nephropathy
Ying Yang, Yinfeng Guo, Zhixia Song, Min Zhou, Xiaoliang Zhang. *Southeast Univ.*

Background: Macrophage, especially its distinct phenotype is involved in the progress of DN. M1 is characterized with pathogenic function, while M2 displays anti-inflammatory. This study tries to examine the macrophage phenotype and its relationship to the renal function and histological changes in human DN.

Methods: We studied retrospectively 46 patients with DN who were confirmed by diagnosis of renal biopsy. Biopsies were divided into I IIa IIb III IV classes according to the pathologic classification of DN. Patients with renal trauma or renal tumor were considered as control group. Serum creatinine, proteinuria were calculated. Kidney tissues were used to assess histological changes and the presence of macrophage marker CD68, M1 marker iNOS, M2 marker CD206, Arg-1, TREM1 and TREM2.

Results: In biopsy renal tissue of human DN, Expression of CD68, M1 were significantly increased in the glomeruli (2.835±1.045/gcs VS 1.203±0.547/gcs for normals P=0.031; 2.330±1.343/gcs VS 0.896±0.548/gcs for normals P=0.046) and interstitium (0.037±0.142%area VS 0.019±0.002%area P= 0.016; 0.018±0.008%area VS 0.009±0.005%area P=0.023). While M2 were mainly observed in the interstitium (0.019±0.008%area VS 0.010±0.004%area P=0.038). Interstitium M2 correlated strongly with interstitium M1 infiltration. Additionally there was a positive correlation between the glomerular CD68, M1 numbers and serum creatinine (r=0.619, p=0.001; r=0.463, p=0.017), proteinuria (r=0.641, P=0.000; r=0.508, P=0.008), mesangial matrix, interstitial collagen deposition. Likewise, the expression of interstitial CD68, M1, M2 also correlated strongly with serum creatinine (r=0.638, P=0.000; r=0.606, P=0.001; r=0.520, P=0.006), proteinuria (r=0.749, P=0.000; r=0.651, P=0.000; r=0.694, P=0.000), mesangial matrix, interstitial collagen deposition. Besides TREM1,2-positive cells were apparent in the interstitium and the expression levels significantly correlated with interstitium M1,M2 expression respectively.

Conclusions: Macrophage infiltration and polarization participate in the development of diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO620

Risk of Diabetes Increased According to the Level of Urinary Albumin Excretion Even Within Normal Range Dong-Young Lee,¹ Beom Kim,¹ Kyoung Hyoub Moon,¹ Sung Keun Park,² Younjoo Jung,¹ ¹Internal Medicine, VHS Medical Center, Seoul, Republic of Korea; ²Total Health Care Center, Kangbuk Samsung Hospital, Sungkyunkwan Univ, School of Medicine, Seoul, Republic of Korea.

Background: Urine albumin creatinine ratio (UACR) as a reliable index of urinary albumin excretion is getting great attention on its predictive role for various diseases related with diabetes. Nevertheless, predictive value of UACR within normal range was not clarified for diabetes yet. Therefore, this study was aimed at examining the clinical association between normal range of UACR and development of diabetes.

Methods: We identified 1,274 non-diabetic Korean men within normal range of UACR in 2005, and followed them up until 2010. All subjects were classified into three categories with respect to baseline UACR, from the lowest to the highest. The incidence rates of diabetes were compared according to the tertile groups of UACR, and the independent hazard ratios (HRs) of UACR levels for diabetes was measured by Cox proportional hazards analysis.

Results: During follow-up, diabetes developed in 97 out of 1,274 subjects (7.6%). Incidence rate of diabetes increased in proportion to the levels of UACR (tertile 1; 4.9%, tertile 2; 7.3%, tertile 3; 10.6%, p<0.001).

	UACR		
	Tertile 1 (<3.17)	Tertile 2 (3.17≤, <4.95)	Tertile 3 (≥4.95)
Age (year)	49.5	52.6	53.9
SBP (mmHg)	113.9	114.6	119.9
DBP (mmHg)	77.0	78.3	81.4
FBS (mg/dL)	96.5	98.5	99.8
HOMA-IR	1.83	1.91	2.07
HbA1C (%)	5.3	5.4	5.4
sCr (mg/dL)	1.16	1.11	1.12
Hypertension (%)	19.8	23.7	37.5
Development of diabetes (%)	4.9	7.3	10.6

table1. Baseline characteristics of participants according to tertile groups of UACR levels (N=1,274)
All variable are shown by mean value. P-value were ≤0.001 except development of diabetes (P=0.002)

The subjects with incident diabetes had the higher normal range of UACR than those without incident diabetes (5.3±4.2 µg/mg and 6.7±4.2 µg/mg, p=0.013). When tertile 1 was considered as reference, HRs for diabetes was higher in tertile 3 (2.06; 1.16-3.37), even after adjusting for age, BMI, total cholesterol, log(HOMA-IR) and eGFR.

Conclusions: Elevated UACR, even within normal range, was significantly associated with the future development of diabetes.

FR-PO621

Albuminuria Is Positively Associated with Elevated Numbers of Circulating Endothelial Pre- and Mature Cells, but Inversely Associated with Circulating Fibrocytes Tine Hansen,¹ Bernt Johan Illum von Scholten,¹ Alexander Rosendahl,² Regine Bergholdt,² Peter Rossing,¹ ¹Steno Diabetes Center, Gentofte, Denmark; ²Novo Nordisk A/S, Måløv, Denmark.

Background: Diabetic nephropathy is characterized as a microvascular disease with enhanced vascular leakiness in the kidney and aberrant tissue remodelling. Abnormal number and function of endothelial cells, stem cells and activation of leukocytes is considered as contributing mechanisms to the “kidney-micro”-vascular leaky syndrome. We determined if circulating endothelial pre- and mature cells, fibrocytes or monocyte sub-populations were abnormally regulated in type 2 diabetic patients with albuminuria.

Methods: Cross-sectional study of 37 type 2 diabetic patients; 18 with normoalbuminuria (<30mg/24h) and 19 with albuminuria (≥30mg/24h). 8-color flow cytometry analysis of peripheral blood was performed. ANCOVA compared expression of cell markers and absolute number of specific cell populations in patients with normoalbuminuria vs. albuminuria.

Results: Expression of VEGFR2 was significantly enhanced in patients with albuminuria (p=0.009). Also, the total number of circulating mature endothelial cells (CEC) was significantly enhanced in albuminuria (p<0.001). Circulating fibrocyte number and collagen-1 expression was inversely associated with albuminuria (p=0.037) and TGFbeta stabilizing and M2-associated galectin-3 expression on M1-like and M0-like monocytes was positively associated with albuminuria (p=0.029). In contrast, expression of the M1-associated marker CD11c (p=0.042) was inversely associated with albuminuria on all monocytes, particularly on M0-like macrophages (p=0.014).

Conclusions: The enhanced number of CEC together with elevated expression of VEGFR2 may indicate an aberrant function of the CEC with reduced capacity to heal the kidney microvascular disease. The imbalanced M2-polarization of monocytes and aberrant fibrocyte count may favour improper repair leading to excessive tissue fibrosis. Hence therapeutic approaches addressing migratory pattern of CEC, providing adjuvant activating signals or restoring the immune balance might provide novel individualized treatment regimes.

FR-PO622

Prognostic Value of Tubulointerstitial Lesions and Urinary N-Acetyl-β-D-Glucosaminidase in Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Nephropathy Koki Mise,¹ Junichi Hoshino,¹ Toshiharu Ueno,¹ Masayuki Yamanouchi,¹ Noriko Hayami,¹ Tatsuya Suwabe,¹ Kenmei Takaichi,² Yoshifumi Ubara.¹ ¹Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Kanagawa, Japan; ²Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: Recently, it has been reported that some biomarkers of renal tubular injury are useful to predict the renal prognosis in the early stage of diabetic nephropathy (DN). However, how closely such biomarkers reflect actual tubulointerstitial damage remains unknown.

Methods: Among 210 patients with type 2 diabetes and biopsy-proven DN, 152 patients were enrolled, 89% of whom had overt proteinuria. The endpoint was defined as a 50% or more decrease of the estimated glomerular filtration rate (eGFR) from baseline or commencement of dialysis due to end-stage renal disease. The Cox proportional hazard model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the death-censored endpoint.

Results: A significant correlation was found between baseline urinary N-acetyl-β-D-glucosaminidase (NAG) excretion and the score for interstitial fibrosis and tubular atrophy (IFTA score) (r=0.39, P<0.001). The influence of urinary NAG on the renal prognosis was attenuated after adjustment for known promoters of progression (+1SD for log NAG, HR: 0.87 [95% CI: 0.66-1.13]). On the other hand, the IFTA score was significantly related to the outcome even after adjustment for those covariates (+1 for IFTA score, HR: 2.20 [1.50-3.21]).

Conclusions: The assessment of urinary NAG excretion did not improve the prognostic power of known indicators of progression, whereas the IFTA score did. The IFTA score may be more useful for predicting the renal prognosis than current tubulointerstitial markers, especially in patients with advanced DN.

Funding: Private Foundation Support

FR-PO623

Is There Any Benefit of Performing Renal Biopsies in Patients with Diabetic Nephropathy when No Other Diagnosis Than Diabetic Nephropathy Is Found? Rosa M. Montero,¹ Dimitrios Anestis Moutzouris,¹ Ranmith Perera,² David Goldsmith.¹ ¹Nephrology & Transplantation, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom; ²Histopathology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom.

Background: The risk of renal biopsy has long been thought to outweigh the benefit of performing these on patients with diabetes mellitus (DM) leading to small numbers of renal biopsies in this population. Those biopsied have a propensity to more proteinuria or haematuria precipitating biopsy. Glomerular lesions alone have long been the hallmark of diabetic nephropathy (DN) however looking back at the biopsy can there be more to see?

Methods: All native renal biopsies diagnosed with DN from 2009-2014 were retrieved from archive at Guy's & St Thomas' NHS foundation trust. Renal biopsies were performed in patients with DM who had heavy proteinuria or haematuria on presentation. Biopsies with a DN diagnosis alone were identified and Tervaert's new DN classification was applied. Clinical outcome data was collected from electronic patient records. Cox regression models were used to perform statistical analysis.

Results: 3000 native kidney biopsies were performed from 2009-2014. 34 DM patients had DN alone on renal biopsy, 12 T1DM and 22 T2DM. 20 male, 14 females. Ethnicity: 35% white, 35% black, 3% asian, 27% other. Age range: 24-86 years (median 55). UPCR 13-1492 mg protein/mmol creatinine (median 392) eGFR 7-74.9 (median 23). 8.8% 5 year mortality. Glomerular IV and Interstitial fibrosis III lesions were significant predictors of renal survival (p=0.013 HR 27.5, p=0.006 HR 21.3, respectively). Renal survival ranged from 1-60 months post renal biopsy (median 3).

Conclusions: Interstitial fibrotic lesions are as important as glomerular lesions in predicting renal survival. Determining the significance of the compartments in predicting outcome may be more sensitive; however few biopsies are undertaken in this population. The role of an earlier renal biopsy showing less well established features in the DN population that could be reversed may need us to review our practice unless sensitive and specific biomarkers are found to correlate with the underlying histopathology.

FR-PO624

Understanding the Relationship Between Histopathology and Renal Function in Hypertension and Diabetes Matthew Palmer,¹ Jordana B. Cohen,² Mendy Liang,² Steven S. Pullen,³ Katalin Susztak.² ¹Pathology, Univ of Pennsylvania, Philadelphia, PA; ²Nephrology, Univ of Pennsylvania, Philadelphia, PA; ³CardioMetabolic Research, Boehringer Ingelheim, Ridgefield, CT.

Background: Much of the literature relating clinical and pathologic variables in patients with diabetes mellitus (DM) and hypertension (HTN) has relied on biopsy series. To gain unbiased insight into the degree of interstitial fibrosis (IF) and glomerular sclerosis (GS) associated with decline of renal function in DM and HTN, we have correlated histopathology with renal function, DM and HTN status in patients undergoing tumor nephrectomies.

Methods: Data and renal tissue were collected on nephrectomy patients from 7 centers. We used Spearman correlation coefficients to compare eGFR with pathologic assessment of IF (estimate) and GS (manual count). Bivariate linear regression was used to assess the association between log-transformed percent IF or GS and eGFR, stratifying by presence of DM or HTN.

Results: Of 251 patients, there were 60 without DM or HTN, 89 with HTN alone, and 102 with DM (+/- HTN). Median age was 62, 42% were female, 60% were Caucasian, median systolic blood pressure was 134 mmHg, and median eGFR was 66.5. There was a significant association between decline in eGFR and both IF (rho=-0.50, p<0.01) and GS (rho=-0.53, p<0.01). eGFR of 60 was associated with a geometric mean (95% CI) IF and GS of 7.3% (5.1-10.3) and 8.3% (5.7-12.1) for patients without DM or HTN, 9.2% (7.5-11.2) and 8.7% (7.0-10.8) for patients with HTN, and 10.9% (8.8-13.5) and 9.6% (8.0-11.6) for patients with DM. Stage 3 CKD was associated with a median IF and GS of 10% (IQR 5-15) and 11.3% (IQR 5.7-18.8) overall, and with median IF and GS of 10% (IQR 5-20) and 11.9% (IQR 5.7-20.8) in DM.

Conclusions: While IF and GS are similar at a given eGFR, patients with DM have a trend toward a greater degree of IF and GS at the same level of eGFR compared to those with isolated HTN. Stage 3 CKD is associated with median IF of 10% though there is high individual variation. This highly variable histopathology should be considered when patients with DM are included into clinical studies, and kidney biopsies might be useful to include in categorization.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim

FR-PO625

Efferent Arterioles Are Special Target for Obesity Noriko Uesugi, Michio Nagata. *Kidney and Vascular Pathology, Faculty of Medicine, Tsukuba Univ, Tsukuba, Ibaraki, Japan.*

Background: The link between obesity and renal disease is unclear. Hyperfiltration is suspected to induce arteriolar hyalinosis and glomerular hypertrophy in moderate to severe obesity. To assess morphological changes in mild obesity, we investigate human non-tumor renal tissue from 7 mild obese cases (Ob)(BMI 27)(Age 61y.o, S-Cre 0.8md/dl. 4 with hypertension) and compared with 7 hypertensive case (HT) and 4 control(Con).

Methods: Total 150 of serially cut paraffin sections were double immunostained with CD34 as endothelial marker, and smooth muscle actin as medial marker, followed by PAS

stain. Incidence of hyalinosis in afferent and efferent arterioles, intraglomerular cystic dilatation connecting to efferent arterioles, segmental sclerosis, sclerotic glomeruli(GS) and average size of glomeruli were assessed using 30-40 glomeruli per case.

Results: The morphological data were as follows; average glomerular diameter 203±26*, 181±19, 156±4 μm, incidence of afferent arteriolar hyalinosis 43±13*, 47±29*, 20±16 % and that of efferent arterioles, 30±10**, 13±14, 5±4% for Ob, HT and Con, respectively (*P<0.05 vs Con, **P<0.05 vs Con and HT). Higher incidence of cystic dilatation near efferent arterioles was noticed in Ob (21±15%) than HT and Con (2±15, 0%, respectively)(P<0.05). Obese cases revealed neither significant intimal thickening nor distortion in the interlobular arteries, no segmental sclerosis, low incidence of GS (11±7%) and minimal interstitial damage(<10%).

Conclusions: Efferent arterioles are targets for obesity, which suggest that specific mechanism of glomerular hyperfiltration involves obese cases, even in mild form.

Funding: Government Support - Non-U.S.

FR-PO626

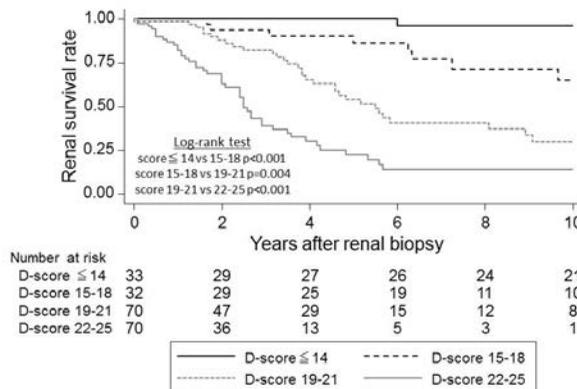
A Pathological Scoring System to Predict Renal Outcome in Diabetic Nephropathy Junichi Hoshino, Koki Mise, Toshiharu Ueno, Keiichi Sumida, Masayuki Yamanouchi, Noriko Hayami, Tatsuya Suwabe, Shigeko Hara, Yoshifumi Ubara, Kenmei Takaichi. *Nephrology Center, Toranomon Hospital, Tokyo, Japan.*

Background: With association between diabetic nephropathy (DN) and renal outcome increasingly clear, we aimed to create a new DN pathological scoring system that could predict renal outcome.

Methods: We studied 205 patients with DN confirmed by renal biopsy between March 1985 and January 2010 who met inclusion criteria. Renal biopsy included clinical parameters and Tervaert classifications. Hazard ratios (HRs) for end-stage renal disease (ESRD) were estimated by adjusted Cox regression. Overall pathological risk score (D-score) was calculated by summing the products of beta-coefficient and bootstrap-inclusion fractions, its predictive utility evaluated by Kaplan-Meier methods and c-statistics with 10-fold cross-validation for 10-year risk of ESRD.

Results: D-scores of glomerular classes 1, 2A, 2B, 3, and 4 were, respectively, 0, 3, 4, 6, and 6. Those of interstitial fibrosis and tubular atrophy classes 0, 1, 2, and 3 were 0, 7, 9, and 11, and those of interstitial inflammation classes 0, 1, and 2, respectively, 0, 3, and 4. D-score of hyalinosis class 2 was 3, and that of arteriosclerosis class 2 was 1. So a patient's D-score could be 0-25.

Figure 1



HRs for ESRD in patients with D-score ≤ 14, 15-18, 19-21, and 22-25 were, respectively, 1.00 (ref.) 16.21 (1.86-140.90), 19.78 (2.15-182.40), and 45.46 (4.63-446.68) after adjusting for clinical factors. When comparing c-statistics, a model that included D-score in addition to age, eGFR, and proteinuria, showed a slight improvement from 0.901 (0.861-0.942) to 0.932 (0.898-0.965). The net reclassification index also showed better reclassification (0.24 (-0.02 to 0.49)).

Conclusions: In addition to clinical parameters, D-score may have improved prediction of 10-year risk of ESRD. Patients with D-score ≤ 14 had excellent renal prognosis.

Funding: Private Foundation Support

FR-PO627

Hyperphosphatemia and Tubulointerstitial Injury in the Progression of Diabetic Nephropathy Song Jiang, Yu Pan, Dandan Qiu, Yu An, Hao Chen, Yongchun Ge, Honglang Xie, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Our aim was to evaluate the relationship between tubulointerstitial injury and hyperphosphatemia in the patients with type 2 diabetes and diabetic nephropathy (T2DN), and investigate the association of hyperphosphatemia with the renal outcome, especially in the T2DN patients with eGFR ≥ 60 ml/min per 1.73m².

Methods: A total of 396 patients with T2D and biopsy-proven DN from Nanjing DN registration system who received follow-up for at least 1 year were recruited and median 5-year follow-up. Renal outcomes were defined by progression to end-stage renal disease and doubling of serum creatinine.

Results: Of the participants, the mean baseline eGFR was 73.86±33.52 mL/min per 1.73 m². The levels of the urinary tubulointerstitial injury markers including the NAG, RBP and NAGL were significantly difference among quintiles of serum phosphorus (P<0.01). The participants whose eGFR≥90 ml/min per 1.73 m² had a higher rate of tubulointerstitial injury (interstitial fibrosis tubular atrophy scores of 2 and 3, P=0.005; interstitial inflammation scores of 1 and 2, P=0.035) in hyperphosphatemia (>1.45 mmol/L) group than in lower phosphorus group (<1.17 mmol/L). Participants with baseline levels of serum phosphorus in higher quintiles had a higher cumulative incidence of ESRD (log-rank, P<0.01). In the analyses adjusted by age, sex, diabetes status, BP, FBG, BMI, proteinuria, cholesterol, and eGFR, the relationship between higher serum phosphorus and an increased risk of ESRD remained. The association between serum phosphorus and ESRD risk persisted and was stronger when the sample was restricted to those with a baseline eGFR equal to 60-90 mL/min per 1.73 m², but not when it was restricted to patients with a baseline eGFR of 30-60 mL/min per 1.73 m².

Conclusions: These findings indicated the baseline serum phosphorus is associated with tubular interstitial injury of T2DN patients. And serum phosphorus >1.45mmol/L is an independent risk factor of ESRD in T2DN, especially in the patients with eGFR≥60 ml/min per 1.73m².

Funding: Government Support - Non-U.S.

FR-PO628

Longitudinal Changes in Estimated Glomerular Filtration Rate in Youth with Type 1 Diabetes Katherine D. Westreich,^{1,2} Nora Fino,^{1,3} Maryam Afkarian,^{1,4} David M. Maahs,^{1,5} Amy K. Mottl.^{1,2} *for the SEARCH for Diabetes in Youth Study;* ¹Univ of North Carolina; ²Wake Forest School of Medicine; ³Univ of Washington; ⁴Univ of Colorado Denver.

Background: Diabetes is the leading cause of kidney disease in the US. The natural history of kidney function early in type I diabetes (T1D) is relatively unknown.

Methods: SEARCH for Diabetes in Youth is a multicenter cohort study of incident diabetes in youth <20 yrs at diagnosis. Cystatin C (CysC) was measured at two study visits; values were calibrated for assay drift and standardized to the reference material. GFR was estimated using the CysC-based Filler equation, the only pediatric equation validated in hyperfiltration. Participants were stratified by change in eGFR: gain of >3ml/min/1.73m²/yr, loss of >3ml/min/m²/yr, or stable. Nominal multinomial regression was used to predict eGFR outcome category. Covariates included gender, race/ethnicity, and follow up age, fasting glucose, HbA1c, insulin sensitivity score, renin-angiotensin inhibition, and systolic blood pressure Z-score (SBPZ).

Results: The analysis included 905 participants with T1D (mean age 14 ±4 yrs; duration 4.2 ±1.9 yrs, HbA1c 8.7% ±1.8%; SBPZ -0.3 ±1.0 and CysC 0.73 ±0.12 mg/L). Follow up CysC was measured 4.6 ±1.3 yrs later. 323 (36%) participants lost eGFR (mean 150±30 fell to 119±23, p<0.0001); 197 (22%) gained eGFR (mean 122±22 rose to 151±29, p<0.0001) and 385 (42%) had stable eGFR. Odds ratios (OR) for predictor variables significant in any pairwise comparison are shown below.

Variable	OR (95%CI) eGFR loss vs stable (ref)	OR (95% CI) eGFR gain vs stable (ref)	OR (95% CI) eGFR loss vs gain (ref)
N	323 vs 385	197 vs 385	323 vs 197
Age (per 1 year)	0.92 (0.88-0.97)	1.07 (1.00-1.14)	0.87 (0.81-0.93)
Female gender	NS	1.64 (1.14-2.38)	0.59 (0.40-0.88)
SBP Z-score (per 1 point)	1.16 (1.03-1.30)	1.15 (1.00-1.33)	1.36 (1.17-1.59)
Fasting glucose (per 100mg/dl)	NS	1.22 (1.01-1.30)	0.80 (0.66-0.98)
HbA1c (per 1%)	NS	1.15 (1.01-1.29)	NS

Conclusions: Changes in eGFR are heterogeneous early in T1D and are predicted in part by SBPZ, age, gender, glucose and HbA1c. Continued follow up will determine whether early changes in eGFR may identify those at risk for subsequent kidney disease.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO629

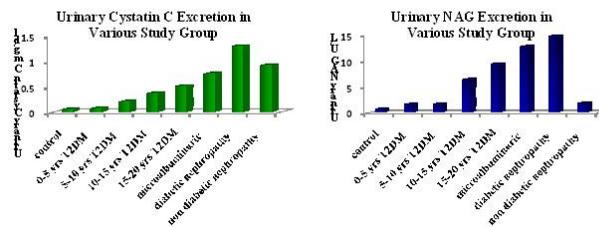
A Cross-Sectional Study for Evaluating the Diagnostic Accuracy of Cystatin C and N-Acetyl β-D Glucosaminidase in Predicting Diabetic Nephropathy Dhara Nrupal Patel, Kiran Kalia. *BRD School of Biosciences, Sardar Patel Univ, Anand, Gujarat, India.*

Background: Diabetic nephropathy (DN) is classified into V stages. Amongst which, stage I-II are reversible proximal tubule damage stages, and III- V are well established irreversible glomerular damage stages. The inability of creatinine and microalbuminuria to detect early reversible stages urges the necessity of new efficient diagnostic biomarkers. Thus, we have selected proximal tubule originated proteins; cystatin c (cyst c) and N-acetyl β-D Glucosaminidase (NAG) to study their efficacy in detecting early manifestations of DN.

Methods: Urinary/serum cyst c and NAG were estimated in total 491 age-matched patients enrolled for our cross-sectional study. Their efficacy was compared with urinary microalbuminuria, serum creatinine and eGFR in patients with varying type 2 diabetes (T2DM) duration and various stages of DN.

Results: Patients with 5-10 yrs of T2DM duration showed a significant increase in cyst c level while urinary NAG increased in T2DM patients with 10-15 yrs of diabetic duration. The ROC curve signifies diagnostic efficacy of urinary cyst c (AUC 0.820) over urinary NAG (AUC 0.678), in detecting T2DM patients susceptible to develop DN.

Figure 1: Comparison of urinary Cystatin c and NAG in various groups



Conclusions: Urinary cyst c in comparison to urinary NAG plays a significant role in predicting the early renal decline in T2DM patients with varying duration of diabetes. Furthermore, the presence of such low molecular weight protein and renal origin enzyme indicates pathogenesis of proximal tubule in early stages of DN.

FR-PO630

The Relationship Between Diabetic Retinopathy and Diabetic Kidney Disease in a Population-Based Study in Korea (KNHANES V2-3) MinJeong Lee,¹ Won June Lee,² Seirhan Kim,¹ Gyu Tae Shin,¹ Heungsoo Kim.¹ ¹Dept of Nephrology, Ajou Univ School of Medicine, Suwon, Republic of Korea; ²Dept of Ophthalmology, 102 Replacement Depot, Republic of Korea Army, Chuncheon, Republic of Korea.

Background: Previous studies of the association between diabetic kidney disease (DKD) and diabetic retinopathy (DR) used only albuminuria/proteinuria as chronic kidney disease (CKD) markers and, hence, did not consider eGFR. This study aimed to evaluate the prevalence of DKD and the association between DKD, as evaluated by both proteinuria and eGFR, and DR in the large cohort of patients with type 2 diabetes from the Korea National Health and Nutrition Examination Survey (KNHANES V).

Methods: From the fifth (2011, 2012) KNHANES, 971 participants with type 2 diabetes were included. Selected samples were weighted to represent the entire civilian population in Korea. DKD was defined as diabetes with the presence of albuminuria and/or impaired GFR. Nonproteinuric DKD was defined as estimated glomerular filtration rate (eGFR) calculated by Modification of Diet in Renal Disease (MDRD) equation < 60 ml/min/1.73m² and no albuminuria. Multivariate logistic regression analysis was performed to determine risk factors, including DR, associated with DN in the Korean population.

Results: Among the 971 DM patients, the prevalence of microalbuminuria was 19.3% and that of macroalbuminuria was 5.5%. The prevalence of eGFR < 60ml/min/1.73m² was 9.1%, and half of those were nonproteinuric DKD. We observed a prevalence of 20.0% for DR and 3.8% for Proliferative DR (PDR). Multiple logistic regression analysis revealed that HTN [aOR = 1.75; 95% CI = 1.19 - 2.59], HbA1c [aOR = 1.24; 95% CI = 1.12 - 1.39], and PDR [aOR = 2.80; 95% CI = 1.32 - 5.96] were independent factors correlated with proteinuric DKD, and the older age [adjusted odds ratio (aOR) = 1.19; 95% confidence interval (CI) = 1.09 - 1.31] and the presence of hypertension [aOR = 5.50; 95% CI = 1.37 - 22.71] were significantly associated with nonproteinuric DKD.

Conclusions: Nonproteinuric renal dysfunction in type 2 DM is not rare. PDR is associated with proteinuric DKD, however, DR and PDR are not significantly associated with nonproteinuric DKD.

FR-PO631

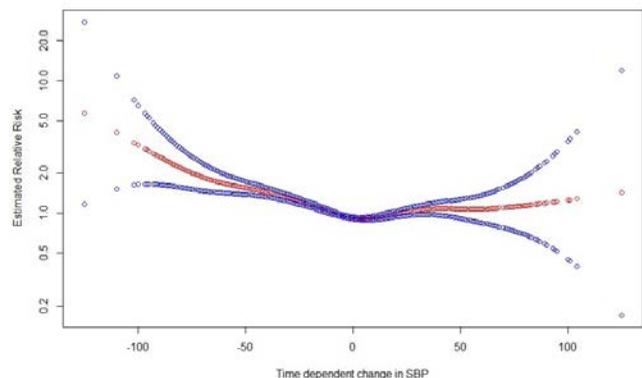
A Decrease in Blood Pressure During Follow-Up Is Associated with an Increased Risk of All-Cause Mortality in Patients with Type 2-Diabetes and Renal Impairment – The Swedish National Diabetes Register (NDR) Hanri Afghahi,¹ Stefan Franzén,² Ann-marie Svensson,² Björn Eliasson,³ Maria Svensson.³ ¹Nephrology, Skaraborg Hospital, Skövde, Sweden; ²Center of Registers, Gothenburg, Sweden; ³Medicine, Sahlgrenska Univ Hospital, Gothenburg, Sweden.

Background: A U-shaped relationship between systolic blood pressure (SBP) and risk of all-cause of mortality has been found in patients with type 2 diabetes (T2D) and renal impairment (RI). We here assess the association between time-dependent mean SBP, change in SBP during follow up and risk of all-cause mortality.

Methods: 27 732 patients with T2D and RI (eGFR<60ml/min/1.73m² MDRD) classified into 10 mmHg intervals according to SBP at baseline were followed for 4.7 years. The risk of all-cause mortality was estimated using time-dependent mean SBP and change in SBP from last observation by time-dependent adjusted cox model. A smoothing spline describe the influence of mean SBP and the change in SBP on the hazard function.

Results: During follow-up 8265 deaths occurred. Using SBP 130-139 mmHg as a reference group a time-dependent mean SBP <130 mmHg was associated with increased risk of all-cause mortality in all (HR 1.28, 95% CI 1.20, 1.36) and in patients without

previous congestive heart failure (n=23 799) (HR 1.26, 95% CI 1.17, 1.36). In addition, a 25-50 mmHg decrease in SBP from the last observation was associated with an increase in risk of all-cause mortality (HR 1.44, 95% CI 1.33, 1.56) compared to a change in the range -10 to 10 mmHg.



Conclusions: A systolic blood pressure < 130 mmHg and a decrease in systolic blood pressure during follow up with or without previous congestive heart failure, is associated with an increase the risk of all-cause mortality in patients with type 2-diabetes and renal impairment. Intensity of hypertensive medication and co-morbidities are important confounders and will be further evaluated.

FR-PO632

Increased Expression of WNT5a in Renal Tubules Is Associated with Diabetic Nephropathy in Humans Malik Asad Anjum,¹ An Xiao,¹ Dean Troyer,^{1,2} Michael J. Solhaug,¹ Anca Dobrian,¹ Jerry L. Nadler,¹ Liwei Huang.¹ ¹Internal Medicine, Eastern Virginia Medical School, Norfolk, VA; ²Pathology, Sentara Norfolk General Hospital, Norfolk, VA.

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease worldwide. In recent years, convincing data has come forward suggesting that inflammatory pathways play a pivotal role in the pathogenesis and progression of DN. Identification of these inflammatory pathways and associated biomarkers may help in the early diagnosis of DN and development of novel targeted therapeutic strategies to help prevent, treat and even slow the progression of DN. Wnt5a, a secreted glycoproteins, plays an important role in normal kidney development and is also a pro-inflammatory factor which has been associated with renal fibrosis and disruption of matrix metabolism. The objective of our study was to investigate the expression of WNT5a in diabetic kidneys in humans.

Methods: 11 subjects with biopsy confirmed DN were included in our experimental group. Normal kidney tissues from non-diabetic subjects who underwent nephrectomy for renal cell carcinoma were used as controls. Exclusion criteria for the experimental group were HIV positivity, chronic/acute inflammatory diseases (including hepatitis C) and steroids/immunosuppressant medication. WNT5a expression was evaluated in paraffin embedded tissues.

Results: Immunohistochemical analysis of WNT5a expression showed positive staining on the apical side of the plasma membrane of the renal tubular epithelial cells in control kidney tissues. The intensity of the staining is increased in patients with DN compared to normal kidney control tissues. In patients with DN, WNT5a expression is localized both in the cytoplasm and on the apical side of the plasma membrane of the renal tubular cells. WNT5a is also expressed on glomerular cells, but there are no differences in Wnt5a expression between the tissues from diabetic subjects and controls.

Conclusions: Our results suggest that WNT5a expression in renal tubules might have a pathogenic role in the development of human renal tubular fibrosis. These studies are the first to demonstrate an increase in WNT5a expression in renal tubules in DN.

Funding: NIDDK Support

FR-PO633

Accuracy of Serum Creatinine and Glomerular Filtration Rate Estimation for Adjusting Metformin Prescription in European Type 2 Diabetics Olivier Moranne,¹ Coraline Fafin,¹ Pierre Delanaye,² Martin Flamant.³ ¹Nephrology, CHU, Nice, France; ²Nephrology, Hospital, Liege, Belgium; ³Physiology, APHP, Paris, France.

Background: There is a debate in the literature about the thresholds of serum creatinine (Scr) above which the drug is contraindicated (1.5 mg/dL in men & ³1.4mg/dL in women). For KDIGO, recommendation is a dose-adjustment between 45 and 30mL/min and a withdrawal below 30mL/min. However, in DM2, estimation of renal function based on Scr alone or on eGFR may vary from the true renal function (mGFR). The purpose of our study was to define the performance of the GFR assessment method (Scr or eGFR calculated with Cockcroft-Gault (CG) or CKD-EPI) in terms of metformin dose adjustment in DM2 who underwent a GFR measurement.

Methods: In 243 DM2 patients, GFR was measured by urinary clearance of ⁵¹CrEDTA. Non indexed GFR was used. We analyzed the agreement between classification of patients based on mGFR and, first, Scr alone with a cutoff value of 1.5mg/dL in men and 1.4mg/dL

in women, second, on eGFR with threshold values of 45 or 30mL/min. When both methods classified the patient in the same subgroup, the data were considered concordant otherwise overprescription (underprescription) was defined for discordance according to mGFR.

Results: Age was 61 ± 12 y/o, median mGFR was 42 [30-61] mL/min. Based on mGFR, the distribution of the patients according the following GFR class: [90-45] 110(45%), [44-30] 74(30%), < 30: 59(24). In patients with a Scr above the cutoff value, mGFR (mL/min) was <30 mL/min in respectively 23/40 women and 33/106 men. With a threshold of 45mL/min then 30 mL/min, concordance was found in 80/85% then 88/88% of the patients for the CG and CKD-EPI. With a threshold of 30 mL/min, discordance was an overestimation [or underestimation] in 22(9%) and 19(8%) [or 14(6%) and 11(5%)] of the patients with the CG and CKD-EPI.

Conclusions: In this population creatinine-derived equations outperformed Scr alone in correctly classifying the patients in prescription subgroups. However, even with creatinine-based equations, discordance with mGFR occurs in 12-20% of the patients. New strategies such as drug concentration monitoring may be necessary to improve appropriate prescription of metformin in DM2.

FR-PO634

The Association Between Changes in Albuminuria and Clinical Outcomes in the ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation) Trial Min Jun,^{1,2} Vlado Perkovic,¹ Mark Woodward,¹ Hiddo Jan Lambers Heerspink,³ Tanvir Chowdhury Turin,² John P. Chalmers,¹ Meg J. Jardine,¹ Braden J. Manns,² Marcello Tonelli,¹ Brenda Hemmelgarn.² ¹George Inst; ²U/Calgary; ³U/Groningen.

Background: Change in albuminuria may have useful prognostic value. We sought to assess the association between change in urine albumin-to-creatinine ratio(UACR) and the risk of all-cause death, cardiovascular disease(CVD), and end-stage renal disease(ESRD) in the ADVANCE trial.

Methods: We defined UACR change(baseline to 2 years) as ³30% decrease, <30% decrease to <30% increase(minor change; reference), and ³30% increase. Follow-up for outcome ascertainment commenced at the second UACR measurement. We used Cox regression to estimate the hazard ratio(HR), after adjustment for demographics, ADVANCE randomized treatment assignments, comorbidities, laboratory measurements(including baseline UACR), and drug use.

Results: From baseline to 2 years, 34% of 9195 patients experienced a UACR decrease of ³30%, 26% experienced a minor change, and 40% experienced an increase of ³30%. Over the next 2.9 years(median), 520 deaths, 524 CVD events, and 12 ESRD events were recorded. An increase of ³30% in UACR was associated with 50% higher mortality when compared to a minor change ([Figure 1] HR 1.50, 95%CI:1.18-1.90). Increase in UACR was not associated with increased CVD or ESRD, although the direction of effect was similar. A ³30% UACR decrease was not significantly associated with the risk of death or CVD when compared to those with minor change but was significantly associated with lower ESRD risk(HR 0.10, 95%CI:0.01-0.79).

Change in UACR	HR (95% CI)	P-value	P-value for trend
All-cause mortality			
Decrease ≥30%	0.92 (0.71 - 1.19)	0.551	
Minor change (<30% decrease to <30% increase)	Reference	-	<0.001
Increase ≥30%	1.50 (1.18 - 1.90)	0.001	
Cardiovascular disease			
Decrease ≥30%	0.87 (0.69 - 1.11)	0.295	
Minor change (<30% decrease to <30% increase)	Reference	-	0.015
Increase ≥30%	1.16 (0.92 - 1.45)	0.194	
End-stage renal disease			
Decrease ≥30%	0.10 (0.01 - 0.79)	0.029	
Minor change (<30% decrease to <30% increase)	Reference	-	0.011
Increase ≥30%	1.47 (0.34 - 6.24)	0.601	

Conclusions: In type-2 diabetes patients, ³30% increase in albuminuria predicted higher mortality while ³30% decrease was associated with decreased ESRD risk. Our results suggest change in albuminuria may be a potential prognostic marker for clinical outcomes in type-2 diabetes.

FR-PO635

Changes in Glycaemia During Haemodialysis (HD) Are Not Associated with Changes in QTc Interval in Insulin-Treated Diabetic Patients Naveen H. Siddaramaiah,¹ Didem Tez,¹ Thanh Phan,¹ Nicholas J. Linker,¹ Mary Bilous,¹ Sue Winship,¹ Sally M. Marshall,² Rudolf W. Bilous.¹ ¹The James Cook Univ Hospital, Middlesbrough, United Kingdom; ²Newcastle Univ, Newcastle upon Tyne, United Kingdom.

Background: QTc prolongation is a risk factor for cardiac arrhythmias, which can lead to sudden cardiac death (SCD). Risk of SCD is higher in the 24hour period before and after the first dialysis of the week perhaps due to greater shifts in electrolyte levels but the impact of changes in glycaemia is not known. **Aim:** To explore the effect of changes in glycaemia and electrolyte levels during HD on QTc interval in C-peptide negative insulin treated diabetic patients.

Methods: 15 diabetic (mean age 54.6yrs) and 5 non-diabetic (mean age 59.6yrs) patients on HD, underwent Holter and continuous glucose monitoring for a week. Blood sampling and 12 lead ECGs were done at the beginning, middle and end of 3 HD sessions. Standard dialysate (5mM glucose) was used. QTc interval was measured taking the mean of 3 consecutive normal QRS complexes.

Results: QTc interval was prolonged significantly at the end of HD in all sessions ($p < 0.001$). Change in glucose level (mean \pm SD -1.8 ± 4.2 vs -1.7 ± 3.0) did not have a significant effect on the change in QTc interval ($p = 0.396$), which was not different in diabetic subjects compared to non-diabetic group ($p = 0.390$). Serum K^+ , Mg^{2+} and Ca^{2+} levels dropped significantly ($p < 0.001$) during all 3 HD sessions. There was no significant difference in the starting level and the drop in K^+ , Mg^{2+} and Ca^{2+} . The change in Mg^{2+} ($p < 0.05$) and Ca^{2+} ($p < 0.05$) levels but not K^+ ($p = 0.202$) were more pronounced in diabetic subjects. The change in Mg^{2+} levels in diabetic subjects was associated with QTc prolongation ($p < 0.05$).

Conclusions: Significant QTc prolongation occurs at the end of HD in people with and without diabetes, often reaching abnormal levels and appears to be related more to changes in blood electrolytes than glycaemia. The fall in serum Mg^{2+} levels during HD had a larger effect on QTc than K^+ or Ca^{2+} and this appears to have a more pronounced effect in diabetic subjects. The changes in QTc may increase the risk of cardiac dysrhythmia and sudden death in HD patients.

FR-PO636

Markers of Inflammation and Endothelial Dysfunction Are Associated with Cardiovascular Morbidity and Mortality in Type 2 Diabetic Patients with Microalbuminuria Bernt Johan Illum von Scholten,¹ Henrik Reinhard,¹ Tine Hansen,¹ Casper Schalkwijk,² Coen Stehouwer,² Hans-Henrik Parving,³ Peter Karl Jacobsen,³ Peter Rossing.¹ ¹Steno Diabetes Center, Denmark; ²Maastricht Univ Medical Center, Netherlands; ³Rigshospitalet, Denmark.

Background: Accumulating evidence suggests that inflammation and endothelial dysfunction link type 2 diabetes (T2D) to cardiovascular disease (CVD). We evaluated the predictive value of markers of inflammation and endothelial dysfunction for combined fatal and non-fatal CVD and for all-cause mortality in patients with T2D and microalbuminuria but without known coronary artery disease (CAD).

Methods: Prospective study including 200 patients. All received intensive multifactorial treatment. Markers of inflammation (TNF- α , ICAM-3, hsCRP, SAA, IL-1 β , IL-6, IL-8) and endothelial dysfunction (thrombomodulin, VCAM-1, ICAM-1, E-selectin, P-selectin) were measured at baseline. Adjusted models included sex, age, total cholesterol, smoking, HbA1c, creatinine, systolic blood pressure and urinary albumin excretion. Fully adjusted models additionally included NT-proBNP and coronary artery calcium score (CAC).

Results: Participants were 76% men, age (\pm SD) 59 ± 9 years, HbA1c was $7.9 \pm 1.3\%$ and UAER (IQR) was 103 (39–230) mg/d. Occurrence of CVD ($n = 40$) and mortality ($n = 26$) was traced after 6.1 years (median). In adjusted Cox analysis, higher TNF- α predicted the CVD endpoint and mortality ($p \leq 0.002$). After fully adjustment higher TNF- α remained predictive of both endpoints ($p \leq 0.007$). Higher thrombomodulin and ICAM-3 were associated with risk of CVD and mortality in adjusted analyses ($p \leq 0.05$) and predicted mortality after fully adjustment ($p < 0.001$). Higher VCAM-1 and ICAM-1 were associated with risk of mortality in adjusted ($p \leq 0.002$) and fully adjusted models ($p \leq 0.005$). The composite z-score of all markers of inflammation and of endothelial dysfunction predicted CVD and mortality ($p \leq 0.008$).

Conclusions: In patients with T2D and microalbuminuria without known CAD, biomarkers of inflammation and endothelial dysfunction were independently associated with risk of CVD and mortality. Especially TNF- α was a robust predictor, even after adjusting for albuminuria, NTproBNP and CAC.

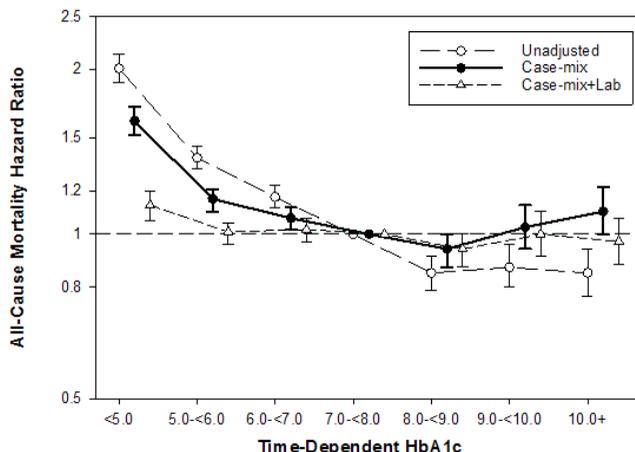
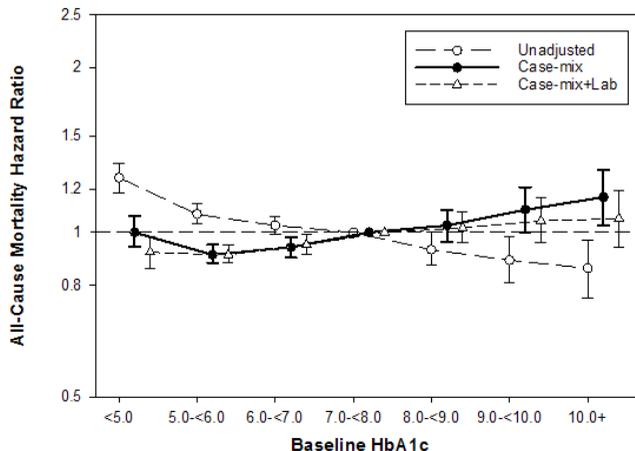
FR-PO637

Predictors of Glycemic Status and Associations with Mortality in Incident Diabetic Hemodialysis Patients Connie Rhee,¹ Steven B. Kim,¹ Rajnish Mehrotra,² Elani Streja,¹ Danh V. Nguyen,¹ Steven M. Brunelli,³ Gregory Brent,⁴ Csaba P. Kovessdy,⁵ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²Univ Washington; ³DaVita Clinical Research; ⁴UCLA; ⁵UTHSC.

Background: In the general population, intensive glycemic targets confer higher mortality in diabetics with cardiovascular risk. In diabetic hemodialysis (HD) patients, some but not all studies show that lower glycemic levels defined by HbA1c are associated with higher mortality. We sought to examine predictors of low glycemic status in HD patients, and hypothesized that lower glycemic levels are associated with higher mortality.

Methods: In a 5-year national cohort (1/2007-12/2011) of incident diabetic HD patients with one or more HbA1c measures during the 1st 91-days of dialysis, we examined predictors of low HbA1c (<6%; ref 6–<8%; $\geq 8\%$ separately examined) using logistic regression. We then examined the association of HbA1c with all-cause mortality. Baseline and time-dependent HbA1c as a proxy of long-term and short-term exposure—mortality associations, respectively, were examined using case-mix+laboratory adjusted Cox models.

Results: Among 63,607 diabetic HD patients, 37% had low HbA1c levels. Female gender and non-Hispanic race/ethnicity; lower BMI and nPCR; and higher serum bicarbonate, creatinine, and albumin were associated with higher risk of low HbA1c. Baseline HbA1c levels <7% were associated with lower mortality. However, time-dependent HbA1c levels <5% were associated with higher mortality.



Conclusions: Baseline HbA1c levels <7% were associated with lower mortality, suggesting that moderately low glycemic status has long-term benefits in diabetic HD patients. Yet time-dependent HbA1c levels <5% were associated with higher mortality, suggesting that very low glycemic status carries short-term risk. Further studies are needed to determine if pharmacotherapies targeting these glycemic ranges reduce mortality in diabetic HD patients.

Funding: NIDDK Support, Private Foundation Support

FR-PO638

Waist-Hip Ratio Is Associated with Renal Hyperfiltration in the Non-Diabetic, Middle-Aged General Population Vidar T. N. Stefansson,¹ Jørgen Schei,¹ Trond G. Jenssen,^{1,3} Toralf Melsom,^{1,2} Bjorn Odvar Eriksen.^{1,2} ¹Metabolic and Renal Research Group, UiT the Arctic Univ of Norway, Tromsø, Norway; ²Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; ³Dept of Organ Transplantation, Oslo Univ Hospital, Oslo, Norway.

Background: Renal hyperfiltration (RHF) is a maladaptive response to increased metabolic stress in the kidneys which may result in chronic kidney disease. Diabetes causes RHF, but whether obesity in non-diabetic persons is a cause of RHF has not been adequately studied in the general population. This study aimed to establish whether RHF assessed by measured glomerular filtration rate (GFR) is associated with obesity independently of metabolic and cardiovascular risk factors.

Methods: We performed a cross-sectional study of a representative sample of 1594 persons recruited from the general population of the municipality of Tromsø, Norway, aged 50-62 without prevalent cardiovascular disease, diabetes or renal disease. GFR was measured by iohexol clearance. Obesity was classified according to body mass index (BMI), waist circumference (WC) and waist-hip ratio (WHR). RHF was defined as >90th percentile of residuals from a linear regression of absolute GFR on age, sex, weight and height.

Results: In multivariable adjusted logistic regression models, the odds ratios (95% confidence intervals) for RHF were 1.56 (1.11-2.18) per 0.10 increase in WHR, 0.82 (0.51-1.32) per 5kg/m² of BMI and 1.23 (0.92-1.65) per 10 cm of WC. WHR was consistently associated with RHF across different models. Higher BMI and WC were significantly associated with RHF only when an alternative definition of RHF, not adjusted for body weight, was used. Higher BMI, WC and WHR were also independently associated with increasing GFR analyzed as a continuous variable.

Conclusions: Central obesity measured as WHR is associated with RHF and higher GFR independently of age, sex, body weight, metabolic indices (including fasting glucose,

insulin and HbA1C) and cardiovascular risk factors (including ambulatory blood pressure, antihypertensive medication and smoking status). WHR may be a better indicator of the renal effects of obesity than BMI or WC.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Private Foundation Support, Government Support - Non-U.S.

FR-PO639

Obesity Associates with High Hemoglobin A1c but Low Alternative Indices in Both Diabetic and Nondiabetic Hemodialysis Patients Mark E. Williams,¹ Neal Mittman,² Lin Ma,³ Julia I. Brennan,⁴ Chinu M. Jani,⁴ Curtis D. Johnson,⁴ Franklin W. Maddux,³ Eduardo K. Lacson,^{3,5} ¹*Joslin Diabetes Center, Boston, MA;* ²*Kidney Care of Brooklyn and Queens, Brooklyn, NY;* ³*Fresenius Medical Care North America, Waltham, MA;* ⁴*Spectra Laboratories, Rockleigh, NJ;* ⁵*Physician, Lexington, MA.*

Background: The GIDE (Glycemic Indices in Dialysis Evaluation) study is evaluating several glycemic markers in hemodialysis (HD) cohorts with and without diabetes. We have reported that alternative glycemic indices may be elevated out of proportion to hemoglobin A1c (HgbA1c). Because obesity is known to affect markers of glycemia, we examined its association with these indices.

Methods: A combined cohort of 2,394 active HD patients (1,424 with diabetes, 970 without) from 26 U.S. FMCNA facilities had baseline indices [HgbA1c; albumin-adjusted and unadjusted fructosamine (AlbF; F) and glycated albumin (GA) or percent GA] measured Jan-Mar 2013 and monthly until April, 2015. Mean of body mass index (BMI) was determined for the entire cohort. Obesity=BMI²≥30kg/m². Cox models adjusted by age, sex, race, ethnicity, vintage, HD catheter, baseline comorbidity and laboratory albumin values were utilized to determine associate between obesity with death outcome.

Results: Average BMI (kg/m², mean±SD) by risk as determined by indices (low=within target range, high=above target range) are shown in (table 1).

Indices	Low Risk	High Risk	p-value
HgbA1c > 7%	28.8 ± 11.4	31.6 ± 8.2	< 0.0001
Percent Glycated Albumin > 15.7%	29.8 ± 12.4	28.9 ± 9.9	< 0.0001
Fructosamine > 285 μmol/L	31.0 ± 14.6	28.7 ± 9.4	< 0.0001
AlbF ≥ 974 μmol/g	29.5 ± 11.8	28.6 ± 7.4	< 0.0001
Glycated Albumin > 300 μmol/L	29.3 ± 11.4	29.2 ± 10.4	0.0008
HgbA1c ≥ 8%	29.1 ± 11.1	31.6 ± 8.7	< 0.0001

The Hazard Ratio (HR) for death was reduced with obesity [HR=0.76, 95%CI (0.62, 0.94), p=0.01].

Conclusions: Obesity is positively correlated with HgbA1c but negatively correlated with other glycemic indices in hemodialysis patients. Further studies are needed to elucidate underlying mechanisms and assess the relationship of these findings to superior survival outcomes in obese HD patients.

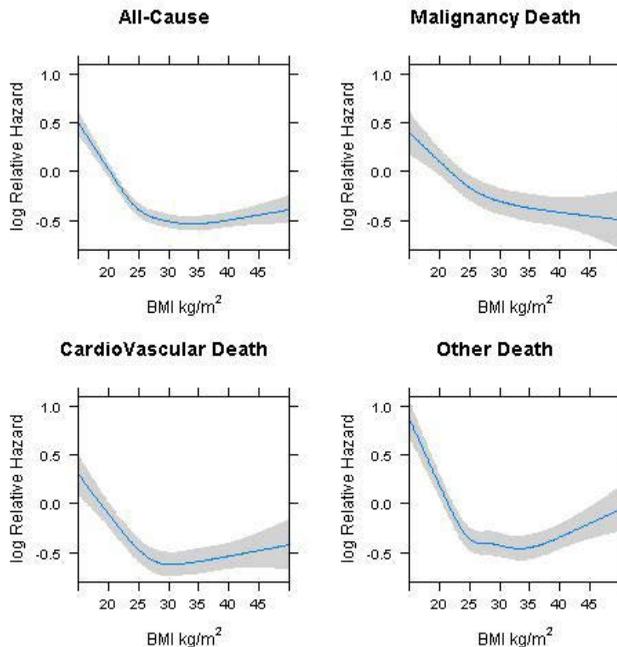
FR-PO640

BMI and Causes of Death in Chronic Kidney Disease Sankar D. Navaneethan,¹ Jesse D. Schold,² Susana Arrigain,² John P. Kirwan,³ Joseph V. Nally,¹ ¹*Nephrology, Cleveland Clinic;* ²*Quantitative Health Sciences, Cleveland Clinic;* ³*Pathobiology, Cleveland Clinic.*

Background: Chronic kidney disease (CKD) is associated with higher risk for cardiovascular related death. In CKD, a higher body mass index (BMI) is associated with a lower risk for death, but cause specific death details are unknown across the BMI range.

Methods: We included 54,506 patients with CKD (two estimated glomerular filtration rate <60 ml/min/1.73 m² 90 days apart; January 2005 – December 2012) from our institutional electronic medical record-based CKD registry. We examined the associations between various causes of death (cardiovascular, malignancy and non-cardiovascular/ non-malignancy related deaths obtained from the State of Ohio mortality files) across the BMI range using the Cox proportional hazards model.

Results: During a median follow-up of 3.7 years (25th percentile-75th percentile: 1.8-5.8), 14,518 patients died. In the multivariable model, an inverted J-shaped association was noted between BMI and overall, cardiovascular, malignancy-related, and non-cardiovascular/ non-malignancy related deaths.



Similar associations were noted for BMI 25-29.9, 30-34.9, and 35-39.9 kg/m² categories. BMI >40 kg/m² was not associated with cardiovascular and non-cardiovascular/ non-malignancy related deaths in CKD. Sensitivity analyses yielded similar results even after including only those with >2 year follow-up, adjusting for proteinuria, and excluding diabetes and hypertension from the models. However, the inverse associations between higher BMI and cardiovascular deaths were not observed among smokers.

Conclusions: In those with CKD, compared to BMI of 18.5-24.9 kg/m², those who are overweight, class 1 and 2 obesity are associated with lower risk for cardiovascular, malignancy-related and non-cardiovascular/non-malignancy related deaths. Future studies are needed to confirm these findings.

Funding: Pharmaceutical Company Support - CCF CKD registry creation was supported by an unrestricted grant from Amgen to the Department of Nephrology and Hypertension at Cleveland Clinic

FR-PO641

Weight Reduction with Low Calorie Diet Reduces Urinary Megalin and Improves Albuminuria in Obese Men Tetsuro Takeda,¹ Akihiko Saito,² ¹*Nephrology, Dokkyo Medical Univ Koshigaya Hospital, Koshigaya, Saitama, Japan;* ²*Applied Molecular Medicine, Niigata Univ, Niigata, Japan.*

Background: Megalin, an endocytic receptor in proximal tubules, is involved in the mechanisms of albuminuria in diabetic nephropathy. A urinary full-length megalin (C-megalin) assay is linked to the severity of diabetic nephropathy and IgA nephropathy. Also, albuminuria is a frequent sign of obese individuals and could be reduced by losing body weight. We investigated the relationship between level of urinary C-megalin and albuminuria on a weight reduction program in obesity.

Methods: Thirty-three obese male volunteers (age 36.6 ± 6.9 years, BMI >25 kg/m²) were enrolled but 30 subjects completed the 12-week weight reduction program. The program consisted of replacement of evening meal by a low calorie formula food (MICRO-S[®]) for first 4 weeks and followed by bi-weekly dietary counseling session with nutritionist. Of these, 20 subjects with metabolic syndrome were included (based on the Japanese criteria). Urinary albumin Cre ratio (ACR) and urinary C-megalin were measured at baseline and after the program.

Results: The mean weight loss was 5.2 ± 2.9 kg (5.6% of the original BW). The baseline ACR ranged from 2.8 to 52.9 mg/gCre. After the program, BMI, waist circumference, BP, total cholesterol, and FFA were significantly decreased. HDL-cholesterol and adiponectin were significantly increased. Overall, ACR was not changed (11.9 ± 12.4 → 8.8 ± 5.3 mg/gCre). However, in the cases with ACR >8 mg/gCre at baseline (n=11), ACR was more effectively reduced (22.9 ± 15.1 → 12.7 ± 6.4 mg/gCre) without a change in eGFR. The reduction of ACR was correlated with the reduction of urinary C-megalin. No other parameters like insulin resistance were associated with the reduction of ACR or C-megalin.

Conclusions: Losing BW with a formula food is effective in reducing urinary ACR in obese men. This improvement of ACR is related to the reduction in urinary C-megalin. Since albumin is excreted into urine by its increased glomerular leakage and/or decreased proximal tubular reabsorption via megalin and cubilin, our observations suggest that megalin metabolism in proximal tubules may determine albuminuria in obesity.

Funding: Pharmaceutical Company Support - Denka Seiken Co. Ltd., Niigata, Japan, Government Support - Non-U.S.

FR-PO642

Obesity Management in Patients with Chronic Kidney Disease (CKD): A National Survey Christopher Lawrence,¹ Helen L. MacLaughlin,² Ken Farrington,¹ Andrew H. Frankel.³ ¹Lister Hospital, United Kingdom; ²Kings College London, United Kingdom; ³Imperial College London, United Kingdom.

Background: Obesity contributes to the development and progression of CKD and may be a barrier to, or increase risks of, transplantation. Evidence for how the renal multidisciplinary team (MDT) should proceed is limited and sometimes counterintuitive i.e. association of increased weight and better survival on hemodialysis. The study assessed approaches to obese patients with CKD across the UK and describes the availability of, and extent of co-working with, bariatric services.

Methods: An online survey tool was designed and sent by the British Renal Society to UK renal clinical directors and dietitians. The survey focussed on patients with CKD stage ≥ 3 , with proteinuria and co-existent Obesity stage II (BMI > 35kg/m²) as these patients are most likely to progress to ESRD.

Results: 58/71 (82%) of UK units responded with respondents split between dietitians (53%) and nephrologists (47%). Most respondents (78%) thought the prevalence of obesity has increased over the last decade. There was no consensus on the BMI cut off for kidney transplantation: £30, 16%; £35, 71%; ≤ 40 , 12%; none, 2%. The 3 most common actions for initial obesity management were: to provide education/motivation (81%); dietetic referral (60%) and test fasting glucose and lipids (43%). Thereafter only 33% would refer to bariatric services. The main perceived barriers to weight loss were: lack of patient motivation (79%); no funding (60%); lack of services (53%). 54% of renal units co-locate with bariatric services. Only 33% of renal units can refer directly to local/regional bariatric service, the remainder were uncertain of referral pathways (27%) or relied on primary care physicians to refer. Only 5 units (9%) have a joint care pathway for obese patients with CKD undergoing bariatric surgery.

Conclusions: The response to obesity in CKD falls short of National (NICE) guidelines. The increasing prevalence of obesity is a challenge to the renal MDT. Strategies to tackle this include wider recognition of the problem; identifying and sharing best practice and development of a robust evidence base to foster investment in renal dietetic and support services.

FR-PO643

Effects of Renin-Angiotensin Blockade (RASB) on the Components of Early Interstitial Expansion in Patients (pts) with Type 1 Diabetes (T1D) Zarah Khan, Michael Mauer, Maria Luiza A. Caramori. *Medicine and Pediatrics, Univ of Minnesota, Minneapolis, MN.*

Background: Interstitial expansion is important for GFR loss in the later stages of a variety of disease processes, including diabetic nephropathy (DN). The Renin-Angiotensin System Study (RASS; NEJM 2009;361:40) considered whether RASB with enalapril or losartan compared to placebo could slow progression of early DN lesions over 5 years (yrs) in 285 normoalbuminuric (NA), normotensive (NT), normal GFR T1D pts. RASS found no treatment benefit of RASB on DN lesions but observed an unexpected ~50% increase in the light microscopic measures of the fractional volume of renal cortex which is interstitium [Vv(Int/Cortex)]. However, possible effects of RASB on individual Int components, i.e., Int collagen (Col), Int cells (C), peritubular capillaries (PTC) and undefined Int space (S) were not assessed. Here we report these additional studies.

Methods: Baseline and 5-yr renal biopsies from 21 RASS pts (52% males), from a single research center, 7 from each treatment group, with a wide range of change in Vv(Int/Cortex), mean age of 34±10 yrs, and T1D for 11±4 yrs were selected. These pts were matched for age and sex, and selected for electron microscopic (EM) measurements of the fractional volume (Vv) of each of the Int components by masked unbiased random sampling and laborious morphometric point counting methods. Renal volume (RV) was measured by ultrasound and calculated using the kidney's length, width, and anterior-posterior diameter by the formula $L \times W \times AP \times 0.523$.

Results: At baseline, 49% of the Int was made up by Col, 12% by C, 26% by PTC, 7% by S, and 2% by artifact. Overall there was no change in Int composition during RASS. Compared across treatment groups, there were no statistically significant effects of treatment group on the Vv of any of the Int components. RV (171±5 cm³) remained stable in all groups.

Conclusions: RASS found that NA, NT, normal GFR T1D pts had surprisingly rapid increases in Vv(Int/Cortex) which was uninfluenced by RASB. Here, using EM morphometric analyses, we showed that RASB also did not affect Int composition, since the Vv of each component at 5 yrs was not different from baseline in any of the groups.

Funding: NIDDK Support

FR-PO644

Liraglutide Improves Glycemic and Blood Pressure Control and Preserves Renal Function and Left Ventricular Function in Patients with Type 2 Diabetes Mellitus with Renal Impairment Takeyuki Hiramatsu, Akiko Ozeki, Kazuki Asai, Akinori Hobo, Hideaki Ishikawa, Shinji Furuta. *Nephrology, Konan Kosei Hospital, Konan, Aichi, Japan.*

Background: Diabetes mellitus(DM) is a progressive multifactorial disease associated with cardiovascular complications. To prevent progression of systemic cardiovascular complications in DM patients, glycemic control is important. However using of anti-diabetic agents was restricted in patients with renal impairment. In this study, we examined the efficacy and safety of the glucagon-like peptide analogue, liraglutide to treat type 2 DM patients with renal impairment.

Methods: Twenty type 2 diabetes patients with renal insufficiency (Age; 65.4y, DM duration; 11.9y, eGFR; 21.6ml/min/1.73m²) were enrolled. Anti-diabetic agents were switched to liraglutide from others. Prior to liraglutide therapy, 9 patients used insulin, 8 used oral antidiabetic agents, and 3 were only diet therapy. During 24 months liraglutide use, we examined the change of blood pressure and renal function. Echocardiography was examined at baseline and 24 months after liraglutide initiation.

Results: Hemoglobin A_{1c}, and systolic/diastolic blood pressure levels were gradually decreased with liraglutide use. Renal function indicated by eGFR was not changed [table1], and the slope of the reciprocal of serum creatinine was improved after use of liraglutide (p<0.001). Moreover Liraglutide induced ameliorating left ventricular function(LVMI and EF).

	baseline	at 12 months	p value	at 24 months	p value
HbA1c (%)	6.90 ± 0.87	6.15 ± 0.65	0.009	6.04 ± 0.52	0.002
SBP (mmHg)	142.3 ± 12.4	130.9 ± 14.9	0.018	125.1 ± 13.4	0.007
DBP (mmHg)	82.6 ± 9.9	75.3 ± 10.0	0.062	71.4 ± 8.8	0.004
eGFR (ml/min/1.73m ²)	21.6 ± 11.4	24.1 ± 14.6	n.s.	22.4 ± 13.0	n.s.
LVMI (g/m ²)	178.6 ± 59.7	n.d.		143.7 ± 40.2	0.047
EF (%)	0.60 ± 0.13	n.d.		0.64 ± 0.15	0.395

No adverse events were seen.

Conclusions: These findings suggest that liraglutide therapy for type 2 diabetes patients with renal impairment was safe and effective for decreasing glucose levels and blood pressure. Moreover it preserved renal function and improving left ventricular function.

FR-PO645

Do SGLT2 Inhibitors Affect GFR and Albuminuria in Diabetic Patients? A Systematic Review and Meta-Analysis Lubin Xu, Yang Li, Peng Xia, Limeng Chen. *Dept of Nephrology, Peking Union Medical College Hospital.*

Background: SGLT2 inhibitors are a new class of antihyperglycemic drugs that lower blood glucose levels by inhibiting renal reabsorption of glucose. SGLT2 inhibitors can have potential renoprotective capacities through modulation of tubuloglomerular feedback and alleviation of hyperfiltration. However, there are also concerns about deleterious effects on renal function caused by volume depletion.

Methods: We performed this systematic review and meta-analysis to assess the effects of SGLT2 inhibitors on estimated GFR (eGFR) and urinary albumin/creatinine ratio (ACR) in diabetic patients. We conducted a systemic search of Pubmed, Embase, Cochrane Central Register of Controlled Trials and Sinomed through April 2015 to identify published randomized double-blind controlled trials of SGLT2 inhibitors reporting renal outcomes. Two reviewers worked independently to extract data and assess the quality of included studies. Random effects model were used in data synthesis.

Results: We retrieved 2279 studies, 53 of which met the predefined criteria. Among included studies, 33 studies examined short-term effect with follow up less than 26 weeks, and 20 studies examined long-term effects with follow-up longer than 48 weeks. 4 studies included subjects with CKD 2-4. SGLT2 inhibitors did not cause statistically significant changes in eGFR (mean change, -0.19 ml/min/1.73m², 95% CI, -0.86 to 0.47) or in ACR (mean change, -23.76 mg/g, 95% CI, -66.75 to 19.23).

FR-PO647

Effects of Statins on Diabetic Kidney Disease in Patients with Type 2 Diabetes Ko Hanai, Tetsuya Babazono, Yasuko Uchigata. *Diabetes Center, Tokyo Women's Medical Univ School of Medicine.*

Background: Renoprotective properties of statins have received much attention; however, a recent large cohort study found no beneficial effect of statins on diabetic kidney disease (DKD). Furthermore, whether there are differences among statins in their effects on the kidneys remains unclear. Here, we compared effects of 4 statins on progression of DKD.

Methods: This was a single-center historical cohort study of Japanese adult ambulatory patients with type 2 diabetes. We studied 412 patients who were newly prescribed one of the following 4 statins: pravastatin, rosuvastatin, atorvastatin and pitavastatin, and who had estimated GFR (eGFR) ≥ 30 mL/min/1.73 m². As the control group, 946 patients without prescription history of statins were enrolled. Two outcomes were defined: 1) annual decline in eGFR and 2) progression to a more advanced stage of albuminuria. To adjust for the effects of confounding factors, we used the propensity score (PS) as the covariate. PS was estimated using a multinomial logistic regression model that included 18 clinical parameters. Furthermore, to take into account the varying number and spacing of eGFR measurements, and the variable follow-up period for each individual, we conducted the linear mixed-effects model regression analysis. The intercept and slope were treated as random effects.

Results: During the median follow-up period of 5.3 years (range, 2.0–8.6 years), the adjusted eGFR decline (\pm standard error) in the control group (1.6 ± 0.1 mL/min/1.73 m²/year) was significantly slower than that in rosuvastatin (2.4 ± 0.2 , $p=0.001$), atorvastatin (2.6 ± 0.3 , $p<0.001$) and pitavastatin group (2.3 ± 0.3 , $p=0.036$), but not in pravastatin group (1.7 ± 0.2 , $p=0.780$). Next, during the median follow-up period of 4.2 years (range, 0.1–8.5 years), 138 patients showed progression of albuminuria stage. The adjusted hazard ratio (vs. control group) for the albuminuria progression was 0.85 ($p=0.690$), 0.86 ($p=0.679$), 1.01 ($p=0.980$), and 0.69 ($p=0.462$) in pravastatin, rosuvastatin, atorvastatin and pitavastatin group, respectively.

Conclusions: Statins may have no beneficial effect on the progression of DKD. Instead, some statins are likely to be associated with faster renal function decline.

FR-PO648

Glucose Targets for Preventing Diabetic Kidney Disease and Its Progression: A Meta-Analysis Marinella Ruospo,^{1,2} Valeria M. Saglimbene,¹ Suetonia Palmer,^{3,4} Salvatore De Cosmo,⁵ Antonio Pacilli,⁵ Mariacristina Vecchio,⁶ Jonathan C. Craig,^{4,7} Giovanni F.M. Strippoli.^{1,4,7,8} *1Diaverum Medical Scientific Office; 2Amedeo Avogadro Univ of Eastern Piedmont; 3Univ of Otago Christchurch; 4Cochrane Kidney and Transplant; 5Scientific Inst CSS; 6Danone Research; 7Univ of Sydney; 8Univ of Bari.*

Background: Diabetes is the leading cause of end-stage kidney disease (ESKD). Blood pressure lowering and glucose control are considered central to protection of kidney function in diabetic nephropathy, however the optimal target range for blood glucose for preventing adverse kidney outcomes among adults with diabetes remains unclear. We evaluated the benefits and harms of intensive versus standard glycemic control for preventing the onset and progression of kidney disease.

Methods: Using standard Cochrane methods, we did a systematic review and meta-analysis of randomized controlled trials that evaluated intensive versus standard glycemic control administered to adults and children with type 1 or type 2 diabetes with or at risk of kidney disease. Intensive glycemic control was defined by a treatment targeting an HbA1c below 7% or fasting glucose levels <120 mg/dL. Effect sizes were calculated using a random-effects model. Studies were critically appraised using Cochrane methods.

Results: 10 studies involving 28,885 participants were eligible for inclusion. In studies at low risks of bias, intensive glycemic control had uncertain effects on doubling of serum creatinine (0.71, CI 0.34-1.47) and end-stage kidney disease (1.21, CI 0.12-11.98). Tight glycemic control reduced the onset (0.82, CI 0.71-0.93) and progression (0.56, CI 0.36-0.87) of microalbuminuria. In absolute terms, treating 1000 patients with tight glycemic control for 1 year might prevent 7 experiencing new-onset albuminuria and 22 with worsening albuminuria.

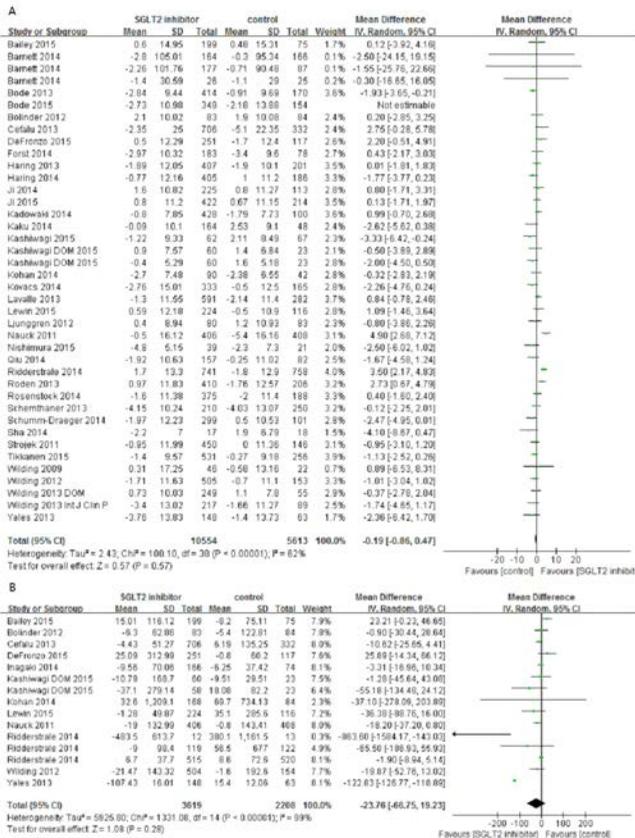
Conclusions: Intensive glycemic control among adults with diabetes had very uncertain effects on developing of ESKD and progression of kidney failure, while providing small clinical benefits on the onset and progression of microalbuminuria.

FR-PO649

Patient Benefits and Cost Savings Predicted for Mineralocorticoid-Receptor Antagonist Treatment of Early and Advanced Diabetic Kidney Disease Michael Blankenburg,¹ Henri J. Folse,² Christina Nowack,³ Bastian Hass.¹ *1Bayer Pharma AG, Berlin, Germany; 2Evidera, San Francisco, CA; 3Bayer Pharma AG, Wuppertal, Germany.*

Background: Exploratory studies suggest that mineralocorticoid-receptor antagonists (MRAs) may improve outcomes in patients with diabetic kidney disease (DKD). Finerenone (BAY 94-8862) is a selective, potent and non-steroidal MRA for the treatment of patients with DKD and is currently being studied in two clinical phase III trials, "FIDELIO" and "FIGARO".

Methods: A Markov cohort model was used to emulate disease history, treatment effects, and outcomes for DKD patients with various disease severities (by albuminuria, measured by urinary-albumin-creatinine ratio [UACR], and chronic kidney disease [CKD] stage, measured by estimated glomerular filtration rate [eGFR]). Efficacy of finerenone is accomplished by reducing albuminuria evidenced by phase 2 trial data. The model has US



Subgroup analysis in CKD patients showed a trend of eGFR decrease (mean change: -1.20 mL/min/1.73m², 95% CI, -2.65 to 0.26) and trend of ACR reduction (mean change: -59.73 mg/g, 95% CI, -144.49 to 25.04), neither of which were statistically significant.

Conclusions: So far, there is not enough evidence of SGLT2 affecting glomerular filtration rate and albuminuria in diabetic patients.

Funding: Government Support - Non-U.S.

FR-PO646

Meglitinides Increase the Risk of Hypoglycemia in Diabetic Patients with Advanced Chronic Kidney Disease Pei-chen Wu,¹ Vincent Wu,² *1Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan; 2Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.*

Background: There are few studies on the safety of short-acting meglitinides in diabetic patients with advanced chronic kidney disease (CKD). The aim of this study was to explore the risk of hypoglycemia in patients with severely impaired renal function taking meglitinides in comparison with that on other antidiabetic agents.

Methods: This was a nationwide cohort study using data from the Taiwan National Health Insurance Research Database. We included diabetic patients with advanced CKD who had a serum creatinine level of > 6 mg/dL (equivalent to an estimated glomerular filtration rate of < 15 mL/min/1.73m²) and a hematocrit level of $\leq 28\%$ and received erythropoiesis-stimulating agent treatment between 2000 and 2010. Fresh users and nonusers of meglitinides were matched using propensity scoring, and the risk of hypoglycemia was analyzed using Cox proportional hazards models with end-stage renal disease and antidiabetic drugs as time-dependent variables.

Results: A total of 2,793 fresh users of meglitinide and 2,793 matched meglitinide nonusers were analyzed. Meglitinide use increased the risk of hypoglycemia (HR, 1.93; 95% CI, 1.56-2.39), and so did sulfonylurea and insulin.

Variable	Hazard Ratio (95% confidence interval)	p-Value
Age (per year)	1.01 (1.01-1.02)	0.001
Male gender	1.20 (1.02-1.41)	0.028
Meglitinide	1.93 (1.56-2.39)	<0.001
Sulfonylurea	1.94 (1.62-2.33)	<0.001
Insulin	2.19 (1.86-2.59)	<0.001
End-stage renal disease	0.53 (0.42-0.65)	<0.001

Conclusions: The use of short-acting meglitinides is also associated with increased risk of hypoglycemia in diabetic patients with advanced CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

settings and a 40-year time horizon. Inputs are from NHANES 1999-2008, USRDS 2009, various registries and trials. Sensitivity analyses explored which patient subpopulation would benefit to what extent from finerenone treatment.

Results: The model predicts that finerenone is an effective treatment option for DKD patients, primarily by virtue of reduced risk of end-stage renal disease (ESRD) and renal death (absolute risk reductions [ARR] of up to 9.7% and 9.3%, respectively, for advanced DKD, i.e. macro-albuminuria and CKD3/4) and increased health-related quality of life, and that it would generate cost savings on renal replacement therapy (up to \$19,100 for advanced DKD). From a clinical outcomes perspective the optimal time point to begin finerenone treatment appears to be after patients have progressed to either macro-albuminuria or CKD stage 3, as represented by both phase III trial populations. Reduced CV events and CV mortality, however, are greatest (ARR of up to 3.8% and 4.5%, respectively) when finerenone treatment is started in early disease states, as represented by the phase 3 trial population "FIGARO".

Conclusions: Treatment with the MRA finerenone appears to be of significant benefit to patients and the healthcare system, particularly if initiated in advanced stages of DKD.

Funding: Pharmaceutical Company Support - Bayer Pharma AG

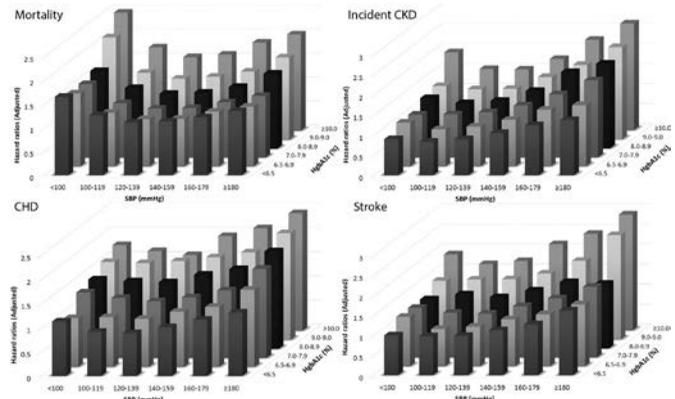
FR-PO650

Independent Association of Systolic Blood Pressure and Hemoglobin A1c Levels on Clinical Outcomes in Diabetic Patients with Normal Kidney Function Aidar Gosmanov,¹ Jun Ling Lu,¹ Miklos Zsolt Molnar,¹ Keiichi Sumida,¹ Praveen Kumar Potukuchi,¹ Kamyar Kalantar-Zadeh,² Csaba P. Kovacs,^{1,3} ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³VA Medical Center, Memphis, TN.

Background: Systolic blood pressure (SBP) goal of <140mmHg is recommended for majority of patients with diabetes mellitus (DM). It is however unknown if glycemic control modifies the association of uncontrolled hypertension (HTN) with mortality and morbidity in DM patients.

Methods: We examined 894,661 US veterans with DM and baseline eGFR >60 ml/min/1.73m² (mean age 66.6±10.9 years, 97% males, 17% African-Americans). The association of mutually exclusive combined categories of hemoglobin A1c (A1c; <6.5, 6.5-6.9, 7.0-7.9, 8.0-8.9, 9.0-9.9, and ≥10%) and SBP (<120, 120-139, 140-159, 160-179, and ≥180mmHg) with the risk of all-cause mortality, incident CKD, coronary heart disease (CHD), and stroke was examined in Cox models adjusted for baseline characteristics, statin use, and co-morbidities, using patients with A1c 6.5-6.9% and SBP of 120-139 mmHg as referent.

Results: A total of 221,983 (25%) patients died, and 178,628 (20%), 43,374 (5%) and 36,936 (4%) developed incident CKD, CHD and stroke, respectively, during a median follow up of 7.4 years. SBP displayed a U-shaped association with mortality in each A1c category. Conversely, SBP >120-139 mmHg was associated with a monotonous increase in the risk of CKD, CHD and stroke in all A1c categories. A1c levels were linearly associated with worse outcomes for all end points and in all SBP categories.



Conclusions: SBP above 120-139 mmHg and higher A1c levels were associated with higher mortality and morbidity in diabetic patients, independent of each other. Tight glycemic control may reduce mortality and morbidity across all SBP categories in patients with normal kidney function.

Funding: NIDDK Support, Veterans Administration Support

FR-PO651

High Acid Diets Increase Urinary Nitrogen Excretion and May Decrease Muscle Mass in Obese Diabetics Lynda A. Frassetto, Umesh Masharani, Anthony Sebastian. UCSF, San Francisco, CA.

Background: We have previously shown that decreasing dietary acid loads with bicarbonate supplements lowers urinary nitrogen (N) excretion in postmenopausal women. Here we examined whether we could lower urinary N excretion in obese diabetics by increasing plant food intake ("Paleo diet") compared with a "usual" acid diet (America Diabetes Association diet).

Methods: 12 obese well controlled type 2 diabetics (7 Paleo, 5 ADA) were enrolled in a 21 day no-weight loss controlled metabolic diet study. Daily protein intake per 2500 kcal averaged 116 g on the Paleo and 127 g on the ADA diets (p=0.7). Fasting arterialized

blood and 24-hour urine samples were collected at baseline (pre, days -2 to 0) and the last 3 diet days (on, +19 to 21). Each subject's tests were averaged by period, and the group averages analyzed by one-way ANOVA and between groups by t-test. Urinary N excretion was adjusted per 70 kg. Body composition [total (T), fat free mass (FFM), kg] was measured by bioimpedance (BIS).

Results: mean±SD. ADA or Paleo pre-on; a, p<0.05; Δ Paleo vs Δ ADA: b, p<0.1; c, p<0.05; d, p<0.01.

Index	Test	ADA pre	ADA on	Paleo pre	Paleo on	Δ Paleo vs Δ ADA
BIS	T	108±37	106±36	92±18	90±18	-0.2±1.0
	FFM	74.5±26.7	73.4±26.0 ^a	58.2±14.0	57.6±15.7	-0.6±1.4
Urine	Cr N, g/d	0.44±0.13	0.46±0.13	0.46±0.15	0.44±0.11	-0.44±0.83
	Cr CL mL/min	168±68	173±80	160±70	145±37	-20±40
	Urea N, g/d	9.5±3.6	11.2±2.6	10.8±5.7	8.8±4.1	-3.7±2.9 ^c
	Urea CL mL/min	57±20	70±29	59±19	52±17	-20±15 ^c
	NH4 N, g/d	0.42±0.10	0.47±0.12	0.43±0.22	0.20±0.06 ^a	-0.28±0.07 ^d
Total N, g/d	10.0±3.6	11.7±2.6	11.3±5.9	9.3±4.2	-2.3±1.5 ^b	
NAE meq/d	118±47	112±52	92±34	31±24 ^a	-55±50 ^a	

Both groups had equally modest nonsignificant declines in weight.

Conclusions: The higher acid diet had significantly greater loss of fat free mass associated with a greater loss of urinary urea and ammonium. A plant based low acid weight loss diet may be better in maintaining lean body mass compared to a usual acid diet.

Funding: Clinical Revenue Support

FR-PO652

Clinical Benefit of Pre-Dilution On-Line Hemodiafiltration for Removal of Low-Molecular-Weight Proteins and Fibroblast Growth Factor-23 Kenji Sakurai,¹ Takeshi Saito,¹ Fumi Yamauchi,¹ Hiromi Hosoya,¹ Yoshitaka Kurihara,¹ Daisuke Ishii,² Kazunari Yoshida,³ Kenichi Kokubo,⁴ Akihiro C. Yamashita,⁵ ¹Hashimoto Clinic, Kanagawa, Japan; ²Urology, Kitasato Univ, Kanagawa, Japan; ³Organ Transplant Medicine, Kitasato Univ, Kanagawa, Japan; ⁴Medical Engineering and Technology, Kitasato Univ, Kanagawa, Japan; ⁵Chemical Science and Technology, Hosei Univ, Tokyo, Japan.

Background: Increased concentration of fibroblast growth factor 23 (FGF-23) is reportedly associated with increased risk of cardiovascular complication and mortality in dialysis patients. Therefore, there is a possibility that reduction of FGF-23 levels may improve prognosis of dialysis patients with elevated its levels. We compared the removal performance of low-molecular-weight proteins (LMWP) and FGF-23 between pre-dilution on-line hemodiafiltration (HDF) and hemodialysis (HD) with super high-flux dialyzer.

Methods: The study involved 31 patients (15:HDF, 16:HD, 4 hrs, Qd:600 mL/min). Blood flow rates were 284±20 for HDF, 281±14 mL/min for HD. Replacement fluid volume in HDF was 49.2±9.9 L/session. Removal rates (RR,%) and removal amounts (RA,mg) of urea nitrogen (UN), creatinine, β₂-microglobulin (β₂-M, MW:11.8kDa), α₁-microglobulin (α₁-M, 33kDa) and FGF-23 (32kDa) were examined. We followed the changes in FGF-23 levels of patients for 4 month period.

Results: Kt/V, RRs of UN and creatinine were significantly higher in HD than in HDF, whereas RRs and RAs of β₂-M, α₁-M, and FGF-23 were significantly higher in HDF. RRs of β₂-M and α₁-M were 80.3±3.7 and 42.0±6.1 for HDF, 73.5±4.1 and 25.0±6.8 for HD, respectively. RR and RA of FGF-23 were 66.9±6.5 for HDF, 51.1±8.3 for HD and 0.11±0.01 for HDF, 0.01±0.01 for HD, respectively.

Conclusions: The results confirmed that HDF was superior to HD in removing LMWP and FGF-23, which are removed mainly by convection. The convection volume can be much easily controlled in HDF than in HD that utilizes internal filtration. The RRs of FGF-23 were 24 points higher than those of α₁-MG in both modes despite the small difference in MW, suggesting that distribution volume of FGF-23 was smaller than that of α₁-MG. No clear tendency was detected in changes of FGF-23 during 4-month observation period.

FR-PO653

Comparison of Removal Performance of Small- to Large-Molecular-Weight Substances Between Pre-Dilution On-Line Hemodiafiltration and Hemodialysis with Super-High-Flux Dialyzer Kenji Sakurai,¹ Takeshi Saito,¹ Fumi Yamauchi,¹ Hiromi Hosoya,¹ Yoshitaka Kurihara,¹ Daisuke Ishii,² ¹Hashimoto Clinic, Sagami-hara Kanagawa, Japan; ²Urology, Kitasato Univ, Sagami-hara Kanagawa, Japan.

Background: In pre-dilution on-line hemodiafiltration (HDF), net dialysate flow rate is reduced, because replacement fluid accounts for 30 to 50% of total dialysate flow (Qdtotal). Therefore, removal efficiency of small-molecular-weight substances by diffusion is reduced, whereas that of low-molecular-weight proteins (LMWPs) by convection is

improved. In hemodialysis (HD) using super high flux dialyzer, the increased blood flow rate (Qb) increases amount of internal filtration, thereby improving the removal efficiency of LMWPs. In this study, we compared the removal efficiency of small- to large-molecular-weight substances between HDF and HD to verify the superiority of HDF.

Methods: The study involved 62 patients (31: HD, 31: HDF). Super high flux dialyzers for HD and high-performance hemodiafilters for HDF were used. Qd was 500 for HD and Qdtotal was 600 mL/min for HDF. Replacement fluid volume for HDF was 44.4 ± 10.0 L/session. Qb was 256 ± 23, 257 ± 25 mL/min and Treatment time was 4.1 ± 0.2, 4.0 ± 0.1 hours in HD and HDF, respectively. Removal rates (RR) of b2-microglobulin(b2-M;11.8kDa), prolactin(PRL;23kDa), α1-microglobulin(a1-M;33kDa) and a1-acid glycoprotein(a1-AGP;44.1kDa) were investigated. Kt/V for urea and plasma clearances (CL) of b2-M, PRL and a1-M were measured.

Results: RR (%) of each substance was significantly higher in HDF than in HD (P < 0.001): b2-M, 79.8 ± 3.2 vs. 70.8 ± 4.7; PRL, 75.3 ± 5.5 vs. 66.2 ± 6.6; a1-M, 40.0 ± 4.1 vs. 31.5 ± 6.4; a1-AGP, 11.9 ± 4.3 vs. 7.4 ± 4.8. Kt/V was 1.56 ± 0.22 (HDF) and 1.51 ± 0.19 (HD). Plasma CLs (mL/min) of b2-M were 95.7 ± 3.6 and 73.6 ± 3.7, those of PRL were 37.3 ± 4.3 and 28.1 ± 5.5 in HDF and HD, respectively.

Conclusions: The performance of HDF in removing LMWPs was superior to that of HD and there was no significant difference in Kt/V in both modes. An increased convection by HDF greatly contributed to improved removal of LMWPs and appropriate control of dialysate flow rate improved the removal efficiency for small molecular substances to the level achieved by HD.

Funding: Private Foundation Support

FR-PO654

The Effect of Increasing Kt/V_{urea} in the HEMO Study on Levels of Non-Urea Solutes Timothy W. Meyer,¹ Tammy L. Sirich,¹ Tariq Shafi,² Tanushree Banerjee,³ Neil R. Powe,³ Thomas H. Hostetter.⁴ ¹Med, Stanford, CA; ²Med, Johns Hopkins, MD; ³Med, UCSF, CA; ⁴Med, Case Western, OH.

Background: In the HEMO study, outcomes were no better in patients randomized to “high dose” thrice weekly hemodialysis providing spKt/V_{urea} 1.73 than in those randomized to “standard” hemodialysis providing spKt/V_{urea} 1.32.

Methods: This study assessed whether “high-dose” treatment lowered levels of non-urea solutes. Solute levels were measured by LC/MS/MS in plasma samples obtained at least 3 months after randomization in 1281 HEMO subjects.

Results: (mean±sd; CI, confidence interval).

Solute	standard	high-dose	% change (95% CI)	p value
Trimethylamine oxide μM	107±63	97±65	-9 (-15, -2)	0.007
Phenylacetylglutamine mg/dl	4.6±3.1	4.3±2.6	-7 (-13, -0)	0.04
Symmetric dimethylarginine μM	4.3±1.4	4.2±1.3	-4 (-7, -1)	0.018
Asymmetric dimethylarginine μM	0.92±0.24	0.93±0.23	-1 (-2, 3)	0.74
p-Cresol Sulfate mg/dl	3.3±1.7	3.4±1.7	+2 (-4, 8)	0.46

Increasing Kt/V_{urea} caused statistically significant but only modest reductions in the levels of trimethylamine oxide, phenylacetylglutamine, and symmetric dimethylarginine. Mathematical modeling showed that limited reduction in the levels of these solutes was a predictable consequence of the intermittency of treatment. Their reduction ratios with standard treatment are high and the increased intensity of treatment reflected by a 30% increase in Kt/V_{urea} in HEMO’s high dose arm could not remove much more solute. Remarkably, increasing Kt/V_{urea} in HEMO caused no reduction in the levels of asymmetric dimethylarginine or p-cresol sulfate, two solutes which have been associated with cardiovascular disease in dialysis patients. Modeling showed that stability of their plasma levels could be accounted for by increased solute production accompanying the increase in Kt/V_{urea} and/or the presence of non-dialytic clearance.

Conclusions: Levels of non-urea solutes may fall only slightly or not at all when Kt/V_{urea} is increased above standard levels for thrice weekly treatment. Treatments that are more effective in reducing solute levels may be required to improve outcomes.

Funding: NIDDK Support, Veterans Administration Support

FR-PO655

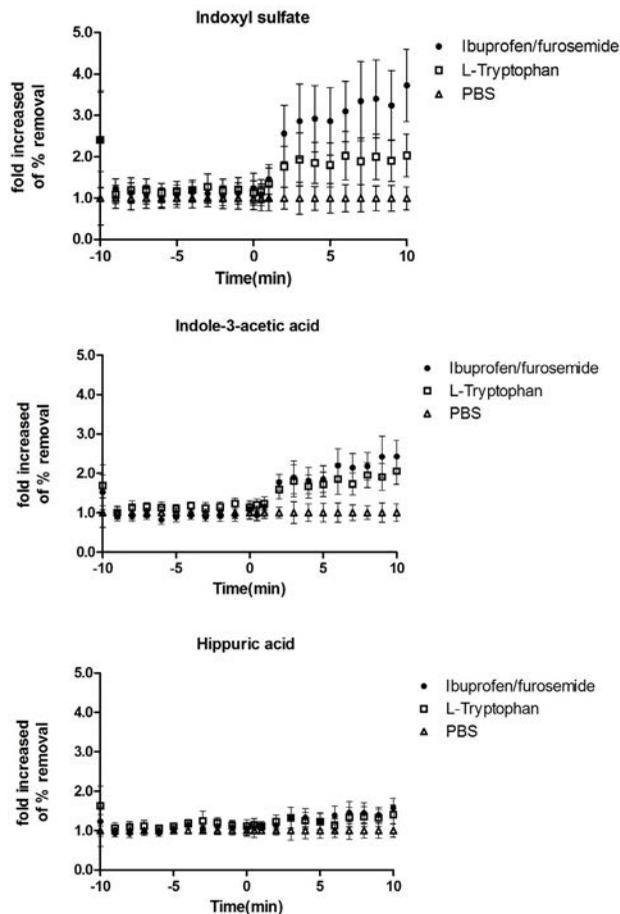
Improved Protein-Bound Uremic Toxins Dialytic Removal with Use of Albumin Binding Competitors: An In Vitro Human Whole Blood Study Xia Tao,¹ Stephan Thijssen,² Peter Kotanko,² Chih-Hu Ho,³ Michael E. Henrie,³ Eric W. Stroup,³ Garry J. Handelman.¹ ¹Univ of Massachusetts, Lowell, MA; ²Renal Research Inst, NY, NY; ³Fresenius Medical Care, Ogden, UT.

Background: Protein-bound uremic toxins (PBUT) are intensively studied retained solutes that accumulate in chronic kidney disease patients. Efficient removal of PBUTs by hemodialysis (HD) is difficult because of limited free fraction in blood. We propose an innovative method for improving the dialytic removal of PBUTs by increasing their free fractions with use of protein binding competitors.

Methods: The binding properties of indoxyl sulfate (IS), indole-3-acetic acid (IAA) and hippuric acid (HIPA), and their binding competitors, ibuprofen (IBU), furosemide (FUR) and tryptophan (TRP) were studied by rapid equilibrium dialysis (RED) to select suitable model compounds for the HD study. The method was then tested in an *in vitro* HD experimental model with human whole blood spiked with PBUTs. After 10 min

baseline test, the binding competitors were introduced upstream of dialyzer blood inlet. The removal of uremic toxins was estimated as the amount leaving dialysate outlet relative to the amount entering blood inlet.

Results: The infusion of IBU and FUR mixture (647μmole/l and 126μmole/l in blood, respectively) in the HD model increased removal of IS from 6.3 ± 0.1 to 15.2 ± 0.3 % (mean ± SEM) (2.4-fold) and IAA removal from 15.9 ± 0.2 to 29.8 ± 0.6% (1.9-fold). TRP (1mmole/l in plasma) infusion increased the removal of IS and IAA to 9.4 ± 0.1% and 26.0 ± 0.3% (1.4- and 1.3-fold, respectively). Only moderate effects were observed in the change of HIPA removal.



Fold change is the ratio of the % removal induced by competitors to PBS. Infusion of competitors started at 0 min. Polysulfone dialyzer (surface area 390cm²), Qb=12.5 ml/min, Qd=25 ml/min.

Conclusions: This method increases the removal of PBUTs and has no effect on non-protein-bound solutes. Achieving higher dialytic removal of PBUTs by infusion of binding competitors is feasible and efficient to apply in current HD settings.

Funding: Pharmaceutical Company Support - Renal Research Institute

FR-PO656

Variable Recovery Time After Hemodialysis Treatment Antonia Harford,¹ Susan Paine,² Ronald Schrader,² Ambreen Gul,² Dana Miskulin,³ Philip Zager.^{1,2} ¹UNM; ²DCI; ³Tufts.

Background: Prolonged recovery time after hemodialysis (HD) may predict adverse clinical outcomes. In the Frequent Hemodialysis Network a patient’s response to the Recovery Question was consistent over time. To determine if this consistency is also present among patients undergoing thrice weekly HD we compared responses to the Recovery Question after each treatment in a given week.

Methods: We asked 256 patients in 3 DCI HD facilities “How long did it take you to recover after your last treatment?” The number of patients who answered the question on the 1st, 2nd, and 3rd treatment was 221, 207, and 200, respectively; 148 patients (57.8%) answered the question on all 3 occasions. Recovery time was categorized as <0.5 hours(h), 0.5 h -< 6 h, and ≥ 6 h.

Results: Among the 148 patients who answered the Recovery Question 3 times, recovery times were 6.9, 4.5 and 9.3 hours after the 1st, 2nd, and 3rd HD. There were 46% of patients who had consistent responses on all 3 treatments; 16%, 15% and 15%, had consistently short (<0.5h), moderate (0.5-<6h) and long (≥ 6h) recovery times, respectively. There were 64% who had similar recovery times on the 1st vs.2nd and 1st vs. 3rd HD of the week. Only 57% had consistent recovery times on 2nd and 3rd treatments.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

		Third Tx in Week Recovery (hours)			
		< 0.5	0.5 - 6-	≥ 6	
Second Tx in Week Recovery (hours)	< 0.5	30	17	24	48%
	0.5 - 6-	1	28	13	28%
	≥ 6	2	6	27	24%
		22%	34%	43%	

Among the patients with consistent short vs. long recovery, there were no differences in age, race, and vintage. There was a trend for women (59%) to be more likely to have recovery ≥ 6h vs. men (33%) (p=0.09). After the 1st dialysis of the week, recovery was more likely (40%) to be ≥ 6h among patients dialyzed with a dialysate sodium concentration (DNa) <140 mEq/L vs. with a (DNa) ≥ 140 mEq/L (22%). However, similar differences were not observed for the 2nd and 3rd treatments.

Conclusions: There is significant variability among individual patients answers during the week when the recovery question is asked after each treatment.

FR-PO657

Quality Control and Improvement Union of Hemodialysis Centers: A New Management Model Liangying Gan, Mei Wang. Dept of Nephrology, Peking Univ People's Hospital, Beijing, China.

Background: With the increasing incidence of end stage renal disease (ESRD) in China, more dialysis facilities are needed. There are huge variations of patient care staffing levels and quality of care. How to maximize the utilization of existing health resources, optimize the management of hemodialysis patients and improve quality control are important issues. The aim of this study was to investigate the feasibility and effects of quality control and improvement union comprised of best hospitals and basic hospitals on patients' medical quality control and improvement.

Methods: The HD union was constructed and specific measures was determined including, 1) Quarterly continuous quality improvement (CQI) meetings, 2) education based on typical cases including extensive discussions, guidelines and latest research results introductions, 3)lectures focusing on key questions, 4) opening green channel and construction of two-way referral system. Paired t-test was used to compare the differences of medical parameters of each hemodialysis center before and two-years after construction of HD union.

Results: The leading center of HD union was the HD center from Peking University People's Hospital. Cooperating centers were other eight centers from class three and class two hospitals. After quarterly CQI meetings, all union members learned how to do medical quality control and improvement, constructed standards and procedures for diagnosis, cure and nursing of their HD center, established the institutions of lab exam and regular round frequency, added necessary examinations and implemented all-around management of HD patients. Green channel for intractable cases transfer were applied successfully. There were statistical improvements of medical quality including dialysis frequency, hemoglobin, calcium, phosphorus, and metabolic acidosis control. Other parameters including Kt/V, iPTH, albumin and Bp improved but without significant difference.

Conclusions: Quality control and improvement union of hemodialysis centers is an effective integrated management model in Beijing China. It can improve medical quality of basic hospitals by balancing the technical advantages of grade A class three hospitals and basic hospitals.

Funding: Government Support - Non-U.S.

FR-PO658

Feasibility of Mindfulness Meditation Training During Dialysis for Patients with Chronic Kidney Disease and Effect on Tolerability of Sessions James C. Wasserman,¹ Daniel Schupack,^{2,3} Andrew E. Williams,⁴ Paul K. Han,^{2,3} George K. Dreher,³ Mary Bitterauf.⁵ ¹Div of Nephrology, Maine Medical Center, Portland, ME; ²Center for Outcomes Research and Evaluation, Portland, ME; ³Maine Medical Center, Portland, ME; ⁴Maine Medical Center Research Inst, Portland, ME; ⁵MaineHealth, Falmouth, ME.

Background: Hemodialysis (HD) for CKD entails ≥12 h of weekly treatment, creating significant distress for patients. Mindfulness-Based Stress Reduction (MBSR) has effectively helped patients with other chronic diseases cope with distressing symptoms and treatments. An abbreviated form of MBSR (Mindfulness Meditation Training, MMT) was incorporated into HD sessions to explore its feasibility, acceptability and potential effectiveness.

Methods: 12 patients were randomly assigned to MMT during HD or usual care. The MMT group underwent weekly 1-h individual sessions during HD for 4 wk. Within-session change in affective response was assessed with the Self-Assessment Manikin, a validated measure of affective valance, arousal and dominance. Anxiety, depression, self-rated health and coping skills were also assessed with validated measures. Patient perceptions were assessed with qualitative interviews at study's end.

Results: In qualitative interviews, patients reported improved tolerability of HD session length, positive intention to continue meditation and no significant issues with

MMT sessions or home practice. There were no significant between-group differences in affective response, anxiety, depression, self-reported health or coping skills at baseline or in change over time. Retention rate was 91.7% overall and 83.3% for the MMT group.

Conclusions: MMT appears to be a feasible and acceptable intervention for CKD patients during HD, although effectiveness remains to be demonstrated. Small sample size and low baseline distress levels in the study population likely limited the power to establish effects of MMT. Further research is needed to determine if abbreviated MBSR is sufficient to benefit tolerability of HD in this population. Focus on patients with higher baseline distress levels in future research would increase the likelihood of observing clinical benefit.

FR-PO659

Fluid Management Parameters Are Associated with Dialysis Recovery Time in Conventional Hemodialysis Wael F. Hussein,^{1,2} Rohini Arramreddy,^{1,2} Marc Reiterman,² Sumi J. Sun,² Brigitte Schiller.^{1,2} ¹Dept of Medicine, Div of Nephrology, Stanford Univ, Palo Alto, CA; ²Satellite Healthcare, San Jose, CA.

Background: Longer dialysis recovery time (DRT) is associated with increased mortality and shorter time to hospitalization. We studied the association of fluid management and hemodynamics with recovery time in conventional hemodialysis (HD) patients.

Methods: Self-reported DRT, obtained by asking "How long does it take you to recover from a dialysis session?", was recorded for 2,689 patients undergoing thrice weekly adequate HD in 46 centers in 3 states. Ordinal logistic regression was used to study the association between patient and dialysis characteristics with DRT. Statistical adjustments were made for patient demographics, comorbidities and body weight.

Results: Forty-three percent of patients were female, 20% were black, median age and vintage were 63 and 3.3 years, median dialysis session length was 203 min (IQR: 180-220). DRT in categories of immediate recovery, >0 to ≤ 2 hours (hrs), > 2 to ≤ 6 hrs, > 6 to ≤ 12 hrs, and > 12 hours, were reported in 27%, 28%, 17%, 9%, and 20% of the patients respectively. In multivariable analysis, longer DRT was associated with female gender, non-black race, lower serum albumin, chronic heart failure, cerebrovascular disease, missed dialysis sessions, higher pre-dialysis systolic blood pressure and larger UF volume. Ultrafiltration rates (UFR) were divided into three categories: <10, 10 to <13, and ≥13 ml/kg/hr. Compared to the lowest UFR category, UFR ≥13 ml/kg/hr was associated with longer DRT; OR of 1.16 (95% CI 0.99 – 1.36) and 1.28 (95% CI 1.06 – 1.54) in the unadjusted and the adjusted analyses respectively. IDH was associated with longer DRT in the unadjusted (per 10% higher frequency, OR 1.04 [95% CI 0.01 – 1.07]) and adjusted analyses (OR 1.03 [95% CI 1.00 – 1.07]).

Conclusions: Long DRT affects a large proportion of HD patients. Optimizing UFR and controlling IDH are critical measures to improve quality of life for these patients.

FR-PO660

Different Adsorptive Properties of Hemodialysis Membranes May Cause Selective Depletion of Plasma Proteins Jan Mares, Lukas Kielberger. Nephrology, Charles Univ, Plzen, Czech Republic.

Background: During hemodialysis (HD) session, plasma proteins are adsorbed to the surface of HD membrane. The resulting biofilm affects both dialyzer permeability and biocompatibility. The aim of this study was to analyze its composition in different HD membranes.

Methods: Twelve long-term HD patients were assigned to 4h HD with three different dialyzers in a cross-over design: ethylene-vinyl-alcohol/EVAL (KF-201-1.8C, Asahi Kasei), polysulfone (F8 HPS, Fresenius), and vitamin E-substituted polysulfone (ViE-18, Asahi Kasei). After HD session, the biofilm was eluted with acetic acid. Obtained proteins (200 µg) were separated by 2-dimensional electrophoresis and fractions showing distinct abundance across groups were identified by tandem mass spectrometry. Blood was sampled along the session to enable subsequent confirmatory studies (ELISA). Data are given as means ± SEM, statistical significance was calculated by ANOVA (general linear model).

Results: The amount of protein eluted from KF dialyzers was higher than from F8 or ViE: 42±9.6, 9±3.3, and 12±6.9 mg, (p<0.001), respectively. Totally, 303 protein fractions were detected, 235 common to all eluates. In 48 fractions, spot intensities varied between groups suggesting different adsorption (p<0.05). Among them, 11 individual plasma proteins were identified: mannose-binding lectin associated serum protease 1 (MASP1 p=0.012), clusterin (p=0.003), retinol-binding protein 4 (RBP4, p=0.018), α1-microglobulin (AMBp, p<0.001), complement factor H (CFH, p=0.004) and its related proteins 1, 2, 5 (FHR, p<0.001), fibrinogen β, γ (p<0.001), and ficolin-2 (FCN2, p<0.001). EVAL membrane bound less FCN2, MASP1, and clusterin but more AMBP, CFH, and FHRs than polysulfone membranes. The most prominent difference was established in FCN2, it was therefore selected for a confirmatory study. It showed a sustained decline of plasma FCN2 levels at all timepoints during HD with F8 but not KF dialyzer to 40±3.6% and 111±5.3% of pre-dialysis levels, respectively (p<0.001).

Conclusions: Different HD membranes show variable binding characteristics for particular plasma proteins. It can be responsible for their increased clearance and temporary depletion as demonstrated in case of ficolin-2.

Funding: Government Support - Non-U.S.

FR-PO661

Mathematical Model of Protein Transport and Plasma Refilling in Hemodialysis Bengt Lindholm,¹ Mauro Pietribiasi,² Malgorzata Debowska,² Alicja Wojcik-Zaluska,³ Wojciech T. Zaluska,⁴ Jacek Waniewski.² ¹*Baxter Novum & Renal Medicine, Karolinska Inst, Stockholm, Sweden;* ²*Inst Biocybernetics & Biomedical Engineering, Warsaw, Poland;* ³*Rehabilitation and Physiotherapy, Medical Univ Lublin, Lublin, Poland;* ⁴*Nephrology, Medical Univ Lublin, Lublin, Poland.*

Background: Mathematical modeling offers a way to estimate quantities we cannot access directly during hemodialysis (HD). Here we propose a whole-body model of vascular refilling describing water and protein shifts across the capillary membrane during HD. The model was applied to reproduce profiles of plasma volume and serum total protein concentration in patients (pts) undergoing HD.

Methods: The double-pool model (vascular and interstitial space) was based on balance equations of protein mass and water volume in each compartment. The net transport across the capillary wall is the sum of the flow through the membrane's pores and lymphatic flow. The capillary membrane is described according to the three-pore theory. Two transport parameters of the model, the relative number of large pores (α LP) and the total permeability surface area product (LpS) of the capillary membrane, were estimated from volumetric data and blood samples collected in 20 stable, non-diabetic pts during 60 HD sessions.

Results: LpS and α LP were estimated to 10.0 ± 8.4 mL/min/mmHg and 0.062 ± 0.041 . The model predicted profiles of plasma volume and serum total protein concentration with an average root-mean-square error < 2%, with larger errors only in pts with very high initial drop in blood volume. When increasing the assumed value of interstitial/serum protein ratio from 0.3 to 0.6, while the total refilling rate remained similar, the value of individual pore flows changed so that filtration through large pores at its peak was 40 % smaller and absorption through small and ultras-small pores was 80 and 60 % higher, respectively.

Conclusions: The model proposes a mechanistic interpretation of fluid transport processes induced by ultrafiltration during HD. The estimated values of individual flows through each kind of pore and lymphatic absorption represent the relative impact of these not-measurable quantities on total vascular refilling.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

FR-PO662

Hemodiafiltration at Increased Plasma Ionic Strength for Improved Protein-Bound Toxin Removal Detlef H. Krieter,¹ Eric Devine,² Thomas Koerner,¹ Marieke Rueth,² Christoph Wanner,¹ Joachim Jankowski,³ Horst-Dieter Lemke.² ¹*Nephrology, Univ Hospital Würzburg, Würzburg, Germany;* ²*eXcorLab GmbH, Obernburg, Germany;* ³*Inst of Molecular Cardiovascular Research, Univ Hospital RWTH Aachen, Aachen, Germany.*

Background: Protein-bound uremic toxin (PBT) removal by hemodialysis (HD) is limited resulting in dialysis associated cardiovascular morbidity. Enhancing ionic strength in the dialyzer decreases protein binding and may result in a larger unbound and removable toxin fraction. This was implemented through high sodium concentration ($[Na^+]$) in the substitute of predilution hemodiafiltration (HDF_{mod}).

Methods: *Ex vivo* predilution HDF with blood tested increasing $[Na^+]$ to demonstrate efficacy and hemocompatibility. Hemocompatibility was further assessed in sheep using two different HDF_{mod} setups and $[Na^+]$ between 350 and 600 mmol/L. Safety and efficacy of para-cresyl sulfate (pCS) and indoxyl sulfate (IS) removal was further investigated in a randomized clinical pilot trial comparing HDF_{mod} to HD and standard HDF.

Results: Compared to physiological $[Na^+]$, *ex vivo* HDF_{mod} at $[Na^+]$ of 500 mmol/L demonstrated up to 50 % higher IS removal. Hemolysis in sheep was low even at $[Na^+]$ of 600 mmol/L, not exceeding 0.016 ± 0.001 g/dL of free Hb. In patients, the reduction rate of free IS was 20 % higher in HDF_{mod} at $[Na^+]$ of 240 mmol/L compared to HD (72.6 ± 6.1 vs. 60.4 ± 16.5 %; $P=0.026$). Compared to HD and HDF (23.0 ± 14.8 and 25.4 ± 10.5 mL/min, resp.), the dialytic clearance of free IS was 37 and 24 % higher in HDF_{mod} (31.6 ± 12.8 mL/min; $P=0.017$), but $[Na^+]$ significantly increased over time (arterial plasma at 0 min and 240 min; 132 ± 2 vs. 136 ± 3 mmol/L; $P<0.001$).

Conclusions: Ionic strength modification with HDF is technically feasible, enhancing PBT removal without adverse effects. More effective HDF_{mod} will require higher temporary $[Na^+]$ in blood, but accumulation of $[Na^+]$ has to be avoided.

Funding: Government Support - Non-U.S.

FR-PO663

A Filter Placed Along the Path of the Water Treatment System Can Reduce Inflammation in Patients on Chronic Dialysis Elena Mancini,¹ Annunziata Tartaglione,² Emanuele Mambelli,¹ Paolo Gaibani,² Annalisa Boneschi,¹ Raffaele Longo,¹ Maria paola Landini,² Antonio Santoro.¹ ¹*Nephrology Dialysis Hypertension, Policlinico S.Orsola-Malpighi, Bologna, Italy;* ²*Inst of Microbiology, Policlinico S.Orsola-Malpighi, Bologna, Italy.*

Background: Contamination of dialysis fluids is one of the most important etiologic factors of chronic inflammation in HD patients, leading to malnutrition/atherosclerosis. Besides intact bacteria and endotoxins, bacterial DNA fragments have to be considered, because, due to their small size, they pass through the most sophisticated water treatment systems.

Methods: We have evaluated the effect on the water quality and patient inflammation of a new ultrafilter placed on the water circuit before the dialysis machine. The filter,

with peculiar characteristics (DSU, Nephros Inc, River Edge, NJ), was applied to all the dialysis seats (n=34; 130 patients) in our Centre (Study period, S). At baseline, during S, and the 3 following months without ultrafilter (control period, C), apart from routine controls, every month we performed both conventional microbiological analyses and bacterial DNA fragment research in the dialysate and in the patients.

Results: Conventional microbiological analyses proved negative at every phase of the study, while the search for bacterial DNA was positive in 8/34 samples at baseline (219 genomic copies/reaction). At the end of S, no dialysate sample was still positive (0.029 genomic copies/reaction; $p=0.04$ sign test). During the following period C, dialysate samples became once again positives. A similar trend was observed in the patient plasma: 113.5 copies/reaction at baseline, 19.9 at the end of S, 84.8 at the end of C ($p=0.013$). C reactive protein measured in each patient was significantly reduced during S ($p=0.04$).

Conclusions: In conclusion, the traditional treatment did not prevent the appearance of bacterial DNA fragments in dialysis fluids. This can foster the onset of inflammation. The ultrafilter tested actually improved the purity of the water and its regular use seems to reduce microinflammation. This could, in turn, have repercussions on different aspects such as resistance to erythropoietin as well as the processes of precocious atherosclerosis.

Funding: Clinical Revenue Support

FR-PO664

Effect of Computationally-Optimized Vibration on Clearance of Solutes During In Vitro Hemodialysis Katherine N. Gharibian,¹ Susan J. Lewis,¹ Joseph L. Bull,² John J. Pitre,² Bridget A. Scoville,³ Thomas Velenosi,⁴ Brad Urquhart,⁴ Noel Perkins,⁵ Bruce A. Mueller.¹ ¹*College of Pharmacy, Univ of Michigan, Ann Arbor, MI;* ²*Dept of Biomedical Engineering, Univ of Michigan, Ann Arbor, MI;* ³*Saint Alexius Medical Center, Hoffman Estates, IL;* ⁴*Dept of Physiology and Pharmacology, Western Univ, London, ON;* ⁵*Dept of Mechanical Engineering, Univ of Michigan, Ann Arbor, MI.*

Background: Our previous *in vitro* studies demonstrated that the addition of vibration enhances dialytic clearance of solutes by a median of 18% during CVVHD. In this study, we applied computational fluid dynamics to determine vibration's effects during hemodialysis and validated them using an *in vitro* hemodialysis model.

Methods: Based on predictions of a computational fluid dynamics model, two vibration settings (120 Hz/0.176 mm & 360 Hz/0.0765 mm) were selected and applied to a F8 dialyzer (1.8 m²; Fresenius) during *in vitro* hemodialysis using blood/dialysate flow rates of 300/600 mL/min, respectively. Mean transmembrane clearances were analyzed for six solutes: urea, creatinine, gentamicin, vancomycin, indoxyl sulfate, and hippuric acid. Albumin, free hemoglobin, and LDH concentrations were measured after 4 hours of dialysis with applied vibration to assess blood and dialyzer integrity.

Results: A one-way ANOVA yielded no significant difference between the control group and non-control vibration groups in solute clearance: urea, $F(2,27)=1.801$, $p=0.184$; creatinine, $F(2,27)=2.525$, $p=0.099$; gentamicin, $F(2,33)=0.273$, $p=0.763$; vancomycin, $F(2,33)=0.003$, $p=0.997$; indoxyl sulfate, $F(2,33)=0.390$, $p=0.680$; hippuric acid, $F(2,33)=0.398$, $p=0.675$. Four hours of vibration had no significant effect on blood and dialyzer integrity as measured by concentrations of albumin ($F(1,22)=0.185$, $p=0.735$), hemoglobin ($F(1,22)=1.038$, $p=0.319$), and LDH ($F(1,22)=0.185$, $p=0.672$).

Conclusions: Although vibration has been shown to enhance solute clearance in CRRT and PIRRT, in this study, computationally-optimized vibration failed to significantly enhance solute clearance in an *in vitro* hemodialysis model using flow rates typically seen with intermittent hemodialysis.

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FR-PO665

Sevelamer Hydrochloride Improves Oxidative Stress in Maintenance Hemodialysis Patients Siren Sezer, Bahar Gurlekdemirci, Cihat Burak Sayin, Emre Tural, Zeynep Bal, Fatma Nurhan ozdemir Acar. *Dept of Nephrology, Baskent Univ Faculty of Medicine, Ankara, Turkey.*

Background: Oxidative stress plays a key role in the pathogenesis of cardiovascular diseases. Superoxide dismutase (SOD) and malondialdehyde (MDA) are well-known antioxidant enzymes that detoxifies advanced glycation end products (AGEs). We thought that avoiding calcium intake and through pleiotropic effects, sevelamer hydrochloride might be a differential influence in terms of oxidative stress. The aim of this study is to evaluate the effects of phosphate binders (PBs) on the components of the oxidative stress and clinical and biochemical parameters including pulse wave velocity in our maintenance hemodialysis (MHD) patients.

Methods: A total of 111 patients (mean age: 52.2 ± 14.3 years; mean duration of dialysis: 9.7 ± 4.6 years) undergoing maintenance hemodialysis and using the same PBs at least one year were enrolled into the study. Patients were divided into two groups according to usage of PBs as sevelamer based PB (group 1; n: 84 and calcium based PB (group 2; n:27). Biochemical parameters were assessed from monthly clinical visits. Serum AGE, MDA and SOD levels were determined by ELISA method. Pulse wave velocity (PWV) was determined by using the SphygmoCor system.

Results: Groups were similar in means of demographic characteristics and URR levels. Patients in group 1 had significantly lower AGE ($p: 0.018$), higher MDA ($p: 0.027$) and SOD ($p: 0.012$) levels. Although both baseline and first year PWV values were similar in two groups, PWV values significantly decreased in group 1 ($p: 0.001$) where increased in group 2 ($p: 0.021$) in the second year analysis. In linear regression analysis, serum AGE levels were detected as the unique predictor of DPWV ($p: 0.005$). For each 1 uM/L of increased level of AGE resulted in 0.53 cm/sec of increased level of PWV ($p: 0.005$, CI: 0.016-0.089).

Conclusions: Despite similar phosphorus levels and dialysis adequacy, sevelamer decreases serum AGE and increases serum MDA and SOD levels as well as improves PWV. Thus, sevelamer improves the oxidative stress and cardiovascular risk by pleiotropic effects when compared to calcium based phosphate binders.

FR-PO666

Preliminary Study About Optimal Dosage of Heparin Locking Solution to Maintain the Patency of Hemodialysis Catheter Jung-woo Noh, Eunjung Kim, Ja-Ryong Koo. *Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym Kidney Research Inst, Seoul, Korea.*

Background: Hemodialysis catheters(HC) are routinely heparin locked to maintain patency. This practice may cause bleeding episodes. The amount of heparin for heparin locking solution at many dialysis centers has been decreased recently to reduce the risk of bleeding. However, the effect of this change on patency of HC is unknown. We compared the patency of HC between four types of heparin amount of 4000, 5000, 7500, and 15000 units(U).

Methods: This observational study included 126 chronic hemodialysis patients using HC in Hallym University Medical Center from March 2011 to July 2014. 29 patients received a 4000 U, 41 patients received a 5000 U, 44 patients received a 7500 U and 41 patients received a 15000 U of heparin. The primary outcome was composite outcome: frequency of thrombolytic instillation, change of hemodialysis line due to dysfunction of HC and HC obstruction due to thrombosis. We also compared activated partial thromboplastin time (aPTT) levels between groups just before and 10 minutes after the end of each hemodialysis.

Results: The composite outcome were 2.44±5.42, 1.06±3.46, 0.40±1.18 and 0.52±1.16 episodes/100 catheter-days, respectively(p=0.03). 4000U group showed especially high rate of events compared to other groups receiving more than 5000 U of heparin. However, event rate of HC obstruction due to thrombosis was not significantly different: zero episodes/100 catheter-days for 4000U and 15000U groups, 0.01±0.05 episodes/100 catheter-days for 5000U group and 0.14±0.61 episodes/100 catheter-days for 7500 IU group. At 10 minutes after heparin lock, prolonged aPTT was observed in all groups. When 10 minutes aPTT levels between 4000 U group and other groups are compared, those of 7500 U(p=0.007) and 15000 U(p=0.004) groups were significantly prolonged. But there were no bleeding complications in those groups.

Conclusions: Low concentration heparin lock solution with total amount of 4000 U do not increase HC obstruction due to thrombosis, but increase in thrombolytic instillation and set change. Higher concentration heparin lock solution with total amount over 7500 U prolonged the aPTT without bleeding complication.

Funding: Clinical Revenue Support

FR-PO667

Association Between Depressive Symptoms and Dependency with Mortality in Hemodialysis Patients After 5 Years of Follow-Up Joaquin Manrique,¹ Maria del cielo Mena,² Eva Cerdán,² Laura Catalan.² *¹Servicio de Nefrología, Complejo Hospital de Navarra, Pamplona, Spain; ²Nursing Staff, Servicio de Nefrología, Complejo Hospital de Navarra, Pamplona, Spain.*

Background: The prevalence of depression and its role in mediating survival of patients with end-stage renal disease (ESRD) has been highly controversial. Moreover, according to the population ages, their limitations in performing daily activities affect their well-being as well as increase the burden on caregivers and the use of health services.

Methods: We determine whether depressive symptoms and dependency are associated with mortality in a longitudinal study of 148 hemodialysis (HD) outpatients followed for 5 years. Depressive symptoms were assessed using the Beck Depression score (BDs), and dependence by Barthel scale (BS) performed by nursing HD staff.

Results: 26.8% of patients had depressive symptoms (BD>10) and the mean baseline BDs was 11.4+/-8.1). 23% patients were moderate or severely dependent (BS<90). 40.5% died during the study follow-up period (a rate similar to that found in this population). We observed a significant association between BS and BDs ($r^2=0.5$; $p<0.001$). Patients with greater disability (BS<90) had worse depressive score ($p<0.001$). After 60 months of follow-up, survival rates were 80.5% for BDs≥8 and 94.3% for BDs < 8 ($p=0.05$), and 71.4% for dependent and 95.5% for no dependent patients ($p<0.001$). Other variables, including age, gender, and dialysis period, were not significantly associated with mortality. Cox proportional hazards regression was performed to predict the mortality hazard associated with baseline level of depressive affect and dependence, controlling for the effects of variation in patient age and dialysis duration.

Conclusions: Our study shows that the disability in self-care and the presence of depressive symptoms are common among patients on haemodialysis. Both of them may act as independent risks factors for mortality. Strategies could be helpful to routinely identify those dialysis patients at risk of functional impairment and depression to limit their disabilities. Self-report scales and those performed by nursing staff could improve the integral treatment of those patients.

FR-PO668

Limitations of Access Recirculation due to a Low Access Flow Rate on Middle Molecule Clearance During Post-Dilution Hemodiafiltration J. Ken Leyppoldt,¹ Markus Storr.² *¹Renal Therapeutic Area, Baxter Healthcare Corporation, Deerfield, IL; ²Research & Development, Gambro Dialysatoren GmbH, Hechnigen, Germany.*

Background: Post-dilution hemodiafiltration (HDF) with a high convective volume (CV) is associated with lower overall patient mortality, potentially due to high middle molecule (MM) clearance from the patient (Kp). A higher CV can most readily be achieved by extending the treatment time or increasing the blood flow rate (BFR); however, the effect of access recirculation due to a low access flow rate (AFR) when increasing the BFR on MM Kp during HDF has not been previously quantified.

Methods: A theoretical mass balance model for assessing the effect of a low AFR on MM Kp was formulated. Access recirculation was assumed to occur when the BFR exceeded the AFR. The model demonstrated that MM Kp was dependent on HDF membrane properties, AFR, BFR, CV and the fluid removal rate from the patient (FRR).

Results: Example results are tabulated for a patient with a hematocrit of 33% at different AFRs and BFRs maintaining a fixed filtration fraction of 25% during a 4-hour HDF treatment with a FRR of 0.5 L/hour. MM filter clearance was assumed to depend on CV with a diffusive clearance of 75 mL/min and a sieving coefficient of 0.7:

AFR (mL/min)	MM Kp (mL/min) at BFR (mL/min)/CV (L)					
	at 300/18.0	at 320/19.2	at 340/20.4	at 360/21.6	at 380/22.8	at 400/24.0
≥400	127.5	131.0	134.5	138.0	141.5	145.0
320	127.5	131.0	129.8	129.0	128.5	128.1

When the AFR is higher than the BFR, MM Kp increases with increasing CV. At low AFR, increasing the BFR above the AFR resulted in a lower MM Kp than expected. Indeed, increasing the BFR above the AFR can even lead to a reduction in MM Kp.

Conclusions: High convective volumes during post-dilution HDF achieved by using high blood flow rates may not result in higher middle molecule clearance if the access flow rate is low. Routine assessment of access recirculation or access flow rate may be necessary during post-dilution HDF with high blood flow rates to improve patient outcomes.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

FR-PO669

Protein Biofilm and Its Relation to Dialyzer Permeability for Middle Molecular Weight Markers in Three Polysulfon Membranes Lukas Kielberger, Jan Mares. *1st Dept of Internal Medicine, Charles Univ Teaching Hospital, Plzen, Czech Republic.*

Background: Membrane permeability, particularly in terms of middle molecular clearances, is largely dependent in vivo on the formation of a protein biofilm. Our aim was to assess its dynamics during HD session together with molecular composition of the biofilm.

Methods: 12 HD patients were assigned in a cross-sectional design to Xevonta® Hi23 (B-Braun, 2.3 m²), CorDiax FX100® (Fresenius, 2.2 m²) and Polyflux® 210H (Gambro, 2.1 m²) dialyzers. Blood pre- and post- dialyzer was sampled at 0, 15, 60, and 240 min; spent dialysate was collected over the first 15 min and then until the end of the session. b2 microglobulin (b2M), myoglobin (MB), retinol-binding protein (RBP), and α1-microglobulin (α1m) levels were determined as permeability markers covering an interval of molecular weight (MW) 11-26 kDa. After HD, protein biofilm was eluted from dialyzer and subjected to proteomic analysis.

Results: At the beginning, Xevonta and FX dialyzers showed significantly higher in vivo sieving coefficients for all MWs up to 26 kDa (α1m) than Polyflux dialyzer ($p<0.01$). After 15 min, Xevonta and FX permeability decreased significantly ($p<0.01$) in all MW classes while in Polyflux, only MW21 kDa (RBP4) were affected ($p<0.01$). The total protein content of membrane biofilm was similar in all three dialyzers: 118±85, 41±10, and 40±17 mg protein per dialyzer for Xevonta, FX, and Polyflux, resp. Significant differences in protein composition were captured in 48 out of 231 protein fractions. Among them, complement factor H-related protein 3 (FHR3), insulin-like growth factor binding protein 4 (IBP4), or multiple fibrin fragments (FDP) were identified. While FDP and IBP4 were prevalent in eluates from FX and Xevonta dialyzers ($p=0.005$ and 0.001 , resp.), FHR3 was abundant in Xevonta only ($p=0.01$).

Conclusions: Even with modern biocompatible dialyzers, in vivo permeability decreases along HD session, probably due to biofilm formation. The decrease occurred irrespective of total protein adsorbed, compromising rather membranes primarily more permeable and higher MWs. Differences in biofilm composition are complex and may impact both dialyzer permeability and biocompatibility.

Funding: Government Support - Non-U.S.

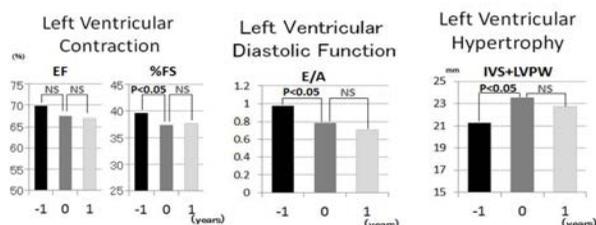
FR-PO670

Protective Effects of Intravenous L-Carnitine (LC) Administration on Development of Cardiomyopathy in Hemodialysis (HD) Patients
 Takuhisa Uchino,¹ Jyunichiro Hashiguchi,¹ Satoshi Funakoshi,¹ Hiroshi Ichinose,¹ Osamu Sasaki,¹ Kenji Sawase,¹ Miki Yano,¹ Yutaka Mori,³ Kazunori Utsunomiya,³ Yoko Obata,³ Tomoya Nishino,² Miwa Shirahama,¹ Takashi Harada.¹ ¹Nagasaki Kidney Center, Nagasaki, Japan; ²Nagasaki Univ Graduate School of Medicine, Nagasaki, Japan.

Background: Due to loss via dialyzer patients on maintenance HD often suffer from dialysis-related carnitine deficiency, causing various clinical symptoms. Carnitine Consensus Conference in 2003 convened by The National Kidney Foundation had reported that the level of evidence was “moderate” for cardiomyopathy. Recent studies have shown that L-carnitine can improve left ventricular (LV) function in HD patients. In this study we aimed to investigate whether intravenous administration of LC can prevent the development of cardiomyopathy in HD patients as assessed by M-mode ultrasound cardiography (UCG).

Methods: Thirty-eight HD patients without reduced left ventricular function were treated with intravenous administration of 1000mg / body of LC at the end of every HD session for 12 months. M-mode UCG assessments were undergone in all subjects at the tree points; 1 year prior to the treatment, the start of LC administration and 1 year after the treatment.

Results: As shown in Figure 1, average %FS (fractional shortening) significantly declined during 1 year before the start of LC, then stabilized after the treatment, suggesting LC administration might protect the progression of LV contraction impairment. Average early diastolic filling velocity (E) / atrial filling velocity (A) ratio showed similar pattern, suggesting LC treatment could be protective in LV diastolic disorder. LC treatment also might delay LV hypertrophy progression.



Conclusions: Intravenous LC administration can be a candidate therapy for protection of the development of cardiomyopathy in HD patients.

Funding: Private Foundation Support

FR-PO671

Symptoms and Quality of Life Among Patients Receiving HD
 Mark L. Unruh,¹ Kim J. Cox,² Stephen H. A. Hernandez,² Sanah Parvez,¹ Mark Parshall,² ¹Div of Nephrology, Univ of New Mexico; ²College of Nursing, Univ of New Mexico.

Background: Health-related quality of life (HRQOL) assessment is a required condition of coverage for HD providers, but standard measures may not adequately reflect the impact of symptoms and treatment on QOL for patients receiving HD or the concerns that matter most to them. The purpose of this qualitative study is to more fully characterize patients’ perspectives on the symptoms and treatment experiences affecting their QOL.

Methods: We conducted semi-structured interviews with a diverse sample of 50 HD patients (48% Female; 42% Hispanic; 30% American Indian; 14% Black; 12% Non-Hispanic White) to elicit their experiences with diagnosis and treatment of ESRD and the symptoms and aspects of treatment that have the greatest impact on their QOL. Interviews were audio-recorded, transcribed, and analyzed for themes using an interpretive-approach.

Results: Participants recalled that the initial diagnosis of ESRD was received with shock and denial. Over time, patients reported that QOL was associated with “taking control” of some features of their treatment. Common symptoms associated with HD, such as cramping and fatigue, were described as potentially manageable when patients were able to participate in decisions about fluid removal and scheduling of HD treatments. Patients who formed a partnership with their providers to negotiate fluid removal reported fewer episodes of severe cramping and improved QOL. Similarly, being able to choose among a variety of days and shifts for HD treatment enabled patients to manage fatigue, work hours, travel, and attendance at social events. These factors were critically important to the QOL in our relatively young sample (median age = 53; median duration of HD treatment = 4 years).

Conclusions: This is one of the largest and most diverse qualitative studies of symptoms among patients undergoing HD. There were few differences in symptoms or the impact of treatment on QOL among racial and ethnic groups. Findings highlighted the importance of fluid management and fatigue to patient experience.

Funding: Pharmaceutical Company Support - Dialysis Clinic Inc.

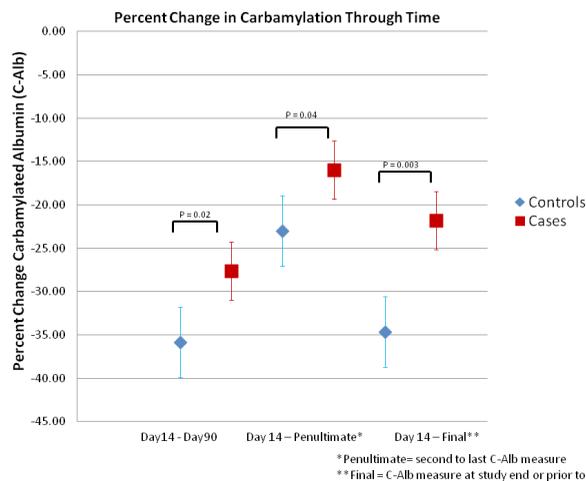
FR-PO672

Longitudinal Measures of Protein Carbamylation and Mortality on Dialysis
 Sahir Kalim,¹ Anders H. Berg,² Rayhnuma Ahmed,¹ Joshua Wibecan,¹ Caitlin A. Trotter,¹ S. Ananth Karumanchi,² Ravi I. Thadhani.¹ ¹MGH; ²BID.

Background: Single time-point measures of carbamylation have recently been associated with mortality in dialysis patients. This study investigated whether repeated measurements of carbamylation over time, allowing calculation of the rate of change, improved on mortality prediction.

Methods: In a nested case-control study, we measured % carbamylated albumin (C-Alb, a measure of carbamylation load) in a cohort of incident hemodialysis patients. 122 subjects who died within 1 year of initiating dialysis (cases) were randomly selected and matched for demographics to 244 individuals who survived at least 1 year on dialysis (controls). C-Alb was assayed within 14 days of dialysis initiation and every 90 days for 1 year or until death. Logistic regression quantified case-control differences.

Results: In adjusted models, there was no case-control difference in day14 C-Alb (P=0.83) and, as expected, carbamylation decreased in both groups with dialysis initiation. By day 90, unit increase in C-Alb was predictive of 1-year mortality (OR 1.7, 95%CI 1.1-2.8; P=0.02) despite no differences in Kt/V. Final C-Alb (last measure taken at study completion or preceding death) was a stronger mortality predictor than C-Alb from any other time point (OR 2.4, 95%CI 1.4-4.0; P=0.003). A smaller % decrease in C-Alb between any 2 time points carried an increased mortality risk (e.g. C-Alb from day 14 to final = -21% in cases vs. -35% in controls; OR 1.6, 95%CI 1.2-2.0; P=0.002). Sensitivity analysis showed follow up time did not bias the results.



Conclusions: C-Alb decreases with dialysis initiation. Smaller decreases in C-Alb over time, resulting in persistently high carbamylation, may herald increased mortality risk during year 1 of dialysis. Because dialysis intensity and amino acid therapy reduce carbamylation, the utility of C-Alb as a therapeutic guide should be investigated.

Funding: NIDDK Support, Other NIH Support - This work was conducted with the support of a KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100), Private Foundation Support

FR-PO673

Recruitment Challenges in the Blood Pressure in Hemodialysis Pilot Study
 Jennifer J. Gassman,¹ Dana Miskulin,² Philip Zager,^{3,4} David W. Ploth,⁵ Manisha Jhamb,⁶ Lavinia A. Negrea,⁷ Mahboob Rahman.⁷ ¹Cleveland Clinic; ²Tufts; ³UNM; ⁴DCI; ⁵MUSC; ⁶Univ of Pittsburgh; ⁷Case Western.

Background: The optimal BP target in hemodialysis (HD) patients is unknown. The Blood Pressure in Dialysis (BID) Pilot Study is an ongoing NIDDK/Dialysis Clinic Inc. funded multi-center randomized trial treating hypertensive HD patients to a standardized predialysis systolic BP (SDUSBP) of 110-140 vs. 155-165 mm Hg, to assess feasibility and safety and inform the design of a full-scale trial.

Methods: We consented 281 participants who entered baseline from 12/2011 to 1/2015. We randomized 126 participants. Achievement of the SDUSBP goal was assessed by determining 2-week running mean SDUSBP in each patient. Participants are followed for 12 months. BP was measured at each dialysis session, home, and ABPM. BP and medications were backtitrated until predialysis SDUSBP was greater than 155 mm Hg. Outcomes include protocol adherence, SDUSBP adherence and left ventricular mass by MRI. To recruit, we identified hypertensive patients, 125 approached for consent refused. Reasons for refusal included perception of study being burdensome 34 (27%) and reluctance to change medications/goals 10(8%).

Results: Of the 281 participants who entered the baseline period 155 (55%) were not randomized, 38(25%) changed their minds, 9(6%) unlikely to adhere, 6(4%) had contraindications to MRI, 6(4%) could not perform required procedures, and 65(42%) were

unable to achieve the lower limit goal of a SDUSBP >155 mm Hg despite backtitration. Retention has been excellent. Patient characteristics are balanced between treatment arms. There is good separation between arms.

Conclusions: We anticipate that a Phase III BID clinical trial will require >1200 participants. MRI will be eliminated and the protocol will be simplified. Routine BPs run higher than SDUSBP and too low a BP was the primary reason for failure to randomize. The anticipated revised protocol will facilitate recruitment and randomization. Clinical sites should plan to enroll twice the number that need to be randomized to achieve the randomization target in the full-scale study.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.

FR-PO674

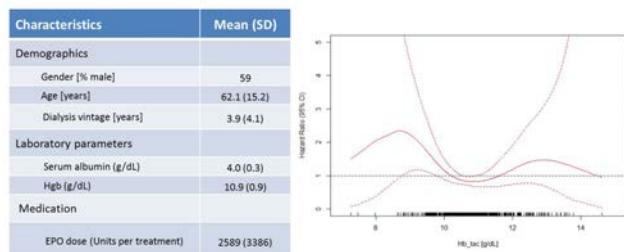
Association of Time-Averaged Concentration of Hemoglobin with Mortality: Results from a Large U.S. Hemodialysis Cohort Hanjie Zhang,¹ Stephan Thijssen,¹ Peter Kotanko,^{1,2} *Renal Research Inst, New York, NY; ²Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: In hemodialysis (HD) patients the time averaged concentration of hemoglobin (Hb_{tac}) can be estimated from pre- and post-HD hemoglobin (Hb) levels. It has been suggested that Hb_{tac} may be an appropriate indicator for anemia management (Siga, Int Urol Nephrol 2014). However, the association between Hb_{tac} and mortality has not yet been evaluated.

Methods: We analyzed Hb data obtained by Crit-Line™ monitor (CLM) in chronic HD patients. A 6-month baseline period with at least 10 CLM measurements preceded a 12-month follow-up during which outcomes were noted. We used Hb values from HD sessions following a short interdialytic interval. Hb_{tac} was computed as follows (Krisper, NDT 2003): Hb_{tac} = Hb_{pre} * 0.5 + Hb_{post} * 0.38 + 1.28. We defined Hb_{pre} as the average Hb between minutes 5 to 20 from the start of the CLM recording, and Hb_{post} as the average of Hb between minutes 5 to 20 from the end of the CLM recording. The relation between Hb_{tac} during baseline and mortality was explored by spline analysis of hazard ratio (HR).

Results: We studied 982 patients (figure 1A) with a total of 19,142 CLM measurements. Average Hb_{tac} was 10.72 g/dL (SD 0.81, range 7.27 – 14.62 g/dL). The mortality rate during follow-up was 11.6 per 100 patient-years. The minimal HR (figure 1B) was 0.82 at Hb_{tac} of 10.87 g/dL. The solid line represents mean HR, the dotted lines 95% confidence intervals.

Figure 1 A: Descriptive statistics (EPO, erythropoietin) **B:** Spline analysis of hazard ratio for mortality as a function of Hb_{tac}.



Conclusions: Hb_{tac} is associated with mortality, levels around 10.9 g/dL are associated with the lowest mortality risk. Studies are required to further explore methods to estimate Hb_{tac} based on Hb measurements by the CLM and the usefulness of Hb_{tac} as an indicator of anemia control.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO675

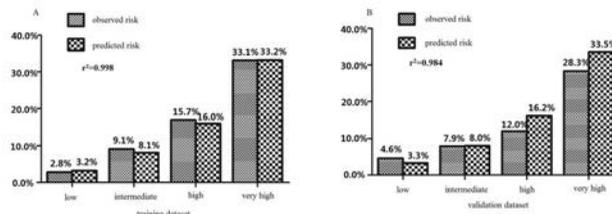
Development and Validation of a Predictive Mortality Risk Score in Chinese Incident Maintenance Hemodialysis Patients Xi Yao. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: We aimed to predict 2-Year all-cause mortality in incident maintenance hemodialysis (MHD) patients by using available clinical and laboratory data, and to establish a risk scoring model.

Methods: Data of incident MHD patients were from Zhejiang Dialysis Quality and Management Center(ZDQM) during the period from January 2008 to June 2012. All patients were >18 years old and survived at least 3 months after starting dialysis treatment, who were followed up for two years. Patients were randomly divided into training dataset (60%, n=2551) and validation dataset(40%, n=1744). The predictive model was developed by using a logistic regression model according to the clinical data in training dataset. The risk model were tested by using the area under the receiver operating characteristic(ROC) curve. The risk scoring model for 2-Year mortality was set up according to the coefficient and rank of variables in the risk model.

Results: In our predictive model, predictors were age, causes of end stage kidney disease(ESRD), vascular access catheter, history of cancer, serum albumin and serum total calcium. The area under the ROC curve of predictive model in training dataset was 0.767, Hosmer-Lemeshow Chi-test, P=0.925, which was highly discriminatory when applied to validation dataset(ROC 0.732), and the sensitivity and specificity were 71.5% and 64.2%, respectively. The risk scores of low, intermediate, high and very high mortality risk strata were <9, 10-13, 14-17 and >18 points, respectively. Observed and predicted mortality risk in the training dataset and validation dataset had a significantly linear relationship(r² = 0.998 and 0.984) across risk strata.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.



Conclusions: The risk-score model can accurately predict 2-Year all-cause mortality in Chinese MHD patients and external validation is needed in future.

FR-PO676

Prediction of Changes in Serum Albumin Levels Among Hemodialysis Patients by Serum Neutrophil Gelatinase-Associated Lipocalin Levels Hirotaaka Imamaki,¹ Akira Ishii,¹ Hideki Yokoi,¹ Masato Kasahara,² Keita P. Mori,¹ Takashige Kuwabara,^{1,3} Kazuwa Nakao,⁴ Masashi Mukoyama,^{1,3} Motoko Yanagita,^{1,4} Kiyoshi Mori.⁴ *¹Dept of Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan; ²Inst for Advancement of Clinical and Translational Science, Kyoto Univ Hospital, Kyoto, Japan; ³Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; ⁴Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.*

Background: Circulating concentration of neutrophil gelatinase-associated lipocalin (NGAL or LCN2) is elevated in acute and chronic kidney diseases. Recently, we reported that, in a cross-sectional study, serum NGAL concentrations in maintenance hemodialysis (HD) patients were determined independently by % creatinine generation rate, white blood cell count and anion gap, indicating that NGAL is a marker of good nutritional conditions. Clinical impact of NGAL was further evaluated in a prospective analysis.

Methods: Correlations of baseline nutritional indices with baseline and follow-up serum albumin levels and with changes in albumin levels after a year were investigated among 87 HD patients using linear regression analysis.

Results: Follow-up albumin levels were positively correlated to baseline NGAL, albumin, geriatric nutritional risk index, creatinine, %creatinine generation rate, anion gap, choline esterase, triglyceride levels and neutrophil counts, and negatively to age. Similar findings were obtained for baseline albumin levels. Importantly, albumin increase was positively correlated to baseline NGAL (r=0.36, P<0.01) and neutrophil but negatively correlated to baseline albumin levels. Typically, some cases with hypoalbuminemia and high NGAL levels experienced elevation in serum albumin levels after recovery from infection (or inflammatory disorders). On the other hand, in some cases with preserved albumin levels and low NGAL levels, serum albumin levels decreased once severe infection developed and reduced albumin levels persisted even after recovery from infection.

Conclusions: Serum NGAL level in HD patients appears to be a unique biomarker allowing prediction of alteration in serum albumin levels in a year.

Funding: Pharmaceutical Company Support - Tanabe Mitsubishi Pharmaceutical Company, Government Support - Non-U.S.

FR-PO677

Race, Health-Related Quality of Life and Mortality in a Large Cohort of Brazilian Multiracial Hemodialysis Population Marcelo Barreto Lopes, Priscila S. Carvalho, Jéssica S. Fernandes, Raissa B. Peixoto, Pedro Guimarães Silva, Jean M. Monteiro, Gildete Barreto Lopes, Antonio Alberto Lopes. *Federal Univ of Bahia, Salvador, BA, Brazil.*

Background: Studies developed in patients undergoing maintenance hemodialysis (MHD) in the United States (US) indicate that the survival and the health-related quality of life (HRQOL) are better in African Americans and other racial minorities than in Whites. Similar to the US, Brazil is a country with a diverse racial population. There is a lack of studies to investigate if there are differences in HRQOL and mortality by race in Brazilian MHD patients. The present study developed in a multiracial Brazilian MHD population investigated associations of race (Whites as reference) with HRQOL and survival.

Methods: A prospective cohort of 1084 MHD patients (11.8% White, 61.3% mixed race and 26.8% Black) enrolled in the Prospective Study of the Prognosis of Chronic Hemodialysis Patients (PROHEMO) developed in nephrology clinics of Salvador, Brazil. The predictor variable was race (White as reference). Outcomes were mortality and HRQOL scores, using the KDQOL-SF. Multivariable linear regression was used for differences in scores and Cox regression for mortality. Associations were adjusted for age, sex, diabetes, heart failure, blood hemoglobin and vintage.

Results: Mean age was significantly lower (P<0.001) in Blacks (49.2±14.0 yr) and mixed races (47.6±14.5 yr) than in Whites (55.0±13.7 yr). In the multivariable linear regression, differences were not observed by race for PCS, MCS, disease burden and effects of kidney disease. For symptoms/problems, a significantly (P=0.043) higher adjusted score (difference=3.6) was observed in Whites (than in Blacks). In the Cox model with complete adjustment for covariates, the hazard ratio (HR) was 0.95 (95% confidence interval (CI) =0.66-1.35) for the comparison between mixed race and White and 1.10 (95% CI=0.75-1.61) for the comparison between Blacks and Whites.

Conclusions: In disagreement with studies developed in the United States, this study developed in a multiracial Brazilian hemodialysis did not show worse HRQOL and higher mortality in whites as compared with patients of mixed race and Blacks.

Funding: Government Support - Non-U.S.

FR-PO678

Low Lymphocyte Counts Are an Independent Predictor of Mortality in Chronic Hemodialysis Patients: A Retrospective Cohort Study Dieter De Clerck, Christian L. Tielemans, Karl M. Wissing. *Nephrology, Univ Ziekenhuis Brussel, Brussels, Belgium.*

Background: Mortality in chronic hemodialysis populations remains high. Lymphopenia has been associated with increased cardiovascular risk in the general population but few data are available on the effect of low lymphocyte counts on long-term survival of hemodialysis patients.

Methods: Retrospective study of a single-center cohort of 689 hemodialysis patients using monthly laboratory results and dialysis parameters extracted from a center database and a national registry. The effect of baseline and time-changing lymphocyte counts on overall mortality was studied using the Kaplan Meier and Cox proportional hazard methods.

Results: Lymphopenia (<1200/ μ L) was present in approximately one third of incident hemodialysis patients and correlated with older age, lower creatinine, lower phosphorus, higher KT/V and a positive history of ischemic heart disease. Lymphopenia was not associated with classical markers of malnutrition-inflammation complex such as albumin, normalized protein catabolic rate, BMI and CRP. Baseline lymphopenia was associated with a 54 percent increase in the hazard of death (HR 1.54 (1.17 to 2.0; P=0.002)) as compared to the tertile of patients with highest lymphocyte counts. Lymphocyte counts tended to decrease during long-term follow up and their introduction as a time-changing variable further increased the HR to 2.1 (1.48 to 2.84; P<0.0001). The association remained significant in the multivariate Cox model after adjustment for age, phosphorus, creatinine, albumin, BMI, CRP, KT/V and history of ischemic heart disease.

Conclusions: Lymphopenia is highly prevalent in hemodialysis patients and is a strong predictor for patient death. The association was stronger when lymphocyte counts were considered as a time-changing variable and independent of other risk factors for patient death. Lymphopenia was not associated with markers of the malnutrition-inflammation complex (MIC) and therefore appears a useful prognostic tool in addition to classical markers such as CRP and albumin levels.

FR-PO679

Current Status of Hemodialysis in China Li Zhang, Delong Zhao, Xueying Cao, Xiang-Mei Chen, Guangyan Cai. *Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases.*

Background: In May 2010, the first nationwide, web-based prospective renal data registration platform, the Chinese Renal Data System (CNRDS) was launched in China. The purpose of this study was to determine the current status of hemodialysis in China by analyzing the data from CNRDS.

Methods: The data from CNRDS were used for dialysis cases including demographic, clinical, and laboratory data. We analyzed the data from CNRDS by the end of 2014.

Results: (1) There were 4047 domestic hemodialysis centers and 339748 survival patients were registered by the end of 2014. (2) In the 339748 patients, 58.85% were male. The average age was 54.9 years and average dialysis duration was 42.2 months. The three leading causes of ESRD were glomerulonephritis, diabetic nephropathy and hypertensive renal diseases. (3) 14322 patients died in 2014, with an average age of 61.9 years and average dialysis duration of 39.7 months. The main causes of death were cardiovascular events and stroke, followed by infection and gastrointestinal bleeding. (4) In the patients, 44.1% had predialysis blood pressure less than 140/90mmHg, 55.4% had hemoglobin concentration ≥ 100 g/L and 80.3% had albumin levels ≥ 35 g/l. 39.6% had serum calcium between 2.10 and 2.50mmol/L. 34.7% had serum phosphorus between 1.13-1.78mmol/L. 53.9% had PTH between 130 and 600pg/ml.

	2011	2012	2013	2014
predialysis blood pressure (mmHg)	148 \pm 21/85 \pm 13	148 \pm 21/85 \pm 13	148 \pm 20/84 \pm 13	148 \pm 21/84 \pm 13
hemoglobin (g/L)	95 \pm 23	97 \pm 22	97 \pm 22	101 \pm 22
serum calcium (mmol/L)	2.15 \pm 0.36	2.15 \pm 0.40	2.15 \pm 0.40	2.17 \pm 0.35
serum phosphorus (mmol/L)	1.92 \pm 0.76	1.91 \pm 0.79	1.91 \pm 0.79	1.92 \pm 0.71
PTH (pg/ml)	394 \pm 452	405 \pm 459	405 \pm 459	402 \pm 455
albumin (g/L)	38 \pm 6	38 \pm 6	38 \pm 6	39 \pm 6

Conclusions: As Chinese National Health and Family Planning Commission have enhanced the basic medical security system on hemodialysis, both the population and the quality of hemodialysis have increased in recent years.

Funding: Government Support - Non-U.S.

FR-PO680

Outcomes and Quality of Care in Rural versus Urban Managed Dialysis Patients James M. Zacharias,¹ Allison Dart,² Harvey M. Chochinov.³ ¹Dept of Medicine, Univ of Manitoba, Winnipeg, MB, Canada; ²Dept of Pediatrics, Univ of Manitoba, Winnipeg, MB, Canada; ³Dept of Psychiatry, Univ of Manitoba, Winnipeg, MB, Canada.

Background: A proportion of patients are managed in remote satellite units in Manitoba, Canada. Urban nephrologists oversee all dialysis care; however family physicians (FP) co-manage patients. This study examines outcomes and quality of care indicators in rural vs. urban managed patients.

Methods: Prospectively collected clinical data from the Manitoba Renal Program and administrative health data housed at the Manitoba Centre for Health Policy were analyzed retrospectively. All adult (>18yo) incident hemodialysis patients on dialysis >90 days, from 1995 to 2010 were included. Individuals dialyzing in rural satellite units (n=510) more than 50% of the time were compared to their urban (n=2629) counterparts. Differences in cohort characteristics were analyzed at baseline as well as differences in primary care quality indicators. Regression analyses examined differences in hospitalizations and days in hospital. Cox proportional hazard models were performed to examine differences in survival.

Results: Patients in rural satellite units vs urban were younger, 58 vs 61 yrs (p=0.002), but were more likely to have DM 69.4 vs 55.3% (p<0.0001), PVD 9.4 vs 4.0% (p<0.001) and IHD (MI, Angiogram or PTCA) 42.8 vs 34.2% (p=0.002). More rural patients accessed a FP at least once per year 85.7% vs 67.3% (p<0.0001) and 85.3% vs 68% (p<0.0001) had at least 25% continuity with the same FP. Despite increased FP utilization Pap smear, mammogram, DM eye exam and use of a Statin post MI were not significantly different. There were no differences in hospitalization outcomes between groups. However, survival was significantly better in the rural cohort OR 0.77 (CI 0.68-0.88, p<0.0001), after controlling for sex, income, charlson, era, age and region at the start of dialysis.

Conclusions: Survival in a cohort of patients dialyzing in remote satellite units was found to be superior to their urban counterparts, after controlling for co-morbidities. A potential reason might be increased primary care involvement, although differences were not seen in traditional quality of care indicators.

Funding: Private Foundation Support

FR-PO681

Applying Hemodialysis Clinical Quality Indicators to Individual Patients: A Useful Mortality Prognostic Tool in Clinical Practice? Tiago Assis Pereira, Artur P. Mendes. *Unidade Linda-a-velha, Diaverum, Linda-a-Velha, Oeiras, Portugal.*

Background: Hemodialysis (HD) care is routinely assessed by a set of clinical and laboratorial parameters, known as Clinical Quality Indicators (CQI). CQI registry and monitoring constitutes an instrument to evaluate the quality of care provided at each HD Unit. The purpose of this study was to determine whether CQI, applied on an individual patient basis, is a predictor of mortality.

Methods: Retrospective study that included 334 patients of a HD Unit from 2011 to 2014. Demographic, clinical and laboratories data were collected. The CQI considered were eleven, whose intended target were: spKt/V ≥ 1.4 ; weekly dialysis time ≥ 720 minutes; Albumin ≥ 3.5 g/dL; Hemoglobin between 10 and 12 g/dL; phosphatemia between 2.5 and 5.5 mg/dL; CaxP product < 55 mg²/dL²; PTH levels between 150 and 600 pg/ml; Ferritin between 200 and 800 mg/dL; Mean arterial pressure < 105 mmHg; interdialytic weight gain (IWG) < 4% and fistulae as vascular access. Single CQI were rated in a binary form (0 = not reached target/1 = reached target) at each monthly evaluation and the average were determined. Ultimately, the eleven parameters were added in a single variable for each patient (CQIp).

Results: During follow-up, 33% of patients died. In the Cox regression model, age (HR 1.09; CI 1.07-1.11; p <0.001), diabetes (HR 2.88; CI 1.92-4.32; p <0.001), peripheral arterial disease (HR 1.63; CI 1.09-2.44; p = 0.016) and CQIp (HR 0.73; CI 0.62-0.87; p <0.001) were shown to be independent predictors of mortality, after adjustment for other clinical and demographical factors. When CQIp was replaced by its constituent variables, albumin (HR 0.016; CI 0.08 -0.32; p <0.001), PTH (HR 2.8; CI 1.10-3.93; p = 0.023), IWG (HR 0.34; CI 0.14-0.83; p = 0.018) and fistulae presence (HR 0.61, CI 0.4-0.93, p = 0.021) presented statistical significance.

Conclusions: A set of parameters, generally applied as a quality care indicators, proved to be an independent predictor of death when applied to individual patients. This should be regarded as an easy and practical prognostic tool to be applied in current practice.

FR-PO682

Association of Estimated Glomerular Filtration Rate at Commencement of Maintenance Dialysis with Mortality Among Patients with Advanced Chronic Kidney Disease in Singapore Tazeen H. Jafar,¹ Jin Ai Zhen,² John C. Allen,¹ Saeideh Tavajoh,¹ Khuan yew Chow.¹ ¹Duke-NUS Graduate Medical School Singapore; ²National Disease Registry Office, Health Promotion Board, Singapore.

Background: Recent evidence suggest that higher estimated glomerular filtration rate (eGFR) at commencement of dialysis may be associated with increased mortality. However, there is scarcity of data on patients of Southeast Asian origin. We analyzed and compared mortality risk in patients with early and late start dialysis as measured by kidney function at dialysis initiation among Southeast Asian population of Singapore.

Methods: We performed a retrospective analysis of patients enrolled in the Singapore Renal Data system database from 2008 to 2011. Patients were classified into groups by eGFR at dialysis initiation.

Results: In this total incident population (n=3708), a total of 1510 individuals died during a median follow-up period of 2.8 years. The hazard ratio (HR) and 95% CI associated with different levels of eGFR at commencement of RRT are shown in table below. The main multivariable model (n=3189 without missing information on covariates) associated with the eGFR at dialysis initiation within the groups: age, gender, level of education, smoking, presence of diabetes, ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, malignancy, hepatitis B, hepatitis C, kidney transplant, and modality of dialysis. Additional models accounted for serum albumin (n=2657), and serum ferritin (n=2462), and serum calcium (n=1628).

eGFR ml/min/1.73m2	Dialysis Patients N=3189	Deaths	Adjusted HR (95%CI)	p trend
<5	1345	395	1.00	<0.0001
5-10	1541	656	1.19 (1.04-1.36)	
>10	303	180	1.81 (1.49-2.19)	

The results were consistent after accounting for serum albumin, serum ferritin, and serum calcium in the multivariable models.

Conclusions: Late initiation of dialysis is associated with a lower risk of mortality in comparison with early dialysis initiation in Southeast Asians in Singapore.

FR-PO683

Predicting Mortality for Patients Who Are on Hemodialysis—A National Cohort Study in Taiwan Jinn-Yang Chen. *Div of Nephrology, Taipei Veterans General Hospital, Taipei, Taiwan.*

Background: Comorbid conditions and medical history provide prognostic information for dialysis patients. The objective of this study was to develop a prognostic model to predict short-term (6-months and 1-year) and long-term (2.5-years) survival for incident hemodialysis (HD) patients.

Methods: Incident Taiwanese hemodialysis patients from 2006 to 2010 were extracted from National Health Insurance claim records. Prognostic model was developed by using comorbid conditions (summarized as Taiwan index), monthly income and medical history during one year before initiation of dialysis. Somer's D statistic was used to assess the discrimination ability of our model.

Results: A total of 36,875 incidence HD patients were included in this study and the last followed-up day was December 31, 2011. More comorbid burden, male gender, history of acute kidney injury, dementia, admitting to intensive care unit, staying at nursing home and ever using ventilator were significant prognostic factors. Monthly income only had marginal effects on survival at 2.5 years. For discrimination ability, our model has Somer's D statistics of 0.76, 0.76, and 0.75 for 6-months, 1-year, and 2.5-years survival, respectively.

Conclusions: Three prognostic models with same covariates for short-term and long-term survival in HD patients were found in this study. The consistency in model performance helps clinicians and patients to make decision.

Funding: Government Support - Non-U.S.

FR-PO684

Twice Weekly Treatment Eligibility for Incident Hemodialysis (HD) Patients Suresh Appasamy, Andrew I. Chin, Thomas A. Depner. *Div of Nephrology, Univ of California, Davis, Sacramento, CA.*

Background: KDOQI guidelines advise that hemodialysis treatments constitute a patient burden and a risk to native kidney function that can be lowered by reducing HD frequency from 3 to 2/week in patients with substantial residual kidney function. To determine eligibility for twice weekly HD we analyzed 24 hour residual urea clearances (Kru) and volume removal requirements in all incident patients with urine output >100 ml/day in 4 HD centers.

Methods: From the years 2000-2014, 420 out of 734 incident patients who survived ≥6 mos, starting HD 3/week had Kru measurements within 1-3 months after starting HD. The fractional weekly renal clearance (KrT/V) was subtracted from the continuous equivalent minimum goal stdKT/V of 2.0 volumes/week to determine the minimum required standard dialyzer clearance (stdKdT/V). With N set as 2/week, eKT/V was back-calculated from the Leypoldt equation for stdKT/V, spKT/V from the Tattersall equation for eKT/V, and Kd from modeled V and T that was limited to a maximum of 4 hours. Patients were excluded if the ultrafiltration (Uf) rate needed to control volume was >10 ml/kg/hr, MAP dropped >10 mm, or the patient exhibited symptoms of nausea, vomiting, or cramps.

Results: Patients: N=420, age 57±15 yrs, 58% male, 51% diabetic, 66% TD Catheters. Urine collections: 974±617 mL, Kru 3.0±2.1 mL/min, KrT/V 0.7±0.5. Uf 2.1±1.2 L/dialysis (3x/week), 2.8±1.6% of dry weight.

Eligibility target for 2/week HD	Patients achieving target
spKT/V <1.4 per 4 hour HD	225 (54%)
Uf rate ≤ 10 mL/kg/hr	206 (49%)
MAP drop < 10 mmHg	343 (82%)
Dialysis symptoms < 10 per month	407 (97%)

In the 225 patients who could achieve the target stdKT/V with 2/week HD, the mean spKT/V required was 0.83±0.36. A total of 105 or 25% of patients with measured Kru met all 4 criteria.

Conclusions: Urine collections disclosed that 225 or approximately 30% of 734 incident patients were eligible for 2/week HD based on solute kinetics alone. Using conservative criteria, half of these were judged ineligible because of Uf requirements or HD-induced symptoms. Opportunity exists for incremental HD in a significant number of incident patients.

FR-PO685

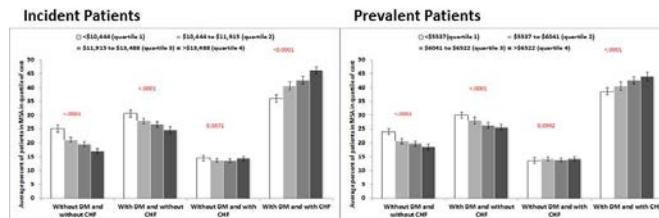
The Relationship of Diabetes and Congestive Heart Failure to Costs of Care in End Stage Renal Disease Patients Sheetal Chaudhuri, Jane Brzozowski, Hao Han, Len A. Usvyat, John W. Larkin, Mahathi Mothali, Terry Ketchersid, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Many Medicare patients (Pts) with end stage renal disease (ESRD) are known to have co-morbidities of diabetes mellitus (DM) and/or congestive heart failure (CHF). Total costs of care for ESRD Pts are likely to be dependent on patient comorbidities and likely to vary by geography. We investigated the relationship of DM and CHF based on Pts' geographic location.

Methods: ESRD Pts with evidence of dialysis at any time during Jan 1, 2010 through Dec 31, 2011 and Medicare as their primary payer were analyzed. Pts were stratified based on Metropolitan Statistical Areas (MSA) and Medicare Part A and B costs were calculated from 100% Medicare data. T-test comparisons were performed for quartiles of total cost of care for eight groups: based on vintage (incident [<90 days on dialysis] or prevalent [>3 years on dialysis]), as well as, comorbidities (no DM and no CHF, with DM and no CHF, no DM and with CHF and with both DM and CHF).

Results: Claims for 107,659 Pts were analyzed. Total cost of care increased significantly as the percent (%) of Pts with CHF and DM increased; cost of care declined significantly as the % of Pts with neither DM nor CHF increased by MSA. Cost of care did not change with the increase in % of Pts without DM and with CHF. Yet, costs of care declined as % of Pts with DM and without CHF increased by MSA. These patterns were observed in both incident and prevalent Pts.

Figure 1. Costs of care by MSA (per member per month)



Conclusions: These results identify differences in association between ESRD related co-morbidities and total costs of care: the % of Pts with both DM and CHF is higher in areas with higher total costs. Surprisingly, costs of care are lower in areas where the % of Pts with DM but without CHF is higher. Risk Adjustments should be considered.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO686

Long Term Outcomes Over 2 Years following a Dialysis Adequacy Quality Improvement Initiative Sajeda Youssouf,^{1,2} Philip A. Kalra,^{1,2} Janet Hegarty,^{1,2} ¹Salford Royal NHS Foundation Trust; ²Manchester Academic Health Sciences Centre.

Background: Dialysis adequacy is known to correlate with clinical outcomes such as mortality. Evidence based guidelines recommend that haemodialysis patients should achieve a urea reduction ratio of >65%. UK Renal Registry data shows wide variation in facility attainment of target URR. In 2010 the Salford Renal Network implemented an ambitious programme to uplift attainment of key quality of care indicators to within the top 10% in the UK; dialysis adequacy was a target in 2 phases of improvement in 2010-2012.

Methods: Our network implemented a quality improvement programme using collaborative methodology. We set four teams a different clinical indicator to work on over 12 month cycles for 2 successive years, guided by QI facilitation input. Unit A worked on URR in phase 1 and developed a package of changes using plan-do-study-act (PDSA) testing that was used for improvement by Unit B in phase 2. We analysed the long-term outcomes in these units for a further 2 years until May 2014.

Results: Both units reached their aim of >90% of patients achieving target URR>65% within their improvement year. Both units sustained the improvements for 2 years with no additional resource input after the collaborative. Changes included protocolised nurse-led changes to dialysis prescriptions, multidisciplinary review of vascular access, a nurse-led anticoagulation protocol, blood sampling protocol, and monthly reports.

	Pre-intervention	Post-intervention	Outcome at 2 years	p value
Percentage of patients with URR > 65% Unit A	75.8%	91.4%	97.8%	0.003
Mean URR, % (SD) Unit A	70.3 ± 8.3	74.5 ± 5.5	74.9 ± 4.9	0.002
Percentage of patients with URR > 65% Unit B	68.9%	91.1%	93.0%	0.002
Mean URR, % (SD) Unit B	69.4 ± 9.1	72.9 ± 9.2	72.8 ± 5.9	0.003

Conclusions: Longer term outcomes from QI interventions are underreported with limited evidence on sustainability. We implemented multifaceted interventions to improve dialysis adequacy in our network to within the top 10% in the UK. Implementing evidence-based changes led by frontline staff trained in QI has sustained these improvements for 2 years after a formal QI intervention, improving quality of care for our patients.

FR-PO687

Clinical Effectiveness of Intermittent Infusion Hemodiafiltration (I-HDF) Compared with Conventional Hemodialysis: A Multicenter Clinical Trial
 Michio Mineshima, Kei Eguchi. *Clinical Engineering, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Intermittent infusion hemodiafiltration (I-HDF) using backfiltration of an ultrapure dialysis fluid has been developed to improve the peripheral circulation of the patient receiving a typical hemodialysis (HD) with repeated intermittent infusion by an automated dialysis machine, GC-110N (JMS Co. Ltd., Tokyo, Japan). In a typical HD treatment, excessive water removal often induces hypotension and muscle spasm. In the I-HDF, some 200-300 mL of ultrapure dialysis fluid was infused into the blood component through the dialysis membrane at a rate of 100 mL/min, every 30 min. I-HDF, namely, means a HDF treatment with small amount of infusion volume, 1.4 to 2.1 L (= 200-300 mL x 7 times/session).

Methods: In this paper, clinical effectiveness of I-HDF was evaluated in comparison with conventional HD (CHD) during a multi-center clinical trial that twenty chronic renal disease patients participated.

Results: A significantly lower value for time-averaged blood volume reduction was obtained with I-HDF compared with CHD in spite of there being no difference in the total amount of water removal. It was due to a higher plasma refilling rate in I-HDF. In addition, increasing peripheral blood flow rate in the patient's toe was detected by a laser flowmeter for each infusion in many patients. The cleared space value defined as amount of normalized solute removal during a treatment were higher with I-HDF than CHD for inorganic phosphate and α 1-MG. Moderate α 1-MG clearance reduction was found in I-HDF due to the prevention of membrane fouling by intermittent backfiltration of the dialysis fluid. No significant difference of albumin leakage between I-HDF and CHD. Reduction ratio of the systolic blood pressure and the number of treatments by medical staff in I-HDF were lower than those in CHD.

Conclusions: Intermittent Infusion HDF using an automated dialysis machine was effective for improvement of the peripheral circulation of patients receiving conventional HD.

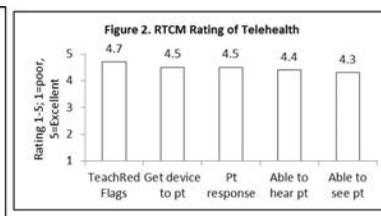
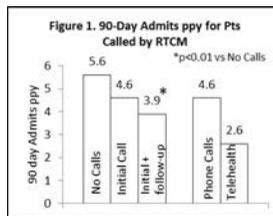
FR-PO688

Impact of Post-Hospital Phone and Telehealth Case Management to Reduce Admissions in Hemodialysis Patients
 Rebecca L. Wingard,¹ Billie Axley,¹ Kathryn A. McDougall,¹ Andrew D. Howard,² Joelle Heilemann,¹ Fern Parlier,¹ Sophia Rosen,¹ Len A. Usvyat,¹ Alexis Porras,¹ Franklin W. Maddux.¹
¹Fresenius Medical Care, Waltham, MA; ²Metropolitan Nephrology Associates, Clinton, MD.

Background: 2012 30-day readmissions for hemodialysis (HD) patients (pts) were high at 35% (USRDS). Right TraC™ (RT) used post-hospital RT case manager (RTCM) calls to reduce post-hospital admissions. Telehealth vs. phone calls was also studied.

Methods: In 28 clinics from Feb-Nov '14, RTCMs attempted weekly phone calls to pts at home or dialysis clinic, or via telehealth in the clinic for 30 days post-hospital. RTCMs assisted pts with discharge instructions and addressed changes in dry weight, medications, nutrition, access, and taught Red Flags (symptoms that signal potential readmission). Telehealth was performed via iPad tablet in the clinic, configured for secure video tele-communication using clinic's local wifi. 90-day admit rates post-hospital adjusted for comorbidities and RTCM telehealth ratings were measured; comparison was done using Poisson models.

Results: For pts with no RTCM calls (n=1702) vs. pts with initial call (n= 801), annualized 90-day admits per pt year (ppy) were 5.6 and 4.6, respectively (p=0.89, Fig 1). 90-day admits ppy for pts with initial call and ≥ 1 follow-up call (n=591) were 3.9 (p=0.0025 vs. no calls). For pts with initial call by phone (n=785) vs telehealth (n=34), 90-day admits ppy were 4.6 and 2.6, respectively (p=0.47). RTCM telehealth ratings ranged 4.3-4.7, and cited enhanced pt-RTCM relationship and assessment (Fig 2). "Able to see pt" rated lowest, due to wifi connectivity.



Conclusions: RTCM calls during 30 days post-hospital showed significantly lower 90-day admits ppy for pts with initial and ≥1 follow-up call. Telehealth had lower 90-day admits ppy vs. phone calls, although not significant. Further study is needed, especially in view of high RTCM ratings.

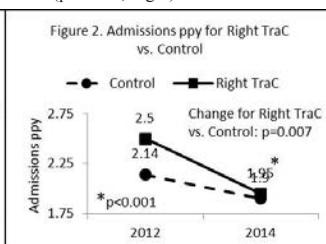
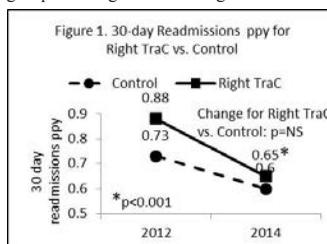
FR-PO689

Reduced Hemodialysis (HD) Patient Hospital Admissions and Readmissions Associated with Right TraC™ Care Transitions Program
 Rebecca L. Wingard,¹ Billie Axley,¹ Kathryn A. McDougall,¹ Andrew D. Howard,² Cathleen Okeefe,¹ Sharon Deluca,¹ Janice B. Sitzlar,¹ Len A. Usvyat,¹ Franklin W. Maddux.¹
¹Fresenius Medical Care, Waltham, MA; ²Metropolitan Nephrology Associates, Clinton, MD.

Background: 30-day readmissions for HD patients (pts) are high at 35% in 2012 (USRDS). The Right TraC (RT) Program addressed factors in the complex process of care transitions, with the aim to reduce hospital admissions and readmissions.

Methods: 26 HD clinics (3682 pts) were in RT. Interventions deployed in 3 phases (Apr '13-Nov '14). I: Pre- and post-hospital checklists for clinics to manage pt teaching, anemia, nutrition, medications, and dry weight. II: Telephonic case management for 30 days post-discharge. III: Dialysis Link™ centralized clinical info exchange among providers. Admission and readmission rates per pt (ppy) for "baseline year" (2012) vs. "full intervention year" (2014) were compared to 18 control clinics (2449 pts) matched for clinic size, admission and readmission rate, and urban vs. rural location at baseline. Poisson models with random effects for pt and clinic, adjusted for age, vintage, race, gender, ethnicity, DM, CHF, and COPD were constructed to assess the difference between baseline and intervention and between RT and control clinics.

Results: 30-day readmissions ppy declined from baseline to full intervention year in RT (0.88 to 0.65, p<0.001) and controls (0.73 to 0.6, p=NS); comparison of the change between groups was not significant (Fig 1). Admissions ppy declined from 2.5 to 1.95 for RT (p<0.001), and 2.14 to 1.9 for controls (p=NS); comparison of the change between groups was significant with greater decline for RT (p<0.001, Fig 2).



Conclusions: RT interventions were associated with significant declines in admissions and 30-day readmissions. The difference in the changes between RT vs. controls was significant for admissions, but not significant for 30-day readmissions.

FR-PO690

Predicting Early Mortality Among Hemodialysis Patients Using USRDS Data
 Fang Wang,^{1,2} Zhi He,³ Jennifer L. Bragg-Gresham,¹ Yuan Yang,³ Haoyu Gu,³ Yi Li,³ Kamyar Kalantar-Zadeh,⁴ Elani Streja,⁵ Rajiv Saran.¹
¹Div of Nephrology-Dept of Internal Medicine and KECC, Univ of Michigan, Ann Arbor, MI; ²Renal Div Dept of Medicine, Peking Univ First Hospital, Beijing, China; ³Dept of Biostatistics and KECC, Univ of Michigan, Ann Arbor, MI; ⁴Univ of California Irvine, Orange, CA; ⁵Harold Simmons Center, Orange, CA.

Background: Higher early mortality of hemodialysis (HD) is recognized. We sought to quantify the risk of early mortality and develop a robust prediction model which could potentially guide clinical decision-making.

Methods: The 2007-2012 data from the United States Renal Data System (USRDS) on incident HD patients, age >18 years, were randomly split as 'training' and 'validation' samples. Cox proportional hazards model with piece-wise constant coefficients was used to model all-cause mortality during day 0-90 and day 91-365 of HD. Those transferred to peritoneal dialysis or transplantation were censored. The resulting model was validated by C statistic.

Results: The mean age (n=611,094) was 63.6±14.9 years, with 130,473 deaths during the first year of HD. Mortality rates were 35 per 100 person-years in the first 90 days and 21 per 100 person-years during day 91-365. The prediction equation for early mortality involved 23 variables including demographics characteristics, pre-ESRD care, laboratory values, co-morbidities as well as institutionalization status. In adjusted analyses, selected variables with significant time-varying effects are listed in the Table.

Table: Hazard ratios for death in the first year of HD

Measures	Adjusted HR (95%CI)		Interaction between time period and individual effect (P value)
	Day 0-90	Day 91-365	
ESRD caused by ATN	1.15(1.10-1.19)	0.98(0.97-1.02)	<0.001
History of diabetes	0.91(0.89-0.93)	1.05(1.03-1.07)	<0.001
Pre-ESRD care	0-5 months	1.52(1.48-1.56)	<0.001
	6-12 months	1.20(1.17-1.24)	<0.001
>12 months	1.00 (as ref)	1.00 (as ref)	
Alcohol dependence	1.95(1.85-2.06)	1.26(1.20-1.33)	<0.001
Serum albumin <3g/dL	1.53(1.50-1.56)	1.31(1.29-1.36)	<0.001

The model was adjusted for age, sex, race, BMI, vascular access, institutionalization, comorbidities including cardiovascular disease, hypertension, cancer and anemia.

The prediction model reached a C statistic of 0.70 (95% CI, 0.57-0.82).

Conclusions: We have developed a predictive model for early mortality in a national cohort of incident HD patients and identified risk factors with time-varying effects. We intend to further refine and validate this model before recommending in clinical practice.

Funding: NIDDK Support

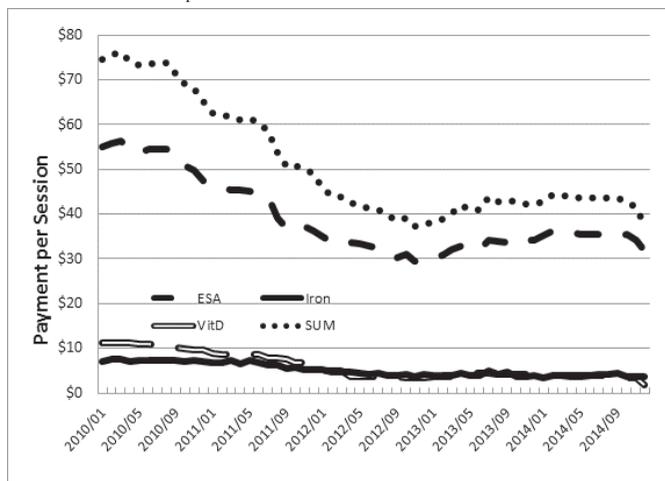
FR-PO691

Recent Evidence on the Impact of Medicare's Bundled, Prospective Payment System for Renal Dialysis Richard Hirth,¹ Tammie A. Nahra,¹ Adam S. Wilk,¹ Marc Turenne,² John Wheeler,¹ Kathryn Sleeman,¹ Wei Zhang,¹ Jonathan H. Segal.¹ ¹Univ of Michigan; ²Arbor Research Collaborative for Health.

Background: Medicare implemented an expanded prospective payment system (PPS) in 2011, including services previously paid by fee-for-service. One intent of the PPS was to incentivize providers to be more efficient in the mix of services provided.

Methods: We used Medicare claims to assess monthly trends from 1/2010-12/2014 for injectable drugs that were previously billed separately. For 2010, we assessed actual spending. For 2011-14, we projected spending based on reported utilization.

Results: ESA use declined in the months immediately pre- and post-PPS, continuing to decline through 2012. In 2013, ESA use leveled off. Use of iron products, often improving the efficacy of ESAs, increased through 2011 and then began to decline. Total drug cost, including ESAs, iron, and vitamin D, fell by more than 50%, from a high of \$76.16 per session in early 2010 to a low of \$37.67 toward the end of 2012. This decline was driven by reduced drug utilization. Since early 2013, total drug costs have risen a bit due to higher drug prices. Beginning in 2013, drug costs have remained at about \$42 per session, reflecting gently declining use and higher drug prices. [Fig.1] The reduction in drug spending of about \$34 per session over a period of 4 years exceeds the Medicare mandated reduction in the base rate over the same period.



Conclusions: The expanded bundle dialysis PPS provided incentives for both lower medication utilization overall and the use of lower cost therapies. These incentives seem to have motivated an immediate movement toward lower cost methods of care. Facilities have been able to maintain a lower cost of care over the last two years. CMS continues to monitor facility costs and will continue to make a reduction to the ESRD PPS Market Basket through CY 2018, in accordance with section 217 of PAMA.

Funding: Other U.S. Government Support

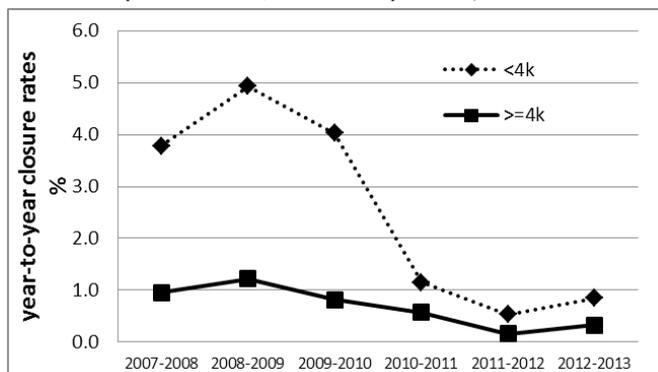
FR-PO692

Effect of Medicare's Payment Adjustment for Low-Volume Dialysis Facilities on Facility Closures Richard Hirth,¹ Tammie A. Nahra,¹ Adam S. Wilk,¹ Marc Turenne,² Jonathan H. Segal,¹ John Wheeler,¹ Kathryn Sleeman,¹ Wei Zhang,¹ ¹Univ of Michigan, Ann Arbor, MI; ²Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Small dialysis facilities may face higher per-treatment costs due to economies of scale. Since 2011 a low-volume payment adjustment (LVPA) raised Medicare payments 18.9% to facilities with <4,000 treatments in each of the 3 prior calendar years. A goal of this policy is to preserve access to care by preventing the closure of small facilities.

Methods: We tested the hypothesis that the LVPA prevented closures by examining the year-to-year closure rates of U.S. dialysis facilities during 2007-2013, before and after the policy, comparing facilities providing <4000 and >4000 annual treatments. Analyses with linear regression relate facility outcomes to prior year size, ownership, for-profit status, hospital affiliation, patient mix, rural location, modality mix and county characteristics, to examine the effect of the LVPA on # of treatments provided by facilities.

Results: Among low-volume facilities, year-to-year closure rates were 3.8%, 4.9% and 4.0% pre-LVPA, falling to 1.1%, 0.5% and 0.8% post-LVPA. Among facilities with >4000 treatments, closure rates also decreased, but to a much smaller extent (from 1.0%, 1.2% and 0.8% pre-LVPA to 0.6%, 0.2% and 0.3% post-LVPA).



Conclusions: In Medicare's bundled payment system, closure rates decreased overall, with a much larger absolute reduction among small facilities. The gap in closure rates between small and large facilities fell from about 3% points before the policy to about 0.5% points after. LVPA appears to have helped prevent small dialysis facility closures, but it may also motivate some small facilities to avoid growing in order to retain the LVPA. Emphasizing a dialysis facility's importance for patient access rather than size alone may help inform payment policy modifications.

Funding: Other U.S. Government Support

FR-PO693

Delayed Thrombectomy Increases Risk for Dialysis Catheter Placement Scott Reule, Sunil Akkina, Andrew J. Esten, Paul E. Drawz. Dept of Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Arteriovenous dialysis accesses (fistulas or grafts) are associated with significant rates of thrombosis. Though timely thrombectomy may have a significant impact on immediate and long-term access survival, it is not always readily available. The goal of this study was to evaluate whether delayed thrombectomy increases risk for loss of dialysis access and subsequent placement of a dialysis catheter.

Methods: All patients at the Fairview Health System with thrombectomy as the primary reason for admission between January 2008 and April 2015 were included in this retrospective observational study. The electronic medical record was reviewed to evaluate type of access, timing of admission and declot, and access on discharge and 6 and 12 months after discharge. Baseline characteristics and proportions were determined for the overall population as well as stratified by tertile of time to thrombectomy, defined as the time from admission to the declot procedure. The outcomes of interest included need for dialysis catheter at discharge and 6 and 12 months after discharge. Logistic regression was used to evaluate the risk for dialysis catheter use adjusting for prior intervention, access type, and time to thrombectomy.

Results: Of 444 patients identified using procedural codes, 122 were admitted primarily for thrombectomy. The mean age was 60.4 years, 65% were male, and 44.3% utilized arteriovenous fistula for access. Mean time to thrombectomy was 0.45 days (range: 0.05-1.13 days). Fifteen patients utilized a catheter for hemodialysis on discharge. Delayed thrombectomy was associated with a two-fold increase in requirement for catheter at discharge (OR 2.02; CI 1.19-3.43) and at 6 months (OR 2.04; CI 1.20-3.48). This association remained present at 12 months (OR 1.75; CI 1.02-3.00).

Conclusions: In this study of patients cared for within a large academic health system, a one day delay in thrombectomy doubled the risk for need for a dialysis catheter at discharge and 6 and 12 months after discharge. These results indicate that a clotted dialysis access should be considered a medical emergency.

FR-PO694

Intradialytic Body Weight Reduction and Outcome of Vascular Access: Analyses of Data from the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS) Manabu Asano,¹ Kenichi Oguchi,¹ Akira Saito,² Yoshihiro Onishi,³ Yosuke Yamamoto,⁴ Shunichi Fukuhara,² Takashi Akiba,² Tadao Akizawa.² ¹Bosei Hospital, Saitama, Japan; ²J-DOPPS Research Group, Japan; ³iHope International, Kyoto, Japan; ⁴Inst for Advancement of Clinical and Translational Science, Kyoto Univ Hospital, Kyoto, Japan.

Background: There is no doubt that large-volume ultrafiltration is one of the important risk factors for vascular access (VA) thrombus in hemodialysis patients. However, the relationships between intradialytic body weight reduction and VA patency are still in the middle of being discussed. We tried to determine whether large-volume ultrafiltration was practically associated with VA failure by means of the results obtained from the phase 3 and 4 J-DOPPS.

Methods: Referring data from the phase 3 and 4 J-DOPPS, the current analyses were limited to 2736 patients who were evaluable for VA patency and body weight change during dialysis. They were assigned to one of the following three groups according to the tertiles (T1-T3) of intradialytic fluid removal per body weight: T1, -9.5% to 3.8%; T2, 3.8% to 5.1%; and T3, 5.1% to 13.7%. The hazard ratio of VA failure was compared across these tertile groups using Cox regression models. The models were adjusted for the following risk factors: age, gender, BMI, diabetes, hemoglobin, phosphorus, Kt/V, ESA use, and antiplatelets use. Primary VA survival was defined as the days until the first VA intervention. Secondary VA survival was defined as the days until new VA creation.

Results: The incidence rates (events/100 person-years) of primary and secondary VA events were 4.7 and 1.3 for T1, 5.6 and 1.6 for T2, and 6.7 and 1.7 for T3, respectively. The adjusted hazard ratios versus T1 for primary VA patency were 1.16 (95% confidence interval [CI], 0.88 to 1.52) for T2 and 1.41 (95% CI, 1.07 to 1.87) for T3. The hazard ratios versus T1 for secondary VA patency were 1.29 (95% CI, 0.78 to 2.13) for T2 and 1.45 (95% CI, 0.86 to 2.45) for T3.

Conclusions: This study shows that large-volume ultrafiltration during dialysis tends to increase VA failure in hemodialysis patients.

FR-PO695

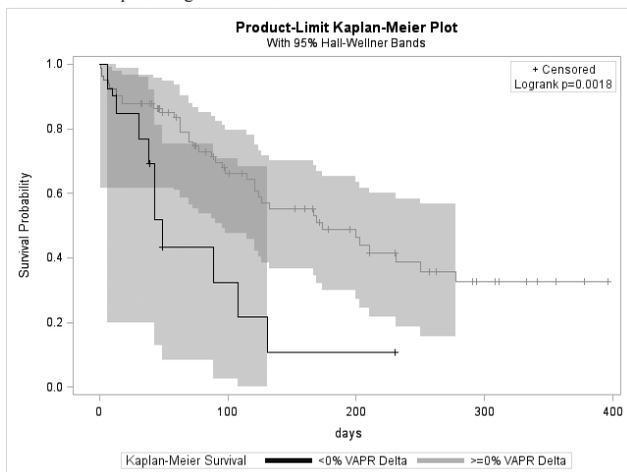
Post-Endovascular Intervention Venous Access Pressure Ratio (VAPR) Predicts Access Survival Lalathaksha Murthy Kumbar,¹ Gerard Zasuwa,¹ Anatole Besarab,² Kim Hirschman,³ Jerry Yee.¹ ¹Henry Ford Hospital, Detroit, MI; ²Stanford, Palo Alto, CA; ³Vasc-Alert, LLC, Evanston, IL.

Background: The Vascular access pressure ratio test identifies vascular access (VA) dysfunction in hemodialysis patients when 3 consecutive VAPR (VAP/MAP) measurements are >0.55. We hypothesized whether a post-interventional VAPR decline predicts VA outcomes in patients with VA dysfunction.

Methods: Retrospective analysis of all VA procedures from 09/2013 to 04/2015. Data collection included demographics, comorbidities, VA features, mean VAPR <30 days pre- and post-procedure, time-to-next procedure, and access patency. Kaplan-Meier arteriovenous graft (AVG) and fistula (AVF) survival curves were compared by the log-rank test. A Cox-proportional hazard model was used to determine the association of VAPR Δ% (Pre-Post)/Pre×100% with access survival.

Results: Analysis of 92 subjects [females 57% (n=53); black 88%; and diabetes mellitus 61% (n=56)] included 46 AVF with 94 procedures and 46 AVG with 86 procedures. Mean VAPR Δ% was 26 ± 61 (SD) and 16 ± 54 for AVF and AVG, respectively. VAPR decline was absent in 13 AVF. AVF with no VAPR decline (<0%) post-intervention when compared to AVF with any decline (>0%) required more subsequent procedures (64% vs 47%), with fewer days to next procedure (75 vs 149 d), and lower survival (p=0.002). For AVG, a post-intervention VAPR decline >10% (p=.04) projected AVG survival. 34% of AVG procedures had <10% decline (n=30) and required more subsequent procedures than AVG with >10% decline (64% vs 39%). AVF without VAPR decline had a 3-fold greater risk of failure (p=0.003). The risk of failure was 2.0-fold greater (p=0.04) for AVG with <10% decline.

Conclusions: A >10% post-intervention reduction of VAPR in AVG and any VAPR reduction in AVF predicts greater VA survival.



FR-PO696

Abnormalities in Mineral Metabolism and Dialysis Arteriovenous Fistula Thrombosis in the HEMO Study Anna Jeanette Jovanovich,^{1,2} Eugene J. Nuccio,² Alfred K. Cheung,^{3,4} Tom Greene,⁴ Michel Chonchol.² ¹Denver VA Medical Center; ²University of Colorado Denver; ³VA Salt Lake City; ⁴Univ of Utah.

Background: Vitamin D deficiency and fibroblast growth factor 23 (FGF23) excess are highly prevalent among patients requiring chronic hemodialysis. This study aims to determine the association of 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)₂D), and FGF23 serum levels with arteriovenous fistula (AVF) thrombosis in hemodialysis patients.

Methods: The HEMO Study was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum 25(OH)D, 1,25(OH)₂D, and intact FGF23 levels were measured in stored serum samples obtained at baseline in 881 patients in this cohort. Cox proportional-hazards models were used to examine the association of 25(OH)D, 1,25(OH)₂D, and FGF23 serum levels with time to first AVF clotting event after controlling for important clinical covariates in the HEMO Study.

Results: Patients had a mean age of 57±14 years, 55% were females, and 46% were white. During a median follow-up of 3.0 years, 111 AVF clotted. Median (IQR) serum 25(OH)D, 1,25(OH)₂D, and FGF23 levels were 19.1 [14.2, 26.6] ng/mL, 6.3 [2.9, 14.5] pg/mL, and 3118 [726, 12928] pg/mL. Among patients with levels in the highest tertiles compared to the lowest tertile, both 1,25(OH)₂D and FGF23 were significantly associated with an increased risk of clotting in adjusted analyses, hazard ratio (HR) 2.79 (95% CI, 1.21-6.46) and HR 1.35 (95% CI, 1.002-1.83), respectively. No statistically significant associations were observed between 25(OH)D serum levels and AVF thrombosis.

Conclusions: Calcitriol and FGF23 excess were associated with an increased risk of AVF thrombosis among chronic hemodialysis patients.

Funding: NIDDK Support, Veterans Administration Support

FR-PO697

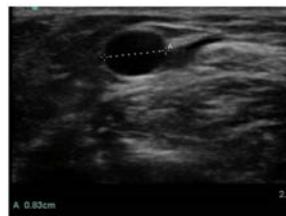
Ultrasound-Guided Evaluation of New AV Fistulas Safely Decreases Time to First Cannulation Farzin Farpour,^{1,2} Roshan A. Patel,^{1,2} George N. Coritsidis.^{1,2} ¹Nephrology, Elmhurst Hospital, Icahn School of Medicine at Mount Sinai, Elmhurst, NY; ²Nephrology, Broadway Atlantic Dialysis Center, Elmhurst, NY.

Background: The use of bedside ultrasonography (USG) in various medical specialties has exploded over the last decade. For the past year, we have been using bedside USG for earlier AV fistula utilization and for diagnosing potential problems. Prior to the use of USG, cannulation was based on physical exam. We were interested to see whether use of bedside USG helps in early cannulation of AVF.

Methods: USG procedures from February 2014 to February 2015 were reviewed. Time to cannulation in the year prior to the introduction of USG (2013 - 2014) was calculated and compared to similar data with USG use. By week 4 all new fistulas underwent the first USG exam. Examinations were performed by the renal attendings and fellows each exam lasting about 5 minutes. SonoSite M-Turbo ultrasound machine was used.

Results: Total of 44 USG examinations were performed on 14 patients while monitoring new AVF maturation. In 10 patients USG-guided cannulation occurred at an average of 6.2 ± 0.9 weeks compare to 10.2 ± 0.9 weeks prior to USG use (P=0.006). There were no complications seen with the earlier USG-guided cannulations. Subsequent cannulations by the nursing staff were successful without USG. In 4 patients failure of maturation was diagnosed by USG at an average of 3.8 ± 0.9 weeks vs 9.6 ± 1.2 weeks prior to USG (P=0.08). Antibiotic dosing occurred 21 times prior to USG compared to 11 times with USG, despite the similar catheter rates for both years.

USG image of mature fistula at 4 weeks



USG image of non-maturing fistula at 4 weeks



Conclusions: USG use facilitates early AVF cannulation with decreased time to first use. Identification of potential AVF issues and their referral are accomplished earlier. This may translate to earlier catheter removal and fewer infections.

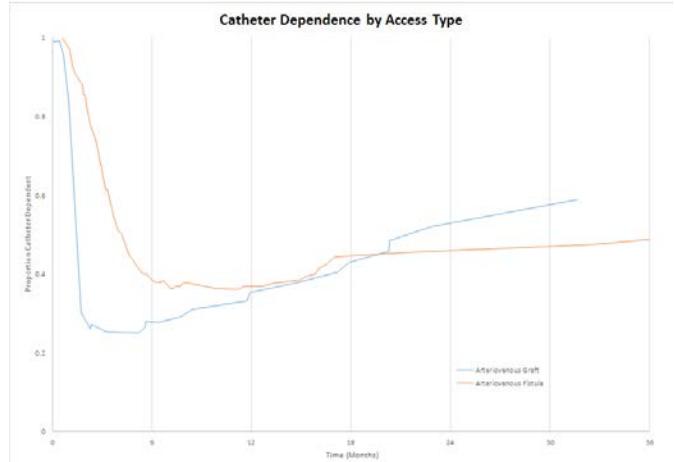
FR-PO698

Arteriovenous Grafts Reduce Catheter Dependence in the Elderly Thomas M. Loh, Matthew E. Bennett, Francis E. Loh, Eric K. Peden. *Vascular Surgery, Houston Methodist, Houston, TX.*

Background: Arteriovenous fistulas (AVF) are the permanent access of choice. The benefits of AVF, durability and longevity, are minimized in the elderly where more than 40% of patients will die within their first year of initiating hemodialysis. We investigate an expanded role for primary arteriovenous grafts (AVG) in this population.

Methods: We retrospectively review consecutive patients over the age of 70 who underwent upper extremity access creation from January 2008 to July 2014. Data collection included demographics, past medical histories, subsequent interventions, volume flows, access usage, and patient survival.

Results: We performed 366 AVF and 124 AVG creations in 442 patients over the age of 70 (197 women, 245 men). There were no significant differences in the comorbidities between the two access types. The AVG group was significantly older and more likely to be female, 79.2 yo vs. 77.2 yo ($p < 0.001$) and 60% vs. 41% ($p < 0.001$) respectively. Patients with AVF were significantly more likely to never use their permanent access, 25% vs. 11% (odds ratio: 2.6, $p = 0.002$) and if utilized, cannulated significantly later, 3.6 ± 0.2 months vs. 1.3 ± 0.1 months ($p < 0.001$). Catheter dependence at 6 months was 40% for AVF and 28% for AVG. (Figure 1) Secondary patency at 18 months was 64% for AVF and 63% for AVG.



Conclusions: Prosthetic grafts should be considered as the preferred permanent access type in the elderly. Better predictors of mortality, including frailty scores, should be investigated for determining the best choice of permanent access in elderly patients.

FR-PO699

Anticoagulation-Free Dialysis Is Not Associated with Failure to Meet Ultrafiltration Target: A Single-Center Inpatient Dialysis Study
 Rozina B. Ali, Akshatha Rao, Sandeep Aggarwal. *Div of Nephrology and Hypertension, Drexel Univ College of Medicine, Philadelphia, PA.*

Background: Conventional outpatient hemodialysis utilizes various forms of anticoagulation to prevent access and extracorporeal circuit clotting. In contrast, to reduce the risk of bleeding events, inpatient dialysis units do not frequently use anticoagulation. We aimed to investigate the consequences of anticoagulation-free dialysis and the factors associated with failure to achieve ultrafiltration target (UFT) in our inpatient unit.

Methods: We performed a retrospective analysis of 250 consecutive hemodialysis treatments in 125 chronic patients. Patients were excluded if they were admitted for initiation of dialysis or required systemic anticoagulation. We looked at both instances of successful achievement and failure of UFT. We looked at the following factors: type of access, episode of intradialytic hypotension (IDH), episode of access clotting, and episode of extracorporeal circuit clotting. No anticoagulation was used in the HD treatments. Correlation analyses were performed and categorical data was analyzed using chi-square test. STATA, version 11, was used for statistical analyses.

Results: Overall the incidence of failure to meet UFT was 35%. Association of failure to meet UFT and episode of IDH was noted ($p = 0.000$, Pearson $\chi^2(1) = 13.5$). There was no correlation between meeting UFT and type of access (graft $r = -0.09$, fistula $r = -0.13$, and catheter $r = -0.07$), access clotting ($r = 0.07$), and extracorporeal circuit clotting ($r = -0.08$).

Conclusions: Our study of 250 anticoagulation-free hemodialysis treatments suggests that access and extracorporeal circuit clotting was not associated with failure to meet ultrafiltration target. However, the failure to achieve ultrafiltration target was significantly associated with intradialytic hypotension. Larger cohort, multi-center prospective trials should be performed to look at causality of failure to meet ultrafiltration targets in the hospitalized patient.

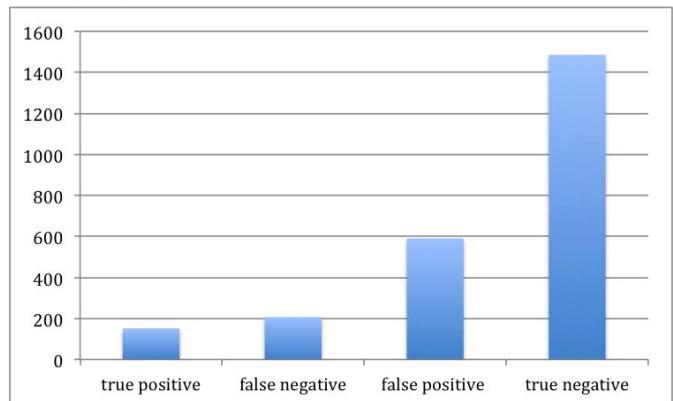
FR-PO700

Evaluation of the Ability of Transonic Monitoring to Predict Dialysis Access Stenoses
 Jerard Zaki Kneifati-Hayek,¹ Gaurav Ghosh,² Stephen Kruger,³ Jeffrey I. Silberzweig.^{1,2,3} *¹Dept of Medicine, New York-Presbyterian Hospital, New York, NY; ²Weill Cornell Medical College, New York, NY; ³The Rogosin Inst, New York, NY.*

Background: Patency of vascular access is critical to successful maintenance hemodialysis. It is well established that lesions are easier to treat if they can be identified prior to thrombosis. Non-invasive evaluation of access blood flow with the Transonic device is established for this purpose. We previously analyzed its performance after two years and demonstrated $>99\%$ sensitivity and specificity¹. We now seek to extend that work by looking at performance over a fifteen-year period.

Methods: Transonic studies are performed on approximately 1500 maintenance dialysis patients with AV grafts or fistulae in our 7 clinics in New York City. Transonic flow rates <600 cc/min or decreases by $>10\%$ from prior readings prompt referral to Interventional Radiology or Vascular Surgery. We report on the sensitivity, specificity and predictive values for patients treated between 1998 and 2012.

Results: Sensitivity was 42%; specificity 72%. Positive predictive value (PPV) was 20%; negative predictive value (NPV) was 88%.



We evaluated our ability to predict stenosis based on decreased dialysis clearance: for Kt/V, PPV was less than 10% and NPV less than 80% for different cutoff points; for URR, PPV was less than 10% and NPV less than 80%.

Conclusions: We hypothesize that the large numbers of false positive and false negative results were caused by scheduled referrals to Interventional Radiology, which have become routine. This study suggests that routine Transonic studies may no longer be as important as they were in 2000; however, Transonic studies provide better predictive ability than reductions in urea-based dialysis clearance.

FR-PO701

Hemodialysis Vessel Mapping in Women and Men
 Rita L. McGill, Robin Ruthazer, Dana Miskulin, Klemens B. Meyer, Daniel E. Weiner. *Tufts Medical Center, Boston, MA.*

Background: Men initiate hemodialysis (HD) with fistulas (AVF) more often than women, and this gap widens following initiation. Angiography and Doppler vessel mapping may promote AVF creation by detecting vessels not found by physical examination. Women may benefit more from imaging, as they are less likely to have veins that are visible upon inspection, even when suitable for AVF construction. We hypothesized that the sex disparity in AVF use may in part reflect a disparity in vessel mapping rates.

Methods: After restricting to patients with pre-dialysis Medicare claims, we used CPT codes to ascertain all vascular imaging during the 2 years before starting HD and up to 12/31/2012, in the subset of adult HD patients entering USRDS in 2010 or 2011 with central venous catheters (CVC) as sole vascular access. Doppler studies performed on the same day as an angiogram were excluded. Angiograms and Dopplers per 100,000 patients-months were calculated. Incidence rate ratios (IRR) between women and men were adjusted for age, race, BMI, diabetes, and vascular disease using Poisson regression.

Results: Among women with preHD claims, 62% had CVC-only and 14% AVF; men had 57% CVC-only and 20% AVF. 18494 men and 16686 women with CVC-only contributed 615257 and 558647 patient-months of data. No imaging was performed in 57% of men and 54% of women. The distribution of studies in men and women showed:

	MEN	WOMEN
N	18494	16686
ANGIOGRAPHY (# studies performed)	5705	5851
# individuals with Angiography	4058 (22%)	3986 (24%)
Crude IRR Angiography	---	1.13 [1.09, 1.17]
Adjusted IRR Angiography	---	1.11 [1.07, 1.15]
DOPPLER VEIN MAPPING (#studies performed)	5815	5746
# individuals with Doppler	4953 (27%)	4743 (28%)
Crude IRR Doppler	---	1.09 [1.05, 1.13]
Adjusted IRR Doppler	---	1.07 [1.03, 1.11]
# individuals with ANY imaging studies	8011 (43%)	7654 (46%)

Conclusions: Vascular imaging was performed in fewer than 50% of individuals starting hemodialysis with CVC. Higher rates of vascular imaging in women were statistically but not clinically significant. Promotion of vein mapping and angiography in women merits exploration as a means to decrease the disparity in fistula rates between women and men.

Funding: Other NIH Support - NIH/NIDDK T32 DK007777 "Epidemiology, Clinical Trials and Outcomes Research In Nephrology"
 Tufts CTSI Grant [UL1 TR001064]

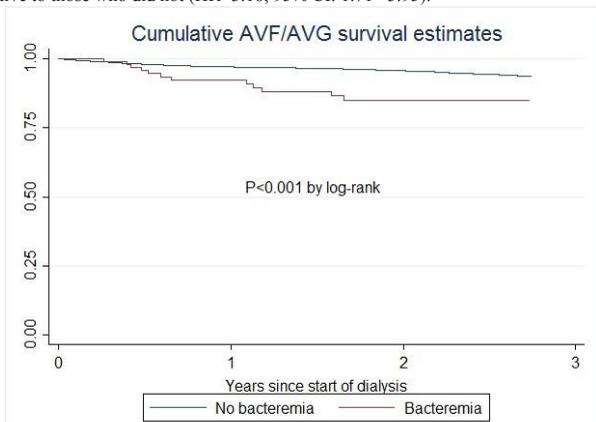
FR-PO702

Association of Bacteremia with Arteriovenous Access Failure in Hemodialysis Patients Syed Mustafa Ahmed, Laura Plantinga, Rachel E. Patzer, Jason Cobb, William M. McClellan. *Emory Univ, Atlanta, GA.*

Background: Obesity, female sex, diabetes, peripheral vascular disease, and pacemakers are known risk factors for arteriovenous fistula (AVF) and arteriovenous graft (AVG) failure. We examined whether bacteremia in hemodialysis (HD) patients with AVF/AVG represents an additional, independent risk factor for subsequent AVF and AVG failure.

Methods: We conducted a retrospective observational study among 29,571 U.S. patients from the United States Renal Data System who started HD with AVF and AVG between 1/1/2009 and 9/30/2010. We used inpatient ICD-9 codes after dialysis start to define bacteremia and AVF/AVG failure. We then used a multivariable Cox proportional hazards model to assess relationship between exposure to bacteremia and time to access failure.

Results: Overall, 12.2% of patients with bacteremia experienced an access failure, compared to 4.0% of patients without bacteremia (P<0.001). This difference persisted over a median follow-up of 582 days. With adjustment for known confounders, patients who had bacteremia after dialysis start were at >3-fold greater risk of subsequent access failure, relative to those who did not (HR=3.18, 95% CI: 1.71– 5.95).



Conclusions: This observational study indicates that decreased AVF and AVG survival may be associated with exposure to bacteremia among HD patients.

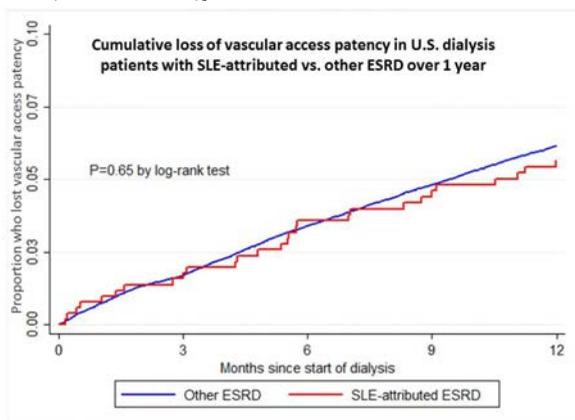
FR-PO703

Comparison of Loss of Vascular Access Patency in Hemodialysis Patients with End-Stage Renal Disease due to Systemic Lupus Erythematosus versus Other Causes Laura Plantinga, Sung S. Lim, Rachel E. Patzer, Stephen O. Pastan, Cristina Drenkard. *Emory Univ, Atlanta, GA.*

Background: Previously we found that U.S. patients with systemic lupus erythematosus (SLE) and end-stage renal disease (ESRD) were 40% less likely than other ESRD patients to have a permanent vascular access in place at the start of dialysis. Here, we examine whether subsequent loss of patency differs in SLE vs. other ESRD patients who have a permanent vascular access.

Methods: A cohort of 106,993 U.S. patients starting hemodialysis with an arteriovenous fistula or graft (7/05-9/11) was identified from a national registry of treated ESRD (United States Renal Data System). Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to estimate the association between SLE vs. other ESRD (by provider-reported attributed cause at start of dialysis) and the time to first inpatient ICD-9 code for loss of vascular access patency, with censoring for death or the end of follow-up.

Results: A total of 597 (0.6%) incident hemodialysis patients with a permanent vascular access had ESRD attributed to SLE. Over a median total follow-up of 1.9 years (IQR, 0.9-3.3 years), SLE vs. other ESRD patients had similar likelihood of loss of patency [HR=0.87 (95% CI, 0.70-1.09)].



Results were similar within the first year of dialysis [HR=0.91, 95% CI, 0.62-1.33] and, with adjustment for demographics and clinical variables, the association remained null [HR=1.13 (95% CI, 0.80-1.65)].

Conclusions: These results suggest that, among those patients who do start dialysis with a permanent vascular access, those with SLE are not more likely than other patients to experience a loss of vascular access patency requiring hospitalization. Further analyses will examine whether these patterns persist when outpatient procedures are included; however, confounding by indication would remain a potential bias.

FR-PO704

The Placement of Tunneled Central Venous Catheters Through Percutaneous Puncture of Superior Vena Cava in Hemodialysis Patients Tianlei Cui, Xiaoxi Zeng, Yanhuan Feng, Ping Fu. *Nephrology Dept, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.*

Background: After the exhaustion of traditional insertion sites of tunneled central venous catheters (tCVCs), it can be challenging to place the tCVCs in exotic locations. A retrospective case series in West China Hospital was studied to assess the placement of tCVCs through percutaneous puncture of superior vena cava (SVC) in patients with innominate veins occlusion.

Methods: Sixteen patients (male: 62.5%; mean age: 64.7 years; mean duration of HD: 5 years) who underwent placement of tCVCs through percutaneous puncture of SVC were retrospectively analyzed. They had either exhausted AV access sites or chosen not to undergo other vascular access placement. All of the patients had occlusion in innominate veins on both sides. The outcomes were function measurements of tCVCs, and safety parameters. The technique: With patients supine, following the guidance of fluoroscopy, a 5-F catheter was placed at the distal end of SVC through the femoral vein, iliac vein or hepatic vein, serving as a fluoroscopic target. Later, guided by fluoroscopy vertically and horizontally, the puncture needle and sheath were placed into SVC through a percutaneous route with the insertion site at 0.5-1.0 cm lateral-inferior to the clavicle head of sternocleidomastoid, allowing the access of the guidewire and the placement of a tCVC.

Results: The procedure succeeded in all of the patients. During the follow-up (mean: 12 months, range: 3-36 months), access failure due to thrombosis was observed in one patient, and the failure was treated by aspirin and Clopidogrel. The remaining continued to function well until the end of the follow-up or until the death of the patients (n=3). The procedure was generally safe. No pneumothorax occurred. The most common complication was mediastinal hematoma after the failure of SVC puncture. The fluoroscopy could reveal the hematoma during the procedure. The largest hematoma was 2cm in diameter in the current series and it resolved spontaneously.

Conclusions: In patients with innominate veins occlusion and exhaustion of the conventional insertion sites, the tCVCs can be safely placed through SVC puncture using percutaneous route.

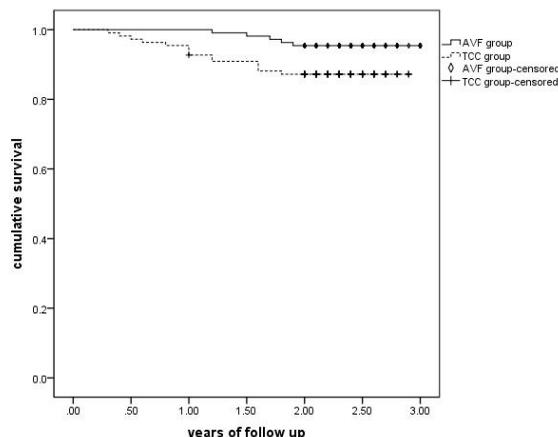
FR-PO705

Analysis of Survival of Cardiac Function in Maintained Hemodialysis Patients with Arteriovenous Fistula and Tunneled Cuffed Catheter Li Hua Wang, Fang Wei, Ai Li Jiang. *Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, 2nd Hospital of Tianjin Medical Univ, Tianjin, China.*

Background: Until now, there is little data of cardiofunction regarding to different type of vascular access. This study was to investigate survival of patients with arteriovenous fistula and tunneled catheter on maintained hemodialysis in terms of cardiofunction.

Methods: A total of 219 patients who received maintained hemodialysis were included in this study. Patients were divided into two groups: arteriovenous fistula group and tunneled catheter group. The baseline anthropometric and laboratory parameters were measured. The time and cause of mortality were documented.

Results: There were significant difference of left ventricular hypertrophy [$\chi^2=6.645$, $P=0.001$], left ventricular systolic dysfunction [$\chi^2=4.007$, $P=0.045$], between two groups. But there was no significant difference of left ventricular diastolic dysfunction between two groups. Kaplan-Meier survival curves showed that the mortality was enhanced among tunneled catheter group.



Patients with left ventricular hypertrophy, left ventricular systolic dysfunction, left ventricular diastolic dysfunction in arteriovenous fistula group have a high survival rate compared with tunneled catheter group. Furthermore iPTH, calcium, systolic blood pressure and diastolic blood pressure were the independent risk factors of mortality for patients on maintained hemodialysis by COX regression model.

Conclusions: Different type of vascular access may have influence on mortality in patients on maintained hemodialysis. Those with tunneled catheters have lower survival rate when left ventricular dysfunction occurred.

FR-PO706

A Retrospective Study of Preferable Alternative Sites to Right Internal Jugular Vein for Tunneled Hemodialysis Catheters Insertion: Right External Jugular Vein versus Left Internal Jugular Vein Yufei Wang, Pei Wang, Xianhui Liang, Xiaoqing Lu, Zhangsuo Liu, Yingjin Qiao, Sijie Zhou. *Blood Purification Center, The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China.*

Background: It has been recommended by the KDOQI guidelines that right internal jugular vein (RIJV) is a preferred insertion site for hemodialysis (HD) catheters, and both right external jugular vein (REJV) and left internal jugular vein (LIJV) are alternative sites for those who have encountered severe thrombosis and/or occlusion of RIJV. The retrospective study aimed to determine if superiority exists in the two alternative sites by comparing the outcomes of tunneled (cuffed) dialysis catheters (TDCs) through REJVs versus LIJVs in HD patients who had failed RIJV.

Methods: From January 1, 2013 to December 31, 2014, 28 LIJV-TDCs and 21 REJV-TDCs were inserted in our hospital. All events were recorded from patient charts until May 31, 2015. Using SPSS 22.0 software, data were analyzed by the Fisher exact test or chi-square test. Event free catheter survival was estimated by the Kaplan-Meier method. Multivariable Cox hazards analysis was fitted to detect the independent risk factors of events. A p-value of <0.05 was considered statistically significant.

Results: A total of 20924 (LIJVs, 11782; REJVs, 9141) catheter-days were evaluated and the mean was 427.02 days. Most of the patients (53.1%) were older than 65 years with an average dialysis time of 25.3 months. The event free catheter survival time was (516.20±55.60)d in REJV-TDCs and (343.91±40.63)d in LIJV-TDCs ($P=0.038$). Mean effective blood flow was higher in REJV-TDCs than that in LIJV-TDCs (270.95±24.93 vs 244.82±30.35ml/min, $P=0.02$). A substantial trend toward statistical significance was found between two groups in incidence of all events, including death, death related to catheter complication and catheter removal. The total historic catheters indwelling time was identified as an independent risk factor for severe TDCs events by Cox regression hazards test ($p=0.01$).

Conclusions: REJV might be superior to LIJV as an alternative insertion site for TDC placement in in HD patients who had failed RIJV.

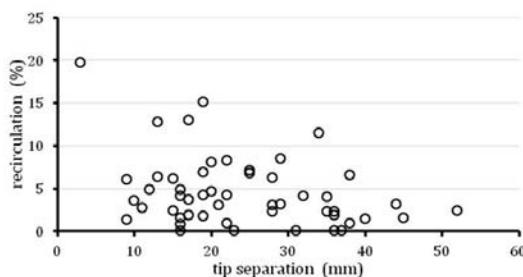
FR-PO707

Haemodialysis Recirculation in Patients with Catheter Access Damien Ashby. *Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom.*

Background: Recirculation is a well described impairment of the haemodialysis circuit which reduces dialysis dose and electrolyte clearance. Catheter tips are designed to minimise recirculation based on in vitro experiment, with most designs having a tip separation of 25mm, but clinical studies of catheter-related recirculation have not been published.

Methods: In a group of stable adult patients receiving haemodialysis by tunneled catheters, recirculation was calculated by 3-sample urea measurement, and analysed in relation to line tip separation (measured by chest X-ray) and routinely collected clinical parameters. All patients were using paired Tesio catheters.

Results: In 54 haemodialysis patients (aged 28-90, 61% male) median recirculation was 3.7% with IQR 1.9-6.3%, range 0-19.7%, and a heavily left-skewed distribution (modal range 0-2%). Greater than 5% recirculation was seen in 30% of patients. Tip separation (range 3-52mm) was strongly associated with recirculation ($R=-0.33$, $p=0.014$), which also appeared to have a weak association with body weight ($R=0.21$, $p=0.13$).



Defining thresholds to avoid high recirculation (>5%): with tip separation over 25mm high recirculation was seen in 6 patients. Increasing threshold tip separation to 30mm reduced the number of patients with high recirculation to 2. The same was achieved using a weight-based tip separation threshold of 0.5mm/kg. High recirculation was associated with high erythropoietin requirement ($R=0.29$, $p=0.030$) but not with low Kt/V ($p=0.26$).

Conclusions: Significant recirculation affects a significant minority of patients dialysing on tunneled catheters, and is closely related to tip separation. A tip separation threshold of

25mm may be inadequate to avoid high recirculation, and 30mm or perhaps a weight-based threshold may be superior. Erythropoietin resistance is a possible consequence of this type of haemodialysis recirculation.

Funding: Clinical Revenue Support

FR-PO708

Risk Factors for Fatal Dialysis Access Haemorrhage Nicole M. Lioufas,¹ Jonathan E.H. Ling,¹ Gail Theresa Read,¹ Matthew D. Jose,^{1,2} ¹Royal Hobart Hospital, Hobart, Tasmania, Australia; ²School of Medicine, The Univ of Tasmania, Australia.

Background: Haemodialysis requires access to the circulation via an arteriovenous fistula or graft, or a synthetic vascular catheter. Annually there are deaths associated with catastrophic bleeding from dialysis vascular access.

Methods: A systematic search strategy including data from the National Coronial Information System (NCIS, containing coroner's reports from all Australian states and New Zealand), the Australian and New Zealand Dialysis and Transplant registry (ANZDATA), published cases from Australia and New Zealand, individual renal units and State Renal Network reports. Data was analysed for all deaths where cause of death was reported as being due to dialysis access haemorrhage from 1st January 2000.

Results: A total of 83 patients (mean age 67 years (range 30 – 89), 55% female) receiving renal replacement therapy died due to dialysis vascular access haemorrhage. These were identified through NCIS 54, ANZDATA 64, State networks 3, Publications 2 and individual renal units 2. Most deaths were attributable to problems with vascular access including infection (22%), dialysis catheter problems (17%), recent access intervention (15%) or use of a thigh arteriovenous fistula (11%). Bleeds commonly occurred at home in people treated with satellite haemodialysis. Modality at the time of death was home haemodialysis in 12 people. Use of Warfarin or cognitive impairment was identified in only 1 death each. Coronial inquests and Root Cause Analyses were identified in only 7 deaths with recommendations involving communication, staffing, clinical policy, practice changes and equipment modification.

Conclusions: Death due to dialysis access haemorrhage is an uncommon, catastrophic, but potentially preventable event. A number are preceded by vascular access infection, vascular access complications or recent intervention. Only a minority of deaths have been investigated, but where they have, critical recommendations for optimising future care are presented.

FR-PO709

Subcutaneous Implantable Electronic Devices in Chronic Kidney Disease and Hemodialysis Patients Rizwan K. Alimohammad, Rahim Dhanani, James O'Brien, Syed S. Haqqie, Arif Asif. *Albany Medical College.*

Background: While epicardial leads have been reported to bypass central venous stenosis, their placement is much more invasive and requires the services of a cardiothoracic surgeon. Recent data have demonstrated successful defibrillation using a subcutaneous ICD (SICD). While the use of these devices is expanding, their insertion in advanced renal failure and hemodialysis patients is somewhat limited. In this analysis, we present 9 CKD and 4 hemodialysis patients treated successfully with an SICD. Demographic characteristics revealed; male=8, diabetes=8, hypertension=13, coronary artery disease=10, peripheral vascular disease=8. Two of the four hemodialysis patients had an AVF while two were dialyzing with a tunneled dialysis catheter. Mean GFR for the CKD patients was 40±3 ml/min. Patients received the SICD device for primary prevention of sudden cardiac death (cardiomyopathy with low ejection fraction). 3/13 patients had non-ischemic cardiomyopathy (CMP) with an ejection fraction of <25% while 10/13 suffered from ischemic CMP with an EF of <30%. There were no procedure-related complications in terms of excessive bleeding, hematoma or infection. At an average follow-up of 6 months, one death has occurred that was unrelated to the procedure or arrhythmia. Subcutaneous ICD is a minimally invasive procedure when compared with an epicardial device. By leaving the venous system untouched, this approach offers the advantage of reduced risk of central venous stenosis and infection over an endocardial ICD with transvenous leads. This approach is particularly helpful for CKD and hemodialysis patients who rely on venous capital for their survival. SICD has been FDA approved and is currently being utilized in the United States and Europe.

Methods: Restrospective evaluation of SICD in patients with CKD and ESRD.

Results: Thirteen patients with CKD and ESRD on dialysis received successful SICD.

Conclusions: SICD can be successfully used in patients on hemodialysis and CKD.

FR-PO710

Modified Non-Transposed Brachio basilic Arteriovenous Fistula for Hemodialysis: A Randomized Controlled Study Dayong Hu,¹ Chunyu Zhou,¹ Chandra Mohan,² Changbin Li,¹ Jie Tang,³ Ai Peng.¹ ¹Shanghai Tenth People's Hospital, Tongji Univ School of Medicine, Shanghai, China; ²Univ of Houston, Houston, TX; ³DHHA-Univ of Colorado School of Medicine, Aurora, CO.

Background: Transposed brachio basilic arteriovenous fistula (BBAVF) is technically challenging. It not only associates with severe arm swelling and pain, but also takes longer to be ready for use. Here we introduce a novel modified non-transposed BBAVF (mNT-BBAVF), and compare its outcomes to those of the standard brachiocephalic arteriovenous fistula (BCAVF).

Methods: From January 2010 to December 2012, 74 identical hemodialysis patients with suitable basilic and cephalic veins were randomized equally into mNT-BBAVF and

BCAVF groups. All participants were followed for 12-months after surgery. The main outcomes were blood flow velocities and volumes, vessel diameters, primary unassisted fistula patency rate (PUFPR), the cumulative fistula survival rate (CFSR) and complications.

Results: The baseline demographic and clinical characteristics were well matched between mNT-BBAVF and BCAVF groups. Blood flow velocities and flow volumes of the corresponding fistula segments increased significantly in both groups. Compared to BCAVF where only proximal cephalic vein increased in size, the proximal cephalic vein, distal cephalic vein and distal basilic vein in mNT-BBAVF all increased significantly compared to baseline over the 12-month period ($p < 0.01$). Therefore, in addition to the proximal cephalic vein, the distal cephalic vein and distal basilic vein were also available for cannulation in mNT-BBAVF. At 12 months, the PUFPR of mNT-BBAVF was significantly better than that of BCAVF (73.0% vs. 45.9%, HR: 2.60; 95%CI: 1.21 to 5.59; $p = 0.01$). Although, the CFSR did not differ between the two groups (91.9% vs. 78.4%, HR: 1.68; 95%CI: 0.55 to 5.17; $p = 0.37$). Finally, there were no significant differences in complications between the two intervention groups at 1 and 12 month follow-ups, other than severe arm pain which was much less reported among patients with mNT-BBAVF at 1 month (vs. BCAVF, $p = 0.03$).

Conclusions: mNT-BBAVF is an effective alternative for the construction of upper arm vascular access.

FR-PO711

Management of Catheter Related Bacteraemias: New Insights into an Old Problem Benjamin A. Oliveira,¹ Conor James Byrne.¹ ¹Renal Medicine, Royal London Hospital, London, United Kingdom; ²Renal Medicine, Royal London Hospital, London, United Kingdom.

Background: Catheter related bacteraemias (CRB) pose a significant risk for those dialysing via such devices. Strategies are needed to minimise this risk as much as possible, especially in light of growing concerns over antibiotic resistance. Our unit routinely uses citrate to lock catheters. We sought to audit our CRB rate and long term complication rate. We believe this contemporary data will be useful to all involved in caring for patients with catheters.

Methods: We retrospectively reviewed all blood cultures taken from our institution's dialysis patients for 1 year (October 2013 and September 2014). The records of patients with positive cultures were reviewed to ascertain if the infection was related to their access. Data was then collected on the type of organism grown, management of the episode, recurrence rate, and any long term complications.

Results: 1014 cultures were taken from approximately 930 haemodialysis patients. 45% of these were dialysing via a catheter. There were 52 instances of CRB giving a CRB rate of 0.34 per 1000 catheter days. 65% were due to gram-positive organisms, 29% were due to gram-negative organisms and 6% were fungal related. The overall recurrence rate was 26%. Catheter removal was performed in 32 instances (62%). Infective complications occurred in 5 (16%) patients with gram-positive infections and 6 (54%) of those with gram-negative infections; a statistically significant difference. The majority of these were endocarditis. CRB accounted for a total of 583 hospital in-patient days.

Conclusions: We observed significantly more infective complications with gram-negative organisms compared with gram-positive. This probably reflects the underlying characteristics of these patients rather than the pathogenicity of the organisms per se (19% of patients with gram-negative infections were intravenous drug users). Never the less our data suggests that gram negative infections are a risk factor for complications and clinicians should consider further investigations in these cases. Our CRB rate was low compared to quoted rates in the literature; this may reflect routine the use of citrate lock in our catheters.

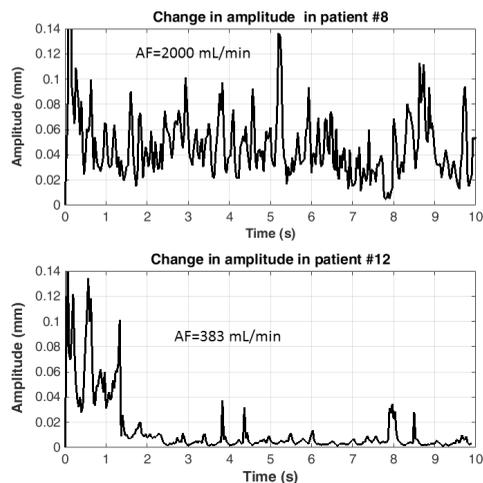
FR-PO712

Assessment of Arteriovenous Fistula Access Flow Using Video Image Processing Technology Schantle Williams,¹ Hannah Putnam,¹ Viviane Calice-Silva,^{1,2} Israel David Campos Gonzalez,¹ Peter Kotanko,^{1,3} Fansan Zhu.¹ ¹Renal Research Inst, NY, NY; ²Pontifícia Univ Católica do Paraná, Curitiba, Brazil; ³Icahn School of Medicine at Mount Sinai, NY, NY.

Background: Vascular stenotic lesions are the main cause of failure in arteriovenous fistulas (AVF). Routine measurement of access flow (AF) is important in the timely detection of changes and planning interventions. The aim of this pilot study was to investigate whether video image processing (VIP) techniques can be used to detect AVF motion and explore the relationship between motion patterns and AF.

Methods: Skin above the AVF was imaged for 1 minute using a digital single lens reflex camera prior to HD. The video was processed using Eulerian video magnification (Wu et al *ACM Trans. Graph.* 31(4), 2012) to amplify AVF motions. Thereafter the motion-amplified video was converted to quantitative waveform data using an algorithm based on change in color of each image (Matlab Image Processing Toolbox). Monthly AF measurements were recorded and correlated with the post-processed AVF waveform pattern.

Results: We studied 12 hemodialysis patients (51.5±11.3 years, 50% male) with a mean±SD AF 1501±392ml/min (N=9; AF was unavailable in 1 subject). Amplitude of skin displacement was 0.069±0.04mm (N=9; technical issues occurred in 2 subjects). While amplitudes of that size are hardly visible to the naked eye, they were clearly discernible in post-processed amplified videos. Amplitude was notably smaller in subjects with lower AF (Fig. 1). Amplitude analysis of the amplified video indicates a relationship with AF ($R^2 = 0.73$, $p < 0.01$; N=9).



Conclusions: Our proof-of-concept study demonstrates this video imaging and analysis technique has potential to provide a quick, noninvasive, low cost way to obtain quantitative information related to AF. Research is underway to assess the impact of clinical interventions of the amplitude pattern.

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FR-PO713

Pre-Emptive Correction of Arteriovenous Access Stenosis: Systematic Review and Meta-analysis of Randomized Controlled Trials Pietro Ravani,¹ Robert R. Quinn,¹ Matthew J. Oliver,² Divya J. Karsanji,¹ Matthew T. James,¹ Jennifer M. MacRae,¹ Suetonia Palmer,³ Giovanni F.M. Strippoli.⁴ ¹U of Calgary, Canada; ²U of Toronto, Canada; ³U of Otago, New Zealand; ⁴Diaverum, Italy.

Background: Elective stenosis correction in an arteriovenous (AV) access that is suitable for hemodialysis may prolong its survival, as compared to salvage procedures postponed to when the AV access becomes dysfunctional.

Methods: We did a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating pre-emptive correction of an AV access stenosis vs. stenosis correction in a dysfunctional access (deferred correction) in adults treated with hemodialysis therapy. We searched the Cochrane Kidney and Transplant Specialized Register (which includes MEDLINE and EMBASE) to 29 October 2014. Outcomes of interest were access loss (primary outcome), access thrombosis, infection, mortality, hospitalization, and access-related procedures. We did sub-group analyses of access outcomes by access type. We summarized the evidence using the Grading of Recommendations Assessment, Development, and Evaluation criteria.

Results: We included 14 studies (involving 1,390 participants; follow-up 6-38 months; N=58-189 participants). Nine studies enrolled adults without access stenosis (primary prophylaxis); three studies including people using fistulas and five enrolled adults with a highly suspected or documented stenosis in a functioning access (secondary prophylaxis); three studies in people using fistulas). Relative to deferred salvage, access surveillance with pre-emptive correction of an AV stenosis did not reduce the risk of thrombosis (RR 0.95; 95% CI 0.8-1.12) or access loss (RR 0.9; 95% CI 0.71-1.15) in grafts (moderate-grade evidence), but reduced the risk of thrombosis (RR 0.5; 95% CI 0.35-0.71) and access loss (RR 0.5; 95% CI 0.29 to 0.86) in fistulas (low-grade evidence). Results were either heterogeneous or imprecise for mortality, rates of infection, procedures and hospitalization. There was unclear or high risk of bias in most studies.

Conclusions: Pre-emptive correction of a new or documented stenosis may not improve graft outcomes, but may prevent fistula thrombosis or loss.

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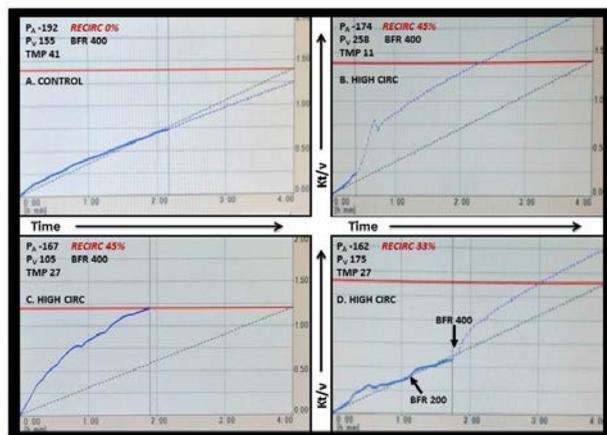
FR-PO714

Real-Time Kt/V Tracking Profile as a Predictor of Dialysis Access Recirculation Abhilash Koratala, Girish Singhania, A. Ahsan Ejaz. *Nephrology, Univ of Florida, Gainesville, FL.*

Background: On-line monitoring of ultraviolet absorption of spent dialysate in routine hemodialysis allows continuous measure of removed solutes from spent dialysate. We studied whether real-time Kt/V tracking profile could be a predictor of dialysis access recirculation.

Methods: End-stage renal disease patients undergoing maintenance dialysis with Dialog (B Braun AG) dialysis machine with a built-in UV-Spectrophotometer (Option Adimea, B Braun AG), high-flux polysulfone dialyzers, and at blood flow rate (Q_b) 400-450ml/min and dialysate flow rate (Q_d) 800ml/min were included in all recording sessions. Real-time Kt/V tracking profile and venous (P_v) and arterial pressures (P_a) were recorded and hemodialysis access recirculation values were biochemically measured using standard protocol.

Results: Distinct real-time Kt/V profiles were identified in patients with significant access recirculation (>5%) vs. none (Control).



In the control profile, real-time Kt/V (Fig 1a, solid line) closely followed the target line (Fig 1a, dashed line) and was associated with normal P_a and P_v . In patients with high access recirculation, real-time Kt/V tracking line deviated widely from the target line (High Recirc Kt/V Profile; Fig 1b, c, d) and remained deviant throughout the treatment session. Fig 1d, demonstrates a case wherein the initial low Q_b provided false impression of normal access function, however increasing Q_b resulted in unmasking of high access recirculation, i.e., appearance of High Recirc Kt/V Profile. High access recirculation was confirmed by biochemical methods. Interestingly, all High Recirc Kt/V Profile events were associated with abnormal recirculation values, but not all were associated with elevated P_a .

Conclusions: Real-time Kt/V tracking profile provides a non-invasive, inexpensive and quick assessment of access recirculation in hemodialysis patients.

FR-PO715

Recurrent Vascular Access Stenosis as a Novel Marker for Cardiovascular Outcome in Hemodialysis Patients Hyo Jin Kim, Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Yon Su Kim, Curie Ahn, Kwon Wook Joo. *Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.*

Background: Vascular access (VA) is essential component and its stenosis is a major complication in hemodialysis (HD) patients. Nevertheless, there are few data for outcomes of patients who had recurrent VA stenosis. We have explored the influence of recurrent VA stenosis on cardiovascular (CV) event, patient death, and VA failure.

Methods: This is a single-center, retrospective study. Patients who had VA operation at Seoul National University Hospital between January 2009 and March 2014 were enrolled. Patients who had two or more instances of percutaneous angioplasty or revision operation within 180 days were categorized recurrent group. The primary outcome was CV events, as coronary artery or heart failure or cerebrovascular, and/or peripheral vascular events. The secondary outcomes were all-cause mortality (ACM), composite of ACM or CV events, and VA failure. The two groups were compared before and after matching with propensity scores (PSM).

Results: A total of 766 patients (59.7% male, age 59.6 ± 14.3 years) were analyzed. Recurrent group patients ($n = 77$; 10.1%) were older and had higher underlying CV disease and dyslipidemia. A total 213 patients (142 in non-recurrent, 71 in recurrent group) were selected by PSM. During 28.7 ± 15.8 months follow-up, 46 patients (21.6%) had CV outcomes, 30 patients (14.1%) died, and 14 patients (6.6%) experienced vascular access failure. After adjustment, recurrent group was an independent risk factor for CV events (adjusted hazard ratio [HR] 2.66; 95% confidence interval [CI] 1.46–4.86, $P = 0.001$) and composite of ACM or CV events (adjusted HR 1.99; 95% CI 1.21–3.27, $P = 0.007$). However, it was not associated with increased ACM and VA failure.

Conclusions: Recurrent VA stenosis was a novel independent risk factor for CV event in HD patients, rather than VA failure. For patients suffered from recurrent vascular stenosis, diligent monitoring should be warranted not only for VA patency but also for CV events.

FR-PO716

Stent Insertion Is an Important Tool in Maintaining Arteriovenous Access Patency Stephen G. John,¹ Kumar Abayasekara,² Peter M. Bungay,³ Mario De Nunzio,³ James E. Kirk,³ John Graham Pollock,³ Peter D. Thurley,³ Paul J. Owen,¹ Richard J. Fluck,¹ Lindsay J. Chesterton.¹ ¹*Nephrology, Royal Derby Hospital;* ²*Vascular Surgery, Royal Derby Hospital;* ³*Radiology, Royal Derby Hospital, Derby, United Kingdom.*

Background: Definitive access for haemodialysis (HD) remains the cornerstone of optimal dialysis. However, HD patients are becoming older, access attempts more problematic and vein preservation remains critical. Clinical examination and access monitoring enable appropriate, timely, endovascular intervention. Stents may be inserted for recurrent stenosis or after endovascular rupture, but their role remains debatable. We report on our single-centre experience of access surveillance and endovascular intervention, highlighting the role of stent insertion.

Methods: Electronic hospital records were retrospectively analysed in all access-related stents inserted from 2006–2014 by 5 vascular radiologists.

Results: 49 stents were inserted during 45 procedures in 39 patients. 12 had diabetes. Mean age was 64.5 ± 25.5 yrs, median dialysis vintage was 1162 ± 1504 days (range 5–5027). Median time from access creation (82% arteriovenous fistula) to stent insertion was 318 ± 926 days (range 31–3752). 34 stents were inserted peripherally (cephalic arch and distally), the majority in the cephalic arch. Equal numbers of covered and bare-metal stents were inserted. 4 stents were placed in thrombosed access. 7 procedures were due to surveillance alone, a further 8 due to surveillance and pressure/flow problems. 12 stents were inserted for rupture or dissection (overall access procedure complication rate 1%). Median time from first stent to access failure/ceased HD was 333 ± 653 days, assisted by median 2 (range 0–11) further procedures. Treatment for rupture was not associated with significantly shorter access longevity. Only 10 patients' access failed during follow-up. Our overall HD definitive access prevalence rate was 86–90%.

Conclusions: Appropriate HD access is essential in minimising HD morbidity. We reserve stent insertion for rapidly-recurring stenosis or rupture during endovascular procedures. Our data suggest that appropriate, judicious stent insertion in an appropriately structured pathway results in access durability and longevity.

FR-PO717

Association of Vascular Access Flow and Volume Status on Fistula Arm by Bio-Impedance Analysis in Hemodialysis Patients Hun Jeong,² Hyung Jong Kim,¹ Eun jung Ko,¹ Younhee Lee.¹ ¹*Internal Medicine, CHA Bundang Medical Center, CHA Univ, Seongnam, Korea;* ²*Internal Medicine, Seoul Bukbu Hospital, Seoul, Korea.*

Background: Multi-frequency bioimpedance is a tool of body composition measure and can monitor changes in extracellular volume during dialysis. Arterio-venous fistulae (AVF) could potentially affect fluid retention in the arm. We investigated whether multi-frequency bioimpedance could detect AVF stenosis or association of AVF with fluid retention in the AVF arm.

Methods: We measured the extracellular water (ECW) and total body water (TBW) in AVF arm following hemodialysis by multi-frequency bioimpedance (Inbody S10[®]) using an eight-electrode contact technique. We measured AVF flow by transonic ultrasonography using an ultrasound dilution technology (HD 03[®]) in hemodialysis.

Results: Total 28 patients (male 13 patients) were enrolled and the mean age of patients was 54.89 ± 13.21 years. ECW/TBW ratio of fistula arm was a significantly higher than ECW/TBW ratio of non-fistula arm (0.389 ± 0.01 vs 0.382 ± 0.001 ; $p < 0.05$). ECW/TBW ratio of fistula arm was a significantly negative correlation with access flow level (mL/min) on fistula ($p < 0.05$). The 5kHz reactance of fistula arm was a significantly positive correlation with access flow level (mL/min) on fistula ($p < 0.05$).

Conclusions: Absolute and also relative extracellular fluid volumes are increased in the fistula arm of hemodialysis. We thought that extracellular fluid volumes in the fistula arm were associated with access flow level (mL/min) and/or relative fistula stenosis. We suggest that multi-frequency bioimpedance can be a useful assistant tool of vascular access flow measure.

FR-PO718

Does Pre- and Post-Angioplasty Doppler Ultrasound Evaluation Help Predicting Vascular Access Outcome? Maria Guedes Marques, Pedro Maia, Fernando Neves, Anibal Ferreira, Carlos Oliveira, Carlos Barreto, João Cruz, Dulce Carvalho, Telmo Carvalho, Pedro M. Ponce. *Vascular Access Center - Nephrocare Lumiar, Portugal.*

Background: KDIGO Guidelines recommend post-angioplasty (PTA) lesion should have $< 30\%$ residual stenosis (RS) and hemodynamic parameters should improve. Access blood flow (ABF) is one of the most used. Primary end point: how post-PTA ABF improvement could predict vascular access (VA) outcome. Secondary: compare doppler ultrasound (DU) and angiography diagnostic accuracy; determine how other factors could predict outcome.

Methods: Prospective study in 80 patients with dysfunctional VA. DU evaluation was performed pre and post-PTA. Several parameters were recorded. Secondary patency verified during first 6 months.

Results: Initial DU in 80 patients; 26 excluded due to abnormalities absence or impossible endovascular approach - final 54. Two thirds male; age 68 ± 15 y; VA time 36 ± 29 months; initial ABF 537 ± 248 mL/min; final ABF 1013 ± 354 mL/min. Number and location of stenosis was highly correlated between DU and angiography (Pearson 0.828; $p < 0.000$); mismatching in central vessels. Overall survival 83% at first trimester and 63% at semester; significantly better for fistulas (76%) than grafts (51.7%), $p < 0.044$. Final angiographic RS $> 30\%$ occurred in 14.8% patients, who had significantly better survival, $p < 0.038$. Initial ABF < 500 mL/min and multiple stenosis didn't affect the outcome ($p < 0.189$ and $p < 0.811$). A > 2 -fold ABF increase had no significant impact on fistulas survival ($p < 0.339$) but it was highly significantly associated with worst outcomes in grafts (23.1% vs 73.5%, $p < 0.009$). VA failure HR was 3.3 for grafts ($p < 0.034$).

Conclusions: DU diagnostic accuracy is highly correlated with angiography. Although less accurate for central lesions, has a key role due to morphologic and hemodynamic assessment. PTA is a powerful therapy with immediate benefit; however final angiographic RS is not predictive of outcome. Grafts have worst patency, demanding more interventions. PTA is associated with mechanical endothelial injury. Higher ABF induce more turbulent flow that is likely to cause more intimal hyperplasia, which could explain the shorter patency, especially in grafts where inflammation is higher.

FR-PO719

Why Are Catheters Still Used to Initiate Hemodialysis Treatment of ESRD?

Tanya Tocharoen Tang, Shubhada N. Ahya, James J. Paparello, Murray L. Levin. *Dept of Medicine/Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.*

Background: Complications of long-term use of tunneled catheters for hemodialysis involve a high risk of infection, thrombosis, hospitalization and expense. This study reviews a single center experience to identify factors that may contribute to the high rate of patients initiated with tunneled HD catheters.

Methods: We conducted a 13-question survey of 47 CKD patients who had been newly initiated on dialysis through a tunneled central vein dialysis catheter during their hospital admission in a university hospital from December 2013-May 2015.

Results: Of 47 subjects, 27 were male and 20 female. Subjects' mean age was 60 years old. Demographics included 26/47 (55%) African Americans, 7/47 (15%) Hispanics, 12/47 (26%) Caucasians and 2/47 (4%) Asian. Ninety-six % of patients (45/47) had been seen by a physician within the past year, and had been told their kidney function was poor. Eighty-three % of patients (39/47) were referred to a nephrologist. Thirty-six patients saw a nephrologist and, of those patients, only 13 patients were referred to a surgeon for access. Of the patients who saw a nephrologist, twenty two % (6/36) did not follow through with access placement secondary to noncompliance. Thus, of 47 patients starting hemodialysis with a catheter, only 7 had actually seen a surgeon for access placement. The largest drop off in the continuum of care of the patient is between seeing the nephrologist and seeing the surgeon. Since half of the patients surveyed received care elsewhere, it indicates this finding is not unique to our institution.

Conclusions: There are numerous points in the path to arteriovenous access where attrition occurs. Nephrologists and primary care physicians must oversee proper follow up and follow through to assure successful access placement. In our study, we found that there is a big attrition point from nephrology to surgery referral. A coordinator to help follow up patients or a joint clinic are options to improve this problematic step.

FR-PO720

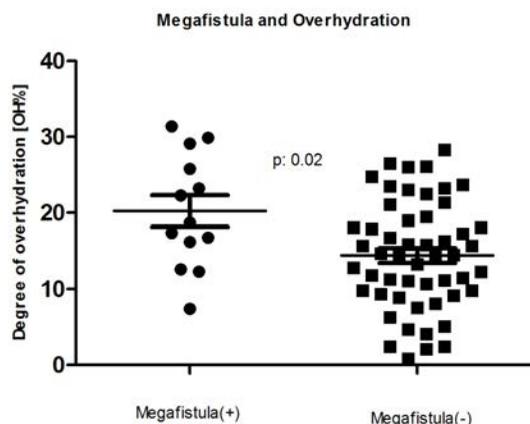
The Association of Overhydration Status with Megafistulas in End-Stage Renal Disease Patients on Hemodialysis

Mihaly B. Tapolyai,¹ Maria Faludi,¹ Melinda Forró,¹ Andras Tisler,² Tibor Fulop,³ Klara Berta.¹ ¹Dialysis, Fresenius Medical Care Semmelweis Univ, Budapest, Hungary; ²Nephrology, Semmelweis Univ, Budapest, Hungary; ³Nephrology, Univ of Mississippi, Jackson, MS.

Background: Megafistulas are tortuous dilated fistulas that fold up on themselves and become visible on the arm and shoulders all the way to the clavicles. They may exacerbate low cardiac output, as well as represent a problematic dilatation of the dialysis access. We sought to investigate the association of bioimpedance apparatus (BCM) measured extracellular fluid volume overhydration (OH%) and the presence of megafistulas.

Methods: In a cross sectional study we compared the pre-dialysis BCM-measured OH% in 12 prevalent chronic dialysis patients with megafistulas (MEGA) who had negative angiographies with that of 52 control dialysis patients (CONTR).

Results: 10/12 MEGA patients had OH% $\geq 16\%$ as compared to 20/52 CONTR patients (Chi square p: 0.02).



The degree of OH% was 20.2 ± 7.4% among the MEGA vs. 14.4 ± 7.1% in the CONTR group (Student t p: 0.01), representing 4.2 ± 3.2 vs 2.8 ± 1.6 L of excess fluid (p: 0.03). MEGA patients took an average of 1.7 ± 1.4 vs 0.8 ± 0.8 (p: 0.002) antihypertensive medications compared to the CONTR patients yet their blood pressure was 156/91 vs 141/78 mmHg (p: 0.03 < 0.0001). We found no difference in fistula vintage, body mass index, age, inflammatory markers, diabetes status or diuretic use. The odds ratio of overhydration being associated with a megafistula is 5.3 (p: 0.01).

Conclusions: There is an association of BCM-measured overhydrated clinical state with the presence of megafistulas; either as an increased volume capacitance or as a potential cause.

FR-PO721

The Observation of the Tunneled Cuffed Catheter Insertion Through Right Innominate Vein in Hemodialysis Patient

Yanhuan Feng, Tianlei Cui, Ping Fu. *Div of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.*

Background: The routine vascular access for hemodialysis is often available due to thrombosis and occlusion after frequent cannulation, which leads to an increase in cost and difficulty of catheterization or recanalization. Further catheterization may accelerate exhaustion of vascular resources. We inserted cuff catheter through right innominate vein in patients with thrombosis or occlusion of right internal jugular vein and subclavian vein so as to preserve precious vascular access at other parts of body. Here we report our observation of right innominate vein catheterization.

Methods: We enrolled patients who had been receiving regular HD in our center and to whom catheter cannot be inserted due to thrombosis or occlusion of internal jugular vein and subclavian vein. We performed cuff catheter insertion by puncturing right innominate vein in 8 patients and recorded their clinical features, lesion position, and efficacy of the treatment.

Results: Among the 8 cases, where mean age is 67.6 years (range from 54-78), 3 of them are male and 5 are female. All the patients received central venous catheterization for more than 2 times, with median time of having a catheter for 36 months. The vascular ultrasound and CTA reveals that all of them suffered thrombosis or occlusion of right internal jugular vein and subclavian vein. By puncturing right innominate vein, all the patients' vascular accesses have been successfully established, with the end of cuff catheter located in the right atrium, superior vena cava(SVC) or SVC/ right atrial junction. No obvious discomfort has been reported, nor did complications such as hematoma and pneumothorax recorded. The mean follow-up period lasts for 12 months, all vascular access of these cases are patency.

Conclusions: For HD patients with limited vascular resources such as thrombosis or occlusion of right internal jugular vein and subclavian vein, the application of tunneled cuffed venous catheter through innominate vein has been proved to be safe and effective. It could preserve vascular access by bypassing the stenotic lesion internal jugular vein or subclavian vein, and reduce the incidence of vascular access exhaustion.

Funding: Government Support - Non-U.S.

FR-PO722

Tunneled Hemodialysis Catheter and Hemodialysis Outcomes

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Background: Studies have reported that tunneled dialysis catheter (TDC) is associated with inferior hemodialysis (HD) patient (pt) survival, as compared to arteriovenous fistula (AVF). Since many cofactors may also affect survival of HD pts, it is unclear whether the risk for the worse survival arises from TDC *per se*, or from associated conditions. Therefore, the aim of this study was to determine the long-term outcome of HD patients, with respect to vascular access (VA).

Methods: This retrospective case-control study included all 156 pts with TDC placed from 2010 to 2012 at Clinical Hospital Merkur. Control group consisted of 97 pts dialyzed through AVF. The groups were matched according to dialysis unit and time of VA placement. The site of choice for the placement of TDC was right jugular vein. Kaplan-Meier analysis with log-rank test was used to assess pt survival. A multivariate Cox regression analysis was used to determine independent variables associated with the pt survival.

Results: Cumulative one-year survival of pts who were dialyzed exclusively through TDC was 86.4 % and of those who were dialyzed exclusively through AVF the survival was 97.1 % (p=0.002). In a multivariate Cox regression analysis, male sex and older age were independently negatively associated with the survival of HD pts, while shorter duration of HD before the creation of the observed VA, hypertensive renal disease and glomerulonephritis were positively associated with survival. TDC turned to be an independent negative risk factor for survival of HD pts (HR 23.037, 95% CI 6.221-85.308).

	TDC	AVF	p
Patient age at the initiation of HD (yrs)*	62.08±14.39	63.85±13.23	0.215
Patient age at current VA creation (yrs)*	63.69±14.20	64.01±13.39	0.737
Sex (m/f)	88/68	64/33	0.081
HD vintage (days)**	658 (374, 1114)	536 (320, 1139)	0.836
Diabetes mellitus	44.2%	40.2%	0.464
Coronary artery disease	20.5%	20.6%	0.851
Cerebrovascular disease	16.7%	4.1%	0.001
Peripheral vascular disease	19.9%	20.6%	0.902
*mean ± SD; ** median with IQR			

Conclusions: TDC is an independent negative risk factor for the survival of patients on HD.

Funding: Government Support - Non-U.S.

FR-PO723

Carpal Tunnel Syndrome Is Associated with Arteriovenous Fistula in Hemodialysis Patients Il Young Kim,¹ Min Jung Kim,¹ Joo Hui Kim,¹ Dong Won Lee,¹ Soo Bong Lee,¹ Su Min Park,² Jong Man Park,² Woo Jin Jung,² Sang Heon Song,² Eun Young Seong,² Harin Rhee,² Ihm Soo Kwak.² ¹Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea; ²Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea.

Background: Carpal tunnel syndrome (CTS) is associated with various systemic diseases such as rheumatoid arthritis, hypothyroidism, peripheral neuropathy and diabetes mellitus (DM). In hemodialysis patients, several factors can contribute to CTS, including amyloid deposition, generalized fluid retention, increased synovial volume, edema around the nerve, and an ischemic or 'steal' effect distal to a dialysis access. This study aimed to evaluate the influence of arteriovenous fistula (AVF) dysfunction on the development of CTS.

Methods: The study included 43 patients (23 male & 20 female) on maintenance hemodialysis via AVF and 97 healthy controls. The median nerves of study population were examined by ultrasonography. Cross-sectional area (CSA) of the median nerve was measured at the distal wrist (CSA-D), and proximal forearm (CSA-P), and wrist-to-forearm ratio (WFR; CSA-P/CSA-D) was calculated for each hand. We also investigated the history of percutaneous transluminal angioplasty (PTA) in them.

Results: The mean age of hemodialysis patients was 60.4 ± 16.0 years. The mean duration on hemodialysis was 48.3 ± 39.6 months. The WFRs in hemodialysis patients were higher than those in healthy controls (1.37 ± 0.45 vs. 1.21 ± 0.25, P < 0.05). The hands with AVF (n = 43) showed higher WFR than those without AVF (n = 43) in hemodialysis patients (1.35 ± 0.47 vs. 1.25 ± 0.26, P < 0.05). The WFRs in patients with a history of PTA were higher than those in patients without a history of PTA (1.46 ± 0.56 vs. 1.23 ± 0.32, P < 0.05).

Conclusions: In maintenance hemodialysis patients, WFR of median nerve was significantly increased in the hand with AVF. Moreover, development of CTS was related not only to AVF itself, but also to AVF function.

FR-PO724

Factors Affecting Patency of Haemodialysis Arterio-Venous Fistulae and Grafts Ayesha Irtiza-Ali, Salman Ahmed, Nicola Ding, Joseph Russell, Nihil Chitalia, Maggi Steele, Hannah R. Wilson, David Makanjuola. *Renal Unit, St. Helier Hospital, Carshalton, United Kingdom.*

Background: Arterio-venous fistulae (AVF) are the preferred access for haemodialysis (HD), and where these cannot be created, arterio-venous grafts (AVGs) are the next best option. AVFs/AVGs however, not uncommonly fail to mature. The causes of this are varied, but loss of patency due to thrombosis and/or significant stenoses are major causes. We investigated the factors affecting patency of AVFs/AVGs in order to identify whether there were any characteristics which were predictive of this.

Methods: All AVFs/AVGs created in our unit between 2006 and 2014 were reviewed. Reasons for loss of primary patency were obtained from the dialysis access database. Characteristics reviewed were age, gender, co-morbidity score, diabetes status and site of AVF. Patients were grouped as follows: patency <30 days, patency <90 days, patency >90 days and patency >365 days.

Results: There were 1897 () AVFs and 251 () AVGs created. 649 (34.2%) of AVFs were lower arm, all the AVGs were upper arm, or lower limb. 1346 (62%) were male. The main reasons for AVF loss were clotted/stenosed vessels in 76% of cases. There was no association between ethnicity or gender with regard to patency rates. Other variables are shown in table 1.

Variable	<30 days	<90 days	>90 days	>365 days
AVF % patent	88%	70%	70%	39%
Age (mean)	72 years	72 years	70 years	71 years
AVG % patent	88%	75%	62%	35%
Age (mean)	70.5 years	70.5 years	66.8 years	67.1 years
Diabetic	31%	36%	35%	34%
Davies Co-morbidity score				
0 (no co-morbidities)	17.3%	13.1%	14.4%	14.3%
1 (1-2 co-morbidities)	60.3%	62.3%	60.9%	64.2%
2 (3 or more co-morbidities)	11%	13.1%	13.8%	13.0%

Conclusions: We did not find any definite predictive factors for loss of primary patency in the variables we studied. In particular, co-morbidity score, age and diabetes showed no association with poorer outcomes. There is quite a significant 'drop off' in primary patency

at 12 months. In the majority of cases, this was due to thrombosis of the HD access. This highlights the importance of close surveillance, as measures to maintain patency (surgical or radiological) are more likely to be required in this period.

FR-PO725

Drug-Eluting Stents versus Bare-Metal Stents During Percutaneous Coronary Intervention in Patients on Dialysis Tara J. Chang,¹ Maria E. Montez-Rath,¹ Mark A. Hlatky,¹ Wolfgang C. Winkelmayer.² ¹Stanford; ²Baylor College of Medicine.

Background: In patients undergoing percutaneous coronary intervention (PCI), drug-eluting stents (DES) reduce the need for repeat revascularization (RR) compared with bare-metal stents (BMS). The effects on death and MI are more controversial, with mixed results from observational studies and generally null results from clinical trials. However, few previous studies have focused patients with end-stage renal disease (ESRD). We compared the effectiveness of DES with BMS in a representative cohort of US patients on dialysis.

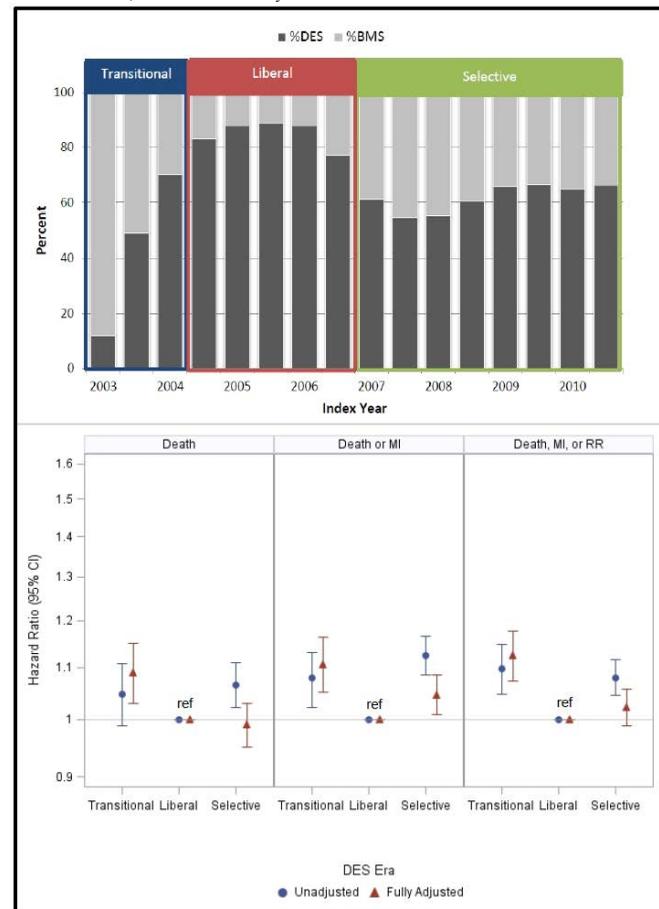
Methods: Using the US Renal Data System, we identified 36,117 patients on dialysis with Medicare Parts A+B who had PCI with stenting after DES became available in the US (4/23/03 – 12/31/10). We used propensity-score matching (PSM) and inverse probability of treatment weighting (IPTW) with Cox regression to examine the association of DES versus BMS on the following 1-year outcomes: death, death or MI, and death, MI or RR. Due to concerns about residual indication bias, we conducted a second, temporal analysis that leveraged the large changes in the prevalence of DES use during three distinct eras: Transitional (4/23/03 -6/30/04); Liberal (7/1/04 – 12/31/06); and Selective (1/1/07 – 12/31/10).

Results: In the PSM and IPTW analyses, DES was associated with lower risks of all three outcomes compared with BMS.

Table: Hazard ratios (95% CI) for DES vs BMS

	Death	Death/MI	Death/MI/RR
PSM	0.82 (0.78-0.86)	0.84 (0.91-0.87)	0.87 (0.84-0.91)
IPTW	0.82 (0.79-0.85)	0.85 (0.82-0.87)	0.88 (0.85-0.90)

DES use varied by era: Transitional=56%, Liberal=85%, and Selective=62%. In the temporal analysis, outcomes in the Liberal DES era were significantly better than in the Transitional Era, but not consistently better than in the Selective Era.



Conclusions: Adoption of DES for PCI was associated with improved outcomes in US patients with ESRD on dialysis.

Funding: NIDDK Support

FR-PO726

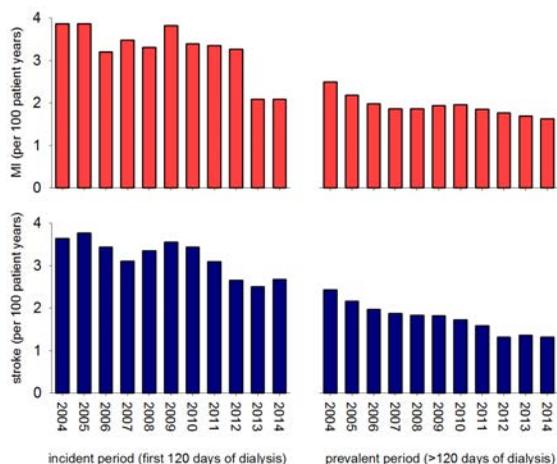
Eleven Year Trends in Myocardial Infarction and Stroke in the Incident and Prevalent Dialysis Population Kevin Chan,¹ Len A. Usvyat,¹ Ann Mooney,¹ Dugan Maddux,¹ Karen G. Butler,¹ Sophia Zhao,² Franklin W. Maddux.¹ ¹Medical Office, Fresenius Medical Care North America, Waltham, MA; ²Div of Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Myocardial infarction (MI) and cerebrovascular (CVA) events are highly prevalent in the chronic dialysis population. We aimed to quantify the annual incidence and trends of MI and CVA events from 2004 to 2014 in a large dialysis population.

Methods: We analyzed >600,000 patients receiving chronic dialysis from a large dialysis provider from January 2004 to December 2014. For each calendar year, we calculated the incidence of MI and CVA (event per 100 patient years) identified by ICD9 code for the population in the first 120 days of chronic dialysis (incident period) and in the subsequent period after the first 120 days (prevalent period). Linear regression was used to quantify statistically significant trends in MI and CVA rate of the eleven year period.

Results: Over an eleven year period in the incident population, the mean incidence of MI and CVA was 3.3 and 3.2 events per 100 patient years respectively. Among the prevalent population, the mean incidence of MI and CVA was 1.9 and 1.8 events per 100 patient years respectively. Using linear regression models, the incidence of MI and CVA was found to decrease by 0.14 (p=0.005) and 0.11 (p=0.0009) per year among incident patients. Similarly, the incidence of MI and CVA was found to decrease by 0.06 (p=0.0007) and 0.10 (p<0.0001) per year among prevalent patients. See Figure 1.

Annual incidence of myocardial infarction and stroke among incident and prevalent dialysis populations



Conclusions: Both MI and CVA rates are decreasing among incident and prevalent dialysis populations over the past eleven years.

FR-PO727

Relationship of Ticagrelor Dose and Platelet Reactivity in Patients with End Stage Renal Disease on Hemodialysis Jin sug Kim, Tae won Lee, Chun-Gyoo lhm, Sang ho Lee, Se yun Kim, Shin yeong Lee, Yu ho Lee, Kyung-hwan Jeong. *Internal Medicine, KyungHee Univ School of Medicine, Seoul, Korea.*

Background: In our previous study, ticagrelor has superiority on platelet inhibition than clopidogrel in patients with end stage renal disease(ESRD) on hemodialysis(HD). One study compared two doses of ticagrelor(90 or 60mg) and placebo, reported that ticagrelor significantly reduced the risk of cardiovascular death, MI, or stroke and increased the risk of bleeding. The rate of bleeding is more frequent in 90mg group. We hypothesized there was some relationship between ticagrelor dose and platelet inhibition. We investigated efficacy and safety of standard and low dose ticagrelor, and clopidogrel in ESRD patients on HD.

Methods: In a single-center, prospective, randomized study, 50 ESRD patients were randomly assigned to receive clopidogrel(75mg once daily), standard dose ticagrelor(90mg twice daily) or low dose ticagrelor(90mg once daily) for 14days. Platelet function assessment which included transmittance aggregometry, and VerifyNow TM P2Y12 assay were then used to serially measure. Maximal platelet aggregation (MPA), inhibition of platelet aggregation (IPA), and P2Y12 reaction units (PRUs) were evaluated.

Results: Baseline characteristics, and concomitant medication of three groups were not significantly different. The standard dose ticagrelor showed significant lower MPA and higher IPA as compared with clopidogrel at 1,5, and 48 hours, and 14days after (p<0.05). Low dose ticagrelor showed significant lower MPA and Higher IPA at 5hours after(p<0.001). Although there was no statistical significance, after 1,48hours and 14days revealed lower MPA and higher IPA, as compared with clopidogrel. There was no significant difference between two ticagrelor doses. Two doses of ticagrelor showed significant lower PRUs, as compared with clopidogrel(p<0.001). 2 patients of standard dose ticagrelor and 1 patient of clopidogrel discontinued study because of bleeding. There was no bleeding in low dose ticagrelor.

Conclusions: Low dose ticagrelor may result in greater platelet inhibition than clopidogrel in ESRD patients on HD. Further studies with large number and various doses of medicine are needed.

FR-PO728

Prognostic Accuracy of Serial versus Single Troponin Measurements in Hemodialysis Patients Thomas A. Mavrakanas,^{1,2} Allan Sniderman,³ Ahsan Alam.¹ ¹Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada; ²Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, GE, Switzerland; ³Div of Cardiology, McGill Univ Health Center, Montreal, QC, Canada.

Background: Cardiac troponin I (TnI) elevation in stable patients receiving chronic hemodialysis (HD) is associated with increased mortality. The frequency of measuring TnI to determine risk is not yet known. This study aimed to assess whether using serial TnI measurements improves the predictive accuracy for mortality compared with a single measurement.

Methods: Pre-dialysis TnI levels were measured in 130 stable HD patients monthly for 3 consecutive months. A value above the laboratory reference range (>0.06 mg/L) was considered to be elevated. To assess the prognostic accuracy of TnI measurement, three different approaches were used to determine high risk: i) only the first month's value was elevated; ii) at least one of three monthly TnI values were elevated; iii) at least two of the three monthly TnI values were elevated. All the patients were followed-up for 12 months. Multivariate Cox proportional hazard analysis was used to examine the association of TnI elevation with the outcomes of mortality or a composite of mortality with major cardiovascular events. The performance of each TnI classification method was compared using net reclassification index (NRI).

Results: Of 130 patients, 36 had an elevated TnI in the first month, 44 had at least one elevated TnI value, and 26 had 2-3 elevated TnI values. The composite outcome was significantly higher in patients with an elevated TnI compared with patients who had normal TnI levels, regardless of the method used [HR i) 3.66 (1.76-7.63) ii) 3.55 (95%CI 1.68-7.52) iii) 3.81 (95%CI 1.83-7.94)]. Similar associations were seen with the outcome of mortality alone. Patients classified as high risk using at least one elevated serial TnI measure, were associated with a NRI of 0.035, as compared with a single TnI measurement. If patients were classified as high risk using at least two elevated TnI values, the NRI was -0.072.

Conclusions: Serial TnI measurements are associated with only marginal improvement in predicting mortality or MACEs as compared with a single TnI measurement.

Funding: Government Support - Non-U.S.

FR-PO729

High Ultrafiltration Rates Are Associated with Increased Troponin Levels in Stable Hemodialysis Patients Thomas A. Mavrakanas,^{1,2} Allan Sniderman,³ Murray L. Vasilevsky,¹ Ahsan Alam.¹ ¹Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada; ²Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, GE, Switzerland; ³Div of Cardiology, McGill Univ Health Center, Montreal, QC, Canada.

Background: An elevated troponin level in asymptomatic patients on hemodialysis is associated with a higher risk of mortality and cardiovascular events. The underlying mechanism for this association has not been elucidated. The objective of this study was to assess whether intra- and inter-dialytic parameters are associated with higher troponin I (TnI) levels.

Methods: Stable chronic hemodialysis patients at 2 tertiary care centers were enrolled in this study. Pre-dialysis TnI levels were measured with monthly bloods for three consecutive months. TnI was measured by immunoassay and was considered to be elevated if it exceeded the laboratory reference range (0.06 mg/L). We examined the association of the dialysis vintage, session duration, intradialytic hypotension (IDH), high ultrafiltration rate (UFR), defined as a UFR ≥ 12.4 ml/kg.h, and interdialytic weight gain (IDWG) using a mixed linear fixed effects model for repeated measures.

Results: 236 patients were enrolled in the study: mean age 67.5 years old, 56% male, 47% had diabetes and 28% had pre-existing coronary artery disease. There were 88 elevated TnI values (13% of all measured) in 52 patients. In univariate analysis, high UFR and dialysis vintage, but not IDH or IDWG, were associated with TnI variability. In multivariate analysis, both high UFR (p=0.02) and dialysis vintage (p=0.01) explained TnI variability. The intraclass correlation coefficient was found to be 1%, suggesting that the observed variability is within and not between subjects, with session related parameters being more important than inter-individual differences.

Conclusions: In this observational study we identify potentially modifiable factors associated with TnI elevation. Strategies to prevent hemodialysis-induced myocardial injury may include efforts to avoid excessive ultrafiltration, minimize IDWG, or offer more frequent dialysis, but these need to be validated by interventional studies.

Funding: Government Support - Non-U.S.

FR-PO730

Prognostic Value of High-Sensitivity Troponin T in Stable Dialysis Patients Titi Chen, Angela Makris. *Dept of Nephrology, Liverpool Hospital, Liverpool, New South Wales, Australia.*

Background: We evaluated the prognostic value of high-sensitivity cardiac troponin T (hs-TNT) in predicting myocardial infarction (MI) and death in dialysis patients after 4 years.

Methods: A retrospective review of a cohort of 354 hemo- (HD, 254) and peritoneal-dialysis (PD, 109) patients was followed up to 4 years after baseline hs-TnT. All-cause mortality, cardiac mortality and new MI were assessed.

Results: The median hs-cTnT was 60 ng/L (interquartile range IQR 38-105 ng/L) with no observed difference between HD and PD patients (P=0.18). Patients dying (n=148) had higher baseline hs-TnT (median 90 vs 50 ng/L, P<0.001). Similar trends were observed for both HD and PD subgroups. Patients with cardiac mortality (n=25) had higher baseline hs-TnT compared with non-cardiac mortality (121 vs 75.5 ng/L, P=0.013). These trends were only observed in the HD subgroup. Patients with a new MI (n=65) had no difference in their baseline hs-cTnT (66 vs 59 ng/L, P=0.064) compared to controls. The group was divided into quartiles based on hs-cTnT. Incremental increase in mortality (P<0.001), cardiac mortality (P<0.001) and MI (P=0.033) were observed with increasing hs-cTnT quartiles. Similar trends were observed for both HD and PD subgroups except MI in the HD subgroup. For every increase of 25 ng/L in hs-cTnT, the unadjusted hazard ratio (HR) was 1.094 for cardiac mortality (P=0.043, 95%CI 1.003-1.192), 1.123 for MI (P=0.000, 95%CI 1.053-1.198). The adjusted HR for MI was 1.107 (P=0.018, 95%CI 1.018-1.205). Kaplan-Meier curves demonstrated increasing hs-cTnT quartiles was associated with an increase in the incidence of cardiac mortality (P=0.014) and MI (P=0.013) but not overall mortality. 178 patients had hs-cTnT repeated at 4 years. There was a significant increase in hs-cTnT from a baseline of 60 ng/L (IQR, 38-105 ng/L) to a 4-year concentration of 64 ng/L (IQR, 42-104 ng/L) (P=0.000). This was true for both patients with (P= 0.008) or without (P<0.001) new MI. Similar trends were observed for both HD and PD subgroup analysis.

Conclusions: Hs-cTnT has a useful role in predicting all-cause mortality, cardiac mortality and MI in stable dialysis population. There was an increase in hs-cTnT level over a 4-year period.

FR-PO731

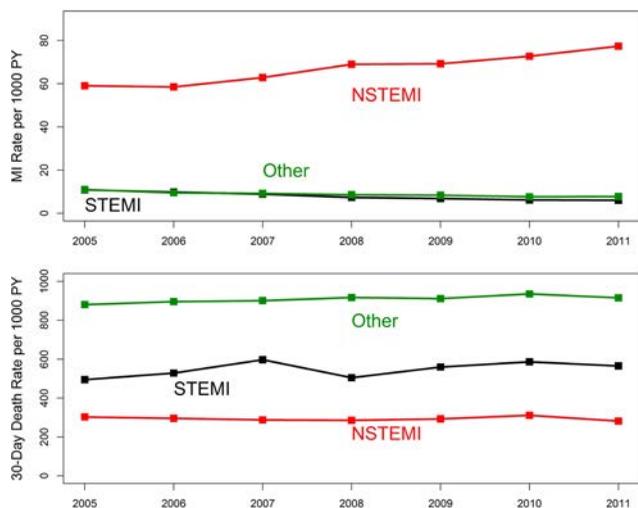
Temporal Trends in Myocardial Infarction Incidence and 30-Day Mortality in U.S. Dialysis Patients Charles A. Herzog,¹ Keri L. Monda,² Anne C. Beaubrun,² Wolfgang C. Winkelmayr,³ Til Stürmer,⁴ Allan J. Collins,¹ Akhtar Ashfaq,² Kenneth J. Rothman,⁵ David T. Gilbertson.¹ ¹Chronic Disease Research Group, MMRF; ²Ctr for Observational Rsrch, Amgen; ³Baylor College of Medicine; ⁴UNC Gillings School of Global Public Health; ⁵RTI Health Solutions.

Background: Acute myocardial infarction (MI) is a catastrophic event in dialysis pts. Few data exist on current MI hospitalization rates. We assessed trends in type of MI (ST-elevation MI [STEMI], non-ST-elevation MI [NSTEMI], and unclassifiable MI [other]), and death rates by type of MI in 2005-2011.

Methods: Using Medicare claims data, we created yearly cohorts of dialysis pts point prevalent on January 1 of each year 2005-2011. We assessed STEMI, NSTEMI, and other MI hospitalization rates, and calculated annualized 30-day death rates following MI.

Results: In 2005 there were 10,275 NSTEMI, 1,892 STEMI, and 1,918 other MI vs 2011 16,235 NSTEMI, 1,269 STEMI, and 1,634 other MI. Demographics: mean age 67; 5% < 45, and 6% > 84 yrs; 47% female; 48% white, 32% black; 55% ESRD from DM. While overall MI rate increased slightly from 2005-2011 (80.1 /1,000 PY in 2005 vs 91.2 in 2011), STEMI and other MI decreased by 44% and 29% respectively, while NSTEMI increased by 31%. Short term mortality was relatively unchanged for NSTEMI (295 deaths/1000 PY), increased slightly for STEMI (495/1000 PY in 2005 to 565/1000 PY in 2011), and was highest following other MI (881/1000 PY in 2005 and 915/1000 PY in 2011).

Conclusions: In the recent treatment era there has been little change in either rates of overall MI hospitalization or 30-day mortality. The increase in NSTEMI rates may be due to greater utilization of more sensitive cardiac biomarkers (cardiac troponins) for MI diagnosis. MI remains a catastrophic event for dialysis pts. Aggressive interventions to reduce the burden of ischemic heart disease and to improve its prognosis in dialysis pts are warranted.



Funding: Pharmaceutical Company Support - Amgen, Private Foundation Support

FR-PO732

Risk of Acute Coronary Events and Coronary Interventions for Overweight and Obese Patients versus Normal Weight Patients Undergoing Dialysis – A National Study Austin G. Stack,^{1,2,3} Mohamed Elsayed,^{1,2} Muhammad Umair Sharif,^{1,2} John P. Ferguson.² ¹Nephrology, Univ Hospital Limerick, Ireland; ²Graduate Entry Medical School, Univ of Limerick, Ireland; ³Health Research Inst, Univ of Limerick, Ireland.

Background: Although elevated body mass index (BMI) is associated with increased risk of cardiovascular events in the general population, it is suggested that the converse may hold true for patients on dialysis.

Methods: We tested this hypothesis in a national cohort of 1,072,737 incident Medicare-eligible US patients, who began dialysis between 5/1995 and 12/2008. Hospitalizations attributed to first myocardial infarction (MI) [ICD 9 codes; 410] and major coronary interventions (coronary angioplasty, stent, and coronary bypass surgery) following first MI were obtained from the US Renal Data System. Multivariable Cox regression compared hazard ratios [HR] of MI and subsequent coronary interventions among BMI categories.

Results: The adjusted HR of MI was highest for underweight patients and lowest for morbidly obese patients, decreasing significantly with increasing BMI category. Overweight patients were significantly more likely to receive a coronary intervention post-MI compared to normal weight individuals but this benefit did not extend to morbidly obese or underweight patients.

		HR of MI	HR of Intervention Post STEMI	HR of Intervention post Non-STEMI
BMI Category (Kg/m ²)	N (%)			
Underweight (< 18.5)	58, 659 (5.7)	1.04 (1.00-1.08)	0.79 (0.56-1.12)	1.00 (0.82-1.24)
Normal (18.5-25)	380, 587 (37.0)	1.00	1.00	1.00
Overweight (25-30)	290, 542 (28.3)	0.96 (0.94-0.98)	1.31 (1.11-1.54)	1.17 (1.06-1.29)
Class 1 Obesity (30-35)	159, 895 (15.6)	0.90 (0.87-0.92)	1.24 (1.01-1.52)	1.01 (0.89-1.15)
Class 2 Obesity (35-40)	75, 823 (7.4)	0.85 (0.82-0.88)	1.20 (0.91-1.59)	1.05 (0.89-1.26)
Class 3 Obesity (> 40)	63, 027 (6.1)	0.84 (0.81-0.88)	1.04 (0.74-1.45)	0.89 (0.72-1.10)

Conclusions: In contrast to the general population, higher BMI is associated with lower risk of major coronary events in US dialysis patients suggesting a protective effect. Furthermore, access to coronary interventions following a major coronary event is not equal across BMI categories.

Funding: Government Support - Non-U.S.

FR-PO733

Propensity-Based Comparison of Haemodialysis and Peritoneal Dialysis with Risk of Haemorrhagic and Ischaemic Stroke Among New Dialysis Patients Austin G. Stack,^{1,2,3} Mohamed Elsayed,^{1,2} Muhammad Umair Sharif,^{1,2} John P. Ferguson.² ¹Nephrology, Univ Hospital Limerick, Ireland; ²Graduate Entry Medical School, Univ of Limerick, Ireland; ³Health Research Inst, Univ of Limerick, Ireland.

Background: The risk of stroke is between 6-10 fold higher in dialysis patients compared to the general population. It is hypothesised that the choice of dialysis modality at initiation may influence the risk of stroke.

Methods: We tested this hypothesis in a national cohort of 1,097,747 US patients (n=86,168 on PD) who were Medicare eligible and began dialysis between 5/1995 to 12/2010 and followed until 9/2011. Hospitalizations attributed to first Haemorrhagic Stroke (H-CVA) and Ischaemic stroke (I-CVA) were obtained from the US Renal Data System files and merged with data from the medical evidence, treatment history and mortality files. Multivariable Cox regression compared the hazards ratio [HR] of H-CVA and I-CVA for PD versus HD with a propensity-matched intent-to-treat (ITT) approach and as-treated analysis. Patients were censored at transplantation, death, recovery of kidney function, or end of study (Sept 1 2011). Approval was received from University Hospitals Ethics Committee.

Results: The adjusted PD/HD HRs for first hospitalized H-CVA using the intent-to-treat model was 0.89 (0.83,0.95) and this decreased from 0.73 (0.61,0.87) in the period 1995-1998 to 0.64 (0.51,0.80) in the period 2007-2010. In contrast, overall HRs for I-CVA were 1.15 (1.12-1.18) and this decreased from 1.20 (1.13-1.27) in the period 1995-1998 to 1.06 (0.97-1.15) in the period 2007-2010. The as-treated model suggested more favourable outcomes for H-CVA with overall HR of 0.61 (0.57,0.67) and for I-CVA with a HR 0.96 (0.93-0.99) in 2007-2010 period. Patients who switched from PD to HD or HD to PD had significantly higher HR of H-CVA, while patients who switched from PD to HD had higher HR of I-CVA.

Conclusions: PD and HD contribute differentially to the overall risk of I-CVA and H-CVA among new dialysis patients. While PD is similar to HD with regard to hazards of I-CVA, it appears to protect against the hazard of H-CVA. These associations should be taken into consideration when choosing treatment options for new dialysis patients.

Funding: Other NIH Support - Health Research Board & Irish Heart Foundation

FR-PO734

Predictors of Sudden Cardiac Death in Hemodialysis Patients with and without Previous Arrhythmia – Results from a Multinational Cohort Viviane Calice-Silva,¹ Stephan Thijssen,² Xiaoling Ye,² Aileen Grassmann,³ Daniele Marcelli,³ Bernard J. Canaud,³ Peter Kotanko,² Roberto Pecoits-Filho.¹ ¹Pontificia Univ Católica do Paraná, Brazil; ²Renal Research Inst; ³Fresenius Medical Care, Germany.

Background: Cardiac dysfunction, rapid electrolyte shifts and high ultrafiltration rates during hemodialysis (HD) are associated with increased vulnerability to arrhythmogenic events. Patients with previous arrhythmia (ARR) are at a higher risk of sudden cardiac death (SCD – Herzog et al, 2011). Our aim was to analyze predictors of SCD in HD patients with and without previous ARR.

Methods: Incident HD patients from the Monitoring Dialysis Outcomes (MONDO) cohort who received in-center treatment between 1/2006-12/2011 and survived at least 90 days on HD were included and followed until 12/2012. Causes of death were classified as SCD according ICD-10/ICD-9. Patients with comorbidity or prior hospitalization due to ARR and/or ARR predisposition were identified. Cox proportional hazards models were constructed to explore associations between baseline parameters and SCD.

Results: We studied 19,129 patients (16 countries). 7,538 patients with complete data were included in the models, 613 died of SCD. Mean age 62.7(±15.5)years, 58.1% male, 48.4% diabetics. Age, ischemic heart disease, albumin, serum sodium, interdialytic weight gain in % of post-HD weight and pre-HD-systolic blood pressure were identified as predictors of death in both subgroups. Distinct predictors are shown below.

Table 1: Predictors of SCD in patients with (N=158) and without ARR history and/or predisposition (N=455).

Parameter	SCD with ARR	
	Hazard Ratio(±SE)	P-value
Serum bicarbonate [mmol/L]	0.07(0.04)	0.04
Leukocytes [1000/mm ³]	0.023(0.005)	<.0001
SCD without ARR		
Hemoglobin [g/dL]	-0.11(0.04)	0.005
Dialysate sodium [mmol/L]	0.093(0.03)	0.0008
Catheter as vascular access	0.41(0.1)	<.0001

Conclusions: Despite the small sample size, some predictors of SCD seem to differ depending on the presence or absence of arrhythmia history or predisposition. These findings may assist the identification of patients at high risk for SCD. Further studies have to be done to corroborate these results.

FR-PO735

The Risks of Acute Health Events After Incident Atrial Fibrillation in Older Hemodialysis Patients Medha Airy,¹ Benjamin A. Goldstein,² Mark A. Hlatky,³ Nisha Bansal,⁴ Alan S. Go,⁵ Wolfgang C. Winkelmayr.¹ ¹Baylor College of Medicine, Houston, TX; ²Duke Univ, Durham, NC; ³Stanford Univ, Palo Alto, CA; ⁴Univ of Washington, Seattle, WA; ⁵Kaiser Permanente Northern California, Oakland, CA.

Background: Limited data exist about whether incident atrial fibrillation/flutter (AF) impacts the risks of major acute health events in patients with ESRD undergoing hemodialysis (HD).

Methods: From the US Renal Data System, we studied older (≥67 years) adults with ≥2 years of uninterrupted Medicare A&B coverage before starting HD (2006-11) and no known AF prior to ESRD. Incident AF was ascertained from ICD-9 diagnosis codes (427.3x) in inpatient claims. We used extended Cox regression adjusted for sociodemographic characteristics and key comorbidities to estimate hazard ratios (HR [95% confidence intervals]) for death, ischemic stroke, myocardial infarction (MI), and hip fracture (as a negative control outcome). AF was treated as a time-varying covariate, with time since first AF diagnosis further categorized as ≤30, 31-90, and >90 days. Patients were censored at time of kidney transplant or end of data (12/31/2011).

Results: We identified 85,377 eligible HD patients; 16.7% developed incident AF and 58.2% died during follow-up. Incident AF was associated with higher adjusted mortality: 8-fold higher during the first 30 days (HR=8.2 [7.9-8.6]), 4-fold higher between 31-90 days (HR=4.2 [4.0-4.4]), and 2-fold higher beyond 90 days after AF diagnosis (HR=2.2 [2.1-2.2]). Incident AF also increased the adjusted rate of ischemic stroke 1.5-2.5-fold: during the first 30 days (HR=2.1 [1.6-2.7]), 31-90 days (HR=2.5 [2.0-3.0]), and beyond 90 days (HR=1.5 [1.3-1.7]). Quantitatively similar findings were obtained for MI. However, the adjusted rate of hip fracture was only marginally increased following AF diagnosis (≤30 days: 1.1 [0.7-1.6]; 31-90 days: 1.4 [1.0-1.8]; >90 days: 1.2 [1.1-1.4]). All associations were attenuated when requiring incident AF to be indicated as principal discharge diagnosis.

Conclusions: While AF was independently associated with higher risks of ischemic stroke, MI, and hip fracture in older ESRD patients on HD, it was more strongly associated with excess all-cause mortality.

Funding: NIDDK Support

FR-PO736

The CRASH-ILR Study: Half a Million Hours of Continuous ECG Monitoring in a Hemodialysis Population Robert Lewis,¹ Darren Green,² Philip A. Kalra,² Donah Zachariah,³ Paul Kalra,¹ Paul R. Roberts.⁴ ¹Portsmouth Hospitals NHS Trust, Portsmouth, United Kingdom; ²Salford Royal NHS Trust, Salford, United Kingdom; ³Royal Bournemouth Hospital, Bournemouth, United Kingdom; ⁴Southampton Univ Hospitals Trust, Southampton, United Kingdom.

Background: Sudden cardiac death (SCD) may cause 25% of all hemodialysis (HD) patient deaths. Multiple potential mechanisms may contribute to the risk of life-threatening arrhythmias in this population. The CardioRenal Arrhythmia Study in Hemodialysis has continuously monitored patients using an Implantable Loop Recorder (ILR) for more than 500,000 hours.

Methods: 30 patients (60% male) aged 67±12 years on established HD for 39 ±44 months with varied etiology of CKD (diabetes 37%, hypertension 23%) and ejection fraction of 56±8% were implanted with a Reveal XT ILR (Medtronic, MN, USA). Patients transmitted data at each HD session and were asked to activate their ILR if symptomatic with palpitations, dizziness or syncope.

Results: Patients were monitored for an average of 17,810±8,108 hours performing 94±92 transmissions. 6 patients (20%) died during the study. The final arrhythmia was VF in 2 patients and agonal bradycardia in 3. One patient died from SCD 2 weeks after device explantation due to infection. All 3 bradycardic deaths occurred in patients during end-of-life care. 1 VF death occurred during a GI bleed: the other was unheralded. A surviving patient received a biventricular pacemaker for 2:1 block detected by ILR. Atrial arrhythmias (AA) were noted in 7 (23%), 4(13%) of which were incident. 1 patient had asymptomatic sustained VT managed with antiarrhythmic drugs. Frequent ectopy was recorded in 2 patients. There were 19 symptomatic activations in 6 patients all corresponding to sinus rhythm (or AA in cases of permanent AF). 6 patients had device explantation, 4 after renal transplantation and 2 due to device infection.

Conclusions: CRASH-ILR is the longest ILR follow up in HD patients to date and provides new insights into arrhythmia and SCD. Arrhythmias occurred in 15 (50%) of the study population. Mortality was high, but this was due to SCD as an expected end-of-life event in 5 of 6 patients.

Funding: Pharmaceutical Company Support - Medtronic, MN, USA

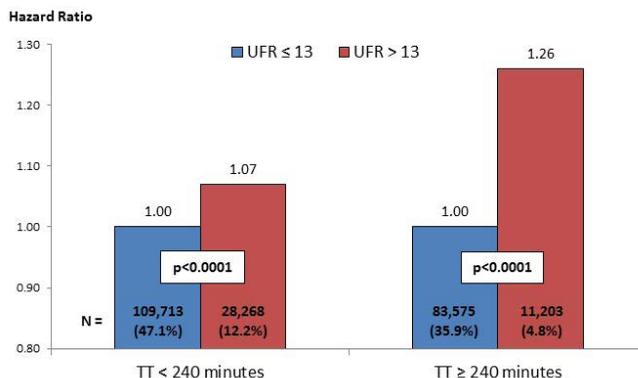
FR-PO737

Revisiting Ultrafiltration Rate (UFR), Treatment Time (TT) and Mortality in Thrice Weekly Hemodialysis Jennifer L. Bragg-Gresham, Brett W. Plattner, Debabrata Ray, Yi Li, Rajiv Saran. *KECC, Univ of Michigan, Ann Arbor, MI.*

Background: UFR and TT are two potentially modifiable practices for improving outcomes in HD. UFR > 13ml/kg/hour has been associated with higher mortality. We re-examined this association, focusing on the effect of higher UFR at TT ≥ 4 hours, as longer TT has been claimed to be ‘protective’, even though TT > 4 hours is logistically difficult to implement in the prevailing US practice setting.

Methods: Using recently available national data from CROWNWeb (CW), we analyzed 232,759 adults on thrice-weekly, in-center HD. Baseline CW data was extracted from June 2012. Patients were followed through December 31, 2013. Cox regression was used to examine the association between UFR (calculated as the intradialytic weight loss / TT and expressed in ml/kg post HD-weight/hr) and mortality, adjusting for demographics, comorbidities, dialysis vintage, interdialytic weight gain (IDWG) and dialysis dose (Kt/V), stratified by TT. Average follow-up was approx 1 year.

Results: Individuals receiving TT ≥ 240 were younger, more likely to be black and male, and had larger BMI. In both strata of TT (< 240 and ≥240) those patients with UFR >13 tended to be younger, non-black race, have a lower BMI, longer HD vintage, higher Kt/V, and higher IDWG than patients with UFR < 13. Congestive heart failure was more prevalent in patients with UFR ≤ 13 regardless of TT. In both strata of TT, patients with a UFR >13 had higher hazard of mortality, with a larger risk found in those with TT ≥ 240.



Conclusions: A higher UFR (>13) was associated with higher mortality irrespective of TT category. The association was surprisingly stronger among those receiving longer TT. In the US, longer TT is prescribed in order to achieve small solute targets (confounding-by-indication) and not necessarily to lower the UFR, as high UFR is a consequence of high IDWG and the average shorter TT.

Funding: NIDDK Support

FR-PO738

Sudden Death and Dialysate Potassium in Hemodialysis: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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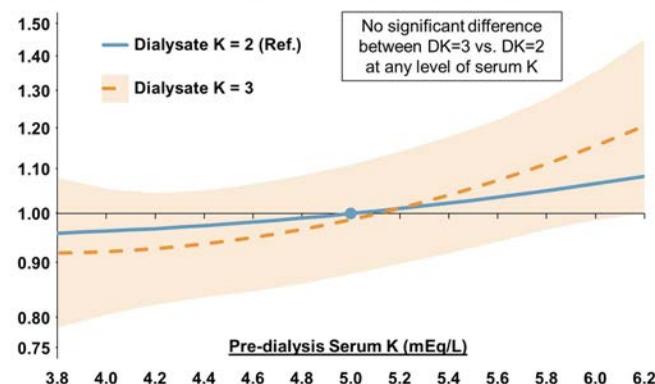
Background: Sudden death (SD) is common in hemodialysis (HD) patients. We investigated trends in dialysate (DK) and pre-dialysis serum (SK) potassium across the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 1-5 (1996-2015) and evaluated whether the risk of SD is higher with lower DK.

Methods: 67,263 patients in 21 countries were studied. Instrumental variable methods were used to model the effect of DK on SK. Adjusted Cox regression was used to test the associations of baseline DK and SK with all-cause death, and an arrhythmia composite (AC) of SD or arrhythmia-related hospitalization.

Results: In the US, DK and SK (mEq/L) have been stable over time (70% DK=2, 25% DK=3; mean±StdDev SK=4.7±0.7). In Europe, DK has increased (currently 15% DK=1-1.5, 45% DK=2, 33% DK=3) while mean SK has decreased from 5.2 to 4.9. SK was only 0.08 mEq/L higher per 1 mEq/L higher DK. SK ≥ 6 (ref 4.5-4.9) was associated with death (HR=1.12, 95% CI: 1.05-1.19) and AC (HR=1.17, 1.04-1.33). Compared to DK=2, DK=3 was not associated with death or AC, overall or at any level of SK (Fig).

Conclusions: In this large international cohort, SK was associated with elevated risk of SD, but risk of SD was similar for DK=2 or DK=3 across SK levels. Because DK had minimal influence on pre-dialysis SK, efforts to limit dietary K intake may be a more effective strategy to lessen the risks associated with high SK.

Hazard Ratio of sudden death or arrhythmia-related hospitalization



HR (95% CI) for Cox model stratified by DOPPS phase*country and adjusted for age, gender, vintage, 13 comorbidities, BMI, nPCR, albumin, Ca, P, Hgb, Kt/V, treatment time; restricted to patients with DK = 2 or 3 mEq/L; covariates include DK, SK, SK*SK, and interactions; HRs compare combinations of DK and SK to the reference of DK=2 and SK=5; 95% CI represents difference between DK=3 vs. DK=2 (ref) at any value of SK

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGfN, Shire, WiNe Institute, Societa Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

FR-PO739

Acute Health Events and the Risk of Incident Atrial Fibrillation in Older Patients Undergoing Maintenance Hemodialysis

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Background: Acute health events might increase the risk of developing atrial fibrillation (AF). We examined the incidence of new onset AF relative to several acute events in patients with ESRD initiating hemodialysis (HD).

Methods: From theUSRDS, we studied older (67+ years) patients with 2 years of Medicare A&B coverage prior to initiating HD (2006-11) who had no documented diagnosis of AF, or claims indicating ischemic stroke, myocardial infarction (MI), or hip fracture prior to ESRD. We used time-varying Cox regression to estimate adjusted hazard ratios for incident AF relative to the acute events of interest, adjusted for socio-demographics and baseline comorbidities. The incidence of AF after either an acute stroke, MI, or hip fracture was modeled in time-varying fashion, during the periods of <=30, 31 to 90, and >90 days after the acute event. Patients were censored at kidney transplantation or end of database (12/31/2011).

Results: 85,377 older HD patients met the inclusion criteria. The risk of AF was approximately doubled in the 90 days after an ischemic stroke, and remained elevated thereafter (Table). The risk of AF after an acute MI followed a similar pattern, with highest risk in the 30 days after the MI. The risk of AF after hip fracture followed a slightly different pattern, peaking between 30 and 90 days after the event, with no significant late hazard after 90 days. These associations were essentially unchanged when requiring that the acute health event be reported as principal diagnosis.

Time since event:	Ischemic Stroke	Myocardial Infarction	Hip Fracture
<=30 days	2.1 (1.7-2.7)	2.9 (2.5-3.4)	1.5 (1.1-2.0)
30-90 days	1.9 (1.5-2.4)	2.3 (2.0-2.6)	2.1 (1.7-2.5)
>90 days	1.5 (1.3-1.6)	1.6 (1.5-1.7)	1.1 (1.0-1.3)

Conclusions: The risk of incident AF among patients on HD is increased after a stroke, MI, or hip fracture. Risks were highest in the first 90 days after the event, and remained elevated >90 days after an ischemic stroke or MI, but not after a hip fracture.

Funding: NIDDK Support

FR-PO740

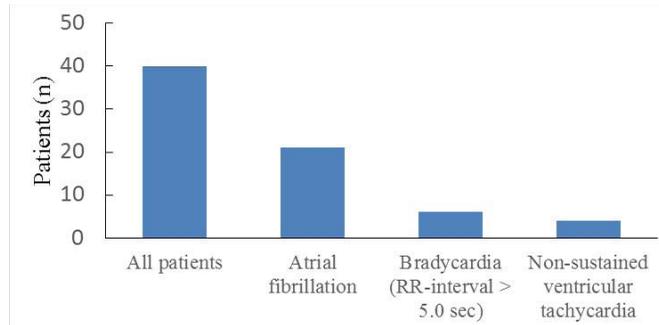
Arrhythmias as a Potential Cause of Dizziness and Syncope in Patients with End-Stage Renal Disease

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Background: It is unknown how often arrhythmias underlie dizziness and syncope in end-stage renal disease. We launched a study to implant subcutaneous loop recorders for their estimation.

Methods: Data is shown for 40 patients (62.4±8.2 years [mean±SD], range 39 to 78 y, 26 M) with stage 4 or 5 renal failure and f-u of > 2 months. Main kidney diseases were diabetic (18), polycystic disease (8) and chronic glomerulonephritis (6). One patient was pre-dialytic, five had peritoneal dialysis, and rest were on hemodialysis. Median time since the start of dialysis was 1.6 years. Seven patients (18%) had either chronic or paroxysmal atrial fibrillation (AF) prior to the implantation of the recorder, being in line with published data.

Results: During the f-u of 14±7 months, recorder revealed bradyarrhythmia in six (15%) patients with an R-R arrest of >5.0 sec with a max. of 9.0 sec; two patients with symptoms thus far received a pacemaker. AF occurred in 21 (53%) patients. The median time to detect new AF was 235 days. Four patients (10%) had non-sustained ventricular tachycardia unknown before the recorder data.



Conclusions: Arrhythmias are more typical than estimated in patients with severe kidney disease. Particularly, symptomatic bradycardia is relatively common and can be easily treated with a pacemaker. AF is three times more common than known before. These findings may change diagnostics and treatment of dizziness in these patients.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO741

Blood Pressure and Risk of Cardiovascular Events Among Hemodialysis Patients: The CRIC Study

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Background: Among hemodialysis (HD) patients, previous studies have reported a U-shaped association between systolic blood pressure (SBP) and risk of mortality. However, the shape of the association between SBP and risk of cardiovascular events (CVD) is not well characterized.

Methods: We studied participants on HD in the Chronic Renal Insufficiency Study (CRIC). SBP was measured at the dialysis unit ("dialysis-unit-SBP", N=403) and at the CRIC study visit ("out-of-dialysis-unit SBP", N=326). We studied the association of SBP

with time to adjudicated CVD (defined as heart failure, myocardial infarction, peripheral vascular disease and stroke), adjusting for demographics, diabetes, smoking, BMI, prior CVD, kt/v, serum albumin and hemoglobin.

Results: Mean age was 60 (±11) years, 42% were women and 64% were Black. There were a total of 121 CVD events over a median time of 1.15 years. The association between dialysis-unit-SBP was U-shaped, with the greatest risk of CVD at the highest and lowest quartiles of dialysis-unit-SBP.

Table. Association between SBP and CVD events

Dialysis-unit SBP (N=403)	Unadjusted		Adjusted for patient characteristics + dialysis variables	
	HR (95% CI)	P value	HR (95%CI)	p value
Q1 SBP (< 138 mm Hg)	1.27 (0.77, 2.11)	0.4	1.26 (0.69, 2.31)	0.5
Q2 SBP (138 - 150 mm Hg)	0.86 (0.50, 1.48)	0.6	1.06 (0.58, 1.91)	0.9
Q3 SBP (151 - 166 mm Hg)	Ref		Ref	
Q4 SBP (>166 mm Hg)	1.52 (0.94, 2.46)	0.09	1.73 (1.01, 2.96)	0.05
Out-of-dialysis-unit SBP (N=326)	Unadjusted		Adjusted for patient characteristics + dialysis variables	
Q1 SBP (< 113 mm Hg)	HR (95% CI)	P value	HR (95%CI)	p value
Q1 SBP (< 113 mm Hg)	1.30 (0.69, 2.47)	0.4	1.40 (0.68, 2.88)	0.4
Q2 SBP (113 - 128 mm Hg)	2.02 (1.13, 3.62)	0.02	2.67 (1.37, 5.22)	0.004
Q3 SBP (129 - 145 mm Hg)	Ref		Ref	
Q4 SBP (>145 mm Hg)	1.98 (1.09, 3.62)	0.03	2.72 (1.35, 5.51)	0.005

Conversely, the association between out-of-dialysis-unit-SBP was linear, with the highest quartile having greater than 2-fold risk of CVD than the lowest quartile.

Conclusions: Among HD patients, the association of SBP measured in the dialysis unit with CVD is U-shaped, while the association of SBP measured outside the dialysis unit with CVD is linear, similar to what has been reported for mortality (Bansal et al, Hypertension 2015). Targeting SBP measured outside the dialysis unit may improve CVD outcomes in HD patients.

Funding: NIDDK Support

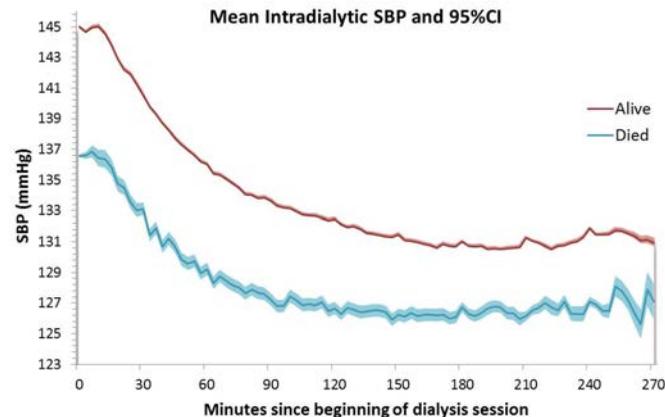
FR-PO742

Intradialytic Dynamics of Systolic Blood Pressure in Hemodialysis Patients Based on Survival Status John W. Larkin,¹ Dugan Maddux,¹ Yue Jiao,¹ Jeroen Kooman,² Frank van der Sande,² Hao Han,¹ Sophia Rosen,¹ Len A. Usvyat,¹ Peter Kotanko,^{3,4} Franklin W. Maddux.¹ ¹Fresenius Medical Care North America (FMCNA), Waltham, MA; ²Maastricht Univ Medical Centre, Maastricht, Netherlands; ³Renal Research Inst, New York, NY; ⁴Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Low systolic blood pressure (SBP) before dialysis has been reported to be associated with worsened outcomes in hemodialysis (HD) patients (Maddux et al., ASN 2014). However, the dynamics of intradialytic SBP and patient outcomes have not been well characterized in this population. We aimed to understand the dynamics of SBP during dialysis in patients based on their survival status.

Methods: We studied HD patients treated at FMCNA facilities in 2014 with recorded intradialytic SBP data. The population mean intradialytic SBP was computed in 20 minute intervals during dialysis per patient per treatment; all treatments were then averaged per patient and thereafter for the entire cohort. Patient survival was recorded in 2014 (i.e. "alive" or "died").

Results: 31,053 and 2,835 patients (338,771 and 20,380 measurements respectively) were used for calculation of the mean SBP at each 20 minute time point in "alive" and "died" groups, respectively. The results show that the mean intradialytic SBP declines to a similar extent in both patients who died and survived, but patients that died exhibited a lower initial predialysis SBP and greater overall intradialytic variability.



Conclusions: These investigations of the dynamics of intradialytic SBP identify increased variability during dialysis and lower starting levels in patients who died. In both patients who were alive and died, SBP declines to a similar extent throughout dialysis. These findings suggest that lower predialysis SBP and intradialytic variability may be associated with mortality in the HD population.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO743

Choosing the Right Analysis of Repeated Events for Clinical Trials in Dialysis George Tomlinson,¹ Stephanie Dixon,² Amit X. Garg,³ Charmaine E. Lok.¹ ¹Medicine, Toronto General Hospital, Toronto, ON, Canada; ²ICES-KDT; ³London Health Sciences Centre.

Background: Cardiovascular (CV) events are a leading cause of morbidity and mortality in hemodialysis (HD) patients. There is a paucity of randomized clinical trials (RCT) in nephrology and fewer positive ones, perhaps due to incorrect choice of endpoints or inadequate power. We simulated RCTs with repeated CV events and competing non-CV death to determine how different analytic methods affected study power (sample size).

Methods: We simulated 1000 RCTs of 1100 patients, with frequency and timing of CV events (CV death, MI, stroke, PVD, CV revascularization, and leg amputation) based on real observations in an Ontario HD administrative cohort (n=9647) from 2004-2011. In simulations, patients were randomized to placebo or a treatment with a known effect and censored at 4 years or non-CV death. We analyzed this data with 1) a Cox model for time to first event, 2) a model with non-CV death as a competing risk, 3) a negative binomial (NB) model and 4) several adaptations of the Cox model for repeated events (e.g., Wei, Lin and Weissfeld, WLW). To check for 2 potential problems (finding a difference when there was none and missing a true difference), we ran simulations in 2 scenarios: 1) with zero treatment effect, we calculated the false positive rate; 2) when the treatment delayed CV events by 33%, we calculated the true positive rate (power) based on the 1000 simulations.

Results: In the source (real) data, 45% of patients had ≥2 CV events; the overall CV event rate was 0.26/yr. When there was no effect of treatment, the NB model had a false positive rate of 11%; for all other models, it was the expected 5%. For the time to first event, competing risk and the WLW marginal Cox model, power was similar (72%) and notably higher than for the remaining Cox-type models (52%-61%).

Conclusions: The WLW Cox model for repeated events was as powerful as models for time to first event but has the advantage of assessing the impact on all (repeated) events a patient experiences. This highlights the importance of choosing the appropriate analytic method when designing a clinical trial in HD patients to maximize the likelihood of both a positive and a meaningful result.

Funding: Government Support - Non-U.S.

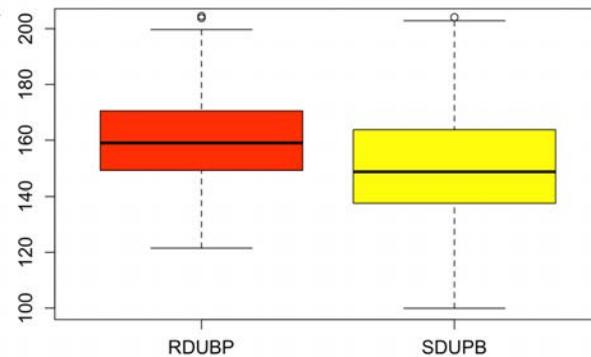
FR-PO744

Routine Predialysis Measurements of Systolic Blood Pressure Are Higher Than Predialysis Standardized Measurements of Systolic Blood Pressure Dana Miskulin,¹ Jennifer J. Gassman,⁴ David W. Ploth,⁵ Manisha Jhamb,⁶ Lavinia A. Negrea,⁷ Mahboob Rahman,⁷ Ronald Schrader,² Susan Paine,² Philip Zager.^{2,3} ¹Tufts; ²UNM; ³DCI; ⁴Cleveland Clinic; ⁵MUSC; ⁶Univ of Pittsburgh; ⁷Care Western.

Background: Measurement of blood pressure (BP) in the dialysis unit does not follow American Heart Association recommendations. We determined the differences between systolic BP (SBP) measured in routine practice versus a standardized procedure.

Methods: The Blood Pressure in Dialysis Study is a pilot, multicenter, randomized clinical trial that assesses treatment of hypertensive HD patients to two BP targets. Measurement of predialysis SBP is done after 5 minutes rest, 3 readings 1 minute apart, with attention to cuff size, placement and patient positioning. We compared the 2-week averaged routine predialysis SBP (RDUSBP) taken immediately prior to enrollment with the 2-week averaged standardized SBP (SDUSBP) in the first 2 weeks of baseline. The within subject variability in SBP, (s_w²) was estimated by mixed linear regression.

Results: We studied 186 patients. The two week averaged RDUSBP was a mean (SD) 10.3 (16.6) mm Hg higher than 2 week averaged SDUSBP (p<0.001).



The RDUSBP was ± 5 mm Hg of the SDUSBP in 20% of patients, 6-15 mm Hg higher in 30%, 15-25 mm Hg higher in 17%, >25 mm Hg higher in 17% and >5 lower in 16%. Estimates of s_w² for RDUSBP (15.7) and SDUSBP (19.6) were not significantly different, (p>0.99). Differences between RDUSBP and SDUSBP tended to be greatest among those with a high body mass index.

Conclusions: SDUSBP were, on average, 10 mm Hg lower than RDUSBP measured in the dialysis unit. Reliance on routine BP measurements may lead to over-treating hypertensive HD patients. More attention to the measurement of BP in dialysis unit is needed.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.

FR-PO745

Comparison of Central and Peripheral Blood Pressure in Predicting Cardiovascular Surrogates in Patients with End-Stage Renal Disease *Kyoung Sook Park, Younkyung Kee, Shin-Wook Kang, Tae-Hyun Yoo. Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Hypertension is an established cardiovascular (CV) risk factor and is closely related with mortality in end-stage renal disease (ESRD) patients. Recent studies have demonstrated that central blood pressure (cBP) is a significant predictor of CV disease in the general population, because cBP reflects the loading conditions of the coronary and cerebral arteries and vascular damage. Therefore, we investigated the association between cBP and CV surrogates compared with peripheral blood pressure (pBP) in patients with ESRD.

Methods: A cohort of 92 ESRD patients from the Cardiovascular and Metabolic Disease Etiology Research Center between November 2013 and February 2015 was selected. cBP was measured by SphygmoCor noninvasively. CV surrogates were determined by carotid intima-media thickness, pulse wave velocity (PWV) and left ventricular mass index (LVMI). Linear regression analysis and Steiger's Z test were used to compare predictive ability of cBP and pBP for CV surrogates.

Results: The mean age was 53.2 years and 52 (56.5%) were male. Mean systolic cBP (cSBP) and central pulse pressure (cPP) was 140.2±28.9 and 57.1±22.8 mmHg. Mean systolic pBP (pSBP) and peripheral pulse pressure (pPP) was 145±25.8 and 65.8±22.2 mmHg. There was an independent association of cSBP and pSBP with PWV (β=0.408, P<0.01; β=0.322, P=0.001) and LVMI (β=0.370, P=0.001; β=0.382, P<0.001). cPP and pPP also were independently associated with PWV (β=0.381, P<0.001; β=0.353, P=0.001) and LVMI (β=0.411, P<0.001; β=0.497, P<0.001) after adjustment for confounding factors. However, there were no significant differences in the predictive value of cSBP and pSBP for estimating PWV (adjusted R², 0.494 vs. 0.431, P=0.07) and LVMI (adj R², 0.215 vs. 0.220, P=0.885). No significant difference was found for cPP and pPP for predicting PWV (adj R², 0.451 vs. 0.429, P=0.546) and LVMI (adj R², 0.220 vs. 0.269, P=0.320).

Conclusions: Although cBP values were closely associated with CV surrogates, these values did not provide additional information beyond pBP in predicting CV risk in patients with ESRD.

FR-PO746

Early Mortality in Hemodialysis Patients Anticoagulated for Atrial Fibrillation *Stanislav S. Bushnik,¹ N. Stanley Nahman,¹ Riad Elmor,² Jennifer L. Waller,² Robert A. Sorrentino,¹ William R. Maddox,¹ Mufaddal F. Kheda,¹ Matthew J. Diamond.¹ ¹Medicine, Georgia Regents Univ, Augusta, GA; ²Biostatistics & Epidemiology, Georgia Regents Univ, Augusta, GA.*

Background: Atrial fibrillation (AF) is prevalent in the Hemodialysis (HD) population and portends a high mortality rate. AF also causes embolic stroke and is treated with lifelong oral anticoagulation (OAT). We have previously shown early increased mortality in HD patients receiving OAT without significant stroke reduction (JASN, 25:609A, 2014). It is unclear why OAT increased early mortality in these patients. To address this question, we queried the USRDS for unique risk factors for mortality in this cohort.

Methods: All incident adult HD cases from the USRDS for 2005-2008 were queried for demographics, access type, risk factors before dialysis, and mortality. Data were derived from ICD9 and CPT codes, or Form 2728. Proportional hazards models were used to estimate the hazard ratio (HR) for death within 90 days.

Results: 34,522 incident HD patients with AF were identified, 6664 (19.3%) of whom died within 90 days of the initiation of dialysis. For the entire group, demographics showed: 83.1% Caucasian, mean age 75.4 years (SD=9.0), and 41.5% female. When controlling for diabetes, cardiomyopathy TIA, pulmonary hypertension, aortic stenosis, CHF, MI, coagulation defects, obesity, cardiac device, age and access type the HR for death in the OAT group was 1.10 (95% CI 1.04 - 1.16). The 1-, 2- and 3-month mortality rates were 6%, 15% and 22% in OAT and 5%, 12% and 19% in non-OAT, respectively. Major bleeding episodes were not significantly associated with mortality (p=0.59).

Conclusions: OAT therapy in HD patients with AF may contribute to the increased death rate observed during the first 90 days of dialysis, but not apparently due to bleeding. We speculate that OAT use may be associated with non-hemorrhagic complications that may lead to increased mortality in the HD population. Defining this level of clinical detail is beyond the scope of an administrative dataset like the USRDS. Future studies addressing non-hemorrhagic effects of OAT may provide new insights on possible causes of early mortality in these patients.

Funding: Private Foundation Support

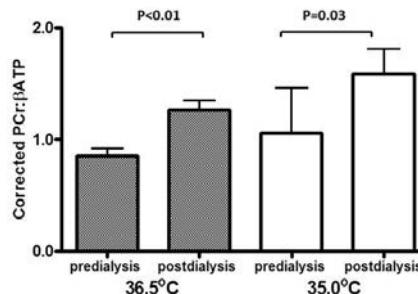
FR-PO747

Reduced Temperature Hemodialysis Augments Dialysis Induced Improvement of Cardiac High Energy Phosphate Levels *Rajan Patel, Elaine Rutherford, Kathryn K. Stevens, Sandosh Padmanabhan, Alan G. Jardine, Patrick B. Mark. Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom.*

Background: ³¹P phosphorus magnetic resonance spectroscopy (³¹P-MRS) measures levels of high energy phosphates, including phosphocreatine:β ATP (PCr:β ATP) ratio which evaluates cardiac metabolic activity. PCr:β ATP is significantly reduced in end stage renal disease (ESRD) patients. Reducing hemodialysis temperature by 1-2°C improves intradialytic hypotension and cardiac function. The effects of reduced temperature dialysis on cardiac metabolism have not been evaluated. We compared myocardial function and PCr:β ATP ratios levels before and after normothermic and reduced temperature dialysis.

Methods: Twelve hemodialysis patients underwent cardiac MRI and ³¹P MRS of their left ventricle (LV) within 30 minutes before (pre) and after (post) three normothermic (36.5°C) and three reduced temperature (35.0°C) maintenance dialysis sessions. Left ventricular dimensions were measured by an observer blinded to intervention. PCr:β ATP were calculated from ³¹P-MR spectra.

Results: Reduced temperature hemodialysis was significantly associated with increased predialysis LV ejection fraction (36.5°C:64.5%±6.6 vs. 35.0°C:69.0%±6.1; p=0.03). At both temperatures, hemodialysis was significantly associated with increased mean LV ejection fraction (36.5°C:pre 64.5%±6.6, post 70.9%±6.8, p=0.002; 35.0°C :pre 69.0%±6.1, post 74.2%±8.3, p<0.01). PCr:β ATP was significantly higher after normothermic (p<0.01) and reduced temperature hemodialysis (p=0.03:). Mean increase in PCr:β ATP was higher after reduced temperature compared to normothermic hemodialysis (+51.5% vs +74.1% respectively).



Conclusions: Hemodialysis is associated with improved myocardial metabolic activity and this effect may be amplified by reducing the dialysate temperature even in patients with no intradialytic hypotension.

FR-PO748

Risk Grading by CHA2DS2_Vasc Score Is Useful in Non-Dialysis Subjects with Atrial Fibrillation while It Is Not Useful in Dialysis Patients Because of Their Very High CHA2DS2_Vasc Scores *Masaki Ohsawa.^{1,2} ¹Dept of Internal Medicine, Iwate Medical Univ, Morioka, Japan; ²Dept of Internal Medicine, Morioka Tsunagi Onsen Hospital, Morioka, Japan; ³Dept of Hygiene and Preventive Medicine, Iwate Medical Univ, Iwate Prefecture, Japan.*

Background: Whether CHA2DS2_Vasc score is useful for predicting the risk of outcomes has not been sufficiently examined in dialysis patients with AF.

Methods: Two prospective studies of 1,109 dialysis patients (AF group (n=35); non-AF group (n=1,074)) and 26,469 community dwellers (AF group (n=26,058); non-AF group (n=411)) living in the same area were conducted. Subjects were subdivided into four groups according to CHA2DS2_Vasc score (G1: CHA2DS2_Vasc score = 0-1; G2: score = 2; G3: score = 3; G4: score = 4+). Crude mortality rates of all-cause and cardiovascular death and crude incidence rates of stroke (per 1000 person-years) were estimated in each group.

Results: Results were shown in the table.

	AF (-)	AF (+)	CHADS2 Vasc 0-1	2	3	4+
community dwellers						
subjects (n)	26058	411	108	133	88	82
all-cause death (mortality rate)	993 (6.8)	57 (26.3)	11 (11.8)	17 (23.4)	12 (26.0)	17 (43.6)
cardiovascular death (mortality rate)	211 (1.5)	27 (12.5)	4 (6.8)	8 (11.0)	6 (13.0)	9 (23.1)
stroke (incidence rate)	692 (4.8)	57 (28.2)	9 (16.2)	18 (26.5)	13 (30.3)	17 (47.8)
dialysis patients						
AF (+) subjects (n)		35	6	1	6	22
all-cause death (mortality rate)		26 (278.9)	2 (81.4)	1 (404.9)	3 (158.1)	20 (423.7)
cardiovascular death (mortality rate)		9 (96.6)	0 (0)	0 (0)	1 (52.7)	8 (169.5)
stroke (incidence rate)		5 (59.7)	0 (0)	0 (0)	0 (0)	5 (132.4)
AF (-) subjects (n)	1074		218	331	242	283
all-cause death (mortality rate)	384 (88.7)		26 (25.9)	83 (58.3)	100 (106.4)	175 (181.8)
cardiovascular death	187 (43.2)		14 (13.9)	41 (28.8)	55 (58.5)	77 (80.0)
stroke (incidence rate)	192 (49.7)		21 (21.5)	49 (37.4)	48 (59.4)	74 (96.4)

Mortality/incidence rates are expressed as per 1000 person-years.

Conclusions: CHA2DS2_Vasc score is useful for predicting the risk of outcomes in non-dialysis subjects with AF and dialysis subjects without AF. Dialysis patients with AF already had very high scores and the risk grading by CHAD2DS2_Vasc score is not useful.

Funding: Government Support - Non-U.S.

FR-PO749

Post Stroke In-Hospital Disability Deterioration and Mortality of Community-Onset Stroke in Patients with and without End-Stage Renal Disease Tomoko Usui,¹ Norio Hanafusa,¹ Hideo Yasunaga,² Masaomi Nangaku.¹

¹Dept of Hemodialysis and Apheresis, The Univ of Tokyo Hospital, Japan; ²Dept of Clinical Epidemiology and Health Economics, School of Public Health, the Univ of Tokyo, Japan.

Background: Increasing evidence suggests that end-stage renal disease is associated with higher risk and severity of cerebrovascular disease. However, the risk factors for post stroke disability and mortality is not clear. We examined the association between risk factors including dialysis treatment and disability deterioration and mortality during hospital stay of community-onset stroke.

Methods: The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data of about 50% of all acute-care inpatients in Japan. Using this database, we extracted data of inpatients age ≥20 years old, admitted within 3 days after community-onset stroke between July 2010 and March 2013. Disability level was divided into modified Rankin Scale (mRS) 0-1, 2-3, 4-5, and 6 (death). Disability deterioration was defined as an increase in disability level. The odds ratio (OR) for in-hospital disability deterioration and mortality was calculated using a logistic regression model.

Results: Out of 438,569 patients, 7,633 (1.7%) had dialysis therapy. The median length of stay was 21 and 20 days for patients with and without dialysis, respectively. During the hospital stay, there were 101,024 (23.0%) disability deterioration and 46,029 (10.5%) death. The patients with dialysis had higher rate of disability deterioration (26.7%) and mortality (13.0%) compared to those without. After adjustment with age, gender, BMI, mRS, Activities of Daily Living, smoking habits, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular complications, antiplatelet, anticoagulant, and thrombolytic medications, multivariate-adjusted ORs of dialysis for deterioration of disability was 1.57 (95%CI 1.48-1.66), and in-hospital mortality was 1.72 (95%CI 1.59-1.86).

Conclusions: Dialysis treatment was an independent risk factor for in-hospital disability deterioration and mortality of community-onset stroke.

FR-PO750

Proportion of Treatments with Low Systolic Blood Pressure and Short Term Mortality in Incident Hemodialysis Patients Dugan Maddux,¹ John W. Larkin,¹ Danqing Xu,² Len A. Usvyat,¹ Frank van der Sande,³ Jeroen Kooman,³ Peter Kotanko,⁴ Franklin W. Maddux.¹

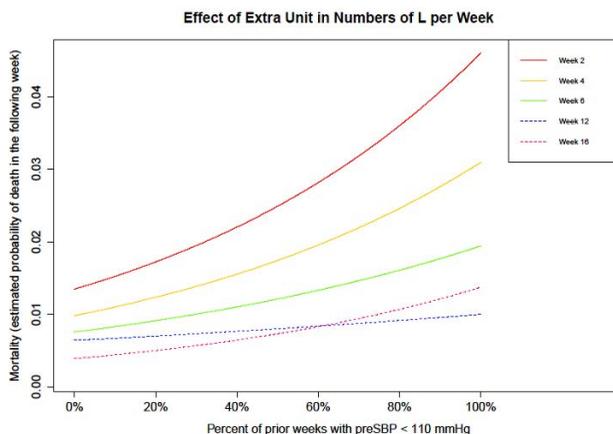
¹Medical Office, Fresenius Medical Care North America, Waltham, MA; ²Univ of California at Santa Barbara, Santa Barbara, CA; ³Maastricht Univ Medical Centre, Maastricht, Limburg, Netherlands; ⁴Renal Research Inst, New York, NY.

Background: Prior studies have associated low mean predialysis systolic blood pressures (preSBP) with increased 120 day risk for mortality in incident hemodialysis (iHD) patients (Maddux et al., ASN 2014). This study aimed to investigate how the percent (%) of low mean preSBP during the prior weeks' hemodialysis (HD) treatments affects the short term risk of mortality in iHD patients.

Methods: For this study, 50,525 iHD patients at Fresenius Medical Care North America (FMCNA) clinics were investigated from 1/1/2004 to 12/31/2010. From the first date of outpatient chronic dialysis (FDD), the % of the prior weeks' mean preSBP <110 mmHg was calculated for the first 4 months of HD. Mortality risk in the following week (7 days) was analyzed by the % of the prior week's mean preSBP <110 mmHg at weeks 2, 4, 6, 12, and 16 from FDD.

Results: We observed that the short term risk for mortality in the following week increases in iHD patients as the % of the prior week's mean preSBP <110 mmHg increases at weeks 2, 4, and 6 from the FDD; the risk for mortality was found to be the greatest at week 2 and was slightly reduced by week 6. Conversely, by week 12 and 16 from the FDD, the % of the prior week's mean preSBP <110 mmHg was not found to be related with the risk of mortality in the next week.

Figure 1: iHD Patient 7 Day Risk of Mortality by the % of the Prior Week's Low preSBP



Conclusions: This study demonstrates that increases in the % of low mean preSBP during the prior weeks' hemodialysis (HD) treatments is associated with heightened short term risks of mortality during the first 6 weeks of iHD, but not during weeks 12 and 16 from the FDD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO751

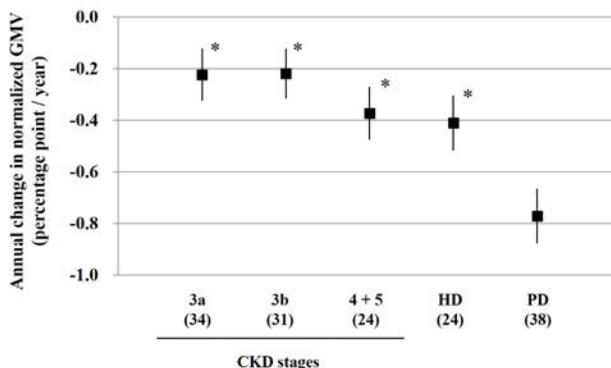
The Possibility of Faster Progression of Brain Atrophy in Patients on Peritoneal Dialysis Compared with Hemodialysis Kazuhiko Tsuruya,¹ Hisako Yoshida,¹ Takanari Kitazono.²

¹Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ²Dept of Medicine and Clinical Sciences, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Brain atrophy has been reported in chronic kidney disease (CKD) patients, especially in hemodialysis (HD) patients. Recently, we reported faster decline in normalized gray matter volume (GMV) in peritoneal dialysis (PD) patients compared with non-dialysis-dependent CKD (ND) (Tsuruya, et al. Am J Kidney Dis, 2015). However, it has not been reported on the comparison of the progression rate of brain atrophy between PD and HD patients. In the present study, we compared it among PD, HD, and ND patients.

Methods: A total of 151 patients of 38 PD patients aged 60 ± 12 years (men 23, diabetes 11), 24 HD patients aged 64 ± 6 years (men 18, diabetes 9), and 89 ND patients (CKD stage 3a, 34; stage 3b, 31; stages 4-5, 24) patients aged 62 ± 11 years (men 46, diabetes 25, eGFR 38.9 ± 11.6 mL/min/1.73m²) were recruited and underwent MRI scanning at baseline and after two years. T1-weighted MRI images were analyzed with statistical parametric mapping software. Total gray matter, total white matter, and cerebrospinal fluid were segmented and each volume was quantified. Normalized GMV was calculated as percentage of intracranial volume to normalize for head size variability. We compared the annual change in normalized GMV among CKD stages.

Results: Annual change in normalized GMV was significantly higher in PD patients than other CKD patients. This finding remained significant even after adjustment for potential confounding factors.



() : number of participants
* : P < 0.05 vs. PD (Dunnnett's test)

Conclusions: Progression of brain atrophy is significantly higher in PD patients than other CKD patients including HD patients, independent of age, gender, diabetes, and blood pressure level.

FR-PO752

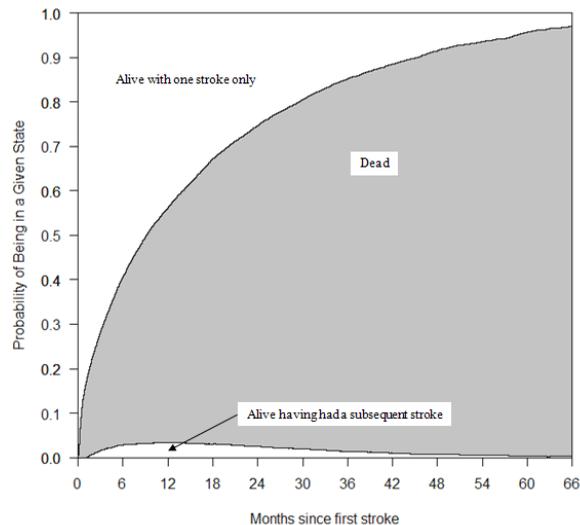
In Centre Nocturnal Haemodialysis: Improving Outcomes and Experience for Patients Matthew P.M. Graham-Brown,^{1,2} Darren Robert Churchward,^{1,2} Alice C. Smith,^{1,2} Richard J. Baines,^{1,2} James O. Burton,^{1,2} ¹John Walls Renal Unit, Univ Hospitals of Leicester, Leicester, United Kingdom; ²Dept of Infection, Immunity and Inflammation, Univ of Leicester, Leicester, United Kingdom.

Background: Extended periods of haemodialysis (HD) improve patient outcomes. Home HD schedules can deliver extended dialysis, but there are patient and physician related barriers that make home therapies impossible for many. We explored in centre nocturnal HD (INHD) as a method of offering extended periods of HD to patients unsuitable for home therapy.

Methods: Ten prevalent HD patients switched from standard HD (3x4 hours) to INHD (3x>5 hours) for four months. Mean ultrafiltration (UF) volumes (L), relative UF rates (ml/kg/hour) and absolute UF rates (ml/hour) were calculated. Additional, biochemical and haematological data, data on dialysis adequacy and blood pressure control were collected. Changes in quality of life (QoL) were assessed using SF12, EQ-5D and the Hospital Anxiety and Depression Score (HADS) questionnaires.

Results: Seven patients completed four months of INHD. Mean dialysis time per session was 355 minutes (SD±43.92). Mean total UF volume increased from 2.0±5.1L to 2.6±3.4L (p=0.02), but there was a reduction in absolute mean UF rates from 513±121ml/hour on standard dialysis, to 356±66 ml/hour on INHD (p=0.03) and a decrease in mean relative UF rates from 6.5±1.7ml/kg/hr to 4.6±1.6ml/kg/hr (p=0.03). Adequacy measured by urea reduction ratio improved from 72±2% to 80±3% (p<0.001), with a trend towards improved phosphate control to within therapeutic targets; from 1.7±0.6mmol/L to 1.2±0.2mmol/L (p=0.08). In addition, there were improvements in all QoL scores. Mean EQ-5D visual analogue score improved from 48±16.9 to 72±13.2 (p=0.003). Mean HADS anxiety score decreased from 9±5.83 to 3.57±3.04 (p=0.03). SF12 physical component score improved from 31.31±3.32 to 41.69±10.19 (p=0.05).

Conclusions: Despite an increase in total UF volume, extended INHD led to an overall reduction in UF rate that has been shown to abrogate HD induced cardiac injury. Other physiological benefits included improved urea clearance and better phosphate control. There were also significant improvements in patient QoL measures over four months.



Transition probabilities (Pr) at different time points after first new stroke

Time in Months	Transitioning from first stroke to subsequent stroke	Transitioning from first stroke to death	Remaining alive with a first stroke only
t=3	Pr = 0.015	Pr = 0.268	Pr = 0.717
t=6	Pr = 0.028	Pr = 0.379	Pr = 0.593
t=12	Pr = 0.033	Pr = 0.529	Pr = 0.438
t=24	Pr = 0.025	Pr = 0.721	Pr = 0.254
t=36	Pr = 0.014	Pr = 0.838	Pr = 0.148
t=48	Pr = 0.007	Pr = 0.908	Pr = 0.085

Funding: NIDDK Support

FR-PO753

Association of Multiple Strokes on Mortality in Incident Hemodialysis Patients: An Application of Multistate Model to Determine Transition Probabilities James B. Wetmore,¹ Jonathan D. Mahnken,² Milind A. Phadnis,² ¹Medicine, Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN; ²Biostatistics, Univ of Kansas Medical Center, Kansas City, KS.

Background: Little is known about the effect of multiple, or subsequent, ischemic strokes in patients receiving dialysis.

Methods: A retrospective cohort study of incident hemodialysis patients with Medicare Parts A and B coverage who had experienced a first ischemic stroke was performed. A multistate model with Cox proportional hazards was used to predict transition probabilities from first ischemic stroke to subsequent stroke or to death. Demographic and clinical factors associated with the respective transition probabilities were determined.

Results: Overall, 12,054 individuals (mean age 69.7 years, 41.3% male, 53.0% Caucasian and 34.0% African-American) experienced a first stroke. Female sex was associated with an increased risk of having a subsequent stroke (adjusted hazard ratio 1.37, 95% confidence intervals 1.20 – 1.56, P < 0.0001); African-Americans, as compared to Caucasians, had lower likelihood of dying after a first stroke (0.81, 0.77 – 0.85, P < 0.0001). A subsequent stroke trended towards having a higher likelihood of transitioning to death compared to a first new stroke on dialysis (1.72, 0.96 – 3.09, P = 0.071). The probability of transitioning to a subsequent stroke increased over the first 6 months, peaked at approximately 12 months, then declined steadily over time (Figure). When a subsequent stroke occurs at 24 months, probability of survival dropped >15%, in absolute terms, from 0.254 to 0.096, with substantial drops observed at subsequent time points such that the probability of survival was more than halved.

Conclusions: Likelihood of subsequent ischemic stroke and of survival in dialysis patients appears to vary by sex and race.

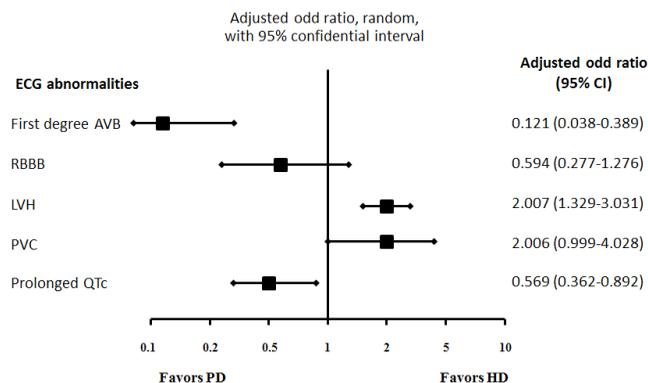
FR-PO754

Electrocardiographic Manifestation in End-Stage Renal Disease Patients with Different Renal Replacement Treatment Thasinas Dissayabuttra,¹ Eiji Kusano,² ¹Biochemistry, Chulalongkorn Univ, Pathumwan, Bangkok, Thailand; ²Internal Medicine, Div of Nephrology, Jichi Medical Univ, Shimotsuke, Tochigi, Japan.

Background: End-stage renal disease commonly coexists with certain type of cardiovascular diseases, partially reflects the burden of cardiac in uremic state and dialysis methods. Hemodynamic changes are different between predialysis state, hemodialysis (HD), peritoneal dialysis (PD) and post-kidney transplant (Post-KT) patients. This study aimed to investigate the cardiac disorders using electrocardiographic (ECG) features between each stage of CKD patients, including HD, PD and Post-KT.

Methods: ECG records were analyzed retrospectively in 974 participants, including (a) 48 Early CKD (CKD stage 1-2), (b) 188 Advanced CKD (CKD stage 3, 4 and 5), (c) 567 Hemodialysis (HD), (d) 112 chronic ambulatory peritoneal dialysis (PD) and (d) 59 post-kidney transplant (KT) patients. ECGs were analyzed by two examiners for major ECG abnormalities.

Results: A few ECG abnormalities were observed in Early CKD, but highly frequent QTc prolongation and first degree atrio-ventricular block (AVB) were detected in Advanced CKD. PD patients developed more left ventricular hypertrophy (LVH) and premature ventricular contraction than HD counterparts.



Four-consecutive-year annual ECGs showed the significant increase of AVB, LVH and QTc prolongation in HD patients. QTc prolongation recovery was observed in KT with the fewer LVH prevalence. We found that the age was a dependent factor for AVB and RBBB development, and the remaining GFR correlated with the prevalence of AVB and QTc prolongation in CKD patients.

Conclusions: Prolonged QTc, first-degree AVB, LVH and PVC were prevalent in ESRD and depended on renal replacement therapy method. The physicians should be cautious and promptly treat to the fatal arrhythmias.

Funding: Government Support - Non-U.S.

FR-PO755

The Relation Between Sclerostin, Peripheral Vascular Calcification, and Cardiovascular Events in ESRD Patients Young Ju Na, Sung Yoon Lim, Myung-gyu Kim, Sang-Kyung Jo, Won-Yong Cho. *Nephrology, Korea Univ Hospital, Seoul.*

Background: Sclerostin, a negative regulator of Wnt signaling pathway produced by osteocyte, is a potent regulator of bone metabolism and a novel candidate for the bone vascular axis in chronic kidney disease patients. Although sclerostin is known as an inhibitor of vascular calcification, recent studies demonstrated conflicting results about the association between sclerostin and cardiovascular events or mortality. In this study we tested the association between sclerostin, peripheral vascular calcification, and cardiovascular events in end stage renal disease (ESRD) patient starting peritoneal dialysis.

Methods: In this prospective study, we included 45 ESRD patients admitted to Korea University Anam Hospital for starting peritoneal dialysis. Circulating sclerostin level was measured in all patients before the start of peritoneal dialysis. Simple vascular calcification score (SVCS) was measured using plain radiographic films of both hands and the pelvis. Median follow up period was 36 months.

Results: Higher sclerostin level was associated with male sex, diabetes mellitus, higher left ventricle (LV) mass index, and lower LV fractional shortening in univariate analysis. ESRD patients with severe vascular calcification (SVCS ≥ 3) had significantly higher prevalence of diabetes mellitus. They had higher pulse wave velocity, alkaline phosphatase, and lower cholesterol levels, LV fractional shortening and in multivariate analysis, the presence of diabetes mellitus (OR, 44.59, $p=0.023$), lower cholesterol levels (OR, 0.94, $p=0.032$) were independent risk factors predicting severe vascular calcifications. In multivariate Cox regression model, higher pulse wave velocity (HR 1.03, $p=0.028$) was significant predictor for cardiovascular events. In addition higher sclerostin group (HR 9.82, $p=0.094$) and lower albumin levels (HR 0.23, $p=0.081$) display a strong tendency of increased cardiovascular events.

Conclusions: This study showed the possible important role of sclerostin in the development of vascular calcification and cardiovascular events in PD patients. Longer term follow up with larger sample size will be needed to clarify this issue.

FR-PO756

Use of Anticoagulants in Patients with Atrial Fibrillation and End Stage Renal Disease: A Study of Real World Data Lloyd P. Haskell,¹ Chris Knoll,² Patrick Ryan,³ Zhong Yuan.³ ¹Cardiovascular, Janssen R and D, Raritan, NJ; ²Epidemiology, Janssen R and D, Raritan, NJ; ³Epidemiology, Janssen R and D, Titusville, NJ.

Background: End stage renal disease (ESRD) in patients with atrial fibrillation (AF) is a significant cause of morbidity and mortality. While these patients are at high risk for stroke, there are limited data with respect to use of anticoagulants in clinical practice and current guidelines are not clear on how to manage them.

Methods: US-based, four large healthcare databases (Truven MarketScan Commercial Claims/Encounters [CCAE], Medicare Supplemental [MDCR], Medicaid [MDCD]) and Optum Clinformatics [Optum]) were used to establish cohorts of patients with AF and ESRD, who were identified using ICD-9 codes. The first encounter with evidence of both conditions during the inception period of 2010-2012 was the index date; patients must have had at least 1 year enrolment prior to and after the index date to be eligible for the study. The use of anticoagulants was examined during the follow-up period.

Results: Table 1 shows patient demographics and use of anticoagulants by data source. As expected, the privately-insured patient populations (CCAE and Optum) as well as the Medicaid population [MDCD] were younger as compared with the Medicare eligible population (MDCR). Across study cohorts, approximately 37% to 40% of patients with AF and ESRD received at least one dispensing of warfarin, with the exception of the Medicaid population (14%). About 3% to 4% of patients (except for Medicaid) received at least one dispensing of novel oral anticoagulant therapy (rivaroxaban, apixaban, or dabigatran).

Table 1. Use of Anticoagulants in Patients with AF and ESRD

Datasource	N	Mean Age [S.D.]	Male, %	Novel Oral Anticoagulants	Warfarin
Commercial	3650	56 [7.7]	66.2%	2.5%	37.7%
Medicare	9866	77 [7.7]	59.7%	3.4%	40.1%
Medicaid	5663	64 [3.7]	41.6%	0.6%	14.0%
Optum	2825	65 [12.4]	66.8%	4.1%	37.5%

Conclusions: Less than 40% of patients with AF and ESRD received anticoagulant therapy. As these are high risk patients, anticoagulant therapy may be underutilized. Further research is necessary to investigate clinical outcomes associated with anticoagulation in these patients.

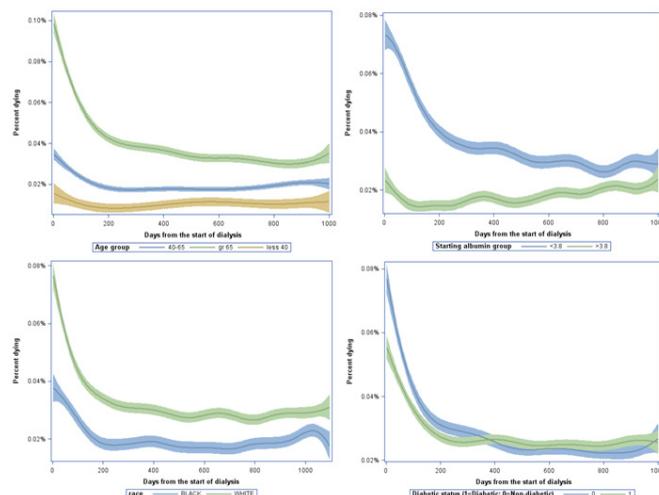
FR-PO757

Factors Determining Changes in Mortality Rates in Incident Hemodialysis Patients Jochen G. Raimann,¹ Len A. Usvyat,² Dugan Maddux,² Jeroen Kooman,³ Frank van der Sande,³ Kevin Chan,² Franklin W. Maddux,² Peter Kotanko.^{1,4} ¹Renal Research Inst; ²Fresenius Medical Care North America; ³Maastricht Univ Medical Centre; ⁴Icahn School of Medicine at Mount Sinai.

Background: The higher risk of death for incident hemodialysis (HD) patients decreases during the first year (Chan, 2011). Next to vintage, risk is also affected by patient characteristics, and the evolution of clinical and laboratory parameters. We analyzed how mortality rates change in different age groups, levels of albumin, in black and white, and in diabetic and non-diabetic patients after HD initiation.

Methods: We analyzed patients commencing HD in Fresenius Medical Care North America clinics between 1/1/2005 and 11/30/2014. We calculated proportions of patients dying from all causes in diurnal intervals starting with the first day on HD up to 1000 days. Only patients who had their first outpatient treatment on day 1 of their first ever HD were analyzed. We analyzed differences in mortality in the following strata: a) age groups (<40, between 40 and 65, and >65 years); b) serum albumin greater and below 3.8 g/dL; c) black and white; and d) diabetic and non-diabetic patients. We fitted penalized B-splines with 95% CIs through all available daily rates.

Results: We studied 334,880 patients. For all groups, mortality rates dropped within the first year. There were differences between groups of age, albumin and between black and white patients, but none between diabetic and non-diabetic patients.



Conclusions: Mortality rates decrease substantially once patients initiate HD. After approximately one year on HD, mortality remains consistent in all groups, but remains lower for those with higher albumin, younger age and black race. Diabetes appears to not affect mortality. Since only patients starting in an outpatient setting were included, selection bias may apply differently to the patient groups.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO758

Strong Association of Geriatric Nutritional Risk Index with the Infection-Related Mortality in Hemodialysis Patients: The Q-Cohort Study Yuta Matsukuma,¹ Shigeru Tanaka,¹ Masatomo Taniguchi,¹ Toshiaki Nakano,¹ Kosuke Masutani,¹ Hideki N. Hirakata,² Kazuhiko Tsuruya,^{1,3} Takanari Kitazono.¹ ¹Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; ²Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; ³Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ, Fukuoka, Japan.

Background: Geriatric Nutritional Risk Index (GNRI) is a simple but useful predictive marker for all-cause and cardiovascular mortality in hemodialysis (HD) patients. However, it is unclear whether the GNRI could predict the infection-related mortality in HD patients. We herein investigated the association between GNRI and the infection-related mortality in Japanese HD patients.

Methods: A total of 3,452 Japanese HD patients aged >18 years were prospectively followed for 4 years. Patients were divided into three groups by tertile of GNRI: Tertile 1 (T1): <92.67; T2: 92.67–98.63; T3: >98.63. We estimated the relationship between GNRI and the all-cause mortality and infection-related mortality using a Cox proportional hazards model. To assess the additional predictive value of GNRI in risk assessment, we compared the c-statistics between serum albumin and GNRI.

Results: During the follow-up period, 566 patients died totally, and 121 patients died of infection-related mortality. All-cause mortality and infection-related mortality increased linearly with lower GNRI levels. After adjusting for confounding risk factors, the GNRI was an independent predictor of not only all-cause but also infection-related mortality (hazard ratio 6.51, 95% confidence interval 3.16–13.4, $p < 0.001$ for T1 vs. T3, and hazard ratio 3.04, 95% confidence interval 1.44–6.43, $p = 0.004$ for T2 vs. T3). When

GNRI was incorporated into a model with potential risk factors instead of serum albumin, the c-statistics increased significantly both in all-cause mortality (0.783 vs. 0.787, p = 0.021) and in infection-related mortality (0.802 vs. 0.812, p = 0.011).

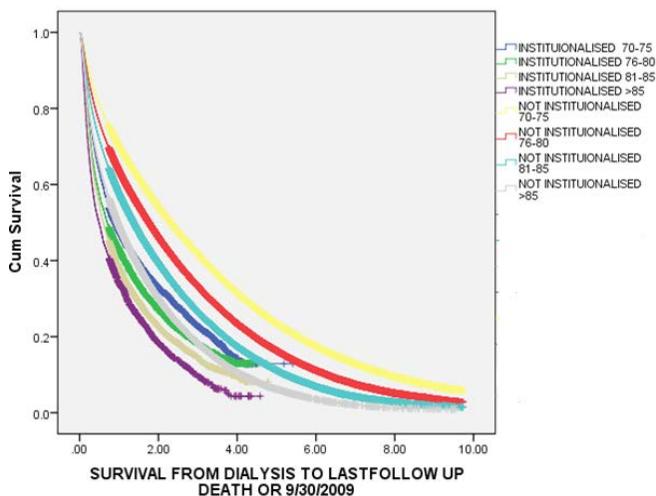
Conclusions: A lower GNRI is strongly associated with infection-related mortality in HD patients, and Our finding suggest that the predictive value of GNRI is superior to serum albumin.

FR-PO759

Survival in Elderly on Dialysis and Impact of Institutionalization
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Background: We hypothesized that in the very elderly dialysis patients in the United States, institutionalization in nursing homes would increase mortality in addition to age alone.

Methods: Data was obtained from the U.S. Renal Data System. Incident dialysis patients from 2001 to 2008 above the age of 70 were included. Follow-up period was from incident dialysis date to either death or last follow up on September 30, 2009. Patients above 70 were categorized into four groups according to age as 70-75 years, 76-80 years, 81-85 years, greater than 85 years and further divided into institutionalized and non-institutionalized.



Results: A total of 349,440 patients were identified above the age of 70 years at the time of initiation of dialysis. Major causes of end stage renal disease were diabetes, hypertension, glomerulonephritis, cystic kidney disease, and urological causes. Mean survival for non institutionalized patients was 3.15 ± 0.01 years for those between 70-75 years of age, 2.55±0.01 years for 76-80 years of age, 2.12±0.01 years for 81-85 years of age and 1.64± 0.01 years for those above 85 years at the time of initiation of dialysis respectively. For institutionalized patients, mean survival was significantly lower, 1.71±0.03 years for 70-75 years old, 1.44± 0.02 years for 75-80 years old, 1.25±0.02 years for 81-85 years old and more than 85 years and 1.04 ±0.02 for > 85 years age group, p=0.0001. The oldest group in non-institutionalized over the age of 85 years had a similar survival as the institutionalized ESRD patients 70-75 years of age.

Conclusions: There was increased mortality in institutionalized elderly patients as compared to non institutionalized elderly patients in the same age group. Keeping with the increased frailty and decreased benefits of therapies in the very elderly especially in those with additional co-morbidities besides age, palliative and end of life care should be considered.

FR-PO760

Geriatric Nutritional Risk Index Is a Simple Predictor of Mortality in Chronic Hemodialysis Patients
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Background: Malnutrition is common in hemodialysis (HD) patients, and it is associated with increasing risk of mortality. The geriatric nutritional risk index (GNRI) has been developed as a tool to assess the nutritional risk. The aim of the present study was to examine the reliability of the GNRI as a mortality predictor in a Japanese HD cohort.

Methods: We prospectively examined the GNRI of 332 maintenance HD patients aged 65.4 ± 13.2 years, 213 males, and followed up on them for 36 months. The patients were divided into quartiles (Q) according to GNRI values (Q1: <91.6, Q2: 91.7-97.0, Q3: 97.1-102.2, Q4: >102.3). Predictors for all-cause mortality were examined using Kaplan-Meier and Cox proportional-hazards analyses.

Results: The GNRI presented a normal distribution. During the follow-up period of 36 months, a total of 76 patients died. The overall mortality at the end of the 3-year observational period was 22.3%. At the 3-year follow-up period, Kaplan-Meier survival rates for all-cause mortality were 72.3%, 79.3%, 84.9%, and 92.6% in Q1, Q2, Q3, and Q4,

respectively (p = 0.0067). Multivariate Cox proportional-hazards analysis demonstrated that the GNRI was a significant predictor of adjusted all-cause mortality (HR 0.958; CI 0.929-0., p < 0.001).

Conclusions: The results of the present study demonstrate that the GNRI is a strong predictor of overall mortality in HD patients. However, cardiovascular mortality was not associated with GNRI values, and did not differ among the GNRI quartiles. The GNRI score can be considered a simple and reliable marker of predictor for mortality risk in Japanese HD patients.

FR-PO761

Frailty and Clinical Outcomes in Chronic Dialysis Patients
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Background: Frailty is a biological syndrome of decreased reserve and resistance to stressors and is independently associated with mortality and hospitalization in the general population. We investigated the relationship between frailty and clinical outcomes in chronic dialysis patients.

Methods: In this prospective study, 1,658 patients receiving chronic dialysis were enrolled. Chronic dialysis was defined as dialysis for more than 6 months. Of the 1,658 patients, 1,255 received hemodialysis. The remainder received peritoneal dialysis. Fried's criteria for frailty as modified by Woods et al. was used. A trained interviewer asked study participants about 5 frailty phenotypes (slowness, weakness, exhaustion, shrinking, and physical inactivity) using the RAND 36-item Short Form.

Results: The mean age was 55.2±11.9, and 55.2% were male. Overall, 577 (34.8%) patients met the study definition of frailty. Another 757 (45.7%) patients were pre-frail. Table 1 shows the prevalence of frailty and its components by age group. During the 30-month follow-up period, 607 patients (79 non-frail, 249 pre-frail, and 279 frail) were hospitalized; and 87 patients (10 non-frail, 24 pre-frail, and 53 frail) died (P<0.001). Frailty was strongly associated with hospitalization (adjusted hazard ratio [HR] 1.80; 95% CI 1.4 to 2.3) and mortality (HR 2.37, 95% CI 1.11 to 5.02) in multivariate analysis. The relationship between frailty and hospitalization was strongest among patients age 40 to 49, with a HR of 3.02 (95% CI 1.48 to 6.20).

Table 1. The prevalence of frailty and its components by age.

	Age group (years)					P value
	< 40	40-49	50-59	60-69	≥ 70	
Frail, %	21.1	20.6	32.8	38.0	63.8	<0.001
Pre-frail, %	57.8	55.9	47.2	41.0	26.5	<0.001
Slowness/Weakness, %	33.0	40.9	35.2	34.6	30.6	0.130
Exhaustion, %	60.8	59.7	65.3	66.2	80.2	0.001
Inactivity, %	58.3	45.6	42.8	35.6	50.6	0.013
Shrinking, %	13.7	7.6	9.8	10.6	10.1	0.777

Conclusions: We found a high prevalence of frailty in chronic dialysis patients across all age groups. The risk of hospitalization and mortality in the 30-month follow-up period significantly increased in frail chronic dialysis patients.

FR-PO762

Outcomes of Early Initiation of Dialysis in Elderly Patients with End-Stage Renal Disease: A Propensity-Matched Analysis of a Prospective Cohort Study
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Background: The optimal timing for initiating dialysis in end-stage renal disease (ESRD) remains controversial, especially in elderly patients. We therefore investigated the effect of dialysis initiation timing on clinical outcomes in elderly patients with ESRD.

Methods: A total of 665 patients aged equal or over 65 years who started dialysis from August 2008 to February 2015 were enrolled in Clinical Research Center for End Stage Renal Disease cohort study in Korea. They were divided into 2 groups based on the median estimated glomerular filtration rate, which was 8.85 mL/min/1.73m². The primary outcome was patient survival and the secondary outcomes were cardiovascular events and Kidney Disease Quality of Life Short Form 36 (KDQOL-36) score.

Results: Overall cumulative survival rates were lower in early initiation group (Log-rank P<0.001). However, the survival rates showed no significant difference after matching propensity score. Additionally, early initiation of dialysis was not associated with survival rates after adjustment for age, sex, Charlson comorbidity index, hemoglobin, serum albumin, serum calcium and phosphorus level. Although the early initiation group showed lower physical component summary in KDQOL-36 at 3 months after dialysis, the difference of the scores was not significant at 12 months after dialysis.

Conclusions: Early initiation of dialysis was not associated with prognosis in elderly patients with ESRD. The physical functioning was worse for 3 months after dialysis but it became similar to late initiation of dialysis at 1 year after dialysis.

FR-PO763

1- and 2-Year Mortality Prediction Models for Patients Starting Chronic Dialysis Mikko Haapio,¹ Jaakko Helve,¹ Carola Gronhagen-Riska,^{1,2} Patrik Finne,^{1,2} ¹Nephrology, Univ of Helsinki and Helsinki Univ Hospital, Helsinki, Finland; ²Finnish Registry for Kidney Diseases, Helsinki, Finland.

Background: Mortality risk of patients with end-stage renal disease (ESRD) is highly elevated compared to patients without ESRD. Taking into account our limited nephrological care resources and the simultaneously increasing number of ESRD patients there is a great need for means of mortality risk estimation to assist both in individualized patient care as well as in sound use of resources. Some mortality prediction models already exist, but many have shown a lack of comprehensiveness in data or in patient recruitment in their development.

Methods: Our objective was to design a prediction model for 1- and 2-year all-cause mortality in patients starting chronic renal replacement therapy. In addition, we aimed to build an easy-to-apply model consisting of only a few variables. We used the comprehensive data of the Finnish Registry for Kidney Diseases with complete coverage of Finnish ESRD patients. Model training group included all incident adult patients who started chronic dialysis in Finland from 1 January 2000 to 31 December 2008 (n=4335). The external validation cohort consisted of all those who started dialysis from 1 January 2009 to 31 December 2012 (n=1768). Prediction algorithms for 1- and 2-year mortality were developed using multivariate logistic regression with stepwise selection of variables. Our primary analyses included 32 variables, from which the most important ones were selected.

Results: Both final prognostic models, including only 6-7 variables, showed adequate discrimination (c-statistic 0.77 and 0.74 for 1- and 2-year mortality, respectively). Because of a significantly lower mortality in the newer (validation) cohort, both models somewhat overestimated mortality risk.

Conclusions: Mortality prediction algorithms could be more widely implemented into clinical treatment-planning of ESRD patients. Our prediction models perform sufficiently and are convenient to use, and could assist in individualized risk-stratification and, furthermore, in equal and fair sharing of limited health care resources.

FR-PO764

Comorbidity Burden at Dialysis Initiation and Mortality: A Retrospective Cohort Study Alwyn Titus Gomez,¹ Bryce A. Kiberd,¹ Talal A. Alfaadhel,² Brenda Hemmelgarn,³ Karthik K. Tennankore.¹ ¹Medicine, Dalhousie Univ, Halifax, NS, Canada; ²Medicine, Univ of Toronto, Toronto, ON, Canada; ³Medicine, Univ of Calgary, Calgary, AL, Canada.

Background: Contemporary assessments of the validity and prognostic value of comorbidity indices in dialysis are lacking. We sought to assess the validity of two comorbidity indices used for dialysis patients and to determine if a high degree of comorbidity was associated with mortality.

Methods: We conducted a retrospective cohort study of incident chronic dialysis patients in a tertiary care institute from 2006-2013. The Charlson Comorbidity Index (CCI) and End-Stage Renal Disease Comorbidity Index (ESRD-CI) were calculated in all patients at dialysis initiation. These indices combine individual medical conditions into an overall score. Comorbid conditions were ascertained using electronic records. The primary outcome was all-cause mortality.

Results: The cohort consisted of 771 patients. Most were male (62%) and Caucasian (91%). Patients had a high prevalence of diabetes (48%) and history of myocardial infarction (31%). The c-index was 0.61 for the CCI, and 0.63 for the ESRD-CI. In an adjusted analysis, ESRD-CI scores of 4, 5 and ≥6 were associated with a similar mortality risk (Table 1). There was a small increased mortality risk for CCI scores of 4, 5 and ≥6.

Conclusions: The CCI and ESRD-CI had a limited ability to discriminate risk of death for incident dialysis patients. Although a higher comorbidity burden was associated with mortality, increases in index scores did not considerably change the risk of death.

Table 1. Multivariable Cox survival analysis for the ESRD-CI and CCI	
End-Stage Renal Disease Comorbidity Index	
Score	Relative Hazard [95% Confidence Interval]*
0/1	Reference
2	1.63 [1.12 to 2.36]
3	1.28 [0.84 to 1.91]
4	1.95 [1.34 to 2.85]
5	1.89 [1.25 to 2.86]
≥6	1.99 [1.41 to 2.81]
Charlson Comorbidity Index	
Score	Relative Hazard [95% Confidence Interval]*
2	Reference
3	1.76 [1.10 to 2.82]
4	1.86 [1.22 to 2.83]
5	2.38 [1.53 to 3.72]
≥6	2.71 [1.81 to 4.06]

*Adjusted for age, sex, race, cause of end-stage renal disease, type of dialysis (hemodialysis or peritoneal dialysis), estimated GFR, albumin, phosphate and hemoglobin

FR-PO765

Cumulative Risk of Death in Propensity-Matched Incident Dialysis Patients: A Nationwide Prospective Multicenter Cohort Study in Korea Hee-Yeon Jung,¹ Sukyung Lee,¹ Ji-Young Choi,¹ Se-Hee Yoon,² Jang-Hee Cho,¹ Sun-Hee Park,¹ Chan-Duck Kim,¹ Yong-Lim Kim.¹ ¹Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; ²Internal Medicine, Konyang Univ, Daejeon, Republic of Korea.

Background: Our previous study reported the superior outcome of peritoneal dialysis (PD) than hemodialysis (HD) in the early dialysis period. This study investigated the impact of dialysis modality after the early period of incident dialysis patients.

Methods: Incident dialysis patients were enrolled from Korean nationwide prospective cohort from September 2008 to December 2013. The patients were stratified by modality at day 90 after the first dialysis or the modality at dialysis initiation if death occurred prior. The survival of PD and HD patients were compared by propensity score matching analysis. Relative risk of death was estimated using the cumulative hazard ratio from the stratified Cox proportional hazard model adjusted for residual confounding.

Results: A total of 1348 patients were matched from 2658 incident dialysis patients with mean follow-up of 29.9 ± 14.1 months. All clinical parameters including baseline residual renal function were comparable between PD and HD patients. The cumulative risk of death was significantly lower in PD than HD from 6 months after dialysis initiation. The cumulative hazard ratio for death was 0.70 (95% confidence interval [CI] 0.41-0.98) at one year for PD compared with matched HD and 0.68 (95% CI 0.46-0.90) at two years. The cumulative survival probability was higher in PD patients for up to 3.5 years on dialysis, with no difference after the period.

Conclusions: Overall survival in maintenance dialysis patients favored PD in the early period of dialysis and the survival advantage lasted to 3.5 years after initiation of dialysis. However, PD and HD patients had similar survival outcomes thereafter.

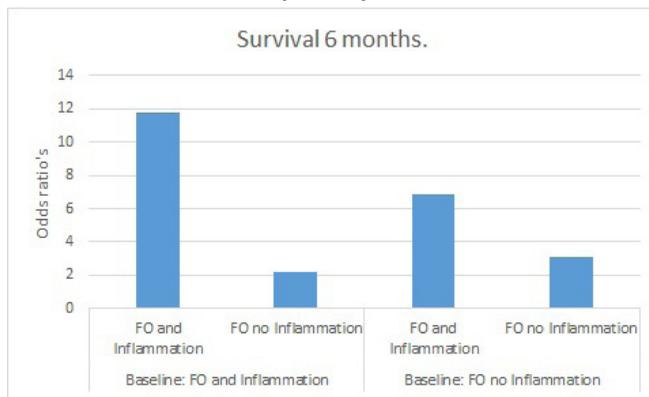
FR-PO766

Inflammation and Fluid Overload a Complex Interaction: Results from the International MONDO Initiative Marijke J.E. Dekker,¹ Len A. Usvyat,^{2,3} Daniele Marcelli,³ Frank van der Sande,⁴ Constantijn Konings,¹ Peter Kotanko,² Jeroen Kooman.⁴ ¹Catharina Hospital Eindhoven; ²Renal Research Inst; ³Fresenius Medical Care; ⁴Maastricht Univ Medical Center.

Background: In hemodialysis (HD) patients, the presence of inflammation or fluid overload (FO) is associated with increased mortality. The combined presence of these two is associated with even a greater risk of death. This study aims to unravel the temporal relationship between fluid status alterations and inflammation.

Methods: We conducted a longitudinal study (baseline and follow-up 3 months each) in a European subset of the MONDO-Initiative. Fluid status was assessed by multifrequency bioimpedance and inflammation by C-reactive protein (CRP). We divided patients into 4 groups based on fluid- and inflammation status. FO was defined as overhydration above >2.5L. Inflammation was defined as CRP >10mg/L.

Results: We included 5954 patients (56.1% male, age 63 years, vintage 5.1 years). At baseline inflammation and FO were jointly present in 1092 (18.3%) patients. 141 (11.8%) developed inflammation during follow up. Of the 1192 (20%) patients with inflammation but with normal fluid status at baseline, 111 (10.2%) had FO during follow up. Inflammation at baseline predicted FO during follow up (odds ratio(OR) 1.20(95% CI 1.05-1.37)). Likewise, FO during baseline predicted inflammation during follow up (OR 1.30 (95% CI 1.15-1.47)). However, in a minor of patients the presence of FO and/or inflammation appears to be a relatively stable condition. The presence of both inflammation and FO during baseline was associated with an increased mortality risk compared to the absence of both.



Conclusions: FO and inflammation are associated in prevalent HD patients. FO is a predictor for inflammation and vice-versa inflammation predicts FO. The combined presence of FO and inflammation is associated with poor survival.

FR-PO767

Blood Volume Analysis as a Guide for Dry Weight Determination in Chronic Hemodialysis Patients Line Malha,^{1,2} Hasan Fattah,³ Frank Modersitzki,¹ David S. Goldfarb,^{1,2} ¹Internal Medicine, Div of Nephrology, NYU School of Medicine, New York, NY; ²Internal Medicine, Nephrology Section, New York Harbor VA Healthcare System, New York, NY; ³Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ Medical Center, Richmond, VA.

Background: Volume overload and depletion both lead to high morbidity and mortality. Achieving euvolemia is a challenge in patients with end stage kidney disease (ESKD) on hemodialysis (HD). Blood volume analysis (BVA) uses radiolabeled albumin to determine intravascular blood volume (BV). The measured BV is compared to an ideal BV (validated in healthy controls). We hypothesized that BVA could be used in HD to evaluate the adequacy of the current clinically prescribed "estimated dry weight" (EDW) and to titrate EDW in order to improve overall volume status. We were also interested in the reproducibility of BVA results in ESKD. This is the first longitudinal study of BVA in HD patients.

Methods: 12 adults on chronic HD were recruited; 10 completed the study. BVA (Daxor, New York, NY, USA) was used to measure BV at baseline. EDW was kept the same if the patient was deemed to be euvolemic by BVA otherwise, the prescribed EDW was changed with the aim that measured BV would match ideal BV. A second BVA measurement was done 1-3 months later in order to measure BV again.

Results: Based on BVA, 6/10 patients were euvolemic at baseline and 5/10 were euvolemic at the second measurement. When comparing patients who had their prescribed EDW changed after the initial BVA to those who did not, both groups had similar differences between measured and ideal BV (P=0.75). BV values were unchanged at the second measurement (P=0.34) and there was no linear correlation between BV change and weight change (r²=0.8).

Conclusions: This pilot study is the first longitudinal measurement of BVA in HD patients. It revealed that changing weight did not proportionally change intravascular BV. BV remained stable for 1-3 months. BVA may not be helpful in clinically stable HD patients but studies on patients with hemodynamic instability and uncertain volume status are needed.

Funding: Pharmaceutical Company Support - Daxor provided BVA equipment and supplies but was not involved in study design or execution and did not participate in the analysis of data or preparation of the manuscript

FR-PO768

Effects of Physician Payment Reform on Provision of Home Dialysis Kevin F. Erickson,¹ Wolfgang C. Winkelmayer,² Glenn Matthew Chertow,¹ Jay Bhattacharya,¹ ¹Medicine, Stanford Univ, Palo Alto, CA; ²Medicine, Baylor College of Medicine, Houston, TX.

Background: Patients with end-stage renal disease can receive dialysis at home or in-center. In 2004 the Centers for Medicare and Medicaid Services reformed physician payment for in-center hemodialysis care from a capitated to a tiered fee-for-service model, augmenting physician payment for frequent in-center visits. We evaluated whether payment reform influenced dialysis modality assignment.

Methods: Using a national cohort of patients starting dialysis in the US in the three years before and after payment reform, we conducted difference-in-difference analyses comparing patients with Traditional Medicare coverage (who were affected by the policy) to others with Medicare Advantage (who were unaffected by the policy). We also examined whether the policy had a more pronounced influence on dialysis modality assignment in areas with lower costs of traveling to dialysis facilities.

Results: Patients with Traditional Medicare coverage experienced a 12% (95% CI, 2% to 21%) reduction in home dialysis use following payment reform compared to patients with Medicare Advantage. Patients living in areas with larger dialysis facilities (where payment reform made in-center hemodialysis comparatively more lucrative for physicians) experienced a 16% (95% CI, 8% to 23%) reduction in home dialysis use following payment reform compared to patients living in areas with smaller facilities (where payment reform made in-center hemodialysis comparatively less lucrative for physicians).

Conclusions: National physician payment reform intended to improve the quality of dialysis care resulted in fewer patients receiving home dialysis. This highlights a major failure of the policy and the importance of considering unintended consequences of future physician payment reform efforts.

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FR-PO769

Characteristics and Outcomes Amongst Patients Who Switch Dialysis Provider Scott Reule, Paul E. Drawz, Robert N. Foley. *Dept of Medicine, Univ of Minnesota, Minneapolis, MN.*

Background: Associations between provider switch and inferior clinical outcome have been demonstrated in primary care settings. It is plausible that similar associations extend into those on renal replacement therapy (RRT) as nephrology care often extends beyond that of RRT management alone. There is a paucity of literature available describing the characteristics and outcomes amongst those whom switch dialysis provider.

Methods: Using USRDS data, a change in provider will be defined the presence of any non-contiguous facility codes while receiving maintenance RRT. As patients transitioning to maintenance RRT may experience early adverse outcomes, only those patients having

initiated RRT with a vintage of at least 1 year were included in the analysis. Means and proportions were calculated for continuous and categorical variables, respectively. Logistic regression was used for adjusted comparisons with adjustments for baseline demographic characteristic including age, sex, and race. All estimates with p-value < 0.05 were considered significant.

Results: Applying these criteria, a total of 187,510 (9.1%) of prevalent patients requiring RRT were identified as having changed provider at least once. The mean age of those who have changed provider (vs. no change) was 41.3 years (vs. 57.3 years), 57% were male (vs. 55.1%), 51.3% were white (vs. 49.1%), diabetes as comorbidity in 29.9% (vs. 49.4%), heart disease in 10.9% (vs. 21.1%), and 23.2% utilized peritoneal dialysis at initiation (vs. 9.75%). Risk of death was lower in those who change provider (OR 0.69; CI 0.68 – 0.70) and odds were higher for both listing for (OR 2.9; CI 2.9 – 3.0) and receipt of renal transplantation (OR 4.1; CI 4.0-4.2).

Conclusions: Patients who switch dialysis providers constitute a distinct population of patients who are younger and lack comorbid conditions frequency observed in those on dialysis. Compared to those who do not switch providers, those who switch are more likely to be listed for and receive renal transplant.

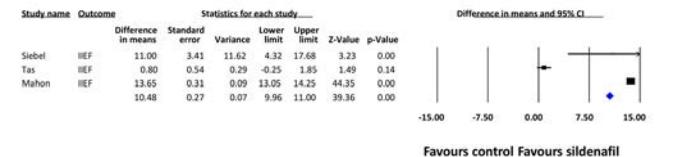
FR-PO770

Effects of Sildenafil in Dialysis Patients with Erectile Dysfunction: A Systematic Review and Meta-Analysis Anawin Sanguankeo,^{1,2} Sikarin Upala,^{1,2} ¹Internal Medicine, Bassett Medical Center and Columbia Univ College of Physicians and Surgeons, Cooperstown, NY; ²Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

Background: Erectile dysfunction (ED) is prevalent in dialysis patients. Sildenafil, a PDE-5 inhibitor, has been shown to be very effective against ED in general population. However, there is some evidence that dialysis patients are resistant to sildenafil treatment. We performed this meta-analysis to evaluate efficacy of sildenafil in dialysis patients with ED compared with control.

Methods: We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published RCT comparing sildenafil therapy to placebo or controls on ED in patients with dialysis. The primary outcome was change in International Index of Erectile Function (IIEF) score. The diagnosis of ED was confirmed with a score of 21 or less in IIEF.

Results: From 153 full-text articles, 3 studies involving 153 dialysis patients were included in the meta-analysis. All included studies were RCT comparing sildenafil with active control in either hemodialysis or peritoneal dialysis patients. A meta-analysis using fixed-effects model was performed. Those who received sildenafil had a significant improvement in IIEF with a MD of 10.48 (95% CI: 9.96 to 11.00, p-value<0.01).



Conclusions: This is the first meta-analysis to show that sildenafil is effective in dialysis patients with erectile dysfunction compared with control. Further study comparing other benefits and side effects of PDE-5 inhibitor in dialysis patients should be conducted.

FR-PO771

Validation of Screening Questionnaires for Sleep Apnea in Hemodialysis Population Farhanah Yousaf, Mitesh K. Patel, Saw H. Mu, Alla Goldberg, Chaim Charytan, Bruce S. Spinowitz. *New York Hospital Queens.*

Background: Sleep apnea hypopnea syndrome (SAHS) is common in end stage renal disease (ESRD). We investigated the validity of Berlin and STOP-BANG questionnaires against nocturnal oximetry in identifying high risk hemodialysis patients for SAHS.

Methods: After obtaining local IRB approval, adult hemodialysis patients who were undergoing regular chronic hemodialysis for at least 3 months were consented and asked to complete Berlin and STOP-BANG questionnaires. Nocturnal oximetry from hemodialysis night using Pulsox 300i wristwatch was also completed. The saturation recordings were downloaded and analyzed using Profox software. The first hour of recording was deleted in efforts to capture oximetry reading from sleep time only. Motion artifacts and aberrant data were also excluded from analysis. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds, per hour. Sensitivity, specificity, positive and negative predictive values were calculated for the Berlin and STOP-BANG questionnaires.

Results: Twenty HD patients (11 males and 9 females) aged 54 ± 13 years with a mean body mass index of 25.5 ± 4.6 kg/m² and neck circumference of 38.4 ± 5.8 cm participated in the study. ODI was ≥ 5 in 80% of patients. Both Berlin and STOP-BANG questionnaires had modest sensitivities (69-71%) but poor specificities (17-50%). Positive predictive value and negative predictive value was 67% and 67% for Berlin questionnaire, respectively. STOP-BANG questionnaire had a positive predictive value of 85% and a negative predictive value of 29%.

Conclusions: Reliable screening tools for SAHS in ESRD population are limited. Both Berlin and STOP-BANG questionnaires lack specificity to be utilized in this setting. Additional studies are warranted to elaborate the role of screening questionnaires for SAHS in end stage renal disease population.

FR-PO772

Moderate to Severe Nocturnal Hypoxemia and Executive Dysfunction in Patients Undergoing Maintenance Hemodialysis Farhanah Yousaf, Mitesh K. Patel, Chaim Charytan, Alla Goldberg, Bruce S. Spinowitz. *New York Hospital Queens.*

Background: Nocturnal hypoxemia and executive dysfunction is common in end stage renal disease. We investigated the impact of moderate to severe nocturnal hypoxemia on executive function in patients undergoing maintenance hemodialysis.

Methods: Following local IRB approval, adult hemodialysis patients were consented to complete 1 night of nocturnal oximetry using Pulsox 300i wristwatch. The first hour of recording was deleted in efforts to capture oximetry reading from sleep time only. Oxygen desaturation index (ODI) was defined as the number of desaturations $\geq 3\%$ from baseline lasting ≥ 10 seconds, per hour. Trail making tests A and B were also completed during dialysis session. Trail making test A and B performance was compared using t-test in patients with ODI < 15 versus those with ODI ≥ 15 . Executive dysfunction was defined as trail making A and B completion time > 75 seconds and 180 seconds, respectively.

Results: Nine of 20 patients aged 45 ± 12 years with a mean body mass index (BMI) of 23 ± 3 kg/m² and neck circumference of 35 ± 4 cm had ODI < 15 . The remaining eleven patients aged 60 ± 12 years with a mean BMI of 28 ± 5 kg/m² and neck circumference of 41 ± 6 cm had ODI ≥ 15 . Patients with ODI ≥ 15 took significantly longer (77 ± 34 seconds) to complete trail making test A versus patients with ODI < 15 (45 ± 23 seconds). Five of 11 (45%) patients with ODI ≥ 15 required > 75 seconds to complete trail making test A compared to only 1 patient out of 9 (11%) with ODI < 15 . Mean duration for completion of trail making B test was also longer in patients with ODI ≥ 15 (157 ± 87 seconds) compared to ODI < 15 (117 ± 67 seconds) [$p=0.3$]. Two of 11 patients with ODI ≥ 15 and 2 of 9 patients with ODI < 15 required > 180 seconds to complete trail making test B.

Conclusions: Patients with ODI < 15 performed better on trail making test A, were younger with a smaller BMI and neck circumference, compared to those with ODI ≥ 15 . Additional research is warranted to confirm these findings. Whether treatment of moderate to severe nocturnal hypoxemia may slow or prevent executive function decline in patients undergoing maintenance hemodialysis remains to be determined.

FR-PO773

Indoxyl Sulfate (Indican) and Sleep Disorders in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study Yunuo Zhu,¹ Tanushree Banerjee,¹ Tariq Shafi,² Timothy W. Meyer,³ Michal L. Melamed,⁴ Thomas H. Hostetter,⁵ Neil R. Powe.¹ ¹UCSF; ²JHU; ³Stanford; ⁴Albert Einstein; ⁵Case Medical Center.

Background: Although sleep disorders are common in dialysis patients, the pathophysiology of sleep disturbance is unclear. Protein-bound solutes inadequately removed during dialysis may contribute to sleep disorders.

Methods: We examined the association of total and free levels of IS with sleep disorder in 1,241 prevalent dialysis patients from the HEMO study. IS levels were measured using mass spectroscopy and modeled as tertiles. Sleep disorder was assessed using a 5-level categorical question in the Short Form (36) Health Survey. We used ordinal logistic regression to assess the relation of IS with sleep disorder, adjusting for confounders including age, race, gender, ICED score, body mass index, diabetes, congestive heart failure, serum albumin, creatinine, and phosphate levels. The lowest tertile of IS was the reference group. Effect modification was tested for IS levels with Kt/V and gastrointestinal (GI) disease (due to IS's GI origin).

Results: Patients were on average 57.5 years old, 62.8% were black, and 43.2% were male. There was a significant association between increasing tertiles of free IS and more severe sleep disorder in both unadjusted [OR 1.44 (95% CI: 1.1-1.89)] and adjusted models [1.78 (1.24-2.58)]. There was effect modification by Kt/V ($p=0.03$) but none by GI disease ($p=0.17$). Similar results were observed with total IS and sleep disorder [2.09 (1.37-3.19)]. Stratified analyses by Kt/V did not show an association between higher tertiles of free IS and sleep disorder in the high Kt/V group [0.72 (0.45-1.14)]. However greater odds of sleep disorder with highest tertile of IS were noted in the low Kt/V group. This relation was also present for total IS; those with low Kt/V had greater odds of sleep disorder with the highest total IS tertile [2.11 (1.29-3.45)] but not with the high Kt/V group [0.91 (0.61-1.35)].

Conclusions: Higher levels of IS are significantly associated with sleep disorder. Patients with a lower dialysis dose may be more susceptible. Further research on whether removal of IS improves sleep outcomes is needed.

FR-PO774

Quantifying Physical Activity Levels and Sleep in Hemodialysis Patients Using a Commercially-Available Activity Tracker Maggie Han,¹ Schantel Williams,¹ Anna Meyring-Wosten,¹ Viviane Calice-Silva,^{1,2} Melissa Mendoza,¹ Hanjie Zhang,¹ Xiaoling Ye,¹ Stephan Thijssen,¹ Peter Kotanko.^{1,3} ¹Renal Research Inst, New York, NY; ²Pontificia Univ Católica do Paraná, Curitiba, Brazil; ³Icahn School of Medicine, New York, NY.

Background: Hemodialysis (HD) patients are less active than their healthy counterparts (Johansen, Kidney Int, 2000). In addition, HD patients frequently experience poor sleep. Our aim was to objectively quantify activity and sleep quality in HD patients.

Methods: The number of steps taken and sleep data were collected by the Fitbit®Flex™ in ambulatory chronic HD patients for 5 weeks. A questionnaire was given at the end of the study. Sleep efficiency is defined as the ratio of sleep duration to time in bed.

Results: We collected data of 22 HD patients (55% males, 86% black, age 54 ± 10 years). Average steps walked were $7,584 \pm 5,429$ (Table 1). 36% of patients were sedentary, walking less than 5,000 steps per day. Patients walked 2,000 steps less on Sundays compared to the rest of the week ($P < 0.0001$). Slightly more steps were taken on HD days. Patients slept less than 6 hours, which was significantly less than the NIH recommendation of 7 hours ($P < 0.0001$). Sleep efficiency was $80 \pm 14\%$, significantly less than 85%, the lower limit of what is defined as poor sleep quality ($P < 0.05$). When asked to what extent they agreed with the statement "I have walked more than usual", 36% replied "not at all", 23% replied "somewhat" or "moderately", and 41% replied "definitely" or "most definitely".

Table 1

All Days	Physical Activity[Steps/d]				Sleep Quality	
	HD Day	Non-HD Day	Monday-Saturday	Sunday	Sleep Duration† [min/day]	Sleep Efficiency‡ [Sleep Duration/time in bed]
7,584±5,429	7,859±5,007	7,390±5,707	7,879±5,508	5,851±4,594**	340±145**	80±14%*

* $P < 0.05$
 ** $P < 0.0001$
 †NIH recommends 420 min/day
 ‡ < 0.85 is poor sleep quality

Conclusions: The activity tracker was well accepted by patients. Programs and interventions to increase activity should target Sundays in particular. The described methodology may assist in identifying patients with poor sleep quality and facilitate the deployment of programs to improve sleep quantity and quality.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO775

Using Decision Tree Analysis to Identify Risk Factors for Functional Impairment in Hemodialysis Patients J. B. Chen. *Div of Nephrology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung Univ College of Medicine, Kaohsiung, Taiwan.*

Background: Hemodialysis (HD) patients frequently developed functional impairment. The study used decision tree analysis to identify risk factors for functional impairment in HD patients.

Methods: A total 1166 maintenance HD patients were enrolled in one hospital-based HD center. The observational period was from 2009 to 2013. Karnofsky Performance Status Scale (KPS) was used to quantify functional status. KPS assessment was based on HD nurse single visit yearly for consecutive five years. High KPS score was defined as ≥ 80 and low score as < 80 . Decision tree analysis was used to analyze odds ratio (OR) of functional impairment from variables in demographics, laboratory test and primary renal disease classification.

Results: Subjects (853) with high KPS scores demonstrated significantly younger age (58.2 vs 71.3 years), longer HD duration (7.2 vs 4.7 years), higher nutritional indices, higher Kt/V (1.65 vs 1.59) and lower cardiothoracic (CT) ratio compared to subjects (313) in low KPS scores. A total 3509 KPS values were collected. 2697 (76.9%) values belonged to high functional scores, 812 (23.1%) values in low functional scores. The first variable chosen by decision tree analysis to split the data was age (67.5 years). There were six leaf nodes and twenty-eight subgroups. In age > 67.5 years group, the orders of consecutive chosen were serum albumin level (≤ 3.75 g/dL, OR 27.58, $p = 1.77E-199$), Cr level (≤ 8.93 mg/dL, OR 5.60, $p = 1.68E-37$), HD duration (≤ 0.95 year, OR 39.40, $p = 1.68E-27$), ferritin (> 664.5 ng/ml, OR 26.26, $p = 2.06E-13$), P level (> 5.35 mg/dL, OR 9.28, $p = 8.88E-24$), Hb level (> 10.85 g/dL, OR 0.89, $p = 1.00$). In age ≤ 67.5 years group, the orders of consecutive chosen were primary renal disease classification, Cr level (≤ 10.43 mg/dL, OR 11.23, $p = 2.03E-72$), age (≤ 58.5 years, OR 1.65, $p = 0.06$), iPTH level (> 356.4 pg/ml, OR 0.44, $p = 0.72$), CT ratio (> 0.44 , OR 11.16, $p = 9.17E-35$).

Conclusions: By decision tree analysis, age was the main risk factor for functional impairment in HD patients. Overall, the weight contribution of different risk factors for functional impairment in HD patients were identified by classification tree analysis.

Funding: Private Foundation Support

FR-PO776

Working Patients and Years on Dialysis: A Review Deborah S. Evans,¹ Duane V. Dunn,¹ Martha Donaho,¹ Laura M. Stewart,¹ Rich Mutell,² Paul J. Broughton,² Allen R. Nissenson,¹ Deborah A. Benner.¹ ¹DaVita HealthCare Partners Inc, Denver, CO; ²Apex Health Innovations, Simi Valley, CA.

Background: Unemployment rates are high among dialysis patients; a 2011 study found approximately 71% of working-age dialysis patients are unemployed.¹ Another study found that dialysis negatively impacts employment status and has the largest effect between dialysis years 1 and 2.² We examined whether prolonged dialysis (dialysis vintage) affected employment status.

Methods: Dialysis vintage data and mean age were obtained from a sample of 16,069 employed patients from a large dialysis organization (Nov 2014-April 2015). Employment status was defined as regular full-time (≥ 30 hrs/wk), regular part-time (< 30 hrs/wk), and per diem (< 24 hrs/wk).

Results: Regular full-time employed patients were older (52.6 yrs) than part-time (49.1 yrs) and per diem (49.0 yrs) patients. Employment status was highest among all patients for all categories of employment during year 1 of dialysis (35.7%) and dropped significantly by year 2 (14.4%) [Table]. Employment status continued to drop as vintage

increased and was lowest in the 10-year group (1.9%). Although there were more full-time employed patients in year 1 (42.4%) than part-time (28.3%) or per diem (28.9%), by year 10, only 1.3% remained employed full-time. Employment status rates were similar among per diem and part-time employees.

Table. Employment Status and Dialysis Vintage Among Surveyed Adult Dialysis Patients at a Large Dialysis Organization

Employment Status	Mean Age (years)	Years on Dialysis (Vintage)										Total	
		1	2	3	4	5	6	7	8	9	10		10+
Regular Full-Time	52.6	n 3553	1191	907	630	469	345	276	206	177	112	507	8373
	%	42.4	14.2	10.8	7.5	5.6	4.1	3.3	2.5	2.1	1.3	6.1	100
Regular Part-Time	49.1	n 1585	787	633	496	437	358	249	197	171	150	537	5600
	%	28.3	14.1	11.3	8.9	7.8	6.4	4.4	3.5	3.1	2.7	9.6	100
Per Diem <24 Hours	49.0	n 605	332	265	191	136	119	96	68	53	43	188	2096
	%	28.9	15.8	12.6	9.1	6.5	5.7	4.6	3.2	2.5	2.1	9	100
Total	50.2	n 5743	2310	1805	1317	1042	822	621	471	401	305	1232	16,069
	%	35.7	14.4	11.2	8.2	6.5	5.1	3.9	2.9	2.5	1.9	7.7	100

Conclusions: Our study found that dialysis vintage negatively impacts employment status and has the largest effect between years 1 and 2. Further study is needed to reveal if any underlying factors contribute toward this decrease, but these results should alert dialysis staff that support and intervention may be needed to help patients stay employed. References: 1) Muehrer RJ et al. Clin J Am Soc Nephrol. 2011;6(3):489-496. 2) van Manen JG et al. Perit Dial Int. 2001;21(6):595-601.

FR-PO777

Provider Visit Frequency During Hemodialysis and Its Effect on End Stage Renal Disease Comorbidities Juan E. Kusnir, Roberto J. Echeverri, Joslyn Wiley, Hazem Abu Grara, Rene Armando Garcia, Alberto J. Sabucedo, Marco A. LadinoAvellaneda. Div of Nephrology, Miami VA Medical Center/Univ of Miami, Miami, FL.

Background: In the United States, patients with End Stage Renal Disease (ESRD) on Hemodialysis visit their Nephrologist one to four times per month during their dialysis sessions. Medicare reimbursement policy encourages frequent provider visits for patients with ESRD on hemodialysis. We believe that increasing the number of face-to-face provider visits improves the care and clinical outcomes of comorbidities related to ESRD (hypertension, hyperphosphatemia, and hyperkalemia).

Methods: We used a Pre and Post-test pilot study design to evaluate the effect on laboratory measurements and blood pressure by increasing the frequency of Nephrologist face-to-face visits at the Miami VA Medical Center. Seventeen patients that were evaluated during a period of six months were included in the analysis. In the initial three months, the patients were evaluated four times per month (usual care). The number of face-to-face visits was increased to eight times per month (or twice weekly) for the following three months.

Results: A paired-sample t-test was conducted to compare the mean systolic blood pressure measure before and after the intervention. Additional provider face-to-face visits per month were associated with a significant difference in the systolic blood pressure before and after the intervention (p= 0.004, t=3.303, Mean=8.235, and Standard Deviation=16). In addition, we found improvement of the phosphorus levels with a difference that was statistically significant (p= 0.028, t=2.419, Mean=0.512, and Standard Deviation=16). Patients reported increased perceived quality of care when they had the opportunity of seeing the Nephrologist more frequently.

Conclusions: Hypertension and electrolyte abnormalities are known risk factors that increase morbidity and mortality in patients with End Stage Renal Disease. Adherence to medications is a major problem in patients on Hemodialysis therapy. Increasing the number of visits per month with the Nephrologist during Hemodialysis sessions increases adherence to a renal diet, medication use and patient satisfaction.

FR-PO778

Response Rate of Hepatitis B Virus Vaccination in Various Stages of Chronic Kidney Disease So Mi Kim,¹ Eun kyoung Lee,² Yun Jung Oh.³ ¹Division of Nephrology, Dept of Internal Medicine, Jeju National Univ Hospital, Jeju, Jejudo, Republic of Korea; ²Division of Nephrology, Dept of Internal Medicine, Dankook Univ Hospital, Cheonan, Chungnam, Republic of Korea; ³Division of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Jedudo, Republic of Korea.

Background: Although hepatitis B virus (HBV) vaccination is recommended for all dialysis patients, the response rate of HBV vaccination in dialysis patients is very low. Therefore, we tried to investigate the necessity of early HBV vaccination in pre-dialysis patients analyzing the response rate of vaccination in various stages of chronic kidney disease (CKD).

Methods: A total of 87 patients in 3 different stages of CKD was enrolled in this study. Patients in stage 3 (n=30) and 4 (n=28) were received the HBV vaccine as standardized schedule, consisting of 1 mL of the recombinant vaccine, Hepavax-gene TF at 0, 1, and 6 months. And then, the patients with stage 5 (n=29) were received the same vaccine for doubling doses at 0, 1, 2, 6 months. Three months after each of the last vaccination, serum level of Anti-HBs was measured in all patients.

Results: There was no significant difference in baseline characteristics including age, sex, presence of DM among the 3 groups. The overall seroconversion rate after vaccination was 79.4%. The seroconversion rate was significantly higher in patients with stage 3 than other patients (stage 3 : 94%, stage 4 : 79%, stage 5: 66%, p=0.031). Analyzing based on dialysis, seroconversion rate was also significantly higher in pre-dialysis patients than that in dialysis patients (pre-dialysis group : 86%, dialysis group: 63%, p=0.02). There was no significant factor to contribute seroconversion in multivariate analysis.

Conclusions: Our study showed the high seroconversion rate after HBV vaccination in CKD patients with stage 3 and pre-dialysis. Therefore, the HBV vaccination should be considered in early CKD stages.

FR-PO779

Hepatitis C Infection in Hemodialysis Patients Is Associated with Increased Anemia-Related Events in the DOPPS Brian Bieber,¹ Michel Y. Jadoul,² Paul Martin,³ Takashi Akiba,⁴ Chizoba Nwankwo,⁵ Jean Marie Arduino,⁵ Ronald L. Pisoni,¹ David A. Goodkin.¹ ¹Arbor Research Collaborative for Health; ²Univ Catholique de Louvain; ³Univ of Miami; ⁴Tokyo Women's Medical Univ; ⁵Merck & Co., Inc.

Background: Hepatitis C virus infection (HCV) remains common among hemodialysis (HD) patients, is associated with elevated mortality risk, and is rarely treated. The association of HCV with anemia-related events is not well characterized.

Methods: The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective cohort study of adult in-center HD patients (pts) in 21 countries, including nations recently joining the DOPPS (China, Russia, Turkey, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates). We studied 67,290 pts in DOPPS phases 1-5 (1996-2015). Pts were considered to have HCV infection (HCV+) at DOPPS enrollment based on an established diagnosis of HCV infection or positive HCV serology. Associations of HCV with transfusions, GI bleed hospitalizations, and Hgb excursions below 8.5 g/dL were estimated via Cox regression (adjustments listed in table).

Results: HCV+ (vs. HCV-) pts were younger (58 vs. 63 yrs), had longer time on dialysis (3 vs. 8 yrs), and were more likely to have hepatitis B (8% vs. 2%) and cirrhosis (9% vs. 1%). Mean baseline Hgb levels for HCV+ pts were similar to HCV- pts (10.8 vs. 10.9 g/dL) and ESA doses by region were similar. In adjusted analyses, HCV+ pts were more likely to be transfused, be hospitalized for a GI bleed, and to have their Hgb drop below 8.5 g/dL (table).

Table: Anemia-related events for HCV+ vs. HCV- patients

Anemia Event	HCV status	N Events	Crude Rate ^a	Unadjusted HR ^b (95% CI)	Adjusted HR ^c (95% CI)
Transfusion ^d	+	237	48.2	1.33(1.16-1.52)	1.43(1.25-1.64)
	-	2600	43.7		
Hgb < 8.5 g/dL ^e	+	1399	239.1	1.11(1.02-1.20)	1.16(1.07-1.25)
	-	13726	208.5		
GI bleed ^f	+	103	12.8	1.16(0.93-1.45)	1.22(0.98-1.51)
	-	988	11.7		

- a. Time to first event (per 1000 patient years)
- b. Stratified by DOPPS country and phase and accounting for facility clustering
- c. Stratified by DOPPS country and phase and accounting for facility clustering; adjusted for age, sex, time on dialysis, 13 summary comorbidities and hepatitis B infection, hemoglobin, albumin, phosphorus, creatinine, and ESA dose
- d. N=46,395 patients; Excludes DOPPS phase 1 where transfusions were not included as an option on the hospitalization worksheet; In DOPPS 2-3 transfusions were only ascertained on the hospitalization worksheet (as inpatient or outpatient events); in phases 4 and 5, transfusion events were additionally captured every month on the interval summary; however, dialysis units may not be aware of or record all blood transfusions that their HD patients receive when transfusions occur outside the dialysis facility; US large dialysis organizations in DOPPS 4 and 5 were excluded due to differential reporting of hospitalization cause
- e. N=59,253 patients; Restricted to patients with baseline Hgb ≥ 8.5 g/dL
- f. N=67,290 patients

Conclusions: The disease burden of HCV+ pts on HD includes a greater likelihood of experiencing anemia requiring transfusion. The reasons for this are unclear but may include gastrointestinal blood loss due to portal hypertension as well as hypersplenism. Anemia in turn may contribute to a reluctance to initiate antiviral therapy for HCV infection.

Funding: Pharmaceutical Company Support - Merck & Co., Inc, Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGFN, Shire, WiNe Institute, Societa Italiana di Nefrologia (SIN). All grants are made to Arbor Research Collaborative for Health., Private Foundation Support

FR-PO780

Outbreaks of Hepatitis C Virus Infection Reported in U.S. Hemodialysis Facilities, 2008-2014 Duc B. Nguyen, Melissa Collier, Anne Moorman, Yury Khudiyakov, Priti R. Patel. US Centers for Disease Control and Prevention.

Background: Hepatitis C virus (HCV) infection is more prevalent among hemodialysis (HD) patients than the general population. HCV transmission of in dialysis units may contribute, and is difficult to detect due to lack of symptoms and systematic screening. We summarized HCV outbreaks reported to CDC to characterize their frequency and factors contributing to transmission in HD facilities.

Methods: We defined a healthcare-associated outbreak as ≥2 new HCV infections (positive anti-HCV 1 year after negative anti-HCV, or positive anti-HCV with acute hepatitis) in the same facility. We reviewed outbreaks in 2008-2014 reported to CDC. For HD unit outbreaks, we summarized type of facility, number of new cases, number of patients notified for HCV testing, infection control lapses identified, and results of HCV molecular testing. Intrafacility transmission was confirmed if there was epidemiologic and molecular evidence of transmission.

Results: During 2008-2014, 22 outbreaks of HCV infection in healthcare settings were reported to CDC; 11 (50%) of these outbreaks occurred in outpatient HD clinics. Seventy-nine (median 4, range 2-21) new HCV infections were identified. More than 1,800 HD patients were notified and screened for HCV in outbreak facilities. Intrafacility HCV transmission was confirmed in all 11 outbreaks. New cases had treatment time and location overlap with their HCV-infected source patient. For 9 outbreaks, lapses in infection control were identified, including environmental disinfection (8), hand hygiene (5), injectable

medication handling (3), separation of clean and contaminated workspaces (2), and vascular access care (1). Multiple lapses were identified in 7 outbreaks. No specific infection control lapses were identified at the time of the investigation in 2 outbreaks.

Conclusions: Outpatient hemodialysis clinics remain a common setting for healthcare-related HCV outbreaks. Infection control lapses were frequently identified in reported outbreaks. Rigorous adherence to recommended infection control practices is needed to protect patients and prevent future outbreaks in this setting.

Funding: Other U.S. Government Support

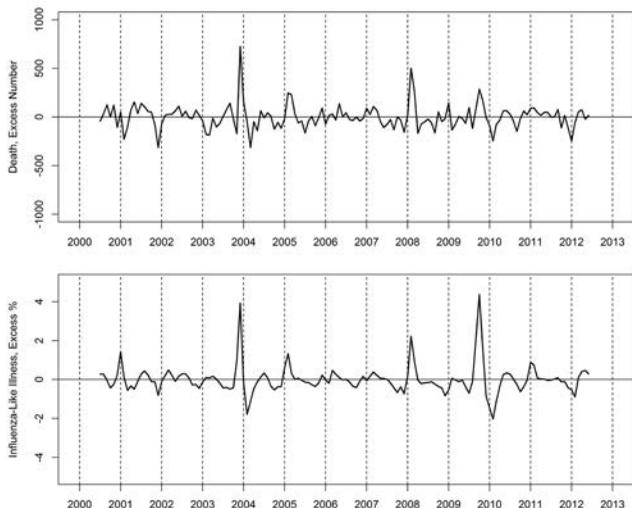
FR-PO781

Influenza and Outcomes in ESRD Patients David T. Gilbertson,¹ Anne C. Beaubrun,² Kenneth J. Rothman,³ Jiannong Liu,¹ Brian D. Bradbury,² Akhtar Ashfaq,² Charles A. Herzog,¹ Allan J. Collins.¹ ¹Chronic Disease Research Group, MMRF; ²Ctr for Observational Rsrch, Amgen; ³RTI Health Solutions.

Background: Yearly influenza vaccination is recommended for all ESRD patients, due to a high risk of influenza-related complications. Through the CDC's Outpatient Illness Surveillance, information on patient visits to health care providers for influenza-like illness (ILI) is collected. These data give estimates of the percent of all OP visits that are for presumed influenza, and give national information on timing and severity of each influenza season. We assessed the association between CDC ILI data and outcomes in ESRD patients.

Methods: We aggregated weekly ILI data from 2000-2012 to monthly, and calculated the monthly number of deaths and hospitalizations among US ESRD patients during the same time period. Using time series decomposition, we subtracted out seasonal and trend components from both series, and computed correlations between the ILI and mortality/hospitalization data.

Results:



The figure displays deaths and ILI data after removing seasonal and trend components. There were 2 influenza seasons (2003-2004 and 2009-2010) during this time period where the peak was at the end of the calendar year (early in the influenza season) instead of at the beginning of the next calendar year. Similar "early" peaks are seen in deaths among ESRD patients. There is also correlation between other peaks and valleys of the ILI data and ESRD deaths; correlation coefficient = 0.63. Correlations were also calculated with cause-specific hospitalizations: 0.69 for ILI-influenza/pneumonia; 0.42 for ILI-any infection; 0.16 for ILI-MI; and 0.02 for ILI-stroke.

Conclusions: The association between ILI and outcomes in ESRD patients is strong. While influenza vaccination rates among ESRD patients have improved over the last decade, the overall rate is still below 70%, suggesting room for further improvement.

Funding: Pharmaceutical Company Support - Amgen

FR-PO782

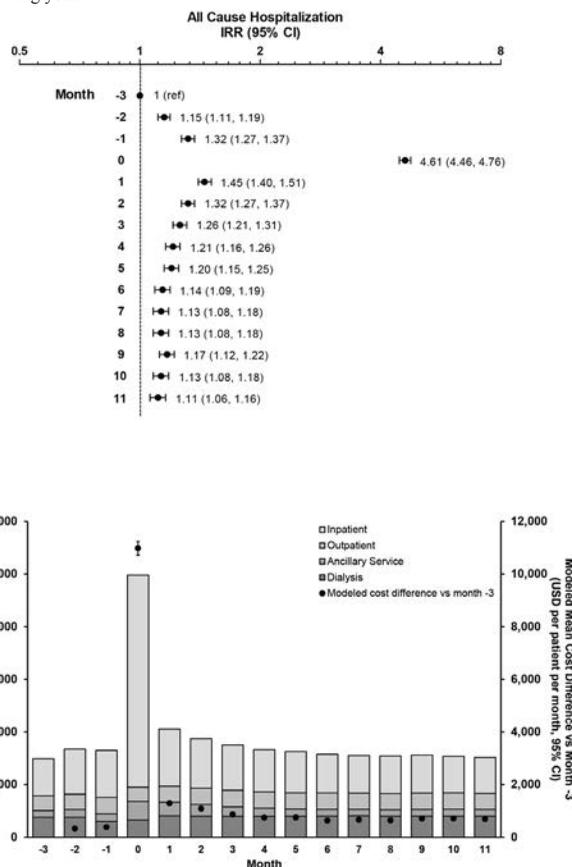
The Burden of Pneumonia in Patients Receiving Dialysis: Incidence, Case Fatality, and Costs to Medicare Scott Sibbel,¹ Reiko Sato,² Abigail Hunt,¹ Wendy Turenne,¹ Steven M. Brunelli.¹ ¹DaVita Clinical Research, Minneapolis, MN; ²Pfizer Inc, Collegetown, PA.

Background: End-stage renal disease patients receiving dialysis are at particular risk for infection. We assessed the clinical and economic burden of pneumonia in a population of Medicare-enrolled ESRD patients with respect to incidence and case fatality rates, rates of all-cause hospitalization, and costs.

Methods: Patients included in the analysis received dialysis between 01 Jan 2009 and 31 Dec 2011, and were enrolled in Medicare Parts A and B. Pneumonia episodes were identified from institutional and supplier claims. Patients were considered at-risk from the first date of Medicare coverage and were censored from the analysis upon transplant, withdrawal from dialysis, recovery of renal function or death. Linear mixed effects models were used to assess hospitalization rates and costs over the 3 months prior to and 12 months following a pneumonia diagnosis.

Results: The pneumonia incidence rate for the study period was 21.4 events/100 patient-years with the majority of episodes (90.1%) requiring inpatient treatment. The 30-day case fatality rate was 10.7%; case fatality rates were higher for older patients and for pneumonia requiring inpatient treatment (11.2%). All-cause hospitalization rates were greater in the month of the pneumonia episode vs month -3 prior to diagnosis (IRR, 4.61; 95%CI: 4.46, 4.76) and remained higher than baseline over the 1-year follow-up period. Mean per patient per month costs were \$10,976 (95% CI: \$10,717, \$11,275) higher in the month of the index episode compared to month -3, largely driven by increased inpatient costs, and remained elevated through end of follow-up.

Conclusions: Pneumonia episodes are frequent among ESRD patients and result in hospital admissions and greater overall costs to Medicare (~\$20,000 incremental) over the following year.



Funding: Pharmaceutical Company Support - Pfizer Inc

FR-PO783

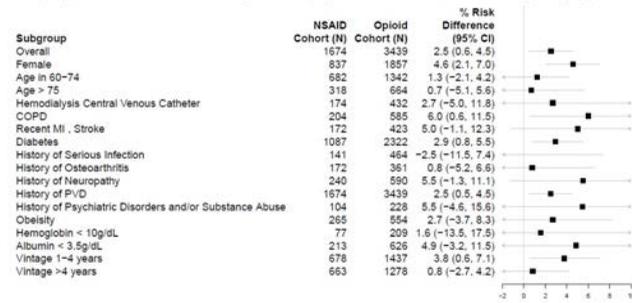
Opioid Use Associates with Infection Related Morbidity and Mortality in Hemodialysis Patients Abhijit V. Kshirsagar, Diane Reams, Magdalene M. Assimon, Anne Mobley Butler, Jennifer E. Flythe, M. Alan Brookhart. Univ of North Carolina at Chapel Hill.

Background: Opiates are frequently prescribed for pain in the US hemodialysis (HD) population but have intrinsic properties that increase risk of infection, a common cause of morbidity and mortality for patients. Data regarding the association of opioids with infection are lacking.

Methods: We conducted a retrospective cohort study using data from a large national dialysis provider linked with the United States Renal Data System and Medicare Part D (2006-2010). We used a new user design—comparing only new users of opioids to new users of prescription non-steroidal anti-inflammatory drugs (NSAIDs) to address confounding, as well as excluding patients with cancer, use of hospice services, or use of > 1 opiate. We assessed treatment effects on infection-related morbidity and mortality using inverse probability of treatment weighted Kaplan-Meier methods, adjusting for many comorbid, lab, and clinical variables.

Results: 5,113 patients met entry requirements, of which 3,439 (67.3%) received an opioid. Relative to new NSAID users, new opioid users had similar baseline laboratory values, but were slightly younger, and had a higher prevalence of comorbidities, including recent infections (8.7% vs 6.8%), diabetes (52.3% vs 49.3%), and chronic obstructive pulmonary disease (COPD), 17% vs 12.2%. After multivariable adjustment, we observed an elevated risk of 90-day infection-related hospitalization, (Risk Difference (RD) 2.5/100 patients, 95% CI 0.6-4.5) (Figure 1), and 90-day risk of infection-related mortality (RD 0.6%, 95% CI 0.3-0.9), no figure. For subgroups, infection-related hospitalizations were elevated among females and patients with diabetes, COPD, and lower dialysis vintage.

Ninety Day Risk of Infection-Related Hospitalization, Opioid versus NSAID, Overall and by Subgroup



Conclusions: Our results suggest that opioid initiation increases the short-term risk of infection-related morbidity and mortality among HD patients.
Funding: Clinical Revenue Support

FR-PO784

A Retrospective Review of the Two-Step Tuberculin Skin Test in Manitoba's Dialysis Population Rukhsana A. Foster,² Thomas W. Ferguson,¹ Claudio Rigatto,^{1,2} Navdeep Tangri,^{1,2} Blake R. Lerner,² Reid Whitlock,¹ Paul Komenda,^{1,2} ¹Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; ²Medicine, Univ of Manitoba, Winnipeg, MB, Canada.

Background: Reactivation of latent *Mycobacterium Tuberculosis* (LTBI) is a health concern for patients on dialysis due to their immunosuppressed state. The most frequently used test for LTBI screening in this population is the Tuberculin Skin Test (TST). The diagnostic accuracy (sensitivity and specificity) and clinical utility of the TST in a contemporary North American dialysis population is unknown.

Methods: We performed a retrospective cohort study of 483 hemodialysis and peritoneal dialysis patients across 4 dialysis units. All patients received a two-step TST and full TB risk assessment between February 2008 and December 2008. We then linked the cohort with the Manitoba Health TB Registry to ascertain if treatment was received for LTBI.

Results: At an induration cut-off of 5mm, 62 (13%) patients had a positive two-step TST. Patients with a BCG vaccination were more likely to test positive (50 vs. 34%, p = 0.05). Using a diagnostic gold standard of an abnormal chest X-ray as a proxy for LTBI, the sensitivity of the TST was only 13.9%, and the specificity was 87.7%. Only 8 of 62 patients (13%) received treatment for LTBI. None of the patients who tested negative were treated.

Conclusions: The TST has limited diagnostic and clinical utility for LTBI screening in patients on dialysis. Further research into the diagnostic accuracy of interferon-gamma release assays, and a revision of LTBI screening guidelines in patients on dialysis should be considered.

FR-PO785

Reliability and Construct Validity of the Coping Strategy Inventory-Short Form in Hemodialysis (HD) Patients in 13 Countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) Elodie Speyer,¹ Hal Morgenstern,^{1,2} Yasuaki Hayashino,³ Peter G. Kerr,⁴ Hugh C. Rayner,⁵ Ronald L. Pisoni,¹ ¹Arbor Research Collaborative for Health; ²Univ of Michigan; ³Tenri Hospital; ⁴Monash Health & Monash Univ; ⁵Birmingham Heartlands Hospital.

Background: In international studies, questionnaires are often translated into several languages without consideration of cultural and linguistic differences that may compromise the reliability and validity of survey instruments, especially those measuring psychosocial factors. The Coping Strategies Inventory-Short Form (CSI-SF) is a 16-item questionnaire, developed in English, and previously validated in US cardiac failure patients. It is scored by computing 4 scales (each with 4 items) to measure 4 different coping strategies. The aim was to assess reliability and construct validity of the CSI-SF in HD patients across 13 countries.

Methods: The CSI-SF was self-administered to HD patients across 13 countries in 9 languages in DOPPS 4 (2009-11). Cronbach's alpha was used to assess internal consistency. Exploratory and confirmatory factor analyses were used to assess the factor structure of the CSI-SF by country and language.

Results: 6,656 HD patients completed the CSI-SF and were included in this analysis (55% male; median age=63, range: 18-96 yrs). Using the English version in 4 countries and the Swedish version, we found good internal consistency ($\alpha=0.63-0.77$) for 3 of the 4 scales; the 4th scale was internally consistent if two items were dropped. In these countries, both types of factor analyses indicated a factor structure perfectly consistent with these same 4 scales. In the 8 other non-English versions, results were very different: internal consistency was lower for the 4 scales; no country showed an exploratory factor structure similar to that found previously, nor was the 4-factor structure confirmed with factor analysis.

Conclusions: The CSI-SF is reliable for measuring coping in HD patients in English and Swedish versions, as tested in the DOPPS. The importance of coping for predicting outcomes in HD patients can now be described in these countries. More research is needed for measuring coping strategies in other countries and languages.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DgN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

FR-PO786

Associations Among Psychosocial/Medical Factors and Quality of Life in Hemodialysis Patients with End-Stage Renal Disease Gun woo Kang, Internal Medicine, Catholic Univ of Daegu School of Medicine, Daegu, Korea.

Background: Patients with end-stage renal disease(ESRD) have a significant impairment in quality of life(QoL). Most previous studies have focused on medical factors mainly. However, quality of life can also be affected by psychosocial problems in the circumstances of chronic illness. The aim of this study was to identify the associations among psychosocial factors, medical factors and QoL in hemodialysis(HD) patients.

Methods: The study included 101 patients with ESRD who were undergoing HD(mean age 57.1 ± 12.1 years). Psychosocial factors were evaluated using the Hospital Anxiety and Depression Scale(HADS), Multidimensional Scale of Perceived Social Support, Montreal Cognitive Assessment and Pittsburgh Sleep Quality Index. In addition, for evaluating caregivers' burden in part of psychosocial factors, HADS and Zarit Burden Interview of main caregivers were administered. We also accessed medical factors(Kt/V and urea reduction ratio, etc.) with laboratory results(body mass index, albumin, hemoglobin, etc.). The QoL was evaluated using WHO Quality of Life-BREF(WHOQOL-BREF). Canonical correlation analysis was used to investigate the patterns of associations.

Results: The canonical correlation between psychosocial factor and QoL was significant. The first canonical correlation was 0.673(proportion = 60.6%, p = 0.001) and the second was 0.519(proportion = 26.9%, p = 0.006). However, the canonical correlation between medical factor and QoL was not significant(the first: p = 0.586, the second: p = 0.713).

Canonical function	Canonical correlation	Proportion	P-value
Between Quality of life and medical factors			
The 1st	0.436	0.382	0.586
The 2nd	0.412	0.332	0.713
Between Quality of life and psychosocial factors			
The 1st	0.673	0.606	0.001
The 2nd	0.519	0.269	0.006

Conclusions: The QoL of patients with ESRD was not associated with medical factor, but psychosocial factor in canonical correlation analysis. This finding may suggest that medical workers should recognize and treat psychosocial problems as well as clinical problems. We also would like to emphasize the comprehensive approach with cooperation between psychiatrists and nephrologists for improvement of QoL in ESRD patients.

FR-PO787

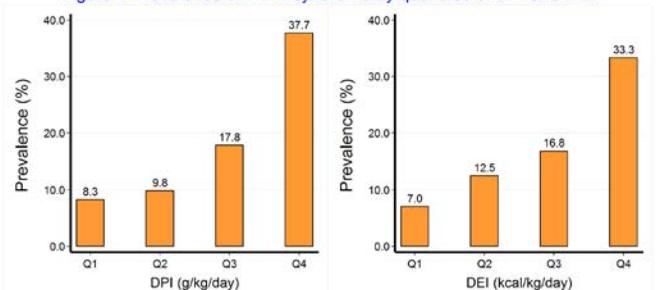
Longitudinal Associations of Dietary Protein and Energy Intake with Protein-Energy Wasting Syndrome in Hemodialysis Patients Srini Beddhu,^{1,2} Xiaorui Chen,¹ G. Wei,¹ Robert E. Boucher,¹ Dominique Ferranti,¹ Kalani L. Raphael,^{1,2} Tom Greene,¹ Michel Chonchol,³ ¹U of Utah; ²VA SLC; ³UC Denver.

Background: Low dietary protein intake (DPI) (<0.6 g/kg/d) and low dietary energy intake (DEI) (<25 kcal/kg/day) are included in the definition of protein-energy wasting (PEW) syndrome. Therefore, we examined the longitudinal associations of baseline DPI and DEI with PEW syndrome (defined by modified criteria that excludes dietary variables) at 1 year of follow-up in 1480 MHD pts in the HEMO Study.

Methods: DPI and DEI were obtained by 24-h dietary recall. PEW syndrome at month 12 was defined as the presence of 2 out of the 3 criteria: serum chemistry (albumin by BCP method < 3.5 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 23 kg/m² or wt loss > 10% over 1 yr), and muscle mass (mid-arm muscle circumference 10% or more less than the 50th percentile of reference population). PEW syndrome at month 12 was related to baseline DPI and DEI in logistic regression models.

Results: 17.4% had PEW at month 12. The prevalence of PEW syndrome at month 12 by baseline DPI and DEI quartiles are summarized in the figure.

Figure 1 Prevalence of PEW syndrome by quartiles of DPI and DEI



The associations of baseline DPI and DEI with PEW syndrome at month 12 in logistic regression models are summarized in table.

Associations of baseline DPI or DEI with the presence of PEW syndrome at month 12*		
	OR (95% CI)	
	Model 1 [§]	Model 2 [#]
DPI < 0.6 g/kg/d	0.39 (0.25, 0.62)	0.40 (0.26, 0.63)
DEI < 25 kcal/kg/day	0.29 (0.21, 0.40)	0.30 (0.22, 0.41)

*Each cell represents a separate logistic regression model, [§] Adjusted for demographics, ESRD duration, Kt/V group, flux group, smoking and alcohol use, [#] Adjusted for above plus diabetes, CAD, CVD, PVD, CHF and arrhythmias

Conclusions: The contrarian finding of lower risk of PEW in those with low DEI and DPI could reflect mathematical coupling (as both DEI and DPI include body wt in the denominator and those with PEW have lower body wt).
Funding: NIDDK Support

FR-PO788

PEW Syndrome, Inflammation and Mortality in Hemodialysis Patients
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Background: The term ‘malnutrition-inflammation complex syndrome’ implies that malnutrition and inflammation are tightly interlinked. Therefore, we examined whether the mortality associations of markers of inflammation and protein-energy wasting syndrome (PEW) are attenuated by each other in 906 maintenance hemodialysis (MHD) patients in the HEMO Study, a multi-center RCT that examined the effects of dialysis dose and dialyzer flux on mortality.

Methods: High sensitivity Creative Protein (hsCRP), tumor necrosis factor (TNF)-a and interleukin (IL)-6 were measured in the month 12 stored samples. Weight loss was estimated from baseline and month 12 post-dialysis weights and hence, PEW syndrome at month 12 was defined as the presence of 2 out of 3 criteria: serum chemistry (albumin by nephelometry < 3.5 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 23 kg/m² or wt loss > 10% from baseline), and muscle mass (mid-arm muscle circumference 10% or more less than the 50th percentile of reference population). Cox models were used to relate month 12 PEW syndrome and hsCRP, TNF-a and IL-6 with subsequent mortality.

Results: Mean age was 57 ± 14 yrs. 45% were women. 67% were black. PEW syndrome was present in 17.4% at month 12. Median (IQR) serum hsCRP was 6.3 (2.6-16.4) mg/L, IL-6 3.3 (2.0-7.6) pg/ml, and TNF-a 31.2 (21.3-46.1) pg/ml. There were 388 deaths over 2189 years of follow-up. PEW syndrome had 2 fold higher risk of mortality which was only marginally attenuated by adjustment for markers of inflammation (table). CRP and IL-6 were associated with higher mortality risk independent of PEW. TNF-a was not associated with mortality.

	Model 1*	Model 2*	Model 3*
PEW syndrome	2.22 (1.78, 2.76)	-	2.09 (1.68, 2.61)
Each doubling of CRP	-	1.10 (1.04, 1.17)	1.10 (1.03, 1.17)
Each doubling of TNF-a	-	1.04 (0.90, 1.19)	1.03 (0.90, 1.17)
Each doubling of IL-6	-	1.13 (1.08, 1.19)	1.12 (1.07, 1.18)

*Adjusted for age, gender, race, duration of ESRD, Kt/v group, smoking, alcohol use, DM, IHD, CVD, PVD, CHF and arrhythmia.

Conclusions: PEW and inflammation are independent predictors of mortality. These results suggest PEW and inflammation might not be tightly interlinked.
Funding: NIDDK Support

FR-PO789

Impacts of Geographic Distance on Peritoneal Dialysis (PD) Utilization: Refining Models of Treatment Selection
 Virginia Wang,^{1,2} Matthew L. Maciejewski,^{1,2} Cynthia Coffman,^{1,2} Linda L. Sanders,¹ Shoou-Yih D. Lee,³ Richard Hirth,³ Joseph M. Messana.³ ¹Duke Univ, Durham, NC; ²Durham VA Med Ctr, Durham, NC; ³Univ of Mich, Ann Arbor, MI.

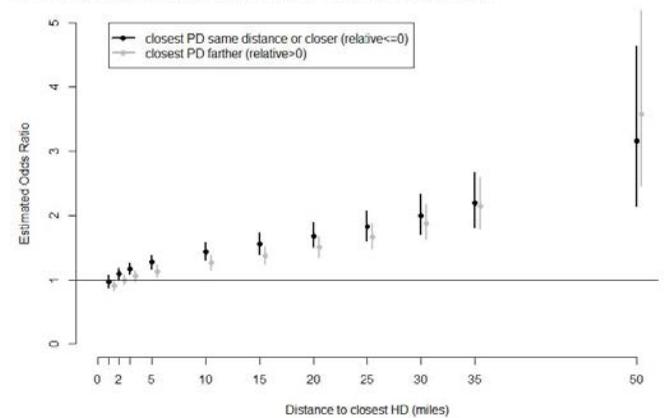
Background: Proximity to dialysis services may ease patient travel burden. Different frequency of visits to dialysis facilities and resulting differences in travel distance may affect patients’ selection of hemodialysis (HD) versus PD. PD has historically been less commonly available in dialysis facilities and less commonly used than HD. We refine methods of prior research to reassess the relationship between patients’ distance to dialysis care and modality choice to better reflect the conditions of patients’ choice set of providers’ location (absolute distance) and available services (relative distance).

Methods: Retrospective cohort of 70,131 patients initiating dialysis and 4,795 dialysis facilities in 2006 using USRDS data. The primary outcome was patient PD use. Independent variables included absolute distance from patients’ home to nearest HD facility, relative distance dichotomized as the nearest PD facility closer or same distance as nearest HD facility, and their interaction. Logistic regression was used to model distance on PD use, controlling for patient and market factors.

Results: 9% of new dialysis patients used PD in 2006. There was a positive, non-linear relationship between absolute distance to closest HD services and PD use (p=0.0006). In

terms of relative distance, odds of PD increased if a PD facility was closer or the same distance as the nearest HD facility (p=0.006). The interaction of absolute and relative distance was not significant.

Figure 1. Predicted Odds of PD Utilization. Estimated odds ratio and 95% confidence limits comparing absolute distance to closest HD facility from 1-50 to 0 miles to closest HD facility (in the same zip code) when distance to closest PD facility is either the same or closer than HD facility (black) or distance to closest PD is farther than closest HD (gray).



Conclusions: Distance is an important factor in patient decision-making when initiating PD, particularly for those living farther away from commonly offered HD services. Analyses of treatment selection must appropriately model distance to reflect logistics of treatment options and service availability to patients.

Funding: NIDDK Support, Other U.S. Government Support

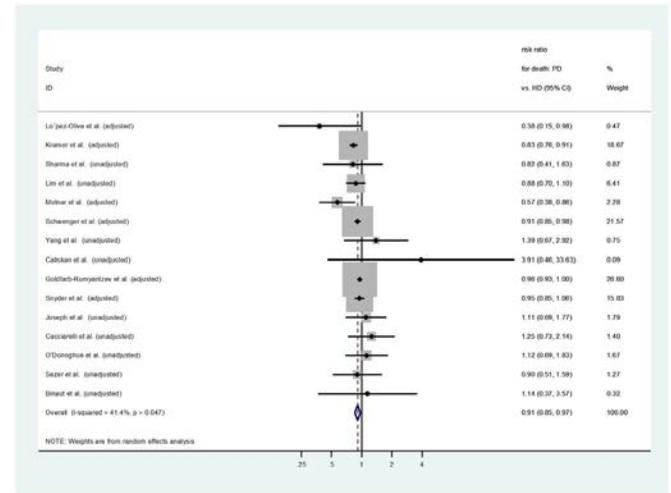
FR-PO790

Association of Pre-Transplant Dialysis Modality and Post-Transplant Outcomes: A Meta-Analysis
 Emily Joachim, Ali I. Gardezi, Sudheer Muduganti, Sana Waheed, Jung-Im Shin, Brad C. Astor, Micah R. Chan. Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Patients who undergo dialysis prior to renal transplant have overall worse outcomes than patients who receive a preemptive transplant. However, individual studies give conflicting results regarding whether post-transplant outcomes differ based on pre-transplant dialysis modality (peritoneal dialysis (PD) versus hemodialysis (HD)).

Methods: We searched English-language literature from January 1, 1980 through August 31, 2014, national conference proceedings and reference lists of all included studies. We used combinations of terms related to dialysis (hemodialysis, peritoneal dialysis, or renal replacement therapy), kidney transplant and outcomes. Studies were included if they measured post-transplant patient mortality for both pre-transplant HD and PD. Studies were excluded if they were not in English or if they included pediatric patients.

Results: A total of 15 studies reported five-year patient mortality. These included 166,531 patients on HD and 51,980 patients on PD pre-transplant. The pooled hazard ratio for five-year patient mortality after renal transplant was 0.91 (CI 0.85-0.97) in favor of pre-transplant PD over HD (p=0.006).



There was moderate heterogeneity among these studies (I²=41.4%, p=0.05). Six studies included an adjusted risk ratio (RR); the pooled RR for these studies was 0.89 (CI 0.82-0.97) in favor of PD (p=0.006). There was significant heterogeneity among these six studies (I²=72.7%, p=0.003).

Conclusions: Based on these results, pre-transplant peritoneal dialysis is associated with better post-transplant survival at five years compared to hemodialysis. Further work should explore potential reasons for this difference and compare additional outcomes such as graft survival, delayed graft function and rejection.

FR-PO791

Impact of Poverty and Health Care Insurance on Pre-End Stage Renal Disease Care in Dialysis Patients Robert Nee,¹ Lawrence Agodoa,² Kevin C. Abbott.¹ ¹Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; ²NIDDK, National Insts of Health, Bethesda, MD.

Background: Access to nephrology care prior to end-stage renal disease (ESRD) is significantly associated with lower rates of morbidity and mortality. We assessed the association of area and individual-level indicators of poverty and types of health care insurance on pre-ESRD care provided by nephrologists.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 739,537 patients initiated on maintenance dialysis from January 1, 2007 through December 31, 2012. We assessed the Medicare-Medicaid dual eligibility status as an indicator of individual-level poverty and ZIP code-level median household income (MHI) data obtained from the 2010 United States Census. We conducted multivariable logistic regression of pre-ESRD care as the outcome variable, as reported on the Centers for Medicare and Medicaid Services Form 2728.

Results: The proportions of dual-eligible and non-dual eligible patients who had pre-ESRD care were 53.06% and 61.82%, respectively (p<0.001). Dual-eligibility was associated with significantly lower likelihood of pre-ESRD care (adjusted odds ratio [aOR] 0.83; 95% confidence interval [CI] 0.82-0.84). Patients in the lowest area-level MHI quintile had an aOR 0.89 (95% CI 0.88-0.90) compared to those in higher quintile levels. Both African American (AA) and Hispanic patients were significantly less likely to have received pre-ESRD care (aOR 0.85, 95% CI 0.84-0.86 and aOR 0.71, 95% CI 0.70-0.72, respectively). Interaction terms for dual eligibility and AA race and Hispanic ethnicity were significant (p<0.001 and p=0.002, respectively).

Conclusions: Individual and area level measures of poverty were independently associated with lower likelihood of pre-ESRD care. Efforts to improve pre-ESRD nephrology care may require focusing on the poor and minority groups. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, Department of the Navy, Department of Defense, or the United States government].

FR-PO792

Development and Validation of the Charlson Comorbidity Scoring System for Korean Incident Peritoneal Dialysis Patients Hyunjeong Cho,¹ Myoung-Hee Kim,² Seung Seok Han,¹ Jae Yoon Park,¹ Hyunjin Ryu,¹ Hyo Jin Kim,¹ Dong-Ryeol Ryu,³ Hajeong Lee,¹ Jung Pyo Lee,⁴ Chun Soo Lim,⁴ Kook-Hwan Oh,¹ Kwon Wook Joo,¹ Yon Su Kim,¹ Dong Ki Kim.¹ ¹Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; ²Dental Hygiene, College of Health Science, Eulji Univ, Gyeonggi-do, Korea; ³Internal Medicine and Ewha Medical Research Inst, School of Medicine, Ewha Womans Univ, Seoul, Korea; ⁴Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea.

Background: The Charlson Comorbidity Index (CCI) has widely used for predicting mortality and adjusting as a confounder in statistical analyses. However, the CCI remains disputed as an index to be applied to ESRD populations because the CCI was developed for general population. In this study, we modified the CCI and developed a modified Charlson comorbidity index in incident peritoneal dialysis patients (mCCI-IPD) to improve risk stratification for mortality.

Methods: The mCCI-IPD was developed based on 7,606 Koreans who received their first peritoneal dialysis treatment between 2005 and 2008. Data were obtained from the Korean Health Insurance dataset. The mCCI-IPD score was the sum of the weights which were assigned to individual comorbidities according to their relative prognostic significance determined by multivariate Cox proportional hazards model. The modified index was validated in an independent prospective cohort (n=664).

Results: The Cox proportional hazards model showed that the CCI comorbidities except ulcers, peripheral vascular disease, dementia and connective tissue disease significantly predicted mortality. Thus, the mCCI-IPD included 11 comorbidities with re-assigned severity weights. In the validation cohort, both the CCI and the mCCI-IPD were correlated with mortality. However, the analyses using continuous net reclassification improvement revealed that the mCCI-IPD improved net mortality risk reclassification by 30.8% (95% CI, 7.6-54.1; P=0.009) relative to the CCI.

Conclusions: The mCCI-IPD performed the better risk stratification for mortality in incident peritoneal dialysis patients than the CCI. It suggests that the mCCI-IPD may be a preferred tool for clinical study of peritoneal dialysis patients.

FR-PO793

Diabetes, Black Race, Female: Risk Factors for Hospitalization After Dialysis Start in a Nationwide Cohort Sample LaTonya J. Hickson,^{1,2} Bjoerg Thorsteinsdottir,^{2,3} Priya Ramar,² Jordan K. Rosedahl,² Cynthia S. Crowson,² Robert C. Albright,¹ Nana-Hawa Yayah Jones,⁴ Rozalina G. McCoy,^{2,3} Suzanne M. Norby,¹ Andrew D. Rule,¹ Amy W. Williams,¹ Nilay D. Shah.² ¹Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Mayo Clinic Kern Center for the Science of Health Care Delivery, Mayo Clinic; ³Primary Care IM, Mayo Clinic; ⁴Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background: Young dialysis patients have a high frequency of hospitalizations and readmissions. Multiple factors likely contribute to this occurrence, but have not been fully elucidated.

Methods: Young, incident dialysis patients aged 20-44 years included in the US Renal Data System with first dialysis service in 2005-2011. Multivariable multinomial logistic regression models examined associations and interactions between baseline predictors and hospitalizations through claims in the first 3-15 months; all p-values <0.05.

Results: For 46,895 patients (mean age: 36; 58% male; 46% black, 48% white, 4% asian, 2% other race, 41% with diabetes, 23% with Charlson score ≥4) mean hospitalization rate was 2.3 per year. Subgroups for low to high utilizers included: 0 (45%), >0-4 (25%), >4-10 (20%) and >10 (10%) per year. Compared to the 0 hospitalization group, the >10 group had more females (48% vs 39%), more blacks (51% vs 45%), fewer Asians (2% vs 5%), more diabetics (52% vs 34%), more with Charlson score ≥4 (41% vs 14%). Diabetics were more likely to be high utilizers (odds ratio [OR]: 1.98(1.84,2.14) adjusting for age (OR:1.30(1.23,1.37) per 10 year decrease; sex (OR:1.23 (1.15,1.32) females vs males), black race (OR:1.24(1.16,1.34) blacks vs whites). Charlson score ≥4 were also more likely to be high utilizers (OR: 7.00(6.25,7.84) vs Charlson score 0-1), with highly comorbid females having nearly twice the risk as highly comorbid males (OR: 12.62 vs 6.23, interaction p<0.001) when compared to low comorbid males.

Conclusions: Hospitalizations are frequent among young incident dialysis patients, particularly among diabetics, blacks, females, and those with multiple comorbidities. Further investigation into socioeconomic factors and causes of hospitalizations is needed to clarify these finding for targeted interventions.

FR-PO794

Does Race Affect the Cause of Mortality in End Stage Kidney Disease? Luxme Nadarajah, Kieran McCafferty, Muhammad M. Yaqoob. *Barts and the London, Nephrology, London, United Kingdom.*

Background: Cardiovascular disease accounts for 50% of mortality in end-stage kidney disease (ESKD). Caucasians (C) are more likely to die from cardiovascular disease, infection and withdrawal compared to Afro-Caribbean's (AC). Little is known about the causes of mortality for Indo-Asian (IA) patients; with the rise in diabetes mellitus (DM) it is inevitable that more patients from IA backgrounds will get ESKD. We aim to investigate whether there are any differences in causes of mortality based on race.

Methods: We performed a single center, prospective, observational study. Electronic case notes were used to extract data to include cause of death, age of initiation of RRT, age of death, dialysis vintage (DV), gender and presence of DM. Patients were excluded if RRT was less than 90 days, or if they were transplanted.

Results: In total 3431 patients commenced RRT during the study period, 802 patients died, 364 were C, 259 IA and 178 were AC. There were no significant differences between the groups for age at initiation, DV, and age of death. Significantly fewer IA died during the follow up period compared to C (p<0.0001) and AC (P<0.0001). More IA and AC were diabetic (p< 0.0001). Cardiovascular deaths were more common in C and AC patients compared to those of IA race (p=0.001). IA's had higher sepsis related deaths when compared C or AC (p< 0.0001).

	Caucasian	Indo-Asian	Afro-Caribbean
Total Number of patients	1055	1616	760
Number of deaths (%)	365 (34)	259 (16)	178(23)
Cardiovascular (%)	101 (28)	48 (19)	54 (30)
Sepsis (%)	79 (22)	97 (37)	36 (20)
Withdrawal (%)	68 (19)	48 (19)	34 (19)
Malignancy (%)	43 (12)	42(16)	17 (10)
CVA (%)	14(4)	8 (3)	10 (6)
Other (%)	59 (16)	16 (6)	27 (15)

Conclusions: Despite the increased prevalence in DM, IA patients do not have worse survival outcomes or cardiovascular deaths compared to C and AC. We believe that the elevated sepsis related mortality in IA patients is secondary to the higher prevalence of diabetes. This data enables stratifying management therapies dependent on race and may help in designing cardiovascular end points trials in racially diverse group of patients.

Funding: Other NIH Support - William Harvey Research Institute

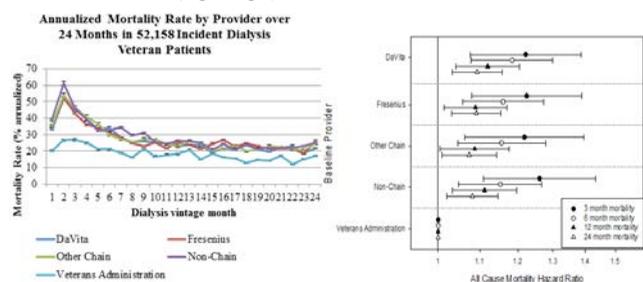
FR-PO795

Association of Dialysis Provider Assignment with Early Dialysis Mortality in U.S. Veterans: A Transition of Care in CKD Study Elani Streja,¹ Melissa Soohoo,¹ Connie Rhee,¹ Vanessa A. Ravel,¹ Joline L.T. Chen,¹ Jennie Jing,¹ Csaba P. Kovessy,² Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC.

Background: Mortality is high during the first months after initiating kidney replacement therapy including in US veterans. Only 10% of veterans receive dialysis therapy in a Veterans Administration (VA) healthcare based dialysis clinic and the majority of veterans are assigned to non-VA centers and dialysis chains.

Methods: We examined all-cause mortality during the 3, 6, 12 and 24 month period after transition in a cohort of 52,158 US veterans who transitioned to ESRD over 4 years (10/2007-9/2011) and the association of dialysis provider assignment. Baseline provider was determined by facility information and divided into 5 categories: DaVita(DV), Fresenius(FR), Other Chain(OC), Non-Chain(NC), and VA. Associations were examined in Cox proportional hazard models and adjusted for age, gender, race, ethnicity, initial vascular access and primary cause of ESRD.

Results: Upon dialysis transition, patients were 70±12 yrs old, 6% female, 25% African-American, 19% initially used AV fistula and 42% had diabetes as the cause of ESRD. At baseline, 24%, 28%, 13%, 21%, and 10% of veterans received treatment at DV, FR, OC, NC, and VA facilities, respectively. Over the first 3, 6, 12 and 24 months after transition, 5489(11%), 9283(18%), 14339(27%) and 21697(42%) veterans died, respectively (Figure left). Compared to patients initiating treatment at the VA, all patients receiving treatment at other facilities had higher risk of mortality through all periods of follow-up, after adjusting for case mix covariates (Figure right).



Conclusions: Veterans transitioning to dialysis treatment in a VA hospital based dialysis center have the best survival over the first 2 years of follow up. Whether the better survival of VA dialysis care is from selection bias versus true superior care in the VA system warrants additional studies.

Funding: NIDDK Support

FR-PO796

Time-Varying Racial/Ethnic Differences in Mortality After Initiation of Dialysis in U.S. Dialysis Patients Guofen Yan,¹ Keith C. Norris,² Alison J. Yu,³ Tom Greene,⁴ Jennie Z. Ma,¹ Wei Yu,¹ Alfred K. Cheung.⁴ ¹Univ of Virginia; ²UCLA; ³Univ of Southern California; ⁴Univ of Utah.

Background: While survival advantage for African Americans (AAs) and Hispanics, compared to Whites, has been observed for decades, our understanding of the mechanism is still incomplete. Using national dialysis patients, we examined whether this survival advantage exists across the entire course of ESRD or just within a certain time interval after initiation of dialysis.

Methods: The study included 1,255,640 adult incident dialysis patients between 1995 and 2010 in the USRDS. We calculated age-specific hazard ratios (HRs) of death for AAs and Hispanics vs. Whites, adjusted for covariates, for every 6-month interval in the first 4 years of dialysis and for the period thereafter.

Results: For each age group above 40 years (Table), lower risk of death for AAs than Whites (HR<1) did not vary greatly across these time intervals. In contrast, in each age group under 40 years, the HR for AAs vs. Whites evolved over time, which was highest in the first year, declined in the second year, and reached stable over time. Hispanics exhibited lower mortality risks in all age groups that remained relatively constant over time (not shown).

Table. Adjusted HRs for AAs vs. Whites

Age Groups	Months after Initiation of Dialysis								
	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	>48
18-30	1.72	1.50	1.14	1.28	1.09	0.92	0.91	0.93	0.93
31-40	1.34	1.32	1.07	0.92	0.86	0.89	0.68	0.72	0.83
41-50	0.89	0.93	0.85	0.76	0.72	0.71	0.70	0.68	0.78
51-60	0.76	0.74	0.70	0.69	0.66	0.66	0.65	0.67	0.76
61-70	0.72	0.73	0.70	0.70	0.70	0.68	0.68	0.71	0.81
71-80	0.76	0.80	0.74	0.76	0.76	0.77	0.78	0.79	0.86
>80	0.84	0.83	0.80	0.78	0.83	0.85	0.81	0.84	0.88

Note: most of these HRs were significant at p<0.05.

Conclusions: AAs over 40 years old and Hispanics of all ages have uniformly lower risks of death than Whites across the course of ESRD. For younger AAs, conversely, their higher-mortality risk period is limited to the first two years of dialysis. Further studies to delineate the factors responsible for excessive mortality associated with racial subgroups will improve care for all dialysis patients.

Funding: NIDDK Support

FR-PO797

Real Threat of ESRD in China: A Ten-Year Experience from Nanjing 3 Million Insurance Covered Population Yu-Chen Han,¹ Ling Sun,¹ Han-Ming Huang,² Kun ling Ma,¹ Bei Wang,³ Bi-Cheng Liu.¹ ¹Zhongda Hospital, Southeast Univ School of Medicine, Nanjing, Jiangsu, China; ²Nanjing Municipal Human Resources and Social Security Bureau, Nanjing, Jiangsu, China; ³Southeast Univ School of Public Health, Nanjing, Jiangsu, China.

Background: In the past decade, Chinese government has made great efforts to provide an affordable and equitable access to renal replacement therapy (RRT) for most of ESRD patients. Here we analyzed the ten years registry data of 3 million Nanjing Urban Employee Basic Medical Insurance (UEBMI) covered population and firstly provided the epidemiological data about ESRD in this developing country.

Methods: Using the electric registry system of UEBMI, we included all subjects insured by UEBMI in Nanjing from 2005 to 2014, and identified subjects who developed ESRD in this cohort. The prevalence and incidence of ESRD was analyzed based on this unique data system.

Results: During the 10-year period, the incidence rate of ESRD in UEBMI cohort in Nanjing gradually declined from 289.3pmp in 2005 to 218.8pmp in 2014. However, the prevalence rate increased steadily from 891.7pmp in 2005 to 1228.6pmp in 2014. The annual mortality rate declined from 138.4 per 1000 patient-years in 2005 to 97.8 per 1000 patient-years in 2014. Long-term survival rate of ESRD fluctuated during the past decade, with 1-year survival rate ranging from 85.1% to 91.7%, 3-year survival rate from 69.9% to 78.3% and 5-year survival rate from 58% to 65.4%.

Conclusions: This study firstly provided an epidemiological data about ESRD based on the complete electric registry data system in large population in China. Due to the lack of a national complete registry data system, the real burden of ESRD in China is still unclear. Nanjing is one of the biggest cities in China. Our present study based on the ten years complete electric registry data system provided a convincing data about the real threat of ESRD in China. According to this study, we estimated that China will probably have over 1.5 million ESRD patients in the near future with the establishment of improved healthcare system. It is therefore utmost important for both medical communities and government to take active measures to control this coming disaster.

Funding: Government Support - Non-U.S.

FR-PO798

An Evaluation of Completeness of Monthly Clinical Data in CROWNWeb, a New Data Source for the United States Renal Data System (USRDS) Valerie B. Ashby,¹ Lingqun Liu,¹ Xizhao Li,¹ Tempie H. Shearon,¹ Bruce M. Robinson,² Douglas E. Schaubel,¹ Yi Li,¹ Rajiv Saran.¹ ¹Univ of Michigan, Ann Arbor, MI; ²Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: CROWNWeb (CW) is a web-based system which collects administrative and clinical data from all Medicare-certified dialysis facilities in the US. It includes patient admission, tracking, and discharge information, CMS forms, and clinical data elements, and is not limited to Medicare patients. Monthly clinical data submission began in May 2012. Previously, monthly clinical data were only available to the USRDS through administrative claims for Medicare patients.

Methods: CMS data were used to analyze 355,846 and 370,610 dialysis patients in 2013 and 2014, respectively, who remained on dialysis the entire year (those who were incident, died, or lost to follow-up were excluded). The percentages of patients with any and high-level reporting of selected CW clinical data were calculated, with 'high-level' defined as 10+ months (except 3+ months for peritoneal dialysis (PD) Kt/V). The percentage of high-level reporting for patient subgroups was also calculated.

Results: The percentages of patients with CW data (any, high) are shown below. All measures had an increase in reporting from 2013 to 2014. High-level reporting in 2014 ranged from 75% (Hemodialysis (HD) Kt/V) to 90% (vascular access type). For all measures, reporting was higher for HD than PD patients, for adults than children, and for patients with (versus without) diabetes as cause of ESRD. 72% of HD patients had high-level reporting for all 6 HD measures. 70% of PD patients had high-level reporting for all 5 PD measures.

Clinical Data	2013		2014		High Level Reporting By Subgroup in 2014					
	Any	High	Any	High	HD	PD	Pediatric	No DM	DM	
Serum albumin	88.4%	79.4%	92.9%	87.0%	87.8%	83.9%	72.0%	87.0%	85.1%	89.3%
Calcium	90.2%	81.0%	93.7%	87.7%	88.6%	84.2%	72.8%	87.7%	85.9%	90.0%
Phosphorus	92.4%	82.9%	94.0%	88.0%	88.9%	84.3%	73.6%	88.0%	86.1%	90.3%
Hemoglobin	83.2%	78.8%	90.8%	86.3%	87.6%	80.2%	69.2%	86.3%	84.6%	88.5%
Vascular Access Type*	94.5%	88.0%	94.8%	89.8%	89.8%	-	81.7%	89.8%	88.1%	91.9%
HD Kt/V**	60.4%	57.7%	78.7%	74.8%	74.8%	-	66.6%	74.8%	73.2%	76.7%
PD Kt/V**	70.4%	59.9%	82.0%	81.3%	-	81.3%	65.2%	81.6%	80.5%	82.8%

*Vascular access type and HD Kt/V are based on 315,850 (2013) and 326,736 (2014) HD patients. **PD Kt/V is based on 25,311 (2013) and 28,514(2014) PD patients. The high level percentage is based on 3 or more months since PD Kt/V is only recommended to be collected every 4 months (3 times per year)

Conclusions: CW is now an integral part of the USRDS. Our study suggests a generally high and improving level of completeness of clinical data elements in CW. These data will enhance the value of the USRDS database for researchers in coming years.

Funding: NIDDK Support

FR-PO799

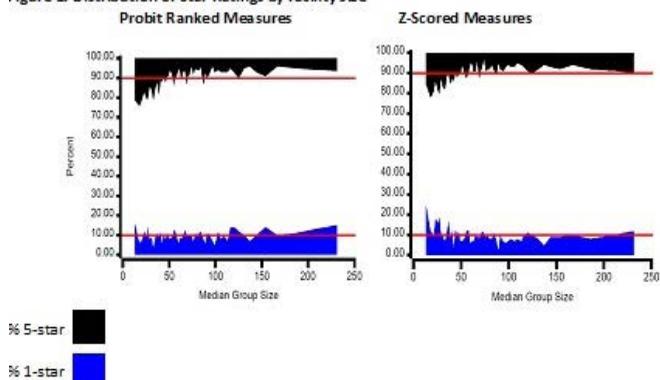
Facility Size and Impact of Extreme Measure Values on DFC Star Ratings
 Christopher J. Harvey,¹ Claudia Dahlerus,¹ Zezhi (zac) Zhang,¹ Joseph M. Messana,¹ Ji Zhu,¹ Cindy Liao,¹ Natalie Scholz,¹ K. A. Wisniewski,¹ Richard Hirth,¹ Elena K. Balovlenkov,² Joel S. Andress,² Yi Li.¹ ¹*Biostatistics, Kidney Epidemiology and Cost Center, Univ of Michigan, Ann Arbor, MI;* ²*Centers for Medicare and Medicaid Services.*

Background: In 2015 CMS implemented star ratings for dialysis facilities to make it easier for consumers to compare dialysis facilities by providing a summary of each facility's performance on a set of 9 DFC quality measures. Our study compares two scoring approaches to the star rating to assess the impact of each on controlling outlying measure values with regard to facility size.

Methods: Fixed percentiles are applied to assign 10% of facilities 1-star or 5-stars based on performance. 2013 data were extracted from the 2015 January DFC file. Probit ranking and z-score transformation were applied to the DFC measures to develop an overall score and final star rating. We compared the final distribution of star ratings for each approach and assessed impact on smaller facilities. We represent the rating by number of patients in each facility contributing to the hospitalization measure, and split ~6000 facilities into groups of ~100 and calculated percentage of each star rating in each group.

Results: Use of original measure values and z-scores allowed skewed measures to highly influence the ratings, but preserved original measure distributions. Probit ranking resulted in giving more 5-star ratings to smaller facilities and z-scored approach resulted in assigning more 1-star and 5-star ratings to smaller facilities (Figure 1).

Figure 1: Distribution of Star Ratings by facility size



Conclusions: Small facilities have more variation in measures and be over represented in the 1 or 2-star categories. Probit ranking (current DFC Star Rating method) controlled impact of outlier measure values. Z-score methods appeared to allow greater impact of extreme values. However, facility size may also be related to quality of care.

Funding: Other U.S. Government Support

FR-PO800

P11 as Marker and Vitamin D as Treatment Option of Depression in Maintenance Dialysis Patients
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Background: Depression is a disabling condition impairing all aspects of human functions. The serotonin system has been implicated in the pathophysiology of depression. Recently, as a member of the S100 family of proteins, P11 is known to have relation to depression by interacting with serotonin receptors and affected by inflammation. Because of nutritional deficiency and limited physical activities, dialysed patients are easy to have vitamin D deficiency. Recent studies reported that vitamin D might play a role in depression. So, we planned this study to assess the possibilities of the P11 as a depression marker and the vitamin D as a treatment option in dialysed patients.

Methods: As a single center cross-sectional study, we examined the peripheral blood mononuclear cells P11 mRNA, IL-6, TNF- α , 25-hydroxycholecalciferol (25-(OH)D₃) of patients with hemodialysis (HD, N=27), peritoneal dialysis (PD, N=39) and healthy group (N=7). Groups were divided by presence of depressive mood and categorized by severity of depressed mood via Beck Depression Inventory (BDI).

Results: In non-depressive group (BDI < 10), The dCt means of P11 were high in HD group (5.51 \pm 0.7 (HD, N=15) vs. 1.39 \pm 0.33 (PD, N=11) and 2.29 \pm 0.37 (control, N=7), p < 0.05). The mean IL-6 levels were low in control group (6.43 \pm 1.34 pg/mL (HD) and 7.53 \pm 1.39 pg/mL (PD) vs. 2.23 \pm 0.49 pg/mL (control), p < 0.05). The mean TNF- α levels were low in control group (4.31 \pm 0.26 pg/mL (HD) and 4.15 \pm 0.25 pg/mL (PD) vs. 1.85 \pm 0.53 pg/mL (control), p < 0.05) respectively. In depressive group (BDI \geq 10), P11 levels showed relationships with depression severity in peritoneal dialysis group (spearman rho=0.2, p

=0.09). In hemodialysis group, 25-(OH)D₃ level was lower in depressive group (11.98 \pm 3.8 vs. 7.5 \pm 2.7, p = 0.005), but there was no difference in peritoneal dialysis group (6.3 \pm 3.3 vs. 7.4 \pm 7.1, p=0.55).

Conclusions: By diagnostic tool, P11 can be used in peritoneal dialysis group as a depression marker despite taking the effect of inflammation into consideration, but not in hemodialysis group. As other treatment option, 25-(OH)D₃ can be used in hemodialysis group for depression management, but not in peritoneal dialysis group.

FR-PO801

Efficacy of Loop Diuretics in the Management of Undocumented End Stage Renal Disease Patients Receiving Emergency Hemodialysis
 Salman Ahmed, Biruh Workeneh. *Dept of Internal Medicine, Section of Nephrology, Baylor College of Medicine, Houston, TX.*

Background: Nearly eleven million undocumented immigrants reside in the United States. An estimated six thousand undocumented patients suffer from End Stage Renal Disease (ESRD). These patients routinely present to public hospitals for life-saving emergent dialysis treatments. Since these patients lack a dialysis unit, they often do not have medication management by a nephrologist. This can result in poorer outcomes.

Methods: We reviewed charts of 93 undocumented patients who presented for at least three emergent hemodialysis (HD) treatments during three consecutive months to the Ben Taub General Hospital, a centrally located county facility in Houston, TX. We abstracted prescription data for furosemide and several commonly prescribed medications. We also abstracted data regarding the number of ER visits, number of HD sessions, and mean, median, and peak potassium values.

Results: On average, the diuretic group had 3.1 (SE=1.8) fewer ER visits during the three-month period for emergency dialysis, compared with subjects not on diuretics (p=0.10). There was no significant relationship between furosemide total daily dose (TDD) and potassium levels. Patients on diuretics were more likely to also be taking ESAs and sevelamer (PE0.05). In a multiple regression model, the diuretic group had significantly fewer ER visits after adjusting for use of ESAs and sevelamer use (p=0.007). The association between diuretic use and ER visits is significantly associated with concomitant ESA use (p=0.04). Among subjects using ESAs, patients on diuretics have about 7.7 (95% CI: 1.9,13.6) fewer ER visits compared with the non-diuretic group.

Conclusions: There was no significant independent association between loop diuretic dosage and number of ER visits, although there was a strong trend. The subset of patients on ESAs and loop diuretics had decreased ER utilization, and this may be explained by increased doctor-patient time, less symptomatology while on ESAs, or other, as-yet-undetermined mechanisms.

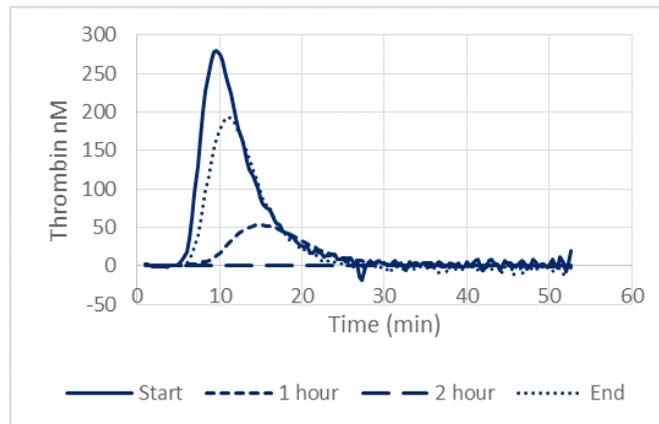
FR-PO802

Unfractionated Heparin May Contribute More to Dialysis-Associated Bleeding Risk Than Low-Molecular Weight Heparin
 Suzanne H. Forbes,¹ Sean Platten,² Michael K. Almond,³ Laura Green,² Neil Ashman.¹ ¹*Nephrology, Royal London Hospital;* ²*Haematology, Royal London Hospital;* ³*Nephrology, Southend Hospital.*

Background: Haemodialysis (HD) patient are well recognised to be at increased risk for major bleeding. The contribution of circuit anticoagulation to this risk is unknown. The use of unfractionated heparin (UFH) vs low-molecular weight heparin (LMWH) is debated. APTT/anti-Xa levels suggest anticoagulation is cleared by the end of HD but these tests are poorly correlated with bleeding phenotype. We used thrombin generation (TG) to assess coagulation throughout HD with UFH or LMWH.

Methods: We studied 127 patients; 60 LMWH, 61 UFH, 6 heparin-free. Blood was taken at t0=pre-anticoagulation, t1=1hr, t2=2hrs, t3=end. TG was performed on platelet poor plasma, measuring lag time, exogenous thrombin potential (ETP) & peak thrombin.

Results: Results are shown in table 1. With LMWH 42% failed to generate thrombin at t3 compared with 57% of UFH, indicating significantly impaired clotting (p=0.05). In those who did generate thrombin at t3, this was considerably below baseline.



The magnitude of this was significantly greater with UFH for lag time (p=0.03), ETP (p=0.06) and peak thrombin (p=0.05). Heparin-free patients showed minimal change.

	UFH	LMWH	Heparin-free
t0			
Lag	4.53	4.63	4.88
ETP	1960	2153	2037
Peak Thrombin	226	325	291
Platelet Count	226	190	248
Hb	10.4	10.7	9.46
Average anticoagulation dose	Bolus 1328u Infusion 991u/hr Lockout time 33mins	3129iu	-
%change t0: t3			
Lag	↑71	↑41	↑10
ETP	↓35	↓29	↓1
Peak	↓65	↓48	↓2

Conclusions: Standard HD anticoagulation results in impaired haemostasis after HD as measured by TG, UFH more so than LMWH, which is not seen in heparin-free patients. This shows the HD process itself does not impact TG, rather exogenous anticoagulation. This should prompt cautious anticoagulation use, especially UFH, in patients at risk of bleeding.

FR-PO803

Anti-Platelet Factor 4 Antibodies: A One HIT Wonder *Suzanne H. Forbes,¹ Sean Platton,² Michael K. Almond,³ Neil Ashman,¹ Laura Green.²* ¹Nephrology, Royal London Hospital; ²Haematology, Royal London Hospital; ³Nephrology, Southend Hospital.

Background: Hemodialysis (HD) patients are exposed to regular anticoagulation, usually unfractionated heparin (UFH) or low-molecular weight heparin (LMWH). For standard HD (4 hrs, 3 days/week) this equates 26 full days exposure/yr. Recently there was interest in the presence of heparin induced thrombocytopenia (HIT) in HD, and the causative anti-platelet factor 4 (PF4) antibody. There are several publications suggesting the presence of the antibody, without the clinical syndrome of HIT, is present in up to 25% HD patients, and may be an independent risk factor for cardiovascular and vascular access morbidity.

Methods: We looked for HIT antibodies in 2 prevalent HD cohorts, one with UFH, one LMWH (line lock sodium citrate). We tested serum for anti-PF4 antibodies using several established tests; STic Expert® (IgG-specific exclusion test), Diamed (particle gel immuno-assay), poly-specific IgGA/M ELISA, IgG-specific ELISA.

Results: We included 127 patients: 60 receiving tinzaparin, 61 receiving UFH and 6 dialysing heparin-free. Serum samples were taken at the start of a standard HD session. The average duration on dialysis was 3.4 years. Results of the various tests are shown.

TEST	UFH	LMWH	Heparin-free
Platelet Count	226	190	248
STic Expert	positive - 52% negative - 48%	positive - 40% negative - 60%	positive - 0% negative - 100%
Diamed	positive - 1% negative - 99%	positive - 1% negative - 99%	negative - 0% positive - 100%
Poly-specific ELISA	median OD - 0.2 (positive>0.4)	median OD - 0.15 (positive>0.4)	median OD - 0.09 (positive>0.4)
IgG specific ELISA	median OD - 0.13 (positive>0.4)	median OD - 0.07 (positive>0.4)	median OD - 0.05 (positive>0.4)

Only 1 patient tested antibody positive (OD 0.5) in the LMWH group. Platelet count and reactivity (using ADP, epinephrine, collagen) did not differ between the STic positive/negative groups, the UFH/LMWH groups, or those with higher or lower tertiles of ELISA OD.

Conclusions: Despite the previously reported concern over the presence of HIT antibodies in HD patient, we comprehensively show here no evidence of antibody positivity in HD patients. Exclusion tests such as STic expert are not useful in these patients.

FR-PO804

Upper Gastrointestinal Bleeding Among Dialysis Patients in an Endemic Area for Chronic Liver Disease: Taiwan National Cohort Study *Chih-Chiang Chien,^{1,2} Chien-Ya Hung,¹* ¹Chung Hwa Univ of Medical Technology, Tainan, Taiwan; ²Chi Mei Medical Center, Tainan, Taiwan.

Background: End-stage renal disease (ESRD) and chronic liver disease (CLD) both increase the risk for upper gastrointestinal (UGI) bleeding. The prevalence of ESRD and CLD are high in Taiwan. The aim of this study was to evaluate the incidence, risk factors, and categories of UGI bleeding in ESRD dialysis patients.

Methods: Using Taiwan's National Health Insurance research database, we enrolled 42,457 incident ESRD dialysis patients who began dialysis between 1999 and 2004. The patients were followed until death, dialysis cessation, or 31 December 2008. Cumulative incidence of UGI bleeding after initiation of dialysis was calculated using Kaplan-Meier methods. Predictors for UGI bleeding were determined using Cox models.

Results: During the follow-up period, 5,528 patients had a UGI bleeding. Male, elderly, receiving hemodialysis (HD) and patient with comorbidities had a higher rate of UGI bleeding. The 1-, 3-, 5- and 7-year cumulative incidence rate of UGI bleeding were 9.8%, 21%, 25.3% and 28% in patients with liver cirrhosis (LC) on HD, 5.8%, 16.2%,

22.2% and 24.4% in patients with LC on PD, 3.7%, 9.2%, 13.2% and 16.4% in patients without LC on HD, and 2.1%, 5.5%, 8.2% and 10.4% in patients without LC on PD (log-rank: p < 0.001). After multivariate adjustment, prior gastrointestinal bleeding (HR 1.731, 95% CI, 1.635-1.834), LC (1.682, 95% CI, 1.524-1.856), alcoholism liver disease (1.536, 95% CI, 1.635-1.834), and receiving HD (1.316, 95% CI, 1.153-1.502) were independently risks for UGI bleeding in ESRD dialysis patient. Gastric ulcers were found to be the most common source of bleeding (50.3%), while bleeding resulting from a gastrojejunal ulcer was least frequent.

Conclusions: ESRD dialysis patients had a higher risk for UGI bleeding, especially those with prior gastrointestinal bleeding, LC, and alcoholism liver disease. In addition, receiving HD is a strong predictor for UGI bleeding. More attention should be paid to select dialysis modality, especially in high risk patients.

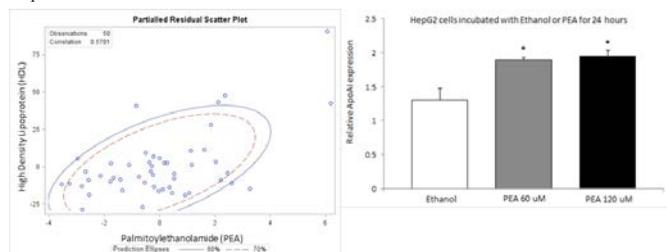
FR-PO805

Palmitoylethanolamide Is a Promising Potential Therapeutic Target for Increasing High Density Lipoprotein Cholesterol Levels *Hamid Moradi,^{1,2} Miki Igarashi,¹ Melissa Soohoo,¹ Elani Streja,¹ Hamid M. Said,^{1,2} Moti L. Kashyap,^{1,2} Daniele Piomelli,¹ Kamyar Kalantar-Zadeh.^{1,2}* ¹UC Irvine; ²VA Long Beach.

Background: End stage renal disease (ESRD) is associated with significant increased risk of cardiovascular (CV) mortality. High density lipoprotein (HDL) deficiency and dysfunction is a major contributor to CV disease in ESRD. Strategies aimed at improving HDL level and function are crucial in improving CV outcomes. Palmitoylethanolamide (PEA) is an anti-inflammatory lipid derived mediator that activates PPARalpha nuclear transcription factor. We hypothesized that serum PEA will correlate with HDL and PEA can increase HDL via activation of apolipoproteinAI (ApoAI) expression.

Methods: Serum PEA concentration was determined in 50 patients on maintenance hemodialysis (MHD) using LC/MS technology and correlated with clinical laboratory indices including a lipid panel. Liver cells (Hepatoma cell line HepG2) were exposed to various concentrations of PEA in-vitro for 24 hours and subsequently mRNA expression of ApoAI, the major protein component of HDL, was measure using real-time PCR.

Results: Serum PEA concentrations strongly correlated with serum HDL levels in MHD patients (r=0.57, p < 0.0001). PEA also correlates with total cholesterol (r=0.36, p=0.009) however not with LDL or triglycerides. In the in-vitro studies, PEA at a concentration of 60 micromolar and 120 micromolar was increased ApoAI expression significantly in HepG2 cells after 24 hours.



Conclusions: For the first time we report that serum PEA concentrations strongly correlate with serum HDL concentrations in MHD patients. Involvement of PEA in HDL production is confirmed in in-vitro studies where incubation of liver cell in PEA resulted in increased ApoA-I expression. These novel findings indicate that PEA may be a promising therapeutic target in HDL deficiency treatment associated with not just ESRD but any proatherosclerotic condition.

Funding: NIDDK Support

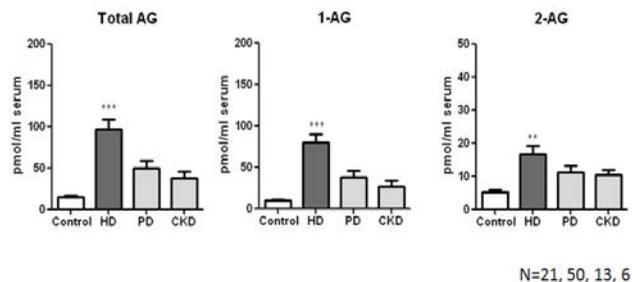
FR-PO806

Arachidonoylglycerol, a Major Activator of the Endocannabinoid System, Is Significantly Increased in Patients with Kidney Disease *Hamid Moradi,^{1,2} Miki Igarashi,¹ Melissa Soohoo,¹ Elani Streja,¹ Connie Rhee,¹ Hamid M. Said,^{1,2} Moti L. Kashyap,^{1,2} Nosratala D. Vaziri,¹ Daniele Piomelli,¹ Kamyar Kalantar-Zadeh.^{1,2}* ¹UC Irvine; ²VA Long Beach.

Background: Chronic kidney disease (CKD) is associated with oxidative stress and inflammation. There is evidence that cannabinoid 1 receptor activation leads to increased oxidative stress and inflammation. We previously showed that 2-arachidonoylglycerol (2-AG), one of the main activators of the endocannabinoid system, is significantly increased in the kidney of animals with ischemia-reperfusion (IR) injury. We hypothesized that serum 2-AG levels will be significantly elevated in CKD patients.

Methods: Serum concentrations of AG were determined in 21 healthy controls, 50 randomly assigned age and gender matched patients on maintenance hemodialysis (MHD), 13 patients on peritoneal dialysis (PD) and 6 patients with CKD stage IV using LC/MS technology. In MHD patients, serum levels of AG were correlated with various laboratory indices.

Results: Serum levels of 1-AG and 2-AG were significantly and incrementally increased with CKD compared to healthy controls. MHD patients had the highest AG levels which positively and significantly correlated with number of treatments per week (r=0.47, p=0.008), AST/ALT (r=0.5, p=0.001), platelet count (r=0.40, p=0.008), ferritin (r=0.36, p=0.016) and negatively with HDL cholesterol (r= -0.43, p=0.04).



Conclusions: For the first time we report that serum AG concentrations are significantly increased in CKD patients. These novel findings are in line with our report on IR acute kidney injury and with a recent study which showed that in an oxidative stress setting, monoacylglycerol lipase, an enzyme responsible for AG breakdown is inhibited leading to increased levels. Moreover, the substantial increase in MHD patients is intriguing given association of MHD with increased oxidative stress, inflammation and platelet activation.

Funding: NIDDK Support

FR-PO807

Newly Launched Cellulose Tri-Acetate Membrane with Asymmetric Structure Dramatically Improves Peripheral Circulation and Hemodynamic Stability During Hemodialysis Ikuto Masakane. *Yabuki Hospital, Nephrology, Yamagata, Japan.*

Background: The most important concern about the biocompatibility of dialysis membrane is the activation of platelets and it would lead hemodynamic instability during dialysis session. The newly launched CTA with asymmetric thick structure (ATA) was produced in order to reduce stimulant property to platelets and the rapid reduction of the serum levels of small uremic solutes by thickening the membrane. We evaluated the solute removal performance and biocompatibility of ATA.

Methods: Seven chronic hemodialysis patients were enrolled to the current study. The conventional CTA was used for the first 4 months and ATA was used for the next 4 months. We evaluated the solute removal property by the clearance of urea, beta-2 microglobulin (B2MG) and removed amount of alpha-1 microglobulin (A1mG) and albumin loss in spent dialysate. The biocompatibility was evaluated by changes in WBC and platelet count, IL-6, Pentoxerine-3 (PTX-3) and high sensitive CRP (hsCRP). The peripheral circulation was estimated by the Skin Perfusion Pressure (SPP) by PAD-3000® (Kaneka Medix, Osaka, Japan). Intra-dialytic hemodynamic stability was evaluated by arterial blood pressure and subjective feelings of the patients.

Results: The clearance of Urea was significantly reduced through dialysis session in both groups but the B2MG clearance was maintained only in ATA. The total removed amount of B2MG and the albumin leakage were not different between 2 groups. The removal of A1mG was significantly higher in ATA than CTA. The platelet count didn't change in ATA during dialysis session but significantly decreased in CTA. WBC counts, IL-6, PTX-3, hs CRP in both groups didn't change. The systolic blood pressure and frequency of intra-dialytic hypotension were not different in both groups whereas some of the patients felt that post-dialytic fatigue improved in ATA. SPP was maintained during dialysis session in ATA but deteriorated in CTA.

Conclusions: The new ATA membrane could reduce the activation of platelets and maintain the peripheral circulation during a dialysis sessions and the time-dependent deterioration of solute removal. The new ATA membrane may improve the QOL and prognosis of chronic dialysis patients.

FR-PO808

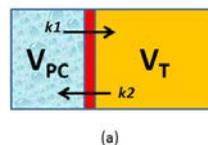
Mathematical Modeling of Fluid Transport in Peritoneal Cavity Fansan Zhu,¹ Samer R. Abbas,¹ Roxana M. Bologa,² Aurelita Lanto,² Peter Kotanko,^{1,3} Nathan W. Levin.¹ ¹Renal Research Inst, New York, NY; ²Rogosin Inst, New York, NY; ³Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The current standard method (peritoneal equilibration test (PET)) is used to obtain transport characteristics of the peritoneal membrane for creatinine, urea and electrolytes, but not for fluid volume. Consequently, ultrafiltration profiles are difficult to obtain because the weight difference between the inlet and outlet dialysate show only net removal during PD. The aim of this study was to investigate whether the rate of change in fluid (V_{PC}) in peritoneal cavity and body tissue fluid volume (V_T) can be simulated with a two compartment model.

Methods: Segmental bioimpedance was continuously monitored in ten PD patients to provide V_{PC} during standard PET in the clinical unit (Zhu, et al, Am J Kidney Dis, 2003). V_T was measured with whole body bioimpedance technique (Hydra 4200). A two compartment model of V_{PC} and V_T (Fig. 1(a)) was established (Eq. 1-Eq.6). Two transport coefficients: k_1 and k_2 represent the rate of fluid shift from V_{PC} to V_T by reabsorption and from V_T to V_{PC} , driven by the glucose gradient. k_1 and k_2 were estimated by best fitting with the actual measurements based on the Marquardt-Levenberg algorithm.

Results: Parameter estimation was successful (residuals<0.01) in all but one patient, who experienced technical problems during the measurements. Fig. 1 (b) shows change in V_{PC} and V_T by modeling simulation in a patient. k_2 correlated inversely with the initial tissue fluid volume V_{T0} ($k_2 = -0.0002 * V_{T0} + 0.0024$, $R^2 = 0.46$, $p < 0.05$).

Conclusions: This model describes dynamics of fluid transport during PD treatment. k_1 and k_2 reflect the characteristics of peritoneal membrane in individual patient. The relationship of k_2 and V_{T0} suggests that fluid status could be a factor affect in ultrafiltration, which could be helpful in clinical practice.



$$\frac{dV_{PC}}{dt} = -k_1 * V_{PC} + k_2 * V_T \quad (1)$$

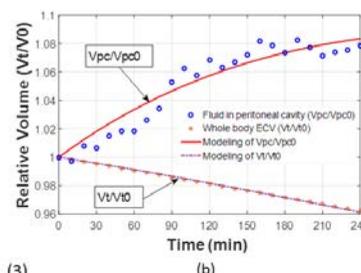
$$\frac{dV_T}{dt} = k_1 * V_{PC} - k_2 * V_T \quad (2)$$

$$\frac{d(V_{PC}/V_{PC0})}{dt} = -k_1 * \frac{V_{PC}}{V_{PC0}} + k_2 * \frac{V_T}{V_{PC0}} \quad (3)$$

$$\frac{d(V_T/V_{T0})}{dt} = k_1 * \frac{V_{PC}}{V_{T0}} - k_2 * \frac{V_T}{V_{T0}} \quad (4)$$

$$\frac{d\lambda}{dt} = -\alpha * \lambda + \beta * \xi \quad (5)$$

$$\frac{d\xi}{dt} = \gamma * \lambda - \delta * \xi \quad (6)$$



$$\lambda = \frac{V_{PC}}{V_{PC0}} \quad \xi = \frac{V_T}{V_{T0}}$$

$$\alpha = k_1 \quad \beta = k_2 * \frac{V_{T0}}{V_{PC0}}$$

$$\gamma = k_1 * \frac{V_{PC0}}{V_{T0}} \quad \delta = k_2$$

FR-PO809

Linagliptin Ameliorated Methylglyoxal-Induced Peritoneal Fibrosis in Mice Takuo Nagai, Shigehiro Doi, Ayumu Nakashima, Takao Masaki. *Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.*

Background: Recent studies have reported that methylglyoxal (MGO) was increased in peritoneal dialysis patients, playing an important role in the development of peritoneal fibrosis. On the other hand, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, exhibits beneficial effects in diabetes patients independent of blood glucose concentration. In this study, we examined whether linagliptin suppressed MGO-induced peritoneal fibrosis in mice.

Methods: Male C57/BL6 mice were divided into three groups: a vehicle group, an MGO injection group, or an MGO injection plus linagliptin group (n=6 per group). Peritoneal fibrosis was induced by a daily intraperitoneal injection of saline containing 40 mmol/L MGO for 21 days. Saline was given in the vehicle group. Linagliptin was administered at a dose of 10 mg/kg by oral gavage once a day.

Results: Immunohistochemical staining revealed that linagliptin suppressed the expression of α -smooth muscle actin and fibroblast-specific protein-1, the deposition of collagen 1 and collagen 3 and infiltration of macrophages (F4/80). In addition, linagliptin reduced TGF- β 1 concentration in peritoneal fluid of MGO-treated mice. Peritoneal equilibration tests showed improvement of peritoneal function in mice receiving linagliptin treatment.

Conclusions: These results suggest that oral administration of linagliptin ameliorated MGO-induced peritoneal fibrosis.

Funding: Private Foundation Support

FR-PO810

Addition of Alanine-Glutamine to Dialysis Fluid Restores Peritoneal Cellular Stress Responses – A Randomized Controlled First-in-Man Trial

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Background: Peritoneal dialysis (PD) fluid cytotoxicity and intermittent bacterial infections contribute to membrane failure and peritonitis in PD patients. Recent meta-analyses revealed no significant influence of newer biocompatible PD fluids on peritonitis rate or peritoneal membrane function, but glutamine addition to standard PD fluids has shown cytoprotective effects both *in vitro* and *in vivo*.

Methods: In this open-label randomized controlled cross-over phase I/II trial (NCT01353638), 20 stable PD patients each underwent two 4 h peritoneal equilibration tests with glucose-based PD fluids supplemented with or lacking 8 mM alanine-glutamine dipeptide (AlaGln), and separated by a 4 week washout phase. Effects of AlaGln on peritoneal inflammation and stimulated cytokine release were also tested in a mouse model of PD-associated peritonitis.

Results: Intraperitoneal (IP) exposure to AlaGln-supplemented PD fluid increased dialysate [glutamine] more rapidly (at 2 h mean 0.55-0.71 mM, $p < 0.05$) and increased heat shock protein expression in peritoneal effluent cells (median 2.12-3.20, $p < 0.05$), but did not alter peritoneal ultrafiltration, small solute transport, cell counts, or biomarkers. AlaGln increased *ex vivo* LPS-stimulated TNF- α release (effect CI 60-100 pg/mL, $p < 0.001$) and, in patients with previous peritonitis, decreased dialysate [IL-8] (effect CI 0.1-4.3, $p < 0.05$). IP AlaGln also reduced inflammation and enhanced cytokine release in the mouse model. No adverse effects of AlaGln were noted.

Conclusions: AlaGln addition to standard PDF acutely attenuated PD-related pathomechanisms in humans and in mice. These data encourage our ongoing phase II trial testing IP AlaGln supplementation as a routine therapeutic intervention in clinical PD.

Funding: Pharmaceutical Company Support - Zytotec GmbH

FR-PO811

Dipeptide Alanine-Glutamine Protects from Peritoneal Fibrosis and Attenuates IL-17 Dependent Pathways During Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is complicated by chronic inflammation and progressive peritoneal membrane damage. Alanine-Glutamine (Ala-Gln), a stable dipeptide commonly used in parenteral nutrition, has immunomodulatory effects and improved resistance of mesothelial cells to PD fluids. Recently, IL-17 was identified as novel player in PD induced peritoneal damage. In this study we investigated if intraperitoneal Ala-Gln administration confers protection against peritoneal damage by modulating IL-17 expression in uremic rodent PD models.

Methods: Uremia was obtained by performing 5/6 nephrectomy and animals were daily instilled with PD fluid enriched or not with Ala-Gln during a period of 5 and 8 weeks respectively for rats and mice. Mice were injected weekly with recombinant IL-17 or with αIL-17. Histological analysis was carried out in parietal peritoneum. Gene expression in the parietal peritoneum biopsies was evaluated by real-time quantitative PCR. Protein levels were determined by ELISA in peritoneal effluents.

Results: Supplementation of PD fluid with Ala-Gln resulted in reduced peritoneal thickness (70.90 ±13.45 vs 16.23 ± 0.70, P<.001), αSMA expression and angiogenesis. Addition of Ala-Gln also showed attenuation of PD induced IL-17 mediated pathways, reflected by substantial reduction/normalisation of peritoneal levels of IL-17 (32.55 ±3.32 vs 7.99 ± 1.59, P<.001), TGFβ, IL-6 and ROR(γ)t. Moreover, repeated exposure of the Ala-Gln treated group to recombinant IL-17 increased peritoneal fibrosis which was however restored upon IL-17 neutralization.

Conclusions: These results suggest that intraperitoneal administration of Ala-Gln ameliorates PD induced peritoneal damage at least in part by modulating IL-17 expression. Therefore, this evidence paves into investigations whether Ala-Gln could be a potential strategy to ameliorate peritoneal deterioration during PD.

FR-PO812

JAK1/2 Inhibitor Preserves Peritoneal Membrane Function in a Non-Uremic Peritoneal Dialysis Rat Model

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Background: We previously showed JAK/STAT pathway activation in the peritoneal membrane (PM) of rats receiving PD with 4.25% Dianeal for 10 days; concomitant treatment with a JAK1/2 inhibitor (JAKi) attenuated PM inflammation, fibrosis, and hypervascularity. We also showed that the mean concentration of MCP-1 was higher in the PD fluid of patients on long-term PD (>6mos) vs new patients (<2wks), demonstrating the potential for clinical relevance (KI.2014). These experiments were performed to determine if a JAKi could prevent deterioration of peritoneal membrane function after longer-term exposure to PD fluid.

Methods: Tunneled PD catheters were placed in rats who received BID infusions of normal saline (n=3), 4.25% Dianeal (n=3), or 4.25% Dianeal + JAKi (n=3) for 12 weeks. Peritoneal equilibration testing (PET) was performed at baseline and again after 12 weeks of fluid instillation. For PET calculations, dialysate glucose was measured enzymatically at time 0 and at 90 minutes after fluid instillation. Plasma and dialysate total protein were measured at 90 minutes after dialysate instillation. D/D₀ glucose and D/P total protein were calculated as [D/D₀ glucose (at 12 wks)]; and [D/P total protein (12 weeks – Baseline)/Baseline] for each rat. Results are expressed as mean + SD for each group.

Results: Both D/Do glucose and D/P total protein functional measurements demonstrate that JAKi protects the peritoneal membrane from the damaging effects of 4.25% Dianeal.

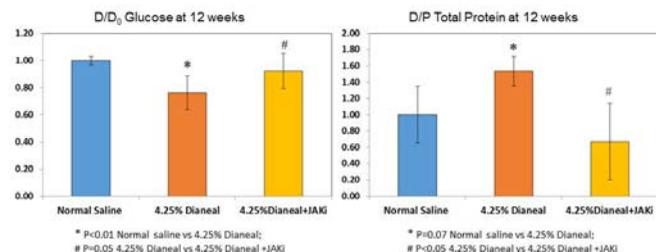


Figure 1

Conclusions: Membrane failure limits the use of PD long-term. Strategies that preserve PD function are critically needed. Together with our prior results, these studies demonstrate the capacity of JAKi to preserve rat PD membrane structure and function during PD fluid exposure.

Funding: Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124, Government Support - Non-U.S.

FR-PO813

MicroRNA Expression Profiling in Peritoneal Fibrosis

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Background: Peritoneal fibrosis (PF) is an intractable complication leading to peritoneal membrane failure in peritoneal dialysis (PD). The aim of this study was to identify the microRNAs (miRNAs) involved in PF.

Methods: miRNA screen was performed using microarray analysis in peritoneal tissue of PF rats induce by intraperitoneally injection of PD fluid containing methylglyoxal (MGO). The expression level of identified miRNAs of serum and drained dialysate were evaluated the association of peritoneal membrane functions measured by peritoneal equilibration test (D/P Cr and D/D₀ glucose) in 33 PD patients. Furthermore, an identified miRNA inhibitor (anti-miRNA-21-5p locked nucleic acid: anti-miRNA-21-LNA) was intraperitoneally injected to PF model mice to investigate its effects for PF.

Results: The initial profiling study identified 6 miRNAs (miRNA-21-5p, miRNA-221-3p, miRNA-223-3p, miRNA-142-3p, miRNA-327 and miRNA-34a-5p) increased more than two fold and no miRNA decreased less than half in peritoneum tissue of PF rats compared with control rats. Among them, serum level of miRNA-21-5p (D/P Cr r=0.44, p=0.01; D/D₀ glucose r=-0.433, p=0.01), miRNA-327(D/P Cr r=0.48, p<0.01; D/D₀ glucose r=-0.50, p<0.01) and miRNA-221-3p (D/P Cr r=0.50, p<0.01; D/D₀ glucose r=-0.50, p<0.01) and drained dialysate level of miRNA-221-3p (D/P Cr r=0.52, p<0.01; D/D₀ glucose r=-0.46, p<0.01) and miRNA-34a-5p (D/P Cr r=0.44, p<0.01; D/D₀ glucose r=-0.48, p<0.01) were significantly correlated with peritoneal membrane functions in PD patients. Anti-miRNA-21-LNA significantly inhibited miRNA-21-5p expression in peritoneum of PF mice. It also inhibited peritoneal fibrous thickening and maintained better peritoneal membrane functions. It significantly increased PPAR-α expression in peritoneum of PF mice.

Conclusions: The results of present study suggested several miRNAs involved in PF, and they may be used as the novel diagnosis biomarkers and therapeutic targets for PF.

Funding: Government Support - Non-U.S.

FR-PO814

Nanoparticules of Lipids Associated with Paclitaxel as an Alternative Strategy to Block Peritoneal Fibrosis

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Background: Peritoneal fibrosis (PF) and loss of ultrafiltration represent important complications of long term peritoneal dialysis, with limited options of treatment. Advances in nanotechnology enabled drug release systems that can provide the release of an active drug in the target tissue. Nanoparticles similar to LDL were developed, linked to Paclitaxel (NanoPACL), an antiproliferative drug. NanoPACL have the ability to bind to LDL receptors present on the cell surface, particularly in immune-inflammatory sites. The aim of this study was to analyze the effect of NanoPACL administration in an experimental model of PF.

Methods: PF was induced in Wistar rats by daily IP injections of chlorhexidine gluconate (CG) at 0.1% during 15 days. Animals (n=20) were divided into 4 groups: Control, normal rats; PF, rats receiving injections of CG; Nano, PF rats treated with nanoparticles without Paclitaxel, via IP; NanoPACL, PF rats treated with NanoPACL (4mg/kg every 3 days, via IP). Euthanasia was performed on day 30. Peritoneal thickness and function, immunohistochemistry and qPCR were analyzed.

Results: NanoPACL significantly reduced peritoneal thickness, α-SMA expression and cell proliferation compared with control groups. Treatment with NanoPACL decreased TGF-β and Smad 3 mRNA expression and preserved peritoneal function characterized by preservation of UF and reduced mass transfer of glucose (MTG).

	Control	PF	Nano	NanoPACL
Peritoneal thickness (µm)	39±5	130±27*	95±10*	40±9**
UF (mL)	4±3	-12±2*	-7±1*	5±1#†
MTG (g/Kg BW)	342±3	406±6*	393±2*	368±2*#†
α-SMA (%)	0±0	8±1*	7±1*	3±1**
PCNA (cells/mm ²)	1±0	234±32*	203±24*	28±10**†
TGF-β	1±0,1	5±1*	4,3±1*	1,8±1**
Smad3	1±0,1	6±1*	6±1*	3±1**

*p<0,05 vs Control; †p<0,05 vs PF; ‡p<0.05 vs Nano.

Conclusions: NanoPACL administration was effective in preventing PF and preserving peritoneal function, possibly by local effect of Paclitaxel.

Funding: Government Support - Non-U.S.

FR-PO815

Vitamin D Receptor Activator (VDRA) Attenuates Epithelial-to-Mesenchymal Transition (EMT) via Modulation of NADPH Oxidase (NOX) Activity and Mitochondrial Dysfunction in Human Peritoneal Mesothelial Cells (HPMC) Duk-Hee Kang, Jiyeon Ko, Hyun-soo Shin, Eun sun Ryu, Hyun-yon Jung, Shina Lee, Dong-Ryeol Ryu, Seung-Jung Kim, Kyu Bok Choi. *Dept of Internal Medicine, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea.*

Background: EMT is known as a key mechanism of peritoneal fibrosis in peritoneal dialysis. Oxidative stress induced by NOX and mitochondrial dysfunction is one of the mechanisms responsible for EMT. Paricalcitol, a selective VDRA, is known to exert antifibrotic effect organ fibrosis, however there are no studies about the role of paricalcitol on peritoneal fibrosis. We investigated whether paricalcitol imposed any effect on TGFβ1-induced EMT of HPMC with an exploration of mechanism of antifibrotic effect of paricalcitol in terms of modulation of oxidative stress.

Methods: EMT was evaluated by morphological changes of HPMCs and the expressions of E-cadherin and α-smooth muscle actin. Intracellular ROS was analyzed by measuring NOX activity, H₂O₂ generation, NOX mRNA expressions with DCF-DA and MitoSox[®] staining. Activation of Erk1/2, p38 MAPK, nuclear translocation of β-catenin and snail expression were assessed by western blotting and immunocytochemistry. Effect of paricalcitol on ROS generation and EMT was analyzed in HPMC exposed to TGFβ1.

Results: TGFβ1 (1ng/ml) induced EMT of HPMCs with an increase in ROS generation and NOX activity from 30 minutes, and mitochondrial ROS production from 6 hours. TGFβ1 also increased the phosphorylation of Erk and p38 MAPK from 1hour, which was followed by nuclear translocation of β-catenin and snail up-regulation in HPMC. Paricalcitol (50nM) ameliorated TGF-β1-induced EMT in HPMC, which was associated with a decrease in both NOX- and mitochondria-mediated ROS production. TGFβ1-induced EMT was partially alleviated by N-acetyl cysteine (5mM) or apocynin (100μM), which was further inhibited by an addition of rotenone (1μM) or paricalcitol.

Conclusions: One of the VDRA, paricalcitol, ameliorated TGFβ1-induced EMT of HPMCs by a decreased in ROS generation in HPMCs. Anti-oxidant effect of paricalcitol seems to be related to the direct inhibition of NOX and mitochondria-mediated ROS production.

Funding: Government Support - Non-U.S.

FR-PO816

Adenosine Monophosphate-Activated Protein Kinase (AMPK) Agonist Attenuated Epithelial-to-Mesenchymal Transition (EMT) of Mesothelium and Peritoneal Fibrosis via an Amelioration of Oxidative Stress Duk-Hee Kang,¹ Jiyeon Ko,¹ Eun sun Ryu,¹ Hyun-yon Jung,¹ Shina Lee,¹ Dong-Ryeol Ryu,¹ Seung-Jung Kim,¹ Kyu Bok Choi,¹ Sun-Hee Park,² Yong-Lim Kim.² *¹Dept of Internal Medicine, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; ²Kyungpook National Univ School of Medicine, Daegu, Republic of Korea.*

Background: Phenotype transition of peritoneum has been regarded as an early mechanism of peritoneal fibrosis. Metformin, one of the AMPK agonists, has recently received a new attention due to an inhibitory effect on EMT of cancer cells. We investigated whether metformin imposed any effect on EMT of HPMC with an exploration of cellular mechanism for anti-fibrotic effect of metformin.

Methods: EMT was evaluated by morphological changes and the expressions of E-cadherin and α-SMA after stimulation of TGFβ1 (1ng/ml). ROS generation was analyzed by DCF-DA, NOX activity, NOX mRNA expressions, and MitoSox[®] staining. Activation of Smad2/3, MAPK, nuclear translocation of β-catenin and snail expression were also assessed. Animal model of peritoneal dialysis (PD) was established by daily infusion of 4.25% glucose-based dialysate for 8 weeks via intraperitoneal catheter. Effects of metformin (50 mg/kg/day, ip) on EMT, peritoneal thickening and an expression of markers of oxidative stress were investigated.

Results: TGFβ1-induced EMT in HPMC was ameliorated by metformin. TGFβ1 increased ROS generation and NOX activity from 30 min, and mitochondrial ROS production from 6 hrs. TGFβ1 increased the phosphorylation of smad2/3 and MAPK, which was followed by nuclear translocation of β-catenin and snail up-regulation. Metformin ameliorated ROS production, the activation of smad2/3 and MAPK, and snail expression. In PD model, metformin decreased peritoneal thickness and EMT with an increase in ratio of reduced to oxidized glutathione and superoxide dismutase activity. Metformin also decreased the expression of nitrotyrosine in peritoneum and 8-OHdG in dialysate.

Conclusions: AMPK may play a role in preservation of peritoneal function by protecting the peritoneum from phenotype transition and fibrosis via an amelioration of oxidative stress.

Funding: Government Support - Non-U.S.

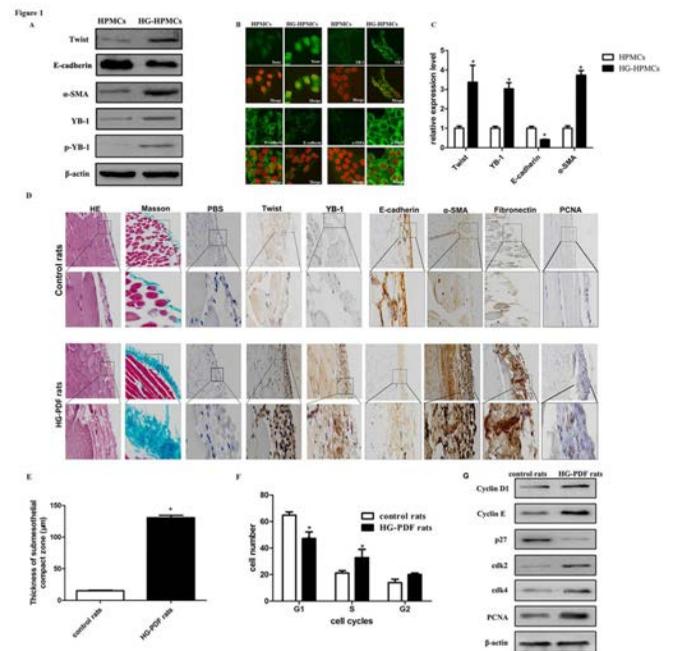
FR-PO817

Twist Accelerates Human Peritoneal Mesothelial Cells Proliferation and Fibrosis by Regulating YB-1 Lijie He. *Dept of Nephrology, Xijing Hospital, Xi'an, China.*

Background: We have previously shown that E-box-binding transcription factor Twist is overexpressed in high glucose damage of human peritoneal mesothelial cells (HPMCs) and is involved in peritoneal membrane (PM) fibrosis in vitro. Here, we further identify its precise function related to peritoneal membranes (PM) fibrosis.

Methods: We have previously shown that E-box-binding transcription factor Twist is overexpressed in high glucose damage of human peritoneal mesothelial cells (HPMCs) and is involved in peritoneal membrane (PM) fibrosis in vitro. Here, we further identify its precise function related to peritoneal membranes (PM) fibrosis.

Results: Here, up-regulated expression and activation of Twist and YB-1 were found in HPMCs under extensive periods of PM fibrosis ex vivo. In immortal HPMCs and in HG-induced PD animal model, Twist and YB-1 were also up-regulated and a transformed fibroblastic phenotype of HPMCs was found stimulated by high glucose (HG, 60 mmol/L).



Evidence from chromatin immunoprecipitation and reporter assays further supported that YB-1 were transcriptionally regulated by Twist directly binding to E-box. Collectively, these data suggested that YB-1 was a major downstream target of Twist. Re-expression of Twist led to decrease HPMCs growth, induced cell cycle arrest and increase PM fibrosis. Silencing of Twist or YB-1 could promote cell cycle progress of HG-induced HPMCs growth, increasing cyclin D1/CDK2 and cyclin E/CDK4 expression and also inhibited PM fibrosis

Conclusions: Our data suggested that activation of Twist/YB-1 pathway might contribute to the growth retardation of HPMCs and the progressive PM fibrosis during PD.

Funding: Government Support - Non-U.S.

FR-PO818

The Expression of miRNA200a in Peritoneal Dialysis Associated Peritoneal Fibrosis Xin Wei. *Nephrology Dept, The First Affiliated Hospital of Nanchang Univ, Nan Chang, China.*

Background: Peritoneal fibrosis (PF) is an almost invariable consequence of peritoneal dialysis (PD), which is an established alternative for the replacement therapy of end-stage renal disease. We know that miR-200a belong to miR-200 family, which is closely related to a variety of fibrotic diseases. However, the role of miR-200a in peritoneal fibrosis is largely unknown.

Methods: The peritoneal fibrosis mouse model associated with PD was established by intraperitoneal injection of lipopolysaccharide + 4.25% peritoneal dialysate. The expression of miRNA was detected by microarray. The expression of miRNA profiles between fibrotic and normal peritoneal tissues was compared (n=3 in each group). The differentially expressed miRNA (miR-200a) was validated by real-time PCR in larger sample size cohorts (n=15). The expressions of miR-200a were also detected in the epithelial-mesenchymal transition (EMT) process of peritoneal mesothelium cells.

Results: In mice model of PD, peritoneal tissue was markedly thickened and with a massive extracellular matrix accumulation. By miRNA microarray analysis, miR-200a was significantly down regulated (3.31 folds change, P<0.05) in fibrotic peritoneal tissues. The down-regulated expression level of miR-200a was also validated by real-time PCR in larger cohorts (P<0.05). Then, the expression level of miR-200a was detected in the EMT process of human peritoneal mesothelium cells. During the process of TGF-β1 induced EMT, miR-200a was significantly down-regulated compared with the control (P<0.05)

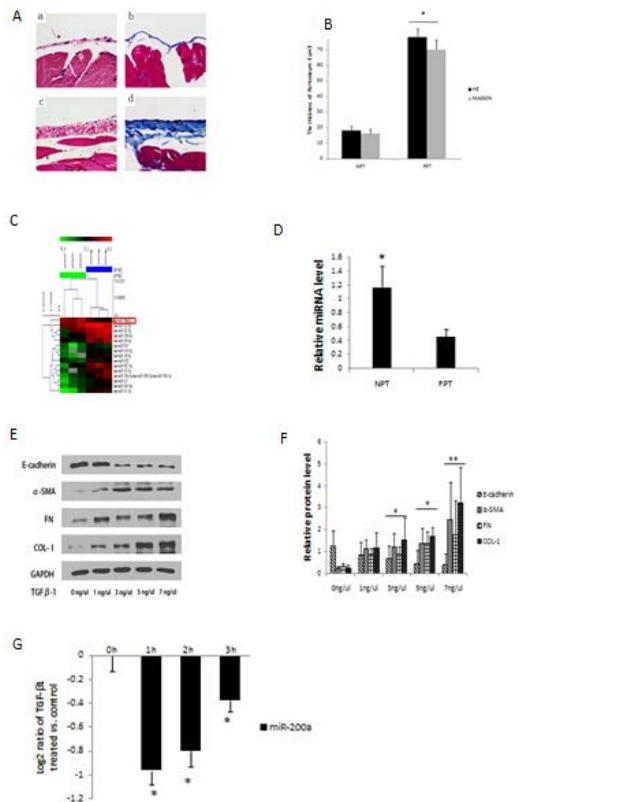


Fig. 1. A,B: peritoneal fibrosis in a mouse model of PD. C,D: peritoneal fibrosis index expression. E, F: EMT index expression during the EMT process of human peritoneal mesothelium cells; G: miR-200a expression level down-regulated during the EMT process. NPT: normal peritoneal tissue, FPT: fibrotic peritoneal tissue, * P<0.05, ** P<0.01.

Conclusions: Down-regulated expression of miR-200a was observed both during peritoneal fibrosis and TGF-β1 induced EMT in vivo and in vitro, suggesting that miR-200a may be involved in the peritoneum fibrosis by regulating the target genes of EMT.
Funding: Government Support - Non-U.S.

FR-PO819

Peritonitis Induces Native and EDA⁺ Fibronectin Synthesis in Human Peritoneal Mesothelial Cells Through PI3K and MAPK Activation
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Background: Peritonitis is a severe complication of peritoneal dialysis (PD), which could lead to progressive structural and functional deterioration of the peritoneum and PD failure. EDA⁺ fibronectin (FN) is induced during disease states, but its expression in PD associated peritonitis has not been investigated. We examined peritoneal expression of native and EDA⁺ FN in an experimental model of peritonitis and their association with mesothelial epithelial-to mesenchymal transition.

Methods: Male C57BL/6 mice were challenged with PBS or lipopolysaccharide (LPS, 500mg) by intraperitoneal injection for 2, 3 and 6 times (n=6), after which time the parietal peritoneum was excised for further studies. Confluent, growth arrested human peritoneal mesothelial cells (HPMC) were stimulated with spent peritonitis PD fluid, LPS, or exogenous TGF-β1 or CTGF (growth factors that are increased during peritonitis) either alone or in combination, for periods up to 72h to investigate their effect on cell morphology, and FN, collagen and SNAIL synthesis.

Results: Mice exposed to six, but not fewer, challenges of LPS exhibited mesothelial denudation, influx of infiltrating cells and substantial submesothelial thickening attributed to increased collagen and native and EDA⁺ FN deposition. Peritonitis PD fluid induced phenotypic changes, and SNAIL, collagen I, and native and EDA⁺ FN synthesis in HPMC. Exogenous TGF-β1, but not CTGF, significantly increased native and EDA⁺ FN by 4.3-fold and 6.2-fold respectively (P<0.05 for both). Cells co-stimulated with TGF-β1 and CTGF showed synergistic increase of native and EDA⁺ FN. This was mediated in part through PI3K, ERK and p38 MAPK activation. TGF-β1 and CTGF neutralizing antibody significantly decreased native and EDA⁺ FN synthesis, but had no effect on collagen I or SNAIL expression in HPMC.

Conclusions: Our data demonstrated that peritonitis, especially when recurrent, induced progressive peritoneal deposition of collagen, and native and EDA⁺ FN. TGF-β1 and CTGF synergistically induced native and EDA⁺ FN synthesis in HPMC, and play important roles in peritoneal fibrosis induced by bacterial peritonitis.

Funding: Government Support - Non-U.S.

FR-PO820

Effects of Astragaloside IV against the TGF-β-Induced Epithelial-to-Mesenchymal Transition in Peritoneal Mesothelial Cells by Promoting Smad 7 Expression
 Lu Zhang,^{1,2} Zhenghong Li,² Weiming He,² Lingdong Xu,² Jing Wang,³ Jun Shi,¹ Meixiao Sheng.^{1,2} *¹the First Clinical Medical College, Nanjing Univ of Chinese Medicine, Nanjing, Jiangsu Province, China; ²Renal Div, Jiangsu Province Hospital of Chinese Medicine, Nanjing, Jiangsu Province, China; ³Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, Jiangsu Province, China.*

Background: To investigate the effect of Astragaloside IV (AS-IV) on the regulation of the TGF-β1 Smad signaling pathway in mesothelial cells with an epithelial-to-mesenchymal transition (EMT).

Methods: EMT of human peritoneal mesothelial cells (HMrSV5) was induced using 2 ng/ml TGF-β1. Cells were randomly divided into a vehicle group, a vehicle group with AS-IV, a TGF-β1 treated group, and a TGF-β1 treated group receiving varied doses of AS-IV or NAC. Real-time quantitative PCR and western blot were used to detect the expression of genes and proteins associated with the TGF-β1/Smad signaling pathway and EMT. DCFH-DA was used to detect the generation of ROS in HMrSV5 cells, and a transwell migration assay was used to verify the capacity of AS-IV to inhibit EMT in HMrSV5 cells. Lentiviruses were used as carriers for the overexpression or knockdown of the Smad7 gene.

Results: Expression levels of E-cadherin (epithelial marker) was decreased and vimentin, α-SMA (EMT markers) and collagen I (extracellular matrix protein) phospho-Smad2/3, Snail1 and Snail2 was increased significantly in the TGF-β1-treated HMrSV5 cells. AS-IV was associated with downregulated expression of vimentin and phospho-Smad2/3 in a dose-dependent manner, while the expression of Smad7 increased. Silenced or forced expression of Smad7 verified its role in the inhibitory effect of AS-IV on TGF-β1-induced EMT in HMrSV5 cells.

Conclusions: AS-IV effectively promotes the upregulation of Smad7 in the TGF-β1/Smad signaling pathway during the EMT of HMrSV5 cells, indicating its potential therapeutic effect for the control of PF.

Funding: Government Support - Non-U.S.

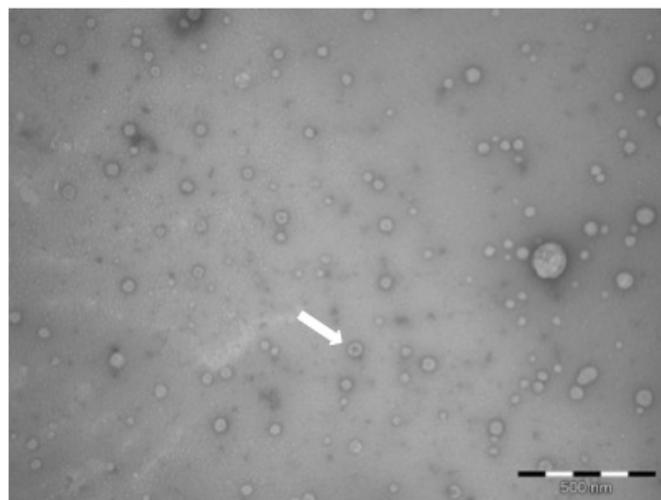
FR-PO821

Extracellular Vesicles in Peritoneal Effluent
 Deirisa Lopes Barreto,¹ Anita N. Böing,² Rienk Nieuwland,² Anita Grootemaat,² Raymond T. Krediet.¹ *¹Nephrology, AMC-UvA, Netherlands; ²Clinical Chemistry, .*

Background: Continuous and long-term exposure to peritoneal dialysis (PD) solutions induces constant low-grade inflammation and remodeling of peritoneal membrane morphology. Although the biochemical composition of peritoneal effluent offers the opportunity to explore the peritoneal membrane status in a simple and non-invasive manner, to date no clinically useful effluent biomarker has been identified that reflects the peritoneal membrane integrity sufficiently. As human body fluids contain extracellular vesicles (EVs), which are now believed to provide novel biomarkers for diseases, we investigated the presence of EVs in peritoneal effluent.

Methods: Peritoneal effluent of a short-term PD patient was collected from a regular dialysis dwell. After centrifugation, aliquots of cell-free effluent were frozen in liquid nitrogen and stored at -80°C until analysis. EVs were isolated by size exclusion chromatography. Thereafter, transmission electron microscopy (TEM) and flow cytometry (comprising markers for epithelial and mesothelial cells, leucocytes, platelets and erythrocytes) were used to detect the presence of single EVs.

Results: EVs and liposomes were identified by TEM and flow cytometry. EVs exhibited their characteristic cup shape. The majority of EVs had a mean diameter <100nm, and were present in similar amounts as in human plasma. Most EVs originate from epithelial and mesothelial cells. Moreover, EVs stained positive for leucocyte antigens, mesothelin and cancer antigen 125.



Conclusions: This is the first study to demonstrate the presence of EVs in human peritoneal effluent. Furthermore, the cellular origin of most peritoneal EVs is established.

We postulate that the presence and composition of such EVs in peritoneal effluent will closely mirror the peritoneal membrane morphology. Future studies will be necessary to investigate the clinical relevance for the detection of peritoneal membrane damage and potential use of these peritoneal EVs in PD patient care.

FR-PO822

miR-200a Negatively Regulates TGF-β1-Induced Peritoneal Mesothelial Cell Epithelial-Mesenchymal Transition by Targeting ZEB1 and ZEB2 Expression Xin Wei, Guojun Hao, Qinkai Chen. *Nephrology Dept, The First Affiliated Hospital of Nanchang Univ, Nan Chang, China.*

Background: Peritoneal fibrosis (PF) is an almost invariable consequence of peritoneal dialysis (PD), which is an established alternative for the replacement therapy of end-stage renal disease. In our previous study, we found that the expression level of miR-200a were down-regulated in fibrotic peritoneum and the epithelial-mesenchymal transition (EMT) process of peritoneal mesothelial cell. However, the role of miR-200a in EMT of peritoneal mesothelial cell and peritoneal fibrosis is largely unknown.

Methods: Human peritoneal mesothelial cell line (HMrSV5) was cultured in the presence or absence of TGF-β1. The protein expression levels of EMT index and E-box-binding homeobox (ZEB) 1/2 were determined by western blot. The level of miR-200a was determined by real-time PCR. miR-200a mimic or inhibitor and its negative control RNA, were transfected into HMrSV5 cells using Lipofectamine 2000.

Results: We found that miR-200a mimic can attenuated TGF-β1 induced peritoneal mesothelial cell EMT and synthesis of extracellular matrix. It was also demonstrated that the miR-200a was responsible for protecting peritoneal mesothelial cells from mesenchymal transition by targeting suppression of ZEB1/2.

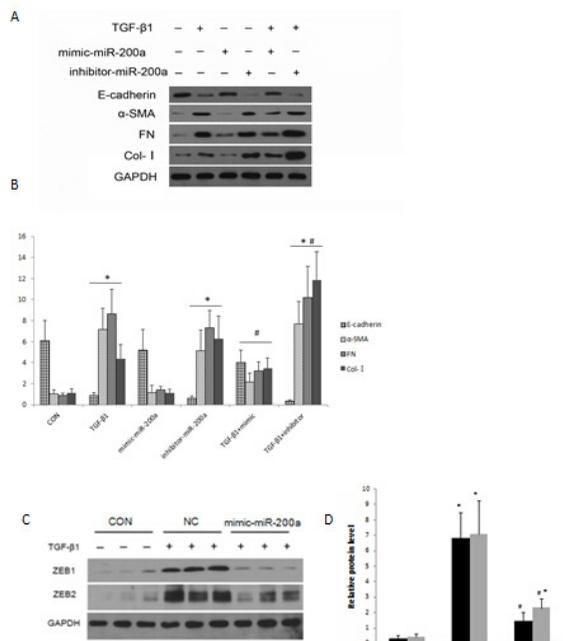


Fig. 1 A-B: EMT index expression after transfection of miR-200a mimic or inhibitor; C-D: ZEB1/2 expression after transfection of miR-200a mimic. * P<0.05, # P<0.01.

Conclusions: The results suggested that miR-200a may not only be a useful biomarker of EMT in ovarian cancer, but also of potential therapeutic value in peritoneal fibrosis. **Funding:** Government Support - Non-U.S.

FR-PO823

Identification and Functional Characterization of Human Peritoneal Fibroblast Subsets According to the Expression of CD90/Thy-1 Edyta Kawka,¹ Andras Rudolf,² Maria Bartosova,³ Rusan Catar,¹ Janusz Witowski,² Duska Dragun,¹ Achim Joerres,¹ Claus P. Schmitt.³ ¹Dept of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany; ²Depts of Pathophysiology and Clinical Immunology, Poznan Univ of Medical Sciences, Poznan, Poland; ³Center for Pediatric and Adolescent Medicine, Universitätsklinikum Heidelberg, Heidelberg, Germany.

Background: The exact origin of myofibroblasts in PD-associated peritoneal fibrosis is unknown. Lineage tracing studies suggest that resident submesothelial fibroblasts may be their major precursors. Here, we set out to identify HPFB subsets in human peritoneum and examined co-expression of CD90/Thy-1 with markers of the myofibroblastic phenotype.

Methods: HPFB were isolated from omentum, purified and then separated (MACS) into CD90/Thy-1⁺ and CD90/Thy-1⁻ populations for assessment of myofibroblastic markers:

qPCR, immunofluorescence, and ELISAs. Moreover, the presence of FSP-1⁺ and CD90/Thy-1⁻ fibroblasts was studied by immunofluorescence in peritoneal biopsies of 12 PD, 5 uremic patients, and 8 healthy controls.

Results: Cells positive for FSP-1 or CD90/Thy-1 were absent in healthy controls, but were detectable in uremic and PD patients. In those, the majority (>95%) of FSP-1⁺ HPFB were also CD90/Thy-1⁻. In vitro studies showed that CD90/Thy-1⁺ HPFB had a 1.2-fold higher proliferation rate (MTT assay; n=12, p<0.05) than CD90/Thy-1⁻. Expression of myofibroblastic markers in CD90/Thy-1⁺ cells was significantly higher with α-SMA, collagen-1 and TGF-β1 being increased (2.5-, 1.6- and 1.8-fold, respectively; n=13, p<0.05). Furthermore, CD90/Thy-1⁺ HPFB revealed increased contractile properties as reflected by 1.2-fold greater reduction in collagen gel contraction assays (n=3).

Conclusions: The vast majority of FSP-1⁺ HPFB detected in the peritoneum of uremic and PD patients expressed CD90/Thy-1. In contrast, this phenotype was not detected in normal peritoneum. In vitro studies demonstrated increased expression of myofibroblastic markers in CD90/Thy-1⁺ HPFB. These cells may thus contribute to peritoneal fibrosis which often develops in patients during chronic PD.

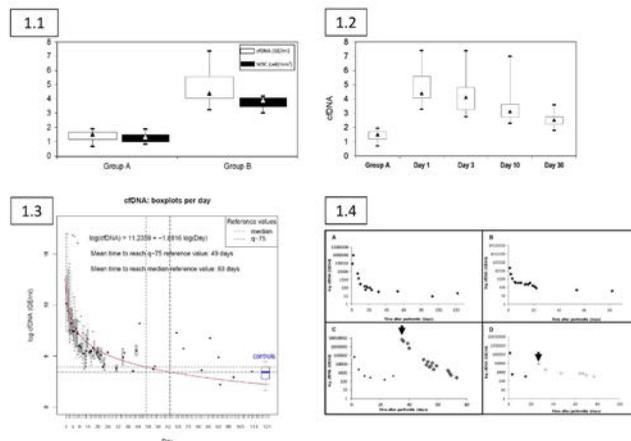
FR-PO824

Innovative Index to Follow the Peritoneal Infections and for Monitoring the Recovery Process After Peritonitis Grazia Maria Virzi, Sabrina Milan manani, Alessandra Brocca, Massimo de Cal, Ilaria Tantillo, Carlo Crepaldi, Claudio Ronco. *Nephrology, San Bortolo Hospital-IRRV.*

Background: Cell-free DNA is present in the peritoneal effluent of stable PD patients, but there is no data on cfDNA in case of peritonitis. We investigated the variation of peritoneal cfDNA (pcfDNA) levels in PD-related peritonitis.

Methods: We enrolled 53 PD patients: 30 without any history of systemic inflammation and peritonitis in the last 3 months (groupA) and 23 with acute peritonitis (groupB). PcfDNA were quantified i by Real-Time PCR. Peritoneal samples on day 1-3-10-30 and until the 120th from the start of peritonitis were collected for WBC counts and pcfDNA evaluation in group B.

Results: Quantitative analysis of pcfDNA showed significantly higher levels in groupB compared with groupA (p<0.01), similarly as WBC. PcfDNA showed significantly higher levels in groupB on day1-3-10 and 30 compared with groupA (p<0.05). A significant positive correlation was observed between pcfDNA level and WBC on day1 (rho=0.89) and day3 (rho=0.5)(both p<0.05). No statistically significant correlation was observed on day10 and 30. In groupB, pcfDNA tends to progressively decrease. From this decreasing curve, we estimated that 49 days are necessary to reach the value of 51 GE/ml (75percentile in groupA) and 63 days to reach 31 GE/ml (median). We observed a new rapid increase of cfDNA level (consistent with WBC) in 5 relapsing patients, at the first day of relapsing peritonitis.



Conclusions: in conclusion, pcfDNA increased in peritoneal effluent in PD-related peritonitis and tended to progressively decrease in relation with membrane repair process. Peritoneal cfDNA could be a new method to determine acute damage and an inverse index of repair process. PcfDNA could help to evaluate functional and structural integrity of peritoneal membrane and to follow the evolution of infections during peritonitis.

FR-PO825

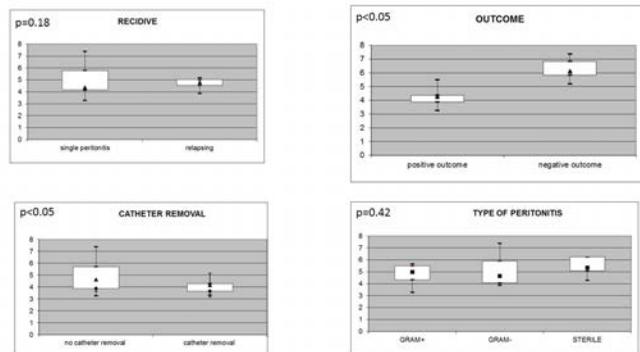
The Role of Cell-Free DNA for Management in PD-Related Peritonitis Grazia Maria Virzi, Sabrina Milan manani, Alessandra Brocca, Massimo de Cal, Ilaria Tantillo, Carlo Crepaldi, Claudio Ronco. *Nephrology, IRIV-Si Bortolo.*

Background: Peritonitis and exit site infections are the major complications of PD and remains the major cause of switch from HD. In this study, we investigated the role of peritoneal cell-free DNA (cfDNA) and its association with peritonitis.

Methods: We enrolled 23 PD patients with peritonitis and without any history of systemic inflammation (14 male, mean age: 68±16yrs). cfDNA were extracted and quantified in peritoneal effluent by Real Time PCR for β-globin gene.

Results: All patients were treated and clinically recovered from peritonitis in 13.5±5.4days. 18/23 patients had a first episode of peritonitis and responded to first-line antibiotics (65% Gram+, 22% Gram- and 13% sterile), whereas 5/23 had a relapsing episode of peritonitis (responded to other course of intra-peritoneal antibiotics). There

was no difference in cfDNA levels between Gram+/Gram-peritonitis; patients with single episode and relapsing peritonitis, but there was a significantly difference in cfDNA between PD patients with positive and negative outcomes (n=4), defined as death (p<0.05). CfDNA showed significantly higher levels in 3 patients required catheter removal (p<0.05). There was no difference in cfDNA levels between PD patients with a negative history of previous peritonitis (n=3) and PD patients with a positive history (n=20) (p=0.48). there was no statistically significant correlation between cfDNA and number of previous peritonitis (rho=0.13, p=0.55).



Conclusions: This pilot study provided substantial basis for further investigations of molecular mechanisms of peritoneal injury and potential clinical application of cfDNA. cfDNA could provide some additional information about patient's outcome and management. These results can be considered hypothesis generating, and stimulate further exploration of a prognostic and predictive role of cfDNA in PD-related peritonitis.

FR-PO826

Epimorphin Expressions in Mice Model of Peritoneal Fibrosis Muneharu Yamada, Takashi Oda, Shuuhei Komatsu, Taito Oshima, Tadasu Kojima, Yasuyo Sudo, Tomohiro Tomiyasu, Noriko Yoshikawa, Masaharu Yoshida. *Nephrology, Hachioji Medical Center of Tokyo Medical Univ, Hachioji, Tokyo, Japan.*

Background: Long-term peritoneal dialysis induces peritoneal fibrosis in submesothelial areas. Epimorphin is a mesenchymal protein that regulates epithelial morphogenesis through epithelial-mesenchymal interactions, has recently attracted attention as an important modulator of tissue repair. We previously reported that epimorphin was involved in the repair of fibrosis in mice (*Lab Invest* 2010). In this study, we evaluated the epimorphin expressions in the peritoneal fibrosis mice model.

Methods: Peritoneal fibrosis was induced by the injection of 0.1% chlorhexidine gluconate in 15% ethanol and 85% normal saline (CG-injected mice) into peritoneal cavity of 10 week-old male C57/Bl6 mice every other day. Control mice received intraperitoneal injection of normal saline. The mice were sacrificed 3 weeks after the first CG injection and peritoneal tissues were dissected out. Morphologic peritoneal changes were assessed by Masson's Trichrome staining. Epimorphin expressions were assessed by immunohistochemically and real-time RT-PCR.

Results: In CG-injected mice, the marked thickening of the submesothelial compact zone was shown in Masson's trichrome staining. IF staining for epimorphin was positive in the submesothelial area corresponding to the fibrotic area. Epimorphin staining was significantly stronger than that in control mice. Such an increase in epimorphin expression was confirmed by and by real-time RT-PCR (n=5, p<0.05 vs control).

Conclusions: These findings suggest that epimorphin expression may have pivotal role in the repair of peritoneal fibrosis similar to that of UUO release model in mice as reported previously.

Funding: Government Support - Non-U.S.

FR-PO827

Peritoneal Mesothelial Cells (PMCs) Injury Induced by Neutral Peritoneal Dialysis Solution (NPDS) and Its Amelioration by Molecular Hydrogen (H₂) Wan-jun Zhu,^{1,2} Kimio Watanabe,¹ Hiroyuki Terawaki,¹ Yoshimitsu Hayashi,¹ Naoki Nakanishi,³ Shigeru Kabayama,² Masaaki Nakayama.¹ *¹Dept of Kidney and Hypertension, Medical School, Fukushima Medical Univ, Fukushima, Japan; ²Medical Device, Nihon Trim Co. Ltd, Osaka, Japan; ³Business Strategy & Management, Nihon Trim Co. Ltd, Osaka, Japan.*

Background: PMCs play pivotal roles in suppression of peritoneal fibrosis, adhesion, and bacterial infection in PD therapy. It is reported that histological changes of peritoneum and incidence of encapsulating peritoneal sclerosis, have been decreased by NPDS introduction. However, meta-analysis did not show superiority of NPDS in incidence of bacterial peritonitis, suggesting bio-incompatibility of current NPDS. H₂ has anti-oxidative effects in biological way, and its clinical application has been studied. The present study aims to examine PMC injury by NPDS, and its ameliorating effect of H₂.

Methods: Male SD rats (n=24) were divided into three groups: control (Con), 2.5% glucose lactate-based NPDS (PD), and the same NPDS with dissolved H₂ (400 ppb) (HPD). The latter two groups were given NPDS or H₂-NPDS intraperitoneally for 10-day

20 mL once a day. Peritoneal tissues were subjected to morphological analysis including immunohistochemistry (cytokeratin, vimentin, proliferation; Ki67, and apoptosis; M30 cytodeath), and PMCs obtained to gene analysis by real time PCR, and microarray assay.

Results: The collagen thickness increased in PD and HPD, however, there were significant changes in stainings of vimentin, M30 cytodeath, and Ki67 in PD as compared to Con, while no change in HPD. In gene cluster analysis, there were changes by 8.7% in whole gene expression between PD and Con, and 3.7% changes between PD and HPD. In PCR, no difference was found in Epithelial-Mesenchymal Transition (Snail, TGF- β , α SMA) among the groups, while wound healing (MMP9, CTGF, Fibronectin, FAK), cytokines (IL1b, TNFa, NFkb) were decreased in PD as compared to Con, but no changes in HPD.

Conclusions: The current lactate-based NPDS may disturb wound healing and local immunity of PMCs, and H₂ dissolved dialysate correct them. H₂ could increase biocompatibility of PDS in preserving physiological function of PMCs in PD therapy.

FR-PO828

Bicarbonate-Buffered Peritoneal Dialysis Solution Suppresses Lactate-Induced Apoptosis via Monocarboxylate Transporter-1 in Human Peritoneal Mesothelial Cells Akihiro Kuma, Tetsu Miyamoto, Ryota Serino, Yumi Furuno, Yoko Fujimoto, Hiromichi Ueno, Yutaka Otsuji, Masahito Tamura. *Dept of Nephrology, Univ of Occupational and Environmental Health, Kitakyushu, Japan.*

Background: Long-term peritoneal dialysis is associated with functional and structural alterations of the peritoneal membrane. Lactate-buffered peritoneal dialysis fluid (L-PDF) has impaired biocompatibility due to the presence of supra-physiological levels of lactate. Although bicarbonate-buffered PDF (B-PDF) has been developed, its biocompatibility remains unclear. Here, we investigated the effects of L- or B-PDF on cell viability and apoptosis in cultured human peritoneal mesothelial cells (HPMCs), focusing on monocarboxylate transporters (MCT).

Methods: HPMCswere cultured in mediums containing 10% fetal bovine serum and L-PDF with 1.5% glucose (L1) or 2.5% glucose (L2), B-PDF with 1.5% glucose (B1) or 2.5% glucose (B2), or no PDF (control). Cell viability and apoptosis were measured with the WST-1 and TUNEL assays, respectively. The roles of MCT-1 and -4 on lactate-induced apoptosis were evaluated by siRNA transfection for MCT-1 and -4.

Results: Cell viability was significantly decreased in cells incubated with L1 (12 \pm 2%, control=100%) and L2 (2 \pm 1%), compared with B1 (74 \pm 2%) and B2 (72 \pm 1%) after 72 h incubation. Apoptotic cells were also increased in L1 (69 \pm 16%), L2 (73 \pm 8%) compared with B1 (3 \pm 0%) and B2 (4 \pm 1%). MCT-1 and -4 protein and mRNA expression levels, examined by Western blotting and real-time-PCR, respectively, were similar in all cells. Protein expression levels of MCT-1 and -4 were almost completely diminished after transfection of siRNAs for MCT-1 and -4, respectively. MCT-1 siRNA increased the levels of cell viability by 3.2–3.7-fold and decreased the amount of apoptotic cells from 64 \pm 8% to 47 \pm 4% in cells treated with L1 for 72 h. Interestingly, MCT-4 siRNA had no effect on cell viability and apoptosis.

Conclusions: Our results showed that L-PDF induced apoptosis by importing lactate via MCT-1 in HPMC, and suggest that B-PDF improved biocompatibility by inhibiting mesothelial cell apoptosis.

FR-PO829

MiRNA-143/145 Gene Cluster Enhances Cell Deformation and Fibrosis of Human Peritoneal Mesothelial Cells via Modulating TPM4 Lijie He, Shiren Sun. *Dept of Nephrology, Xijing Hospital, Xi'an, Shaanxi, China.*

Background: In this study, we work for the function and mechanism of miR-143/145 gene cluster in human peritoneal mesothelial cells (HPMC), who were as possible triggers for peritoneal membrane fibrosis.

Methods: To investigate if miR-143/145 gene cluster could promote PM fibrosis, all these immortal HPMCs were characterized by fibrosis related markers and tested the expression of miRNA-143/145 cluster and tropomyosin4 (TPM4) by real time PCR or Western blot. We also used PD dialysis rat model to observe the response of PM to miR-143/145 gene cluster and their possible target.

Results: Here, we found that miR-143/145 gene cluster, which are examined to be highly expressed in HG-induced HPMCs (HG, 60 mmol/L) and in PD animal model. TPM4 were found significantly lower expression in HG-induced HPMCs. So our study showed that high glucose from PD fluid could promote the expression of miR-143/145 of HPMCs and reduce the expression of TPM4, compared with normal glucose-cultured HPMCs. Reporter assays further supported that TPM4 were post-transcriptionally regulated together by miR-143/145 gene cluster. Collectively, these data suggested that TPM4 was a downstream target of miR-143/145 gene cluster. Re-expression of miR-143/145 gene cluster by miR-143 or miR-145 mimic led to cell deformation, and reduced cell adhesion, following the down-regulating expression of TPM4 and E-cadherin, but up-regulating expression of α -SMA, CTGF, collagens and fibronectin which might increase PM fibrosis. Depletion of miR-143/145 cluster in HG-induced HPMCs enhanced cell adhesion, marking by up-regulating E-cadherin and TPM4 but down-regulating α -SMA, CTGF, collagens and fibronectin in vitro. Mechanistically, miR-143/145 gene cluster were characterized to target the messenger RNA TPM4 to contribute to the cell adhesion, deformation and fibrosis.

Conclusions: Our data suggested that miR-143/145-TPM4 pathway might contribute to the cell deformation of HPMCs and the progressive PM fibrosis during PD.

Funding: Government Support - Non-U.S.

FR-PO830

Mitochondrial DNA Copy Number Is Associated with Peritoneal Dialysis Failure in Younger and Metabolically Healthier Peritoneal Dialysis Patients

Jae Eun Um,¹ Jong Hyun Jhee,² Kyoung Sook Park,² Chang-Yun Yoon,² Mi Jung Lee,² Jung Tak Park,² Shin-Wook Kang,^{1,2} Tae-Hyun Yoo.^{1,2} ¹Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea; ²Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Insulin resistance and inflammation are known to be closely related to adverse outcomes in peritoneal dialysis (PD) patients. Recently, mitochondrial function has been reported to play a key role in glucose metabolism as well as systemic inflammation in various populations. However, the clinical consequences of mitochondrial function in PD patients are not well known. Therefore, this study was aimed to investigate the relationship of mitochondrial DNA (mtDNA) copy number and clinical outcome in PD patients.

Methods: A total of 120 prevalent PD patients were recruited. mtDNA copy number was counted by a PCR based method. Primary outcome was PD catheter removal due to ultrafiltration failure. Metabolic syndrome was defined using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Cox proportional hazard analysis was performed to determine the independent association of mtDNA copy number with primary outcome.

Results: The mean age was 52.3 years and 52 patients (42.5%) were male. The mean mtDNA copy number was 29.1±14.9. During a mean follow-up duration of 59.4±39.3 months, primary outcome was observed in 54 patients (45.0%). There were no significant differences in baseline characteristics between non-PD failure and PD failure group except for serum adiponectin levels (20.5±7.3 vs. 17.5±7.3 mg/mL, P=0.028). mtDNA copy number was not significantly associated with PD failure in multivariate Cox analysis [hazard ratio (HR)=0.995, 95% confidence interval (CI)=0.976-1.015, P=0.634]. However, a subgroup analysis revealed that mtDNA copy number was an independent predictor of PD failure in patients younger than 55 years without metabolic syndrome (HR=0.819, 95% CI=0.692-0.970, P=0.020) after adjustment for confounding factors.

Conclusions: mtDNA copy number may be associated with ultrafiltration failure in younger and metabolically healthier patients treated with PD.

FR-PO831

IL-6 Induces VEGF Production by Human Peritoneal Mesothelial Cells During Peritonitis Through SP4-Mediated Trans-Signaling with sIL-6R

Rusan Catar,¹ Janusz Witowski,^{1,2} Nan Zhu,¹ Christian Luecht,¹ Andras Rudolf,² Duska Dragun,¹ Achim Jorres.¹ ¹Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany; ²Pathophysiology, Poznan Univ of Medical Sciences, Poznan, Poland.

Background: Vascular endothelial growth factor (VEGF) has been implicated in peritoneal angiogenesis and membrane remodeling in peritoneal dialysis (PD). Human peritoneal mesothelial cells (HPMC) have been identified as a major source of VEGF in the peritoneum. However, the exact mechanism of VEGF induction in HPMC is unclear. Since IL-6 concentrations in the drained dialysate correlate with VEGF levels, the link between the two has been suggested. While HPMC do not bear classical IL-6 receptor, they can respond to IL-6 trans-signaling that involves soluble IL-6 receptor (sIL-6R). Here, we have examined whether this mechanism can underlie VEGF synthesis by HPMC.

Methods: HPMC were isolated from normal omentum. Dialysate effluent was obtained from stable PD patients and during peritonitis. VEGF mRNA and protein levels were measured by RT-qPCR and ELISA, respectively. The involvement of transcriptional factors was assessed by EMSA, transient transfections with VEGF promoter constructs, and siRNA silencing.

Results: IL-6 and sIL-6R alone had no effect on VEGF release by HPMC. However, the exposure to IL-6+sIL-6R resulted in a time- and dose-dependent induction of VEGF mRNA and protein. The combination of IL-6+sIL-6R activated the VEGF promoter region that contained high affinity binding sites for the transcription factor SP4. Specific mutation of the SP4 binding site eliminated VEGF promoter activation. In turn, the induction of SP4 was controlled by STAT3. Exposure of HPMC to dialysate effluent obtained during acute peritonitis and containing increased levels of IL-6 and sIL-6R resulted in a dose-dependent VEGF induction. This effect was significantly attenuated in cells treated with siRNAs for either SP4 or STAT3.

Conclusions: Dialysate IL-6 and sIL-6R act through the trans-signaling pathway controlled by the STAT3-SP4 axis to up-regulate mesothelial VEGF production during peritonitis.

Funding: Government Support - Non-U.S.

FR-PO832

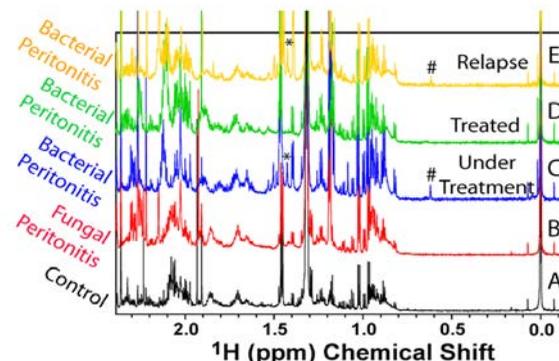
¹H NMR Based Metabolome Can Predict Relapsing Peritonitis and Differentiate Bacterial and Fungal Peritonitis as Well

Narayan Prasad,¹ Raj K. Sharma,¹ Amit Gupta,¹ Dinesh Kumar.² ¹Nephrology and Renal Transplantation, SGPGIMS, Lucknow, UP, India; ²CBMR.

Background: Conventional culture methods for microbes are inherently slow and inefficient. Treatment of bacterial (BP) and fungal peritonitis (FP) are different and quick differentiation is needed. Presently, there is no biomarker to predict relapsing peritonitis (RP). Bacteria and fungus may have different metabolome as one is prokaryotic and other eukaryotic.

Methods: Five unused PD fluid, 13 effluent from normal PD and 45 effluents from 15 patients (at baseline, 1 week and 2 weeks of therapy) with BP including 3 who relapsed and 3 FP were included. Half of each was subjected to total and differential WBC count and culture; and half was frozen at -80°C for NMR analysis. BP and FP was diagnosed based on identification of organism. RP was defined as per standard definition. High Resolution NMR spectra were recorded at 298 K on a Bruker Avance III 800 MHz spectrometer. Standard 1D ¹H NMR spectra were acquired using the Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence. To confirm the assignment of marker peak, two-dimensional (2D) 1H-1H TOCSY and 1H-13C HSQC spectra were also acquired.

Results: Five unused and 13 normal PD effluents after 6 hours of dwell did not show any marker peak at NMR spectra at 0.67 ppm while 15 cases of BP showed marker peak; however marker peak disappeared after resolution of peritonitis at 1 week and 2 weeks of antibacterial therapy except for 3 cases who relapsed in whom marker peak was persisting despite absence of clinical peritonitis. The 3 cases of FP did not show any such marker peak differentiating it from BP. Marker signal represent trans-methylene protons of cyclopropane ring moiety as reported earlier and depicted in Figure 1.



Conclusions: The cyclopropane signal at 0.67 ppm can be marker signal to differentiate BP and FP and persistence of this signal at 2 weeks after clinical resolution of peritonitis predicts RP.

FR-PO833

Peritoneal Mesothelial Cell Sodium Glucose Co-Transporter 1 (SGLT1) Regulates VEGF Production: Potential Target in Ultrafiltration Failure

Eric L. Wallace,¹ Phillip H. Chumley,¹ Leslie J. Jackson,¹ Juling Zhou,¹ Michal Mrug,¹ Jeremy Goodman,¹ Joanne E. Murphy-Ullrich,¹ Edgar A. Jaimes.² ¹Univ of Alabama at Birmingham; ²Memorial Sloan Kettering Cancer Center.

Background: D-glucose and vascular endothelial growth factor (VEGF) are important in the development of ultrafiltration failure (UFF) in peritoneal dialysis (PD). The role of glucose transport in peritoneal mesothelial cells (PMC) in UFF is unknown. Herein we hypothesize that the glucose transporter SGLT1 is increased in response to high glucose and regulates VEGF production.

Methods: PMC, obtained from omental digestion of non-PD patients and from spent PD dialysate, were incubated for 48 hrs under 200mM D-glucose or L-glucose, 200mM mannitol, 200mM 3OMG a non-metabolizable glucose analog transported by SGLT1, 7.5% icodextrin, with and without 50µM phlorizin (Ph), an SGLT1 inhibitor. VEGF was measured by ELISA. mRNA for VEGF and SGLT1 was measured by RT-PCR. Immunofluorescence microscopy for cytokeratin and SGLT1 was performed on human peritoneal biopsies performed at PD catheter insertion (CI) and at catheter revision (CR) after 6 months of PD.

Results: SGLT1 expression was minimal in PMC in biopsies at CI, but abundantly present in PMC in biopsies at CR. PMCs cultured under 200 mM D-glucose had a 6 fold increase in SGLT1 mRNA vs 5mM D-glucose and an increase in VEGF: 70 ± 1.9 pg/mg to 2,456 ± 189 pg/mg (p<0.05). D-glucose stimulation of VEGF was partially inhibited by 50 µM Ph: 6,098 ± 405 pg/mg to 3,991 ± 289 pg/mg (p=0.003). 3OMG also stimulated VEGF: 71 ± 1.9 pg/mg to 1,474 ± 160 pg/mg (p < 0.01) that was inhibited by Ph 623 ± 74 pg/mg, suggesting Ph inhibition of VEGF is partly independent of glucose metabolism (p<0.05). 200mM L-glucose stimulated VEGF less than D-glucose (543 ± 35pg/mg, p < 0.01). This stimulation was inhibited by Ph (123 ± 12 pg/mg). 7.5% icodextrin vs 5mM Glucose did not stimulate VEGF production (47 ± 5.1 pg/mg, p<0.005).

Conclusions: SGLT1 expression in PMC is upregulated in response to high D-glucose *in vivo* and *in vitro*. Glucose transport regulates VEGF production under high D-glucose conditions, which may provide a therapeutic target for UFF.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corp

FR-PO834

Correlation Between Fibroblast Growth Factor-23, Endothelial Dysfunction, and Inflammatory Markers in Chronic Peritoneal Dialysis Patients and Their Response to Antioxidant Therapy

Mitul Bora.¹ Nephrology, Ayur Sundra Super Speciality Hospital, Guwahati, Assam.

Background: Cardiovascular disease (CVD) is the major cause of morbidity and mortality in dialysis patients. Various non-traditional factors like inflammation, acute phase reactants and endothelial dysfunction have been proposed for this increased incidence of

CVD. Increased intact parathyroid hormone and FGF-23 levels are associated with the progression of vascular calcification in peritoneal dialysis (PD) patient. N-acetylcysteine (NAC) acts on atherosclerosis and also improves the endothelial functions. This study was designed to evaluate the correlation between FGF-23, endothelial dysfunction and markers of inflammation in chronic PD patients and to evaluate the effect of three months of therapy of NAC on these parameters.

Methods: All patients underwent Doppler studies to assess endothelial function by the flow mediated dilatation (FMD) of the brachial artery and carotid arterial intima media thickness (CMT). Brachial artery was imaged during reactive hyperemia (endothelium-dependent, flow-mediated dilatation, FMD) and during glyceryl trinitrate-mediated dilatation (nitroglycerine-mediated dilatation, NMD, endothelium-independent) in all PD patients. NAC was given in the dose of 1200 mg in two divided doses for a period of three months. The associations between different parameter were analyzed using Spearman correlations. All these parameters were repeated after three months of therapy with NAC.

Results: A total of 73 chronic PD patients were enrolled in this study. FGF-23 showed strong positive correlation with serum homocysteine level ($r=1.00$, $P<0.001$), hsCRP ($R=0.977$, $P<0.001$). Endothelium Dependent Dilatation [(EDD) ($r = 0.968$, $P < 0.001$)] and CMT ($r = 0.994$, $P < 0.001$), but negatively correlated with Endothelium Independent Dilatation (EID) and Vitamin D level. All these parameters including FGF-23, hsCRP, homocysteine, CMT and EDD were significantly reduced after three months of therapy with NAC.

Conclusions: FGF-23 correlated well with inflammatory markers and endothelial function. With three months of therapy, NAC significantly reduces the CMT, inflammatory markers and improves the endothelial function in chronic PD patients.

FR-PO835

SRF Enhances Cell Adhesion, Migration and Peritoneal Fibrosis via Modulating miRNA-199a/214 Cluster in Human Peritoneal Mesothelial Cells Lijie He, Shiren Sun. *Dept of Nephrology, Xijing Hospital, Xi'an, Shaanxi, China.*

Background: Our previous work showed that serum response factor (SRF) was involved in fibrosis of peritoneal membrane, but the exact underlying mechanism were still unclear. Here we further study the role of miR-199a/214 cluster and the relationship of SRF in peritoneal fibrosis.

Methods: We isolated HPMCs from the effluents of end-stage renal disease (ESRD) patients with peritoneal dialysis (PD), and also used PD dialysis rats model to observe the response of PM to miR-199a/214 cluster and the predicted target CDH1 and CLDN2.

Results: In this study, we found that miR-199a-5p/214 cluster, which was examined to be highly expressed in HG-induced HPMCs by real time PCR, was directly regulated by SRF after HG stimulation. All these HG induced immortal HPMCs became scatter, have the migration ability, lost cell-cell adhesion, and characterized by phenotype markers change with the elevated expression of miRNA-199a/214 cluster, which were also found in these long time treatment of CAPD patients ex vivo or in PD rats. The overexpression of miR-199a/214 cluster led to the lower expression of the cell-cell adhesion markers E-cadherin and claudin-2 protein, and the silencing of miR-199a/214 cluster by lentivirus could inhibit HG-induced damage and alleviate fibrosis in PD rats. Depletion of miR-214/ miR-199a cluster in HG stimulated HPMCs reduces cell to cell adhesion, migration and phenotypic transition by up-regulating E-cadherin, claudins and downregulating α -SMA in vitro. While overexpression of miR-214 and miR-199a-5p by mimic into HPMCs caused the opposite effects. ChIP and luciferase reporter assays revealed that the active and overexpression of SRF directly promotes the transcription of miR-199a/214, which are examined to be highly expressed in HG-induced HPMCs. Mechanistically, miR-199a-5p and miR-214 were characterized to target the E-cadherin and claudin-2 messenger RNA CDH1 and CLDN2 to contribute to the adhesion of cell to cell or cell to matrix induced by HG of HPMCs in vitro.

Conclusions: Together, this study reveals a new SRF-miR-199a/miR-214 cluster-CDH1/CLDN2 EMT axis which highlights the potential damage of HG and fibrosis in PD.

Funding: Government Support - Non-U.S.

FR-PO836

Therapeutic Targeting of EGFR Protects against Peritoneal Fibrosis in Rats Li Wang,¹ Na Liu,¹ Andong Qiu,¹ Shougang Zhuang.¹ *¹Dept of Nephrology, Shanghai East Hospital, Tongji Univ School of Medicine, Shanghai, China; ²Dept of Medicine, Rhode Island Hospital and Alpert Medical School, Brown Univ, Providence, RI.*

Background: Long-term PD leads to peritoneal damage and subsequently to peritoneal fibrosis that is characterized by fibroblast activation, collagen fibril accumulation, inflammation, and angiogenesis, but there is still no available treatment for peritoneal fibrosis thus far.

Methods: In the current study, we explored the therapeutic effect of gefitinib, a specific inhibitor of epidermal growth factor receptor (EGFR), on the development and progression of peritoneal fibrosis induced by chlorhexidine gluconate (CG) and high-glucose dialysis fluid in rats.

Results: Daily intraperitoneal injections of CG or high-glucose dialysis fluid induced peritoneal fibrosis as indicated by thickening of the submesothelial area with an accumulation of collagen fibrils and activation of myofibroblasts. This was accompanied by time-dependent EGFR phosphorylation. Administration of gefitinib, a specific EGFR inhibitor, immediately after injury prevented the onset of peritoneal fibrosis, and delayed treatment until a certain degree of peritoneal fibrosis has occurred halted the progression of peritoneal fibrosis. Gefitinib treatment abrogated increased phosphorylation of EGFR, Smad3, STAT3 and nuclear factor (NF)- κ B during peritoneal fibrosis. Gefitinib also

inhibited overproduction of transforming growth factor- β 1 and multiple proinflammatory cytokines as well as infiltration of macrophages to the injured peritoneum. Moreover, gefitinib significantly reduced peritoneal increase of CD31 (+) blood vessels and vascular endothelial growth factor (+) cells after injury.

Conclusions: These results demonstrate that EGFR contributes to peritoneal fibrosis, inflammation and angiogenesis and suggest that EGFR inhibitors may have therapeutic potential in peritoneal fibrosis.

Funding: NIDDK Support

FR-PO837

Effects of Alanyl-Glutamine Addition in Peritoneal Dialysis Fluid on Peritoneal Immune Modulation – A Pilot Clinical Trial Klaus Kratochwill,^{1,2} Rebecca Herzog,^{1,2} Manoj K. Bhasin,³ Seth L. Alper,³ Andreas Vychytil,¹ Christoph Aufricht.¹ *¹Medical Univ of Vienna, Vienna, Austria; ²Zytoprotec GmbH, Vienna, Austria; ³Beth Israel Deaconess Med. Ctr., Harvard Medical School, Boston, MA.*

Background: Low peritoneal glutamine levels may contribute to reduced immune defense and increased inflammation in the peritoneal cavity. As a pilot clinical trial, PD patients were treated with PD fluid supplemented with 8 mM alanyl-glutamine (AlaGln) and the effect on peritoneal cell immuno-competence was studied by functional assays and transcriptomics using RNA-seq (RNAseq) and microRNA (miRNA) profiling of cells derived from PD effluents.

Methods: In an open-label, randomized, crossover clinical trial at the Medical University of Vienna (Eudract-2012-004004-36), 6 stable PD patients received either standard PD fluid (Physioneal40 3.86%, Baxter) or AlaGln-supplemented PD fluid for an overnight dwell followed by a 4 h peritoneal equilibration test. Cytokine release from ex vivo-stimulated effluent cells was assessed as a measure of immuno-competence. Cells were also analyzed by RNAseq (TruSeq Single-end mRNA, Illumina) and miRNA microarray analysis (Affymetrix) using an integrated bioinformatics workflow developed in the Bhasin Lab.

Results: AlaGln treatment significantly increased cytokine release following ex-vivo stimulation, consistent with restoration of previously suppressed peritoneal immunocompetence. Peritoneal effluent cell transcripts of 9,797 genes were identified. Unsupervised clustering and principal component analysis revealed partial separation between treatments. Supervised analysis using the paired approach identified 13 differentially expressed miRNAs and 41 differentially expressed genes with >1.5-fold change ($P<0.01$). Functional enrichment analysis of these genes indicated pathways linked to immune response and modulation.

Conclusions: In summary, AlaGln-mediated improvement in peritoneal leukocyte immuno-competence was correlated with changes in peritoneal leukocyte transcriptome status in well-described clinical samples. To strengthen these promising data, larger numbers of patients will be treated with AlaGln for a prolonged period in an international multi-center RCT.

Funding: Pharmaceutical Company Support - Zytoprotec GmbH

FR-PO838

Choice of Dialysis Modality for Children with End Stage Renal Disease Julien Hogan,^{1,2} Cécile Couchoud.² *¹Pediatric Nephrology, Robert Debré Hospital, Paris, France; ²REIN Registry, Agence de la Biomédecine, La Plaine Saint Denis, France.*

Background: Despite many studies that aim to assess the best modality of dialysis, results remain conflicting both in adults and in children. This lack of medical evidence leads commentators to emphasize the importance of patients' choice in the decision process. Thus, we try to assess factors that impact the choice of the dialysis modality in children and to determine which from medical factors, center practices or patients' or families' wishes plays the major role.

Methods: All incident patients <20 years old at start of dialysis, recorded in the French ESRD registry between 2002 and 2013 were included. We used multivariate hierarchical logistic regression models to study patients and centers characteristics associated with the probability of starting with peritoneal dialysis (PD). The effect of centers was assessed by including centers as a random effect.

Results: Among 806 patients treated in 177 centers, 601 (74.6%) started with hemodialysis (HD) and 205 (25.4%) with PD. A higher probability of PD was found in younger children while starting treatment in emergency was associated with a low use of PD. Low and high educational level of the town of residence were both associated with less probability of PD when compared with average educational level. There was a significant variability between centers, that was not explained by patients' case-mix. Being treated in specialized pediatric centers was associated with less probability of PD, while the probability of PD was proportional to the rate of PD in the center.

Conclusions: Although little evidence exists to favor a dialysis modality over the other in children, HD remains the predominant modality in France. PD is still mostly offered to the youngest children while it remains underused in patients starting RRT in emergency. However, we found that besides medical factors, centers practices play a major role in the choice of dialysis modality. This raise concerns about the place left to patients' and families' choices and to what extent doctors may influence the final decision. Further pediatric studies focusing on children and parents' wishes are needed in order to provide cares as close as possible to there expectations.

FR-PO839

Clinical Course of Children Born with Chronic Kidney Disease – A Single Centre Experience Christina Taylan,¹ Bernd Hoppe,² Eva Maria Haffner,² Lutz Thorsten Weber.¹ ¹*Pediatric Nephrology, Univ Hospital of Cologne, Cologne, Germany;* ²*Pediatric Nephrology, Univ Hospital of Bonn, Bonn, Germany.*

Background: The number of babies born alive suffering from chronic kidney disease (CKD) is constantly increasing.

Methods: We analyzed the outcome of infants with CKD and renal replacement therapy (RRT) started within their first year of life. Between 2007 and 2013 17 infants (11 male; 6 female) developed end-stage renal disease resulting in RRT in our department.

Results: All of them received peritoneal dialysis (PD) initially at a median age of 34 [1-334] d. During follow-up 10 children underwent renal transplantation (RTx), 1 child was still on PD at last follow-up, 1 child had to go back to hemodialysis after graft loss and 2 had a recovery of renal function. 3 out of 17 children died during the PD period. Causes of death were severe sepsis twice and one cerebral bleeding. The mean GFR at last follow-up (2.2±0.73 years) of patients who underwent RTx was 105±22.8 ml/min/1.73 m². Mean time on dialysis was 17.8±14.3 months before RTx, mean age at transplantation was 29.2±14.2 months. Mental development was measured by Mental Development Index T1 (Bayley Scales of infant development BSID-II) at an average age of 12 [9-16] months and showed developmental delay at the motor, mental and behaviour rating scale. At time of transplantation 6/10 infants had tube feeding, 9/10 were <3. percentile of height, 3/10 were <3. percentile of body weight.

Conclusions: RRT started in the first year of life was associated with reasonable outcome and should be offered to all infants with end stage renal disease. It is, however, associated with a high risk of developmental delay. This work emphasizes the great demands made on an interdisciplinary team of pediatric nephrologists, psychologists and social workers.

FR-PO840

Altered Myogenesis and Oxidative Stress in a Rat Model of Chronic Kidney Disease Keith Avin,¹ Neal X. Chen,² Jason M. Organ,³ Kalisha O'Neill,² Sharon M. Moe.^{2,4} ¹*Dept Physical Therapy, Indiana Univ, Indianapolis, IN;* ²*Div of Nephrology, Indiana Univ, Indianapolis, IN;* ³*Dept of Anatomy, Indiana Univ, Indianapolis, IN;* ⁴*VAMC, Indianapolis, IN.*

Background: Skeletal muscle atrophy and impaired muscle function are associated with lower quality of life, and greater disability and mortality risk in those with chronic kidney disease (CKD). However, the pathogenesis of atrophy is unknown.

Methods: We used a slowly, progressive, naturally occurring, CKD rat model (*Cy⁺* rat) and its normal littermate (NL). At 35 weeks, we tested muscle strength, sacrificed and collected tissues and blood. RNA and protein were isolated from skeletal muscle and real time PCR and western blot performed.

Results: CKD rats developed sarcopenia evident by reduced cross sectional area ($p<0.05$), increased connective tissue deposition on histology ($p<0.05$), and impaired strength ($p<0.05$). Strength was defined as the maximal amount of force produced during maximal, electrically stimulated dorsiflexion. These findings of atrophy can be explained by reduced regeneration, increased catabolism, or differentiation of muscle stem cells toward myofibroblasts. By PCR, there was increased activation and differentiation of muscle stem cells (reduced Pax-7, increased MyoD and myogenin ($p<0.05$)) and increased proteolytic markers (Atrogin-1 and MuRF-1 ($p<0.05$)). Fibrosis may be enhanced via decreased miR-29b ($p<0.05$) and increased Wnt5a ($p<0.01$). Finally myostatin was increased in blood and muscle RNA expression yet no difference in the activin type IIB. The long term consequences of the impaired balance of increased proteolysis and inadequate regeneration is further supported by mitochondrial derangement (electron microscopy) and increased mitochondria complexes I, II and IV ($p<0.05$) despite increased expression of the antioxidant nuclear erythroid 2-related factor 2 ($p<0.05$).

Conclusions: In a rat model of CKD, sarcopenia was present despite the activation of myogenic factors. The atrophy is due to a combination of factors including increased myostatin, increased expression of atrogens, and the presence of oxidative damage. Augmentation of the myogenic and antioxidant responses through treatments may prevent progressive sarcopenia in CKD.

Funding: Other NIH Support - NIH R01AR058005

FR-PO841

Can Calcitriol and Calcidiol to Regulate Toll Like Receptors 7, 9 and IL-6 and IFN- γ Expression on Lymphocytes Incubated with Uremic Serum? Maria Dalboni,^{1,3} Marion Schneider,¹ Lilian Cuppari,¹ Caren Cristina Grabulosa,¹ Silvia Regina Manfredi,¹ Edgar Maquigussa,¹ Danilo Takashi Aoiike,¹ Miguel Cendoroglo Neto,^{1,2} Jose Tarcisio Giffoni.¹ ¹*Div of Nephrology, Univ Federal São Paulo, Sao Paulo, Brazil;* ²*Medicine, Tufts-New England Medical Center, Boston;* ³*Medicine, Univ Nove de Julho, Sao Paulo, Brazil.*

Background: The uremic environment has been reported to induce an inflammatory response and TLR is one of the mechanisms that may be involved in this response. In addition, it has been recognized that low levels of this vitamin can be associated with the deregulation of the inflammatory response. Thus, the purpose of this study was evaluate the effect of 25 (OH)D₃ and 1,25 (OH)₂D₃ on lymphocytes B and T for IL-6, IFN- γ TLR-7, TLR-9, VDR, CYP27 and CYP24 expression in presence of uremic serum.

Methods: PBMC isolated by Ficoll-Hipaque from health subjects were used to analyze lymphocytes. These cells were incubated with normal or uremic serum in presence

or absence of 25 (OH)D₃ or 1,25 (OH)₂D₃ for 24 h in a 37°C, 5% CO₂. We use flow cytometry to evaluate IL6, IFN- γ , TLR7, TLR9, VDR, CYP27 and CYP24 expression on lymphocytes B and T.

Results: Uremic serum induced a significant increase in IL6, IFN γ , TLR7, TLR9, VDR, CYP27 and CYP24 expression in B and T lymphocytes ($p<0.05$). Both lymphocytes incubated with 25 (OH)D₃ or 1,25 (OH)₂D₃ had a significant reduction in IL-6 and TLR9. As CYP24 had a higher expression and this can to induce a degradation of 1,25 (OH)₂D₃, we did a CYP24 silencing, and observed an additional decreased in IL6, IFN γ , TLR7 and TLR9 expression on B and T lymphocytes for both treatment when compared to effect of these vitamins alone ($p<0.05$). In the same condition, we also observed an increase VDR expression.

Conclusions: Our results suggests that both 25 (OH)D₃ and 1,25 (OH)₂D₃ had immunomodulatory effects in B and T lymphocytes. This *in vitro* model confirm the anti-inflammatory role of Vitamin D in uremia environment. However, these effects of Vitamin D were enhanced after CYP24 silencing. So, this data support that CYP24 inhibitors may also be a target of treatment in association with vitamin D supplementation to improve a immunological response mechanisms.

FR-PO842

Toll Like Receptors 2, 4, TNF- α , IL-6 and IL-10 Expression on Leukocytes from Hemodialysis and Pre-Dialysis Patients Maria Dalboni,^{1,3} Jose Tarcisio Giffoni,¹ Silvia Regina Manfredi,¹ Jacqueline Ferritto Rebello,³ Rodrigo Barbosa de oliveira Brito,³ Miguel Cendoroglo Neto,^{1,2} Caren Cristina Grabulosa.¹ ¹*Nephrology Div, Univ Federal de São Paulo, Sao Paulo, Brazil;* ²*Medicine, Tufts-New England Medical Center, Boston;* ³*Medicine, Univ Nove de Julho, Sao Paulo, Brazil.*

Background: Toll-like receptors (TLR) are involved in immunologic response. The TLRs expression and cytokines association in neutrophils and monocytes from CKD patients is unclear. To evaluate TLR-2, TLR-4, TNF- α , IL-6 and IL-10 expression in neutrophils (PMN) and monocytes (MN) from Hemodialysis (HD) and Pre-dialysis (PD) patients.

Methods: Blood samples from 43 hemodialysis (HD) patients (collected before the beginning of the second week hemodialysis session), 46 pre-dialysis (PD)(estimated by *Modification of Diet in Renal Disease* (MDRD) and 70 age-and gender-matched healthy volunteers (CONT) were analyze for TLR2 and TLR4 expression on PMN and MN by Flow cytometry. The TNF- α , IL-6 and IL-10 cytokines were analyzed by ELISA.

Results: The expression of TLR2 and TLR4 on neutrophils from HD patients was higher than PD and CONT patients ($p<0.001$). In monocytes, TLR-2 expression was higher in HD patients compared to others groups ($p<0.001$) and TLR4 expression was higher in PD patients compared to the CONT and HD patients ($p<0.001$). Regarding to cytokines, we observed that HD patients showed an increase of TNF and IL-6 levels compared to CONT (4.6±5.3 vs 1.9±1.3 and 6.0±3.2 vs 2.5±2.1; $p<0.001$, respectively) and IL-10 from HD patients were higher than PD and CONT patients (115± 166 vs 36±82 and 27±62, respectively). We also observed a significant correlation between TLR2 and TLR4 and TNF- α on neutrophils ($r = 0.30$; $p = 0.02$ and $r = 0.34$; $p = 0.01$, respectively). In respect to monocytes, only TLR2 had correlation with TNF- α and IL-6 ($r = 0.30$; $p = 0.02$ and $r = 0.24$; $p = 0.03$, respectively).

Conclusions: It is possible that the deregulation of TLR2 and TLR4 expression on leukocytes may be caused by uremic toxins in CKD population. Besides, the high expression of TLR2 and TLR4 in these cells resulted in an increase of TNF- α and IL-6 levels, suggesting that TLRs are associated with inflammatory mechanisms in uremic patients.

FR-PO843

Effect of Cholecalciferol Supplementation on Toll-Like Receptors 7, 9 Expression and IL-6 and IFN- γ Intracellular on B and T Lymphocytes on Chronic Dialysis Patients Maria Dalboni,^{1,3} Marion Schneider,¹ Lilian Cuppari,¹ Caren Cristina Grabulosa,¹ Silvia Regina Manfredi,¹ Edgar Maquigussa,¹ Danilo Takashi Aoiike,¹ Miguel Cendoroglo Neto,^{1,2} Jose Tarcisio Giffoni.¹ ¹*Div of Nephrology, Univ Federal de Sao Paulo, Sao Paulo, Brazil;* ²*Medicine, Tufts-New England Medical Center, Boston;* ³*Medicine, Univ Nove de Julho, Sao Paulo, Brazil.*

Background: Vitamin D deficiency is highly prevalent among patients in all stages of CKD. Studies have reported that the Vitamin D deficiency is associated with mortality and morbidity in CKD patients and may modulate TLRs that are involved in inflammatory responses. Thus, the purpose was evaluate the effect of cholecalciferol on IL-6, IFN- γ TLR-7 and TLR-9 expression in lymphocytes B and T in patients on dialysis with vitamin D hipovitaminosis.

Methods: In a randomized, placebo-controlled, double-blind study, we investigated the effect of cholecalciferol (100,000 UI once per week or placebo) for 3 months, in patients on chronic dialysis, who had nutritional vitamin D deficiency. The 25(OH)D₃ detection was performed by quimioluminescence and IL6, IFN- γ , TLR7, TLR9, VDR, CYP27 and CYP24 expression by flow cytometry on lymphocytes B and T.

Results: After 3 months of treatment, Cholecalciferol increased 25(OH)D₃ levels (16,00±4,44 vs 42,81±13,06, $p=0,01$) and reduced PTH levels (525,3 (128-1775) vs 484,8 (86-2264, $p=0,03$), but have no impact on FGF23 levels. Additionally, we observed a reduced expression of TLR7 (305±78 vs 252±45, $p=0,01$), TLR9 (1864±700 vs 1084±370, $p=0,001$ and CYP24 (284±136 vs 200±86, $p=0,01$), and increased of VDR (730±360 vs 965±440, $p=0,006$) and CYP27 (245±38 vs 442±380, $p=0,04$) expression.

Conclusions: Cholecalciferol treatment in dialysis patients showed to be efficient to correct hipovitaminosis D. In addition, we observed impact of 25(OH)D₃ repletion on reduction of expression of the TLR7, TLR9, IFN- γ and improve of regulatory mechanisms

associated with intracellular production of vitamin D on lymphocytes from CKD patients. These results suggest that cholecalciferol treatment play an important role on TLRs expression as an anti-inflammatory and that this may contribute to a better systemic inflammation response in CKD patients.

FR-PO844

The Effect of Selenium Deficiency on Thyroid Hormone and Cardiovascular Diseases in Hemodialysis Patients So Mi Kim,¹ Eun kyoung Lee,² Yun Jung Oh,³ Ja Seon Kim.⁴ ¹Div of Nephrology, Dept of Internal Medicine, Jeju National Univ Hospital, Jeju National Univ School of Medicine, Jeju, Jeju-do, Republic of Korea; ²Div of Nephrology, Dept of Internal Medicine, Dankook Univ Hospital, Cheonan, Chungnam, Republic of Korea; ³Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Jeju-do; ⁴Div of Nephrology, Dept of Internal Medicine, Incheon sarang Hospital, Incheon, Kyongkido, Republic of Korea.

Background: Selenium deficiency is known to associate with impairment of thyroid hormone and cardiovascular diseases such as ischemic heart disease (IHD), cardiomyopathy or sudden death. In hemodialysis (HD) patients, various causes may contribute to selenium deficiency, including malabsorption, alteration of metabolism, and removal through dialysis itself. Therefore, we tried to investigate the effect of selenium deficiency on thyroid hormone and cardiovascular diseases in HD patients.

Methods: This cross-sectional study enrolled 83 HD patients. They were divided into two groups based on serum selenium levels: 62 patients were normal level and 22 patients were selenium deficient. Thyroid hormones such as TSH, free T4 were measured. And cardiovascular diseases, including IHD, heart failure or cardiomyopathy, were evaluated.

Results: Thyroid hormone impairment, including hypothyroidism and subclinical hypothyroidism, showed higher tendency in selenium deficient group than that in non-selenium deficient group. (27% vs 10% P=0.06) The prevalence of IHD was significantly higher in selenium deficient group than that in the non-selenium deficient group. (59% vs 21%, p=0.04) But there was no difference in heart failure and cardiomyopathy. The patients with thyroid hormone impairment showed high prevalence of IHD, and the coincidence of thyroid hormone impairment and IHD was also significantly higher than that in selenium deficient group than that in non-selenium deficient group. (18% vs 4%, p=0.014).

Conclusions: This study showed the significant high prevalence of thyroid hormone impairment and IHD in HD patients with selenium deficiency. Selenium deficiency may affect heart disease, associating with thyroid hormone impairment.

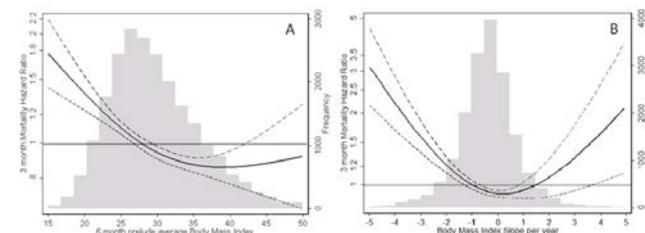
FR-PO845

Associations of Prelude (Pre-ESRD) BMI and Weight Change with Early Dialysis Mortality Among U.S. Veterans: A Transition of Care in CKD Study Elani Streja,¹ Melissa Soohoo,¹ Joline L.T. Chen,¹ Amanda R. Tortorici,¹ Jennie Jing,¹ Danh V. Nguyen,¹ Csaba P. Kovessy,² Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC.

Background: In end stage renal disease (ESRD) lower body mass index (BMI) portends a higher risk of mortality while obesity is protective, the so-called obesity paradox. However, the association of BMI and change in BMI over time in the pre-ESRD period and early post-ESRD mortality is unknown. We hypothesized that lower and decreasing BMI prior to transition to ESRD may be associated with higher early dialysis death.

Methods: In a cohort of 22,716 US veterans who transitioned to dialysis between 10/2007 and 9/2011 with available BMI values within the last 2 year prelude period (prior to ESRD transition), we examined the association of 6 month average BMI and 2 year BMI slope as continuous predictors of all-cause mortality in the first 3 months after transition, using restricted cubic spline analyses and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region. In the models of BMI slope, we also adjusted for BMI level at the time of transition.

Results: The mean±SD age was 69±11 yrs, 27% were African-American, 7% Hispanic, and 49% diabetic. There was a reverse J-shaped association between BMI and mortality, where patients with BMI <27 kg/m² were at higher risk of death (Figure A). When examining changes in weight over the 2-year prelude there was a U-shaped association where patients with little to no-change in BMI (-1 to +1 kg/m² per year) exhibited the best survival (Figure B).



Conclusions: Among veterans transitioning to dialysis, obese patients and those patients with little to no weight change in the last 2 years prior to ESRD have the greatest survival in the first 3 months post transition. Weight change in late stages of pre-dialysis CKD, possibly due to uremic wasting and fluid gain, portend poor outcomes, and could be used to identify at-risk patients.

Funding: NIDDK Support

FR-PO846

Nutritional Assessment for Incident Elder Dialysis Patients Ikuto Masakane,¹ Yuya Sakai,² Miho Suzuki.² ¹Yabuki Hospital, Nephrology, Yamagata, Japan; ²Yabuki Hospital, Dept of Health and Nutrition.

Background: Nutritional status is one of the most powerful predictors of patient survival in chronic dialysis patients especially in elders. It is generally accepted that aging itself is one of the risk factors of malnutrition. Recently the patients who started dialysis have become older and older as the average age of incident dialysis patients in Japan is nearly 70 years old. It is very meaningful to evaluate the status of malnutrition in new elder dialysis patients, its time-course and to establish strategies for preventing progression of malnutrition.

Methods: The nutritional status of 257 incident dialysis patients in YHG was retrospectively evaluated by MIS. The nutritional status on 37 patients out of the 257 patients has been followed for 3 years. The "malnutrition" was diagnosed as "moderate-severe" in MIS and fulfill of the diagnosis of PEW. Patients greater than 75 years old were categorized as Elder and patients under 75 years old were as Non-elder. The statistical significance of time-dependent changes in nutritional status was evaluated by paired-T test.

Results: The prevalence of malnutrition at the point of dialysis initiation by MIS in average was 7%, 12% in Elder and 5% in Non-elder. The nutritional status had been improved in the non-elder but not in the elder. The lean body mass had decreased in the first year of dialysis vintage in both groups and had remained the same in the following 2 years. Body fat mass had increased consistently for 3 years in non-elderly. It had increased for the first 2 years but had begun to decrease in the third year in the elder. Protein and energy intake per ideal body weight were lower in elder dialysis patients.

Conclusions: Malnutrition in elder dialysis patients was often accompanied by the initiation of chronic dialysis therapy and would gradually develop in the maintenance period. In order to protect the progression of malnutrition several proposals were addressed as the proper timing of the initiation of dialysis before the deterioration of daily activities; nutritional education for sufficient energy and protein intake, exercise education and sufficient dialysis prescription with biocompatible dialysis membranes.

FR-PO847

Uric Acid Is a Determinant of Glomerular Filtration Rate in Inflammatory Conditions Suad Ma Hannawi,¹ Issa AL Salmi. ¹Medicine, The Ministry of Health, Dubai, United Arab Emirates; ²The Renal Medicine Dept, The Royal Hospital, Muscat, Oman.

Background: The presence of gout or a baseline serum uric acid in the upper range are possibly stronger predictors of first CV events than some traditional CV risk factors or parameters of inflammation. Presence study analysis UA determinants in relation to GFR.

Methods: Patients attending the only centre of MOH in Dubai were studied during their OPD rheumatology visit from Jan 2014 till Dec 2014. Many laboratory tests including UA were performed. MDRD formula was used to get eGFR. Simple statistical and regression models were performed. Variables that not normally distributed being log transformed.

Results: 79 (88.6%F,11.4%M) were recruited with mean age46.4(13.4) years. Mean UA was249.8 (84.4), eGFR137.1(50.5)(59.6,306.1).

Regression analysis found a negative relationship between UA and GFR (P<0.001,-0.004,-0.002) and positive relationship between uric acid and age (p=0.032, 0.001-0.011), urea (p<0.001,0.041-0.137), microalbuminuria (p=0.046,0.000-0.001), microalbumin/cr (p=0.024,0.001-0.013), SBP(P=0.014,0.001-0.009), DBP(p=0.025,0.001-0.014), age at Dx RA (P=0.028,0.001-0.010), monocyte% (p=0.009,0.013-0.088), monocyte count (p=0.003,0.015-0.776) TG (p=0.034,0.009-0.216), BUT also negative with cholesterol (p=0.033,-0.148,-0.007).

Uric acid multiple model has maintained a strong correlation with eGFR (p=0.005), monocyte count (0.009), cholesterol (p.007),microalbuminuria(p=0.01), after adjustment for all the above mentioned variables.

Conclusions: UA is determined by eGFR and other renal parameters in inflammatory condition. On the other hand, uric acid increase the risk of renal impairment and CVD in inflammatory condition. Thus, uric acid level might be an elemental key factor that result in high renal and CV associated morbidity and mortality in the inflammatory diseases. UA is a powerful independent predictor of prevalent renal dysfunction but was also a significant predictor of progression of renal disease. UA may not be just an innocent bystander but may be an active player in the pathogenesis of renal disease by causing endothelial dysfunction, intrarenal vascular disease and renal impairment in inflammatory conditions.

FR-PO848

Does Nutritional Status and Serum Electrolytes Change when Dialysis Patients Reduce Their Fluid Overload? Penny Faith Sheppard,¹ Suzette Thompson,² Laura Rosales,¹ Nathan W. Levin,¹ Peter Kotanko,¹ Fansan Zhu.¹ ¹Renal Research Inst, New York, NY; ²Fresenius Vascular Care, New York, NY.

Background: Electrolyte balance between the intracellular (ICV) and extracellular (ECV) fluid compartment is essential in the control of normal physiological functions. Nutritional status is mainly reflected by ICV. In hemodialysis (HD) patients the relationship between electrolyte control and management of fluid balance is not completely understood. We aimed to evaluate whether the degree of reduction of fluid overload affects the measurement of ICV, and concentrations of serum albumin (Alb), sodium, potassium, and calcium.

Methods: Fifty six HD patients were studied. At baseline (BL), the fluid status was evaluated by calf bioimpedance spectroscopy (cBIS). If patient's dry weight (DW) was not reached by criteria of cBIS DW, the post target weight was gradually reduced (Zhu et al,

Physiol Meas, 29:S530-S516, 2008). At six months follow up, the patients either reached DW or did not (NDW) due to difficulty in prolonging treatment time. ECV and ICV, weight, and systolic blood pressure (SBP) were measured pre and post HD. Comparison of all parameters between BL and follow up were made using student *t* test.

Results: Thirty one patients reached DW and 25 did not. Weight and ECV were significantly reduced during follow up. However, ICV, electrolytes and Alb concentrations did not change between different fluid statuses. Post HD SBP significantly decreased from BL to the end of the study in DW but not in NDW groups.

Conclusions: Although extracellular fluid (ECV) was largely reduced, the ICV and serum concentrations of sodium, potassium, and calcium did not differ significantly. This implies that there is no fluid or mass shift from ICV to ECV, suggesting over all isotonic removal of sodium and that nutritional status is not changed by attainment of dry weight.

Table 1

	Na+ (mEq/l)	K+ (mEq/l)	Ca++ (mEq/l)	Alb (mEq/l)	kt/V	Pre HD ECV (L)	Pre HD ICV (L)
BL (n=31)	138.2±3.8	4.7±0.8	9.1±0.6	3.9±0.4	1.63±0.3	16.8±3.6	18.5±5.4
DW	138.7±3	4.7±0.7	9.3±0.6	4.0±0.3	1.7±0.3	15.8±3.1**	18.1±5.1
BL (n=25)	139.3±2.2	4.4±0.7	8.95	4±0.05	1.28±0.3	19.8±3.1#	18.4±5.2
NDW	140.5±3.1	5.0±1.1	8.8±0.6	3.9±0.3	1.53±0.3	20.1±3.5**#	18.9±4.9

*and** indicate significant (p<0.05, or p<0.01) difference between BL and DW or BL and NDW.
indicate difference (p<0.05) between DW group and NDW group.

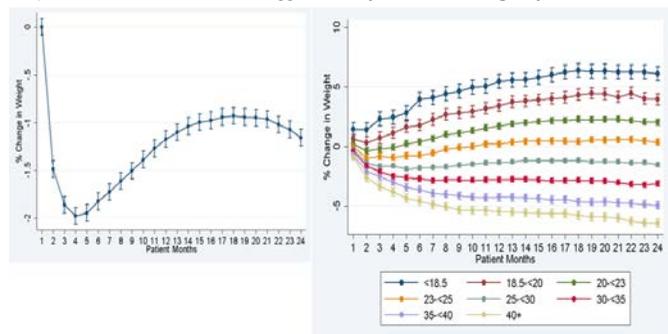
FR-PO849

Trends in Weight Change During the First Two Years of Transition to Hemodialysis Treatment Vyvian Ngo,¹ Elani Streja,¹ Anna Mathew,² Tae Hee Kim,¹ Yoshitsugu Obi,¹ Connie Rhee,¹ Csaba P. Kovessy,³ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine, ²Hofstra North Shore LIJ Health System, ³UTHSC.

Background: Some hemodialysis patients may undergo rapid weight loss in the first few months of starting dialysis, but the nature of this trend has not yet been characterized in large nationally representative studies. We hypothesized the trajectory of weight change during the first 24 months of hemodialysis therapy may differ by baseline body mass index (BMI).

Methods: We examined percent post-dialysis weight (kg) change from baseline in 37,759 incident hemodialysis patients who initiated dialysis in a large US dialysis organization in calendar years 2007-2011 and who survived the first 2 years of hemodialysis. Trends of percent weight change over time were analyzed using crude and case-mix adjusted mixed effects models. Baseline BMI was categorized into 8 categories (<18.5, 18.5-<20, 20-<23, 23-<25, 25-<30, 30-<35, 34-<40, 40+ kg/m²).

Results: Patients were 60±14 years old, 64% diabetics, 44% female, and had an average starting weight of 82±22 kilograms. Patients reached a nadir of weight at the 5th month of dialysis with an average 2% weight loss from baseline. At 14 months, patients' weight stabilized at an average of 1% drop from baseline. However, trends differed across groups of baseline BMI groups. Underweight (BMI <18.5) did not experience weight loss but instead gained approximately 6% of their weight by the 24th month. Obese patients (BMI >40) did not reach a nadir and lost approximately 6% of their weight by the 24th month.



Conclusions: Baseline BMI can affect the trajectory of weight change over the first two years in hemodialysis patients. Further studies are needed to better understand the cause of these differences and their impact on clinical outcomes.

Funding: NIDDK Support

FR-PO850

Significance of Renal Autonomic Nerves in the Reduction of Body Weight by SGLT2 Inhibitors Aika Hagiwara, Kazutoshi Miyashita, Masaaki Sato, Hiroyuki Inoue, Kentaro Fujii, Masanori Tamaki, Hiroshi Itoh. *Nephrology, Endocrinology and Metabolism, School of Medicine, Keio Univ, Shinjuku, Tokyo, Japan.*

Background: Sodium-glucose co-transporter (SGLT) 2 inhibitors decrease not only serum glucose level but also body weight significantly. Similarly, it is reported that renal denervation (RDN) decreases body weight, in addition to blood pressure. The urinary glucose might have a relationship with sympathetic activation that controls body weight. However, the relationship has not been elucidated.

Methods: The present study examined the roles for renal autonomic nerves in the weight reduction by SGLT2 inhibitors through performing RDN on mice fed on a high-fat diet. The C57BL/6 mice fed on a high-fat diet were divided into 4 groups; control group, RDN group, SGLT2 inhibitor group and SGLT2 inhibitor with RDN group. The body weight, glucose tolerance, tissue weights, tissue hormone sensitive lipase (HSL) activity and noradrenalin concentration were examined. The SGLT2 inhibitor (tofogliflozin 50 mg/kg pellet) was administered to mice from 8 weeks old mixing it in the high-fat diet (60 Kcal% fat). RDN was performed at 7 weeks old by surgically stripping the renal arteries and coating the vessels with a solution of 10% phenol in ethanol.

Results: The body weight at 16 weeks old significantly decreased in the SGLT2 inhibitor group. In that group, the catecholamine levels in subcutaneous fat and the activity of HSL which was measured by the phosphorylation level were increased. On the other hand, RDN with SGLT2 inhibitor group significantly weakened the degree of the reduction of body weight by the SGLT2 inhibitor associated with suppression of the catecholamine levels and the activity of HSL in the adipose tissue. In RDN without SGLT2 inhibitor group, the body weight significantly decreased; however, HSL in the adipose tissue was not activated.

Conclusions: These results indicate that HSL activation in the adipose tissue mediated by the renal autonomic nerves was involved in the mechanism of weight-reduction by SGLT2 inhibitors. The renal autonomic nerves were suggested to have a role in the control of tissue HSL activity and body weight.

FR-PO851

The Combination of Walking Exercise and Branched Chain Amino Acid Recovered Response of Protein Synthesis in Low Protein Diet Fed Chronic Kidney Disease Model Rats Takuya Yoshida, Hiromichi Kumagai. *Dept of Clinical Nutrition, Univ of Shizuoka, Shizuoka, Japan.*

Background: Low protein diet (LPD) protects progression of renal injury in patients with chronic kidney disease (CKD). However, LPD may accelerate muscle wasting in these patients. The exercise and branched chain amino acid (BCAA) are known to increase the muscle synthesis by activating mTOR signals pathway. The aim of this study is to investigate whether walking exercise and BCAA would increase muscle protein synthesis in LPD fed CKD (5/6 nephrectomized) rats.

Methods: CKD rats were fed LPD or LPD fortified with BCAA diet (BD), and about half of the each group were loaded with the walking exercise (7 weeks of treadmill, 15 m/min, 1 hour/day, 5 days/week). After 7 weeks, the kidney and the soleus muscle were collected to evaluate the renal fibrosis and the muscle protein synthesis, respectively.

Results: The renal function and fibrosis were not different between LPD and BD fed CKD rats, and the walking exercise did not accelerate renal damage in both LPD and BD fed CKD groups. The walking exercise increased the phosphorylation of p70s6kinase, a biomarker of mammalian target of rapamycin complex 1 activity, in soleus muscle of LPD and BD fed CKD rats. However, the phosphorylation of p70s6kinase was lower in LPD fed CKD rats when compared with sham-operated groups and BD fed CKD group.

Conclusions: CKD reduces activation of muscle protein synthesis. Combination of walking exercise and BCAA recovered the muscle protein synthesis in CKD rats. These results suggest combination of walking exercise and BCAA may be beneficial to improve the muscle protein synthesis in CKD.

Funding: Government Support - Non-U.S.

FR-PO852

Unacyl-Ghrelin: A Key Molecule in Uraemic Cachexia in Children and Adolescents Alice Monzani,¹ Michela Perrone,² Sara Testa,² Fabio Paglialonga,² Silvia Consolo,² Gianluigi Ardissino,² Francesca Tel,² Marta Lepore,² Stefani Rotondo,² Antonietta Biasuzzi,² Luciana Ghio,² Gianni Bona,¹ Alberto Edefonti.² ¹Div of Pediatrics, Univ del Piemonte Orientale, Novara, Italy; ²Pediatric Nephrology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Background: Cachexia and poor growth are common in children with chronic kidney disease (CKD). Several mechanisms are involved, including loss of appetite and poor food intake. Unacyl-ghrelin (UAG) is known to produce an inhibitory effect on feeding. We measured UAG levels in children and adolescents with CKD stage II-IV on conservative treatment (CKD-CT), on haemodialysis (CKD-HD) and after transplantation (Tx), compared to healthy controls, in relation to biochemical and anthropometric parameters.

Methods: Plasma UAG levels were measured by ELISA in 43 CKD-CT, 20 CKD-HD, 48 Tx and 43 healthy children. Urea and creatinine levels were measured in all subjects and GFR was calculated by Schwartz formula. Weight, height and bicipital, tricipital, subscapular and suprailiac folds were measured, and BMI z-score, fat-mass and fat-free mass pro body weight (FM/BW and FFM/BW, respectively) were calculated.

Results: Mean UAG levels were significantly higher in CKD-HD (1444.75±1211.44 pg/ml) than in CKD-CT (582.24±546.93 pg/ml, $p=0.001$), in Tx (491.05±532.82 pg/ml, $p<0.0001$) and controls (245.29±181.07 pg/ml, $p<0.0001$). UAG levels were positively correlated with serum creatinine and urea and negatively correlated with GFR, also after adjustment for gender, age, pubertal status and BMI z-score ($p<0.0001$ for each model). A negative correlation was found between UAG and BMI z-score ($R=-0.371$, $p<0.0001$) and between UAG and both FM/BW and FFM/BW ($R=-0.518$, $p<0.0001$ and $R=-0.319$, $p=0.004$, respectively).

Conclusions: UAG seems to be a promising inverse biomarker of nutritional status in children with CKD, strictly related to the degree of renal impairment.

FR-PO853

Visceral Fat Area Is Associated with Renal and Cardiac Function in a Population with Normal or Mildly Impaired Renal Function Sung jun Kim,^{1,2} Yunju Nam,¹ Hyeon Seok Hwang,¹ Seok Joon Shin,^{1,2} Hye Eun Yoon.^{1,2} ¹Internal Medicine, The Catholic Univ of Korea, Seoul, Korea; ²Internal Medicine, Incheon St. Mary's Hospital, Incheon, Korea.

Background: Visceral fat is involved in the development of metabolic and cardiovascular diseases. This study was to evaluate the association between visceral fat area (VFA) and renal and cardiac function and arterial stiffness in a population with normal or mildly impaired renal function.

Methods: This cross-sectional study included 719 middle-aged adults who underwent a voluntary health check-up program. Participants with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m² were excluded. VFA was measured using bioimpedance analysis. Subjects were divided into tertiles according to their VFA. The associations between VFA and eGFR, brachial-ankle aortic pulse wave velocity (baPWV), and echocardiographic parameters were investigated.

Results: Across the tertiles of VFA, there was a significant trend for decline in eGFR ($P<0.001$), increase in baPWV ($P<0.001$) and left ventricular mass index (LVMI, $P<0.001$), and decrease in the ratio of early mitral inflow velocity to peak mitral annulus velocity (E/E', $P<0.001$). VFA showed significant correlations with eGFR ($r=-0.15$, $P<0.001$), baPWV ($r=0.28$, $P<0.001$), LVMI ($r=0.31$, $P<0.001$), and E/E' ($r=0.21$, $P<0.001$). In multivariate analysis, VFA was linearly associated with eGFR ($\beta=-0.06$, 95% confidence interval [CI] -0.11 - -0.01, $P=0.02$), LVMI ($\beta=0.08$, 95% CI 0.06 - 0.10, $P<0.001$), and E/E' ($\beta=0.01$, 95% CI 0.006 - 0.019, $P<0.001$), after adjustments for cardiovascular risk factors. In contrast, total body fat was not associated with eGFR.

Conclusions: VFA is associated with renal and cardiac function in middle-aged adults with normal or mildly impaired renal function. Measuring VFA may predict risks of renal and cardiac diseases.

Funding: Government Support - Non-U.S.

FR-PO854

Serum Ferritin <70 µg/L Predicts Functional Iron Deficiency in Patients with Chronic Kidney Disease Neha Garg, Mrinalini Kotru, Om Prakash Kalra, Meera Sikka. *Pathology, UCMS and GTBH, Delhi, New Delhi, India.*

Background: Chronic Kidney Disease (CKD) is a major public health problem with anemia occurring early in the course of disease. Its most common cause is erythropoietin deficiency which can be effectively treated with erythropoiesis stimulating agents. However most of the patients do not respond adequately due to development of Functional Iron Deficiency (FID). The current diagnostic criteria for FID as recommended by KDOQI 2006 tend to miss the diagnosis of FID. The study was conducted to explore the role of hsCRP and Interleukin-6 (IL-6) along with Serum Ferritin (SF) in improving the efficacy of this criteria.

Methods: 77 clinically diagnosed patients of CKD (Stage 3, 4 and 5) of either sex, age >18 years with Hb <11 g/dL were included in the study. Complete clinical history and physical examination was done. Complete hemogram with peripheral smear, serum iron, total iron binding capacity, Transferrin Saturation (TSAT), SF, transferrin receptors (sTFR), hsCRP, IL-6, ESR were estimated.

Results: sTFR/log ferritin (taken as gold standard) detected 31/77 patients as having iron deficient erythropoiesis. Out of these 31 patients, 12 patients had SF <12 µg/L indicating absent iron stores. Remaining 19 patients had FID. In these cases, TSAT <20% and SF >100 µg/L detected FID in only 2 patients with a sensitivity of 6.45%. SF at a cut-off <70 µg/L showed the best sensitivity (83.87%) and specificity (73.91%) in detecting FID in these patients and identified 14/19 cases of FID. The 5 FID cases who were missed had raised hsCRP. In the absence of raised hsCRP, SF <70 µg/L had very good sensitivity (100%). However, in the presence of raised hsCRP sensitivity was reduced (79.16%).

Conclusions: TSAT <20% and SF >100 µg/L had a sensitivity of only 6.45%. However, SF <70 µg/L emerged as the most sensitive and specific in identification of iron deficient erythropoiesis. SF >12 µg/L - SF <70 µg/L was able to identify 14/19 cases of FID. Also, hsCRP could be used to stratify the CKD group in which FID could be detected with high sensitivity and specificity.

Funding: Government Support - Non-U.S.

FR-PO855

Chronic Inflammation Is Associated with Poor Clinical Outcomes Independent of Mineral Metabolism Abnormalities in the HEMO Study Anna Jeanette Jovanovich,^{1,2} Eugene J. Nuccio,² Alfred K. Cheung,^{3,4} Tom Greene,⁴ Michel Chonchol,² Kristen L. Nowak.² ¹Denver VA Medical Center; ²Univ of Colorado Denver; ³VA Salt Lake City; ⁴Univ of Utah.

Background: Epidemiological studies show a high prevalence of chronic inflammation, vitamin D deficiency, and fibroblast growth factor 23 (FGF23) excess in hemodialysis patients. Whether the relationships of high circulating C-reactive protein (CRP) and interleukin-6 (IL-6) with all-cause mortality and cardiac and infectious events are attenuated in the presence of circulating markers of mineral metabolism is unknown.

Methods: We studied the association of inflammatory markers (CRP and IL-6) with all-cause mortality, and cardiac and infectious hospitalizations and deaths among 1340 subjects from the Effect of Dialysis and Membrane Flux in Maintenance Hemodialysis (HEMO) trial. Cox regression models adjusted for important confounding variables: demographics, comorbidities, Kt/V, dialyzer, smoking, albumin, and mineral metabolism markers including serum calcium, phosphorus, intact parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and FGF23.

Results: Mean age was 58±14 years, 56% were female, and 63% were black. Median (IQR) CRP and IL-6 levels were 6.1 (2.6-15.2) mg/L and 3.2 (1.7-6.9) pg/mL, respectively. Over mean 2.84 years follow-up, there were 582 deaths, 514 cardiovascular events, and 499 infectious events. Among subjects with levels in the highest quartile compared to the lowest quartile, both CRP and IL-6 were significantly associated with all-cause mortality in adjusted analyses, odds ratio (OR) 1.96 (95% CI, 1.27-3.02) and OR 1.51 (95% CI, 1.02-2.23), respectively. However, only CRP was associated with cardiovascular disease events (OR 1.90; 95% CI, 1.04-3.44) and infectious events (OR 3.84; 95% CI, 1.37-10.74) among subjects with levels in the highest quartile compared to the lowest quartile.

Conclusions: CRP and IL-6, were significantly associated with all-cause mortality independent of mineral metabolism abnormalities. Only CRP was significantly associated with cardiovascular disease and infectious disease events independent of mineral metabolism abnormalities among subjects in the HEMO trial.

Funding: NIDDK Support, Veterans Administration Support

FR-PO856

Assessment of Protein-Energy Wasting: Comparing a New PEW Score and the MIS in Chronic HD Patients Camiel LM de Roij van Zuijdewijn,¹ Muriel P. Grooteman,¹ Peter J. Blankestijn,² Menso Jan Nubé,¹ Pieter M. Ter Wee.¹ ¹Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; ²Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands.

Background: the assessment of protein-energy wasting, a syndrome of decreased bodily protein and energy fuels, remains debated. Recently, a French group introduced a new PEW score, encompassing BMI, serum creatinine, nPNA and serum albumin. In a cohort of chronic hemodialysis patients, we compared the predictive value of this score with the Malnutrition Inflammation Score (MIS) using all-cause mortality as end point. Furthermore, we investigated which of these scores correlates best with quality of life (QOL).

Methods: from data of the CONvective TRANsport STudy (CONTRAST), the new PEW score and the MIS were determined at baseline. QOL was measured with the Kidney Disease QOL-Short Form 36, which results in 2 general and 12 kidney-disease specific domains of QOL. Discrimination and calibration for mortality were tested by Harrell's C Statistic and the Hosmer-Lemeshow Goodness-of-Fit test, respectively. Spearman's rank correlation coefficient ρ was used to determine correlations between a test and the various QOL domains.

Results: 489 out of 714 patients were analyzed. 183 died during follow-up (mean 3.15±1.78 years). Discrimination for mortality was higher for MIS than the new PEW score (Harrell's C statistic 68.0 [95% CI 65.7-69.8] and 61.0 [95%CI 59.0-63.3], respectively). Furthermore, mortality calibration was adequate for MIS ($p=0.65$), but not for the new PEW score ($p=0.03$). Lastly, MIS correlated with 13 domains of QOL (ρ 's between -0.47 and -0.12), whereas the new PEW score only correlated with the physical component score (ρ 0.18).

Conclusions: both the MIS and the new PEW discriminate for mortality, but the MIS performs better. Furthermore, only the MIS is properly calibrated. Third, the MIS correlates with more QOL domains with higher correlation coefficients. Therefore, we conclude that MIS is preferred over the new PEW score in assessing PEW.

FR-PO857

Change in MIS Over 1 Year Is Not Associated with Mortality in Chronic Hemodialysis Patients Camiel LM de Roij van Zuijdewijn,¹ Muriel P. Grooteman,¹ Menso Jan Nubé,¹ Peter J. Blankestijn,² Pieter M. Ter Wee.¹ ¹Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; ²Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands.

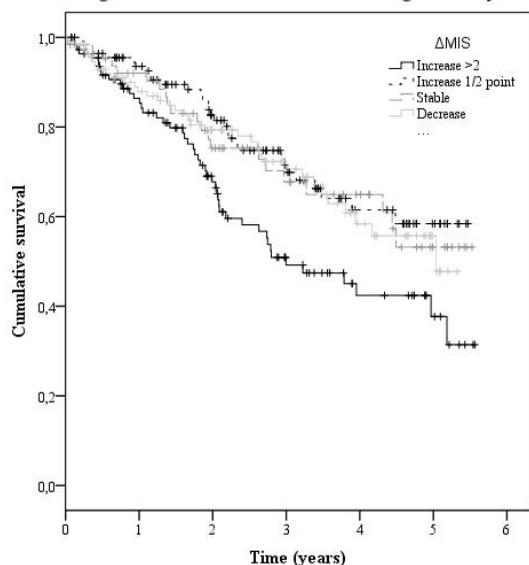
Background: protein-energy wasting, a state of decreased bodily protein and energy fuels, has been associated with increased mortality as measured by the Malnutrition Inflammation Score (MIS), a composite, clinical, nutrition-related score. Longitudinal data on this score, however, are limited. We checked whether a change in MIS over 1 year of follow-up is associated with mortality.

Methods: data from CONTRAST were used, a well-defined cohort of end-stage kidney disease patients. Patients were selected for analysis if MIS was available at baseline (M0) and at 12 months (M12). Delta (Δ) MIS was calculated as MIS (M12) - MIS (M0). As the

association between Δ MIS and mortality was not linear, patients were divided into quartiles of Δ MIS. Cox proportional hazards models, crude and adjusted for potential confounders, were used to calculate hazard ratios (HRs) of patients with severe deteriorating MIS (increase >2 points), mild deteriorating MIS (increase of 1 or 2 points), stable MIS versus patients with an improving MIS.

Results: 404 patients were available for analysis. Mean age was 63.0 \pm 13.5 and 62.4% were male. During follow-up (median 3.1 years), 135 patients died. Median Δ MIS was 1.0 (IQR -1.0 to 3.0). Survival curves are shown in fig 1. HR of patients with a mild deteriorating or stable MIS versus patients with an improving MIS was 0.85 (95%CI 0.53-1.39) and 0.97 (95%CI 0.56-1.67), respectively; for patients with a severe deteriorating MIS, HR was 1.63 (95%CI 1.02-2.51). After correction for age, sex, dialysis vintage and dialysis modality, this association did not remain significant ($p>0.1$).

Figure 1: survival curves of MIS change over 1 year



Conclusions: a change in MIS over 1 year is not associated with mortality in a multivariable survival analysis.

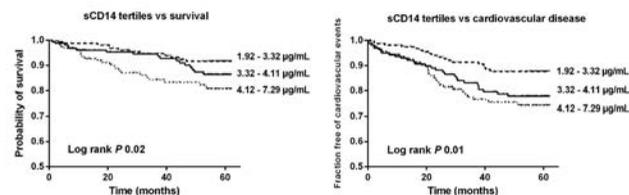
FR-PO858

Soluble CD14, a Marker of Endotoxemia, Associates with Survival and Cardiovascular Disease in CKD Patients Ruben Poesen,¹ Ian Barrows,² Ali Ramezani,² Pieter Evenepoel,¹ Kathleen Claes,¹ Bjorn Meijers,¹ Dominic S. Raj.² ¹Nephrology, Univ Hospitals Leuven, Belgium; ²Renal Diseases and Hypertension, George Washington Univ.

Background: CKD goes along with gut microbial dysbiosis and gut barrier dysfunction, possibly contributing to endotoxin translocation. Subsequent binding of endotoxin to toll-like receptor-4 and its co-receptor CD14 activates the innate immune system. As half-life of systemic endotoxin is very short, soluble CD14 (sCD14) has been proposed as better marker of endotoxin exposure. Whether sCD14 relates to adverse outcome in CKD patients not yet on dialysis is unknown.

Methods: We performed a prospective study in CKD patients stage 1-5. Plasma sCD14 was determined with ELISA. Determinants of sCD14 were examined with regression analysis. The relationship between sCD14, survival and cardiovascular disease (CVD) was explored using Kaplan Meier and Cox PH analysis.

Results: 495 CKD patients were followed from 2005 until 2010. Median plasma sCD14 was 3.72 μ g/mL (IQR 3.15-4.40). Lower eGFR and higher CRP were the strongest determinants of higher sCD14 (both $P<0.0001$). During follow-up, we observed 53 deaths (Tertile 1/2/3: 12/17/24 events, log rank $P=0.02$, see figure). In Cox PH analysis, sCD14 remained a significant predictor of death (univariate HR per SD increase of 1.809 (1.356-2.413), $P<0.0001$), even after adjustment for renal function, Framingham risk factors, CRP and albumin (HR 1.899 (1.316-2.739), $P=0.0006$). We also noted 78 CV events (Tertile 1/2/3: 18/29/31 events, $P=0.01$, see figure). This association remained borderline significant in the fully adjusted model (HR 1.299 (0.999-1.689), $P=0.05$).



Conclusions: Plasma sCD14 is elevated in patients with advanced CKD, suggesting increased endotoxin exposure. sCD14 is independently associated with survival and CVD, pointing to a role of endotoxemia as driving force behind adverse outcome in CKD.

Funding: Government Support - Non-U.S.

FR-PO859

Gut Microbiota Derived Trimethylamine-N-Oxide Is Not a Biomarker for Mortality and Cardiovascular Disease in European CKD Patients Ruben Poesen, Pieter Evenepoel, Bjorn Meijers. *Nephrology, Univ Hospitals Leuven, Belgium.*

Background: Trimethylamine-N-oxide (TMAO) is a gut microbiota derived metabolite of dietary choline, lecithin and L-carnitine with recent evidence suggesting involvement of TMAO in development of atherosclerosis. Recently, TMAO has been associated with mortality and cardiovascular disease in a general US population as well as in US CKD patients not yet on dialysis. As there may be population-specific differences in diet and/or microbial metabolism, we questioned whether TMAO also relates with adverse outcome in European CKD patients.

Methods: We performed a single-center prospective study in patients with CKD stage 1-5. Baseline serum levels of TMAO were determined using LC-MS. Correlation between eGFR and serum TMAO was explored using Spearman's rank correlation analysis. The relationship between TMAO, survival and cardiovascular disease was examined using Cox proportional hazard analysis.

Results: 488 CKD patients were followed from November 2005 until December 2010. Median serum level of TMAO was 11.6 μ M (IQR 5.7-21.8). We observed a highly significant inverse correlation between eGFR and serum TMAO ($\rho=0.71$, $P<0.0001$). During follow-up, we noted a total of 51 deaths and 75 cardiovascular events. In univariate cox proportional hazard analysis, TMAO was a significant predictor of mortality (HR 1.521 (1.183-1.956), $P=0.001$) and cardiovascular disease (HR 1.570 (1.283-1.921), $P<0.0001$). However, significance was lost after adjustment for eGFR for overall mortality (HR 1.126 (0.795-1.595), $P=0.50$), as well as for cardiovascular events (HR 1.256 (0.958-1.647), $P=0.10$).

Conclusions: Serum levels of TMAO rise in parallel to a declining renal function and further analysis of 24h urine samples is ongoing to elucidate its renal handling. In this European cohort of CKD patients, we were not able to find an association between TMAO and adverse outcome that is beyond renal function, which is in contrast to previous observations in US populations, both general and CKD. This may question the validity of TMAO as a universal biomarker for cardiovascular disease, possibly due to population-specific differences in diet and/or microbial metabolism.

Funding: Government Support - Non-U.S.

FR-PO860

Microbiota Derived Phenylacetylglutamine Associates with Survival and Cardiovascular Disease in CKD Patients Ruben Poesen, Pieter Evenepoel, Bjorn Meijers. *Nephrology, Univ Hospitals Leuven, Belgium.*

Background: Lately, there is increasing interest in gut microbiota derived uremic retention solutes as driving force behind adverse outcome in CKD. Both p-cresyl sulfate and indoxyl sulfate are considered representatives of this group, also commonly referred as to protein-bound solutes due to their high protein binding and dependence on active tubular secretion for renal clearance. Phenylacetylglutamine is another microbial metabolite subjected to high tubular secretion, although protein binding is rather low. We questioned whether this solute also relates to adverse outcome in CKD patients not yet on dialysis.

Methods: We performed a prospective study in CKD patients stage 1-5. Serum levels of phenylacetylglutamine were determined using LC-MS. Correlation between eGFR and serum phenylacetylglutamine was explored using Spearman's rank correlation analysis. The relationship between phenylacetylglutamine, survival and cardiovascular disease (CVD) was examined using Kaplan Meier and Cox PH analysis.

Results: 488 CKD patients were followed from November 2005 until December 2010. Median serum level of phenylacetylglutamine was 6.2 μ M (IQR 3.0-13.2). We observed a highly significant inverse correlation between eGFR and serum phenylacetylglutamine ($\rho=-0.76$, $P<0.0001$). During follow-up, we noted a total of 51 deaths and 75 CV events with a gradual and significant increase with higher tertiles of phenylacetylglutamine (both log rank $P<0.0001$). In univariate Cox PH analysis, phenylacetylglutamine was a significant predictor of mortality (HR 1.962 (1.481-2.598), $P<0.0001$) and CVD (HR 1.997 (1.590-2.508), $P<0.0001$), even after adjustment for renal function, Framingham risk factors, calcium-phosphorus-PTH, CRP and albumin (HR 1.611 (1.140-2.275), $P=0.007$ for mortality and HR 1.668 (1.295-2.149), $P<0.0001$ for CVD).

Conclusions: Serum levels of microbiota derived phenylacetylglutamine are elevated in patients with more advanced CKD. Serum phenylacetylglutamine is also a strong and independent risk factor for mortality and CVD. Further analysis of 24h urine samples is ongoing to differentiate between impact of higher urinary excretion as surrogate of intestinal generation vs. impact of lower tubular secretion.

Funding: Government Support - Non-U.S.

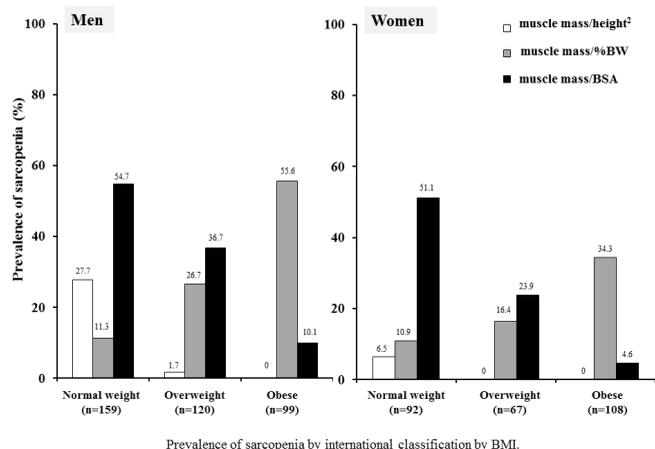
FR-PO861

Sarcopenia Among Prevalent Hemodialysis Patients: Weighing the Evidence Piyawan Kittikulnam,¹ Juan Jesus Carrero,² Glenn Matthew Chertow,³ George A. Kaysen,⁴ Kirsten L. Johansen.¹ ¹UCSF; ²Karolinska Inst; ³Stanford Univ; ⁴UC Davis.

Background: There is no consensus on the best way to define sarcopenia in ESRD. Use of muscle/height²(Ht²) is suggested by geriatric societies but may underestimate sarcopenia, particularly in the setting of excess adiposity. We compared three definitions of sarcopenia in a prevalent HD cohort.

Methods: ACTIVE/ADIPOSE enrolled HD patients from San Francisco and Atlanta from 6/09 to 8/11. Bioelectrical impedance spectroscopy was performed before a midweek dialysis session (n=645), and total-body muscle mass was estimated using an equation containing age, sex, body weight (BW), and intracellular water. We defined sarcopenia as muscle mass ²SD below sex-specific means for adults 18-49 y from NHANES data indexed to Ht², %BW, and body surface area (BSA) by DuBois formula. We compared the prevalence of low muscle mass among the three methods and assessed their correlation with handgrip strength.

Results: Mean age was 57±14 years, 41% were women, 61% black. The prevalence of sarcopenia was 8% by muscle/Ht², 25% by muscle/%BW and 32% by muscle/BSA. Most sarcopenic patients by muscle/BSA method had normal BMI, while >50% of sarcopenic patients by %BW were obese. Almost none of the overweight or obese patients were identified as sarcopenic by muscle/Ht².



Patients who were classified as sarcopenic by muscle mass/BSA but not Ht² had significantly higher BMI and %body fat than those who were sarcopenic by both methods (25.2 vs 21.3 kg/m², p<0.001 and 31.1 vs 24.4%, p<0.001, respectively). Handgrip strength was moderately correlated with muscle/BSA (r=0.6) but weakly correlated with muscle/Ht²(r=0.3) and %BW (r=0.4).

Conclusions: Skeletal muscle mass normalized to Ht² may underestimate the prevalence of sarcopenia, particularly in overweight HD patients. Detection of sarcopenia among overweight/obese patients requires adjustment for body size or adiposity.

Funding: NIDDK Support

FR-PO862

Does a Probiotic Supplementation Alter the Indoxyl Sulfate Levels in Non-Dialysis Chronic Kidney Disease Patients? A Randomized Placebo-Controlled Clinical Trial Denise Mafra,¹ Natalia Alvarenga Borges,¹ Milena Barcea Stockler-Pinto,² Denis Fouque,⁴ Amanda F. Barros.² ¹Medical Sciences Graduate Program, Federal Univ Fluminense, Rio de Janeiro, Brazil; ²Cardiovascular Sciences Graduate Program, Federal Univ Fluminense, Rio de Janeiro, RJ, Brazil; ³Post Graduate Program in Dentistry, Estácio de Sá Univ, Rio de Janeiro, RJ, Brazil; ⁴Dept of Nephrology, Centre Hospitalier Lyon Sud, Univ Claude Bernard, Lyon, France; ⁵Graduate Program in Science Applied to Health Products, Federal Univ Fluminense, Rio de Janeiro, RJ, Brazil; ⁶Medicine Faculty, Federal Univ Fluminense, Rio de Janeiro, RJ, Brazil.

Background: The imbalance in gut microbiota associated with alterations in colonic epithelium contributes to the accumulation of gut-derived uremic toxins in chronic kidney disease (CKD) patients. Therapeutic strategies like probiotic supplementation may modulate the gut microbiota and reduce the toxins levels. To determine the effect of probiotics supplementation on indoxyl sulfate (IS) plasma levels in non-dialysis CKD patients.

Methods: In this double-blind, placebo-controlled trial, 29 non-dialysis CKD patients were recruited. Patients were randomized to receive probiotic (1 capsule, containing 30 billion of colony forming units - *S. thermophilus*, *L. acidophilus*, and *B. longum*, n= 17) or placebo (n= 12) for 3 months. IS plasma levels were quantified with HPLC, calprotectin and protein C reactive were analyzed by immunoenzymatic assay. Five patients in probiotic group and three in placebo were lost to follow-up.

Results: Plasma IS increased significantly in patients who received probiotics whereas the other parameters did not change.

Parameters	Probiotic (N=12)		Placebo (n=9)	
	Before	After 3 months	Before	After 3 months
Total IS (mg/L)	8.0 (0.1 - 99.5)	72.0 (6.1 - 240.0)*	5.5 (0.64 - 21.2)	15.8 (4.9 - 84.3)
Calprotectin (ng/dL)	12.8± 4.6	14.0± 6.5	12.2 ± 4.8	11.4 ± 3.1
CRP (mg/dL)	4.8 (1.3 - 6.1)	3.6 (1.2 - 6.0)	1.2 (0.4 - 3.7)	0.4 (0.4 - 6.8)

Conclusions: Data from this randomized study suggest that administration of probiotics alone may increase plasma IS levels in non-dialysis CKD patients. These findings support the need for more studies with probiotics in CKD patients.

Funding: Government Support - Non-U.S.

FR-PO863

Prevention of the Progression of Both Renal Dysfunction and the Atherosclerotic Change in Chronic Kidney Disease (CKD) Stage 3-4 Patients due to Benign Nephrosclerosis Yoshihiko Inoue, Tomoaki Miyazaki, Shinya Omiya, Kiyoko Inui, Daisuke Komukai, Ashio Yoshimura. *Div of Nephrology, Showa Univ Fujigaoka Hospital, Yokohama, Kanagawa, Japan.*

Background: Effect of EPA for CKD patients is not fully known. We studied the efficacy of EPA to prevent the progression of both renal impairment and atherosclerosis in CKD stage 3-4 patients due to benign nephrosclerosis (BNS).

Methods: 31 CKD stage 3-4 patients due to BNS with dyslipidemia were followed for 3 years after the start of EPA treatment. The dosage of 1800 mg/day of EPA was newly prescribed. T-cho, LDL-cho, Triglycerides (TG), eGFR, the amount of proteinuria, EPA, arachidonic acid (AA), Dihomo-gamma-linolenic acid (DGLA) and docosa hexaenoic acid (DHA) were studied. Both right and left (RL) brachial-ankle pulse wave velocity (baPWV), RL maximum carotid intima-media thickness (max IMT), RL maximum carotid plaque thickness and RL ankle-brachial index (ABI) were evaluated at before treatment (baseline), after 1,2-year and at the end of the study (3-year).

Results: EPA, EPA/AA ratio, TG, RL baPWV, RL max IMT and eGFR showed significant improvement at 3-year (table 1).

	Baseline	End of the study (3-year)	P
EPA (µg/ml)	70.4±38.7	236.8±99.2	<0.01
EPA/AA	0.39±0.23	1.39±0.56	<0.01
TG (mg/dl)	243.8±127.0	136.7±37.3	<0.01
Right baPWV (cm/s)	1686.0±369.2	1580.3±289.4	<0.05
Left baPWV (cm/s)	1723.4±378.8	1618.2±245.0	<0.05
Right max IMT (mm)	0.96±0.35	0.79±0.26	<0.05
Left max IMT (mm)	0.92±0.31	0.76±0.24	<0.05
eGFR (ml/min/1.73m ²)	44.0±11.2	48.5±14.6	<0.05

Furthermore, both EPA and DHA levels were significantly low in eGFR exacerbation patients group (n=9) compared with the improvement group (n=22) at both baseline and 3-year. Patients showing the highest EPA levels at baseline (EPA: 124.6±18.8 mg/ml, n=8) showed significant improvement in both eGFR and baPWV compared with those with the lowest EPA levels (30.1±8.1 mg/ml, n=8). There was no difference on both plaque thickness and ABI between baseline and 3-year.

Conclusions: EPA powerfully prevents the progression of both renal dysfunction and the atherosclerotic change in CKD stage 3-4 patients due to BNS.

FR-PO864

Relationships Between Composition of Gut Microbiota and Uremic Toxins Mami Kikuchi,¹ Ryoko Tateoka,¹ Yoshiharu Itoh,¹ Wataru Suda,^{2,3} Masahira Hattori.^{2,4} ¹Kureha Corporation, Tokyo, Japan; ²The Univ of Tokyo, Chiba, Japan; ³Keio Univ, Tokyo, Japan; ⁴Waseda University, Tokyo, Japan.

Background: Gut microbiota is known to function in producing uremic toxins (UTs) and their precursors, such as indoles, phenols and so on. However the relationships between specific bacteria and UTs are not clear. To elucidate the production of UTs by gut microbiota, we collected blood, urine and feces samples in normal rats, rats subjected to 5/6 renal removal. AST-120, a spherical carbon adsorbent of intestinal small-molecular-weight UTs and/or their precursors, was used to evaluate the effects of UTs on gut microbiota.

Methods: Serum and urine levels of UTs were quantified by SRM of LC/ESI-MS/MS. Gut microbiota from feces were analyzed using 454-pyrosequencing of a hypervariable V1-V2 region of the 16S rRNA gene in combination with barcode sequences. We used the GLSEARCH program and self-build 16S sequences database and genome database to determine the closest species. We identified the indole and/or phenol producing species using BLASTX.

Results: In CKD rats, urinary excretion and serum concentrations of UTs, such as indoxyl sulfate and phenyl sulfate, were higher than control rats. In AST-120-administered CKD rats, urinary excretion and serum concentrations of UTs decreased compared to CKD

rats. The overall bacterial community composition was compared according to the UniFrac distance metric among control rats, CKD rats, and CKD + AST-120 rats. A principal coordinate analysis plot revealed clustering of each group. We identified the intestinal microbiome containing tryptophanase and/or tyrosine phenol-lyase gene in the genome sequences from NCBI bacterial genome. These enzymes metabolize tryptophan to indole and tyrosine to phenol, respectively.

Conclusions: Our data suggest that UT production is not only the cause of uremic symptoms but also correlated with a subset of indigenous gut microbes and affects the composition of gut microbiota.

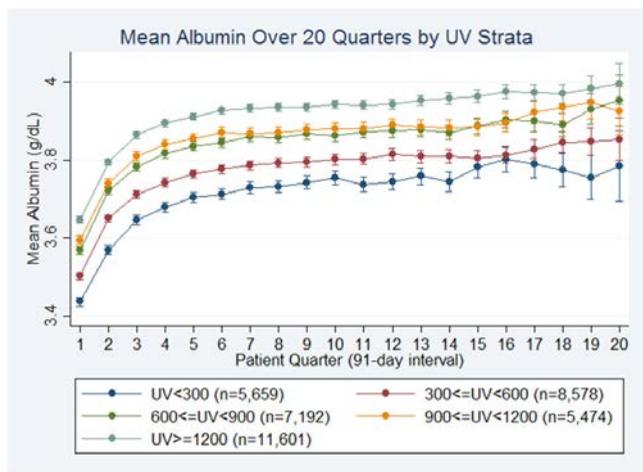
FR-PO865

Association of Urine Volume at the Start of Dialysis and Subsequent Changes in Serum Albumin Level in Incident Hemodialysis Patients Rieko Eriguchi,¹ Yoshitsugu Obi,¹ Connie Rhee,¹ Steven M. Brunelli,² Joline L.T. Chen,¹ Anna Mathew,³ Tae Hee Kim,¹ Elani Streja,¹ Csaba P. Kovcsdy,⁴ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²DaVita Clin Research; ³Hofstra North Shore-LIJ Health System; ⁴UTHSC.

Background: Previous studies have shown that low serum albumin(Alb) levels are associated with higher mortality in hemodialysis (HD) patients. While serum Alb is a critical inflammatory and nutritional marker, low Alb may also result from albuminuria. It is unknown if a change in serum Alb over time is due to the loss of residual kidney function. While data on urine Alb was unavailable, we hypothesized that higher urine volume (UV) is associated with a decrease in Alb.

Methods: Among 38,504 incident HD patients receiving care from a large dialysis organization from 2007-2011, we examined serum albumin level trajectory over 5 years (divided into 20 patient quarters) across five strata of baseline UV: <300, 300-<600, 600-<900, 900-<1200, ≥1200 mL. The association between baseline UV and serum albumin trend was examined using mixed effects models with adjustment for age, gender, race, diabetes, and insurance type.

Results: Patients were 62±15 years old, 38% female, 28% black, and 46% diabetic. Higher baseline UV was incrementally associated with higher Alb levels across strata: 3.44±0.48g/dL, 3.50±0.46g/dL, 3.57±0.44g/dL, 3.59±0.45g/dL, and 3.65±0.46g/dL, respectively. [Figure] Serum Alb increased over the first 6 patient quarters (18 months) on dialysis and then stabilized. Patients with higher UV not only had a higher baseline serum Alb level, but also maintained a higher serum Alb level over follow-up.



Conclusions: Higher baseline UV appears to be associated with sustained higher serum Alb levels over time. Improvement in hypoalbuminemia as a result of transition to dialysis therapy appears to be independent of residual kidney function and may suggest an inherent advantage of dialysis initiation.

Funding: NIDDK Support

FR-PO866

Individual Variation of Hippuric Acid and P-Cresyl Sulfate Plasma Levels Correlate with Variation of Intestinal Microbial Phylotypes in Hemodialysis Patients Griet Lrl Glorieux,¹ Sara Vieira-Silva,² Sunny Eloit,¹ Eva Schepers,¹ Annemieke Dhondt,¹ Raymond C. Vanholder,¹ Jeroen Raes,² Geert Huys,³ Marie Joossens.² ¹Renal Div, Ghent Univ Hospital, Ghent, Belgium; ²Microbiology and Immunology, KU Leuven, Leuven, Belgium; ³Microbiology, Ghent Univ, Ghent, Belgium.

Background: In chronic kidney disease (CKD), a myriad of metabolites accumulate in the circulation. A substantial part is generated by intestinal microbiota. We hypothesize that there is a link between plasma levels of these uremic metabolites and the composition of the intestinal microbiota.

Methods: Over 4 months, up to 8 consecutive plasma and fecal samples from 16 hemodialysis patients (14M/2F; 74±10y; vintage: 43±30mo) were collected. Uremic metabolites were quantified by UPLC. Fecal microbial DNA was amplified for 16S rDNA (V4 hypervariable region) sequencing (Illumina MiSeq). After quality and chimera filtering

(UCHIME), data was rarefied to 10,000 reads/sample and taxonomically annotated (RDP). Correlation between the maximum intra-patient variability of metabolite levels and the corresponding time-points of fecal microbial phylotypes was assessed. In addition, cross-sectional correlations at t0 were evaluated. Statistical analyses were performed with R package phyloseq, using Spearman correlation, with multiple testing correction (FDR) per metabolite for the number of genus-level phylotypes.

Results: Within this patient group, we observed a strong positive correlation between an increase in total hippuric acid and unclassified *Peptostreptococcaceae* (p=0.83; corrected p-value=0.012). We also found a positive trend for total p-cresyl sulfate and unclassified *Clostridiales* and unclassified *Ruminococcaceae* (p=0.77 and 0.74; corrected p-value=0.074 and 0.078, respectively). Cross-sectionally at t0, strong negative correlations between indoxyl sulfate, indole acetic acid and specific unclassified bacterial phylotypes (p=-0.79 and -0.84; corrected p-value=0.028 and 0.004) were observed.

Conclusions: There is a link between plasma levels of specific uremic metabolites and fecal bacterial phylotypes, suggesting that these microbiota might be a target for reducing uremic metabolite levels in patients with CKD. Data needs validation on larger patient groups.

Funding: Government Support - Non-U.S.

FR-PO867

Decreased Vitamin K Intake in Italian Hemodialysis Patients Maria Fusaro,¹ Claudia D' Alessandro,² Marianna Noale,¹ Giovanni Tripepi,⁴ Lucia Bonfante,³ Nicola Veronese,⁶ Irene Santinello,³ Sabina Zambon,⁵ Sandro Giannini,³ Maurizio Gallieni,⁶ Adamasco Cupisti.² ¹CNR - Padua, Italy; ²Div of Nephrology Dept of Clinical and Experimental Medicine, Univ of Pisa; ³Nephrology Unit, Univ of Padua; ⁴CNR-IFC Clin. Epid. and Physiopath. of Renal Dis. and Hypert. of Reggio Calabria; ⁵Clinica Medica 1, Univ of Padua, Italy; ⁶Univ of Padova; ⁷Dialysis Unit St Carlo, Milan, Italy.

Background: Vitamin K is involved in the production of Bone and Matrix Gla Proteins (BGP and MGP, respectively), regulating bone and vascular health. We carried out a pilot study to evaluate vitamin K intake in hemodialysis (HD) patients.

Methods: We measured vitamin K1 intake (7-day food record) in 78 Italian hemodialysis patients (48 M, 30 F) compared to intake in 39 healthy adults (28 M, 11 F).

Results: HD patients had a mean (± SD) age of 62.8±15.0 years, median dialytic age of 97 months, mean BMI of 25.4±4.5 Kg/m². Mean serum levels of interest for CKD-MBD were: Ca 9 mg/dL, P 4.3 mg/dL, PTH 231.5 pg/mL, ALP 81.5 U/L. Control group mean age was 54.6±13.9 years. HD patients had a significantly lower intake of vitamin K1 compared to controls (see Table). We also evaluated and compared between HD patients and controls the intake of other fat soluble vitamins and of nutrients closely associated with bone and mineral disorders in CKD patients (see table). All were decreased in HD patients.

Data	Patients	Controls	p value
Vitamin K1 (mcg/day) [Median]	70.1	109.2	0.0009
Vitamin A (mcg/day) [Median]	306	495.0	<0.0001
Vitamin D (mcg/day) [Median]	1.2	1.74	0.0326
Active Vitamin E (mcg/day) [Median]	7.1	11.24	<0.0001
Calcium (mg/day) [Median]	364.5	587.8	<0.0001
Phosphorus (mg/day) [Median]	749.2	1079.2	<0.0001
Magnesium (mg/day) [Median]	144.9	212.7	<0.0001

Conclusions: This Vitamin K intake study is the first carried out on Italian diet. We found a decreased intake of Vitamin K1 in HD patients. This finding supports the hypothesis of supplementing vitamin K for the prevention of vascular calcifications and bone disorders in HD patients. Benefits of vitamin K supplementation should be proved by a randomized trial.

FR-PO868

Association of Geriatric Nutrition Risk Index with Body Fluid Composition, Renal Adverse Outcomes and Mortality in Patients with Chronic Kidney Disease Reibin Tai,¹ Yasushi Ohashi,¹ Toshiyuki Aoki,¹ Shizuka Kobayashi,¹ Atsushi Aikawa,¹ Ken Sakai.¹ *Dept of Nephrology, School of Medicine, Faculty of Medicine, Toho Univ, Tokyo, Japan.*

Background: Decreased body stores of protein and energy fuels may express by the geriatric nutritional risk index (GNRI) consisting of body mass index (BMI) and serum albumin levels. We studied the association of the GNRI with body fluid composition, renal adverse outcomes and all-cause mortality in patients with chronic kidney disease (CKD).

Methods: Body fluid composition was measured in 306 patients with CKD from 2005 to 2014 and was separated into three components – (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW) content, and (c) extracellular water (ECW) content. Patients were categorized according to tertiles of GNRI levels. Of those, 275 patients were followed until March 2015. The adverse renal outcomes were defined by a decline of 50% or more from baseline glomerular filtration rate or initiation of renal replacement therapy.

Results: Patients with the lower tertiles of the GNRI levels were more likely to be higher age, have a lower BMI, diastolic blood pressure, serum albumin, hemoglobin, glomerular filtration rate, and proteinuria (P < 0.05). In the body fluid composition, those tended to have lower free water mass (r = 0.73, P < 0.001) and the ratio of extracellular water to

intracellular water ($r = 0.37, P < 0.001$). Compared with patients with the middle tertile of the GNRI levels during a median 2.5-year follow-up, the lowest tertile of the GNRI levels had higher mortality (6.8 vs. 1.7 per 100 patient-years, $P < 0.001$), but had no worse adverse renal outcomes (16.5 vs. 9.0 per 100 patient-years, $P = 0.08$). In multivariate analysis, the lower GNRI levels independently remained as a risk factor for all-cause mortality (hazard ratio, 3.16; 95% CI, 1.30–8.84; $P < 0.001$).

Conclusions: The GNRI may be a simple and useful tool for predicting the risk of mortality even in CKD population including patients with massive proteinuria. These findings emphasize the importance of adequate body stores of protein and energy fuels in patients with CKD.

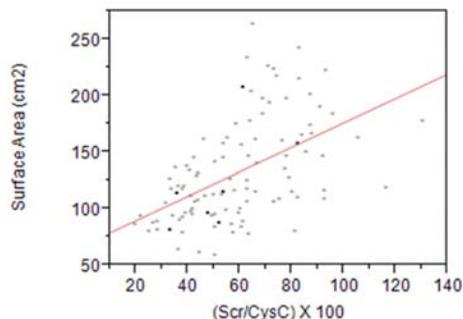
FR-PO869

A Novel Index for Estimation of Muscle Mass Using Biomarkers of Kidney Function: Sarcopenia Index Kianoush Banaei-Kashani,^{1,2} Lucie Kukralova,³ Erin N. Frazee,⁴ Rahul Kashyap.² ¹Div of Nephrology and Hypertension, Dept of Internal Medicine, Mayo Clinic, Rochester, MN; ²Div of Pulmonary and Critical Care, Dept of Internal Medicine, Mayo Clinic, Rochester, MN; ³Faculty of Medicine in Hradec Kralove, Charles Univ, Prague, Czech Republic; ⁴Dept of Pharmacy, Mayo Clinic, Rochester, MN.

Background: Sarcopenia is associated with poor patients' outcomes in Intensive Care Unit (ICU). Tools to evaluate sarcopenia are DXA scan, CT and MRI, which may not be feasible for critically ill patients. We hypothesize a novel index which can be used as a surrogate for sarcopenia among ICU patients.

Methods: This is a secondary analysis of prospectively enrolled critically ill patients. Adult ICU patients (>18 years) with shock, sepsis, use of IV antibiotics and contrast media exposure, in 24 hours of enrollment, intra-abdominal hypertension or severe Trauma were included. We excluded patients with pre-existing acute kidney injury, pregnancy, and kidney transplant, or those who were on dialysis or were moribund. We measure paraspin muscle surface area at L3 level, using Slice-O-Matic software (TomoVision®, Magog, Canada). Sarcopenia Index (SI) was calculated as [Serum Creatinine (Scr) ÷ Cystatin C (CysC)] X 100.

Results: A total of 226 patients met the inclusion criteria. Among these enrollees, 110 patients who had abdominal CT within ± 4 weeks of their index ICU admission were included in the final analysis. The median age (IQR) was 67 (57-77) years and 59 (54%) were male. SI and Paraspinal Muscle Surface Area were found to be statistically correlated ($R^2 = 0.26, p < .0001$).



Conclusions: SI has a fair correlation with gold standard in critically ill patients. This index would be a surrogate for sarcopenia for patients who cannot tolerate transfer to imaging testing.

FR-PO870

Association with Activities of Daily Living and Geriatric Nutritional Risk Index Improves the Prediction of Mortality in Patients on Hemodialysis Kaoru Yasuda,¹ Shoichi Maruyama,² Kunio Morozumi.¹ ¹Nephrology, Masuko Memorial Hospital, Nagoya, Aichi, Japan; ²Nephrology, Nagoya Univ, Nagoya, Aichi, Japan.

Background: Protein energy wasting (PEW) is a typical status of Malnutrition seems to be a prevalent complication in end-stage renal disease (ESRD), and is associated with poor prognosis. We previously reported that Geriatric Nutritional Risk Index (GNRI) is useful marker for the assessment of malnutrition status in hemodialysis (HD) patients. However the interaction between actual activities of daily living (ADL) and GNRI is uncertain. We investigated the prognostic value of the ADL and GNRI, and hypothesized that the combination of both indicators could improve predictive values for mortality in HD patients.

Methods: A total of 304 stable HD patients were enrolled. They were divided into tertiles according to the ADL defined by the Renal Data Registry of Japanese Society for Dialysis Therapy; tertile A: < independence, B: care-needed (mild) and C: care-needed (moderate or severe). They were also divided into tertiles of GNRI levels; L: <91.7, M: 91.7-97.8 and H: >97.8, and GNRI were 95.9±7.6, 94.9±5.8, 87.1±11.0 in A, B and C of ADL, respectively ($p < 0.0001$ in both).

Results: During the follow-up period (40 month), 59 patients were died (19.4%). Kaplan-Meier survival rates for 4 years were 88.9%, 82.1% and 53.1% in A, B and C of ADL, and were 63.5%, 82.8% and 88.8% in L, M and H of GNRI, respectively ($p < 0.0001$ in both). The adjusted HR for mortality was 3.21 (95% CI, 1.57-6.95, $p = 0.0006$, C vs

A) and 3.24 (95% CI, 1.62-7.06, $p = 0.0019$, L vs H). In the combined setting of ADL and GNRI with 9 groups (3x3), the risk of mortality was 8.02-fold (95%CI 2.56-35.4, $p = 0.0001$, C+L vs A+H).

Conclusions: ADL and GNRI could strongly predict the mortality, and combination of both setting also improved the prediction of mortality with ESRD patient on HD.

	Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value
Life activity (vs. A)		<0.0001		0.0006
B	1.69 (0.82-3.60)	0.15	1.15 (0.54-2.51)	0.71
C	5.80 (3.02-11.8)	<0.0001	3.21 (1.57-6.95)	0.0012
GNRI (vs. >97.9)		<0.0001		0.0019
91.7-97.9	2.31 (1.29-4.32)	0.0042	1.65 (0.75-3.79)	0.21
<91.7	3.99 (2.04-8.54)	<0.0001	3.24 (1.62-7.05)	0.0006

FR-PO871

Delta Neutrophil Index Is a Predictive Marker of Disease Severity in Patients with Acute Pyelonephritis SulA Lee,¹ Jong Hyun Jhee,¹ Jae Eun Um,² Meiyun Wu,² Hyung Jung Oh,¹ Jung Tak Park,¹ Seung Hyeok Han,¹ Shin-Wook Kang,^{1,2} Tae-Hyun Yoo.¹ ¹Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; ²Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Delta neutrophil index (DNI) is the fraction of immature granulocytes provided by a complete blood count analyzer. Previous studies demonstrated that DNI was a novel marker to predict clinical outcomes in sepsis patients. Therefore, this study was aimed to evaluate DNI as a predictive marker of disease severity in patients with acute pyelonephritis (APN).

Methods: Patients who were diagnosed with APN at Severance Hospital from December 2009 to July 2012 were retrospectively investigated. DNI levels were measured at the time of admission. Patients were classified into two groups according to the median value of DNI. Severe APN was defined as one or more of following conditions; bacteremia, acute kidney injury, hypotension requiring use of vasopressors, and admission of intensive care unit. Independent risk factors for severe APN were determined by multivariate logistic regression analysis. Area under the receiver operating characteristic curves (AUC) was compared among DNI, white blood cell (WBC) count, and C-reactive protein (CRP).

Results: A total of 258 patients were included in this study. The median age was 61.0 (19.0 – 87.0) years, and 237 patients (91.9%) were female. The median DNI levels were 2.5%. Severe APN was significantly more prevalent in the high DNI group. Multivariate analysis showed that DNI independently predicted severe APN (per 1% increase, odds ratio=1.287, 95% confidence interval=1.135-1.458, $P < 0.001$). Furthermore, DNI was a better predictive marker of severe APN than WBC count [AUC (95% confidence interval); 0.697 (0.637-0.753) vs. 0.562 (0.499-0.624), $P = 0.001$] and not inferior to CRP levels [0.697 (0.637-0.753) vs. 0.633 (0.571-0.692), $P = 0.118$].

Conclusions: DNI at admission could be a valuable predictor of disease severity in patients with APN.

FR-PO872

An Improved Magnesium Formulation for Mitigating Cisplatin-Induced Renal Epithelial Cell Injury Malvika H. Solanki,^{1,2,3} Rachel Lauren Mintz,² Xiangying Xue,² Prodyot K. Chatterjee,² Christine N. Metz.^{1,2,3} ¹Elmazzi Graduate School of Molecular Medicine, NY; ²Feinstein Inst for Medical Research, NY; ³Hofstra-North Shore-LIJ School of Medicine, NY.

Background: Cisplatin is a potent chemotherapy for treating cancer. It causes nephrotoxicity in ~25% and hypomagnesemia in ~90% patients. This hypomagnesemia is treated with oral magnesium (Mg) chloride (MgCl₂) and/or i.v. Mg sulfate (MgSO₄). Poor Mg intake and Mg deficiency are not uncommon in the US. Our previous studies revealed the beneficial effects of MgSO₄ in reducing cisplatin-induced acute kidney injury (AKI) (Solanki et al, *AJP Renal* 2014). This study compared the efficacy of various Mg formulations in reducing cisplatin-induced renal epithelial cell injury.

Methods: LLC-PK₁ renal epithelial cells were maintained in media containing 100% Mg (i.e. the amount of Mg found in growth media) or 10% Mg (Mg-deficient) for 3 days. To mimic Mg replacement, the 10% Mg cells were restored to 100% Mg using: MgSO₄, Mg-L-threonate (MgT), MgCl₂, and Mg gluconate (MgG) (keeping elemental Mg equal) and then treated with vehicle or cisplatin. Oxidative stress, cytotoxicity and inflammation were measured by DCF-DA assay, MTT assay and TNF α production, respectively. ERK activation was measured by in-cell-western.

Results: Cisplatin-induced oxidative stress, cytotoxicity, and inflammation were exacerbated by Mg deficiency, while Mg supplementation with all formulations consistently and significantly attenuated these effects. MgT was the most effective Mg-formulation for reducing cisplatin-induced oxidative stress and inflammation. Mechanistic studies revealed that cisplatin-induced ERK activation was modulated by Mg status and MgT was most protective.

Conclusions: Mg supplementation protected against cisplatin-induced oxidative stress, cytotoxicity and inflammation in renal epithelial cells. This is the first study to reveal the effectiveness of MgT over other Mg-formulations in reducing cisplatin-induced renal

epithelial cytotoxicity. Note: MgT has significantly lower GI-effects (bloating and diarrhea) than other Mg formulations. These results warrant further in vivo and clinical studies to investigate the beneficial role of MgT in protecting against cisplatin-AKI.

Funding: Private Foundation Support

FR-PO873

Impact of Uremic Serum on the Barrier Function and Inflammation in Human Colonocytes *Laila Santos Andrade,¹ Maria Dalboni,² Jose Tarcisio Giffoni,² Caren Cristina Grabulosa,² Lilian Cuppari.^{1,2}* ¹*Nutrition Graduation Program, Federal Univ of São Paulo, São Paulo, Brazil;* ²*Medicine, Div of Nephrology, Federal Univ of São Paulo, São Paulo, Brazil.*

Background: In chronic kidney disease (CKD) it has been suggested that alterations of the gut are associated with inflammatory state and uremic toxicity. Studies suggest that uremia may impair the intestinal barrier function, by promoting increased intestinal permeability. In this study we aimed to evaluate the in vitro effect of uremic serum on the transepithelial electrical resistance (TER), inflammation and apoptosis in the intestinal epithelial cells.

Methods: Pools of serum were prepared from blood samples from patients maintained on hemodialysis (Pre-HD and Post-HD), and of patients with CKD stage 4 (NND-CKD). A pool of serum from healthy individuals served as control (CTL). When the TER exceeding 1,000 Ω /cm² was reached, the T84 cells were incubated for 24 h in medium containing 10% pool of serum from each group. At the conclusion of the incubation period, the TER was measured again and the following parameters were determined by flow cytometry: expression of toll-like receptor (TLR), production of reactive oxygen species (ROS) and apoptosis. TNF- α and IL-6 in the culture supernatant was determined by ELISA. A total of nine experiments were performed.

Results: No differences among groups were found regarding TER ($p=0.443$), apoptosis ($p=0.751$), ROS ($p=0.999$), expression of TLR-2 ($p=0.493$), TLR-4 ($p=0.418$) and TLR-9 ($p=0.937$) and secretion of TNF- α ($p=0.438$). IL-6 secretion was higher ($p<0.001$) by cells incubated with post-HD pool (2.07 \pm 0.93pg/ml) when compared with cells incubated with CTL pool (0.67 \pm 0.35), NND-CKD (0.61 \pm 0.53) and pre-HD (0.11 \pm 0.45).

Conclusions: The results obtained from this model suggest that uremic serum *per se* does not seem to impair the integrity of intestinal epithelial cells. The increased IL-6 secretion in post-HD condition may be a consequence of pro-inflammatory stimulus of the dialysis process.

Funding: Government Support - Non-U.S.

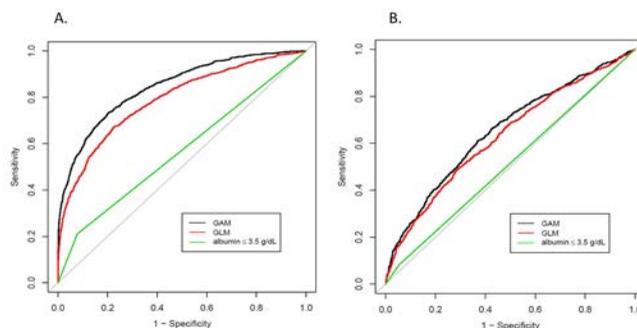
FR-PO874

Prediction of One-Year Mortality and Hospitalization Risk Using Nutritional Indicators and Their Trajectories in a Large Prevalent Hemodialysis Cohort *Michelle M.Y. Wong,¹ Stephan Thijssen,¹ Yuedong Wang,² Len A. Usvyat,³ Qingqing Xiao,¹ Peter Kotanko,¹ Franklin W. Maddux.³* ¹*Renal Research Inst;* ²*Univ of California - Santa Barbara;* ³*Fresenius Medical Care North America.*

Background: Existing nutritional scores developed in the hemodialysis (HD) population do not consider temporal trajectories of nutritional parameters. We aimed to develop predictive models for mortality and hospitalization using readily available nutritional indicators and their rates of change.

Methods: Using retrospective data from a large US HD provider, a cohort with HD vintage ≥ 1 year ($N=21,082$ and $N=23,384$ in mortality and hospitalization analyses, respectively) was randomly split 2:1:1 for model development, testing and validation. Parameters included demographics, nutritional/inflammation parameters, and slopes of all continuous variables over 6 months. Follow-up period was January-December 2012. Performance of generalized linear models and generalized additive models (GAM) was evaluated with area-under-the-curve (AUC), sensitivity and specificity.

Results: For both mortality and hospitalization prediction, GAM performed best. The best mortality model included neutrophil:lymphocyte ratio (NLR) slope, serum bicarbonate slope, albumin, creatinine, age, sex and vintage (AUC 0.85, 95% CI 0.83-0.86; sensitivity 0.70; specificity 0.83). The best hospitalization model included NLR slope, albumin, congestive heart failure, serum bicarbonate slope, creatinine, serum phosphate slope, vintage, diabetes, serum phosphate, volume of urea distribution, age and enPCR (AUC 0.70, 95% CI 0.62-0.79; sensitivity 0.41; specificity 0.88).



Receiver-operator characteristic curves for A) mortality and B) hospitalization models. Predictive performances of generalized additive models (GAM) (black line), generalized linear models (GLM) (red line), and albumin ≤ 3.5 g/dl alone (green line) are shown.

Conclusions: We developed novel and accurate predictive models for mortality and hospitalization using nutritional indicators and their slopes over time. Future studies are needed to assess if its application can improve nutritional intervention allocation and outcomes in HD patients.

Funding: Pharmaceutical Company Support - Renal Research Institute

FR-PO875

Extracellular Fluid/Intracellular Fluid (ECF/ICF) Volume Ratio Is a Novel Risk Indicator of Death and Highly Related to Malnutrition-Inflammation-Arteriosclerosis (MIA) Complex in Hemodialysis (HD) Patients *Eunjung Kim, Soyoon Rhee, Jiwoon Ryu, Hee Jung Jeon, Jung-woo Noh, Ja-Ryong Koo.* *Nephrology, Hallym Univ Hospital, Dongtan/Seoul, Korea.*

Background: Fluid overload and malnutrition are well recognized risk factors contributing to the high mortality in HD patients. Recent studies suggest pathophysiological link between fluid overload and malnutrition as a part of MIA complex. Because the ECF and ICF volume can represent fluid volume and nutritional status respectively, ECF/ICF ratio could be defined as a novel integrated marker reflecting both fluid overload and malnutrition. Accordingly we investigated the relationship of ECF/ICF ratio to survival in the context of MIA complex in chronic HD patients.

Methods: 77 HD patients (age 53 \pm 13 year, diabetes 38%) were prospectively enrolled. ECF/ICF volume was measured by multi-frequency bioimpedance analysis. Nutrition, inflammation, arteriosclerosis and volume status were measured by serum albumin, C-reactive protein (CRP), pulse wave velocity (PWV) and serum B-type natriuretic peptide(BNP) respectively.

Results: Mean ECF/ICF ratio was 0.56 \pm 0.06 and cut-off value for maximum discrimination of survival was 0.57 by ROC curve. As compared with low ECF/ICF group (ratio<0.57, 58%), high ECF/ICF group (ratio \geq 0.57, 42%) had higher all-cause mortality, CRP, PWV, BNP and lower serum albumin level. During the 5-year follow-up, 24 all-cause death occurred (18 in high ECF/ICF group versus 6 in low ECF/ICF group, log rank $P<0.001$). In Cox analysis adjusted for age, diabetes, BP and cardiac function, the ECF/ICF ratio was an independent predictors of all-cause death (HR=1.25, 95% CI=1.10-1.54, per $\Delta 0.01$ in ECF/ICF ratio) and nullify the effect of MIA component and volume marker on survival. The degree of malnutrition (albumin), inflammation (CRP), arteriosclerosis (PWV) and fluid overload (BNP) were correlated well with ECF/ICF ratio.

Conclusions: Chronic HD patient with high ECF/ICF ratio is not only fluid overloaded but malnourished and have stiff artery with more inflammation. As a novel integrated marker of fluid overload and malnutrition, ECF/ICF ratio is highly related to MIA complex and a major risk indicator of death in chronic HD patients.

FR-PO876

Weight Gain After Listing Independently Predicts Pre-Transplant Sensitization Status *Priitika Shrivastava,¹ Krista L. Lentine,² Ankit Sakhuja,¹ Fidel Barrantes,³ Diane M. Cibrik,¹ Yihung Huang,¹ Abhijit S. Naik.¹* ¹*Univ of Michigan;* ²*Saint Louis Univ;* ³*Renal Medical Associates, NM.*

Background: Non-alloimmune stimuli such as infections, vaccinations and pro-inflammatory events cause sensitization to HLA antibodies and increased panel reactive antibodies. Obesity is recognized as an inflammatory state. Given relationship between obesity and inflammation we speculated that weight gain on the waitlist may increase sensitization status at the time of transplantation.

Methods: Using national data from the Organ Procurement and Transplantation Network we identified first time kidney only transplant recipients, aged 18-70, transplanted between January 1,2009 and June 30,2013. Previous non-renal transplants were excluded. A calculated panel reactive antibody of 20% or more at the time of transplant was considered to be "sensitized". Using *a priori* chosen variables we performed a logistic regression model with sensitized status at time of transplantation as the dependent variable and change in BMI from listing to transplantation, BMI at transplant, recipient age, prior transfusion status, prior pregnancy, dialysis time and race as independent variables.

Results: Among 55,894 patients transplant recipients, 39.45 % were female of which 67.33 % were previously pregnant. Overall 15.12 % had received prior blood transfusions. Mean BMI at wait listing and transplantation was similar at 28.4± 5.5 kg/m². Greater than 50 % patients with BMI ≥ 30 kg/m² at listing had an increased their BMI by time of transplantation, while >50 % patients in BMI <30 kg/m² had lost weight. A 1-unit increase in BMI (kg/m²) after transplantation was associated with an increased risk of being sensitized, aOR: 1.01 (1.01-1.02). Other independent predictors included prior transfusion aOR: 1.25 (1.18-1.33), AA race aOR: 1.26 (1.19-1.32), pregnancy aOR: 3.32 (3.04-3.63), dialysis time aOR: 1.23 (1.11-1.14).

Conclusions: The majority of obese patients gain weight on the waitlist. We identified weight gain on the waiting list to be associated with a small but statistically significant increase in odds of being sensitized. Further studies are needed to determine the impact of malnutrition-inflammation complex on pretransplant sensitization.

FR-PO877

High Salt Diet Impairs the Immune Defense against Uropathogenic *Escherichia coli* in Murine Pyelonephritis *Katarzyna Jobin, Katharina Hochheiser, Maik Giesing, Christian Kurts. Inst of Experimental Immunology, Univ of Bonn, Bonn, Germany.*

Background: Recent studies demonstrated that NaCl stimulates immune responses, for example by promoting Th17 cells differentiation, macrophage recruitment into tissues and pro-inflammatory cytokine release from epithelial cell lines. Specially, high salt diet (HSD) exacerbated experimental autoimmune encephalomyelitis and improved immune defense against *L. major* infection. Little is known about the influence of HSD on anti-microbial responses in the kidney – an organ with extremely high sodium chloride concentration.

Methods: Wild type female mice were given normal salt diet (NSD) or HSD one week prior to infection with uropathogenic *E. coli* into the bladder resulting in pyelonephritis development. 20 h after the infection, kidneys were harvested and analyzed for CFU and immune cell subsets by flow cytometry.

Results: HSD exacerbated pyelonephritis as measured by CFU. Additionally, in kidney medullas of mice fed HSD the number of PMNs, Ly6c^{hi} macrophages and NK cells was significantly decreased in comparison with NSD fed mice. Although PMNs from mice given HSD produced more ROS than PMNs from mice on NSD, in vitro studies demonstrated that less medullary PMNs from mice fed HSD than NSD were able to perform phagocytosis.

Conclusions: Contrary to the expectations, HSD worsened experimental pyelonephritis, possibly through affecting immune cell activation and/or migration into the kidney medulla. This finding may be of clinical significance and, if confirmed in human studies, decreasing salt intake during bladder infection or pyelonephritis could support antibiotic therapy. Further studies are needed to elucidate the immune mechanisms underlying the negative effect of HSD on pyelonephritis.

Funding: Government Support - Non-U.S.

FR-PO878

Gut Microbiota *Lactobacillus* Protects against the Progression of Renal Impairment in Rats Through the Modulation of TLR2-Mediated Gut Barrier Stability in Rats *Ayumi Yoshifuji, Shu Wakino, Junichiro Irie, Takaya Tajima, Kazuhiro Hasegawa, Hirobumi Tokuyama, Hiroshi Itoh. Keio Univ Japan.*

Background: Gut microbiota has been shown to have some role in the pathogenesis of various diseases and previous study demonstrated that *Lactobacillus* (*Lact*) decreased in number in CKD. In this study, we elucidated the significance of *Lact* in the pathogenesis of CKD.

Methods: Six-week-old spontaneously hypertensive rats (SHR) were rendered CKD by 5/6th nephrectomy (Nx). The SHRs were divided into three groups; sham-operated SHR (SHR), SHR with Nx (Nx) and Nx given *Lact* (Nx+*Lact*). After 12 weeks, biochemical parameters, urinary protein excretion, IL-6, histological changes in the kidney, and molecular changes of tight junctions and TLR2 expression were explored. Furthermore, concentrations of fecal uremic toxins were measured. To confirm the effect of *Lact*, rats are administered with broad antibiotics as pseudogerm-free condition and kept for 8 weeks with *Lact*. Human colon cell line, Caco-2 cells were treated with uremic toxin precursor, indole in the presence or absence of *Lact* or OxPAPC, an inhibitor of toll-like receptor, putative receptor recognizing *Lact*. The expressions of colon tight junction proteins were examined by immunoblotting.

Results: The gut flora analysis revealed that the decrease in *Lact* in Nx, which was restored in Nx+*Lact*. However, fecal uremic toxins did not show significant changes. Both serum indoxylsulfate and IL-6 increased in Nx. These increases were ameliorated in Nx+*Lact*. The decreases in the tight junction proteins Occludin and Zo-1 as well as in TLR2 in Nx were mitigated by *Lact*. In the pseudogerm-free condition, *Lact* decreased the urinary protein excretion. In Caco-2 cells, the downregulations of Occludin and ZO-1 by indole were ameliorated by *Lact*. OxPAPC inhibited the *Lact*-induced restoration of these tight junctions.

Conclusions: The supplementation of *Lact* improves the gut environment through the activation of TLR2 pathway. This improvement would contribute to the decrease in systemic uremic toxin levels, systemic inflammation and urinary protein excretion. This probiotic therapy can provide novel therapeutic strategy against the progression of CKD.

Funding: Government Support - Non-U.S.

FR-PO879

Relationship Between Serum Uric Acid Change and Renal Injuries: An Observational Cohort Research from Pinggu District, Beijing *Xiaohong Fan, Wenling Ye, Jianfang Cai, Jie Ma, Ying Sun, Xuewang Li, Xuemei Li. Dept of Nephrology, Peking Union Medical College Hospital.*

Background: Hyperuricemia is thought to be a risk factor of CKD and ESRD. This research aims to demonstrate the relationship between serum uric acid change (Δ UA) based upon baseline from general population and indexes of renal injuries.

Methods: This cohort research was based on 5 years' follow up of an epidemiological study in 2008 in Pinggu District, Beijing. Baseline population was 7086, and 5364 subjects were followed up in 2014. All subjects were interviewed with questionnaires, tests of anthropometric indicators, blood and urine sample collection. Serum creatinine, cystatin C, etc were tested. Urine sample was used to test ACR, α 1mG, and NAG. Hyperuricemia is defined as serum uric acid is above 420mmol/L for men, and above 360mmol/L for women. According to baseline of 2008 and blood uric acid level of 2014 (Normal, N; High, H), patients were grouped as: N/N, H/N, N/H, H/H (group 1-4). One-way ANOVA was applied to evaluate differences of indexes among all groups. Risk factors of CKD (ACR^{3.39}mg/mmol & eGFR <60ml/min/1.73²) were evaluated with Multiple Logistic regression analysis.

Results: 1. 5364 patients (M:F 1:1.1) were included. In 2008 prevalence of hyperuricemia was 5.9% (7.0% for men, 5.0% for women), and prevalence of hyperuricemia was 6.2% (8.5% for men, 4.2% for women) in 2014. 2. Δ eGFR of group N/H, H/H were significantly higher than that of group N/N, H/N, indicating that GFR of hyperuricemia patients following up in 2014 declined more than that of patients without hyperuricemia; serum cystatin C in 2014 increased significantly from group 1 to group 4; there was no significant difference among all groups in α 1mG, NAG/Cr. 3. Δ UA, age, BMI, hypertension, DM were independent risk factors of CKD. HR of CKD in group N/H, H/H was 1.87 times (95%CI 1.30-2.68, P=0.001) and 4.2 (95%CI 2.60-6.70, P<0.001) times of group N/N.

Conclusions: In general population, elevation of serum uric acid is the independent risk factor of GFR decline and serum cystatin C ascent. It is also the independent risk factor of the development of CKD, and the decline of uric acid in the blood may reduce the risk of renal injuries.

Funding: Government Support - Non-U.S.

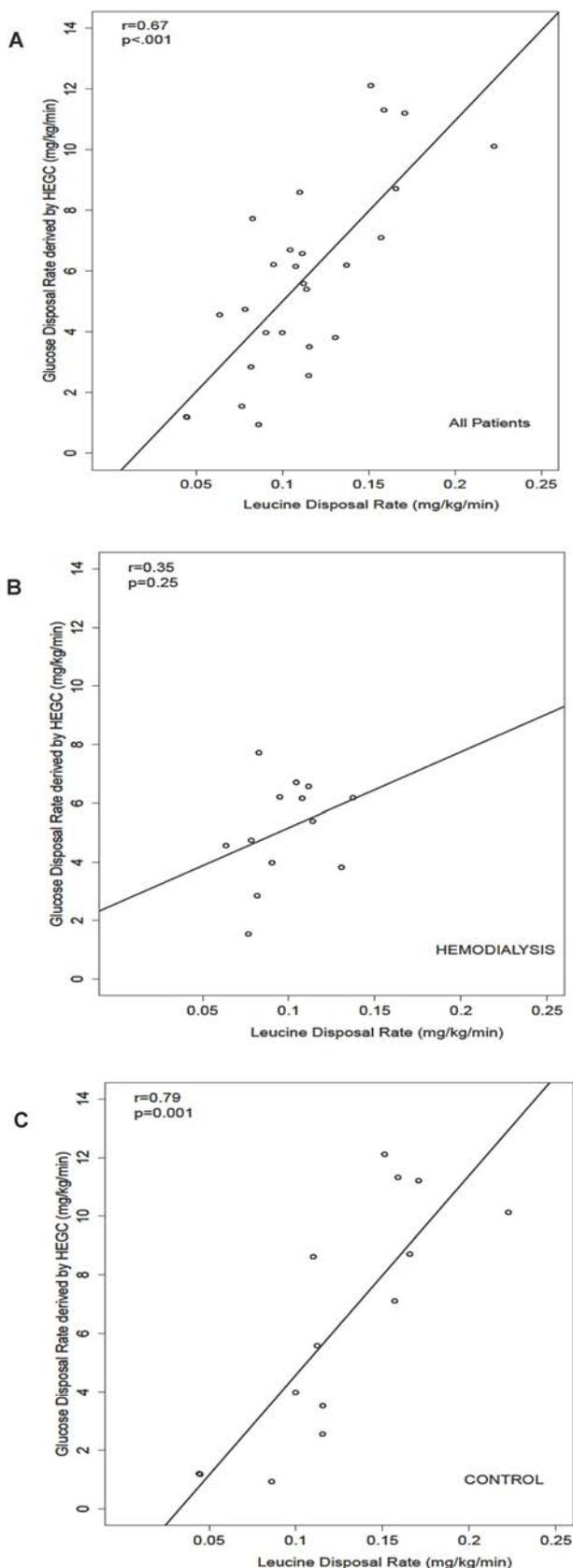
FR-PO880

Leucine Disposal Rate for Assessment of Amino Acid Metabolism in Maintenance Hemodialysis Patients *Gerald Denny,¹ Serpil Muge Deger,^{1,2} Feng Sha,¹ Cindy Booker,^{1,2} Charles D. Ellis,¹ Talat Alp Ikizler,^{1,2} ¹Nephrology, Vanderbilt Univ, TN; ²Veteran Affairs, TN.*

Background: Protein energy wasting (PEW) is common in patients undergoing maintenance hemodialysis (MHD) and is closely associated with poor outcomes. Insulin resistance and associated alterations in amino acid metabolism is a potential pathway leading to PEW. In this study we hypothesized that measurement of leucine disposal rate (LDR) during a hyperinsulinemic-euglycemic-euaminoacidemic clamp (HEAC) procedure would accurately measure the sensitivity of insulin for its actions on concomitant carbohydrate and protein metabolism in MHD patients.

Methods: We examined 15 MHD (aged 52±13 years, BMI 29±5 kg/m²) patients and 16 control subjects (aged 46±10 years and BMI 28±7 kg/m²) by hyperinsulinemic euglycemic clamp (HEGC) procedure followed by HEAC clamp procedure to obtain glucose disposal rate (GDR) and LDR, respectively.

Results: The GDR by HEGC was 4.9±1.9 mg/kg/min in the MHD subjects compared to 6.3±4.1 mg/kg/min in the controls (P=0.47). The LDR during HEAC was 0.09±0.03 mg/kg/min for MHD patients vs 0.12±0.05 mg/kg/min for control (P=0.11). The GDR derived by HEGC and LDR correlated well in the control population (r=0.793, P=0.001), but less so in the MHD subjects (r=0.346, P=0.25).



Conclusions: Leucine disposal rate reliably measures amino acid utilization in MHD patients. The lack of correlation between GDR versus LDR in MHD subjects requires further investigation for understanding the effects of insulin signaling on protein metabolism in MHD patients.

FR-PO881

Age and Dependence on Dialysis Are More Important Predictors of Immune Response to Influenza Vaccine Than Inflammation and Iron Status
 Jaromir Eiselt,¹ Lukas Kielberger,¹ Daniel Rajdl,² Jaroslav Racek.² ¹Internal Dept 1, Charles Univ, Plzen, Czech Republic; ²Dept of Biochemistry, Charles Univ, Plzen, Czech Republic.

Background: The immune response to influenza vaccine is not uniform and may be influenced by many factors, e.g. comorbidities, age, inflammation or iron metabolism. The aim of our study was to identify factors associated with low production of hemagglutination-inhibition antibodies (HIA) after vaccination in hemodialysis (HD) patients and controls.

Methods: We evaluated the immune response to the influenza vaccine in a total of 122 stable HD patients and in 37 subjects without renal dysfunction. To identify factors associated with immune response, a stepwise backward and forward algorithm for a linear regression model was used with postvaccination increase in HIA titre against H1N1 vaccine strain as dependent variable and following independent variables: age, dependence on dialysis, diabetes, iron, transferrin, transferrin saturation, ferritin, hepcidin, interleukin-6, C-reactive protein, albumin, prealbumin and pre-vaccination HIA protective titre.

Results: The rate of HIA production was lower in HD patients than in controls. Factor increases in geometric mean titer for the H1N1 strain were 2.9 in HD and 6.6 in controls ($p<0.001$), with the respective figures being 2.8 and 3.1 ($p=ns$) for the H3N2 strain, and 2.4 and 4.7 ($P<0.05$) for the B strain. Also, post-vaccination seroconversion rates were lower in the HD group than in controls (43% versus 73% against the H1N1 strain; $p<0.05$; 43% versus 53% against the H3N2 strain; $p=ns$; and 36% versus 62% against the strain B; $p<0.05$). According to the regression model (adjusted R^2 0.298, $p<0.00001$), the predictors of low HIA production against H1N1 strain were high age ($p<0.0001$), dependence on dialysis ($p=0.011$) and high transferrin saturation ($p=0.03$).

Conclusions: The immune response to the influenza vaccine was lower in HD patients than in controls. Besides dependence on dialysis, the most significant predictors of low antibody production were high age of vaccinated subjects and high transferrin saturation. Immune response was independent of other markers of iron metabolism and inflammation.

Funding: Government Support - Non-U.S.

FR-PO882

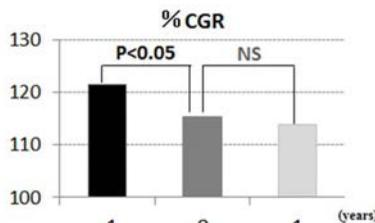
Intravenous Administration of L-Carnitine (LC) May Maintain the Muscle Volume in Hemodialysis (HD) Patients
 Jyunichiro Hashiguchi,¹ Takuhisa Uchino,¹ Miki Yano,¹ Satoshi Funakoshi,¹ Osamu Sasaki,¹ Hiroshi Ichinose,¹ Kenji Sawase,¹ Yoko Obata,² Tomoya Nishino,² Yutaka Mori,³ Kazunori Utsunomiya,³ Takashi Harada.¹ ¹Nagasaki Kidney Center, Nagasaki, Japan; ²Nagasaki Univ Graduate School of Medicine, Nagasaki, Japan; ³Jikei Univ, Tokyo, Japan.

Background: Patients on maintenance HD usually suffer from dialysis-related carnitine deficiency, causing various clinical symptoms. At Carnitine Consensus Conference in 2003 convened by The National Kidney Foundation, the level of evidence was strongest for the treatment of anemia, and weakest for the response of muscle weakness. We hereby investigated whether intravenous administration of LC can maintain the muscle volume in HD patients as assessed by % creatinine generation rate (CGR).

Methods: Thirty-eight HD patients were enrolled in this study after appropriate informed consent. Subjects were treated with intravenous administration of 1000mg / body of LC at the end of every HD session for 12 months, then assessed by %CGR. Normalized protein catabolic rate (nPCR), geriatric nutritional risk index (GNRI) as well as serum albumin or hemoglobin levels were measured at the tree points; 1 year prior to the treatment, the start of LC administration and 1 year after the treatment.

Results: As shown in Figure 1, average %CGR significantly declined during 1 year before the start of LC, and then stabilized 1 year after the treatment, suggesting LC administration might prevent the loss of muscle volume. Serum albumin, hemoglobin, nPCR and GNRI stayed the same level during observation period.

Total Muscle Volume



	-1	0	1	(years)
Albumin (g/dL)	3.5±1.1	3.4±0.9	3.6±1.1	NS
Hb (g/dL)	10.8±1.7	11.0±0.7	11.1±1.1	NS
GNRI	93.3±10.4	92.9±9.8	94.0±11.1	NS
nPCR (g/day)	1.2±0.2	1.3±0.4	1.4±0.2	NS

Conclusions: Intravenous LC administration may potentially maintain the muscle volume in patients undergoing HD.

Funding: Private Foundation Support

FR-PO883

Nutrition Analysis Mobile Application in Patients with Chronic Kidney Disease Chayakrit Krittanawong,¹ Sakkarin Chirapongsathorn,^{2,3} Zhen Wang,⁴ Hua Ann Jenny Lu.⁵ ¹Div of Cardiovascular Disease, Mayo Clinic, Rochester, MN; ²Div of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; ³Div of Gastroenterology, Dept of Medicine, Phramongkutklao Hospital and College of Medicine, Royal Thai Army, Bangkok, Thailand; ⁴Dept of Healthcare Policy and Research, Mayo Clinic, Rochester, MN; ⁵Div of Nephrology, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Background: While mobile phone applications have become increasingly important in the last decade, few eating healthy mobile applications exist for patients. Yet in their daily lives, patients on a restricted diet often lack instant access to health information with regards to the food that is in front of them. It is therefore an objective of this pilot project to introduce a device that patients can utilize to overcome such problems.

Methods: The nutrition analysis application is named "GoFoody Project" and primarily consists of two functions: a scanning system and a recommendation system.

Results: The first major component of this invention is the food scanning and recognition process, which is comprised of two sub-processes: a photo recognition and a barcode scanning. In the photo recognition, the user can take a picture of food and send it to the cloud database for further processing, regardless of their location. Second, the recommendation system compares the patient's medical profile with their consumptions records in order to make health and dietary suggestions.

Conclusions: Over the next few years, we anticipated that this invention will be popular in grocery stores such as Walmart, Target, etc. We plan to demonstrate our invention to the healthcare industry by using the example of computer vision technology and cloud database.



FR-PO884

Lipoxin A₄ Attenuates Obesity-Induced Adipose Inflammation and Associated Liver and Kidney Disease Emma Borgeson,^{1,2} Kumar Sharma,¹ Catherine Godson.² ¹Center for Renal Translational Medicine, Inst for Metabolomic Medicine, UC San Diego, San Diego, CA; ²Diabetes Complications Research Centre, Conway Inst, Univ College Dublin, Dublin, Ireland.

Background: Visceral obesity and adipose inflammation is considered a driving force of systemic disease, e.g. chronic kidney disease (CKD). Inflammatory resolution is actively regulated by specialized pro-resolving mediators (SPMs), including the lipid LXA₄. Impairment of SPMs may underlie development of obesity-related pathology. Here we explored the therapeutic potential of LXA₄ in experimental obesity-induced systemic disease, e.g. liver cirrhosis and CKD.

Methods: C57BL/6 or Adiponectin^{-/-} mice were fed a standard (10% fat) or high fat (60% fat) diet for 12 wks. LXA₄ (5ng/g) and benzo-LXA₄ analogue (1.7 ng/g) were given as interventional therapeutics i.p. 3 times weekly, between wk 5-12. Furthermore, omental adipose tissue biopsies were isolated from obese (BMI 35-50) bariatric surgery patients (n=4). Adipose explants were incubated with vehicle or LXA₄ (1 nM) for 6h at 37 °C, and leukocytes were characterized by flow cytometry.

Results: Obesity caused distinct pathologies, including impaired glucose-tolerance, adipose inflammation, fatty liver and CKD. Lipoxins attenuated obesity-induced CKD; reducing glomerular expansion, mesangial matrix and urinary H₂O₂. Furthermore, LXA₄ reduced liver weight, serum alanine-aminotransferase and hepatic triglycerides. LXA₄ decreased obesity-induced adipose inflammation, attenuating TNF-α and CD11c⁺ M1-macrophages (MFs), while restoring CD206⁺ M2-MFs and increasing Annexin-A1. Lipoxins did not affect renal or hepatic MFs, suggesting protection occurred via attenuation of adipose inflammation. Lipoxins restored adipose expression of autophagy markers LC3-II and p62. LX-mediated protection was demonstrable in adiponectin^{-/-} mice, suggesting that the mechanism was adiponectin independent. The ongoing clinical studies are characterizing whether Lipoxins promote an M1-to-M2 MFs phenotype shift in human omental adipose tissue.

Conclusions: In conclusion, Lipoxins protect against obesity-induced systemic disease and these data support a novel therapeutic paradigm for treating obesity and associated CKD.

Funding: Other NIH Support - NIH DP3 award (DK094352-01), Veterans Administration Support, Government Support - Non-U.S.

FR-PO885

Prevalence of Protein-Energy Wasting Syndrome and Its Association with Anemia, Erythropoietin Resistance, Overhydration and Body Composition in Hemodialysis Patients Carlos Adrián Chávez-Mendoza, Jose Luis Ortega Vargas, Jorge Osvaldo Montes rivera, Ricardo Correa-Rotter, Olyнка Vega-Vega. Nephrology and Mineral Metabolism, National Inst of Medical Science and Nutrition Salvador Zubiran, Mexico City, Mexico.

Background: The prevalence of protein-energy wasting syndrome (PEW) in Mexican hemodialysis (HD) patients is unknown. Accordingly, there is no information on which clinical, biochemical, quality of life (QL), and body composition (BC) variables are associated or predictive of PEW in this population.

Methods: Observational comparative study that included 191 prevalent HD patients. BC was determined by BIS employing (BCM,Fresenius®), QL was measured with KDQOL-36 and presence of PEW according to ISRN criteria.

Results: General characteristics are shown in Figure 1, prevalence of PEW was 22%(n=41). No differences between groups (with or without PEW) were present in: age, Charlson index, number and type of drugs employed, time on dialysis, vascular access, history of PD or kidney transplant and hospitalization days in the last year. PEW patients had a higher prevalence of DM(p=0.04), lower Hb(p=0.006) and higher EPO requirements(p=0.04) despite similar iron reserves. In terms of BC, PEW patients had more overhydration (OH) and higher extracellular water (ECW), and lower lean and fat tissue indexes (LTI,FTI). Surprisingly, QL indicators were not different between groups. In a Cox multivariate logistic regression model analysis, predictors of PEW were:degree OH(OR 3.2,95% CI 1.2-8.3,p<0.001), and ECW(OR 0.51,95% CI 0.22-0.89,p<0.01).

Figure 1. Differences between PEW and No PEW patients in chronic HD

	RRT – HD n= 191	PEW n= 41	No PEW n= 150	p
Age, years	54 ± 16	54 ± 17	54 ± 16	0.92
Sex (female), %	85 (44.5)	24 (58.5)	61 (40.6)	0.55
Diabetes Mellitus, %	97 (50.8)	24 (58.5)	73 (48.6)	0.04
Body mass index, kg/m ²	25.8 ± 4.7	22.7 ± 5	26.6 ± 4.2	< 0.001
Interdialytic weight gain, kg	2.23 ± 0.9	1.71 ± 1.1	2.37 ± 0.8	<0.001
Interdialytic wet weight gain, ml/kg	33.46 ± 17.4	32.93 ± 22.1	34.84 ± 12.2	0.46
Serum Albumin, mg/dL	3.5 ± 0.4	3.2 ± 0.4	3.6 ± 0.3	<0.001
nPNA, g/kg/d	1.02 ± 0.4	0.85 ± 0.3	1.07 ± 0.4	<0.001
Serum P, mEq/L	5.3 ± 1.8	4.6 ± 1.5	5.4 ± 1.8	0.04
PTH, pg/mL	597.5 ± 526.7	585.5 ± 622.0	600.8 ± 499.7	0.87
Total body water [TBW], L	33.9 ± 7.6	29.37 ± 6.2	34.94 ± 7.6	<0.001
Total body water [TBW], ml/kg	514.92 ± 85.2	540.04 ± 99.5	514.09 ± 85.3	0.17
Overhydration [OH], ml/kg	30.4 ± 24.2	43.05 ± 26.5	27.39 ± 22.8	<0.001
Extracellular water [ECW], ml/kg	246.46 ± 31.9	263.13 ± 39.6	246.17 ± 31.9	0.01
Intracellular water [ECW], ml/kg	268.43 ± 59.2	277.12 ± 66	267.89 ± 59.2	0.47
Lean tissue index [LTI], kg/m ²	13.70 ± 3.6	12.21 ± 3.2	14.03 ± 3.7	0.02
Fat tissue index [FTI], kg/m ²	11.82 ± 6.2	9.61 ± 5.7	12.33 ± 6.2	0.04
Body cell mas [BCM], kg	19.9 ± 7.8	16.3 ± 5.7	20.7 ± 8	0.009
Hemoglobin, mg/dL	10.1 ± 1.7	9.5 ± 1.6	10.3 ± 1.6	0.005
EPO, UI/ kg/wk	156.49 ± 73.8	171.2 ± 100.6	142.6 ± 59.8	0.04
Ferritin, ng/ml	360 ± 547.8	463 ± 660.8	331.4 ± 511.1	0.17
Transferrin saturation, %	27.3 ± 20.3	31.7 ± 29.1	26.1 ± 17	0.12
Physical Composite	35.5 ± 10	35.4 ± 11	35.5 ± 10	0.95
Mental Composite	50.0 ± 12	49.6 ± 11	50.0 ± 12	0.85
Handgrip strength, kg	26.5 ± 9.3	22.5 ± 7.1	28.1 ± 9.6	0.002

Conclusions: Prevalence of PEW in the studied population was lower compared to other series. PEW patients exhibit a state of overhydration which is given by increased ECW, and accompanied by loss of LTI and FTI. No PEW impact on QL was observed. PEW patients have increased anemia and higher requirements of EPO possibly associated to chronic inflammation.

FR-PO886

Efficacy of Nutrition Counseling on Protein Intake Restriction in Chronic Kidney Disease Patients – Niigata Part of SOFT-J (Study on Regional Variation of FROM-J Intervention by JSN) Ryohei Kaseda,¹ Michihiro Hosojima,¹ Toshiko Murayama,¹ Akihiko Saito,¹ Yoshiki Suzuki,¹ Kunihiro Yamagata,² Ichiei Narita.¹ ¹Niigata Univ, Japan; ²Tsukuba Univ, Japan.

Background: Low adherence is frequently observed in patients with chronic kidney disease (CKD) who are following a diet therapy. This study evaluated the efficacy of nutrition counseling focused on protein restriction for CKD patients in clinics by national registered dietician using iPad and textbook used in FROM-J (Frontier of Renal Outcome Modification in Japan) study, aiming at promoting relationship between home doctor and nephrologist.

Methods: 47 patients with CKD stage3 (eGFR 30-59 ml/min/1.73m²), age 40-85 were recruited. Nutrition counseling was conducted once for 30 min by national registered dieticians using iPad and textbooks in clinics without any dieticians in the staff. Optimal protein and energy intake were prescribed as 0.9 g/kg/day and 25-30 kcal/kg/day, respectively. The amount of protein intake was estimated from dietary records and by 24 hours urine collection before and 2 months after counseling (pre/post, respectively).

Results: All patients recorded their daily diets, 26/47 provided 24 hours urine collections. Counseling significantly decreased protein intake (record pre 1.10±0.23 g/kg/day post 1.00±0.26 p=0.001, urine pre 1.02±0.29 post 0.91±0.22 p=0.04). Although energy intake slightly decreased (record pre 31.9±6.4 kcal/kg/day post 30.1±5.2 p=0.03), this was not below the prescribed optimal calories. Salt intake decreased in recorded data but not in urine data (record pre 8.4±2.8 g/day post 7.6±2.7 p=0.03, urine pre 9.0±4.2 post 9.1±4.4 p=0.86, respectively). There was no significant difference in body mass index, eGFR, HbA1c (diabetic patients), LDL cholesterol, uric acid and blood pressure.

Conclusions: iPad and textbook counseling by dieticians is effective in reducing protein intake without compromising necessary caloric requirements, even in clinics without regular nephrologist or dietary staff. Informational technology may be an effective method of delivering on-demand nutritional counseling that can directly benefit patient care.

FR-PO887

Activin B Has a Functional Role in Hecpudin Induction by Inflammation Jodie L. Babbitt, Susanna Canali, Amanda B. Core, Maria Merkulova, Kimberly Zumbrennen-Bullough. *Nephrology Div, Program in Membrane Biology, Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.*

Background: Induction of the iron regulatory hormone hepcidin contributes to the anemia of chronic kidney disease by restricting iron availability. Bone morphogenetic protein 6 (BMP6) signaling is a central transcriptional regulator of hepcidin. Recently, the transforming growth factor-β (TGF-β)/BMP superfamily member Activin B was implicated in hepcidin induction by inflammation via noncanonical SMAD1/5/8 signaling, but its mechanism of action and functional significance *in vivo* remain uncertain.

Methods: Hep3B cells and primary hepatocytes were treated with Activin B, BMP6, or Activin A, without or with siRNA knockdown of Activin/BMP pathway components, and were tested for SMAD2/3 versus SMAD1/5/8 phosphorylation and hepcidin expression. Liver Activin B expression was measured and the effect of the Activin inhibitor follistatin-315 was examined in multiple rodent models of anemia of inflammation.

Results: Activin B, but not Activin A, stimulated SMAD1/5/8 signaling and hepcidin expression in liver cells to a similar degree as canonical SMAD2/3 signaling, and with similar potency and kinetics compared with BMP6. Activin B induced hepcidin via classical Activin type II receptors ACVR2A and ACVR2B, noncanonical BMP type I receptors ALK2 and ALK3, and SMAD5. The co-receptor hemojuvelin (HJV) bound directly to Activin B and facilitated Activin B-SMAD1/5/8 signaling. Activin B-SMAD1/5/8 signaling occurred selectively in hepatocyte-derived cells and was not enabled by HJV in other cell types. Liver Activin B mRNA expression was increased in multiple rodent models of inflammation associated with increased hepcidin and hypoferrremia. Follistatin-315 had no effect on basal hepcidin expression, but blunted hepcidin induction by inflammation in mice.

Conclusions: Our data elucidate a novel mechanism for noncanonical SMAD activation by BMP/TGF-β superfamily members, and support a functional role for Activin B in hepcidin induction by inflammation *in vivo*. Targeting the Activin B-hepcidin pathway may lead to new therapies for anemia of inflammation including the anemia of chronic kidney disease.

Funding: NIDDK Support

FR-PO888

Effects of a Very Low Protein Diet Supplemented with Amino and Keto Acids on Skeletal Muscle Protein Synthesis and Degradation in Patients with Chronic Kidney Disease Giacomo Garibotto,^{1,2} Antonella Sofia,² Valeria Cademartori,² Emanuele L. Parodi,² Francesca Ansaldo,² Daniela Verzola.¹ ¹DIMI, Nephrology Div Genoa Univ, Genoa, Italy; ²Dept Intern. Med., IRCCS AOU San Martino-IST, Genoa, Italy.

Background: Chronic kidney disease (CKD) is characterized by progressive loss of muscle mass, an effect which could be accelerated by low (LPD) and very low protein diets (VLPD), even if essential amino/keto analogue (AA/KA) supplements are used. However, to what extent skeletal muscle protein metabolism adapts to a supplemented VLPD in CKD patients is still unexplored.

Methods: To determine the muscle responses to a supplemented VLPD (0.45 g/kg+0.1 g/kg AA/KA, 35 kcal/Kg/day), as compared to a standard (0.55 g/kg, 35 kcal/Kg/day) LPD,

forearm [2H]phenylalanine kinetics were evaluated in six CKD patients(5M/2F, age 71±1 yrs, eGFR 11±1 ml/min) assigned to a LPD (4 weeks), followed by a 4- week supplemented VLPD period. Studies were performed after an overnight fast (post-absorptive state) and results express basal rates of protein turnover.

Results: After supplemented VLPD, as compared to a standard LPD: a) whole body protein turnover declined only slightly (0.51±2 vs. 0.55±2 μmol/min/kg, VLPD vs. LPD, p=NS); b) forearm protein net balance, i.e. the difference between protein synthesis and degradation, was less negative by 18% (from -11±3 to -9 ±2 nmol/min.100 ml, p<0.02); c) the efficiency by which amino acids are cycled back from protein degradation into protein synthesis increased by 15% (p<0.05); d) muscle protein degradation was unchanged (from 44±4 to 46±5 nmol/min.100 ml, p<0.02); e) Protein synthesis increased by 17% (from 33±1 to 38±4 nmol/min.100 ml, p<0.05).

Conclusions: Our data show that in patients with CKD stage 5 the response of muscle protein turnover to a AA/KA supplemented VLPD, as compared to a standard LPD, is characterized by similar reduced rates of protein degradation, but an increase in muscle protein synthesis, with enhanced recycling of amino acid derived from catabolism. Net protein balance is less negative, which suggests that the use of AA/KA supplemented VLPD may be nutritionally safer than a standard LPD.

Funding: Pharmaceutical Company Support - Fresenius-Kabi Ketosteril Award 2012, Government Support - Non-U.S.

FR-PO889

Risk of Anemia and Blood Transfusion following Reduction of Maximum ESA Doses Kelvin C.W. Leung, Robert R. Quinn, Braden J. Manns, Jennifer M. MacRae, Pietro Ravani. *Medicine, Univ of Calgary, Calgary, AB, Canada.*

Background: The cost of providing erythropoietin stimulating agents (ESAs) for renal patients is currently covered in the province of Alberta, Canada. Due to the high costs associated with therapy, the provincial funding agency reduced the maximum weekly ESA dose by 50%. We sought to determine the clinical impact of this policy change on the risk of severe anemia (hemoglobin [HGB] <90g/L) and transfusions.

Methods: All patients in the Southern Alberta Renal Program with a HGB >90g/L and receiving more than darbepoetin 75ug/wk or epoetin 15000 units/wk were reduced to an equivalent of darbepoetin 75ug/wk in September 2013. Serum HGB, iron stores, serum albumin, and parathyroid hormone assessed at baseline, 3 months, and at 6 months (end of study). Blood transfusion data was extracted from provincial electronic records. Patients were returned to a higher ESA dose when the HGB declined to ≤90g/L. We performed Kaplan-Meier analysis and multivariable regression analysis to calculate the median time to a drop in HGB level to ≤90g/L (primary outcome) and the receipt of blood transfusions (secondary outcome) following ESA dose reduction. ESA doses were re-established in people who reached the primary end-point.

Results: patients (mean age 61±16 years) met the inclusion criteria. The majority of patients were treated with hemodialysis (75%) and received darbepoetin (81%). The mean baseline darbepoetin dose (or equivalent for those treated with epoetin) was 110±28ug/week; mean baseline HGB was 106±12g/L. A HGB of ≤90g/L was reached in 50% of the cohort by 4.1 months (median 1.8 months, IQR 0.4-2.8 months). Blood transfusions occurred in 15% of the cohort during the study and 12% in preceding 3 months (p=0.77). In multivariate analysis, only higher baseline HGB levels were associated with reduced hazard of a drop in HGB to ≤90g/L. Baseline ESA dose, magnitude of ESA dose reduction, and baseline iron stores was not independently associated with our primary outcome.

Conclusions: HGB declines below 90 g/L in about four months following ESA dose reduction. The short-term risk of blood transfusion remains similar. The clinical and economic implications of this policy remain to be determined.

FR-PO890

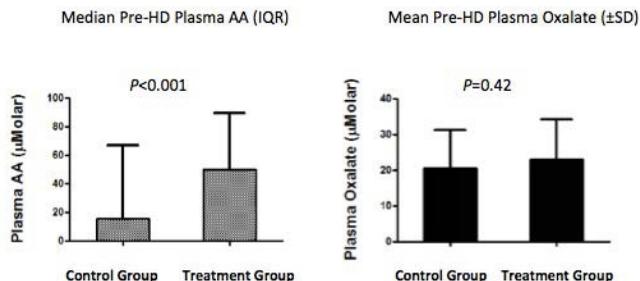
Association of Moderate Ascorbic Acid Supplementation with Plasma Ascorbic Acid and Oxalate Levels in Prevalent Hemodialysis Patients William D. Sirover,¹ Yuguan Liu,² Amanda Logan,³ Krystal Hunter,³ Craig B. Langman,⁴ Lawrence S. Weisberg,¹ Garry J. Handelman.² ¹Nephrology, Cooper Univ Healthcare, Camden, NJ; ²Nutrition, Univ of MA Lowell, Lowell, MA; ³Cooper Research Inst, Cooper Univ Healthcare, Camden, NJ; ⁴Nephrology, Northwestern Univ, Chicago, IL.

Background: Ascorbic acid (AA) supplementation may improve anemia in hemodialysis (HD) patients. Oxalate (Ox), an AA-metabolite, is excreted in the urine and is also removed during HD. When the plasma Ox concentration (plasma [Ox]) reaches 30 μM, Ox may deposit pathologically in organs. Moderate oral AA supplementation--up to 100 mg of AA/day--is often prescribed to HD patients. Of concern, patients who received earlier forms of HD could develop pre-HD Ox levels of 30 μM or higher when taking this degree of AA. We hypothesize that moderate AA use is not associated with an increase in pre-HD plasma [Ox] when patients receive high-flux HD.

Methods: In 2011, we surveyed outpatients on HD regarding AA supplement use. Pre-HD AA and Ox levels were measured. The treatment group consisted of patients who took up to 100 mg of oral AA/day. Patients who took no AA comprised the control group.

Results: There was no difference in pre-HD plasma [Ox] (mean±SD) between the treatment and the control groups, 21.9±10.1 μM vs. 20.6±10.6 μM, respectively (P=0.42). Median plasma AA concentration was 47.2 μM (IQR 24.6-83.6) in the treatment group and 15.8 μM (IQR 8.5-67) in the control group, (P<0.001).

	Treatment Group(N=132)	Control Group(N=54)	P-value
AA supplementation (number) 50-75 mg/day 100 mg/day	19 113	-- --	
Age(yrs)	61±15	61±17	0.98
spKt/V	1.76±0.27	1.73±0.31	0.50
Albumin(gm/dL)	3.9±0.3	3.9±0.4	0.38
BMI(kg/M ²)	28.6±7.8	28.4±8.1	0.90



Conclusions: These findings support the notion that moderate AA supplementation may be able to safely and effectively raise plasma AA levels.
Funding: Private Foundation Support

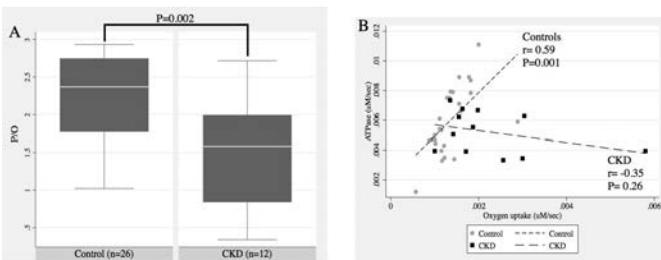
FR-PO891

Chronic Kidney Disease Is Associated with Altered Muscle Mitochondrial Energetics by Functional MR Spectroscopy and Optical Spectroscopy
Baback Roshanravan,¹ Bryan R. Kestenbaum,¹ Jorge Gamboa,² Jonathan Himmelfarb,¹ Ian H. De Boer,¹ Kevin Conley.¹ ¹Medicine, Kidney Research Inst - Univ Washington, Seattle, WA; ²Vanderbilt Univ, Nashville, TN.

Background: Exercise intolerance and muscle weakness are frequent clinical complications of CKD associated with adverse health outcomes, yet the pathophysiology underlying these conditions is poorly understood.

Methods: Cross-sectional study of *in vivo* muscle mitochondrial energetics using ³¹P Magnetic Resonance Spectroscopy and optical spectroscopy (MRS/OS) in 12 subjects with non-diabetic CKD (eGFR<60) and 26 controls. ³¹P MRS and OS were performed on the hand muscle under controlled ischemia. ATPflux (ATPase rate) was measured from phosphocreatine breakdown. Hemoglobin and myoglobin desaturation rates were assessed by OS to measure muscle oxygen uptake (O₂ uptake). The primary outcome was the coupling efficiency of mitochondrial oxidative phosphorylation ATP production (ATPflux) per unit of oxygen consumed (O₂ uptake) or P/O ratio. Grip strength and timed up and go were assessed. Pearson's correlation coefficient was calculated for univariable associations. We used multivariable linear regression adjusting for age.

Results: Mean age of CKD patients was 53±13yrs. Physical performance of the CKD group was no different from predicted normal values. Mean P/O values were 1.46±0.7 in the CKD group vs. 2.22±0.6 in the control group (age-adjusted P=0.002). The strongest correlates of P/O ratio age (ρ=0.42), followed by eGFR (ρ=0.32). In contrast to controls, patients with CKD had higher O₂ uptake (P=0.03) without concomitant change in ATPase rate.



Conclusions: Application of non-invasive tools reveals that CKD is associated with greater muscle O₂ uptake reflecting uncoupling of oxidative phosphorylation. These results suggest altered mitochondrial respiration in skeletal muscle of patients with CKD prior to dialysis.

Funding: NIDDK Support

FR-PO892

Improving Outcomes with Nutrition in Older People with Advanced Chronic Kidney Disease – Baseline Data from a Pilot Randomised Controlled Trial
Lina Johansson,¹ Mary Hickson,¹ Edwina A. Brown.² ¹Nutrition and Dietetics, Imperial College Healthcare NHS Trust, London, United Kingdom; ²Imperial Kidney and Transplant Centre, Imperial College Healthcare NHS Trust, London, United Kingdom.

Background: It is difficult to determine when to start dialysis in older people as creatinine and eGFR can be misleading. Dialysis start is often determined by weight loss, symptoms, potassium and fluid overload, all of which are potentially modifiable with nutrition. This pilot RCT aims to determine whether dietary interventions can result in improved patient outcomes, including time to dialysis, in older people with advanced chronic kidney disease (CKD).

Methods: Patients ≥65 years, with eGFR 10-20mls/min were randomised to an observational or intervention group (greater dietetic input). Data will be collected every 6 months for up to 2 years: nutritional status (Subjective Global Assessment), symptoms (Palliative Outcome Scale – Symptoms Renal), function (4 metre walk gait speed test and Jamar handgrip dynamometer) and fluid overload using Body Composition Monitor (Fresenius).

Results: 80 patients were recruited, baseline data presented. The 2 groups have statistically similar baseline demographic and clinical characteristics. Overall, 30% have malnutrition of which 58% are overweight/obese. 28% have nutritionally relevant potentially uraemic symptoms (nausea, vomiting and/or poor appetite). Fluid overload (>2L) was observed in 22% of those that were assessed (n=58).

Demographics	Control (n =40)	Intervention (n=40)
Male n (%)	27 (67.5)	26 (65.0)
Age years, mean (SD)	74.5 (6.8)	76.0 (7.4)
Diabetes n (%)	19 (47.5)	18 (45.0)
Biochemistry		
eGFR mls/min, mean (SD)	16 (4)	16 (3)
Potassium >5.5mmol/L %	10	5
Nutritional status and symptoms		
Subjective Global Assessment (SGA) malnourished %	38	23
Nausea, vomiting and/or poor appetite %	25	30
Physical function		
Gait speed <0.8m/sec, indicative of gait impairment %	45	48
Handgrip strength ≤20kg women or ≤ 30kg men, indicative of weakness %	50	58

Conclusions: There is a high prevalence of indications for dietetic interventions within older people with advanced CKD at baseline which may positively affect outcomes within two years.

Funding: Government Support - Non-U.S.

FR-PO893

Retention of Acetylcarnitine in Chronic Kidney Disease Causes Insulin Resistance in Skeletal Muscle
Yasunori Miyamoto,¹ Teruo Miyazaki,² Akira Honda,² Homare Shimohata,¹ Kouichi Hirayama,¹ Masaki Kobayashi.¹ ¹Nephrology, Tokyo Medical Univ Ibaraki Medical Center, Ami, Ibaraki, Japan; ²Joint Research Center, Tokyo Medical Univ Ibaraki Medical Center, Ami, Ibaraki, Japan.

Background: Insulin resistance occurs frequently in patients with chronic kidney disease (CKD) and ameliorates after introduction of hemodialysis (HD). However, the mechanisms of insulin resistance associated with CKD are unclear. An increased mitochondrial acetyl-CoA/CoA ratio causes insulin resistance in skeletal muscle, and this ratio is regulated by carnitine acetyltransferase (CAT), which transfers excess acetyl moieties to carnitine (CT). Because the resulting acetylcarnitine (AcCT) is excreted in urine, we hypothesized that retention of AcCT might be a cause of insulin resistance in patients with CKD.

Methods: Serum samples were collected from 64 patients with CKD (including 14 HD patients) and 31 control subjects who underwent a medical examination. CT and AcCT concentrations in sera were measured by HPLC-ESI-MS/MS. The effects of exogenous AcCT (0-300 μM) on insulin-dependent 2-deoxyglucose (2DG) uptake, mitochondrial CT and AcCT levels, and the mitochondrial acetyl-CoA/CoA ratio were examined in a cultured skeletal muscle cell line (C2C12 myotubes).

Results: The serum concentration of AcCT, but not that of CT, significantly increased with reduction of renal function, as classified by eGFR (stage E2 3.7 ± 0.6 μM, stage 3a 6.1 ± 1.1 μM, stage 3b 10.9 ± 1.9 μM, stage 4 16.3 ± 2.1 μM, stage 5 28.2 ± 5.9 μM, mean ± SEM). After introduction of HD, the increased AcCT levels were significantly reduced (pre 16.8±2.5 μM, post 6.3 ± 0.7 μM). In vitro experiments in skeletal muscle cell lines showed that uptake of 2DG was significantly and dose-dependently inhibited by addition

of AcCT. The added AcCT was converted to CT through the reverse reaction of CAT, and thus the acetyl-CoA concentration and acetyl-CoA/CoA ratio in mitochondria were significantly elevated.

Conclusions: The results suggest that increased AcCT in patients with CKD causes insulin resistance in skeletal muscle by stimulating the reverse reaction of CAT, which leads to accumulation of acetyl-CoA in mitochondria.

Funding: Government Support - Non-U.S.

FR-PO894

High Protein Intake in Relation to Incident End-Stage Renal Disease (ESRD) Among Blacks and Whites in the Southern Community Cohort Study (SCCS) Rakesh Malhotra, Edmond Kato Kabagambe, Kerri L. Cavanaugh, William J. Blot, Talat Alp Ikizler, Loren Lipworth. *Vanderbilt Univ Medical Center.*

Background: Dietary composition could contribute in part to observed racial disparities in ESRD incidence. Diabetes, a major risk factor for ESRD, may lead to differences in dietary intake and metabolism. We examined whether protein intake is associated with ESRD risk and whether the association varies by race and diabetes.

Methods: We conducted a nested case-control study of ESRD within the SCCS, a prospective study of low income blacks and whites in the southeastern US (2002-2009). Through 2012, 1,074 incident ESRD cases were ascertained by linkage with the USRDS, and matched to 3,230 controls on age, sex and race. A validated food frequency questionnaire was administered at baseline. Odds ratios (OR) and 95% confidence intervals (CI) for ESRD were computed in relation to protein intake, expressed as daily % of total energy intake and modeled in 1 standard deviation (SD) increments in unconditional logistic regression models stratified by race and diabetes. ORs were adjusted for age, sex, BMI, education, income, hypertension, total energy intake and % energy from saturated and polyunsaturated fat.

Results: Median daily % energy intakes from protein were higher among whites than blacks and those with vs without diabetes, but differences between ESRD cases and controls were small (15.9 and 15.7%, respectively, for blacks with diabetes, 14.6 and 14.6% for blacks without diabetes, 16.6 and 16.4% for whites with diabetes, and 15.1 and 15.1% for whites without diabetes). For a 1 SD (3.17%) increase in daily % energy intake from protein, adjusted ORs (95% CI) for ESRD were 1.18 (1.05-1.34) for blacks with diabetes, 1.06 (0.93-1.21) for blacks without diabetes, 0.89 (0.61-1.30) for whites with diabetes and 1.00 (0.74-1.33) for whites without diabetes.

Conclusions: Our results raise the possibility that among blacks with diabetes, a diet higher in protein is associated with increased incidence of ESRD. If confirmed, future studies might examine contributors leading to adverse outcomes associated with high protein intake in this subpopulation.

Funding: Other NIH Support - Grant R01 CA92447 from the National Cancer Institute (NCI), including American Recovery and Reinvestment Act funding (3R01 CA029447-08S1)

FR-PO895

Effects of Lanthanum Carbonate on Intestinal Bacterial Flora in Chronic Renal Failure Mice Minoru Satoh, Hiroyuki Kadoya, Seiji Itano, Atsushi Uchida, Yuji Sogawa, Hajime Nagasu, Tamaki Sasaki, Naoki Kashihara. *Dept of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.*

Background: The intestinal microbial flora consists of diverse bacterial species that inhabit the gastrointestinal tract. These bacteria are integral to the ontogeny and regulation of the immune system, and maintenance of intestinal homeostasis. In the chronic kidney diseases, changes of the intestinal bacterial flora have been reported, which contribute to nutritional disorder, systemic or local inflammation, and the uremic toxin production. Phosphate promotes a bacterial growth. So, by phosphate adsorption, intestinal bacterial flora may be changed. We examined whether phosphorus adsorption with lanthanum carbonate could change intestinal bacterial flora in renal failure mice.

Methods: We used 5 weeks old male ICR-derived glomerulonephritis (ICGN) mice (n=10) for renal failure group and ICR mice (n=10) for control group. Each group mice were fed with standard diet or diet supplemented with 3% lanthanum carbonate for 10 weeks. Gene expression patterns of a whole bacterial flora in the intestine were analyzed by terminal restriction fragment length polymorphism analysis method. Fecal bacteria products (phenol, para-cresol, indole and skatole) were examined by quantitative chemical analysis.

Results: The ratio of "bad" bacteria clostridia was increased, and the ratio of opportunistic pathogen bacteroides was decreased in intestinal bacterial flora of ICGN mice. By the lanthanum carbonate administration, the ratio of clostridium was decreased, and the ratio of beneficial bacterium lactobacilli was increased. Fecal bacteria products phenol and para-cresol were increased in feces of ICGN mouse, but indole was not changed. Skatole was not detected in feces of both mice. Among intestinal bacterial flora, the ratio of clostridium showed a positive correlation, and the ratio of bacteroides showed a negative correlation of phenol production.

Conclusions: The intestinal bacterial flora in chronic renal failure mice was changed by lanthanum carbonate administration. The change of the bacterial flora affected the fecal bacteria products, which may contribute the production of serum uremic toxin.

FR-PO896

High-Fat Diet Induces the Production of IKK ϵ by Macrophages to Promote Nephrotoxicity Xin Wan,¹ Binbin Pan,¹ Changchun Cao.¹ ¹Nanjing Hospital Affiliated to Nanjing Medical Univ (Nanjing First Hospital).

Background: The NF- κ B activation may participate in lipid nephrotoxicity which may be regulated by inhibitor kappa B kinase epsilon (IKK ϵ). To investigate the role of IKK ϵ in this procession, mice experiment was performed.

Methods: Mice were grouped: (1) wild-type with normal fat diet (WN), (2) wild-type with high fat diet (WH), (3) IKK ϵ knockout with normal fat diet (KN), (4) IKK ϵ knockout with high fat diet (KH). Renal function, lipid, histological changes and tubular proliferation were analysed. IL-1 β , TNF- β , p50 and p65 were determined by western blot. NF- κ B level was tested by EMSA. Expression of IKK ϵ was evaluated via immunohistochemistry and immunofluorescence.

Results: Cystatin C levels were significantly higher in WH group than others. Staining with hematoxylin-eosin revealed that tubular lesions in WH group (3.53 \pm 0.21) were more severe than in WN group (0.32 \pm 0.11). By Immunohistochemistry, WH group exhibited marked macrophages infiltration than WN, KN and KH groups. Western blot showed significant increase of IL-1 β , TNF- β and marked increment in the expression of NF- κ B pathway components consists of p50 and p65 in WH group, while these increases were blocked in KN and KH groups. Furthermore, NF- κ B level in WH group was higher than other groups. WH group exhibited remarkable macrophages infiltration than other groups by Immunofluorescence. Immunohistochemistry showed remarkable increases in the expression of IKK ϵ in the WH group compared with other groups. Immunofluorescence analysis demonstrated that the expression of IKK ϵ was located around macrophages.

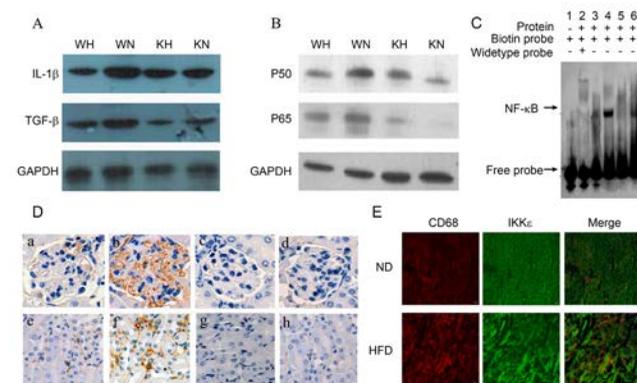


Figure 1A.

HFD induce inflammation and infiltration of macrophage.

Expression levels of IL-1 β and TNF- β were significantly increased in the WH group compared to the WN group of mice after normalization to GAPDH, which can be attenuated in KN or KH group.

Figure 1B.

Protein expression of NF- κ B cascade components determined by Western blotting.

Expression levels of P50 and P65 in kidney tissue, after normalization to GAPDH, were all significantly increased in the WH group compared to the WN group of mice, which can be decreased in KN and KH groups.

Figure 1C.

Activation of NF- κ B determined by EMSA.

NF- κ B activation in mice kidneys. Lane 1, labeled probe with no extract; lane 2, labeled probe with extract from WH group renal tissues plus 200-fold excess of unlabeled probe; lanes 3-6, NF- κ B activities in each group: lane 3, WN group mice; lane 4, WH group mice; lane 5, KN group mice; and lane 6, KH group mice.

Figure 1D.

Expression of IKK ϵ in tubulointerstitium and glomerulus of mice via immunohistochemical analysis after 24 weeks.

a, e: A small quantity of IKK ϵ expressed in glomerulus and interstitium in WN group; b, f: Tubulointerstitium and mesangial region of mice revealed obvious expression of IKK ϵ in WH group; c, g: No expression of IKK ϵ was found in KN group; d, h: No expression of IKK ϵ was found in KH group.

Figure 1E.

Immunofluorescence of IKK ϵ and macrophage in kidneys of WN and WH.

No obvious expression of IKK ϵ in WN, some macrophages were observed. Obvious expression of IKK ϵ was located around macrophage in interstitium and glomerulus in WH group.

Conclusions: IKK ϵ mediates lipid nephrotoxicity by HFD induced macrophages infiltration to activate NF- κ B signal pathway.

Funding: Government Support - Non-U.S.

FR-PO897

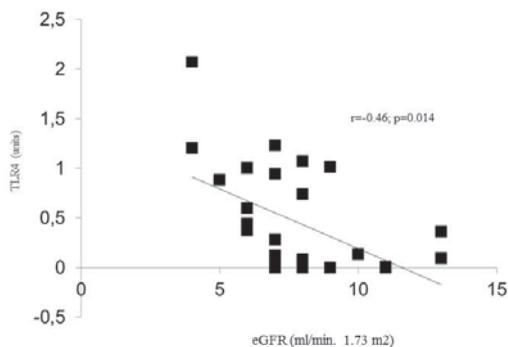
Clinical Determinants of Toll Like Receptor 4-Mediated Inflammatory Response in Skeletal Muscle of Patients with Chronic Kidney Disease Daniela Verzola,¹ Alice Bonanni,¹ Antonella Sofia,¹ Francesca Ansaldo,¹ Elisa Veziano,¹ Valeria Cademartori,¹ Emanuele L. Parodi,¹ Giuliano Brunori,² Chiara Venturelli,² Giacomo Garibotto.¹ ¹DIMI, Nephrology Div., Univ of Genoa, Genoa, Italy; ²Nephrology Div., Santa Chiara Hospital, Trento, Italy.

Background: Inflammation in skeletal muscle is implicated in the pathogenesis of insulin resistance and cachexia. We previously observed that the Toll-like receptor-4 (TLR4) dependent muscle signaling is upregulated in muscle of CKD subjects.

Methods: We studied the associations between muscle (*rectus abdominis*) TLR4 protein (western blot and immunohistochemistry) and gene (rt-PCR) expression and clinical parameters in 38 CKD stage 5 patients (23M/15F, eGFR 8 \pm 1 ml/min).

Results: CKD subjects had significantly elevated TLR4 gene expression and protein content in muscle (-4-fold increase vs. controls p<0.05). LogTLR4 protein content in

muscle was inversely related to Subjective Global Assessment (SGA) ($r=-0.410$, $p<0.03$), eGFR ($r=-0.46$; $p=0.014$), hemoglobin ($r=-0.380$, $p<0.05$) and directly related to cholesterol levels ($r=0.398$, $p<0.05$).



There was no relationship between muscle logTLR4 and age, BMI, muscle area, nPNA, calorie intake, albumin, CRP, BUN, bicarbonate, triglycerides, fibrinogen, and phosphate levels. At multivariate analysis SGA and eGFR only contributed significantly to the prediction of TLR4 expression in muscle ($p<0.003$).

Conclusions: Both low SGA score (which indicates an overall concept of nutritional status) and eGFR (an index of residual renal function) play an independent role to predict TLR4 content in muscle of CKD patients. TLR4 content in muscle rises progressively along with progressive decline of residual renal function, with a 2-fold increase in TLR4 as eGFR declines from 12 to 5 ml/min. Both wasting and progressive loss of residual renal function are predictive of muscle inflammation.

Funding: Government Support - Non-U.S.

FR-PO898

Randomized, Double-Blind, Crossover Clinical Trial on Oral Rice Endosperm Protein Supplementation to Patients on Maintenance Hemodialysis Michihiro Hosojima,¹ Hisaki Shimada,² Shigeru Miyazaki,² Yoshitsugu Obi,³ Hazuki Kondo,⁴ Mikio Fujii,⁴ Reiko Watanabe,⁵ Shoji Kuwahara,⁶ Ryohei Kaseda,¹ Ichiei Narita,⁷ Yoshiki Suzuki,⁸ Motoni Kadowaki,⁹ Akihiko Saito.⁶ ¹Dept of Clin Nutr Sci, Niigata Univ, Japan; ²Shinraku-en Hospital, Japan; ³Univ of California; ⁴Kameda Seika Co., Ltd., Japan; ⁵Univ of Niigata Prefecture, Japan; ⁶Dept of Appl Mol Med, Niigata Univ, Japan; ⁷Div of Clin Nephrol & Rheumatol, Niigata Univ, Japan; ⁸Health Admininstr Center Div, Niigata Univ, Japan; ⁹Faculty of Agriculture, Niigata Univ, Japan.

Background: Protein-energy wasting, a state of metabolic and nutritional derangements, is an important risk factor that affects outcomes of patients with CKD, particularly in ones with ESRD and on maintenance dialysis (MHD). Purified rice endosperm protein (REP) contains less phosphorus (150 mg/100g) compared with soybean (787 mg/100g) and casein (737 mg/100g) proteins, and may improve nutritional status without imposing further metabolic derangements.

Methods: We carried out a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effect of REP supplementation (5 g per day × 4 weeks) on nutritional and metabolic status in 50 MHD patients (UMIN000010876). The primary outcome was the change in urea kinetic-based normalized protein nitrogen appearance (nPNA), an indicator of protein intake in MHD patients. The inclusion criteria were: (1) nPNA < 1.2g/kg/day, (2) serum albumin concentration ≤ 3.8mg/dL, (3) body mass index ≥ 19 kg/m² and < 23 kg/m², (4) < 5% variation in dry weight during the period of preceding 6 months, and (5) duration of MHD ≥ 2 years.

Results: By intention-to-treat analyses, REP increased nPNA by 0.07 (95%CI, 0.03-0.11) g/kg/day compared with placebo, whereas Dserum phosphorus concentration was not significantly different between the groups [0.18 (95%CI, -0.23-0.58) mg/dL]. REP did not show significant effects on other nutritional parameters. Per-protocol analyses yielded similar results. There were no specific complications associated with the REP supplementation.

Conclusions: Purified REP may be useful for dietary supplementation in MHD patients. Further studies are warranted to evaluate its long-term or high-dose efficacy.

Funding: Government Support - Non-U.S.

FR-PO899

Association of Serum Phosphate Levels and Mortality Risk in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis Anawin Sanguankeo,^{1,2} Sikarin Upala.^{1,2} ¹Internal Medicine, Bassett Medical Center and Columbia Univ College of Physicians and Surgeons, Cooperstown, NY; ²Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.

Background: Abnormalities of serum phosphate are associated with increased risk for mortality in end stage renal disease (ESRD) or dialysis patients. Use of phosphate binders has shown to reduce risk of mortality in these population and is recommended in several

guidelines. However, there is still controversy on the management of serum phosphate in patients with chronic kidney disease (CKD). This meta-analysis evaluated the impact of serum phosphate on mortality in patients with CKD not requiring dialysis.

Methods: We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published RCT and prospective cohort studies assessing effects of high serum phosphate (compared to normal range) and a 1-mg/dL increase in phosphorus level in patients with CKD (eGFR < 60 ml/min/1.73 m²). We excluded ESRD, dialysis, or renal transplant patients. The primary outcome was risk of all-cause mortality. We used hazard ratio (HR) or risk ratio (RR) in the multivariate model as an effect estimate.

Results: From 15 full-text articles, five studies involving 6,536 patients were included in the meta-analysis. All were prospective cohort studies of CKD stage 3 or 4 patients. There was an increase all-cause mortality risk in higher phosphorus levels (HR = 1.36, 95% CI: 1.24 to 1.0, $p<0.01$, $I^2=0\%$) compared with normal phosphorus levels. A 1-mg/dL (0.1 mmol/L) elevation in serum phosphate also increases mortality risk with HR=1.23 (95% CI: 1.14-1.34, $p<0.01$, $I^2=0\%$).

Conclusions: Elevated serum phosphate levels were independently associated with increased mortality risk among patients with CKD. Randomized controlled trials are needed to assess the benefits of using phosphate lowering therapy in patients with CKD before developing ESRD or dialysis.

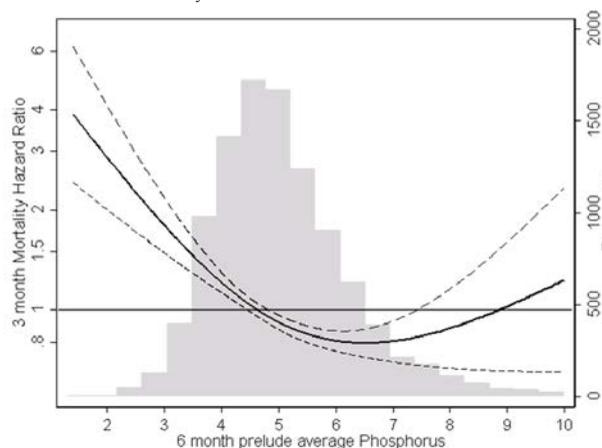
FR-PO900

Serum Phosphorous Levels prior to Transition to Dialysis and Early Dialysis Mortality Among U.S. Veterans: A Transition of Care in CKD Study Amanda R. Tortorici,¹ Yoshitsugu Obi,¹ Melissa Soohoo,¹ Connie Rhee,¹ Elani Streja,¹ Jennie Jing,¹ Rajiv Saran,² Bruce M. Robinson,² Yi Li,² Danh V. Nguyen,¹ Keith C. Norris,³ Csaba P. Kovacs,⁴ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UM-KECC; ³UCLA; ⁴UTHSC.

Background: Previous studies have shown that higher phosphorous (Phos) levels were monotonically associated with higher risk of death in patients with chronic kidney disease and end-stage renal disease (ESRD). However, the impact of pre-ESRD Phos levels on early post-ESRD mortality is not known.

Methods: In US veterans who transitioned to dialysis between 10/2007 and 9/2011, we identified 10,724 patients with available Phos measurements within the last 6 month prelude period (prior to transition). We examined the association of Phos (averaged over 6 months) as a continuous predictor of all-cause mortality within the first 3 months post transition, using restricted cubic spline analysis and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region of residence.

Results: The mean±SD age of the cohort was 66±11 years, among whom 34% were African-American, 8% were Hispanic, and 52% had diabetes listed as their primary cause of ESRD. We observed a reverse J-shaped association between pre-ESRD Phos and 3-month post-ESRD mortality risk. Patients with Phos levels < 4.7 mg/dL had a higher risk of mortality, and patients with Phos levels > 9.0 mg/dL trended towards a higher risk of mortality as well. However, patients with Phos levels between 4.7 and 7.2 mg/dL demonstrated lower mortality risk.



Conclusions: Among veterans transitioning to dialysis, both lower and higher Phos levels were associated with higher risk of early post-ESRD mortality, while patients with Phos levels between 4.7 to 7.2 mg/dL had the lowest risk of mortality. Further studies are needed to determine if using dietary and medication interventions to attain this Phos range confers higher survival in this population.

Funding: NIDDK Support

FR-PO901

The Comparison of Serum Calcium, Phosphorus and Intact Parathyroid Hormone Between Peritoneal Dialysis Patients and Hemodialysis Patients

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Background: In this study, we compared the serum calcium, phosphorus and intact parathyroid hormone between peritoneal dialysis patients and hemodialysis patients to study the difference in MBD biochemical variables between PD and HD.

Methods: 507 patients were enrolled from July 1, 2014 to December 31, 2014, including 148 patients received peritoneal dialysis and 359 patients received hemodialysis patients (HD) more than 3 months. Basic clinical information, data of dialysis, serum calcium, phosphorus and iPTH levels were collected in all patients, and comparative analysis was carried out based on those information.

Results: The age and the dialysis vintage was significantly higher in HD group than in the PD group (P<0.001). Serum phosphorus was lower, percentage of phosphorus in target was higher and percentage of calcium in target was lower (P=0.271) in PD group than in HD group (P<0.001). The serum phosphorus levels of PD patients with peritoneal high transport characteristics or high average transport were much lower than those with low transport or low average transport (P=0.0167). The levels of serum phosphorus (P<0.001), iPTH (P=0.0167) and alkaline phosphatase (P<0.001) were much lower in patients with RRF²2ml/min than those with RRF<2ml/min. The levels of serum calcium (P<0.01), corrected calcium (P<0.01), phosphorus (P=0.025), iPTH (P<0.001) and alkaline phosphatase (P<0.01) were much lower in patients with urine volume ³100ml/d than those <100ml/d. There was a negative correlation between RRF and serum phosphorus (r=-0.291, P<0.001) and iPTH (r=-0.271, <0.01) in PD group. The weekly total KT/V (r=-0.201, P=0.019) and weekly total creatinine clearance (Cr) (r=-0.407, P<0.001) negatively related to serum phosphorus. The Cr (r=-0.241, P<0.01) negatively correlated with serum iPTH.

Conclusions: The serum levels of phosphorus is lower and the percentage of achieving target of serum phosphorus is higher in PD patients than HD patients. The peritoneal high transport characteristics, RRF²2ml/min, urine volume ³100ml/d and the nutrition status have obvious influence on the serum phosphorus and iPTH levels in PD patients.

FR-PO902

Increased Risk of Cerebral Hemorrhage in Hemodialysis Patients with Hyperphosphatemia: The Q-Cohort Study

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Background: Mounting evidences have shown that hyperphosphatemia, an established component of CKD-MBD, accelerates cardiovascular disorders in dialysis patients. However, previous studies did not separately determine the effects of hyperphosphatemia on the onset of cerebrovascular disorders and cardiovascular disorders in dialysis patients.

Methods: The present study is an observational study consisting of 3431 outpatients undergoing hemodialysis. The associations between the baseline serum phosphate (Pi) level and the onset of cerebral bleeding and infarction were examined. Independent variable was serum Pi level. Dependent variable was the onset of cerebral hemorrhage and infarction. Age, sex, diabetes mellitus, history of cardiovascular events, dialysis vintage, Kt/V for urea, systolic blood pressure, hemoglobin, serum levels of calcium, parathyroid hormone, albumin, alkaline phosphatase, creatinine, and C-reactive protein, and use of vitamin D and Pi-binder were used as covariates. Cox proportional hazard model was used for analyses. All statistical analysis was conducted by JMP11.2 (SAS institute).

Results: The mean age of the examined population was 63.7±12.8 years, female was 41%, and the proportion of diabetes mellitus was 29%. Mean serum levels of calcium, Pi, and intact parathyroid hormone were 9.41±0.76 mg/dL, 4.92±1.2 mg/dL, 168±210 pg/mL, respectively. During the mean observational period of 3.1 years, 77 patients newly developed brain hemorrhage and 140 developed brain infarction. Hyperphosphatemia (Pi≥6 mg/dL) did not increase the risk of brain infarction, but increased the risk of brain hemorrhage by 2.2 fold, compared with the target Pi range (3.5≤Pi<6.0 mg/dL), even after adjustment for the potential confounders.

Conclusions: Hyperphosphatemia is closely associated with the onset of cerebral hemorrhage but not with cerebral infarction. Our results highlight the importance of Pi management in the prevention of cerebral hemorrhage in dialysis patients.

Funding: Private Foundation Support

FR-PO903

Development and Evaluation of Novel Correction Equations for Serum Calcium Concentrations in Hemodialysis Patients

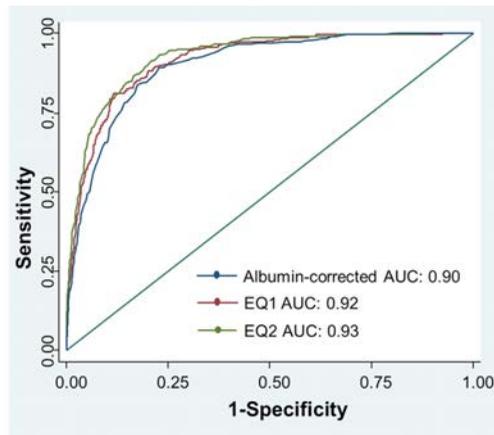
Yoshitsugu Obi,¹ Wei Ling Lau,¹ Elani Streja,¹ Connie Rhee,¹ Steven M. Brunelli,² Csaba P. Kovessy,³ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²DaVita Clinical Research; ³UTHSC.

Background: Ionized calcium (iCa), but not total calcium (tCa), is the physiologically relevant component of blood calcium. However, these measurements correlate poorly in hemodialysis patients even after correction for serum albumin, which may be partly explained by electrolyte and acid-base derangements in this population.

Methods: In 1,366 patients who initiated conventional HD over four years (1/2007-12/2010), we identified 6,830 iCa measurements where serum albumin, tCa, sodium, chloride, phosphorus, and bicarbonate were measured simultaneously. We randomly divided patients into a derivation set (n=681) or a validation set (n=685) to develop and

evaluate new correction equations for serum tCa concentrations by comparing correlation r and Bayesian information criterion (BIC) in linear regression analysis as well as receiver operating characteristic (ROC) curves for hypercalcemia determined by iCa (≥5.28 mg/dL).

Results: Albumin was associated with iCa, but its coefficient was -0.15, not -0.8 as shown in the conventional correction equation. Furthermore, albumin-corrected tCa showed lower correlation than uncorrected tCa with iCa (r=0.69 and 0.76, respectively). Two equations were developed from the derivation set as follows: [EQ1] 1.1*tCa - 0.12*(phosphorus + 1) and [EQ2] 1.1*tCa - 0.08*(anion gap - 2). In the validation set, EQ1 and EQ2, compared to the conventional correction by albumin, showed better correlation with iCa (r=0.78 and 0.80, respectively), lower BIC (96% and 92%, respectively), and higher area under the ROC curve for iCa-defined hypercalcemia (P<0.01 for both).



Conclusions: Novel correction equations for tCa show better association with iCa and hypercalcemia evaluated by iCa. Its clinical usefulness needs to be evaluated in further studies.

Funding: NIDDK Support

FR-PO904

Relationship Between Dietary Phosphorus Intake and Protein and Energy Intakes in Hemodialysis Patients

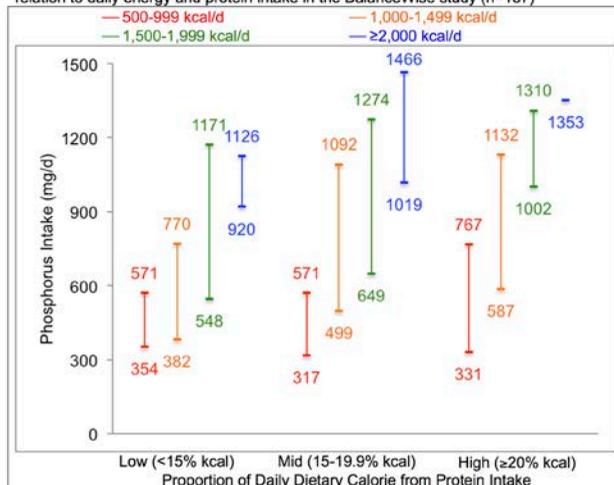
David E. St-Jules,¹ David S. Goldfarb,^{2,3} Mary Lou Pompeii,¹ Kathleen Woolf,⁴ Kamyar Kalantar-Zadeh,⁵ Mary A. Sevick.¹ ¹NYU School of Medicine; ²NY Harbor VA Medical Center; ³NYU Langone Medical Center; ⁴NYU Steinhardt; ⁵UCLA School of Public Health.

Background: Excess dietary phosphorus may contribute to mineral and bone disorders in hemodialysis (HD) patients. However, many high phosphorus foods are also important sources of dietary protein, which raises concerns that phosphorus restriction may compromise protein status.

Methods: We conducted a cross-sectional study of 190 African American and white men and women on intermittent HD for >3 months. Dietary data were collected by three 24-hour recalls, which were analyzed using NDSR®. Only participants who completed all three recalls and reported intakes >500 kcal/d were included (n=137).

Results: Dietary phosphorus and protein were highly correlated (R²=0.73). Based on linear regression, a 1,000 mg/d phosphorus restriction would provide about 78 g protein/d (or 1.1 g protein/kg/d for a 70-kg person). When adjusting for energy intake, the association of dietary phosphorus and protein was far less apparent (R²=0.42). Further, the highest phosphorus intake was about two times greater than the lowest phosphorus intake for each energy and protein intake level (500 kcal and 5% of kcal increments), reaching 600 mg/d for some groups.

Figure 1. Ranges in reported dietary phosphorus intake of hemodialysis patients in relation to daily energy and protein intake in the BalanceWise study (n=137)



Conclusions: Although dietary phosphorus and protein are highly correlated, this relationship appears to be driven in part by the amount of Calories consumed. Moreover, phosphorus intake ranges widely within energy and protein intake increments, suggesting that reductions in dietary phosphorus may be achieved in many HD patients without compromising the protein status.

Funding: NIDDK Support, Other NIH Support - NIH/NINR/R01-NR010135, NIH/NINR/NIDDK/NHLBI/NIA- K24-NR012226, NIH/NIA/R01-AG027017, NIH/NIA/P30-AG024827, NIH/NIA/K07-AG033174

FR-PO905

Assessment of Barriers to Phosphorus Control in Dialysis Patients Rashmi Bisla, Jasmin Sandhu, Vinod K. Bansal, Stephanie Kliethermes, Anuradha Wadhwa. *Loyola Univ Medical Center, Maywood, IL.*

Background: High phosphorus levels are associated with increased cardiovascular and all-cause mortality but Phosphorus control continues to be a challenge amongst dialysis patients. In this study, we conducted a survey to assess phosphorus control and identify barriers to phosphorus control in patients receiving dialysis at Loyola outpatient dialysis unit.

Methods: The study consisted of 17 question survey evaluating patients knowledge and understanding of phosphorus control, self care practices and social support as potential barriers to phosphorus control. Patients were approached during dialysis to participate. Objective patient data and laboratory data was collected from electronic medical records. Study was approved by Loyola IRB.

Results: Of the 99 eligible subjects, 57 completed the survey. Mean age of the participants was 62 years, 52% were males and 75% were African Americans. Patients were categorized into uncontrolled (phosphorus >= 5.5 mg/dL) and controlled phosphorus group. The two groups had similar demographics, co-morbidities, dialysis adequacy and medication pill burden. Approximately 80% of patients with uncontrolled phosphorus were aware of normal phosphorus levels in dialysis patients, complications associated with high phosphorus and identified majority of foods with high phosphorus compared to 53%, 43% and 57% in the controlled phosphorus group, respectively. Patients with uncontrolled phosphorus frequently identified cheating on diet and missed medication dose as reasons for lack of phosphorus control. There was no difference among the two groups relative to social support or self-care practices. 75% patient in controlled and 55% in uncontrolled group were interested in learning more about phosphorus control.

Conclusions: Patients with uncontrolled phosphorus had significantly greater knowledge and understanding of phosphorus control. While continued education of patients regarding phosphorus control is important, qualitative research to study patients' behavioral aspects is needed to better understand barriers to phosphorus control.

FR-PO906

Use of a Simple, Widely Available Laboratory Test to Quantify and Explain Variation in Phosphorus Levels in Beverages Elizabeth J. Lindley,¹ David Francis Keane,¹ Tracey Ying,² John W. MacD. Agar,² Gunnar H. Heine,³ Juergen Geisel.³ ¹Leeds Teaching Hospitals NHS Trust, United Kingdom; ²Geelong Hospital, Australia; ³Saarland Univ Medical Centre, Germany.

Background: Restriction of dietary phosphorus (P) is essential in the management of hyperphosphataemia in CKD. Beers and wines contain inorganic P that is readily absorbed but data on these beverages, and less well-known soft drinks, is difficult to obtain. An assay used routinely in hospital laboratories has been validated for measurement of P in a range of beverages (Lindley, J Ren Nutr 2014) enabling renal unit staff to compile information on locally sourced products and investigate variation between brands.

Methods: Beverages were processed as if they were urine samples and tested using the standard phosphomolybdate assay. 12 beers popular in the German Saarland were tested to find out if lower P brands could be identified. 10 wines from a micro-winery in New South Wales containing little or no di-ammonium phosphate (DAP, a widely-used yeast nutrient) were compared with 8 Australian wines from UK supermarkets. Classic Coca-Cola, which is strictly regulated world-wide, was used to check agreement between analysers in different countries.

Results: The P content of alcoholic beers in the Saarland selection varied from 12 to 27 mg/dL. There was no association between P and alcohol level. P levels in the non-alcoholic beers tested to date were 9 and 18 mg/dL. DAP-free white wines contained 6 to 8 mg/dL P, while reds contained 14 to 20 mg/dL. DAP increased the P level by about 2 mg/dL for every 100 mg/L added to the wine must. Much higher P levels in the supermarket wines (up to 31 mg/dL) suggest routine addition of 500 to 700 mg/L DAP.

Conclusions: Phytic acid in cereal grains and grape pips provides P for the seedlings. Inorganic P is released from this indigestible molecule by the enzyme phytase during malting (sprouting) and fermentation. Biological variation, differences in production that affect the breakdown of phytic acid and addition of DAP contribute to the wide range of P content in beer and wines. Until appropriate labelling becomes mandatory, tables of measured P content by brand could help patients trying to restrict their P intake.

Funding: Government Support - Non-U.S.

FR-PO907

Recruitment and Retention to a Randomised Trial of Low versus High Serum Phosphate Levels in Hemodialysis Patients Ramya Bhargava,¹ Paul E. Brenchley,¹ Philip A. Kalra,² Alastair J. Hutchison.¹ ¹Manchester Royal Infirmary, United Kingdom; ²Salford Royal Hospital, United Kingdom.

Background: High phosphate is linked with increased mortality in dialysis patients in retrospective observational studies but cause and effect is unproven. A large scale RCT of high versus low serum phosphate would be required to determine whether serum phosphate reduction improves length or quality of life of dialysis patients. We performed a feasibility study to investigate whether such a large scale RCT might be possible in the future.

Methods: After consent, 104 HD patients were randomized to low (2.5-4.4 mg/dL) or high phosphate (5.6-7.5 mg/dL) groups. Non-calcium binders, and an adherence self-help program were used to titrate to target PO₄ over 8 weeks. A 10 month maintenance period followed. Primary endpoint; % patient months within target range over 10 months. Secondary end points: % nephrologists agreeing to enrol patients, % eligible patients willing to participate, drop-out rate over 12 months, pill burden per subject.

Results: 768 HD patients were screened, 263 suitable, 202 approached, 128 consented, and 104 randomised (13.5% of screened). 21 of 24 nephrologists (87.5%) agreed to enrol patients after assessing the protocol.

	High PO ₄	Low PO ₄
Randomised N	51	53
Completed follow-up N, (%)	31 (60.8)	38 (71.7)
Premature trial exit N, (%)	20 (39.2)	15 (28.3)
Transplanted N, (%)	4 (7.8)	1 (1.9)
Deceased N, (%)	8 (15.7)	2 (3.8)
Withdrew consent N, (%)	4 (7.8)	8 (15.1)
Withdrawn by investigator N	4 (7.8)	1 (1.9)
% pt mths within PO ₄ range	49.5	35.7

Conclusions: Less than 50% of PO₄ levels were within target range over 10 months, and this will be analyzed as time-averaged results. More patients withdrew consent in the low PO₄ group, with GI side-effects plus high pill burden being possible contributory factors. 65% patients completed the study with a drop-out rate of 35%. Drop-out due to death was substantially greater in the high PO₄ group, but randomization was not stratified for other risk factors, and the overall mortality rate of 10% is lower than the expected dialysis rate of 13-17% per annum.

Funding: Pharmaceutical Company Support - Shire pharmaceuticals provided an unrestricted educational grant towards the salary of the research fellow for 12 months., Government Support - Non-U.S.

FR-PO908

Randomization to High or Low Phosphate Control in Hemodialysis: Is Such a Study Feasible? Ramya Bhargava,¹ Paul E. Brenchley,¹ Philip A. Kalra,² Alastair J. Hutchison.¹ ¹Manchester Royal Infirmary, United Kingdom; ²Salford Royal Hospital, United Kingdom.

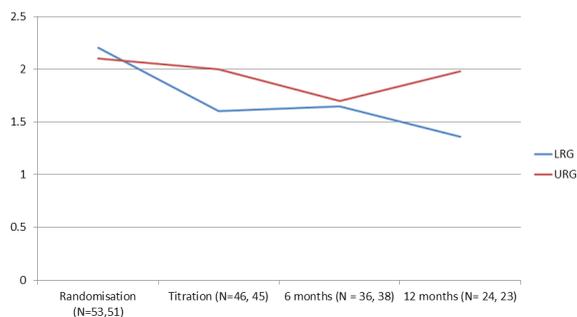
Background: High phosphate is linked with increased mortality in dialysis patients in retrospective observational studies but cause and effect is unproven. A large scale RCT of high versus low serum phosphate would be required to determine whether serum phosphate reduction improves length or quality of life of dialysis patients. We performed a feasibility study to investigate whether such a large scale RCT might be possible in the future.

Methods: From a pool of 768 HD patients, 104 were suitable and consented to a binder washout period, and were randomized to low phosphate (2.5 to 4.4 mg/dL) or high phosphate (5.6 to 7.5 mg/dL) groups. Subjects were titrated to target over 8 weeks with lanthanum or sevelamer binders only, then followed for 10 months. The pill burden in each group and secondary hyperparathyroidism were assessed. Serum albumin as a measure of nutritional status was recorded.

Results:

	HRG	LRG	P value
Number randomised	51	53	
Randomisation PO ₄ (mg/dL)	2.1 +/- 0.1	2.2 +/- 0.1	
Week 8 PO ₄ (mg/dL)	2.0 +/- 0.4	1.6 +/- 0.4	<0.05
Randomization PTH(pg/ml)	436 +/- 62	424 +/- 54	
Week 8 PTH(pg/ml)	362 +/- 258	472 +/- 380	
Randomization Albumin(g/L)	32 +/- 0.8	32 +/- 0.8	
Week 8 Albumin(g/L)	34 +/- 0.6	34 +/- 0.7	
Week 8 Pill burden	6 (2,15)	1.5 (0,9)	<0.05
Mortality	8	2	

Serum phosphate in the two groups



Conclusions: 1. Statistically significant separation in serum phosphate was achieved between the two groups (fig 1) with no apparent increase in secondary hyperparathyroidism. 3 patients in the HRG commenced Cinacalcet during the course of the study because serum PTH > 1200mg/dL. 2. As expected, LRG had a significantly larger pill burden than the HRG, with 20 patients in the LRG taking 9 or more binder pills. 3. Despite increased pill burden, albumin levels were not different between groups. 4. Crude mortality 4 times higher in the HRG.

Funding: Pharmaceutical Company Support - Shire pharmaceuticals provided an unrestricted educational grant towards the research fellow's salary for 12 months., Government Support - Non-U.S.

FR-PO909

Efficacy and Safety of PT20: A Novel Iron-Based Phosphate Binder Geoffrey A. Block,¹ George G. Hon,² Nuno Faria,³ Jonathan Powell,³ ¹Denver Nephrologists PC, Denver, CO; ²Kidney Wellness Center, Long Beach, CA; ³Human Nutrition Research, Medical Research Council, Cambridge, United Kingdom.

Background: PT20, a novel iron based phosphate binder (P-binder), has been specifically engineered with adipic acid substitution to improve phosphate binding capacity and affinity of ferric oxides. PT20 has shown high binding affinity for phosphate in preclinical studies.

Methods: Patients were on hemodialysis with serum phosphate (P) levels between 4.0 and 8.0mg/dL plus serum ferritin levels <1000 ng/mL at their screening visit. All patients were then washed out of previous P-binders and required to have an increase in serum P of at least 1.0 mg/dL to enter study. 153 subjects were randomized to either 400mg, 800mg, 1600mg, 3200mg PT20 or placebo, each taken TID with meals for 28 days. Doses were not modified during the treatment period. Primary end point was change in serum P from Baseline to Day 29. Secondary endpoints assessed safety as well as haematological parameters.

Results: PT20 treatment significantly reduced serum P levels and demonstrated a dose response effect (ITT population; p<0.001). All dose groups showed a reduction in mean serum P levels greater than placebo. Mean reduction in P over the 28 days was (mg/dL) 1.36 / 3200mg; 1.29 / 1600mg; 0.59 / 800mg; 0.40 / 400mg and 0.17 / Placebo dose. Limited iron absorption from PT20 was observed across all groups. Adverse events (AE) were mostly GI in nature but generally uncommon and not dose related (diarrhoea (15 and 6%; P binder average and placebo); discoloured faeces (10 and 0 %); Vomiting (4 and 0 %); nausea (4 and 0%); constipation (1 and 11 %)). 12 patients' experienced serious adverse events that were not considered related to PT20.

Conclusions: Use of adipate-modified iron oxide (PT20) resulted in a statistically significant and dose-dependent reduction in serum phosphate over a 28 day period. The safety profile and tolerability were acceptable with AEs being mostly GI in nature, with no pattern of serious adverse events related to treatment. Limited iron absorption from PT20 was observed.

Funding: Pharmaceutical Company Support - Phosphate Therapeutics Ltd

FR-PO910

Phase III Study to Investigate the Efficacy, Safety, and Tolerability of PA21 (Sacroferric Oxyhydroxide) Compared with Sevelamer Hydrochloride in Japanese Hemodialysis Patients with Hyperphosphatemia Fumihiko Koikiwa,¹ Masafumi Fukagawa,² Keitaro Yokoyama,³ Tadao Akizawa,⁴ Akira Terao.⁵ ¹Div of Nephrology, Dept of Medicine, Showa Univ Fujigaoka Hospital, Yokohama, Japan; ²Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; ³Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; ⁴Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan; ⁵Biostatistics, Faculty of Pharmaceutical Sciences, Josai Univ, Sakado, Japan.

Background: An open-label, randomized, parallel-group, multicenter, active-controlled phase III study was performed to assess the efficacy, safety, and tolerability of the non-calcium, iron-based phosphate binder PA21 (sacroferric oxyhydroxide: SFOH) vs sevelamer hydrochloride (SEV) in Japanese hemodialysis (HD) patients with hyperphosphatemia.

Methods: In total, 213 patients were randomized to SFOH (750–3000 mg/day; starting dose 750 mg/day; 250 mg tablets; n=108) and SEV (3–9 g/day; starting dose 3 g/day or 6 g/day; 250 mg tablets; n=105) for 12 weeks. Doses were titrated during Weeks 2–8 to reach predefined serum phosphorus (sP) concentrations of 3.5–6.0 mg/dL, but were unchanged during Weeks 8–12.

Results: Mean sP concentrations at the last evaluation were 5.00 mg/dL for SFOH vs 5.34 mg/dL for SEV (between-group difference: -0.34 mg/dL). Moreover, the value was significantly lower in the SFOH compared to the SEV (an analysis of covariance with sP concentrations at Week 0 as a covariate, P = 0.02). The average number of tablets was 4.8 tablets/day for SFOH vs 17.6 tablets/day for SEV.

Conclusions: Study met the non-inferiority primary end point. SFOH showed even a larger serum phosphorus reduction in Japanese HD patients, compared with SEV (p=0.02), and was associated with a lower pill burden and good tolerability.

Funding: Pharmaceutical Company Support - Kissey Co, Ltd

FR-PO911

Phase III Study to Investigate the Long-Term Efficacy, Safety, and Tolerability of PA21 (Sacroferric Oxyhydroxide) in Japanese Hemodialysis Patients with Hyperphosphatemia Fumihiko Koikiwa,¹ Masafumi Fukagawa,² Keitaro Yokoyama,³ Tadao Akizawa.⁴ ¹Div of Nephrology, Dept of Medicine, Showa Univ Fujigaoka Hospital, Yokohama, Japan; ²Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; ³Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; ⁴Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan.

Background: An open-label, multicenter study was performed to assess the long-term efficacy, safety, and tolerability of the non-calcium, iron-based phosphate binder PA21 (sacroferric oxyhydroxide: SFOH) after 52-weeks of treatment in Japanese hemodialysis (HD) patients with hyperphosphatemia.

Methods: In total, 161 patients were treated with SFOH (750–3000 mg/day; starting dose 750 mg/day; available as 250 mg and 500 mg tablets). SFOH was administered at Week 0, after treatment with any prior phosphate binders had been discontinued. Doses of SFOH were titrated to maintain predefined serum phosphorus (sP) concentrations of 3.5–6.0 mg/dL.

Results: Mean sP concentrations decreased from 5.46 mg/dL at Week 0 to 5.00 mg/dL at the last evaluation. Mean sP concentrations were maintained within the target range of 3.5–6.0 mg/dL throughout the 52-weeks treatment period. The average number of SFOH tablets was 3.3 tablets/day, and the average dose of SFOH was 1,141 mg/day. Overall, the incidence of adverse events and adverse drug reactions was 94.4% and 32.9%, respectively. Frequently observed adverse drug reactions were diarrhea (22.4%) and constipation (2.5%); no severe diarrhea or constipation was reported. Despite slight increases in serum ferritin and transferrin saturation, no clinical signs of iron accumulation or overload were observed at 52 weeks.

Conclusions: SFOH demonstrated a sustained sP-lowering effect 52-weeks of treatment in Japanese HD patients, and was associated with a low pill burden and good tolerability.

Funding: Pharmaceutical Company Support - Kissey pharmaceutical Co, Ltd

FR-PO912

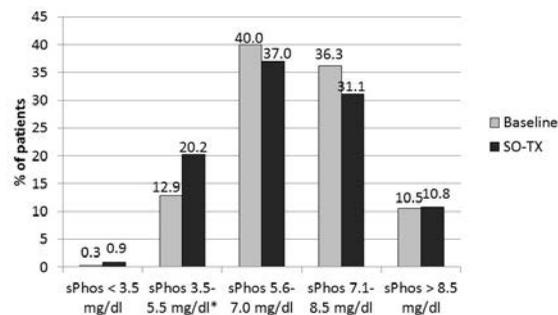
Improved Serum Phosphorus Control and Decreased Phosphate Binder Pill Burden Amongst African American Hemodialysis Patients Taking Sacroferric Oxyhydroxide Linda H. Ficociello, Lin Ma, Vidhya Parameswaran, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. Fresenius Medical Care North America (FMCNA), Waltham, MA.

Background: A retrospective database study was conducted on the real-world effectiveness of sacroferric oxyhydroxide (SO) in controlling serum phosphorus (sPhos) among hemodialysis (HD) patients (pts). This analysis focuses on the subset of patients who self-reported race as Black or African American.

Methods: All patients were prescribed SO as part of standard care at FMCNA clinics and had ³¹P sPhos measured during SO use. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and phosphate binder pills per day (PPD) were assessed 3-months before (baseline; BL) and 3-months during SO treatment (SO-TX).

Results: On average, pts (n=1015) were 51 years old with a dialysis vintage of 5.2 years and hyperphosphatemia (BL sPhos= 6.93 mg/dl). BL phosphate binder used were: sevelamer (52.1%), calcium acetate (26.3%), calcium carbonate (4.7%), lanthanum (7.2%), dual PB therapy (4.1%) and no PB specified (5.5%). As shown in Figure, pts in-range for sPhos increased from 12.9 to 20.2% (57%, p<0.001). Significant decreases in mean sPhos (6.93 to 6.73 mg/dl) and PPD (8.5 to 3.7 pills) were observed (p<0.001 for both). There was minimal change in sCa (9.3 to 9.27 mg/dl, p=0.05) or iPTH (685.3 to 700.9 pg/ml, p=0.15). Iron indices increased (FER: 1010.7 to 1076.3 ng/ml, p<0.001; TSAT: 33.6 to 34.8%, p<0.001). In pts not receiving IV iron, changes in TSAT (35.1 to 34.2%) and FER (1245.1 to 1193.6 ng/ml) were not significant.

Distribution of sPhos during baseline compared to sucroferic oxyhydroxide (SO)-treated follow-up for African American HD patients (N=1015)



*Change in %in-range and %out of range baseline compared to SO-treated follow-up, p<0.001

Conclusions: In a cohort of African American hemodialysis patients prescribed sucroferic oxyhydroxide, a 57% increase in patients with in-range (3.5-5.5 mg/dl) serum phosphorus (p<0.001) along with a decrease in pill burden (4.8 fewer pills, p<0.001) was observed.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO913

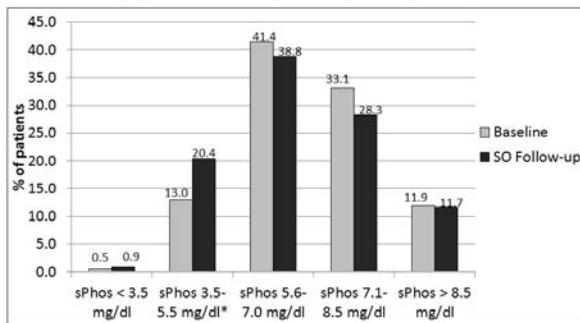
Real-World Use of Sucroferic Oxyhydroxide in Hemodialysis Patients: Changes in Serum Phosphorus Control and Phosphate Binder Pill Burden
 Linda H. Ficociello, Lin Ma, Vidhya Parameswaran, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America (FMCNA), Waltham, MA.*

Background: Approximately 40% of US dialysis patients (pts) do not achieve serum phosphorus (sPhos) goals (US-DOPPS Practice Monitor, 4/2015). This retrospective database analysis assessed the real-world effectiveness of sucroferic oxyhydroxide (SO) to control sPhos in hemodialysis (HD) pts.

Methods: In-center HD pts prescribed SO as part of routine clinical practice at FMCNA clinics with ³¹P sPhos during SO use were included. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and phosphate binder (PB) pills per day (PPD) were assessed 3-months before (baseline) and 3-months during SO treatment (follow-up).

Results: On average, pts (n=3151) were 54 years old with 4.3 years dialysis vintage and hyperphosphatemia (baseline sPhos = 6.94 mg/dl). PB prescribed at baseline were: sevelamer (47%), calcium acetate (26%), calcium carbonate (6%), lanthanum (7%), other PB (.1%), dual PB (7%), and no PB specified (7%). Pts with in-range sPhos (3.5-5.5 mg/dl) increased from 13 to 20.4% (57% increase). Mean sPhos (6.94 to 6.73 mg/dl, p<0.001) and mean sCa (9.21 to 9.18 mg/dl, p=0.003) decreased significantly. iPTH changed minimally (594.6 to 604.9 pg/ml, p=0.06). TSAT and FER increased (both p<0.001) from 33.6 to 35.1% and 947.9 to 1005.3 ng/ml, respectively. In pts not receiving IV iron, there was no significant change in TSAT (35.5% to 34.6%) and minimal decrease in FER (1122.9 to 1063.7 ng/ml, p=0.008). PB PPD decreased by 4.7 pills (8.4 to 3.7 pills, p<0.001).

Distribution of sPhos during baseline compared to sucroferic oxyhydroxide (SO)-treated follow-up for HD patients (N=3151)



*Change in %in-range and %out of range baseline compared to SO Follow-up, p<0.001

Conclusions: In a large HD patient cohort prescribed sucroferic oxyhydroxide as part of routine clinical care, in-range serum phosphorus increased by 57% (13 to 20.4%, p<0.001) and mean pills per day decreased by 4.7 pills (8.4 to 3.7 pills, p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO914

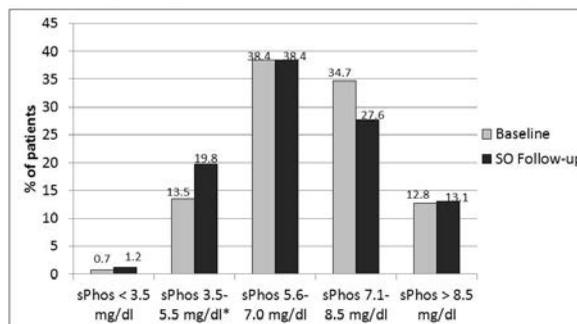
Serum Phosphorus Control and Phosphate Binder Pill Burden Among Hemodialysis Patients Who Switched from Calcium Based Phosphate Binders to Sucroferic Oxyhydroxide
 Vidhya Parameswaran, Lin Ma, Linda H. Ficociello, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America, Waltham, MA.*

Background: A retrospective database analysis of in-center hemodialysis (HD) patients (pts) who switched from calcium-based phosphate binders (PB) to sucroferic oxyhydroxide (SO) was conducted to study the real-world effectiveness of SO in controlling serum phosphorus (sPhos).

Methods: In-center HD pts who had ≥ 1 sPhos measured during SO treatment and switched from calcium-based PB were included. Comparisons were made between baseline (3 months prior to SO) and follow-up (3 months during SO) levels of sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pills per day (PPD).

Results: Analyzed pts (n=1011) were, on average, 54 years old with dialysis vintage of 4.5 years and hyperphosphatemia (baseline sPhos=6.98 mg/dl). Prior therapy included 81.7% calcium acetate and 18.3% calcium carbonate. There was a significant decrease in sPhos (6.98 to 6.77 mg/dl, p<0.001) and PB PPD (8.2 to 3.7 pills, p<0.001). A 47% increase (13.5% to 19.8%, p<0.001) in the number of pts with in-range sPhos (3.5-5.5 mg/dl) was observed. Levels of iPTH (539.3 to 552.9 pg/ml) and sCa (9.12 to 9.1 mg/dl) did not change significantly. Significant differences in TSAT (34.0 to 34.8%, p-value=0.007) and FER (931.7 to 973.1 ng/ml, p<0.001) were observed. In pts not receiving IV iron (n=103), there were no significant changes in TSAT (34.5% to 33.4%) and FER (1039 to 1003.4 ng/ml).

Distribution of sPhos during baseline compared to sucroferic oxyhydroxide (SO)-treated follow-up for HD patients who switched from calcium-based PB (N=1011)



*Change in %in-range and %out of range baseline compared to SO Follow-up, p<0.001

Conclusions: In a HD cohort switched from calcium-based binders to sucroferic oxyhydroxide as part of routine clinical care, a 47% increase (p<0.001) in the number of patients with in-range serum phosphorus and reduction of serum phosphorus (0.21 mg/dl, p<0.001) was observed. Pill burden decreased significantly (4.6 fewer pills, p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO915

Phosphate Binder VS-505 Prevents Hyperphosphatemia from Altering Aortic Gene Expression in 5/6 Nephrectomized Uremic Rats
 J. Ruth Wu-Wong,¹ Xiaoran Ruan,² Yung-wu Chen,¹ Jerry Wessale.¹ ¹Vidasym; ²Jackson Lab.

Background: Chronic kidney disease (CKD) patients are known to have impaired vascular function. Clinical studies have linked hyperphosphatemia to a higher cardiovascular mortality in CKD.

Methods: We compared gene expression profiles in aorta isolated from 5/6 nephrectomized (NX) uremic Sprague Dawley rats fed a normal diet vs. a high phosphate (Pi) diet. Real-time RT-PCR analysis was conducted on selected genes in aorta prepared from 5/6 NX uremic rats on a high Pi diet for 4 weeks treated with or without the phosphate binder VS-505, a non-absorbable, calcium- and aluminum-free, chemically-modified, plant-derived polymer currently being evaluated in hemodialysis patients.

Results: An increase in serum Pi was observed in uremic rats on the special diet (3.92 ± 0.42 vs. 3.29 ± 0.55 mmol/L on normal diet). A total of 135 target genes were affected (out of 15923 genes; 2-fold change, p<0.01) by increased serum Pi, with 122 up-regulated and 13 down-regulated. Target genes fell into various categories including carboxylic acid metabolism, lipid metabolism, mitochondrion, and oxidoreductase activity. In a separate study, VS-505 (0.2 - 5% by weight in food) prevented the increase in serum Pi (3.06 ± 0.30 mmol/L in the 5% VS-505 group vs. 3.74 ± 0.68 mmol/L in the vehicle-treated group, p<0.01), and it increased fecal Pi in a dose-dependent manner in the uremic rats on high-Pi diet (2.48 ± 0.60 mmol/24 hr in the 5% VS-505 group at Week 4 vs. 0.84 ± 0.55 mmol/24 hr at pre-dosing, p<0.001). VS-505 did not affect food/water consumption, feces appearance, intestine histomorphology and NPT2b gene expression. VS-505 treatment prevented the effects of hyperphosphatemia on altering the expression of aortic genes related to oxidative stress and inflammation such as activin A receptor-type 1c, glycogen synthase 2, heat shock 70KD protein 1A, stearoyl coenzyme A desaturase 1, and uncoupling protein 1.

Conclusions: These results suggest that hyperphosphatemia affects aortic gene expression linked to oxidative stress and inflammation, and that the adverse cardiovascular effects of high serum Pi may be prevented by oral treatment with the phosphate binder VS-505.

Funding: NIDDK Support

FR-PO916

Fractional Excretion of Phosphorus Misrepresents Hormonal Effects on Phosphate Reabsorption in Chronic Kidney Disease Kenneth R. Phelps,^{1,2} Darius Mason,^{1,2,3} Sun J. Kang,¹ ¹Stratton VAMC, Albany, NY; ²Albany Medical College, Albany, NY; ³Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: The serum P concentration ($[P]_s$) = E_p/C_{cr} + TR_p/C_{cr} , where E_p/C_{cr} and TR_p/C_{cr} are rates of urinary excretion and tubular reabsorption of P per volume of filtrate. E_p/C_{cr} is proportional to filtrate [P] in the cortical distal nephron ($[P]_d$); we have argued that [PTH] correlates with E_p/C_{cr} for this reason in CKD. Fractional excretion of P (FE_p), usually calculated as $[P]_d[cr]_d/[P]_s[cr]_s$, also equals $1/(1 + (TR_p/C_{cr})/(E_p/C_{cr}))$. Since E_p equals influx of P (I_p), the second expression shows that both I_p and TR_p determine FE_p . We hypothesized that FE_p correlates with [PTH] and [FGF23] in CKD because I_p affects all 3 variables.

Methods: We measured fasting $[cr]_s$, $[cr]_u$, $[P]_s$, $[P]_u$, [PTH]1-84 (Scantibodies) and intact [FGF23] (Immutopics) in 30 patients with stages 3-4 CKD. We calculated E_p/C_{cr} as $[P]_u[cr]_d/[cr]_u[cr]_s - E_p/C_{cr}$, and FE_p as $[P]_u[cr]_d/[P]_s[cr]_s$. We performed simple linear regressions as in the table and a multilinear regression of FE_p on E_p/C_{cr} , TR_p/C_{cr} , [PTH], and [FGF23].

Results: FE_p correlated directly with [PTH], [FGF23], and E_p/C_{cr} , and inversely with TR_p/C_{cr} . [PTH] and [FGF23] correlated directly with E_p/C_{cr} . TR_p/C_{cr} was not associated with [PTH] or [FGF23]. In the multilinear regression, E_p/C_{cr} and TR_p/C_{cr} caused > 90% of variation in FE_p ; [PTH] and [FGF23] did not contribute significantly.

Regression	R ²	P	Regression	R ²	P
FE_p on [PTH]	0.24	0.006	[PTH] on E_p/C_{cr}	0.28	0.003
FE_p on [FGF23]	0.17	0.02	[FGF23] on E_p/C_{cr}	0.26	0.004
FE_p on E_p/C_{cr}	0.76	< 0.001	TR_p/C_{cr} on [PTH]	0.07	0.15
FE_p on TR_p/C_{cr}	0.34	< 0.001	TR_p/C_{cr} on [FGF23]	0.001	0.84

Conclusions: TR_p/C_{cr} was unrelated to [PTH] and [FGF23] even though both hormones reduce P reabsorption. Although FE_p varied inversely with TR_p/C_{cr} , correlations of FE_p with [PTH] and [FGF23] did not result from effects of the hormones on TR_p/C_{cr} , and therefore did not reflect quantitative relationships between hormone concentrations and P reabsorption. The correlations occurred because FE_p , [PTH], and [FGF23] were associated with E_p/C_{cr} . FE_p should not be used to relate P reabsorption to hormones in CKD.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

FR-PO917

Attributes of the Walton-Bijvoet Nomogram at Normal and Reduced Glomerular Filtration Rate Kenneth R. Phelps,^{1,2} Darius Mason,^{1,2,3} Sun J. Kang,¹ ¹Stratton VAMC, Albany, NY; ²Albany Medical College, Albany, NY; ³Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: The serum P concentration ($[P]_s$) is the sum of E_p/C_{cr} and TR_p/C_{cr} (urinary excretion and tubular reabsorption of P per volume of filtrate). In Bijvoet's infusion studies, observed TR_p/C_{cr} equaled maximum TR_p/C_{cr} (Tm_p/GFR) at fasting fractional P excretion (FE_p) > 20%; as FE_p fell, $(Tm_p/GFR) - (TR_p/C_{cr})$ rose. These observations were incorporated into a nomogram that derives Tm_p/GFR from $[P]_s$ and FE_p . Although the nomogram was based on data obtained at $GFR > 40$ mL/min, it is used to assess P reabsorption in CKD. We examined this practice.

Methods: We collected fasting morning serum (s) and urine (u) from 30 patients with stages 3-4 CKD and 28 controls with MDRD eGFR > 60. We calculated E_p/C_{cr} as $[P]_u[cr]_d/[cr]_u[cr]_s - E_p/C_{cr}$, and FE_p as $[P]_u[cr]_d/[P]_s[cr]_s$. After ascertaining Tm_p/GFR from the nomogram, we calculated $(Tm_p/GFR)/[P]_s$, $(Tm_p/GFR - TR_p/C_{cr})$, and $(Tm_p/GFR)/(TR_p/C_{cr})$. We performed group comparisons with the Mann-Whitney U test.

Results: In CKD, E_p/C_{cr} and FE_p were higher, and eGFR, TR_p/C_{cr} , Tm_p/GFR , $(Tm_p/GFR)/[P]_s$, $(TR_p/C_{cr})/(E_p/C_{cr})$, $(Tm_p/GFR - TR_p/C_{cr})$, and $(Tm_p/GFR)/(TR_p/C_{cr})$ were lower than in controls. $[P]_s$ was not different in the 2 groups. In CKD, FE_p was > 20% in 27/30 patients; mean $(Tm_p/GFR - TR_p/C_{cr})$ and $(Tm_p/GFR)/(TR_p/C_{cr})$ approximated 0 and 1, respectively.

Parameter	CKD*	Controls*
eGFR, ml/min/1.73m ²	29.5 (1.7)	86.0 (1.9)
$[P]_s$, mg/dL	3.5 (0.1)	3.4 (0.1)
E_p/C_{cr} , mg/dL	1.4 (0.1)	0.4 (0.03)
TR_p/C_{cr}, mg/dL ($[P]_s - E_p/C_{cr}$)	2.2 (0.1)	3.1 (0.1)
$(TR_p/C_{cr})/(E_p/C_{cr})$	2.1 (0.3)	8.8 (0.9)
FE_p , %	40 (3)	11 (0.7)
Tm_p/GFR, mg/dL (nomogram)	2.1 (0.1)	3.4 (0.1)
$(Tm_p/GFR)/[P]_s$	0.63 (0.03)	0.97 (0.02)
$(Tm_p/GFR) - (TR_p/C_{cr})$, mg/dL	0.02 (0.01)	0.3 (0.05)
$(Tm_p/GFR)/(TR_p/C_{cr})$	1.0 (0.003)	1.1 (0.02)

*Values are mean (SEM). $P = 0.73$ for $[P]_s$ and < 0.001 for all other comparisons.

Conclusions: FE_p is > 20% at $(TR_p/C_{cr})/(E_p/C_{cr}) < 4$. In this circumstance, $Tm_p/GFR = TR_p/C_{cr} = [P]_s - E_p/C_{cr}$ whether E_p/C_{cr} is increased by P influx or low C_{cr} . Use of the nomogram and calculation of TR_p/C_{cr} require the same variables. In CKD, the nomogram is accurate but unnecessary if $(TR_p/C_{cr})/(E_p/C_{cr})$ is < 4.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

FR-PO918

Role of KHSRP and Pin1 in Mediating the Parathyroid Hormone Response in the Proximal Tubule Rebecca Murray,^{1,2} Michael Merchant,² Syed J. Khundmiri,^{1,2,3} Barbara Clark,⁴ Eleanor D. Lederer,^{1,2,3} ¹Physiology & Biophysics, Univ of Louisville, Louisville, KY; ²Medicine, Univ of Louisville, Louisville, KY; ³Robley Rex VAMC, Louisville, KY; ⁴Biochemistry & Molecular Biology, Univ of Louisville, Louisville, KY.

Background: Parathyroid hormone (PTH) regulates the type IIa sodium-phosphate cotransporter (Npt2a), the major regulated proximal tubule phosphate transporter, at both the protein and mRNA level. We previously identified KHSRP as a PTH-responsive phospho-protein that binds Npt2a mRNA and may mediate its degradation. Pin1, a peptidyl-prolyl isomerase, is the upstream regulator of KHSRP function and localization. Non-phosphorylated Pin1 binds KHSRP, promoting KHSRP dephosphorylation and maintaining its cytosolic localization. We hypothesize that PTH stimulates Npt2a mRNA destabilization through PKA-mediated phosphorylation of Pin1.

Methods: To address this hypothesis, we treated opossum kidney (OK) cells, a proximal tubule cell line, with 100nM PTH or 10μM 8-bromo-cAMP (8-Br [to directly activate PKA]) in the presence or absence of 1μM H-89 (a PKA inhibitor).

Results: 2h PTH induced a 2.5-fold increase in Pin1 phosphorylation. IP of KHSRP followed by immunoblot for Pin1 showed that Pin1 associates with KHSRP under basal conditions, but not following 2h PTH or 8-Br treatment. Pre-treatment with H-89 blocked the PTH/8-Br-induced disassociation. 2h PTH did not alter total expression of KHSRP, but stimulated its translocation to the nucleus.

Conclusions: We conclude that PTH-mediated destabilization of Npt2a mRNA likely involves PKA-mediated regulation of Pin1 and KHSRP activity. Funding provided by VA to EDL.

Funding: Veterans Administration Support

FR-PO919

Phosphate Depletion-Induced Metabolic Acidosis and Alkali Urine May Be Caused by Inappropriate Stimulation of Apical Cl⁻/HCO₃⁻ Exchanger (Pendrin) in Mouse Kidney Type B Intercalated Cells (IC-B) Yukiko Yasuoka,^{1,2} Tomomi Oshima,¹ Yuichi Sato,³ Hiroshi Nonoguchi,⁴ Katsumasa Kawahara.^{1,2} ¹Physiol., Kitasato U. Sch. of Med., Sagamihara, Japan; ²Cell & Mol. Physiol., Kitasato U. Grad. Sch. of Med. Sci., Sagamihara, Japan; ³Mol. Diag., Kitasato U. Grad. Sch. of Med. Sci., Sagamihara, Japan; ⁴Internal Med., Kitasato U. Medical Center, Kitamoto, Japan.

Background: Mice treated with a low phosphate (P_i) diet can maintain normal levels of plasma P_i concentration via stimulation of bone reabsorption, but show hypercalcemia, hypercalciuria, and hypophosphaturia. Recently, the Ca-sensing receptor (CaSR) was found to be localized in the basolateral membrane of IC-B as well as in the thick ascending limb of Henle's loop (Yasuoka et al, 2014). This study was aimed to determine whether hypercalcemia and/or hypercalciuria affect urine pH as expected in mice treated with either dietary P_i depletion or CaCl₂-loading.

Methods: C57Bl/6J mice (10 wks, male) were divided into three groups: (1) normal diet (1% P_i, n=6), (2) low-P_i (LP) diet (0.02% P_i, n=4), (3) CaCl₂-loading (1% P_i, +1% Ca (CaCl₂), n=6). All diets contain 1% Ca (CaCO₃). On day 7, a 24-hr urine, blood, and kidney samples were collected.

Results: Serum and urinary Ca were markedly and significantly increased in the LP and CaCl₂ groups [serum, 9.1 and 8.9 mg/dl; and urine, 2,400 and 2,140 μg/day], compared with control [serum, 7.6 mg/dl; urine, 108 μg/day]. Although serum pH decreased similarly and significantly to 7.25 and 7.20 in both groups, pH of the urine decreased to 5.6 (P < 0.05) in the CaCl₂ group and, surprisingly, increased to 7.4 (P < 0.05) in the LP group (control, serum pH 7.35; urine, pH 6.3). Kidney histology and immunohistochemistry showed that

the IC-A cell height and basolateral Cl⁻/HCO₃⁻ exchanger type 1 (AE1) staining significantly increased in the CaCl₂ group, whereas the IC-B cell height and apical Pendrin and basolateral AE4 staining significantly increased in the LP group.

Conclusions: P_i-depletion induced metabolic acidosis may be due to imbalanced urinary alkalization and acid absorption caused by inappropriate stimulation of Pendrin and AE4 through the hypercalcemia-induced activation of the basolateral CaSR in IC-B.

FR-PO920

MUC1N1 Increases Renal Calcium Channel TRPV5 Activity to Enhance Calcium Reabsorption in a Galectin-3 Dependent Fashion Matthias Wolf,¹ Mingzhu Nie,¹ Zhufeng Yang,² Jie Liu,¹ Denise K. Marciano,² Manjot S. Bal,¹ ¹Pediatrics, UTSW Medical Center, Dallas, TX; ²Internal Medicine, UTSW Medical Center, Dallas, TX.

Background: MUC1N1 (MUC1) mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD-MUC1), a condition similar to a nephropathy caused by *Uromodulin* (UMOD) mutations (ADTKD-UMOD). We previously showed that UMOD may protect against calcium-containing kidney stones by increasing TRPV5 cell surface abundance and tubular calcium reabsorption, which may decrease the risk of urinary supersaturation. The role of MUC1 in kidney is unclear. As UMOD and MUC1 share characteristics regarding disease phenotype, protein function, and structure, we examined the hypothesis that MUC1 enhances TRPV5 channel activity.

Methods: We expressed TRPV5 and MUC1 variants in HEK293 cells and studied TRPV5 current density by whole-cell patch-clamp recording.

Results: MUC1 coexpressed with TRPV5 resulted in a higher TRPV5 current density compared to mutant MUC1+C or control. MUC1 increased TRPV5 current density when applied extracellularly and required TRPV5 N-glycan for upregulation. Immunofluorescence imaging showed apical MUC1 expression along the distal nephron which is compatible with TRPV5 regulation in DCT. To test if MUC1 affects TRPV5 endocytosis, we tested if MUC1 upregulates TRPV5 in caveolin-1 deficient fibroblasts, as TRPV5 undergoes endocytosis via caveolin-1. While MUC1 alone had no effect, cotransfection of recombinant caveolin-1 with MUC1 restored TRPV5 upregulation by MUC1. The extracellular domain of MUC1 contains variable number tandem repeats (VNTRs) which bind galectin-3, a lectin involved in lattice formation of channels. Using galectin-3 siRNA, we identified galectin-3 as a prerequisite for TRPV5 upregulation by MUC1. This was confirmed by the inability of MUC1 lacking VNTR to upregulate TRPV5. In urine samples of patients with calcium-containing kidney stones we found less urinary MUC1 compared to control individuals.

Conclusions: MUC1 upregulates TRPV5 by extracellular lattice formation with TRPV5 N-glycan via galectin-3 which impairs TRPV5 channel endocytosis. These data are consistent with MUC1 contributing to protection against calcium-containing kidney stones.

Funding: NIDDK Support

FR-PO921

NCC Activity Modulation as a Mechanism for PTH Regulation of DCT Calcium Transport Benjamin S. Ko,¹ Robert S. Hoover,² ¹Dept of Medicine, Univ of Chicago, Chicago, IL; ²Dept of Medicine, Emory Univ, Atlanta, GA.

Background: The distal convoluted tubule (DCT) is a major site of both calcium and sodium transport. While altered DCT calcium handling is not required for thiazide-induced hypocalcemia, studies have documented increased DCT calcium reabsorption in response to thiazide administration. This suggests that DCT sodium transport does affect DCT calcium transport, and while thiazide induced hypocalcemia is due to a proximal effect, modulation of NCC activity may affect DCT calcium transport by TRPV5. Since parathyroid hormone (PTH) is known to increase TRPV5 activity and decrease NCC activity, we theorized that decreased NCC-mediated sodium reabsorption may contribute to the enhanced TRPV5 calcium reabsorption seen with PTH administration.

Methods: Radiotracer uptake and biotinylation in mDCT15 cells were used to measure sodium and calcium uptake as well as surface expression of NCC and TRPV5.

Results: mDCT15 cells expressed ruthenium red sensitive ⁴⁵Ca²⁺ uptake of 5.9±0.2 nmol/mg/min and surface expressed TRPV5. PTH increased ⁴⁵Ca²⁺ uptake to 8.8±0.7 nmol/mg/min (n=4, p<0.01 compared to control) and decreased NCC activity from 75.4±2.7 to 20.3±1.3 nmol/mg/min (n=4, p<0.01 compared to control). Knockdown of RasGRP1, the pathway by which PTH affects NCC, had no baseline effect on ⁴⁵Ca²⁺ uptake but significantly attenuated the increased ⁴⁵Ca²⁺ uptake response to PTH from a 45% increase (6.0±0.2 to 8.7±0.4 nmol/mg/min) in non-targeting controls to only a 20% increase (6.1±0.1 to 7.3±0.2 nmol/mg/min (n=4, p<0.01 compared to non-targeting treated groups)). Inhibition of PKC and PKA, the known pathways by which PTH acts upon TRPV5, resulted in further attenuation of the PTH effect.

Conclusions: Here, through the use of a cell model with native NCC and TRPV5 activity, we report that modulation of NCC activity does indeed contribute to the TRPV5 response to PTH, implying a role for hormonal modulation of NCC activity in distal calcium handling. Further study is needed to determine the mechanism for these findings.

Funding: NIDDK Support, Veterans Administration Support

FR-PO922

How Disruption of Distal Nephron Salt Reabsorption Causes Calcium Wasting, Tubule Calcification and Skeletal Changes Sharon L. Barone,^{1,2} Jie Xu,¹ Mujan Varasteh kia,¹ Saeed Alshahrani,¹ Marybeth Brooks,¹ Kamyar A. Zahedi,^{1,2} Manoocher Soleimani,^{1,2} ¹Internal Medicine, Univ of Cincinnati, Cincinnati, OH; ²Research Services, Veterans Affairs Medical Center, Cincinnati, OH.

Background: Carbonic anhydrase II/sodium chloride co-transporter (NCC) and pendrin/NCC double knockout mice (dKO) develop salt wasting and are growth retarded. We propose that the disruption of sodium and chloride reabsorption in these mice causes phosphate and calcium wasting and leads to bone and skeletal anomalies.

Methods: Renal alterations that lead to distorted calcium and phosphate reabsorption and contribute to tubular calcification and growth retardation in the dKO mice were examined.

Results: dKO mice are volume depleted, exhibit kidney hypoperfusion, and have increased urinary calcium and phosphate excretion. These mice also exhibit skeletal anomalies and osteopenia and develop tubular calcium phosphate deposits. Parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) levels are normal in dKO mice. The urinary content of prostaglandin E₂ (PGE₂) is significantly elevated, along with the expression of microsomal prostaglandin synthase 1, while the sodium phosphate transporter IIa (NaPi-IIa) is downregulated in the kidneys of dKO mice. qRT-PCR analyses revealed that the expression levels of NKCC2 variants A and F are reduced while NKCC2-B levels are increased in dKO animals. The latter changes lead to decreased NKCC2 activity in the medullary thick limb and increased calcium excretion, while NaPi-IIa downregulation reduces the reabsorption of phosphate in the proximal tubules. Placement of dKO mice on a high salt diet or their treatment with indomethacin corrected the above derangements. These results show an important role for salt wasting and dehydration-induced PGE₂ synthesis in renal calcium and phosphate excretion as well as in bone calcium mobilization.

Conclusions: Our studies suggest the presence of PGE₂-mediated pathways, which are activated in response to salt wasting and volume contraction and independent of PTH and FGF-23 activity can lead to anomalous mobilization and excretion of calcium and phosphate, and ultimately lead to skeletal abnormalities and growth retardation.

Funding: NIDDK Support, Veterans Administration Support

FR-PO923

Hypercalcemia-Induced Natriuresis Is Mediated by Endothelin-1 (ET-1) Natsuko Tokonami, Lydie Cheval, Pascal Houillier. ERL 8228 – U1138 Équipe 3, Univ Pierre-et-Marie-Curie, Univ Paris Descartes, INSERM, CNRS, and Centre de Recherche des Cordeliers, Paris, France.

Background: Acute hypercalcemia commonly increases urinary sodium and water excretions. We previously showed that targeting the calcium receptor CaSR does not affect sodium transport in the renal tubule (Loupy, et al., JCI, 2012), suggesting that the natriuretic effect of hypercalcemia does not involve CaSR. Since hypercalcemia increases the renal expression of ET-1, we tested if ET-1 mediates the natriuretic effect of hypercalcemia.

Methods: Forty-two 8 week-old, male C57Bl6 mice were studied. Osmotic minipumps were implanted to infuse hPTH(1-34) and maintain the concentration of PTH to normal range throughout the experiment. Hypercalcemia was induced by the oral administration of dihydroxycholesterol (DHT: 7.5mg/kg food/day). Eighteen mice were treated with an ET-1 receptor antagonist, macitentan (Maci, 27mg/kg BW/day), with or without DHT.

Results: On 3rd day of treatment, mice treated by DHT developed hypercalcemia (5.0±0.1 vs 2.4±0.1 mmol/L control mice) and exhibited increased water and sodium excretion as compared to control mice (2.0 ± 0.1 vs 1.4 ± 0.1 mL/day and 46±4 vs 36±2 mmol Na/mmol creatinine, respectively, p<0.01 for both). Mice treated with Maci+DHT had similar levels of hypercalcemia and polyuria as mice treated with DHT only. However, mice treated with Maci+DHT showed no increase in urinary sodium excretion. Mice treated with Maci only were similar to control mice. A 3-4 fold increase in the renal level of ET-1 mRNA was observed in mice treated with DHT and Maci+DHT.

Conclusions: Hypercalcemia increases the renal production of ET-1, which is likely responsible for the increase of urinary sodium excretion. In contrast, ET-1 is not involved in hypercalcemia-induced polyuria.

Funding: Government Support - Non-U.S.

FR-PO924

The Uremic Toxin Indoxyl Sulfate (IS) Activates the Extracellular Regulated Kinase 1/2 (ERK1/2) Pathway in Primary Human Endothelial Cells (ECs) by Stimulating Ca²⁺-Influx via the Na⁺/Ca²⁺ Exchanger (NCX) Luxme Nadarajah, Steven Michael Harwood, Petros Andrikopoulos, Muhammad M. Yaqoob. William Harvey Research Inst, Barts and the London School of Medicine, London, United Kingdom.

Background: Cardiovascular complications are a major cause of morbidity/mortality in CKD and endothelial dysfunction is a major contributing factor. The uremic toxin IS accumulates in the plasma of end-stage renal disease (ESRD) patients and causes oxidative stress and endothelial dysfunction. However, the underlying molecular mechanism(s) are largely unknown. We recently reported that Ca²⁺ influx through the ion transporter NCX activated the ERK1/2 pathway in ECs stimulated with thrombin in a reactive oxidant species (ROS)-dependent manner (Andrikopoulos et al., 2015 JBC). In the present study we investigated whether ERK1/2 activation in response to IS also required Ca²⁺-influx via NCX.

Methods: Primary human umbilical vein endothelial cells (HUVECs) were serum starved in a physiological buffer and preincubated with reverse-mode (Ca²⁺ influx) NCX inhibitors SN-6 or SEA0400 and the general NCX inhibitor ORM-10103. NCX1 protein was knocked down using siRNA. ERK1/2 activation was determined by western blot. [Ca²⁺]_i was measured in ECs loaded with the fluorescent Ca²⁺ indicator Fluo-4N.W.

Results: We report that IS, at concentrations found in the plasma of ESRD patients (25mg/ml) activated the ERK1/2 pathway and extracellular Ca²⁺ was required for activation. Furthermore, inhibitors of reverse-mode NCX suppressed IS-induced activation of ERK1/2 in a time- and dose-dependent manner and attenuated IS-induced Ca²⁺ transients. Knock-down of NCX1 (the main NCX isoform in HUVECs) by siRNA confirmed the pharmacological data.

Conclusions: We propose that Ca²⁺ influx through reverse-mode NCX is required for IS-induced ERK1/2 activation. Given the known role of ERK1/2 activation in the expression of pro-inflammatory molecules such as COX-2 and VCAM-1 in ECs, reverse-mode NCX could be a novel target for improving endothelial function in CKD.

FR-PO925

Chronic Kidney Disease Impairs Myocardial Perfusion and Disturbs Cardiac Calcium Handling Melissa Verkaik,^{1,2,4} Maarten Oranje,² Desiree Abdurrachim,³ Pieter M. Ter Wee,¹ Etto C. Eringa,² Marc G. Vervloet.¹ ¹Dept of Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; ²Dept of Physiology, Inst of Cardiovascular Research ICar-VU, VU Univ Medical Center, Amsterdam, Netherlands; ³Biomedical NMR, Dept of Biomedical Engineering, Eindhoven Univ of Technology, Eindhoven, Netherlands; ⁴On behalf of the NIGRAM Consortium.

Background: The molecular and microcirculatory changes that may underlie the increased prevalence of heart failure and cardiac mortality in CKD are ill-defined. We hypothesized that CKD directly impairs both myocardial perfusion and disturbed cardiac diastolic and systolic function due to disturbed calcium fluxes across the myocardial sarcoplasmic reticulum.

Methods: Eight week old C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery, and after 6 weeks mice were subjected to myocardial contrast echocardiography (MCE) to test myocardial perfusion. Cardiac function was assessed using Cine MRI. In single intact cardiomyocytes diastolic and systolic function, as well as intracellular Ca²⁺ transients were measured by fura-2 loaded cardiomyocytes.

Results: No difference was found between groups for heart weights over tibia length, neither for ejection fraction, cardiac output, end diastolic and systolic volume, and E/A ratio. Sham mice increased myocardial blood volume during acetylcholine infusion, which was absent in 5/6Nx mice (D17%, p=0.023). In isolated cardiomyocytes, time to reach systole was increased in 5/6Nx mice (52.3±0.8 vs. 56.7±0.8 ms, p<0.001), which is explained by a decrease in velocity of cytosolic Ca²⁺ increase (78.8±2.2 vs. 66.0±2.0 Fura340/380/s, p<0.001). The removal of Ca²⁺ from cytosol during diastole was slower in 5/6Nx mice (-7.12±0.23 vs. -5.74±0.18 Fura340/380/s, p<0.001), due to reduced phosphorylation of the SERCA-regulating protein phospholamban (p=0.024), as shown by semiquantitative WB.

Conclusions: CKD compromises both myocardial microvascular perfusion reserve, and systolic and diastolic function in cardiomyocytes. Calcium fluxes across the sarcoplasmic membrane are disturbed, due to a reduced amount of phosphorylated phospholamban, which activates the sarcoplasmic reticulum Ca²⁺ channel SERCA.

FR-PO926

Recessive Mutations in SLC34A1 (NaPi-IIa) as a Cause of Idiopathic Infantile Hypercalcemia Karl P. Schlingmann,¹ Birgitta Kranz,² Martin Kaufmann,³ Elisabeth A.M. Cornelissen,⁴ René J. Bindels,⁵ Asaf Vivante,⁶ Robert Kleta,⁷ Elena N. Levchenko,⁸ Glenville Jones,³ Carsten A. Wagner,² Martin Konrad.¹ ¹General Pediatrics, Wilhelms Univ, Munster, Germany; ²Inst of Physiology, Univ of Zurich, Zurich, Switzerland; ³Biomedical and Molecular Sciences, Queen's Univ, Kingston, Canada; ⁴Pediatric Nephrology, Radboud Univ, Nijmegen, Netherlands; ⁵Physiology, Radboud Univ, Nijmegen, Netherlands; ⁶Children's Hospital Boston, Boston; ⁷Univ College London, London, United Kingdom; ⁸Pediatric Nephrology, Univ Hospitals, Leuven, Belgium.

Background: Idiopathic infantile hypercalcemia (IIH) is characterized by severe hypercalcemia with failure to thrive, vomiting, dehydration, and nephrocalcinosis. Initially, mutations in *CYP24A1* encoding the vitamin D catabolizing enzyme 25-hydroxyvitamin D₃-24-hydroxylase were discovered that lead to an accumulation of active 1,25-(OH)₂D₃ with subsequent hypercalcemia and hypercalciuria.

Methods: In a subgroup of IIH patients without mutations in *CYP24A1* we now performed a positional candidate gene approach in order to identify a second IIH gene locus.

Results: We identified a shared homozygous interval on chromosome 5q35 with a maximum LOD score of 6.91. The sequence analysis of *SLC34A1* encoding proximal-tubular sodium-phosphate co-transporter NaPi-IIa revealed recessive mutations in the 4 index cases as well as in 18 additional sporadic IIH patients. The clinical reevaluation revealed renal phosphate wasting but no signs of rickets. Functional studies of mutated NaPi-IIa in *Xenopus* oocytes and OK cells demonstrated a disturbed membrane trafficking as well as a loss of phosphate transport activity. The reexamination of *Slc34a1* knockout mice highlighted the critical role of phosphate depletion and FGF-23 suppression. In affected patients, clinical and laboratory findings persist after omitting vitamin D prophylaxis but rapidly respond to phosphate supplementation.

Conclusions: Therefore, an early differentiation between *CYP24A1* (24-hydroxylase) and *SLC34A1* (NaPi-IIa) defects appears crucial for an effective therapy in children with IIH.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

FR-PO927

Identification of SLC41A3 as a Novel Player in Renal Magnesium Homeostasis Jeroen H.F. De Baaij, Anke Lameris, René J. Bindels, Joost Hoenderop. Dept of Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Hypomagnesemia is a common clinical cause of muscle cramps, epilepsy and cardiac arrhythmias. In the distal convoluted tubule (DCT) of the kidney, transcellular reabsorption of Mg²⁺ regulates the body Mg²⁺ balance by determining the final urinary Mg²⁺ excretion. In the DCT, Mg²⁺ is reabsorbed from the pro-urine via the apical Mg²⁺ channel TRPM6. Until now, the basolateral Mg²⁺ extrusion mechanism in DCT is still unknown, but recent findings suggest that proteins of the SLC41 family may contribute to cellular Mg²⁺ extrusion. The aim of this study was, therefore, to investigate the role of SLC41A3 in Mg²⁺ homeostasis using the *Slc41a3* knockout mouse.

Methods: The *Slc41a3* knockout mice were studied by serum and urinary electrolyte analysis. To determine the effect of SLC41A3 on intestinal Mg²⁺ absorption, the Mg²⁺ absorption capacity was measured using the stable ²⁵Mg²⁺ isotope.

Results: Tissue expression screening was performed by RT-PCR, showing that *Slc41a3* is the only SLC41 isoform with enriched expression in DCT compared to other segments in the kidney. Interestingly, serum and urinary electrolyte determinations demonstrated that *Slc41a3* knockout mice suffer from hypomagnesemia due to renal Mg²⁺ wasting. Serum and urinary Na⁺, K⁺ and Ca²⁺ levels were not affected. ²⁵Mg²⁺ uptake was similar in wild type and knockout mouse, although *Slc41a3* knockout animals exhibited increased intestinal expression of Mg²⁺ transporters *Trpm6* and *Slc41a1*. Remarkably, 10% of the *Slc41a3* knockout mice developed severe unilateral hydronephrosis, as demonstrated by the presence of transitional epithelium lining the fluid cavity. Feeding the *Slc41a3* knockout mice a low Mg²⁺ diet may have instigated the formation of hydronephrosis.

Conclusions: In conclusion, SLC41A3 was established as a new important factor for renal Mg²⁺ handling, suggesting that SLC41A3 is the basolateral Mg²⁺ extrusion mechanism in the DCT. *Slc41a3*^{-/-} mice provide the first mouse model with isolated hypomagnesemia, without concomitant electrolyte disturbances. In the future, *SLC41A3* mutations should be considered in patients with unilateral hydronephrosis and/or hypomagnesemia.

Funding: Government Support - Non-U.S.

FR-PO928

Dietary Inulin Supplementation Stimulates Magnesium Absorption in Patients with Proton Pump Induced Hypomagnesemia Jeroen H.F. De Baaij,¹ Mark Wilhelm Hess,¹ Joost Hoenderop,¹ Joost P.H. Drenth,² René J. Bindels.¹ ¹Dept of Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Dept of Gastroenterology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Hypomagnesemia is a common and severe side effect of patients using proton pump inhibitors (PPI), causing severe muscle cramps and depression. Given that PPI-users are dependent on PPIs for gastric acid protection, drug withdrawal or antacid switching is often not possible to prevent hypomagnesemia. This study, therefore, aimed to restore serum Mg²⁺ levels during PPI use by the dietary application of fructose-oligosaccharide-enriched inulin fibers.

Methods: This clinical trial prospectively determined serum Mg²⁺ concentrations in 133 patients using PPIs. Under maintenance of PPIs, eleven identified cases of PPI-induced hypomagnesemia were exposed to 2 repetitive dietary supplementations with inulin for 14-days each followed by 14-days washout and compared to 10 healthy non-PPI users. The primary endpoint was serum Mg²⁺. Secondary endpoints were serum Ca²⁺, K⁺, and Na⁺ levels.

Results: Hypomagnesemia is present in 13% of the study population. Dietary supplementation with inulin significantly enhanced mean serum Mg²⁺ levels by +0.1 mmol/L in PPIH patients and by +0.06 mmol/L in healthy controls. Moreover, in patients with PPIH concomitant treatment effects were observed for serum Ca²⁺ (+0.09 mmol/L) and serum K⁺ (+0.07 mmol/L), no effects were seen on serum Na⁺. Patients with PPIH had adequately renal excretion of Mg²⁺ and Ca²⁺, which increased due to inulin following increases in serum levels. Additionally, two SNPs in TRPM6 (rs3750425 and rs2274924) were identified that cause a 4.75 times higher risk to develop hypomagnesemia.

Conclusions: Inulin fibers are a new promising prebiotic treatment strategy to treat intestinal- and renal-caused hypomagnesemia. For the first time we provide a successful alternative for oral Mg²⁺ supplementation.

Funding: Government Support - Non-U.S.

FR-PO929

The Distal Convoluted Tubule Plays a Key Role in Tacrolimus-Induced Hypomagnesemia and Hypercalciuria Rebecca A. Lazelle,¹ Sabina K. Jelen,² Chao-Ling Yang,¹ Joost Hoenderop,² René J. Bindels,² David H. Ellison.^{1,3} ¹Div of Nephrology & Hypertension, Oregon Health and Science Univ, Portland, OR; ²Radboud Inst for Molecular Life Sciences, Radboud Univ Medical Center, Nijmegen, Netherlands; ³Renal Section, Portland VA Medical Center, Portland, OR.

Background: The immunosuppressive drug tacrolimus, used to prevent graft rejection, often leads to hypomagnesemia and can also cause hypercalciuria. A decrease in renal Mg²⁺ and Ca²⁺ reabsorption is thought to be involved, but the molecular mechanisms are unclear. Tacrolimus requires a binding partner, FKBP12, to inhibit its canonical target, calcineurin. We generated a mouse model in which FKBP12 can be deleted along the

nephron (KS-FKBP12^{-/-}). We then tested if either FKBP12 disruption or calcineurin inhibition along the nephron alters the mRNA abundance of renal ion transport proteins leading to hypomagnesemia and hypercalciuria.

Methods: KS-FKBP12^{-/-} mice were generated using an inducible CRE/LOX system driven by the Pax8 promoter. Mice were treated with doxycycline (KS-FKBP12^{-/-}) or vehicle (control). We tested the effects of tacrolimus (3 mg/Kg daily for 18 days) on plasma [Mg²⁺], urinary Ca²⁺ excretion, and mRNA abundance of renal proteins involved in ion transport using metabolic cages, colorimetric assays and qRT-PCR.

Results: As expected, tacrolimus caused hypomagnesemia and hypercalciuria in control mice. Effects which were absent in KS-FKBP12^{-/-} mice (P<0.05 2-Way ANOVA). In control mice, tacrolimus reduced the mRNA abundance of proteins involved in Mg²⁺ and Ca²⁺ transport by the distal convoluted tubule (DCT) including, TRPM6, calbindin-28K and the Sodium Calcium Exchanger-1. In contrast, tacrolimus had no effect in KS-FKBP12^{-/-} mice (p<0.05 by 2-way ANOVA). The abundance of mRNA encoding Claudin 16 and 19, thick ascending limb (TAL) proteins involved in Mg²⁺ and Ca²⁺ handling, were not affected by tacrolimus treatment in either group.

Conclusions: Tacrolimus reduces the abundance of mRNA encoding proteins involved in Ca²⁺ and Mg²⁺ transport by the DCT. These effects require FKBP12, suggesting that calcineurin inhibition is essential. The results show that the DCT plays a key role in these troubling side effects.

Funding: NIDDK Support, Private Foundation Support

FR-PO930

Regulation of Magnesium Reabsorption and Transient Receptor Potential M6 Channel Activity by Protein Kinase A Signaling Joost Hoenderop,¹ Maxime G. Blanchard,¹ Wararat Kittikuluth,² Anil V. Nair,¹ Jeroen H.F. De Baaij,¹ Jonathan R. Genzen,³ Donald E. Kohan,² René J. Bindels.¹ ¹Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Nephrology, Univ of Utah, Salt Lake City, UT; ³Pathology, Univ of Utah, Salt Lake City, UT.

Background: The transient receptor potential melastatin type 6 (TRPM6) epithelial magnesium (Mg²⁺) channel participates in Mg²⁺ transport in kidney and intestine. Previous reports have suggested a hormonal cAMP-dependent regulation of Mg²⁺ reabsorption in the kidney. The molecular details of this process are, however, unknown. Adenylate cyclase type 3 (Adcy3) has been shown to colocalize with the Na⁺Cl⁻ cotransporter (NCC), a marker of the distal convoluted tubule, the principal site of TRPM6 expression.

Methods: Given the critical role of TRPM6 in Mg²⁺ reabsorption, an inducible kidney-specific Adcy3 deletion mouse model was characterised for blood and urinary electrolyte disturbances under normal and low Mg²⁺ diet. Using patch clamp, cell surface biotinylation and Total Internal Reflection Fluorescence (TIRF) live cell imaging of transfected HEK293 cells TRPM6 channel activity was measured.

Results: Urinary Mg²⁺ excretion was increased (~1.7-fold) in AC3 deleted mice compared to controls where as serum Mg²⁺ concentrations were not different. Renal TRPM6 mRNA levels were increased by ~2-fold in AC3 deleted mice. Serum Mg²⁺ was significantly lower in AC3 deleted animals for 7 days on the low Mg²⁺ diet compared to the control animals. In HEK293 cells, it was demonstrated that cAMP signaling rapidly potentiates the activity of TRPM6 by promoting its accumulation at the plasma membrane and by increasing its single channel conductance. Comparison of electrophysiological data between the phosphorylation-deficient S1252A and phosphomimetic S1252D mutants suggests that phosphorylation at this intracellular residue participates in the observed stimulation of channel activity.

Conclusions: These data support a physiologically relevant magnesiotropic role of cAMP signaling in the kidney by a direct stimulatory action of protein kinase A on the plasma membrane trafficking and function of TRPM6 ion channels in the distal convoluted tubule.

Funding: Government Support - Non-U.S.

FR-PO931

Renal Handling of Magnesium in Individuals on Long Term Proton Pump Inhibitor Therapy Saubhik Sural, Nephrology, Peerless Hospital & B K Roy Research Centre, Kolkata, West Bengal, India.

Background: Proton Pump Inhibitors (PPI) are a group of very commonly used medication. Recently the US---FDA has issued warning regarding the risk of hypomagnesemia in patients receiving long term PPI therapy. The present study was conducted with the objective of evaluating the serum magnesium and renal handling of magnesium in long term PPI patients.

Methods: The study was designed as a case control study consisting of adult patients on long term PPI therapy (Omeprazole; Rabeprezole; Pantoprezole etc) for more than 1 year. Patients on PPI with diabetes, chronic kidney disease or on diuretics were excluded. Age and sex matched healthy controls not on any medication were included as controls. Serum Magnesium and Urinary Fractional Excretion of magnesium (FE---Mg) were measured using an automated clinical chemistry autoanalyser. Study was conducted for one year followed by statistical analysis of data with Graph-pad software.

Results: The mean age of the long term PPI group was 47.5years and 45.9years in the control population with no statistical difference between the two groups. Among study patients long term PPI users (n = 43) had a mean(SD) Mg level of 1.79 (0.17) mg/dL; and non---users (n = 43) 2.06 (0.30) mg/dL; p = 0.001. PPI use was associated with lower serum Mg levels (95% CI = 0.30 to 0.19). The FE---Mg of long term PPI users had a mean (SD) of 1.37(0.65) % and the control population 2.72(0.88); p = 0.001. Among the PPI group 9 patients (20%) had a serum Mg less than the lower limit of our population reference interval (1.7 mg/dl). None of them were clinically symptomatic for hypomagnesemia. The serum

magnesium levels showed a negative correlation with the duration of PPI therapy (r = -0.502 ; p 0.01). The FE---Mg of the PPI group is significantly reduced suggesting increased renal conservation of magnesium in order to maintain near normal serum levels.

Conclusions: Compensatory renal conservation of Mg occurs in long term PPI receiving patients. Thus if patients with impaired renal handling of Mg (diabetes; CKD or those on diuretics) receive long term PPI therapy they might possibly be at a greater risk of clinically significant hypomagnesemia.

FR-PO932

Magnesium Protects against Phosphate-Induced Kidney Injury in Mice with Uninephrectomy Yusuke Sakaguchi,¹ Takayuki Hamano,² Isao Matsui,¹ Akihiro Shimomura,² Yasuo Kusunoki,¹ Sayoko Yonemoto,¹ Daisuke Mori,¹ Hiromi Rakugi,¹ Yoshitaka Isaka.¹ ¹Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; ²Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: We have recently reported that the risk of progression of CKD associated with high serum phosphate (P) was significantly attenuated in patients who had higher serum magnesium (Mg) levels (Kidney International in press), although the causality remains unclear. Here we studied whether Mg protects against kidney injury induced by P overload.

Methods: Eight-week-old C57BL/6 mice underwent uninephrectomy and were divided into 4 groups: 1. high P (1.25% P)-normal Mg (0.05% Mg) diet; 2. high P (1.25% P)-low Mg (0.005% Mg) diet; 3. low P (0.25% P)-normal Mg (0.05% Mg) diet; 4. low P (0.25% P)-low Mg (0.005% Mg) diet. Twenty-four-hour urine samples were collected for the measurement of daily urinary excretion of P. After 6 weeks of dietary intervention, mice were sacrificed and kidney tissues were harvested for histological analysis and mRNA quantification.

Results: Mice fed with the high P-low Mg diet showed severe tubular injury, interstitial fibrosis, and a marked accumulation of F4/80 positive cells in the interstitium; these changes were largely attenuated in mice in the high P-normal Mg diet group. Creatinine clearance in the high P-low Mg diet group was significantly lower than that in the high P-high Mg diet group (0.04±0.02 vs 0.27±0.14; p<0.05). Both TGF-β1 and TNF-α mRNA expression levels in the whole kidney were upregulated in the high P-low Mg diet group compared with those in the high P-normal Mg diet group. No histological evidence of kidney injury was found in both of the low P groups. Since urinary P excretion in the high P-low Mg diet group was equivalent (at 3 weeks) to or even lower (at 6 weeks) than that in the high P-normal Mg diet group, it is unlikely that the exacerbation of kidney injury in the high P-low Mg diet group was owing to an increased intestinal absorption of P.

Conclusions: Low Mg diet aggravates phosphate-induced kidney injury. Mg may be beneficial to reduce the phosphate toxicity to the kidney.

FR-PO933

Low Serum Magnesium Is Associated with an Increased Risk of Death from Coronary Heart Disease and Sudden Cardiac Death Brenda C.T. Kieboom,^{1,2} Robert Zietse,² Oscar Franco,¹ Albert Hofman,¹ Bruno H. Stricker,^{1,2} Ewout J. Hoorn.² ¹Epidemiology, Erasmus MC, Univ Medical Center Rotterdam, Rotterdam, Netherlands; ²Internal Medicine, Erasmus MC, Univ Medical Center Rotterdam, Rotterdam, Netherlands.

Background: Low serum magnesium has been associated with cardiovascular disease (CVD) mortality in population-based studies. However, results are conflicting and it remains unclear if this effect is mediated by an effect on atherosclerosis or heart rhythm.

Methods: We examined the relationship between serum magnesium and CVD mortality in 9,820 participants aged ≥ 45 years from the population-based Rotterdam Study. We used multivariable-adjusted Cox proportional hazard regression models and divided serum magnesium into quartiles, with the second and third quartile combined as reference group.

Results: During a median follow-up of 8.7 years, 780 participants died of CVD, including 431 deaths from coronary heart disease (CHD) and 217 sudden cardiac deaths (SCD). Low serum magnesium (≤ 0.80 mmol/L) was associated with an increased CVD mortality risk (HR 1.25, 95% CI 1.05-1.50), including both death from CHD (HR 1.42, 95% CI 1.04-1.95) and SCD (HR 1.68, 95% CI 1.20-2.37). Low serum magnesium was associated with an increased QTc-interval, due to a strong effect on heart rate (RR interval -7.7 ms, 95% CI -14.7 to -0.7), but additional adjustment for heart rate did not change the association with SCD. Low serum magnesium was associated with increased intima media thickness (0.01 mm, 95% CI 0.004-0.020), and this explained part of the effect of magnesium on CHD mortality. Notable, high serum magnesium (≥ 0.89 mmol/L) was also associated with an increased risk of SCD (HR 1.50, 95% CI 1.05-2.16), but reduced risk of death from CHD (HR 0.64, 95% CI 0.43-0.95).

Conclusions: Low serum magnesium is associated with an increased risk of death from CHD, which is partly explained by an effect on atherosclerosis. Both low and high serum magnesium are associated with an increased risk of SCD. Although serum magnesium strongly affects heart rate, this did not explain the relationship between serum magnesium and SCD.

FR-PO934

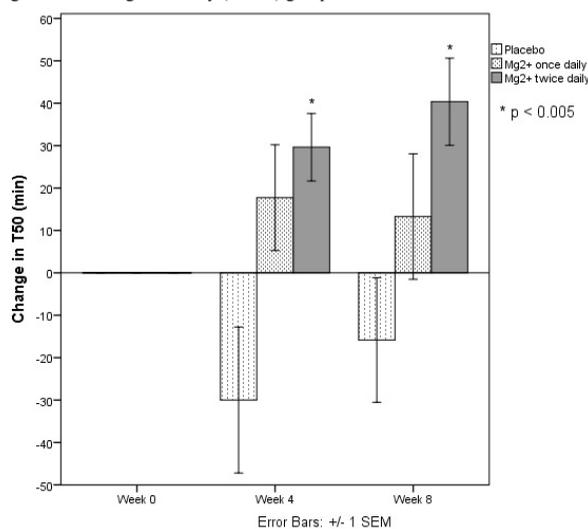
Oral Magnesium Supplementation Improves Serum Calcification Propensity in Chronic Kidney Disease Stage 3-4

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Background: In previous experimental studies of chronic kidney disease (CKD) magnesium has been shown to improve vascular calcification. Serum calcification propensity measured using the T50 analysis has been shown to predict all-cause mortality among patients with chronic kidney disease (CKD) stage 3-4.

Methods: In a proof-of-concept randomized placebo-controlled double-blinded trial of placebo versus slow-release magnesium oxide at two different doses (360 mg once daily or 360 mg twice daily) for eight weeks in 34 subjects with CKD stage 3-4 and plasma magnesium <0.82 mmol/L, T50 was measured to examine whether magnesium supplementation affects serum calcification propensity.

Results: In subjects randomized to magnesium 360 mg twice daily (n = 11) plasma magnesium increased by 0.11 mmol/L (confidence interval; 0.05 - 0.17, p = 0.003) and T50 increased by 40 minutes (confidence interval; 18 - 63, p = 0.003) after eight weeks of treatment (Figure 1), while there were no changes in plasma phosphate, calcium or parathyroid hormone. There were no significant changes in T50 in the placebo (n = 12) or magnesium 360 mg once daily (n = 11) groups.



Conclusions: Oral magnesium oxide 360 mg twice daily improves serum calcification propensity in CKD stage 3-4 after eight weeks of treatment. Larger, long-term trials are needed to assess whether this translates into reductions in vascular calcification (e.g. coronary artery calcium score or pulse wave velocity) and cardiovascular endpoints.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO935

The Novel NaPi-IIb Inhibitor ASP3325 Does Not Mitigate Hyperphosphatemia in Chronic Kidney Disease Patients on Hemodialysis

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Background: The sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) is considered an important mediator of active inorganic phosphate (Pi) transport and absorption in the small intestine. ASP3325 is a novel NaPi-IIb inhibitor effective for reducing the plasma Pi level in a rat model of adenine-induced renal failure and is currently in development for the treatment of hyperphosphatemia in chronic kidney disease (CKD).

Methods: Two phase 1 studies were conducted. Study 1 was a randomized double-blind placebo-controlled single and multiple ascending dose study in healthy subjects (HS). Dose levels ranged from 1-600 mg as a single dose and from 10-100 mg t.i.d. for 7 days. Study 2 was a multicenter open-label study in hyperphosphatemic CKD patients on hemodialysis. After an initial washout period of Pi binders, 100 mg ASP3325 was administered t.i.d. for 14 days.

Results: In Study 1, 124 HS were randomized either to ASP3325 (n=90) or placebo (n=34). ASP3325 was absorbed with a t_{max} ranging from 1.4 to 6.7 h; $t_{1/2}$ ranged from 15.5 to 22 h following single dosing under fasted conditions. AUC and C_{max} increased almost dose proportionally following dosing up to 100 mg t.i.d. under fed conditions. Urinary and fecal Pi excretion did not change following ASP3325 administration for 7 days. In Study 2, 9 patients received ASP3325 just before a meal while 10 patients received ASP3325

just after a meal. ASP3325 was generally well tolerated, however gastrointestinal related adverse events were reported in 21.1% of the patients. ASP3325 did not reduce the serum Pi level irrespective of timing of administration in relation to meals.

Conclusions: ASP3325 showed no effect on Pi parameters in both HS and CKD patients on hemodialysis. The role of orally administered NaPi-IIb inhibitors as treatment for hyperphosphatemia in humans remains uncertain.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc.

FR-PO936

Novel NaPi-IIb Inhibitor ASP3325 Inhibits Phosphate Absorption in Intestine and Reduces Plasma Phosphorus Level in Rats with Renal Failure

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Background: The sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) is considered to be an important mediator of intestinal inorganic phosphate (Pi) absorption and therefore recognized as a target molecule for treatment of hyperphosphatemia. We evaluated the pharmacological characteristics of ASP3325, a novel NaPi-IIb inhibitor being developed to treat hyperphosphatemia in chronic kidney disease (CKD).

Methods: The inhibition ratio of ³²P-Pi uptake during AP3325 (0.03-1000 nmol/L) treatment was measured in HEK293 cells stably expressing rat or human NaPi-IIb. To assess the contribution of NaPi-IIb to intestinal Pi absorption, ASP3325 and ³²P-Pi were orally administered in sequence, and then serum ³²P-Pi levels were measured. For normal rats, an ASP3325 containing-diet was provided for three days and the rate of Pi excretion in urine was measured on the final day. For rats with adenine-induced renal failure, an ASP3325 containing-diet was provided for two weeks after which plasma levels of phosphorus were measured.

Results: ASP3325 inhibited ³²P-Pi uptake with an IC₅₀ value of 7.0 nmol/L in HEK293 cells expressing human NaPi-IIb and an IC₅₀ value of 88 nmol/L in HEK293 cells expressing rat NaPi-IIb. In normal rats, oral administration of ASP3325 at 1 and 3 mg/kg significantly reduced the area under the concentration curve of serum ³²P-Pi levels from 0 to 30 min post ³²P-Pi administration. ASP3325 (0.001%-0.01%) reduced urinary Pi excretion dose-proportionally, and treated with 0.01% ASP3325 reduced excretion by 31.2% compared to vehicle (P<0.01). In rat with adenine-induced renal failure, ASP3325 (0.001%-0.01%) exhibited a dose-related reduction in plasma levels of phosphorus. Following two weeks of treatment, plasma level of phosphorus in the vehicle-treated group was 11.43 ± 0.66 mg/dL and in the 0.01% ASP3325-treated group was 6.61 ± 0.47 mg/dL (P<0.01).

Conclusions: ASP3325 inhibited NaPi-IIb-mediated Pi transport and decreased plasma levels of phosphorus in rats with renal failure as well as urinary Pi excretion in normal rats. ASP3325 might therefore be a novel candidate for the treatment of hyperphosphatemia in humans.

FR-PO937

Statin Therapy Reduces Phosphate Levels in Dialysis Patients: Results from the Epidemiological Vitamin K Italian Study (VIKI Study)

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Background: Statin therapy is the mainstay approach to reduce VC and prevent CV events in patients with dyslipidemia. The aim of this study was to investigate an association between statin therapy and plasma phosphate levels in patients on hemodialysis recruited in the VIKI Study.

Methods: The VIKI Study is a multicenter, cross-sectional study in 387 CKD patients on hemodialysis from 18 hospitals in Italy. We determined plasma levels of vitamin 25(OH) D, vitamin K, osteocalcin (bone-Gla-Protein or BGP), matrix-Gla-protein (MGP) and routine biochemistry. Assessment of VC was centralized (Wittman's method: by measuring the length of calcific deposits along the anterior and posterior wall of the aorta). Plasma phosphate levels were dichotomized according to the median value (>4.6 vs <4.6 mg/dl).

Results: 33% of the VIKI Study population (n=126) was on statin therapy. Patients on statin had significantly lower HDL cholesterol (mean±SD: 40.4±11.1 vs 43.3±13.4 mg/dl, p=0.0473) and higher plasma triglyceride levels (median: 164.0 vs 142.0 mg/dl, p=0.0041) than those not on statin. Plasma phosphate levels were significantly lower in patients on statin therapy (4.57±1.12 vs 4.86±1.33 mg/dl, p=0.0365). The analysis of the vitamin K components showed that patients on statin therapy had higher plasma MK7 levels (median: 1.16 vs 0.84 ng/ml, p=0.0241), while concentrations of vitamin 25(OH)D were significantly reduced (median: 26.0 vs 30.7 nmol/L, p=0.0198). In a multivariate analysis adjusted for BMI, angina, LDL, BGP and antibiotics, statin therapy was significantly associated with lower plasma phosphate levels (OR 0.61, 95%CI 0.38-0.98, p=0.0411), while BMI (OR 1.06, 95%CI 1.01-1.12, p=0.0250) and serum BGP levels ≥ 182 mcg/L (OR 1.58, 95%CI 1.01-2.48, p=0.0472) were associated with higher phosphate concentrations.

Conclusions: To our knowledge this is the first evidence of an association between statins and reduced plasma phosphate levels in CKD patients.

FR-PO938

Epidemiology of Kidney Stone Disease in Icelandic Children 1985-2013 Solborg E. Ingvarsdottir,¹ Olafur S. Indridason,² Runolfur Palsson,^{2,3} Vidar O. Edvardsson.^{1,3} ¹Children's Medical Center, Landspítali – The National Univ Hospital of Iceland; ²Div of Nephrology, Landspítali – The National Univ Hospital of Iceland; ³Faculty of Medicine, Univ of Iceland, Reykjavik, NA, Iceland.

Background: The aim of the study was to examine time trends in the incidence and prevalence of kidney stone disease in Icelandic children and adolescents over the past 3 decades.

Methods: Computerized databases of all major hospitals and medical imaging centers in Iceland covering the years 1985 to 2013, were searched for ICD, radiologic and surgical procedure codes indicative of kidney stones for subjects <18 years of age. Incidence was calculated for the time periods 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009 and 2010-2013, based on population information for Icelandic children in these years. Prevalence was calculated for the years 1999-2013.

Results: From 1985 to 2013, there were 186 incident patients, 110 (59%) of whom were female. Median (range) age at diagnosis was 15.0 (0.2-17.99) years. The annual incidence increased from a mean of 3.7/100,000 in the first 5 years to 11.0/100,000 in the years 1995-2004, but decreased thereafter and was 7.8/100,000 in 2010-2013. This trend was more pronounced in boys, for whom the incidence was 4.7/100,000 in the first time period, 11.0/100,000 during 2000-2004 and only 2.4/100,000 in 2010-2013. The incidence for girls increased from 2.7/100,000 in the first time period to 14.2/100,000 in 1995-1999 and has since then leveled off and was 13.6/100,000 in 2010-2013. The largest incidence rise was seen in girls aged 14-17 years, for whom it increased from 9.8/100,000 in 1985-1989 to 39.2/100,000 in 2010-2013. The mean annual prevalence of kidney stone disease in 1999-2013 was 44/100,000 for boys and 51/100,000 for girls.

Conclusions: The incidence rise observed and current incidence of kidney stones in Icelandic children is similar to that recently reported in the USA. A significant incidence increase was observed for both genders in the late 1980's and early 1990's but thereafter trended downwards in boys and remained stable in girls. These trends can not be adequately explained and warrant further study.

Funding: Government Support - Non-U.S.

FR-PO939

Kidney Stone Recurrence in Icelandic Children Solborg E. Ingvarsdottir,¹ Olafur S. Indridason,² Runolfur Palsson,^{2,3} Vidar O. Edvardsson.^{1,3} ¹Children's Medical Center; ²Div of Nephrology, Landspítali – The National Univ Hospital of Iceland; ³Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland.

Background: The 5-year recurrence rate of kidney stones in adults is in the range of 30-50%. No population-based data are available on the recurrence of childhood kidney stone disease. The purpose of this study was to examine the recurrence rate of stone disease in Icelandic children.

Methods: Patients were identified by searching computerized databases of all the major hospitals and the only freestanding radiology clinic in Iceland for diagnostic, radiologic and surgical codes indicating kidney stones in 1985-2013. We subsequently examined medical records of patients with kidney stone disease for information on stone recurrence. A recurrent stone event was defined as radiologic signs of a new stone or a new episode of flank pain and hematuria. The Kaplan-Meier method was used to assess stone-free survival and the log-rank test to compare groups.

Results: We identified 186 children with stone disease during the study period. There were 76 boys with a median (range) age of 14.6 (0.2-17.9) years and 110 girls aged 15.4 (0.8-17.9) years. The follow-up time was 13.0 (0-36) years. A total of 67 children (37%) experienced a second stone event, at a median of 1.9 (0.9-18.9) years after the initial diagnosis. The recurrence rate was 26%, 35%, 41% and 46% after 5, 10, 15 and 20 years of follow-up, respectively. There was no significant difference in recurrence rate between boys and girls ($p=0.24$) and those aged under and over 13 years at diagnosis ($p=0.56$), but a significant difference between patients diagnosed in 1985-1994, 1995-2004 and 2005-2013 was observed, with a 5-year recurrence rate of 9%, 24% and 38%, respectively ($p=0.002$).

Conclusions: In our population-based pediatric study, the recurrence rate of kidney stones is similar to that reported in adults. Further, the rate of recurrence appears to be increasing as has recently been reported for the incidence of childhood stone disease. Increased recurrence rate may be related to improved diagnosis and documentation of stone events and/or environmental factors affecting urinary lithogenicity.

Funding: Government Support - Non-U.S.

FR-PO940

Clinical Stone Events in Patients Diagnosed with Asymptomatic Nephrolithiasis Berglind Eik Gudmundsdottir,¹ Rebekka Sigrún Lynch,² Runolfur Palsson,^{2,3} Vidar O. Edvardsson,^{1,2} Olafur S. Indridason.³ ¹Children's Medical Center, Landspítali; ²Faculty of Medicine, Univ of Iceland; ³Div of Nephrology, Landspítali - The National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: More frequent use of high-resolution medical imaging in recent years has resulted in increased detection of asymptomatic kidney stones (KS). The purpose of this study was to investigate the frequency of clinical stone events in incident patients with asymptomatic KS.

Methods: We searched databases at all major hospitals and imaging centers in Iceland for radiologic and diagnostic codes indicative of KS in the years 2000-2008. We found 2550 incident cases, review of medical records identified 218 patients with no past history of nephrolithiasis or symptoms consistent with KS, who, therefore, were considered to have asymptomatic KS. The patients' records were then thoroughly reviewed for the development of a clinical stone event defined as abdominal/flank pain and hematuria associated with stone passage and/or a stone removal procedure. End of follow-up was between June 2014 and April 2015 or at patient's death. Event-free survival was examined by the Kaplan-Meier method.

Results: Of the 218 patients, 54.6% were men, the median (range) age was 65 (11-91) years. The diagnosis of KS was made by computed tomography in 156 (71.6%), ultrasound in 49 (22.5%) and by plain X-ray in 13 patients. The median follow-up time was 6.0 (0.0-14.5) and 6.7 (0.0-14.9) years for men and women, respectively. Twenty patients (9.2%) underwent a stone removal procedure shortly after diagnosis. Additional 29 patients (13.3%) had a clinical stone event at a median of 2.8 (0.2-14.4) and 1.2 (0.1-9.3) years following diagnosis for men and women, respectively. When a procedure performed to remove an asymptomatic stone was considered a clinical event, a total of 49 patients experienced a clinical stone event, and the 5 and 10 year event-free survival was 80% (95% CI, 74-85) and 73% (95% CI, 65-80), respectively.

Conclusions: Approximately 10% of asymptomatic KS were considered clinically significant at diagnosis. In the remaining patients, a clinical stone event was unlikely to occur over a decade following diagnosis of asymptomatic stone disease.

FR-PO941

Population Attributable Fraction of Modifiable Risk Factors for Kidney Stones Pietro Manuel Ferraro,^{1,2} Eric N. Taylor,² Giovanni Gambaro,¹ Gary C. Curhan.² ¹Div of Nephrology, Catholic Univ of the Sacred Heart, Rome, Italy; ²Channing Div of Network Medicine, Harvard Medical School, Boston.

Background: Several dietary and lifestyle factors are associated with a higher risk of developing kidney stones. In this study, we estimated the population attributable fraction (PAF) of modifiable risk factors for kidney stones including body mass index (BMI), fluid intake, DASH-style diet, dietary calcium intake and intake of sugar-sweetened beverages (SSB).

Methods: We used data from three large ongoing cohorts, the Health Professionals Follow-up Study (41,937 men) and the Nurses' Health Studies (NHS) I (59,864 older women) and II (90,449 younger women). Information on risk factors and incident kidney stones was obtained from validated questionnaires. Cox proportional hazards regression models adjusted for age, race, geographic area, history of diabetes, history of hypertension and use of thiazides were used to estimate the association of each risk factor with development of kidney stones. PAF estimates were obtained by published equations.

Results: The study included 192,250 participants who contributed a total of 3,079,449 person-years of follow-up, during which 6,225 participants developed incident kidney stones. All the modifiable risk factors were independently associated with incident stones in each of the cohorts. The PAF ranged from 5.1% for higher SSB intake to 25.2% for lower fluid intake; the PAF for all the five risk factors combined was 58.1% in HPFS, 46.5% in NHS I and 44.2% in NHS II.

Conclusions: Modifiable risk factors, specifically BMI, low fluid intake, low DASH-style diet, low dietary calcium intake and high intake of SSB, account for about 50% of incident kidney stones in three large prospective cohorts, suggesting that a large proportion of kidney stones could be prevented. Assuming a causal relation, these estimates suggest that prevention measures aimed at reducing those factors could effectively reduce the burden of kidney stones in the general population.

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FR-PO942

Assessment of Health-Related Quality of Life (HRQoL) in Rare Kidney Stone Formers (RKSF) Frank Modersitzki,¹ Alicia Meek,² David S. Goldfarb.¹ ¹Medicine, New York Univ School of Medicine, New York, NY; ²Medicine, Mayo Clinic, Rochester, MN.

Background: Assessment of HRQoL in RKSF is important for following disease course and evaluating treatments. We previously showed that SF with cystinuria reported lower HRQoL than non-cystinuria SF. We now report on baseline characteristics of RKSF in the Rare Kidney Stone Consortium (RKSC) Registries, to be followed prospectively.

Methods: Patients were enrolled from 3 RKSC registries: primary hyperoxaluria (PH), cystinuria and Dent disease. In adults, HRQoL is measured using the SF-36v2 and in children, the SF-10. Participants choose between online assessment or paper-based questionnaire. Results are calculated as norm-based scores (NBS) based on US Standard Population = 50.

Results: 280 participants were enrolled; 200 adults, 80 children; 163 males, 118 females. Mean age was 34 years: for adults 44y and children 10y. 189 adults and 68 children were included in the baseline analysis: PH: 145, cystinuria: 71, Dent: 41. Domain scores for children are presented without cystinuria ($n<10$). For all participants, SF-36 NBS and summary scores for adults are below 50, except for the domain Physical Functioning (mean = 51.2). The lowest total domain score was in General Health with 45.8 +11.8. Adults had significantly different results in Role-Physical, Bodily Pain, Vitality, Social Functioning, Mental Health and Mental Component Score based on disorder. The lowest score was found in cystinuria for General Health (mean = 43.9). The summary scores for Physical Health (PHS) and Psychosocial (PSS) in children were 47.4 +14.2 and 51.80 +9.6 with

lowest summary scores for Dent disease 46.5 PHS and 48.8 PSS. The PSS was lower in Dent disease than PH and cystinuria (p = 0.03). PHS was significantly different in SF-10 specific age groups (p=0.05).

Conclusions: RKSF have worse HRQoL than US adults. HRQoL profiles in adults vary with genetic disorder. Cystinuria was associated with the worst domain and summary scores. Children RKSF have lower HRQoL PHS compared with adults, with the worst results in children with Dent Disease. We will correlate HRQoL with stones and disease course in the next 4 years.

Funding: NIDDK Support, Other NIH Support - NCATS

FR-PO943

Supplemental Calcium Increases the Growth Rate of Renal Calculi in Stone Formers Christopher J. Loftus, Josephine Volovetz, Alexander Chaitoff, Jennifer C. Hu, Carol Swetlik, Joseph Roy Abraham, Manoj Monga, Juan C. Calle. *Glickman Urology and Nephrology Inst, Cleveland Clinic, Cleveland, OH.*

Background: Though dietary calcium is associated with a decreased risk of stone formation, post-menopausal women supplemented with calcium have an increased risk of urinary tract stones. Prior studies have examined the effect of supplemental calcium on the risk of passing symptomatic stones but its role in the pathogenesis of stone formation is not clear.

Methods: We retrospectively identified 6050 patients with a history of urolithiasis. Eligible patients had 2 unenhanced CT scans greater than 30 days but less than 2 years apart during the time of supplementation. For those on no supplementation, the most recent data were used. Of these, 426 patients met the criteria: 195 on calcium, 127 on vitamin D only, and 104 on none. Patients on calcium received 439mg/d± 2793IU vitamin D3/d or 5607IU D2/d and patients on vitamin D only received 3085 IU D3/d or 6296 IU D2/d. Stone burden was calculated as the sum of the maximum diameters of all stones on CT, and rate of stone growth was calculated by the change in consecutive stone burdens divided by the elapsed time between scans.

Results: Stone composition was similar among all groups: 65.5% calcium oxalate, 20.0% calcium phosphate, and 11.8% uric acid. Stone formation rate in mm/year±standard deviation was 7.8±20.8 for calcium group, 3.3±11.4 for vitamin D, and 4.49±13.8 for none. Those supplemented with calcium had a higher rate of stone formation than those supplemented with vitamin D alone, p=0.0105. Supplement group was statistically significant when controlling for serum PTH and calcium on multiple logistic regression. BMI, gender, age and dose of calcium were not significantly associated with stone formation rate while dose of vitamin D3 had an inverse association, p=0.0490.

Conclusions: Supplementation with calcium was associated with a significant increase in stone growth rate in stone formers. Vitamin D supplementation showed no added risk and may potentially have a protective effect. Though the pathophysiology is unclear, these data suggest patients at risk of stone formation should be cautious of supplementation use.

Funding: Private Foundation Support

FR-PO944

Effects of Calcium and Vitamin D Supplementation on Known Stone Formers Christopher J. Loftus, Josephine Volovetz, Alexander Chaitoff, Carol Swetlik, Jennifer C. Hu, Joseph Roy Abraham, Manoj Monga, Juan C. Calle. *Glickman Urology and Nephrology Inst, Cleveland Clinic, Cleveland, OH.*

Background: While high dietary calcium has protective effects against kidney stone formation, the effect of supplementation with calcium and vitamin D on the risk of kidney stone formation remains unclear. Post-menopausal women supplemented with calcium have an increased risk of urinary tract stones; however, there is conflicting evidence for the effects of supplementation on urinary excretion of calcium.

Methods: We identified 6050 patients with a history of urolithiasis by CT scan, 2061 of which had 24-hour urine collections before and after starting supplementation. For patients on no supplement, the most recent data were used. A total of 1,486 patients were supplemented with calcium, 417 with vitamin D only, and 158 with no supplementation. Patients on calcium received an average of 460mg/d± 2726IU vitamin D3/d or 5678IU D2/d and patients on vitamin D only received 3005IU D3/d or 6307IU D2/d.

Results: Stone composition did not differ among groups: 70.0% calcium oxalate, 16.6% calcium phosphate, and 10.8% uric acid stones. There was a significant decrease in urinary calcium excretion in patients supplemented with calcium (p=0.021) and vitamin D (p=0.011) and significant decreases in urinary oxalate in those supplemented with calcium (p<0.0001) and vitamin D (p<0.0001). No differences were seen in the amount of change between supplemented groups for any urinary excretion values.

	Calcium	Vitamin D	None	p-value difference between groups
serum Calcium (mg/dL)	-0.005	-0.005	0.01	0.86
serum Vitamin D (ng/mL)	3.7	7.6	-1.2	<0.0001*
serum PTH (pg/mL)	8.1	-0.43	-5.3	0.024*
urinary Calcium (mg/d)	-5.1	-8.9	5.3	0.19
urinary Oxalate (mg/d)	-4.2	-3.1	-2.0	0.38

The table shows changes from baseline. Among all groups, higher serum calcium was associated with higher urinary calcium excretion (p<0.0001); higher serum calcium (p=0.0007) and vitamin D (p=0.026) were associated with and lower oxalate excretion.

Conclusions: Both calcium and vitamin D supplementation decreased urinary calcium excretion. High serum calcium but not vitamin D was associated with higher urinary calcium excretion in both men and women.

Funding: Private Foundation Support

FR-PO945

Tolvaptan Therapy Effectively Decreases Urinary Calcium Oxalate, Calcium Phosphate, and Uric Acid Supersaturations in Stone Formers Visit Cheungpasitporn,¹ Stephen B. Erickson,¹ Andrew D. Rule,¹ Felicity T. Enders,² John C. Lieske.¹ ¹Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Dept of Health Sciences Research, Mayo Clinic, Rochester, MN.

Background: Drinking large amounts of fluids is universally recommended for urinary stone prevention but can be difficult to do for many stone formers. Tolvaptan, a V2 receptor antagonist, blocks water reabsorption in the collecting duct. This in turn should increase serum osmolality and stimulate thirst. The net effect should be lower supersaturation of stone forming salts, but this has not been proven.

Methods: This double blind, randomized, placebo-controlled, crossover study was conducted in 21 adult calcium urinary stone formers, stratified as majority calcium oxalate (CaOx, n=10) or calcium phosphate (CaP, n=11). Patients were randomized to receive tolvaptan 45 mg/day or placebo for week 1, followed by washout week 2, and then crossover to drug or placebo for week 3. The 24 hr urine volume and chemistries were assessed at the end of week 1 and week 3.

Results: Tolvaptan versus placebo decreased urinary osmolality (204±96 vs 529±213 mOsm/kg, P<0.001) and increased urinary volume (4.8±2.9 vs 1.8±0.9 L, P<0.001). However, the majority of urinary salt excretion rates (mg/24 hrs) including sodium and calcium did not significantly change. Thus, urinary CaOx SS (-0.01±1.14 vs 0.95±0.87, P<0.001) and CaP SS (-1.66±1.17 vs -0.13±1.02, P<0.001) both decreased. Urinary Uric Acid (UA) SS also fell (-2.05±4.05 vs -5.24±3.12, P=0.03). The tolvaptan treatment effect on urinary supersaturation did not differ between CaOx and CaP stone types (P>0.05 for all interactions). Serum sodium increased slightly while on tolvaptan (142±3 vs 141±2 mEq/L, P=0.01).

Conclusions: Use of tolvaptan increased urinary volume but did not appreciably change daily excretion of urinary constituents. The net effect was thus a fall in CaOx, CaP and UA SS. This study highlights the dramatic benefit increased free water ingestion alone can have on urinary supersaturation. Use of tolvaptan or other V2 receptor antagonists could be a useful strategy for selected stone formers not responsive to intensive dietary and/or behavioral counseling.

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FR-PO946

Effect of Increasing Doses of Cystine Binding Thiol Drugs (CBTDs) on Cystine Capacity (CysCap) in Patients with Cystinuria Deepa A. Malieckal,^{1,2} Felicity T. Enders,³ Frank Modersitzki,¹ John R. Asplin,⁴ David S. Goldfarb.^{1,2} ¹Internal Medicine, Div of Nephrology, New York Univ School of Medicine, New York, NY; ²Internal Medicine, Div of Nephrology, NY Harbor VA Healthcare System, New York, NY; ³Health Sciences Research, Div of Biomedical Statistics & Informatics, Mayo Clinic, Rochester, MN; ⁴Litholink Corp, Chicago, IL.

Background: We have proposed that CysCap is a superior measure of lithogenicity when using CBTDs in cystinuria. CBTDs significantly increase urinary CysCap compared to no CBTD. We studied the effect of increasing doses of CBTDs on CysCap in patients with cystinuria.

Methods: 6 patients on CBTDs took 4 different doses of their usual CBTD over 4 weeks: 0, 1, 2, and 3gm for 7 days in random order. On day 6 and 7 they reproduced a self-selected diet and on day 7 of each of the 4 weeks, they did a 24h urine collection to measure CysCap. CysCap values were compared for each of the 4 weeks. 3 patients took tiopronin and 3 patients took d-penicillamine. Alkali doses were unchanged.

Results: All patients had more positive CysCap when switched from 0 to 1gm of CBTDs (p<0.03). There was no further change in CysCap with doses >1gm. Generalized least squares regression demonstrated that only the dose of CBTDs was a predictor of CysCap (p<0.03). Although reproducibility of diet and collections was not attained (based on 24h urine sodium and creatinine), urine sodium and volume were not predictors of CysCap. Those patients with the most negative CysCap values had the greatest positive effect when taking 1gm compared with 0gm CBTD.

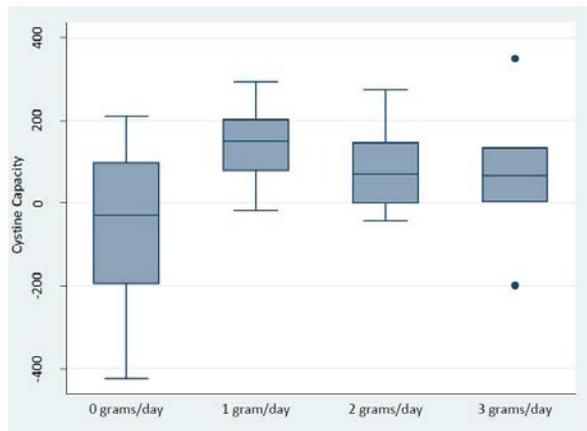


Figure 1. Effect of CBTD dose on CysCap. Length of box: IQR; whiskers: range; line in box: median; ●: outliers.

Conclusions: Prescribing doses of CBTDs greater than 1 gm did not improve lithogenicity significantly. Higher doses may not have clinical benefit. Prescribing the minimum effective dose based on CysCap can potentially decrease the adverse effects often associated with CBTDs.

Funding: NIDDK Support, Other NIH Support - Rare Diseases Clinical Research Network - Rare Kidney Stone Consortium

FR-PO947

Claudin-14 Gene Polymorphisms May Regulate Urine Calcium Excretion
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Background: Claudins are a family of proteins that form paracellular calcium channels in tight-junctions and may thus regulate tubular permeability to divalent cations. Claudin-14 is expressed in the ascending limb of Henke’s loop and inhibits calcium reabsorption. A previous GWA showed that two polymorphisms (SNPs) of *CLDN14* (rs219778 e rs219781) were associated with kidney stones and calcium excretion in an Iceland population. The present study is aimed to explore the effect of *CLDN14* SNPs on calcium excretion.

Methods: We ha performed a retrospective study on 380 hypertensive patients never treated with antihypertensive drugs. These patients underwent a saline load test (i.v. infusion with NaCl 0.9% 2 litres in 2 hours) to evaluate sodium sensitivity. Kidney stones in their clinical history was ascertained by interview. Calcium was measured in 24-h urine and in every 2 hours during the saline load test. Patient genotypes of the *CLDN14* gene were obtained from the GWA data.

Results: Kidney stones were reported by 9.3% of patients. No association was found between *CLDN14* SNPs and stones. As previously observed, rs219778 was associated with 24-hour calcium excretion that was also associated with many SNPs of the *CLDN14* gene. The most significant association occurred with rs219755 (GG 5.62±3.10, GA 4.86±2.49, AA 3.11±1.82 mmol/24h; p=0.00014). The association with calcium excretion was also observed when calcium excretion after saline load was considered (considering rs219755: GG 0.75±0.51, GA 0.72±0.46, AA 0.44±0.27 mmol/2h; p=0.02).

Conclusions: *CLDN14* genotype is associated with calcium excretion. This association is observed even after saline load test, a well known stimulus to urinary calcium excretion. Minor alleles of these SNPs could cause a reduction of calcium excretion and could be protective against kidney stones and hypercalciuria. The lack of association among stones and *CLDN14* SNPs could be due to the method used to identify stone formers.

FR-PO948

Independent Effect of Blood Glucose Level on Urinary Citrate and pH
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Background: Urinary citrate is an important kidney stone inhibitor and its excretion is influenced by systemic acid base status and diet. However, the effects of demographics and other factors on urinary citrate excretion are not well defined, including the independent influence of blood glucose.

Methods: Twenty-four hour urine samples were collected from non-Hispanic white sibships in Rochester, MN. Height, weight, blood pressure, blood glucose, serum creatinine and cystatin C were measured. Diet was assessed using the Viocare food frequency questionnaire. The effects of blood glucose, demographics and diet on urinary citrate excretion, urine pH and net gastrointestinal (GI) alkali absorption were evaluated in bivariate and multivariable models, plus interaction models that included age, sex, and weight.

Results: Samples were available from 709 individuals (mean age 66±9 years). In general urine citrate and urine pH correlated positively with higher net alkali absorption (p<0.0001). Urine pH was higher in women for any given net alkali absorption value, but

not after adjustment for covariates. In multivariable models urinary pH decreased with higher serum creatinine, blood glucose, dietary protein and increased with dietary potassium. Meanwhile, in multivariable models urinary citrate increased with age, weight, eGFR_{Cys}, blood glucose and decreased with loop diuretic and thiazide use. Association of urinary citrate and age was influenced by blood glucose (p=0.01).

Conclusions: In our study urinary citrate and pH correlated positively with net GI alkali absorption. Blood glucose had independent effects on urine pH and urinary citrate. This study provides the first evidence that blood glucose could influence stone risk independent of urinary pH and uric acid crystallization. These observations could provide new insights into the association of obesity and urinary stone disease.

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FR-PO949

Renal Oxalate Secretion Reduces Risk of Systemic Oxalosis in Primary Hyperoxaluria
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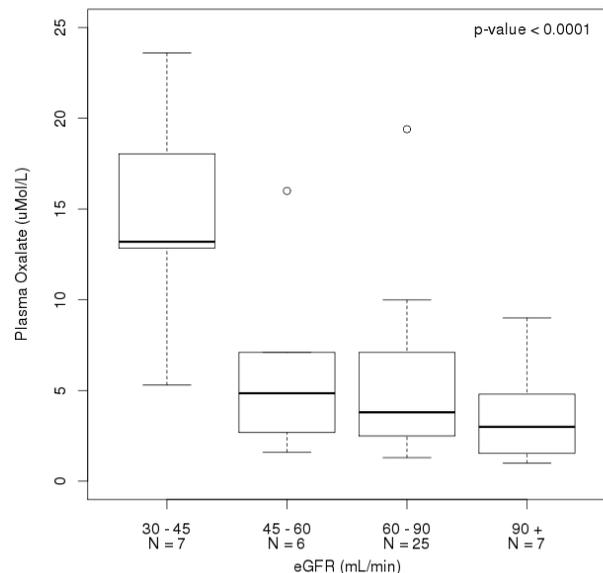
Background: Primary Hyperoxaluria (PH) is a rare genetic disease causing high hepatic production of oxalate. Renal excretion of oxalate keeps plasma oxalate (Pox) controlled but leads to stones and often ESRD. Systemic oxalosis occurs when GFR is reduced and Pox rises above the supersaturation threshold (approximately 45 mmol/L). Renal handling of oxalate in relation to GFR is poorly understood.

Methods: PH patients ≥ 12 years without ESRD were identified from the Rare Kidney Stone Consortium registry. We used the most recent simultaneous Pox, serum creatinine and 24 hour urine oxalate (Uox). Net oxalate secretion (Sox) equals Uox-GFR×Pox. Proximal tubular oxalate (PTox) is Uox corrected for creatinine and estimated proximal tubule water absorption. eGFR is by CKD-EPI (adults) or modified Schwarz (adolescents). We grouped patients by CKD stage and balanced eGFR groups. Analysis was by Fischer exact test and ANOVA.

Results: 45 patients were identified (33 PH-1; 5 PH-2; 7 PH-3). Median age was 23.2 (IQR: 16.7, 32.9) and eGFR was 66.1 mL/min/BSA (54.4, 80.8). Pox, Sox and Uox rose sharply when eGFR fell below 45 mL/min. Similar results were seen in eGFR groups. PTox and Pox increased proportionally (p<0.001).

CKD stage (n)	CKD 1 (7)	CKD 2 (25)	CKD 3a (6)	CKD 3b (7)	p value
PH type 1	6	16	5	6	0.505
Uox mmol/day (SD)	1.01 (0.52)	1.40 (0.72)	1.38 (0.58)	2.60 (0.98)	0.0008
Pox μmol/L (SD)	3.67 (2.82)	5.12 (4.09)	6.18 (5.20)	14.84 (5.85)	<0.0001
PTox μmol/L (SD)	0.21 (0.15)	0.47 (0.29)	0.55 (0.22)	1.26 (5.85)	<0.0001
Sox mmol/day (SD)	0.36 (0.62)	0.88 (0.72)	0.92 (0.32)	1.74 (0.95)	0.007

Plasma Oxalate by eGFR group



Conclusions: Compensation for high oxalate production in PH is maintained through CKD stage 3a. Higher PTox in CKD stage 3b may accelerate proximal tubular CaOx crystallization. Risk for systemic oxalosis is low until at least CKD stage 4.

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FR-PO950

Effect of Antibiotic Treatment on *Oxalobacter formigenes* Colonization
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Background: Kidney stones are a disease of worldwide prevalence with significant public health implications. About 60–80% of stones are composed of calcium oxalate (CaOx). Hyperoxaluria is a major risk factor. *Oxalobacter formigenes* (OF), a member of the human colonic microbiota, plays a major role in net colonic oxalate absorption and secretion. We now report OF colonization rates in a young healthy population, the stability of colonization, and the effects of antibiotic treatment on OF colonization.

Methods: We followed 64 healthy subjects tested for *Helicobacter pylori* (HP), who were treated with antibiotics (Amoxicillin and clarithromycin for 2 weeks) for HP eradication. Using species-specific PCR, we tested for OF colonization at baseline and at follow-up.

Results: Of the 64 subjects (M/F: 24/40; mean age 25.0 + 5.5y) tested for OF, 25 (39%) were positive at baseline. Of 7 OF+ subjects at baseline, subject to HP elimination, 6 became OF-negative at 6 wks, only 2 reverted to positive at week 24, and 4 patients remained negative at follow up (Mean 21.0 + 6wks). Of 16 untreated positive people, 12 (75%) remained positive at follow up (Mean 18.8 + 7.7w), but of 26 untreated negative subjects, only 6 (23%) were positive at follow up (mean 19.7 + 6.6wks), significantly fewer than the untreated positives (p=0.001 by Fisher exact test).

Conclusions: We conclude that OF status remains stable over a follow-up period of several months, with antibiotics suppressing colonization in the majority of people in the short term. The differential long-term effect of antibiotics on OF colonization and its effect on urinary oxalate excretion, will be important to evaluate.

FR-PO951

Identification of Calcium-Oxalate Binding Proteins in Human Urine That Prevent Crystal Adhesion in an *In Vitro* Model of Kidney Stone Formation
 Scott R. Manson, Joel F. Koenig, Qiusha Guo, Katelynn H. Moore, Paul F. Austin. *Dept of Surgery, Div of Urology, Washington Univ, St. Louis, MO.*

Background: There are limited therapeutic options for the treatment of stone disease and about 50% of patients experience at least one recurrence. Existing treatment protocols focus on altering urine concentrations, which presents challenges due to the idiopathic nature of many stones and the variety of underlying factors. In this study, we examine the hypothesis that there are naturally occurring urinary proteins capable of binding calcium oxalate crystals, promoting their clearance, and preventing stone formation. Elucidating these interactions may provide novel therapies.

Methods: Calcium oxalate monohydrate (COM) crystals and fluorescently-labeled derivatives (COM-FITC) were synthesized *in vitro*. Stone formation was modeled *in vitro* by assessing the adhesion of COM-FITC crystals to confluent monolayers of inner medullary collecting duct (IMCD) epithelial cells. Affinity chromatography was used to isolate COM-binding proteins from human urine.

Results: COM and COM-FITC crystals synthesized *in vitro* exhibited the typical prismatic morphology of urinary crystals. Incubation of IMCD cells with COM-FITC crystals resulted in rapid binding to the cell surface with high affinity. The addition of urinary proteins purified from human urine inhibited COM-FITC binding by 76.2%. Furthermore, urinary proteins inhibited the growth of COM crystals in free solution by 63.7%. In using affinity chromatography to isolate COM-binding proteins, we found that this technique was highly specific as only 17.2% of urinary proteins exhibited binding activity. The bound fraction was eluted, purified by electrophoresis, and four prominent proteins were identified (97 kD, 69 kD, 56 kD, 45 kD).

Conclusions: This study demonstrates that urinary proteins bind to COM crystals and inhibit their adhesion to the renal epithelium. Further characterization of these proteins may facilitate the design of peptide-based therapies that prevent crystal adhesion and stone formation as well as the development of diagnostic biomarkers that stratify patients and guide treatment decisions in at-risk populations.

Funding: NIDDK Support, Private Foundation Support

FR-PO952

Hydroxyapatite Induces Tolerance in Primary Human Monocytes Exposed to Calcium Oxalate Crystals
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Background: Although most crystal deposits within tissue produce inflammation, renal interstitial hydroxyapatite deposits do not, accumulating as Randall's plaque. To further explore this lack of response, we investigated the effect of oxalate, hydroxyapatite, and combination of both on time dependent, immunological responses in human THP-1 (monocyte) cells, the precursors to tissue macrophages.

Methods: Using 1 ug/ml LPS and untreated as positive and negative controls, THP-1 cells were exposed to varying concentrations of soluble potassium oxalate (KOx) or CaOx and HA crystals (10, 100, and 1000 ug/ml). In addition, a group of primary human monocytes cells were pre-treated with 100 ug/ml of HA or CaOx followed by secondary treatment with 100 ug/ml HA, 100 ug/ml CaOx, and 1 ug/ml LPS. THP cells were collected at 2, 4, and 8 hours after various treatments, and RNA was analyzed by quantitative real time PCR.

Results: THP-1 cells responded strongly to CaOx in a dose dependent manner producing TNF α , IL-1 β , IL-8, and IL-10 with little to no response to KOx and HA. Pre-

exposure of human monocytes to HA had little effect on cytokine response to subsequent CaOx and LPS exposure; however, pre-exposure to CaOx followed by HA negated all further cytokine production.

Conclusions: In our human monocyte model, the order of CaOx and HA exposure affects monocytic response. HA neither stimulates cytokine production nor inhibits cytokine production when pre-treating monocytes prior to CaOx exposure. Pre-treated CaOx monocytes, however, had decreased cytokine and chemokine expression when secondarily treated with HA. This tolerance mechanism may partially explain the lack of capillary inflammation in the pathogenesis of Randall's plaque.

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FR-PO953

A Low Sodium Diet Inhibits Stone Formation in Genetic Hypercalciuric Stone-Forming Rats
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Background: Increasing dietary (D) sodium (Na) intake results in greater urine (u) calcium (Ca) excretion, leading to the recommendation that D Na be restricted in hypercalciuric stone formers to decrease stone recurrence. However, there is no direct clinical evidence that reduction in D Na intake alone will reduce recurrent stone formation.

Methods: To determine if D Na restriction reduces kidney stone formation, we utilized 101st generation genetic hypercalciuric stone-forming (GHS) rats fed either a low (LNa, 0.05%) or normal (NNa, 0.4%) Na D for 18 wks. Urine was collected at 6 wk intervals; a mean was determined for each analyte and then an overall 18 wk mean calculated. Radiographic analysis for stone formation was done at 18 wks.

Results: As anticipated, LNa decreased mean uNa (NNa=2.48±0.03 mmol/24h; LNa=0.39±0.02, p<0.001) and uCl (NNa=2.65±0.13 mmol/24h; LNa=1.19±0.06, p<0.001). Overall mean uCa was lower with LNa than NNa (NNa=17.3±0.5 mg/24h; LNa=15.2±0.5, p<0.01) as was u phosphate (P) (NNa=16.5±0.6 mg/24h; LNa=13.8±0.4, p<0.001). Urine oxalate (Ox), pH, NH₄⁺, citrate and volume did not differ with diet Na. There were no significant differences in u supersaturation with respect to CaP or CaOx. Serum Ca was slightly increased with LNa (NNa=10.9±0.1 mg/dL; LNa=11.4±0.1, p<0.01) though there were no differences in serum P, PTH or FGF23. Radiographic analysis of kidneys demonstrated a significant decrease in calcification with LNa (calcification scores with a range of 0-3: NNa=1.14±0.15; LNa=0.32±0.12, p<0.001).

Conclusions: Thus a low Na diet reduced uCa and stone formation in GHS rats even though urine supersaturation was not altered. These data, in a genetic model of hypercalciuria and stone formation, lend support to the use of dietary Na restriction to prevent recurrent Ca nephrolithiasis.

Funding: NIDDK Support

FR-PO954

Ethylene Glycol Induced Hyperoxaluria in Rats: A Transcriptional Study
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Background: Hyperoxaluria, if remains undiagnosed, can cause renal injury and inflammation leading to a number of diseases including advanced stages of renal failure. In order to look into the different pathways and molecular mechanisms involved in the kidneys of hyperoxaluric rats, we performed genome wide analysis of differentially expressed genes in the kidneys of rats fed ethylene glycol (EG).

Methods: Male rats were divided into two groups. Rats in one group were fed normal diet and the other group diet supplemented with 1.25% EG. Urinary assays were done at different time intervals and after 14 and 28 days rats were euthanized, kidneys explanted and total RNA extracted for micro array analysis using Agilent 8 x 60K single color arrays. Data was analyzed using bio-conductor Limma (Linear models for micro array analysis) package using R. Gene ontology (GO) and KEGG pathway analyses was also performed. Immunohistochemical (IHC) and Eosin and Hematoxylin (E & H) staining was also done for highly significant genes.

Results: All rats became hyperoxaluric from day 7 and had crystal deposition at different time intervals. Urinary LDH, sodium and creatinine were significantly different in the EG group as compared to the control. There was significant expression of different genes encoding for macromolecular modulators such as osteopontin (OPN), monocyte chemoattractant protein-1 (MCP-1), lipocalin 2 (Lcn-2), fibronectin (Fn-1), clusterin (CLU) and kidney injury molecule-1 (KIM-1) along with nicotine amide dinucleotide phosphate (NADPH) oxidase-4 (NOX-4) and glutathione peroxidase (Gpx-2). Gene analysis showed 17 and 33 differentially expressed pathways for day 14 and day 28 respectively.

Conclusions: Results highlight that the EG treated rats showed heavy deposition of crystals and there were 15 pathways that were common between day 14 and day 28 giving a deep insight into the molecular mechanisms and pathways activated in hyperoxaluric rats.

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FR-PO955

Sulfate and Thiosulfate Competitively Inhibit Oxalate Transport via a *Drosophila* Prestin (dPrestin, dSlc26a6)-Dependent Mechanism Greg M. Landry,^{1,2,3} Taku Hirata,^{1,3} Jacob B. Anderson,¹ Christopher Joseph roel Gallo,¹ Michael F. Romero.^{1,2,3} ¹Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN; ²Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN; ³O'Brien Urology Research Center, Mayo Clinic College of Medicine, Rochester, MN.

Background: Nephrolithiasis affects approximately 12% of men and 6% of women in industrialized countries with the majority of stones being composed of calcium oxalate (CaOx).

Methods: Using *Drosophila melanogaster* as a robust and translatable model of CaOx nephrolithiasis, we studied the effects of sulfate and thiosulfate on oxalate transport, and subsequent CaOx crystal formation, as a proof of principle in providing a nidus to identify new therapeutic interventions.

Results: Results indicate that dPrestin transports thiosulfate with a much higher affinity than sulfate (dPrestin sulfate $K_m = 8.65 \pm 3.87$ mM compared to dPrestin thiosulfate $K_m = 0.23 \pm 0.03$ mM). Additionally, both sulfate (48 h) and thiosulfate (24 and 48 h) were effective at decreasing Malpighian tubule CaOx crystallization with the opposite results observed at 48 h in Malpighian tubules where dPrestin was not expressed indicating a role for principle cell-specific dPrestin in luminal oxalate transport.

Conclusions: Given the higher affinity of thiosulfate for dPrestin when compared to those which are reported for oxalate (dPrestin average K_m for oxalate = 0.87 ± 0.16 mM and for thiosulfate = 0.22 ± 0.03 mM), we have concluded that the ability of thiosulfate to act as a competitive inhibitor of oxalate at the transporter level, specifically dPrestin, may explain the decrease in CaOx crystallization seen in the presence of thiosulfate, but not sulfate. Overall, our findings predict that thiosulfate or oxalate-mimics may be effective as therapeutic competitive inhibitors of CaOx crystallization.

Funding: NIDDK Support

FR-PO956

Complement Receptor 3 Mediates Renal Protection in Experimental C3 Glomerulopathy Thomas D. Barbour, Guang Sheng Ling, Marieta Milkova Ruseva, Liliane Fossati-Jimack, H. Terence Cook, Marina Botto, Matthew C. Pickering. Centre for Complement and Inflammation Research, Imperial College, London, United Kingdom.

Background: C3 glomerulopathy (C3G) is a progressive form of glomerulonephritis (GN) that is frequently associated with abnormalities in regulation of the alternative pathway (AP) of complement. Mice with deficiency of factor H (*Cfh*^{-/-}), a negative AP regulator, are an established experimental model of C3G in which abundant complement C3 accumulates along the glomerular basement membrane.

Methods: We examined the spontaneous renal phenotype in *Cfh*^{-/-} mice with and without accompanying deficiency of complement receptor 3 (CR3), the main receptor for iC3b. We performed accelerated serum nephrotoxic nephritis (ANTN) in CR3-deficient mice to assess the role of CR3 in glomerular injury outside the setting of FH deficiency. The effect of iC3b ligation of CR3 on macrophages and other leukocytes during inflammation was assessed *in vitro*.

Results: In 8-month old *Cfh*^{-/-} mice, accompanying CR3 deficiency was associated with significantly increased albuminuria, glomerular hypercellularity and macrophage influx, and mortality. Bone marrow (BM) transplantation experiments in *Cfh*^{-/-} recipients indicated that the protective effect of CR3 was dependent on BM-derived cells. ANTN produced severe, crescentic nephritis in CR3-deficient mice (but not wild-type mice). *In vitro* ligation of CR3 using iC3b-coated particles down-regulated the proinflammatory cytokine response of both murine and human macrophages to lipopolysaccharide stimulation *in vitro*. These cytokine-modulating effects were cell-type specific, an observation that may reconcile some of the conflicting reports concerning the immune role of CR3 in the literature.

Conclusions: Deficiency of CR3 unexpectedly enhanced the severity of both experimental C3G and immune complex GN. Our findings suggest that pharmacological potentiation of the CR3-iC3b interaction could be therapeutically useful in patients with chronic GN.

FR-PO957

Two Autoimmune Forms of C3-Glomerulopathy Are Defined by Complement Convertases Deregulating Autoantibodies Christine Skerka,¹ Fei Zhao,¹ Giuseppe Remuzzi,² Rossella Piras,² Peter F. Zipfel.^{1,3} ¹Dept of Infection Biology, Leibniz Inst for Natural Product Research and Infection Biology, Jena, Germany; ²Laboratory of Immunology and Genetics of Transplantation and Rare Diseases, IRCCS- Istituto di Ricerche Farmacologiche, 24020- Ranica (Bergamo), Italy; ³Friedrich Schiller Univ, Jena, Germany.

Background: In C3Glomerulopathy (C3G) defective complement activation on level of the C3 convertase is caused by mutations in genes coding for complement components or regulators as well as by autoantibodies. C3 nephritic factor (C3NeF) has been reported in 50-80% of C3G patients. Notably also autoantibodies to C3b and Factor B were identified in C3G patients, which do not score in the standard C3NeF assay. Here we compare how the new C3 convertase reacting antibodies and also C3NeF affect complement regulation on the level of the C3- and the C5 convertases.

Methods: The autoantibodies were isolated from the serum of C3G patients (n=34), assayed for binding to the C3 convertase by ELISA and further characterized by using a number of functional complement assays.

Results: Among the 34 C3G patients, 19 patients were identified with autoantibodies which bind to the C3 convertase, but lack C3NeF. 15 patients were identified C3NeF positive. According to the binding to the C3 convertase, high titer (HT) and low titer (LT) antibodies were identified among isolated autoantibodies from all 34 C3G patients. HT as well as LT antibodies strongly activated the C5 convertase and enhanced C5a generation. Interestingly all antibodies bound to the C3 convertase, but only HT and not LT antibodies enhanced C3 convertase activity. The HT but not the LT antibodies increased C3 convertase assembly, stabilized the convertase and increased C3a generation.

Conclusions: Two classes, HT and LT, of complement C3 convertase binding autoantibodies were identified in C3NeF- positive and negative C3G patients. These antibodies deregulate complement by two different mechanisms: HT antibodies activate complement on the C3- and C5 convertase levels, while LT antibodies activate only on C5 convertase level. We speculate that these functional different autoimmune forms explain responder and non-responder types to therapeutic C5 inhibitors.

Funding: Government Support - Non-U.S.

FR-PO958

Autoimmune C3 Glomerulopathy: Can Complement Inhibiting Drugs Reduce Complement Activation by C3 Convertase Autoantibodies? Friederike Sophie Schulze,¹ Fei Zhao,¹ Giuseppe Remuzzi,² Marina Noris,² Christine Skerka,¹ Peter F. Zipfel.^{1,3} ¹Hans Knöll Inst, Jena; ²Mario Negri Inst for Pharmacological Research, Bergamo; ³Friedrich Schiller Univ, Jena.

Background: C3 glomerulopathy is a severe kidney disorder that is caused by deregulation of the alternative complement pathway. Identified causes include genetic mutations, copy number variations in the CFHR gene cluster as well as autoimmune factors. Some patients but not all respond to therapy with the complement inhibitor Eculizumab. Recently a new class of C3 convertase antibodies was identified in C3G patients who lack classical C3Nephritic factor (C3Nef). We aim at characterising how these new autoantibodies cause complement deregulation and how complement inhibitors affect the action of these autoantibodies.

Methods: IgGs were purified from patients with C3 convertase antibodies lacking C3Nef (n=19) and also from C3Nef+ patients (n= 15). These purified IgGs were tested for their impact on complement activity and the effect of soluble CR1 (sCR1) and Eculizumab was examined by ELISA, Western blot and complement activation assays.

Results: C3 convertase antibodies from patients lacking C3Nef deregulated complement. Some antibodies stabilized the C3 convertase and all activated the terminal complement pathway. C3Nefs activated complement in a related manner. In probes with C3 convertase antibodies sCR1 did inhibit excessive complement activity. Also Eculizumab prevented antibody mediated complement activation. Both inhibitors blocked C3Nef-mediated complement deregulation in a related manner. For some probes from either C3NeF+ or C3NeF- patients a higher dose of sCR1 was necessary to affect C3 convertase activity.

Conclusions: A subgroup of C3G patients present with C3 convertase-binding antibodies but lack C3Nef. Some C3 convertase antibodies deregulate the C3 convertase and all stabilize the C5 convertase. The complement inhibitors sCR1 and Eculizumab reduced complement activity. Patients with antibodies causing only excessive C5 convertase activity may benefit from Eculizumab, whereas patients with excessive C3 convertase may require additional C3 convertase inhibition.

Funding: Government Support - Non-U.S.

FR-PO959

Respiratory Syncytial Virus May Exacerbate Kidney Damage in IgA Nephropathy Through C3a/C3aR and C5a/C5aR Signaling Amplifying the Effects of Th17 Cells Xiaozhao Li,¹ Xinyue Hu,² Ting Meng,¹ Juntao Feng,² Qiaoling Zhou.¹ ¹Dept of Nephrology, Xiangya Hospital of Central South Univ, Changsha, Hunan, China; ²Dept of Clinical Laboratory, Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: The exacerbation of IgA nephropathy (IgAN) is related to respiratory tract infection with respiratory syncytial virus (RSV), but the mechanism is unknown. In this study we investigated the role of complement activation products C3a/C5a and their receptor C3aR/C5aR in response to the effect of T helper 17 (Th17) cells in the pathogenesis of IgAN associated with RSV.

Methods: IgA nephropathy was induced in BALB/c mice with lipopolysaccharide, carbon tetrachloride and bovine serum albumin. Then the mice were sensitized with C3aRA (C3aR antagonist) and C5aRA (C5aRA antagonist) respectively and infected with respiratory syncytial virus (RSV) in sequence. Urine Albumin-Creatinine ratio and sediments were measured. The pathological changes in kidney and lung tissues were observed under microscopy. C3aR and C5aR proteins in kidney tissue were examined by immunohistochemical staining. Th17 cells and regulatory T cells (Tregs) in kidneys were tested by flow cytometry. C3a, C5a, IL-17A, IL-6 and IL-21, IL 22 in the kidneys were detected by ELISA.

Results: The IgAN mice had albuminuria and microscopic hematuria, renal mesangial proliferation, IgA deposition, high electron dense deposition in glomerular mesangial region, decreased frequency of Tregs, increased frequency of Th17 and Th17-Treg ratio. Furthermore, C3a, C5a, C3aR, C5aR and Th17-related cytokines IL-17A, IL-6 and IL-21 were all increased in the kidneys of IgAN mice. Compared with IgAN mice, the manifestations in RSV-IgAN mice were more severe, but alleviated in C3aRA-treated groups and C5aRA-treated groups respectively.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: RSV infections may exacerbate kidney damage in IgAN through C3a/C3aR and C5a/C5aR signaling amplifying the Effects of Th17 Cells. The first two authors contributed equally to this work.

Funding: Government Support - Non-U.S.

FR-PO960

Functional Glomerular Decay Accelerating Factor Induction by Heme: Role of HO-1 Maria Detsika,¹ Giouli Makri,¹ Vasileios Atsaves,¹ Pu Duann,² Elias A. Lianos.^{1,2} ¹Medicine, Univ of Athens, Greece; ²Medicine, Rutgers Biomedical and Health Sciences, NJ.

Background: In hemolytic disorders and glomerular injury associated with hematuria intraglomerular free heme increases and may activate the alternative complement (C) pathway. Rat glomeruli express decay accelerating factor DAF in glomerular epithelial cells (GEC). We assessed whether heme upregulates glomerular DAF to minimize C activation and explored underlying mechanisms.

Methods: *hmx1*^{-/-} and *hmx1*^{+/-} rats were generated by Zinc Finger Nuclease (ZNF)-mediated HO-1 gene disruption and rats with GEC targeted HO-1 overexpression (GEC^{HO-1}) by Sleeping Beauty Transposon mediated transgenesis using a nephro promoter. Wild type (WT) or *hmx1*^{+/-}, *hmx1*^{-/-} or GEC^{HO-1} glomeruli were treated for 18 h with heme (hemin, FePP) or non-iron porphyrins with opposite effects on HO activity: 1) HO inducers, Cobalt (CoPP) and the non-metal protoporphyrin IX (PPIX) and 2) HO inhibitors: Zinc (ZnPP), Tin (SnPP) protoporphyrins, Tin (SnMP) and Chromium (CrMP) mesoporphyrins. C3b deposition in glomeruli was triggered by exposure to 10% rat serum. DAF, HO-1 and C3b levels were assessed by western blotting or Real-time PCR. HO enzyme activity was measured by standard methods.

Results: Constitutive DAF (mRNA and protein) decreased in both *hmx1*^{+/-} and *hmx1*^{-/-} and increased in GEC^{HO-1} glomeruli. Heme, at concentrations encountered in hemolytic disorders (50-400 μM), increased DAF expression in WT glomeruli. This effect was attenuated in both *hmx1*^{+/-} and *hmx1*^{-/-} and augmented in GEC^{HO-1} glomeruli. Heme-mediated DAF induction in *hmx1*^{+/-} glomeruli persisted despite complete HO-1 absence. Of the non-Fe porphyrins, CoPP, ZnPP, and PPIX increased DAF and HO-1. SnPP induced DAF but not HO-1. SnMP and CrMP had no effect on either protein. Hemin or SnPP-mediated DAF induction reduced C3b deposition. This was reversed by PI-PLC which removed membrane bound DAF.

Conclusions: HO-1 regulates constitutive DAF expression and heme-mediated DAF induction. The latter is independent of metal moiety and HO enzyme activity, requires the porphyrin ring and may also occur via a HO-1 independent mechanism. DAF induction by heme is functional and attenuates C-activation.

Funding: Government Support - Non-U.S.

FR-PO961

Complement Activation Impairs Endothelial Cell Migration – Possible Role in TMA Pathogenesis Magdalena Riedl, Daniel Schlam, Fred G. Pluthero, Walter H. Kahr, Christoph Licht. *Cell Biology Program, The Hospital for Sick Children, Toronto, ON, Canada.*

Background: Cell migration is a key requirement in multiple physiological scenarios including angiogenesis and endothelial cell repair. Thrombotic microangiopathy (TMA) is characterized by endothelial cell (EC) activation and injury, in atypical hemolytic uremic syndrome caused by complement activation on ECs. We hypothesized that EC injury in aHUS was – at least in part – caused by complement-mediated inhibition of cell migration.

Methods: To test this hypothesis blood outgrowth ECs were exposed to complement by blocking EC surface regulators (CD46, CD55, CD59) and incubating ECs with 50% normal human serum (NHS; complement active). Heat inactivated serum (HIS; complement inactive), C5-depleted serum (terminal pathway inactive) and media served as controls.

Results: Wound healing assay in fluidic conditions (wound infliction via trypsin/EDTA) showed within 1.5h a wound area decrease to 62.5±4% when perfused with media. Subsequent (1.5h) HIS perfusion allowed for further wound area reduction to 38±6%, similar to C5-depleted serum (46±5%). In contrast, exposure to complement (NHS) inhibited further wound closure (wound area 63±7%, p<0.05). The proliferation rate (% BrdU positive cells after 2 h) was similar between controls and complement-exposed ECs (20±2 vs. 21±3%), and no apoptosis or necrosis was detected within a 30min - 4h observation period (Annexin V, live dead aqua dye). However, we demonstrated an instantaneous but transient cell membrane perforation (via C5b-9, FM1-43X dye) with subsequent Ca²⁺ influx (Fura-2). Consequences of this sublytic C5b-9 deposition caused immediate and sustained (2h) cyto-skeletal (live cell imaging of F-actin, Rho-GTPases), cell-cell contact (decreased VE-Cadherin expression, decreased transendothelial resistance) and cell motility abnormalities (live cell imaging) in complement-exposed ECs, all leading to defective cell migration.

Conclusions: Our data suggest that sublytic EC complement exposure results in impaired cell migration leading to EC injury and defective EC repair – findings extending our current concept of TMA pathogenesis.

FR-PO962

Uncommon Features in Antigen Binding Sites of Human Anti-Glomerular Basement Membrane Autoantibodies Mary H. Foster, Elizabeth Sarah Buckley, Amy G. Clark. *Medicine, Duke Univ Medical Center and Durham VAMC, Durham, NC.*

Background: Detection of pathogenic anti-α3(IV)NC1 collagen autoAb in the serum and kidneys is required for diagnosis of anti-GBM nephritis and Goodpasture Syndrome, yet little is known about the origin and structure of human autoAb in these diseases. The heterogeneity of serum Ig, lack of ready access to key tissues in patients, and inability to reproduce complex immunological microenvironments in vitro present formidable barriers. Humanized models provide a novel platform to circumvent these obstacles.

Methods: We generated Hu-HSC mice by injection of human CD34+ hematopoietic stem cells into immunodeficient NOD-scid-gamma hosts. Mice with an established human immune system (mean blood chimerism 15.0±15.9% at 3 mos post-injection) were immunized twice with α3(IV)NC1 collagen prior to tissue harvest. Human B cells were EBV transformed using CpG oligos and kinase inhibitors, screened for antigen binding, electrofused with a human heterohybridoma, and subcloned. The mAb sequences were determined using PCR of cDNA with published primer panels and analyzed using IMG/QUEST.

Results: Sequence analysis of 6 non-clonally related human anti-α3(IV)NC1 mAb reveals skewed gene use and unusual motifs in the critical HCDR3 that is predominantly responsible for antigen binding. 4 of 6 (67%) human mAb are encoded by an IGH J6 allele, the extended sequence of which enriches for aromatic tyrosine residues in HCDR3. The HCDR3 are exceptionally long, with mean length 26.4 amino acids (a.a.) compared to average human HCDR3 of 15.2 a.a., and include hydrophobic motifs, an autoimmunity signature uncommon in Ig repertoires of healthy individuals and of unimmunized Hu-HSC mice. Similar motifs were observed in murine anti-α3(IV)NC1 mAb, despite substantial species differences in Ig gene loci and a.a. composition.

Conclusions: Our results suggest that binding of α3(IV)NC1 collagen by human anti-GBM autoAb requires unusual structural motifs that can access recessed hydrophobic epitopes and that are normally excluded from the healthy human immune repertoire. Similar motifs in man and mouse suggest origins by convergent selection.

Funding: NIDDK Support, Veterans Administration Support

FR-PO963

Antigenicity Alteration of Deglycosylated Myeloperoxidase Juntao Yu,¹ Zhao Cui,² Minghui Zhao.² ¹Academy for Advanced Interdisciplinary Studies, Peking Univ, Beijing, China; ²Renal Div, Peking Univ First Hospital, Beijing, China.

Background: Myeloperoxidase (MPO) is a kind of enzyme located in the azurophilic granules of neutrophils, which is the most common target antigen of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in Chinese patients. Native MPO possesses five N-glycans at positions 323, 355, 381, 483 and 729. The alteration of MPO antigenicity after deglycosylation of these glycans is not elucidated.

Methods: We prepared deglycosylated MPOs via glycosidases based on commercial human-derived intact MPO, and then detected the antigenicity of deglycosylated MPOs in 40 patients with anti-glomerular basement membrane (GBM) disease without MPO-ANCAs.

Results: We found antibodies against deglycosylated MPOs existed in patients with anti-GBM disease. 12/40 (30%) patients were positive for MPO treated with PNGase F (naked MPO without hydrocarbon side-chain). 12 (30%) patients were positive for MPO treated with Endo H (MPO with one GluNac only). Antibody against the intact native MPO was not detectable in all these patients. Furthermore, clinical analysis presented that the levels of antibodies against deglycosylated MPOs were positively associated with renal dysfunction. The plasma levels of antibodies against naked MPO without glycan were positively correlated with the concentrations of serum creatinine ($P=0.006$, $R^2=0.178$). The plasma levels of antibodies against MPO with one GluNac only were also positively correlated with the concentrations of serum creatinine ($P=0.002$, $R^2=0.234$).

Conclusions: The existence of patients' antibodies towards deglycosylated MPO first discovered the new epitope exposure of MPO after the loss of hydrocarbon side-chain, explicating the possible reasons for antigenicity alteration, and then prompting some clinical significance of these antibodies.

Funding: Government Support - Non-U.S.

FR-PO964

Autoantibodies to a Cryptic Myeloperoxidase-Specific Immunodominant Epitope Correlate with Disease Activity in Patients with MPO-ANCA Vasculitis Jacob J. Hess, Meghan E. Free, Olivier Lardinois, Donna O. Bunch, Caroline J. Poulton, JulieAnne G. McGregor, J. Charles Jennette, Ronald J. Falk, William Franklin Pendergraft. *UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.*

Background: ANCA vasculitis is commonly characterized by polyclonal autoantibody reactivity to one of two autoantigens, proteinase 3 (PR3) and/or myeloperoxidase (MPO). ANCA positivity has been observed in patients with active and quiescent disease. A subset of MPO-ANCA in many patients recognize a peptide sequence referred to as KIV. This peptide is buried within MPO suggesting that this epitope may be exposed by mechanisms that are not yet understood. We assessed human anti-KIV reactivity longitudinally in a large cohort of patients with MPO-ANCA vasculitis to better understand the temporal association of the autoantibody response.

Methods: Serum, plasma, and extensive clinical data from patients with ANCA vasculitis were prospectively collected every 3 months. A highly sensitive and specific indirect ELISA using KIV peptide was developed to longitudinally screen patient samples for reactivity over their disease course. To minimize non-specific antibody signal, reactivity to a scrambled peptide of the same amino acid composition was also measured. A positive signal was defined as two standard deviations above the healthy control mean (HC n=85).

Results: Of 67 patients with MPO-ANCA vasculitis, 28 were positive for human anti-KIV autoantibodies at least once during their disease course spanning an average follow-up of 3.3 years. The majority of these patients displayed positivity during initial stages of disease that receded over time while other patients exhibited recrudescence of reactivity. Further structural analysis of autoantibody binding to native MPO confirmed this peptide to be a cryptic epitope.

Conclusions: These findings suggest that conformational changes in MPO that expose this cryptic epitope may be important in the pathogenesis of MPO-ANCA vasculitis and may provide insight into the etiology of this disease. Furthermore, this assay could help to more clearly define temporal disease activity.

Funding: NIDDK Support

FR-PO965

An Anti-GBM Autoantibody Gene Contributes Risk to Distinct Anti-Collagen Responses Amy G. Clark, Inge M. Wormi-Schudel, Mary H. Foster. *Medicine, Duke Univ Medical Center and Durham VAMC, Durham, NC.*

Background: The mechanism by which anti-GBM nephritis is initiated and regulated remains an enigma. Recent studies indicate that anti-GBM patients' serum IgG react with multiple collagen chains and with atypical alpha3(IV)NC1 epitopes, and that diverse murine anti-collagen autoAb are genetically linked. We examined these relationships in a novel autoAb transgenic (Ig Tg) model expressing an IGKV3 gene used at low frequency in adult mice but enriched in anti-GBM Ig and arthritogenic anti-collagen II IgG.

Methods: Mice expressing an IGKV3-encoded Ig kappa light chain Tg were bred with B6 kappaKO mice, such that all kappa is Tg-derived, and use of lambda chains reflects regulation by editing. Purified B cells or whole splenocytes were cultured +/- Toll-like receptor ligands (TLR4L or TLR7/TLR9L). Quantitation of Tg autoAb binding to alpha3(IV)NC1 collagen or collagen II was performed by ELISA (expressed as OD405 on Ag-coated minus diluent-coated wells, n=6-10 mice/group, mean ± SD).

Results: Tg receptor expression was detected on 65±14% of B cells, with in vivo regulation suggested by low serum kappa levels (µg/ml, 27±28 vs 1029±611 for nonTg kappa+ controls, p<0.01). AutoAb were not detected in supernatants from unstimulated cells (mean OD 0.003±0.006), but were detected after TLR stimulation. AutoAb specificity varied according to TLR and with: (1) B cell surface lambda (editor) expression: anti-collagen II Ig, OD 0.271±0.122 vs 0.037±0.056, p<0.001, for high-lambda-expressing mouse Tg lines L16/L21 (mean lambda+ 47.5±12.4% of cells) vs low-lambda line L24 (mean 25±11.7% lambda+); and, (2) Presence of non-B cells: anti-alpha3(IV)NC1 collagen Ig, OD 0.124±0.104 vs 0.038±0.033, p<0.001, for whole splenocyte cultures vs purified B cells (all data shown for TLR7/TLR9L).

Conclusions: This new model confirms a role for IGKV3 genes in determining different anti-collagen specificities, including reactivity to GBM. This and data not shown suggest that the different specificities are not crossreactive, arise from non-overlapping cell populations, and are regulated in vivo by mechanisms that can be overcome by TLR or hematopoietic cell interactions.

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FR-PO966

Autoantibodies Target Multiple Epitopes in THSD7A in Primary Membranous Nephropathy Hong Ma, David J. Salant, Laurence H. Beck. *Medicine, Renal Section, Boston Univ Medical Center, Boston, MA.*

Background: Thrombospondin type-1 domain-containing 7A (THSD7A) is a large type 1 transmembrane glycoprotein expressed by the podocyte. It serves as the *in situ* antigen in a subset of primary membranous nephropathy patients. Its extracellular domain consists of a regularly repeating structure composed of thrombospondin type-1 and F-spondin repeats, as well as a highly basic region. We sought to investigate the location(s) of the humoral epitopes targeted by anti-THSD7A antibodies in membranous nephropathy.

Methods: N- and C-terminal truncation mutants of THSD7A, as well as constructs comprising single or multiple adjacent domains, were expressed in HEK293T cells. Reactivity with human autoantibodies was assessed by western blot, dot blot, and immunoprecipitation.

Results: Patient sera displayed varying degrees of reactivity to these recombinant constructs, with most sera reacting with 2 or more distinct domains in the more C-terminal, extracellular region of the molecule. A subset of patients also recognized an additional epitope in the N-terminal portion of the molecule. Reactivity with the larger constructs, such as THSD7A serially truncated from the N- or C-termini, was stronger than that against constructs composed of 1 to 4 adjacent domains, and could be detected by western blot, dot blot, and immunoprecipitation. Reactivity with single domains or several multiple adjacent domains was most prominent when detected by immunoprecipitation, and less consistently detected by western blot, which may suggest the presence of conformation-sensitive epitopes within the molecule.

Conclusions: As in PLA2R-associated membranous nephropathy, the humoral response to the target antigen THSD7A involves multiple epitopes within the molecule. Reactivity with autoantibody appears to depend on the conformation of an extended THSD7A

extracellular region. Further analysis of additional anti-THSD7A positive sera will help to better define the dominant epitopes within the molecule, understand the pathogenesis of this autoimmune disease, and identify potential targets for novel therapeutics.

Funding: NIDDK Support

FR-PO967

Intramolecular Epitope Spreading in Phospholipase A₂ Receptor in IMN Quansheng Zhu,¹ Hong Tang,¹ Phat H. Duong,¹ Meryla Waldman,² ¹Medicine, UCLA, Los Angeles, CA; ²NIDDK/Kidney Disease Section, National Insts of Health, Bethesda, MD.

Background: Idiopathic membranous nephropathy (IMN) is an organ specific autoimmune disease. The major antigen responsible for developing IMN in patients has been identified to be the phospholipase A₂ receptor (PLA₂R) expressed in the glomerular visceral epithelial cells. Clinical studies demonstrated that over 70% of IMN patients possess circulating autoantibodies that target PLA₂R triggering immune complexes formation in situ and deposition in the glomerular subepithelial spaces. The immunodominant epitope in PLA₂R was recently located to the extreme N-terminus of the receptor encompassing the CysR-FnII-CTLD1 region. In the rat model of MN, epitope spreading was detected in the antigenic protein, megalin that is correlated with the disease progresses. Whether epitope spreading occurs in human IMN and its relationship to disease progresses is unclear.

Methods: Serum samples from biopsy-proven IMN patients were collected and screened for anti-PLA₂R antibodies using Western-blot and epitope-specific ELISA assays. The reaction of autoantibody and PLA₂R epitope protein was further analyzed using immunoprecipitation and immunoblocking assays.

Results: Western-blot analysis using patient sera against full-length PLA₂R or the dominant epitope region indicated that, 3 of the 12 serum samples that were positive with anti-PLA₂R autoantibodies failed to recognize the dominant epitope protein. Further test of these 3 samples against a series of truncated PLA₂R extracellular domains on Western-blot demonstrated that the autoantibodies bind strongly to the CysR-FnII-CTLD1-3 region of PLA₂R. Interestingly, serial analysis of sera from a patient with worsening proteinuria showed that, the autoantibodies first recognized the CysR-FnII-CTLD1-3 region and then spread to the CysR-FnII-CTLD1 region, suggesting epitope spreading is associated with the disease progresses.

Conclusions: Our results demonstrate for the first time that intramolecular epitope spreading occurs in PLA₂R in IMN. This finding supports the important role of the dominant epitope in IMN pathogenesis and disease progresses.

FR-PO968

Demonstration of a High Titer Low Affinity Anti-PLA₂R Autoantibody in an IMN Patient En Route to End-Stage Renal Disease Michael Shye,¹ Theresa L. Nilson,¹ Ritu Vahi,¹ Miguel Fernando Palma Diaz,² P.C. Pham,¹ Phat H. Duong,¹ Liyo Kao,¹ Douglas Yao,¹ Ira Kurtz,¹ Quansheng Zhu,¹ ¹Medicine, Univ of California, Los Angeles, Los Angeles, CA; ²Pathology, Univ of California, Los Angeles, Los Angeles, CA.

Background: Clinical studies have established that over 70% of patients with idiopathic membranous nephropathy (IMN) possess high levels of circulating autoimmune antibodies targeting phospholipase A₂ receptor (PLA₂R) in the glomerular visceral epithelial cells (podocyte). Binding of autoantibodies to PLA₂R triggers immune complex formation in situ that impairs podocyte biology resulting in foot process effacement and subsequently proteinuria in patients. In this study, we monitored the fluctuation of autoantibody level in a patient progressing to the end-stage renal disease (ESRD) under the supportive treatments.

Methods: Serum samples from an IMN patient progressing to ESRD under supportive treatments over a period of 6 month were collected (5 clinical visits) and tested for the level of anti-PLA₂R antibodies using western-blot, indirect immunofluorescence staining and epitope-specific ELISA assay. The reaction of autoantibodies toward the dominant epitope region of PLA₂R was further analyzed using immunoprecipitation under the non-denaturing and denaturing conditions.

Results: A sharp decline of autoantibody reactivity toward PLA₂R in sera from the last two visits was detected on Western-blot as the patient approaching ESRD. In contrast, an epitope-specific ELISA assay indicated that the autoantibodies were remained at high levels in these two serum samples, and this observation is further confirmed by the immunofluorescence staining analysis. Test of epitope-antibody reaction under the non-denaturing and denaturing conditions revealed that, the properties of the autoantibodies in the last two visits differ significantly from that in the first three visits, which have low affinity toward PLA₂R and only bind to the non-denatured form of the epitope.

Conclusions: Our results demonstrate that a high titer low affinity anti-PLA₂R autoantibody presents in an IMN patient at the late stages of IMN approaching ESRD under the supportive treatments. This autoantibody has altered reactivity toward PLA₂R that only binds to the non-denatured immunodominant epitope of the receptor.

FR-PO969

Immune Complex Binding to Renal Endothelial Cells Induces TRAIL and Promotes Apoptosis Scott E. Wenderfer, Adisak Suwanichkul. *Pediatrics, Baylor College of Medicine, Houston, TX.*

Background: Circulating immune complexes (IC) deposit in the glomeruli of the kidney in many autoimmune diseases, leading to proliferative glomerulonephritis. IC binding can promote proliferation or induce apoptosis in human macrovascular EnCs.

Tumor necrosis family (TNF) superfamily members regulate proliferation and apoptosis, and both ligands and receptors are produced by glomerular endothelial cells (EnC). Tnfrsf10/ TRAIL is up-regulated in the kidneys of patients with IC disease.

Methods: Renal EnCs were cultured from C57BL/6 mice and primary human glomerular EnCs were obtained commercially. Cells were treated with heat aggregated IgG or peroxidase anti-peroxidase IC. Quantitative RT-PCR was used to measure mRNA levels of TNF superfamily members. A cellular ELISA was used to assess TRAIL protein expression on EnC surfaces. Apoptosis was assessed using XTT and H2AX phosphorylation, and caspase 3 activity assays, as well as TUNEL staining. *In vitro* findings were validated in a non-inflammatory murine model of acute IC kidney injury.

Results: TRAIL mRNA expression is up-regulated by renal endothelial cells *in vitro* in the presence of IC binding and *in vivo*. Membrane TRAIL expression on EnCs also increases after treatment with IC in a dose dependent manner. Receptors for TRAIL, DR5, DR6 are also expressed by EnCs at RNA and protein level. Using XTT cell proliferation assays, there is a modest decrease in EnC metabolism or proliferation after treatment with IC. Caspase 3 activity and DNA double strand breaks were both increased in cultured EnCs after treatment with IC in a dose dependent manner. Results were similar for both murine and human glomerular EnCs.

Conclusions: Results suggest that IC binding to glomerular EnCs *in vitro* is pro-apoptotic. Several TNF superfamily members known to promote apoptosis and their receptors are also up-regulated on EnCs treated with IC. Targeting TRAIL binding to DR5 and its downstream signaling pathways may reduce EnC activation or injury in IC kidney diseases.

Funding: NIDDK Support

FR-PO970

Paired Immunoglobulin-Like Type2 Receptor α (PILR α) Negatively Regulates Immune Complex-Mediated Glomerulonephritis Yutaka Sugiyama, Naotake Tsuboi, Yutaka Kamimura, Shoichi Maruyama, Seiichi Matsuo. *Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.*

Background: PILR α expressed mainly on macrophages, dendritic cells and granulocytes, has been described for its regulatory functions for leukocyte β 2 integrin activation in acute inflammation including LPS-induced endotoxin shock model. Here, we investigated roles of PILR α in immune complex (IC)-mediated glomerular inflammation.

Methods: IC-mediated glomerulonephritis was induced by intravenous administration of nephrotoxic serum (NTS) after pre-immunization with rabbit IgG in C57BL/6 (WT) and PILR α ^{-/-} mice. Functional analysis for renal injury was performed by urine albumin and serum creatinine (sCr) concentrations at day 7, 14 and 21. Diseased kidneys from both mouse strains were harvested for histology, renal leukocyte infiltrates by flow cytometry and renal cytokine profiles by ELISA after induction of NTS glomerulonephritis. *In vitro*, $\alpha_{m\beta 2}$ integrin-dependent neutrophil adhesion on IC was evaluated in both mouse strains.

Results: BUN and sCr concentrations were significantly elevated in PILR α ^{-/-} mice compare to wild type mice at day 14 and day 21 and those were highly associated with deteriorated proteinuria. In histological analysis, glomerular damages, corroborated with both glomerular PAS deposits and glomerular crescent formation, were more severe in PILR α ^{-/-} mice at day 21 (p<0.05). Moreover, glomerular neutrophil accumulation was remarkably observed in PILR α ^{-/-} mice compare to WT mice at day 21. In addition, total infiltration of Ly6G^{high} neutrophils, F4/80⁺ macrophages and CD3⁺CD4⁺ T cells in whole kidneys were increased in PILR α ^{-/-} mice than WT mice at day 14 and day 21. Renal proinflammatory cytokine profiles for IL-1 β and IL-6 on day 21 also demonstrated severe renal inflammation in PILR α ^{-/-} mice. *In vitro*, PILR α deficient neutrophils showed enhanced adhesion and spreading on IC compared to WT.

Conclusions: PILR α ^{-/-} deficiency resulted in deteriorated renal damage in mouse IC-mediated glomerulonephritis compare to WT mice, indicating that PILR α negatively regulates IC-mediated leukocyte recruitment by inhibition of $\alpha_{m\beta 2}$ integrin activation.

FR-PO971

Role of Interferon Regulatory Factor 5 and Toll-Like Receptor 7 in Immune-Complex Glomerulonephritis Abraham Cohen-Bucay, Barry K. Horne, Yao Xie, Prachi Shukla, Ian R. Rifkin, Ramon G. Bonegio. *Renal Section, Boston Univ Medical Center, Boston, MA.*

Background: Immune-complex glomerulonephritis (ICGN) is a common cause of glomerular inflammation characterized by the *in situ* formation of immune complexes and activation of the complement cascade. Interferon regulatory factor 5 (IRF5) is a transcription factor acting downstream of toll-like receptors 7 (TLR7) to trigger an inflammatory response. Recent genetic studies have associated systemic lupus erythematosus and other autoimmune syndromes with gain-of-function polymorphisms in the IRF5 gene. We therefore hypothesized that deletion of IRF5 or TLR7 would ameliorate ICGN.

Methods: We induced nephrotic nephritis using an endotoxin-free IgG1 fraction of sheep nephrotoxic serum (NTS) in Fc γ R1b^{-/-} mice that either express (Control) or do not express IRF5 (IRF5-KO) or TLR7 (TLR7-KO). During the first five days following tail-vein injection of NTS, at a time when the heterologous antibody response peaked, we euthanized the mice and compared histology, albuminuria, renal immune cell infiltrate and gene expression.

Results: The control mice developed severe glomerulonephritis characterized by massive albuminuria, prominent kidney mononuclear cell infiltration and presence of crescents or necrosis in 28±6% of glomeruli. In contrast, TLR7-KO and IRF5-KO developed significantly less severe disease with crescents/necrosis in only 6±2% of glomeruli (p<0.01),

and significantly decreased mononuclear cell infiltration (including both patrolling and resident monocytes). Albuminuria was similar in the control and IRF5-KO mice, but significantly lower in the TLR7-KO mice.

Conclusions: IRF5 and TLR7 signaling is required for the development of glomerular inflammation during the heterologous phase of ICGN. However, proteinuria was only ameliorated in the TLR7-KO, but not in the IRF5-KO mice. Therefore an IRF5-independent pathway downstream of TLR7 is responsible for the proteinuria. Consequently, we conclude that the TLR7/IRF5 pathway may represent a novel therapeutic target for the control of glomerular inflammation.

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FR-PO972

Therapeutic TLR9 Inhibition Prevents the Establishment of Anti-Myeloperoxidase Autoimmunity and the Development of Glomerulonephritis in Mice with Established Autoimmunity Sharon Lee Ford,^{1,2} Poh-Yi Gan,² A. Richard Kitching,^{1,2} Stephen R. Holdsworth,^{1,2} Shaun A. Summers.^{1,2} ¹Depts of Medicine & Nephrology, Monash Health, Clayton, VIC, Australia; ²Centre for Inflammatory Diseases, Monash Univ, Clayton, VIC, Australia.

Background: We have shown TLR9 ligation enhances anti-myeloperoxidase (MPO) autoimmunity (AI) and glomerulonephritis (GN) through dendritic cell (DC) activation. We assessed therapeutic TLR9 inhibition on both the development of anti-MPO AI induced through DC vaccination and subsequent development of GN by TLR9 responsive innate effector cells.

Methods: Injection of MPO/Freud's Adjuvant or transfer of MPO/CpG (TLR9 ligand) pulsed bone marrow derived DCs established anti-MPO AI. To stimulate effector cells, intraperitoneal (IP) CpG or MPO/Freud's Adjuvant was injected after inducing anti-MPO AI, prior to triggering renal injury (using anti-glomerular basement membrane globulin). TLR9 signaling was inhibited with an inhibitory oligodeoxynucleotide before both induction of AI and triggering renal injury.

Results: Mice receiving MPO/CpG DCs + IP CpG compared to MPO/CpG DCs + IP CpG (Control) developed heightened immune responses (cells/spleen: 5.4±6 vs 3.6±5x10⁶, p<0.05) and renal injury (urea: 31±7 vs 11±0.3µmol/L, p<0.05; abnormal glomeruli: 93±3 vs 15±3%, p<0.0001) confirming effector cell TLR9 ligation is required for disease induction and a target for therapeutic inhibition. TLR9 inhibition prevented MPO/FCA induced systemic anti-MPO autoimmunity measured by MPO specific dermal DTH swelling (2.6±1 vs 18.6±3Dmm, p<0.05) and decreased frequency of MPO stimulated IL-17A producing cells (6±1 vs 21±3cells, p<0.01) compared to control. TLR9 inhibition prevented IL-17A driven AI in mice receiving MPO/CpG DCs (DTH: 2.3±1 vs 18.6±3Dmm, p<0.001, IL-17A: 21±6 vs 43±8cells, p<0.05). The TLR9 inhibitor was effective at preventing injury when given to mice with established anti-MPO AI compared to control (DTH: 3±1 vs 13±4mm footprint swelling, p<0.05, urea: 26±1 vs 34±3µmol/L, p<0.05, abnormal glomeruli: 43±9 vs 79±5%, p<0.01).

Conclusions: Therapeutic TLR9 inhibition prevents the development of anti-MPO AI and is a therapeutic option to prevent the development of renal injury once anti-MPO AI is established.

Funding: Government Support - Non-U.S.

FR-PO973

TLR9 Activation Aggravates Murine IgA Nephropathy; Possible Role of BAFF Mediated Pathway Yuko Makita, Hitoshi Suzuki, Akiko Takahata, Toshiki Kano, Satoshi Horikoshi, Yusuke Suzuki. *Div of Nephrology, Dept of Internal Medicine, Juntendo Univ School of Medicine, Bunkyo-ku, Tokyo, Japan.*

Background: Contribution of Toll like receptors (TLRs) which play a key role in the innate immune system has been discussed in the pathogenesis of IgAN. We recently demonstrated that TLR9 is importantly involved in progression of kidney injuries in IgAN prone mice. On the other hand, role of B cell activating factor (BAFF) is discussed in the pathogenesis of human IgAN. Present study examined the contribution of BAFF in the TLR9 mediated progression of IgAN using IgAN prone mice.

Methods: Commercially available quiescent IgAN prone mice (ddY mice) at 4 weeks of age were used for this study. They were divided into two groups with (n=8) or without (n=8) TLR9 ligand (CpG-ODN) for 12 weeks. Renal histological lesions and serum levels of IgA, IgG and IgA-IgG immune complexes (IC) were evaluated at 16 weeks of age. Serum levels of aberrantly glycosylated IgA was measured by the binding of Sambucus nigra bark lectin and Ricinus communis agglutinin I. Splenic expressions of TLR9, MyD88, BAFF and its receptor (TACI) were also quantitatively evaluated.

Results: CpG-ODN treated, but not non-treated mice, showed mesangial deposition of IgA, IgG and C3. Moreover albuminuria and renal histological scores based on mesangial proliferation and mesangial matrix expansion in CpG-ODN treated mice were significantly higher than those in non-treated mice. The expressions of MyD88, BAFF and TACI were also significantly increased by treatment with CpG-ODN. Interestingly there were significant correlation between BAFF expression and serum levels of aberrantly glycosylated IgA and IgA-IgG IC.

Conclusions: Present study indicated that TLR9 activation exacerbates murine IgAN via increase of aberrantly glycosylated IgA and nephritogenic IC. In addition, present findings also suggested that TLR9 mediated BAFF expression may be involved in the nephritogenic IgA and IC production.

FR-PO974

Key Role of Apoptosis Inhibitor of Macrophage in Phlogogenic Action of Glomerular Nephritogenic IgA in IgA Nephropathy Akiko Takahata,¹ Kento Kitada,² Chieko Nogi,¹ Satoko Arai,² Yuko Makita,¹ Hitoshi Suzuki,¹ Junichirou Nakata,¹ Satoshi Horikoshi,¹ Toru Miyazaki,² Yusuke Suzuki.¹
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Background: Apoptosis inhibitor of macrophage (AIM), a protein mainly produced by macrophages, has been reported to be related to autoimmune diseases as well as arteriosclerosis.

Methods: We evaluated the role of AIM in IgA nephropathy (IgAN) using IgAN prone mice, *grouped ddY (gddY)* (*J Am Soc Nephrol*, 2012(8):1364-74). Serum of *gddY* mice was injected to AIM-deficient (AIMKO) and wild-type (WT) mice, and proteinuria and glomerular depositions were evaluated over time. In addition, nephritogenic IgA, produced by *gddY* splenic B cells hybridomas, was injected to AIMKO and WT to perform the same evaluation.

Results: We found excessive expression of AIM in *gddY*, which were co-localized with glomerular IgA. Glomerular IgA depositions were observed in AIMKO and WT 2h after the injections of *gddY* serum and purified nephritogenic IgA. The depositions were cleared soon thereafter in WT but later in KO after being accumulated. However, proteinuria was confirmed in WT, but not in KO. Moreover, CD45⁺ macrophages infiltration was significantly delayed and less in KO than in WT. To identify the role of macrophages in the clearance of the glomerular immunoglobulin depositions, Gr1⁺/FcγIV⁺ macrophages were depleted by injecting WT mice with clodronate liposomes and later with *gddY* serum. However, the depletion of macrophages did not change the degree of glomerular depositions in WT, as in non-depleted WT.

Conclusions: These findings suggest that AIM is a critical molecule in the glomerular IgA clearance and subsequent inflammatory triggering induced by infiltrating macrophages in IgAN. Furthermore, AIM may also contribute to such inflammatory responses by glomerular resident cells such as mesangial cells.

Funding: Government Support - Non-U.S.

FR-PO975

Expression of Mesangial Tissue Transglutaminase Is Independent of Aberrantly Glycosylated IgA in Patients with IgA Nephropathy Akihiro Kato,^{1,2} Kazuo Takahashi,^{1,2,3} Tomohiro Mizuno,^{1,2} Stacy D. Hall,³ Yoshiyuki Hiki,⁴ Kiyotaka Hitomi,⁵ Jan Novak,³ Yukio Yuzawa.¹
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Background: It has been reported that tissue transglutaminase (TG2) is essential for mesangial deposition of IgA1 and development of mesangial inflammation in a mouse model of IgA nephropathy (IgAN). We have shown that some IgAN patients have an active form of TG2 in the mesangial area and that mesangial TG2 activity is associated with elevated proteinuria and proliferation of mesangial cells (MC). The impact of aberrantly glycosylated IgA1 on mesangial TG2 expression merits investigation, as circulating immune complexes, including those containing aberrantly glycosylated IgA1, are deposited in the mesangium in IgAN.

Methods: To understand the role of mesangial TG2 in IgAN, expression of TG2 in cultured MC stimulated by sera from IgAN patients with mesangial TG2 activity (IgAN-TG2A), IgAN patients without mesangial TG2 activity (IgAN-TG2N), disease controls (DC), or healthy controls (HC) were assessed. Expression of TG2 in MC stimulated by purified serum IgA1 or enzymatically deglycosylated IgA1 was also assessed. Furthermore, we characterized hinge-region (HR) O-glycosylation profiles of serum IgA1 from IgAN-TG2A and IgAN-TG2N using high-resolution mass spectrometry.

Results: MC stimulated with sera from IgAN-TG2A showed more binding of IgA and expressed more TG2 than those stimulated with sera from IgAN-TG2N, DC, or HC ($P < 0.01$). Mass spectrometric analysis identified 13 IgA1 HR O-glycoforms with up to 3 galactose-deficient glycans. The number of galactose-deficient glycans was not significantly different between IgA1 from IgAN-TG2A and IgA1 from IgAN-TG2N (0.76 vs. 0.79 mol/HR). Enzymatically deglycosylated IgA1 did not change TG2 expression on MC compared to IgA1 from HC.

Conclusions: Sera from IgAN patients enhanced mesangial TG2 expression. Aberrantly glycosylated IgA1 alone was insufficient to increase TG2 expression by MC.

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FR-PO976

Characterization of a Signaling Network That Enhances Production of Galactose-Deficient IgA1 in IgA1-Secreting Cells from Patients with IgA Nephropathy Koshi Yamada,^{1,2} Colin Reilly,¹ Zhi qiang Huang,¹ Joshua Charles Anderson,¹ Milan Raska,^{1,3} Hitoshi Suzuki,^{1,2} Bruce A. Julian,¹ Christopher D. Willey,¹ Jan Novak.¹
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Background: Interleukin (IL)-6, leukemia inhibitory factor (LIF), and oncostatin M (OSM) cytokines are likely involved in the pathogenesis of IgA nephropathy (IgAN). IL-6/LIF/OSM cytokines activate B cells through similar receptors and the downstream JAK/STAT pathways. We identified key roles of STAT transcription factors in IL-6/LIF/OSM-mediated enhancement of production of IgA1 with galactose-deficient O-glycans (Gd-IgA1) by IgA1-secreting cells from IgAN patients. Our study defines how these signaling pathways influence IgA1 O-glycosylation.

Methods: IgA1-secreting cells from IgAN patients and healthy controls (HC) were stimulated with IL-6/LIF/OSM with or without JAK/STAT inhibitors. Gd-IgA1 levels were determined by lectin ELISA. Cell lysates from IgAN and HC cells were analyzed by global tyrosine-kinome profiling using PamStation@12 platform and Western blotting. The role of STAT3 or STAT1 in mediating IL-6/LIF/OSM, signaling was confirmed by siRNA knock-down (k/d).

Results: siRNA k/d of STAT3 and STAT1 reduced production of Gd-IgA1 in IgAN cells induced by IL-6 and LIF/OSM, respectively. A specific inhibitor of JAK/STAT signaling reduced IL-6/LIF-enhanced production of Gd-IgA1, but only in IgAN cells. Global tyrosine-kinome profiling identified nine target peptides that were selectively inhibited by the tested JAK/STAT inhibitor in the IgAN cell lysates. Bioinformatics analyses and pathway mapping identified abnormal signaling in JAK/STAT and MAPK cascades as the highest ranked pathway.

Conclusions: IL-6/LIF/OSM cytokines enhanced production of Gd-IgA1 via overactivation of JAK/STAT pathways in IgAN cells. Global tyrosine kinomic profiling validated this finding and also indicated participation of MAPK. Elucidating the mechanisms of abnormal signaling associated with Gd-IgA1 production in IgA1-secreting cells may provide new targets for treatment of IgAN.

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FR-PO977

TGF-β1 Has the Same Effect with IL-4 on Alteration of IgA1 Glycosylation Through Down-Regulation of Core 1 β1, 3-Galactosyltransferase and Cosmc Jun Xiao,
Nephrology, Dept of Nephrology, the First Affiliated Hospital of Nan Chang Univ, Nanchang, Jiangxi, China.

Background: Aberrantly glycosylated IgA1 plays a pivotal role in the pathogenesis of IgA nephropathy (IgAN). Transforming growth factor-β1 (TGF-β1) mediates the progression of IgAN is well established as a critical IgA isotype switching factor. The effect of TGF-β1 on IgA1 glycosylation has not been illuminated and related mechanism is still unknown.

Methods: We analysed the mRNA levels of Core1β1, 3-galactosyltransferase (C1GalT1) and its molecular chaperone Cosmc and subsequent O-glycosylation of IgA1 in a human B-cell line stimulated with TGF-β1. The surface IgA1-positive human B-cell line was cultured with different concentration of recombinant human TGF-β1 (5, 10, 15, 30ng/ml). The production and glycosylation of IgA1 were determined by sandwich ELISA and enzymelinked lectin binding assay, respectively. The mRNA levels of C1GalT1 and Cosmc were quantitatively measured by real-time PCR.

Results: IgA1 production was stimulated by low concentration of TGF-β1 (5, 10ng/ml), while was suppressed by high concentration (15,30ng/ml). The terminal glycosylation of secreted IgA1 was altered in response to TGF-β1. TGF-β1 stimulation significantly decreased the mRNA levels of both C1GalT1 and Cosmc.

Conclusions: TGF-β1 may play a key role in controlling glycosylation of the IgA1, and may be partly due to the down-regulation of C1GalT1 and Cosmc.

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FR-PO978

Epigenetic Modulation of Vitamin D Receptor (VDR) in HIV-Associated Nephropathy (HIVAN) Nirupama Chandel, Kamesh R. Ayasolla, Shabirul Haque, Rivka Lederman, Ashwani Malhotra, Pravin C. Singhal.
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Background: HIV has been reported to induce podocyte injury through down regulation of VDR in HIVAN. However, the exact mechanism is not clear. Since HIV has been reported to modulate gene expression via epigenetic phenomena, we hypothesized that HIV would be down regulating podocyte VDR expression in HIVAN via chromatin modifications.

Methods: Renal tissues and cortical sections from four week old control (FVB/N) and HIV-transgenic (Tg26) mice (n=4) were evaluated for the expression of SNAIL, VDR, trimethylation of histone 3 at lysine 4 residue (H3K4me³). Human podocytes (HPs) transduced with either empty vector (EV) or HIV (HIV/HPs) were evaluated for the expression of SNAIL, VDR, and H3K4me³. Stably transfected 293T cells (SNAIL/293T) were evaluated for the same profile. Genomic DNAs of HPs were evaluated for cytosine methylation by Epitect kit and bisulphite pyrosequencing. Composition of SNAIL repressor complex was determined by immunoprecipitation (IP) studies. Trimethylation at SNAIL

promoter and binding at VDR promoter were evaluated by ChIP assays. To reverse the VDR expression, HIV/HPs were treated with either VDR agonist (VDA) alone or in combination with either an HDAC inhibitor or a demethylating agent.

Results: Renal tissues of Tg26 mice displayed enhanced expression of SNAIL and H3K4 me³ but down regulation of VDR. Podocytes in renal cortical sections of Tg26 mice displayed enhanced expression of SNAIL and down regulation of VDR. HIV/HPs and SNAIL/293T displayed upregulation of SNAIL but down regulation of VDR. HIV/HPs displayed H3K4 trimethylation at SNAIL promoter and enhanced expression of histone deacetylase (HDAC) 1, DNA methyl transferase (Dnmt) 3b. IP studies revealed the association of HDAC1, Dnmt3b, Dnmt1, and mSin3A with the SNAIL. VDR agonists, HDAC inhibitor, and demethylating agents alone could not reverse VDR expression optimally, but could do so, when used in combination.

Conclusions: SNAIL recruits multiple chromatin enzymes to form a repressor complex that down regulate VDR expression in HIV milieu. To upregulate VDR optimally in HIV milieu, reversal of chromatin modifications are deemed essential.

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FR-PO979

ANCA Disease Patients Demonstrate a Higher Frequency of CD33+ Myeloid Cells with Variable Suppressive Abilities Meghan E. Free,¹ Katie Stember,² JulieAnne G. McGregor,¹ J. Charles Jennette,² Ronald J. Falk,¹ Maureen Su,³ ¹UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; ²Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; ³Pediatrics, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Myeloid-derived suppressor cells (MDSCs), or CD33+ myeloid cells, have been extensively studied in cancer as potent suppressors of T cell activation. Regulatory T cells do not control T cell proliferation in patients with anti-neutrophil cytoplasmic autoantibody (ANCA) disease, therefore we sought to determine the role of CD33+ myeloid cells in ANCA disease as an alternative suppressive mechanism.

Methods: Analyses were performed using flow cytometry on peripheral blood mononuclear cells (PBMCs) from 63 patients stained with relevant antibodies. Suppressive potential of CD33+ myeloid cells was assessed with a standard T cell suppression assay.

Results: Flow cytometric analysis of PBMCs revealed an increased population of lineage negative, HLA-DR negative, CD11bhigh and CD33+ myeloid cells in patients with ANCA disease compared to healthy controls (mean 2.72% versus 0.18% of PBMCs). This CD33+ myeloid cell population also contained MPO and PR3. Suppression assays utilizing patient CD33+ myeloid cells and autologous T cells have demonstrated variable suppressive capacities with the majority of patients exhibiting modest (30-60%) suppression.

Conclusions: CD33+ myeloid cells are increased in patients with ANCA disease and represent a potential source of T cell suppression not previously investigated. Intriguingly, the patients who demonstrated the highest frequency of CD33+ myeloid cells were those who had sequentially received rituximab and cyclophosphamide.

Funding: NIDDK Support

FR-PO980

Endothelial NF-κB Induction by ANCA-Activated Neutrophils Mira Choi,¹ Adrian Schreiber,¹ Claudia Eulenberg,² Ralph Kettritz,¹ Claus Scheideleit,³ ¹Dept of Nephrology, Charité Berlin, ECRC, Berlin, Germany; ²Experimental and Clinical Research Center (ECRC), Berlin, Germany; ³Max-Delbrück Center, Berlin, Germany.

Background: Activation of the NF-κB/Rel family and subsequent transcriptional upregulation of inflammatory mediators plays a central role in vascular diseases. ANCA vasculitis is an inflammatory condition where ANCA-activated neutrophils (PMN) interact with the endothelium resulting in necrotizing vasculitis. We hypothesized that ANCA-activated PMN promote endothelial NF-κB and vascular inflammation.

Methods: NF-κB activation was assessed by IκBα degradation, EMSA, RT-PCR and IHC. NF-κB was studied in renal tissue from mice and patients with ANCA-induced NCGN, ANCA-stimulated PMN and endothelial cells.

Results: In kidney extracts from mice in which we had induced anti-MPO Ab-mediated NCGN, we observed a significant correlation between the percentage of crescents and NF-κB activity by EMSA (R²=0.72, n=20). Similar correlations were found for crescents and upregulation of the NF-κB dependent genes TNFα and IκBα. In renal biopsies from patients with ANCA-induced NCGN, we observed strong phospho-p65 staining in the glomerular convolute. Regarding the importance of PMN-EC interactions in ANCA vasculitis, we studied NF-κB activation in PMN and ECs in vitro. Low-dose TNFα priming resulted in little IκBα degradation in PMN, but this effect was not further increased by mAb to PR3/MPO. We studied NF-κB activation in EC when co-incubated with mAb-stimulated PMN and observed significant IκBα degradation in EC (n=10). We confirmed this with human ANCA preparations. Cell-free PMN supernatants were sufficient for endothelial NF-κB activation indicating that direct cell-cell contact was not required. Consequences of endothelial NF-κB activation were the upregulation of endothelial TNFα and IL-8 mRNA and its release as cytokines into the supernatant, which lead to increased recruitment and adhesion of new PMN.

Conclusions: Renal NF-κB activation and NCGN severity were closely correlated. Our in vitro data demonstrate that ANCA-activated PMN induce endothelial NF-κB activity thereby promoting vascular inflammation by recruiting more PMN. Inhibiting endothelial NF-κB may help limiting the ANCA-mediated damage.

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FR-PO981

Ubiquitin C-Terminal Hydrolase-L1 Controls Dendritic Cell Cross Priming of the CD8⁺ T Cell Response Anna Reinicke,¹ Malte Mühlig,¹ Pina Schmucker,¹ Timo Lischke,² Elisabeth Mettke,³ Christian Kurts,³ Hans-willi Mittrücker,² Catherine Meyer-Schwesinger,¹ ¹Nephrology, III. Medical Clinic, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; ²Immunology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; ³Experimental Immunology, Inst for Experimental Immunology, Bonn, Germany.

Background: Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) is a central deubiquitinating enzyme of the ubiquitin proteasomal system. UCH-L1 is thought to regulate the pool of ubiquitin. Within the kidney, UCH-L1 is *de novo* expressed in glomerular podocytes in human and rodent glomerulonephritis. Mice with constitutive UCH-L1-deficiency exhibit an exacerbated course of immune-complex nephritis suggesting that UCH-L1 affects the ability to mount an effective renal immune response. Aims of the study were 1. To identify the origin of renal tubulo-interstitial UCH-L1-expressing cells, 2. To analyze the response of UCH-L1-deficient mice to a bacterial infection, 3. To analyze the role of UCH-L1 in dendritic cells (DCs).

Methods: Constitutive UCH-L1-deficient mice were generated by Cre-Lox technology. The immunologic phenotype was investigated by challenging UCH-L1-deficient mice with *Listeria monocytogenes*. Cross presentation and cross priming assays were performed *in vitro* and *in vivo*. The DC phenotype was assessed in naïve and stimulated DCs by FACS, Western, proteasomal and deubiquitinase-based activity assays, and real-time PCR.

Results: UCH-L1 is expressed in DCs isolated from kidney and spleen, and in bone-marrow derived cultured DCs. UCH-L1 expression in bmDCs is regulated by IFN-γ and LPS. UCH-L1 activity is upregulated by LPS stimulation while other deubiquitinating enzymes upregulate their activity in the absence of UCH-L1. DCs are specially equipped to cross present antigen to stimulate a CD8⁺ T cell response. Cross-presentation of cell-associated antigen in UCH-L1-deficient DCs is significantly reduced *in vitro* and *in vivo* while activation of a CD4⁺ T cell response is unaffected. Finally, exposure to *L. monocytogenes* results in a significantly decreased generation of antigen-specific CD8⁺ T cells.

Conclusions: We describe a hitherto unrecognized role for UCH-L1 in controlling CD8⁺ T cell activation by DCs.

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FR-PO982

CD103+ Dendritic Cells Elicit CD8⁺ T Cell Responses to Accelerate Kidney Injury in Adriamycin Nephropathy Qi Cao,¹ Qing Li,¹ Xin M. Wang,² Chengshi Wang,¹ Yuan Min Wang,³ Stephen I. Alexander,³ Yiping Wang,¹ David C. Harris,¹ ¹Centre for Transplant and Renal Research, Westmead Millennium Inst for Medical Research, The Univ of Sydney, Sydney, NSW, Australia; ²Flow Cytometry Facility, Westmead Millennium Inst for Medical Research, The Univ of Sydney, Sydney, NSW, Australia; ³Centre for Kidney Research, Children's Hospital at Westmead, Sydney, NSW, Australia.

Background: CD103+ dendritic cells (DCs) in non-lymphoid organs exhibit two main types of function, namely maintaining tolerance by induction of regulatory T cells and protecting against tissue infection through activation of CD8 T cells. However, the characteristics and functions of CD103+ DCs in kidney remain unclear.

Methods: Adriamycin nephrosis (AN) was induced in BALB/c mice. The distribution, phenotype and function of kidney CD103+ DCs were assessed in normal and AN mice. CD103+ DCs were depleted by neutralizing CD103-saporin (SAP) antibody in AN mice to examine their role *in vivo*.

Results: In the present study, we showed that CD103+ DCs are one of four subpopulations of renal mononuclear phagocytes in normal kidney; they expressed DC-specific surface markers, transcription factors and growth factor receptors, and were found in kidney cortex but not medulla. The number of kidney CD103+ DCs was significantly increased in mice with Adriamycin nephropathy (AN) and depletion of CD103+ DCs attenuated kidney injury in AN mice. The possible mechanisms underlying the pathogenic role of CD103+ DCs were examined. *In vitro*, kidney CD103+ DCs preferentially primed CD8 T cells, and did not directly induce tubular epithelial cell apoptosis. Adoptive transfer of CD8 T cells significantly exacerbated kidney injury in AN SCID mice, whereas depletion of CD103+ DCs impaired activation and proliferation of transfused CD8 T cells, and thereby reduced kidney injury in AN SCID mice treated with CD8 T cells.

Conclusions: Kidney CD103+ DCs display a pathogenic role via activation of CD8 T cells in Adriamycin nephropathy.

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FR-PO983

Advanced Glycation End Products Induced the Imbalance Between Th17 and Treg Cells via RAGE Pathway in Diabetic Nephropathy Yanlin Zhang, Ao Cheng. *Dept of Nephrology, The First Affiliated Hospital of Xiamen Univ, Xiamen, Fujian, China.*

Background: There was imbalance of Th17/Treg cells in patients with diabetic nephropathy, but the mechanism was still unclear. Advanced glycation products (AGEs) often accumulated in the patients with diabetic nephropathy. The main purpose of this experiment is to explore whether AGEs can cause the imbalance of Th17/Treg cells through RAGE signaling pathway.

Methods: (1) Recruitment of 20 healthy adults and 40 diabetic nephropathy patients of CKD stages 3 to 5, and detection AGE-HSA content and ratio of Th17 cells / Treg cells to verify the correlation. (2) Prepared AGE-HSA in vitro and isolated and cultured the initial CD4⁺ T cells from healthy volunteers peripheral blood to explore the effect of AGE-HSA on the differentiation of initial CD4⁺ T cell: AGE-HSA with different dose and time stimulated initial CD4⁺ T cells, or pretreatment with RAGE-siRNA or RAGE neutralizing antibody, and to detect the ratio of Th17 cell and Treg cells by flow cytometry and determine the expression mRNA of RORgt and Foxp3, and the expression of mRNA and protein of STAT3 and HIF-1 α .

Results: (1) In patients with diabetic nephropathy, there is accumulation of AGEs and increasing of Th17 cells and the reduction of Treg cells. The ratio of Th17 cells and Treg cell is imbalance (increase in the proportion). There was a positive correlation between the concentration of AGEs and ratio of Th17 cells and Treg cells; (2) the AGE-HSA in a dose dependent manner induced the initial CD4⁺ T cells to differentiate Th17 cells, and blocking RAGE could mitigate this effect; (3) AGE-HSA increased the expression of RORgt in the initial CD4⁺ T cells, but had no effect on Foxp3. After blocking RAGE, it could inhibit the expression of RORgt induced by AGE-HSA; (4) the expression of STAT3 and HIF-1 α was raised in the initial CD4⁺ T induced by AGE-HSA, while blocking RAGE, expression of STAT3 and HIF-1 α induced by AGE-HSA was inhibited.

Conclusions: In the patients with diabetic nephropathy, there was positively correlated between the content of AGEs and the proportion of Th17 cells and Treg cells, and AGE-HSA can induce the initial T CD4⁺ cells to generate Th17 cells by RAGE- RORgt signaling.

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FR-PO984

RORgt Activation in biTregs Promotes Lupus Nephritis Malte A. Kluger, Anna Nosko, Paul Diefenhardt, Boeren Goerke, Matthias C. Meyer, Michael Luig, Rolf A. Stahl, Oliver M. Steinmetz. *Nephrology, Hamburg Univ Medical Center.*

Background: We recently characterized Foxp3⁺ regulatory T cells, co-expressing the Th17 characteristic transcription factor RORgt, as an independent and bi-functional T cell lineage (biTregs). biTregs secrete both, anti-inflammatory (IL-10, IL-35), but also pro-inflammatory (IL-17) cytokines. Studies in a model of acute crescentic glomerulonephritis suggest that pro-inflammatory biTreg functions are mediated by RORgt. This is of high clinical relevance, since multiple RORgt blocking agents are currently under development.

Methods: Systemic lupus erythematosus (SLE)/Pristane in biTreg^{ROR}-mice.

Results: Time course analyses showed increasing infiltration of biTregs into kidneys of pristane injected mice with a maximum at around 5 months. Subsequently percentages decreased and were back to baseline at 8 months. To study the functional role of RORgt in biTregs, Foxp3^{Cre} x RORC^{fl/fl} mice were generated (biTreg^{ROR}). Renal histology at 8 months showed severe proliferative glomerulonephritis in pristane injected wild type mice. Histological injury in the biTreg^{ROR} group, in contrast, was significantly ameliorated. Renal leukocyte infiltration and albuminuria were also reduced by knockout of RORgt in biTregs. As one possible explanation for the improved outcome, we found that biTregs from wild type mice produced pro-inflammatory IL-17 at all observed time points, while biTregs from biTreg^{ROR} mice did not. In order to assess effects of biTreg expressed RORgt on development of systemic auto-immunity, we studied humoral immune responses. Analyses, however, showed unaltered serum anti-U1-RNP auto-antibody levels of all isotypes. Likewise, renal IgG and complement C3 deposition remained unchanged. This indicates that RORgt activation in biTregs directs renal injury by cellular effectors but does not play a major role for generation of humoral auto-immunity.

Conclusions: Our data provide first evidence for presence and functional importance of biTregs in SLE. Importantly, biTreg expressed RORgt was identified as a factor promoting development of renal injury. Our data therefore favor RORgt directed interventions as innovative new therapeutic option for lupus nephritis.

FR-PO985

IL-2/Anti-IL-2 Complex Attenuates Lupus Nephritis by Expansion of Regulatory T Cells Hye Jin Lim, Ji-Jing Yan, Hyunjin Ryu, Tai Yeon Koo, Kyungok Min, Jae-Ghi Lee, Bohae Kang, Curie Ahn, Jaeseok Yang. *Transplantation Center, Seoul National Univ Hospital, Republic of Korea.*

Background: Regulatory T(Treg) cells play an important role in the pathogenesis and control of autoimmune diseases. Systemic lupus erythematosus(SLE) is an autoimmune disorder characterized by the production of antibodies to self-nucleic acids, immune complex deposition, and tissue inflammation such as glomerulonephritis. We therefore hypothesized that the IL-2/anti-IL-2 complex(IL-2C), a mediator of Treg expansion, can ameliorate progression and reduce the mortality of lupus-prone mice.

Methods: NZWF1 female mice progressively produce high levels of autoantibodies and resultant deposition of immune-complexes drives lupus-like glomerulonephritis. NZWF1 female mice were treated intraperitoneally with IL-2 /anti-IL-2 mAb(JES6-1) 4 times a week starting at 24 weeks of age, and were analyzed at 36 weeks of age. Lupus-like disease progression was assessed by measurement of proteinuria, dsDNA, cytokine levels and kidney histology, as well as by flow-cytometric analysis of cellular infiltration.

Results: IL-2C induced an effective and sustained expansion of CD4⁺Foxp3⁺CD25⁺ Tregs in both kidney and spleen. Compared with the vehicle-treated controls, NZWF1 female mice treated with IL-2C showed less proteinuria, less acute and chronic pathological lesions in the kidney and better survival. There were significant differences in glomerular injury, tubular injury and vasculitis scores, as well as in the quantitative analysis of IgG and C3 deposition between the two groups. Disease activity markers were reduced in serum of the IL-2C group. IL-2C treatment reduced plasma cell populations in spleen, inhibition of B and T cell infiltration of the kidney tissue, and suppressed IFN- γ CD4⁺ and

Th17⁺CD4⁺ cells in both spleen and kidney. When compared with combination therapy of steroid and mycophenolate mofetil, IL-2C treatment showed similar or better outcomes. Depletion of Tregs with anti-CD25 antibodies abrogated the beneficial effects of IL-2C.

Conclusions: IL-2C protects lupus-prone mice against lupus nephritis by expanding Tregs and suppressing inflammation. Therefore, IL-2C could have a therapeutic potential in lupus nephritis.

FR-PO986

Hyporesponsive T-Cell Phenotype Predicts a Subset of Focal Segmental Glomerulosclerosis (FSGS) Patients Responsive to Rituximab Chang-Yien Chan,¹ Isaac Liu,¹ Lourdes Paula Real Resontoc,¹ Kar Hui Ng,¹ Yiong Huak Chan,¹ Yew Weng Perry Lau,¹ Stanley C. Jordan,² Kong Peng Lam,³ Wee Song Yeo,¹ Hui Kim Yap.¹ ¹Paediatrics, National Univ of Singapore, Singapore; ²Cedars Sinai Medical Center; ³Bioprocessing Technology Inst, A-Star, Singapore.

Background: Rituximab has been used with variable success in difficult FSGS, but the immunological basis of its efficacy is poorly characterized. This study aimed at identifying T-cell subsets in pediatric FSGS patients in order to define an immunological signature predictive of a favorable response to rituximab.

Methods: 22 FSGS patients (median age 14.4 years, range 6.2-25.0 years) were recruited prospectively to receive rituximab (375mg/m² fortnightly to a maximum of 4 doses). Median duration of follow-up was 26.7 months (range 6.5-66.6 months). Baseline immunological subsets were compared with 30 healthy controls, and subsequently examined for association with response to rituximab. Good response was defined as complete resolution of proteinuria accompanied by cessation of prednisolone and calcineurin inhibitors within 3 months.

Results: Of the 22 patients, 12 (54.5%) responded to rituximab therapy. Activated CD154⁺CD4⁺CD3⁺ subsets before rituximab were significantly lower in responders (54.9 \pm 8.10%) compared to non-responders (78.9 \pm 5.18%) (p=0.03) and controls (75.7 \pm 2.49%) (p<0.001). IFN- γ CD3⁺ subsets were similarly decreased in responders (0.55 \pm 0.24%) compared to non-responders (7.21 \pm 2.11%) (p=0.005) and controls (12.4 \pm 2.15%) (p<0.001). IL-2⁺CD3⁺ subsets were also lower in responders (0.24 \pm 0.14%) compared to non-responders (4.42 \pm 1.59%) (p=0.007) and controls (6.3 \pm 1.5%) (p=0.003). Significant recovery of all 3 activation subsets occurred 3 months post-rituximab treatment. Using ROC curve analysis, activated CD154⁺CD4⁺CD3⁺ (AUC 0.82, 95% CI 0.63-1.00), IFN- γ CD3⁺ (AUC 0.86, 95% CI 0.67-1.00) and IL-2⁺CD3⁺ (AUC 0.82, 95% CI 0.63-1.00) were good predictors of response to rituximab.

Conclusions: We have identified prognostic markers which define a subset of FSGS patients bearing an immunological signature representing hyporesponsiveness to T-cell stimulation, with good response to rituximab therapy.

FR-PO987

Cytokine Profiling in Rituximab-Treated Pediatric Focal Segmental Glomerulosclerotic Nephrotic Patients Wee Song Yeo, Chang-Yien Chan, Hui Kim Yap. *Pediatrics, Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore, Singapore.*

Background: Focal segmental glomerulosclerosis (FSGS) is the most common histological pattern seen in pediatric steroid-dependent and steroid-resistant nephrotic patients. In recent years, rituximab is increasingly used in nephrotic patients who have failed therapy with conventional immunosuppressants. This study aimed to examine the cytokine profile in rituximab-treated pediatric FSGS nephrotic patients and elucidate the cytokine profile differences between responders and non-responders.

Methods: Our study population consisted of 13 pediatric FSGS patients who underwent rituximab therapy. Plasma cytokine profiling was performed on each of these patients utilizing multiplexed Luminex[®] Cytokine Human 27-Plex assay pre- and post-rituximab therapy. Statistical analysis was performed using Wilcoxon signed-rank test with a p-value of less than 0.05 considered as statistically significant.

Results: Five (38%) of the patients responded to rituximab, defined as having achieved complete resolution of proteinuria accompanied by cessation of prednisolone and calcineurin inhibitors within 3 months. All patients in the study demonstrated an increase in plasma interferon-gamma-inducible protein (IP)-10 levels post-rituximab therapy (554.3 \pm 62.4 pg/ml (pre) vs 793.4 \pm 125.5 pg/ml (post), p=0.008). Comparing the cytokine profile between responders and non-responders, responders demonstrated a positive mean-fold change in macrophage inflammatory protein (MIP)-1 α , in contrast to non-responders which demonstrated a negative mean fold change (0.23 \pm 0.16 vs -0.17 \pm 0.08, p=0.04). There were, otherwise, no noted significant differences in the other cytokines i) pre-/post-rituximab and ii) between responders and non-responders.

Conclusions: Our study results suggest the development of a pro-inflammatory state in our patients post-rituximab therapy. The increase in plasma IP-10 in patient post-rituximab may account for the phenomenon of rituximab-associated colitis. The finding of increased plasma MIP-1 α in responders compared to non-responders is novel. Further mechanistic studies are required to ascertain the role of MIP-1 α in the mechanism of action of rituximab.

Funding: Government Support - Non-U.S.

FR-PO988

Gut-Kidney Axis in the Pathogenesis of IgA Nephropathy Gabriella Lauriero,¹ Eustacchio Montemurno,¹ Maria De angelis,² Valentina Maranzano,¹ Lucia Vannini,³ Loreto Gesualdo.¹ ¹DETO-Nephrology Unit, Univ of Bari, Italy; ²DiSSPA, Univ of Bari, Italy; ³Dept of Agricultural and Food Sciences, Univ of Bologna, Italy.

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. It is characterized by deposition of deglycosylated IgA1 and IgG antibodies in the glomeruli and its pathogenesis is only partially defined. Intestinal microbiota could be involved in IgAN, as suggested by the observation that B-cell activation factor (BAFF) transgenic mice had high levels of aberrantly glycosylated serum polymeric IgA, the presence of commensal flora and the circulation of corresponding specific IgA antibodies being essential for the development of IgA deposits. BAFF is an important regulator of B cell maturation, survival and function. The aim of the study was to analyze the role played by gut-kidney axis in the pathogenesis of IgAN.

Methods: 16 healthy controls (HC) and 32 IgAN patients (16 non progressors - NP and 16 progressors - P) were included in the study. Serum creatinine, estimated Glomerular Filtration Rate, 24h-proteinuria and histological lesions following Oxford Classification (MEST score) were analyzed. Gut microbiota, urinary and fecal metabolome of all subjects were characterized by 16S sequencing, Biochrom 30 series amino acid analyzer and gas-chromatography mass spectrometry/solid-phase microextraction (GC-MS/SPME). Galactose-deficient IgA1 (Gd-IgA1) were measured by helix aspersa agglutinin binding assay. BAFF serum levels were quantified by ELISA.

Results: Some traits of the gut microbiota and urinary and fecal metabolome profiles significantly differed between P, NP and HC. Gd-IgA1 and BAFF were significantly higher in IgAN patients, particularly in P, compared to HC (Gd-IgA1: $p \leq 0.01$ P vs HC; $p \leq 0.05$ NP vs HC; BAFF: $p \leq 0.01$ P vs HC). IgAN patients with histological grade at diagnosis M1, E1, S1 and T1 had significantly higher levels of serum BAFF than HC. Moreover, serum BAFF levels were positively correlated with 24h-proteinuria ($r = 0.47$, $p = 0.0069$) and with the levels of fecal phenolic metabolites ($r = 0.61$, $p = 0.0003$).

Conclusions: Gut-kidney axis might play an important role in the pathogenesis of IgAN.

FR-PO989

Intestinal Macrophages Polarized to Activation of Pro-Inflammatory and Had Dysfunction of Phagocytosis Leading to Aggravate Microinflammation and Assist Bacterial Translocation as Carrier in Uremia Rats Lingshuang Sun, Hongli Jiang, Hua Liu, Meng Wei. *Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of Medicine School.*

Background: This study investigated whether intestinal macrophages are related to low-grade inflammation and bacterial translocation (BT) during uremia, and whether probiotics can alter the macrophage activity.

Methods: Male Sprague-Dawley rats were randomly divided into 3 treatment groups: sham, uremia (untreated), and uremia + probiotic. The expression of cell surface antigen CD11a (a.k.a., lymphocyte function-associated antigen 1 [LFA1]), inducible nitric oxide synthase (iNOS), ICAM1, and TGF- β were analyzed by immunohistochemistry. Gene and protein expression of early growth response protein 1 (EGR1) and TLR4 in intestinal specimens were determined. Density of labeled macrophages and tracer bacteria in intestinal and extraintestinal tissues were examined by immunofluorescent microscopy, and macrophage micromorphology were examined by transmission electron microscopy.

Results: Intestinal segments of the uremia exhibited markedly high intensity of CD11a, iNOS, ICAM1, and TGF- β staining. Gene and protein expression levels of intestinal TLR4 and EGR1 were also highest in this group. Intestinal segments of uremic rats exhibited high density and broad distribution of tracer bacteria and macrophages. Intestinal macrophages in untreated rats showed fewer cytoplasmic protrusions and pseudopodia. Administration of probiotics resulted in restoration of macrophage classic activation and phagocytosis that was associated with a reduction in BT.

Conclusions: In the uremic state, intestinal macrophages are polarized toward a proinflammatory phenotype that results in low-grade inflammation. Abnormal intestinal macrophage activation and impaired phagocytic function are associated with increased BT. Probiotics may reduce BT by enhancing phagocytosis of intestinal macrophages.

Funding: Government Support - Non-U.S.

FR-PO990

Linking PI3K/AKT Signaling to RNase 7 Production and Urinary Tract Sterility Tad Eichler, Robert Easterling, Brian Becknell, John David Spencer. *The Research Inst at Nationwide Children's, Columbus, OH.*

Background: Antimicrobial peptides (AP) play a role in shielding the uroepithelium from uropathogenic *E. coli* (UPEC). We have identified RNase 7 (R7) as a potent, epithelial-derived AP that is secreted by the bladder urothelium and renal intercalated cells. R7 serves as front-line shield to protect the urothelium from UPEC. Currently, there is a limited understanding of the mechanisms that regulate R7 production, and if dysregulated R7 production increases UTI risk. Using a chemical inhibitors transcriptome PCR array, we identified the PI3K/AKT pathway as a unique regulator of R7. Here, we confirm that PI3K/AKT regulates R7 expression and relate changes in R7 to UTI pathogenesis.

Methods: To evaluate the role of PI3K/AKT in regulating R7, we treated primary human renal epithelial cells (REC) with insulin, a known PI3K agonist and/or insulin+wortmannin (wort), a PI3K/AKT inhibitor. PI3K/AKT activation was confirmed by Western blot. qRT-PCR and ELISA quantitated R7. UPEC growth in insulin and/or insulin+wort treated REC

media was assessed. Since patients with diabetes mellitus (DM) have decreased PI3K/AKT activity and increased UTI risk, we measured serial urinary R7 levels in new onset Type 1 DM ($n=16$) before and after starting insulin.

Results: Insulin-dependent phosphorylation of the PI3K/AKT in REC was detected by 1hr. Insulin induced R7 gene expression and protein expression 3-fold (25.23 ± 3.16 ng/mL to 72.12 ± 16.20 ng/mL, $p=0.026$). R7 induction was abolished with wort, confirming PI3K/AKT involvement in R7 production. Media from insulin treated REC suppressed UPEC growth compared to media from REC pretreated with wort or vehicle control, suggesting that PI3K/AKT and R7 is involved in UTI pathogenesis. Urinary R7 levels were significantly lower in DM patients compared to healthy controls (13.61 ± 3.94 vs 71.95 ± 15.40 ng R7/mg UCr, $p < 0.02$). After 24-hr of insulin, urinary RNase7 levels increased.

Conclusions: PI3K/AKT activation is required for R7 induction. R7 induction suppresses UPEC growth. Diabetics, with decreased PI3K activity, have lower urinary R7 levels. These data may indicate why UTIs are more prevalent with DM and may provide new regulatory targets for UTI treatment.

Funding: NIDDK Support

FR-PO991

Serum Acetate and Lipopolysaccharide Levels Correlate with Disease Activity in Patients With Lupus Nephritis Daniel Tak Mao Chan, Ping Lung Chan, Qing Zhang, Kin Yi Au, Desmond Y.H. Yap, Mel Chau, Susan Yung. *Dept of Medicine, The Univ of Hong Kong, Hong Kong.*

Background: Lupus nephritis is a severe manifestation of systemic lupus erythematosus and is associated with poor prognosis. The gut microbiota has been implicated in the etiology of autoimmune diseases. Bacterial products from the gut may enter the circulation and induce inflammatory responses. Acetate is a short chain fatty acid (SCFA) produced by gut microbiota and lipopolysaccharide (LPS) is a component of the outer wall of Gram-negative bacteria. We measured serum acetate and LPS levels and intra-renal expression of their cell surface receptors in lupus nephritis patients to investigate the potential relationship between gut microbiota and lupus nephritis pathogenesis.

Methods: Serum acetate and LPS levels were measured in patients with biopsy-proven severe proliferative lupus nephritis, patients with non-lupus glomerular diseases and healthy controls ($n=50$ for each group). Intra-renal expression of LPS-binding protein (LBP) and GPR-41 and GPR-43 (SCFA receptors) was also examined.

Results: Serum acetate and LPS levels were significantly higher in patients with lupus nephritis compared to levels in patients with non-lupus renal diseases ($P < 0.05$, for both) and healthy subjects ($P < 0.01$, for both). In lupus nephritis patients, serum acetate and LPS levels were significantly higher during disease flare ($P = 0.04$ and $P = 0.0015$ respectively compared to levels during remission). Serum LPS level correlated with acetate level ($r = 0.52$, $P < 0.001$), and inversely correlated with that of IgG ($r = -0.61$, $P < 0.01$). Renal LBP, GPR-41 and GPR-43 expression was markedly increased in lupus nephritis patients compared to healthy controls, and was predominantly detected in the tubulo-interstitium, associated with inflammatory cell infiltration, fibrosis and tubular atrophy. LBP, GPR-41 and GPR-43 expression showed similar staining intensities and localization in patients with lupus nephritis and those with non-lupus renal diseases.

Conclusions: Our data suggest that acetate and LPS may be involved in the pathogenesis of lupus nephritis and non-lupus glomerular diseases.

Funding: Government Support - Non-U.S.

FR-PO992

Noninvasive Assessment of Macrophage Activation in Experimental Glomerulonephritis Using Optical Imaging with Near-Infrared Light Serves as a Surrogate of Disease Activity Sebastian Braehler, Dongyue Huang, Matthew David Cheung, Walter J. Akers, Alfred Hyoungju Kim. *Washington Univ School of Medicine, St. Louis, MO.*

Background: Glomerulonephritis (GN) represents a major cause of morbidity & mortality. The standard for diagnosing GN is through renal biopsy, but this is not performed uniformly across many centers. There is an unmet need to identify a noninvasive approach for recognizing GN. Recent advances in deep tissue imaging using probes detected by near-infrared (NIR) wavelengths have enabled the noninvasive probing of biologic activity. Macrophage infiltration of the kidney is observed in early GN and once activated, express the cysteine protease cathepsin B. Thus, renal macrophage activation can be assessed using an NIR probe that becomes fluorescent upon cleavage by cathepsin B. We tested the ability of using NIR optical imaging to assess renal macrophage activation as a noninvasive marker for early-stage GN.

Methods: GN was induced in 129 mice by nephrotoxic serum (NTS) delivered intravenously (IV). Proteinuria was assessed using albumin ELISA & chromogenic creatinine assay. H&E and PAS stained slides of mouse kidneys were observed using light microscopy. Presence of renal macrophages was confirmed using FACS. NIR optical imaging of anesthetized mice was performed following IV administration of a cleavable sensor for cathepsin B & fluorescence intensity of kidney regions quantified.

Results: In mice with uninflamed kidneys, we confirmed the paucity of renal macrophages. Accordingly, there was minimal renal fluorescence signal as determined by fluorescent molecular imaging of cathepsin B activity. 3 days post-NTS administration, we observed a massive influx of macrophages into the kidney, along with nephrotic range proteinuria. This correlated with a significant increase in renal fluorescence intensity signal in NTS mice compared to control mice.

Conclusions: Induction of GN by NTS caused significant macrophage infiltration, which was detected noninvasively by a cathepsin B-activatable probe and NIR optical imaging. These data establish the proof-of-principle that NIR optical imaging may represent a translatable approach to establishing early stages of GN.

Funding: Private Foundation Support

FR-PO993

Improved Tissue Clearing and 2-Photon Imaging of Mouse Kidneys Reveals Immune Cell Architecture in Nephrotoxic Nephritis Matthew David Cheung, Dongyue Huang, Alfred Hyoungju Kim. *Rheumatology, Washington Univ School of Medicine, St. Louis, MO.*

Background: Tissue clearing approaches such as CLARITY renders tissue transparent, and in combination with two-photon microscopy, enables microscopic visualization deep internal structures within unaltered organs. These cutting edge approaches have drastically improved the understanding of cellular circuits in the brain. However, application of this approach has only recently been described for the kidney. Here, we clear mouse kidneys to better understand the immune cell architecture following induction of nephrotoxic nephritis (NTN) using a modified lipid removal approach that also worked for human kidney fragments.

Methods: 129 mice were injected intravenously with nephrotoxic serum to induce NTN. Mice were perfused with an acrylamide monomer solution to form the basis of the hydrogel. Lipid removal was accomplished using 8% sodium dodecyl sulfate (SDS). An aminoalcohol solution was used to quench light absorbing heme in red blood cells trapped within the tissue. Cleared mouse kidneys were stained with antibodies specific for B cells, T cells, macrophages, and dendritic cells (DCs). Human kidney fragments were incubated in acrylamide monomer solution, then cleared as mentioned above. Cleared tissue was imaged using two-photon microscopy.

Results: Compared to previously published protocols, perfusion of acrylamide monomers into mice significantly accelerated the tissue clearing process. Enhanced tissue clearing was observed when we incubated kidneys in aminoalcohols. We observed vast networks of lymphocytes, macrophages, and DCs in cleared NTN kidneys compared to control kidneys. Human kidneys also were cleared using this approach, and we noted DC networks in healthy donor controls.

Conclusions: We identified a new protocol that enhanced and accelerated tissue clearing in mouse and human kidneys. Using this approach, we found elaborate networks of lymphocytes and monocyte-derived cells in NTN mouse kidneys. We also observed DC networks in healthy human kidney donor fragments. These data demonstrate the utility of tissue clearing in evaluating cellular architecture in mouse and human kidneys.

Funding: Private Foundation Support

FR-PO994

Natural IgM Mediates Ischemic AKI Lindsey R. Goetz,¹ Jennifer Laskowski,¹ Brandon Renner,¹ Rachel A. Woolaver,¹ Liudmila Kulik,¹ Kazuo Takahashi,² Matthew C. Pickering,³ Joshua M. Thurman.¹ ¹Dept of Medicine, Univ of Colorado Denver School of Medicine, Aurora, CO; ²Dept of Radiology, Massachusetts General Hospital, Boston, MA; ³Centre for Complement and Inflammation Research, Imperial College London, London, United Kingdom.

Background: Glomerular IgM deposition occurs in numerous “non-immunologic” kidney diseases and has been shown in chemical and inflammatory models of injury. We recently demonstrated that complement activation within the kidney leads to neo-epitope formation. Because the alternative complement pathway is activated in renal ischemia/reperfusion (I/R) injury, we hypothesized that complement activation during renal I/R generates neo-epitopes recognized by natural IgM antibodies that then exacerbate inflammatory injury.

Methods: To investigate this hypothesis, we used a 24 minute I/R model.

Results: We first subjected soluble IgM deficient (sIgM^{-/-}) mice to renal I/R and found a trend toward less severe injury in these mice vs. wild type (wt) controls (mean BUN of 135 ± 39 [SD] and 152 ± 26 mg/dL, respectively; n ≥ 6, p = NS). To accentuate complement activation in this model, we then exposed mice heterozygous for complement regulatory protein factor H (fH^{+/-}) to the same I/R protocol and found that the fH^{+/-} mice sustained worse renal injury and had greater glomerular IgM deposition than wt controls (mean BUN of 114 ± 46 and 63 ± 48 mg/dL, respectively; n ≥ 14, p = 0.009 and mean glomerular IgM RFUs of 44 ± 7 and 22 ± 7, respectively; n = 8, p = 0.0002). To further evaluate IgM pathogenicity, we induced I/R injury in mice deficient in both factor H and IgM (fH^{+/-}/sIgM^{-/-}) and noted a trend toward attenuation of renal injury in the fH^{+/-}/sIgM^{-/-} vs. fH^{+/-} mice (mean BUN of 106 ± 69 and 127 ± 52 mg/dL, respectively; n ≥ 7, p = NS) with data collection ongoing.

Conclusions: These data suggest that natural IgM contributes to ischemic renal injury by binding neo-epitopes generated during complement activation in the kidney. This adds to a growing body of evidence suggesting a common final pathway of IgM-mediated glomerular injury in a variety of “non-immunologic” renal disorders and offers a novel therapeutic target for the treatment of these diseases.

Funding: NIDDK Support

FR-PO995

Activation of Toll-Like Receptor 2 in the Pathogenesis of Contrast-Induced Nephropathy Kristina Angela Rathmell,¹ Altaf-M Khan,¹ Federico Jose Teran,¹ Kathleen S. Hering-Smith,¹ Eric E. Simon,^{1,2} Vecihi Batuman.^{1,2} ¹Medicine, Nephrology & Hypertension, Tulane Univ, School of Medicine, New Orleans, LA; ²VA, SLVHCS, New Orleans, LA.

Background: Innate immunity mediated by Toll-like receptors (TLRs) is involved in the pathophysiology of contrast-induced nephropathy (CIN). We studied the expression of TLRs and associated molecules in CIN using human renal proximal tubule epithelial cells (RPTECs) and aged diabetic (db/db) mice.

Methods: We cultured RPTECs in normal (5 mM) or high (35 mM) glucose media for 24 h and then exposed them to nonionic (iodixanol or iohexol) and ionic (Urografin) contrast media (CM) at a dose of 25–100 mg iodine/ml for another 24 h in the same media. 24-wk-old male db/db mice were given nonionic CM i.v. (3 g of iodine/kg bw) after 24 h water deprivation. All mice were sacrificed 24 h after CM injection.

Results: The mRNA expressions of TLR2 increased by 2.5 fold ($p < 0.05$), TICAM-1 by 1 fold ($p < 0.01$) and TNF- α by 1.7 fold ($p < 0.05$) in RPTECs exposed to iohexol compared to untreated RPTECs in a dose-dependent fashion. RPTECs in high glucose for 48 h and exposed to iodixanol showed significantly increased apoptosis compared to RPTECs in normal glucose. 24-wk-old db/db mice became obese, polyuric, glucosuric, ketonuric, and had increased GFR, systolic blood pressure, urine NGAL, and renal tubular damage compared to nondiabetic (db/m) control mice. 24 h after iohexol injection, db/db mice showed a significant decrease in GFR, metabolic acidosis and significant increases in serum creatinine, urine and kidney KIM-1 levels and kidney damage histologically compared to control db/db mice. After iohexol administration, the mRNA level of TLR2 was significantly increased by 2.4 fold ($p < 0.01$) in kidney compared to control mice but there was no change in TLR4 expression. The expression of CD11b and CD68 were also significantly upregulated in kidney.

Conclusions: High glucose RPTECs and diabetic (db/db) mice are vulnerable to CIN. Innate immunity mediated by TLR2 plays a major role in the pathogenesis of CIN as demonstrated by *in vitro* and *in vivo* studies. TLR2 may prove to be a promising drug target for the development of new therapeutics against CIN.

Funding: Private Foundation Support

FR-PO996

Heparanase Deficiency Improves Renal Function During Experimental Glomerulonephritis Marjolein Garsen,¹ Marilen Benner,¹ Henry Dijkman,² Jin-ping Li,³ Ton J. Rabelink,⁴ Israel Vlodavsky,⁵ Jo H.M. Berden,¹ Angelique Rops,¹ Michael Elkin,⁶ Johan Van der Vlag.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Pathology, Radboud Univ Medical Center, Nijmegen, Netherlands; ³Medical Biochemistry and Microbiology, Uppsala Univ, Uppsala, Sweden; ⁴Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; ⁵Cancer and Vascular Biology Research Center, Bruce Rappaport Faculty of Medicine, Haifa, Israel; ⁶Sharett Inst, Hadassah-Hebrew Univ Medical Center, Jerusalem, Israel.

Background: Heparanase (HPSE), a heparan sulfate (HS)-specific endoglucuronidase, mediates the onset of proteinuria and renal damage during experimental diabetic nephropathy. Glomerular HPSE expression is increased in the majority of proteinuric diseases. The exact role of HPSE in the development of other inflammatory glomerular diseases is still unknown.

Methods: Here, we evaluated the role of HPSE in two models of experimental glomerulonephritis, being anti-glomerular basement membrane and lipopolysaccharide (LPS)-induced glomerulonephritis, in wild type (WT) and HPSE-deficient mice.

Results: Induction of experimental glomerulonephritis led to an increased HPSE expression in WT mice, which was associated with a decreased glomerular HS expression and albuminuria. Albuminuria was reduced in the HPSE-deficient mice in both models, which was accompanied by a better renal function and less renal damage. Notably, glomerular HS expression was preserved in the HPSE-deficient mice. Glomerular leukocyte and macrophage influx was reduced in the HPSE-deficient mice, which was accompanied by a reduced expression of both Th1 and Th2 cytokines. *In vitro*, tumor necrosis factor (TNF)- α and LPS directly induced HPSE expression and increased transendothelial albumin passage in a HPSE-dependent manner.

Conclusions: Our study shows that HPSE deficiency ameliorates proteinuria and renal damage in experimental glomerulonephritis by preserving glomerular HS expression, and reducing leukocyte and macrophage influx, and by affecting the local cytokine milieu.

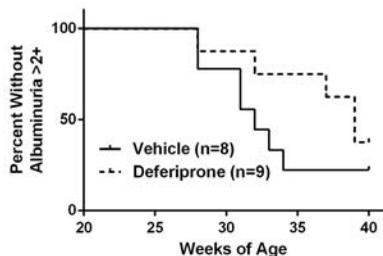
FR-PO997

Iron Chelation as a Novel Renoprotective Strategy in Lupus Nephritis Erika L. Boesen. *Cellular & Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.*

Background: Poorly liganded iron damages tissue via several mechanisms. Multiple iron homeostasis proteins have been proposed as urinary biomarkers of lupus nephritis, and we have previously found that renal tissue iron levels are increased in the (NZBxNZW)F1 mouse model of lupus nephritis. Anemia is also common in lupus patients. Together, these data suggest that dysregulation of body iron homeostasis may occur in lupus. This pilot study tested whether (i) iron chelation is renoprotective in the (NZBxNZW)F1 model of lupus nephritis, and (ii) whether this therapy adversely affects hematological parameters.

Methods: Female (NZBxNZW)F1 mice were treated with the iron chelator deferiprone from 20 weeks of age onwards. Albuminuria was monitored in 24h urine samples collected weekly, and mice were sacrificed at >2+ (>100mg/dL by dipstick) or 40 weeks of age, whichever was sooner. Hematocrit, red cell hemoglobin, plasma non-heme iron concentration as well as kidney and liver iron concentrations were measured at sacrifice.

Results: As shown in Figure 1, there was a trend towards later onset of albuminuria in deferiprone-treated mice compared with vehicle treated mice (median onset of albuminuria 39 and 32 weeks, respectively).



Liver iron concentration was significantly lower in deferiprone-treated mice than vehicle-treated mice, consistent with effective iron chelation. Renal cortical and outer medullary iron concentrations were not significantly different between groups. Unexpectedly, hematocrit was significantly improved by treatment with deferiprone (48±1% versus 39±3% in vehicle-treated mice; P<0.01), whereas red cell hemoglobin and plasma non-heme iron concentrations were not different between groups.

Conclusions: Our pilot data suggest that iron chelation may delay the onset of albuminuria in a mouse model of lupus nephritis without adversely affecting hematological parameters.

Funding: Private Foundation Support

FR-PO998

IKK2 Inhibition Inhibits the Initiation, but Aggravates the Progression of Crescentic Glomerulonephritis Janine Gotot,¹ Eveline Piotrowski,² Gisa Tiegs,³ Ulf Panzer,² Christian Kurts,¹ Friedrich Thaiss,² *Rheinische Friedrich-Wilhelms-Univ, Inst of Experimental Immunology, Bonn, Germany;* ²*Universitätsklinikum Hamburg-Eppendorf, III Medizinische Klinik, Hamburg, Germany;* ³*Univ Medical Center Hamburg-Eppendorf, Inst of Experimental Immunology and Hepatology, Hamburg, Germany.*

Background: The NFκB transcription factor family facilitates the activation of dendritic cells (DC) and CD4⁺ T helper (Th) cells, which are important for protective adaptive immunity. Inappropriate activation of these immune cells may cause inflammatory disease, and NFκB inhibitors are promising candidate drugs.

Methods: Here, we investigated whether inhibiting the NFκB component IKK2 can attenuate crescentic glomerulonephritis, a severe DC- and Th cell-dependent kidney disease by induction of the paasive and the accelerated NTN mouse model.

Results: Prophylactic pharmacological IKK2 inhibition reduced DC activation, Th cell activation and ameliorated glomerulonephritis in mice. However, therapeutic IKK2 inhibition during ongoing disease, which is relevant for clinical situations, unexpectedly aggravated the nephritogenic immune response and disease symptoms. This resulted from systemic loss of regulatory T cells (T_{reg}), which have been previously shown to protect against crescentic glomerulonephritis and which require IKK2 as well.

Conclusions: In conclusion, although IKK2 inhibition can suppress the induction of nephritogenic immune responses in vivo, it may aggravate such responses in clinically relevant situations, because it also impairs T_{reg} and thereby unleashes pre-existing nephritogenic responses. Our findings argue against using IKK2 inhibitors in chronic glomerulonephritis, and perhaps also in other immune-mediated diseases.

Funding: Government Support - Non-U.S.

FR-PO999

Transfused M2 Macrophages Ameliorate Renal Injury in Murine Nephrotoxic Serum Nephritis Qiuna Du, Naotake Tsuboi, Yutaka Sugiyama, Seiichi Matsuo, Shoichi Maruyama. *Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.*

Background: Glomerular leukocyte infiltration is a hallmark of glomerulonephritis. In addition to the effector roles of glomerular macrophages (Mφ) for tissue injury, recent studies found involvement of alternatively activated macrophages (M2 Mφ) in resolution of kidney inflammation. The aim of this study is to directly assess the potential of M2 Mφ to protect against renal injury in murine nephrotoxic serum (NTS) nephritis.

Methods: Bone marrow (BM)-derived Mφ and mouse iPS-derived Mφ were obtained under the stimulation of IL-4/IL-13 to differentiate M2a Mφ with high expression of CD206. FACS and RT-PCR were performed to assess efficient Mφ differentiation. 0.6 x 10⁶ of M2a Mφ were intravenously transferred 4 days after NTS nephritis induction. Immunostaining was used to detect Mφ, T cell and neutrophil infiltration. Renal cytokines were determined by ELISA. BM-derived M2a Mφ from EGFP transgenic mice (EGFP+M2a Mφ) was exploited to investigate the cell distribution. To investigate in vitro function of M2a Mφ on other leukocyte subsets, BM-derived M1 Mφ and splenic CD4+CD25-T cell were co-cultured with EGFP+M2a Mφ.

Results: M2a Mφ expressed higher levels of arginase-1 and IL-10/IL-12 mRNAs than M0 Mφ. Proteinuria was significantly attenuated by injection of M2a Mφ compared with disease-control mice at day 14 and day 21. Treatment with M2a Mφ prevented glomerular neutrophil and T cell accumulation. In addition, renal levels of IL-6, MCP-1, IL-1β and TNF-α were significantly decreased in M2a Mφ-treated mice on day 21. EGFP+ M2a Mφs were seen in the kidney and spleen 24h after cell injection. M1 Mφs were demonstrated phenotypic conversion to an M2a cells following the co-culture with EGFP+M2a Mφ, while EGFP+M2a phenotype was relatively stable. M2a Mφ suppressed T-cell proliferation and promoted induction of Tregs in vitro. Immunostaining displayed that Foxp3+ T cells were significantly increased in spleen in mice treated with M2a Mφ compared with disease control group.

Conclusions: Administration of M2 Mφ may have therapeutic potency for glomerular injury by further M2 cell conversion and induction of regulatory T cells.

FR-PO1000

Electroacupuncture (EA) and Moxibustion (MO) Decrease the Mortality Rate and Attenuate Inflammation on Already Established Chronic Kidney Disease Josne Carla Paterno, Marcelo Andery Naves, Rafael Luiz, Nestor Schor, Vicente De paulo castro Teixeira. *Nephrology, UNIFESP/EPM, Sao Paulo, Brazil.*

Background: Chronic kidney disease (CKD) is now considered a serious worldwide public health and associated high morbidity and mortality. Traditional Chinese Medicine (TCM) has been increasingly recognized as an effective therapeutic in several fields of medicine. Among its therapeutic strategies are electroacupuncture (EA) and moxibustion (MO). The aim of this study was to investigate the effects of EA and MO on inflammatory factors in CKD model.

Methods: Male wistar rats were submitted to 5/6 nx and divided into three groups: Control (NX); only 5/6 nx; Sham-EA-MO (NX-Sham): 5/6 nx and twice weekly 30 min EA-MO session in sham-points; and EA-MO (NX-ACUP): 5/6 nx and twice weekly 30 min EA-MO session in three real acupuncture points. All procedures began 4 weeks after 5/6 Nx, when the chronic lesions were already established. We measured 24h-proteinuria, tail cuff blood pressure (TBP), renal transforming growth factor-β1 (TGF-β1), IL-1, IL-6, IL-2, MCP-1 and mortality rate. The statistical significance of the results was evaluated by ANOVA followed by Tukey test. Values were expressed as mean± SD.

Results:

Parameters	NX	NX-Sham	NX-ACUP
24h-proteinuria (mg/24h) initial	11.4±4.1	12.7±3.1	12.3±4.7
24h-proteinuria (mg/24h) final	198.7±15.3	175.8±9.8	78.3± 10.2*
TBP (mmHg) initial	104.7±6.8	107±8.4	106.5±9.6
TBP (mmHg) final	237.9±13.3	219.9±14.9	135.9±10.7*
TGF-β1 (pg/mL)	572.4±39.2	581.3±45.7	347.9±39.8*
IL-1 (pg/mL)	137.8±11.8	130.8±12.8	40.4±10.9*
IL-2 (pg/mL)	397.8±41.1	391.8±39.8	220.6± 61.2*
IL-6 (pg/mL)	335.8±59.5	297.7±52.6	188.4±54.1*
MCP-1 (pg/mL)	379.6±53.4	369.1±58.3	214.5±43.5*
Mortality Rate (%)	58.9±7.8	54.3±8.9	17.7±6.3*

* (p<0.05) vs NX and NX-Sham

Conclusions: EA and MO modulated immune and inflammatory responses in CKD, leading to lower production of intrarenal TGF-β1, IL-1, IL-6, IL-2, MCP-1 and decrease mortality rate. Thus, it is reasonable to suggest that EA and MO could be an additional strategy to be employed in CKD.

Funding: Government Support - Non-U.S.

FR-PO1001

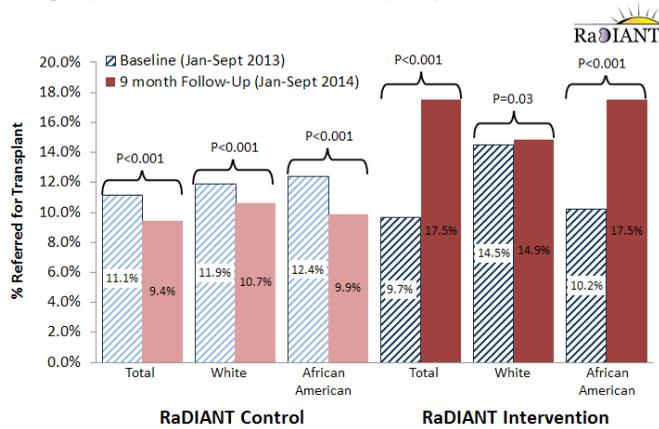
A Randomized Multicomponent Intervention to Reduce Disparities in Transplant Referral: Results from the RaDIANT Community Study Rachel E. Patzer,¹ Leighann Sauls,² Jennifer C. Gander,¹ Laura Plantinga,¹ Sudeshna Paul,¹ Eric M. Gibney,³ Laura L. Mulloy,⁴ Stephen O. Pastan.¹ *¹Emory Univ;* *²Southeastern Kidney Council;* *³Piedmont Hospital;* *⁴Georgia Regents Univ.*

Background: The Reducing Disparities In Access to kidney Transplantation (RaDIANT) Community Study is a dialysis facility-level randomized clinical trial to test the effectiveness of a multicomponent intervention in improving kidney transplant (KTx) referral and reducing racial disparities in referral in Georgia.

Methods: In 2013, 134 dialysis facilities were randomized to receive either usual KTx education (n=67) or a multicomponent intervention conducted by, consisting of KTx education and engagement activities targeting dialysis facility leadership, staff, and patients (n=67) over 12 months. Paired t tests, overall and by race [white and African-American (AA)], were used to compare referral at 9 months of intervention vs. baseline, in intervention and control facilities.

Results: Facilities that received the intervention had a greater absolute increase in referral over 9 months than facilities that performed usual KTx education (+7.8% vs. -2.5%).

Figure 1. Change in Proportion of dialysis patients referred for kidney transplantation among dialysis facilities in the RaDIANT Community Study: Baseline to 9 Months



A total of 51 of the 67 (76.1%) intervention facilities improved their percentage of patients referred for KTx over the 9 month study period. Intervention vs. control facilities had a greater increase in referral among AA (+7.3% vs. -2.5%) than white (+0.4% vs. -1.2%) patients over 9 months. Among the 26 dialysis facilities that had an AA vs. white racial disparity in referral at baseline, 69.2% no longer had a racial disparity in referral by 9 months.

Conclusions: Data from RaDIANT Community Study intervention facilities suggest that a large, randomized, quality improvement program among dialysis facilities in GA may improve KTx access. Availability of data after 12 months of the intervention will allow final assessment of the effectiveness of the intervention.

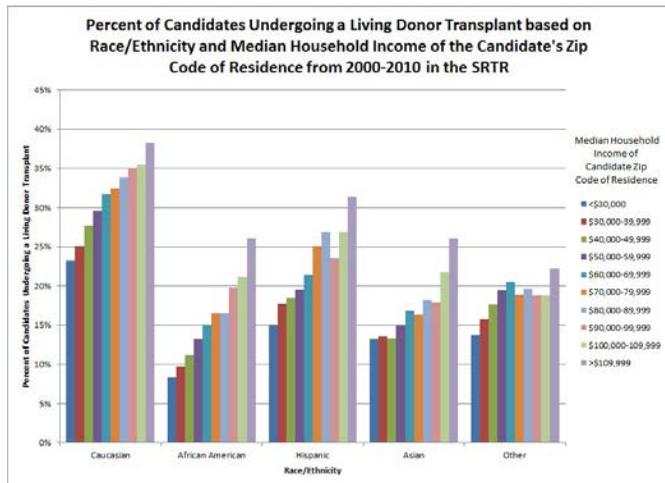
FR-PO1002

Association of Neighborhood Poverty and Living Donor Kidney Transplant Rates by Race Douglas Scott Keith, Angie G. Nishio-Lucar, Gayle M. Vranic. Medicine, Univ of Virginia, Charlottesville, VA.

Background: Despite a growing shortage of deceased donor kidneys in the US, living donation (LD) rates have declined steadily since 2004. We sought to understand the impact of candidate socioeconomic environment on living donation rates.

Methods: We identified all candidates listed for kidney or kidney pancreas transplant in the SRTR database from 2000-2010. Data was linked to US census data on median income by zip code. Candidate zip code of residence was used as a surrogate for neighborhood poverty. Univariate and Cox regression analyses were performed to evaluate the independent effects of candidate age, race/ethnicity [Caucasian, African American (AA), Hispanics, Asian, Other], gender, etiology of ESRD, dual listing for pancreas, level of educational attainment, insurance type, PRA, initial listing status (active vs. inactive), dialysis status at listing, first organ procurement organization of listing, year of listing, and median income of zip code by decile. Sensitivity analyses comparing zip code to candidate insurance type and educational status, other markers of socioeconomic status, were performed and yielded similar results.

Results: Increasing median income of candidate zip code was associated with higher rates of LD for all racial and ethnic groups. Overall LD rates were highest among Caucasians followed by Hispanics and Asians. AA had by far the lowest overall LD rates with LD rates of AA candidates living in the wealthiest neighborhoods only slightly higher than rates seen from the lowest quintile median income areas for Caucasians.



Conclusions: Neighborhood poverty is associated with decreased likelihood of LD. This impact was most pronounced among AA. Efforts should be made to remove financial disincentives to living donation to address racial and socioeconomic disparities in access to the life-saving treatment of transplant.

FR-PO1003

Deceased Donor Renal Transplant eGFR at Six Months Has Improved in the Last 13 Years in Spite of Declining Donor Quality Douglas Scott Keith, Gayle M. Vranic, Angie G. Nishio-Lucar. Medicine, Univ of Virginia, Charlottesville, VA.

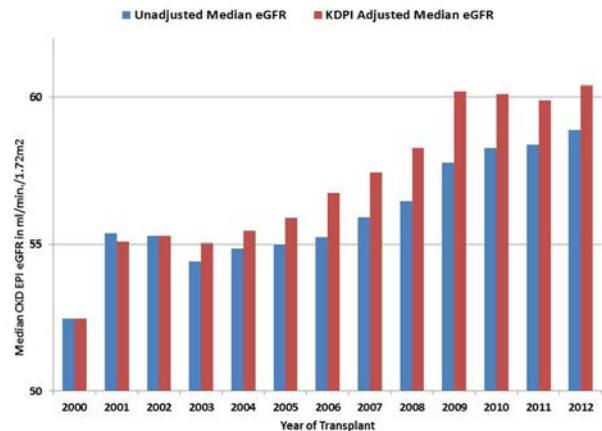
Background: Deceased donor quality has declined in the last decade but long-term graft outcomes are improving. We sought to analyze the trend in graft function at six months post-transplant in relation to this improvement.

Methods: All adult deceased donor kidney transplant recipients with at least six months graft survival recorded in the SRTR databased between 2000 and 2012 were analyzed. The CKD EPI eGFR was determined based on the patient characteristics and serum creatinine at six months post-transplant. KDPI of the donors was also calculated. Linear regression was used to determine the effect of covariates on eGFR.

Results: 111,678 deceased donor recipients were identified. 4918 (4.4%) recipients with no six month creatinine recorded were excluded. The median eGFR improved from 54.5 ml/min/1.72m2 in 2000 to 58.9 in 2012 (p<0.001) while the median KDPI increased from 41% to 46%(p<0.001). The use of tacrolimus/mycophenolate derivative also increased from 33.1% to 89.8%. Every 10 unit increase in KDPI resulted in a 3 ml/min/1.72m2 decline in eGFR.

Linear Regression Analysis	B ml/min/1.72m2	Std. Error
Constant	73.87	0.59
KDPI	-0.304	0.002
Acute Rejection in First Six Months	-10.94	0.23
En Bloc Pediatric Kidney	25.82	0.49
Dialysis in the First Week Post-Transplant	-4.91	0.14
Tacrolimus/Mycophenolate Derivative	1.08	0.58
Neoral/Mycophenolate Derivative	-4.74	0.60
CNI/mTOR	-4.69	0.64
CNI/Azathioprine	-2.93	0.78
Other combination	-2.10	0.60

KDPI adjusted median eGFR increased 13%.



Conclusions: Graft function improved significantly over the 13 year period in spite of declining donor quality and appears to be an important factor in the improvement in long-term graft survival. The transition to tacrolimus/mycophenolate derivative as the dominant maintenance immunosuppression appeared to be an important factor in this improvement.

FR-PO1004

Recipient Age and KDPI Are the Most Potent Predictors of Early Acute Rejection in Deceased Donor Kidney Transplantation Douglas Scott Keith, Gayle M. Vranic, Angie G. Nishio-Lucar. Medicine, Univ of Virginia, Charlottesville, VA.

Background: The rate of acute rejection in first six months after deceased donor kidney transplant is now under 10% in the modern era of immunosuppression. We sought to determine the factors predictive of acute rejection in this era.

Methods: All recipients transplanted between 2001 and 2012 in the SRTR database were included in the analysis. Logistic regression was performed to determine the odds ratio of acute rejection in the first six months adjusting for multiple covariates.

Results: The acute rejection rate was 7.1% during the study period. KDPI and recipient age were the most important factors influencing rejection rates with recipients under 30 years old having a rate of rejection more than double that of recipients 60 years or older and recipients receiving donor kidneys with a KDPI over 90% having a 2 fold increase in rejection rate over those receiving a kidney with a KDPI less than 30%.

	Odds Ratio	Lower C.I.	Upper C.I.
Age in Years (Reference 70 or older)			
0-17	2.30	2.00	2.66
18-29	2.18	1.92	2.48
30-39	1.65	1.47	1.86
40-49	1.37	1.22	1.53
50-59	1.19	1.07	1.32
60-69	0.99	0.89	1.11
KDPI Group (Reference 0-9%)			
10-19%	1.00	0.91	1.11
20-29%	1.07	0.96	1.18
30-39%	1.22	1.10	1.36
40-49%	1.33	1.20	1.47
50-59%	1.39	1.26	1.54
60-69%	1.53	1.38	1.69
70-79%	1.52	1.37	1.69
80-89%	1.80	1.61	2.00
90-100%	2.03	1.81	2.28
Other Covariates in model: Recipient gender, race, retransplant, cause of ESRD, duration of dialysis, delayed graft function, pra, HLA mismatch, induction, maintenance immunosuppression, and transplant year			

The only factors in the KDPI determination associated with rejection were donor age, donor hypertension, HCV seropositivity, and black donor race, with age accounting for most of the effect.

Conclusions: KDPI and recipient age are the most important factors associated with rejection. Risk stratification for donor recipient pairs based on age and KDPI should be considered when determining induction and maintenance immunosuppression needs.

FR-PO1005

Transplantation of Cadaveric Kidneys from Infants and Toddlers into Adults in the Era of Extreme Donor Shortage Jimena A. Blandon,¹ Nader Najafian,² Neerja Agrawal.³ ¹Nephrology, Cleveland Clinic Florida, Weston, FL; ²Nephrology, Cleveland Clinic Florida, Weston, FL; ³Nephrology, Cleveland Clinic Florida, Weston, FL.

Background: Kidney transplantation is the treatment of choice for patients with ESRD. The number of patients in the waiting list for a deceased donor kidney transplant continues to increase. In this era of extreme donor shortage we present our experience with transplantation of cadaveric kidneys from infant and toddler into adult recipients.

Methods: This was a retrospective study of twelve adult deceased donor kidney transplant recipients from pediatric donors ages 0-5 years. Medical records were reviewed from visits previous to transplantation to the most recent follow up after transplant.

Results: Twelve consecutive adult patients were transplanted with pediatric end stage kidneys from donors 0-5 years between February 2014 to February 2015. Ten of the donors were standard criteria brain death (DBD) and two were donors with cardiac death (DCD), KDPI scores ranged from 47 to 87%, donor age from 6 months to 5 years, weight 6 to 15 Kg. Recipients were equally distributed by gender, average age 56 years, mean BMI 22. All patients were followed in average 6 months to 1 year. In the early post transplant period 9 recipients were noted to have glucosuria with normal blood glucose and mild metabolic acidosis. These findings were noted on average up to 3 to 6 months after transplant and resolved thereafter. Nine patients had follow up renal ultrasound with finding of increase in kidney size 0.3 to 1.2 cm on average at 3-6 months in follow up. There were no perioperative complications, allograft failure, rejection, vascular complications or recurrence of the primary disease. The average serum creatinine remains at 0.89 to date.

Conclusions: We report excellent outcomes after adult kidney transplant from cadaveric donor ages 0 to 5 years of age. Younger age and low weight of the donors did not adversely affect our results. No vascular complications, rejection or allograft loss was noted. All of our patients have excellent allograft function 6-12 months post transplant.

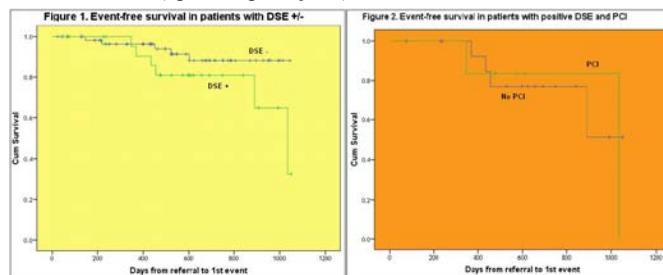
FR-PO1006

The Role of Dobutamine Stress Echo in Identifying Cardiac Ischaemia, Cardiovascular Events and Role of Subsequent Cardiac Angiography Maria Ventura, Robin Ramphul, Sami Firoozi, Juan Carlos Kaski, Rajan Sharma, Debasish Banerjee. *Renal and Cardiology Depts, St. George's Univ Hospitals NHS Foundation Trust.*

Background: Dobutamine Stress Echo (DSE) is an established method of identifying cardiovascular (CV) risk in patients undergoing kidney transplantation, however the role of coronary angiography (CA) is not clear. The aim of this study was to investigate the role of DSE and CA in predicting cardiac ischaemia and CV events in this population.

Methods: We reviewed data on all patients, 92 out of 233, that were referred between 1/2/2012 and 31/12/2014 and underwent DSE on risk stratification according to our protocol.

Results: 92 high risk patients underwent DSE. 28 of 92 patients had a positive DSE (i.e. suggestive of myocardial ischaemia) and 6 of these 28 had an event (event rate 13% per year) whereas there were only 5 events amongst the 64 patients in the DSE negative group (event rate 5% per year) (figure 1; log rank p=0.13). There were no perioperative events. 23 of 28 patients with a positive DSE had a CA, 14 had significant (> 50% stenosis) coronary artery disease (CAD) and another 3 had non-significant CAD (<50% stenosis). 7 of 14 patients with significant CAD had coronary stents; and 6 of 14 had events (event rate 26% per year). There was no difference in survival between the patients stented and those who were not (figure 2; log rank p=0.9).



Conclusions: DSE is a suitable method to stratify cardiovascular risk and predict significant CAD on CA, however subsequent PCI does not conclusively show decreased event rates. Larger studies are required to establish the role of revascularisation.

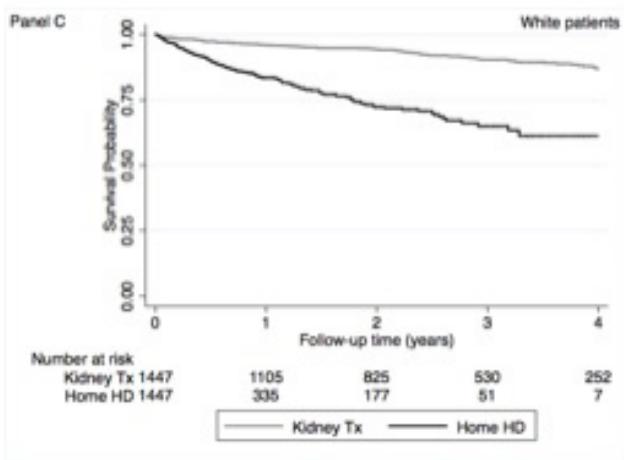
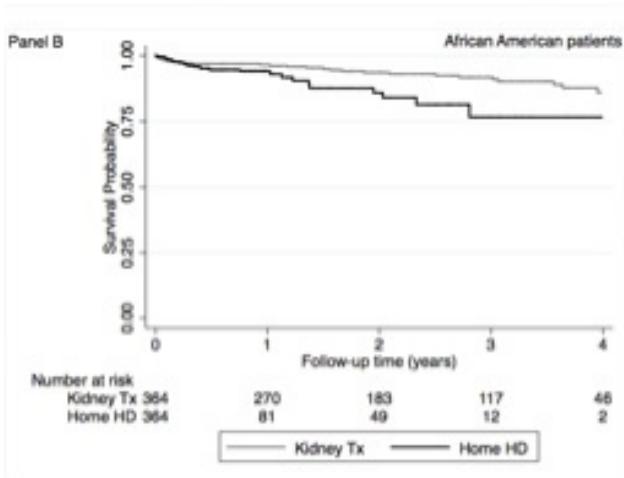
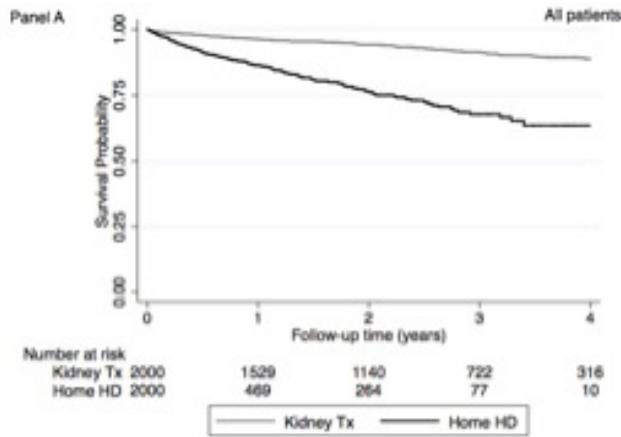
FR-PO1007

Racial Differences in Survival of Incident Home Hemodialysis and Kidney Transplant Patients Miklos Zsolt Molnar,¹ Vanessa A. Ravel,² Elani Streja,² Csaba P. Kovacs,¹ Rajnish Mehrotra,³ Kamyar Kalantar-Zadeh.² ¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³Univ of Washington, WA.

Background: Previous studies have indicated that patients on maintenance dialysis have worse survival compared to kidney transplant (KTx) recipients. However, none of these studies have compared mortality in United States(US) patients using alternative dialysis modalities such as home hemodialysis(HD) with KTx recipients.

Methods: Comparing patients who started home HD with those who received KTx in the US between 2007-2011, we created a 1:1 propensity-matched cohort of 4,000 patients and examined the association between treatment modality and mortality using Cox proportional hazard models.

Results: The mean±SD age of the matched home HD and KTx patients at baseline were 54±15 and 54±14 years, 65% were male (both groups), 70% and 72% of patients were white and 19% were African American (both groups), respectively. Over 5 years of follow-up, home HD patients had 4-times higher mortality risk compared to KTx recipients in the entire patient population (HR:4.06, 95%CI:3.27-5.04), and similar differences were found across each race stratum (Figure).



However, during the first year of therapy, while white home HD patients had higher mortality risk (HR:4.21, 95%CI:3.10-5.73) compared to their KTx counterparts, there was no significant difference in mortality risk between African American home HD and KTx patients (HR: 1.62, 95%CI:0.77-3.39). These results were consistent across different types of kidney donors.

Conclusions: Among all patients, home HD is associated with 4 times higher mortality compared to KTx regardless of the type of kidney donor, whereas among African Americans home HD and KTx have similar survival during the first year of therapy. Further studies on racial disparities of home HD and KTx are warranted.

Funding: Other NIH Support - R21AG047306 and R01DK95668

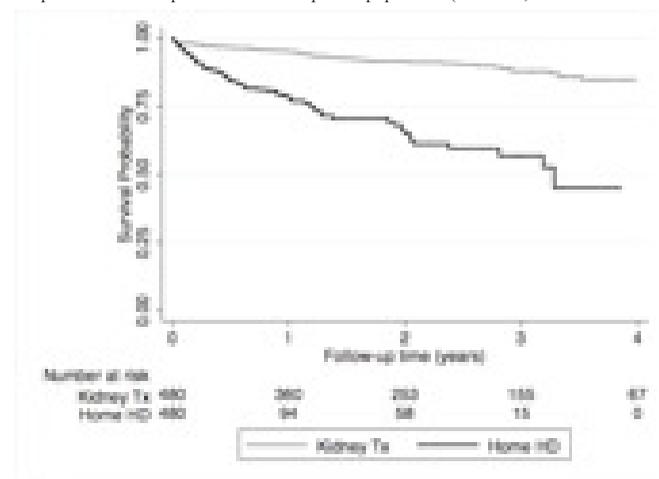
FR-PO1008

Survival of Elderly Incident Home Hemodialysis and Kidney Transplant Patients Miklos Zsolt Molnar,¹ Vanessa A. Ravel,² Elani Streja,² Csaba P. Kovcsdy,¹ Danh V. Nguyen,² Rajnish Mehrotra,³ Kamyar Kalantar-Zadeh.²
¹Univ of Tennessee Health Science Center, Memphis, TN; ²Univ of California, Irvine, CA; ³Univ of Washington, WA.

Background: The proportion of elderly (≥65 years) patients with kidney failure is increasing. Previous data suggest that the projected increases in the life spans of kidney transplant (KTx) patients compared to conventional dialysis were 2.8 and 1.1 years for patients aged 65-69 and 70-74 years, respectively. However, no studies have compared mortality of elderly patients using alternative dialysis modalities such as home hemodialysis (HD) with KTx recipients.

Methods: Comparing elderly patients, who started home HD with those who received KTx in the US between 2007-2011, we created a 1:1 propensity score (PS) matched cohort of 960 elderly patients (480 KTx and 480 HD) and examined the association between treatment modality and all-cause mortality using Cox proportional hazard models.

Results: The mean±SD age of the PS matched home HD and KTx patients at baseline were 71±6 years and 71±5 years, 69% were male (both groups), and 81% and 79% of patients were whites in home HD and KTx group, respectively. Median follow-up time was 205 days (IQR: 78-364 days) for home HD patients and 795 days (IQR: 366-1,221 days) for KTx recipients. There were 97 deaths (20%, mortality rate 253 [297-309]/1000 PY) in the home HD group, and 48 deaths (10%, 45 [34-60]/1000 PY) in the KTx group. Over 5 years of follow-up, home HD patients had almost 5-times higher mortality risk compared to KTx recipients in the entire patient population (HR: 4.74, 95%CI:3.25-6.91).



These results were consistent across different types of kidney donors and recipients characteristics.

Conclusions: Elderly home HD patients appear to have almost 5 times higher mortality compared to KTx recipients regardless of the type of kidney donor.

Funding: Other NIH Support - R21AG047306 and R01DK95668

FR-PO1009

Beyond the Bones – The Association Between Vitamin D, Graft Outcomes and Vascular Disease Aravind Cherukuri,¹ Santhanakrishnan Balasubramanian,² Rebekah Molyneux,² Richard J. Baker.² ¹Univ of Pittsburgh; ²Univ of Leeds.

Background: Vitamin D deficiency in KTRs is an emerging theme. The purported associations between Vitamin D deficiency and various metabolic, cardiovascular and non-metabolic adverse events have not been thoroughly studied in kidney transplant recipients (KTRs).

Methods: Here, we examined the association between Vitamin D deficiency and graft loss, mortality, NODAT, cardiovascular events and development of cancers.

Results: 504 KTRs had their vitamin D checked in 2008 and were followed up for 6 years. Vitamin D deficiency was defined as a level <50nmol/L. In this population, the prevalence of vitamin D deficiency was high at 66.5% with a significantly higher prevalence in older (71.9% vs. 60.9%, P=0.006) and female recipients (male 62.1% vs. female 73.2%, P=0.006) and in relatively new transplants (recent transplants 72.3% vs. old transplants 60.6%, P=0.003). KTRs who were vitamin D deficient had significantly worse overall (77% vs. 92%, P<0.0001), death censored graft survival (89% vs. 96%, P=0.009), development of NODAT (19.8% vs. 10% p=0.005) and cardiovascular events (9.9% vs. 2.9%, p=0.002) when compared to those with normal levels. In a stratified analysis, this was noted to be worse in KTRs on maintenance steroids, with relatively worse baseline renal function and proteinuria, with secondary hyperparathyroidism, deceased donor transplants and earlier vs. late transplants. Although vitamin D deficiency is not associated with a higher incidence of malignancy, it is associated with higher mortality in those with cancer (33.3% vs. 12.9%, p=0.005). In a multivariate Cox model, vitamin D deficiency was associated with significantly worse overall graft (HR 2.7, P=0.001) and death censored graft survival (HR 2.4, P=0.04), NODAT (HR 2.3, p=0.03) and cardiovascular events (HR 4.0, P=0.004) independent of age, PTH levels, gender, graft number, type of transplant, time since transplantation, graft type and renal function measured by both proteinuria and eGFR.

Conclusions: In conclusion, vitamin D deficiency which is highly prevalent in KTRs is associated with adverse clinical outcomes. Our study stresses the need for a prospective trial of vitamin D replacement in KTRs.

Funding: Private Foundation Support

FR-PO1010

Acute Tubular Necrosis Changes in Living Kidney Donor Implant Biopsy Associates with Higher Rejection Rates Post-Transplant Chunping Yu, Nissreen Elfadawy, Andres G. Chiesa-vottero, Leal C. Herlitz, Emilio D. Poggio. *Dept of Nephrology and Hypertension, Glickman Urological and Kidney Inst, Cleveland Clinic, Cleveland, OH.*

Background: Ischemic injury may occur during organ retrieval. In deceased kidney donor transplants, delayed graft function, a form of acute tubular necrosis (ATN), associates with acute graft rejection. Histological changes consistent with ATN can also be seen in implant biopsies of living donors(LD), however, the influence of ATN-like changes at time on donation from LD on recipient graft outcomes is unclear, especially its impact on graft rejection.

Methods: We retrospectively studied all LD kidney transplants at our center from Jan 2005 to Dec 2014 who had an implant biopsy. We perform protocol biopsies at 3-6, 12 and 24 months post-transplant and for cause biopsies in all of our patients. Post-transplant biopsy results were reviewed, and patients with subclinical and clinical borderline and/or BANFF scored graft rejection were captured.

Results: The study included 350 LD kidney transplant recipients, the mean age was 47.8±13.7 years (range 10-75) and 224(64%) were male. The incidence of ATN in implant biopsies was 16% (n= 56). Patients with ATN had a trend toward higher risk of graft rejection in post-transplant biopsy compared with those without ATN (32.1% vs. 21.7%, p=0.09). When the study population was stratified by time interval from transplant to post-transplant biopsy, there was a statistically significant higher incidence of graft rejection in those biopsies performed between 1 and 24 months post-transplant (31.0% in the ATN group vs. 17.8% in the non-ATN group, respectively, p=0.02). No statistical correlation was found between ATN and graft rejection after 24 months post-transplant. Importantly, implant ATN has no impact on GFR at 3, 6, 12, 24 months post-transplant.

Conclusions: Histological changes consistent with ATN in LD kidney implant biopsy are associated with higher rates of graft rejection between 1 and 24 months post-transplant. However, ATN does not affect graft function at 3, 6, 12, or 24 months.

FR-PO1011

Impact of Pre-Transplant Cardiovascular Risks on Renal Allograft Survival: A Multi-Center Prospective Study Jung Nam An,^{1,2} Song Vogue Ahn,³ Chun Soo Lim,^{1,2} Yon Su Kim,² Young hoon Kim,⁴ Jung Pyo Lee.^{1,2} *¹Seoul National Univ Boramae Medical Center; ²Seoul National Univ College of Medicine; ³Yonsei Univ Wonju College of Medicine; ⁴Asan Medical Center and Univ of Ulsan College of Medicine, Republic of Korea.*

Background: Cardiovascular (CV) disease is a leading cause of mortality in patients with end-stage renal disease. Even after successful renal transplantation, CV risks can induce CV morbidity and mortality in renal transplant recipients. However, the impact of pre-transplant CV risks on renal allograft outcomes has not been reported.

Methods: We analyzed the graft outcomes of 2902 renal transplant recipients who were enrolled in a multi-center cohort from 1997 to 2012. We calculated pre-transplant CV risk scores by the Framingham risk model using age, sex, total cholesterol levels, smoking and a history of hypertension. Cox proportional hazard models were used to assess hazard ratios (HRs) with and without competing risks of post-transplant CV deaths, adjusting for risk factors of allograft failure including recurrence of glomerulonephritis and acute rejection.

Results: Hypertension and vascular disease (a composite of ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) were noted in 84.1% and 6.5% of the patients, respectively. During a median 6.4 years of follow-up, 122 (4.2%) patients died and 286 (9.9%) patients developed allograft failure. In multivariable-adjusted models, pre-transplant vascular disease was associated with increased risk of renal allograft failure (HR 2.43; 95% confidence interval [CI] 1.58-3.71). The HR for renal allograft failure comparing the highest with the lowest tertiles of pre-transplant CV risk scores was 1.49 (95% CI 1.11-2.00). In competing risk models, the HR of pre-transplant vascular disease was 2.01 (95% CI 1.20-3.36) and the HR for renal allograft failure comparing the highest with the lowest tertiles of pre-transplant CV risk scores was 1.44 (95% CI 1.05-1.98).

Conclusions: Both pre-transplant CV risk and vascular disease are independently associated with renal allograft failure in this multi-center prospective study. Pre-transplant CV risk assessment could be useful to predict renal allograft failure.

FR-PO1012

Blood Pressure (BP) Control in Kidney Transplant Recipients: A Single Centre Experience Kristin Vibeke Veighey, Jacqueline C. Nevols, Panagiotis Chondrogiannis, Amanda Jane Laird, Irene Synodinou, Doreen Zhu, Katherine A. Alington, Nichola Dawn Pugh, Chuin ying Ung, Gopalakrishnan Venkat-Raman. *Wessex Kidney Unit, Portsmouth Hospitals NHS Trust, Portsmouth, United Kingdom.*

Background: Cardiovascular disease is the leading cause of death among kidney transplant recipients (KTRs), however there remains uncertainty regarding optimal BP targets. Current UKRA, KDIGO and KDOQI guidelines advocate BP control to 130/80

in KTRs; UKRA/KDIGO advocate tighter control (125/70) in proteinuric KTRs. We examined BP control and proteinuria in all KTRs under longterm follow up at one centre, and adherence to these recommendations.

Methods: As of 1 March 2015, 839 KTRs were attending for regular clinic review (excluding recent KTRs<1yr). We performed a retrospective database review of BP, proteinuria, renal function and antihypertensive use.

Results: The cohort was 60% male with mean allograft age 10±0.28 years. Mean decline in eGFR was 0.83ml/min/m² per year (p=0.0004). Mean SBP was 134±0.56, DBP 79±0.37. 48% had SBP <130, 62% DBP <80, 39% both. 78% received ≥1 antihypertensive, 42% 2-3, 4% ≥4 agents. Only 9% had PCR measured. In those with PCR≥50, 19% had BP treated to 125/75. Dipstick proteinuria was recorded in 58% and showed a significant association with SBP (p=0.01). There were significant correlations between reducing eGFR and increasing PCR (R²=0.11, p<0.0001), and between PCR and ACE/ARB use (p= 0.0002). There was no correlation between CNI level and BP (CyA p=0.88, FK506 p=0.49). There was a significant stepwise decrease in renal function (sCr p=0.005, eGFR p=0.01) and increase in dipstick proteinuria (p=0.03) when data were analysed in SBP groups <120, 120-140 and >140. In terms of DBP, the stepwise decrease in renal function remained (sCr p=0.01, eGFR p<0.0001) when data were analysed in groups <70, 70-90 and >90. DBP≥90 had the most significant impact on eGFR. DBP was not associated with proteinuria.

Conclusions: The optimal BP target remains uncertain. Adherence to current guidelines is reasonable in our unit but could be improved. This study again demonstrates that SBP is the key risk factor for proteinuria, however increases in DBP >90 were most strongly associated with graft dysfunction.

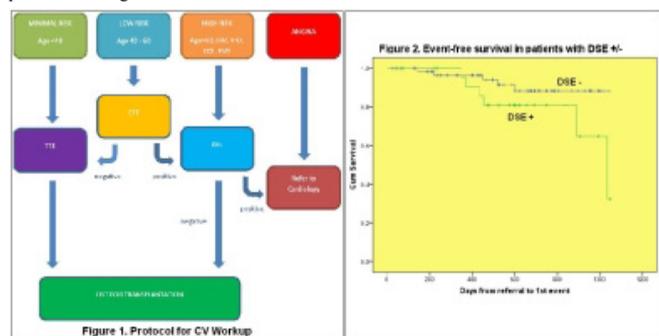
FR-PO1013

Dobutamine Stress Echocardiography (DSE) Significantly Reduces the Need for Coronary Angiography in Renal Transplant Recipients Robin Ramphul, Maria Ventura, Sami Firoozi, Juan Carlos Kaski, Rajan Sharma, Debasish Banerjee. *Renal and Cardiology Unit, St. Georges Univ Hospitals NHS Foundation Trust, United Kingdom.*

Background: There is significant controversy regarding optimal cardiac workup strategy for kidney transplantation. Some centres perform coronary angiograms (CA) in all patients whereas others have adopted a tailored approach using non-invasive techniques such as Exercise Tolerance Testing (ETT) and ischaemia assessment with cardiac imaging. This study examines the role risk stratification and DSE for cardiac workup in this patient group.

Methods: We analysed data on patients referred between 1/2/2012 and 31/12/2014 who were risk stratified and investigated according to the protocol (figure 1).

Results: Of 233 patients referred 92 were high risk and went on to have DSE. All other patients underwent echocardiography with/without ETT (35 ETT, 122 echocardiography and 33 CA). 16 patients had CV events, but none were perioperative. Overall event rate was 4% per year. 11 of 92 patients who had DSE had events. 11 of 33 patients who had CA had event. 28 of 92 patients had a positive DSE (i.e. suggestive of myocardial ischaemia) and of these 23 went on to CA. 6 of 28 patients with a positive DSE and 5 of 64 with a negative DSE had an event (figure 2, log rank p=0.1). 25 of 33 patients had evidence of coronary artery disease (CAD) at CA of which 13 received coronary artery stents. There was no significant difference between those with significant (>50% stenosis) CAD on CA who had events (8 of 21 patients) compared to those without significant (<50% stenosis) CAD who had events (3 of 12) (log rank p = 0.7). 6 patients with significant CAD who had PCI had events. 35 patients underwent ETT, 4 had CA following positive ETT. One patient with negative ETT had an event.



Conclusions: A careful risk stratification and using DSE decreases the need for CA and achieves very low event rates.

FR-PO1014

Levels of Indoxyl Sulfate in Kidney Transplant Patients, and the Relationship with Hard Outcomes Sophie Liabeuf,¹ Lucie Desjardins,¹ Ziad Massy,² François Brazier,¹ Dimitri Titeca Beauport,¹ Momar Diouf,¹ Griet Lrl Glorieux,³ Raymond C. Vanholder,³ Maite Jaureguy,¹ Gabriel Choukroun.¹ *¹Nephrology, Amiens; ²Nephrology, Ambroise Paré; ³Nephrology, Gent.*

Background: Kidney transplant recipients are at greater risk of cardiovascular disease (CVD). Indoxyl sulfate (IS) is a protein-bound uremic toxin that is known to be associated with the risk of CVD and mortality in both pre-dialysis and dialysis patients. Data on levels of protein-bound uremic toxins in kidney transplant patients are scarce. The objective

of the present study was to evaluate the levels of IS in kidney transplant patients and their relationships with biochemical parameters and hard outcomes (including mortality, cardiovascular (CV) events and graft loss).

Methods: In 311 consecutive kidney transplant patients, total and free IS levels were measured immediately before transplantation (T0) and then 1 month (M1) and 12 months (M12) afterwards. In a case controlled substudy (n=90), IS levels in transplant patients were compared with those in non-transplant patients with chronic kidney disease matched for age, gender and estimated glomerular filtration rate (eGFR). Over a mean ± standard deviation follow-up period of 113 ± 29 months, 55 deaths, 70 CV events and 71 graft losses were recorded.

Results: We observed a rapid, consistent, significant decrease in IS levels after kidney transplantation. Majority of IS levels were below or near the normal value at M1 and M12. We did not observe a correlation between IS levels and eGFR at M1 and M12. Total and free IS levels at M12 were significantly higher in non-transplant patients (0.34±0.23 mg/dl and 0.04±0.007 mg/dl, respectively) than in transplant patients (0.21±0.17 mg/dl and 0.01±0.1 mg/dl; (p=0.003 and <0.0001 respectively), despite having similar eGFRs. Lastly, IS levels were not associated with overall mortality, CV events or graft loss at T0, M1 or M12.

Conclusions: Free and total IS levels were significantly lower in transplant recipients than in non-recipients matched for, age, gender and renal function - suggesting that kidney transplantation protects against an increase in IS levels. Importantly, serum IS levels were not associated with hard outcomes at any of the three time points.

FR-PO1015

Identification of Metabolic and Cardiovascular Risk in Pediatric Kidney Transplant Recipients: Body Mass Index, Waist Circumference, or Waist-to-Height ratio? Kristen Sgambat, Asha Moudgil. *Children's National, Washington DC.*

Background: In the general population, abdominal obesity is more closely associated with metabolic and cardiovascular (CV) risk than high BMI. The ideal measure of obesity to identify risk in pediatric kidney transplant (Tx) recipients, who have impaired growth and altered body composition, has not been established. In this prospective study we compared ability of BMI, Waist Circumference (WC), and Waist-to-Height ratio (WHR) to identify metabolic and CV risk in pediatric kidney Tx recipients.

Methods: Kidney Tx recipients 3-20 years old and 0-30 months post-Tx had WC, BMI, WHr, blood pressure (BP), fasting lipids, leptin, HbA1c%, standard and speckle echocardiogram and carotid intima-media thickness (CIMT) measured. Patients were classified as obese or lean by 3 methods: WC (ATP cut-point males>94th%ile, females>84 th%ile), WHr(CDC cut-point>0.539), and BMI(≥95th%). Logistic regression determined association of groups with metabolic and CV risk factors.

Results: The study group comprised of 33 Tx recipients, age 13.6±0.3 years. Prevalence of obesity by BMI, WC, and WHr was 21.2%, 33.3%, and 48.5%. Prevalence of hypertriglyceridemia(TG) was 24.2%, high LDL 15.2%, low HDL 57.5%, high leptin 39.3%, high HbA1c% 12.1%, left ventricular hypertrophy(LVH) 30.3%, hypertension(HTN) 69.6%, and high CIMT 48.4%. In all groups (WHR, WC, and BMI), obese children were more likely than lean to have HTN(OR4.5,2.2,3.6,p<0.01),LVH(OR5.4,7.4,4.8,p<0.001), low HDL(OR5.0,7.4,3.8,p<0.001), and high leptin(OR19,13.1,7.3,p<0.001). Obese children in WHr and WC groups, but not BMI group, had greater chance of high TG(OR5.4,3.2,p<0.01), high CIMT(OR2.0,4.5,p<0.05), and impaired myocardial strain(OR1.2,1.1,p<0.01). Five patients with short stature (height z -2.56) and CV risk factors (3.0±0.5 factors/patient) were not identified as obese by WC criteria(height z-0.08,p=0.003).

Conclusions: WC and WHr are more effective than BMI for detecting metabolic and CV risk amongst pediatric Tx recipients. We may underestimate prevalence of obesity in children of short stature, and therefore WHr may be a more sensitive method for identification of children with increased metabolic and CV risk in the kidney Tx population.

FR-PO1016

Knowledge About Benefits of Kidney Transplant: A Survey of Dialysis Patients Naman Trivedi, Fareeha Khalil, Ming Wang, Eric Chang, Nasrollah Ghahramani. *Pennsylvania State Univ College of Medicine.*

Background: Kidney transplant (KT) is the treatment of choice for end stage renal disease (ESRD). Knowledge of dialysis patients about the benefits of KT is an important determinant of their active engagement in the decision making process. We studied factors associated with patients' knowledge about benefits of KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants fulfilling inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent variables were demographic factors, distance to dialysis unit, and modes of education about options. In multivariate analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of responding correctly to each of 4 questions about benefits of KT.

Results: 673 participants responded to questions about overall survival benefit of KT (correct: 32%), benefits of KT for diabetic patients (correct: 46%), for patients > 60 (correct: 29%) and for patients transplanted pre-emptively (correct: 17%). Receiving 3 or more modes of education about KT was associated with higher likelihood of correct response to questions about overall survival benefit of KT (OR:2.19;CI:1.50 to 3.20), survival benefits of KT for diabetics (OR:2.04;CI:1.39 to 3.01) and patients transplanted pre-emptively (OR:1.67;CI:1.06 to 2.64). White race was associated with higher likelihood of correct response to questions about overall survival benefit of KT (OR:1.59;CI:1.11 to 2.28) and the benefit of KT for patients > 60 (OR:1.54;CI:1.07 to 2.21). Age > 60 was associated with lower likelihood of correct response to the question about overall survival benefit of

KT (OR:0.65;CI:0.45 to 0.94), benefits of KT for diabetics (OR:0.54;CI:0.38 to 0.77), and for patients > 60 (OR:0.64;CI:0.44 to 0.93). Patients on dialysis > 5 years were less likely to be aware of the benefit of KT for diabetics (OR:0.68;CI:0.48 to 0.98).

Conclusions: Dialysis patients' knowledge about survival benefits of KT is rather limited. The most significant modifiable contributor to improvement in knowledge is diversity of modes of education about KT. Other factors include race, age and number of years on dialysis.

Funding: NIDDK Support

FR-PO1017

Pretransplant HbA1c Predicts New-Onset Diabetes After Transplantation Among Renal Transplant Recipients Jung-Im Shin, Mari Palta, Arjang Djamali, Brad C. Astor. *Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: New-onset diabetes after transplantation (NODAT) is a common complication among renal transplant recipients and is associated with a higher risk of cardiovascular events and poorer graft and patient survival. The association of pretransplant HbA1c with NODAT remains unclear. Identifying recipients at greatest risk of NODAT may help guide monitoring and treatment strategies to prevent or delay the onset of NODAT.

Methods: We assessed the association between pretransplant HbA1c and NODAT in 1522 non-diabetic recipients using data from the United States Renal Data System (USRDS) from 2004-2011. Cox proportional hazards models adjusted for demographics, cause of ESRD, year of transplantation, number of prior transplants, duration of pretransplant dialysis, comorbidities, lipid levels, hemoglobin level, body mass index, HCV and CMV serostatus, donor type and age, HLA mismatch, and posttransplant steroid and tacrolimus use.

Results: Median HbA1c was 5.4% and 531 (34.9%) patients had HbA1c ≥ 5.7% (i.e., prediabetes). A total of 404 (26.5%) patients developed NODAT during a median follow-up of 1.7 years. Pretransplant HbA1c was associated with the risk of NODAT in a non-linear fashion. The adjusted hazard ratio (HR) associated with 1% higher pretransplant HbA1c was 0.94 (95% confidence interval (CI): 0.62, 1.42) for HbA1c lower than 5.4% and 1.87 (95% CI: 1.30, 2.68) for HbA1c higher than 5.4%.

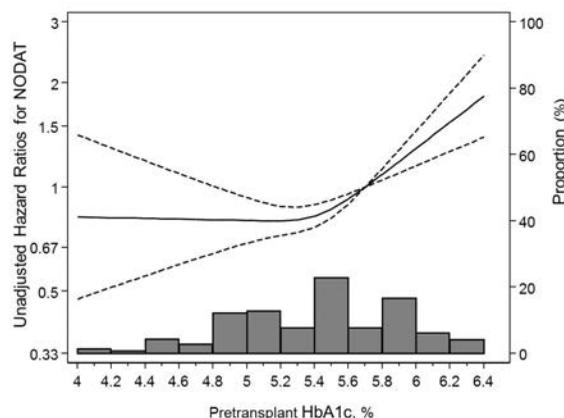


Figure 1. Unadjusted hazard ratio (solid line) with 95% CI (dashed line) for development of NODAT, by pretransplant HbA1c.

Conclusions: Pretransplant HbA1c is independently associated with the risk of NODAT among renal transplant recipients. A continuous relationship between pretransplant HbA1c and the risk of NODAT suggests that greater risk starts at levels below the standard threshold for prediabetes.

FR-PO1018

Choice of Equation to Estimate Kidney Function Has Large Impact on Timing of Kidney Transplant Waitlist Qualification Benjamin J. Lee,¹ Charles E. McCulloch,² Isabel Elaine Allen,² Sindhu Chandran,¹ Chi-yuan Hsu.¹ ¹Medicine, UCSF, San Francisco, CA; ²Epidemiology and Biostatistics, UCSF, San Francisco, CA.

Background: Because mortality on the kidney transplant waitlist is high (4-6% per year), being placed on the waitlist earlier versus later has important clinical consequences. Per U.S. Organ Procurement and Transplantation Network (OPTN) rules, patients begin accruing time on the waitlist when renal function declines beyond a threshold defined as "measured (actual urinary collection) creatinine clearance level or calculated glomerular filtration rate (Cockcroft-Gault or other reliable formula) less than or equal to 20 mL/min".

Methods: We assessed the relative performance of three commonly used kidney-function equations (Cockcroft-Gault, MDRD, and CKD-EPI). We first compared the equations mathematically to determine under what age and serum creatinine combinations each pair of equations yields discordant waitlist qualification statuses (i.e., a patient would qualify for the waitlist if one equation were used but not the other). We then applied the equations to serial creatinine measurements from three patient cohorts: one of waitlisted patients at a major U.S. academic center and two national, multicenter cohorts of CKD patients (the NIH-sponsored AASK and MDRD studies).

Results: Mathematically (assuming average weights), the Cockcroft-Gault equation almost always yields higher numeric values compared with the MDRD and CKD-EPI equations. When applied to the three actual patient cohorts, Cockcroft-Gault consistently disadvantaged patients, delaying average time to waitlist qualification by 1 to 2 years.

Conclusions: This study identified a potential source of significant inequity (on the order of 1-2 years) in wait-time accrual for kidney transplantation that stems from imprecise rules for waitlist qualification. The OPTN may need to revise the language in their kidney transplantation policies so that consistent methods to assess renal function are adopted and patients are not inadvertently disadvantaged.

Funding: NIDDK Support

FR-PO1019

New Onset Diabetes Has Unfavorable Effect on Patient but Not on Allograft Survival Thomas Dienemann,^{1,2,3} Naohiko Fujii,^{1,2} Roy D. Bloom,^{1,2} Harold I. Feldman,^{1,2} Yimei Li.² ¹Dept of Medicine, Perelman School of Medicine- Univ of Pennsylvania, Philadelphia, PA; ²Dept of Epidemiology and Biostatistics, Perelman School of Medicine, Philadelphia, PA; ³Dept of Renal Medicine and Hypertension, Univ of Erlangen, Erlangen, Germany.

Background: New onset diabetes after transplantation (NODAT) has been linked to higher rates of graft loss and shorter patient survival. More recent awareness, improvements in care, and changes in immunosuppression may have modified this association.

Methods: Retrospective single center analysis of 1427 (age>18) first time renal transplant recipients (KTR) without pre-transplant(Txp) diabetes. Patients with <1 year of follow up and those with allograft failure in the first year post-Txp were excluded. NODAT was defined as prescription of a glucose lowering medication 1 year after Txp. Cox models adjusted for mult. potential confounders were used to examine the relationship of NODAT with allograft and patient survival.

Results: The incidence of NODAT was 16.1%. Median follow up was 5.9 years(IQR3.5-9.2) for allograft and 6.3(IQR3.8-9.8) for patient survival. Age, BMI, non-white race and HCV were independently associated with NODAT (all p<0.01). Compared with KTRs without DM NODAT was not associated with an increased risk of overall graft failure (aHR1.15, CI0.86-1.52) or death censored graft survival (DCGS) (aHR1.12, CI0.73-1.71) in multivar. analysis. NODAT remained borderline significant after adj. for multiple other factors for patient survival (aHR1.39, CI1.00-1.91 p=0.049), but not for death with functioning graft (aHR1.34, CI0.89-2.02). The associations between NODAT and outcomes were not detectably different over time (p=0.095 for patient survival and p=0.25 for DCGS).

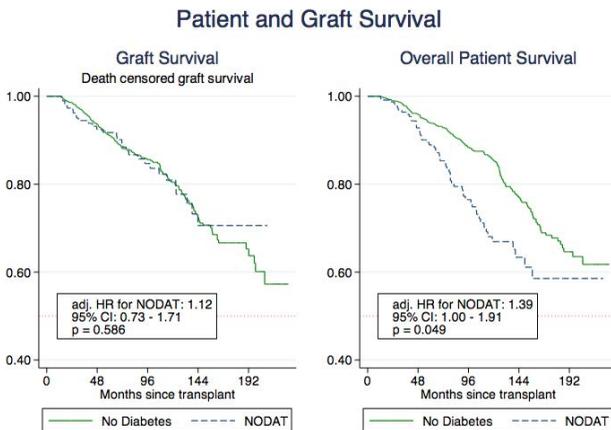


Figure 1. Kaplan-Meier curves for death censored graft survival and overall patient survival

Conclusions: In this cohort of KTRs NODAT had no impact on graft survival but was indep. associated with reduced overall survival.

FR-PO1020

Frequency of Hospital Readmission Post Kidney Transplantation Essy Mozaffari,¹ Jay Lin,² Melissa Lingohr-Smith.² ¹Chimerix Inc., Mendham, NJ; ²Novosys Health, Green Brook, NJ.

Background: Early hospital readmission following kidney transplantation has been identified to be a strong predictor of adverse sequelae that can have significant clinical and economic implications. Our goal was to quantify the frequency of hospital readmissions post kidney transplantation, as well as the reasons for the rehospitalizations.

Methods: Patients who received a kidney transplant between Jan 2009 and Sept 2013 were identified from the Premier Hospital database by ICD-9-CM code. The first transplant procedure was defined as the index event. The frequency and causes for hospital readmissions were evaluated during the first 12-month after index transplant hospitalization using hospital discharge records.

Results: Of patients who received kidney transplant (n=5,402; mean age: 50.8 years) 61% were male. Most patients received transplant in urban (98%), large (>=600 beds: 61%), teaching hospitals (84%). During index transplant hospitalizations 35 deaths occurred, resulting in 5,367 evaluable patients. Among this study population, 43% had a hospital

readmission for any cause during the 12 months following kidney transplant, with 41% occurring within 1 month and 67% occurring within the first 3 months. Readmissions were most frequently related to opportunistic infections (25%) including viral infections (6%), followed by renal impairment (25%), and neutropenia (4%). Among the readmissions related to viral infections, the majority were related to CMV (79%). Readmission of patients with high severity APR-DRG levels of 3 (major) and 4 (extreme) at 30% and 9%, respectively (severity of illness level rated 1-4: minor, moderate, major, and extreme).

Conclusions: Over 4 in 10 of the kidney transplant recipients in this study were rehospitalized post transplantation. A significant number of the readmissions occurred in the first month post-transplant and the majority were within the first three months; almost 4 in 10 readmissions were classified as major or extreme severity level. Among hospital readmissions, more than half of them were related to an opportunistic or viral infection, underscoring unmet needs for the prevention of these infections.

Funding: Pharmaceutical Company Support - Chimerix Inc.

FR-PO1021

Role of Non-Invasive Cardiac Stress Studies During Assessment for Kidney Transplantation in Pre-Dialysis Recipients Talvinder S. Bhogal, Simon James Gray, Patrick Hamilton, Durga A.K. Kanigicherla. *Manchester Inst of Nephrology & Transplantation, United Kingdom.*

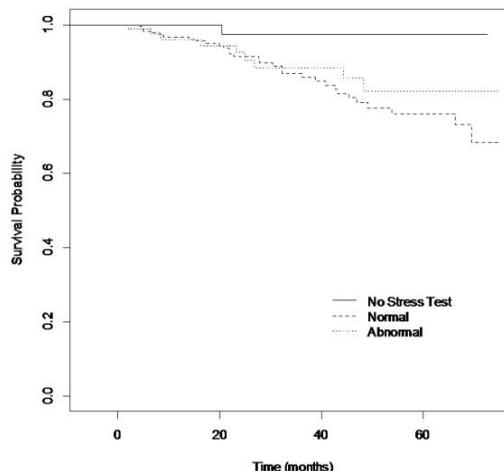
Background: Non-invasive cardiac stress studies (NISS) are routinely undertaken during listing of patients for kidney transplantation. Although guidelines recommend NISS in high risk patients based on studies reported on patients on RRT. However role of NISS in pre-dialysis population is unknown. We analysed the role of NISS in listing process and impact on longer term outcomes.

Methods: Retrospective study of all patients undergoing assessment for kidney transplantation at our centre between 2009 and 2014. 695 patients were assessed, including 397 who were pre-dialysis (naïve to RRT).

Results: 306 (77.1%) patients underwent NISS (98% were myocardial perfusion studies). Baseline and outcomes during follow-up are below.

	No NISS	Normal NISS	Abnormal NISS
Number of patients	91	225	81
Baseline % or Median			
Age	36	57	60
Males	59	51	69
BMI	27	28	30
Diabetes	5	31	53
Any vascular disease	3	24	31
Follow up			
Follow-up (in months)	34	25	29
Coronary intervention before listing	0	0	4
Number listed for kidney Tx	77	71	53
Transplants completed	57	28	17
Cardiovascular events	0	7	19
Death	1	14	11

Only 3 patients with abnormal NISS (1% of all who had NISS) had flow limiting lesions, needing interventions (2CABG and 1PCI). At last follow up, compared to those with normal NISS, patients with abnormal studies a) were less likely to be listed for kidney transplantation, b) had increased cardiovascular events (p=0.01). But there was no significant difference in patient survival.



Conclusions: Our study illustrates lack of benefit of non-invasive myocardial perfusion studies in identifying treatable coronary artery disease during pre-transplant assessment in pre-dialysis patients. Better risk stratification strategies are needed to inform assessment of kidney transplantation.

FR-PO1022

Longitudinal Association of Recipient Nonmuscle Myosin IIA Gene rs5756168 with Transplanted Kidney Doppler Ultrasound Blood Flow Indexes Joanna Pazik,¹ Ewa Nowacka-Cieciora,¹ Zbigniew Lewandowski,² Monika Oldak,³ Dominika Ozi?b?o,⁴ Magdalena Durlik.¹ ¹Transplantation Medicine and Nephrology, Medical Univ of Warsaw, Warsaw, Poland; ²Epidemiology, Medical Univ of Warsaw, Warsaw, Poland; ³Histology and Embryology, Medical Univ of Warsaw, Warsaw, Poland; ⁴Inst of Physiology and Pathology of Hearing, Warsaw, Poland.

Background: MYH9 gene polymorphisms associate with nephron injury in hypertensive nephrosclerosis and FSGS. We have shown the association of rs5756168 with transplanted kidney eGFR(ATC 2015). MYH9 gene polymorphisms correlate with cerebrovascular blood flows. In transplanted kidneys resistance and pulsatility indexes predict graft function.

Methods: The study aims at evaluating the association of donor/recipient MYH9 SNPs (rs3752462, rs11089788, rs5756168, rs136211 rs2239784) and transplanted kidney pulsatility (PI) and resistive (RI) indexes. Recipients engrafted 2007-2012 with available: donor/recipient DNA, kidney spectral Doppler ultrasound (US) were included. For genotyping custom TaqMan genotyping assays were used. Mixed models were used to assess relations of SNPs and PI, RI values.

Results: Genotyping was performed in 295 kidney recipients and their donors, in 202 at least one US was done. In the longitudinal observation between first day and 2 years after engraftment, recipients carrying two T alleles in rs5756168 showed significantly different PI indexes in opposition to allele C carriers, $p=0.04$, for RI the differences did not reach statistical significance ($p=0.14$). In two-factor analyses the effects of rs5756168 was maintained in first transplants for RI ($p=0.02$) and PI ($p=0.02$), in recipients with TTT >24h ($p=0.03$ and 0.07 , respectively), with grafts from donors >55 years old ($p=0.05$ for PI only), with panel reactive antibodies <20% ($p=0.01$ and 0.04 for PI and RI), patients on immunosuppression without induction ($p=0.07$ for PI only) and on tacrolimus treatment ($p=0.05$ for PI $p=0.05$).

Conclusions: Identified association of transplanted kidney blood flow parameters and MYH9 polymorphism additionally confirms MYH9 effect on graft functioning shown in our previous study cited above. The study supported by grant from National Science Center NN402566840.

Funding: Government Support - Non-US.

FR-PO1023

Determinants of Hcpidin, the Key Regulator of Iron Homeostasis, in Renal Transplant Recipients Michele F. Eisenga,¹ Stefan P. Berger,¹ Robin P.F. Dullaart,¹ Aiko P.J. De Vries,² Stephan J.L. Bakker,¹ Carlo A. Gaillard.¹ ¹Internal Medicine, UMCG; ²Internal Medicine, LUMC.

Background: Hcpidin is synthesized in the liver and secreted into the circulation. Circulating concentrations may be influenced by body iron availability, inflammation, insulin resistance and tissue hypoxia. Moreover, hcpidin is a small 2.8 kD molecule. Therefore, renal clearance may be an important additional determinant of circulating hcpidin. We aimed to investigate whether markers of iron availability (ferritin), inflammation (C-reactive protein (CRP)), insulin sensitivity (fasting insulin), tissue hypoxia (erythropoietin) and estimated glomerular filtration rate (eGFR) are determinants of serum hcpidin in a population of renal transplant recipients (RTR) with a large variation in renal function.

Methods: The study was performed in an extensively phenotyped RTR cohort recruited in the University Medical Center Groningen. Serum hcpidin was assessed by ELISA ECL immunoassay. Statistical analyses were performed using univariable linear regression followed by stepwise backward linear regression. P-values for inclusion and exclusion were set at 0.2 and 0.1, resp.

Results: We included 561 RTR (age 51 ± 12 years; 55% males at 7.8 ± 6.4 years after Tx). Mean hemoglobin (Hb) was 8.6 ± 1.0 mmol/l. Median [IQR] serum hcpidin was 7.2 [3.2 - 13.4] ng/mL. Mean eGFR was 47 ± 16 ml/min/1.73m². In univariable analysis, ferritin ($\beta=0.69$, $p<0.001$), CRP ($\beta=0.24$, $p<0.001$), eGFR ($\beta=-0.14$, $p=0.001$), Hb ($\beta=-0.12$, $p=0.006$), EPO ($\beta=0.12$, $p=0.006$), fasting insulin ($\beta=-0.09$, $p=0.03$) and age ($\beta=0.09$, $p=0.03$) were associated with serum hcpidin. In multivariable analysis, concentrations of ferritin ($\beta=0.66$, $p<0.001$), CRP ($\beta=0.19$, $p<0.001$), erythropoietin ($\beta=-0.13$, $p<0.001$), fasting insulin ($\beta=-0.08$, $p=0.01$) and Hb ($\beta=-0.06$, $p=0.06$) (total model $R^2=0.53$) were identified as independent determinants of serum hcpidin, while the univariable association of eGFR was lost.

Conclusions: Despite large variation in eGFR, fifty-three percent of the variation in serum hcpidin concentrations in RTR can be attributed to variation in iron status, inflammation, insulin sensitivity and tissue hypoxia reflected by erythropoietin, rather than to variation in renal clearance.

FR-PO1024

Associations of Serum Soluble α -Klotho, Fibroblast Growth Factor 23, and 25 (OH) Vitamin D with Kidney Function and Left Ventricular Hypertrophy in Japanese Kidney Transplant Recipients Makoto Tsujita,¹ Shoichi Maruyama.² ¹Transplant Surgery, Nagoya Daini Red Cross Hospital, Japan; ²Nephrology, Nagoya Univ School of Medicine, Japan.

Background: Deterioration of kidney function and left ventricular hypertrophy (LVH) is crucial for kidney transplant recipients. Any marker for predicting kidney function and LVH is needed to prevent complications.

Methods: This was a retrospective cohort study. Forty-seven consecutive patients were enrolled in this study at Nagoya Daini Red Cross Hospital in 2011.

Table 1. Study population characteristics (n=47)

	Value
Age, years	51.8 \pm 11.6
Gender (male), n	32
DM ^{II} , n	9
Systolic BP, mmHg	127.0 \pm 11.5
Diastolic BP, mmHg	77.5 \pm 7.7
Corrected Calcium, mg/dl	9.6 \pm 0.7
Phosphate, mg/dl	3.4 \pm 0.4
Intact parathyroid hormone, pg/ml	110.0 \pm 133.3
Triglyceride, mg/dl	122.5 \pm 65.6
Low Density Lipoprotein Cholesterol, mg/dl	96.0 \pm 17.3
Hb, g/dl	12.3 \pm 1.6
Urinary protein, g/day	0.12 \pm 0.25
Soluble α -Klotho, pg/ml	516.3 (412.8, 612.0)
Fibroblast growth factor 23, pg/ml	58.7 (47.6, 68.5)
25(OH)vitamin D, ng/ml	5.7 (4.2, 11.3)
eGFR(1y), ml/min/1.73m ²	43.0 \pm 12.8
eGFR(3y), ml/min/1.73m ²	43.2 \pm 14.3
LVMI at 1 year, g/m ²	105.2 \pm 27.1
LVMI at 3 year, g/m ²	100.2 \pm 24.2
Use of Cyclosporine / tacrolimus, n	27 / 20
Use of mycophenolate mofetil, n	45
Use of ARB, n	33
Use of statin, n	25

Serum intact fibroblast growth factor (FGF) 23, soluble α -Klotho(saKlotho), 25(OH) Vitamin D[25(OH)D], estimated glomerular filtration (eGFR), left ventricular mass index (LVMI) and other clinical parameters after 1 year and eGFR after 3 years since kidney transplantation were measured to investigate the usefulness of these markers for predicting kidney function and LVH.

Results: The median serum saKlotho, intact FGF23, 25(OH)D were 516.3 pg/ml, 58.7 pg/ml, and 5.7 ng/ml, respectively. Serum saKlotho levels were associated with difference between eGFR after 1 year and after 3 years (DeGFR) ($r=0.37$, $p=0.01$), but not with difference between LVMI after 1 year and after 3 years (Δ LVMI). Patients were divided into two groups based on median serum FGF23 level. Higher serum intact FGF23 levels were associated with Δ LVMI. Serum 25(OH)D levels were associated with eGFR after 1 year ($r=0.34$, $p<0.05$), but not with DeGFR and Δ LVMI. Multivariate regression analysis revealed that serum saKlotho was the strongest predictor of kidney function and serum intact FGF23 was that of LVMI.

Conclusions: Serum saKlotho may be a good marker for kidney function and intact FGF23 for LVH in Japanese kidney transplant recipients.

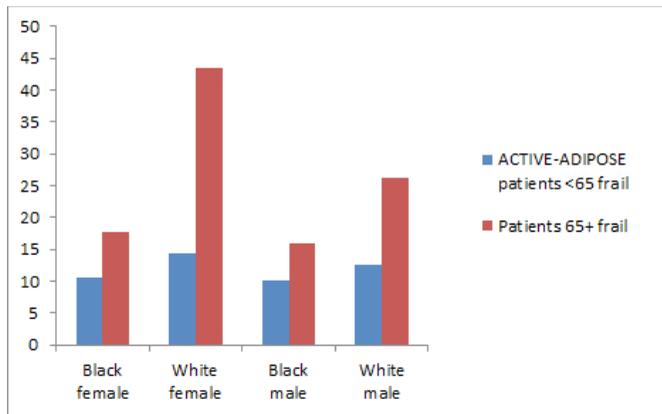
FR-PO1025

Lower Frailty Risk but Fewer Kidney Transplants in Blacks: USRDS Special Study Data Nancy G. Kutner, Rebecca H. Zhang, Janice P. Lea, Stephen O. Pastan, Rachel E. Patzer. Emory Univ, Atlanta, GA.

Background: Frailty, a measure of physiologic reserve, may indicate risk for adverse outcomes among kidney transplant (KT) recipients according to recent research. Non-frailty may therefore be a preferred characteristic of candidates for KT. Frailty status, age, race, and KT receipt were investigated during the 2009-13 USRDS study of a maintenance hemodialysis (MHD) cohort (ACTIVE-ADIPOSE study).

Methods: Frailty was assessed at study enrollment in 745 prevalent MHD patients (Atlanta and San Francisco areas; mean [SD] age = 57.1 [14.1]) using the Fried index (includes recent unintentional weight loss, reported exhaustion, low measured grip strength, slow measured walk speed, low reported physical activity; these indicators are both performance-based and patient-reported, and presence of 3+ criteria indicates frailty). Additional (1-2) frailty assessments were obtained annually for participants who remained on MHD post baseline. KT following most recent frailty assessment was monitored in the USRDS through February, 2013.

Results: % frail varied by age, gender, and race (Figure). 95% of the 40 KT recipients during the study period were non-frail; 82.5% were <65 years old; 52% were men. Among all non-frail patients <65 (n=115 whites and 358 blacks) in the study cohort, 10.7% of whites and 3.1% of blacks received a KT. However, a multivariable regression analysis, with adjustment for a large number of demographic, treatment and clinical variables, showed that blacks had lower odds for frailty compared with whites (OR 0.58; 95% CI 0.34-0.99; $p=0.04$).



Conclusions: Most study participants who received a KT were non-frail, but the proportion of black KT recipients was small despite blacks' lower observed risk for frailty compared with whites. Closer alignment of frailty status with support for KT access may have implications for reducing racial disparity in KT rates.

Funding: NIDDK Support

FR-PO1026

Circulating Inflammatory Cell Subsets Are Associated with Cardiac Function in Renal Transplant Recipients Jill Neale,¹ Danielle Richler-Potts,¹ Maurice Dungey,¹ Patrick Highton,¹ N. Martin,² Nicolette C. Bishop,² Alice C. Smith.¹ ¹Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; ²School of Sport, Health and Exercise Sciences, Loughborough Univ, United Kingdom.

Background: Cardiovascular (CV) disease is a major cause of mortality and morbidity in renal transplant recipients (RTRs). Systemic and vascular inflammation is paradoxically common despite immunosuppression and is an important non-traditional CV risk factor. Monocytes are heterogeneous: the intermediate phenotype (CD14⁺⁺CD16⁺) is particularly pro-atherogenic and pro-inflammatory compared to the classical phenotype (CD14⁺⁺CD16⁻). Regulatory T-cells (TRegs) maintain peripheral tolerance and minimise tissue damage. This study aimed to explore the association of circulating inflammatory cell subsets with cardiac function in RTRs.

Methods: 18 stable RTRs (Mean age 55 years, 61% male) and 5 healthy controls participated. Blood monocytes and T cells were analysed by flow cytometry, and cardiac hemodynamic function measured by bioreactance (NICOM).

Results: Circulating pro/anti-inflammatory cell subsets differed significantly in RTRs and controls. Mean %[SEM] intermediate monocytes was higher in RTRs (7.2[0.8]) vs controls (3.2[0.5], p=0.01), while classical monocytes and TRegs were lower in RTRs (83.2[1.3] vs 89.1[1.6], p=0.03 and 2.8[0.2] vs 5.0[1.0], p=0.001 respectively). In RTRs, % intermediate monocytes was inversely correlated with stroke volume (SV: r=-0.48, p=0.05) and cardiac output (CO: r=-0.52, p=0.03) and positively correlated with total peripheral resistance (TPR: r=0.50, p=0.04), while the opposite was seen with % classical monocytes (SV r=0.56, p=0.02; CO r=0.62, p=0.006; TPR r=-0.54, p=0.02).

Conclusions: Our results reveal a significant bias towards pro-inflammatory circulating leucocyte subsets in RTRs (increased intermediate monocytes, reduced classical monocytes and TRegs), which likely promotes an atherogenic environment. Furthermore, the observed significant correlations between pro- and anti-inflammatory monocyte subsets and indices of cardiac function strongly support an important pathogenic role for these cell subsets, which represent a potential therapeutic target in this vulnerable population.

Funding: Private Foundation Support

FR-PO1027

Iron Deficiency Is Associated with Mortality Independent of Anemia in Renal Transplant Recipients Michele F. Eisenga,¹ Stefan P. Berger,¹ Jenny E. Kootstra-Ros,² Else van den Berg,¹ Gerjan Navis,¹ Peter Van der Meer,³ Stephan J.L. Bakker,¹ Carlo A. Gaillard.¹ ¹Nephrology; ²Clinical Chemistry; ³Cardiology, UMCG.

Background: Anemia and iron deficiency (ID) are highly prevalent in renal transplant patients (RTR). Anemia is associated with poor outcome, but the role of ID is unknown. Therefore, we aimed to investigate the association of ID, irrespective of anemia, with all-cause mortality in RTR.

Methods: In a previously defined cohort of RTR, with hemoglobin data available, we additionally assessed serum iron, transferrin and ferritin. ID was defined as transferrin saturation (TSAT)<20% and ferritin <300 ng/ml. Anemia was defined as Hb<13 g/dL (M) or <12 g/dL (F). Cox regression analyses were used to investigate prospective associations with all-cause mortality.

Results: We included 701 RTR (age 53±13 years; 57% males at 8.1±7.5 years after renal transplantation). Mean Hb was 8.2±1.1 mmol/L, serum iron 15.3±6.0 μmol/L, and ferritin 118 (55-222) μg/L. Prevalences of anemia, ID, and iron deficiency anemia (IDA) were 34%, 30%, and 13%, resp. During follow-up for 3.2±0.8 yr, 81 (12%) of RTR died. In univariable analysis, ID was associated with mortality (HR 2.04 [95%CI 1.31-3.16],

p=0.001; fig. 1). Furthermore, both anemia (1.72 [1.11-2.66], p=0.02) and IDA (2.43 [1.48-4.00], p<0.001) were associated with mortality. After adjustment for age, gender, BMI, eGFR and anemia, the association of ID with mortality remained (1.82 [1.16-2.85], p=0.009). In contrast, the association of anemia with mortality disappeared after adjustment for eGFR and ID (1.15 [0.71-1.86, p=0.57], while the association of IDA remained after adjustment for eGFR (1.83 [1.10-3.05], p=0.02).

Conclusions: ID is highly prevalent among RTR and is associated with an increased risk of mortality, independent of anemia. Since iron deficiency is a modifiable factor, correction of iron deficiency could be a target to improve survival.

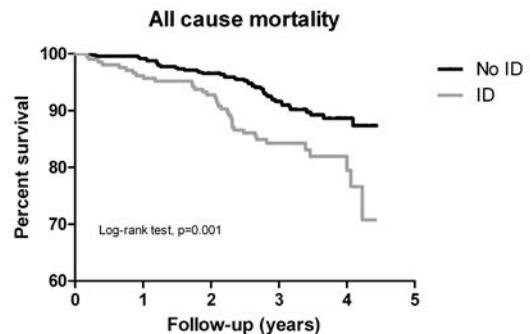


Figure 1: Survival curve for all-cause mortality based on the presence of ID

FR-PO1028

Indoleamine 2,3-Dioxygenase Activity and Late Graft Failure After Kidney Transplantation Laura V. de Vries,¹ Claude P. Van der Ley,² Casper F.M. Franssen,¹ Gerjan Navis,¹ Stephan J.L. Bakker,¹ Ido Peter Kema.² ¹Dept of Nephrology, UMCG, Netherlands; ²Dept of Laboratory Medicine, UMCG, Netherlands.

Background: Long-term graft survival after kidney transplantation remains a major clinical problem. Therefore, markers that allow for early identification of patients at risk for late graft failure (LGF) are urgently needed. Indoleamine 2,3-dioxygenase (IDO) catabolizes tryptophan along the kynurenine pathway. Recent studies found IDO activity associated with occurrence of acute rejection and renal function decline shortly post-transplant. We hypothesized that IDO activity could also be a marker for LGF after kidney transplantation.

Methods: We prospectively included outpatient renal transplant recipients (RTR) with a functioning graft >1 yr, between 2001-2003. Follow-up was recorded until May 2009. Death-censored GF was defined as return to dialysis or re-transplantation. Serum kynurenine (KYN) and tryptophan (TRP) were measured with LC-MS/MS; KYN/TRP is a widely accepted measure of IDO activity.

Results: We studied 562 RTR (age 51±12 yrs, 56% men, 6.0 [2.6-11.6] yrs post-transplant). Baseline concentration of serum KYN was 1.8 [1.4-2.2] μmol/l, that of TRP was 40.0 [34.5-46.0] μmol/l, and KYN/TRP was 44.3 [35.0-57.9] μmol/mmol. In multivariable linear regression analyses, KYN/TRP was positively associated with proteinuria (β=0.17, P<0.001) and waist circumference (β=0.12, P<0.001), and inversely with eGFR (β=-0.54, P<0.001) and HDL-c (β=-0.14, P<0.001). During follow-up for 6.9 [6.1-7.4] years, 51 (9.2%) RTR developed GF. In multivariable Cox-regression analyses, KYN/TRP was positively associated with GF (age, sex, eGFR, and proteinuria adjusted HR 3.6 [95% CI 1.3-9.9], P=0.01). Further adjustment for waist circumference and HDL-c did not materially change this association (HR 3.1 [95% CI 1.3-8.9], P=0.02).

Conclusions: IDO activity, as measured by KYN/TRP, is cross-sectionally associated with eGFR, proteinuria, waist circumference, and HDL-c. Prospectively, it is associated with increased risk for LGF after kidney transplantation. Increased IDO activity may not only be a marker for LGF, but also an interesting target for intervention to prevent decline of renal transplant function leading to LGF.

FR-PO1029

The Significance of Preoperative Left Ventricular Diastolic Dysfunction and Left Atrial Enlargement on Clinical Outcomes in Kidney Transplantation Jin Ho Hwang,¹ Jung Nam An,² Jaeseok Yang,³ Curie Ahn,³ Chun Soo Lim,² Yon Su Kim,⁴ Young hoon Kim,⁵ Jung Pyo Lee.² ¹Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; ²Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea; ³Transplantation Center, Seoul National Univ Hospital, Seoul, Republic of Korea; ⁴Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea; ⁵Surgery, Asan Medical Center and Univ of Ulsan College of Medicine, Seoul, Republic of Korea.

Background: In spite of improved survival of kidney transplant (KT) recipients, cardiovascular mortality is the leading cause of death following KT. Echocardiography is commonly performed as a screening test to evaluate cardiac function before KT. However, there are only limited data on echocardiographic parameters to evaluate the effect of left ventricular diastolic dysfunction (LVDD) and left atrial enlargement (LAE) on the long term outcome in KT recipients.

Methods: A total of 2,779 adult recipients who underwent pretransplant echocardiography from 1997 to 2012 were evaluated. We divided the patients into two groups by two different categories: LVDD grade 0-1 vs. 2-3, and LA size >38 mm. Post-KT fatal/non-fatal acute coronary syndrome (ACS), graft failure (GF), and all-cause mortality was evaluated.

Results: During a mean follow-up of 4.5 years, fatal/non-fatal ACS was occurred in 49 (1.8%) patients. A total of 231 (12.4%) patients experienced GF and 116 (6.2%) died. The recipients with LVDD grade 2-3 (P=0.005) and LAE (P=0.001) showed higher occurrence of fatal/non-fatal ACS after KT. Graft failure and all-cause mortality was not different between the groups depending on both the LVDD grades and LAE. In a multivariate analysis, increased age (P<0.001), previous history of CV event (P<0.001) and LVDD of grade 2-3 (hazard ratio[HR]:2.98, 95% confidence interval[CI]:1.535-5.787;P=0.001), and LAE (HR:1.052, 95% CI:1.006-1.101;P=0.025) were associated with ACS. However, none of LVDD and LAE was significantly associated with mortality and GF in a multivariate analysis.

Conclusions: In patients of KT candidate, pretransplant LVDD and LAE were independently associated with high occurrence of ACS after KT.

FR-PO1030

Effect of Dietary Sodium Restriction on Blood Pressure and Urinary Protein Excretion in Renal Transplant Recipients on RAAS-Blockade Laura V. de Vries,¹ Linn Charlotte Dobrowolski,² C.T.P. (Paul) Krediet,² Frederike J. Bemelman,² Stephan J.L. Bakker,¹ Gerjan Navis.¹ ¹Dept of Nephrology, UMCG, Netherlands; ²Renal Transplant Unit, AMC, Netherlands.

Background: In CKD patients on RAAS-blockade, it is well established that dietary sodium restriction exerts renoprotection by reduction of blood pressure (BP) and by reduction of urinary protein excretion (UPE), which is partly independent of BP. In renal transplant recipients (RTR), the effect of sodium restriction is not well-documented. We therefore studied the effects of dietary sodium restriction on BP and UPE in RTR.

Methods: We performed a randomized, cross-over trial in stable outpatient RTR with creatinine clearance >30 ml/min, BP >120/80 mmHg, UPE <1.5g/day, and use of RAAS-blockade. Exposures consisted of a 6-week regular sodium (RS) diet (target: 150 mmol/24h) and 6-week low sodium (LS) diet (target: 50 mmol/24h). End points were BP, UPE, urinary albumin excretion (UAE), and eGFR at the end of each diet period. Dietary compliance was assessed by 24h urinary sodium excretion.

Results: We randomized 23 RTR, of which 22 RTR (age 58±8 yrs, 50% men, eGFR 51±21 ml/min) completed the study. One patient dropped out, due to orthostatic complaints on the LS diet. Sodium intake was 156 [130-193] vs. 68 [55-86] mmol/24h on RS vs. LS diet resp. (P<0.0001). Sodium restriction significantly reduced systolic and diastolic BP. There was, however, no material change in UPE, UAE and eGFR.

	RS	LS	P-value
SBP (mmHg)	140±14	129±12	<0.0001
DBP (mmHg)	86±8	79±8	<0.0001
Serum creatinine (µmol/l)	123 [108-146]	125 [107-157]	0.3
eGFR (ml/min*1.73)	50±18	49±20	0.8
UPE (g/24h)	0.2 [0.0-0.3]	0.2 [0.0-0.3]	0.9
UAE (mg/24h)	29 [11-99]	22 [13-94]	0.3

Conclusions: Dietary sodium restriction effectively reduces BP in stable RTR on RAAS-blockade, but, at variance with findings in CKD, has no material effect on UPE or UAE, even with strict dietary compliance. This discrepancy might be due to relatively low UPE in the study population, or differences in pathogenesis of UPE/UAE or co-medication in RTR. Sodium restriction, therefore, is relevant to BP management in RTR on RAAS-blockade, but our data do not support independent renoprotective effects.

FR-PO1031

Individual Blood Calcification Propensity in a Cohort of Renal Transplanted Patients Carlo M. Alfieri,¹ Andreas Pasch,² Anna Regalia,¹ Maria Meneghini,¹ Maria Teresa Gandolfo,¹ Valentina Binda,¹ Deborah Mattinzoli,¹ Masami Ikehata,¹ Piergiorgio Messa.¹ ¹Nephrology, Dialysis and Renal Transplantation, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy; ²Nephrology, Hypertension and Clinical Pharmacology, Univ Hospital and Univ of Bern, Bern, Switzerland.

Background: Vascular calcifications and related cardiovascular disease have a strong impact in kidney transplantation(KTx).Calciprotein particle maturation time(T50) is a new measure of individual blood calcification propensity.Our aim is to explore in a cohort of KTx patients:1)the levels of T50 and their modifications during the 1st year of KTx;2)the relationship between T50 and routine clinical and biochemical parameters;3)the relationship between T50,bone mineral density(BMD)and aortic calcifications(ACI).

Methods: 70 KTx pts(M=38,Age:48±12 yrs),transplanted between 2005 and 2009 were recruited.Along with T50 evaluation,routine clinical and biochemical parameters and FGF-23,OPG, fetuin A and 25-(OH)-Vitamin D were tested at 1st,6th and 12thmonth after KTx. At 1st and 12th mth, femoral Dual X-ray absorptiometry and vertebral column X-ray for BMD(g/cm²) and ACI(Kaupilla) evaluation were performed.T50(min.) was determined using a Nephelostar nephelometer(BMG Labtech, Offenburg, Germany) in the laboratory of one of the authors.

Results: T50 at 1st6th and 12th mth were of 243[72-283],218[79-275] and 227[79-279] resp.,with a reduction of T50 at the 12thmth of KTx(p=0.04).In multivariate analysis,T50 was influenced by acid uric and fetuin-A(1st mth:p=0.02 and 0.001), by alkaline phosphatase,fetuin-A and 25-(OH)-Vitamin D (6th mth:p=0.01, p=0.001 and p=0.03 resp.), and by estimated glomerular filtration rate,body mass index and 25-(OH)-Vitamin D(12th mth:p=0.01, p=0.03 and 0.01 resp).Both at baseline and at 12thmth of KTx a direct correlation between BMD and T50 was demonstrated (p=0.002-p=0.04 respectively).No correlation between T50 and ACI score was demonstrated.

Conclusions: The main results of our study are that 1)during the 1st year of KTx,T50 decreases significantly, and 2)has a strong and direct relation with Fetuin-A and 25OH vitamin-D,both implicated in bone-vascular axis;3)T50 is associated with BMD but not of ACI status.

FR-PO1032

Prediction of Acute Rejection in Kidney Transplant Recipients Using a Multicenter Cohort Kyung Don Yoo,¹ Junhyug Noh,² Hajeong Lee,¹ Dong Ki Kim,¹ Chun Soo Lim,¹ Young hoon Kim,³ Yon Su Kim,¹ Gunhee Kim,² Jung Pyo Lee.¹ ¹Seoul National Univ College of Medicine; ²Seoul National Univ College of Engineering; ³Ulsan Univ College of Medicine.

Background: More than 20% of kidney transplant recipients (KTR) are likely to have rejection episode, which is associated with graft loss. However, the impact of risk factors on acute rejection had not been well clarified. Here, we aimed to build new prediction models through considering variables related to immunologic and non-immunologic factors using machine learning methods.

Methods: This multicenter cohort study included adult KTR admitted to 2 major experienced tertiary hospitals in Korea between 1997 and 2014. A total of 3,117 KTRs were enrolled. Biopsy-proven acute rejection (BPAR) of these recipients were investigated by the individual learners such as decision tree, logistic regression, and ensemble learners such as random forest.

Results: We analyzed 2,045 recipients' records, with more than 50 attributes. Among them, we chose 21 independent attributes which could affect BPAR incidence for building our models. In the decision tree model for the prediction of BPAR after three years of KT, HLA DR mismatch was found to be the most important predictor. In the case of HLA DR mismatch, donor specific antibody (+) predicted in 66.6% of BPAR incidence at three year after transplantation, and also posttransplant infection episode showed significant association with BPAR. In the case of HLA full matched, old age with heavy weighted recipient showed high probability of BPAR (71.4%). The final modeling represent AUC performance 0.670 (logistic regression) and 0.665 (random forest) in the BPAR prediction.

Conclusions: In this study, machine learning modeling could present an accurate and versatile tool for forecasting probability of having BPAR episode during the early years following the transplant.

FR-PO1033

Prediction of Long-Term Prognosis of the Kidney Transplantation Using Comorbidity Score Jae Yoon Park, Eunjin Bae, Sejoong Kim, Dong Ki Kim, Chun Soo Lim, Kwon Wook Joo, Yon Su Kim, Jung Pyo Lee. *Seoul National Univ College of Medicine, Seoul, Korea.*

Background: Comorbidity assessment is important to the informed interpretation of kidney allograft outcomes. Weights assigned to comorbidities to predict survival may vary based on the type of index disease and advances in the management of the comorbidities. We aimed to develop a modified Charlson comorbidity index (CCI) in renal allograft recipients (mCCI-KT), thereby improving risk stratification for mortality.

Methods: A total of 3,765 recipients in multicenter cohort were included to develop comorbidity score. The weights of comorbidities per the CCI were recalibrated using a Cox proportional hazards model. The modified score was validated in an independent nationwide cohort (n=1,538).

Results: The Cox proportional hazards model revealed that peripheral vascular disease, mild liver disease, and diabetes with end-organ damage in the CCI significantly predicted mortality. Thus, the mCCI-KT included 3 comorbidities with recalibrated severity weights. In the validation cohort, both the CCI and the mCCI-KT were correlated with mortality. The mCCI-KT showed modest increases in c statistics compared with the CCI (0.565 versus 0.534, P=0.002).

Conclusions: The mCCI-KT stratifies the risk better for mortality in renal allograft recipients compared with the CCI, suggesting that it could be a preferred index for use in clinical practice.

FR-PO1034

Patient Uncertainty Regarding Kidney Transplantation Associated with Length of Dialysis prior to Transplant Evaluation Laura J. McPherson,¹ Mohua Basu,¹ Stephen O. Pastan,¹ Sumit Mohan,² Rachel E. Patzer.¹ ¹Emory Univ, Atlanta, GA; ²Columbia Univ, New York, NY.

Background: End stage renal disease (ESRD) patients' uncertainty about undergoing kidney transplantation (KTx) ---i.e., decisional conflict---may be affected by cumulative time spent on dialysis prior to KTx evaluation. We aimed to investigate the association between time from dialysis start to KTx evaluation and decisional conflict.

Methods: In an ongoing clinical trial of study patients measuring the effectiveness of a shared decision tool at a single KTx center, ESRD patients were asked 10 questions assessing decisional conflict related to KTx, with possible scores ranging from 0 (none)

to 100 (high). Patients were dichotomized as having (score > 0) or not having (score = 0) decisional conflict. Time from dialysis start to KTx evaluation was abstracted from electronic medical records, and time on dialysis prior to evaluation was categorized as never on dialysis, <1 year, and >1 year. Logistic regression was used to assess odds ratios (ORs) for decisional conflict by time on dialysis prior to KTx evaluation.

Results: Of 70 surveyed patients, 64% were male, 62% were African American, and 66% had hypertension; the average age was 51 years. Patients with any decisional conflict (65%) were more likely to be male and African American in addition to having lower literacy and numeracy scores. Crude logistic regression showed that, compared to patients who had never been on dialysis prior to KTx evaluation, patients on dialysis for <1 year and >1 year evaluation were 1.4 (95% CI: 0.4, 4.9) and 2.5 (95% CI: 0.7, 9.2) times more likely to have decisional conflict, respectively.

Conclusions: Results suggest that longer time on dialysis prior to KTx evaluation may be associated with decisional conflict regarding KTx. Identifying characteristics of patients with longer time on dialysis prior to KTx evaluation could help inform intervention efforts to improve patients' abilities to make decisions about treatment of their kidney disease.

Funding: Private Foundation Support

FR-PO1035

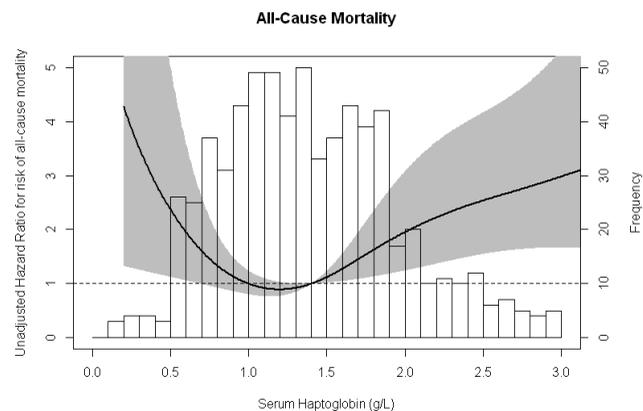
Haptoglobin and Long-Term Outcomes in Renal Transplant Recipients

Isidor Minovic,¹ Ineke J. Ripphagen,¹ Else van den Berg,¹ Jenny E. Kootstra-Ros,² Ido Peter Kema,² Andy P. Levy,³ Johanna M. Geleijnse,⁴ Gerjan Navis,¹ Stephan J.L. Bakker.¹ ¹Nephrology, UMCG, Netherlands; ²Laboratory Medicine, UMCG, Netherlands; ³Medicine, Technion, Israel; ⁴Human Nutrition, Wageningen Univ, Netherlands.

Background: Haptoglobin (Hp) is a hepatocyte-derived protein that protects against oxidative damage by binding free hemoglobin (Hb). Being an acute-phase protein, Hp is upregulated by inflammation. We hypothesized that both low and high Hp are risk factors for all-cause mortality and graft failure in renal transplant recipients (RTR).

Methods: Hp was measured using a turbidimetric immunoassay in a well-characterized prospective RTR cohort. Cox regression analysis was used to assess the association of Hp with endpoints.

Results: We included 707 RTR (57% male, age 53±13 y, eGFR 49±18 ml/min/1.73m² and 58% used a calcineurin inhibitor). Median Hp was 1.4 [IQR 1.0-1.8] g/L. Hp phenotype 1-1, 1-2, and 2-2 distribution was 18%, 50%, and 33% resp., with Hp levels of 1.7 [1.3-2.1], 1.4 [1.1-1.8] and 1.1 [0.9-1.7] g/L resp. (P<0.001). After median 38 [32-46] months follow-up, 81 (12%) RTR died and 45 (6%) developed graft failure. Hp showed a U-shaped association with mortality (P=0.01, fig. 1), but not with graft failure (P=0.7). Accordingly, the lowest (<0.9 g/L) and highest (>1.6 g/L) quintile of Hp levels were associated with mortality (HR 2.65 [95% CI 1.11-6.35] and 3.30 [1.41-7.72], resp.). Adjustment for sex, age, hsCRP, serum albumin, eGFR, BMI, HbA1c, LDH and Hp polymorphism did not materially influence the association of low Hp with mortality (HR 3.55 [1.42-8.84]). However, adjustment for hsCRP and serum albumin markedly weakened the association of high Hp with mortality (HR 2.06 [0.84-5.08]).



Conclusions: Low Hp is independently associated with mortality, but not graft failure, in RTR. High Hp was also associated with mortality, but this association largely depended on hsCRP and serum albumin.

Funding: Private Foundation Support

FR-PO1036

Pre-Transplantation Flow-Citometry Crossmatch Can Be a Predictor of Outcome when Donor-Specific Antibodies Are Present

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Background: Clinical relevance of pre-transplant (Tx) donor-specific-antibodies (DSA) detected by single antigen beads (SAB) when pre-Tx CDC-AHG crossmatch (XM) is negative is still unclear. The aim of this study was to evaluate the importance of a positive flow-citometry-XM (FCXM) in patients with DSA over patient and graft survival.

Methods: Retrospective study, performed between Jan09 and Dec13 evaluating FCXM influence over antibody-mediated rejection (AMBR) incidence, and over graft and patient survival. Biopsies were classified according to Banff'09 criteria and DSA by Luminex SAB.

Results: From 2009-2013, 1002 kidney transplants (Tx) were performed in our center. 261 (26%) were sensitized (PRA>0%) and 87 (8.7%) presented pre-Tx DSA. 60 (69%) of them had FCXM performed with serum collected before transplantation: 22 (36%) positive and 38 (64%) negative. There was no difference between the highest DSA-MFI between Tx with positive or negative FCXM [FCXM+ 5080 (1046-13560) vs FCXM- 3120 (597-14600)], or between the sums of all DSA-MFI of each patient between these groups [FCXM+ 6589 (1046-13560) vs FCXM- 3247 (597-15669); P 0,05]. DSA+/FCXM+ Tx had a significantly higher incidence of ABMR than DSA+/FCXM- Tx [FCXM+ 12 (54.5%); FCXM- 9 (23.7%); p 0.024]. After a median follow-up time of 34 mo, graft survival (GS) between Tx with positive and negative FCXM differed significantly (41% vs 92%; p < 0.0001). Among FCXM+ patients, GS was not influenced by ABMR (p=0,256). However, among patients with ABMR, FCXM+ had worse graft survival than FCXM- (FCXM+ 25% vs FCXM- 90%; p 0.011). Patient survival did not differ between FCXM+ (82%) and FCXM- (95%) neither was affected by ABMR.

Conclusions: A positive pre-Tx FCXM is related to a higher incidence of ABMR in the first year after Tx and to worse graft survival, and did not influence patient survival.

FR-PO1037

Pre-Transplant Mental Health Disorders and Non-Adherence and Post-Transplant Outcomes in Kidney Transplant Recipients

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Background: Mental health disorders (MH) and non-adherence (NA) have been associated with lower access to kidney transplantation (KT) and poorer clinical outcomes. We examined the relationship between history of MH problems, NA, and post-transplant outcomes (i.e., biopsy proven acute rejection: BPAR; death censored graft failure: DCGF; or total graft failure: TGF).

Methods: This was a single-centre retrospective cohort study of adult patients transplanted at our KT program from July 1, 2004 and Dec 31, 2012, and followed up until June 30, 2014. Patients with complete information about pre-transplant MH problems or pre-transplant history of NA in their medical record (n=955) were included. Univariable and multivariable associations between MH, NA and time to event (for BPAR, TGF and DCGF) were explored using log rank analysis and Cox proportional hazards models.

Results: The mean (±SD) age was 50.5 (±13.4) years, 61% of patients were male and 27% had a history of diabetes. Twenty-two percent had a positive history of MH disorders and 11% had a history of NA. Fifteen percent of the patients had BPAR, 5.6% had DCGF and 13% had TGF (death or DCGF). Participants with a history of pre-transplant NA but not with history of MH had higher risk for BPAR (log rank test p = 0.049 and p=0.46 for NA and MH, respectively). This difference, however, was not significant after adjusting for socio-demographic characteristics, donor type and HLA mismatch: adjusted HR (95% CI) 1.36 (0.84-2.23) and 1.16 (0.77-1.75) for NA and MH, respectively. Neither the history of pre-transplant MH nor pre-transplant NA was associated with DCGF or TGF. These results remained qualitatively unchanged after multivariable adjustment : adjusted HR (95% CI) 1.81 (0.96-3.42) and 0.99 (0.58-1.70) for NA and MH, respectively.

Conclusions: A history of pre-transplant mental health disorders or non-adherence are not associated with poor post-transplant outcome in a select group of patients who are cleared for transplantation. Patients with such problems should have equal access to kidney transplantation compared to patients with no MH problems.

Funding: Government Support - Non-U.S.

FR-PO1038

HLA Profile and Short and Long Term Outcomes in African American Donors and Recipients

Rabi Yacoub, Girish N. Nadkarni, John C. He, Paolo Cravedi, Rebecca L. Kent, Ioannis Konstantinidis, Karen Lok yee Keung, Sander Florman, Peter S. Heeger, Barbara T. Murphy, Madhav C. Menon. Mount Sinai, NY.

Background: We have previously reported the apparent greater impact of HLA-matching over HLA-mismatching on both early allograft events as well as graft survival in the United Network for Organ Sharing database (UNOS). Here, we specifically studied the influence of HLA-matching and mismatching on allograft outcomes among African-American (AA) recipients and AA-donor organs in deceased donor kidney transplantation (DDKT).

Methods: We utilized data from the UNOS database (1995 – 2012), and analyzed 10 year death censored graft survival (DCGS), 1 year clinical acute rejection (1y-AR), and delayed graft function (DGF) using Cox-regression and logistic regression in a combined multivariable model including HLA-matching and mismatching adjusted for key covariates. We performed sensitivity analysis using a subgroup of DDKT patients after 2003 with less heterogeneous HLA nomenclature, and resampling analysis using bootstrapping.

Results: We had complete data (outcomes and predictors) for 96236 recipients (Age 49.23±15.13, 60.4% male). AA-recipients constituted 30.2% while AA-donor organs were utilized 13.1% of DDKT (n=29071&12575, respectively). Similar to the whole UNOS cohort, among AA-recipients both HLA-matching and -mismatching individually had significant stepwise association with all outcomes (10-yr DCGS, 1y-AR & DGF). However, distinct from the whole cohort, we identified that when added in a combined model along with other covariates and adjusted for each other, HLA-matching and -mismatching had equal effects on each of the three examined outcomes. Among AA-donors, neither HLA-

matching, nor –mismatching had any effect on the three examined outcomes in either individual or combined multivariable models. Sensitivity analysis in the 2003-2012 cohort showed similar results.

Conclusions: Our analysis in this large cohort reports for the first time the absence of any effect from HLA-matching or –mismatching on allograft outcomes among AA-donor kidneys. These findings suggest that the allocation algorithm for AA-donor organs may need to be re-evaluated without including HLA-match status.

FR-PO1039

Femoral Bone Mineral Density Is Related with Aortic but Not with Coronary Calcifications in KTx Patients Carlo M. Alfieri, Anna Regalia, Maria Meneghini, Maria Teresa Gandolfo, Valentina Binda, Masami Ikehata, Deborah Mattinzoli, Piergiorgio Messa. *Nephrology, Dialysis and Renal Transplantation, Ospedale Maggiore Policlinico, Milan, Italy.*

Background: Our study wants to evaluate in a cohort of kidney transplanted(KTx) patients, undergone to femoral DEXA: 1) the prevalence of bone mineral anomalies; 2) the factors related to femoral bone mineral density (f-BMD) 3) the relationship of f-BMD with aortic calcifications (ACI) and coronary calcifications (CAC). Lumbar DEXA was not considered to avoid confounders between abdominal vascular calcifications (VC) and BMD.

Methods: 293 pts (M=170) transplanted in our Unit (2004-2013) were evaluated. Clinical and routine biochemical exams (plus PTH, FGF-23, Fetuin and VitD) were tested at 1(T0) and 12(T1) months of KTx. At the same time, DEXA, lumbar X-Ray (193pts) and coronary tomography (86pts) for f-BMD (g/cm²), ACI (Kauppila) and CAC (Agatston) evaluations were performed. ACI increase (ACI-Prog), any increase in ACI, Presence of CAC (CAC+), Agatston score >400, CAC increase (CAC-Prog) assessed using Sevrukov formula.

Results: At T0 and T1, OPN in 53% and 52%, OPR in 15% and 12% of pts resp. f-BMD was associated with: age, alkaline phosphatase (ALP) (at T0 and T1), fetuin and P (at T0). A logistic regression with BAbn (OPN+OPR as a whole) as dependent variable confirmed age and ALP as the only independent associated variables (T0 and T1). ACI were found in 55% and 61% of pts (T0-T1). ACI were higher in BAbn (T0 and T1). ACI-Prog (26%) had lower f-BMD (T0 and T1). f-BMD showed a discriminatory role in ACI-Prog (ROC-Curve, T0: AUC 0.66, p=0.02; T1: AUC=0.70, p=0.005). CAC+ was found in 13%, 20% and 28% of pts at T0, T1 and T2. CAC-Prog was found in 13% at T1 and in 49% of pts at T2. f-BMD did not correlate with CAC at T0, T1, T2, and both at T1 and at T2 its levels weren't different between CAC-Prog and CACnot-Prog.

Conclusions: High prevalence of BAbn and VC from the beginning of KTx is present. Age and ALP are strongly associated with f-BMD; 2) ACI and CAC progress in a high % of patients, in the early post-KTx period; 3) However, though f-BMD was significantly related with ACI-Prog, no association was observed with CAC worsening, possibly suggesting that different mechanism(s) might underlie VC processes at different sites.

Funding: Private Foundation Support

FR-PO1040

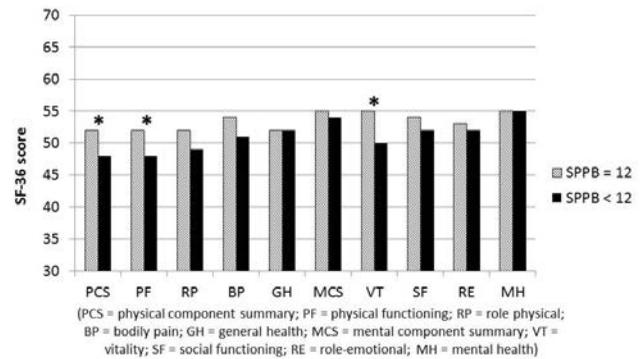
Relationship Between Pre-Transplant Physical Function and Quality of Life Following Kidney Transplant Elizabeth C. Lorenz, Andrea L. Cheville, Walter K. Kremers, Fernando G. Cosio, Nathan Lebrasseur. *Mayo Clinic, Rochester, MN.*

Background: Decreased physical function predicts adverse outcomes following non-transplant surgery. The goal of this study was to assess whether pre-transplant physical function predicts impaired quality of life (QOL) following kidney transplant.

Methods: We conducted a prospective cohort study involving all recipients of living donor kidney transplants at our center from 2012 until 2014. Physical function was measured using the Short Physical Performance Battery (SPPB), a composite measure of gait speed, balance and chair rise time (score range 0-12, with higher score indicating better physical function). QOL was measured 12-months post-transplant using the Short Form 36 Health Survey (SF36) with standardized scores adjusted for age and gender. Below-average physical and mental QOL was defined as physical (PCS) and mental component summary scores (MCS) < 45, respectively.

Results: Among the cohort of 140 patients, mean age was 51 ± 15 years, 61% were male, 91% were Caucasian, 21% had diabetes and 26% had a pre-transplant SPPB score < 12. A pre-transplant SPPB score < 12 was associated with a significantly lower 12-month PCS score (48.1 ± 9.0 vs 51.6 ± 8.5, p=0.04) but not a lower MCS score (54.2 ± 9.4 vs 55.2 ± 8.4, p=0.90).

Relationship between pre-transplant physical function and post-transplant SF-36 score



Below-average physical QOL at 12-months was observed in 23% of patients and was associated with pre-transplant BMI (OR 1.12 per 1 kg/m² increase, CI 1.02-1.23, p=0.02) and a pre-transplant SPPB score < 12 (OR 3.05, CI 1.17-7.97, p=0.02). In contrast, pre-transplant dialysis, diabetes, maintenance steroids and 12-month eGFR were not associated with physical QOL.

Conclusions: Decreased pre-transplant physical function predicts impaired physical QOL one year after kidney transplant. Further studies are needed to determine whether physical rehabilitation interventions can improve post-transplant QOL.

FR-PO1041

1st Report of Korean Organ Transplantation Registry (KOTRY) Tai Yeon Koo,¹ Hye Jin Lim,¹ Kyungok Min,¹ Hyunjin Ryu,¹ Jong Cheol Jeong,² Jaeseok Yang,¹ Myoung Soo Kim,³ Jae-Joong Kim,⁴ Curie Ahn,¹ Kotry Study Group.⁵ *¹Transplantation Center, Seoul National Univ Hospital; ²Dept of Nephrology, Ajou Univ School of Medicine; ³Dept of Surgery, Yonsei Univ College of Medicine; ⁴Division of Cardiology, Asan Medical Center; ⁵Korean Organ Transplantation Registry, Republic of Korea.*

Background: The Korean Organ Transplantation Registry (KOTRY) were launched in 2014 to construct the nationwide transplant database system which encompasses outcomes of various transplanted organs by support of the Korea Centers for Disease Control and Prevention.

Methods: In 2014, kidney, liver and heart transplant cohorts were established with participation of 29/58 centers for kidney, 13/35 centers for liver, and 4/8 centers for heart, covering more than 80% of total cases. Lung and pancreas transplant cohorts are also in progress since 2015. A web-based database system and attached biobank system have been developed. Annual data report and related information of database development process are available at <http://www.kotry.org>. From July 2014 to December 2014, 419 transplants in kidney transplantation (KT), 430 in liver transplantation, and 77 in heart transplantation were registered.

Results: Among 419 KT, deceased donor (DD) was performed in 156 patients (37.2%). Mean age was 47.7±11.2 and 56.8% of transplants were males. Diabetic recipients were 23.2%, and 5.5% of transplants were older than 65 years. Their original kidney disease was most often chronic glomerulonephritis (39.6%), followed by diabetic nephropathy (18.6%). Preemptive KT was 29.3% among living donor KT. The high panel-reactive antibody (>50%) accounted for 9.8% of transplants. Positive results of T or B flow cytometric crossmatch were found in 1.9% and 4.5% of transplants, respectively. ABO incompatible KT was performed in 21.7% of living donor KT. Mean age of donors was 45.3±13.2 and 59.9% were males. Among DD, expanded-criteria donor was 23.7%. Mean serum creatinine of living donor before and after KT were 0.81±0.18mg/dl, and 1.16±0.27mg/dl, respectively.

Conclusions: The KOTRY is expected to provide infrastructures for research in the field of KT and invaluable data for the Asian organ transplantation field.

Funding: Government Support - Non-U.S.

FR-PO1042

Pre-Transplant Midodrine Use: A Newly Identified Risk Marker for Complications After Kidney Transplantation Tarek Alhamad,¹ Daniel C. Brennan,¹ Zaid Brifkani,¹ Mark Schnitzler,² Vikas R. Dharnidharka,¹ Krista L. Lentine.² *¹Washington Univ; ²St. Louis Univ.*

Background: Midodrine is increasingly prescribed to decrease the severity and complications of hypotension in dialysis patients. The impacts of midodrine use before kidney transplantation on graft and patient outcomes early after transplantation are not well described.

Methods: We analyzed linked national U.S. transplant registry, pharmacy records and Medicare claims data to follow 16,322 kidney transplant recipients (2005-2008), of whom 308 (1.9%) had filled midodrine prescriptions in the year prior to transplantation. We examined associations of midodrine use with DGF, graft survival and death as reported to the registry, and with clinical complications captured in Medicare claims.

Results: At 3mo, patients who used midodrine before transplant had higher rates of DGF, 32% vs. 19%; hypotension, 14% vs. 4%; acute myocardial infarction (AMI), 4% vs. 2%; cardiac arrest, 2% vs. 0.9%; graft failure, 5% vs. 2%; and death, 4% vs. 1% than the non-users (P<0.05). After multivariate adjustment including recipient, and donor factors, as well as for the propensity of midodrine exposure, pretransplant midodrine use was independently associated with risks of DGF (aOR 1.95; CI 1.49-2.56), death-censored graft failure (aHR 1.94; CI 1.14-3.27), death (aHR 3.55; CI 1.99-6.33), as well as many potentially mediating complications. Patterns were similar at 12mo.

FIGURE 1A: INCIDENCE OF COMPLICATIONS AT 3-MO & 12-MO POST-TRANSPLANT, ACCORDING TO PRE-TRANSPLANT MIDODRINE USE

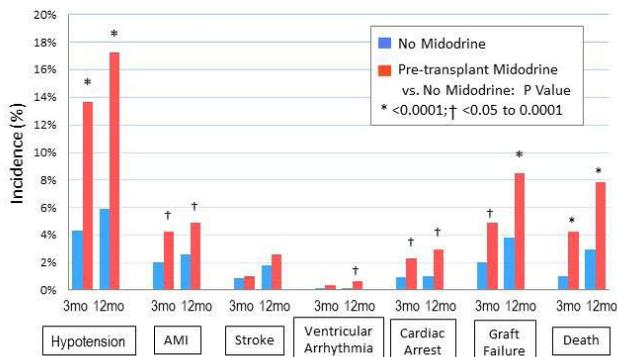
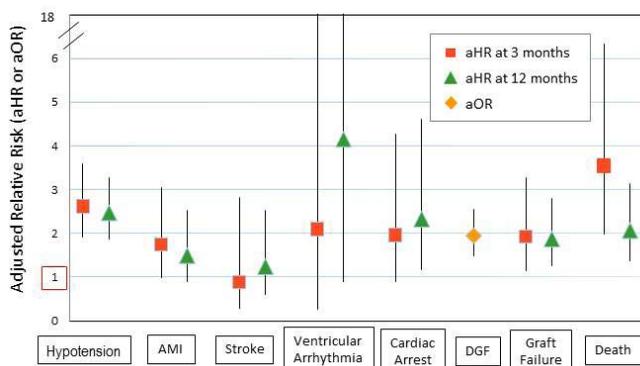


FIGURE 1B: ADJUSTED ASSOCIATIONS OF PRE-TRANSPLANT MIDODRINE USE WITH POST-TRANSPLANT COMPLICATIONS



Conclusions: Although associations may in part reflect underlying conditions, the need for midodrine before kidney transplantation is a bio-marker for increased risks of complications including graft failure and death. As the new KAS is expected to increase ESRD duration at the time of allocation for many patients, monitoring recipient comorbidity burden through novel methods including pharmacy claims, and associated impacts on transplant outcomes, are important priorities.

Funding: NIDDK Support

FR-PO1043

Impact of Proton Pump Inhibitors on Hypomagnesemia and Arterial Stiffness in Renal Transplant Recipients Siren Sezer,¹ Bahar Gurlekdemirci,¹ Saliha Uyanik,² Mehtap Erkmen Uyar,¹ Mehmet Haberal.³ ¹Dept of Nephrology, Baskent Univ Faculty of Medicine, Ankara, Turkey; ²Dept of Internal Medicine, Baskent Univ Faculty of Medicine, Turkey; ³Dept of General Surgery, Baskent Univ Faculty of Medicine, Turkey.

Background: Hypomagnesemia predicts cardiovascular morbidity and mortality in the general population and accelerated loss of kidney function in renal transplant recipients (RTRs). Proton pump inhibitors (PPIs) or H₂ receptor blockers (H₂RBs) are frequently used agents after RT. The aim of this study was to evaluate the effects of PPIs on serum magnesium levels and arterial stiffness in RTRs.

Methods: We performed a retrospective study of 354 maintenance RTRs (mean age: 38.6 ± 10.7 years) with stable allograft function who had received their transplant at least 36 months previously. All acute cellular and humoral rejections were excluded. According to using stomach-protecting agents (SPAs), patients were divided into three groups: PPIs (Group 1, n: 164), H₂RBs (Group 2, n: 96) and control group who don't receive SPAs (Group 3, n: 94). Estimated glomerular filtration rate (eGFR) was calculated by using the MDRD4 equation. Pulse wave velocity (PWV) was determined from pressure tracing over carotid and femoral arteries using the SphygmoCor system.

Results: Groups were similar in means of demographic characteristics and eGFR levels. Mean serum magnesium levels were significantly lower in group 1, however similar in group 2 and 3 (1.5 ± 0.04 mg/dl, 1.7 ± 0.02 mg/dl and 1.7 ± 0.01 mg/dl, respectively). PWV values were significantly higher in group 1, whereas similar in group 2 and 3 (7.3

± 0.2 cm/sec, 6.3 ± 0.1cm/sec and 6.2 ± 0.1 cm/sec, retrospectively). In linear regression analysis; type of SPAs (p: 0.001), serum calcium (p: 0.031), magnesium (p: 0.07) and folic acid levels (p: 0.013) were detected as the predictors of PWV.

Conclusions: We concluded that PPIs inhibit magnesium absorption independent from calcium metabolism in RTRs. Moreover, PPIs leads to increased arterial stiffness and cardiovascular risk in RTRs. Thus physicians should be aware of the side effects of PPIs to scale down the cardiovascular morbidity and mortality.

FR-PO1044

Comorbidity Burden of Kidney Transplant Recipients Predicts Emergency Usage Despite increased Family Physician Visits Hatem A. Alnasser,¹ Sita Gourishankar,¹ Kevin C. Wen.¹ ¹Univ of Alberta, Canada; ²King Fahad Specialist Hospital, Saudi Arabia.

Background: Kidney transplant(KTX) recipients utilize many aspects of the healthcare system, especially emergency(ER) visits. Unterman et al showed that within a four year period, 378 KTX recipients generated 828 ER visits. This study aims to understand factors leading to ER usage by KTX recipients.

Methods: This is a single center retrospective study in conjunction with patient questionnaire, collected from March 2012 - 2013. The questionnaire inquired the frequency of the family physician(GP) visits and ER usage within the past year. Patient demographics and comorbidities were collected from chart reviews. Univariate logistic regression was used to define factors that are predictive of ER usage. Significant covariates were then used in multivariate backward stepwise logistic regression model to predict ER visits.

Results: Number of GP visits(OR = 1.6, p=0.003), diabetes(OR = 1.7, p=0.016), coronary artery disease(OR = 2.5, p=0.001), below knee amputation(OR = 4.3, p=0.037), and number of comorbidities(OR = 1.35, p=0.001) significantly predict ER visits. Number of transplant clinic visits does not significantly decreased ER visits(p=0.32). By multivariate backward stepwise logistic regression, number of GP visits(OR = 1.5, p=0.007) and coronary artery disease(OR = 2.1, p=0.011) remain significantly predictive of ER usage.

Conclusions: This single center study showed that KTX recipients with more comorbidities have increased ER usage, particularly coronary artery disease, despite higher frequency of GP visits. However, kidney transplant recipients with more ER usage are not seen more frequently by our transplant clinic. The results suggest that KTX recipients with higher comorbidity burden may need to be followed more closely by transplant clinics, rather than relying on GP's, to improve effective usage of ER visits.

1. Unterman S, Zimmerman M, Tyo C, et al. A descriptive analysis of 1251 solid organ transplant visits to the emergency department. West JEM 2009; 10: 48.

Funding: Government Support - Non-U.S.

FR-PO1045

Stroke Predictors and Outcome in Renal Transplant Recipients Mark Duncan Findlay,^{1,2} Peter C. Thomson,² Patrick B. Mark.^{1,2} ¹Univ of Glasgow, Glasgow, United Kingdom; ²Glasgow Renal and Transplant Unit, Glasgow, United Kingdom.

Background: End-Stage renal disease is associated with a high incidence of cerebrovascular disease. Conventional risk factors do not always apply & established preventive strategies may be ineffective. The incidence, predictors & outcomes following stroke in those with a functioning renal transplant is not well described.

Methods: All adult patients with a renal transplant attending Glasgow Renal and Transplant Unit between 1st Jan 2007 and 31st Dec 2012 were identified using the electronic patient record. Clinical, demographic & laboratory data were collected including presence of diabetes, cardio- or cerebrovascular disease (CeVD), atrial fibrillation, deprivation, serum renal and bone chemistry and use of immune suppressants. Stroke was identified via discharge codes, cerebral imaging or death certification. Independent predictors of stroke were identified via multivariable regression analysis. Fatality & causes of death are presented.

Results: 636 patients were identified, mean age 38 years (SD 12.9). 60.5% were male and 9.1% had AF. During follow-up 7.1% received a transplant as first RRT modality. 24 patients experienced a stroke during 3455 patient years of follow-up. 83.3% were ischemic. Stroke incidence was 6.9/1000 patient years for all stroke and 3.76/1000 patient years for first stroke. A stepwise backward regression revealed predictors of stroke as older age (HR 1.05, p=0.025) and previous CeVD (HR 18.16, p<0.001). Significant independent predictors for first stroke were age, diabetes and AF (p<0.05). There were no cases of SAH in PCKD. AF associated with time to stroke (p=0.003), but there was no detectable benefit from use of warfarin. 134 died during follow-up. 62.5% deaths followed stroke with 7, 28 and 365 day fatality of 20.8, 25 and 45.8%. Cardiovascular (75%) or malignancy (13%) were the cause of death in most cases.

Conclusions: Renal transplant recipients have a high incidence of stroke and poor outcome following stroke. Risk factors include prior CeVD, age, diabetes and AF. Although AF associated with time to stroke, the role of warfarin in prevention is poorly defined, requiring further study.

FR-PO1046

Factors Influencing Racial Disparities in Renal Transplantation Outcomes

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Background: Kidney transplants from African American (AA) deceased donors have worse outcomes than kidneys procured from donors of other ethnic groups; deceased-donor kidney transplants (DDKTs) engrafted into AAs fare worse than kidneys placed into recipients of other ethnic groups. The role of biological and environmental factors in these disparities remains unclear. We sought to identify factors contributing to these ethnic differences in AA and European American (EA) recipients of kidneys from AA and EA donors in a study using donor-matched design to eliminate donor-specific confounding effects.

Methods: We compared allograft survival of DDKTs in 4 types of donor/recipient pairs (TDRP) (AA/AA, AA/EA, EA/AA and EA/EA). Models were fitted using a mixed effect Cox model with particular focus on effect modifiers of the TDRP association with allograft survival.

Results: We identified 669 AA and 3,383 EA donors resulting in 669 AA/AA, 669 AA/EA, 3,383 EA/AA and 3,383 EA/EA DDKTs. In agreement with previously reported trends, AA donors were more likely to be younger, male, hypertensive, and with higher serum creatinine, while EA recipients were more likely to be employed (46 and 45% vs. 37 and 33%) and less likely to experience delayed allograft function (DGF) (19 and 18% vs. 28 and 23%). Adjusted analyses controlling for donor and recipient characteristics identified strong interaction effects between the TDRP and incidence of DGF (P=0.009) and between the TDRP and employment status (P=0.04). Observed hazard ratios varied from 0.9 for an employed (EA/EA) pair without DGF to 4.3 for an unemployed (AA/AA) pair with DGF.

Conclusions: Ethnic differences in employment status and incidence of DGF were the strongest effect modifiers of the association between the TDRP and allograft survival for DDKTs. These differences partially explain the observed racial disparity in outcomes for DDKTs.

Funding: Other NIH Support - NIH RO1 DK070941 (BIF), NIH RO1 DK084149 (BIF), NIH RO1 MD009055 (JD, BIF), NIH/NIAD Genomics of Transplantation 5U19-AI070119 (AKI)

FR-PO1047

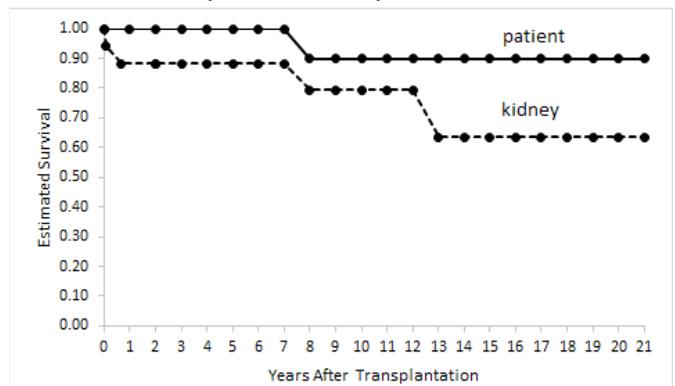
Renal Transplantation in Bardet-Biedl Syndrome

Robert M. Haws,¹ Aditya Joshi,¹ Siddharth A. Shah,³ Omar M.A.A. Alkandari,⁴ Martin A. Turman.² ¹Dept of Pediatrics, Marshfield Clinic, Marshfield, WI; ²Dept of Pediatrics, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; ³Dept of Pediatric Nephrology, Univ of Louisville, Louisville, KY; ⁴Dept of Pediatrics, Mubarak Al-Kabeer Hospital & Hamid Al-Essa Transplant Center, Safat, Kuwait.

Background: Bardet-Biedl syndrome (BBS) is a rare, multisystemic genetic disorder frequently associated with chronic kidney disease (CKD). Data regarding renal transplantation (RT) in BBS is lacking and reports tend to highlight complications. We report RT outcomes in the largest BBS cohort examined to date.

Methods: An international BBS registry was interrogated to identify individuals that had undergone RT and capture age, gender, body mass index (BMI), transplant and patient survival, donor source, and comorbidities.

Results: RT was performed in 19/171 (11%) registry subjects (mean age 9 y; range 2-25 y). RT patients were younger (9 vs. 17.9 y, p<0.05) and more likely to be female (82% vs. 50%). Deceased donors provided 12/21 kidneys; one patient received a combined liver/renal transplant. Two patients that underwent RT in the 1980s and died at <10 y of age were excluded from further analysis. Patient and kidney survival is shown.



Thrombosis and infection resulted in graft loss in the first year in 1 patient with 2 kidneys. One patient died awaiting a second RT. Acute reversible rejection in the first year occurred in 1/17 kidneys. Diabetes, hypertension, and obesity were present in 18%, 71%, and 88% of subjects, respectively. Malignancy was not observed (mean follow-up 9.8 y; range 1-21 y). BMI was increased compared to age-matched BBS patients without RT (42.2 vs. 35.2, p < 0.05).

Conclusions: Outcomes following RT in patients with BBS is favorable. Female predominance raises questions regarding gender as a potential modifying factor impacting CKD prevalence.

Funding: Private Foundation Support

FR-PO1048

Kidney Transplant Recipient Hospital Readmission: Examination of Discharge-Level Factors

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Background: Early rehospitalization after kidney transplantation (KTx) is common and is considered a quality metric. Few studies have examined preventability or discharge factors associated with early rehospitalization.

Methods: We performed a single-center, retrospective cohort study between 2011-2015 of adult KTx recipients. The primary outcome was at least one readmission within 30 days after discharge. Secondary outcomes were reason for readmission, potential for process improvement to reduce readmission, and all-cause graft failure.

Results: Of 462 KTx, 31.4% were readmitted within 30 days of discharge. The reason for readmission was surgical in 20.1%. Of those with non-surgical reasons, 21.7% were from infection, 20.9% graft dysfunction, 21.7% gastrointestinal, 21.7% metabolic, and 13.9% other. Readmission was significantly associated with all-cause graft failure (p=0.006). The assessment of preventability showed that the reason for readmission was present at the time of discharge in 11.7%, additional hospital resources may have abrogated the readmission in 15.8%, and 12.4% could have been managed as outpatient. On univariate analysis, risk factors for rehospitalization were: presence of comorbidities (p=0.03), complication during hospitalization (p<0.001), discharge electrolyte abnormalities (p<0.001) and kidney function at discharge (p=0.003), Table 1. On multivariate analysis, the presence of 3 comorbidities pre-KTx (aOR 2.01 95% CI 1.84-3.86), electrolyte abnormalities at discharge (aOR 1.77 CI 1.17-2.69), delayed graft function (aOR 1.65 95% CI 1-2.7), and post KTx complication (aOR 1.7 95% CI 1.1-2.61) were associated with increased risk of readmission

Table 1: Comparison of Patients Requiring Readmission versus No Readmission

Characteristic N(%) or mean +/- SD	Readmission No N=317	Readmission Yes N=145	p-value
Recipient Age, years	53.8 ± 13.2	53.4 ± 13.5	0.7933
Recipient, Male	188 (59.3)	90 (62.1)	0.5735
Recipient race			0.3011
Black	131 (41.3)	69 (47.6)	
Hispanic	116 (36.6)	49 (33.8)	
White	45 (14.2)	13 (9.0)	
Other	25 (7.9)	14 (9.7)	
Any Recipient Comorbidity	217(68.5)	113(77.4)	0.0364
Recipient BMI > 35 kg/m ²	32 (10.1)	18 (12.4)	0.4634
Recipient Diabetes mellitus	137 (43.2)	81 (55.9)	0.0115
Recipient, Prior Solid Organ Transplant	32 (10.1)	17 (11.7)	0.5976
Recipient, Cardiovascular Disease	89 (28.1)	41 (28.3)	0.9646
Recipient, peripheral vascular disease	35 (11.0)	28 (19.3)	0.0162
Recipient HIV, HCV, or HBV	32 (10.1)	14 (10.0)	0.8836
Recipient, pre-transplant albumin <3.5, g/dL	10 (3.4)	7 (5.3)	0.3382
Recipient, pre-transplant hemoglobin < 10 g/dL	48 (15.1)	27 (18.6)	0.3467
Recipient time on list, days			0.9954
Low < 483	122 (38.5)	57 (39.3)	
Medium 483-1579	130 (41.0)	60 (41.4)	
High > 1579	65 (38.5)	28 (19.3)	
Recipient, ATG Induction	160 (50.5)	71 (49.0)	0.7636
Kidney Type			0.8486
Standard criteria donor	182 (67.7)	87 (60.0)	
Expanded criteria donor	79 (24.9)	35 (24.1)	
Living donor	56 (17.7)	23 (15.9)	
Hospitalization Complication	159 (50.2)	98 (67.6)	0.0005
Hospitalization, length of stay > 7 days	65 (34.5)	50(34.5)	0.0013
Hospitalization, intensive care unit location	34 (10.7)	19 (13.1)	0.4567
Hospitalization surgical or radiologic intervention	23 (7.3)	20 (13.8)	0.0248
Hospitalization infection	8 (2.5)	6 (4.1)	0.1771
Hospitalization, blood transfusion	112 (35.3)	67 (46.2)	0.0260
Discharge, any electrolyte abnormality	131 (41.3)	87 (60.0)	0.0002
Discharge, Na < 135 or > 145	63 (19.9)	44 (30.3)	0.0133
Discharge, K < 3.5 or > 5.0	34 (10.7)	17 (11.7)	0.7506
Discharge, Mg < 1.7	26 (8.2)	16 (11.0)	0.3257
Discharge, Ca < 8.0 or > 11	37 (11.7)	38 (26.2)	<0.0001
Discharge, glucose < 70 or > 200	33 (10.4)	20 (13.8)	0.2897
Discharge WBC < 4 or > 12	51 (16.1)	33(22.8)	0.0845
Kidney Function at discharge			0.0032
DGF but recovery by time of discharge	76 (24.0)	37 (25.5)	
DGF and not recovered by time of discharge	69 (21.8)	51 (35.2)	
No DGF	172 (54.3)	57 (39.3)	
Follow-up duration, days	286.0±203.8	285.8±245.8	0.3346*

*Wilcoxon log rank

Conclusions: Early readmission is associated with worse graft survival. Many readmissions may be preventable and review of process improvement may reduce early readmission after KTx.

FR-PO1049

Kidney Transplant Outcomes for Patients with Amyloidosis – A United Network for Organ Sharing Database Analysis Ali Khalil, Tim E. Taber, Muhammad Ahmad Mujtaba, Muhammad S. Yaqub, Asif A. Sharfuddin. *Medicine/Neph, Indiana Univ, Indianapolis, IN.*

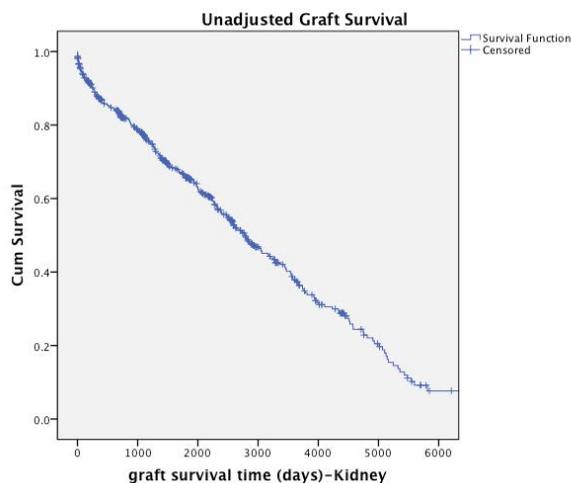
Background: Outcomes of patients with Amyloidosis who receive a kidney transplant have not been extensively studied. We examined UNOS database for outcomes of such recipients.

Methods: UNOS database was queried for recipients with code “3016” which corresponds to “Amyloidosis”. Duration of study period was Nov 1987 to Dec 2014.

Results: A total of 625 recipients were identified as in the table.

Variable	Result
Mean Age at time of transplant (yrs) SD	54.8±11.1
Mean Donor Age	40±15.1
Median Time On Wait List (days)(range)	261(0-2706)
Caucasian/African American/Hispanic/Other (%)	80.5/7.2/9.1/3.2
Deceased/Living (%)	56.5/43.5
M/F (%)	62.4/37.6
On Dialysis at time of transplant (%)	80.2
Mean BMI (SD)	25.7±4.8
Diabetes (%)	6.3
Repeat Kidney Transplant (%)	3.8
PRA >80 (%)	3.6
Zero Mismatch (%)	8.6
Blood Type A/AB/B/O (%)	40.7/5.3/12.5/41.6
ECD Donor/DCD (%)	9.6/2.9
Multi-Organ Transplant (%)	6.6
- Heart(n)	- 21
- Liver(n)	- 23
- Panc(n)	- 2
Delayed Graft Function (%)	14.6
Serum Creatinine (mg/dL) at discharge (SD)	2.3±2.1
Treated for Rejection within 6mo (%)	11.2
Treated for Rejection within 1 yr (%)	12.8
Death With Functioning Graft (%)	28.3
Unadjusted 1 yr/3yr/5yr/10 yr Graft Survival (%)	87.5/79.3/71.2/58.2
Actual Patient Survival 1yr/3 yr/5yr/10 yr	91.0/83.0/75.8/61.2

After excluding multi-organ transplants, the 1 year unadjusted graft survival was 88.6% and the 1 year patient survival was 92.1%. Kaplan Meier Survival Curves are in the Figure.



Conclusions: Although 1 year graft and patient survival of kidney transplants in recipients with Amyloidosis is inferior to standard outcomes, long-term outcomes are not remarkably different. Careful selection of this population can lead to satisfactory outcomes. To our knowledge this is the first and largest report on the outcomes of these patients from the US national database.

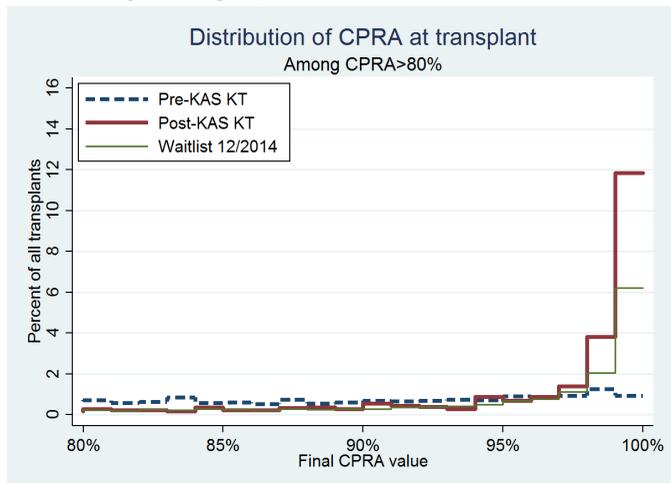
FR-PO1050

Early Experience with the New Kidney Allocation System Allan Massie, Dorry L. Segev. *Johns Hopkins.*

Background: On December 3, 2014, major changes to deceased donor kidney allocation were implemented under the new Kidney Allocation System (KAS).

Methods: Using national registry data, we compared changes in rate of DDKT among adult kidney-only waitlist registrants 1/2011-3/2015 pre vs post-KAS via Poisson regression, adjusting for age, sex, race, ABO blood type, calendar year, calculated panel reactive antibody (CPRA), and wait time. We compared donor service area-level geographic disparity pre vs post-KAS using multilevel Poisson regression and median incidence ratio (MIRR). We also compared CPRA of DDKT recipients pre vs post-KAS, and incidence of delayed graft function (DGF).

Results: Pre-KAS, access to DDKT was poorer for women (IRR=0.91 0.92 0.94), African-Americans (AAs) (IRR=0.86 0.88 0.90), and Hispanics (IRR=0.77 0.79 0.81, all p<0.01). Access was best for patients of ABO type AB (IRR vs O=2.19 2.29 2.39, p<0.01) and worst for ABO type B (IRR vs O=2.19 2.29 2.39, p<0.01). KAS was associated with no change in overall DDKT access (p=0.7), but with improved access for AAs (IRR=1.09 1.16 1.24, interaction p<0.001) and patients of ABO type AB (IRR=1.11 1.29 1.50, interaction p=0.001). Geographic disparity declined post-KAS (MIRR=1.76 pre-KAS, 1.64 post-KAS). Median CPRA at transplant was 0 both pre and post-KAS; the proportion of recipients with CPRA 80-99 decreased from 13.6% to 10.1% (p<0.001), but the proportion with CPRA>99 rose from 1.6% to 14.0% (p<0.001, Figure 1).



DGF incidence increased from 26.5% pre-KAS to 31.6% post-KAS (chi² p<0.001); in a multilevel (center-level) model, DGF increased 37% (OR=1.21 1.37 1.55, p<0.001).

Conclusions: After recent changes to kidney allocation, DDKT access improved for AA patients and geographic disparity declined. Women and Hispanic patients are still disadvantaged, and disparity by ABO type worsened. The proportion of recipients with CPRA>99 rose dramatically. Increase in DGF may suggest risk of poorer long-term outcomes.

Funding: NIDDK Support

FR-PO1051

Kidney Transplantation Tourism: High Risk and Bad Outcome for the Recipients Amgad E. ElAgroudy. *Internal Medicine Dept, College of Medicine and Medical Sciences, Arabian Gulf Univ, Manama, Bahrain.*

Background: While the ethical aspects of transplant tourism have received much attention recently, less has been written about the medical safety of this practice. We retrospectively evaluated the outcomes of patients who purchased organs internationally and presented to our center for follow-up care.

Methods: We report the outcome parameters of 270 local recipients of unrelated kidney (URT) vendor transplants presenting to our institute between 1986 and 2014. Their outcome was compared with 123 recipients of living-related donor transplants matched for age, gender and transplant duration done in our center as controls (RT).

Results: Age of unrelated recipients was 42.6 ± 13.4 years with Male % of 68. The country of transplant was mainly in Philippines (n = 85), Pakistan (n = 56), India (n = 57), Iran (n = 40) and Egypt (n= 25). Comparison of commercial recipients with controls showed high co morbidities (P = 0.01) with hepatitis-C (n=2 vs. 0) and hepatitis-B (n=2 vs. 0) and cytomegalovirus (n=4 vs. 1). Donor age was 25.9 ± 3.8 vs. 34.6 ± 8.6 years (P = 0.0001) and 90.4% were male. Biologic agents induction in 74 (27.4%) vs. 123 (100%) (P = 0.00001), acute rejections in 65 (24.1%) vs. 26 (21.1%) (P = 0.7), while recurrent rejection in 13 (4.8%) vs. 1 (0.8%) (P = 0.04), surgical complications including lymphocele 16 (5.9%) vs. 0 (0%) (P = 0.0001), ureteral obstruction 7 (2.6%) vs. 0 (0%) (P = 0.007), hematoma 4 (1.5%) vs. 1 (1.1%) (P = 0.06) and recurrent urinary tract infection 18 (9.9%) vs. 6 (6.8%) (P = 0.3). Overall 1- and 10-year for graft survival was 91% and 22% vs. 98% and 44% and for patient survival 96% and 70% vs. 98% and 78% in URT and RT, respectively (P = 0.001).

Conclusions: Although recent developments increased success in renal transplantation, receiving a kidney from a paid living donor at a commercial transplant center still carries great risks for the recipient.

FR-PO1052

The Negative Effect of First Transplant Nephrectomy for Second Transplant Outcome Masaki Muramatsu,^{1,2} Michael Sheaff,³ Arun Gupta,⁴ Atsushi Aikawa,² Carmelo Puliatti,¹ Muhammad M. Yaqoob.¹ ¹*Nephrology and Transplantation, The Royal London Hospital, London, United Kingdom;* ²*Nephrology, Toho Univ Faculty of Medicine, Tokyo, Japan;* ³*Cellular Pathology, The Royal London Hospital, London, United Kingdom;* ⁴*Clinical Transplant Laboratory, The Royal London Hospital, London, United Kingdom.*

Background: The impact of failed renal allograft nephrectomy on the outcome of retransplant is unclear. This single center study was conducted to address this question.

Methods: We analyzed 93 patients who received a 2nd transplant at The Royal London Hospital between November 1994 and January 2015. 59 patients did not receive primary transplant nephrectomy (TNx) and had failed allograft in-situ at the time of second graft (group A) whilst 34 patients underwent TNx prior to second graft (group B). 2nd transplant survival was the primary end point. Sensitization, waiting time for 2nd graft, graft function and rejections were secondary end points.

Results: Group A patients had significant longer graft survival than group B (100.6 months vs 40.2 months, *p*<0.001). Waiting time from primary graft loss to second transplant in group A was shorter than group B (36.7 months vs 59.1 months, *p*=0.013). In total, 35 patients had pre-formed anti-HLA antibodies (low titer). Group B had significantly higher rate of pre-formed anti-HLA antibodies than group A (50.0% vs 29.3%, *p*=0.047). The rate of HLA class I in group B was also significantly higher than that in group A (47.1% vs 25.7%, *p*=0.038). Group B had numerically higher rate of acute rejection than group A (32.4% vs 15.3%, *p*=0.053). eGFR between both groups did not differ until 3 years post-transplant. In group A, 2nd graft survival rates at 6month, 1, 3 and 5 years were 94.9%, 93.0%, 87.0% and 82.3%, and were significantly better group B (73.3%, 70.0%, 60.6% and 46.8%, *p*<0.001). On multivariate analysis, waiting time for second transplant, TNx, second transplant donor age and delayed graft function were independently associated with second graft survival. TNx had highest hazard ratio (2.83, 95% CI 1.22-6.67, *p*=0.015).

Conclusions: Prior TNx is associated with inferior 2nd renal graft survival in this observational study and calls for an urgent randomized control trial.

FR-PO1053

Induction Agent Use, Mortality and Acute Rejection in Older KT Recipients Mara McAdams-DeMarco, Xun Luo, Babak Orandi, Dorry L. Segev. *Johns Hopkins.*

Background: Induction agents are commonly used as an initial intensive immunosuppression after kidney transplantation (KT) to prevent acute organ rejection; this practice is mostly off label. Little is known about induction agent use in older KT recipients.

Methods: Data on 19,546 older KT recipients (2005-2013) was ascertained from the Scientific Registry of Transplant Recipients. Induction agents were classified as thymoglobulin/ATG, IL-2, or other induction agents. The risk of mortality was estimated using a Cox Proportional Hazards model (hazard ratio (HR)) adjusting for all recipient and KT factors (age, sex, race, BMI, peak PRA, history of diabetes, years on dialysis) and KT factors (HCV, HLA mismatches, cold ischemia time, donor type, donor age, and donor sex). The relative risk (RR) of 1 year acute rejection was estimated using modified Poisson regression adjusting for all recipient and KT factors.

Results: The mean age was 69 (SD=3.8 years), 36% female, 19% black and 27% live donor recipients. There is an increasing utilization by year of induction agents, with 84% use in older recipients. Compared to those who did not receive induction, the risk of mortality for older recipients was decreased for those who received thymoglobulin/ATG (HR=0.86, 95%CI:0.79-0.94), IL-2 induction agents (HR=0.89, 95%CI:0.81-0.97), and other induction agents (HR=0.85, 95%CI:0.75-0.97). Additionally, compared to those who did not receive induction, the risk of 1 year rejection for older recipients was increased for those who received IL-2 induction agents (HR=1.36, 95%CI:1.15-1.61), as well as other induction agents (HR=1.27, 95%CI:1.03-1.57) but not thymoglobulin/ATG (HR=1.06, 95%CI:0.90-1.25).

Conclusions: For older KT recipients, there is an increasing trend in the use of induction agents and a decreased risk of mortality regardless of the type of induction agent used. However, there is little evidence for a protective effect of induction agent use for 1 year acute rejection.

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FR-PO1054

Immunosuppression and the Elderly – Can They Take It? Mariana C. Chiles, Shefali Patel, Sumit Mohan, Russell J. Crew. *Columbia Univ, New York, NY.*

Background: The aging immune system has fewer naïve T cells, more memory T cells, and less T cell receptor variability. Older transplant patients tend to have more comorbidities and less functional reserve. This combination makes them more difficult to immunosuppress with higher risk of infection, and potentially increased mortality from rejection treatment.

Methods: In order to determine the impact of rejection treatment on outcomes in our transplant recipients >70 years of age, we reviewed the outcomes of patients transplanted at our center from 1/2009-12/2013. Induction regimens varied; maintenance immunosuppression consisted of tacrolimus, mycophenolate, and rapid steroid withdrawal.

Results: During this time period, we transplanted 110 over 70 years of age. Of these, 27 patients had rejection—24 ACR, 1 combined AMR/ACR, 1 AMR, 1AMR followed by ACR (see table). 11 of these patients received Tecll depleting agents, the rest received IV steroids +/- IVIg. There was no difference in age, race, donor type, prior transplant, or induction therapy between the two groups. Mean creatinine was higher in the rejection group. However, treatment appeared to stabilize function- the rate of decline in estimated GFR after rejection treatment was no different between groups. Within 6 months of rejection treatment, there were 12 infectious complications, only 3 of which required hospitalization (urosepsis-2, CMV-1). There were no differences in rates of BK viremia, CMV viremia, graft survival, or mortality. 7 of the 27 patients died at some point after rejection. only one was related to infection >1 year later and not related to treatment.

Conclusions: Among our >70 patients, rejection treatment appeared well tolerated with few complications requiring hospitalizations and no treatment related mortalities. In addition, it appeared that treatment stabilized function in the majority of patients.

	Non Rejectors N = 83	Rejectors N = 27	P value
Age ± SD	73.50±2.90	74.12±3.41	0.3503
Gender (% male)	60 (72.3)	20 (74.1)	1.0000
Race (% white)	55 (66.3)	15 (55.6)	0.2373
History of Prior Transplant (%)	10 (12.1)	3 (11.1)	1.0000
Donor Type (%DDRT)	55 (66.3)	23 (85.2)	0.1686
Induction (%)			
Basiliximab	27 (32.5)	14 (51.9)	0.2697
Thymo/thymo ritux	52 (62.7)	12 (44.4)	
Campath	3 (3.6)	1 (3.7)	
Simulect	1 (1.2)	0 (0.0)	
Follow up time, years (SD)	3.1±1.7	2.9±1.7	0.6270
Creatinine ± SD			
6 month	1.50±0.60	1.93±0.70	0.0033
3 year	1.32±0.49	2.44±1.05	0.0016
Change eGFR over time (cc/min/1.73m ² /year)	0.29(±11.2)	-2.1(±6.8)	0.21
Patient survival (% alive)	64 (77.1)	19 (70.4)	0.4798
Graft survival (% functioning)	75 (90.4)	23 (85.2)	0.4839
ACR Rate (%)	0 (0.0)	26 (96.3)	<.0001
Grade (%)			
Borderline		7(26.9)	----
1a		7 (26.9)	
1b		3 (11.5)	
2a		8 (30.8)	
2b		1 (3.9)	
Time to ACR, days ± SD		204.7±21.8	----
Infection within 6 months after Tx of ACR (%)	0 (0.0)	10 (37.0)	<.0001
AMR Rate (%)	0 (0.0)	3 (11.1)	0.0136
Infection within 6 months after Tx of AMR (%)		3 (11.1)	----
Bk Viremia (%)	16 (19.3)	6 (22.2)	0.7841
CMV (%)	9 (10.8)	5 (18.5)	0.3256

FR-PO1055

Mortality After Kidney Allograft Failure and Return to Dialysis Amarपाली Brar,¹ Edem Nguamon Timpo,¹ Rahul M. Jindal,³ Nabil Sumrani,² Fasika M. Tedla,¹ Moro O. Salifu.¹ ¹*Medicine, SUNY Downstate Medical Center, Brooklyn, NY;* ²*Surgery, SUNY Downstate Medical Center, Brooklyn, NY;* ³*Surgery, Uniformed Services Univ of Health Sciences, Bethesda, MD.*

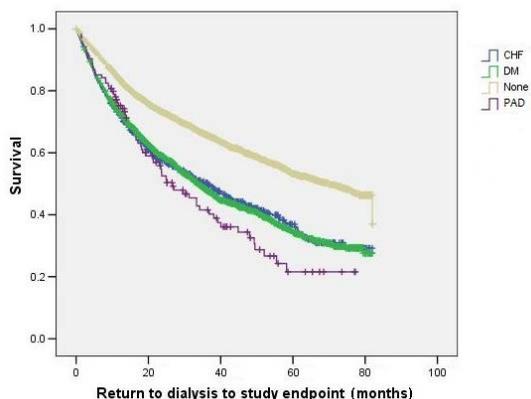
Background: Our hypothesis was that kidney allograft failure (KAF) and return to dialysis (RTD) results in greater mortality versus patients with end-stage renal disease (ESRD). We also sought to identify variables associated with mortality after KAF.

Methods: We used an incident cohort of patients from the United States Renal Data System who initiated any form of dialysis between Jan 2003 and Dec 2008 after KAF. We followed patients until retransplantation, death or Sept 2009. Multivariable Cox analysis was used for statistical associations.

Results: 7,156 patients were followed for a mean of 30.8 ± 22.6 months. 3,622 (50.6%) patients died; main causes of death cardiac (47.0%), infectious (17.5%), other (16.4%) and metabolic/endocrine (7.9%) causes. Predictors of all-cause mortality included age at KAF [hazard ratio (HR)= 1.03, 95% confidence interval (CI) 1.03-1.04], diabetes (DM) as cause of kidney failure (HR= 1.52, CI 1.3-1.8), congestive heart failure [CHF] (HR= 1.19, CI 1.04-1.36), peripheral arterial disease [PAD] (HR= 1.23, CI 1.04-1.55), stroke (HR= 1.27,

CI 1.05-1.55), employment (HR=0.80, CI 0.67-0.96), BMI (HR=0.98, CI 0.97-0.99) and serum albumin (HR=0.82, CI 0.75-0.90). Mortality was higher in those with either DM or CHF, and increased further in those with PAD (P<=0.0001).

Figure 1. Adjusted all-cause mortality (Kaplan-Meier curve)



Gender, number of transplants, donor type (deceased, living), ESRD duration prior to transplant, tobacco use, drug or alcohol abuse and erythropoietin use did not predict all-cause mortality.

Conclusions: DM, CHF and PAD are associated with increased mortality after KAF and RTD. Prevention and early management of these conditions may increase survival. Prospective studies are needed to confirm our findings.

Funding: Private Foundation Support

FR-PO1056

Current Trends in Waiting List of Kidney Transplantation and Mortality in Asian: A National Population-Based Cohort Study Using the Korean Network for Organ Sharing (KONOS) Database Kyung Don Yoo, Sunhwa Lee, Jung Nam An, Yun Kyu Oh, Chun Soo Lim, Yon Su Kim, Jung Pyo Lee. *Seoul National Univ College of Medicine.*

Background: Kidney transplantation has been increasing, globally. However, the clinical outcome of wait-listed patients for deceased donor kidney transplantation has not been well described in Asian patients with end-stage renal disease (ESRD).

Methods: We reviewed the detailed trends of wait-listed patients and conducted survival analysis in kidney transplant recipients using KONOS (The Korean Network for Organ Sharing) database which is a complete enumeration survey. We compared the outcomes according to the transplant era as followings: 2000-2004, 2005-2009, 2010-2014.

Results: From 2000 to 2014, a total of 34,843 patients registered in the waiting list, and 5,164 patients received transplantation from deceased donor. The proportion of deceased donor kidney transplantation has increased up to 45.9% in 2013 from 4.6% in 2000. The number of waiting list for kidney transplantation has increased continually more than 3,000 ESRD patients per year. The mean waiting time of deceased donor kidney transplantation was 54.9 months and has been getting longer. A total of 18,687 patients were remained on the waiting list until Jan 2015. Recently, diabetic nephropathy was the leading cause of primary disease on the waiting list, and the mean age of new registrants was getting older. The crude annual mortality rate during waiting time was 8.4%. The survival analysis revealed that there was no difference of patient survival according to the transplant era in kidney transplant recipients. However, the cumulative survival rate of the recently registered wait-listed patients was significantly improved even though they were older and had more proportion of diabetes (P<0.001, HR 0.51 95% CI 0.46-0.57).

Conclusions: In Korea, deceased donor kidney transplantation has increased. Donor organ is still seriously insufficient, therefore, it is necessary to encourage organ donation. In addition, more meticulous management needs to be provided to wait-listed patients.

FR-PO1057

Factors Affecting Mortality During Waiting Time for Kidney Transplantation: A Nationwide Population-Based Cohort Study Using the Korean Network for Organ Sharing (KONOS) Database Sunhwa Lee,¹ Kyung Don Yoo,¹ Jung Nam An,¹ Yun Kyu Oh,² Chun Soo Lim,² Yon Su Kim,¹ Jung Pyo Lee.² ¹Div of Nephrology, Dept of Internal Medicine, Seoul National Univ Hospital; ²Dept of Internal Medicine, Seoul National Univ Boramae Medical Center.

Background: Longer waiting times for kidney transplant have been suggested to be more deleterious than shorter waiting times. We analyzed the impact of waiting time on the post-transplant outcome and investigated risk factors for mortality during waiting time based on complete enumeration survey in Korea.

Methods: We analyzed all persons over 18-years-old deceased donor kidney transplant cases enrolled in Korean Network for Organ Sharing (KONOS) data between Jan 2000 to Jan 2015. The primary end point was all cause of death after enrollment.

Results: Of the 24,296 waiting-listed dialysis subjects, 5,255 patients including 588 re-transplant cases received kidney transplantation from deceased donor with median waiting

time of 4.5 years. Ten year overall survival was 81.3% in kidney transplant recipients, whereas 68.1% in dialysis patients. Unlike previously known data, the effect of waiting time on mortality after transplantation was insignificant. During waiting time, however, various demographic and clinical factors are associated with increased mortality. Diabetic patients are more likely to die before transplantation (HR 2.25, 95%CI 1.37-3.70, P=0.001). Aging is another significant risk factor for mortality. Only 56% of people aged 65 survive after 10 year of waiting, whereas 86% of people aged 35. Men are more likely to die than women during waiting time (HR 1.22, 1.13-1.31, P<0.001). Moreover, Patients with Rh negative blood type shows higher mortality rate than those with Rh positive (HR 1.60, 1.06-2.42, P=0.024). Pre-transplant experienced patients, however, showed better survival during waiting time (HR 0.63, 0.46-0.86, P=0.003).

Conclusions: Longer waiting times on dialysis do not affect survival after transplantation although transplant itself shows better overall survival. It should be emphasized to have more attention to the patients who are diabetic, old, men, or Rh negative with higher risk for mortality during waiting time.

FR-PO1058

Normal Saline versus Lower-Chloride Solutions for Kidney Transplantation Susan Wan,^{1,2} Matthew A. Roberts,³ Peter F. Mount.¹ ¹Dept of Nephrology, Austin Health, Melbourne, Victoria, Australia; ²Central Clinical School, Univ of Sydney, Sydney, New South Wales, Australia; ³Eastern Health Clinical School, Monash Univ, Box Hill, Victoria, Australia.

Background: The ideal intravenous (IV) fluid for kidney transplantation (KTx) has not been defined, despite the common use of normal saline (NS) in the perioperative period. The high chloride content of NS is associated with an increased risk of hyperchloraemic metabolic acidosis, which may increase the risk of hyperkalaemia and delayed graft function (DGF). Balanced electrolyte solutions (BES) have a lower chloride content, which may decrease this risk and avoid the need for dialysis due to hyperkalaemia. Randomised controlled trials (RCTs) have used biochemical outcomes to compare fluids and have been underpowered to address patient-centred outcomes such as DGF. We systematically reviewed the effect of BES versus NS on DGF, hyperkalaemia and acid-base status in KTx recipients.

Methods: We searched the Cochrane Renal Group's Specialised Register to 24th March 2015. We included RCTs of KTx recipients that compared perioperative IV lower-chloride solutions to NS. Two independent investigators assessed studies for eligibility and risk of bias. Data were extracted using standardised forms and pooled according to a published protocol.

Results: Six studies (477 participants) were included in the review. All participants were adult KTx recipients and 70% received live-donor KTx. The overall risk of bias was low for selection bias and unclear for remaining domains. There was no difference in the risk of DGF (RR 1.03, 95%CI 0.62-1.70, P=0.91) or hyperkalaemia (RR 0.48, 95%CI 0.04-6.10, P=0.57) for participants who received BES compared to NS. Compared to NS, BES were associated with higher blood pH (mean difference pH 0.07, 95%CI 0.05-0.09, P<0.00001), higher serum bicarbonate (mean difference HCO₃ 3.04mEq/L, 95%CI 2.13-3.94mEq/L, P<0.00001) and lower serum chloride (mean difference chloride -9.93mmol/L, 95%CI -19.96-0.11mmol/L, P=0.05).

Conclusions: Intraoperative balanced electrolyte solutions are associated with less hyperchloraemic metabolic acidosis compared to normal saline. However, these data do not support their use to reduce clinical events.

FR-PO1059

Risk Factors for Delayed Graft Function in Kidney Transplantation Marcos A. Meniconi,¹ Vitoria C. Vilela,¹ J. Medina-Pestana,¹ Miguel Cendoroglo Neto,^{1,2} Miguel A Goes.^{1,2} ¹Nephrology Div, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; ²Nephrology Div, Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil.

Background: Renal failure persisting after transplantation necessitating dialysis within the first week is called delayed graft function (DGF). **Objective:** To assess the impact of erythropoietin usage on DGF after renal transplantation.

Methods: A total of 196 maintenance hemodialysis patients who underwent renal transplantation at one center (Hospital do Rim) were prospectively analyzed pre and post-renal transplantation. Data on demographics, ESRD etiology, pre-transplantation hemodialysis, recombinant human erythropoietin (rHuEPO) use, type of donor kidney and immunosuppression regimen were reported. Two-sample t test were used to compare differences between two groups (DGF versus non-DGF groups) and X² to analyze categorical variables. Binary logistic regression was used to determine the impact of factors on outcome-DGF.

Results: The mean time duration on maintenance hemodialysis was 18+6 months. The main causes of ESRD were diabetes (37%) and hypertension (15%) followed by chronic glomerulonephritis (9%). There were transplants from deceased-donor kidneys (47%), living unrelated kidney donation (43%) and living related donors (10%). 41 patients necessitated dialysis within the first week after renal transplantation (DGF group). We observed that 131 patients (67%) used recombinant human erythropoietin until one week before renal transplantation. We observed that DGF group was older (39+15; p=0.007), higher cold ischemia time (23+10h, 12+10h; p<0.001), longer time on dialysis (4+4, 2+1 yr; p=0.001) and higher rHEPO dose (4930+447, 1658+844 IU; p<0.001). DGF group had higher use of rHuEPO (p<0.001). Cold ischemia time (p=<0.001) was an independent predictor of DGF.

Conclusions: This study shows that rHuEPO was not associated with DGF-protection in renal transplant patients. Cold ischemia time is an independent predictor of DGF.

FR-PO1060

Outcomes of Kidney Transplant Recipients from Donation After Circulatory Death Donors without Pre-Agonal Heparin Administration *Layla Kamal, Joel Lindower, Maria Ajaimy, Michelle L. Lubetzky, Graciela De Boccardo, Enver Akalin, Liise K. Kayler. Montefiore-Einstein Center for Transplantation.*

Background: Protocols of organ donation after circulatory death (DCD) are considerably varied. Heparin administration during the pre-agonal phase has been recommended to improve organ perfusion and prevent blood clots; however some protocols avoid heparin before verification of death based on legal or professional concerns. We assessed outcomes of kidney transplant recipients who received DCD kidneys recovered with and without heparin.

Methods: We retrospectively evaluated recipients of kidney transplants between 2011 and 2014 from controlled DCD donors who received (n=23) or did not receive (n=29) pre-agonal heparin.

Results: All kidneys underwent machine perfusion. No Heparin donors had a similar kidney donor profile index but were more likely to have mild histologic changes, elevated terminal machine perfusion resistive index, and to be imported from non-local donor service areas compared to the Heparin donors. Recipients of no Heparin kidneys were more likely to be female, sensitized, prior solid organ recipients, and to receive thymoglobulin induction but were less likely to have diabetes. None of these differences reached statistical significance. Post-transplantation, 1 patient died early due to a cardiac event (no Heparin group). Graft failure occurred in 2 patients in the no Heparin group (one each of sepsis/intraparenchymal venous thrombosis and chronic histologic changes suggestive of donor disease) and 1 patient in the Heparin group (renal artery thrombosis). Between group differences were small in terms of delayed graft function, 6-month acute rejection, and estimated GFR at 3, 6, and 12 months.

Table: Transplant Characteristics and Outcomes by Group

Characteristic % or mean +/- SD	Heparin No N=29	Heparin Yes N=23	P- Value
Kidney Donor Profile Index	61.7±21.9	59.4±30.0	0.63
Warm ischemia time	28.2±5.98	35.3±16.4	0.21
11-25% Arteriosclerosis or 11-25% Interstitial Fibrosis or ≥ 5% Glomerulosclerosis	38.5	27.8	0.54
Kidney from non-local Donor Service Area	86.2	69.6	0.78
Machine Perfusion Terminal Resistive Index			
<0.2 mm Hg/mL/min	41.7	52.2	0.46
0.21-0.35 mm Hg/mL/min	41.7	43.5	
>0.35 mm Hg/mL/min	16.7	4.4	
Recipient, Black race	51.7	56.5	0.21
Recipient, Female	51.7	30.4	0.16
Recipient Age, years	54.3±16.3	55.4 ± 10.1	0.78
Recipient, Diabetes Mellitus	44.8	56.5	0.58
Prior Solid Organ Transplant	10.3	0	0.25
Thymoglobulin Induction	55.2	30.4	0.10
Panel Reactive Antibody > 0%	27.6	4.4%	0.03
Human Leukocyte Antigen mismatch > 4	58.6	34.8	0.10
Cold Ischemia Time-hours			
<30	37.9	47.8	0.21
30-40	27.6	39.1	
40-54	34.5	23.1	
Delayed Graft Function	65.5	60.9	0.78
Cumulative incidence of acute Rejection at 6 months	12.0	5.0	0.62
Overall death Censored Graft Failure	6.9	4.3	0.10
Estimated Creatinine Clearance (Cockcroft-Gault)			
3-months	50.4±16.4	58.1±15.2	0.12
6-months	54.7±18.6	61.2±16.7	0.24
12-months	61.9±15.7	58.6±11.1	0.58
Follow-up duration, days	292.4±395.6	233.5±305.1	0.45

Conclusions: Our findings suggest that DCD kidneys recovered without pre-agonal heparin are not at increased risk for primary non-function or thrombosis.

FR-PO1061

Effects of Dopamine Donor Pretreatment on Graft Function After Kidney Transplantation: Five-Year Follow-Up of a Randomized Controlled Trial *Urs Benck, Bernhard K. Krämer, Peter Schnuelle. ¹V. Medical Clinic, Univ Medical Center Mannheim, Mannheim, Germany; ²Nephrology, Center for Renal Diseases, Weinheim, Germany.*

Background: [For the study Group]: A previous multicenter randomized controlled trial reported reduced dialysis requirements after kidney transplantation with dopamine donor pretreatment. Data on long-term outcomes are needed.

Methods: We calculated five-year graft survival from follow-ups at 60 European centers. We analyzed intention-to-treat and on-study-medication and produced survival estimates as tertiles of dopamine exposure because infusion times varied by treatment arm (range 0-1,929 min). Recipients with functioning grafts at three months were analyzed separately to differentiate early events from long-term consequences of the trial intervention.

Results: Follow-up was complete in 99.2%. Overall graft survival was 72.6 vs. 68.7%, (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.61-1.19; p=0.35), and

death-censored graft survival was 83.3 vs. 80.4%, (HR 0.84, 95%CI 0.54-1.29; p=0.42) in the treatment and control arms, respectively. The HR decreased to 0.46 (95%CI 0.23-0.94; p=0.03) in recipients with functioning grafts at three months, whose donor had received dopamine >270 min. It remained significant after adjusting for donor age (HR 1.05, 95%CI 1.02-1.08; p=0.001), delayed graft function (HR 2.05, 95%CI 1.12-3.73; p=0.02), biopsy-proven rejection (HR 2.13, 95%CI 1.16-3.93; p=0.02), and repeat transplants (HR 2.49, 95%CI 1.19-5.20; p=0.02). There were no differences of graft survival on intention-to-treat.

Conclusions: Dopamine administered for >270 min provided a long-term graft survival advantage independent of early events after Transplantation.

FR-PO1062

Does Calcineurin Inhibitor Timing Matter? Single Center Experience with En-Bloc Kidney Transplantation *Maya Campara,¹ Oksana A. Kucher,¹ Sanjeev Akkina,² Ignatius Yun-Sang Tang,² ¹Pharmacy Practice, Univ of Illinois at Chicago; ²Medicine, Nephrology, Univ of Illinois at Chicago.*

Background: En-bloc kidney transplantation (KTx) has excellent outcomes. To minimize vascular complications and nephrotoxicity, calcineurin inhibitor (CNI) therapy is often delayed. The purpose of our study is to investigate the impact of CNI initiation timing on 1-year graft outcomes.

Methods: This is a single-center, retrospective review of adult en-bloc KTx between 2001 and 2013. Timing of CNI initiation was decided by the operating surgeon. Patients were divided into two groups, those that received CNI therapy early (<48 hours) or delayed (>48 hours) posttransplant. The primary objective was to compare one year estimated glomerular filtration rate (eGFR) between the groups. Secondary outcomes included graft and patient survival, CNI levels, incidence of delayed graft function (DGF), rejection and graft failure rates.

Results: Twenty-one en-bloc KTx recipients were included in the analysis. Ten patients received CNI therapy within 48 postoperative hours (Early CNI Group). There was no difference in age, race, gender, PRA, cause of ESRD or BMI between the groups. Only 50% of Early CNI patients received lymphocyte depleting therapy vs. 100% in the Delayed CNI group (p = ns). In the Early CNI Group, 3 patients were on cyclosporine; all other patients received tacrolimus and mycophenolate maintenance. There was no difference in eGFR between groups at one year or at any other time points. Comparable therapeutic tacrolimus trough was observed at 5, 10 and 30 days posttransplant. There was no difference in DGF or rejection incidence. In the delayed CNI group, one patient died of sepsis at 6 months.

Conclusions: Timing of CNI initiation had no impact on one year graft function and patient survival.

	Early CNI (n = 10)	Delayed CNI (n = 11)
FK506 trough POD-5, ng/ml	5.75+/-2.65	7.34+/-4.9
FK506 trough POD-10, ng/ml	11.5+/- 4.9	12.1+/-7.5
FK506 trough POD-30, ng/ml	9.3+/-1.4	9.9+/-3.7
eGFR POD-30 Days, ml/min/m2	59.7+/-22.3	50.9+/-25.7
eGFR POD-365 Days, ml/min/m2	84.9+/-27.8	80.5+/-21.4
Rejection 1st year, n(%)	2(20)	3(27)
BPAR, n(%)	1(10)	1(9)

FK506-tacrolimus; POD-postoperative day; BPAR-biopsy proven acute rejection

FR-PO1063

Reduction of Pediatric Renal Transplantation Vascular Thrombosis Rates Utilizing Low Dose Heparin Infusion *Philip D. Acott,^{1,2} James B. Tee,^{1,2} Philip Wornell,^{1,2} John F.S. Crocker.^{1,2} ¹Pediatrics, Dalhousie Univ, Halifax, NS, Canada; ²Pediatrics, IWK Health Center, Halifax, NS, Canada.*

Background: Pediatric renal allograft thrombosis rates are 4-10% and often result in allograft loss. Thrombotic risk factors are smaller native vessel size, deceased donor source (DD), delayed renal allograft function, acute rejection, and small centre size (<50 transplants/decade). In our pediatric program from 1971 – 1992, 5 of 69 consecutive renal transplants (7.2%) were lost to vascular thrombosis. This study assesses if low dose continuous heparin reduces the risk and outcome of thrombosis in pediatric renal transplants.

Methods: Over 22 years (1993-2015), 44 of 100 consecutive children post renal transplant received low dose continuous heparin (10 units/kg/hour) for 1 week for thrombotic risk: 1) age < 6yr (n=24); 2) laboratory profile of hypercoagulability (n=10); 3) oliguric delayed function (n=5); 4) surgical complications with venous or arterial anastomosis or double artery (n=4); or 5) patient history of access thrombosis or vasculitis (n=1). Renal scans were obtained on days 1, 3, 5 and when clinical deterioration occurred.

Results: Only 2 thrombotic events were noted which did not cause graft loss: 1) 2yr LRD transplant- venous thrombosis immediately post-op on heparin with successful thrombectomy at 2hr and allograft recovery; 2) 17yr DD double renal artery allograft arterial thrombosis of smaller inferior renal artery on day 10 (heparin stopped day 7). One patient on heparin infusion required laparotomy 3hrs after surgery for thrombosis external to the anastomosis. One patient not on heparin also required laparotomy in the first 24hrs post-op for hematoma evacuation. One patient in each group had primary non-function/surgical loss with removal of the kidney within the first 3 days post transplant. Graft survival at 1yr was 96% and no allograft was lost due to thrombotic complications.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Identification of pediatric patients with who are at high risk of thrombosis post renal transplant appears warranted. We achieved a low thrombosis rate and no thrombotic organ loss, despite a high proportion of high-risk patients < 6yr, utilizing low dose continuous heparin for 1 week post transplant.

FR-PO1064

The Influence of Induction Immunosuppressive Therapies and Diabetes on Graft Loss After Kidney Transplant Hosam A. Farag,¹ Nasrollah Ghahramani,¹ Tarek Alhamad.¹ ¹Public Health Dept, Penn State College of Medicine, Hershey, PA; ²Nephrology Dept, Penn State College of Medicine, Hershey, PA; ³Public Health Dept, Penn State College of Medicine, Hershey, PA; ⁴Nephrology Dept, Washington Univ, St. Louis, MO.

Background: Induction therapy plays a significant role to reduce the rate of acute rejection in kidney transplant (KT). Understanding differences in outcomes associated with induction agents may lead to improvement in long-term care. Our objectives were to examine the influence of various induction therapies and diabetes on graft and patient survival after KT.

Methods: We used the 2000-2013 United Network for Organ Sharing (UNOS) data to evaluate the effectiveness of induction therapies and diabetes on graft and patient survival after KT. The patients were divided into four groups based on induction therapy: Basiliximab (n=24,484), alemtuzumab (n=3,321), rabbit anti-thymocyte globulin (r-ATG) (n=54,974) and daclizumab (n=13,358). Also the patients were divided into four groups based on diabetic status: non-diabetic (n=192,333), type1 diabetes (n=11,863), type 2 diabetes (n=43,543) and new onset of diabetes (n=10,509). The main outcome were the risk of graft loss and death at 1,3,5,10 years. Cox proportional hazards model was used to estimate the hazard ratios.

Results: Graft loss was significantly higher in alemtuzumab group (HR=1.171 ; P= 0.002) and rabbit anti-thymocyte globulin group (HR=1.109 ; P< 0.0001) versus basiliximab group. Daclizumab group showed significantly lower risk for graft loss (HR=0.902%; P< 0.0001) than basiliximab. Death was significantly higher in rabbit anti-thymocyte globulin group (HR=1.075 ; P< 0.0094) versus basiliximab group. Daclizumab group showed significantly lower risk for death (HR=0.850 ; P< 0.0001) than basiliximab group. Graft loss was significantly higher in type 2 diabetes (HR=1.451 ; P< 0.0001).

Conclusions: Induction immunosuppressive therapies and diabetic status play significant role in long-term graft and patient survival. Basiliximab and daclizumab as IL-2 RA receptor antagonists have better long-term graft and patient survival outcomes.

FR-PO1065

Does Induction Type Influence Outcomes in Kidney Transplant Recipients at Different Phases of Hepatitis B Infection? Kalathil K. Sureshkumar, Richard J. Marcus, Bhavna Chopra. *Nephrology and Hypertension, Allegheny General Hospital, Pittsburgh, PA.*

Background: Host response to hepatitis B virus (HBV) infection is variable with some patients progressing to chronic liver disease. Immunosuppression associated with kidney transplantation in such patients may increase the risk of disease progression. We aimed to analyze the impact of potent depleting vs. non-depleting antibody induction on the outcomes in kidney transplant recipients (KTRs) at different serological stages of HBV infection.

Methods: Using UNOS database, we identified adult KTRs from 2001 to 2011 who at the time of transplantation were in one of the 3 serological stages of HBV infection: HBsAg+/HBeAb-, HBsAg+/HBeAb+ and HBsAg-/HBeAb+. All patients received peri-operative induction followed by calcineurin inhibitor/mycophenolate mofetil-based maintenance with/without steroids. Using multivariate Cox model, graft and patient survivals were compared for depleting (antithymocyte globulin or alemtuzumab) vs. non-depleting (basiliximab or daclizumab) antibody induction among the 3 HBV serological groups. Donor, recipient and transplant related confounders including lamivudine therapy were adjusted in the model.

Results: Adjusted graft and patient survivals for depleting vs. non-depleting induction among the 3 groups are shown in the table.

Outcome	HBsAg+/HBeAb- group (depleting=652; non-depleting =446)		HBsAg+/HBeAb+ (depleting = 250; non-depleting = 216)		HBsAg-/HBeAb+ (depleting = 3562; non-depleting = 2555)	
	HR	95% CI	HR	95% CI	HR	95% CI
Overall graft survival	0.97	0.78-1.26	0.81	0.55-1.18	0.96	0.86-1.05
Death-censored graft survival	1.20	0.83-1.60	0.59	0.32-1.12	1.00	0.88-1.14
Patient survival	0.92	0.66-1.30	0.95	0.60-1.49	0.92	0.80-1.05

All p-values non-significant

Conclusions: Our study did not show adverse graft and patient survivals associated with depleting as compared to non-depleting antibody induction in KTRs with either HBsAg+/HBeAb- (early infection), HBsAg+/HBeAb+ (inactive carrier or immune tolerant)

or HBsAg-/HBeAb+ (clearing infection) sero-status. These findings support a practice of choosing induction type based on the immunological risk in such recipients rather than the serological status following HBV infection.

FR-PO1066

Health Economic Analysis of Rabbit Antithymocyte Globulin (Thymoglobulin) versus Basiliximab (Simulect) in Renal Transplantation – A German perspective Friedrich Thaiss,¹ Thomas Benzing,² John Reitan,³ Thomas Paivanas,⁴ Meghan E. Gallagher,⁵ Michael Sean Wiesener,⁶ Nikolai Zink.⁶ ¹Univ. Hospital, Nephrology, Hamburg, Germany; ²Univ. Hospital, Nephrology, Cologne, Germany; ³RJM Group, Crown Point; ⁴TAP & A, Annandale; ⁵Sanofi, Cambridge; ⁶Univ. Hospital, Nephrology, Erlangen-Nuernberg, Germany.

Background: Kidney transplantation is now accepted as a proven therapeutic modality prompting a greater need to understand the cost-effectiveness of different treatment approaches.

Methods: The primary objective of this study was to quantify the economic consequences of acute rejection and adverse events in patients undergoing cadaveric kidney transplantation and receiving ATG (Thymoglobulin - Thymo) compared with those receiving basiliximab (Simulect - Sim). Health economic data were collected according to reimbursement calculations from 3 German sites in an existing database (Brennan et al NEJM, 2006).

Results: Based on the clinical data from the Brennan trial, the study quantified current data and changes in treatment patterns. Results demonstrate that at 12 months the cost of the Thymo-regimen is €5,753 more than that of the Sim-regimen. However, costs of delayed graft function, nonfatal graft failure events and post-graft failure dialysis are lower among Thymo treated patients. Thymo treated patients incurred higher graft maintenance costs, consistent with their longer graft survival. In total the associated cost-offset from lower rejection events with Thymo offset the added cost from drug treatment and therefore Thymo is a more cost-efficient resource vs Sim due to cost-avoidance. To further evaluate differences between the two groups we considered quality-adjusted life year differences. The Thymo cohort is projected to enjoy 405,714/ QALY after 1 year. After a decade, the Thymo cohort is projected to cost 332,232 Euros less than the Simulect cohort while enjoying 10.8 more QALYs.

Conclusions: This analysis was intended to provide information that should be considered when weighing the costs and benefits of two immunosuppressive regimens and to investigate if treatment changes might result in more cost-effective care.

Funding: Pharmaceutical Company Support - Sanofi and RJM

FR-PO1067

Design and Rationale of Athena Study: A 12-Month Study Evaluating Everolimus versus Standard Regimen in De Novo Renal Transplant Recipients-Baseline Data Friedrich Thaiss,¹ Claudia Sommerer,¹ Barbara M. Suwelack,¹ Duska Dragan,¹ Ingeborg A. Hauser,¹ Peter Schenker,¹ Daniel Baeumer,² Björn Nashan.¹ ¹Athena Study Group; ²Novartis Pharma Germany.

Background: Long-term use of standard calcineurin inhibitor (CNI) post-kidney transplant (KTx) is associated with an increased risk for malignancies, cardiovascular disease, and renal failure. Previous studies have shown everolimus (EVR) to allow CNI reduction and thereby preserve renal function without affecting efficacy. ATHENA study evaluates the renal function comparing EVR with reduced CNI exposure (tacrolimus [TAC] or cyclosporine A [CsA]) vs a standard treatment protocol with mycophenolic acid (MPA) and TAC in de novo (day 0) KTx recipients (KTxR).

Methods: This is a 12-month (M), multi-centre, open-label, prospective study in KTxR (>18 years) receiving renal allografts from deceased or living donors. Patients were randomised prior to Tx to one of three treatment arms (1:1:1): TAC+MPA+steroids (n=204) or EVR+TAC+steroids (n=204) or EVR+CsA+steroids (n=204) (all with basiliximab). The primary objective is to demonstrate non-inferiority in renal function (eGFR, Nankivell) in one of the EVR arms vs TAC+MPA+steroids arm at M12 post-KTx. Secondary objectives are treatment failure (BPAR, graft loss or death) at M12 post-KTx.

Results: Study recruitment is completed in Germany and France. A total of 658 patients were enrolled, of which 614 patients were randomised. To-date, baseline data was available for 367 treated patients (TAC+MPA, 125; EVR+TAC, 116; EVR+CsA, 126); of which 66% were male (65%, 67%, and 66%, respectively). The mean age was 54 years (TAC+MPA, 55 years; EVR+TAC, 54 years; EVR+CsA, 53 years). At baseline mean BMI was 26.8 kg/m² (TAC+MPA, 26.7 kg/m²; EVR+TAC, 26.7 kg/m²; EVR+CsA, 26.8 kg/m²). Overall, 18% patients received allograft from living donor (TAC+MPA, 18%; EVR+TAC, 17%; EVR+CsA, 20%). The mean HLA mismatch was 2.8 (TAC+MPA, 2.6; EVR+TAC, 2.8; EVR+CsA, 3.0) The preliminary results of this ongoing trial are expected in 2016.

Conclusions: ATHENA is the largest European renal transplant study and the first study evaluating the non-inferiority of renal function as a primary objective in a de novo EVR-based immunosuppressive protocol.

Funding: Pharmaceutical Company Support - Novartis Pharma Germany

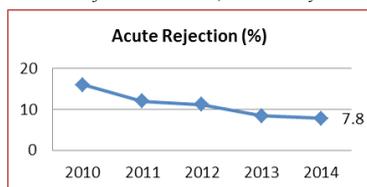
FR-PO1068

Thymoglobulin Induction Therapy; Results for 5 Years – Improving the Survival of Renal Allograft and Patient Virginia Ibarra Pedroza, Benjamin Gomez-Navarro. *Nephrology and Transplantation, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, Mexico.*

Background: The factor that impacts the survival of renal allograft is the presence of acute rejection. In our city, using Thymoglobuline has offered to patients at high immunological risk, and through the years has sought to reduce adverse events use. The objective is to evaluate the frequency of acute rejection during the last 5 years in patients receiving Thymoglobuline induction.

Methods: An ambispective cohort, patients transplanted in UMAE HE-CMNO, Jalisco, Mexico is included in the period June 2010 to June 2014 who received received induction therapy with Thymoglobulin. Was recorded the frequency of acute rejection, the frequency of infections, use of Filgrastim(rG-CSF), graft loss and death at 12 months of transplantation.

Results: A 370 patients were included, which received initial doses of Thymoglobulin 0.6mg/kg-1.5mg/kg. In 2013, by multivariate analysis Thymoglobuline dose that was associated with a lower incidence of acute rejection was analyzed and found that 1mg/kg for 4 days (cumulative dose 4mg/kg) is a protective factor for the occurrence of acute rejection (IC 95%; 0.11- 0.60, OR 3.7, $p < 0.001$), for this reason almost patients received this dose. In 2010, the rate of rejection was 16%, and actually is 7.8% ($p < 0.05$);



Infections disease was reduced about 30%. Currently few patients use of rG-CSF because leukopenia- neutropenia, lost the renal graft or die during the first year.

	2010	2011	2012	2013	2014
Infetions (%)	62	42	48	34	32
Use of rG-CSF (%)	16	15	13	9.4	4.5
Graft loss (%)	8	8	5.6	3.7	2.2
Death (%)	8	3.7	4.5	2.8	0

Conclusions: Interestingly, in our hospital, we observed a lower rate of acute rejection and improved patient survival and allograft. Apparently finding the right dose in our patients has allowed thymoglobulin induction is safe and minor complications.

FR-PO1069

Randomized Trial of Tacrolimus/Everolimus versus Tacrolimus/Enteric-Coated Mycophenolate Sodium to Prevent Biopsy-Proven Acute Rejection and Chronic Allograft Injury in Adult, Primary Kidney Transplantation Giselle Guerra,¹ Jeffrey J. Gaynor,² David Roth,¹ Warren L. Kupin,¹ Adela D. Mattiazzi,¹ Michael J. Goldstein,² Linda J. Chen,² George William Burke,² Gaetano Ciancio.² ¹Dept of Medicine, Miami Transplant Inst, Miami, FL; ²Dept of Surgery, Miami Transplant Inst, Miami, FL.

Background: It was of interest to determine whether everolimus(EVL) might reduce the incidence of biopsy-proven acute rejection(BPAR) during the first 12mo post-kidney transplant.

Methods: We performed a single-center, open-label randomized trial comparing two maintenance immunosuppression regimens: TAC(tacrolimus)/EVL(Group A) vs. TAC/EC-MPS(enteric coated mycophenolate mofetil)(Group B). In both treatment arms, dual induction therapy (anti-thymocyte globulin plus basiliximab) was given along with planned early corticosteroid withdrawal.

Results: Among 30 eligible adult participants (15 per treatment arm), median follow-up was 11mo(range: 3-20mo). Mean TAC levels were 5-8ng/ml in both arms; mean EVL level in Group A was 4-6ng/ml. One patient in Group A vs. 3 patients in Group B experienced BPAR - actuarial estimates at 12mo were 10%+9% vs. 20%+10%, respectively($P= .31$). All 3 BPAR's in Group A occurred prior to 6mo vs. the single BPAR in Group B occurring after 6mo (logrank $P= .09$ during the first 6mo post-transplant). A slight trend for more favorable renal function(eGFR) was also observed in Group A at 1-3mo post-transplant ($P= .06$, .10, and .18, respectively). No graft failures or deaths have been observed. Regarding the incidence of NODAT, a slight trend against Group A was observed (2/15 vs. 0/15 in Group B, $P= .13$), and higher mean cholesterol and triglyceride levels also occurred in Group A during 2-12mo($P < .10$ at various times).

Conclusions: Although a relatively favorable performance for the experimental maintenance regimen of TAC/EVL in terms of a low BPAR rate during the first 12mo post-transplant was observed, it may occur at the expense of possibly higher rates of NODAT and lipidemia.

FR-PO1070

Early Conversion to Everolimus in De Novo Renal Transplant Recipients: 24-Month Results from the ELEVATE Study Johan W. De Fijter, Hallvard Holdaas, Patricia M. Lopez, Cesar Escrig, Zailong Wang, Josep M. Cruzado, Markus van der Giet. *For the ELEVATE Study.*

Background: Long-term therapy with calcineurin inhibitors (CNIs) is associated with nephrotoxicity i.e., glomerulosclerosis and interstitial fibrosis (IF). We present the 24 month results from the ELEVATE study (NCT01114529), which compared an early conversion to everolimus (EVR) vs standard CNI in renal transplant recipients (RTxR).

Methods: ELEVATE, a 24M, multicenter, open-label trial, randomized *de novo* RTxRs 10-14 weeks post-Tx to convert from CNI to EVR (n=360; C₀ 6-10 ng/mL) or standard CNI (n=357; C₀: TAC 5-10 ng/mL, CsA 100-250 ng/mL); all received enteric-coated mycophenolate sodium and steroids. Primary endpoint was change in eGFR (MDRD4) from RND to M12. Main secondary endpoint a composite efficacy of treated biopsy-proven acute rejection (tBPAR; Banff ≥IB), graft loss, or death and safety.

Results: At M12, the clinical benefit observed in eGFR did not achieve statistical significance (1.70, 95% CI: -0.53, 3.93, $p=0.134$) whilst eGFR at M24 for EVR was significantly better ($p < 0.006$). The composite efficacy endpoint was comparable at M12 & M24. Overall acute rejection rates were very low with more tBPAR in EVR, but mild in severity (Banff IA & IB). In both the groups, number of patients with *de novo* DSAs at M12 or M24 was low and unrelated to outcomes. At M24, rate of CAN (IF/TA) was significantly higher in the CNI versus EVR (35.1 vs 26.7%, $p=0.029$).

Conclusions: Early conversion to EVR at 3 months vs continued CNIs better preserved renal function with comparable overall efficacy and safety up to 2-years.

Table: Outcomes at M12 and M24

	M12			M24		
	EVR	CNI	p-value	EVR	CNI	p-value
Mean eGFR (mL/min/1.73m ²)	64.0	60.4	0.054	62.5	57.4	0.006
Composite efficacy ^a (%)	6.2	3.8	0.172 ^b	8.1	4.5	0.057
tBPAR ≥IB (%)	4.9	2.0	0.034	5.2	2.3	0.041
Graft loss (%)	0.6	1.2	0.407	1.2	1.1	0.935
Death (%)	2.0	1.5	0.725	2.6	2.6	0.964
Any AE/infection (%)	89.0	83.6	-	91.3	88.9	-
SAEs (%)	42.5	40.7	-	54.3	49.0	-
Proportion of patients with <i>de novo</i> DSA^a (MFI ≥500)						
HLA A (%)	2.9	0.5	-	2.8	0	-
HLA B (%)	2.6	0	-	0.8	0	-
HLA DR (%)	0	0	-	1	1.4	-
HLA DQ (%)	0	4.3	-	0	1.7	-

^aDefined as tBPAR ≥IB, graft loss or death. ^bp-value of z-test for non-inferiority is <0.001
^cPatients with MFI=0 at randomization and MFI ≥500 at post-RND measurement

Funding: Pharmaceutical Company Support - Novartis

FR-PO1071

Early Conversion from Cyclosporine to Everolimus following Living-Donor Kidney Transplantation: Outcomes at Five Years Post-Transplant in the Randomized ZEUS Trial: A Post-Hoc Analysis Ingeborg A. Hauser,¹ Frank Lehner,¹ Wolfgang Arns,¹ Klemens Budde,¹ Ute Eisenberger,² Rudolf P. Wuthrich,² Petra Reinke,¹ Rolf A. Stahl,¹ Anja Susanne Mühlfeld,¹ Heiner H. Wolters,¹ Barbara M. Suwelack,¹ Katharina M. Heller,¹ Martina Porstner,³ Oliver Witzke,¹ Claudia Sommerer.¹ ¹ZEUS Study Group, Germany; ²ZEUS Study Group, Switzerland; ³Novartis Pharma, Germany.

Background: To study renal function and patient outcome after 5 years in living-donation subgroup of kidney de novo transplant recipients after conversion to an everolimus (EVR) based regimen and withdrawal of calcineurin inhibitor therapy.

Methods: Post hoc subgroup analysis from the prospective, open-label, controlled, multi-center study ZEUS. 300 renal transplant (Tx) patients were randomized at month (mo) 4.5 post Tx to either receive EVR plus enteric coated-mycophenolate sodium (EC-MPS) or cyclosporine (CsA) plus EC-MPS regimen. Of these were 80 living donation recipients (EVR group n=42; CsA group n=38). Patients could enter an observational follow-up (FU) period where outcome on patients' safety and efficacy was recorded until mo 60 post Tx.

Results: Adjusted eGFR (Nankivell) in living-donation subpopulation at mo 60 was 67.2 (95% CI [62.5, 71.9]) mL/min/1.73m² in EVR vs 60.8 (95% CI [56.0, 65.6]) mL/min/1.73m² in CsA patients, resulting in a difference of +6.4mL/min/1.73m² in favor of EVR patients ($p=0.031$, ANCOVA). Unadjusted mean eGFR after 5 years was 69.5 ml/min for EVR vs 60.6 ml/min for CsA ($p=0.006$, Wilcoxon). BPARs during FU since mo12 occurred in 4 patients of the EVR and 3 of the CsA group, all BANFF grade IA except one BANFF grade IIA among EVR patients. From randomization to mo 60 one death occurred in CsA living-donor recipients, two in the EVR living-donation subgroup; one graft loss occurred in the EVR, none in the CsA group. Overall safety profile was similar between both treatment groups.

Conclusions: The presented analysis shows that EVR-based regimen with early elimination of CNI-therapy in living-donor kidney transplant recipients is associated with a significant benefit on renal function maintained over 5 years post Tx without compromising safety and efficacy.

Funding: Pharmaceutical Company Support - Novartis Pharma GmbH

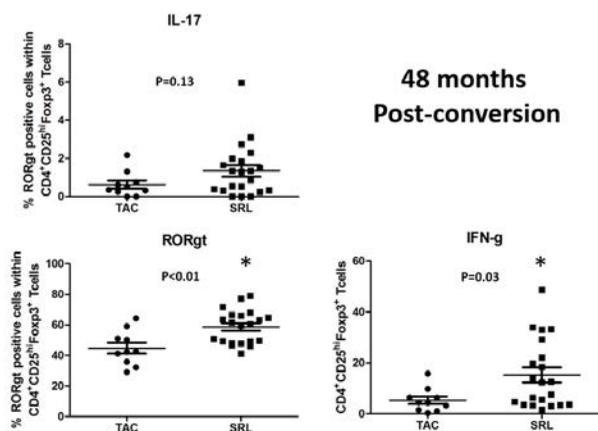
FR-PO1072

Co-Expression of RORgt and IFN-Gamma in Regulatory T Cells of Long-Term Sirolimus-Converted Kidney Transplant Recipients *Opas Traitanon, Ekamol Tantisattamo, Mohammed Javeed Ansari, Lorenzo G. Gallon. Medicine-Nephrology, Northwestern Univ, Chicago, IL.*

Background: Tacrolimus(TAC) and Sirolimus(SRL) are commonly used immunosuppressive drugs in kidney transplantation. SRL has been shown to induce the expansion of regulatory T cells in post-transplant recipients converted from TAC to SRL.

Methods: This study included 84 renal transplant recipients from a randomized trial of SRL conversion(n=55) or TAC maintenance(n=29). The conversion started at 12 months post-transplant. PBMC were collected at 0(baseline), 6, 12, 24, 36 and 48 months post-randomization. T cell subpopulations were analyzed by flow cytometry.

Results: At baseline, frequencies of CD4⁺25^{hi}Foxp3⁺ T cells were similar in both groups (0.63±0.06(SRL) VS 0.66±0.12(TAC) % of Lymphocytes, p=0.79). SRL conversion led to a significant increase in CD4⁺25^{hi}Foxp3⁺ T cells at 6, 12 and 24 months post conversion with highest frequencies observed at 12 months post-conversion (2.23±0.23 (SRL) VS 0.68±0.12 (TAC) %, p<0.01). However, we observed a decline of CD4⁺25^{hi}Foxp3⁺ T cells started at 24 months and the differences were no longer significant compared to the TAC group at 36 and 48 months post-conversion (1.41±0.60 (SRL) VS 1.07±0.44 (TAC) %, p=0.24). Intracellular staining for Interferon Gamma (IFN-γ), Interleukin 17 (IL-17) and RAR-related orphan receptor gamma 2 (RORgt) showed no difference at 24 months. However, at 48 months, we found that PMA-stimulated CD4⁺CD25^{hi}Foxp3⁺ T cells in SRL-converted group had more percentage of cells that co-expressed IFN-γ and RORgt which are Th1 and Th17 markers respectively.



Conclusions: Switching from TAC to SRL results in an expansion of CD4⁺25^{hi}Foxp3⁺ T cells which peaked at 12 months post-conversion but no significant frequency differences were observed at 48 months follow-up and we observed more percentage of regulatory T cells that co-expressed IFN-γ and RORgt in the SRL group.

FR-PO1073

Pulmonary Complications in Kidney Transplant Recipients: Role of Everolimus *Gianni Cappelli, Andrea Solazzo, Fabio Nava, Decenzio M. Bonucchi. Nephrology Dialysis & Renal Transplant Unit, Univ Hospital of Modena, Modena, Italy.*

Background: Kidney transplant recipients are at higher risk to develop pulmonary complications as drug related side-effects.

Methods: 500 kidney transplanted patients were retrospectively analyzed for pulmonary complications based on chest RX and HRCT, BAL, oximetry and clinical data. Results were classified as parenchymal, interstitial and neoplastic complications.

Results: We found 168 pulmonary complications in 161 pts (32%): 137 parenchymal pneumonia, 29 interstitial lung diseases (IP) and 2 cancers. Most pneumonia were bacterial, 96 cases (70%) required hospitalization. IP were from infections in 13 cases (45%) and Pneumocystis jirovecii was present in 42,85 %; 16 cases of IP (55%) resulted as drug-induced IP (DI-IP); all IP and cancer cases required hospitalization. According to antirejection protocols DI-IP occurred in 7 pts (43,7%) while on triple regimen [steroids, Everolimus (EVL) and Cyclosporine (CyA)] and in 7 pts on double regimen (steroid and mTORi: Sirolimus or EVL) (43,7%). In IP cases EVL (through concentration: EVL^{TL}) and CyA (2-hour concentration: CyA^{2h}) levels were higher than in patients in the same regimen but with no-IP: EVL (ng/mL) 9.84 vs 6.85 and CyA (ng/mL) 303.97 vs 298.56; using the combined blood levels of both drugs (Everolimus^{TL} + (CyA^{2h}/100) there is a significant difference between pts groups: 12.88±1,61 vs 9.83±1,91. Applying ROC analysis for optimal model to detect risk of developing IP using EVL or the sum of both drugs we obtained a ROC-AUC respectively of 0.9082 (p=0.0028) and 0.8622 (p=0.0081) and a threshold value of 9,03 ng/ml or 11,41ng/ml.

Conclusions: Pulmonary side-effects are frequently drug related and a relationship of IP to EVL concentration is obtained. Based on ROC analysis pts on EVL/CyA combined protocol show a risk of IP when EVL concentration is >9.03 ng/ml or the summatory of both drugs is >11.41 ng/ml and support the use of this formula for better prevention of IP in clinical practice.

FR-PO1074

High Doses of M-TOR Inhibitors May Induce Pulmonary Pro-Fibrotic Effects in Renal Transplant Recipients: Result of a Translational Comparative Research Approach Between Everolimus versus Tacrolimus *Gianluigi Zaza,¹ Valentina Masola,¹ Simona Granata,¹ Gloria Bellin,¹ Maurizio Onisto,² Giovanni Gambaro,³ Antonio Lupo.¹ ¹Renal Unit, Dept of Medicine, Univ of Verona, Italy; ²Dept of Biomedical Sciences, Univ of Padova, Italy; ³Div of Nephrology and Dialysis, Columbus-Gemelli Hospital Catholic Univ, School of Medicine Rome, Italy.*

Background: Pulmonary fibrosis is a quite frequent adverse effect occurring in mTOR-I-treated renal transplant (RT) recipients. It has been suggested that epithelial to mesenchymal transition (EMT) in airway cells may determine this condition. However, the exact biological machinery involved is not completely clarified.

Methods: We performed a translational study. First we analyzed the in vivo pulmonary pro-fibrotic potential of Everolimus (EVE) by computing a pulmonary fibrosis index score (PFIS), obtained by using several computerized tomography, hemogasanalytic and spirometric parameters, in 13 RT patients in EVE treatment and 13 patients treated with Advagraf (ADV). Subsequently, we carried out an in vitro study in which we assessed whether EVE at low- (5, 10 nM) or high-dosage (100 nM) or Tacrolimus (5 nM, 500 nM e 5 μM) was able to induce EMT in bronchial epithelial cells (Nuli-1) and human type II pneumocyte-derived A549 cells. Additionally, microarray analysis was performed to identify new elements involved in this complex machinery.

Results: In the in vivo part of the study, we found that the PFIS was higher in EVE-treated patients compared to those treated with ADV (mean±SD 2.58±1.83 versus 1.21±1.25). This effect was positively correlated to the trough levels (TL) in EVE-treated patients (R2=0.35). The higher PFIS score was measured in patients treated with EVE that reached a TL≥6. Interestingly, in vitro, only very high doses of EVE were able to induce up-regulation of alpha-SMA, Fibronectin and Vimentin at gene and protein level in A549. No effects were seen in Nuli-1. Interestingly, microarray analysis confirmed the above-mentioned results.

Conclusions: All together, our data suggested that only very high doses of EVE may induce pulmonary fibrosis and that this effect could be mediated by EMT in pneumocyte cells.

FR-PO1075

Efficacy and Safety of Three Different Treatment Regimen in De Novo Renal Transplant Patients: 48 Months Follow-Up Results of the HERAKLES Trial *Wolfgang Arns,¹ Volker Kliem,¹ Claudia Sommerer,¹ Johannes Jacobi,¹ Bruno Vogt,² Ingeborg A. Hauser,¹ Petra Reinke,¹ Rolf A. Stahl,¹ Thomas Rath,¹ Martina Porstner,³ Martin G. Zeier,¹ Frank Lehner,¹ Klemens Budde,¹ Oliver Witzke.¹ ¹HERAKLES Study Group, Germany; ²HERAKLES Study Group, Switzerland; ³Novartis Pharma, Germany.*

Background: To compare safety and efficacy of 3 different immunosuppressive regimen at month (mo) 48 after kidney transplantation (KTx).

Methods: 802 patients (pts) were included in this 1 year, prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to mo 60 post Tx. After induction therapy all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium(EC-MPS) and steroids. 3 mo post Tx, 499 pts were randomized 1:1:1 to either a) continue standard CsA(100-180ng/ml)+EC-MPS(n=166) (STD) or convert b) to a calcineurin inhibitor (CNI)-free regimen with everolimus (EVR) (5-10ng/ml) + EC-MPS (n=171) or c) to a CNI-reduced regimen with EVR (3-8ng/ml) + reduced CsA (50-75ng/ml; n=162). All pts continued on steroids. At time of mo 48 FU interims-analysis data were available from 110(73%) STD, 117(79%) CNI-free and 111(76%) CNI-low treated pts of the FU ITT population.

Results: From randomization to mo 48 BPAR was reported in 19/151(13%) STD, 24/149(16%) CNI-free and in 23/147 (16%) CNI-reduced pts (ITT; p=ns). 5 deaths (3%) occurred in STD, 3(2%) in CNI-free and 6(4%) in the CNI-reduced group. 9(6%) graft losses were observed in the STD, 6(4%) in the CNI-free and 2(1%) in the CNI-reduced group. Composite failure (BPAR, death, graft loss, loss to FU) occurred in 32(21%) STD, 36(24%) CNI-free and in 39(27%) CNI-reduced treated pts. Premature discontinuation due to AEs was reported for 5(3%) of STD, 5(3%) of CNI-free and 1(1%) of CNI-reduced patients (safety-population) since mo 12 to 48. eGFR (Nankivell, LOCF) was significantly improved by +6.8mL/min in favor of the CNI-free regimen at mo 48 (ITT;p=0.02).

Conclusions: Mo48 results from HERAKLES show that immunosuppressive regimen using EVR with reduced-dose or without CNI-exposure reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized immunosuppression to minimize CNI-exposure.

Funding: Pharmaceutical Company Support - Novartis Pharma

FR-PO1076

SparTacus: Multicentre, Prospective Randomised Study Comparing Tacrolimus Hexal® versus Prograf® Based Regimen in De Novo Renal Transplant Recipients *Wolfgang Arns,¹ Thomas Rath,¹ Lars C. Rump,¹ Klemens Budde,¹ Daniel Baeumer,² Peter Schenker.¹ ¹Spartacus Study Group; ²Novartis Pharma Germany.*

Background: In a transplant (Tx) setting, studies evaluating pharmacokinetic (PK) parameters and therapeutic equivalence of generic tacrolimus vs the reference drug are lacking. SparTacus (NCT01649427) study was designed to compare PK profile of tacrolimus hexal® with prograf® in renal Tx recipients (RTxR).

Methods: In this prospective, two-phase open-label study, 76 de novo RTxR were randomised to receive tacrolimus hexal® (n=35) or prograf® (n=41), both in combination with enteric-coated mycophenolate sodium + corticosteroids + basiliximab induction therapy. Starting dose of tacrolimus was 0.15 mg/kg/day, adjusted to target trough levels (C₀) of 8–12 ng/mL from Tx to month (M) 1; 5–10 ng/mL up to M3; and 5–8 ng/mL up to M6. Primary objective of the study in phase 1 was to demonstrate comparable PK (ratio of AUC_{0-12h}, one month period) of tac. hexal® vs prograf®. Here we present the PK results of the first month.

Results: At M1, the dose-normalised tacrolimus 12-h-AUC (h/10³×3XL) was comparable between tac. hexal® vs prograf® (adjusted log-transformed LS mean, 2.9 vs 3.0; difference, 0.076; 90% CI: -0.169, 0.321, p = 0.605; adjusted back-transformed LS mean, 19.0 vs 20.5; ratio, 1.079; 90% CI: 0.844, 1.378, p = 0.605). LS mean value for C_{max} (1/10³×3XL) and mean 12 h tacrolimus C₀ (mg/L) at M1 were comparable between tac. hexal® vs prograf® (C_{max}, 1.1 vs 1.2; difference, 0.150; 90% CI: -0.134, 0.435; p = 0.377; C₀, 12.2 vs 11.1, respectively). Of 76 patients, 40 (PK-Set 40 pts.) to date completed 6-M treatment; tac. hexal®, n = 19; prograf®, n = 21. At M6, tacrolimus hexal® vs prograf® had a comparable incidence of composite events (ITT, n=76) (5.7% vs 9.8%, p = 0.681) and its individual components (BPAR [5.7% vs 7.3%], graft loss [0.0% vs 2.4%], death [0.0% vs 2.4%]). Incidence adverse events (AEs, SAE) were comparable (AEs: 97.1% vs 100%; serious AEs: 37.1% and 42.1%).

Conclusions: Tacrolimus hexal® has a PK profile similar to that of prograf®, with comparable efficacy and safety in de novo RTxR.

Funding: Pharmaceutical Company Support - Novartis Pharma Germany

FR-PO1077

Monitoring of Cyclosporin by NFAT-Regulated Gene Expression Reduces the Cardiovascular Risk – The CIS Trial Claudia Sommerer,¹ Janina Brocke,¹ Stefan Meuer,² Martin G. Zeier,¹ Thomas Giese.² ¹Nephrology, Univ Hospital, Heidelberg, Germany; ²Immunology, Univ Hospital, Heidelberg, Germany.

Background: Adequate monitoring tools are required to optimize the immunosuppressive therapy of an individual patient. A new pharmacodynamic monitoring tool has been established to measure directly the functional effect of cyclosporin A (CsA) in an individual patient. This is the first randomized controlled study comparing standard pharmacokinetic monitoring by CsA trough (C₀) levels to pharmacodynamic monitoring by NFAT-regulated gene expression.

Methods: Stable renal allograft recipients were included in this 6-month, prospective, open-label, randomized, controlled study. All patients received triple immunosuppression (CsA, MPA, steroids). Patients were randomized 1:1 to either continue a) CsA therapy monitored by CsA C₀ (80–150ng/ml) or b) CsA therapy monitored by NFAT-regulated gene expression (15–30%). The expression of the NFAT-regulated genes (IL2, IFN γ , GM-CSF) were determined by qRT-PCR at CsA C₀ and C2. The cardiovascular risk was assessed by change of pulse wave velocity (PWV) from baseline to month 6.

Results: 55 patients were enrolled (35 male; Age 51.5±12.9y; time after transplantation 69.8±73.7m). CsA dose was 96±25ng/mL in the NFAT-group and 93±22ng/mL in the standard-group. Residual NFAT-regulated gene expression was 13±9%. Patients monitored by the pharmacodynamic assay with NFAT-regulated gene expression showed a significant decline in PWV from baseline to month 6 compared to the standard group (-1.68±2.02 vs. 0.38±1.42 m/s, p<0.0001). Renal function was stable in both study cohorts. An acute rejection episode occurred in one patient of the NFAT-group who refused to increase CsA dose according to results of NFAT regulated gene expression.

Conclusions: Renal allograft recipients on CsA therapy monitored by the residual NFAT-regulated gene expression showed a significantly better cardiovascular risk assessed by PWV compared to patients on standard CsA C₀ monitoring. NFAT-regulated gene expression proved in this first randomized controlled trial as an efficacious and safe approach to individualize CsA therapy with the opportunity to improve the cardiovascular risk profile.

FR-PO1078

Follow-Up Results of HERAKLES Trial on Three Different Treatment Regimen and Switching Off Behaviour in De Novo Renal Transplant Patients After 4 Years Claudia Sommerer,¹ Oliver Witzke,¹ Johannes Jacobi,¹ Wolfgang Arns,¹ Bruno Vogt,² Petra Reinke,¹ Ingeborg A. Hauser,¹ Rolf A. Stahl,¹ Thomas Rath,¹ Martina Porstner,³ Frank Lehner,¹ Volker Kliem,¹ Klemens Budde,¹ Martin G. Zeier.¹ ¹HERAKLES Study Group, Germany; ²HERAKLES Study Group, Switzerland; ³Novartis Pharma, Germany.

Background: To compare switching off 3 different immunosuppressive (IS) regimen 4 years after renal transplantation (Tx).

Methods: 802 patients (pts) were included in this prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to month (mo) 60 post Tx. All pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids; at 3 mo post Tx 499 pts were randomized 1:1:1 to either a) continue standard CsA (100–180ng/ml) +EC-MPS(n=166) (STD) or convert b) to a calcineurin inhibitor (CNI)-free regimen with everolimus (EVR) (5–10ng/ml) + EC-MPS(n=171) or c) to a CNI-reduced regimen with EVR (3–8ng/ml) + reduced CsA (50–75ng/ml;n=162). All pts continued on steroids.

Results: At 48 mo post Tx, 40% CNI-free, 30% CNI-reduced and 55% of STD treated pts were still on their initial assigned treatment and available for mo 48 analysis. Drop-out frequency among FU ITT population from randomization to mo 48 was 17%, 15% and 14% for STD, CNI-free and CNI-reduced groups, respectively. Premature discontinuation due to AEs occurred in 5(3%) of STD, 5(3%) of CNI-free and 1(1%) of CNI-reduced pts (safety-population) from mo 12 to 48. The CsA trough levels in CNI-reduced group were in the higher end of target levels (50–75 ng/mL) in non-switcher population; whereas in

switcher population they were beyond the target levels. In non-switcher population, eGFR (Nankivell) was significantly improved by +13.7 mL/min in favor of CNI-free regimen at mo 48 (p<0.001).

Conclusions: Mo 48 HERAKLES results show that IS regimen using EVR with reduced-dose or without CNI-exposure reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized IS to minimize CNI-exposure. Drop-out rates over 4 years post Tx showed relative similar adherence rates between groups. Pts that never switched off the assigned CNI-free regimen reached a markedly improved GRF.

Funding: Pharmaceutical Company Support - Novartis Pharma

FR-PO1079

Intensified Dosing of Mycophenolate Mofetil Is Associated with Slower Progression of Chronic Renal Allograft Injury – Results from a Randomized Controlled Trial Mladen Knotek,¹ Miha Arno,² Jadranka Buturovic-Ponikvar,² Danica Galessic Ljubanovic,³ Nika Kojc.³ ¹Dept of Medicine, Renal Div, Univ of Zagreb Medical School, Merkur Univ Hospital, Zagreb, Croatia; ²Dept of Nephrology, Univ Medical Centre Ljubljana, Ljubljana, Slovenia; ³Inst of Pathology, Univ of Ljubljana Medical Faculty, Ljubljana, Slovenia; ⁴Dept of Pathology, Dubrava Univ Hospital, Univ of Zagreb Medical School, Zagreb, Croatia; ⁵Univ of Zagreb School of Medicine, Dubrava Univ Hospital.

Background: Interstitial fibrosis (ci) is a major histological predictor of long-term graft outcome. This randomized controlled trial (NCT01860183) was designed to evaluate the effect of intensified mycophenolate mofetil (MMF) dosing on progression of ci during the first year post kidney transplant (KT).

Methods: Immunologically low-risk KT recipients were randomized on MMF 3g/d, or 2g/d during the first year post KT. Immunosuppression consisted of basiliximab induction, with tacrolimus, MMF ± steroids. Protocol biopsies were performed at implantation, and at 12 months post KT and were scored according to the Banff. Progression of ci (Dci) was calculated as ci12-ci0. MMF dose was calculated as an average dose at 1, 3, 6 and 12 months. Difference in Dci with respect to MMF dose was analyzed in an ITT population using one-way ANOVA.

Results: Here we report interim results from patients who completed 12 month follow-up by June 1st 2015. Patient and KT data are were similar in MMF 3g and MMF 2g group, except for average MMF dose, which was higher in the 3g group (2697.1±321.6 vs. 1745.5±359.0 g, p<0.001). In an overall study population ci progressed during first 12 months post KT from 0.45±0.51 (ci0) to 1.41±0.87 (ci12) (p<0.001). Dci was lower in the MMF 3 g group (0.60±0.74) as compared with MMF 2g group (1.36±0.93; p=0.021). Serum creatinine at 1 year was similar in both MMF groups (116.5±25.0 vs. 115.1±33.7; p=0.899). Incidence of acute rejection was similar and no significant differences were seen in common adverse events between both groups.

Conclusions: Intensified dosing of MMF (3g daily) during the first posttransplant year in a tacrolimus-based regimen may be associated with slower progression of chronic allograft injury.

Funding: Government Support - Non-U.S.

FR-PO1080

Safe Conversion from Tacrolimus to Belatacept in Kidney Transplant Recipients with Allograft Dysfunction Anil Regmi, Dhiren Kumar, Hasan Fattah, Anne L. King, Pamela Kimball, Ankur Atal Gupta, Gaurav Gupta. Virginia Commonwealth Univ, Richmond, VA.

Background: Belatacept might be an alternative to Calcineurin Inhibitors (CNI) to avoid short and long-term nephrotoxicity. Prior data on low immunologic risk de-novo kidney transplant recipients (KTxp) with stable graft function switched from a CNI to belatacept demonstrated improved renal function. There is minimal data on the use of belatacept for sensitized patients and those with impaired graft function [estimated glomerular filtration rate (GFR) <35].

Methods: EBV seropositive patients were converted to belatacept from tacrolimus for biopsy proven presumed acute CNI toxicity and/or interstitial fibrosis/tubular atrophy. Belatacept was initiated based upon prior published protocol (Grinyo et al., Transpl Int. 2012 Oct). Mycophenolate dose was increased from baseline dose of 1–2g/d to a dose of 2–3g/d to minimize risk of rejection.

Results: Seventeen (mean age=46±10 years) patients were switched from tac to belatacept at a median of 4 months post-KTxp. A majority were African-American (13/17; 76%) and received deceased donor KTxp (76%). Seven patients (41%) were sensitized (median PRA=31%; range=0–99%). Renal function improved significantly from a peak mean GFR of 28±12 mL/min/1.73m² to an GFR of 42±16mL/min/1.73m² (p=0.001) at a median follow-up of 15 (range=7–30) months post-conversion. Surveillance biopsies performed in 7/17 patients did not show rejection or worsening of chronicity. No evidence of de-novo donor specific antibody (DSA) was noted in 16/17 (94%) patients. One patient with pre-existing DSA and stable creatinine had rising DSA after a viral infection. A biopsy showed subclinical antibody-mediated rejection. There were no cases of BK viremia, CMV disease or malignancies.

Conclusions: In this first study on KTxp patients with significantly reduced GFR we report remarkable improvement in renal function in patients converted from tacrolimus to belatacept with acute CNI toxicity and chronic allograft fibrosis without a significant concurrent increase in risk of rejection, worsening chronicity and DSA. Further studies with protocol biopsies are needed to ensure safety and wider applicability of this approach.

FR-PO1081

Home Infusion of Belatacept in Kidney Transplant Recipients
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Background: Belatacept (bela) is an IV administered selective T-cell co-stimulation blocker approved for preventing organ rejection in EBV-positive adult kidney transplant recipients. The logistics of IV maintenance therapy are challenging for some pts/clinicians; the safety of home infusion has not been well described. Phase 2/3 study participants could have received home infusion of bela under certain circumstances. Here, we compare the safety of bela infused in the home vs a facility.

Methods: Pts in the 008 (BENEFIT/NCT00256750), 027 (BENEFIT-EXT/NCT00114777), 010 (NCT00402168), and 034 (NCT00455013) studies were eligible to receive bela home infusion if the site sought IRB approval and if the pt lived ≥2 hrs from the site and had been exposed to bela for >28 wks in 008 or 027, >16 wks in 010, or >6 wks in 034. 008 and 027 compared bela with CsA regimens with basiliximab induction. In 010, pts receiving a stable CNi regimen were switched to a bela regimen. 034 compared bela with tacrolimus steroid-sparing regimens under thymoglobulin induction. Rate and time to pre-specified peri-infusional AEs and peri-infusional serious AEs were recorded in pts who received bela in the home (N=66) or in a facility (N=672).

Results: Pts administered bela in the home received a median of 32.5 (range, 1-61) infusions. No pre-specified or serious peri-infusional AE was reported, including in the 034 study.

Conclusions: No pt (irrespective of steroid use) receiving home infusion of bela had a pre-specified or serious peri-infusional AE. These data suggest that bela was safely administered in the home.

	Facility-Based (N=672)		Home Infusion (N=66)	
	n (%)	Median time to event, days	n (%)	Median time to event, days
Specified Peri-Infusional AEs				
Total patients with an event	1 (0.1)	557	0	0
Device malfunction	0	0	0	0
Device-related infection	0	0	0	0
Infusion site reaction	1 (0.1)	557	0	0
Peri-Infusional Serious AEs				
Total patients with an event	5 (0.7)	783	0	0
General disorders and administration site conditions	2 (0.3)	937	0	0
Pyrexia	2 (0.3)	937	0	0
Nervous system disorders	1 (0.1)	1650	0	0
Dizziness	1 (0.1)	1650	0	0
Vascular disorders	2 (0.3)	159	0	0
Hypertension	1 (0.1)	117	0	0
Hypotension	1 (0.1)	201	0	0

*Pts administered bela in a facility were included in this analysis if they had been exposed to bela for >28 wks in 008 or 027, >16 wks in 010, or >6 wks in 034.

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FR-PO1082

Optimizing the Immunosuppression Regimen with Belatacept
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Background: Belatacept with basiliximab induction plus maintenance MMF/corticosteroids is associated with a higher 3-year eGFR compared to cyclosporine but a higher 1-year incidence of acute rejection. In an attempt to optimize the belatacept immunosuppression regimen we investigated the safety and efficacy of a novel combination utilizing belatacept with rATG induction (3 mg/kg) and maintenance everolimus ± corticosteroids.

Methods: Retrospective single center analysis of the first 33 patients to receive our belatacept regimen compared to a historical control group of 66 patients matched for donor type, KDPI, ESRD cause, CIT, and corticosteroid protocol who met our belatacept criteria (EBV seropositive and low immunologic risk [first transplant, no DSA ≥500 MFI, cPRA ≤30%]) but received basiliximab induction with maintenance tacrolimus/MMF ± corticosteroids. We compared the 6-month eGFR and the rates of rejection and infection between the groups.

Results: Demographic and transplant characteristics were similar. Mean tacrolimus trough (SD) at months 3 and 6 were 8.7 (2.5) and 8.4 (2.8), respectively. Mean everolimus trough (SD) at months 3 and 6 were 5.5 (2.6) and 5.3 (2.6), respectively. Eleven patients didn't tolerate everolimus and were placed on MMF. Rejection occurred in 3 belatacept (1 of each: type 1a, type 1b and type 2b) and 1 tacrolimus patient (type 2a) (P=0.07). The belatacept rejections occurred in patients who didn't tolerate everolimus and occurred after everolimus was discontinued. By month 6 two grafts were lost in the tacrolimus group with a 100% patient survival for both groups. eGFR at month 6 for belatacept and tacrolimus treated patients was 61.9 (15.3) and 60.1 (21.2), respectively (P=0.51). The incidence of CMV infection, BK viremia, and UTI was similar between the groups.

Conclusions: The findings suggest that a belatacept regimen with limited T cell depletion and an mTORi can maximize efficacy and maintain safety. These results of a synergistic effect of costimulation blockade and mTOR inhibition are consistent with experimental studies and phase 2 data. A larger prospective trial is warranted to fully evaluate this approach.

Funding: Pharmaceutical Company Support - BMS

FR-PO1083

A Change in Insulin Sensitivity and Lipid Profile in Renal Transplant Recipients Converted from Cyclosporine or Standard Release Tacrolimus to Once-Daily Prolonged Release Tacrolimus
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Background: New-onset diabetes after transplantation may be associated with the use of tacrolimus (Tac) causing impaired insulin release or reduced insulin sensitivity. And, dyslipidemia commonly occurred after transplantation. Such effects in insulin sensitivity and lipid profile have not been studied in renal transplant recipients receiving traditional twice-daily tacrolimus (TacBID) or cyclosporine and then compared to the new once-daily prolonged release formulation of tacrolimus (TacOD).

Methods: We performed an observational prospective study of 15 stable non-diabetic renal transplant recipients on change in insulin sensitivity and lipid profile in renal transplant recipients converted from cyclosporine or standard release tacrolimus to once-daily prolonged release tacrolimus. We evaluated the level of HbA1c, total cholesterol, HDL, LDL, TG, apolipoprotein A1, apolipoprotein B, serum creatinine, fasting plasma glucose, fasting insulin and HOMA-β at base line, two and four months. To analyze differences in parameter, we performed a t-test in both groups (cyclosporine to TacOD conversion group/ TacBID to TacOD conversion group), and GLM-repeated measures ANOVA. HOMA-β = (360 X Fasting insulin)/(Fasting glucose-63) HOMA-IR (insulin resistance) = (Fasting glucose X Fasting insulin)/405.

Results: At baseline, parameters were not different in both groups (cyclosporine to TacOD conversion group/TacBID to TacOD conversion group). In GLM-repeated measures ANOVA, the result did not show and any change in insulin sensitivity and lipid profile after conversion at baseline, two and four months.

Conclusions: Conversion from standard TacBID or cyclosporine to TacOD is safe. In spite of a reduced Tac exposure, there was no change in insulin sensitivity and lipid profile in renal transplant recipients.

FR-PO1084

Tacrolimus Dose Requirement Based on the CYP3A5 Genotype in Renal Transplant Patients
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Background: Tacrolimus and cyclosporin A (CsA) are widely used to protect graft function after renal transplantation. The aim of the present study is to determine whether CYP3A5*A and CYP3A5*G genotype is a predictive index of tacrolimus dose requirement, and even the selection accordance of tacrolimus or CsA treatment.

Methods: We tested archival peripheral blood of 218 kidney recipients for CYP3A5 genotyping with PCR-SSP. The doses and blood concentrations of tacrolimus and CsA for recipients were measured at day7, 1st month, 3rd month, 6th month and 12th month after renal transplantation, as well as hepatic and renal function. In addition, we also observed the incident of acute rejection happening on these participants.

Results: 123 patients took tacrolimus treatment and 95 patients took CsA treatment after renal transplantation. In tacrolimus treatment group, genotype CYP3A5*GG was associated with low tacrolimus dose-adjusted concentration after transplantation, showing lower acute rejection rate compared to CYP3A5*AA/AG group but with no significant difference (P=0.154). In CsA treatment group, there was no significant difference in acute rejection rates between CYP3A5*AA/AG and CYP3A5*GG (P=0.494) with no difference in dose-adjusted concentration as well. For CYP3A5*GG patients, tacrolimus treatment cause lower acute rejection rate than CsA treatment (P=0.030), taking shorter time to get a stable immune situation than CsA treatment. For CYP3A5*AA/AG patients, tacrolimus treatment cause similar acute rejection rate with CsA treatment (P=0.982), but took longer time to get a stable immune situation than CsA treatment. What's more, tacrolimus treatment costs much than CsA treatment.

Conclusions: These results indicate that CYP3A5*AA/AG carriers need higher tacrolimus dose than CYP3A5*GG homozygote to achieve the target blood concentration. CYP3A5*GG carriers preferred to tacrolimus treatment and CYP3A5*AA/AG carriers preferred to CsA treatment depended on the incomes. CYP3A5 genotyping is a new approach for detecting tacrolimus dose requirement and a predictive index for the tacrolimus or CsA treatment selection in the kidney recipients.

FR-PO1085

Intrapatent Tacrolimus Level Variability in Pediatric Kidney Recipients Predicts Allograft Loss After Transfer to Adult Care Hilda E. Fernandez,¹ Sandra Amaral,² Pamela A. Shaw,³ Roy D. Bloom,³ Alden Michael Doyle,⁴ Sumit Mohan,¹ Susan L. Furth.² ¹Columbia Univ; ²CHOP; ³PENN; ⁴Hahnemann Univ.

Background: Allograft loss is especially common in 17-24 year olds and is associated with non-adherence around the time that transplant care is transferred from the pediatric to adult setting. We explored whether coefficient of variation of tacrolimus (CV TAC) levels prior to transfer, as a marker of non-adherence, predicted allograft loss in a cohort of pediatric kidney recipients transferring to adult transplant centers.

Methods: Retrospective cohort of transplant recipients at Children's Hospital of Philadelphia transplanted 1999 to 2011 who transferred care to University of Pennsylvania or Hahnemann University Hospital, identified by chart review. CV TAC was calculated as SD divided by mean TAC over 12 mos. Date of transfer was defined as the last pediatric visit. We compared pre-transfer TAC CV in those that subsequently lost their graft to those that did not (t-test).

Results: 24 of 65 subjects had sufficient data for analysis. Median age at transplant was 15.9y (8.5-18.9). The cohort was primarily male (66%), White (77%), had CAKUT (8%), and 46% had LRKT. Median age at transfer was 20y (17.4-22.1). Four patients had allograft loss within 365 days post-transfer. Pre-transfer CV TAC for subjects with allograft loss post-transfer (n=4) was significantly higher as compared to subjects without allograft loss (n=20) (49.4% vs 26.2%, p = 0.0275).

Conclusions: CV TAC may aid in identifying patients at risk for allograft loss post-transfer. Future analysis will investigate the effect of race, age at transfer, rejection, *de novo* DSA pre-transfer that may also help predict adolescent kidney transplant recipients at risk for allograft loss following transfer to adult transplant centers.

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FR-PO1086

High Tacrolimus Level Variability in the Early Post-Transplant Period Is Associated with Reduced Patients and Graft Survival After Kidney Transplantation Benaya Rozen-zvi,¹ Avry Chagnac,¹ Ruth Rahamimov.^{1,2} ¹Nephrology and Hypertension, Rabin Medical Center, Petach-Tikva, Israel; ²Organ Transplantation, Rabin Medical Center, Petach-Tikva, Israel.

Background: The effect of Tacrolimus levels variability in the early period after kidney transplantation was not properly studied. We sought to evaluate whether increased drug level variability is associated with reduced graft survival and evaluated the relative effect of exposure to high and low drug levels.

Methods: We screened the Rabin Medical Center registry database for adult patients from 2001 to 2013 that were treated with tacrolimus, micophenolate mofetil and corticosteroids and had at least 6 values of drug level during the first six months after the transplantation. Variability was defined as the time average of the absolute value of the difference from the mean and this value was divided by the mean to get the variability index. Univariate and multivariate Cox proportional hazard model was used with the combination of death and graft failure as composite outcome.

Results: We identified 803 patients who met the inclusion criteria, ninety eight (12.2%) of them reached the end point during median follow up time of 3.7 years (range 0.5 to 12.9 years). Increased variability index was associated with increased hazard of death or graft failure by univariate (Hazard Ratio (HR) 1.029 per 1%, 95% Confidence Interval (CI) 1.006-1.052, p=0.013) and multivariate models (HR 1.036 per 1%, 95% CI 1.01-1.062, p=0.006). Variability was still significantly associated with reduced graft survival after introducing acute rejection into the model (HR 1.038 per 1%, 95% CI 1.008-1.056, p=0.008). Introducing exposure to levels above 15 ng/ml into the model didn't change the association between variability index and the composite outcome while introducing exposure to levels below 5 ng/ml eliminated the association and made it non-significant (p=0.18).

Conclusions: High variability index in the first six month after kidney transplantation is associated with increased mortality and graft loss. This association is, probably, mediated by exposure to low drug levels.

FR-PO1087

Decision Tree Analysis of Renal Transplantation Recipients Outcomes: A Single Center Data Mining Jingyi Zhou, Jianghua Chen. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, China.*

Background: Results from former literature on factors influencing renal transplant outcomes are quite confusion and few include factors influencing outcomes of rejection cases. This study was intended to get the factors in order and to provide reliable predictive models for clinical practice with decision tree analysis, and attempted to discuss about decision tree integrated with renal transplant database to fulfill the dynamic model growth and to serve personal medical care in big data era.

Methods: Renal transplant recipients registering between May 1988 and April 2014 in Kidney Center of the First Affiliated Hospital of Zhejiang University were included. Living state, rejection state, state post rejection and overall outcomes were analyzed by decision tree.

Results: Totally 3921 cases were included. The loss-to-follow rate is 9.7%. With survival rate as the object, we got the most important factor, steroids (P < 0.01). Patients in the following factor combination showed the highest survival rate: steroids, mycophenolate mofetil (MMF), stenting, warm ischemic time (WIT) ≤ 6.5min, cold ischemic time (CIT)

≤ 300min, and aspartate aminotransferase (AST) 6 months post operation ≤ 34U/L (survival rate 100%, 305 cases). Patients had the lowest acute rejection rate when in the factor combination: steroids, antihuman thymocyte globulin or basiliximab induction, no blood transfusion history and female (0%, 83). Patients with acute rejection were regarded as a new database. The patients who took steroids and received stents shows similar outcomes with patients who had no rejection. Important factors that could be intervened for long-term outcomes included stenting, statins, steroids, etc.

Conclusions: Decision tree analysis is an outstanding choice for risk stratification, prognosis prediction and dynamic follow-up. Immunosuppression therapy was regarded as the most important factor for renal transplant recipients' survival, rejection and other outcomes. Factors should be considered in combination for each specific patient.

FR-PO1088

Comparison of Clinical Outcome Between ABO Incompatible and Compatible Spousal Donor Kidney Transplantations Ji Hyun Yu,¹ Byung ha Chung,¹ Bum soon Choi,¹ Curie Ahn,² Sung-joo Kim,⁵ Chul Woo Yang.¹ ¹Transplantation Research Center, Internal Medicine, Nephrology, Seoul St. Mary's Hospital, Seoul, Republic of Korea; ²Transplantation Center, Seoul National Univ Hospital, Seoul, Republic of Korea; ³Surgery, Severance Hospital, Yonsei Univ College of Medicine, Seoul, Republic of Korea; ⁴Organ Transplantation Center, Busan Paik Hospital, Inje Univ School of Medicine, Busan, Republic of Korea; ⁵Surgery, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea.

Background: Spousal donor is an important source to overcome shortage of living donor in kidney transplantations (KTs). We aimed to compare the clinical outcomes in ABO incompatible KT (ABOi-KT) to those of ABO compatible KT (ABOc-KT) from spousal donors.

Methods: We analyzed 580 KT from spousal donors among 3043 living donors KT registered in the Korean Organ Transplantation Registry. Clinical outcome between ABOi-KT and ABOc-KT were compared by episodes of acute rejection (AR), graft function, grafts and patients survival rates.

Results: The proportion of spousal donors in ABOi-KT was higher than that of ABOc-KT (40.9% vs. 21.4%, P < 0.001). The biopsy proven AR -free survival rate in ABOi-KT was comparable to ABOc-KT (79.7% vs. 82.3%, P=0.188). The renal allograft function showed no difference until 36 months after KT. The 3-year graft survival (92.5% vs. 95.7%), and patient survival (96.4% vs. 98.5%) were not significantly different between ABOi-KT and ABOc-KT groups (P > 0.05, respectively). Multivariate analysis revealed that ABOi-KT from spousal donors did not affect the graft, patient survival and BPAR-free survival rate.

Conclusions: The results of our study show that the ABOi spousal donor is an important source of living donor, and can be a good alternative of overcoming donor organ shortage.

FR-PO1089

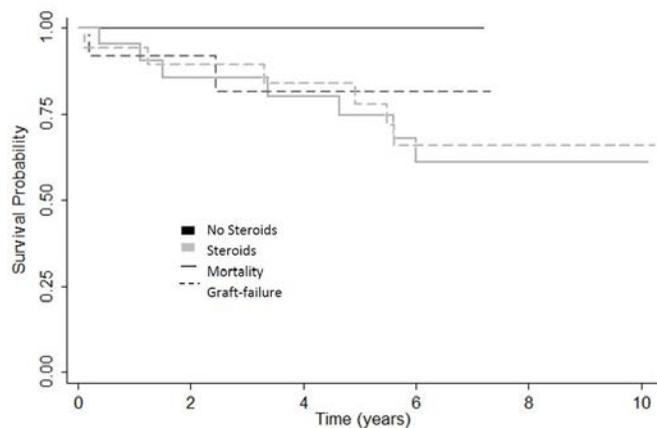
3-Year Outcomes After ABO Incompatible Kidney Transplantation without Steroids Shefali Patel, Mariana C. Chiles, Sumit Mohan, Russell J. Crew. *Columbia Univ, New York, NY.*

Background: Early steroid withdrawal paired antibody induction therapy provides comparable outcomes to steroid maintenance patients. However, ABOi transplantation is considered higher immunologic risk, and it unclear if a steroid free regimen is appropriate for this population.

Methods: We performed 40 ABOi transplants with pre-transplant plasmapheresis (PP) with IVIG to an isohemagglutinin titer 1:16 and 2 post-tpx PP/IVIG treatments, immunosuppression with tacrolimus, mycophenolate, and intraoperative rituximab (375mg/m²). Prior to 2008, patients received an IL-2 receptor blocker, and prednisone tapered to 5 mg by 6 months. After 2008, induction included Thymoglobulin® (6 mg/kg in 4 divided doses) and steroid withdrawal by postop day #3. Patients underwent protocol biopsies at predefined intervals. We compared outcomes at 3 years between those who had and had not received maintenance steroids.

Results: 24 patients received maintenance steroids and 16 underwent rapid steroid withdrawal. There were no differences in sex, starting isohemagglutinin titer, or blood group mismatch between the groups. Antibody mediated rejection was more common in the steroid maintenance group (41% vs 31%) as was cellular rejection (50% vs 47%), though not significantly different. At 3 years, renal function was similar between those with and without steroids- eGFR 46±25 cc/min vs 52±15 cc/min, respectively. Approximately 50% of patients underwent protocol biopsy at 3 years. There were no differences in the degrees of interstitial fibrosis, glomerulosclerosis, or transplant glomerulopathy between groups. Graft survival, patient survival, and infectious complications were also similar.

Conclusions: Even in higher immunologic risk ABOi transplant recipients, rapid steroid withdrawal appears to provide similar medium term results as steroid maintenance therapy without the longterm side effects.



FR-PO1090

Three Year Outcome of a Pioneer ABOi Renal Transplant Programme in Malaysia Si-Yen Tan,¹ Mohan Rao,² Eng-Thye Koh.² ¹Medicine, Prince Court Medical Centre, Kuala Lumpur, WP, Malaysia; ²Surgery, Prince Court Medical Centre, Kuala Lumpur, WP, Malaysia.

Background: ABO incompatible (ABOi) renal transplantation increases organ donor pool and is an option for patients with no blood group compatible donors. We report here results of a pioneer ABOi renal transplant programme in Malaysia which was first established in Prince Court Medical Centre in 2011.

Methods: Ten patients entered into our ABOi programme between July 2011 and December 2013. Data were analyzed to determine the number of therapeutic plasma exchange (TPE) and/or immunoadsorption (IA) with Glycosorb columns to achieve target pre transplant ABO antibody titres of < 1:16 and ABO titres post transplant. Graft function and rejection rates together with graft and patient survival at 3 years were also determined.

Results: Median baseline ABO titres was 1:128 and all patients achieved target pre transplant ABO titres of < 1:16 after a median of 4 TPE and/or IA. Median follow up was 32 months with all patients maintaining ABO titres of < 1:16 at follow up with no protocol post transplant TPE/IA. There was 1 case (10%) of acute cellular rejection at one year which was reversed with steroids but none had antibody mediated rejection. Patient and graft survival was 100% at 3 years with current median serum creatinine 108umol/L.

Conclusions: The results of our pioneer ABOi renal transplant programme with graft and patient survival of 100% at 3 years is extremely encouraging and suggest that graft and patient outcome is similar to ABO compatible renal transplants. The use of ABO incompatible donors may effectively increase organ donor pools especially in countries where both cadaver and living related kidney transplant rates remain poor. Our results also suggest that national ABOi renal transplant programmes may be effectively introduced and led by a private medical centre to complement and support more established renal transplant programmes in government institutions which are now beginning to perform their own ABOi renal transplants in light of our success.

Funding: Clinical Revenue Support

FR-PO1091

Improved Graft Outcome After Blood Transfusion: Still in Effect? Gowrie Balasubramaniam,¹ Arun Gupta,² Neil Ashman,² Raj Thuraisingham.² ¹Dept of Medicine, Southend Univ Hospital, Southend, Essex, United Kingdom; ²Dept of Nephrology and Transplantation, Barts and The Royal London Hospital, London, United Kingdom.

Background: Blood transfusions can lead to sensitisation in potential transplant patients. We previously quantified the risk of sensitisation from transfusion per se by looking at a cohort of male patients on the transplant waiting list and ascertaining the transfusion history from electronic records and questionnaires. Prior to standard triple immunosuppression, transfusions were associated with overall better graft outcome possibly by a tolerogenic effect or by selecting non-sensitisers. The majority of patients who were transfused do not become sensitised, we wanted to characterise graft outcome in this group.

Methods: We obtained graft outcome information on the original cohort of patients. Data was collected prospectively as part of routine surveillance.

Results: 100 out of the initial 126 male patients were transplanted. 10 were excluded from further analysis due to death or graft loss in the immediate post-transplant period. 11 of remaining 90 patients were DSA prior to transplantation, 8 also had a history of previous blood transfusion. 4 of the 8 patients with a previous blood transfusion and DSA had a rejection episode (2 AMR and 2 ACR). Of the remaining 79 patients who were DSA negative prior to transplantation, 26 had a previous transfusion (TR+ DSA-) and 53 did not have a history of transfusion (TR- DSA-). Comparison between the two groups is shown in (table 1).

	TR+ DSA-	TR- DSA-
Rejection rate	2/26	15/53
ACR	2	12
AMR	0	3
Recipient age	50.1 ± 11.5	48.2 ± 9.9
Donor age	49.0 ± 13.2	45.1 ± 14.4
Donor type		
LT	2	10
HB	13	28
NHB	11	15
CIT	768.1 ± 284.5	730 ± 368.6
Immunosuppression		
Induction		
ATG	11	17
IL-2 agent	15	35
Campath	0	1
Maintenance	23	50
Cya, MMF, Pred	3	0
FK, MMF, Pred	0	2
FK, Aza, Pred	0	1
FK, Pred		

Conclusions: Lack of sensitisation with a history of leuco-depleted transfusion is associated with a lower risk of rejection post-transplantation. This suggest that previous mechanisms of transfusion tolerance or “non-sensitisers” are still relevant in the modern immunosuppression era.

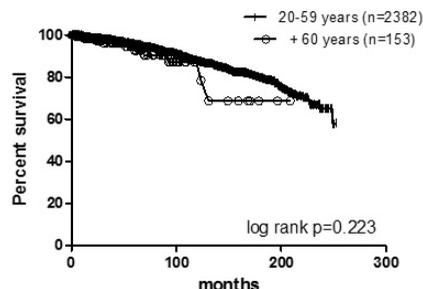
FR-PO1092

Geriatric Renal Transplantation in Deceased Donor Showed Compatible Clinical Outcomes to Younger Recipients Hyungjin Cho, Eunhye Shin, Hyosang Kim, Su-Kil Park. *Dept of Internal Medicine, Div of Nephrology, Asan Medical Center, Seoul, Republic of Korea.*

Background: According to USRDS annual report, while 50.3% of patients who start hemodialysis were aged over 65 years, only 19.3% of patients who underwent renal transplantation was aged over 65 years. Elderly ESRD patients still are not under renal transplantation as much as younger recipients. There were many previous studies about geriatric renal transplantation outcome in white, however data in Asian were limited. The aim of this study is analysis of geriatric kidney transplantation outcome in Korea.

Methods: From May 1993 to December 2013, kidney transplantations performed in Asan medical center were retrospectively reviewed. Recipients younger than 20 years and who underwent other organ transplantation were excluded. Binary logistic regression was used for evaluating risk factors of graft failure before half-life. Half life of kidney allograft was defined as 10 years according to previous study.

Results: Regardless of donor type, there is no statistically significant difference in death censored graft survival between geriatric population and younger recipients.



Multivariate analysis of deceased donor recipients revealed that recipients aged over 60 years was not a significant risk factor for graft failure before half-life.

	univariate analysis			Multivariate analysis		
	p	Hazard ratio	95% CI	p	Hazard ratio	95% CI
+ 60 years	0.604	1.263	0.522-3.056			
Female	0.219	0.767	0.503-1.171			
Cold ischemic time	0.655	1.000	0.999-1.001			
Donor age	0.031	1.018	1.002-1.035	0.036	1.017	1.001-1.033
Re-transplantation	0.531	1.272	0.599-2.705			
Diabetes mellitus	0.002	2.841	1.475-5.473			
Hypertension	0.931	0.959	0.376-2.447			
HLA DR mismatch	0.932	1.035	0.473-2.266			
Dialysis before transplantation	0.382	2.085	0.402-10.826			

Conclusions: Renal transplantation in geriatric population can be encouraged in Asian ESRD patients.

FR-PO1093

Long-Term Survival and the Associated Risk Factors for Death in Patients (pts) with Kidney Transplantation (Tx) Tanja Abeling,¹ Irina Scheffner,¹ Verena Broecker,² Michael Mengel,³ Hermann G. Haller,¹ Anke Schwarz,¹ Wilfried Gwinner.¹ ¹Hannover Medical School, Germany; ²Cambridge Univ, United Kingdom; ³Univ of Alberta, Canada.

Background: Deaths over a period of up to 10 years (yrs) and the related risk factors were studied in Tx pts with protocol biopsies (Bx) (total observation: 4805 patient-yrs).

Methods: 892 pts with kidney Tx in 2000-2007 were included. Protocol Bx were taken at 6 weeks, 3 and 6 months post-Tx (n=2251). 862 Bx for cause were taken in the 1st year and 262 thereafter. Lost-to follow-up was negligible (n=15). All acute rejections and clinical borderline cases in protocol Bx were treated.

Results: Patient and graft survival was 80% at 5 yrs and 68% at 10 yrs. Patient survival was 92% at 5 yrs and 82% at 10 yrs. 99 deaths occurred, relating to infection (24%), cardiovascular disease (15%), malignancy (16%), other specified causes (8%). Deaths were less in living-donor or kidney/pancreas Tx and more frequent for extended donor criteria-Tx. A three-level multivariate Cox regression model was created in a stepwise fashion, using significantly different variables from the pre-Tx, peri-operative, and long-term post-Tx period between survivors and deceased pts. Pre-Tx variables in the final model included recipient age, HLA-DR mismatches, diabetes, coronary heart disease, heart failure, and peripheral arterial disease. A significant peri-operative variable was cold ischemia time. In the long-term course, variables for death included increased loss of graft function, urinary tract infection, and higher PTH levels. Compared to the survivors, deceased pts received more therapies for rejection seen in protocol Bx (0.30 vs. 0.43 per patient) and in Bx for cause (0.29 vs. 0.34 per patient), however, this was not a significant factor in the final model. Also, the proportion of anti-rejection treatments was not higher in pts who died from infections, compared to pts dying from other causes. Concordance of the final model was 0.79; 200-fold bootstrapping confirmed its applicability.

Conclusions: Based on these results a tool is presented that readily allows risk calculation and stratification of individual pts, as a pre-requisite for individualized and optimal pre- and post-Tx care.

Funding: Government Support - Non-U.S.

FR-PO1094

Causes of Death-Censored Kidney Allograft Failure: A Matched Case-Control Study of 340 Kidney Allograft Recipients Mohamad M. Alkadi,¹ Jim Kim,² Choli Hartono,¹ Thangamani Muthukumar,¹ Meredith J. Aull.¹ ¹Medicine, Weill Cornell Medical College, New York, NY; ²Surgery, Weill Cornell Medical College, New York, NY.

Background: Causes of kidney allograft failure in the current era of immunosuppression have not been clearly defined.

Methods: We did a matched case-control study of death-censored allograft failures among the 1672 adult kidney transplants at our center between 11/2001 and 12/2011. The cases and controls were matched 1:1 for age, donor type and year of transplant. We reviewed the charts and used the last available biopsy diagnosis for each case to determine the cause of graft failure. We divided the causes of graft failure into 8 categories; (i) acute rejection, (ii) transplant glomerulopathy, (iii) IF/TA, (iv) glomerular diseases, (v) BK nephropathy, (vi) others/unclassified, (vii) surgical and (viii) medical causes. We used conditional logistic regression analysis to determine the odds ratio.

Results: We identified 175 graft losses during the study period and matched 170 of them (cases) 1:1, with 170 controls. There was no statistically significant differences between cases and controls in terms of donor sex, recipient sex, donor race, recipient race, number of transplants, induction therapy or maintenance therapy. 86% of patients received antithymocyte globulin induction. The median follow up in the cases and controls was 22 months and 56.5 months, respectively. 72% of cases had a biopsy done within 12 months of graft failure. The proportion of cases and controls in the 8 diagnostic categories and their respective conditional odds ratio is shown in the table below.

	Cases	Controls	OR (95% CI)	P value
Acute Rejection	36	11	4.5 (2-10.3)	< 0.001
Transplant Glomerulopathy	15	4	3.7 (1.2-11.2)	0.01
Glomerular Disease	29	4	7.2 (2.5-20.6)	< 0.001
BKV Nephropathy	10	1	9.9 (1.2-78.1)	0.02
Primary IFTA	7	1	6.9 (0.8-56.8)	0.07
Surgical Causes	18	0	-----	-----
Medical Causes	24	0	-----	-----
Other Histology	31	22	1.5 (0.8-2.7)	0.1

Conclusions: In the modern era of immunosuppression, allo-immune rejection and auto-immune glomerular disease continue to be significant factors associated with graft failure.

FR-PO1095

Effect of Simultaneous Native Nephrectomy on the Outcome of Kidney Transplant Recipients with Autosomal Dominant Polycystic Kidney Disease Jeong Ho Kim, Bum soon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim, Byung ha Chung. *Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea.*

Background: End stage renal disease (ESRD) patients with autosomal dominant polycystic kidney disease (ADPKD) required native nephrectomy because of limited space for renal allograft. However, the appropriate timing for nephrectomy and also its effect on allograftand patient survival has not been fully investigated.

Methods: We retrospectively analyzed 41 kidney transplant recipients with ADPKD in whom transplantation was done either simultaneously, after or without native nephrectomy at Seoul St. Mary's hospital between January 1987 and February 2014. We divided patients into 2 groups; simultaneous nephrectomy group (group A, n=13), after or without nephrectomy group (group B, n=28) and compared the perioperative outcome, post-transplant complications, allograft survival rate.

Results: The mean operative time was significantly longer in group A than group B (6.48 ± 1.84 vs. 5.27±0.84 hours; P = .048). The mean intraoperative blood transfusions was also significantly more needed in group A than B (3.66±3.43 vs. 0.75 ±0.26 units; P = .018). However, there were no differences in the incidence of acute rejection and other complications such as post-operative bleeding, infectious complication between the two groups (P > .05, for all). The graft survival rate also did not differ between the two groups (P > .05).

Conclusions: Our study suggests that the complication rates were acceptable and there was no significant negative impact on graft survival rate when native nephrectomy was done during kidney transplantation in ADPKD patients with ESRD. Therefore, if native nephrectomy is needed in ADPKD for kidney transplantation it can be done safely during transplantation.

FR-PO1096

Predictors of Renal Function Change After Kidney Transplantation Yoshifumi Hamasaki,¹ Kent Doi,² Akihiko Matsumoto,³ Daigoro Hirohama,¹ Nobuhiko Sato,¹ Daisuke Katagiri,¹ Rei Isshiki,¹ Wakako Kawarazaki,¹ Eisei Noiri,¹ Masaomi Nangaku.¹ ¹Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; ²Emergency and Critical Care Medicine, The Univ of Tokyo, Tokyo, Japan; ³Urology, The Univ of Tokyo, Tokyo, Japan.

Background: Several perioperative factors including histological findings of allograft biopsy are known to be associated with graft function and graft survival after kidney transplantation (KT). Urinary L-type fatty acid binding protein (uL-FABP) was reported to be correlated with serum creatinine, serum cystatin C, and estimated glomerular filtration rate (eGFR) in a cross sectional study evaluating post-KT patients. It is unclear what factors in post-KT period predict the longitudinal change of renal function.

Methods: The data from post-KT patients followed at The University of Tokyo Hospital were collected retrospectively. Patients followed-up less than 6 months after KT were excluded. To identify predictors of the longitudinal change of renal function, we analyzed data including clinical parameters measured at each outpatient visit. The primary outcome was determined as the change of eGFR during 6 months period.

Results: 32 post-KT recipients were analyzed in this study. Age and eGFR at baseline of these patients were 51.3 ± 12.7 years old and 41.2 ± 16.1 ml/min/1.73m² (mean ± SD), respectively. The duration from KT to collection of clinical parameters was 6.8 ± 7.3 years (mean ± SD). Changes of eGFR were evaluated 6 months after. When patients were divided into two groups with (N = 15) and without (N = 17) eGFR decline after 6 months, uL-FABP and urinary protein were significantly higher in the eGFR decline group (uL-FABP; 11.6 vs 5.1 mg/ml, and urinary protein; 272.7 vs 97.2 mg/gCr, respectively). On ROC analysis, uL-FABP and urinary protein predicted eGFR decline after 6 months (AUC [95%CI] = 0.78 [0.60-0.96] and 0.70 [0.51-0.89], respectively). On multiple regression analysis, uL-FABP and urinary protein were significantly correlated with the absolute and relative eGFR changes during 6 months observation period.

Conclusions: uL-FABP and urinary protein measured at outpatient clinic can predict the change of renal function of post-KT patients.

FR-PO1097

Plasma Proenkephalin and Poor Long-Term Outcome in Renal Transplant Recipients Lyanne M. Kieneker,¹ Joachim Struck,² Ron T. Gansevoort,¹ Michel M. Joosten,¹ Rudolf A. de Boer,³ Oliver Hartmann,² Stephan J.L. Bakker.¹ ¹Nephrology, UMC Groningen, Netherlands; ²Sphingotec GmbH, Germany; ³Cardiology, UMC Groningen, Netherlands.

Background: Enkephalins are well-known endogenous opioid peptides. Recent evidence indicates that they are not only involved in regulation of pain, but also in homeostasis of the immune system and the circulation. Proenkephalin (pro-ENK) is stable in plasma and has been established as reliable surrogate marker for unstable enkephalins. Recent studies found associations of pro-ENK with acute kidney injury and prognosis after myocardial infarction. We aimed to investigate whether pro-ENK could be linked to chronic kidney injury and poor long-term outcome in renal transplant recipients (RTR).

Methods: We included 664 RTR who were 8.1±7.6 years after transplantation. Plasma levels of pro-ENK were measured with a double monoclonal sandwich immunoassay.

Results: Mean age was 53±13 years, 56% was male, estimated glomerular filtration rate (eGFR) 49 ml/min/1.73m² (interquartile range [IQR]: 37-64 ml/min/1.73m²) and

urinary albumin excretion (UAE) 40 mg/24h (IQR: 10-196 mg/24h). Median pro-ENK was 110 pmol/L (IQR: 85-148 pmol/L). Pro-ENK was correlated with both eGFR ($r = -0.73, P < 0.001$) and UAE ($r = 0.35, P < 0.001$). During a median follow-up of 3.1 years (IQR: 2.7-3.9 years), 45 RTR developed graft failure and 76 died. Pro-ENK was both associated with increased risk of graft failure (hazard ratio per standard deviation increment of the logarithm of pro-ENK, 2.76; 95% confidence interval, 1.69-4.53) and all-cause mortality (1.83; 1.24-2.69), independent of age, sex, eGFR, and UAE. These associations remained materially unchanged after additional adjustment for body mass index, alcohol consumption, smoking, systolic blood pressure, antihypertensive drug use, use of calcinurin inhibitors, and high-density lipoprotein.

Conclusions: High concentrations of pro-ENK are linked to chronic kidney injury as reflected by correlations with eGFR and UAE. In addition, pro-ENK was independently associated with increased risk of graft failure and mortality in RTR. Pro-ENK is an interesting new biomarker which may aid in early identification of RTR at risk for late graft failure and premature mortality.

Funding: Private Foundation Support

FR-PO1098

Serum Albumin Level Has Association with Both Graft Failure and Mortality in Kidney Transplant Recipients Hee Jung Jeon,¹ Soyon Rhee,¹ Eunjung Kim,¹ Jung Pyo Lee,² Ja-Ryong Koo,¹ ¹Dept of Internal Medicine, Hallym Univ of College of Medicine, Seoul, Republic of Korea; ²Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea.

Background: The studies concerned the association between post-transplant serum albumin concentration and post-transplant outcomes in kidney transplant recipients (KTRs) are scarce.

Methods: To evaluate the impact of serum albumin level on graft and patient survival, we performed a retrospective multi-center cohort study in Seoul National University Hospital, Asan Medical Center, and Kangdong Sacred Heart Hospital. A total of 2815 KTRs who underwent renal transplantation from Jan 1997 to Jan 2012 were classified into two groups according to the level of serum albumin at 1 year after transplantation (higher albumin group, ≥ 4.0 g/dL, n=1978 vs. lower albumin group, < 4.0 g/dL, n=837). The Cox proportional hazard model was adjusted with age and gender of recipient, donor type, age of donor, diabetes mellitus, and estimated glomerular filtration rate (eGFR) at 1 year after transplantation.

Results: The mean age of the recipients was 41.7±11.3 (range, 18-73) years, and 59.1% were male. The rate of graft failure was higher in lower albumin group compared to higher albumin group (Hazard ratio [HR] 1.840, 95% confidence interval [CI] 1.367-2.477, $P < 0.001$), even though eGFR at 1 year after transplantation was not different between the two groups (61.7±19.8 vs. 62.1±15.8 mL/min, $P = 0.615$). Both all-cause mortality and non-cardiovascular mortality rates were higher in lower albumin group (HR 2.227, 95% CI 1.258-3.943, $P = 0.006$, and HR 2.784, 95% CI 1.254-6.179, $P = 0.012$, respectively). Every 1.0 g/dL higher serum albumin concentration was associated with 69.2% lower all-cause mortality (HR 0.308, 95% CI 0.196-0.483, $P < 0.001$).

Conclusions: Serum albumin level at 1 year after transplantation is a prognostic factor for graft failure and patients' mortality in KTRs. Therefore, evaluation and management for hypoalbuminemia should be considered to improve outcomes in KTRs.

FR-PO1099

Brain Effects of Renal Transplantation: Association Between Cognition and White Matter Integrity Amiti Gupta,¹ Rebecca J. Lepping,² David K. Johnson,³ Alan S.L. Yu,¹ William M. Brooks,² Jeffrey M. Burns,³ ¹Kidney Inst; ²Hoglund Brain Imaging Center; ³KU Alzheimer's Disease Center; ⁴Univ of Kansas Medical Center.

Background: Cognitive impairment is present in up to 87% patients with end stage renal disease (ESRD). Magnetic resonance imaging (MRI) using diffusion tensor imaging (DTI) shows lower fractional anisotropy (FA) values in these patients. FA values measure structural integrity of white matter and are associated with cognitive impairment. In this study we examine the effect of renal transplantation on cognitive function and determine whether changes in white matter integrity underlie the observed cognitive changes.

Methods: Adults with ESRD were recruited from the renal transplant waiting list. Subjects were evaluated before transplantation and 3 months after transplantation with neuropsychological (NP) tests and a brain MRI. Two-tailed paired t-test was used to analyze changes in NP tests and FA values before and after transplantation. Pearson correlation coefficients were calculated.

Results: Two hundred patients were screened and eighteen enrolled. Ten subjects, 57±11 years of age have been transplanted and have completed the study. After transplantation, there was a significant improvement in NP tests for memory and executive function.

Test	Pre-Transplant	Post-Transplant	P value
Logical Memory I	10.5±4.6	13.9±4.5	0.011
Logical Memory II	8.5±5.2	13±4.8	0.007
Stroop color	68.9±16	74.9±14.5	0.028
Digit Symbol	43.3±11	48±11.5	0.002

There was a significant increase in the FA values in the body of corpus callosum ($P = 0.017$), forceps minor ($P = 0.058$) and left cingulate gyrus ($P = 0.002$). Furthermore, the improvement in NP tests positively correlated with the increase in FA values in these tracts.

Conclusions: Memory and executive function improve after renal transplantation. FA, a DTI metric representing white matter integrity also increases in brain regions important for these functions. This study provides insight into the neural mechanisms underlying cognitive impairment in ESRD and its improvement after transplantation.

FR-PO1100

Pre-Kidney Transplant Left Ventricular Ejection Fraction, Long-Term Allograft Function, and Survival Asjad Sardar, Maha A. Mohamed, Arjang Djamali, Sandesh Parajuli, Didier A. Mandelbrot, Brad C. Astor. *Div of Nephrology, Univ of Wisconsin Hospitals and Clinics, Madison, WI.*

Background: End stage kidney disease patients with low left ventricular ejection fraction (LVEF) are considered high risk for poor outcomes following kidney transplantation (KT). No consensus exists on the level of systolic dysfunction below which patients are at increased risk of unfavorable allograft outcomes.

Methods: We studied 387 KT patients transplanted from 1/02 to 12/09 who underwent pre-transplant invasive and non-invasive cardiac assessment of LVEF. Outcomes included Delayed graft function (DGF), allograft survival, patient survival and allograft function.

LVEF	N	DGF	Patient Survival	Graft Survival	Mean Difference and (95% CI) in Cr		
					OR (95% CI)	HR (95% CI)	HR (95% CI)
<45%	36	1.66 (0.44, 6.26)	1.03 (0.43, 2.49)	0.99 (0.47, 2.02)	-0.10 (-0.66, -0.64)	-0.41 (-1.0, 0.21)	-0.1 (0.66, 0.64)
45-60%	215	1.29 (0.56, 2.94)	0.78 (0.43, 1.42)	0.89 (0.57, 1.40)	0.01 (0.13, 0.15)	-0.22 (-0.56, 0.11)	0.07 (-0.30, 0.44)
>60%	136	Ref	Ref	Ref	Ref	Ref	Ref
P-trend		0.42	0.81	0.80	0.70	0.12	0.86

CI: Confidence Interval, Ref: Reference

Data adjusted for age, sex, race, PRA, Duration of RRT, DM, CAD, LVH and Induction Therapy.

Associations between different LVEF values.

Results: A total of 136 (35.1%) patients had LVEF > 60%, 215 (55.5%) had LVEF between 45-60% and 36 (9.3%) had LVEF < 45% before KT. Patients with low EF were more likely to have DM, CAD, LVH and longer duration of dialysis. During median follow up of 4.4 years there were 122 graft losses including 71 deaths. 73 patients (18.9%) had DGF. There was no significant difference in rate of DGF, serum creatinine, allograft survival and patient survival.

Conclusions: Low LVEF does not appear to significantly effect patient and allograft survival and function, suggesting that patients with low LVEF should not be excluded from transplantation.

FR-PO1101

Progression of Coronary Artery Calcification in Renal Transplant Recipients – A Follow-Up of 7 Years Sibel Gulcicek, Nurhan Seyahi. *Dept of Internal Medicine, Div of Nephrology, Istanbul Univ, Cerrahpasa Medical Faculty, Istanbul, Turkey.*

Background: In the general population coronary artery calcification (CAC) and its progression is associated with cardiovascular and all cause mortality. We conducted a study to determine the progression of CAC in renal transplant recipients; we also examined the factors associated with progression and the impact of the analytic methods used to determine CAC progression.

Methods: We used multi-detector computed tomography to examine CAC in 113 prevalent renal transplant recipients, who did not have a documented cardiovascular disease. A baseline and a follow-up scan were performed and changes in CAC scores were evaluated in each patient individually, to calculate the incidence of CAC progression. Univariate and Multivariate logistic regression analysis was used to evaluate the determinants of CAC progression.

Results: Baseline CAC prevalence was 34.5 % and the mean CAC score was 47.08 ± 135.25. At follow-up scan that was performed after an average of 6.9 ± 0.5 years, CAC prevalence increased to 47.6% and the mean CAC score to 140.18 ± 332.11. Progression of individual CAC score was found between 32.7 and 34.5 %, depending on the method used to define progression (Hokanson and Sevrakov). In patients with baseline CAC, median annualized rate of CAC progression was 13.8. Based on univariate analysis, age, presence of baseline CAC, high baseline CAC score, high body mass index were significantly associated with CAC progression defined according to both the Hokanson and Sevrakov methods. Moreover, HDL cholesterol level were significantly associated with CAC progression when progression was defined according to Hokanson's method and donor type, high triglyceride levels and systolic blood pressure were significantly associated with CAC progression according to Sevrakov's method. Based on multivariate analysis baseline CAC and high triglyceride were the independent determinants of CAC progression.

Conclusions: Progression of CAC is the usual evolution pattern of CAC in renal transplant recipients. Beside baseline CAC, high triglyceride level were also associated with progression of CAC.

Funding: Clinical Revenue Support

FR-PO1102

Adiponectin Fractions Influence the Development of Cardiovascular Disease in Japanese Renal Transplant Recipients Hiroki Adachi, Yuki Matsui, Norifumi Hayashi, Keiji Fujimoto, Junko Imura, Hideki Yamaya, Hitoshi Yokoyama. *Div of Nephrology, Kanazawa Medical Univ, Uchinada, Ishikawa, Japan.*

Background: Although the risk for morbidity and mortality has been studied in subjects with renal transplantation (RTx), a few study has investigated the role of adiponectin (ADPN) for cardiovascular disease (CVD) in RTx recipients.

Methods: We studied 57 adult RTx subjects (39 males, 18 females; 10 cadaveric donors) with at least three years of allograft survival (median 251 months). We examined clinical backgrounds such as treated drugs, blood pressure (BP, mmHg), body mass index (BMI), and blood chemistry including cholesterol (total, LDL-C, HDL-C), glucose, glycated hemoglobin (HbA1c), and serum high- and low-molecular-weight(HMW-/LMW-) ADPN fractions with regard to the associations of the visceral and subcutaneous fat areas on CT scan. We also analyzed the associations of CVD and post-transplant diabetes mellitus (PTDM) with ADPN fractions and the fat areas.

Results: The visceral fat area was inversely correlated with serum HMW- and LMW-ADPN levels ($r=-0.400$, $p=0.002$ and $r=-0.296$, $p=0.025$, respectively). Furthermore, the visceral fat area was inversely correlated with the HMW ratio and positively with the LMW-ADPN ratio ($r=-0.444$, $p<0.001$ and $r=0.467$, $p<0.001$, respectively), but no significant correlation was noted between the subcutaneous fat area and the ADPN ratio. On multiple regression analysis, eGFR and the visceral fat area were significant reducing factors of HMW-ADPN levels, and the alteration of eGFR was identified as an increasing factor of HMW-ADPN levels. Patients with CVD had larger visceral fat area ($p=0.004$), lower HMW-ADPN ratio ($p=0.022$) and higher LMW-ADPN ratio ($p=0.049$), but not in the subcutaneous fat area. On multiple logistic analysis, the higher HMW-ADPN ratio and statin treatment were identified as reducing factors of the development of CVD, but the LDL-C level was an aggravating factor. Moreover, the higher LMW-ADPN ratio and the visceral fat area were aggravating factors of PTDM.

Conclusions: Even in Japanese renal transplant recipients, visceral fat area and ADPN fractions were significant factors for the development of both CVD and PTDM.

Funding: Government Support - Non-U.S.

FR-PO1103

Obesity Before Renal Transplantation: Is Bariatric Surgery the Solution? Ian Thomas, Jeffrey J. Gaynor, David Roth, Warren L. Kupin, Linda J. Chen, George William Burke, Michael J. Goldstein, Gaetano Ciancio, Giselle Guerra, Tameka Joseph. *Univ of Miami, Miami, FL.*

Background: Post transplant outcomes, in obese chronic kidney disease (CKD) patients having bariatric surgery (BS) as a bridge to renal transplantation, have not been widely reported.

Methods: The database at our center of renal transplant recipients having BS prior to transplant from was reviewed. Control group: all obese renal transplant recipients not having BS with body mass index (BMI) greater than 37 at time of transplant. BMI, patient and graft survival, time on wait-list, acute rejections and infections requiring hospitalization were compared between both groups. Immunosuppressant drug levels were assessed in both groups.

Results: 11 patients had BS prior to transplant. There were 25 obese controls. Median follow up post transplant was 12 months (range 2 to 39 months) in BS group versus 63 months (range 48 to 75 months) in the controls. There were no deaths in the BS group but 5 deaths among controls, of which 4 had functioning grafts at time of death. No significant difference in patient survival was found ($P = 0.18$). There were 2 graft losses in the BS group versus 6 in the controls ($P = 0.77$), 4 of which were due to death with functioning grafts. Death-censored graft survival was borderline worse in the BS group ($P = 0.05$). Rejections were more frequent in the BS group. 4/11 patients had acute rejections in the BS group versus 3/25 in the control group ($P = 0.01$). Tacrolimus levels were at target in cases seen in BS group except in 1 patient who was non-adherent. Tacrolimus levels were lower in cases of rejection seen in the controls. There were no significant differences in time on waitlist, BMI prior to BS or mean eGFR at 6 months (60.6 in BS and 64.8 mL/min/1.73 m² in controls). However, the rate of infections was significantly higher in the BS group, 9/11 versus 10/25 in the control group ($P = 0.02$).

Conclusions: Despite possible increased transplant candidacy in obese CKD patients having BS, higher rejection rates and inferior death-censored graft survival compared to matched controls seen in this study suggest that vigilance is mandatory. Further investigation is required.

FR-PO1104

Association Between Serum Magnesium Level and the Risk of New-Onset Diabetes After Renal Transplantation in Korea Hoon Yu, Hyungjin Cho, Eunhye Shin, Su-Kil Park. *Div of Nephrology, Asan Medical Center, Univ of Ulsan College of Medicine.*

Background: New onset diabetes mellitus after transplantation (NODAT) is a serious complication following renal transplantation. Association between serum magnesium level and new-onset diabetes after renal transplantation is controversial. The aim of this study was to identify the association between serum magnesium level and the development of NODAT in Korea.

Methods: The recipients who underwent living donor kidney transplantation between January 2009 and April 2012 were reviewed. Diagnosis of NODAT is defined by American diabetes association criteria. Serum magnesium level were measured at pretransplant, 3 days, 7days and 3 months posttransplant. Univariate and logistic regression analysis were performed to examine the association between serum magnesium level and NODAT at 1 year posttransplant.

Results: Total 419 patients were enrolled. NODAT was diagnosed in 85(20%) patients. Mean magnesium level at 3 and 7 days after transplantation was significantly lower in patients who diagnosed with NODAT. On logistic regression analysis, Age >40, Obesity, pretransplant glucose were associated with NODAT. However, there is a no association between serum magnesium and NODAT.

Table 1. Risk factors of new-onset diabetes - univariate analysis

	Non-NODAT	NODAT	P-value
Number of patients (%)	334 (80)	85 (20)	
Age, years	40.83± 10.52	47.82±10.75	<0.001
Sex, male (%)	117 (53)	53 (62)	0.143
Family history of Diabetes (%)	50 (15)	21 (24.7)	0.036
Tacrolimus (%)	230 (68.9)	59 (69.4)	1.000
Cyclosporine (%)	104 (31.1)	26 (30.6)	1.000
Mycophenolate mofetil (%)	273 (81.7)	64 (75.3)	0.181
Azathioprine (%)	30 (9.0)	11 (12.9)	0.306
Corticosteroids (%)	315 (94.3)	83 (97.6)	0.273
Impaired fasting glucose, pretransplant	12 (3.6)	11 (12.9)	0.002
Glucose, pretransplant	88.7±10.4	96.7±13.5	<0.001
Obesity, pretransplant	51 (15.3)	35 (41.2)	<0.001
Mg, pretransplant	2.17±0.35	2.22±0.34	0.201
Mg, 3 days	1.77±0.20	1.83±0.23	0.026
Mg, 7 days	1.77±0.20	1.82±0.23	0.037

Conclusions: A lower magnesium level at posttransplant may be associated with NODAT after renal transplantation in Korea.

FR-PO1105

Is NODAT Really Associated with Acute Rejection in Kidney Only Transplantation? Rosa M. Montero,¹ Florence R. Delaney,² Manohursingh Rungllal,² Paula Mobillo,³ Syed K. Hasan,² Paramit Chowdhury,¹ Maria P. Hernandez-Fuentes,^{2,3} ¹Nephrology & Transplantation, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom; ²NIHR Comprehensive Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital, London, United Kingdom; ³MRC Centre for Transplantation, DTIMB, King's College, London, United Kingdom; ⁴King's Clinical Trials Unit, Biostatistics Dept, King's College, London, United Kingdom; ⁵Nephrology & Transplantation, King's College Hospital NHS Foundation Trust, London, United Kingdom; ⁶Nephrology & Transplantation, East Kent Hospitals Univ NHS Foundation Trust, London, United Kingdom.

Background: Previous reports suggest an association with New Onset Diabetes After Transplantation (NODAT) and rejection however it is unclear whether this effect is secondary to hyperglycaemia or a result of previous episodes of treated rejection. This observational study aims to determine the association between acute rejection(AR) and NODAT.

Methods: 381 renal transplant recipients(RTR) from the KALIBRE study were analysed. Clinical details and laboratory results were collected in this cohort from 2010-2014. Episodes of AR were identified by renal transplant biopsies; Banff 2009 Categories 2&4 and 3 that were treatment responsive. NODAT was defined as HbA1C>6.5% 3months post renal transplant. Cox's regression proportional hazards was used for survival analysis.

Results: 381 RTRs (39%female, 64%white, 39%non-white, Age at transplant range:17-75). 47 patients were diagnosed with NODAT (13.1%) and 93 (24.4%) with AR. 17/47 (36.2%) patients with NODAT had AR. Rejection free survival in NODAT group was significantly lower than patients without NODAT ($p=0.036$ HR 1.75). Mean tacrolimus

levels between rejectors and non-rejectors were not significantly different (10.1 and 10.3 ng/mL means, respectively). T1DM and T2DM combined did not increase the rates of rejection in the cohort.

Conclusions: An association between NODAT and AR has been observed that was independent of tacrolimus levels. RTRs with diabetes mellitus did not have the same effect on AR rates suggesting a different underlying mechanism specific to NODAT rather than just hyperglycaemia.

Funding: Other NIH Support -

1. Guy's & St Thomas' Charity, Grant number R090782 (Title: Clinical Validation of non-invasive peripheral biomarkers to predict and diagnose rejection following renal transplantation).

2. National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London

3. GSTT Kidney Patient Association

4. Quest Diagnostics

FR-PO1106

Insulin Resistance: Is It a Risk Factor for Left Ventricular Hypertrophy in Pediatric Renal Transplant Recipients? Lale Sever, Nur Canpolat, Gulseren Pehlivan, Salim Caliskan. *Pediatric Nephrology, Istanbul Univ Cerrahpasa Faculty of Medicine, Istanbul, Turkey.*

Background: Renal transplantation reverses uremia-related risk factors for cardiovascular disease; however, immunosuppressive therapy causes metabolic abnormalities such as insulin resistance, hyperglycemia and dyslipidemia. The aim of the present study was to evaluate the effects of these metabolic abnormalities as a risk factor for left ventricular hypertrophy in pediatric renal transplant recipients.

Methods: This is a retrospective study involving 31 renal transplanted children and adolescents (19 male; age 4-20 years) and 19 healthy controls. Anthropometric indices, office blood pressure (BP) and laboratory measurements and also left ventricular mass index (LVMI) at the same time were recorded from the patients' file. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Insulin resistance was defined as a HOMA-IR ≥ 2.5 . Dyslipidemia was defined as HDL-C < 40 mg/dL, and/or LDL-C > 130 mg/dL, and/or TG > 150 mg/dL.

Results: Age at transplantation was 12.4 \pm 4.4 years with a median follow-up of 27 months. One patient received pre-emptive transplantation, 25 were on PD and 5 on HD before transplantation; 25 patients received a kidney from living donor. Triple immunosuppressive therapy was used in all patients, except two who were not using steroids at time of the enrolment. Patients had significantly higher BMI-SDS, fasting glucose, fasting insulin, HOMA-IR and TG as well as lower HDL-C levels than controls ($p < 0.05$ for all). Nine patients (29%) had insulin resistance; 11 (42%) were dyslipidemic; and 15 (56%) were hypertensive. LVMI was significantly higher in the patients than the controls (40.0 \pm 9.1 vs. 25.8 \pm 5.71; $p < 0.001$); left ventricular hypertrophy was noted in 11 patients (48%). LVMI was correlated only with indexed diastolic BP ($r = 0.433$, $p = 0.039$), however, not with any of the lipid parameters or HOMA-IR. HOMA-IR was correlated with only BMI ($r = 0.381$, $p = 0.035$). There was no association between HOMA-IR and steroid doses.

Conclusions: Although insulin resistance and dyslipidemia are prevalent in pediatric renal transplant recipients, hypertension appears to be the main risk factor for left ventricular hypertrophy.

FR-PO1107

Mediterranean Type Diet Is Associated with Low Risk of New-Onset Diabetes and Mortality After Renal Transplantation Maryse Osté,¹ Eva Corpeleijn,¹ Gerjan Navis,¹ Charlotte A. Keyzer,¹ Sabita Soedamah-muthu,² Else van den Berg,¹ Daan Kromhout,^{1,2} Stephan J.L. Bakker.¹ ¹Univ of Groningen; ²Univ of Wageningen, Netherlands.

Background: The incidence of new-onset diabetes after transplantation (NODAT) and cardiovascular events leading to premature mortality is high in renal transplant recipients (RTR). We hypothesized that a Mediterranean type diet protects against development of NODAT and premature mortality in RTR.

Methods: In a prospective cohort study consisting of 707 adult stable RTR with a functioning graft for > 1 year, dietary intake at baseline was assessed with a 177 item validated food frequency questionnaire. Patients were divided into two categories, low resemblance (0-4 points) and high resemblance (5-9 points), based on a 9-point score according to the degree that their dietary pattern resembles that of a Mediterranean type diet. RTR with missing dietary data, diabetes mellitus at baseline or who underwent combined pancreas-kidney transplantation were excluded from analyses, leaving 474 RTR. Cox multivariable regression analyses were used to study the association of the Mediterranean diet with the development of NODAT and mortality.

Results: In total 474 RTR (56.8% men) were included with a mean \pm SD age of 51.5 \pm 13.2 years. At baseline, 256 (54%) had a high resemblance to that of a Mediterranean type diet. During median follow-up of 3.8 (interquartile range [IQR], 3.0-4.6) years from baseline, 28 (6%) developed NODAT and 52 (11%) patients died. RTR with ≥ 5 points were both significantly associated with a lower risk of developing NODAT (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.20-0.94; $P = 0.04$) and mortality (HR, 0.54; 95% CI, 0.31-0.95, $P = 0.03$), both adjusted for age and sex. The results of multivariable analyses, in which we adjusted for potential confounders including total energy intake, physical activity and smoking status, did not materially change the results of the analyses adjusted for age and sex.

Conclusions: Dietary habits that resemble the Mediterranean type diet may protect against NODAT and mortality after kidney transplantation. More attention should be directed to the nutritional habits of renal transplant recipients.

FR-PO1108

Parathyroidectomy for Tertiary Hyperparathyroidism in Kidney Transplant Recipients Brian M. Zwecker,¹ Zahra Deen,¹ Sreedhar A. Mandayam,¹ Luan D. Truong,² A. Osama Gaber,² Emad H. Asham,² Dana M. Hong,² Venkat Ramanathan.¹ ¹Nephrology, Baylor College of Medicine; ²Transplant, Houston Methodist Hospital.

Background: Secondary hyperparathyroidism associated with ESRD improves after kidney transplantation (KT) in most patients. However, in some patients, high PTH persists post-KT to cause a tertiary hyperparathyroidism (ThPT) state, leading to hypercalcemia and worsening post-transplant bone disease. New calcimimetic drugs are often denied by insurance post-KT leaving few options for physicians.

Methods: In this retrospective study, we identified kidney transplant recipients between 2008 and 2013 who underwent parathyroidectomy (PTx) for ThPT.

Results: We identified 26 (2.5%) patients who underwent PTx, out of 1001 patients who underwent KT at our center. Pre-surgery mean calcium and iPTH levels were 10.4 \pm 1.3 mg/dl and 508 \pm 404 pg/ml respectively. Post-KT, median time to PTx was 482 days (Q1,Q3: 225,909); 65% underwent PTx greater than one-year post-KT. PTx indications included persistent hypercalcemia despite medical therapy (62%) and worsening osteoporosis (42%). Sestamibi scan showed hyperplasia and adenoma in 50% and 34% respectively. However, surgical pathology showed hypercellular parathyroid tissue in 25/26 (96%) patients. Predictive value of the Sestamibi scan was poor (Cohen's kappa index 0.1). PTx complications included hypocalcemia (19%), transient renal failure (12%), and temporary nerve paresis (4%). There was no deleterious effect on long-term allograft function after PTx: compared with baseline values, serum creatinine was identical at 1 month (1.3 \pm 0.5 vs. 1.3 \pm 0.6, NS) and 1 year (1.3 \pm 0.8 vs. 1.3 \pm 0.6 $p = NS$). Seven patients had follow up post-surgical DEXA scans revealing an improvement in femur bone mass by 7.5%.

Conclusions: In one of the largest case series, we have shown that (a) Parathyroidectomy is required for tertiary hyperparathyroidism to treat hypercalcemia refractory to medical therapy and worsening osteoporosis (b) Sestamibi scan is inaccurate in differentiating between hyperplasia and adenoma and (c) Parathyroidectomy is well tolerated with no long-term deleterious effect on allograft function.

SA-PO001

Intra-Abdominal Hypertension and Renal Dysfunction in Pregnancy Wonggarm Kittanamongkolchai,¹ Elliott G. Richards,² Mari Charisse B. Trinidad,² Wendy White,² Vesna D. Garovic.¹ ¹*Nephrology, Mayo Clinic, Rochester, MN;* ²*Maternal Fetal Medicine, Mayo Clinic, Rochester, MN.*

Introduction: The effects of high intra-abdominal pressure(IAP) on renal function have been known for over a century. However, the diagnosis of peripartum intra-abdominal hypertension(IAH)/abdominal compartment syndrome(ACS) is challenging due to the lack of well-established normative values of IAP in pregnancy.

Case Description: A 32 year old obese primigravida with a twin pregnancy at 33 weeks gestation was admitted for intractable nausea and vomiting. She was oliguric and unresponsive to IV fluid. Her blood pressure was normal. Cr increased from a baseline of 0.5 to 0.9 mg/dL. Urinalysis was bland. A FeNa obtained after fluid resuscitation was 0.02%. Renal ultrasound showed patent renal vessels and no hydronephrosis. A diuretic was given with slight improvement in urine output. IAP measured by an intravesical catheter was 35 mmHg, and abdominal perfusion pressure(APP) (difference between mean arterial pressure and IAP) was 46 mmHg(normal > 50-60mmHg). She was suspected to have IAH/ACS and was closely monitored. 2 days later, she developed hypertension, an increase in liver transaminases, and proteinuria. The decision was made to proceed with delivery due to severe preeclampsia. IAP measured immediately after C-section decreased to 18 mmHg, and it was 7 mmHg prior to dismissal. Urine output increased to 2.5 L per day and Cr declined to 0.7 mg/dL after delivery.

Discussion: Animal and human studies indicate that oliguria and acute kidney injury are frequent consequences of IAH/ACS, and can be present at relatively low levels of IAP. In our case, the IAP of 35 mmHg was quite extreme compared to IAP of 4-28 mmHg observed in cohort studies of peripartum patients. We suspected that obesity and twin pregnancy contributed to the extreme IAH. Her APP was significantly low and restoration of renal function was readily observed after reduction of IAP. Our case may support the theory that IAH plays a role in preeclampsia, as it developed after IAH was detected. Renal dysfunction from IAH is probably underrecognized as IAP is not routinely measured. Further study is needed to elucidate the impact of IAH in pregnancy.

SA-PO002

Diabetes, Deafness and Renal Disease – A Case Report Iolanda Godinho, Joana Gameiro, Noélia Lopez Santos, Sofia C.A. Jorge, Fernando Abreu, Estela Nogueira, Maria Alice Fortes, Jose António Lopes, Patricio Aguiar, Dolores López Presa, António Gomes da costa. *Hospital Santa Maria, Lisboa, Portugal.*

Introduction: Deafness and kidney disease as well as diabetes and kidney disease are associations of which the Nephrologist is well aware. However, the concomitance of the three is not as usual, neither is a family history of these diseases.

Case Description: We present the case of a 47-year-old woman with non-nephrotic proteinuria, no haematuria, normal renal function, slowly progressive bilateral sensorineural hearing loss and recently diagnosed diabetes and maculopathy and a maternal family history of deafness, diabetes and renal disease. The patient progressed with increasing proteinuria despite antiproteinuric measures and a renal biopsy was performed, revealing Focal and Segmental Glomerulosclerosis (FSGS). Alport syndrome and Fabry disease investigation was negative. Facing the personal and maternal family history, the mitochondrial mutation m3243A>G was pursued and identified in heteroplasmy and maternally inherited diabetes and deafness (MIDD) with renal involvement as FSGS diagnosed. Renal biopsy ultrastructural study is ongoing. While waiting the etiologic investigation because of symptomatic nephrosis the patient was started on prednisolone 1mg/kg/d with no antiproteinuric response and with side effects causing her to interrupt this medication.

Discussion: Mitochondrial diseases constitute a group of rare diseases in which renal involvement is uncommon, although possible. This is the case with MIDD, in which patients present with non-insulin dependent diabetes and sensorineural hearing loss, which may be accompanied by other manifestations as cardiomyopathies or maculopathy. Renal involvement is possible, mostly as tubulointerstitial nephritis or less frequently presenting as glomerulopathy, namely FSGS. In this type of FSGS, the proteinuria is usually non-nephrotic, with scarce response to antiproteinuric measures, and slow progression to chronic kidney disease. The association of FSGS with mitochondrial diseases is not well known to the nephrologic community. Its timely diagnosis is particularly important to avoid exposure to ineffective and toxic immunosuppression.

SA-PO003

Chronic Inflammatory Demyelinating Polyneuropathy Associated with Advanced Focal Segmental Glomerular Sclerosis Albert Ndzengu,¹ Rada Petrinjac-Nneadic,² Lekha K. George,¹ Elvira Gosmanova.¹ ¹*Nephrology, UTHSC, Memphis, TN;* ²*Neurology, Tri-State Neurology, PLLC, Memphis, TN.*

Introduction: Chronic demyelinating polyneuropathy (CIDP) is rarely reported in patients with nephrotic syndrome (NS). CIDP tends to manifest concomitantly with NS. We report a case of CIDP developing at a time of focal segmental glomerular sclerosis (FSGS) progression to ESRD and mimicking uremic neuropathy.

Case Description: A 23-yo male with NS due to biopsy proven 1ry collapsing FSGS and serum creatinine (Scr) 1mg/dL was initiated on oral prednisone and lisinopril. He was lost to follow up and returned 1.5 years later complaining on burning pain and numbness in both feet for 4 weeks. Physical exam was normal except for unsteady gait, inability to perform tandem gait, decreased sensation from feet to upper legs, depressed Achilles and ankle flexor reflexes. Laboratory tests showed Scr 44mg/dL, hyperkalemia, metabolic acidosis, normocytic anemia, and normal creatinine phosphokinase. A diagnosis of ESRD

due to progression of untreated FSGS was made and dialysis was started. CT head and MRI spine were normal. Cerebrospinal fluid had protein of 74 mg/dL and 1WBC/ μ L. Electromyography (EMG) showed absent compound muscle action potential (CMAP) and F-waves in both peroneal and tibial nerves, active denervation in tibialis anterior, gastrocnemius and extensor digitorum brevis muscles, and prolonged distal latencies and motor conduction velocity with normal amplitude of CMAP on both arms. Sensory nerves action potentials on sural and peroneal nerves were absent with prolongation of peak latencies on other nerves. The constellation of clinical, EMG and normal inflammatory, infectious and autoimmune laboratory markers was consistent with diagnosis of CIDP. Plasmapheresis was performed with partial improvement of neurological symptoms and was followed by intravenous immunoglobulin infusion as a maintenance therapy.

Discussion: CIDP should be considered in patients presenting with peripheral neuropathy and history of FSGS. Correct diagnosis of CIDP is critical as untreated CIDP leads to inability to walk. Autoimmune mechanisms may be responsible for CIDP and glomerular damage in FSGS but remain to be proven.

SA-PO004

Alloimmune Membranous Nephropathy in Fabry Disease Zubin T. Lathara,¹ Josephine M. Ambroz,² Eric P. Cohen.¹ ¹*Medicine, Medical College of Wisconsin, Milwaukee, WI;* ²*Pathology, Nephropath, Little Rock, AR.*

Introduction: Use of enzyme replacement therapies may cause allo-reactivity that causes illness superimposed on the primary disease.

Case Description: A 20 year old male with Fabry disease developed proteinuria. He has the 3.1 kb alu- α deletion including exon 2. His most recent agalactosidase serum enzyme activity was low at 0.8 nmol/hour/ml (normal 6.2 to 18.6). He has chronic arthralgia and abdominal pain. He has been on treatment with agalsidase beta enzyme since age 10. His medications also include cholecalciferol, dicyclomine, and carbamazepine. He has had infusion reactions with back pain and painful diarrhea. He was premature at 32 weeks gestation. His dizygotic twin sister has no manifestations of Fabry disease. His maternal grandfather has Fabry disease and is on dialysis. On exam, his blood pressure was 127/67 mmHg. There was minimal peripheral edema. Urinalysis showed small blood, 100 mg/dl protein, 0-2 wbc, 0-2 rbc, and free fat. His serum creatinine was 0.78 mg/dl. He had 1 gram of urine protein per gram of urine creatinine. His proteinuria had ranged from 1.3 to 2.9 gram/gram over the preceding four months. Serological testing showed a negative RPR, negative tests for hepatitis B and C, and an antinuclear antibody of 1:640 titer. A kidney biopsy showed Fabry disease and superimposed membranous nephropathy. Lisinopril 2.5 mg/day was started. Rheumatological evaluation showed no evidence of lupus erythematosus. The most recent urine protein to creatinine ratio was 0.71 gram/gram, with a serum creatinine was 0.8 mg/dl.

His kidney biopsy stained positive for anti-agalsidase, but normal control kidney did not. He had anti-agalsidase antibodies in his serum that did not block agalsidase activity. Immunofluorescence for the phospholipase A2 receptor (PLA2r) was negative within the glomeruli and his serum did not have antibodies to PLA2r.

Discussion: Enzyme replacement therapies may lead to allo-reactivity. Membranous nephropathy has been described in three such patients but not in Fabry disease. Its occurrence may change the therapy of the primary disease and force specific treatment of the membranous nephropathy.

Funding: Veterans Administration Support, Clinical Revenue Support

SA-PO005

Silicone Implant Associated Acute Kidney Injury in a Male Transgender Patient Frank J. O'Brien, Brian Y. Young. *Div of Nephrology, Santa Clara Valley Medical Center, San Jose, CA.*

Introduction: Obstructive kidney disease secondary to nephrolithiasis is a well-described cause of acute kidney injury. Stone formation is often due to dietary or metabolic factors, often no predisposing factors are found. We describe a rare case of obstructive acute kidney injury associated with hypercalcemia and hypercalcemia in a 32-year-old transgender patient. Patient was found to have granulomatous disease associated with silicone implants.

Case Description: 32-year-old male to female transgender patient presented to our institution with fatigue. Routine labs showed creatinine 11 mg/dl, BUN 140 mg/dl, K 7 mmol/L. She was emergently dialyzed, and imaging showed obstructing ureteric calculi, requiring bilateral stent insertion. Patient had a history of silicone implants to hip, buttocks and thigh 5 years previous. These were inserted by a non health care professional. There was no history of calcium product ingestion or hormonal therapy use. Diagnostic work up for nephrolithiasis revealed; 24 hour urinary calcium 866 mg/24 hours, serum calcium 12.5mg/dl, ionized calcium 1.7 mmol/L. Other 24-hour urine values were normal. ACE level was 216 units/L. CXR was normal. PTH and malignancy work up was negative. CT abdomen revealed subcutaneous edema in lower back/gluteal area, around the sites of previous silicone implants, and inguinal lymphadenopathy. Subsequent gallium scan showed tracer uptake around inguinal area, buttock and hips, consistent with granulomatous activity around silicone implants. Excisional lymph node biopsy revealed foreign body type giant cells consistent with granulomatous disease. Empty vacuoles were noted within the giant cell cytoplasm consistent with silicone induced granulomas. Hypercalcemia was managed with calcitonin and intravenous fluids and definitive therapy with prednisone was commenced when diagnosis was made.

Discussion: Hypercalcemia due to silicone implant associated granulomatous disease is a rare, but important presentation. Our patient developed symptoms years after initial implant insertion. With the growing prevalence of cosmetic surgery, particularly in the transgender community, physicians need to be increasingly aware of the associated long term complications.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

SA-PO006

Isolated Diplopia Caused by Calcineurin Inhibitor Therapy in a Patient with Idiopathic Membranous Nephropathy Nader S. Bahri, Ashwani K. Gupta. *Nephrology and Hypertension, Univ of Florida, Jacksonville, FL.*

Introduction: Neurotoxicity is a common side effect of treatment with calcineurin inhibitors. Tremors are frequently reported as the most common manifestation. Variable presentations can include headaches, seizures, visual hallucinations or blindness. Sixth nerve palsy has been reported in previous cases of bone marrow and cardiac transplant patients receiving calcineurin inhibitors. In many of these previously reported cases, the drug was administered intravenously and very high drug levels were found.

Case Description: 42 year-old Caucasian female with biopsy proven idiopathic membranous nephropathy (iMGN) who was being treated with tacrolimus and prednisone for nephrotic syndrome. Her tacrolimus levels were maintained between 6-8 ng/mL. Her urine protein/creatinine ratio of 8 gm/gm was successfully reduced to less than 1 gm/gm with therapy. She continued to be in complete remission but after 3 months of therapy she presented with diplopia. The diplopia was binocular and vertical. The patient was seen for an ophthalmologic evaluation. Her visual acuity was 20/20. Pupils were equal and reactive to light and accommodation. No nystagmus was observed. Visual fields and color vision was also normal in both eyes. Assay for Acetyl-choline receptor antibody was negative. The patient remained compliant with her medications despite the side effects. At this time she was switched to low dose Cyclosporin (CyA) in anticipation that similar side effects may not be observed. Trough CyA levels were 44 ng/mL and 59 ng/mL on two occasions but her symptoms did not resolve. A consultation with neuro-ophthalmology was sought and the patient was instructed to discontinue CyA. The symptoms completely resolved 4 days after stopping CyA.

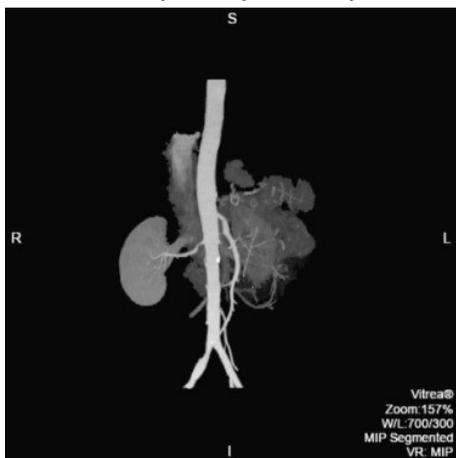
Discussion: This is the first reported case of isolated diplopia secondary to calcineurin inhibitors in low doses for treatment of iMGN. Monitoring of serum concentrations of these drugs has not been correlated with toxicity. The mean duration to onset of symptoms can be as much as 70 days suggesting accumulation of the drug in the central nervous system plays a role. Recognition of this condition is important for prompt diagnosis and appropriate management.

SA-PO007

Bilateral Renal Artery Stenosis in a Patient Treated with Nilotinib for Chronic Myeloid Leukemia Omar M. Shahateet, Milos N. Budisavljevic. *Medical Univ of South Carolina.*

Introduction: The use of tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 oncoprotein has been successful in chronic myeloid leukemia (CML). Nilotinib is a second generation TKI designed and used to overcome deficiencies of imatinib such as resistance or intolerance. Nilotinib also received approval in chronic phase (CP)-CML for superior response rate and less progression to blast crisis compared to imatinib. Reports suggest peripheral artery disease (PAD) as an adverse drug reaction associated with the use of nilotinib. We describe a case of bilateral renal artery stenosis in a patient treated with nilotinib.

Case Description: A 45 year old Caucasian male diagnosed with BCR-ABL positive CML at age 31. He was treated with Hydreia followed by Gleevec and was in complete remission (CR) for 4 years when he developed ALL transformation necessitating chemotherapy and peripheral blood stem cell transplantation. He was in CR for 5 years being maintained on dasatinib which was switched to nilotinib due to intolerance from GI upset. He developed worsening creatinine and high blood pressure after being on nilotinib for 2 years. His blood pressure was 170/90, heart rate of 64/min. The remainder of his physical exam was unremarkable for cardiovascular, pulmonary or abdominal findings, including bruits. Creatinine 2.7mg/dl. CT angiogram revealed 70% stenosis of the right and occlusion of the left renal artery with atrophic left kidney.



Discussion: Renal artery stenosis (RAS) is common in elderly patients. RAS due to fibromuscular dysplasia in the renal artery is most commonly observed in younger women. Recent data suggest that nilotinib bind to discoidin domain receptor 1 (DDR1) which has been implicated in plaque formation in atherosclerosis. Nilotinib blocks the receptor kinase KIT which regulates histamine and heparine release. This depresses vascular repair system and predisposes to arterostenotic events.

SA-PO008

A Case of Minimal Change Disease After the Administration of Anti RANKL Monoclonal Antibody Keisuke Horikoshi, Norihiko Sakai, Yasuyuki Shinozaki, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Miho Shimizu, Kengo Furuichi, Takashi Wada. *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.*

Introduction: Receptor activator of nuclear factor kappa B (RANK)-RANK ligand (RANKL) has emerged as an important regulator of bone mineral density and microarchitecture. In addition to that, recent study has revealed that RANK-RANKL may contribute to the podocyte survival signal after its injury. Here we report a case that RANKL inhibition might contribute to the onset of nephrotic syndrome.

Case Description: A 59-year-old male without any episodes of proteinuria was given denosumab, a fully human monoclonal antibody to RANKL to treat osteoporosis. Two weeks after its administration, he showed bilateral pretibial edema. Laboratory tests revealed that he had microscopic hematuria, severe proteinuria (15g/gCr), hypoproteinemia (4.0g/dL) and hypoalbuminemia (1.5g/dL). The proteinuria selectivity index was below 0.1, indicating that he had selective proteinuria. Based on the results, he was diagnosed to have nephrotic syndrome. Renal biopsy showed minor glomerular abnormality with less tubulointerstitial damage, indicating minimal change disease (MCD). Taken altogether, glucocorticoid therapy of prednisolone 50 mg/day had started. After four weeks of treatment, the level of urinary protein was still high (4.1g/gCr), but it decreased gradually to the range of partial remission (1.2g/gCr) with another 8 weeks treatment of prednisolone.

Discussion: This may be a rare case to report the association of RANKL inhibition with MCD. The responsiveness to glucocorticoid therapy was not good enough to promptly induce complete remission, suggesting that podocyte injury due to RANKL inhibition could be responsible at least in part for MCD in this case.

SA-PO009

Eculizumab in Management of Thrombotic Lesions in Kidney Allograft of Patient with Anti-Phospholipid Syndrome Anju Yadav, Ravi Sunderkrishnan, Andres Rodrigo Caero. *Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.*

Introduction: Thrombotic microangiopathy (TMA) is one of the hallmark vascular lesions of anti-phospholipid syndrome (APLS). These lesions are at high risk of recurrence after kidney transplantation. The complement pathway is thought to be active in this process by deposition and by presence of apoptotic and vascular cell markers on sequential transplant biopsies. Eculizumab is a humanized anti-C5 monoclonal antibody which has been used in atypical hemolytic uremic syndrome. Recently, there have been reports of use of Eculizumab in transplant patients with APLS/TMA.

Case Description: We present a case of a 58 year old Caucasian man with history of systemic lupus erythematosus, APLS on warfarin, hypertension, rheumatoid arthritis, transient ischemic attack, coronary artery disease with triple vessel bypass, chronic kidney disease stage 5 for which he received pre-emptive living unrelated kidney transplant. After an uneventful post-transplant course, he was discharged on warfarin. He presented to the hospital 4 days later, with acute renal failure, pain over the graft and sub-therapeutic INR. A perinephric collection was drained. Cytomegalovirus and BK polyoma viremia were ruled out. Transplant kidney biopsy, revealed TMA with segmental necrosis and small vessel fibrin thrombi and no acute rejection. High dose steroids along with aggressive anticoagulation were started. He received two sessions of plasmapheresis. After meningococcal meningitis immunization, Eculizumab 900mg/week was started. After 4 doses, Eculizumab was changed to 1200mg/two weeks. Creatinine trended down from 7.3 to 3.0 mg/dl and dialysis was stopped after 7 sessions. He was positive for IgG anticardiolipin, beta-2 glycoprotein, and lupus anticoagulant and was started on daily aspirin and warfarin with INR goal of 2.5-3.5.

Discussion: Treatment with Eculizumab and plasmapheresis resulted in a relatively rapid and dramatic improvement of graft function in our patient and should be considered in difficult to manage TMA/APLS in transplant patients. Its use permits a safer approach of controlling the complement final common pathway.

SA-PO010

Transient Gestational Diabetes Insipidus in a Patient with Pre-Eclampsia Anju Yadav, Ravi Sunderkrishnan, Andres Rodrigo Caero. *Dept of Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.*

Introduction: Diabetes insipidus (DI) is manifestation of post pituitary insufficiency characterized by polyuria and hypotonic urine. DI can be neurophysic, nephrogenic, polydipsia related or gestational (GDI). L-deamino-8-d-arginine- vasopressin (DDAVP) is a vasopressin analogue which had higher and prolonged anti-diuretic activity with no effects on smooth muscle. An increase in urine osmolality by at least 50% following administration of DDAVP is diagnostic of disorder.

Case Description: We present a case of 22-year-old African American primigravida woman with no past medical history, in 32nd week of pregnancy, admitted with pre-eclampsia with no liver injury. On admission, blood pressures were between 140-165/60-79mmHg. After an uneventful delivery she had urine output ranging 6-9 liters along with polydipsia. Both of these were present all through out her third trimester. On exam there was no evidence of volume overload or dehydration. Labs were sodium 137mEq/L, Potassium 2.8mEq/L, Alb 3.0mg/dl, TSH 4.16, urea nitrogen <0.3, creatinine 0.4, serum osmolality 284, urine osmolality 141, tsp urine protein creatinine ratio of 0.8. With one dose of sub-cutaneous DDAVP increased urine osmolality to 385 within 24hrs. Oral DDAVP

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

doses were titrated based on clinical response and labs. Hypokalemia was managed with oral repletion and resolved later. On discharge urine osmolality increased up to 523 with 2 liters urine output and no excessive thirst.

Discussion: GDI is attributed to decreased thirst threshold, secretion of vasopressinase from placental cells (cystine amino-peptidase) along with reduced vasopressin secretory capacity, increased degradation of vasopressin by placenta derived vasopressinase, decreased responsiveness to vasopressin by physiologically increased prostaglandin E2 activity in kidney and polyuria with hypokalemia renders collecting ducts resistant to vasopressin. Subclinical DI can manifest itself under the influence of physiological pregnancy changes. DDAVP is the only treatment, as it is not degraded by vasopressinase. Timely diagnosis with high index of suspicion can help with appropriate management and shorter length of stay.

SA-PO011

A Case Report of Baclofen Toxicity in a Hemodialysis Patient Sweta Carpenter, Sandeep Aggarwal. *Nephrology and Hypertension, Drexel Univ.*

Introduction: The dangers of baclofen toxicity in patients with advanced kidney disease and in particular patients on dialysis remain underappreciated by many physicians.

Case Description: We present a case of a 64 year old male who developed an uncommon case of altered mental status during his hospitalization. His medical history included ESRD for which he was receiving in-center hemodialysis, diabetes and hypertension. He initially presented to the hospital with complaints of shortness of breath and hiccups. His shortness of breath was attributed to volume overload and resolved with two consecutive days of dialysis with fluid removal. For his intractable hiccups, he was started on baclofen. During his hospitalization, he became lethargic and was unable to move his lower extremities. Laboratory data including serum sodium, potassium, glucose, calcium, BUN, phosphorus, liver transaminases, thyroid function tests, troponins, infectious work up and ammonia levels were unremarkable. Neuroimaging, including CT head and brain MRI, were unchanged from previous studies and revealed moderate diffuse cerebral atrophy. An EEG was also performed and did not suggest signs of epileptic activity. Further investigation revealed that he had received a total of 20 mg of baclofen over 2 days. After other etiologies were ruled out, we determined that he may have suffered from baclofen induced encephalopathy. His baclofen was stopped and he was prescribed daily sessions of hemodialysis for three days with the intent of clearing baclofen. He was dialyzed for 4 hours during each dialysis session with a high flux dialyzer. After his first session of dialysis, the patient was more alert and would follow simple commands. At 3 days, the patient's mental status returned to baseline and he was able to move his extremities.

Discussion: Although the kinetics of baclofen elimination during hemodialysis are not well understood, this case demonstrates the resolution of baclofen induced encephalopathy with frequent and consecutive dialysis. Furthermore, we hope this case raises awareness among physicians of the toxic effects that baclofen can cause in dialysis patients.

SA-PO012

Utility of Hemodialysis in Urea Cycle Disorders Chintan Shah, Zeinab M. Tamam, Inder Patel, Yahya M. Osman Malik, Nashat Burhan Imran. *Wayne State Univ.*

Introduction: Urea cycle disorders (UCDs) are rare pediatric diseases but partial enzyme deficiency can persist throughout adulthood. Little has been published about the role of hemodialysis in addressing the acute complications of UCDs in adulthood. Catabolic states are well known trigger factors for the life-threatening acute hyperammonemia.

Case Description: We are reporting a 32-year old male patient with history of partial ornithine transcarbamylase deficiency diagnosed at age of 6 months. He presented with altered mental status due to acute hyperammonemia (108mcg/dl). He was treated with a pre-specified protocol (infusion of Na Phenylacetate/benzoate and Arginine HCl, fasting for 36 hours along with intravenous administration of lipids and glucose followed by protein restricted diet of 35 grams per day and Na phenyl butyrate & L-citrulline). This decreased Ammonia level to 34mcg/dl. Later, patient underwent a procedure and was kept NPO without intravenous calorie supplements and developed fever. Due to both of these catabolic states, he developed a second acute hyperammonemia (270mcg/dl). He was treated with the same protocol which was successful initially but due to worsening infection his ammonia continued to worsen regardless of the treatment (258mcg/dl) and developed tonic clonic seizure requiring intubation and mechanical ventilation. He was promptly started on a 7.5-hour hemodialysis session followed by a 5-hour session in following day. He was kept on CVVHD during the second night. Ammonia level decreased to 0 mcg/dl and patient regained consciousness.

Discussion: Partial Ornithine transcarbamylase deficiency is a very rare disorder among adults and its complications can be life-threatening like cerebral edema and herniation. Prompt dialysis is indicated as an emergency treatment or after failure of medical management to prevent such complications. Given the molecular characteristics of ammonia, prolonged (>5hours) hemodialysis sessions are more effective. Subsequent continuous modalities might be required as a maintenance to prevent the potential rebound elevation. Discontinuation of dialysis is a clinical judgment after considering resolution of both the life-threatening condition and the catabolic event.

SA-PO013

Treatment of Atypical Hemolytic Uremic Syndrome Early in Pregnancy with Eculizumab Rahul N. Pawar,¹ Savneek S. Chugh,¹ Amy R. Patel,¹ Prachi Kale,² ¹Nephrology, Westchester Medical Center, New York; ²Internal Medicine, Westchester Medical Center.

Introduction: Atypical Hemolytic Uremic syndrome (aHUS) is known to cause acute thrombotic microangiopathy (TMA) in pregnancy with adverse maternal and fetal outcomes. A French study showed that aHUS usually occurs postpartum when activity of placental related complement regulatory proteins decreases. We present a case of a young lady early in pregnancy with severe thrombocytopenia and acute renal failure suspicious for TTP, but later diagnosed with aHUS, which improved with eculizumab.

A 30 year old G11P5A5L5 10 weeks pregnant with a past medical history of 5 first trimester miscarriages presents with nausea, vomiting and watery diarrhea whose labs show a hemoglobin (Hgb) 7.8 g/dL, platelet (PLT) count 15K/uL, BUN 65 mg/dL, and serum creatinine 2.44 mg/dL along with a LDH of 1,847 U/L, haptoglobin <8 mg/dL, and albumin 3.2 g/dL. Liver function tests (LFTs) and coagulation studies were normal. She was suspected to have TTP and transferred to our tertiary medical center. Urinalysis revealed 3+ protein and 3+ blood. Blood smear showed schistocytes. A diagnosis of TMA was made and plasmapheresis was started. Serologies for lupus and anti-phospholipid antibody syndrome were negative and LFTs remained normal, ruling out HELL.P. The ADAMTS-13 activity level was noted to be 129%. Renal function declined requiring the initiation of hemodialysis(HD). On the basis of ongoing hemolytic anemia with thrombocytopenia, renal failure and a negative ADAMTS-13, she was started on Eculizumab. After 2 doses, her renal function and urine output improved and HD was stopped. At discharge, her Hgb was 8.5 g/dL, PLT 150 K/uL, and BUN/creatinine 23/1.84 with the plan to receive monthly eculizumab infusions.

Discussion: aHUS is caused by activation of the complement system due a genetic deficiency of its regulatory proteins, specifically complement factor H, factor I, and/or membrane cofactor protein. It can lead to TMA causing multi-organ failure and the potential for death if not managed in time. Pregnancy can cause aHUS in any trimester. One should maintain a low suspicion for aHUS in a pregnant patient with prompt initiation of eculizumab to prevent negative outcomes.

SA-PO014

I've Got a Fever and the Only Prescription Is More Colchicine: Familial Mediterranean Fever Related Pauci-Immune Glomerulonephritis Ashvin Baru, Anam Khan, Celia A. Peña, Rajeev Raghavan. *Nephrology, Baylor College of Medicine, Houston, TX.*

Introduction: Relatively few renal manifestations have been detected in Familial Mediterranean Fever (FMF). We present a case of biopsy proven pauci-immune glomerulonephritis (GN) in a patient with clinically diagnosed FMF and review past treatments of pauci-immune GN in FMF patients.

Case Description: We present an interesting case of a 22 year old man who had suffered for nearly seven years a constellation of symptoms including fever, nausea, vomiting, abdominal pain, arthralgias, chest pain, and an erythematous rash consistent with a clinical diagnosis of Familial Mediterranean Fever. He had a normal serum creatinine of 1.0 mg/dL which peaked at 2.0 mg/dL. Repeated urinalysis indicated 6-10 RBCs per high powered field (phf) and 6-21 WBCs phf. Laboratory testing revealed only an elevated C-reactive protein. A kidney biopsy was performed which revealed 41% of the total glomeruli globally sclerosed and 54 % of the viable glomeruli with active crescents and 25% interstitial fibrosis with tubular atrophy. Immunofluorescence revealed minimal C3 staining. This was consistent with Pauci-Immune Glomerulonephritis or ANCA negative GN. He was treated with Colchicine, pulse steroids, and maintained with mycophenolate mofetil as detection for mutations in the MEFV gene in the diagnosis of FMF is ongoing. He has had no relapse of his FMF with initiation of colchicine and now has had resolution of his hematuria, proteinuria, and acute kidney injury.

Discussion: In the literature, there is minimal knowledge about the renal manifestations of Familial Mediterranean Fever and fewer documented reports on the treatment protocols for ANCA negative vasculitis in FMF. We were able to treat ANCA negative vasculitis in a patient with FMF with only pulse steroids and maintenance immunosuppression with mycophenolate mofetil with great response.

SA-PO015

Stress of Surgery – Is It Just Mental or Can It Be Renal as Well? Mitul Natu Patel, Maria M. Picken, Kavitha Vellanki. *Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Introduction: Waldenstrom's macroglobulinemia (WM) is a rare clinicopathological disorder with a reported annual incidence of 3 per million people. It is characterized by Ig M monoclonal gammopathy in the blood and lymphoplasmacytic lymphoma in the bone marrow. Clinical manifestations are non-specific and generally related to Ig M infiltration of hematopoietic tissues. While deposits of Ig M in the glomerular basement membrane may be seen, renal failure per se is unusual. Here, we present a unique case of recurrent episodes of acute kidney injury (AKI) post-operatively in a patient with underlying WM with spontaneous recovery each time.

Case Description: 75 year old woman with WM, hypertension, obstructive sleep apnea and paroxysmal atrial fibrillation presented for an elective surgery for lumbar stenosis to our center. Her post-operative course was fairly uncomplicated and she was transferred to rehabilitation floor on day 3. She had gradual worsening of lower extremity swelling and shortness of breath and repeat labs showed a serum creatinine of 3.32 mg/dl (0.94

mg/dl, 5 days prior) and renal service was consulted for AKI. She had a prior episode of AKI with knee replacement in 2008, dialysis dependent for 33 days with subsequent spontaneous recovery. Further work up revealed fairly active urine sediment with new onset 24 hour urine protein of 3.3 grams. C3 was normal, C4 < 5 mg/dl, cryoglobulin was positive, rheumatoid factor of < 20 ug/dl, serum Ig M were elevated at 646 mg/dl (normal 46-304 mg/dl) and serum immunofixation showed an abnormal restricted band between the beta and gamma regions. Kidney biopsy showed strongly PAS positive hyaline-like precipitates in the glomerular capillaries with immunofluorescence strongly positive (3+) for IgM and lambda light chains. There were abundant, confluent electron dense deposits in the mesangium and subendothelial space. Her symptoms improved with diuresis and she refused any other major intervention. Renal function eventually improved with serum creatinine of 1.2 mg/dl at the time of discharge.

Discussion: In conclusion, we believe the stress of surgery precipitated intraglomerular deposition of Ig M leading to AKI with spontaneous resolution thereafter.

SA-PO016

New Causes of Secondary Hyperparathyroidism: Unforeseen Effects of New Drugs on the PTH-Calcium Axis Muthanna M. Saraireh, Harold M. Szerlip. *Nephrology, Baylor Univ Medical Center, Dallas, TX.*

Introduction: Calcium homeostasis is a function of the interplay between GI absorption, renal excretion and bone resorption. Although numerous effectors control these processes, PTH is primarily responsible. PTH affects the kidney and bone through PTH receptor 1. In the kidney PTH decreases phosphorus reabsorption, increases calcium reabsorption and stimulates 1-hydroxylation of vitamin D. In the bone PTH up-regulates expression of RANKL and decreases expression of osteoprotegerin. This process increases RANKL binding to RANK on osteoclast precursors stimulating them to become osteoclasts that increase bone resorption. New drugs that inhibit RANK are used to treat osteoporosis and bone metastases. We describe two patients treated with recently developed chemotherapeutic agents who developed severe hypocalcemia, and secondary hyperparathyroidism with hypophosphatemia due to renal PO4 wasting. We hypothesize that these drugs inhibit RANK.

Case Description: Case 1: A 72 y/o woman with metastatic leiomyosarcoma received Trabectedin, an experimental agent which interacts with DNA. She subsequently complained of weakness. Labs are shown. **Case 2:** A 73 y/o man with ALL positive for BCR-ABL was started on the tyrosine kinase inhibitor Dasatinib. He subsequently developed the laboratory abnormalities shown.

	Ionized calcium	Pi	Urine Ca	FePi	25-Vit D	1,25-Vit D	PTH
patient 1	0.84 mmol/L	0.9 mg/dl	< 5 mg/dl	44%	33 ng/ml	110 pg/ml	832 pg/ml
patient 2	0.95 mmol/L	1.3 mg/dl	< 5 mg/dl	46%	32 ng/ml	101 pg/ml	509 pg/ml

Creatinine was 0.7 mg/dl in patient 1 and 0.8 mg/dl in patient 2

Discussion: Both patients developed secondary hyperparathyroidism. The renal effects of PTH appeared to be intact with increased calcium resorption, phosphorus excretion and hydroxylation of 25-Vitamin D. The effects of PTH on bone resorption, however, appeared blunted. Because PTH acts on both kidney and bone through the same receptor, we believe that this represents a post receptor phenomena involving the RANKL/osteoprotegerin system. The tyrosine kinase inhibitor, Imatinib, has been shown to decrease bone resorption through a similar mechanism. As new drugs are developed it is important to recognize potential untoward effects.

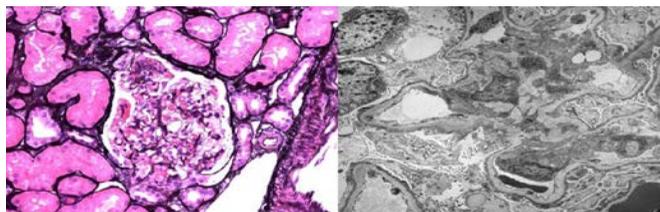
Funding: Clinical Revenue Support

SA-PO017

Connection or Coincidence: Behçet’s Disease and Focal Segmental Glomerulosclerosis with Nephrotic Syndrome Deanne Leonard, Cherise M. Cortese, Xochiquetzal J. Geiger, Nabeel Aslam. *Mayo Clinic, Jacksonville, FL.*

Introduction: Behçet’s Disease (BD) often presents with aphthous and genital ulcers, uveitis, and erythema nodosum. Rarely, renal amyloidosis, IgA nephropathy and crescentic glomerulonephritis result. Here we present a case of nephrotic syndrome from focal segmental glomerulosclerosis (FSGS) in a patient with BD with evidence to suggest a direct connection.

Case Description: 49 y/o female with history of hypertension and BD on etanercept, colchicine and carvedilol. Following a recent prednisone taper, she developed oral ulcers, uveitis, pathergy reaction and proteinuria. Physical exam: Blood pressure: 170/90, aphthous ulcer, uveitis, and 3+ bilateral leg edema. Laboratory data: serum albumin 3.3 g/dL, total cholesterol 282mg/dL, serum creatinine 1.1 mg/dL. Urinalysis: 3+ proteinuria, 10 RBC/hpf and a random protein:creatinine ratio of 8.5. Normal complement levels, DS-DNA, SS-A, SS-B, Sm Ab, RNP Ab, Scl 70 ab, and Jo Ab. Renal biopsy: Light microscopy: focal segmental lesions. Immunofluorescence: IgM trace mesangial granular staining, consistent with immunoglobulin trapping. IgG, IgA, C3, C1q, kappa, and lambda: negative. Electron microscopy: near total visceral epithelial cell foot process effacement with villous formation.



Treatment included losartan and prednisone 1 mg/kg/day which resulted in resolution of edema and reduction of protein to creatinine ratio to 0.14 along with resolution of oral ulcers and uveitis.

Discussion: At present, there is no proven correlation between BD and FSGS with nephrotic syndrome. Our patient presented with BD flare coinciding with the development of nephrotic syndrome both of which improved simultaneously with steroids suggesting a direct connection. Therefore, the clinician should be aware of this possible link and screen accordingly for proteinuria both qualitatively and quantitatively to detect early renal involvement in patients with BD.

SA-PO018

Reversal of Dialysis-Dependent Renal Failure and Nephrotic Syndrome after Conservative Therapy in an Adult with Proliferative Glomerulonephritis with C3-Dominant Deposition Eriko Takehara,¹ Shintaro Mandai,² Shinichi Uchida.² ¹*Dept of Nephrology, Shuuwa General Hospital, Saitama, Japan;* ²*Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.*

Introduction: C3 glomerulonephritis (C3GN) is a recently described entity in a reclassification of membranoproliferative glomerulonephritis, characterized by isolated or predominant glomerular C3 deposits. Although abnormalities in the alternative pathway are known to be involved in the pathogenesis, efficient therapeutic approaches have yet to be established.

Case Description: In December 2012, a 55 year-old man was admitted with rapidly progressive glomerulonephritis and nephrotic syndrome. In May 2011, his serum creatinine (SCR) was 0.63mg/dl. Seven weeks previously, he was admitted to another hospital with hemorrhagic gastric ulcer accompanied by renal failure (SCR 4.61 mg/dL, urinary protein 15 g/gCr, and moderate hematuria), in the absence of preceding infection. At admission to our hospital, SCR increased to 7.60 mg/dL. ANCA, anti-nuclear antibody, and decrease in complement factors were absent. A renal biopsy specimen showed crescentic and endocapillary proliferative GN with dominant C3 and trace IgG. Conservative therapy was started, given the repeated hemorrhagic ulcer, and decreased rate of renal function decline. Hemodialysis was initiated on hospital day 20 because of oliguria, but was ceased on day 60 with recovery of kidney function. SCR decreased to 1.2 mg/dL, and urinary protein decreased to <1 g/gCr. One year after discharge, he developed nephrotic-range proteinuria, and the second renal biopsy revealed the increased sclerotic glomeruli and fibrous crescents with isolated C3 deposits.

Discussion: To our knowledge, this report is the first to describe reversal of dialysis-dependent renal failure after conservative therapy in a C3GN patient. Similarly to the present case, the histological morphology and clinical presentation infrequently mimic the picture of postinfectious GN, although the transient recovery is usually partial. A novel classification of such cases among C3GN may be needed to avoid an unbeneficial immunosuppression.

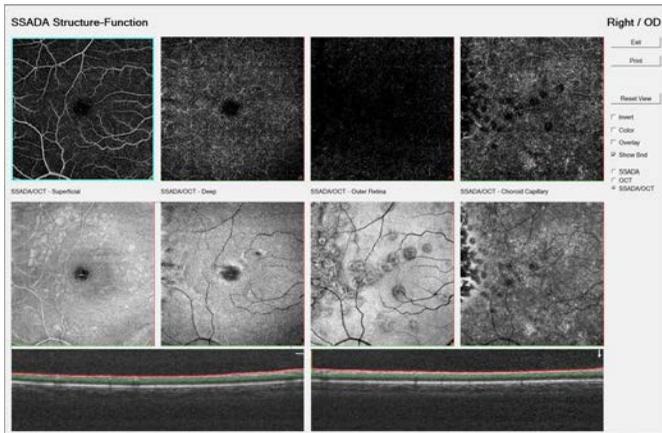
SA-PO019

Optical Coherence Tomography and En Face Retinal Findings in Membranoproliferative Glomerulonephritis Type 2 Paula Delegrago Borba, João Rafael De oliveira dias, Eduardo Amorim Novais, Andre Romano, Gianna Mastroianni-kirsztajn, Rubens Belfort De mattos. *Ophthalmology and Visual Sciences Dept, Univ Federal de Sao Paulo - UNIFESP, Sao Paulo, Brazil; Nephrology Dept, Univ Federal de Sao Paulo - UNIFESP, Sao Paulo, Brazil.*

Introduction: Membranoproliferative glomerulonephritis type 2 (MPGN II) is a condition with electron dense deposits in the glomerule basal membrane that usually affects youngsters of 5-15 years old. Patients may have asymptomatic retinal drusen-like deposits but 10% of cases may have choroidal neovascularization that leads to visual loss. We evaluated patients with a high-speed spectral-domain optical coherence tomography (SD-OCT) device and en face OCT imaging of the retina.

Case Description: Four eyes of 2 patients with MPGN II were scanned using a high-speed 840-nm-wavelength SD-OCT (RTVue XR Avanti; Optovue, Inc, Fremont, USA). The split-spectrum amplitude-decorrelation angiography algorithm was used to detect blood flow. Fluorescein angiography (FA) (HRA System, Heidelberg Engineering) images were obtained in search for drusen-like deposits in the Bruch membrane or choroidal neovascularization.

Both patients (female, 34 years old and male, 25 years old) had best corrected visual acuity of 20/20 in both eyes, unremarkable anterior biomicroscopy, RPE mobilization and macular drusen-like deposits. There was no choroidal neovascularization at the FA. En face OCT showed hyperreflective dots with a hyperreflective ring at the RPE that corresponds to drusen-like deposits underneath the RPE and dilated choroidal image.



Discussion: MPGN II may cause drusen and choroidal neovascularization. Eye examination is useful to diagnose visually threatening complications. The newer high-speed spectral-domain optical coherence tomography instrument may define the precise location of the drusen-like deposits when using En face OCT.

SA-PO020

Severe Hyponatremia following the Treatment of Pulmonary Strongyloides Stercoralis Infection Renu Regunathan-Shenk, Woojin Ahn, Sumit Mohan. *Nephrology, New York Presbyterian-Columbia Univ Medical Center, New York, NY.*

Introduction: Strongyloides stercoralis is a soil transmitted nematode which can cause serious infection in immunocompromised patients through skin penetration. The helminth can cause abdominal and pulmonary symptoms and can continue to autoinfect patients if untreated. It has been infrequently reported to cause hyponatremia which resolves with treatment of the infection.

Case Description: A 59-year-old Dominican man with a history of single lung transplant and chronic abdominal pain was admitted for treatment of pulmonary strongyloides infection found on routine outpatient bronchoscopy. On admission he was found to have an E. Coli bacteremia which was attributed to gastrointestinal translocation. The patient was started on ivermectin (15 mg/day orally) and piperacillin tazobactam (4.5 grams every 8 hours intravenously in 5% dextrose solution). He developed a rapid decline in his serum sodium concentration from 135 mmol/L prior to admission to 109 mmol/L on hospital day 5. Physical exam at this time was notable for euvolemic appearance, lethargy, and inattention. Laboratory evaluation confirmed a hypo-osmolar hyponatremia with elevated urine osmolality (576mOsm/kg) consistent with Syndrome of Inappropriate ADH Secretion (SIADH). Thyroid studies and cerebral fluid studies were unremarkable. He was treated with hypertonic saline and desmopressin until he achieved normonatremia. He has been continued on weekly ivermectin treatment, daily salt tablets, and furosemide tablets.

Discussion: Strongyloides stercoralis induced SIADH in an under-recognized cause of euvolemic hyponatremia, especially in patients who have traveled to endemic areas or who are immunocompromised. Prior case reports have shown resolution of hyponatremia with strongyloides treatment, however we present a patient who worsened after bronchoscopy and initiation of ivermectin. We propose that this may have occurred due to increased systemic parasite exposure after the bronchoscopy procedure.

SA-PO021

A Case of Disseminated HSV Infection in PD Patient with Bullous Pemphigoid Yujiro Machida,¹ Kentaro Fujii,¹ Ayumi Yoshifuji,¹ Naoki Washida,¹ Hirobumi Tokuyama,¹ Matsuhiko Hayashi,² Shu Wakino,¹ Hiroshi Itoh.¹ ¹Dept of Internal Medicine, Keio Univ School of Medicine, Tokyo, Japan; ²Apherisis and Dialysis Center, Keio Univ School of Medicine, Tokyo, Japan.

Introduction: Patients with end stage renal disease (ESRD) are affected by various infections with high mortality because of the immunodeficiency. We report a rare case of disseminated Herpes simplex virus (HSV) infection in peritoneal dialysis (PD) patient, who was treated with high-dose steroid for bullous pemphigoid (BP).

Case Description: A 72-year-old man under the treatment with PD for 2 months for ESRD caused by nephrosclerosis was admitted to our hospital because of blisters and ulceration on his whole body for two weeks. He had had BP and been treated with 60 mg of prednisolone. Twenty-nine days after the admission, peritoneal fluid became yellowish-brown and peritonitis was suspected from the elevation of inflammatory markers. Though the cell count of peritoneal fluid was within the normal range, multinuclear, frosted glass-formed cells were detected in PD fluid, which indicated HSV pritonitis. Serum HSV-DNA elevated to 6x10⁵ copies and he was diagnosed as disseminated HSV infection. After 200 mg of Acyclovir daily was administered, he had a severe disturbance of consciousness. Although differential diagnosis between acyclovir encephalopathy and HSV encephalitis was difficult, the results of spinal fluid tap and head MRI concluded acyclovir encephalopathy. Introduction of hemodialysis recovered his consciousness. HSV-DNA was decreased, although he developed multiple complications of hemophagocytic syndrome, bacterial infection and invasive pulmonary aspergillus, and died 56 days after hospitalization.

Discussion: We experienced a rare case of disseminated HSV infection and PD-related HSV peritonitis. The combination of immunodeficient factors of ESRD, high-dose steroid and BP contributed to the severe immune-compromised state and disseminated HSV infection. Since an early diagnosis determines the prognosis of disseminated HSV infection, cell pathology in peritoneal fluid would assist preemptive therapy.

SA-PO022

Use of Rituximab in Goodpasture's Disease with Pulmonary Hemorrhage Scherly Leon, Vadim Abramov, Farouk Talakshi, Mary C. Mallappallil, Moro O. Salifu. *Medicine, Renal Div, Downstate Medical Center, Brooklyn, NY.*

Introduction: Goodpasture's syndrome (GPS) or anti-GBM disease is a rare autoimmune disease, where pathogenic autoantibodies deposit in the basement membrane. It presents with rapidly progressive glomerulonephritis, with or without pulmonary hemorrhage. The current standard treatment of Anti-GBM disease is immunosuppression to reduce antibody production and plasmapheresis to remove existing antibodies in circulation. Rituximab, a monoclonal antibody directed against CD-20 antigen present on B-lymphocytes, approved for various B-cell lymphoproliferative diseases has been used in ANCA associated vasculitis with success; however it's use in anti-GBM disease is scarce and data regarding safety and efficacy is lacking. We report use of Rituximab in the treatment of GPS with pulmonary hemorrhage.

Case Description: A 35 year-old man presented in 2012 with two week history of nausea, vomiting, intermittent fevers and dark urine. Laboratory findings were creatinine 18 mg/dl, potassium 6.1 mmol/L, Hgb 11.6 g/dL, and platelet count 288 x 10³ per µL. Urinalysis showed nephritic urine sediment. Serology test including ANCA was negative. Anti-GBM antibodies levels were greater than 8 with peak 27. CT chest with pulmonary hemorrhage. He was given pulse dose steroids and initiated on dialysis. Renal biopsy was consistent with GPS (crescentic GN linear anti-GBM on IF). Plasmapheresis was initiated and patient received four doses of Rituximab. Anti-GBM level on discharge from hospital was 2.9. Since initial presentation, patient had two admissions to the hospital in 2014 and 2015 with undetectable Anti-GBM levels.

Discussion: Patients with anti-GBM renal disease have high mortality, especially when pulmonary involvement is present. The use of steroid, immunosuppressives and plasmapheresis alone or in combination has led to a significant improvement of both patient survival and clinical symptoms. Anti-GBM disease is a rare fulminant disease, data regarding the safety and efficacy of alternative therapies are lacking. There are few reported cases of anti-GBM disease treated with rituximab. We present a case of anti-GBM disease with pulmonary hemorrhage successfully treated with Rituximab.

SA-PO023

A Rare Case of Aluminum Toxicity Khurram Saleem, Khaled Boobes, Yazan M. Alia, Muhammad H. Hasan, Jennifer A. Tuazon. *Nephrology, Northwestern Memorial Hospital, Chicago, IL.*

Introduction: Aluminum toxicity was initially described in encephalopathic patients with renal failure, overdosing of aluminum-based phosphate binders and attributed to contamination of water used for dialysis treatments. Use of alum irrigation for the treatment of refractory hemorrhagic cystitis was first reported in 1982. It was described as a safer alternative to formalin bladder irrigation. We report a case of bladder perforation after alum irrigation, leading to intra-peritoneal aluminum exposure. Our patient expired despite chelation and renal replacement therapy. Her serum aluminum concentration is the highest reported level to date.

Case Description: 67 year old female with cervical cancer, admitted for uresepsis, was noted to have hematuria and urinary retention. Her catheter was changed due to clot obstruction and bladder irrigated with saline. Following day continuous bladder irrigation was instituted for persistent hematuria. She underwent cystoscopy with fulguration for persistent hematuria secondary to radiation cystitis. Her CBI resumed with alum irrigant. Overnight, alum irrigant was placed on a pump for infusion. Hours later, patient transferred to ICU for hypotension. CT abdomen revealed free intraperitoneal air, large volume of new fluid, air around bladder suspicious for bladder perforation, and absence of contrast outside of the bowel. Bilateral percutaneous nephrostomy performed for urinary diversion and to evacuate free fluid. Aluminum levels were drawn. Patient was intubated, placed on vasopressors. Had non-gap metabolic acidosis and worsening renal function, concerning for aluminum toxicity due to intra-abdominal bladder perforation in the setting of alum irrigation. Deferoxamine was started and CVVH for acidosis. However patient developed refractory shock, and expired. Shortly before her death, aluminum level resulted 163.7mcg/L (normal 0 to 20mcg/L). Subsequent levels peaked at 1455.2mcg/L.

Discussion: We report systemic absorption of alum-containing irrigant following bladder perforation. Large aluminum load to the peritoneum resulted in systemic toxicity, multi-organ failure and death. Chelation therapy and CVVH were inadequate. We report the highest serum aluminum level to date.

SA-PO024

Primary Glioblastoma Multiforme in a Renal Transplant Patient Hermes Garcia-Sanchez, Arshad Ali, Stephen O. Pastan. *Nephrology, Emory Univ, Atlanta, GA.*

Introduction: Glioblastoma multiforme is the most common and most aggressive malignant primary Brain tumor in humans, involving glial cells and accounting for 52% of all functional tissue brain tumor cases and 20% of all intracranial tumors. Incidence of 2-3 cases per 100,000. The principal neoplasm involving the CNS of transplant recipients is non-Hodgkin lymphoma while glial tumours are rarely described.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Case Description: We describe 54 year old Male with a history of Deceased Donor Renal transplant in 1999 whose kidney disease was secondary to Hypertensive nephrosclerosis. Donor information is not available. The patient had been in his usual state of health until one week prior to presentation, when he started feeling weak and became confused, reason for hospitalization.

An MRI brain confirmed a large mass measuring 5.4 x 2.9 cms, in the corpus callosum splenium and second lesion 8 x9 mm, in the left parietal region. He had a biopsy done which revealed a GBM. Neurosurgery was consulted and mass was found to be unresectable. Neuro-Oncology was consulted and he was advised radiation therapy and possible chemotherapy, however he decided to seek second opinion. His Post transplant period has been remarkable for a borderline rejection with donor specific antibodies, treated with plasmapheresis and IVIG. His immunosuppressant medications were Cyclosporine, Mycophenolate mofetil and prednisone.

Discussion: Review of the literature indicates that gliomas do not seem appear in an early post-transplant period. These tumors have been reported mostly after 4–20 years from renal transplantation. Increased risk of tumour occurrence may be related immunological disorders such as HIV, and also to the administration of immunosuppressive drugs. Few studies have shown that cyclosporine may induce phenotypic changes in different tumoural and normal line cells and may play a role in modulating the neoplastic course. There seems to be the existence of a relationship between glioblastoma development and kidney transplant, but this association needs to be studied further. With increasing life expectancy of transplant recipients, evaluation of the risk of serious complications such as glial tumors is necessary.

SA-PO025

Eculizumab in Gemcitabine-Induced Thrombotic Microangiopathy
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Introduction: Thrombotic microangiopathy (TMA) is a pathological process involving thrombocytopenia, microangiopathic hemolytic anemia and microvascular occlusion particularly the kidney and brain. Eculizumab, a complement C5 inhibitor, has been used to successfully treat cases of atypical HUS but its use has not been widely reported in drug induced TMA. We report a case of Gemcitabine induced TMA treated with Eculizumab.

Case Description: A 68 y/o male with h/o hypertension, Diabetes mellitus, CKD with a baseline Cr 1.9, Prostate Ca. s/p Whipple procedure, receiving gemcitabine as neo adjuvant chemotherapy was sent to the hospital for worsening creatinine, 20 lbs. weight gain and worsening pedal edema over the duration of one month. On admission, he was in hypertensive urgency with BP 235/110. Labs showed Hb 9, platelet 201, Na 136, K 5.4, Cl 114, HCO₃ 18, BUN 53 and Cr of 3.0. Urinalysis showed 3+ blood and 4+ protein. Further workup revealed normal complements, negative ANA, ANCA, hepatitis panel and HIV serology, elevated LDH and low haptoglobin. Occasional schistocytes were noted on the peripheral smear. Renal ultrasound showed mildly echogenic kidneys. Urine protein/creatinine ratio was 7.5. A renal biopsy was performed, which showed TMA, clinically suspected to be secondary to gemcitabine. The patient was started on Eculizumab regimen but renal function deteriorated requiring RRT. After 3 months of therapy, his LDH and haptoglobin have improved but he is still on Dialysis.

Discussion: The mechanism of chemotherapy induced TMA is presumed to be a dose dependent direct endothelial injury rather than deficient ADAMTS 13 activity or complement dysfunction. So, Therapeutic plasma exchange is usually not recommended. There are rare case reports of Gemcitabine induced TMA that improved with TPE. This indicates that patients who do get TMA while on Gemcitabine likely have some complement dysfunction or a serum factor induced by Gemcitabine that is responsible for endothelial injury. There might be a role for Eculizumab in underlying complement dysregulation in chemotherapy induced TMA, which needs further studies.

SA-PO026

Improvement of Renal Function with Treatment of Hypothyroidism
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Introduction: Association of subclinical hypothyroidism and chronic kidney disease is increasingly being recognized. Early data suggests improvement in renal function with thyroid hormone replacement in patients with clinical and subclinical hypothyroidism. We present a case of dramatic improvement of renal function upon successful treatment of hypothyroidism.

Case Description: 33 y/o AA male with past medical history of nasopharyngeal carcinoma and cisplatin nephropathy (baseline creatinine 2.4 mg/dL) presents with sustained elevation of creatinine kinase (CK). No improvement was noted after stopping statin and reported intense exercise regimen. No detectable urine myoglobin. CK remained about 40,000 IU/L, with gradual worsening of creatinine up to a peak of 3.2 mg/dL. Work up revealed primary hypothyroidism with TSH 117 uU/ml (N=.34 - 5.6) and Free T₄ < 0.4 ng/dL. Muscle biopsy showed type II muscle fiber atrophy and loss which can be correlated with biochemical lack of L-thyroxine. The patient was started on levothyroxine replacement and within days demonstrated improvement in CK and Scr. Seven weeks after initiation of therapy there is ongoing improvement in CK, TSH and Scr to levels of 3271 IU/L, 15.4 uU/ml, and 1.9 mg/dL.

Discussion: Experimental evidence suggests that hypothyroidism is associated with changes in renal function and decrease nephron mass. Similarly, hyperthyroidism can result in glomerular hypertrophy by enhanced expression of renin mRNA. Hypothyroidism blunts compensatory hypertrophy after unilateral nephrectomy in remnant kidney models. Developmentally, thyroid hormone also has important role in tubular function including maturation and density of many tubular transporters. We demonstrate continued

improvement in renal function upon thyroid hormone replacement. Subclinical and overt hypothyroidism may be under recognized in CKD and ESRD. Further studies are needed to understand these complex interactions.

SA-PO027

A Case of Rapidly Progressive C3 Glomerulonephritis
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Introduction: C3 glomerulonephritis (C3GN) is a rare glomerular disease, characterized by predominant C3 deposition within the glomerulus. It is thought to be caused by uncontrolled activation of the alternative complement pathway. Eculizumab, a humanized monoclonal C5 antibody, has advanced the treatment of complement mediated diseases such as complement-mediated hemolytic uremic syndrome, and has emerged recently as a treatment option for C3GN.

Case Description: A 74 year old retired software engineer with history of atrial flutter, and nephrolithiasis was transferred to our center with 2 weeks history of sore throat, fatigue, fever and rigors. Laboratory studies were significant for WBC 19U/L with left shift, platelets 40,000/UL, and serum creatinine 2.2 mg/dl, which rapidly increased to 11 mg/dl over 4 days. Blood cultures grew Streptococcus pyogenes. Further tests revealed a high ASO titre at 800, ANA 1:160, and low C3 and C4. Hemodialysis was started for uremic symptoms and a kidney biopsy was performed. The biopsy revealed an acute glomerulonephritis with C3 predominance, with tubulointerstitial nephritis, there were also features of post infectious GN evident by subepithelial humps. Intravenous Methylprednisolone was started but he remained dialysis dependent. With the consideration that the infection likely induced unregulated activation of the alternative complement pathway. We started eculizumab 900 mg. Patient received a total of six hemodialysis treatments. After 1 dose of eculizumab, the serum creatinine plateaued without dialysis treatment at 3.9 mg/dl, dialysis treatment was discontinued and plan was made to continue weekly infusions of eculizumab.

Discussion: Disorders of alternative complement pathway regulation are becoming increasingly recognized. There are no proven therapies for C3GN, but targeting terminal complement is an attractive approach given the known causes of C3GN. There are few reported cases of the benefit of eculizumab in C3GN and often describe the agent's efficacy earlier in the course. This case represents a unique instance of effective treatment of dialysis-dependent C3GN with early restoration of renal function.

SA-PO028

Nephrotic Syndrome After Scorpion Sting
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Introduction: Scorpion venom is a water soluble, anti-genic and heterogeneous mixture. The reported incidence of scorpion sting in India is 0.6%. Scorpion sting resulting in acute renal failure has been reported in the past, but not the nephrotic syndrome.

Case Description: A 49-year-old gentleman, non-diabetic and not a hypertensive, presented with history of scorpion sting over the fourth digit of the left hand. Patient had immediate intense local pain, swelling and redness. Within one hour he had hypersalivation, sweating, vomiting and diarrhoea. After three days, the patient complained insidious onset of abdominal distension, followed by pedal oedema and facial puffiness over next one week. There was no history of oliguria, dysuria and haematuria. Investigations revealed serum creatinine: 2.9 mg/dL, 24 hour urine protein was: 9.90 g. He was subjected to renal biopsy at that institute. The diagnosis was minimal change with acute tubular necrosis. He presented to our institute with breathlessness and ansarca. On examination BP 140/90mmHg and bilateral crackles on auscultation. Serum creatinine: 7.0 mg/dL, blood urea: 148 mg/dL, total serum proteins: 5.5 g/dL, serum albumin: 2.5 g/dL, total cholesterol: 237 mg/dL, triglycerides: 182 mg/dL, haemoglobin: 12.0 g/dL and 24 hour protein: 2872 mg. He was dialyzed for three sessions and subjected to renal biopsy and diagnosed to have minimal change disease and acute tubular necrosis, the patient was continued on dialysis. Urine output improved after three more weeks. Serum creatinine stabilized to 2.0 mg/dL after eight weeks of scorpion sting.

Discussion: The scorpion venom is composed of varying concentration of neurotoxin, cardiotoxin, nephrotoxin, haemolytic toxin, phosphodiesterase, phospholipases, hyaluronidases, glycosaminoglycans, histamine, serotonin, and tryptophan and cytokine releasers. Acute renal failure after scorpion sting is reported but nephrotic syndrome is not reported. We report a patient of nephrotic syndrome after scorpion sting. The lacunae in the present knowledge linking scorpion sting venom with nephrotic syndrome would only be replenished with publications of similar reports.

SA-PO029

Diffuse Crystals Accumulation in the Proximal Tubules, Podocytes, and Interstitial Histiocytes of a Patient with a Multiple Myeloma
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Introduction: Light chain proximal tubulopathy with crystals formation is a rare condition, accompanied by paraproteinemia. In particular, observation of crystal inclusions in the podocytes has seldom been reported. We present a distinct case that revealed diffuse crystal inclusions in a variety of kidney cells of a multiple myeloma (MM) patient, including the proximal tubular cells, podocytes, and interstitial histiocytes.

Case Description: A 66-year-old Japanese woman was admitted to our hospital and diagnosed with gradual deteriorated kidney function (serum creatinine, 2.0 mg/dL), proteinuria (urinary protein, 1.3 g/d), and mild hematuria (urinary red blood cells, 10-19/hpf). Urinary b2-microglobulin was notably elevated (117,700 mg/L); however, Fanconi's syndrome was not detected. Elevated serum IgG levels (IgG 2,559 mg/dL) with IgA and IgM suppression were confirmed, and serum immunoelectrophoresis revealed monoclonal IgG-κ. Examination of kidney biopsies revealed crystal inclusions in the proximal tubules, podocytes, and interstitial histiocytes. The crystals tested negative for eosin, periodic-acid Schiff, and trichrome staining. No segmental glomerulosclerosis was observed. Immunofluorescence staining of both κ and λ was negative. Similarly, immunohistochemistry, using an antigen retrieval method, failed to detect either κ or λ. Transmission electron microscopy revealed highly electron dense crystals that diffusely accumulated in the proximal tubules, podocytes, and interstitial histiocytes. By bone marrow biopsy, the patient diagnosed as MM. Bortezomib treatment attenuated kidney dysfunction and proteinuria. Sequential DNA analysis confirmed that the patient had Vκ subgroup I restriction.

Discussion: Monoclonal light chains are internalized into the lysosomes of proximal tubular cells by receptor-mediated endocytosis, where they form protease resistant crystals. Our case suggests that podocytes can engulf crystals in a similar manner, despite lacking the receptors found on proximal tubular cells.

SA-PO030

Erythematous Skin Rash and Gastrointestinal Bleeding as Presenting Features of ANCA Negative Pauci-Immune Glomerulonephritis Anusha Lakshmi Badveli, Chanchal Kumar Jana. *Internal Medicine, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India.*

Introduction: Pauci-immune glomerulonephritis (PGN) is one of the common causes of RPGN. In most patients with PGN, circulating antineutrophil cytoplasmic autoantibody (ANCA) is present, however 10% of the patients are ANCA-negative. Usually extra renal manifestations in ANCA negative PGN are rare, but the case reported here is a rare presentation having skin rash and gastrointestinal (GI) manifestations.

Case Description: A 50-year-old female was admitted with low-grade intermittent fever, erythematous maculopapular rash all over the body and asymmetrical arthralgia involving large and small joints for about 3 months. She had one-week history of pain abdomen and melena followed by decreased urine output and generalized edema. On examination BP 156/94 mmHg, Birmingham Vasculitis Activity Score of 23/63. Investigations: Hb 9.9 g/dL, serum creatinine 4.0 mg/dL, urinalysis - protein ++, RBC 2-3/hpf, 24 hour urinary protein 4.75gm/day. Serum uric acid & C3 were normal. Serum ANA, pANCA, cANCA, and RA factor were negative. Skin biopsy for IgG, IgM, IgA, C3, C1q was negative. USG showed normal sized kidneys. Renal biopsy: Light microscopy showed segmental fibrinoid necrosis and early cellular crescents with mild increase in cellularity of mesangial matrix. Immunofluorescence: IgG, IgM, IgA, C3, C1q, kappa and lambda chains were negative. Diagnosis of ANCA negative pauci-immune GN with crescents was made and patient was started on systemic steroids and cyclophosphamide pulse therapy. Patient improved symptomatically and creatinine levels gradually declined.

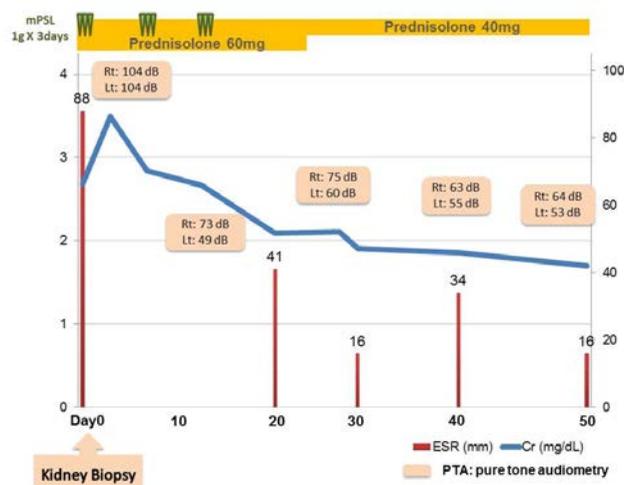
Discussion: Patients with ANCA negative PGN rarely present with skin and GI manifestations. In a study done in China comparing clinical features of ANCA negative patients only 7% were found to have GI manifestations and 17.9% had skin rash. These patients were treated similarly to ANCA-positive patients, although no study has focused specifically on the treatment of ANCA-negative patients. Such patients could be easily confused as other forms of systemic vasculitis and therefore early identification and prompt treatment could prevent many life threatening complications and improve prognosis.

SA-PO031

A Case of ANCA-Associated Nephritis Mainly Localized to the Tubulointerstitial Area, Successfully Treated by Steroid Therapy Tomo Nakajima, Yosuke Nakagawa, Takuya Isegawa, Masahiro Koizumi, Masafumi Fukagawa. *Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.*

Introduction: The typical pathological findings of antineutrophil cytoplasmic antibody (ANCA)-associated nephritis consist of extracapillary proliferation and necrotizing crescent formation. Nevertheless, a few cases of ANCA-associated nephritis, in which the tubulointerstitial area was mainly affected, are reported. Here, we present such a case of ANCA-associated tubulointerstitial nephritis, and review its characteristics compared to ANCA-associated glomerulonephritis.

Case Description: A 74 year-old generally healthy female developed bilateral hearing loss, and thereafter suffered from persistent fever. With a diagnosis of bacterial pneumonia, she was admitted to another hospital and treated with several broad-spectrum antibiotics without improvement. Four weeks later, she was referred to our hospital. On admission, weight loss and peripheral numbness and weakness was noted in addition to advanced hearing loss and fever. Serum creatinine level was elevated to 3.5 mg/dL, while urinalysis revealed mild proteinuria with few red blood cells and no cast in the sediment. Sinusitis and alveolar hemorrhage were observed by CT scan. Immunological tests demonstrated positive myeloperoxidase (MPO)-ANCA (104 U/ml). In view of multiple organ involvements, ANCA-associated vasculitis was suspected. Renal biopsy showed diffuse interstitial infiltrates and remarkable vasculitis in small arteries and capillaries with only a small number of crescentic glomeruli, which was consistent with ANCA-associated tubulointerstitial nephritis. Steroid therapy ameliorated not only kidney dysfunction, but also hearing loss.



Discussion: In an atypical case of ANCA-associated nephritis with near normal urinalysis, we need to consider the possibility of tubulointerstitial nephritis.

SA-PO032

Treatment of Severe Resistant Idiopathic Membranous Glomerulopathy with Adrenocorticotropic Hormone Gel: A Case Report Blaitthin A. McMahon,¹ Adam R. Berliner.² *¹Div of Nephrology, Johns Hopkins School of Medicine, Baltimore, MD; ²Nephrology Center of Maryland, Baltimore, MD.*

Introduction: Idiopathic membranous glomerulonephritis is a frequent cause of nephrotic syndrome. Therapy is based on Ponticelli protocol or other immunosuppressive therapies. Adrenocorticotropic hormone has been used with some success for the treatment of resistant idiopathic membranous nephropathy. We present here a case of a 39 year old Caucasian man presenting with severe resistant idiopathic membranous glomerulonephritis who encountered only a partial response with cyclosporine but had a complete remission with single therapy corticotropin.

Case Description: Medical history included chronic kidney disease stage IIIA and hypertension. He attended a work-associated physical examination that revealed proteinuria and subsequent 24hr urine collection revealed 18g of proteinuria. His physical examination was notable for stage 3 hypertension, no chest, cardiac or abdominal abnormalities. He had bilateral +2 pitting edema to the knees. Renal biopsy showed thickened capillary walls with spikes and holes in the glomerular basement and subepithelial deposits. All inflammatory and infectious serological studies were negative. Treatment included corticosteroids and cyclosporine 100mg twice daily. His glomerular filtration rate was 58 ml/min per 1.73/m². His proteinuria improved from 18g to 5g over an eight week period after initiation of cyclosporine, however, five months later he relapsed to 10g and later to 15.9g. After stopping his cyclosporine, his proteinuria worsened to 20g/24hr urine collection. Magnetic resonance imaging of his renal veins were negative for thrombus. PLA2 receptor antibody testing was negative. At our institution, he was treated with corticotropin (ATHACAR H.P.) 80 unit/mL injectable gel subcutaneously twice weekly. A complete remission was achieved within 12 months. Patient characteristics and clinical course is reviewed.

Discussion: Randomized controlled trials are needed to evaluate the therapeutic efficacy of corticotropin for resistant idiopathic membranous glomerulonephritis.

SA-PO033

HCV-Related Cryoglobulinemic Glomerulonephritis and B Cell Lymphoma: Early Antiviral Therapy Crucial Sixto G. Giusti, Ivo Lukitsch. *Nephrology, Ochsner Clinic Foundation, New Orleans.*

Introduction: Untreated chronic Hepatitis C Virus (HCV) infection often leads to a spectrum of severe extra hepatic manifestations related to B cell dysregulation, which include cryoglobulinemia, renal diseases, and lymphoproliferative disorders. Type I membranoproliferative glomerulonephritis (GN) associated with type II mixed cryoglobulinemia is the most common HCV related kidney disease, with membranous nephropathy and MPGN without cryoglobulinemia being less frequent.

Case Description: A 58 year-old Caucasian man with history of hypertension, recent biopsy proven membranous nephropathy, and treatment naïve chronic HCV infection Genotype 3a diagnosed 5 yrs ago, presented with complaints of intermittent vasculitis rash in his legs for a year as well as worsening paresthesias of his palms and soles. Initial evaluation showed microscopic hematuria, red blood cell casts, 1.2 grams of proteinuria, and serum creatinine (SCR) of 1.0 mg/dL. Serum C4 was low, and serum positive for type II cryoglobulins. Repeat kidney biopsy was showed a diffuse proliferative GN with characteristics of cryoglobulinemic GN. The patient was referred to hepatology for antiviral treatment, which was delayed due to myocardial infarction requiring bypass surgery. During this time he developed worsening renal function (SCR of 3 mg/dL) with increase in proteinuria to 2-3 gm prompting the decision for immunosuppressive therapy. Rituximab (1 gm) was administered and he was started on ledipasvir 90 mg/sofosbuvir 400 mg with prompt viral response and an improvement of renal function (SCR 1.6). Weeks after, he presented with AKI and diffuse alveolar hemorrhage and was treated with high

dose steroids, plasma exchanges, and a second dose of Rituximab, with clinical and renal improvement. One month after discharge, he was re admitted with ARDS and diagnosed with B-cell lymphoma.

Discussion: There is a paucity of data on anti-HCV therapy in patients with renal failure often resulting in a delay of antiviral therapy. Immunomodulatory therapies may provide transient improvement of symptoms but bear the risk of significant adverse reactions. Early initiation of antiviral therapy is vital in order to prevent spectrum of HCV related complications.

SA-PO034

A Case of Membranous Nephropathy with an Adjacent Smooth Muscle Cell Tumor Laiith Al-Rabadi,¹ Cathryn J. Byrne-Dugan,² Stanley D. Crittenden,¹ Helmut G. Rennke,² Laurence H. Beck.¹ ¹*Boston Medical Center;* ²*Brigham and Women's Hospital.*

Introduction: Different stromal tumors can occur in the kidney and potentially skew the true extent of parenchymal injury induced by different glomerular diseases. Most of these stromal tumors are benign. The value of renal biopsy in assessing interstitial sequelae may be compromised by the mass effect of the infiltrating tumor cells.

Case Description: We describe a case of a 65 year old male patient, with a history of primary membranous nephropathy 20 years ago. He had initially been treated with the Pontocelli protocol with favorable response. He continued to be in remission until a few months prior to presentation when he developed anasarca. His 24 hour urine collection revealed 8 grams of protein, and creatinine was 1.8 mg/dl. The decision was made for the patient to undergo a kidney biopsy which confirmed recurrence of primary membranous nephropathy with positive staining for PLA2R. It also revealed advanced chronic changes that included focal global glomerulosclerosis (87%) in addition to interstitial fibrosis 80%. However, adjacent to this atrophic area, there was a tumor of spindle-shaped cells with smooth muscle characteristics. There was no atypia or mitosis and no clear capsule but the tumor cells appeared to infiltrate and surround the tubules and vasculature. This was labeled by the pathologist as a fragment of a smooth muscle cell tumor of undetermined malignant potential. The possibility of leiomyosarcoma could not be ruled out. MRI abdomen and pelvis did not show any evidence of extra renal involvement. The possibility of the parenchymal tissue being significantly influenced by its close proximity to the tumor prompted us to pursue another renal biopsy from the other kidney. Surprisingly, repeat biopsy showed only 15% of tubular atrophy and interstitial fibrosis. The patient was initiated on Rituximab and tolerated two courses of treatment. He achieved partial remission with UPCr less than 3 gram with stable Cr at 1.8 mg/dl.

Discussion: Coexistence of smooth muscle tumors and membranous nephropathy is rare. The extent of parenchymal involvement should be confirmed, with repeat biopsy, when there are concerns about tissue distortion by neighboring tumor.

SA-PO035

Freezing Point: Sjögren's Disease Leads to Cryoglobulin Induced Membranoproliferative Glomerulonephritis Manuel A. Fernandez Palmer, Roberto L. Collazo-Maldonado. *Nephrology, Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Sjögren's disease is chronic autoimmune inflammatory disorder mainly affecting salivary and lacrimal glands but rarely it can present with systemic manifestations including kidney involvement. The kidney manifestations may include hypokalemic RTA, interstitial disease and rarely MPGN.

Case Description: This is a 30 year old woman with no medical history who arrived to ER complaining of a three day history of SOB and increasing edema on lower extremities. She denied toxic habits. Review of systems positive for lower extremity rash in the preceding weeks. P/E was pertinent for elevated BP at 159/90 mmHg, 94% O2Sat on NC at 2LPM, bibasilar crackles with decreased breath sounds at bases and lower extremity pitting edema. Labs showed HGB of 10 g/dL, creatinine of 1.32 mg/dL with normal electrolyte, albumin levels 3.4 mg/dL, UA with proteinuria and hematuria, and a BNP that was markedly elevated. CXR showed pulmonary edema and bilateral moderate pleural effusions. Patient was admitted and workup performed, including CT which was negative, lower extremity Doppler that was negative for DVT. Creatinine increased to 2.6 and proteinuria was quantified at 4 g/24hrs. Serologic work up was negative except for low Complement levels, along with a positive rheumatoid factor, positive anti-SSA. Clinical presentation and labs consistent with a diagnosis of Primary Sjögren's disease. Cryoglobulin levels were negative but kidney biopsy was performed and results consistent with Membranoproliferative Glomerulonephritis with intra capillary thrombi highly suggestive of cryoglobulins. Patient was started on high dose steroids and received five plasma exchanges. Afterwards, Rituximab 375 mg/m² was administered at weekly intervals times four. At the time of discharge creatinine had stabilized at 0.95 mg/dl.

Discussion: Despite being rare, Sjögren's Disease can lead to cryoglobulin formation and subsequent deposition in different tissues of the body. Nephrologists must consider this rare complication when evaluating patients with proteinuria, especially when there is worsening renal function and other systemic symptoms.

SA-PO036

Postinfectious Glomerulonephritis Associated with *Escherichia coli* Infection Caused by Transurethral Prostatectomy Eleni Chelioti, Alexia Papalexandrou, Evdokia Efthimiou, Maria Sotiraki, Ioannis Xatzis, Maria Tsilivigou. *Dept of Nephrology, General Hospital of Piraeus, Athens, Greece.*

Introduction: Postinfectious glomerulonephritis (PIGN) is an immune-mediated glomerulonephritis (GN) caused by non-renal bacterial infection. In adults, PIGN is more common in immunocompromised patients, particularly diabetics. The major site of infection is the skin, followed by the lungs and the urinary tract. In terms of causative agents, Staphylococcus is the most common cause in elderly people, followed by Streptococcus. Gram-negative bacteria, including *Escherichia coli* (*E. coli*), are responsible for up to 10% of cases of adult PIGN and 5% of cases in the elderly. We report a patient with PIGN associated with *E. coli* infection caused by transurethral prostatectomy.

Case Description: A 76-year-old Caucasian man with a history of coronary artery disease and recent transurethral prostatectomy was admitted with complaint of fever, and uremic symptomatology that necessitated dialysis therapy. Blood and urinary cultures were positive for *E. coli* and resumed antibiotic therapy. After one week, he was afebrile, without amelioration of renal function and with signs of glomerular involvement: urine red blood cells= 20-40/HPF, 24-hour urine proteins=1.7g. Immunological analyses were negative, except for decreased C4. The diagnostic approach led to a renal biopsy that findings were consistent with PIGN: endocapillary proliferative and exudative GN on LM; C3-dominant glomerular staining on IF and hump-shaped subepithelial deposits on EM. After urinary tract infection was controlled by antibiotic therapy, oral methylprednisolone was initiated, and the patient's renal function and nephritic syndrome subsequently gradually improved.

Discussion: For a diagnosis of PIGN, at least three of the following five criteria must be satisfied: 1) clinical or laboratory evidence of an infection preceding the onset of GN 2) decreased serum complement levels 3) endocapillary proliferative and exudative GN on LM 4) C3-dominant or co-dominant glomerular staining on IF and 5) hump-shaped subepithelial deposits on EM. In the present case, all criteria were met. Moreover, recently reported that rarely, *E. coli*, also cause this type of GN.

SA-PO037

A Patient Presenting with Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome and Leptospirosis Ali Veyysel Kara,² Yasar Yildirim,² Zülfükar Yılmaz,² Melike Elif Celik,² Erdal Bodakci,² Ali Kemal Kadiroglu,² Mehmet Emin Yilmaz.² ¹*Nephrology, Dicle Univ, Diyarbakir, Turkey;* ²*Internal Medicine, Dicle Univ, Diyarbakir, Turkey.*

Introduction: There are very rare case reports in the literature about leptospirosis in association with TTP-HUS. We present a case report of TTP-HUS syndrome in a patient with leptospirosis.

Case Description: A 27 years old female patient was transferred to our clinic due to progressive deterioration in the general status and kidney functions. On admission, she was oriented and cooperated. She had blood pressure of 130/65 mmHg, heart rate of 90/min, temperature of 38.3 C and respiratory rate of 25/min. Patient had no urine output. There is minimal swelling on the dorsum of right hand of the patient. When we detailed history about this finding, she remembered that she saw mice in her working place in the night shift. Peripheral blood smear showed large numbers of fragmented red blood cells. Disseminated intravascular coagulation panel was normal. Viral hepatitis markers and serological tests for anti-nuclear anticor, anti-double stranded DNA and also Toxoplasma, Rubella, Cytomegalovirus, Herpes panel were all negative. C3 and C4 levels were normal. There was no reproduction in the blood cultures. ADAMS 13 level was reported as normal. Plasmapheresis was initiated immediately with the preliminary diagnosis of TTP/HUS. Also patient was empirically treated with antibiotics and on the 3rd day of treatment; doxycycline 200 mg orally per day was added to therapy because of the positive result of Leptospira IgM ELISA test. After 14 days of antibiotherapy and a total of 10 sessions of plasmapheresis, patient general status improved and laboratory findings come to near normal levels. Patient was discharged with the normal laboratory findings.

Discussion: In conclusion; leptospirosis and TTP-HUS can present with the same clinical findings and differential diagnosis is crucial to initiate the right treatment. Also, it is important to consider co-occurrence or association of these two disease in the light of patient's history and laboratory findings although there are very rare reports in the literature.

SA-PO038

For the Eye Altering, Alters the All Marie-Angélique De Scheerder, Anne Marie Bogaert. *Internal Medicine, UZ Gent, Gent, Belgium; Nephrology, Sint-Elisabethziekenhuis, Zottegem, Belgium.*

Introduction: We describe the case of a 26-year-old African female that was treated successfully with belimumab in a case of severe membranous lupus nephritis, resistant to first line therapy.

Case Description: She presented initially with chronic dacryoadenitis and screening showed nephrotic range proteinuria. Biopsy of the kidney confirmed the diagnosis of membranous lupus nephritis. Clinical features (joint pain, dacryoadenitis and lupus nephritis) in combination with serology (positive anti-DNA antibodies, hypocomplementemia) confirmed diagnosis of systemic lupus erythematosus (SLE). Treatment was initiated with glucocorticosteroids (GCS), mycophenolate mofetil (MMF) and Hydroxychloroquine sulphate (Plaquenil®). Tacrolimus was associated but no effect was observed with the proteinuria remaining in nephrotic range and secondary effects of the GCS becoming a real concern. Patient was started on add-on belimumab with quasi-immediate effect on the

proteinuria, making it possible to decrease dosage of the other immunosuppressants and gradually stop them, even the GCS. Patient is now in complete remission after 2 years of treatment with no signs of relapse after stopping additional medication.

Discussion: Belimumab is indicated in treatment of seropositive active SLE in addition to standard therapy, when lack of clinical improvement despite optimal standard therapy. Two large, phase 3, multicenter, prospective, randomized, controlled trials (BLISS-52 and BLISS-76) compared belimumab with placebo in patients with SLE who were receiving standard therapies. Both studies showed significant improvement in SRI (Systemic Lupus Erythematosus Responder Index) with 10mg/kg of belimumab as compared with placebo. A phase 3 study (BLISS-LN) is recruiting patients with lupus nephritis since these post-hoc analysis of the BLISS trials suggest that belimumab may offer renal benefit in patients with SLE. The treatment is so far not recommended in these cases. We can conclude that our case shows excellent results of belimumab in lupus nephritis with persistent nephrotic range proteinuria under conventional treatment. Alternatives are scarce and mostly limited due to toxic effects and by failure to control disease.

SA-PO039

Overlap Syndrome or Drug Reaction? Varun Gaur, Michael T. Eadon, Jesus H. Dominguez. *Medicine, Indiana Univ, Indianapolis, IN.*

Introduction: The overlap of ANCA-Associated Vasculitis (AAV) with other autoimmune diseases is well known. However, the association of AAV with the use of TNF- α antagonists in Rheumatoid Arthritis (RA) patients is less understood.

Case Description: A 44 y/o white female with RA had prior treatment with methotrexate (3 yr), adalimumab (2 yr) and etanercept (2 yr). She concluded all DMARD therapy 3 yr prior to presentation (PTP), and then her RA flared 5 months PTP. After initiation of leflunomide and steroids, she had partial resolution. Two weeks PTP, she received golimumab for onset of severe neurological manifestations including right foot drop, distal extremity numbness, and a right 4th digit ischemic lesion. Upon presentation, she was admitted with persistence of these symptoms. Her serum creatinine increased from 0.9 (mg/dl) to 1.4 with 2 gm proteinuria. Her urinalysis had hematuria and serology was positive for PR3-positive cANCA. Her renal function deteriorated with a peak creatinine of 6.7, necessitating intermittent dialysis. A biopsy revealed pauci-immune diffuse necrotizing and crescentic glomerulonephritis consistent with AAV. She received pulse solumedrol, cytoan, and plasma exchange. Her neurological symptoms improved after a month of therapy. After 6 weeks, she did not require dialysis and her serum creatinine was 2.4.

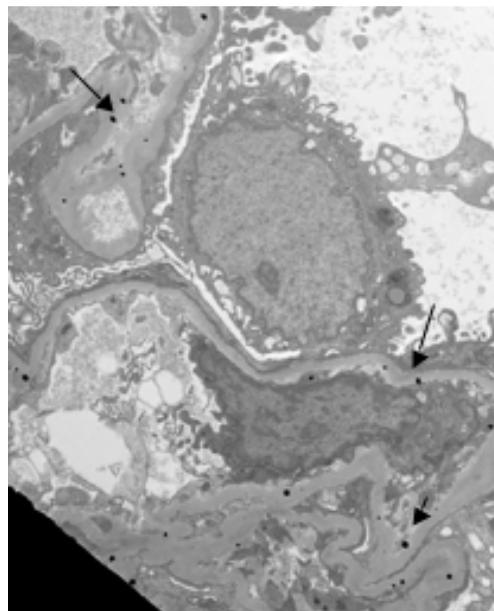
Discussion: We present a case of a patient previously treated with TNF- α inhibitors who then developed PR3-positive AAV years later. An association between AAV and RA has been described and RA may precede AAV by up to 8 years. Different theories explain this association. One reason may be the common genetic predispositions to autoimmunity, involving HLA or PTPN22 genes, reported in a series of both RA and AAV. A second theory suggests TNF antagonists may predispose one to develop secondary autoimmunity. In our case, the patient discontinued DMARDs 3 yr PTP, although had recently received Leflunomide and Golimumab. There are no reports that associate leflunomide use with AAV and only one case report suggests an association of golimumab with AAV. Our case highlights the need to further understand the importance of AAV in RA patients, and the potential role of TNF inhibitors on the development of AAV.

SA-PO040

Pauci Immune Crescentic Glomerulonephritis in a Patient with T-Cell Lymphoma and Argyria Tamer Rezk, James J. Penton, Mark Alan Little, John Cunningham, Alan D. Salama. *Centre for Nephrology, Royal Free Hospital, London, United Kingdom.*

Introduction: Silver is a transition metal element with a range of industrial and ornamental uses and is known to be toxic when ingested in significant amounts. Silver exposure causing argyria (skin deposition) and argyrosis (eye deposition) is well-recognized but the renal consequences of silver toxicity are poorly understood.

Case Description: A 47 year old woman with a T-cell lymphoma who refused conventional chemotherapy for 18 months but self-medicated with a remedy containing colloidal silver was admitted with acute dialysis-dependent kidney injury. The serum silver concentration was strikingly elevated at 127.1 nmol/l (reference value <2.8 nmol/l). Kidney biopsy demonstrated a pauci-immune crescentic glomerulonephritis and glomerular tufts with fine, dark, granular material scattered within the mesangium and along the glomerular basement membrane (GBM). Electron microscopy confirmed the presence of electron-dense granules in the mesangium and along and within the GBM.



Electron probe microanalysis demonstrated that these granules contained predominantly silver. The patient recovered independent renal function following immunosuppression with cyclophosphamide and steroids.

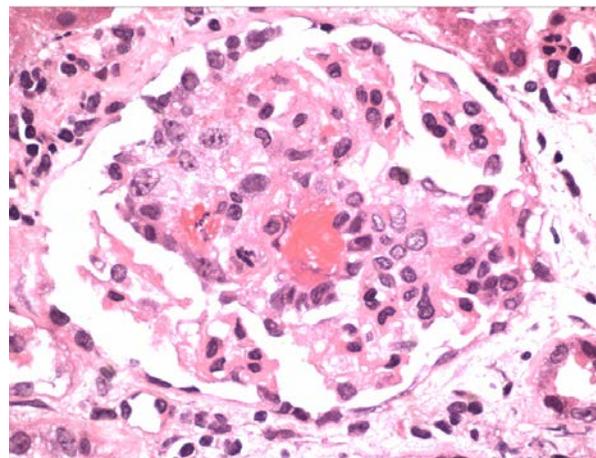
Discussion: Crescentic glomerulonephritis results from disruption of the GBM which may be induced by immune complexes or by cellular mediators. However our patient had no autoantibodies, and no deposited immunoproteins. Our case therefore represents a pauci-immune crescentic glomerulonephritis with intense silver deposition along the GBM. Between 5-10% cases of pauci-immune glomerulonephritis are ANCA negative. The pathogenesis in these cases may be related to other autoantibodies (such as anti-endothelial antibodies) or to direct leukocyte-induced GBM damage via soluble mediators, which in this case we believe was due to a combination of T cell lymphoma and argyria.

SA-PO041

PR3-ANCA Vasculitis following Influenza Vaccination Karim El Hachem, Eduardo J. Zouain, Isha Gupta, Steven D. Smith. *Nephrology, Mount Sinai- St Luke's Hospital, New York, NY.*

Introduction: Influenza vaccination has been associated with the development of autoantibodies and autoimmune rheumatic disease. We report a case of PR3-ANCA associated vasculitis following influenza vaccination.

Case Description: The patient is a 45 year old Hispanic male with no known medical history who presented with subacute onset pleuritic chest pain and shortness of breath. Four weeks prior to presentation, he had received his annual injectable influenza vaccine and reports feeling weak since. On presentation, he was hemodynamically stable. His exam was notable for bibasilar crackles. He had positive Rheumatoid Factor. His CT chest was notable for multiple ground glass nodules at the right upper lobe. His creatinine was 1.64 mg/dL. His urine albumin to creatinine ratio was 225 mg/gm creatinine and his urine protein to creatinine ratio was 500 mg/gm creatinine. He had 25-30 RBC/hpf with no dysmorphic RBCs. He had strongly positive PR3-ANCA antibody (>8 AI). His kidney biopsy revealed acute focal segmental necrotizing crescentic GN, pauci-immune type.



The patient was treated with pulse IV methylprednisolone and Rituximab 375mg/m2 weekly for four doses. Three months following induction therapy his creatinine improved from a peak of 3.6mg/dL to 1.4 mg/dL. His CT findings and hematuria resolved. His PR3-ANCA slowly decreased and became negative 6 months after induction.

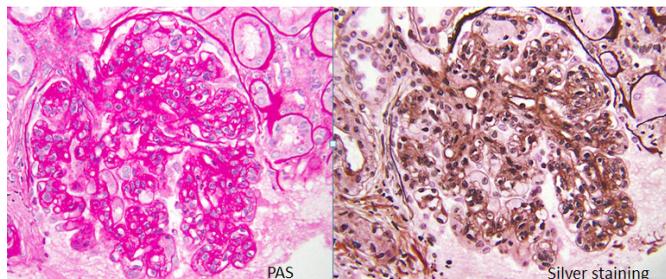
Discussion: This patient's presentation with lung nodules on chest CT, necrotizing crescentic GN on kidney biopsy and high serum level of PR3-ANCA support a diagnosis of Granulomatosis with Polyangiitis with a strong temporal relationship to vaccination against influenza. This is the 9th case of ANCA associated vasculitis following influenza vaccination reported in the literature. Clinicians should be aware of the possible association between systemic vasculitis and influenza vaccination.

SA-PO042

C3 Glomerulonephritis Associated with Monoclonal Gammopathy Aumyot Prongdong,¹ Weeraporn Srisung,¹ Mustafa G. Aly,¹ Irfan Warraich,² Faisal Jamal.¹ ¹Nephrology, Texas Tech Univ Health Sciences Center, Lubbock, TX; ²Pathology, Texas Tech Univ Health Sciences Center, Lubbock, TX.

Introduction: A case of C3 glomerulonephritis associated with monoclonal gammopathy responding effectively with immunosuppressive therapy.

Case Description: The patient is a 65 year-old Hispanic female who presented with lower extremity edema and dyspnea. She had acute kidney injury with nephritic urinary sediments. C3 and C4 were low. Hepatitis B & C profile, ANA, ANCA, anti-GBM and SPEP were within normal limits. There was a faint monoclonal band in the gamma region on UPEP. Kidney biopsy was consistent with membranoproliferative glomerulonephritis (MPGN), of an undetermined etiology. Patient was readmitted with similar complaints and a rapidly declining renal function. Repeated UPEP showed a significant IGG kappa monoclonal protein and an elevated serum free light chain with kappa/lambda ratio of 2.52. Bone marrow biopsy revealed atypical plasmacytosis without overt myeloma. Repeated kidney biopsy showed global proliferative changes along with splitting of glomerular basement membrane. C3 deposits were seen on immunofluorescence. No reactivity was seen for IgA, IgG, IgM, C1q, C4, fibrinogen and albumin. Electron microscopy showed subendothelial and mesangial immune complex deposits.



Diagnosis was determined as C3 glomerulonephritis associated with monoclonal gammopathy. Patient was successfully treated with pulse glucocorticoids followed by oral glucocorticoids and mycophenolate mofetil. C5b-9 was elevated whereas factor H, C3 nephritic factor, and factor B were within normal limits.

Discussion: C3 glomerulonephritis is related to dysregulation of alternative pathway of complement (AP) that can be associated with monoclonal gammopathy. Treatment of underlying monoclonal gammopathy may be of benefit in such a situation. Genetic studies for dysregulation of AP might be helpful.

SA-PO043

Late-Onset Fabry Disease with a R112H *GLA* Mutation and Mild Increase in Plasma Globotriaosylsphingosine Akifumi Onishi,¹ Reika Takemoto,² Tsutomu Hiromasa,² Hidetoshi Kagawa,² Hiroki Maruyama,³ Ichiei Narita,³ Hitoshi Sugiyama,¹ Jun Wada.¹ ¹Okayama Univ Graduate School, Okayama, Japan; ²Himeji Red Cross Hospital, Himeji, Japan; ³Niigata Univ Graduate School, Niigata, Japan.

Introduction: Fabry disease (FD), a lysosomal storage disorder caused by α -galactosidase A (*GLA*) gene variants, has a heterogeneous phenotype. *GLA* variants can lead to a late-onset and non-classical phenotype. We herein describe a 42-year-old patient with FD diagnosed by a renal biopsy exhibiting a R112H *GLA* mutation and a mild increase in plasma globotriaosylsphingosine (Lyso-Gb3).

Case Description: A 42-year-old Japanese male was referred to our hospital due to proteinuria. He had never experienced neuropathic pain, cutaneous angiokeratomas, or hypohidrosis. He had no family history of FD. At 32 years of age, positivity for urinary protein was noted on a health checkup. Thereafter, his urinary protein was annually positive, however, it was untreated because he had no other symptoms. The urinary protein was 0.62 g/gCr, serum creatinine 1.27 mg/dL, and the eGFR 51 mL/min/1.73m². Microscopic findings of a renal biopsy showed foamy change and numerous lamellar inclusions in the cytoplasm of podocytes. A significantly low level of leukocyte *GLA* activity (1.0 nmol/mgP/hr), normal level of plasma globotriaosylceramide (Gb3) (2.7 mg/ml), mildly high level of plasma Lyso-Gb3 (4.1 ng/ml), and the c335G>A, p.R112H mutation of *GLA* were found. He was diagnosed with late-onset FD without signs of the classical symptoms, cardiac hypertrophy or cerebrovascular disorder. He began taking enzyme replacement therapy of agalsidase beta every 2 weeks, and his renal function has remained stable for 8 months.

Discussion: FD patients with the R112H *GLA* mutation do not exhibit classical symptoms and are considered to have a late-onset phenotype (*Clin Genet* 2014) with higher

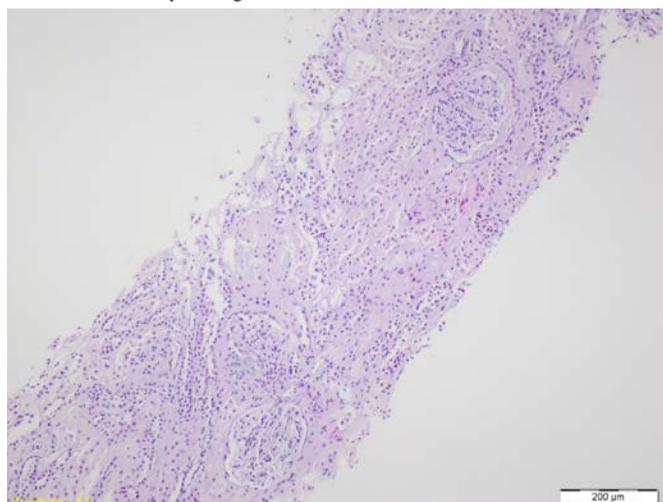
plasma Lyso-Gb3 levels than healthy subjects (*PLoS One* 2015). Undiagnosed FD patients may exist because their symptoms are restricted to proteinuria alone, as shown in this case. Further familial examination will help us elucidate this case as sporadic or familial FD to make an earlier diagnosis and treatment.

SA-PO044

Another Enemy for Kidneys: Synthetic Cannabinoids Alper Alp,¹ Hakan Akdam,² Aysegul Ormeci,³ Ibrahim Meteoglu,³ Alparslan Unsal,⁴ Yavuz Yenicierioglu.² ¹Nephrology, Van Region Education and Research Hospital, Van, Turkey; ²Nephrology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; ³Pathology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; ⁴Radiology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey.

Introduction: Synthetic cannabinoids(SC) are widely used especially among young population. These substances have various physiological, metabolic and psychiatric(addictive) effects. In last few decades SC related acute kidney injury(SC-RAKI) is pronounced more often.

Case Description: A 20-yo man without a medical history presented to ED with abdominal discomfort, nausea and vomiting for 3-4 days. On physical examination; arterial tension was 150/60 mm/Hg, HR 86/min, without orthostatic signs. He denied any nephrotoxic drug use, OTC medication or contrast media exposure. He has been a synthetic cannabinoid(Bonzai) smoker for last 2 weeks. On admission he was oliguric and creatinine was 7.71mg/dl with normal creatinine kinase levels. Urinary analyse revealed pH 5.5, protein +, leu 3, ery 1. Renal ultrasound showed normal size kidneys with increased echogenities, without hydronephrosis. Intermittent hemodialysis therapy was started. Autoimmune antibodies were negative. Renal biopsy revealed acute interstitial nephritis with increased mesangial matrix. Vascular structures were normal, no specific immunohistochemistry staining was detected.



After 6 sessions of HD his urinary output increased and creatinine levels regressed without a specific therapy. 24-h urinary proteinuria was 529,2mg/d. On the 11th day of hospitalisation his creatinine level was 0.6mg/dl.

Discussion: SC-RAKI is usually reported as a consequence of prerenal conditions or rhabdomyolysis. In general renal histopathology reveals acute tubular necrosis. However, rarely these patients may present with interstitial nephritis. In our case complete cure of the patient without specific therapy was quite interesting.

SA-PO045

A Unique Case of Granulomatous Acute Interstitial Nephritis from Ipilimumab Kenneth Ralto,¹ Seymour Rosen,² Melanie P. Hoenig.¹ ¹Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; ²Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Introduction: Ipilimumab is a CTLA-4 inhibitor which is used for the treatment of melanoma. We report a case of granulomatous interstitial nephritis due to ipilimumab, which developed after the first dose and featured a prominent component of granulomatous vasculitis.

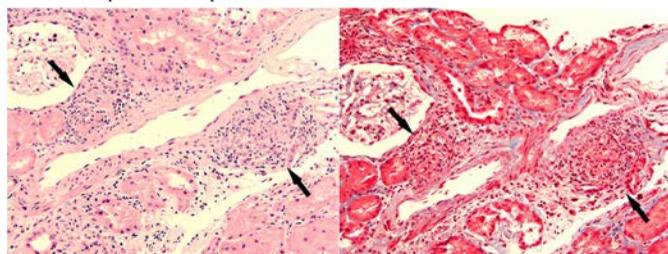
Case Description: A 70 year old man with stage IV melanoma presented with low grade fevers and malaise. He was found to have acute kidney injury with a creatinine of 6.0 mg/dL. Two months earlier, he had received a single dose of ipilimumab at which time his creatinine was 0.9 mg/dL. Laboratory data was notable for the absence of eosinophilia. Urinalysis showed 5-10 WBCs/hpf and many hyaline casts. A renal biopsy showed granulomatous interstitial nephritis with a component of granulomatous vasculitis (figure: H&E, Masson trichrome). He was treated with high-dose prednisone, which resulted in improvement of his renal function without the need for hemodialysis. After ten weeks of steroid therapy, his creatinine had decreased to 1.6 mg/dL.

Discussion: Ipilimumab is a potent activator of T cells and can interfere with the immune system's tolerance of self-antigens. This drug is known to cause a variety of immune-related adverse events including hypophysitis, hepatitis, colitis and dermatitis. Interstitial nephritis is a rare diagnosis, but has been reported to occur after exposure to

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

ipilimumab. Additionally, there have been reports of a sarcoidal-type response involving the lung and skin. This injury pattern is typified by angiocentric non-necrotizing well formed granulomas. Steroid therapy is effective at treating these immune-related adverse events and does not appear to impair the antineoplastic effects of ipilimumab. With the increasing use of immune-modulating antibodies for treatment of malignancies, it is important to be aware of this potential complication.



SA-PO046

Severe Rhabdomyolysis Secondary to Adenovirus Infection Daniel Tseytlin,¹ Sharon E. Maynard.² ¹Dept of Medicine, Lehigh Valley Health Network, Allentown, PA; ²Div of Nephrology, Lehigh Valley Health Network, Allentown, PA.

Introduction: A 38-year-old male presented with renal failure in the setting of a flu-like illness. Urinalysis showed myoglobinuria and granular casts. His CPK was markedly elevated. He is diagnosed with rhabdomyolysis from adenovirus and requires hemodialysis.

Case Description: A 38-year-old AA male presented to the ER with a 4-day history of weakness, subjective fever, and diffuse myalgias as well as recent left eye viral conjunctivitis. He noted dark urine and poor urine output. On arrival to the ER his vitals were stable. He had full muscle strength and no neuro deficits. He was oliguric. His Scr 5.04, CPK 1,149,533 despite volume resuscitation including bicarb-containing fluid. He required HD. Workup was positive for adenovirus. Muscle biopsy was deferred in setting of known cause. He required 4 weeks of HD and was able to come off with impaired GFR of 67.

Discussion: Two cases of rhabdomyolysis from adenovirus have been reported. Most commonly manifests as a febrile illness with pharyngitis. Management strategies have been adopted from studies on crush injury victims. Early volume resuscitation is recommended to mitigate renal failure. Despite the theoretical benefits of bicarbonate-containing resuscitation fluids, no consensus exists. Adenoviral infection can lead to rhabdomyolysis with severe acute kidney injury. Respiratory viral panel should be included in workup of rhabdomyolysis when no other cause is evident. Treatment relies on supportive care, intravenous fluid resuscitation, and hemodialysis in cases of severe renal failure.

Serum Parameter	Day 1	Day 2	Day 3	Day 17 (discharge day)	Day 64 (outpt f/u off dialysis)
Sodium (mmol/L)	125	124	122	136	137
Potassium (mmol/L)	4.7	7.3	6.7	4.2	4.1
Chloride (mmol/L)	89	83	84	104	102
Bicarbonate (mmol/L)	17	20	26	24	26
BUN (mmol/L)	40	52	58	40	17
Creatinine (mg/dL)	5.04	5.79	8.50	9.52	1.32
Albumin (g/dL)	3.3				4.3
Anion Gap	19	17	12		9
CPK (U/L)	857,200	360,000	1,149,533		245
Phosphorus (mg/dL)	14.4	>16	14.6		3.5
Calcium (mg/dL)	5	<5		8.2	9.4
Ionized Calcium (direct)			<2.24		
Magnesium (mg/dL)	2.8	2.9	2.9		1.7
AST (U/L)	3,107				
ALT (U/L)	279				
Lactate (mmol/L)	3.1	2.1	1.5		

SA-PO047

Acute Respiratory Distress Syndrome and Posterior Reversible Encephalopathy Syndrome following Rituximab Therapy Eoin D. O Sullivan,¹ Katrina E. Wardrope,¹ Lynn Manson,² Wendy Metcalfe.¹ ¹Dept of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; ²Scottish Blood Transfusion Service, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.

Introduction: The anti CD20 monoclonal antibody Rituximab is an increasingly used therapy in modern medicine. It is associated with rare but potentially serious adverse events, notably Posterior Reversible Encephalopathy Syndrome (PRES), and Acute Respiratory Distress Syndrome (ARDS).

Case Description: A 60 year-old female was admitted with symptoms of peripheral oedema, arthralgia and mucosal bleeding. She was noted to have a widespread vasculitic rash, nephrotic range proteinuria and new acute kidney injury. Renal biopsy demonstrated mesangiocapillary glomerulonephritis with multifocal extraglomerular necrotising vasculitis, in keeping with cryoglobulinemia. She was commenced on plasma exchange, prednisolone and Rituximab. 2 days after the initial dose of Rituximab she developed acute respiratory distress and was found to be in florid pulmonary oedema. This was managed with ultrafiltration, furosemide and oxygen therapy. She received a second dose of Rituximab 1 week later, and rapidly developed tonic-clonic seizures, a further episode of flash pulmonary oedema, encephalopathy and hyperreflexia. MRI brain revealed subcortical white matter high T2 and FLAIR signal in the occipital and posterior parietal lobes consistent with PRES. She received no further Rituximab. Her cryoglobulin levels remained detectable despite alternate day plasma exchange for 2 weeks, prompting the initiation of cyclophosphamide. Following 1 dose of cyclophosphamide the cryoglobulin titre fell to undetectable levels. All reported cases of PRES and ARDS were identified and are presented as a review.

Discussion: There are 7 reported cases of PRES complicating rituximab use. The onset of PRES occurred from immediately to 21 days after administration. All patients recovered completely, and rituximab was reintroduced in half of the cases. Mean recovery time was 4 days, and an additional risk factor was present in 5 cases. The occurrence of ARDS in association with rituximab is rare, only 3 confirmed cases exist. ARDS may occur as a delayed reaction.

SA-PO048

Atypical Hemolytic Uremic Syndrome Associated with Rituximab Kristina Angela Rathmell, Shilpa Gadde. *Nephrology, Tulane, New Orleans, LA.*

Introduction: Hemolytic uremic syndrome (HUS) is classified as a thrombotic microangiopathies (TMA). Atypical HUS (aHUS) occurs in 0.5 to 2 per million population per year, 50% progress to end-stage renal disease (ESRD), and 25% may die in the acute phase. Atypical HUS is linked to uncontrolled activation of the complement system. A variety of genetic abnormalities of the alternative pathway of complement have been described in aHUS, occurring in 60% of cases. aHUS is diagnosis when *toxin producing bacterial infections*, ADAMTS13 deficiency, and systemic-associated diseases are all excluded.

Case Description: A 57 year-old woman with a history of dermatomyositis and associated interstitial lung disease (ILD) was being treated for her ILD with Rituximab. She presented with altered mental status, shortness of breath, and fatigue after receiving an infusion of Rituximab. She was noted on physical exam to have peripheral edema and crackles on lung exam. On laboratory evaluation, her creatinine was 4.5 (baseline 1), hemoglobin 7, and platelets 20 with schistocytes on peripheral smear and a low C3 and C4. ADAMTS13 showed normal activity. She was initially treated with high dose steroids and plasmapheresis. She was started on Eculizumab. She required hemodialysis. Renal biopsy showed thrombi consistent with thrombotic microangiopathy as well as mild acute tubular necrosis. She is still hemodialysis dependent.

Discussion: Overall outcomes of this rare diagnosis vary widely. Initial treatment is usually plasmapheresis and corticosteroids. Confirmed aHUS is usually treated with Eculizumab. Our unique case entertains Rituximab, a monoclonal antibody, as a possible trigger for aHUS. Knowing the mechanism of action of Rituximab, it is possible it mediated a complement imbalance. More investigation is needed to determine Rituximab's causality in inducing aHUS. Given the increasing use of Rituximab for various autoimmune conditions and malignancies it will be notable to see if more cases like this arise. 1. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med.* 2009;361:1676-1687. 2. Constantinescu AR, Bitzan M, Weiss LS, et al. Non-enteropathic hemolytic uremic syndrome: Causes and short-term course. *Am J Kidney Dis.* 2004;43: 976-982.

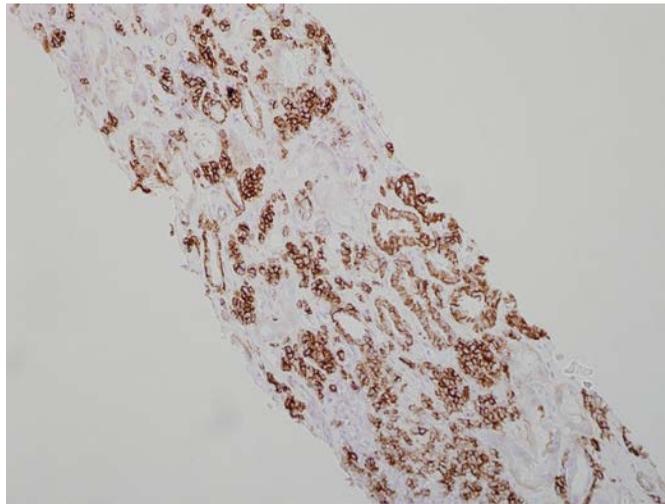
SA-PO049

Acute Renal Failure Associated with Parenchymal Involvement of Lambda-Restricted Neoplastic Plasma Cells Mark C. Sievert, Amanda K. Hall, Mazdak A. Khalighi, Josephine Abraham. *Div of Nephrology, Univ of Utah, Salt Lake City, UT.*

Introduction: The pathogenesis of renal disease in multiple myeloma (MM) is diverse, but biopsies show that cast nephropathy, light chain amyloidosis and monoclonal Ig deposition are most often responsible. Renal function often correlates to the degree of cellular injury, not the degree of cast burden, amyloidosis or light chain deposition and direct involvement by plasma cells is rare. We present a case of diffuse interstitial involvement by neoplastic plasma cells, contributing to renal failure.

Case Description: A 70-year-old male with MM presented with acute renal failure. He was diagnosed with IgG lambda myeloma 8 years prior but refused therapy until 7 months ago. He failed CyBorD (M-protein remained at 9g/dl) prior to starting Carfilzomib-Revlimid.

On day 8 of therapy he was admitted with a Cr of 3.4, acutely elevated from 1.7. He denied hematuria, oliguria, fevers, edema or NSAID use. Renal ultrasound was without obstruction. He underwent renal biopsy. Pathology revealed diffuse interstitial involvement by lambda-restricted neoplastic plasma cells and minimal cast nephropathy, but no significant interstitial fibrosis, tubular atrophy or monoclonal deposition disease. Congo red studies were negative for amyloid. There were no features of TMA. Chemotherapy was resumed.



CD138 IHC stain showing plasma cells.

Discussion: Kidney disease with MM is common but it is rare to see involvement of plasma cells in the renal parenchyma. Several review articles list renal parenchymal involvement of plasma cells as a cause of renal failure and, to our knowledge, one case report suggests the same. It is unknown the extent to which parenchymal involvement by plasma cells contributes to the pathogenesis of renal failure. To our knowledge, this is one of only several cases of renal failure that can be attributed to neoplastic plasma cell involvement.

SA-PO050

AL Amyloidosis with Rapidly Progressive Renal Failure and Massive Liver Involvement: A Case Report Matteo Floris,¹ Maura Conti,¹ Riccardo Cao,¹ Anna Maria Asunis,² Elisabetta Tamponi,² Alice Atzeni,¹ Patrizia Melis,¹ Gianfranco Pili,¹ Valeria Matta,¹ Nicola Lepori,¹ Doloretta Piras,¹ Andrea Angioi,¹ Antonello Pani.¹ ¹*Nephrology, G. Brotzu Hosp, Italy;* ²*Pathology, G. Brotzu Hosp, Italy.*

Introduction: AL amyloidosis is a plasma cell disorder clinically dominated by organized deposits of light chains, mainly in renal and cardiac tissues. Although hepatic disease is described, clinical manifestations are usually mild and frequently undetected. We report a severe case of AL amyloidosis with a massive hepatic involvement and rapidly progressive renal failure (RPRF).

Case Description: One month before coming to our attention, a 67 year old male was admitted to another institution for ascites and scrotal edema. Past medical history included hypertension, previous hepatitis B virus infection and estimated daily alcohol intake of 60g. Renal function was normal (serum creatinine [SCr] 0.7 mg/dl), while hepatic lysis indexes were moderately positive. A serum monoclonal component IgA kappa (0.21 g/dl) was detected and the bone marrow aspirate showed 10% plasma cell infiltration. Hepatic ultrasound showed hepatomegaly and portal hypertension. Final diagnosis was compensated alcoholic liver disease. After discharged, nephrotic syndrome (NS) (albumin 2.4 g/dl, proteinuria 12 g/24h), RPRF (SCr 1.6 mg/dl) and cholestasis appeared (ALP 1359 IU/L, GGT 462 IU/L, AST-ALT normal). The patient was admitted to our institution and renal biopsy was performed revealing AL amyloidosis, with prominent IgA(+) and Kappa(++) mesangial deposits, coherently with the serology. The hepatic disease was rediscussed, and the liver biopsy revealed coarse deposits of amyloid as for the kidney. Other organs, heart included, appear to be spared at the time. In accordance with hematologists, a CyBorD based regimen was started. Due to worsening kidney dysfunction, hemodialysis was initiated.

Discussion: This case highlights a rare presentation of AL amyloidosis with severe renal and hepatic involvement. Liver amyloidosis should be suspected in any patient with NS and unexplained cholestasis. Therefore, renal and hepatic biopsies should be considered when the clinical diagnosis is obscure, especially if rapid evolution to multiorgan failure is documented.

SA-PO051

Pulmonary-Renal Syndrome: A Rare Case Joana Gameiro,¹ Sofia C.A. Jorge,¹ Miguel Bigotte Vieira,¹ Estela Nogueira,¹ Maria Alice Fortes,¹ Helena Sousa Viana,² Fernanda Carvalho,² Jose António Lopes,¹ Antonio Gomes Da Costa.¹ ¹*Service of Nephrology and Kidney Transplantation, Hospital Santa Maria, Portugal;* ²*Service of Nephrology, Hospital Curry Cabral, Portugal.*

Introduction: Pulmonary-renal syndrome (PRS) is characterized by acute renal and pulmonary involvement of immunological or non-immunological causes.

Case Description: A 35-year-old African woman with 6-month history of edema, bilateral arthralgias in her knees, shoulders and hands, creatinemia 2.6mg/dL and nephrotic proteinuria referred to Portugal for medical care presenting with bilateral erythematous non pruriginous macular lesions in both thighs. Investigation confirmed renal failure (creatinemia 7mg/dL), nephrotic proteinuria (4.7g/24h), haematuria, hypoalbuminemia, hyperlipidemia, normal sized kidneys with increased parenchymal echogenicity. She began hemodialysis and was transferred to ICU due to pulmonary hemorrhage requiring mechanical ventilation. Plasmapheresis and intravenous high-dose steroids were started. Pneumococcal pneumonia was also diagnosed and began antibiotic. Immunologic and serologic tests were negative or normal range. Serum protein electrophoresis showed hypogammaglobulinemia. Echocardiogram revealed type II diastolic dysfunction. Renal biopsy showed nodular glomerulosclerosis. Investigation of haematological disease revealed serum kappa light chain band and urine Bence Jones kappa. Free kappa light chains, serum kappa/lambda ratio and serum Beta-2-microglobulin were elevated. Bone marrow biopsy and aspirate showed 10% monoclonal plasmacytosis. No lytic lesions or masses were detected. Immunofluorescence of the renal biopsy revealed linear staining for kappa light chains along the tubular basement membrane and scarcer in the glomeruly. Electron microscopy is underway. Multiple myeloma was diagnosed and started chemotherapy with Bortezomib. Although there was maintained remission of pulmonary hemorrhage she remained on dialysis.

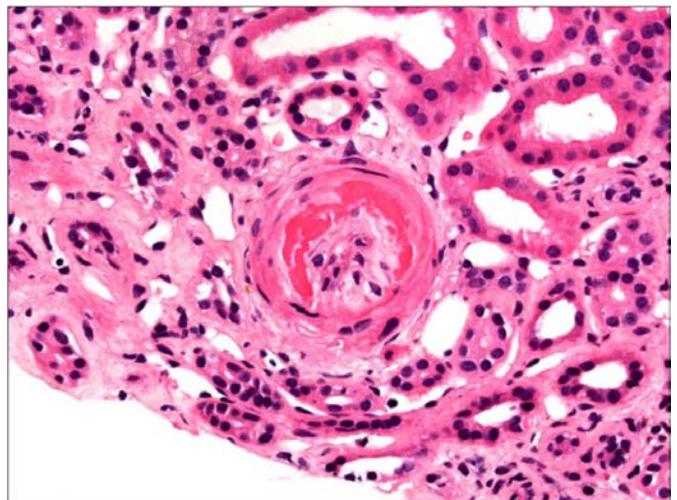
Discussion: Light chain deposits disease (LCDD) should be considered in the differential diagnosis of PRS. Renal involvement is typical in LCDD with nodular glomerulosclerosis as the common pathologic finding. Pulmonary haemorrhage is unusual and might suggest coexistence of fibrillary glomerulonephritis.

SA-PO052

Acute Cadrilateral Syndrome as a Presenting Symptoms for Scleroderma Renal Crisis Muhammad H. Hasan, Khurram Saleem, Khaled Boobes, Yazan M. Alia, Sadaf S. Khan. *Nephrology and Hypertension, Northwestern Univ, Chicago, IL.*

Introduction: Systemic scleroderma is known to have renal manifestations including scleroderma renal crisis. Acute decompensated heart failure was not described in the literature as the presenting symptom.

Case Description: 50 year-old female with benign past history was diagnosed with new acute decompensated diastolic heart failure and hypertension 160/89 and acute kidney injury with elevated serum creatinin (SCr) 2.6 mg/dL from normal kidney function 2 months prior. Right heart catheterization showed elevated right heart pressures. Endomyocardial biopsy showed small vessel vasculitis. Urinalysis was bland. Renal ultrasound was unremarkable. Renal artery Duplex showed high resistant signals with low velocity. Subsequent immunology screen showed elevated antinuclear antibodies >1:1280, elevated RNA Polymerase III >80 and normal C3 and C4. Renal biopsy showed changes consistent with systemic sclerosis; the glomeruli were ischemic in general and one was sclerosed, the arteriols were with marked walls thickening and swelling of the intima, some undergone occlusive changes with onion skinning of their walls, while others undergone focal fibrinoid necrosis, the tubules were with mild to moderate atrophy, the interstitium was diffusely scarred, with mild to moderate focal and scattered cellular of lymphocytes. (biopsy). Retrospectively, the patient reported skin tightening noticed 6 months prior to admission. Blood pressure was controlled with nicardipine drip, captopril, diuretics and bosentan. SCr peaked up to 6.72 mg/dL but renal replacement therapy was avoided. She was discharged on bosentan, amlodipine and lisinopril. SCr improved to 1.78 mg/dL after 8 months.



Discussion: Scleroderma renal crisis can present as acute cardiorenal syndrome.

SA-PO053

Dent's Disease: An X-Linked Tubulopathy Sambhavi Krishnamoorthy, Tingting Li. *Renal Div, Washington Univ in St. Louis, Saint Louis, MO.*

Introduction: Dent's disease is an X-linked recessive disorder of the proximal tubule characterized by low-molecular weight proteinuria, hypercalciuria, nephrocalcinosis/nephrolithiasis, and progressive renal failure. This disorder is caused by mutations in either the CLCN5 gene, or less commonly the OCRL1 gene, leading to disruption of tubular endocytosis and the characteristic clinical findings.

Case Description: We describe an interesting case of a 24 year old Caucasian male with a longstanding history of excessive thirst and polyuria. He had no known history of renal disease. He denied history of urinary tract infections, nephrolithiasis, or NSAID use. Physical examination was unremarkable. Laboratory data showed a serum creatinine of 1.6. Hemoglobin A1c was normal. Urinalysis showed 2+ blood and 2+ protein. Urine osmolality was 277 mOsm/kg. A 24 hour urine collection showed proteinuria of 1.7 g/day. ANA, ANCA, and hepatitis panel were all negative. Renal ultrasound showed multiple bilateral renal calculi and nephrocalcinosis. Further testing showed a daily urinary calcium excretion of 735 mg, phosphate 2150 mg and sodium 257 mg. His urine beta microglobulin level was significantly elevated at 29817 mcg/L. The presence of significant low molecular weight proteinuria, hypercalciuria, hyperphosphaturia, nephrolithiasis/nephrocalcinosis, hematuria/subnephrotic proteinuria, and chronic kidney disease fulfilled criteria for the diagnosis of Dent's disease. No obvious X-linked pattern had been noted in his family history. Further genetic testing is pending at this time. On initiating hydrochlorothiazide, urinary calcium excretion reduced by 50%. Polyuria, which we attributed to nephrogenic diabetes insipidus in the setting of nephrocalcinosis, also improved significantly with the thiazide.

Discussion: This case report highlights the importance of recognizing this rare X-linked tubulopathy when presenting in adulthood. Commercially available genetic testing can be utilized for supporting the diagnosis and for appropriate genetic counseling for family members. The treatment focuses on reducing urinary calcium excretion and formation of nephrocalcinosis/nephrolithiasis with the ultimate goal of slowing progression to end stage renal disease.

SA-PO054

Phlegmasia Cerulea Dolens: Complication of Femoral Vein Catheterization Chaitanya Vemuri, Boju Sangeetha lakshmi, Hari Krishna Reddy Mogili, Ram R, Siva Kumar Vishnubhotla. *Dept of Nephrology, Sri Venkateswara Inst of Medical Sciences, Tirupati, Andhra Pradesh, India.*

Introduction: There are three manifestations of acute massive venous thrombosis and obstruction of the venous drainage of an extremity. They are phlegmasia alba dolens, phlegmasia cerulea dolens (PCD) and venous gangrene.

Case Description: We present a 55-year-old hypertensive, presented with paedal oedema and breathlessness. About a month ago, she fell down and had dislocation of left patella. She was treated with a plaster cast and immobilization for 3 weeks. Her serum creatinine was 8.8 mg/dL. She was initiated on haemodialysis via two single lumen catheters placed in left femoral vein. The femoral vein catheters were removed after third session of haemodialysis. On fourth day, the patient complained pain and blue discoloration of left toes. Examination revealed that the left lower limb was swollen, discoloured and cold up to ankle joint. The left dorsalispedis and posterior tibial arteries were not palpable. Within next 12 hours, the signs extended to upper one-third of left leg and there were blebs.



Doppler revealed thrombosis of left common, external iliac, femoral, popliteal, anterior, posterior tibial vein and superficial veins. The left lower limb was elevated and anticoagulation was started but blebs increased and limb became blue. Below knee amputation of left lower limb was performed.

Discussion: The causative factor in phlegmasia is massive thrombosis and occlusion of major venous channels. Perkins et al reported that in 10 percent of patients no cause is found. It is common in women between fifth and sixth decades of age. Swelling, pain and cyanosis are the triad of PCD. Amputation rates are 12-50%. In our patient the effect of immobilization is compounded by femoral vein catheterization. PCD after femoral vein catheterization for haemodialysis has not been reported yet.

SA-PO055

Successful Treatment of Ischemic Hand Ulcer by Paclitaxel Coated Balloon Jie Cui,¹ Fengyong Liu,² Zubin Irani.³ *¹Nephrology, Massachusetts General Hospital, Boston, MA; ²Interventional Radiology, Chinese People's Liberation Army General Hospital, Beijing, China; ³Div of Vascular Imaging and Intervention, Massachusetts General Hospital, Boston, MA, China.*

Introduction: Hand ischemia is a common complication in end stage renal disease (ESRD) patients. Steal syndrome from dialysis access is the most common cause of ischemic hand and is usually treated with banding procedure. However, exclusion of peripheral arterial disease (PAD) prior to banding is crucial.

Case Description: A 74 year-old woman with history of ESRD due to diabetes mellitus on hemodialysis presented to access clinic for right hand ulcer. She had a right side brachiobasilic graft placement 3 years ago and has been dialyzed through this graft without any issues. However, 3 months prior to the presentation, she started to notice severe right hand pain, especially during dialysis treatment. Four weeks ago, she developed an ulcer in the 2nd finger of her right hand.

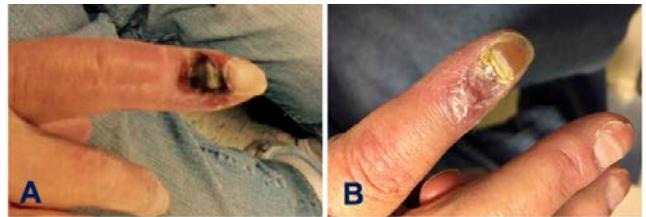


Figure The patient presented with a black ulcer on the second finger of her right hand. The ulcer completely healed 4 weeks later after paclitaxel-coated angioplasty balloon.

Given the concerns for steal syndrome, she was referred for a banding procedure. On physical exam, the graft had good thrill and bruits. Right radial artery pulse was very weak. A black ulcer was noticed on the 2nd finger of the right hand. Decreased sensation in the 1st, 2nd and 3rd fingers of the right hand. Fistulogram was performed which demonstrated occluded lesion in the proximal right radial artery, which was recanalized and angioplastied with 2mm, 3mm and 4mm balloon. However, at one-month clinic follow up, her ulcer only had minimal improvement. Repeat arteriogram showed moderate radial artery stenosis, which was angioplastied with 4mm paclitaxel coated-angioplasty balloon. The ulcer healed completely 1 month later.

Discussion: Paclitaxel coated balloon was recently approved by FDA to treat PAD in the lower extremities. This case report showed upper extremity PAD can also be treated successfully with paclitaxel coated angioplasty balloon.

SA-PO056

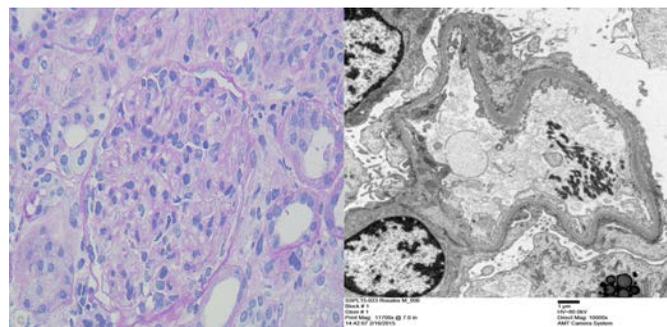
Minimal Change Disease Associated with Invasive Ductal Carcinoma of the Breast: A Case Report and Literature Review Siddhesh R. Lotlikar,² Julian D. Rose,¹ Soumya Patnaik,² Supakanya Wongrakpanich,² Mary Carolina Rodriguez Ziccardi,² Mark S. Morginstin,² Rasib Raja,² Eric J. Bloom.² *¹Sidney Kimmel Medical College; ²Albert Einstein Medical Center, Philadelphia.*

Introduction: A tenth of malignancies have been associated with nephrotic syndrome, the diagnosis of which may precede the detection of cancer. In an adult with Minimal Change Disease (MCD), paraneoplastic etiology should be explored. Here, we describe a rare case of MCD associated with breast cancer.

Case Description: Our patient is a 72-year-old Caucasian female who presented with bilateral lower extremity edema for 1 week. Home medications were notable for occasional Diclofenac use. Urinalysis on admission showed nephrotic-range proteinuria. MCD was suspected and confirmed on renal biopsy. CT ruled out lymphoma and thymoma. MCD was presumed secondary to Diclofenac use and she was discharged on daily prednisone with instructions to avoid NSAIDs. Two months later, she presented with a pulmonary embolus and CT showed concerning breast changes. Biopsy confirmed a stage IIIC invasive ductal adenocarcinoma. She was tapered off steroids, continued on furosemide and started on Paclitaxel.

Discussion: Breast cancer mainly causes antibody-mediated paraneoplastic syndromes. Yet, studies have shown intratumoral IFN- α expression correlates with induction of autoreactive T-cells, presenting a route for breast cancer to cause a T-cell mediated process such as MCD. Our patient had no lymphoma or thymoma and the lack of evidence of AIN and failure of improvement on discontinuation of NSAIDs argue against NSAID-induced MCD. The relationship of MCD with breast carcinoma is reinforced by her improved proteinuria with chemotherapy.

Time	MCD dx	1 month after dx	1.5 months after dx	1 week after first chemo (week 1)	2nd cycle of chemo (week 2)	3rd cycle of chemo (week 3)	1 week after 3rd cycle of chemo
Urine Protein (mg/dl)	1270.1	1773.4	1407.3	55	35.8	10.6	0



SA-PO057

A Case of Donor-Derived Enterococcal Pyelonephritis in an HIV-Positive Kidney Transplant Recipient Akshatha Rao,¹ Shilpa A. Chaudhari,² Dong Heun Lee,² Karthik M. Ranganna,¹ Alden Michael Doyle.¹ *Div of Nephrology, Drexel Univ, Philadelphia; ²Division of Infectious Disease, Drexel Univ, Philadelphia.*

Introduction: Donor-derived infections are an unusual but recognized complication of solid organ transplantation. Between 2005-2011, there were 118 reported donor bacterial infections, of which 34 recipients had confirmed transmission of infection and 9 deaths due to donor derived bacterial infections. Herein, we describe a unique case of donor-derived enterococcal pyelonephritis in a kidney transplant recipient with HIV infection.

Case Description: 47 year old male with history of HIV infection (CD4 -534 cells/mm³, VL<20 copies), ESRD on peritoneal dialysis, hypertension had deceased donor kidney transplantation. Post-op patient was given 1 dose of cefazolin as surgical prophylaxis. Basiliximab and intravenous immunoglobulin was used for induction therapy. Patient was started on tacrolimus, mycophenolate mofetil and prednisone for maintenance therapy. POD#3 we were notified by organ procurement organization (OPO) that donor urine culture grew >100,000 colonies /ml of Enterococcus faecalis. Our patient was started on intravenous ampicillin to complete a total of 6 days antibiotic course. POD #17 patient was readmitted to the hospital with urinary retention and elevated serum creatinine 2.2.

Renal ultrasound showed no hydronephrosis. Urinalysis showed 2+ leukocyte esterase, WBC 11-20, with occasional bacteria. Blood and urine culture grew Enterococcus faecalis that had same susceptibility pattern of that from donor kidney. Patient was started on intravenous ampicillin to complete a total of 14 days. Serum creatinine improved with treatment.

Discussion: There is no clear consensus on treatment regimens for donor-derived infections. This case demonstrates transmission of donor-derived enterococcal infection despite timely initiation of appropriate antimicrobial therapy. Because of increased morbidity and mortality associated with post-transplant infection extended duration of antimicrobial therapy should be considered in these patients.

SA-PO058

Peritoneal Dialysis: A Better Modality of Renal Replacement Therapy for Liver Cirrhotics with End Stage Renal Disease? Akshatha Rao, Sweta Carpenter, Alden Michael Doyle. *Divison of Nephrology, Drexel Univ, Philalphia.*

Introduction: Managing patients with end stage liver disease associated with portal hypertension, ascites and end- stage kidney disease requiring renal replacement therapy is challenging for a number of reasons including chronic hypotension, poor nutrition, coagulopathy, high infection rates, and encephalopathy. It is difficult to assess accurate dry weights because of the large variation patient weights depending on how much ascites they have at the time of dialysis, with weight fluctuations in excess of 10 kg. There is also a reluctance on the part of the transplant community to utilize PD because of the perception that these patients may not be able to go on to receive a successful liver transplant.

Case Description: Herein, we report our experience with 5 consecutive patients with decompensated cirrhosis who progressed to ESKD and required dialysis support. One patient did not tolerate HD and was switched to PD, the other 3 started with de novo PD. In each case, the patients were admitted to hospital for PD catheter placement with a surgeon experienced with patients who had advanced liver disease and stayed in the hospital for initial recovery period with IV albumin to support blood pressure. By our protocol, ascites fluid was drained in the OR and then drained each morning for the next 2 weeks before dialysis was initiated. Blood pressures ranged from 80/50-110/65 mmHg, patients remained asymptomatic. All patients received oral midodrine for BP support.

Adequate ultrafiltration achieved and edema improved. Serum albumin was monitored at regular intervals, ranged from 2.5-3. One patient had peritonitis from time of surgery, which was treated successfully; no other cases of peritonitis were noted.

Discussion: We suggest that PD should be considered in selected patients who have ascites and end-stage kidney disease. Further research is warranted regarding long term outcomes and potential effects of PD on the ability for these patients to get transplanted.

SA-PO059

Focal Segmental Glomerulosclerosis Presenting Concurrently with Chromophobe Renal Cell Carcinoma Itunu O. Owoyemi, Denise J. Thomson, Hiren J. Joshi, M.J. Barchman. *Nephrology, East Carolina Univ/Vidant Medical Center, Greenville, NC.*

Introduction: Chromophobe renal cell carcinoma (CHRCC) is a rare variant of RCC with distinct histochemical, ultrastructural and genetic characteristics. CHRCC accounts for approximately 4% of all kidney neoplasms. Glomerulopathies are often diagnosed in patient with malignances, particularly hematological cancers with membranous nephropathy being the most common variety. We present a case of resistant hypertension in a young adult male found to have focal glomerulosclerosis (FSGS) with concurrent CHRCC. This case highlights the association and emphasis of screening for secondary hypertension in resistant patients, early referral and the pitfalls of percutaneous biopsy for solid renal masses.

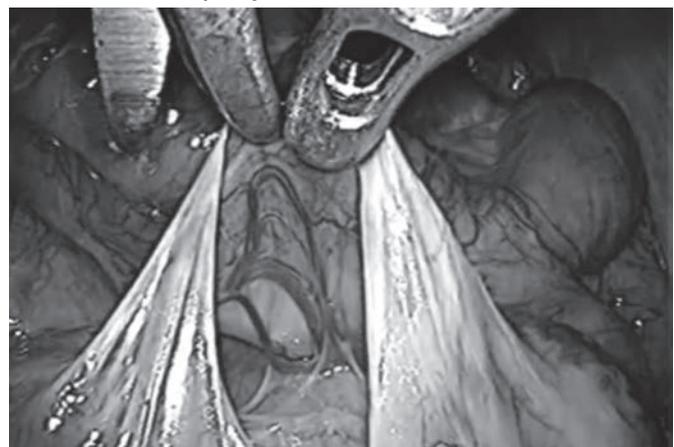
Case Description: A 34 year old Nigerian male initially presented to the Internal Medicine clinic to establish care in 2011. His past medical history was significant for hypertension and gross hematuria. He was subsequently referred to Nephrology due to persistent microalbuminuria, hematuria and passage of blood clots in his urine. On presentation to Nephrology, he was found to have nephrotic range proteinuria. Renal ultrasound was significant for several lesions in the right kidney with the largest measuring 3 cm. Percutaneous renal biopsy performed for proteinuria revealed focal segmental glomerulosclerosis with moderate tubulointerstitial scarring. He initiated on steroids however he was lost to follow up for approximately 9 months. Upon return, his renal lesions were readdressed with a MRI of the abdomen which could not exclude multiple solid masses in the right kidney. A subsequent ultrasound-guided fine needle aspiration and core biopsy of the right kidney lesion diagnosed chromophobe renal cell carcinoma. He underwent a right nephrectomy with biopsy result negative for metastasis.

Discussion: We were able to unravel this unique finding of FSGS co-presenting with chromophobe renal cell carcinoma. The prevalence of FSGS in RCC has not been established with precision. This case highlights the importance of timely evaluation of secondary hypertension and biopsy of suspicious renal masses.

SA-PO060

A Case of Peritoneal Dialysis Patient with Unknown Membrane-Like Structure Covering Intestinal Tract Yu Honda, Nanae Matsuo, Yudo Tanno, Yasuyuki Nakada, Taketo Uchiyama, Izumi Yamamoto, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Introduction: A 24-year-old male developed end-stage renal disease (ESRD) and was initially started on hemodialysis (HD). Since he had found difficulty to continue HD because of disdialysis syndrome, he switched to the combination therapy with peritoneal dialysis (PD) and weekly HD on 17years of dialysis duration. Seven years later, he was converted to HD alone. He had no episode of peritonitis. He had no episode of ileus and was not diagnosed with encapsulating peritoneal sclerosis (EPS). Generally the macroscopic appearance of EPS is the whole bowel trapped in a thick, tough peritoneal cocoon. Since his PD duration was long, laparoscopy was performed when his PD catheter was removed. We found his agglomerated small intestine was coated with thin membrane-like structure. It was soft, elastic and easy to separate from intestine.



We performed biopsies of the structure. Surprisingly its histology looked like the normal peritoneum. On the surface of the biopsy, a single layer of mesothelial cells was present. There are no apparent fibrosis (thickening) and sclerosis. This case suggests that his peritoneum-like membrane might be the very early stage of sclerosing capsule of EPS. Since little has been known about transition from a normal state to EPS through pre-EPS state, this case is valuable to identify one part of the mechanisms of EPS. We report this rare case with some literature review.

SA-PO061

Abdominal Compartment Syndrome: An Overlooked Culprit of Acute Kidney Injury in Immediate Post-Liver Transplantation Ekamol Tantisattamo,¹ Praveen Ratanasrimetha,² Siwadon Pitukweerakul.³
¹Nephrology, Northwestern Univ; ²Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; ³Presence St. Francis Hospital, Evaston.

Introduction: Acute kidney injury (AKI) is a common complication after liver transplantation and often times, dialysis is required. Abdominal compartment syndrome (ACS) is a treatable cause of prerenal AKI without dialysis needed.

Case Description: A 60-year-old man with HCV and alcoholic cirrhosis underwent an OLT. He had massive blood loss during the uncomplicated operation and required massive transfusion and fluid resuscitation. Postoperatively, renal function initially was stable at the baseline serum creatinine (SCr) of 0.8 mg/dL. However, hemoglobin dropped from 9.1 to 5.7 g/dL and tacrolimus level elevated up to 53 ng/mL on postoperative day (POD)4. SCr rose up to 1.3 mg/dL and urine output (UOP) decreased on POD7. Renal function continued to decline with a peak BUN and SCr of 120 and 2.73 mg/dL on POD14, respectively (Figure 1). Dialysis was initially planned. However, he had progressively increased ascites with markedly tense abdomen. Bladder pressure revealed intraabdominal hypertension (IAH) with the pressure of 20 mmHg. FE_{Na} and FE_{crea} were 0.7% and 21%, respectively. Therefore, abdominal paracentesis was performed with an 8 L of yellowish clear ascites fluid removed. UOP significantly increased shortly after paracentesis. SCr had trended down and dialysis was not required.

Discussion: Our patient presented with prerenal AKI secondary to perioperative hypovolemia concomitant with supratherapeutic tacrolimus level. Massive blood transfusion and fluid resuscitation in the setting of major abdominal surgery caused IAH and subsequently ACS contributing to worsening prerenal AKI. Bladder pressure is a bedside diagnostic tool to detect IAH. AKI could be reversed and dialysis could be avoided by abdominal paracentesis.

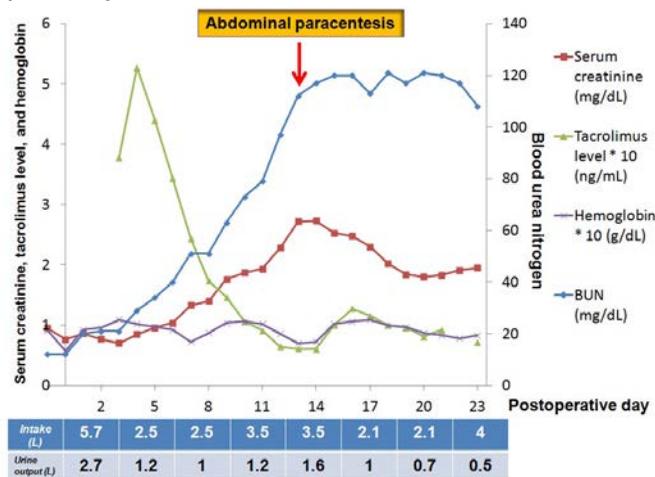


Figure 1: Clinical course during perioperative orthotopic liver transplantation.

SA-PO062

Rasburicase: A Salvage Strategy to Prevent Renal Allograft Loss in Acute on Chronic Urate Nephropathy Ekamol Tantisattamo,¹ Praveen Ratanasrimetha,² Siwadon Pitukweerakul.³ ¹Nephrology, Northwestern Univ; ²Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; ³Presence St. Francis Hospital, Evaston.

Introduction: Chronic hyperuricemia can lead to chronic kidney disease (CKD) and acute on chronic hyperuricemia potentially causes renal failure. Rasburicase is an effective uric lowering agent indicated for the treatment of acute hyperuricemia especially in tumor lysis syndrome. We report a case of kidney transplant recipient with acute hyperuricemia-related acute kidney injury (AKI) which was resolved with rasburicase.

Case Description: A 51-year-old man with ESRD secondary to type 2 diabetes status post renal transplant was admitted with diffuse muscle cramping. Maintenance immunosuppression included cyclosporine (CsA) and mycophenolate mofetil. The baseline serum creatinine (SCr) was 2.5 mg/dL after 2 episodes of borderline changes detected from transplant renal biopsy at 1 and 2 years posttransplant, respectively. However, over the past 9 months, SCr had gradually trended up to 4.4 mg/dL. He had asymptomatic hyperuricemia with a serum uric acid of 9.1–12.5 mg/dL. Two days after admission, he developed severe pain on the right first metatarsal joint presumed from acute gouty arthritis which responded to oral prednisone. However, SCr continued rising up to 4.8 mg/dL. Urinalysis showed a pH of 6 and Sp.Gr. of 1.011. Serum and urine BK virus were undetectable. Transplant renal ultrasound was unremarkable. Serum uric acid was markedly elevated up to 17.7 mg/dL. Given worsening renal function in the setting of acute hyperuricemia, rasburicase was initiated. Serum uric acid had been decreased to 8.1 and 4.5 mg/dL within 20 and 30 hours, respectively and SCr returned to the baseline of 2.5 mg/dL.

Discussion: Our patient presented with AKI on CKD in the setting of symptomatic acute on chronic hyperuricemia. Acute hyperuricemia leads to AKI which was resolved by

rapidly lowering uric acid level with rasburicase. AKI in the patient with underlying chronic hyperuricemia should raise a suspicion for acute hyperuricemia-related AKI. Rasburicase should be considered as a salvage therapy to avoid renal allograft loss.

SA-PO063

The Effect of Taurine on Haemodialysis Filtration in Patients with Chronic Heart Failure: A Case Study Shunji Shiohira,^{1,2} Kosaku Nitta,¹ Ken Tsuchiya.¹
¹Dept of Medicine IV, Tokyo Women's Medical Univ, Shinjuku, Tokyo, Japan; ²Dept of Blood Purification, Joban Hospital, Iwaki, Fukushima, Japan.

Introduction: Taurine, an important factor in the living body, is essential for cardiovascular function and development and function of skeletal muscle, retina and central nervous system. In the present study, its effect on cardiovascular function was specifically taken into consideration. In haemodialysis filtration (HDF) patients, the effect of taurine on patients with chronic heart failure (CHF), in whom dry weight was difficult to control, was evaluated.

Case Description: All patients who were subjected to regular HDF for 4 h three times per week at Joban hospital in this study. Patients with chronic heart failure, in whom dry weight was difficult to control (n = 4), were included in the evaluation of clinical status. X-ray and echocardiography were determined before and after taurine treatment.

Almost all cases were taking nitric acid, warfarin, anti-platelet and vasopressor. Because vital signs were unstable in chronic heart failure, all cases withheld antihypertensive drugs during HDF. For unstable vital signs during HDF, pulmonary congestion was chronically recognized. After taurine was started, vital signs stabilized and lowering of dry weight was possible. In addition, X-ray and cardiac diastolic failure on echocardiography improved.

Discussion: Taurine was effective for CHF patients on HDF in whom dry weight was difficult to control in spite of various medications.

SA-PO064

Immune Complex MPGN Associated with Hashimoto's Thyroiditis in a Young Female Samuel Chakola, Iris J. Lee, Jean Lee, Xu Zeng, Duncan B. Johnstone, Lleras A. Samuels. *Nephrology, Temple Univ, Philadelphia, PA.*

Introduction: Glomerular disease associated with Hashimoto's Thyroiditis (HT) is a rare occurrence infrequently reported in the literature. We present a case of membranoproliferative glomerulonephritis (MPGN) that was thought initially to be due to systemic lupus erythematosus (SLE) in a young woman.

Case Description: A 38 year old female presented in 2013 with leg edema and two grams of proteinuria. Creatinine (Cr) was 1.3 mg/dl. Of note, her thyroid function tests were consistent with severe hypothyroidism, with a TSH of 129 IU/ml and thyroid peroxidase and thyroglobulin antibodies >900 IU/ml. Serologic workup for hepatitis B, C and HIV and complements were negative. She had a history of Raynaud's but did not fulfill clinical and immunological criteria for SLE. Kidney biopsy was consistent with immune complex MPGN with immunofluorescence positive for IgG and C3 only. Patient was non-compliant with thyroid replacement therapy and was lost to follow-up. She reappeared in 2015 with arthralgias, dyspnea, and leg edema. Her Cr had worsened to 1.7 mg/dl with 16 gram proteinuria. She was found to have a pericardial effusion. TSH was 174 IU/ml. Repeated testing for SLE was negative and a repeat renal biopsy demonstrated an immune complex mediated MPGN with minimal staining for full house immunoglobulins. She was placed on thyroxine hormone and also initiated on mycophenolate mofetil, given that both her thyroid and renal disease appeared to be driven by an autoimmune antibody mediated process.

Discussion: HT, immune complex MPGN and clinical findings in our patient were initially thought to be due to SLE however patient failed to fulfill any immunologic criteria for SLE. HT is rarely associated with MPGN and specific mechanisms remain unclear. Proteinuria in glomerular disease associated with HT is not correlated with levels of thyroid hormone. However, deposition of thyroglobulin and thyroid-peroxidase antibodies has been found in the kidney in HT. This supports the theory of an autoimmune basis for MPGN in HT, and reinforces that immunosuppression may be required to adequately treat both diseases.

SA-PO065

Hypervitaminosis D – A Rare Complication of PJP in a Transplant Patient Khaled Boobes, Khurram Saleem, Yazan M. Alia, Muhammad H. Hasan, Aneesha A. Shetty, Mohammed Javed Ansari. *Nephrology, Northwestern Univ/Northwestern Memorial Hospital, Chicago, IL.*

Introduction: Pneumocystis Jiroveci Pneumonia (PJP) is a known complication in immunocompromised hosts including transplant recipients, usually in the first six months of transplant. Hypercalcemia (HcA) is not a classic symptom of the disease. We present a case of a patient with simultaneous kidney and pancreas transplantation nineteen years ago who presented with PJP and developed HcA (highest value 14.8mg/dl [8.3-10.5] mg/dl). Parathyroid Hormone (PTH) was appropriately suppressed with a level of (6; [12-88] pg/ml). 1,25-(OH) vitamin D concentration was elevated (123; [18-72] pg/ml). After treatment with trimethoprim-sulfamethoxazole her Calcium concentration returned to normal along with PTH and 1,25-(OH) vitamin D. It is thought that, like other granulomatous disease-induced HcA, it is likely that endogenous extrarenal production of 1-alpha-hydroxylase by activated macrophages and by interferon-gamma involved in granuloma formation results in increased conversion from 25-(OH) vitamin D to 1,25-(OH) vitamin D and, consequently, in HcA and suppression of PTH secretion. Although only few cases of PJP-associated HcA have been reported to date, it is possible that this association is more frequent than previously thought. Hypercalcemia in transplant recipients with pulmonary symptoms must raise suspicion of PJP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

SA-PO066

A Rare Case of Tubulointerstitial Nephritis Associated with Primary Biliary Cirrhosis Jatinder K. Hothi,¹ Jingyin Yan,¹ William F. Glass,² ¹Dept of Nephrology, Baylor College of Medicine, Houston, TX; ²Dept of Nephrology, Baylor College of Medicine, Houston, TX; ³Dept of Pathology, Univ of Texas Health Science Center, Houston, TX.

Introduction: Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease characterized by positive antimitochondrial antibodies (AMA), immune-mediated epithelial damage of small bile ducts, which leads to liver cirrhosis as the disease advances. In addition to liver injury, other autoimmune diseases, such as Sjögren's syndrome and Raynaud's syndrome, are reported in approximately 2-20% patients with PBC. However, the association of PBC and renal injury is rarely documented.

Case Description: Here we present a case of tubulointerstitial nephritis (TIN) in a patient with PBC. A 35-year-old female with past medical history of PBC developed sub-nephrotic range proteinuria and chronic kidney disease stage 3. A renal biopsy showed moderate to severe renal cortical and focal medullary tubulointerstitial inflammation with infiltration of lymphocytes, plasma cells and occasional eosinophils, as well as significant tubulitis.

The patient was treated with a short course of oral prednisone and her renal function improved.

Discussion: This case highlights a very rare cause of TIN and suggests that steroid therapy is effective in this setting.

SA-PO067

Plasma Exchange as Adjunctive Therapy for Crescentic IgA Nephropathy Jicheng Lv, Xinfang Xie, Fude Zhou, Minghui Zhao, Hong Zhang. Renal Div, Peking Univ Inst of Nephrology.

Introduction: Recent KDIGO guidelines recommend an aggressive immunosuppressive therapy in patients with crescentic IgA nephropathy (CreIgAN). While large cohort study from our center suggest that even with such a therapy, the 1- and 5-year renal survival rates remained low at 65% and 28%, respectively. Especially patients who present with serum creatinine (SCr)>580umol/L hardly recovered from dialysis. In this study we aim to evaluate the efficacy of plasma exchange(PE) in severe CreIgAN.

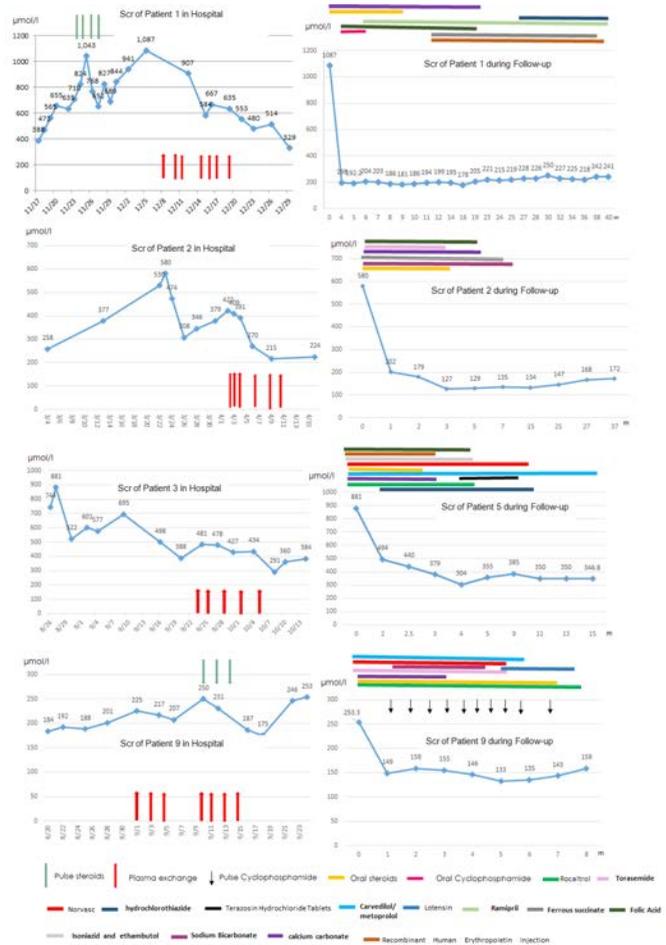
Case Description: In this pilot study we give PE as adjunctive therapy to patients with severe CreIgAN on the back of high dose steroids and cyclophosphamide. Severe CreIgAN is defined as diffuse crescent forming with kidney failure that needs dialysis or presents kidney function declining even with high dose steroids and cyclophosphamide therapy.

Overall ten patients with severe crescentic IgA nephropathy received PE from 2011 to 2015.

Pa-tients	Age	Gender	Dialy-sis	Scr (μmol/L)	Crescents (%)	Course of PE	Pulse of steroids	Follow-up months
1	57	M	Y	1087	61	7	Y	40
2	64	M	Y	580	55	6	N	37
3	26	M	Y	756	67	6	Y	6
4	24	M	Y	710	81	10	Y	6
5	58	M	Y	881	90	5	N	15
6	23	M	N	449	85	7	Y	6
7	39	M	N	394	85	6	Y	6
8	66	F	Y	775	89	7	N	6
9	40	F	N	253	54	7	Y	8
10	44	M	Y	589	43	10	Y	1

Y: yes, N: No

Among them 7 patients reached dialysis at presentation with serum creatinine (768±176mmol/L). Another 3 cases showed progressively kidney decline even after an aggressive immunosuppressive therapy. Patients received 5-10 PEs. After a mean 13 month follow-up, 4 of the 7 patients who had dialysis successfully recovered from dialysis. One of the 3 patients with persistent kidney progression showed serum creatinine decline.



No severe adverse event was observed during the follow-up.
Discussion: Plasma exchange as adjunctive therapy may achieve benefit for patients with severe crescentic IgAN.

SA-PO068

Fibrillary Glomerulonephritis Associated with Demyelinating Polyneuropathy Sixto G. Giusti, Pradeep Vaitla, Jorge C. Garces. Nephrology, Ochsner Clinic Foundation, New Orleans.

Introduction: Fibrillary glomerulonephritis (FGN) is characterized by nonbranching randomly arranged fibrils along the mesangium and glomerular capillary walls that do not stain for Congo red, have a diameter of 16-24 nm, and usually show polyclonal IgG, C3, and light chain deposition by immunofluorescence. Found in ≤ 1% of native renal biopsies, FGN is usually idiopathic, although some cases are associated with malignancy, monoclonal gammopathy, and autoimmune diseases. Association of FGN with demyelinating neuropathy has been rarely described.

Case Description: A 38-year-old Indian man with 3-year history of hypertension and 10-month history of end stage renal disease attributed to hypertension, presented to our institution with a 3-week history of progressive, bilateral lower extremity weakness. During his hospital stay, he was diagnosed with non-infectious pleural and pericardial effusions. Lab work revealed normal Anti nuclear antibody, anti double stranded DNA antibody, serum complements, anti nuclear cytoplasmic antibodies. Serologies for hepatitis and human immune deficiency virus were negative. Electromyography revealed demyelinating sensorimotor polyneuropathy. Chest, abdomen and pelvis imaging was unrevealing for malignancy. No monoclonal peaks on serum and urine electrophoresis or immunofixation. Fat pad biopsy negative for amyloid. Bone marrow biopsy showed 60% cellularity with tri lineage hematopoietic activity, no B cell clonality or T cell aberrancy. He was started on high dose steroids with gradual improvements of weakness. Renal biopsy showed findings of chronic FGN with IgG4 dominant deposition. 44 of 48 glomeruli were globally sclerosed with 80% fibrosis and no activity. Sural nerve biopsy results are still pending.

Discussion: FGN is a rare and leads to ESRD in the majority of cases. There are very few cases describing FGN in association with demyelinating polyneuropathy without associated plasma cell dyscrasias. Although FGN renal prognosis remains poor, early identification is important as it may help identify an underlying malignancy or systemic autoimmune disorder with potential for treatment. FGN may be a precursor for future lymphoproliferative disorder.

SA-PO069

Acute Inflammatory Polyarthrititis following Kidney TransplantationPaul P. Maraj. *Nephrology, Baylor College of Medicine, Houston, TX.*

Introduction: An acute inflammatory polyarthrititis develops one month after deceased donor kidney transplantation in a 54 year old male. He had no prior diagnosis of any form of arthritis, crystalline, inflammatory or otherwise. Following workup he was diagnosed with Rheumatoid arthritis and improved with an increased dose of steroids. To date there are no case reports which describes rheumatoid arthritis precipitated by kidney transplantation. This case report describes this unique clinical scenario and the dilemmas with diagnosis.

Case Description: 54 year old man with a medical history of end stage renal disease secondary to hypertensive nephrosclerosis who underwent deceased donor kidney transplant one month prior is admitted for joint pains. During kidney transplantation he had induction with thymoglobulin, plasmapheresis and rituximab as per institutional protocol for positive DSA. Maintenance immunotherapy consisted of tacrolimus, mycophenolate mofetil and prednisone taper dose. Following transplantation he was asymptomatic until one month after transplantation when he developed bilateral shoulder pains which then migrated to elbows and wrist; this was associated with significant morning stiffness and malaise. Xrays which were negative for bony abnormalities, MRI wrist revealed small to moderate joint effusion. Fluid analysis was negative for septic arthritis and crystals. Serum uric acid was within normal limits. Autoimmune workup negative including ANA, C3, C4. Rheumatoid factor was positive to titer 1:4, anti CCP was significantly positive at >250. He was treated with oral steroids which resulted in resolution of his symptoms.

Discussion: To date there have been no reports of rheumatoid arthritis in the immediate post-transplant period. There have been reports of an acute inflammatory syndrome related to mycophenolate use which improved on discontinuation, anti-CCP titers were unknown in these cases. Mycophenolate was continued in this patient and his symptoms did not recur after steroid taper making a reaction to mycophenolate less likely. Anti CCP is very specific for diagnosis of rheumatoid arthritis but its validity post transplant is unknown. The temporal relation with transplantation also raises the possibility of a drug induced reaction.

SA-PO070

IgM Nephropathy: A Neglected Pathology of Nephrotic SyndromeKrystahl Z. Andujar, Carlos Antonio Cortes Sanchez, Hector R. Cordova. *Medical Service, VA Caribbean Healthcare System, San Juan, PR.*

Introduction: IgM nephropathy is defined by the presence of immunoglobulin M (IgM) as the dominant immunoglobulin in the mesangium of the glomeruli in a diffuse and global distribution. Clinically, a poor response to steroids distinguishes this disease from Minimal Change Disease.

Case Description: An 80-year-old man with past history of Hypertension, Alzheimer's dementia, and benign prostatic hypertrophy complained of progressive shortness of breath associated with severe bilateral lower extremity edema and decreased urine output. Vital signs revealed blood pressure of 171/77mmHg. Lung auscultation was remarkable for bibasilar rales. The patient had anasarca. Laboratory tests showed serum creatinine at 2.2mg/dL (baseline of 1.2mg/dL), BUN of 36mg/dL and albumin of 2.2g/dL. Urinalysis showed microscopic hematuria and proteinuria (> 500 mg/dl). Renal sonogram revealed normal kidney size without hydronephrosis or nephrolithiasis. The 24-hour urinary protein excretion was 6.7gms/day. Serum creatinine rose to 7.7mg/dL a week later. Kidney biopsy was performed and steroid pulse therapy was started. Hemodialysis was initiated. Renal biopsy results showed mild increase in mesangial matrix and interstitial fibrosis. Sections stained for IgG, IgA, albumin C1q and kappa and lambda light chains were negative. Staining for IgM showed granular deposits in the mesangial areas compatible with a diagnosis of IgM Nephropathy. Hemodialysis was discontinued after two sessions since the patient had rapid recovery of kidney function after the 3 day steroid pulse therapy. Steroid therapy was tapered and eventually discontinued. Three months later, 24 hour urinary protein excretion was normal and the serum creatinine was 1.6mg/dL.

Discussion: Patients with IgM Nephropathy are less likely to respond to immunosuppressive agents. The presence of mesangial IgM deposits and interstitial fibrosis entails a worse prognosis. However, in our case, the patient had a prompt response to steroid therapy with resolution of the nephrotic syndrome and recovery of renal function.

Funding: Veterans Administration Support

SA-PO071

Renal Infarct from Traumatic Renal Artery DissectionEduardo J. Zouain, Isha Gupta, Karim El Hachem, Germaine Z. Chan, Steven D. Smith. *Nephrology Dept, Mt. Sinai St. Luke's Hospital and Icahn School of Medicine at Mt. Sinai, New York, NY.*

Introduction: Renal infarction is an uncommon condition associated with a thromboembolic event (i.e.: related to atrial fibrillation), hypercoagulable state, renal artery dissection or fibromuscular dysplasia.

Case Description: A 26 y/o male with no significant PMHx presented with left flank pain for 3 days. The pain was described as 10/10 and associated with intermittent nausea. He fell from his motorcycle onto his left side 2 weeks prior. On exam there was a healing laceration over the left knee and tenderness to palpation over the left lower quadrant and L flank. The remainder of his exam including blood pressure was unremarkable. Blood work was pertinent for a WBC of 13.3K/uL and an elevated CRP of 2.5mg/dl. Urinalysis was positive for 30mg/dl protein, and trace blood with 5 RBC/HPF. A basic metabolic panel was normal with a creatinine of 1.1mg/dl. After a non-contrast CT a CT angiogram of the L renal artery was performed.

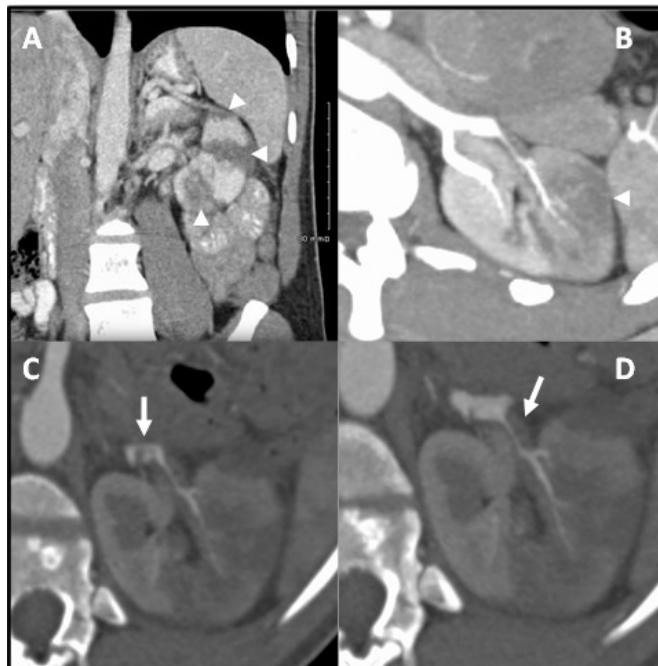


Figure 1. High resolution 3D Vitrea Reconstructions of Computer Tomographic Angiogram. Image A: Multiple areas of hypoattenuation (Arrow head). Image B: Renal Infarct (Arrowhead). Image C: Intimal tear (Arrow). Image D: Thrombosis distally of the false lumen (Arrow).

Discussion: Renal infarcts are characterized by acute onset of flank or generalized abdominal pain, nausea, vomiting, and occasionally fever and hypertension. Elevated WBC, CRP and LDH have also been associated. Renal artery dissection secondary to trauma is rare and has been associated with anatomical variations and acceleration/deceleration injury leading to intimal tearing. The two goals of treatment are organ preservation and improvement of renovascular hypertension. The treatment options include surgical reconstruction, endovascular repair, or conservative treatment. Our patient was initially placed on empiric anticoagulation with heparin. After hypercoagulable disorder, vasculitis, and embolic source was ruled out, anticoagulation was stopped. The patient was discharged on conservative treatment.

SA-PO072

Persistent Fever in a Patient with Wunderlich SyndromeMarijeta Pekez,¹ Kshitij Thakur.¹ *¹Dept of Medicine, Crozer Chester Medical Center, Upland, PA; ²Clinical Renal Associates, Crozer Chester Medical Center, Upland, PA.*

Introduction: Wunderlich syndrome is spontaneous, nontraumatic renal hemorrhage confined to the subcapsular and perirenal space. We present a case of a patient with a Wunderlich syndrome complicated by renal abscess.

Case Description: Patient was a 43 year old male who presented with nausea and generalized weakness, found to have sepsis secondary to urinary source. Ultrasound obtained during work up showed a old right perinephric hematoma. Patient continued to be febrile despite IV antibiotics. Repeat imaging with CT scan showed large abscess in place of the previously described subcapsular hematoma. Successful CT-guided drainage of the abscess led to marked improvement and resolution of fever.

Discussion: Wunderlich syndrome is secondary to neoplastic and non-neoplastic causes. It usually presents as mild flank pain, flank tenderness, or hematuria. Depending on blood loss, symptoms, of hypovolemic shock may develop. Treatment varies according to severity, ranging from monitoring of the hematoma to nephrectomy. Our case is interesting since Wunderlich syndrome provided a nidus for infection and eventual abscess formation causing persistent fevers and flank pain with preserved hemodynamic stability. It demonstrated the need for CT imaging in order to fully appreciate the extent of the hemorrhage which in this case converted into an abscess. In the right clinical scenario, Wunderlich syndrome should be evaluated as a possible factor in infectious presentations.

SA-PO073

Gaucher's Disease and Lupus, Two Diseases in the Same Scope?Ana Pocinho Pimentel, Ana Cabrita, Teresa M. Jeronimo, Joana Vidinha, Viriato J.V. Santos, Pedro L. Neves. *Nephrology, Centro Hospitalar do Algarve, Faro, Portugal.*

Introduction: Gaucher's disease is a rare inherited lysosome storage disease caused by genetic mutations that encodes for glucocerebrosidase enzyme. It's deficiency leads to glucocerebroside (GC) accumulation in mononuclear macrophage system, including liver, spleen and bone marrow. Kidney involvement is usually rare. Systemic lupus erythematosus

(SLE) is an autoimmune disorder where similarly, sphingolipid accumulation occurs when there is glomerular disease. The authors describe a case of a woman with both Gaucher's disease type 1 and SLE.

Case Description: A 32-year-old woman with Gaucher's disease diagnosed at 17 years old, having velaglucerase, presented several clinical clues suggesting SLE. Months later started presenting face and limbs edema and hypertension. She was admitted with microcytic and hypochromic anemia, 77000 platelets, creatinine serum levels of 1.38mg/dL and hypocalcemia. The urinalysis showed hematuria and proteinuria of 7628mg in the 24h urine collection. The patient had positive anti-nuclear antibodies, Anti-Sjögren's syndrome-related antigen and negative anti-double stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, viral serologies. Both complement levels were low. A kidney biopsy was performed.

It has been suggested that progressive accumulation of GC may trigger macrophage activation resulting in enhanced cytokine secretion and subsequent clonal B-cell expansion leading to chronic stimulation of the immune system. GC changes natural killer T cell function, a regulatory lymphocyte that have a role in infectious, neoplastic and inflammatory processes, therefore having a potential role in inducing other autoimmune disease. NKT lymphocytes are considered to be a link between innate and adaptive immune responses and were shown to have a role in a number of immune-mediated disorders. In an animal model of SLE, a selective reduction in NKT cells precedes the development of autoimmune phenomena.

Discussion: This case highlights a possible immunologic proximity between Gaucher's disease and SLE, bringing up the already existing doubt that the defects in lipid metabolism, could contribute to the development of autoimmunity.

SA-PO074

Chronic Periaortitis, a Known Cause of Obstructive Uropathy Margaret Duffy,¹ Smita Mahendrakar,¹ Mandeep Samra,¹ Michael Yudd.²
¹*Nephrology, Rutgers-New Jersey Medical School, Newark, NJ;* ²*Nephrology, East Orange Veterans Administration Hospital, East Orange, NJ.*

Case Description: A 59 year-old man with hypertension presented with one week of gradually decreasing urine output, nausea, generalized weakness, and vague dull left lower quadrant pain with radiation to the left flank. He was afebrile with blood pressure of 170/90 mmHg, pulse of 79 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. His abdominal exam was unremarkable except for non-tender scrotal swelling bilaterally. Laboratory studies were notable for the following values: WBC $12.1 \times 10^9/L$, BUN 62mg/dL, SCr 13.8mg/dL (baseline SCr 1.1mg/dL), ESR 57mm/hr, CRP 67mg/dL, U/A clear, yellow, specific gravity 1.01, pH 6, moderate blood, negative protein, leukocyte esterase, or nitrites. A renal ultrasound showed moderate hydronephrosis with patent renal arteries and veins bilaterally. CT of the abdomen and pelvis revealed moderate bilateral hydronephrosis, an abdominal aortic aneurysm (3.6cm), and a periaortic soft tissue mass measuring 2 cm in diameter with associated ureteral obstruction. There was no inguinal iliac lymphadenopathy or suggestion of discrete malignancy. Based on combined clinical and radiographic evidence the patient was diagnosed with chronic periaortitis and retroperitoneal fibrosis. He was started on mycophenolate mofetil and prednisone taper with complete resolution of symptoms within 6 months.

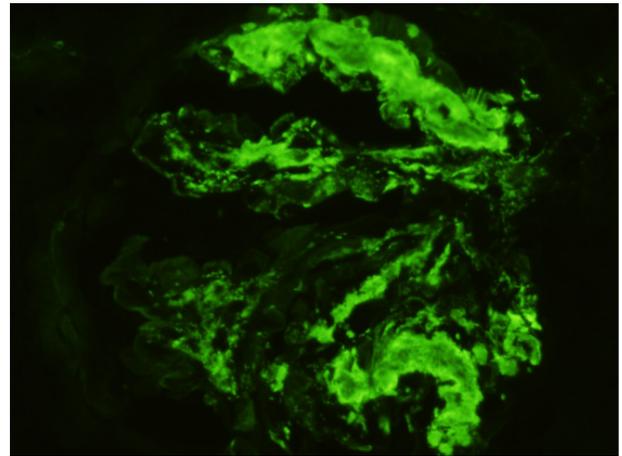
Discussion: Retroperitoneal fibrosis (RPF) is a relatively rare condition characterized by the presence of fibrosis and inflammation of the retroperitoneal tissues that often surrounds the ureters and other abdominal organs and can lead to renal failure in advanced cases. Our case demonstrates the importance of considering RPF as an etiology of flank pain and renal failure as medical treatment is effective in reversing obstructive uropathy.

SA-PO075

IgA Nephropathy in HIV Positive Patient with Acute Kidney Injury Giovanna Y. Arteaga Muller,¹ Lilia Maria Rizo Topete,¹ Elisa Maria Guerrero Gonzalez,¹ Concepcion Sanchez Martinez,¹ Jesus Cruz Valdez,¹ Gabriela Alarcón-Galván.² ¹*Nephrology, Univ Hospital José E. González UANL, Monterrey, Mexico;* ²*Anatomic Pathology, Univ Hospital José E. González UANL, Monterrey, Mexico.*

Introduction: Acute kidney injury is common in patients with HIV, being prerenal variety the predominant etiology. Among the intrinsic causes are thrombotic microangiopathy, the antiretroviral drugs associated and the immune complexes associated (3.5%-10%) being the collapsing focal segmental glomerulosclerosis the most frequently found.

Case Description: Male 41 year old, with use of cocaine, marijuana, benzodiazepines tattoos and high-risk sexual behavior, diagnosed with HIV nine years ago, treated with antiretrovirals which suspended two years ago. Begins 3 months before with malaise, a week prior to his admission presented progressive dyspnea on moderate to high stresses accompanied by productive cough and fever. Chest radiography showed fine interstitial infiltrate, compatible with pneumocystis jiroveci, laboratories: Hb9.4g/dL, creat.3.0 mg/dL, BUN30 mg/dL, urine protein 4.79g/24 hrs, the urinalysis reported reddish urine, with granular casts, hematuria and pyuria. Hepatitis B, Hepatitis C, CMV and tuberculosis tests were all negative and the renal ultrasonography was normal. Renal biopsy revealed IgA nephropathy.



Direct immunofluorescence technique (400X). Mesangial granular staining (4+) for IgA. Early treatment with anti-proteinuric general measures and prednisone improved renal function with a decreased in creatinine to 1.3mg/dL.

Discussion: The immune complexes associated nephropathy in patients with HIV is more common due to the start of antiretroviral therapy, however IgA nephropathy remains uncommon in this patients. In our patient the indication for renal biopsy was the erythrocyturia and the proteinuria in nephrotic range. Early detection and treatment can prevent progression to ESRD.

SA-PO076

Ketorolac Induced Mesangiolytic: A Clinical Example of Anti-Thy 1.1 Model of Mesangio-Proliferative Glomerulonephritis Fatima Khalid. *Dept of Medicine, Univ of Rochester School of Medicine, Rochester, NY.*

Introduction: NSAIDs are known cause of acute kidney injury, but do not usually cause glomerulonephritis. We share an unusual presentation of glomerulonephritis after only one dose of ketorolac. No renal biopsy findings in acute ketorolac-related acute kidney injury appear to have been published based on an Ovid literature search.

Case Description: This is a 42 year old male with past medical history of nephrolithiasis and urethral stricture, who presented to the hospital for a cystoscopy procedure. The patient had urinary obstruction after the procedure and developed oliguric acute kidney injury with serum creatinine of 3.1 mg/dl (baseline 0.8 mg/dl). Of note, the patient also received one dose of ketorolac during the procedure. Urinalysis showed 2+ blood with many red blood cells, and 9 grams of proteinuria as TP/creatinine ratio. Lab work demonstrated high LDH, low haptoglobin but stable hematocrit and platelet count. Peripheral smear did not reveal schistocytes. Urine microscopy showed RBC casts. Renal ultrasound showed normal sized kidneys with no hydronephrosis. Kidney biopsy showed acute tubule-interstitial nephritis with tubular necrosis and mesangiolytic. Electron microscopy showed patent capillary loops with focal epithelial foot process effacement, visceral epithelial cells with cytoplasmic vacuolization, dilated capillaries with endothelial apoptosis and mesangial lysis. Glomerular basement membrane thickness was increased. There was evidence of acute tubular injury. No electron dense deposits, thrombi or crescents were identified. Immunofluorescence of glomeruli was negative. The patient remained oliguric and required renal replacement for short term followed by full recovery of renal function.

Discussion: Renal toxicity of ketorolac has been described, and appears generally to be reversible, but could lead to glomerulonephritis in a rare setting. The pathological findings in the glomeruli resemble those described in experimental animals with Thy-1 induced glomerulonephritis treated with rofecoxib (COX-2 inhibitors). In this model, glomerular disease is initiated by immune-mediated mesangial cell damage, resulting in mesangiolytic.

SA-PO077

Disseminated Cytomegalovirus Disease in Induction Treatment with Mycophenolate Mofetil in a Lupus Nephritis Patient Ana Pocinho Pimentel, Joana Vidinha, Teresa M. Jeronimo, Ana Cabrita, Ana Paula Silva, Pedro L. Neves. *Nephrology, Centro Hospitalar do Algarve, Faro, Portugal.*

Introduction: Mycophenolate mofetil (MMF) is an immunosuppressive agent that exerts relatively selective antiproliferative effects on T and B lymphocytes and is increasingly being associated with higher incidence of tissue-invasive cytomegalovirus (CMV) disease in transplant recipients and other immune-mediated diseases. The case presented is a patient who developed CMV enteritis while receiving MMF and corticosteroids for lupus nephritis (LN).

Case Description: 59 year-old man with LN class IV G(a) + V under MMF (2,5g/day) and prednisolone (60mg/day) when started having weight loss, diarrhea, nausea, dysphagia and haematochezia. The blood count showed severe anemia and leucopenia. Comprehensive chemistry profile revealed PCr 2.7mg/dL improving proteinuria from 11.7 to 2g/day and normal urinary sediment. CMV serology IgM came positive (PCR CMV: 834 copies/mL). Immunology tests were negative. Upper endoscopy and colonoscopy were performed. Biopsies showed CMV infection signs and esophageal candidiasis. MMF was tapered to 1g/day and prednisolone to 20mg/day. The patient was started on intravenous ganciclovir

and fluconazole, with favorable clinical response. Proteinuria then worsened to 7.9g/day. Renal biopsy was repeated showing relapse of LN class V. Renal function improved PCR 1.6mg/dL having 2g MMF and prophylactic oral valganciclovir.

CMV virus directly infects the bowel causing mucosal erosions or ulcerations. We can only find little evidence that CMV disease explains the gastrointestinal adverse event profile associated with MMF but we bring up again the hypothesis that high local concentrations of MMF have a direct toxic effect on cells of the small intestine, causing gastrointestinal upset. Data on the incidence of CMV disease with the MMF induction protocol for LN are scarce.

Discussion: Similarly to transplant recipients receiving MMF, LN patients presenting gastrointestinal upset demand exclusion of CMV infection. This report highlights the importance of clinical follow-up of lupus patients with GI symptoms undergoing intense immunosuppression and accurate serological and histological diagnosis.

SA-PO078

Cryoglobulinemic Nephropathy with Successful Childbirth After Recurrent Episodes of Nephrotic Syndrome During Pregnancy Miho Karube, Shinya Kaname, Kazuhito Fukuoka, Hideki Shimizu, Yoshinori Komagata, Yoshihiro Arimura. *The First Dept of Internal Medicine, Kyorin Univ School of Medicine, 6-20-2 Shinkawa Mitaka-city, Tokyo, Japan.*

Introduction: It is unknown whether pregnancy affects clinical course of cryoglobulinemic nephropathy and how to treat pregnant patients complicated with it.

Case Description: A 35-year-old woman was admitted to our hospital because of massive proteinuria that developed during the third pregnancy. The previous two pregnancies had been terminated for similar episodes of nephrotic syndrome. No history of hypertension was observed, but during the course she presented cryoglobulinemia, a high titer of RF and low serum complements. The renal biopsy performed 10 days after the third termination revealed MPGN-like lesions with lobulation in glomeruli, double contour of GBM, endotheliosis, and moderate mesangial cell proliferation. Immunofluorescence study showed IgG, IgA, IgM, C3, C4, and C1q all positive mainly along the glomerular capillaries, and subendothelial deposits were confirmed by EM, thus she was diagnosed as cryoglobulinemic nephropathy. Because the histological findings of repeated renal biopsy were not improved two months after the disappearance of proteinuria, treatment with 30 mg/day of PSL was started, followed by intravenous cyclophosphamide 6 times and plasma exchange, since she had a desire for baby. Finally at the fourth pregnancy, she bore a healthy baby weighing 2,342g on vaginal delivery at 36 weeks despite of recurrent appearance of nephrotic syndrome. After delivery, she was given 30 mg/day of PSL and proteinuria subsided.

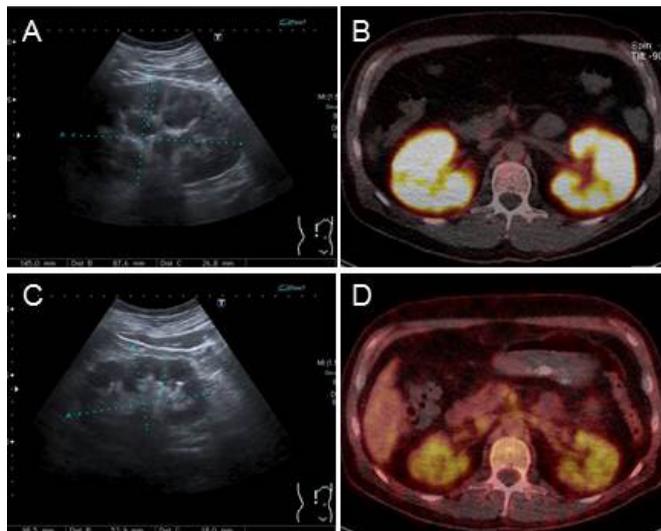
Discussion: We experienced a rare case of type III cryoglobulinemic nephropathy that repeatedly developed nephrotic syndrome during pregnancy, but finally bore a baby after immunosuppressive therapy. Although the pathogenesis of pregnancy-induced exacerbation of cryoglobulinemic nephropathy was not clear in this patient, aggressive treatment may have been helpful for ameliorating it, leading to successful delivery.

SA-PO079

Renal Recurrence of Acute Lymphatic Leukemia Anna Bertram,¹ Jan H. Braesen,² Ansgar Reising.¹ ¹*Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany;* ²*Pathology, Hannover Medical School, Hannover, Germany.*

Introduction: Renal complications of hematologic neoplasia can be therapy- or neoplasia-associated. We report a case of acute kidney injury (AKI) in the long term follow-up of a patient with acute lymphatic leukemia (ALL).

Case Description: The 42y old patient was diagnosed with ALL in 2009 and treated according to recommendations with chemotherapy and peripheral blood stem cell transplantation. In 2012, extramedullary ALL recurrence in his right knee was treated with irradiation. Starting from September 2014, molecular markers of minimal recurrence without evidence of lymphoblasts were found in bone marrow biopsies, and the patient received donor lymphocytes to induce graft vs. host reaction. In December 2014, ramipril was started for newly diagnosed hypertension, after which creatinine increased within several days to 290µmol/L. Because of this association, we suspected renal artery stenosis, toxic AKI, or acute interstitial nephritis. Ultrasound revealed diffusely swollen and dense kidneys (Fig.1A). Renal artery stenosis could be excluded, but - untypical for interstitial nephritis - segmental arteries seemed compressed. Kidney biopsy revealed ALL recurrence with extensive lymphoblast infiltration. DOTA-CXCR4-PET-CT confirmed diffuse infiltration of both kidneys (Fig.1B) without bone marrow affection. After starting chemotherapy, creatinine rapidly ameliorated. Ultrasound and PET-CT-controls 10 weeks after starting therapy confirmed good treatment response (Fig.1C-D).



Discussion: This exceptional case of isolated renal ALL recurrence highlights the importance of early evaluation with ultrasound and biopsy in patients with hematologic neoplasia and AKI. An empiric treatment for suspected interstitial nephritis would have delayed chemotherapy and thereby endangered the patient.

SA-PO080

A Rare Cause of Acute Kidney Injury in Non-Renal Solid Organ Transplantation Sameer Gupta, Wasay Humayun, Ramapriya Sinnakirouchenan, Liliانا Osadchuk. *Nephrology, Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Acute kidney injury (AKI) is a frequent complication of non-renal solid organ transplantation (SOT). Here we report a case of rapidly progressive renal failure leading to end stage renal disease (ESRD) due to acute oxalate nephropathy (AON) in a patient with non-renal SOT.

Case Description: A 63 year old female with past history of pulmonary fibrosis status post bilateral lung transplant, obesity status post Roux en Y gastric bypass (RYGB) surgery, and hypertension presented with worsening kidney function with BUN and creatinine of 55 mg/dl and 6.18 mg/dl respectively. She had normal kidney function with serum creatinine of 0.5mg/dl prior to transplant 8 months ago. Induction regimen included Basiliximab followed by tacrolimus, prednisone and mycophenolate (MMF) as maintenance therapy. Ensuuing transplantation, she had multiple episodes of AKI attributed to calcineurin inhibitor (CNI) toxicity and hypovolemia from MMF and clostridium difficile associated diarrhea. Her average tacrolimus trough level was 12 ng/ml. Several urinalyses showed acute tubular necrosis casts. Renal ultrasound revealed bilateral echogenic small kidneys compared to normal kidney size prior to transplant. Her kidney biopsy unexpectedly revealed oxalate nephropathy. She is currently on hemodialysis.

Discussion: AON has been poorly described in patients with RYGB surgery and SOT. In our patient with prior RYGB, chronic diarrhea, and numerous antibiotics unveiled AON. This superimposed with CNI toxicity resulted in rapid progression to ESRD. Antibiotic use depletes colonization of oxalate consuming bacteria (Oxalobacter formigenes). This combined with fatty acid malabsorption from prior RYGB increases colonic oxalate absorption resulting in hyperoxaluria. Diarrhea causes hypovolemia and metabolic acidosis leading to low urinary pH and hypocitraturia promoting calcium oxalate crystallization. Additional steps should be taken for SOT patients with RYGB, like diet modification, probiotic use, citrate supplementation, administration of fatty acid binding agents, and monitoring for hyperoxaluria. High suspicion for AON in patients with risk factors may lead to early diagnosis and treatment.

SA-PO081

Paraneoplastic Membranous Nephropathy and Myelodysplastic Syndrome – A Rare Combination Krishna K.R. Manda, Madhuri Manne, Dagmar Klingler. *Renal Medicine, Univ of Massachusetts Medical School, Worcester, MA.*

Introduction: We report a case of Membranous Nephropathy(MN) seen in association with Myelodysplastic Syndrome(MDS). This occurrence is rare and only 3 cases have been reported in literature previously. Up to 5-20% of adults with MN have been reported to have most commonly a solid tumor and less frequently, a hematologic malignancy.

Case Description: Our patient is a 58 y/o man who has chronic kidney disease of unclear etiology with serum creatinine(Scr) of 1.3 and MDS. He was admitted with acute kidney injury in the setting of pneumonia and had nephrotic range proteinuria along with dysmorphic red blood cells on the urinary sediment. Renal biopsy showed MN with relatively recent immune complex deposition. There was no colocalization of IgG4 membranous deposits with phospholipase A2 receptor. He was hospitalized again with pancytopenia, marked inflammatory markers and infectious complications. Although bone marrow biopsy was not diagnostic, this syndrome was diagnosed as hemophagocytic

lymphohistiocytosis by clinical criteria and therapy was initiated with high-dose steroids and etoposide. During the hospitalization SCr peaked to 4 but did not require renal replacement therapy. Following this treatment SCr improved to 0.7.

Discussion: MN is the most common cause of the nephrotic syndrome in nondiabetic adults. Histologic change on light microscopy is glomerular basement membrane thickening with little or no cellular proliferation. Patients without known cancer who are diagnosed with MN should undergo age-appropriate cancer screening and this could be life saving. MDS, a group of heterogeneous hematopoietic stem cell disorders, are characterized by abnormal bone marrow differentiation & maturation, morphologically and functionally changed progenitors and a variable risk of evolution to acute leukemia. Paraneoplastic Glomerulonephritis (PGN), a rare secondary cause of glomerulonephritis and a complication of cancer remains a challenge to both nephrologists and oncologists. Studies to identify diagnostic biomarkers of PGN in blood, urine, or kidney biopsy samples by use of proteomic or other approaches are critically needed to facilitate the early diagnosis of this disease.

SA-PO082

Eculizumab in Gemcitabine Induced Atypical Hemolytic Uremic Syndrome aHUS Mohit Gupta, Rupesh Raina, Natthavat Tanphaichitr. *Dept of Nephrology, Akron General Medical Center, Cleveland, OH.*

Introduction: HUS (aHUS) is caused by endothelial damage due uncontrolled activation of complement system. Gemcitabine a nucleoside analog induced HUS (GIHUS) is rare. We report a patient with unresectable, locally advanced pancreatic cancer who developed a HUS after 1 months of gemcitabine.

Case Description: A 64 year-old female was diagnosed with 4 cm mass adenocarcinoma of the pancreatic head, after extensive evaluation of recurrent abdominal associated with clay colored stool. She underwent three cycles of gemcitabine at 1,000 mg/square meter. Her condition deteriorated over the following 1 weeks and developed microangiopathic hemolysis, rapidly declining renal function with proteinuria and hematuria, and renal biopsy of the last dose. Other markers of hemolysis namely LDH and bilirubin had dramatic improvement after 2 treatment of Eculizumab.

Pt was consequently treated with Eculizumab for management of atypical HUS. She received 1 dose of Eculizumab IV every week after which she was transitioned to once monthly for a total of nine doses. Pt's Creatinine Clearance was closely monitored and had significantly improved from 14 mL/min at the time of onset to 60 mL/min by the time of the last dose. Other markers of hemolysis namely LDH and bilirubin had dramatic improvement after 2 treatment of Eculizumab.

Discussion: HUS associated with gemcitabine is quite rare and no consistent risk factors have been identified. Conventional treatment with hemodialysis, or corticosteroids or plasmapheresis as minimal response. The rapid clinical response to eculizumab supports the concept that GIHUS might involve aberrant and autonomous complement activation. The dramatic resolution of symptoms after eculizumab administration suggests that chemotherapy induce aHUS is an area deserving further careful investigation of therapeutic complement blockade.

SA-PO083

A Case of Rapidly Progressive Idiopathic Membranoproliferative Glomerulonephritis Effectively Treated with High-Dose Steroid Therapy Bernice Kim, Kyung Soo Kim. *Div of Nephrology, Dept of Internal Medicine, Dongguk Univ Ilsan Hospital, Goyang, Republic of Korea.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) is an uncommon kidney disorder which can be idiopathic or secondary in etiology. As diagnostic methods improved over time, secondary cause of MPGN is increasingly defined and the truly idiopathic form is now a very rare condition. Because of the rarity of idiopathic MPGN, treatment guidance is based mainly on case series and the natural history of the disease is unclear. We present a case of rapidly progressive idiopathic MPGN effectively treated with high-dose steroid.

Case Description: A 73-year-old male was admitted because of subtrochanteric fracture. On admission, he had normal kidney function with serum creatinine (sCr) level of 1.02 mg/dL. 5 days after the operation of fracture, he was referred to the nephrology department due to abruptly increased level of sCr. On postoperative day 10, despite adequate intravenous hydration, he became anuric and sCr rose to 4.40 mg/dL requiring hemodialysis. Serum C3 level was low (38mg/dL). Kidney biopsy revealed mesangiocapillary proliferation, duplication of the glomerular basement membranes, subendothelial deposits and predominant C3 immunofluorescent staining suggestive of MPGN type I. Secondary causes such as infection, autoimmune disease, monoclonal gammopathy, neoplasia, complement dysregulation were excluded. He was diagnosed as idiopathic MPGN type I and high dose steroid therapy (40mg/day of prednisolone) was initiated. After 17 days of therapy, urine output was increased and dialysis was discontinued accordingly. Prednisolone was gradually tapered to 5mg over 1 month and he was discharged with sCr of 1.39 mg/dL.

Discussion: The early trials of the treatment of idiopathic MPGN have given inconsistent results, and should be interpreted with great caution since many of the reports likely included cases of secondary MPGN. The clinical presentation of MPGN is variable, from benign and slowly progressive to rapidly progressive, and different therapeutic approach should be applied in regard of the disease course. Studies are needed to identify the natural course and effective treatment of MPGN.

SA-PO084

A Case of Advanced IgG4 Related Tubulointerstitial Nephritis Complicating Multiple Lymphadenopathy and Intrathoracic Nodule, Mimicking Malignant Lymphoma Shigeto Horita, Hiroshi Fujii, Yuhei Fujisawa, Satoshi Hara, Yasunori Suzuki, Kazunori Yamada, Mitsuhiro Kawano. *Div of Rheumatology, Kanazawa Univ Graduate School of Medicine, Kanazawa, Ishikawa, Japan.*

Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disorder characterized by mass-forming lesions with IgG4-producing plasma cells. We describe a patient with IgG4-RD associated with advanced tubulointerstitial nephritis, membranous nephropathy, and multiple lymphadenopathy, mimicking malignant lymphoma.

Case Description: Four months prior to this admission, an 81-year-old male experienced anorexia and weight loss. Enhanced CT revealed gastric cancer, intrathoracic nodule, multiple defects of contrast medium in the kidneys and abdominal periaortitis. The patient's serum Cr level was 1.1 mg/dl and IgG4 level was 390 mg/dl. One month prior to this admission, the patient had received gastrectomy. After gastrectomy, decreased renal function (Cr 2.09 mg/dl), elevation of IgG4, and hypocomplementemia were detected. A renal biopsy showed marked infiltration by IgG4-positive plasma cells, spiking and bubbling on PAM staining, and granular deposits of IgG on immunofluorescent staining. The patient was diagnosed with IgG4 related tubulointerstitial nephritis and membranous nephropathy. PET showed accumulation of fluorodeoxyglucose in the submandibular glands, lymph nodes, kidneys, abdominal aorta and prostate, which were hard to distinguish from malignant lymphoma. Biopsy of the largest lymph nodes in the axilla and intrathoracic nodule showed reactive lymphadenopathy with IgG4 positive plasma cell infiltration. One month after starting prednisolone (25 mg/day), Cr level was partially decreased to 1.1 mg/dl and, the size of the lymph nodes and intrathoracic nodule reduced.

Discussion: Findings of IgG4-RD often mimic those of malignancies, so the differentiation of malignancies from IgG4-RD is important. In this regard, pathological findings of the affected organs are important to make the correct diagnosis. As severe renal dysfunction might develop during a several month period, IgG4-related kidney disease should be considered as a cause of renal dysfunction of unknown origin, especially in elderly men.

SA-PO085

Presence of PLA-2R Autoantibodies in a Patient with Clinical and Histopathological Evidence Suggestive of Secondary Membranous Nephropathy Kristen P. Tamura, Niti Madan. *Nephrology, UC Davis Medical Center, Sacramento, CA.*

Introduction: Differentiating between secondary membranous and idiopathic membranous nephropathy (IMN) is based on histopathology showing proliferative features in mesangium, full-house staining pattern, electron dense deposits in the mesangium and tubular basement membrane. Phospholipase A2 receptor (PLA2R) has been identified is a major target antigen involved in IMN pathogenesis. We describe here a patient with clinical history and histopathology suggestive of secondary membranous and positive anti-PLA2R antibody suggestive of IMN.

Case Description: A 56 year old Caucasian man with history of colon tubular adenoma, NHL- status post chemotherapy and radiation 30 years back, hypothyroidism presented with new-onset nephrotic-range proteinuria. He was not taking any medications and physical exam noted generalized edema. Laboratory exam as noted in table 1.

	Proteinuria in 24 hrs	Creatinine	Albumin	Anti-PLA2R IFA titres
At Diagnosis	9 gms	0.85 mg/dL	1.8 g/dL	1:1000
6 months of conservative therapy	11 gms	1.3 mg/dL	1.6 g/dL	
3 months of Ponticelli regimen	7.3 gms	1.5 mg/dL	2.2 g/dL	1:20

A renal biopsy showed variable-sized electron dense deposits in subepithelial, intra-membranous, mesangial and paramesangial locations. This finding strongly suggested a secondary etiology for the membranous nephropathy. Workup for infectious, autoimmune and neoplastic causes of membranous nephropathy was negative. Proteinuria worsened to 11 g/24h despite six months of conservative therapy with lisinopril and low protein diet. Additional labs obtained came back positive for PLA2R autoantibodies (IFA 1:1000, ELISA 976.6 RU/ml). Kidney stained positive for PLA2R glomerular deposits suggesting IMN. The patient was then treated with a modified Ponticelli protocol using alternating monthly prednisone and oral cyclophosphamide (2 mg/kg/d) for six months. After three months, proteinuria, albumin and edema improved.

Discussion: Relying on histopathologic differences to distinguish between idiopathic and secondary membranous nephropathy may lead to incorrect diagnosis and delay in treatment. The presence of circulating and tissue PLA2R autoantibodies may be more reliable in diagnosing IMN than histopathology.

SA-PO086

Silent Malakoplakia in a Recipient of Kidney-Pancreas Transplant Diagnosed on Surveillance Biopsy of Kidney Allograft: A Patient-Centered Approach to Treatment of Malakoplakia Jun Shoji,¹ Ravinder K. Wali,² ¹Dept of Kidney Disease and Hypertension, George Washington Univ, Washington, DC; ²Inova Transplant Center, Inova Fairfax Hospital, Falls Church, VA.

Introduction: Malakoplakia is an inflammatory disease leading to chronic morbidity and organ dysfunction. It was originally described in association with genitourinary tract infections with coliform bacteria and can manifest as acute pyelonephritis, acute or chronic renal failure, or renal mass. We present a case of a 40-year-old female recipient of simultaneous pancreas-kidney transplant who developed an acute rise in serum creatinine without apparent cause and found to have malakoplakia on kidney allograft biopsy. Patient-centered treatment resulted in reversal of allograft dysfunction and resolution of histological features of malakoplakia.

Case Description: 40-year-old Caucasian female with type 1 diabetes mellitus and end-stage renal disease on peritoneal dialysis underwent SPK transplant. After induction with thymoglobulin, she was maintained on tacrolimus and mycophenolate mofetil. Two months later, she was treated for acute T-cell mediated rejection (Banff Grade IA) with thymoglobulin. Serum creatinine returned to baseline and maintenance prednisone was added to her regimen. Her posttransplant course was complicated by multiple infections including parvovirus B19 infection, primary CMV infection, two episodes of urinary tract infections, and influenza A pneumonia. Due to an increase in serum creatinine without apparent cause, a kidney allograft biopsy was performed which revealed lesions consistent with malakoplakia.

Discussion: Treatment of malakoplakia in kidney transplant recipients is not well established but include surgical resection and use of antimicrobial agents. In the era of cyclosporine and azathioprine, it was speculated that the use of azathioprine may be associated with the development of malakoplakia. Discontinuation of azathioprine was shown to restore bactericidal activity of mononuclear cells. This case report illustrates that in the era of immunosuppression with tacrolimus and mycophenolate mofetil, the maintenance therapy with tacrolimus may be continued while treating for malakoplakia.

SA-PO087

Common Weight Loss Medication Pill "Qsymia" Causing Hypokalemia and Renal Tubular Acidosis Jyotsana Thakkar, Mala Sachdeva. Div of Nephrology, North Shore -LJ School of Medicine, Great Neck, NY.

Introduction: The obesity epidemic is growing. Aside from the traditional diet and exercise, weight loss pills are more commonly prescribed. Qsymia is one such weight loss pill consisting of topiramate and phentermine. We report potentially life threatening side effects of Qsymia causing severe hypokalemia, proximal renal tubular acidosis (pRTA), and cardiac dysrhythmia.

Case Description: A 68 year old female with history of hypertension presented with complaints of tingling of her left arm and jaw of one day duration. Her home medications included Aspirin and Hyzaar (Losartan and Hydrochlorothiazide). She had self discontinued the Hyzaar five days prior to presentation. Patient was recently started on the weight loss medication "Qsymia" three months prior. She denied any alcohol use. On initial presentation, she was noted to be in atrial fibrillation (HR 150s) and hypotensive (BP 84/43 mmHg) requiring cardioversion. Subsequent cardiac catheterization and echocardiogram were unremarkable. Initial lab data showed severe hypokalemia-2.4 mmol/L, creatinine 1.08 mg/dL, bicarbonate 22 mmol/L, phosphorus 2.1 mg/dL, magnesium 2.2 mg/dL, and calcium 8.9 mg/dL. Urinalysis showed pH 8 with glucosuria. Urine Lytes showed potassium 38 mmol/L, chloride 43 mmol/L, and sodium 141 mmol/L.

It was suggested that patient's clinical presentation and electrolyte disorders were due to the weight loss medication, and Qsymia was discontinued. Qsymia was approved by FDA in 2012 for weight loss. Most common side effects reported include paresthesia, dizziness, insomnia, constipation and dry mouth. In the U.S., drug label contains warnings for increased heart rate. Topiramate is known to cause pRTA. Our patient had mild acidosis, hypophosphatemia and glucosuria which we believe was a result of an early pRTA, induced by topiramate. Although hydrochlorothiazide is known to cause hypokalemia, our patient was not taking the medication for five days.

Discussion: Weight loss medications are now being more commonly used to treat obesity. Prescribers should be aware of the potential nephrotoxic side effects of Qsymia. Monitoring serum potassium and bicarbonate levels regularly should be taken into consideration.

SA-PO088

Multiple Myeloma as the Underlying Cause of Thrombotic Microangiopathy Venkata Buddharaju, Liga Yusvirazi, Anastasios Papanagnou, Savneek S. Chugh, Rahul N. Pawar. Nephrology, Westchester Medical Center, Valhalla, NY.

Introduction: Thrombotic microangiopathy (TMA) describes a pathological process of microvascular thrombosis, consumptive thrombocytopenia and microangiopathic hemolytic anemia, leading to end-organ ischemia and infarction affecting particularly the kidney and brain. TMA is a pathological feature of a number of clinical disorders including Hemolytic uremic syndrome (HUS) and atypical HUS. Rare but important, TMA may also occur in malignancy, connective tissue disease, malignant hypertension, and renal transplantation (rejection or drug toxicity). We present a rare case where patient developed AKI from TMA but found to have plasma cell dyscrasia as possible underlying etiology.

Case Description: A 42 y/o man with h/o myopathy, questionable mixed connective tissue disorder on prednisone and cellcept, Pulmonary Hypertension on home oxygen,

CHF with preserved EF and Anemia requiring multiple transfusions went to an outside hospital with SOB and pedal edema found to have AKI with serum creatinine of 4 and 2+ proteinuria. Serologies were negative except for anti-RNP and ESR; with no improvement in renal function the patient had a renal biopsy which showed TMA, mild fibrosis and atherosclerosis. The patient was Started on RRT and then transferred to Westchester medical center for treatment with Eculizimab for atypical HUS. After reviewing the labs we ordered Serum and urine protein electrophoresis which showed monoclonal Ig M spike, the patient underwent bone marrow biopsy which showed Plasmacytoma with 18% Plasma cells. The patient's renal function improved in the hospital stay and stabilized with creatinine of around 2.0 mg/dl, but unfortunately the patient had a severe sepsis and passed away before initiation of management for Multiple myeloma.

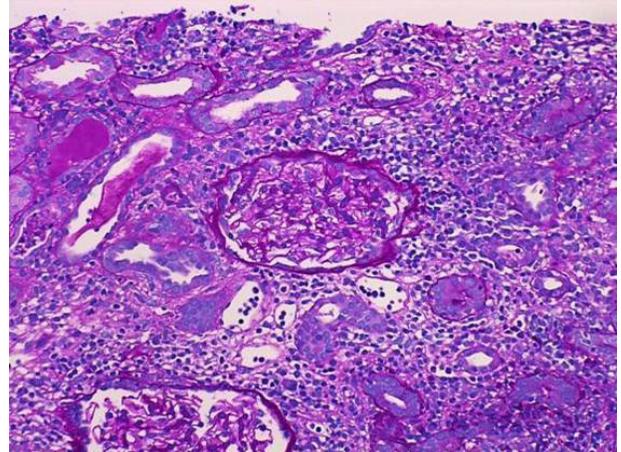
Discussion: Multiple Myeloma accounts for 10% of hematological malignancies. At least 50% of patients with MM have evidence renal insufficiency and more than 80% have proteinuria. Multiple myeloma can present as has wide range of renal manifestations including myeloma cast nephropathy, Immune deposition disease, CKD Fanconi syndrome. Though rare Multiple myeloma can cause TMA and the Pathogenesis still remains unclear.

SA-PO089

Drug-Induced Acute Interstitial Nephritis Managed with Early and Aggressive Steroid Therapy Radhika Vemuri, Abhilash Koratala, Keerti K. Bhanushali, William L. Clapp, Saraswathi Gopal. Nephrology, Univ of Florida, Gainesville.

Introduction: Pantoprazole (PPZ), a Proton Pump Inhibitor, is known to cause acute interstitial nephritis (AIN). We report a case of PPZ induced AIN in a young adult with just 3 doses of drug exposure.

Case Description: A 21 year old Asian American male with no past medical history was sent to the hospital by his Internist for elevated serum creatinine (Scr). He had nausea and abdominal pain 3 weeks earlier and was prescribed PPZ, which he took for 3 days. He denied use of any other medications including herbal supplements and NSAIDs. Laboratory data showed BUN of 82 mg/dL, Scr 15 mg/dL (baseline 0.6), bicarbonate of 15 mmol/L and no serum osmolal gap. Urinalysis showed sterile pyuria with no eosinophils, glycosuria with normal blood glucose, mild proteinuria (900mg/24 hrs). Serum and urine toxicology, protein electrophoresis, auto-immune work up were unremarkable. A Renal biopsy revealed diffuse expansion of the interstitium due to accumulation of cellular infiltrates consisting of lymphocytes, plasma cells and eosinophils with accompanying tubulitis consistent with AIN.



He received pulse steroids for 3 days and was continued on prednisone 1mg/kg/day with a plan to taper over 8-12 weeks. He required a few sessions of renal replacement therapy before his renal function started to recover, 6 weeks later his Scr was 1.4 mg/dl.

Discussion: Any drug can cause AIN, although the categories of antibiotics, diuretics and NSAIDs are most commonly implicated. Drug-induced AIN is not dose dependent, and recurrence can occur with a second exposure to the same or a related drug. The data on time of initiation, dosage and duration of steroids in drug induced AIN is limited due to lack of randomized control trials. On review of literature and our experience, we conclude that stopping the culprit agent and early steroid use confers better prognosis in drug induced AIN.

SA-PO090

Metastatic Sarcomatoid Carcinoma of Urothelial Origin in Failed Renal Allograft Venkata Buddharaju, Rajat Lamba, Daniel G. Glicklich. Nephrology, Westchester Medical Center, Valhalla, NY.

Introduction: Renal cell carcinomas are more common in ESRD than the general population and renal transplant patients with enhanced longevity may be at particular risk. Sarcomatoid renal cell carcinoma represents 1-15% of all renal cell carcinomas but has been very rarely described in renal allograft. The median age at diagnosis is 60years with 45-77% of patients with locally advanced or metastatic disease at the time of diagnosis. We describe a case sarcomatoid tumor of urothelial origin in a transplanted renal allograft.

Case Description: A 54 y/o man with ESRD from polycystic kidney disease, HTN, aortic dissection repair, mechanical AVR, paroxysmal Afib, who had 2 failed renal transplants in the past and was on dialysis for past 12 years, was admitted for left lower quadrant pain, fever and leukocytosis for which he was started on vancomycin and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

aztreonam. On imagine, he was found to have a mass around the left transplant kidney, ascites, omental caking, retroperitoneal lymphadenopathy and heterogeneous liver lesions. Retroperitoneal lymph node biopsy and ascitic fluid cytology was negative for malignant cells. Left kidney mass could not be biopsied because of technical difficulties and he had biopsy of the liver lesions which showed sarcomatoid tumor. He developed respiratory failure and septic shock requiring pressor support and expired. An autopsy was performed which showed Metastatic Sarcomatoid carcinoma of urothelial origin.

Discussion: Malignancy in post transplant is related to direct effects of immune-suppressants as well as their effects to suppress immune surveillance and to stimulate the activation of oncogenic viruses. It is generally recommended that patients on the active transplant list and renal transplant recipients be screened every several years for renal tumors. However after allograft failure, it is unclear how often to do cancer screening tests. Although in this particular case it is unclear whether screening would have made a difference in outcome, we recommend routine screening for renal cell carcinoma even if the renal allograft has failed.

SA-PO091

Parathyroidectomy on a Patient with Sickle Cell Disease and End Stage Renal Disease Farouk Talakshi, Mary C. Mallappallil, David Kau, Moro O. Salifu. *Suny Downstate Medical Center, Brooklyn, NY.*

Introduction: Patients with End Stage Renal Disease (ESRD) can develop elevated parathyroid hormone (PTH) levels with hypercalcemia. Some fail or cannot tolerate medical therapy. They eventually require parathyroidectomy. Tertiary hyperparathyroidism (3HPT) is the autonomous function of the parathyroid gland due to increased mass. Our case is unique as there are no reported cases of tertiary hyperparathyroidism in sickle cell patient, where symptoms of renal osteodystrophy mask vaso-occlusive crisis which improved with parathyroidectomy. 25 year old man with sickle cell disease, ESRD on hemodialysis since 2012, (3HPT), presents after many admissions for sickle cell pain crisis. Cause of ESRD was unknown but attributed to sickle cell nephropathy. Current admission for knee pain, imaging of which showed “sclerotic appearance of the bones, likely due to renal osteodystrophy”. Intact PTH (iPTH) consistently > 4000 pg/mL, and patient non adherent to cinacalcet, agreed to parathyroidectomy after many admissions for presumed vasoocclusive crisis. CT neck: “moderately enhancing foci inferior to the left and right thyroid lobes, and superior to the left thyroid lobe, could be compatible with parathyroid adenomas. “Sestamibi scan:”equivocal slow washout focus in region of right lower pole of thyroid gland extending posteriorly. Suspicious for but not definitive for parathyroid adenoma”. On the day prior to surgery, iPTH =4078 pg/mL with serum calcium (Ca)=10.3 mg/dl. Immediately after surgery, iPTH=265 pg/mL with Ca=8.9 mg/dl. The first day after surgery, iPTH=36 pg/mL with Ca=7.6 mg/dl. Patient admitted for 3 weeks due to his requirement of intravenous calcium and daily hemodialysis. Since discharge, patient has had fewer admissions for pain. He has however, remained hypocalcemic and is on 5 grams of calcium carbonate, 4 mgc of doxercalciferol, and is dialyzed with a 3 mEq/L calcium bath.

Discussion: 3PTH is common in ESRD patients that can leave them debilitated. Those who fail medical therapy may benefit from resection. In sickle cell disease symptoms of 3PTH was masked by vaso-occlusive crises and could be distinguished by marked reduction in symptoms after resection.

SA-PO092

Synthetic Cannabinoid (SC) in End Stage Renal Disease Chyi Chyi Chong,¹ Pallavi D. Shirsat,¹ Ramesh Marahatta,¹ Neville R. Dossabhoj,^{1,2} *LSU Health Science Center, Shreveport; ²VA Medical Center, Shreveport.*

Introduction: Synthetic cannabinoid (SC) are drugs of abuse especially among young adults. They are affordable, widely available and mostly importantly undetectable by standard urine toxicology screen. The avoidance of detection in the urine contributes to their allure and abuse. Acute kidney injury (AKI) related to synthetic cannabinoids has been reported. However, effect of synthetic marijuana in end stage renal disease (ESRD) patients remains unknown.

Case Description: We present a case of severe high anion gap metabolic acidosis (HAGMA) with acute respiratory failure in an ESRD patient. A 37-year-old African American female with ESRD, hepatitis C and hypertension was found smoking synthetic marijuana under a tree, and in a confused state. Upon arrival to the emergency room, patient was severely hypertensive with blood pressure of 230/140 mmHg, and subsequently developed acute respiratory failure requiring intubation. Chest x-ray showed bilateral pulmonary edema. Laboratory data revealed: WBC 18K/uL, Na 138 mEq/L, K 3.6 mEq/L, Cl 104 mEq/L, CO2 10 mEq/L, Anion Gap 24. On Blood Gas: pH 6.95, pCO2 42 mmHg, pO2 73 mmHg, HCO3 8.3 mmHg. Urine drug screen was positive for benzodiazepine and cannabinoid. Patient required emergent hemodialysis for severe high anion gap metabolic acidosis. Patient required dialysis consecutively for 2 days and anion gap metabolic acidosis resolved. She was also successfully extubated on third day of admission.

Discussion: Synthetic Cannabinoids are sold under different trade names and the exact compounds contained in these products change frequently and are frequently unknown. Therefore, risks and adverse consequences of consuming synthetic cannabinoids are unpredictable and can be deadly. Acute tubular necrosis and interstitial nephritis are most common findings for patients who developed synthetic cannabinoid related AKI. Treatment is supportive management. However, effects on ESRD patients remain unknown. Our patient developed (HAGMA), which could very well be related to synthetic marijuana use. Physicians should be aware of designer drugs use in ESRD patients.

SA-PO093

Focal Segmental Glomerulosclerosis Associated with Cocaine Abuse: A Case Report Teg Marcos Veiga, Nathalia K.N. Alecrim, André Luiz De Andrade Araújo, Gisele Vajgel Fernandes, Luis H.B.C. Sette, Lucila Maria Valente, Maria Alina G.M. Cavalcante. *Nephrology, Univ Federal de Pernambuco, Recife, Pernambuco, Brazil.*

Introduction: Cocaine exists in two major forms: cocaine hydrochloride and alkaloidal freebase (crack). Cocaine abuse causes many well recognized systemic adverse effects and acute kidney injury is usually due to rhabdomyolysis, malignant hypertension with thrombotic microangiopathy and renal infarction. In addition, it has been described ANCA-positive vasculitis induced by levamisole-adulterated cocaine causing nephrotic syndrome. We report a case of focal segmental glomerulosclerosis in a patient with history of cocaine use.

Case Description: A 49 year-old man of admixture race presented with progressive edema and dyspnea for the past five months. Lab tests showed Scr 7.0 mg/dL (baseline: 0.9 mg/dL), hypoalbuminemia, hypercholesterolemia and nephrotic range proteinuria (13g/24h). The patient had started using illicit drugs (marihuana and crack) three months before the symptoms begun. There was no sign of infection or hypovolemia. All serologic tests were normal or negative, including complement, antinuclear antibodies, anti-DNA antibody, c-ANCA, p-ANCA, hepatitis B and C, HIV, syphilis and there was no evidence of monoclonal serum spike. Renal ultrasound was normal. The patient underwent hemodialysis and received methylprednisolone. Renal biopsy showed 13 glomeruli, 6 globally sclerotic and 5 with segmental sclerosis and synechiae of the glomerular tuft, tubular atrophy and moderate interstitial fibrosis. Immunofluorescence was negative. There was no recovery of renal function.

Discussion: Although it has been described nephrotic syndrome due to ANCA-positive vasculitis induced by levamisole-adulterated cocaine, we have reported a case that showed association between the use of cocaine and focal segmental glomerulosclerosis.

SA-PO094

A Rare Case of Tumor Lysis Syndrome in a Patient with Angiosarcoma Bilal J. Alturkmani,¹ Michael A. Mao,² Edward T. Casey,² *Alfaisal Univ, Riyadh, Saudi Arabia; ²The Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Introduction: To report a rare case of tumor lysis syndrome (TLS) developing in a patient with angiosarcoma and metastasis to the liver.

Case Description: A 63-year-old male presented to his primary care physician complaining of fatigue, night sweats, fever, and newly developed RUQ pain. An ultrasound of the abdomen revealed hepatic lesions and a subsequent CT scan showed two large masses in the liver and a mass in the pancreas. A liver biopsy was obtained and findings were consistent with metastatic angiosarcoma and he was therefore initiated on palliative chemotherapy. The patient then presented to his local hospital with abdominal pain and abdominal bruises. His hemoglobin was 4.9 g/dL and he was found to be bleeding from the liver biopsy site. He was transferred to our institution for embolization in setting of intra-abdominal bleeding and multiorgan dysfunction. His clinical presentation, along with laboratory findings, was consistent with anuric renal failure secondary to TLS.

Table 1			
Laboratory Values	Three days prior to hospitalization	On admission to Mayo	Reference Ranges, Units
Creatinine	1.4	2.7	[0.8-1.3], mg/dL
Potassium	4.3	6.6	[3.6-5.2], mmol/L
Uric Acid	-	16.3	[3.7-8.0], mg/dL
Calcium	8.2	-	[8.9-10.1], mg/dL
Ionized Calcium	-	4.29	[4.65-5.30], mg/dL
Phosphorus	-	8.4	[2.5-4.5], mg/dL

The patient was initiated on allopurinol, rasburicase, and continuous veno-venous hemofiltration (CVVH). He progressively deteriorated during his 11-day hospital course with recurrent episodes of arrhythmia, persistent encephalopathy, continued mechanical ventilator and hemodialysis dependence, and refractory septic shock with candidemia. The family elected for comfort care and the patient expired the next day.

Discussion: TLS is a constellation of laboratory and/or clinical manifestations that can arise either spontaneously or secondary to cancer treatments. Patients with hematological malignancies have a higher tendency to develop this syndrome due to the rapid turnover of cell growth and death. However, patients with solid tumors occasionally present with TLS. To our knowledge, this is the first case report of TLS associated with angiosarcoma.

SA-PO095

Leukocyte Chemotactic Factor 2 (LECT2)-Associated Renal Amyloidosis: A Case Report Alejandro Pepen Romero,¹ James Drakakis,¹ Joseph Mattana.¹
¹Nephrology Dept, Winthrop Univ Hospital, Mineola, NY; ²Pathology Dept, Columbia Univ, New York, NY.

Introduction: ALECT2 amyloidosis is a frequent form of systemic amyloidosis, represents 2.7-10% of all cases of renal amyloidosis. Most patients are elderly who presents with chronic renal insufficiency and bland urinary sediment.

Case Description: We report a 76-year-old Egyptian male who presented after a recent hospitalization for self limited gastroenteritis and severe acute renal failure presumed secondary to acute tubular necrosis. Due to non-improving renal function and uremic symptoms, renal biopsy was done and showed patchy Interstitial amyloidosis deposits that did not stain for IgG, IgM, IgA, Kappa, Lambda chains or Amyloid A; sample was sent to Mayo Clinic where Liquid chromatography tandem mass spectrometry detected a peptide profile consistent with ALECT2 Amyloidosis.

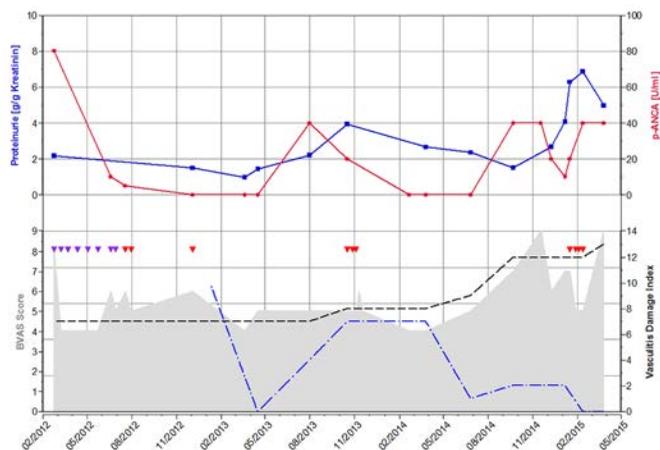
Discussion: This case suggests that ALECT2 Amyloid can present with bland urinalysis and non-nephrotic range proteinuria in elderly patients.

SA-PO096

Monitoring Disease Activity in ANCA Associated Vasculitis (AAV): A Case for Activated Circulating Monocytes? Florian Gunnar Scurt,¹ Leon Brian Schubert,¹ Noemi Rose Emma Doll,¹ Marius Früh,¹ Tobias Hölscher,² Andreas Jeron,² Dunja Bruder,² Peter R. Mertens,¹ Christos D. Chatzikyriou.¹
¹Nephrology, Hypertension, Diabetes and Endocrinology, Otto-von-Guericke Univ Magdeburg; ²Inst of Microbiology, Otto von Guericke Univ Magdeburg.

Introduction: We are still in need for more reliable markers to monitor disease activity in AAV.

Case Description: The clinical course of a patient with therapy refractory AAV is presented.



Disease activity was assessed by means of the BVAS and VDI score and by serial measurements of the CD19/CD20 cell count and the MPO titer. The last renal flare was on 11/2014 and was corroborated by renal biopsy. Monocyte subsets were also identified by flow cytometry with the use of the surface markers CD 14, CD 16 CCR2 and CxCR3. The expression of different proteins reflecting antigen presentation or activation status as well as scavenger receptor and toll like receptor functions was quantified in the monocyte subpopulations. Blood samples of a healthy individual were used as controls. Results of the antigen presentation marker HLA-DR and the monocyte activation marker CD 11b are presented here.

Renal and pulmonary disease progressed despite the use of an impressive immunosuppressive therapy. The CD19/CD20 cell count and the MPO titer did not predict relapse. The intermediate CD14++CD16+CCR2lowCXCR1+ monocyte subpopulation was increased but expressed less of the HLA-DR protein. The CD11b antigen expression was reduced in the classical monocyte subpopulation CD14++CD16+CCR2highCXCR1-, whereas no differences in the HLA-DR and CD 11b expression were observed in the non-classical monocyte subpopulation CD14+CD16+CCR2lowCXCR1high.

Discussion: There appear to be functional alterations in the different monocyte subpopulations during relapse of AAV. Their pathophysiological significance remains to be elucidated.

SA-PO097

A Case of Rhabdomyolysis Induced AKI with Two Questions: Serum Myoglobin versus CPK and the Potential Role for Rasburicase Mehdi Nouri kolouri. Nephrology, Baylor College of Medicine, Houston, TX.

Introduction: Rhabdomyolysis induced AKI is a common scenario. The mechanisms include myoglobin and uric acid crystal induced tubular injury. The role of uric acid lowering agents in such condition remains to be defined. Here we describe such a case, in which

uric acid lowering agent successfully lowered uric acid level and possibly contributed to renal function recovery. In this case CPK level was not high enough to justify AKI and a very high serum myoglobin level established the diagnosis.

Case Description: a 37 years old man without known history was brought to ER with agitation and delusional/combatative behavior. Vital signs included temp=100.4, BP=165/85, RR=32/min and PR=120/min. On examination, he was mildly volume deplete. He was found to have AKI with BUN=76, Cr=4, K=6.7 and metabolic acidosis. Urine toxicology was positive for amphetamines. CPK level was 4200 U/L and uric acid level was 21 mg/dL. Supportive management including aggressive IV fluids was initiated for amphetamine toxicity with resultant rhabdomyolysis. Urine exam showed several coarse granular casts. Serial CPK levels were not high enough to justify AKI. However serum myoglobin level was very high at >20000 ng/mL and confirmed severe rhabdomyolysis. one session of dialysis was done due to persistent metabolic acidosis and hyperkalemia. However uric acid level remained high at same range. We used a dose of Rasburicase at 3 mg which reduced uric acid level to 5.5 six hours later. After few days, renal function and clinical status started to improve and he was discharged in stable condition.

Discussion: There may be a therapeutic/prophylactic role for uric acid lowering agents in rhabdomyolysis induced AKI. In our case, Rasburicase successfully lowered uric acid level after it had remained high post-dialysis. Similar results have been reported in the past, however further research is needed in the future. Besides, Although AKI in rhabdomyolysis is usually seen with CPK levels>20000, our patient had much lower levels and a very high serum myoglobin established the diagnosis of severe rhabdomyolysis. Serum myoglobin is more accurate to determine the severity of rhabdomyolysis and predict the risk of AKI.

SA-PO098

Exploring the Utility of Albuminuria Saman Sarani,¹ Ruchika Bhasin,¹ Afsaneh Haftbaradaran,¹ Golriz Jafari,¹ P.T. T. Pham,² P.C. Pham.¹ ¹Div of Nephrology and Hypertension, Olive View-UCLA Medical Center, Sylmar, CA; ²Kidney Transplant, UCLA Medical Center, Los Angeles, CA.

Introduction: Patients with underlying glomerular diseases often present with acute kidney injury from either acute tubular necrosis (ATN) due to hemodynamic compromise such as diuretic overuse versus exacerbation of underlying disease. The clinician is often faced with the difficult decision to either provide fluids and supportive care vs. intensification of immunosuppressive therapy. Whereas proteinuria associated with ATN is presumably predominantly non-albumin protein, proteinuria associated with glomerular disease exacerbation is predominantly albuminuria. We follow a case with biopsy proven minimal change disease and concurrent ATN and evaluate sequential urine albumin to creatinine (MAC) ratio to protein to creatinine (PCR) ratio MAC/PCR over the course of treatment for changes.

Case Description: A 63 year old Hispanic male presented with anasarca and blood pressure 214/104 mm Hg. Routine evaluation was significant for a serum creatinine (Scr) of 1.4 mg/dl, peaked at 1.77 mg/dl, PCR of 12.8 g/g Cr, and MAC of 7.9 g/gCr. Physical examination was significant for anasarca. There was no lymphadenopathy noted. Routine proteinuria evaluation for hepatitis B and C, RPR, HIV, C3, C4, CH50, ANCA, serum free light chains, serum and urine protein electrophoresis and immunofixation were negative. A kidney biopsy performed revealed minimal change disease with evidence of marked ATN. Patient was treated with a course of prednisone at 1m/kg/day tapered over a 6 month period. Patient went into full remission without any complications. Over the course of disease, sequential MAC/PCR was noted to increase as PCR and Scr decreased. Presentation: Scr 1.44-1.77, MAC=7.9 g/g Cr, PCR=12.8 g/gCr, MAC/PCR=0.62; 2-month follow-up: Scr 1.3, MAC=1.6, PCR=1.7, MAC/PCR=0.95; 3-month follow-up: Scr 1.3, MAC=1.4, PCR=0.8, MAC/PCR=1.6.

Discussion: The current case indicates that a higher degree of albuminuria relative to proteinuria is noted with eventual resolution of ATN. We suggest that MAC/PCR may be used as a marker of associated ATN complicating underlying GN. Further studies are needed.

SA-PO099

Idiopathic Eosinophilic Peritonitis After Peritoneal Dialysis Catheter Placement Nader S. Bahri, Charles W. Heilig. Nephrology and Hypertension, Univ of Florida, Jacksonville, FL.

Introduction: Idiopathic Eosinophilic peritonitis (IEP) typically occurs soon after initiation Peritoneal Dialysis (PD) with variable presentation mimicking bacterial or fungal peritonitis. The main etiology of IEP is unclear and many have speculated that it represents an allergic reaction to possible plasticizers in the PD bags or catheter or an eosinophilic reaction to the solutions, methods of catheter placement or air exchanges during the exchanges.

Case Description: 42 year-old AAF with ESRD from T2DM and hypertension in 9/2009 was started on hemodialysis (HD) via fistula. She underwent PD training and started CAPD on 9/18/2010 with Baxter Ultra bag dextrose solution after laparoscopic placement of Quinton Curl PD catheter on 9/2/2010. During follow on 9/30/2010 cloudy PD fluid recognized. The patient didn't have any symptoms of abdominal pain, nausea, vomiting, constipation, diarrhea or fatigue. Vital signs were stable. Physical exam didn't show any evidence of site infection or abdominal tenderness and no skin allergic reaction. There were no new medications or no current antibiotic therapy since placement of PD catheter. PD fluid cell count showed total WBC count of 480/mm³ with 49% eosinophil and 1% neutrophil. Gram stain and all bacterial, fungal and AFB cultures were negative. CBC showed normal WBC count of 9900/mm³ with 8.9% eosinophilia. The patient kept on PD with close follow ups. empiric antibiotics were discontinued. Repeat PD fluid cell count showed total of WBC 327/mm³ with 20% eosinophil and 6% neutrophil with all repeated- cultures negative. AT this point the patient has switched to HD on 11/04/2010 via available fistula and PD catheter was kept in place. By 12/28/2010 a sample of peritoneal fluid obtained which showed declining of WBC count to 123/mm³ with 7% eosinophil with

complete resolution of eosinophilia while the patient was on HD. In 3/28/2011, the patient resumed PD via same catheter and same solution, follow up PD fluid sample on 4/07/2011 showed normal WBC count and 4% eosinophil.

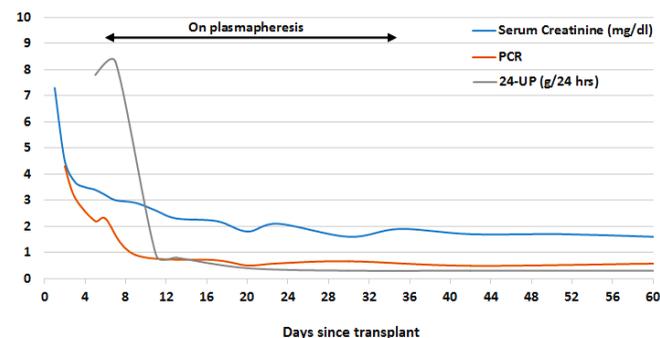
Discussion: Our case suggests IEP was a transient reaction to the catheter placement rather than a reaction to the PD set or solution.

SA-PO100

Post Renal Transplant Follow Up in Focal Segmental Glomerulosclerosis with 24 Hour Urine Protein Collection – Traditional and True Ravinder Pal S. Bhatti, Manisha Singh, Lakshmi P. Nadimpalli, Sameh R. Abul-Ezz. *Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Random Urine Protein Creatinine Ratio (PCR) is commonly used to estimate proteinuria compared to 24 hour urine protein measurement (24-UP). However, there are concerns over the diagnostic accuracy and reliability of such an approach in post-transplant setting. We present a case of post-transplant focal segmental glomerulosclerosis (FSGS) illustrating this.

Case Description: A 39 year old male with primary FSGS, on peritoneal dialysis for 4 years received a cadaveric kidney transplant. His panel reactive antibody was 0% and HLA cross-match was negative. Peri-operative course was uneventful. Given the history of FSGS, PCR was monitored. By post-op day 5, serum creatinine had decreased from 7.3 mg/dl to 3.2 mg/dl and PCR from 4.3 to 2.8. However, his 24-UP came back 8 g, which was markedly different.



Early recurrence of FSGS was diagnosed. A biopsy was withheld to avoid delay in timely management and risk of bleeding with plasmapheresis which was immediately initiated. He was switched from tacrolimus to cyclosporine. He required plasmapheresis for 5 weeks and had satisfactory recovery in the ensuing months.

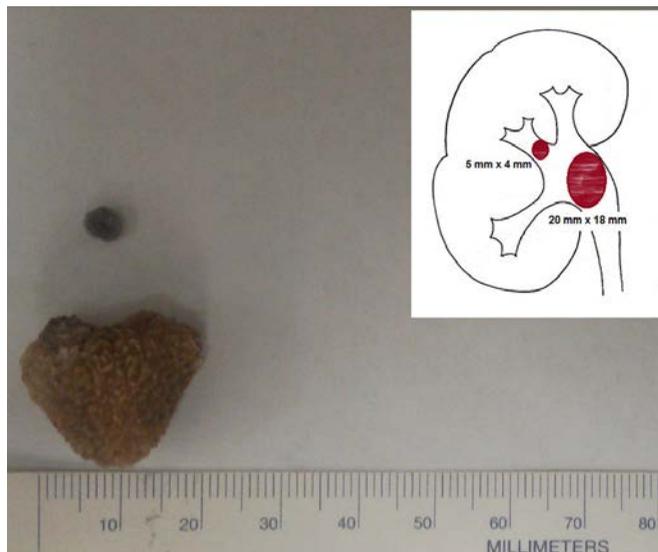
Discussion: Logistics have led to the widespread use of PCR in follow-up of kidney transplant recipients. However changing creatinine excretion with recovering renal function, lower precision with heavier proteinuria, and limited data on accuracy compared to 24-UP, potentially limit its utility at detecting early post-transplant recurrence of FSGS. Our case highlights marked discordance between the PCR and 24-UP, detection of which allowed a timely change in management. We conclude that it is prudent to monitor proteinuria by timed urine collection in preference to random PCR in the immediate post-transplant setting for recipients with primary FSGS.

SA-PO101

Donor Kidney Lithiasis: A Case of Throwing Out the Baby with the Bathwater? Ravinder Pal S. Bhatti,¹ Sameh R. Abul-Ezz,¹ Lakshmi P. Nadimpalli,¹ Gary Wickens Barone,² ¹*Nephrology;* ²*Transplant Surgery, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Cadaveric kidneys account for a majority of transplants in the United States. However, only 10% of waitlisted patients receive one annually, making optimal utilization critical. Donor nephrolithiasis represent a small yet significant proportion of kidneys discarded. We present a patient who received such a kidney which otherwise could have been discarded.

Case Description: The donor was a healthy 31 year old female who suffered anoxic brain injury in a motor vehicle accident. Her CT abdomen showed 2 stones in the right kidney as represented in the figure's inset. The kidney became available to us on a regional list after it was declined locally due to concerns over kidney quality. Our recipient was a 50 year old female with hypertensive nephropathy, on hemodialysis for the past 2 years. Her panel reactive antibody was 90% and HLA cross match was negative. Intra-operatively, a large stone measuring 2 cm was identified in the hilum of the donor kidney and was extracted via pyelotomy. A smaller middle calyceal stone was localized by fluoroscopy and successfully removed by irrigation.



There were no perioperative complications and the recipient had excellent immediate graft function. Her creatinine progressively improved by time of discharge, remaining normal in subsequent months.

Discussion: The new kidney allocation policy aims to address organ shortage by reducing donor and graft survival mismatch. Traditionally, donor hemodynamics, age, serum creatinine and histopathology have influenced decisions on accepting a kidney. The perceived quality and utilization techniques widely vary for deceased donor kidneys with lithiasis. Our case illustrates how this can lead to non-acceptance of an otherwise healthy kidney, which can be transplanted with a favorable outcome.

SA-PO102

A Peritoneal Dialysis Catheter Leak Complicated by *Burkholderia Gladioli* Peritonitis Ravinder Pal S. Bhatti, Dumitru Rotaru. *Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Dialysate leaks can occur any time after peritoneal dialysis (PD) catheter placement. Early leaks usually manifest as an exit site leak, though may also present with air in the PD catheter. Leaks increase the risk for exit site infections (ESI) and peritonitis. We present such a patient developing peritonitis with an unusual pathogen.

Case Description: A 74 year old male who had been on Continuous Cycling Peritoneal Dialysis for 3 years, presented with exit site erythema a week after trying to push in an extruded cuff. Prophylactic antibiotics were started but he declined surgery. The ESI recurred soon after completing 3 weeks of antibiotics. He agreed to catheter replacement with an exit site change. He was started on low volume exchanges. Two weeks later, he noted air bubbles in the PD catheter upon draining.



A small pinhole was found at the exit site, suspected to be from a sharp injury during dressing change. He was planned for surgical revision but soon started having turbid drainage. Instilled dialysate was cultured, broad spectrum intravenous antibiotics were started and he was switched to hemodialysis. During surgery, the damaged catheter was spliced to new tubing proximal to the exit site. The cultures grew *Burkholderia Gladioli* by now. PD was resumed the next day. The peritonitis resolved during the 3 weeks of antibiotics. He continued PD uneventfully over ensuing months.

Discussion: A rare observation, air in a PD catheter is almost pathognomic of a dialysate leak. Our case highlights several key points in such a scenario. Firstly, use of sharps is a major risk factor and should be discouraged. Secondly, an increased risk of peritonitis

including by rare pathogens warrants appropriate antibiotic prophylaxis and lastly a more limited approach than catheter exchange may be used even for leaks close to exit sites based on the location and local experience.

SA-PO103

Enteric Hyperoxaluria Related to Celiac Disease Causing Acute Kidney Injury After Kidney Transplantation *Ashvin Baru, Venkat Ramanathan. Nephrology, Baylor College of Medicine, Houston, TX.*

Introduction: Acute kidney injury (AKI) after kidney transplantation can occur from myriad of causes. We present an interesting case of a young woman with history of Celiac disease who developed AKI and biopsy-proven oxalate nephropathy within 3 months post-transplantation, as a result of enteric hyperoxaluria associated with gluten noncompliance.

Case Description: A 35 year-old woman with type 1 diabetes mellitus, and celiac disease underwent living unrelated kidney transplantation for ESRD related to biopsy-proven diabetic nephropathy. Her original renal ultrasound did not show nephrocalcinosis. After transplantation, nadir serum creatinine was 1.0 mg/dL. Three months later, she presented with six-day history of diarrhea and AKI. Serum creatinine peaked at 2.6 mg/dL. Since volume replacement did not improve her allograft function and she had high panel reactive antibody levels pre-transplant, a kidney biopsy was performed that showed acute tubular injury with significant oxalate crystalline deposits. Initial serum oxalate level was undetectable, but 24-hour urine oxalate excretion was elevated at 98 mg/dL. Pending gene testing, she was treated with intravenous fluids, low oxalate diet, gluten free diet, vitamin B6, oral alkali and calcium carbonate. Subsequent gene testing did not reveal gene mutation in the oxalate pathway. Her urine output was maintained between 3 to 4L per day. With strict gluten avoidance and low oxalate diet, urine alkalinization and oral calcium, her allograft function has improved to baseline.

Discussion: Celiac disease exacerbation and subsequent malabsorption can lead to significant gut oxalate absorption and hyperoxaluria. Resulting oxalate nephropathy is a rare cause of AKI after kidney transplantation.

SA-PO104

Unusual Presentation of Tumor Related Membranous Nephropathy *Tahir Zaman,¹ Frederic Clayton,² Josephine Abraham.¹ ¹Nephrology, Univ of Utah, Salt Lake City, UT; ²Pathology, Univ of Utah, Salt Lake City, UT.*

Introduction: The literature is laden with evidence of several solid tumors causing secondary membranous nephropathy. It is also described in the literature that solid tumors could also ANA positivity.¹

Case Description: A 62-year-old male with a history of hypertension presented with oliguric renal failure following an episode of gastroenteritis. History was unremarkable with patient denying smoking or other vices. Urine analysis revealed rare dysmorphic RBC's and minimal proteinuria (spot protein/creatinine ratio 0.5 gms). Serologic workup revealed +PR3 (ANCA negative) and abnormal Kappa/Lambda Ratio thus renal biopsy was performed, which revealed membranous nephropathy and acute tubular necrosis (ATN). Immunofluorescence was positive for C3, IgG, though negative for PLA-2R, IgA and C1q. ANA was strongly positive (1:10240 speckled pattern), HIV serology was negative. Sublingual mass was found which revealed squamous cell carcinoma. Bone marrow biopsy revealed smoldering multiple myeloma. The patient's ATN resolved and he subsequently underwent left partial glossectomy. His cancer was staged at T2N0 and he is undergoing chemotherapy and radiation therapy.



Sublingual mass.

Discussion: Secondary membranous nephropathy has a known association with solid tumors. The positive ANA raised the concern of concomitant connective tissue disease but C1q negativity on the biopsy made this diagnosis unlikely. Ultimately treatment of the underlying condition is paramount. Imai, H. *et al.* Nucleolar antigens and autoantibodies in hepatocellular carcinoma and other malignancies. *Am. J. Pathol.* 140, 859–70 (1992).

SA-PO105

A Case of Severe Adrenal Insufficiency due to Long-Term Glucocorticoid Administration for Pediatric Nephrotic Syndrome *Yuko Fujii,¹ Akira Ashida,¹ Hideki Matsumura,¹ Akihiko Shirasu,¹ Hyogo Nkakura,¹ Motoshi Hattori,² Hiroshi Tamai.¹ ¹Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; ²Pediatric Nephrology, Tokyo Women's Medical Univ, Shinjyuku, Tokyo, Japan.*

Introduction: One of the adverse effects of long-term glucocorticoid therapy in supra-physiologic doses is suppression of the hypothalamic-pituitary-adrenal axis, although symptomatic adrenal insufficiency is considered to be an unusual complication of glucocorticoid therapy for nephrotic syndrome in pediatric patients. Here we describe a case of secondary adrenal insufficiency due to long-term glucocorticoid therapy for steroid-dependent nephrotic syndrome.

Case Description: A 12-year-old boy who had developed steroid-dependent nephrotic syndrome at the age of 2 years had been treated repeatedly with corticosteroid, cyclosporine and mizoribine. On relapse of the disease at 4 years of age, the nephrotic syndrome had been resistant to steroid therapy including 2 mg/kg prednisolone and 4 courses of methylprednisolone pulse therapy, but had responded to additional cyclophosphamide therapy at 7 months after relapse onset. During tapering of the glucocorticoid therapy, the patient had shown various symptoms, including general fatigue, facial edema, decreased urine volume, appetite loss, and dizziness from the age of 5 years. At that time, the basal value of cortisol was not detectable and a rapid ACTH loading test elicited a low response. In the CRH and insulin loading test, the basal value of ACTH was not detectable and an over-response of ACTH was demonstrated. Therefore the patient was diagnosed as having glucocorticoid-induced hypothalamic adrenal insufficiency and treated with cyclosporine, a decreased dose of prednisolone, and hydrocortisone supplementation. The serum ACTH and cortisol values increased gradually. An insulin loading test at the age of 12 years demonstrated normal responses of the ACTH and cortisol levels.

Discussion: The very long-term nature of the therapy for this patient with idiopathic nephrotic syndrome resulted in glucocorticoid-induced adrenal insufficiency. Periodic evaluation of adrenal function and re-evaluation of the treatment is important for patients with nephrotic syndrome receiving steroid therapy.

SA-PO106

Henoch-Schönlein Purpura in Adult, from a Clinical Case *Miguel Goncalves, Pedro Vieira, Jose Duraes, Luis Resende, Nuno Rosa, Jose Alves Teixeira, Gil Silva. Nephrology, Hospital Dr. Nélito Mendonça, Funchal, Portugal.*

Introduction: Henoch-Schönlein purpura is a small vessel vasculitis mediated by IgA-immune complex deposition with multisystemic involvement. Rare in adults, is characterized by purpura, arthralgias, abdominal pain, and renal involvement. Viral infections have been reported as triggers.

Case Description: The authors present the case of a 25 years old male, without relevant medical history, admitted to the Nephrology Department in May 2014 by severe hypertension, renal failure (creatinine 6.7mg/dL), erythrocyturia and proteinuria. Renal ultrasound was normal. Renal biopsy revealed IgANephropathy (M1E1S1T2). Our investigation revealed chronic hepatitis B virus (HBV) of vertical transmission origin (viral load 150 IU/mL). Corticosteroid therapy was started, with slight improvement in renal function. He was readmitted 2 months later by asthenia, epistaxis, weight loss, pallor, generalized edema, ascites, and oral and nasal ulcers. Laboratory tests revealed hemoglobin 9.2g/dL, creatinine 4.3mg/dL, normal transaminases, albumin 20g/L, urinary spot protein:creatinine ratio 1300mg/g, hypocomplementemia, negative p-ANCAs, c-ANCAs and cryoglobulins, HBV load 379.980IU/mL. During hospitalization the patient initiated progressive pancytopenia, diffuse abdominal pain, generalized skin purpura and fever (with no identifiable infectious origin and interpreted as immunologic). We made clinical diagnosis of Henoch-Schönlein purpura and started with cyclophosphamide and entecavir. A few days later appeared hypoxemia and oliguria, requiring urgent dialysis. Cranial CT scan showed microangiopathic leukoencephalopathy of unspecified etiology and alveolar hemorrhage in chest CT scan. Due to life threatening multisystemic involvement we started methylprednisolone pulses, intravenous immunoglobulin and plasmapheresis. Patient completely recovered, but remained dependent on dialysis. 6 monthly cycles of cyclophosphamide were maintained, with no signs of recurrence.

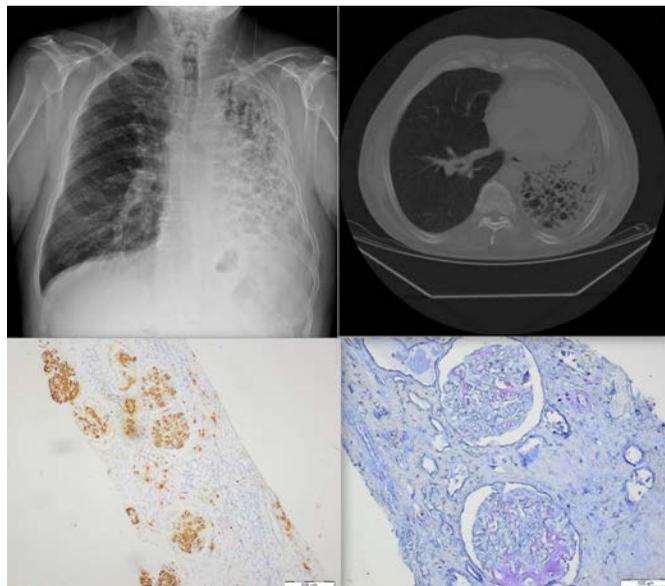
Discussion: We emphasize the rare severe multisystemic involvement of a Henoch-Schönlein purpura in an adult, the onset of the disease with exacerbation of viral infection, and the therapeutic challenge of an HBV patient with a vasculitis.

SA-PO107

Rare Etiology for Chronic Kidney Disease: Bronchiectasis Related Secondary Amyloidosis *Alper Alp,¹ Hakan Akdam,² Aysegul Ormeci,³ Ibrahim Meteoglu,³ Alparslan Unsal,⁴ Yavuz Yenicerioglu.² ¹Nephrology, Van Education and Research Hospital, Van, Turkey; ²Nephrology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; ³Pathology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; ⁴Radiology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey.*

Introduction: Here we present an elderly patient with a known posttuberculosis-bronchiectasis. Nephrotic-range proteinuria and renal failure was detected. Renal biopsy revealed AA amyloidosis. Tuberculosis and tuberculosis related systemic disorders still have clinical impact in nephrology practice especially in developing countries.

Case Description: A 67 yo man was referred to our hospital with renal failure and proteinuria. PMH was remarkable for tuberculosis (41 years ago) and posttuberculosis-bronchiectasis for long years. On physical examination pretibial edema was evident. Chest X-ray, thorax CT revealed left sided total bronchiectasis and pulmonary nodules. Malignancy was excluded with PET/CT and bronchoscopy. On admission biochemical tests: urea: 220mg/dl, creatinine: 5.86mg/dl, potassium: 4.8mmol/L, GFR 10.3ml/min/1.73m², ANA 1/100 positivity (cytoplasmic). Renal ultrasonography revealed bilateral echogenic kidneys with normal size and shape. 24 hour urinary proteinuria, albuminuria was 7924 was mg/dl, 4789mg/dl, respectively. Renal biopsy was compatible with AA amyloidosis (segmental homogeneous deposits of amyloid in the glomeruli and interstitium). Immunohistochemistry was positive for staining of AA amyloid. There was no immunofluorescence staining with IgG-A-M, C3, fibrinogen.



Tunneled catheter was placed and hemodialysis was started.

Discussion: FMF and rheumatological disorders are the leading causes of amyloid AA in Turkey. However other rarely seen etiologies should not be missed in clinical practice. Secondary amyloidosis as a multisystemic disease has a high mortality risk. Renal manifestations include nephrotic syndrome and renal failure.

SA-PO108

Sunitinib Induced Acute Renal Failure and Nephrotic Syndrome in a Patient with Metastatic Neuroendocrine Tumor: A Case Report and Review of the Literature Srijita Mukherjee,¹ Carla L. Ellis,² ¹Nephrology, Emory Univ Hospital and School of Medicine, Atlanta, GA; ²Pathology, Emory Univ Hospital and School of Medicine, Atlanta, GA.

Introduction: Sunitinib is a chemotherapeutic agent used to treat advanced malignancies via inhibition of tyrosine kinase phosphorylation. We present a case of sunitinib induced acute renal failure with nephrotic syndrome, occurring within one week of initiation for persistent carcinoid syndrome secondary to hepatic metastasis of a primary small intestinal neuroendocrine tumor.

Case Description: A 63 year old man with metastatic neuroendocrine tumor was initiated on sunitinib to treat persistent carcinoid syndrome despite initial therapy. Within one week of initiation, he developed new onset peripheral edema, 20 pound weight gain and acute renal failure with nephrotic range proteinuria. Baseline creatinine was 1.0, and on presentation, had increased to 3.0. There were over 10 grams of proteinuria on urine protein to creatinine ratio. Sunitinib was discontinued, but renal failure progressed, with peak creatinine of 7.1 prior to starting hemodialysis. A kidney biopsy was performed, which showed diffuse podocyte foot process effacement, focal global glomerulosclerosis and acute tubular injury. The patient remains dialysis dependent as of this report.

Discussion: Literature review reveals reports that vary both in time to onset and degree of resolution of renal disease after initiation and discontinuation of sunitinib therapy, respectively. Renal pathology also varies, including acute tubular necrosis, acute interstitial nephritis, diffuse podocyte foot process effacement and thrombotic microangiopathy. Our patient developed a greater severity of renal failure than most reported, including a higher peak serum creatinine, longer duration of renal replacement therapy and current lack of renal recovery. To our knowledge, this is also the first report of the onset of renal failure in the specific clinical scenario described. Given the near immediate adverse effect of sunitinib in our patient, we recommend monitoring of creatinine and urine protein at baseline and within the first three to five days of medication initiation.

SA-PO109

Cryoglobulinemic Glomerulonephritis After Successful Treatment of Hepatitis C Nupur Gupta, Chad A. Zarse, Allon N. Friedman. *Nephrology, IU School of Medicine, IN.*

Introduction: The optimal treatment of cryoglobulinemic glomerulonephritis (GN) in the setting of Hepatitis C (Hep C) with sustained viral response (SVR) is unknown. Only expert opinion obtained from case reports provide guidance to the clinician. Some reports suggest treatment with Rituximab may be beneficial.

Case Description: 58yo male with h/o treated Hep C currently with an undetectable viral load, gastric ulcer, anemia, and HTN presented to clinic for evaluation of CKD. Hep C was initially diagnosed when he was found to have leukocytoclastic vasculitis on a skin biopsy of skin rash. Labs were positive for serum cryoglobulins, rheumatoid factor, low C4, and Hep C viral load. Renal function was normal and he was successfully treated for cryoglobulinemic vasculitis due to Hep C with interferon alpha, telaprevir and ribavirin and achieved a SVR. He presented 1 year later with renal insufficiency (creatinine -2.2 mg/dL) and 500mg proteinuria. He had intermittent flares of vasculitis. SPEP revealed IgM kappa monoclonal with negative UPEP. C4 was low and cryoglobulins remained positive. Kidney biopsy showed immune complex GN with organized deposits. Bone marrow biopsy was negative for lymphoproliferative disease. He was diagnosed with cryoglobulinemic GN with SVR. Initially, he was treated with prednisone followed by Rituximab and plasmapheresis. He failed the treatment and was started on hemodialysis.

Discussion: Cryoglobulinemic GN is frequently due to Hep C but is rare in patients achieving a SVR. In our case an underlying B cell lymphoma was ruled out and it was felt that B cell immune dysregulation due to Hep C was the culprit, in part due to prior published cases. However, in our case treatment with rituximab and plasmapheresis was unsuccessful. It remains possible, as others have demonstrated, that the virus may persist within the liver, macrophages, lymphocytes, and even kidney. The pathological basis for persistent vasculitis in setting of a SVR requires further study so that targeted and more effective treatment strategies can be designed.

SA-PO110

Diagnostic Intrapartum Dilemma: Distinguishing Glomerulonephritis from Preeclampsia in Pregnancy Suzanne L. Katsanos, Fernanda Payan Schober, William Franklin Pendergraft, Volker Nickleit, JulieAnne G. McGregor, Harsharan Kaur Singh. *UNC Kidney Center, Chapel Hill, NC.*

Introduction: Distinguishing glomerular disease from preeclampsia intrapartum can be challenging due to overlap of clinical findings. Unfortunately, this diagnostic dilemma can result in unwarranted early delivery. Here we present 5 cases of glomerulonephritis (GN) complicating pregnancy.

Case Description: 3 patients (ages 22, 31 and 33) presented during pregnancy with proteinuria, dysmorphic hematuria and, in 2 cases, acute kidney injury. In all 3 cases, the concern for preeclampsia prompted induction of labor (IOL), and postpartum kidney biopsy showed IgA nephropathy. 2 patients were treated with steroids and ACE inhibitors (ACEI) with improvement in proteinuria. The one with the most severe kidney dysfunction was treated with cyclophosphamide (CYC). Unfortunately, she became dialysis-dependent 1 month postpartum. The fourth patient (age 20) presented with HELLP syndrome at 25 weeks and underwent IOL. 5 months post-partum, she developed clinical symptoms of lupus in the setting of proteinuria, dysmorphic hematuria and persistent kidney dysfunction. Kidney biopsy showed diffuse proliferative lupus nephritis, which was treated with IV CYC. Unfortunately, she continued to have renal dysfunction despite treatment. The fifth patient (age 37) had minimal change disease (MCD) and was in remission at the time of pregnancy. She did well on cyclosporine until 25 weeks gestation when she developed hypertension, edema, and nephrotic-range proteinuria. It was unclear whether this represented preeclampsia or a MCD flare so she underwent IOL. Subsequent placental pathology failed to show signs of preeclampsia. She was treated postpartum with steroids and ACEI and re-entered remission.

Discussion: Here we show that pregnancy can aggravate (as in the case of our patient with MCD) or unmask (as in the other 4 cases) underlying glomerular disease. Diagnosis can be delayed due to risks related to kidney biopsy during pregnancy, and treatment is complicated by safety concerns for the developing fetus. Further work is needed to identify meaningful mechanisms to accurately differentiate preeclampsia from GN during pregnancy.

SA-PO111

A Case of Rapidly Progressive Glomerulonephritis Associated with Metastatic Lung Cancer Eduardo J. D. de Sa Carneiro Filho, Victor Longo Silva, Lilian Cordeiro, Veronica T. Costa e Silva, Elerson Costalonga. *Univ of São Paulo, Nephrology Division, São Paulo, Brazil.*

Introduction: Several solid malignancies have been associated with glomerular diseases. Rapidly progressive glomerulonephritis (rPGn) has been reported in association in particular with renal cell carcinoma and lung cancers. We report a case of rPGn associated with metastatic lung cancer treated with chemotherapeutic agents.

Case Description: A 57-year-old male with metastatic epidermoid lung cancer, treated previously with paclitaxel plus carboplatin, cisplatin plus gemcitabine and four cycles of docetaxel, was admitted with dysuria and hematuria for last 1 week. Upon physical examination: edema of the lower limbs. Laboratory results demonstrated normal liver function, positive anti-Hbc, negative HbsAg and anti-Hbs, hemoglobin 6.5 g/dL, serum creatinine of 3.78 mg/dL (baseline 1.5), C3 154 mg/dL, C4 24.8 mg/dL, negative cANCA. Urinalysis showed proteinuria (>1 g/L), more than 100 leukocytes per field and more than 100 red cells even after antibiotic treatment for presumed urinary infection. Due to persistent

proteinuria (3.7g/24h), evidence of dysmorphic hematuria and worsening of renal function (Cr 4.1 mg/dL), he received methylprednisolone 1g for three days and renal biopsy was proposed. It revealed pauci-immune crescentic glomerulonephritis. Immunofluorescence showed mesangial deposition of C3 (3+) and lambda chains (1+). Treatment was followed by monthly i.v. cyclophosphamide and proteinuria decreased to 0.87 g/24h. cANCA became positive (1/160) 4 months after diagnosis.

Discussion: Membranous nephropathy is the most commonly reported glomerulopathy especially with pulmonary cancer, but several reports suggest an association between rPnG and malignancies. The increased risk for malignancy has been confirmed in a retrospective review of 200 patients with ANCA-associated vasculitis, demonstrating a significantly increased relative risk (6.02) compared with age-matched controls. Biava et al reported seven cases of rPnG associated with a coexisting nonrenal malignancy (6 carcinomas and 1 lymphoma). The pathogenetic mechanisms by which neoplasms lead to the development of ANCA-associated vasculitis and rPnG are largely unknown.

SA-PO112

A Case of Encapsulating Sclerosing Peritonitis in a Type I Diabetic on Peritoneal Dialysis Zachary Freestone, Josephine Abraham, Akram M. Shaaban. *Nephrology, Univ of Utah, Salt Lake City, UT.*

Introduction: Encapsulating sclerosing peritonitis (ESP) is a rare disorder associated with PD. It is characterized by peritoneal fibrosis and encasement of the bowel. Symptoms associated with ESP are non-specific and may be attributed to other etiologies. Abdominal imaging is required to evaluate ESP and diagnostic confirmation is achieved by laparoscopy. ESP should be considered in patients on peritoneal dialysis with symptoms involving the gastrointestinal tract, weight loss, or inadequate solute clearance.

Case Description: A 34 year old Caucasian male on PD presented to the clinic with complaints of nausea and abdominal pain. He had a history of type I DM, ESRD, neuropathy, and gastroparesis. He was started on PD 8 years ago and has had 3 prior episodes of peritonitis. The patient appeared ill and malnourished. His abdomen was soft on examination and non-tender to palpation. An abdominal x-ray indicated that he had calcification in the abdomen and pelvis. CT imaging showed calcification of the parietal peritoneum, abdominal cavity, omentum, and bowel. The patient underwent exploratory laparotomy with simultaneous PD catheter removal. The visual examination revealed a brown, inflamed rind encompassing the peritoneum, omentum, bowel, and colon. Peritoneal dialysis was discontinued and the patient was transitioned to hemodialysis.



Discussion: Encapsulating sclerosing peritonitis (ESP) is a condition associated with peritoneal dialysis. Its presenting symptoms are often non-specific and may be attributed to other causes. Abdominal imaging is necessary to evaluate for suspected ESP, CT being the preferred method. ESP is characterized by peritoneal thickening and fibrosis that encases the bowel. Treatment includes cessation of PD with transfer to hemodialysis and bowel rest. Other attempted treatments of this disease have included steroids and total enterolysis.

SA-PO113

Acute Kidney Injury from Enterovesical Fistula Secondary to Squamous Cell Carcinoma of Bladder Eleni Chelioti, Evdokia Efthimiou, Alexia Papalexandrou, Maria Sotiraki, Ioannis Xatzis, Maria Tsilivigou. *Dept of Nephrology, General Hospital of Piraeus, Athens, Greece.*

Introduction: Squamous cell carcinoma (SCC) of the bladder is a relatively rare tumor. Predisposing factor is chronic irritation of the bladder by urinary infection, calculi and long-term indwelling catheterization. Enterovesical fistula (EVF) usually has flow from intestine to the bladder and commonly manifests with recurrent urinary tract infections(UTI), fecaluria and pneumonia. We report a case with SCC of bladder who developed EVF, leading to acute kidney injury(AKI).

Case Description: A 56 year old Caucasian female with hypertension, diabetes mellitus and recurrent UTI was admitted in a uremic state that necessitated the immediate start of hemodialysis. Further clinical and laboratory findings revealed hematuria, pyuria, bacteriuria and fecaluria after placing a Foley catheter. Ultrasound scan of the abdomen showed two kidneys of normal size and parenchymal thickness. CT scan of the abdomen and pelvis showed a markedly contracted and nodular bladder with a large bladder wall defect and

the Foley catheter extending through the bladder wall into a small bowel loop. A diagnosis of EVF with reverse flow from the bladder to intestine was made. She subsequently underwent to a long surgery with total cystectomy, a ileo-hemicolectomy and creation of an ileal conduit. Histopathology examination of specimens revealed SCC of bladder and metastasis in the colon. After surgical intervention, she became hemodialysis dependent, refused further therapy and she is well 6 months later.

Discussion: In the western world SCC represent less than 5% of all bladder tumors. There are no specific diagnostic tests and it is usually diagnosed in advanced stage. Although distant metastasis is infrequent but the prognosis is poor and most patients die. In our case the only proved predisposing factor is chronic irritation of the bladder by UTI. EVF rarely can have reverse flow leading to urine excretion via GI tract in patients with diminished bladder capacity. The diverted urine stimulates metabolic disorders causing AKI.

SA-PO114

Postoperative Bilateral Ureteroenteric and Enterovesicular Fistulas Complicated by Hydronephrosis and Urosepsis Aya M. Zarm, Muner Mohamed, Rohini Chawla, Sunithi Krishnan, Richard E. Seguritan, Vinay N. Kikkeri. *Medicine/Nephrology Div, Richmond Univ Medical Center, Staten Island, NY.*

Introduction: Lower urinary tract fistulas are serious complications of abdominopelvic surgeries, often resulting in poor outcomes.

Case Description: This is a case of a 65-year-old man with a history of colorectal cancer who underwent colon resection with colostomy placement, chemotherapy and radiotherapy. The patient was admitted with signs and symptoms of Urosepsis with MDR Klebsiella and oliguric acute kidney injury. CT abdomen/pelvis demonstrated moderate bilateral hydronephrosis and hydroureter with cystitis and inflammatory changes within the pelvis. Patient was noted to have minimal urinary output after a Foley catheter placement and worsening renal failure due to which a bilateral percutaneous nephrostomy catheter was placed by Interventional Radiology. During this procedure, the patient was found to have bilateral Ureteroenteric and Enterovesicular fistulas (Figure 1, 2) with associated cystitis.

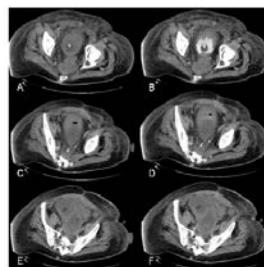


Figure 1. Axial slices of a CT cystogram with pre-contrast (Figures 1A, 1C, and 1E) and post-contrast (Figures 1B, 1D, and 1F) images demonstrates contrast filling within the non-dependent portion of the bladder without visualization of extra-vesicular extravasation, even on delayed imaging (not shown). Figure 1A and 1B shows contrast filling within the non-dependent portion of the bladder, suggesting higher density debris within the bladder. Figure 1C and 1D shows a focus of air within the dome of the bladder and dilated contrast material on Figure 1D without any extra-vesicular contrast extravasation. Figure 1E and 1F demonstrate the superior portion of the dome of the bladder and an additional hypodense complex fluid collection just anterior to the bladder. Additionally, 1E and 1F demonstrate an irregularly thick and nodular bladder wall. Furthermore, there is a focus of air seen on the post-contrast image (1F) that was not visualized on pre-contrast imaging (1E), suggesting a possible communication with the collection.

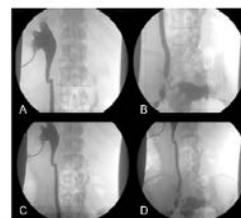


Figure 2. Sequential fluoroscopic spot images of a left percutaneous antegrade nephrostogram during a bilateral percutaneous nephrostomy tube placement procedure. Figure 2A shows normal contrast filling of the left kidney and proximal ureter. Figure 2B shows contrast filling within the mid to distal left ureter and an abnormal collection of contrast projecting over the pelvis. The abnormal collection does not assume the shape of the bladder even with consideration of the contour and irregularity of the bladder dome as demonstrated on prior imaging. Further investigation with real-time fluoroscopic imaging demonstrated active contrast reflux into the mid and distal right ureter. Fluoroscopic spot images were obtained (Figure 2C) demonstrating reflux up to the mid right ureter along with contrast movement within the abnormal collection assuming a tubular shape (Figure 2D) suggesting bilateral ureteral finalization with bowel lumen.

In order to confirm the diagnosis of these bilateral ureteroenteric fistulas, a sample of colostomy fluid was checked for Creatinine levels. The Creatinine level from the colostomy fluid was equivalent to the urine creatinine level hence confirming the diagnosis. Patient was further treated with intravesical Polymyxin for cystitis.

Discussion: Lower urinary tract infections are a serious complications in patients undergoing abdominopelvic surgeries. However, they are mainly associated with patients undergoing chemotherapy and radiation therapy for colorectal malignancies. These complications can be lethal and have a very poor prognosis.

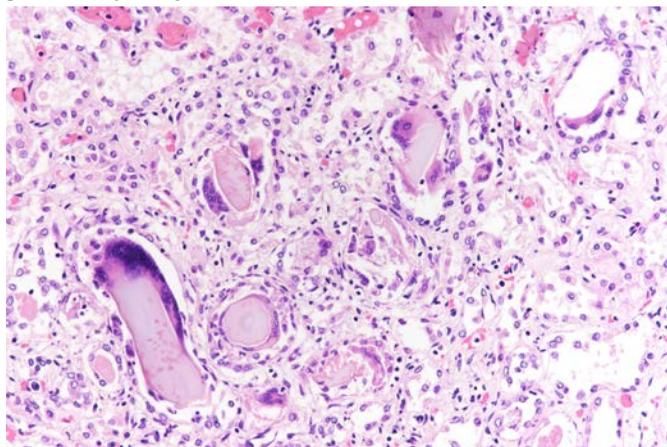
SA-PO115

Clinicopathological Feature of a Patient with IgD-Lambda Type Multiple Myeloma Showing Kidney Involvement Kaori Yamaguchi,¹ Toshiya Okumura,¹ Kengo Furuichi,² Takashi Wada,² Yasunori Iwata,² Taichiro Minami.¹ *¹Nephrology, Tonami City Hospital, Tonami, Toyama, Japan; ²Nephrology, Kanazawa Univ, Kanazawa, Ishikawa, Japan.*

Introduction: Kidney involvement sometimes occurs in patients with multiple myeloma (MM). MM associated kidney diseases encompass diverse manifestations, such as cast nephropathy, amyloidosis and immunoglobulin deposition disease. Since the frequency of IgD type MM is relatively low, renal manifestation, especially, renal pathology has not been fully understood. Here, we reports the autopsy case of IgD type MM with kidney involvement.

Case Description: A 81 years old women admitted the hospital because of systemic pain and appetite loss. Laboratory data showed serum Cr 5.14 mg/dl, urea nitrogen 57.2 mg/dl and corrected Ca 16mg/dl. Urine protein was 1+ with dipstick analysis and 9.7 g/gCr. Serological test revealed a monoclonal IgD-lambda chain. Proliferated plasma cells with the positivity of IgD-lambda chain was increased (16%) in bone marrow. After the Ca lowering therapy, dexamethasone (20mg/day X 4days) was administered to the patient. While serum levels of IgD was decreased by the therapy, renal function deteriorated, requiring dialysis. She died of infection at 64 day after admission. Autopsy specimen of kidney showed cast

formation in tubular lumens with severe tubular atrophy. Cell accumulation and fibrotic lesion were also detected in interstitium. Mesangial matrix was mildly expanded in glomeruli. Amyloid deposition was not observed.



Discussion: Herein, we showed clinical course and renal pathology of the patient with IgD-lambda type MM. Although steroid pulse therapy decreased serum levels of IgD, renal function did not improve. Renal pathology showed cast nephropathy, interstitial fibrosis and cell infiltration. The renal manifestation of IgD type MM requires further investigation.

SA-PO116

Sunitinib-Induced Nephrotic Syndrome and Acute Kidney Injury in a Malignant Insulinoma Patient: A Case Report Wakana Shoda, Naofumi Yui, Shotaro Naito, Soichiro Iimori, Koichiro Susa, Takayasu Mori, Naohiro Nomura, Eisei Sohara, Tomokazu Okado, Tatemitsu Rai, Shinichi Uchida. *Dept of Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.*

Introduction: Sunitinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFR), has been proven to be effective in the treatment of several types of cancer, including pancreatic neuroendocrine tumors. However, its risk of renal complications, such as proteinuria, renal dysfunction, and hypertension, are underestimated.

Case Description: A 71 year-old man with malignant insulinoma treated on sunitinib for six months, developed proteinuria, acute kidney injury and hypertension. Kidney biopsy showed thrombotic microangiopathy (TMA) like lesions such as double contours, edematous endothelial cells and microaneurysms, suggesting injuries induced by sunitinib. Decreased VEGF expression in podocytes was demonstrated by immunohistochemistry, supporting the diagnosis. Sunitinib was discontinued and partial remission of the renal complication was achieved in two weeks. However, the patient mandatorily needed to restart sunitinib because of poor control of blood glucose level due to pancreatic cancer exacerbation. By reducing the dose of sunitinib and administering losartan concurrently, the patient was able to maintain stable renal function with serum creatinine level of 1.4 mg/dl and urinary protein level under 1.0g/day.

Discussion: VEGF blockade by sunitinib is featured by adverse effects including hypertension and renal injury. In the present case, renal injury partially improved after discontinuing sunitinib. Reducing the dosage of sunitinib and administering losartan made it possible to restart sunitinib treatment while controlling its renal side effects. VEGF, which is expressed and secreted by podocytes, is an important factor for development and maintenance of glomerular endothelium. Renal biopsy in this case showed down regulation of VEGF in podocytes. Although the mechanism of renal dysfunction and proteinuria caused by anti-VEGF therapy is not well elucidated, the findings of this case might provide insights into the mechanism of renal toxicity by sunitinib.

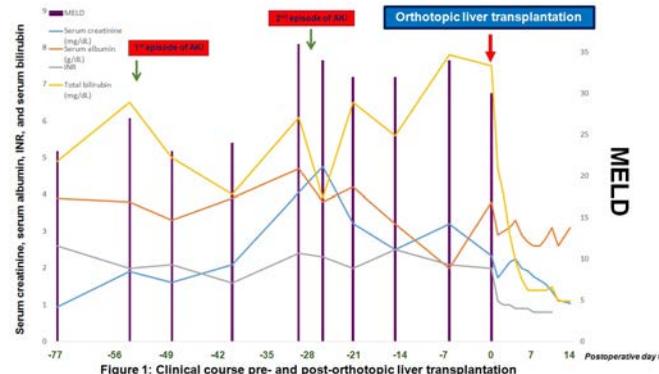
SA-PO117

Liver-Kidney versus Liver Transplant Alone: Decision Making in the Operating Room Ekamol Tantisattamo,¹ Siwadon Pitukweerakul,² Praveen Ratanasrimetha,³ ¹Nephrology, Northwestern Univ; ²Presence St. Francis Hospital, Evaston; ³Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

Introduction: Acute kidney injury (AKI) is a common complication of decompensated chronic liver disease and hepatorenal syndrome (HRS) is one of the leading causes. Liver transplantation (LT) is a definitive treatment for HRS; however, simultaneous liver-kidney transplantation (SLK) is pursued due to the severity of preoperative AKI with uncertainty of postoperative renal recovery.

Case Description: A 60-year-old Caucasian woman with ESLD due to alcoholic cirrhosis had been readmitted twice over 2.5 months with AKI from HRS. Even though, she was treated with albumin, midodrine, and octreotide, serum creatinine (SCr) had been elevated from the initial baseline of 1 mg/dL and had never returned to the baseline. Instead, it was worse every times she had AKI (Figure 1). After the last episodes of AKI, SCr had been stable at 2.5 mg/dL and she was listed for SLK. One week later, she was offered for SLK. After the LT, she started making a significant amount of urine immediately; therefore, the kidney was not transplanted and transferred to other potential kidney transplant recipient in another transplant center. Postoperatively, SCr had trended down to 1.1 mg/dL.

Discussion: Even though, our patient had recurrent episodes of AKI from HRS and persistently elevated SCr even <3 months period, it was thought that the chance of meaningful renal recovery was small and SLK was initially planned. Fortunately, her renal function was recovery immediately after the LT alone. Preoperative evaluation for SLK versus LT alone sometimes becomes uncertainly. Intraoperative finding of signs of renal recovery after LT is crucial as it can avoid unnecessarily kidney transplantation and provide an opportunity to utilize kidney organ to other potential kidney transplant recipients.



SA-PO118

Is Portopulmonary Hypertension Patient a Good Candidate for Liver Transplantation? Ekamol Tantisattamo,¹ Praveen Ratanasrimetha,² Siwadon Pitukweerakul,³ ¹Nephrology, Northwestern Univ; ²Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; ³Presence St. Francis Hospital, Evaston.

Introduction: Portopulmonary hypertension (PPH) is one of the most feared complications of end-stage liver disease (ESLD). Liver transplantation (LT) may reverse this complication with uncertain outcomes. We report a case of ESLD women complicated by severe pulmonary arterial hypertension (PAH) secondary to PPH and acute kidney injury (AKI) who had prolonged pre- and post-operative simultaneous liver-kidney transplantation (SLK) with partial liver improvement, un-meaningful renal recovery, and bed bound with reconditioning.

Case Description: A 48-year-old woman with ESLD from cryptogenic cirrhosis complicated by portal hypertension, PAH-related to PPH and sarcoidosis presented with AKI requiring CRRT. She was treated with treprostinil, sildenafil, and ambrisentan until suitable for SLK. Postoperatively, liver and renal allografts worked well and PA pressure was decreased. However, she still required treprostinil and diuresis to control PAH and volume status. After 5 months of ICU stay, she developed severe deconditioning and malnutrition. She had AKI with SCr of 0.5 mg/dL up to 1 mg/dL over 3 weeks. Calculated average clearance from 24-hour urine collection was 15 ml/min. Transplant renal allograft biopsy revealed moderate ATN and borderline changes. Diuretic dose was decreased and SCr was improved to 0.7 mg/dL. She still required treprostinil as well as intensive rehabilitation and nutritional supplementation. She remains in ICU for the majority of the time posttransplantation.

Discussion: PPH is one of the challenging scenarios for ESLD requiring LT. Reversibility from PPH after LT is uncertainty. It is still a dilemma in managing this difficult situation between LT to prolong life with poor quality and conservative management. LT is a life-saving surgery but may not always reverse a severe complication of ESLD such PPH and thus prolongs no postoperative quality of life. Therefore, LT in such a complex underlying condition needs to be individualized.

SA-PO119

Flash Pulmonary Oedema in Renal Artery Stenosis: An Indication for Stenting? Elise Chua, Martine David, Neil Chapman. *Medicine, Imperial College, United Kingdom.*

Introduction: Renal artery stenosis (RAS) is an unusual but potentially treatable cause of flash pulmonary oedema. Although national guidelines recommend percutaneous revascularization (level of evidence B), we present a case of recurrent flash pulmonary oedema which suggests a need for further evidence to support use of revascularization therapy in elderly patients with multiple comorbidities.

Case Description: A 78 year old woman presented with a fourth episode of sudden onset dyspnoea in 4 months. Her medical history included CAD, AF, hypertension (HTN) and severe pulmonary HTN due to heart failure with preserved ejection fraction (HFPEF). On admission, there were bilateral respiratory crackles and pulmonary congestion on chest XR. BP was 164/95, creatinine 110umol/L, eGFR 42. Echocardiogram showed concentric LVH, preserved EF and raised PAP. Because of recurrent symptoms despite apparently adequate medical management of HFPEF, she underwent CT angiography which revealed bilateral ostial RAS (70% right, 40% left). Following multidisciplinary team discussion, bilateral balloon angioplasty with stent insertion was performed with radiologically successful results and she was discharged on rivaroxaban for stroke prevention. Since then, she has had no further episodes of pulmonary oedema. However, renal function has deteriorated post-procedure (max creatinine 226umol/L, eGFR 18 at 6 weeks; no evidence of in-stent thrombosis) and she has diuretic-resistant pedal oedema severely impacting quality of life.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Discussion: This case highlights the importance of recognizing RAS as a cause of flash pulmonary oedema, especially in bilateral disease due to lack of compensatory mechanisms. Observational studies and case series have demonstrated that angioplasty +/- stenting reduces the incidence of flash pulmonary oedema. However, there is limited literature to guide management (eg. on risks and benefits of unilateral vs. bilateral intervention, degree of stenosis) and limited experience in the elderly in whom comorbidities may increase the risks of procedural complications such as deterioration of renal function due to contrast nephropathy and/or cholesterol emboli.

SA-PO120

Complement Mediated Hemolytic Uremic Syndrome Secondary to SLE

Aala Jaber, Jean M. Francis, Craig E. Gordon. *Nephrology, Boston Medical Center, Boston, MA.*

Introduction: Complement-mediated hemolytic uremic syndrome (CM-HUS) is a life-threatening disease. Rapid diagnosis and early treatment impact patient outcomes. CM-HUS is often caused by defects in the complement regulatory system leading to uncontrolled activation of the alternative complement pathway, resulting in systemic thrombotic microangiopathy (TMA).

Case Description: 64-year-old female with well-controlled HIV on HAART, presented with new pancytopenia, thrombocytopenia and acute kidney injury. On examination she had no neurological symptoms and no diarrhea. Preliminary blood tests revealed WBC 2.9K/UL, hemoglobin 6.6g/dl, platelets 64 K/UL, and serum creatinine at 4.0 mg/dl. LDH was elevated at 600U/L, haptoglobin was undetectable, with Coombs test negative. Peripheral blood smear revealed numerous schistocytes. Further work up revealed an elevated ANA (>1:2560), and hypocomplementemia. Anti-Smith antibody elevated at >8. These laboratory studies and the presence of lymphadenopathy and pancytopenia established a diagnosis of SLE. Patient received pulse methylprednisolone, but creatinine increased to 6 mg/dl. A kidney biopsy revealed TMA. The patient was treated with plasma exchange but developed uremia and was started on hemodialysis. Neither renal function nor hemolysis improved. In the absence of anti phospholipid antibody, normal ADAMTS13 level and activity, well-controlled HIV, and in the presence of positive serologies for SLE with complement consumption, the diagnosis of CM-HUS secondary to SLE was the most explanation of the patients' presentation, a decision was made to treat with eculizumab. Patient received one treatment, with no immediate improvement in her renal disease or hematologic parameters. Unfortunately her clinical status deteriorated and patient opted to be made comfort measures only and ultimately expired.

Discussion: This case emphasizes the importance of early consideration of CM-HUS as well as prompt initiation of treatment to block terminal complement upon recognition of the syndrome. As clinicians, this class of diseases is challenging and complicated, requiring our rapid attention to aid timely identification and rapid management.

SA-PO121

Idiopathic Nodular Glomerulosclerosis Presenting with Nephrotic Range Proteinuria and Normal Renal Function

Hassan E. Osman, Dany H. Issa. *Dept of Internal Medicine - Div of Nephrology, Saint Louis Univ, Saint Louis, MO.*

Introduction: Idiopathic Nodular Glomerulosclerosis (ING) is a well-established but uncommon entity that has been described in 1985 by Chan JY et al. It is common in older white men with history of long-standing hypertension, obesity, and smoking and typically presents with renal insufficiency & Nephrotic Range Proteinuria. Multiple reports and meta-analyses of patients with ING demonstrate an average creatinine > 2.0 mg/dl and progressive kidney dysfunction leading to ESRD.

Case Description: We report a case of a 57 year old Caucasian obese female who presented with edema and heavy proteinuria (9 grams/day). She is a 40-pack year smoker with long-standing hypertension with variable control. Serum Creatinine on presentation was 0.7 mg/dl. HbA1c was 6.0% and fasting/random sugars never met criteria for overt Diabetes Mellitus. Urine showed 3-10 rbc/hpf and none where dysmorphic with an otherwise bland urine sediment. She had a negative work up for paraproteinemias and all other causes of proteinuria. Kidney biopsy showed Class III nodular sclerosis (KW lesions) and moderate atherosclerosis by light microscopy. Immunofluorescence and Congo red staining were negative while EM showed ultra-structural features of Diabetic Nephropathy.

Treatment with diuretics and ACE-Inhibitor lead to improvement in volume status and proteinuria. Nine-months into follow up renal function remain stable.

Discussion: Our case illustrates that Idiopathic Nodular Sclerosis is not limited to male gender and can occur in the setting of preserved renal function, contrary to the common observation revealed in previous case reports.

References (among other reviewed data) include:

[1] Clin Exp Nephrol. 2014 Dec;18(6):865-75. doi: 10.1007/s10157-013-0929-y. Epub 2014 Jan 10.

[2] Diabetes Care. 1985 Jul-Aug;8(4):385-90.

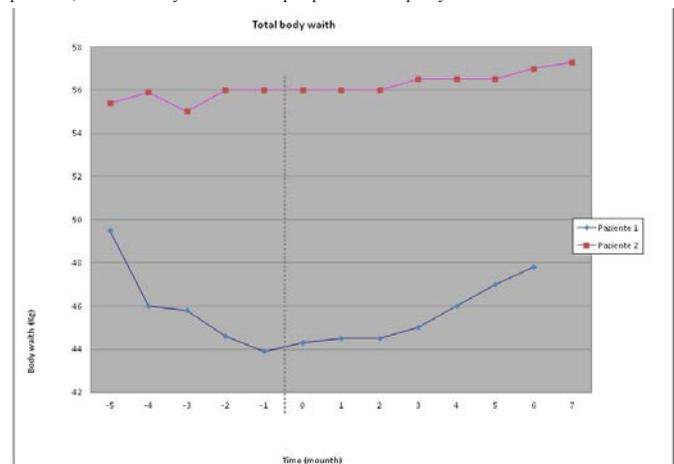
SA-PO122

Hemofiltration Reinfusion Acuilbrum Can Be an Answer to Malnutrition and Hypotension in Dialysis

Nicoletta Pertica. *Dept of Nephrology, Verona Hospital (AOUI VR), Verona, Italy.*

Introduction: We analyze the impact of A-HFR on intradialytic tolerance, nutritional status and on the clinical condition of two malnourished patients of our dialysis center.

Case Description: We performed an observational study for 12 months on 2 patients shifted to A-HFR caused by dialysis intolerance towards other methods. We monitored Blood Gas (pre and post treatment), clinical, biochemical, and dialytic data. **Patient 1** 62 years old man: on dialysis since 2008, suffering from malnutrition and anorexia due to cerebellar stroke (BMI 15.8) with intra and interdialytic hypotension. On February 2014 he started IDPN (IntraDialytic Parental Nutrition) + HDF online without any clinical improvement. On June 2014 he shifted to A-HFR+IDPN with improved hemodynamics control, weight (10% compared to its initial), nutritional and inflammatory indexes. In addition, he improved his quality of life with disappearance of hypotensive episodes and reduced consumption of EPO. **Patient 2** 44 years old Woman: kidney-pancreas transplanted, on dialysis since 2011. In 2012 she started an antibiotic therapy for curing a pulmonary TBC, burdened by malnutrition and severe peripheral neuropathy with persistent hypotension, also during dialysis. In 2013 she shifted to A-HFR and improvements regarding bodyweight, blood pressure, inflammatory markers and peripheral neuropathy were observed.



Discussion: A-HFR has dynamic profiles of ultrafiltration and conductivity of the dialysate; this aspect creates an iso-osmolar dialysate, ensuring a better peripheral refilling and improving compliance during the dialysis treatment. This is due to the use of biosensors. A-HFR also reduces the Amino acids loss. This report has numerical limitations but provides encouraging data on the use of AHFR in malnutrition and disequilibrium syndromes. This experience underlines the importance of further efforts towards customized dialysis procedures.

SA-PO123

Monoclonal Gammopathy of Renal Significance: The Significance Is Not Always Unknown

Umair S. Ahmed. *Nephrology, West Virginia Univ, Morgantown, WV; Nephrology, West Virginia Univ, Morgantown, WV.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury noted on microscopy. It is less commonly associated with monoclonal gammopathies, including monoclonal gammopathy of unknown significance (MGUS).

Case Description: Patient is a 67 years old female, with a history of rheumatoid arthritis, on Methotrexate, who presented to an outside facility with progressively worsening fatigue for four months. Investigations showed pancytopenia, following which she was transferred to our hospital for further management. On arrival at our hospital, patient was noted to have an acute kidney injury. A random urine protein/creatinine ratio showed 5.5 gm proteinuria. Serum protein electrophoresis showed a monoclonal spike, with an Ig M kappa clone. Immunoglobulin (Ig) G was low at 161 mg/dl, while Ig M was increased at 378 mg/dl. Bone marrow biopsy done showed 5% plasma cells, with no morphological features of a plasma cell neoplasm, leukemia or lymphoma. Kidney biopsy done showed MPGN, with positive immunofluorescence for IgM, C3, kappa, along with large subendothelial and mesangial deposits. Both C3 and C4 were low. Work up was negative for hepatitis B and C. Serum cryoglobulin levels were normal. No evidence of lupus was noted. Infectious work up was also unremarkable. Patient was diagnosed as having MGUS by the hematology service. MPGN was assessed to be secondary to MGUS in the absence of other possible etiologies. Patient was started on high dose steroids for 3 days followed by a taper, along with intravenous Rituximab 375 mg/m² weekly for 4 weeks. Due to worsening renal functions patient was started on hemodialysis. Unfortunately due to lack of renal recovery, patient was declared as having end stage renal disease.

Discussion: MGUS is the most common plasma cell disorder and may be a precursor for myeloma. It is characterized by a lack of end organ damage. A small subset of patients, however, may rarely have renal involvement, with MPGN being noted on renal biopsy. MGUS can therefore be associated with morbidity and mortality, and therefore its significance may not always be unknown.

SA-PO124

A Case of Chronic Unilateral Hematuria Treated by Segmental Renal Artery Embolization Hansae Kim,¹ Joon Seok Oh,² Yong Ki Park,² Dongyeol Lee.¹ ¹*Nephrology, Bongseng Memorial Hospital, Busan, Korea;* ²*Nephrology, Dongrae Bongseng Memorial Hospital, Korea.*

Introduction: Chronic unilateral hematuria is characterized by intermittent or continuous hematuria that cannot be diagnosed using standard radiologic and hematologic methods. Unilateral hematuria is probably a benign condition that seldom requires surgical treatment, but some cases were managed with partial or total nephrectomy. Recently, a variety of treatments, including the ureteroscopic interventions have been attempted if the bleeding focus is identified. However, if not identified on ureteroscopy, surgical treatment has been considered a priority. We report the case of treatment of chronic unilateral hematuria with segmental renal artery embolization.

Case Description: We experienced a case of chronic unilateral hematuria in a 42-year-old woman who was admitted to our hospital due to intermittent gross hematuria and anemia for 31 months. About 29 and 19 months ago she already underwent CT scan, renal angiography, and renal biopsy at other tertiary hospitals, but didn't find any other specific abnormalities repeatedly except some blood clots in left renal pelvis on ureteroscopy. She underwent CT urography, renal arteriography, cystoscopy and ureteroscopy again. Ureteroscopic findings only showed bleeding in the upper third of left renal calyces but definite bleeding focus could not be identified. Thus we decided to manage with segmental renal artery embolization than partial nephrectomy to minimize the reduction in renal function and to reduce operational risk. The superior and superoanterior segmental renal arteries were successfully embolized with 3mm coils and gelatin sponge. Gross hematuria disappeared on the 4th day after the procedure, microscopic hematuria disappeared on the 5th day. In 11th day, infarction in the upper third portion of left kidney was confirmed on CT scan. In 13th day, the patient was discharged. Thereafter serial urinalysis showed no hematuria.

Discussion: Patients with chronic unilateral hematuria often require surgical or upper urinary tract endoscopic procedures. Segmental renal artery embolization will be a better treatment for patients unable to identify the bleeding focus on the upper urinary tract endoscopy.

SA-PO125

An Unusual Cause of Acute Kidney Injury in a Patient Several Months Post Renal Transplant Sweta Carpenter, Karthik M. Ranganna. *Nephrology, Drexel Univ.*

Introduction: Urinary anastomosis leaks after kidney transplants are no longer a common phenomenon. Due to advancements in reconstruction techniques, urologic complications after renal transplant are now reported to occur in only 2-2.5% of patients. If a urinary anastomotic leak were to develop, it frequently occurs within one month of the transplant and is usually due to technical error or ischemia to the ureter.

Case Description: We present a case of a 60 year male with a history of a living unrelated kidney transplant who developed acute kidney injury 5 months after transplant. He had a baseline creatinine of 1.5-1.7 mg/dL and initially presented to the hospital with fevers and a creatinine of 2.96 mg/dL. A fungal urinary tract infection with *Candida Albicans* was deemed the culprit of his symptoms and so he was promptly started on fluconazole with only a slight improvement in his creatinine. A renal ultrasound of the allograft revealed that the patient had a 7x5 cm perinephric fluid collection. A perinephric drain was placed in the collection and culture of the fluid grew *Candida Albicans*. The large amount of perinephric drainage led to concerns of an anatomic urinary leak. Further testing on the perinephric fluid showed similar levels of creatinine in the perinephric fluid and the patient's urine. Cystoscopy later revealed that the patient had a large ureteral anastomotic leak. He underwent a percutaneous nephrostomy tube and nephroureteral stent placement. The patient's perinephric fluid collection subsequently resolved and he was discharged home with a creatinine of 1.47 mg/dL.

Discussion: Improvements in surgical techniques have decreased but not eliminated the incidence of anatomic surgical complications. Urinary anastomotic leaks are a rare but serious complication of kidney transplantation. This case highlights the need for diligence in diagnosing such a leak and favorable outcomes with prompt treatment. Since urinary leaks are uncommon months after kidney transplant, a question could be raised about the possible causative association between the fungal urinary tract infection and the anastomotic leak.

SA-PO126

Early Onset Kidney Stone Formation in Severe Ulcerative Colitis: Prevention Better Than Cure Akshatha Rao, Rozina B. Ali, Ziauddin Ahmed. *Div of Nephrology, Drexel Univ, Philadelphia.*

Introduction: Incidence of kidney stones is higher in patients with inflammatory bowel disease (IBD) than in general population. Studies using screening ultrasound showed 38% of Crohn's disease and 37% of Ulcerative Colitis(UC) patients had asymptomatic renal calculi mostly calcium oxalate and/or uric acid stones. Active inflammation was the important risk factor for renal calculi.

Case Description: In our case report we describe a 40 year old male with no significant past medical history except newly diagnosed ulcerative colitis with severe proctocolitis on colonoscopy 3 months ago. His proctocolitis was treated with steroids and Infliximab therapy with significant improvement of his symptoms. Subsequently patient was readmitted to the hospital with severe abdominal pain, radiating from loin to groin. CT abdomen and

pelvis showed multiple bilateral kidney stones, largest measuring 7mm, and a 5mm stone at the ureterovesical junction on the left with hydronephrosis. His serum creatinine (SCr) increased from 1.2 to 4 mg/dl.

Patient underwent cystoscopy, left retrograde pyelogram for renal stone extraction and stent placement with improvement of creatinine. A 24-hour urine collection 4 weeks after the acute episode showed high normal urinary calcium and oxalate excretion and low citrate excretion. A repeat 24 hour collection 8 weeks after the remission of UC showed normal both calcium and oxalate excretion but citrate excretion remained low and urine of pH 6.5. Patient was told to increase fluid intake to 3L /day and potassium citrate was added to his regimen.

Discussion: This case suggests that stone formation may be an early phenomenon in UC. We think there might be a benefit in obtaining 24-hour urine collection for stone analysis following diagnosis of IBD, as this may help us identify patients at increased risk of stone formation. Early simple intervention like increasing fluid intake may prevent stone formation. Benefits from empiric treatment with potassium citrate are not well known. Further studies need to be done for the better understanding and preventing renal stones formation in patients with active and severe IBD.

SA-PO127

Bilateral Renal Artery Stenosis due to Takayasu Arteritis Complicated by Complete Renal Artery Occlusion with Complete Spontaneous Renal Recovery Saifullah Kazi, Ghulam Akbar, Paul Robbins. *Nephrology, Lankenau Medical Center, Wynnewood, PA.*

Introduction: 53 year old female who had established diagnosis of severe bilateral renal artery stenosis from unknown cause, admitted for elective repair of the aortic root aneurysm and aortic valve replacement for severe aortic regurgitation developing acute renal failure from complete renal artery occlusion post operatively due to ischemic insult followed by spontaneous recovery.

Case Description: 53 year old female with past medical history of multiple CVA and negative embolic workup, presented with syncope at an outside hospital. Workup with echocardiogram revealed severe aortic regurgitation. CT angiogram revealed multiple small ulcerations within the aorta starting from ascending aorta until iliac artery bifurcation with severe stenosis of superior mesenteric artery, celiac artery and bilateral renal arteries. Her serum creatinine was at 0.9 and an ultrasound revealed right and left kidneys size to be at 11.4cm and 9.4cm respectively. Her serologies for vasculitis were negative. She underwent elective repair of the aortic root and aortic valve. Immediately in post operative period, patient became anuric due to complete occlusion of the right renal artery based on CT angiogram. She was taken to catheterization laboratory with unsuccessful attempt to open right renal artery. She was started on hemodialysis next day. A week later, reattempt to open right renal artery was again unsuccessful. She was placed on prednisone as her biopsy revealed Takayasu Arteritis. After 2 weeks into her course, patient started to have spontaneous recovery with renal function and she was taken off the hemodialysis.

Discussion: Renal artery stenosis as a manifestation of systemic vasculitis is rare. With an aggressive surgical approach, combined with glucocorticoid therapy, mortality due to Takayasu arteritis is less than 10%. In our patient, it is most likely that slow progression of renal artery stenosis occurred over time with an acute embolic occlusion postoperatively. However, her best functioning kidney on right side likely had spontaneous recovery after ischemia based on renal angiograms and potential benefit of steroids by reducing inflammation.

SA-PO128

A Case of Kidney Dysfunction and Visual Loss Patrick Kosciuk,¹ Muhammad Sohaib Karim,¹ Micah R. Chan,¹ Anthony Krentz,² ¹*Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health;* ²*PreventionGenetics.*

Introduction: Senior-Loken syndrome is a rare hereditary nephronophthisis (ophtho-renal syndrome) often presenting with autosomal recessive inheritance, a reduction in urinary concentrating ability with bland urinary sediment, and chronic tubulointerstitial nephritis with typical progression to end-stage renal disease (ESRD) in individuals younger than 20 years old. It was first described in 1961 by Senior et al., and Loken et al.

Case Description: A 29 year old male and his seeing eye dog presented to the kidney clinic with uncontrolled hypertension, creatinine of 2.6mg/dl and a history of Leber congenital amaurosis since the age of four. Physical exam was unremarkable other than nystagmus and severe visual impairment with 5-degree visual field and 20/300 acuity. Patient was currently pursuing his PhD via braille and did not appear to have any mental impairment. Family history was remarkable for a healthy sister in her 20s, a paternal uncle who passed away from renal failure in his 20s, and his paternal cousin (son of his deceased uncle) who had been born with hearing loss. Further evaluation was undertaken, which revealed normal electrolytes, unremarkable UA (notably with specific gravity <1.005 and absence of proteinuria, hematuria, leukocyte esterase, nitrates, and pyuria), but findings of minimal proteinuria (urine protein to creatinine ratio of 0.55). A renal ultrasound revealed a 12.4 cm R and 12.6cm L kidney with multiple cysts. Taking into account the history of renal dysfunction, visual impairment and renal cysts, patient was referred to a geneticist. Genetic studies revealed two autosomal recessive heterozygous mutations in the IQCB1 gene. A frameshift mutation was seen in c.424_425 del ITT resulting in premature protein mutation. Another chromosomal mutation was found as a nonsense mutation in IQCB1 as c.1090C>T. This was consistent with a diagnosis of Senior-Loken syndrome.

Discussion: There is no specific treatment for Senior-Loken Syndrome. Uniform progression to ESRD is inevitable, and patients are often good renal transplant candidates as there is no recurrence of the disease.

SA-PO129

Clostridium Difficile Associated Peritonitis in a Patient on Peritoneal Dialysis Dimpu M. Patel, Gaurav Jain. *Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.*

Introduction: Culture negative infectious peritonitis (CNP) is a common and serious complication in peritoneal dialysis (PD) patients. It is usually a result of samples failing to reach the threshold of microbiological detection, recent antibiotic exposure, or simply unusual organisms not routinely tested for. Clostridium difficile (C. diff) infections have become more frequent, and more refractory to treatment, and dialysis patients are often affected by C diff secondary to repeated exposure to antibiotics, as well as hospitalizations. C diff infection should be considered in the differential for CNP in dialysis patients.

Case Description: A 41 AA male on PD since 2012 presented to PD unit with complaints of abdominal pain and cloudy fluid. He was started on intraperitoneal antibiotics (Vancomycin and Ceftazidime) as an outpatient, though his symptoms of abdominal pain worsened requiring a hospital admission within 48 hrs of onset of symptoms. He complained of non-bloody diarrhea for 12 hrs on the day of admission. On exam, he was diffusely tender in his abdomen, with no guarding/rigidity. Lab data was significant for peritoneal fluid WBC count of 7,130 with 85% polys and he was continued on broad-spectrum IV antibiotics. Stool C diff toxin resulted positive on day 2 of hospitalization and he was started on IV metronidazole. His abdominal pain persisted, and a recheck of PD fluid cell counts on Day 3 revealed a WBC count of 17,671 with 79% polys. The PD fluid cultures from the PD unit as well as the hospital were negative for any growth. Microbiology lab was asked to check his PD fluid for C diff, and the C diff PCR from the PD fluid was positive. The vancomycin and ceftazidime were stopped, and oral vancomycin added to the metronidazole. His abdominal pain and diarrhea both improved and he was discharged to complete a 14 day course of PO metronidazole and vancomycin.

Discussion: Our case study describes culture negative peritonitis in a patient with C diff diarrhea that did not respond to broad spectrum IV antibiotics. This prompted further investigation of C. difficile peritonitis that was confirmed on lab testing. This case highlights the importance of suspecting C diff peritonitis in PD patients with CNP.

SA-PO130

Adequacy of Australian Nephrology Training Nicholas A. Gray,¹ Thomas Joseph Beaton,¹ Rathika Krishnasamy,¹ Nigel David Toussaint,³ Richard K.S Phoon.² ¹Renal Unit, Sunshine Coast Hospital and Health Service, Nambour, Queensland, Australia; ²Renal Unit, Westmead Hospital, Westmead, New South Wales, Australia; ³Renal Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia.

Background: There has been an increase in the number of doctors training in nephrology in Australia. This study aimed to assess the adequacy of nephrology training by measuring self-determined competency and skill relevance among recently graduated nephrologists.

Methods: A survey was developed by the Nephrology Advanced Training Committee of the Royal Australasian College of Physicians. The survey was administered on-line in 2015 via the annual subscription to the Australian and New Zealand Society of Nephrology. Nephrologists who were awarded Fellowship after 2002 were invited to participate.

Results: 113 of a 306 eligible Fellows (37%) completed the survey. 8 respondents had trained overseas and were excluded. Median age was 41 years (interquartile range 37-44) and 63% were male. Medical school was completed in Australia (59%), India (15%), and New Zealand (7%). 35% received at least some training in a rural area and 25% were qualified in another specialty (mainly internal medicine). 56% had completed and 21% commenced a higher degree. Higher degrees were undertaken for career development (43%) and desire for a research career (30%). Respondents indicated good training and competency in most clinical skills that were relevant to their practice. Training in home hemodialysis (37%) and living kidney donor assessment (51%) were considered less adequate, despite these areas being considered very relevant to practice. There was a greater mismatch identified between training and importance of skills for management and research. This included inadequate training in managing complaints (82%), managing a private practice (98%), health system knowledge (86%) and regulations (93%), medical directorship (94%), ethics approval (76%), research funding (88%), and quality assurance (73%).

Conclusions: Nephrology training in Australia meets the clinical needs of new specialists. Similar to findings in USA, training in management and research was considered insufficient for the practices of new specialists and should be addressed in updates of the curriculum.

SA-PO131

Pediatric Nephrology Workforce and Training: An International Perspective Dorey A. Glenn,¹ Adam R. Weinstein,² Maria E. Ferris,³ ¹Univ of North Carolina at Chapel Hill; ²Dartmouth Hitchcock Medical Center; ³Univ of North Carolina at Chapel Hill.

Background: There is a shortage of pediatric nephrology providers in a number of areas around the world. We sought to determine pediatric nephrologists' perspectives on this issue.

Methods: A voluntary web-based survey was deployed via the Qualtrics™ survey engine. Members of the International Pediatric Nephrology Association responded anonymously to questions about their geographic location, time spent on training, practice setting, and impressions on local workforce challenges and opportunities.

Results: The number of responses to date was 38, representing 21 countries from all continents. Six percent of the respondents treat both children and adults. The number of years required to train in pediatric nephrology was reported as: 2 years (35%), 3 years

(58%) and 4 years (8%). Nearly 80% of practices were associated with academic settings. Sub-specialty training programs are reported in 63% of the respondents' institutions and 50% of those with training programs stated that it was difficult or very difficult to recruit trainees. Forty two percent of the respondents stated that it was difficult or very difficult to find a job after training. The themes most frequently cited on qualitative analysis include low availability and interest in the field by trainees, poor compensation, demanding schedule and competing family demands.

Conclusions: In this preliminary study of an international cohort of pediatric nephrologists, our data suggests a perception of a decreased pediatric nephrology workforce. There is also a perceived shortage of available positions in the field. Further data collection on workforce issues as it pertains to country-related factors is needed.

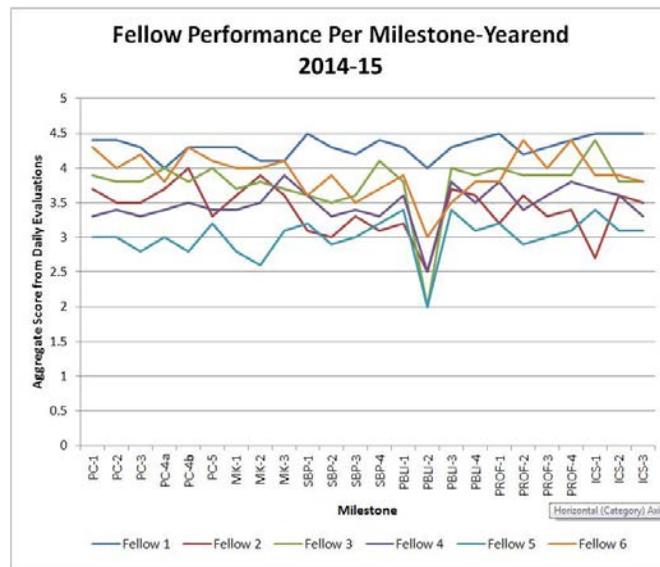
SA-PO132

Take Guessing Out of Milestone Ratings – Simplify the Evaluation System to Easily Achieve the Next Accreditation System (NAS) Report Samantha J. Thompson, Laura J. Maursetter. *Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: In an effort to translate into competency-based training, the ACGME has developed 24 milestones specific to fellowship. While the milestones are comprehensive, it is challenging to determine an individual's rating through faculty evaluations; many of whom are untrained in this system. We aimed to create a simple scoring system that translates the milestones into observable nephrology activities that can be completed daily on a handheld device.

Methods: For each nephrology rotation, a list of 5-10 frequent activities was developed. For every activity, a description for the five levels of competency was written to standardize the score. The activities were mapped to 1-4 NAS milestones. The evaluations were built in Google Forms and delivered daily to supervising faculty members. Using a four-click system, the observer can submit a fellow evaluation with most done on mobile devices. If faculty members wish to express a narrative, a free-text response box is provided for comments.

Results: Of the 914 possible evaluations over a nine-month period of time 727 evaluations were returned. This provided data points to distinguish scores among all fellows in all of the NAS milestones.



In Clinical Competency Committee meetings thus far, 1 of 276 scores have been adjusted from the scores provided by the evaluation system.

Conclusions: This is an easy to use scoring system that has resulted in immediate feedback that is activity-specific and feed into NAS milestones easily and effectively. By translating the evaluation system into specific activities that any nephrologist can observe, a robust amount of valuable data has been obtained. The 4-click system has yielded an excellent response rate with more narrative comments than were previously obtained with monthly evaluations.

SA-PO133

American Society of Nephrology In-Training Exam for Fellows 2010-2014: Scoring and Item Statistics Suzanne M. Norby,¹ Troy J. Plumb,² Nancy Day Adams,³ Ryan Russell,⁴ Mitchell H. Rosner,⁵ Mark G. Parker.⁶ ¹Mayo Clinic; ²Univ of Nebraska Medical Center; ³Univ of Connecticut Health Center; ⁴American Society of Nephrology; ⁵Univ of Virginia School of Medicine; ⁶Maine Medical Center.

Background: Since 2009, the American Society of Nephrology (ASN) In-Training Exam (ITE) has been administered annually to fellows. This study reports 2010-2014 overall scale scores, item difficulty, item discrimination, and reliability.

Methods: ITE annual reports provided by the National Board of Medical Examiners were reviewed and summarized.

Results: Scale score for all was 480±104 (mean ± SD); 1st-year fellows (Y1, n=2,020) 445±96, 2nd-year (Y2, n=2,005) 515±100, and 3rd-year and higher (n=112) 509±113. Standard error of the mean ranged 41-45. The 2010 ITE had 150 core items only. 2011 and 2012 ITE had separate 20-item urinalysis and renal pathology modules administered to Y1 and Y2 respectively (not included in total test statistics). In 2013 and 2014, all completed two 10-item modules on these topics (included in statistics). A mean of 6.6 core items (4.4%) were deleted per year after adjudicating items with high difficulty or negative discrimination. Content areas aligned with American Board of Internal Medicine Certification Exam: General Aspects of Chronic Kidney Disease (CKD), Glomerular/Vascular (G/V), Tubulointerstitial/Cystic (TI/C), Acute Renal Failure/ICU Nephrology (ARF/ICU), Kidney Transplant, Hypertension, Sodium/Water (Na/H₂O), Acid-Base/Potassium (A-B/K), Mineral Metabolism (MM), and Clinical Pharmacology (CP), plus Ethics. Though examinee abilities typically vary yearly, overall total test average p value was 0.67. ARF/ICU, Na/H₂O, MM, and CP tended to be less difficult (average p value 0.7) and TI/C more difficult (average p value 0.58). Total test mean item discrimination biserial correlation averaged 0.21, highest for A-B/K (0.28) and lowest for CKD (0.18). Total test reliability (α) averaged 0.81; highest for G/V (0.46) and lowest for TI/C (0.25).

Conclusions: As expected, scale scores were higher for Y2 than Y1 fellows. Over 95% of administered items were scored; among those, mean item difficulty, item discrimination, and reliability varied among content areas.

Funding: Private Foundation Support

SA-PO134

What Are We Doing? A Survey of U.S. Nephrology Fellowship Program Directors Scott E. Liebman, Mahrukh Rizvi, Catherine A. Moore, Rebeca D. Monk. *Medicine- Nephrology Div, Univ of Rochester, Rochester, NY.*

Background: Recent years have seen a decrease in Nephrology fellowship applicants. Long work hours may be partially responsible, and may affect the educational mission of the fellowship. Our survey addresses fellow work load and educational experiences to further explore these issues.

Methods: We distributed a survey for nephrology program directors via the Training Program Directors' website. The survey addressed fellows' service load and the scope of educational activities offered by the fellowship.

Results: 57 out of 147 programs responded (39%). Most are 2 years long, with a mean of 7 fellows, and are "front loaded"- 64% require ≥ 7 months of inpatient service during year one. Inpatient services are usually (93%) covered by one fellow with significant resident involvement. NP's and PA's help cover about 15% of services. The busiest services have about 21-25 patients, although 13% of programs averaged ≥ 26 patients. At their busiest, these services have more than 30 patients, occasionally surpassing 50 patients. About one quarter of programs cap the number of patients and/or notes for which a fellow is responsible. Night call is most often divided equally among all years. Weeknight call is typically one night at time (74%) covering a single hospital (66%). Fellows in the call rotation typically cover ≥ 10 nights over a three month period and ≥ 1 week-end a month. Most fellows do one weekly half day clinic, averaging 4-6 patients per session with a faculty: fellow ratio typically $\leq 2:1$. Clinic structure is not usually modified during fellows' inpatient service. Longitudinal coverage of HD and PD patients is provided by 82% and 61% of program respectively. Educational conferences ranged from 2-6 hours per week. Faculty didactic teaching varies from < 1 hour a week to 5 hours per week; one hour is typical. Fellows usually give 2-6 formal presentations yearly, although in some programs this is significantly more.

Conclusions: Our survey underscores the large variety in work load, practice patterns and frequency of educational conferences at different institutions and provides a framework to help address the service/education balance during nephrology fellowship.

SA-PO135

Perceptions of Nephrology Among Internal Medicine Residents Michael N. Daniels,¹ Ivan E. Porter,² Nabeel Aslam,² Deepika Jain,¹ Charity Curtis,³ Hope Kincaid,³ Sharon E. Maynard.¹ ¹*Div of Nephrology, Lehigh Valley Health Network/ Univ of South Florida, Allentown, PA;* ²*Div of Nephrology and Hypertension, Mayo Clinic College of Medicine, Jacksonville, FL;* ³*Network Office of Research and Innovation, Lehigh Valley Health Network/ Univ of South Florida, Allentown, PA.*

Background: As interest in nephrology declines, we sought to identify factors influencing career interest among internal medicine (IM) residents.

Methods: This is a repeated cross-sectional survey of IM residents to assess perceptions of nephrology and the impact of these perceptions on career decisions. All categorical internal medicine residents at two institutions were invited to participate in 2012, prior to the initiation of a nephrology fellowship program (Group 1); and in 2015, three years following initiation of a nephrology fellowship program (Group 2).

Results: 131 of 156 residents (84.0%) completed the survey. A total of 14.8% (19/131) of residents indicated an interest in a nephrology career, with 6.25% (8/131) indicating Nephrology as their first choice. Cardiology (21.1%) and Hospitalist (12.5%) were the most popular career choices. The presence of a Nephrology Fellowship program did not increase resident career interest in nephrology (14.5% in Group 1 vs. 15.1% in Group 2). Residents' perceptions of nephrology were not significantly different in Group 1 vs. Group 2. Negative perceptions of nephrology most commonly endorsed by residents were: renal pathophysiology is too complex (22.9%), poor preparation in medical school (22.14%), few opportunities for procedures (26.7%), long work hours (24.4%), and long hours/burdensome call for nephrology fellows (27.5%). The majority of residents (83.2%)

reported exposure to positive role models in nephrology. Experiences cited as having a high impact on career choice included: mentors/role models in the field (71.65% of residents) and rotations during residency (57.14%).

Conclusions: The presence of a nephrology fellowship program had no effect on IM residents' interest in nephrology careers. Residents endorsed several negative perceptions of nephrology which may affect career choice.

SA-PO136

Insight into the Declining Interest in Nephrology Sherry Mansour, Yeunjung Kim, Mark A. Perazella. *Nephrology, Yale School of Medicine, New Haven, CT.*

Background: The decline of interest in nephrology is very concerning with an increasing number of unfilled fellowship spots every year. Identifying the reasons behind such decline is crucial to reverse this trend and preserve the future nephrology workforce. Several surveys have attempted to isolate this problem but none targeted US IM residents. We present the results of a survey targeting IM residents.

Methods: A web-based survey was conducted using survey monkey. 10 questions designed to help understand the reasons behind the decline of interest in nephrology were utilized. The survey link along with recruitment letter and consent form were sent to all US IM residency programs. Email addresses were obtained from the Alliance for Academic Internal Medicine website.

Results: 531 residents responded to the survey. 81% of those who completed the survey answered "No" to the question asking if they had interest in nephrology. The most common reason cited was a disheartening patient population, followed by salary, work hours & lack of understanding. 50.9% found nephrology "difficult" with the most challenging topics being glomerulonephritis (GN), acid/base & transplant. The respondents noted that exposure to interventional nephrology; transplant & GN might increase their nephrology interest. Of those interested, more exposure to GNs during residency was felt to likely reinforce their interest.

Conclusions: These survey results demonstrate that most IM residents aren't interested in nephrology and that restructuring of nephrology electives in residency programs to include enhanced exposure to GNs, transplant, and nephrology procedures might increase interest. Nephrology rotations are primarily an inpatient experience with exposure to critically ill AKI patients or complicated ESRD patients with significant recidivism. This experience leads to the perception that the nephrology population is disheartening. Since this is the most common reason why residents lack interest, changing the structure of nephrology electives in IM residencies to allow for more outpatient exposure with emphasis on GNs and transplant might be crucial for enhancing interest in nephrology fellowship training and a career in this subspecialty.

SA-PO137

Challenges and Opportunities in the Training and Retaining of Nephrology Workforce in Developing Countries: A Review of the Current Trends and Implications for Optimal Kidney Disease Care Julius Oluoch Okel,¹ Bilal Qarni,¹ Timothy Olusegun Olanrewaju,² Aminu K. Bello.¹ ¹*Univ of Alberta, Canada;* ²*Univ of Ilorin, Nigeria.*

Background: Nephrology education has undergone rapid advancement leading to the development of comprehensive curricula and standards towards a high quality patient-centered care. These standards are often lacking on issues critical to the practice of nephrology in developing countries.

Methods: We evaluated nephrology training programs within the context of the healthcare systems across 25 upper-middle and high income countries to identify best practices and opportunities for adoption in developing nations. We further reviewed training guidelines from the major professional societies (ISN, major national societies) on content and process of training. Data were obtained from multiple sources (government reports, published literature, and websites of professional/licensing authorities, World Federation for Medical Education (WFME) and its Regional branches. The WFME 3-set of Global Standards on medical education at all levels were applied in evaluating training programs on the domains of training process, assessment, and evaluation.

Results: We found 5 key thematic problems with the current training model in developing countries that included 1)an emphasis on factual information, memory and recall (core knowledge content), 2) absence of needs assessment and evaluation, 3)structure and organization of training is a product of established tradition than of evidence and not in congruent with health system changes and dynamics, 4) a didactic and opportunistic instructional model with other core areas of competencies (professionalism, collaboration, advocacy, managerial skills and of scholarship are not formally taught, and 5) application of summative rather than formative assessment methods.

Conclusions: There are similarities and differences in structure, content and process of training programs across both developed and developing countries. The results have implications for re-design of training programs in the developing world for quality education and better clinical care delivery in patients with kidney diseases addressing local needs and priorities.

SA-PO138

Creating and Enhancing Interest in Nephrology Careers: A Novel Nephrology Elective Experience for Medical Students

Hitesh H. Shah, Kenar D. Jhaveri. *Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY.*

Background: Interest in nephrology careers continues to decline in the United States (US). The type of nephrology elective that US medical students experience may play an important role in creating and enhancing interest in nephrology careers.

Methods: At our institution, we created a novel 4-week nephrology elective experience for medical students. Our redesigned elective included both 2-week inpatient (IP) and 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of various nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of kidney donor evaluation clinic, 2 half-days of peritoneal dialysis clinic and 3 half-days of outpatient hemodialysis unit rounding. The redesigned elective also included education conferences. From 7/2012 to 2/2015, nine 4th year medical students (all from different US medical schools) completed our redesigned nephrology elective. To evaluate the novel elective experience, all medical students were asked to complete an anonymous on-line survey upon completion of their rotation.

Results: All students responded to our survey. All reported adequate OP nephrology exposure during their elective. 89% had worked with 1 or 2 faculty members during the IP setting. In comparison, 78% were exposed to at least 4 different faculty members during the OP experiences. All students had interacted with at least 3 fellows. All reported that the elective experience enhanced their exposure and knowledge in nephrology and that they would recommend this elective to other medical students. They also thought that this elective structure provided them with a better insight into what nephrologists do in practice. 78% reported that this elective experience created an interest in nephrology career. 56% responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: We believe that the restructured nephrology elective provides the medical student with a much needed and realistic exposure to nephrology careers. Based on our experience, we recommend all training programs to consider this elective structure for medical students.

SA-PO139

Journal Publication of Nephrology Fellows Case Report Presentations at ASN Kidney Week 2012-2013

Hitesh H. Shah,¹ Nairuti H. Shah,² Rushang Parikh,³ Kenar D. Jhaveri.¹ *¹Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY; ²Colgate Univ, NY; ³SUNY Upstate Medical Univ, NY.*

Background: The inception of the fellows case report (CR) category at the ASN Kidney Week (KW) occurred in the year 2012. However, the number and types of CR abstracts accepted for presentation at ASN KW 2012-2013 is not known. Peer-reviewed journal publication (PR-JP) of these previously presented CR abstracts at ASN KW is also not known.

Methods: All previously accepted fellows CR abstracts from ASN KW 2012-2013 were reviewed and further categorized as follows: glomerular diseases (GN), tubulointerstitial diseases (TIN), acute kidney injury (AKI), fluid-electrolyte and acid-base disorders (FE-AB), dialysis (D), kidney transplant (KT), genetic disorders (GD), mineral diseases (MD), and other (O) cases. To determine the PR-JP rate of these CR abstracts, a literature (PubMed) search was performed in May 2015.

Results: A total of 415 abstracts were presented in the fellows CR category at the ASN KW 2012-2013. Compared to KW 2012, there was a 7.5% increase in CR abstract presentations at KW 2013. Over these previous two KW meetings, nearly one-third (31.6%) were GN related case presentations. The remaining abstracts were FE-AB (15.2%), AKI (14.4%), KT (11.8%), D (11.8%), TIN (5%), MD (4%), O (4%), and GD (2.2%) related presentations. Compared to KW 2012, there was increase in GN related presentations (from 55 to 76) at KW 2013. So far, only 72 (17.3%) out of the 415 abstracts have been published as papers in peer-reviewed journals. One abstract was published as a letter to the editor format. Of those that were published, 31.5% were GN related case reports. Interestingly, 22% of these journal publications did not list the lead author of the KW CR abstract as the primary author of the paper.

Conclusions: Based on our study, it seems that there is an increased interest among fellows to present CR abstracts at ASN KW. Nearly one-third were GN related case presentations. However, so far, less than one-fifth of the fellows CR abstracts presented at KW 2012-13 have been published in peer-reviewed journals. Reasons for this low publication rate is not known. Measures to enhance CR publications need to be considered.

SA-PO140

Analysis of Published Medical Student Related Nephrology Medical Education Research

Sarah D. Bayefsky,¹ Hitesh H. Shah,^{1,2} Kenar D. Jhaveri.^{1,2} *¹Hofstra NSLIJ School of Medicine; ²Nephrology, Hofstra NSLIJ School of Medicine.*

Background: Undergraduate (medical student) related medical education research in nephrology is not well studied. This analysis aims to assess the rigor of the studies describing teaching methods used in medical student education in nephrology.

Methods: A review of the English literature on nephrology education of medical students was conducted on two major online academic search engines (PubMed and ERIC). References of the papers discovered in this search were also reviewed. Conference abstracts were not investigated. The empirical studies were categorized by subject within nephrology. The research design of each study was then recorded.

Results: 26 original studies were found in which a method of teaching nephrology to medical students was described. The studies dated from 1977 to 2015. The focus of these teaching experiences was as follows: anatomy (3.3%), physiology (23.3%), pathophysiology (26.7%), pathology (10%), treatment (20%), and general nephrology (16.7%). 4 of the pathophysiology studies were also classified under other categories, so there were 30 total topics. The papers were also categorized into types of assessments, with two papers containing two different types of studies for a total of 28 types of assessment. 14.2% had either no assessment of the educational experience or had a description too vague to categorize it; 3.6% involved a questionnaire about the existing educational approach before a novel method was implemented; 57.1% involved surveys or questionnaires after a practice was carried out; 7.1% assessed the method both before and after; 10.7% were case studies or ethnography; and 7.1% included a randomized controlled trial. The randomized controlled trials involved teaching techniques focused on the pathophysiology of renal disease. Overall, students responded positively to teaching that is interactive.

Conclusions: Rigor is lacking in most studies done in medical student education research in nephrology. Over 50% of the studies done had a survey-based design. More randomized controlled trials are needed to assess reliably the effectiveness of the educational techniques in nephrology medical education research.

SA-PO141

Participation in the Open, Online, Twitter-Based, Nephrology Journal Club, NephJC

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Background: We established an online nephrology journal club, NephJC, in April 2014 that meets twice monthly to discuss emerging research and clinical practice guidelines. We invite content experts and manuscript authors to the discussion. The meeting occurs on the public forum Twitter, allowing any interested individual to join. The purpose of NephJC is to provide a recurring, academically-minded event on Twitter to help establish this communication channel as one for serious nephrology discourse. In addition, online journal clubs are becoming a critical route for post publication peer review. In order to assess the impact of NephJC we reviewed participation in the discussions over the first year.

Methods: We searched the Symplur analytics database for all tweets with the hashtag #NephJC from March 16, 2014 to June 2, 2015. We measured the numbers of participants, number of tweets and assessed participation over the first 27 NephJC sessions.

Results: From April 29th to June 2nd, 2015, 27 topics were discussed. 27 Chats were at 9PM Eastern for the Americas and starting Dec 18, 2014 a Europe and Africa chat was added at 8PM GMT. 10 GMT chats have been held, generally one day after the American chat. 1,022 Twitter accounts have used the hashtag #NephJC a total of 14,891 times. The median journal club chat has 41.5 (IQR 30.5-56.5) participants and 353.5 (IQR 268.5-633.5) tweets. The number of participants and tweets increased over time (P<0.01). The addition of the GMT chat was responsible for some of that growth (median number of tweets increased from 273 to 662.5, P<0.001, participants from 35 to 60.5, P<0.001).

Conclusions: NephJC has established itself as an integral part of the online digital mentorship curricula. The sustained usage and growth in participation of NephJC demonstrates the positive value of Twitter in medical education.

SA-PO142

Three Years' Experience with the Online Educational Game, NephMadness

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Background: NephMadness is an educational project that leverages social media and Free Open Access Medical Education (FOAMed) to highlight advances and important issues in nephrology. NephMadness 2015 was the third year of this project.

Methods: The curriculum takes the form of an online game that mimics the NCAA basketball tournament, March Madness. Participants attempt to predict the winners of hypothetical contests between nephrology concepts. The NephMadness field consists of 64 concepts from 8 different domains of nephrology: cardiorenal, onconephrology, nutrition, obstetrics, infectious disease, vascular surgery, genetics, and critical care. The theme for 2015 was nephrology's interaction with other specialties of medicine. The editorial content was created by a team of nephrologists with experience in social media. Additionally, content experts assisted in building the field (selection committee) and fact-checked the editorial content. A blue ribbon panel of nephrologists determined the winners of each match-up. Engagement in the contest was assessed by participation, website traffic and use of the hashtag #NephMadness on Twitter.

Results: There were 342 entries in NephMadness (25% increase over 2014) representing 26 countries with three quarters from the US. Gender breakdown was 31% female, 69% male. 46% of the contestants were attendings, 24% fellows, 10% residents and 9% medical students. The hashtag #NephMadness was tweeted 4,297 times (190% increase) by 401 people (144% increase) between Jan 16 and June 16. Web traffic to the hosting site was triple its monthly average and included the single highest traffic day ever.

Conclusions: NephMadness is increasing engagement on three unique metrics. We believe this indicates that pairing social media with freely available, expert-generated content can stimulate interest in nephrology.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

SA-PO143

Awareness of AKI in Low Resource Settings: A Global Survey

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Background: The ISN has set a goal of eliminating preventable deaths from AKI by 2025—the “0X25” initiative. However, there is limited awareness of the challenges presented by AKI in terms of diagnosis, treatment and management in low resource settings (LRS).

Methods: We reached out to nephrologists working in LRS using a web-based instrument of 18 questions. Responders were asked what strategies should be considered to increase the awareness of AKI in LRS and recommend approaches to heighten this awareness. 26 respondents were from 5 WHO world regions, including 54% from Africa.

Results: The major barriers to raising awareness cited by all were inadequate training, shortage of adequately trained health workers and lack of awareness of the significance of AKI by healthcare workers, government officials and the general public. Additional factors cited were limited patient access to health facilities, limited diagnostic and treatment facilities, lack of support for AKI programs, lack of clinical practice guidelines for AKI, poor communication systems, limited research funding and lack of linkages of AKI programs to other health projects. Health centers (HCs) were broken down into rural, district and regional HCs. Supplies available for diagnosis (serum creatinine and BUN) and management (IV fluids, antibiotics, anti-venom) of AKI are limited in rural HCs. All noted that hemodialysis services were available but only in selected, large urban centers. Peritoneal dialysis was limited to regional HCs.

Conclusions: Increasing the awareness of AKI in local, district, and regional HCs requires a multi-faceted approach, reaching out to government officials, hospital administrators, physicians, nurses, local health care workers, community leaders, international organizations and the general public. The success of this initiative involves the development of meaningful and targeted educational programs, training materials, and treatment guidelines tailored to the local situations. Alliances will need to be formed with governmental agencies, non-profit organizations and global health programs. Support needs to be provided for additional research programs.

SA-PO144

Acute Kidney Injury Education to Nursing and Assistant Health Care Staff

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Background: Acute Kidney injury (AKI) is a global healthcare problem. It carries significant mortality and incurs heavy costs to the National Health Service. Extensive work has been done recently both at undergraduate and postgraduate level to ensure front line medical staff have better understanding in managing AKI. One such important area of focus involves the need for training nursing and assistant healthcare staffs who care for patients presenting with AKI.

Purpose of the study: To gauge the understanding of AKI amongst nursing and healthcare assistants working on busy acute medical admissions unit.

Methods: The anonymous questionnaire was aimed at the nursing and assistant health care staff working on the admissions unit at two large district hospitals. The length of time since qualification ranged from few weeks to 16 years. The questionnaire was followed by planned teaching, simulation training and workshop sessions. The process was carried out within a period of 2 months.

Results: The Questionnaire was completed by 50 staff members. It included series of questions aimed at defining and managing AKI from a nursing perspective. 24 out of 50 were able to define AKI. Only 5 out of 50, have never cared for patients with AKI. Not all were aware of the symptoms of AKI; common answers given by 40 respondents were “reduction in urine output” and “dehydration.” All participants answered “yes” to monitoring urine output and understood the significance of fluid monitoring but all admitted more needed to be done to ensure accurate documentation in the patient’s notes. Other questions asked were if nurses check patient’s blood results on the system server to which most replied “no” and if medications were regularly reviewed during drug rounds. Surprisingly, not all were aware of nephrotoxic medications and only 20 respondents would regularly review drug charts in the context of renal failure.

Conclusions: The questionnaire and the training sessions identified lack of better understanding of AKI and its management. There needs to be a stronger emphasis on the introduction of AKI and its management during their training years and development of mandatory online e-learning modules.

SA-PO145

Evaluation and Management of Acute Kidney Injury – A Trainee Survey

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Background: Aki occurs in 1-in-3 hospitalized patients, and majority of those are managed by non-nephrology specialties, including trainees.

Methods: The renal fellowship program designed an online anonymous survey, distributed to trainees (students, residents, fellows), to understand their level of knowledge in recognition and management of AKI. 37 questions were classified into following categories: knowledge of guidelines; prognostic factors; and drug safety. Results are represented as aggregate proportions.

Results: 104 trainees responded to the online survey; 50% were male, 84% US medical graduates and 70% were residents/fellows. 50% were affiliated to medical specialties;

and 53% had spent at least one elective in nephrology. In terms of AKI definition: 51% use serum creatinine (SCr) as the most important factor to diagnose AKI, whereas 20% use urine output. Majority (76.1%) agreed that rise of 0.3 mg/dl or 1.5 times of baseline SCr was clinically relevant, in concordance with current guidelines. RIFLE criteria were most commonly used (42%), followed by KDIGO (13%); and 90% agreed that guidelines help in standardization, and management of patients. 85% concurred that AKI impacts short and long-term outcomes, however, majority (60%) felt dialysis requirement was the most important clinical predictor of outcome. Majority (67%) felt that early involvement of nephrology services is helpful in AKI management; 66% sought nephrology input to determine the cause of AKI/co-management, and 7% viewed nephrology role purely for procedural delivery of dialysis. As for drug safety, 89% reported to pay attention to renal function while drug dosing, but 70% felt that this was the responsibility of either pharmacy or ordering team. In terms of follow-up 61% of subjects felt that follow-up was only needed in moderate to severe AKI cases or in non-recovery; 86% preferred that in < 30 days, and 64% preferred that to be with primary care.

Conclusions: Most of the trainees displayed good knowledge of AKI guidelines (RIFLE), seek timely nephrology involvement and view it to be beneficial. More work needs to be done in terms of improving knowledge/practice about drug safety and follow-up care in AKI.

SA-PO146

Adherence to Care Bundles for AKI – Challenges in Supporting Education and Measuring Compliance

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Background: AKI typically occurs as a consequence of intercurrent illness in patients with multiple comorbidities and risk factors. The use of clinical guidelines to assist medical and nursing staff in AKI management has been adopted by most secondary care institutions in the UK. We have previously presented our use of e-alerts for AKI as a prompt to improve AKI care (Mulgrew *et al*, ASN, 2013). Clinical guidelines were prompted by the e-alert and widely publicised to staff.

Methods: In a model similar to the NHS Safety Thermometer, snapshots of compliance with 6 key elements of the AKI guidelines on 4 medical wards was measured by identifying patients from AKI e-alerts. These included documentation of AKI, medication review, clinical assessment and ongoing investigation/monitoring. Awareness was supported by an AKI Education nursing team, working with medical and nursing staff. Monthly compliance was assessed over a period of one year.

Results: Mean compliance for all elements of the guidelines improved from 52% to 69% over the year. Significant variability was seen, often associated with notable workforce challenges such as new medical staff or periods of increased activity.



Variability in compliance with individual elements of the care bundle also existed in different clinical areas. Analysis allowed for targeted support and education to clinical teams.

Conclusions: Supporting medical and nursing teams to manage AKI in secondary care in order to prevent progression and treat promptly remains challenging. A number of external factors frequently impact upon adherence to guidelines and support needs to be planned in order to continue to maintain high standards and optimise patient care. The use of a Safety Thermometer, allowing performance to be analysed and comparisons made between clinical areas, may continue to be useful in improving performance and patient outcomes in AKI.

SA-PO147

Internal Medicine Residents Knowledge of Vein Preservation in Chronic Kidney Disease Patients

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Background: Vein preservation is important among CKD patients for future arteriovenous fistula potential. House staff plays critical role in managing these patient population and preserving their vein for future arteriovenous fistula. Their knowledge and current practices directly affects the outcome for vein preservation among these patients.

Methods: We conducted a survey among 44 internal medicine residents to understand their baseline knowledge and current practices regarding vein preservation. The survey was conducted at Geisinger Medical center, Danville, PA.

Results: 44 residents were included in the survey. Only 6.8% (3) were able to correctly identify patient population, on whom we should avoid particular arm for IV draws, BP measurements, peripherally access or peripherally inserted central catheters. Two-third (27) answered non-dominant arm to avoid for these procedure and 13.5% (6) responded side does not matter. 81.8% (36) answered that nephrology should be consulted prior to peripherally inserted central catheters placement for CKD 4 patient. 93.1% (41) answered

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Underline represents presenting author.

correctly that peripherally inserted central catheters can damage peripheral veins. 52% (23) knew alternative of PICC line was tunneled internal jugular catheter, however 34% (15) answered tunneled subclavian catheter as an alternative. 55% (24) did not know preferred site for peripheral access, blood draws. 63% (28) has never written orders for nurse to request to avoid particular arm for IV draws, BP measurements in advanced CKD patients or patients on HD, 90%(31) have never requested a bedside sign to avoid particular arm for these patients.

Conclusions: Baseline knowledge was poor regarding vein preservation in CKD patients and very few residents have engaged in practices to preserve veins. More resident education is needed to engage them in vein preservation for CKD patients.

SA-PO148

Vascular Access and Transplant Referral Rates in CKD: An Ongoing Performance Improvement Project for Nephrology Fellows Nardos Belayneh, Anuj Regmi, Jusmin Patel, Divakar Jammalamadaka, Elias Ugwu, Noble Iwuagwu, John Jason White, N. Stanley Nahman, Lu Y. Huber. *Medicine, Georgia Regents Univ.*

Background: Referral for vascular access (Ac) and kidney transplantation (Tx) are important management facets of CKD. We previously conducted a performance improvement project assessing Ac and Tx referral rates (RR) in CKD patients from the Nephrology fellows' clinics. Following an educational intervention, there was an improvement in transplant RR (JASN 25:786A, 2014). To evaluate the sustainability of this initiative, we conducted a follow-up analysis.

Methods: This performance improvement project was conducted in 3 phases at the Charlie Norwood VAMC; Phase 1 (baseline, 1/1-4/30, 2013), Phase 2 (post-intervention, 8/1-11/30, 2013) and Phase 3 (follow-up, 1/1-4/30, 2015). Data extraction was conducted by three, 2-fellow teams, each reviewing the other's RR for all patients seen in the previous 4-month period. The analysis was sorted by eGFR (ml/min/1.73m2): for eGFR<15, both Ac and Tx RR were recorded. In addition, Tx RR for eGFR 15-20 was documented.

Results: 1114 total records were reviewed (349, 361, and 404 for Phases 1, 2 and 3, respectively). Table 1 indicates the number of patients and RR in those with GFR<20. RR for Ac through all 3 phases were steady at 72-73%. Tx RR were improved after intervention and were sustained in Phase 3.

	Phase 1		Phase 2		Phase 3	
	GFR 15-20	GFR<15	GFR 15-20	GFR<15	GFR 15-20	GFR<15
N	79	36	30	22	18	29
Transplant referral	9 (11%)	18 (50%)	11 (37%)	15 (67%)	8 (44%)	19 (66%)
Vascular Access referral	-	26 (72%)	-	16 (73%)	-	21 (72%)

Conclusions: Referral rates for kidney transplantation by Nephrology fellows improved after a chart review and educational intervention were performed. Vascular access referrals from this study remained stable. This work suggests that outpatient performance improvement projects conducted by Nephrology fellows confer peer review accountability for outpatient practice habits, heightens trainee awareness of key referral issues, and appears to help sustain or improve referral rates for vascular access and kidney transplantation.

SA-PO149

Impact of Standardized Electronic Documentation in an Academic Nephrology Setting Leslie P. Wong,¹ Emilio D. Poggio.^{1,2} ¹*Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH;* ²*Transplant Center, Cleveland Clinic, Cleveland, OH.*

Background: Reimbursement depends on documentation and billing based on complexity of care. Academic nephrologists are under pressure to improve productivity measured by revenue and relative-value based units (RVUs). Incorrect documentation or billing may result in loss of revenue and RVUs despite services having been provided. Standardized electronic templates were introduced in an academic nephrology setting to help address this issue.

Methods: Standardized templates based on Medicare 1997 Guidelines were introduced in July 2014 for all inpatient nephrology encounters. A training presentation was provided to teach nephrologists proper use of the templates. 73,314 inpatient charges submitted by 22 academic nephrologists between January 2012 and March 2015 were reviewed. Data included the current procedural terminology (CPT) code specifying the type of service, the identity of the nephrologist and any adjustments made by the coding department. Adjusted charges were accompanied by the reason for adjustment, the corrected CPT code and a revenue change based upon Medicare reimbursement. RVUs were calculated using the Medicare National Physician Fee Schedule.

Results: Before July 2014, 6.2% of charges were adjusted compared to only 2.8% after July 2014. The mean work RVU loss per adjustment decreased from 1.15 to 1.00 (p<0.01). The mean revenue loss per adjustment improved from \$270.88 to \$229.56 (p<0.01). Multivariate regression identified factors associated with worse productivity adjustments: encounters before July 2014, more than 10 years of academic experience

and transplant nephrology (all p-values <0.01). Factors associated with improvement in adjustments were encounters after July 2014, ICU encounters and less than 10 years of academic experience (all p-values <0.01).

Conclusions: Standardized templates led to significant reductions in revenue/work RVU losses per encounter at a large academic nephrology center. Nephrologists with more than 10 years of academic experience and transplant nephrologists performed worse than their peers. Efforts to improve documentation and billing may have important implications for academic nephrologists.

SA-PO150

Nephrology Documentation and Billing Educational Needs at an Academic Medical Center Leslie P. Wong,¹ Emilio D. Poggio.^{1,2} ¹*Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH;* ²*Transplant Center, Cleveland Clinic, Cleveland, OH.*

Background: Reimbursement in nephrology depends on accurate documentation and billing. Academic nephrologists are under increasing pressure to meet financial productivity targets. An analysis of nephrology reimbursement was performed at an academic medical center to find deficiencies and identify targets for education.

Methods: 75,097 inpatient nephrology encounters by 22 nephrologists from January 2012 and March 2015 were reviewed. Data included the current procedural terminology (CPT) code specifying the type of service and any charge adjustments made by the coding department. Adjusted charges were accompanied by the reason for adjustment, the corrected CPT code and a gross revenue adjustment based upon Medicare reimbursement. Relative value units (RVUs) were calculated using the Medicare National Physician Fee Schedule. Multivariate regression analysis was performed to identify factors associated with RVU adjustments.

Results: 5615 (7.5%) of encounters were adjusted by coders. 3832 (68%) were due to incorrect documentation or billing and 1683 (32%) were due to services performed but not billed by nephrologists. For submitted charges, revenue was reduced by \$995,976 and 4227 work RVUs as a result of incorrect documentation or billing. The potential loss of revenue from unbilled services was \$693,014 and 2823 work RVUs. Inadequate documentation of physical exam (p=0.01) and inadequate documentation of supervision of medical students/residents/fellows (p<0.01) were independently associated with RVU adjustments. Incorrect charge selection, duplicate charges, competing charges from another nephrologist and conflicting discharge/observation/post-operative care CPTs were also independently associated with RVU adjustments (p<0.01).

Conclusions: There was a substantial loss in gross revenue and work RVUs due to incorrect documentation and billing in an academic nephrology setting. These reductions in reimbursement and productivity might be avoided through better physician education and training. Specific targets include documentation of physical exam and supervision of trainees, correct CPT charge selection and ensuring all services performed are billed.

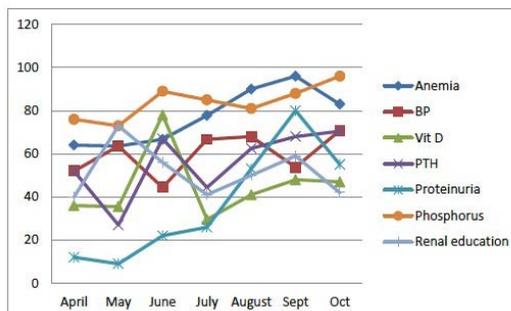
SA-PO151

Reaching Renal Goals – A Quality Improvement Project Mihran V. Naljayan, Oksana I. Nimkevych, Vechev Fedorchenco, Sara Jacob Coulon, Kimberly Cox Fremin, Zachary M. Al Shaijal. *Medicine, LSUHSC School of Medicine, New Orleans, LA.*

Background: The purpose of this study was to improve our patient care in a renal clinic at a large university hospital by using three of the core competencies- patient care, systems based practice, and practice based learning and improvement.

Methods: A check-out sheet was developed and given to all trainees in the nephrology clinic. Data was collected for 174 visits over 6 months. Data include age, gender, eGFR, and CKD stage. Each patient's blood pressure, hemoglobin, phosphorus, Vitamin D, PTH, bicarbonate, and the extent of renal replacement therapy planning were acquired and further analyzed to determine whether nephrology goals were met based on KDOQI/KDIGO guidelines.

Results: Achievements in goals for CKD 3-5 as per KDIGO/KDOQI guidelines based on a percentage value of the patients seen each month. Data are from April to October. Hemoglobin of >10 g/dL were met in 64%, 64%, 67%, 78%, 90%, 96% and 83%, respectively. Blood pressure of <140/90 mmHg (or <130/80) were met in 52%, 64%, 45%, 67%, 68%, 54% and 71%, respectively. Vitamin D of ≥30 ng/mL were met in 36%, 36%, 78%, 30%, 41%, 48% and 47%, respectively. PTH of ≤150 were met in 52%, 27%, 67%, 44%, 63%, 68% and 71%, respectively. Proteinuria (<300 mg/day) were met in 12%, 9%, 22%, 26%, 53%, 80%, and 55%. Phosphorus of ≤5.5 mg/dL were met in 76%, 73%, 89%, 85%, 81%, 88% and 96%, respectively. Attending renal education classes were met in 40%, 73%, 56%, 41%, 50%, 59% and 42% respectively.



Conclusions: Our project was helpful in educating trainees in the treatment goals and guidelines for patients in the renal clinic and standardized an approach to patient care. Overall, the results show a trend towards improvement in all goal areas except for renal education. This study did not account for patients who were new to our clinic and therefore had never received renal education previously.

SA-PO152

A Simulation Exercise to Assess Renal Replacement Therapy and Kidney Biopsy Communication Skills Lisa K. Prince,¹ Maura A. Watson,¹ Anna M. Howle,² Christina M. Yuan.¹ ¹*Nephrology, Walter Reed National Military Medical Center, Bethesda, MD;* ²*Medical Simulation, Walter Reed National Military Medical Center, Bethesda, MD.*

Background: We piloted a nephrology-specific “Breaking Bad News” simulation to assess Interpersonal Communication Skills and Professionalism during renal replacement therapy (RRT) and kidney biopsy (Bx) counseling. Assessment tools were a 9-point Likert Mini-Clinical Examination Exercise (Mini-CEX) adapted for RRT and Bx counseling, and the Essential Elements of Communication-Global Rating Scale 2005 (EEC-GRS).

Methods: There were three cases: 1) a middle-aged woman with polycystic kidney disease and CKD5, 2) a critically-ill elderly man with AKI whose wife was his surrogate decision maker, and 3) a previously healthy soldier with nephrotic syndrome. There were 5 nephrology fellow examinees. One patient actor performed for each case, assessing each examinee with the EEC-GRS. One faculty assessed all examinees for one case using the EEC-GRS and mini-CEX. Encounters lasted 15 minutes, followed by 5 minutes for examinee counseling by the actor and faculty.

Results: Post-simulation, 3/3 faculty surveyed felt that the exercise met objectives, and was an excellent assessment tool. 4/5 examinees felt the exercise was “good” and met objectives. 5/5 felt that simulation time was too short to assess communication skills. 2/5 felt that a mini-CEX assessing a real patient encounter was superior. Median examinee EEC-GRS performance assessed by actors and faculty was 4 (range 3-5). Median mini-CEX performance was 6 (range 5-9).

Conclusions: Based on feedback, the original mini-CEX was too detailed for a 15-minute encounter, and was simplified. Instructions now stress that, because of encounter brevity, counseling is unlikely to be completed, and completion is not required for satisfactory grading. A second set of scenarios was developed to permit a yearly simulation in a two-year cycle. We plan to test the revised simulation in a larger group of nephrology fellows within the next year. *The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense or the United States Government.*

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SA-PO153

Implementation of KDIGO CKD Guidelines Leads to Decreased Diagnosis of CKD Heather M. Mascio, Deepti S. Moon, Ryan J. Altenburg, Lisa K. Prince, Dustin J. Little. *Nephrology Service, Walter Reed National Military Medical Center, Bethesda, MD.*

Background: Estimated glomerular filtration rate (eGFR) is used to diagnose and classify CKD. The accuracy of creatinine-based eGFR (eGFR-Creat) is inferior to eGFR calculated using multiple renal filtration markers. CKD guidelines suggest using serum creatinine and serum cystatin C to evaluate for CKD in select patients, but methods for, and results of guideline implementation have not been reported.

Methods: We reviewed new patient nephrology clinic encounters for a three month period to establish baseline guideline adherence. Combined creatinine/cystatin C eGFR (eGFR-CreatCysC) was considered indicated in patients with eGFR-Creat 45-59 mL/min/1.73m² and no albuminuria, urine sediment abnormalities, or other markers of kidney damage. Consultation review was modified such that a nephrologist reviewed every referral request, with the option of ordering labs to be obtained prior to a clinic visit. During a six-month implementation period, guideline awareness was targeted via didactics, signs posted in exam rooms, and “cystatin C—just check it” t-shirts. Seven months of charts were reviewed following the intervention period, and pre and post-intervention adherence was compared using Fisher’s exact test. Patients with eGFR-CreatCysC ≥ 60 mL/min/1.73m² were considered to have no evidence of CKD. Inpatients for whom eGFR-CreatCysC was obtained, mean eGFR-Creat and eGFR-CreatCysC were compared using paired t test.

Results: Guideline adherence was significantly higher in the post-intervention compared to the pre-intervention period (testing obtained in 30 of 40 (75%) vs. 12 of 32 (37.5%) indicated cases; p = 0.002). Mean eGFR-CreatCysC was significantly higher than eGFR-Creat (77.3 ± 15.3 vs. 58.3 ± 9.1 mL/min/1.73m²; p < 0.001). eGFR-CreatCysC was ≥ 60 mL/min/1.73m² in 85.3% of cases.

Conclusions: By modifying our consult review process and raising awareness among nephrology providers, we significantly increased implementation of eGFR-CreatCysC guidelines and determined that the vast majority of tested patients had no evidence of CKD. Our results suggest testing as suggested in the guidelines has the potential to markedly decrease the number of inaccurate CKD diagnoses.

SA-PO154

Improving Pathology Curriculum for Nephrology Fellows Enrica Fung,¹ Orlando Camacho,¹ Michelle M. O’Shaughnessy,¹ Adetokunbo A. Taiwo,¹ Gabriela Velez,¹ Neeraja Kambham,² Timothy W. Meyer.^{1,3} ¹*Nephrology, Stanford;* ²*Pathology, Stanford;* ³*Nephrology, VA Palo Alto.*

Background: Stanford fellows were previously exposed to renal pathology through attendance at monthly hour-long “biopsy conferences” where faculty and fellows discussed difficult cases; and informal quarterly “fellows-only conferences” where fellows asked pathologists questions on core topics. Our project sought to improve fellows’ education in renal pathology.

Methods: Twelve first to third year fellows participated in this project. Two renal pathologists led five orderly review sessions, dedicated to fellows only: 1. Common renal pathology; 2. Primary glomerulonephritis; 3. Secondary glomerulonephritis; 4. Plasma cell dyscrasia-related renal disease; 5. Renal transplant pathology. Second year fellows helped in preparation of teaching material. Fellows were encouraged to ask questions. Participants completed a survey to measure their satisfaction with renal pathology teaching and their confidence in interpreting renal biopsies before and after this project. Five 10-question pre-session quizzes and a comprehensive 40-question post-project final measured knowledge acquisition.

Results: Prior to our project, 55% of fellows felt “somewhat satisfied” to “satisfied” with the current pathology conferences, and 10% of fellows felt “somewhat confident” in their abilities to interpret biopsy findings. Most fellows (83%) viewed renal pathology to be an “important” or “very important” part of their overall nephrology training. After the project, 100% of fellows felt “somewhat satisfied” to “very satisfied” with the project, and 60% of fellows felt “somewhat confident” in their abilities to interpret biopsy findings. To date, fellows answered 63% of quiz questions correctly prior to the project and 60% of final questions correctly after the project.

Conclusions: Survey of nephrology fellows revealed poor confidence in interpreting renal pathology prior to our project despite perceived importance of the topic. To date, post project evaluation suggested improved confidence in renal pathology but lack of significant change in knowledge base. This may be due to issues with knowledge acquisition, inter-test comparability or instruction method.

SA-PO155

Improving the Communication Skills of Nephrology Fellows by Utilizing MBTI Training Anna Marie Burgner, Julia Lewis. *Vanderbilt Univ School of Medicine, Nashville, TN.*

Background: Communication skills can both positively and negatively affect the patient-physician relationship. Although many things impact successful communications, individuals’ personality types affect the way they communicate and the way they interpret the communications of others. It has been suggested that a lack of understanding of the basic difference between personality types contributes to poor communication and unsuccessful interactions. Nephrologists work in a unique environment in the dialysis unit with a complex interdisciplinary team and a “captured” audience of anywhere from 10-40 patients in a single room. In the dialysis unit, communication between the multi-disciplinary team and the patients and between the multidisciplinary team’s individual members impacts the successful achievement of dialysis outcomes.

Methods: Eleven nephrology fellows underwent a curriculum designed to increase their awareness of their own Myers Briggs Type Indicator (MBTI) personality preferences, their knowledge of the different basic personality preferences, and how those differences impact communication. Knowledge of the MBTI preferences was tested pre-intervention, immediately post intervention, and 8 weeks post intervention. Communication skills were measured prior to the intervention and 8 weeks post intervention by dialysis nurses observing fellow-real patient interactions. Fellows were also asked to describe how they used their knowledge at 8 weeks post intervention.

Results: The intervention led to a sustained increase in the nephrology fellows’ MBTI personality preference knowledge. At 8 weeks post intervention, fellows reported utilizing their personality preference knowledge to improve their communication with their patients as well as with members of their team. However, nephrology fellows’ communication skills, as measured by the Kalamazoo Essential Elements Communication Checklist Adapted (KEECC-A), did not change.

Conclusions: Although training in MBTI personality preferences led to a significant, sustained increase in MBTI knowledge and fellows continued to report utilizing their knowledge at 8 weeks post intervention, there was no change in their measurable communication skills utilizing nurse observations.

SA-PO156

Lung Ultrasound: A New Skill for Nephrologists for Volume Overload Quantification in End Stage Renal Disease Patients on Hemodialysis Marc M. Saad, Wissam Mansour, Elias Moussaly, Jeanne Kamal, Boutros Karam, Cara Brown, Monica Kapoor, Elie El-Charabaty, Suzanne E. El Sayegh. *Internal Medicine/Nephrology, Staten Island Univ Hospital, Staten Island, NY.*

Background: Many methods have been tried to assess the volume status in patients on hemodialysis (HD). While the estimated dry weight is still the only method widely used, it is often inaccurate and poses a clinical challenge. Pulmonary congestion detected as B lines on ultrasound (BLUS) is rising as a novel parameter for assessing volume status; we evaluate the accuracy and reliability of measuring BLUS performed by residents following a short training course.

Methods: Residents underwent a 3 hour course under the supervision of ultrasound-fellowship trained Emergency Physicians (EP). The course included a didactic section, a simulation hands-on training, and an Objective Structured Clinical Examination prior to enrolling the trainees as investigators; Residents performed lung ultrasound (LU) on ESRD patients post HD sessions in a supine position over 28 intercostal windows. They obtained at each window a 6s clip that were reviewed by 2 blinded EP. BLUS were summed up categorizing patients into different classes of pulmonary congestion:mild (0-14), moderate (15-30) and severe (>30).

Results: A total of 81 ESRD patients on HD were scanned. 71.6% were males; mean age 59.74 years, mean BMI 28.59±5.62 kg/m²; mean test duration was 15 min. The B-lines score found by the study investigators and EPs was 15.8±21.3 and 12.06±21 respectively. The difference was 3.77±16.8 (0.0475). When categorized into the 3 classes, there was no significant difference between both classification (0.085), and were in moderate agreement-kappa 0.56 [0.42-0.71].

Conclusions: B-lines visualized on bedside LU can provide a reliable and quantifiable assessment for lung congestion. Our study shows that a short training course can render novice users of ultrasound capable of performing this quick evaluation. This can aid in objectively assessing volume overload in a timely manner in HD patients who present a unique clinical challenge. LU has emerged as a new technic, readily available at bedside, providing immediate results, yet is an easily learned skill.

SA-PO157

Renal Pathology: What We Think and What Is Ambarish Athavale, Kalyani Perumal, Peter D. Hart, Amit J. Joshi, Albert M. Osei. *Nephrology, John H. Stroger Jr. Hospital of Cook County, Chicago, IL.*

Background: Percutaneous kidney biopsy is the gold standard for diagnosis of kidney disease but is underutilized due to wariness of complications. Based on clinical and laboratory data, Nephrologists try to predict the renal pathology (clinical gestalt). However, no study has compared the diagnostic accuracy of the clinical gestalt with the kidney biopsy result. **Aim:** To compare pre-biopsy diagnosis (PBD) by Nephrologist with final histologic diagnosis. To assess if accuracy of PBD improves with increasing years in clinical practice.

Methods: Division of Nephrology at Stroger Hospital of Cook County conducts a monthly biopsy conference. Three case summaries are presented followed by discussion and presentation of the biopsy findings. Between September 2014 and April 2015, using a structured form Fellows and Nephrologists were asked to provide their top diagnosis for each case and this was compared with the actual histologic diagnosis. All physicians apart from the primary Nephrologist were blinded to the diagnosis. The study was deemed exempt by IRB.

Results: 23 cases were discussed in the biopsy conference involving 13 unique diagnoses and 286 unique responses were obtained. Overall diagnostic accuracy was 53.49% (153/286); Fellows (52.5%) and Nephrologists (54.36%). Diagnostic accuracy for nephrologists was 100% for ANCA vasculitis and Minimal Change Disease (MCD) and 86% for Diabetes but < 50% for stages of Lupus and other seronegative GNs.

Biopsy Diagnosis	Pre-biopsy diagnostic accuracy (%)
ANCA vasculitis	100
MCD	100
DM	86
Lupus class II	80
Amyloid	57.14
Lupus class III +V	50
Idiopathic Membranous	45.45
HIVAN	42.85
IgA	38.46
Lupus class V	33.33
HTN	33.33
Fibrillary GN	25
Normal	0

Nephrologists with > 10 years' experience tended to more accurately predict the diagnosis than those with < 10 years' experience (64.4 vs. 48.3%, p=0.07).

Conclusions: Nephrologists more accurately diagnosed ANCA vasculitis, MCD & Diabetes by clinical gestalt, but were less accurate for stages of lupus and other seronegative GNs. Regardless of training and experience kidney biopsy is still the diagnostic tool of choice in patients with kidney disease.

SA-PO158

Out-Patient Clinic Based Multidisciplinary Patients' Education for Advanced DM Nephropathy Is Effective and Efficient for Reducing ESRD Fumika Taki, Takuya Fujimaru, Masataka Hasegawa, Miyuki Futatsuyama, Yuki Heath, Masahiko Nagahama, Yasuhiro Komatsu. *Nephrology, St. Lukes' International Hospital, Tokyo, Japan.*

Background: Diabetes Mellitus (DM) is the most common etiology of CKD. Patients educations for these patients are known to be important, however, effectiveness and efficiency of them are still unclear. We established multidisciplinary out-patient clinic based education system, specialized for advanced diabetes nephropathy, and assessed their clinical outcomes.

Methods: Education system were started from May 2012, in St. Lukes' International Hospital, Tokyo, Japan. All CKD patients with DM were asked to meet nurse and dietitian, before seeing physicians, on every visit of the CKD clinic. Nurse and dietitian give the specific advices for each patients, within 15 minutes, by using our original short text or materials. Initiation of renal replacement therapy (RRT) were assessed for the primary end point, comorbidity, HbA1c, eGFR, type of RRT were also analyzed, retrospectively.

Results: From May 2012 to March 2015, total 372 individual patients were participated. Their baseline eGFR were 36.5±12.5ml/min, mean age 65.5±13.2 y.o. and 68% of them were male. Two hundred and ninety seven, 82% of patients were educated and their average of frequency of education was 4.3±2.1 times/year. Comparison of educated and non-educated groups, baseline eGFR, HbA1c or other comorbid did not differ. However, preservation of renal function were better in educated group ; delta eGFR: Educated vs. Non-educated: -3.26±1.21 vs. -8.2±3.25 ml/min/1.73m²/year, P=0.04, T-Test. More, incidence of ESRD is lower in educated group ; Initiation of Dialysis: Educated vs. Non-educated: 9.4% vs. 33.3%, P=0.033, Chi-Square test. Furthermore, in non-educated group, none of the patient selected peritoneal dialysis or transplants for the RRT.

Conclusions: Our out-patient clinic based education system is simple and useful for diabetic CKD patients for reducing ESRD.

SA-PO159

Our Stories Our Way: Creation of a Digital Story CKD Educational Intervention Stacey Jolly,¹ Marcia Oleary,² Ashwini R. Sehgal.³ ¹General Internal Medicine, Cleveland Clinic, Cleveland, OH; ²Missouri Breaks Industries Research Inc, Eagle Butte, SD; ³Center for Reducing Health Disparities, MetroHealth Medical Center, Cleveland, OH.

Background: Chronic Kidney Disease and End Stage Renal Disease disproportionately affects American Indian communities, yet there are few culturally appropriate educational interventions for this population.

Methods: Digital storytelling combines first person narrative with digital images and music and can be done with a community-based, learner-centered approach. With these digital tools, people create personal narratives that are powerfully compelling, emotionally engaging, and provide another view or perspective on a topic. We recruited 10 men and women with diverse life experiences related to health and kidney disease from an American Indian community to create digital stories. Each participant was mailed a pre-workshop information sheet about digital storytelling and were encouraged to bring pictures.

Results: We held a 3 ½ day digital story workshop with our partner nDigiDreams, LLC in Nov 2013 at a tribal college. Participants, their family members, and research staff worked together with the facilitators to create their personal digital story related to health and kidney disease in their words. A total of 10 digital stories were created. The process encompassed four areas: develop story idea, gather media such as pictures and music, record the voice parts/edit the digital story, and share or screen the digital stories among the group. Five stories about life on dialysis, having a kidney transplant, and making changes to control diabetes were selected to be in the final DVD.

Conclusions: We created a unique educational tool in the form of digital stories. The DVD has been used in an ongoing pilot observational educational trial looking at the impact on chronic kidney disease knowledge and health behaviors among American Indians.

Funding: NIDDK Support

SA-PO160

The Effect of Nephrology Specialty Clinics on Patient Care and Trainee Experiences Frederick H. Kuo, Rajeev Raghavan, Wolfgang C. Winkelmayr, Jose Jesus Perez. *Dept of Medicine-Nephrology, Baylor College of Medicine, Houston, TX.*

Background: As medicine evolves, there has been a trend towards the creation of special clinics which streamline care in hopes of improving patient survival through clinical trials and increased time with "super-specialists". From a trainee perspective, a Nephrology clinic focused on a particular disease affords fellows a unique perspective on disease pathophysiology and treatment and can be a wonderful tool to recruit residents or students into Nephrology. We hypothesized that a majority of Nephrology training programs across the US utilize such subspecialty clinics, and we aimed to characterize the patient and trainee experience by conducting a nationwide survey.

Methods: An e-mail detailing the study's aims and an anonymous 7-question online survey were sent to the 139 program directors of ACGME-accredited nephrology fellowship programs in July 2014.

Results: 54 of 139 program directors (39%) replied. We found Transplant clinics to be the most common subspecialty clinic (83%), followed by Stone clinic (63%), Advanced CKD clinic (50%), and Glomerulonephritis clinic (38%). Transplant clinics were oldest on average, with 67% in existence for over 10 years. Less common clinics included those

for lupus, polycystic kidney disease, and genetics. Regarding patient compliance within specialty clinics, 40% indicated no change, 40% improved, and 20% much improved. On patient satisfaction, 32% indicated no change, 49% improved, and 19% much improved. No respondents perceived decreased patient compliance or satisfaction. Trainees participated in 98% of specialty clinics with a 91% satisfaction rate; 29% were very satisfied. 45% of specialty clinics had ongoing research projects, with an average of 5.5 research projects in those clinics.

Conclusions: Subspecialty clinics can be an invaluable tool for both trainees and patients; both groups reported high satisfaction levels. These clinics also enable research by providing an established database of patients with specific disease processes. Access to such information is essential to quality research and may streamline the development of key clinical trials.

SA-PO161

The Impact of a Patient Education Program on Chronic Kidney Disease Patients' Plans to Initiate Dialysis – Prospective Study (2012-2014) Abdallah Guerraoui, Hallonet Patrick, Agnes Caillette-Beaudoin. *Néphrologie-Dialyse, Calydia, Vienne, France.*

Background: The distribution of renal replacement therapy (RRT) modalities among patients varies from country to country, and is often influenced by non-medical factors. In our department, patients progressing towards end-stage renal disease (ESRD) go through a structured Pre-Dialysis Education Program (PDEP). This PDEP is conceived with patients association and nursing educator.

Methods: Forty nine patients with CKD who were receiving care in a multidisciplinary predialysis clinic (mean age 73.5, 63% men). The participants are accompanied by family members. They have an initial educational evaluation, followed by two workshops in groups and a final educational evaluation. The workshops are carried out in groups of 6 to 10 patients. The PDEP consisted of: (1) psychosocial assessment, (2) education about dialysis and choice of modalities, (3) counseling sessions with patient, family members, (4) education about dietetic and dialysis.

Results: - Choice of the substitution method at the end of the workshops: 61% peritoneal dialysis, 18% haemodialysis and 21% absence of choice. - 94% of the patients began the substitution treatment with a chosen modality. - 100% Satisfaction of the patients, 26% decrease of the anxiety. ($p < 0,0005$), 25% ($p < 0,0001$) increase in the consent for the treatment, 61% increase in the engagement in the treatment (patient ready to receive treatment) ($p < 0,00001$), 47% increase knowledge of RRT ($p < 0,00001$).

Conclusions: Most studies dealing with the pre-dialysis information show a balanced choice of the RRT, but only 50% of the patients actually begin DP. Our workshops of help and assistance to the choice enable to significantly reduce the anxiety linked to the dialysis and thus increase the adherence and engagement for the chosen method RRT. A two-phase educational intervention can increase the proportion of patients who intend to initiate dialysis with self-care dialysis. In our centre offering all treatment RRT modalities, a high percentage of patients exposed to a structured PDEP start with a self-care RRT modality.

SA-PO162

Frequency of Use of Social Media in CKD Patients on Hemodialysis: Pilot Study in Ecuador Fabian A. Ortiz-Herbener,¹ Juan Carlos Calderon,² Walter Morquecho,³ Julio Israel Merino,³ Byron Josué Haz,² Ivan Manuel Cherez,^{2,3} ¹Inst Ecuatoriano de Diálisis y Transplantes, Guayaquil, Guayas, Ecuador; ²Respiralab, Guayaquil, Guayas, Ecuador; ³School of Medicine, Univ de Especialidades Espíritu Santo, Samborondón, Guayas, Ecuador.

Background: CKD on dialysis is defined as <15% of kidney function. In Latin America, 461 per million are on dialysis. Region is the third largest Internet user. Social Media includes communications spread electronically, shared by individuals and discussed by a committed population. Hispanic Americans with CKD used it, to inform and be informed, and for supporting each others.

Methods: Observational, cross sectional, pilot study. Patients were recruited in dialysis center in Guayaquil. Survey included demographic and clinical items, Charlson score and 4 questions about frequency of use of social media were included. Also, questions about obtaining information; and interest in receiving or asking physician questions related to illness in social media. Frequencies and mean (SD) were employed. Chi-square, ANOVA and M-W U was used for comparisons. Also, Cronbach were calculated.

Results: 34 patients participated, with mean age of 56.5 (SD 16.3), mean years on dialysis of 3.9 (SD 4). 52.9% were women. Comorbidity's rate was very high (82.4%). 70.6% of patients believed that dialysis control symptoms of disease. 11.8% hadn't got cellular-phone neither Internet. 61.8% hadn't got SMS. Almost half of patients had smartphones. Women had a high comorbidity (41.2%), $p > 0.05$. Around 30.0% reported using SMS, Facebook, YouTube, email an Internet at least once a week. 46.7% use Internet as principal source of information, YouTube (20.0%) and email (16.7%). 40.0% of patients reported high interest in receiving information by SMS, Facebook (33.3%) and email (26.6%). 33.3% reported high interest in asking by SMS, email (26.7%) and Facebook (20.0%). Finally, 43.5% reported interest in receiving information and asking by whatsapp. Cronbach was 0.884.

Conclusions: Internet use is very common for searching information related to disease. Whatsapp, SMS, Facebook and email were reported as new tools for providing illness related information to the patient. The survey had a good reliability and consistency.

SA-PO163

The Impact of Predialysis Education on Patient Understanding, Preparedness, and Decisional Conflict Regarding Renal Replacement Therapy Options Syed Amir Hamid Ali Shah,¹ Ion D. Bucaloiu,¹ Amanda Young,² Jamie Alton Green.¹ ¹Nephrology, Geisinger Medical Center, Danville, PA; ²Center for Health Research, Geisinger Medical Center, Danville, PA.

Background: Predialysis education is recommended to prepare patients with advanced chronic kidney disease (CKD) for initiation of renal replacement therapy; however, the impact of various approaches on medical decision-making is unknown.

Methods: We surveyed 91 advanced CKD patients before and after a 2-hour nurse led group education class to assess patient understanding of renal replacement therapy options (1=poor to 5=excellent), preparedness to make a decision (1=not at all to 5=very prepared), and decisional conflict using a validated scale (0=no decisional conflict to 100=extremely high). The class included a combination of direct verbal instruction and video presentation, tailored to patients with a variety of health literacy and sociodemographic backgrounds. Content included the advantages/disadvantages of hemodialysis (HD), peritoneal dialysis (PD), transplant, and conservative management.

Results: Mean age was 66, 58% male, 94% white, 44% had a high school or lower level of education, and 46% had low health literacy. Mean level of understanding increased significantly for all modalities pre-post (2.02 vs. 4.10 for HD, 1.95 vs. 4.14 for PD, 2.35 vs. 4.15 for transplant, and 2.10 vs. 4.12 for conservative management; all $p < 0.001$). Decision preparedness also increased significantly from 2.44 to 3.50 ($p < 0.001$). Improvements were similar regardless of age, gender, educational level, or health literacy. At the end of the class, overall decisional conflict was low (median score 10; IQR 0, 20). Equal proportions of patients preferred HD (24%) or PD (22%), compared with transplant (12%) and conservative management (4%), yet nearly (30%) of patients remained unsure of their decision.

Conclusions: Despite significant improvements in patient understanding and preparedness about renal replacement therapy options, a substantial number of patients remain unsure of their decision after routine predialysis education. Additional decision supporting interventions may be needed to improve decision-making in advanced CKD patients.

SA-PO164

Chronic Kidney Disease Knowledge Among English and Non-English Speakers Anushya Jeyabalan, Pranav S. Garimella, Lesley Inker. *Nephrology, Tufts Medical Center, Boston, MA.*

Background: Patient education regarding CKD is an important part of pre-dialysis care. While educational interventions have also shown to improve clinical outcomes among dialysis patients, there is little information however, on health literacy in CKD populations.

Methods: We performed a cross-sectional survey of patients identifying themselves as primarily English or Chinese (Cantonese or Mandarin) speakers visiting an outpatient nephrology clinic at a single tertiary hospital. A validated Kidney Knowledge Survey (KiKS) that has been used to assess CKD knowledge in previous studies was translated into Chinese and then self-administered in English or Chinese. All patients had at least 1 prior visit with a nephrologist.

Results: 102 participants completed the survey of which 70 were English speakers and 32 were Chinese speakers. Chinese speakers were older, more likely to have less than high school education and had a greater prevalence of diabetes (Table). Estimated glomerular filtration (eGFR) and urine albumin creatinine ratio were not different between groups. Mean KiKS score was lower in Chinese speakers compared to English speakers (11.9 vs. 17.2, $p = 0.001$). Chinese speakers scored lower in all domains of the KiKS; general kidney knowledge (6.2 vs. 4.5), knowledge of kidney function (5.5 vs. 4.0) and knowledge of symptoms (5.4 vs. 3.7).

Conclusions: While our results for CKD knowledge among English speakers are comparable to previously published data (mean score 18.6), scores among non-English speaking CKD patients is lower than English speakers. Whether this finding is associated with differences in care management and clinical outcome needs to be evaluated. Furthermore, educational material and programs may need to be tailored to specific populations to improve health literacy.

SA-PO165

Follow-Up with Doppler Ultrasound of Asymptomatic Arteriovenous Fistula (AVF) After Renal Biopsy (RB) Maite Rivera,¹ Saul Enrique Pampa,¹ Virginia López de la Manzanara Pérez,² Victor Burguera,¹ Nuria Rodríguez Mendiola,¹ Cristina Galeano,¹ Ingrid Viviana Raoc Michaels,¹ Rodrigo Hernandez Loyola,¹ Fernando Liano.¹ ¹Nephrology, Hospital Univ Ramon y Cajal, UAH, Madrid, Spain; ²Nephrology, Hospital Univ San Carlos, Madrid.

Background: RB is an essential percutaneous technique in Nephrology that entails major and minor complications, one being the AVF which is usually asymptomatic and underdiagnosed because of the absence of routine Doppler examination post RB. We analyzed the natural history of asymptomatic AVF post RB of native kidney (NK) and transplanted (RT) detected by Doppler examination following RB.

Methods: We analyzed the presence of AVF on 327 RB between January 2011 and December 2014 included in our database. 47 (14%) RB developed AVF detected by Doppler ultrasound performed at 24h post RB. We studied the following data: AVF size and its relation to the needle caliber and time to spontaneous closure and its relationship to the AVF size. All RB were real-time ultrasound-guided RB performed with a biopsy gun (Acecut Tsk, Japan), the RT caliber 16G and 14G in the NK.

Results: 45 AVF were asymptomatic (96%), whereas 2 (4.2%) had to be embolized by their large size. Of the 45 asymptomatic AVF, 28 were of RT (62.2%). 69% were male. AVF 28 (62%) were followed until its closure with Doppler. 75% sized <1cm and corresponded to RT (16 G-needle). We noticed that the 50% of AVF had closed at 3 months post RB at an average of 49 days. AVF with a size between 1.1 and 1.9 cm (17.7% of the total) took longer time to close (mean 67 days). Among the 17 patients without follow-up five had died, 3 lost the renal graft and 9 were lost in the evolution. Seven of the 9 patients without follow-up were studied by Doppler after contacting them by phone, 28 months post-biopsy. In the seven AVF had spontaneously closed.

Conclusions: Contrary to published, AVF after RB is a frequent complication but asymptomatic and rarely requires surgery. All asymptomatic AVF closed spontaneously. The size of AVF were related with the caliber of the needle and with the time to close. No AVF grew in evolution. The routine use of Doppler following RB is essential to identify and standardizing management of AVF.

SA-PO166

The Role of Post Biopsy Ultrasound in Predicting Complications After Percutaneous Renal Biopsy of Native Kidneys Umar Hayat, Hafiz I. Ahmad, Syed Rizwan Bokhari, Syed A. Khalid. *Dept of Nephrology, Allama Iqbal Medical College/ Jinnah Hospital Lahore, Lahore, Pakistan.*

Background: The percutaneous renal biopsy (PRB) of native kidneys has been an essential tool in the diagnosis and management of renal diseases. Despite all advances, clinically evident bleeding complications do occur in up to 30% of patients after PRB of native kidneys. Traditionally patients are kept under observation for 24 hours after the procedure. An earlier investigation to anticipate the likelihood of complications will help to reduce the length of stay for these patients and thus the resource burden. Post PRB ultrasound has been studied for this purpose. We conducted a study to evaluate the role of early post PRB ultrasound to predict procedure related complications in our patient population.

Methods: 46 patients undergoing renal biopsy at department of Nephrology, Jinnah Hospital were considered for this study. Renal biopsy was performed using a 16-gauge automated core biopsy needle. After the biopsy, patients were closely monitored in recovery room and after 1 hour, the biopsied kidney was examined by ultrasound. These patients were admitted and were kept under observation to assess any complications for next 23 hours.

Results: Of these 46 patients, 24 (52%) were males with mean age 39 (16 to 60 years). More than 3 cm hematoma was seen in 2 (4.3%) patients at 1 hour post biopsy ultrasound scan. Of these 2 patients, only 1(2%) patient had major complications including hypotension, decrease in hemoglobin etc. Thus 45 (97.8%) patients had uneventful recovery. Sensitivity of more than 3 cm hematoma formation at 1 hour post biopsy in predicting major complications was 100% with specificity of 97.7%.

Conclusions: Our study showed that the frequency of major complications was minimal in patients without >3 cm hematoma formation at one hour post-PRB. Post-PRB ultrasound is a non-invasive, accurate diagnostic tool in predicting procedure related major complications.

SA-PO167

A Multidisciplinary Clinic for Children with Lupus Nephritis (LN) – A Step Towards Personalized Medicine? Nicole A. Hayde,¹ Tamar Rubinstein,² Janice Berthe Desir,¹ Dawn Wahezi,² Katherine Steigerwald,² Beatrice Goilav.¹ ¹*Pediatric Nephrology, Children’s Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY;* ²*Pediatric Rheumatology, Children’s Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY.*

Background: Most children with SLE develop LN, which significantly worsens morbidity and mortality. Progression to ESRD occurs in 5-10%. Early diagnosis and treatment improve long-term outcomes, thus prompt evaluation is essential. Therefore, a combined pediatric nephrology/rheumatology clinic (LN Clinic) was started in 2013. The primary aim was to evaluate the number of days between onset of proteinuria (first-am urine p/c >0.2) and performance of a renal biopsy (bx) for SLE patients (pts), pre- and post-establishment of the LN Clinic. We aimed for a 20% reduction in time to renal bx within 2yr of establishment of this clinic. The secondary aim was a reduction of steps in the referral process.

Methods: SLE pts with an outpt renal bx were identified by an EMR query. Pts were selected if a bx was performed within 5yr pre or 16mo post establishment of the LN clinic. Our sample selection was cross-referenced with an established lupus registry. A chart review provided the date of proteinuria onset, disease activity markers, and LN class. Pts diagnosed in the inpt setting were excluded. A process map determined the number of steps occurring between new-onset proteinuria and first evaluation by a nephrologist.

Results: We show that pre LN clinic, the median number of days between onset of proteinuria and renal bx was 51 (IQR=25–83.5d), compared to 34 (IQR=14–48d) post (p=0.057). This is a 33% decrease in time. There was a negative association between amount of proteinuria and days to bx (r=-0.5826, p<0.001). There was no association between hematuria or markers of disease activity and days to bx. There was also no association between LN class and days to bx. Pre LN clinic, a referral required 10 steps, which was reduced to 6.

Conclusions: The LN clinic has resulted in earlier renal bx and fewer steps in the referral process. For pts with proliferative LN, this translates to earlier initiation of treatment and a chance at improved outcome.

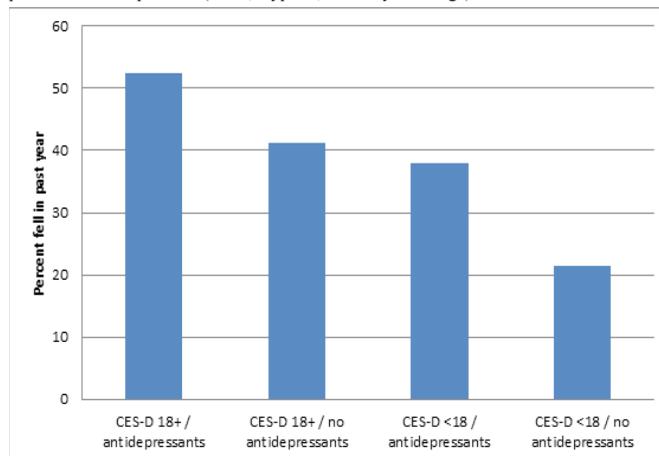
SA-PO168

Antidepressant Efficacy and Safety Observations: USRDS ACTIVE-ADIPOSE Study Nancy G. Kutner,¹ Rebecca H. Zhang,¹ Yijian Huang,¹ C. Barrett Bowling,^{1,2} ¹*Emory Univ, Atlanta, GA;* ²*Atlanta VA Medical Ctr.*

Background: Although depression is a prominent issue, depression management in advanced CKD and ESRD patients is not well understood. Antidepressant medications are the most frequent therapy, but efficacy and safety data are limited (Hedayati et al. 2012).

Methods: The primary exposure of interest was use of antidepressant medications among 771 maintenance hemodialysis (MHD) patients ages 20-92 in 14 outpatient clinics who were enrolled 2009-2011 in the ACTIVE-ADIPOSE special study (median ESRD treatment 3.2 years). Gender distribution and ESRD etiology were similar to the overall MHD population, but the proportion non-white and younger than age 65 was higher in the study cohort. Medication efficacy was defined by participants’ scores (<18 vs. 18+) on the Center for Epidemiologic Studies-Depression (CES-D) scale (Hedayati et al. 2006). Adjusted odds for recent falls observed in association with antidepressant use and CES-D score provided an indicator of safety.

Results: Antidepressants were prescribed for 15% of study participants. 40% of those with prescribed antidepressants had an elevated CES-D score, suggesting lack of drug efficacy. Efficacy did not appear to vary by patients’ age or vintage, but more whites had elevated CES-D scores. Recent falls were more frequent among patients on antidepressants with elevated CES-D score (adjusted odds ratio 2.27 [1.05, 4.90], p = 0.04, compared with patients not on antidepressants and CES-D score <18). Fall risk was similar across type of prescribed antidepressant (SSRI, atypical, and tricyclic drugs).



Conclusions: Efficacy of antidepressant medications was unclear for 40% of those with these drugs prescribed, and safety hazard was suggested by increased fall risk. Continued evaluation of nonpharmacologic as well as pharmacologic options for depression management in MHD patients, the focus of a current PCORI trial, is important.

Funding: NIDDK Support

SA-PO169

Sofosbuvir Use in Patients with Hepatitis C Virus Infection and Severe Chronic Kidney Disease Alberto J. Sabucedo, Marie Essie Antoine, Delvis Jorge, Aileen Andreu, Fernando E. Pedraza, Maria Del Pilar Hernandez, Lennox Jeffers, Marco A. LadinoAvellaneda. *Dept of Medicine. Divs of Nephrology and Hepatology, Miami VA Medical Center/Univ of Miami, Miami, FL.*

Background: Chronic hepatitis C virus (HCV) infection is a major health problem. The use of new direct acting antiviral (DAA) based regimens has been shown to provide a high sustained virologic response with less adverse reactions compared to interferon-ribavirin regimens. The American Association for Study of Liver Diseases recommends expert consultation on patients with eGFR less than 30 mL/min because safety and efficacy data are not available on these patient populations. We propose that these DAAs are safe to use in patients with advanced kidney disease.

Methods: A total of 23 patients with HCV and estimated glomerular filtration rate (eGFR) less than 45 ml/min were treated with sofosbuvir and simeprevir, dose of sofosbuvir was adjusted to 200 mg PO daily or 400 mg PO every other day for patients with eGFR less than 30 ml/min by Hepatology and Nephrology services. These patients were monitored closely by both services.

Results: A cohort of 23 HCV positive patients had the following descriptive statistics, 20 males (87%) and 3 females (13%). 15 patients had Genotype 1a (65%), 7 patients had Genotype 1b (31%) and 1 patient had Genotype 2b (4%). 3 patients (13%) had End Stage Kidney Disease (ESKD) and were on hemodialysis, 9 patients (39%) had Chronic Kidney Disease grade IV (CKD IV - eGFR <30 ml/min) and 11 patients (48%) had Chronic Kidney Disease grade IIIB (CKD IIIB - eGFR <45 ml/min) The HCV viral load of the 23 patients (100%) had a statistically significant decrease as the therapy progressed through completion with a statistically significant T-test with a p < 0.05. No side effects were present on the patients during DAA therapy. Patients with CKD grades IIIB and IV on DAA treatment had a preserved kidney function by the end of therapy.

Conclusions: Sofosbuvir is safe and effective in patients with Hepatitis C Virus infection and severe Chronic Kidney Disease, co-management and close monitoring by Hepatology and Nephrology is imperative due to the lack of data in safety and efficacy.

SA-PO170

Enoxaparin as Bridging Therapy in Veterans with Advanced Kidney Disease
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Background: Patients with CrCl < 30ml/min on anticoagulation require temporary bridging perioperatively. Low-molecular weight heparins (LMWH) have longer half-lives and predictable anticoagulant effect but require anti-Xa monitoring in CKD. This study aims to evaluate the safety and efficacy of lovenox as a bridge therapy in patients with CrCl < 30ml/min.

Methods: A retrospective study was conducted from Jan 1, 2012 to Dec 1, 2014. Patients with CrCl < 30 mL/min, received enoxaparin 1 mg/kg/day as a bridge therapy to warfarin, and had at least one anti-Xa level checked were included in the study. Patients were excluded if they had major bleeding or thromboembolism in previous 3 months before enoxaparin, history of bleeding disorders, or used enoxaparin for other indications. A dosing nomogram was used to guide dosage adjustment to keep anti-Xa levels within the target range (0.5 -1.0 mcg/ml). The primary outcomes are # of minor/major bleeds and thromboembolic events. The proportion of anti-Xa levels within goal range was assessed. Descriptive statistics were used to compare outcomes to the literature.

Results: 12 patients met inclusion and exclusion criteria. The mean age was 62.4 ± 11.9 years, 91.7% were male, 58% were diabetic and 46% had congestive heart failure. 50% were on both warfarin and aspirin. The mean treatment duration of enoxaparin was 11.4 ± 4.6 days, the average CrCl was 17.6 ± 4.5 mL/min. A total of 19 anti-Xa levels were included for analysis. There were 2 (16.7%) bleeding events, 1 (8.3%) major and 1 (8.3%) minor bleed. None of the patients developed thromboembolic complications. The most common adverse event was bruising at the injection site that did not lead to any early discontinuations of therapy. Seventeen of the anti-Xa levels (89.4%) were in the target range.

Conclusions: Majority (83.3%) of patients had minimal or no adverse events and none with thromboembolic outcomes. In patients with bleeds, no correlation was seen with the anti-Xa levels. The dosing protocol is effective, with 89.4% of anti-Xa levels within goal range. The results of this study support the safety and efficacy of the enoxaparin dosing protocol as a bridge therapy perioperatively in patients with CKD.

Funding: Veterans Administration Support

SA-PO171

Thiopurine Methyltransferase (TPMT) Genotyping to Predict Myelosuppression Risk in Chinese Patients with Nephropathy
Xuemei Li, Jie Ma. *Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: Pharmacogenetic study in nephritis is mainly focused on genes involved in the metabolism of Azathioprine (AZA). Use of AZA is limited by its toxicity. Variants in the Thiopurine S-methyltransferase (TPMT) have been associated with AZA toxicity. The aim of this study was to determine the contribution of TPMT variants in the development of AZA-related myelosuppression in Chinese patients with nephropathy.

Methods: Variants associated with the decrease of enzyme activity in TPMT genes were genotyped in 4 nephritis patients treated with AZA, and correlated with the clinical response and development of adverse drug reactions in a retrospective case-control study. Three common mutation alleles of TPMT [TPMT* 3A (G460A/A719G), TPMT* 3B (G460A), TPMT* 3C (A719G)] were detected by polymerase chain reaction-high resolution melting and sequencing in 12 patients, included 4 patients with myelotoxicity and 8 patients without myelotoxicity.

Results: Genotypic analysis showed only one of the 4 patients with myelotoxicity was detected TPMT*3C polymorphisms, no TPMT*2, *3A, *3B or *3C polymorphisms were detected in any of the 11 patients.

Conclusions: Single-nucleotide polymorphisms of TPMT could not explain the azathioprine-related adverse events.

SA-PO172

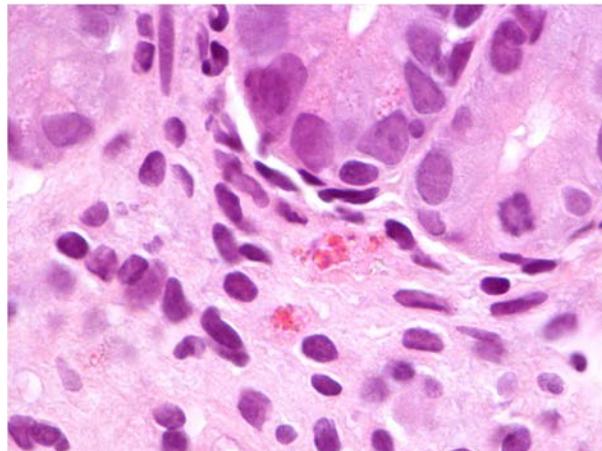
Lanthanum Carbonate-Induced Granulomatous Gastritis
Francesco Iannuzzella,¹ Loredana De Marco,² Sonia Pasquali.¹ *¹Dept of Internal Medicine, Nephrology and Dialysis Unit, Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia, Italy; ²Dept of Human Pathology, Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia.*

Background: Long-standing non-calcium based phosphate binders administration has been recently associated with a number of different gastroduodenal lesions. We describe a rare case of lanthanum carbonate-induced granulomatous gastritis.

Methods: A 58-year-old woman was admitted to our hospital because of nausea, vomiting, and progressive weight loss. Because of a well-known stage 5 chronic kidney disease, she was started on peritoneal dialysis. About one month later, CAPD was well-tolerated with an adequate dialysis dose. Nevertheless, she continued to complain of nausea, vomiting and dyspepsia. A gastroscopy revealed chronic gastritis with superficial erosions and an histopathology consisting of non-necrotizing, sarcoid-like granulomas with aggregates of multinucleated giant cells. Orange crystalline material was seen within granulomas. Special stains for fungus and mycobacteria were negative. Her previous medical history was only significant for hypertension and type 2 diabetes mellitus. Physical examination was unremarkable. A chest X-ray was normal. A tuberculin skin test was

negative. ANCA titres was negative and serum angiotensin converting enzyme (ACE) level was in the laboratory reference range. At the time of our evaluation, she had been receiving lanthanum carbonate 1 g bid for about 6 months.

Conclusions: At the best of our knowledge, so far, only 7 cases have been described in the literature.



The histopathologic picture in our patient was compatible with a lanthanum carbonate-induced gastritis with some peculiar characteristics: a granulomatous reaction and the appearance of lanthanum carbonate crystals not only within histiocytes/multinucleated giant cells but also inside the cytoplasm of the epithelial glandular cells.

SA-PO173

Relative Incidence of Adverse Events with Ferumoxytol versus Other Intravenous Iron Products in Non-Dialysis-Dependent Chronic Kidney Disease
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Background: All intravenous (IV) iron products confer risk of hypersensitivity reaction (HSR). The relative safety of ferumoxytol versus other IV iron products is not established. We used Medicare claims to assess relative safety of ferumoxytol versus other IV iron products in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: We analyzed a 20% sample of Medicare Parts A and B claims in 2009-2012. Patients received a first dose of IV iron between Jan 1, 2010, and Nov 30, 2012, and had diagnosed NDD-CKD without IV iron treatment during the 1 year before first dose. For each ferumoxytol user, we identified 1 propensity score-matched control who used another IV iron product; the score included demographics, comorbidity, and concomitant IV medication. Patients were followed until change in IV iron product, end stage renal disease, death, or Dec 15, 2012. With Cox regression stratified by matched pair and cumulative number of prior IV iron doses, we assessed relative incidence of anaphylaxis, HSR symptoms, hypotension, emergency room (ER) visit, hospitalization, and death within 1 day of first dose and within 1 day of each subsequent dose.

Results: We identified 7358 ferumoxytol users and 7358 matched controls. Baseline characteristics were balanced across groups. There were too few cases of anaphylaxis and death to permit comparisons. However, after first dose, hazard ratios (ferumoxytol users vs. matched controls) were 0.90 (95% confidence interval, 0.80-1.01) for HSR symptoms, 1.06 (0.66-1.72) for hypotension, 0.72 (0.55-0.94) for ER visit, and 0.78 (0.60-1.02) for hospitalization. After subsequent doses, corresponding hazard ratios were 1.07 (0.90-1.27) for HSR symptoms, 0.91 (0.50-1.67) for hypotension, and 0.86 (0.64-1.15) for ER visit, and 0.97 (0.70-1.35) for hospitalization.

Conclusions: Relative to other IV iron products, ferumoxytol was not associated with excess risk of adverse events in NDD-CKD patients, following both first dose and subsequent doses. The incidence of anaphylaxis and death was very low in ferumoxytol users and matched controls.

SA-PO174

Efficacy, Safety and Pill Burden of Sucroferic Oxhydroxide, an Iron-Based Phosphate Binder, Over 52 Weeks in African American Dialysis Patients
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Background: A *post hoc* analysis of data from a randomized, open-label, Phase 3 study and its extension investigated the efficacy and safety of the iron-based phosphate binder sucroferic oxhydroxide (SFOH; VELPHORO®) vs sevelamer carbonate (SEV; Renvela®) in African American dialysis patients.

Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12 weeks' dose titration then 12 weeks' maintenance. Eligible patients enrolled in a 28-week extension study.

Results: Of the 549 patients who completed the extension study, 100 were African American patients, equally distributed between the treatment groups despite the 2:1 randomization (n=48, SFOH; n=52, SEV). Serum phosphorus decreased rapidly and to a similar extent with SFOH and SEV, and remained relatively constant thereafter (Table). Mean ± standard deviation number of tablets/day was lower for SFOH (3.4 ± 1.35) vs SEV (7.6 ± 2.92) over 52 weeks. The incidence of serious or severe treatment emergent adverse events and deaths were similar in both treatment groups. Gastrointestinal-related disorders were the most frequently observed adverse events for SFOH and SEV.

Conclusions: SFOH efficacy was maintained long-term, with a lower pill burden than SEV and similar safety profile, in African American dialysis patients. *Post hoc* results reflect those from the overall study population.

Table: Treatment efficacy and safety in African American patients.

Efficacy (completer set; N=100)	SFOH (n=48)	SEV (n=52)
Phosphorus, mg/dL*		
Baseline	7.4 (1.97)	7.3 (1.36)
Δ at Week 12	-2.0 (1.88)	-2.3 (1.76)
Δ at Week 24	-2.1 (2.26)	-2.0 (1.79)
Δ at Week 52	-2.1 (2.58)	-2.1 (1.58)
Safety parameters (safety set; N=205), %	SFOH (n=130)	SEV (n=75)
Withdrawal due to AEs	18.5	8.0
Severe AEs	14.6	20.0
Serious AEs	27.7	30.7
Deaths	3.1	2.7
Anemia	1.5	9.3
Hyperparathyroidism	9.2	14.7
Gastrointestinal-related adverse events	43.1	44.0
Diarrhea	15.4	10.7
Discolored feces	13.8	1.3
Nausea	9.2	14.7
Vomiting	6.9	9.3
Constipation	3.8	8.0

*Mean (standard deviation) serum levels. AEs, adverse events; SEV, sevelamer carbonate; SFOH, sucroferriic oxyhydroxide.

Funding: Pharmaceutical Company Support - Vifor Pharma

SA-PO175

Integrated Dialysis Unit Module and Module Compartment Structure
 Stanley Shao-Ying Lee,¹ Ming-cheng Wang,² ¹Chi-Hsien Hemodialysis Center, Taiwan; ²College of Medicine, National Cheng Kung Univ, Tainan, Taiwan.

Background: Conventional set-up of hemodialysis (HD) center requires intensive manpower and tedious workload due to the intricate fluid and electricity layouts, and the fixed partitions structure. It is vital to design an integrated module considering rapid assembly, patient privacy and easy access to the fluid pipes and electricity lines for routine maintenance.

Methods: The Integrated Dialysis Partition System was designed for HD center. To ensure patient privacy, an easy-assembled partitions with a herringbone seating arrangement was used to position the HD seats partially and equally askew in one direction. The mobile modules of fluid pipes and electricity lines allow easy access for routine maintenance. Eighty uremic patients were enrolled to examine the differences between conventional and new HD unit in terms of psychological adjustment including depression, anxiety, mood, and illness intrusiveness.

Results: The state-of-the-art HD center with 40 seats could be established within one day.



For the entire patients, BDI scores were significantly higher when dialyzed in the conventional HD unit (M = 13.3 :t 0.9) than in the new HD unit with integrated dialysis partition system (M = 10.3 :t 1.2; t = 1.95, p = 0.014). In the conventional HD unit, patients recorded higher anxiety and lesser positive mood. There were no significant differences regarding negative mood or illness intrusiveness.

Conclusions: The intergrated dialysis unit module allows for rapid assembly, easy pipeline maintenance, and improved patients' quality of life.

SA-PO176

Safety and Adherence in End Stage Renal Disease Patients on Chronic Hemodialysis
 Kamran Karimi, Yezina T. Nigatu, Catherine Miranda, Kerri Fico, Leonard A. Arbeit, Nand K. Wadhwa. *Nephrology, Stony Brook Univ Medical Center, Stony Brook, NY.*

Background: Missed hemodialysis and abbreviated hemodialysis sessions are common in end stage renal disease patients on maintenance hemodialysis. Dialysis non-adherence has been associated with increased mortality and morbidity in chronic hemodialysis patients. Our quality assessment performance improvement data revealed that on an average 15% of patients missed and abbreviated hemodialysis (HD) sessions over a period of 6 months.

Methods: We evaluated patients' perception about missed and abbreviated sessions, and safety during HD sessions at our dialysis center. A questionnaire regarding patients' views about missed, abbreviated and safe hemodialysis sessions using a visual analog scale (0-100 mm, where 0 means 'No' and 100 means 'Yes') was conducted in-person by a nephrology fellow or a social worker on all HD patients. Data are presented as (mean ± SD).

Results: Ninety patients participated in the survey. Sixty eight (75.6%) patients with a mean score of 78+ 29.6 felt like coming for their HD sessions during the last one month. Fifteen of 89 (16.9%) did not know why they came for HD sessions. Twenty seven percent came because they wanted to live while 18% came because they did not want to die. Eighty nine (98.9%) patients with a mean score of 94.5 + 17.3 felt safe during the HD sessions. Seventeen (18.9%) patients indicated missing the HD sessions. Thirty six of 83 (43.4%) patients with a mean score of 71 + 37.6 wanted to miss HD sessions during the last one month. Fifteen of 89 (16.9%) signed against medical advice for the abbreviated HD sessions during the last one month.

Conclusions: Data suggest that safety of HD sessions does not appear to be a factor for missing HD sessions. Lack of patients' understanding of importance of HD treatments as well as lack of their active participation likely leads to non-adherence and abbreviation to HD sessions. The safety of HD treatment was not the core issue behind increasing patients' absenteeism. Active patients' participation and individualization of HD sessions may improve adherence to HD sessions.

SA-PO177

Validation of a Tool to Assess Nursing Workload in Hemodialysis
 Clara Bohm,¹ Brett M. Hiebert,¹ Joe A. Buetti,¹ Jan Schneider.² ¹Univ of Manitoba; ²Winnipeg Regional Health Authority.

Background: Patient classification scales (PCS) to assess nursing workload predict staffing needs and facilitate transparency in assignments resulting in improved work environment, patient safety and quality of care. Few validated PCS tools exist for hemodialysis (HD). This study validates a point-of-care PCS developed for in-centre HD at a Canadian tertiary care centre.

Methods: Using LEAN framework, from Sept 1, 2013 to Mar 1, 2014 at the Health Sciences Centre in Winnipeg, Canada, iterative consultations with stakeholders resulted in creation of a PCS consisting of 9 domains and 67 subdomains. At each HD session between April 7-21, 2014, bedside HD nurses completed both a visual analogue scale (VAS), which assessed general level of nursing care required, and the PCS tool. Karnofsky scale and time-series studies were completed in 50 and 28 randomly selected HD patients, respectively. *Analysis:* Internal consistency and reliability were assessed using Cronbach's alpha and Intraclass Correlation Coefficient (ICC), respectively. Multi-trait multi-method analysis (MTMM) determined item homogeneity. Spearman's correlation of PCS with VAS, Karnofsky Score and time-series studies assessed criterion and predictive validity. Linear regression was performed to determine the association of each subdomain with PCS score.

Results: PCS and VAS data for 1640 HD sessions (380 patients) was obtained.

	PCS Score	VAS Score	Karnofsky Score	Time Series
Mean (SD)	10.7 (5)	3.7 (1.9)	66 (14.4)	89 min (48)
N	380	380	50	27

PCS correlated well with VAS (0.769). Correlation of PCS with Karnofsky scale and time-series studies was -0.56 and 0.39, respectively. ICC was 65%. MTMM identified 4 subdomains never used and 2 which were redundant. Linear regression identified 16 subdomains with minimal contribution to overall PCS score. Reconsultation with stakeholders resulted in a revised 41-item PCS tool. Correlation between the revised tool and VAS, Karnofsky score and time-series was similar to the original model (0.77, -0.51 and 0.316, respectively).

Conclusions: Preliminary results suggest excellent reliability and validity of this PCS tool. Validation studies at other HD centres with expanded time-series and reliability studies continue.

SA-PO178

Feasibility of a Hemodialysis Safety Checklist for Nurses and Patients Samuel A. Silver,¹ Alison Thomas,¹ Andrea Rathe,¹ Pamela L. Robinson,¹ Ron Wald,¹ Chaim Bell,² Ziv Harel.¹ ¹Nephrology, St. Michael's Hosp, Toronto, ON, Canada; ²Medicine, Mt.Sinai Hosp, Toronto, ON, Canada.

Background: In 4% of ESRD patient deaths, the cause of death is a result of a preventable hemodialysis complication. These include errors related to communication, organization and human factors. We recently developed a hemodialysis safety checklist (Hemo Pause) to be completed by nurses and patients at specified intervals throughout a hemodialysis session, with the goal to improve dialysis unit safety culture. Our objective was to determine the feasibility of using Hemo Pause during every hemodialysis session for 3 months.

Methods: We conducted a single center, prospective time series study. A convenience sample of 14 nurses and 22 prevalent in-center hemodialysis patients participated. All participants were trained in the administration of Hemo Pause, completed the checklist at every hemodialysis session for 3 months and were free to suggest checklist modifications consistent with quality improvement methodology. The primary outcome was Hemo Pause completion, which was determined weekly using the percentage of checklists in the patient chart with all 17 items assessed. We also measured Hemo Pause acceptability using local patient safety surveys.

Results: There were 799 hemodialysis treatments pre-intervention and 757 post-intervention. The checklist was completed for 556 of 757 (73%) treatments. The most common reasons for non-completion were the availability of nursing staff trained in Hemo Pause and patient admission to hospital. Among hemodialysis nurses, 93% (13/14) agreed that Hemo Pause was easy to use and 79% (11/14) agreed it should be expanded to other patients. Among hemodialysis patients, 73% (16/22) agreed that Hemo Pause made them feel safer and should be expanded to other patients. Negative comments by nurses or patients occurred on 4% (7/200) of survey responses.

Conclusions: A hemodialysis safety checklist (Hemo Pause) was acceptable to both nurses and patients over a 3 month period. Our next step is to spread Hemo Pause locally, and conduct a mixed methods study to determine mechanisms by which Hemo Pause may improve safety culture, patient engagement, and reduce adverse events.

Funding: Government Support - Non-U.S.

SA-PO179

Community-Based Parenteral Anti-Infective Therapy (COPAT) for ESRD Patients Evamaria Anvari, Reza Anvari, Laura Ferreira Provenzano, Juan C. Calle. *Nephrology, Cleveland Clinic Foundation, Cleveland, OH.*

Background: Infections are the leading cause of hospital admissions for patients with ESRD. The majority will need to continue antimicrobial therapy when discharged. Community-based parenteral anti-infective therapy (COPAT) refers to the practice of administering antimicrobial therapy in the outpatient setting. It requires a multidisciplinary and the goals are to improve outcomes, reduce toxicity, drug resistance, and decrease hospital stay. ESRD patients have the advantage that IV antibiotics can be given at their dialysis units. The downfall is that every outpatient dialysis provider has their own policies for the approval of IV/IP therapy. Patients are frequently discharged with an order to continue therapy but it is not continued, leading to adverse outcomes.

Methods: We investigated the policies from the main dialysis providers in our community.

Results:

	Fresenius Medical Care	Davita	Centers for Dialysis Care
IV/IP drugs in unit	Vancomycin, Cefazidime, Cefazolin, Gentamycin	Vancomycin, Cefazidime, Cefazolin, Gentamycin	Vancomycin, Cefazolin, Gentamicin, Tobramycin (IP), Cefazidime (IP)
IV/IP drugs in formulary	Amikacin, Tobracycin, Ceftriazone, Cefepime, Meropenem, Daptomycin, Aztreonam, Ampicillin, Levofloxacin, Amphotericin B, Fluconazol, Ganciclovir, Pentamidine	-Any other medication needs pre-approval -Daptomycin will <u>not</u> be approved	Any other antimicrobial drug will be approved
Time for drug arrival	24-48 hrs.	-Pre-approval 24-48 hrs. -Day after approval	48 hrs.
Requirement	Hospital order	-ID consult -Organism with sensitivity -Rational for using other antimicrobial	Hospital order
IP drugs	Receive in unit	-Loading dose in unit and continue self-administer -Drugs orderd Monday - Thursday will arrive at their home the following day -If ordered after 3PM Friday it will arrive Monday	Loading dose in the unit and are given a 5-7 day supply to self-administer
Home Hemo	Dialyze in center for therapy	Dialyze in center for therapy or trained to self-administer	Dialyze in center for therapy

Conclusions: Readmissions and complicated infections in ESRD patients can be prevented if the multidisciplinary team coordinates care with the outpatient dialysis unit before discharge.

SA-PO180

Rapid Response and Cardiac Arrests in In-Patient Hemodialysis - A Retrospective Review Justin Chen,¹ Ladan Golestaneh,^{1,2} Lewis Ari Eisen.^{1,3} ¹Albert Einstein College of Medicine, Bronx, NY; ²Nephrology, Montefiore Medical Center, Bronx, NY; ³Critical Care, Montefiore Medical Center, Bronx, NY.

Background: Patients with renal dysfunction requiring hemodialysis are known to be at increased mortality and morbidity risk. Few studies have examined rapid response (RR) and cardiac arrest (CA) events in inpatient hemodialysis. The purpose of this study is to evaluate patient characteristics and predictive factors of RR and CA in inpatient hemodialysis units.

Methods: A retrospective review of all available RR/CA events in two separate hospitals over a 3-year period was performed. Charts were reviewed for abnormalities in vital signs or laboratory values during hemodialysis sessions and for a 24-hour period prior to RR/CA events.

Results: In total, 16 RR and 13 CAC events were recorded for 26 unique patients (average age 64±16 years). Of the 29 total RR/CA events, 9 events resulted in survival <24 hours (31%). Common medical comorbidities included hypertension (92%), diabetes (73%), chronic heart failure (50%), and coronary artery disease (50%). The most common inciting factors for RR/CA activation were altered mental status (72%), systolic blood pressure < 90 (45%), and respiratory distress (31%). Vital sign abnormalities identified prior to hemodialysis included need for supplemental oxygen (72%), respiratory rate > 20 (34%), and systolic blood pressure < 90 (3%). Vital sign abnormalities identified during hemodialysis included systolic blood pressure < 90 (34%) and heart rate < 40 (3%). Of those with labs available, the most common lab abnormalities included low hemoglobin and hematocrit (100%), elevated direct bilirubin (71%), elevated troponin-T (62.5%), and elevated PT (60%).

Conclusions: Our data suggest there are characteristics amongst patients undergoing inpatient hemodialysis that predispose them to RR/CA events. Simple, objective measures such as requirement for supplemental oxygen and abnormal vital signs may be important indicators that patients are at risk for serious adverse events. Knowledge of these factors can aid in decision-making regarding pursuit of dialysis and lead to the study of strategies to prevent patient harm.

SA-PO181

Monitoring of Protective Levels of Hepatitis B Antibody Titre in Pre-Dialysis and Dialysis Patients Ravindra Mukkunda, Zahra Jabir. *Renal Medicine, Doncaster and Bassetlaw NHS Foundation Trust, Doncaster, Yorkshire, United Kingdom.*

Background: Patients on dialysis are at risk of hepatitis B virus infection. Hence it is widely recommended to vaccinate chronic kidney disease (CKD) patients who might need renal replacement therapy. Antibody titre of >10iu/L is generally regarded as protective against Hepatitis B infection. The frequency of antibody level monitoring remains unclear. Once adequate antibody response achieved levels would wane with time. We monitored antibody levels in pre-dialysis and dialysis patients who achieved antibody response of >100iu/L, yearly for 2 years in order to explore the sustainability of the levels.

Methods: We selected 112 predialysis and dialysis patients who had Hepatitis B antibody response of >100 iu/L and has had antibody titres checked subsequently for 2 consecutive years. Results analysed retrospectively to see how long the protective antibody levels lasted.

Results: Total number of patients who had antibody response of >100 iu/L from 2007 to 2015 was 112 from our dataset at Doncaster Royal Infirmary Renal Unit. Of these 34% (38) of patients had hepatitis B antibody titres checked for 2 consecutive years. Patients maintaining antibody level of atleast >10iu/L for 2 years or more were 95%(36 out of the 38).

Conclusions: The outcome of this study confirms that protective antibody levels (>10iu/L) are maintained in 95% of those monitored for 2 years. This result reiterates the need for more robust evidence to inform nephrologists about the appropriate frequency of antibody monitoring in CKD patients.

SA-PO182

Improving Emergency Room (ER) to Dialysis Flow in a Busy Inner City ER Anjali Acharya,¹ Cherryll Moore,² Raymond McClinton,¹ Naheed Ansari,¹ Bonnie Carnes.² ¹Nephrology, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; ²Nephrology, Atlantic Dialysis, Queens, NY.

Background: Delays in access to hemodialysis during hospitalization are not uncommon and negatively impact on quality of patient care and lead to avoidable complications and unnecessary hospitalizations. Triple Aim is a sought after goal for health organizations to optimize health system performance. We hoped to target one of the three components which is to improve the experience of care.

Methods: The objective was to ensure initiation of dialysis for all non-emergent patients within four hours of ER triage. We analyzed retrospectively in a 8 week observation period, Electronic Medical Record (EMR) data on all hemodialysis patients >18 years of age presenting to the ER, with emphasis on time from triage to initiation of dialysis (TID). We also analyzed factors contributing to delays in dialysis initiation. Data were collected daily on each patient and tabulated weekly. We instituted two measures to address the obstacles.

These were-i) educating the ER staff about timeliness of informing the renal team and ii) the second was to institute a tracking system to systematically gather detailed data on patient transport metrics such a time to patient pick up from initial contact with the transport office.

Results: Baseline data revealed average TID from triage was 8 hours. Two major contributory factors identified were late notification by ER to renal team and delays in transport. By instituting measures targeting these, we were able to achieve being able to provide dialysis within 4 hours of triage in over 80% of our non-urgent hemodialysis patients.

Conclusions: We were able to improve the patient experience and care with simple measures. This has a positive impact on patient safety by minimizing late treatments and staff fatigue. Though Triple Aim is a goal at the population and health care delivery level, we believe processes can be implemented at a local level that align with the CMS goals of triple aim. In today's environment it is incumbent upon us to make efforts to innovate for better patient care and to minimize health care costs.

SA-PO183

Quality Improvement Project in Dialysis: Improving Access to Dialysis for Patients Presenting to the Emergency Room (ER) Nikulkumar Chaudhari,¹ Bonnie Carnes,² Cherryll Moore,² Roshni Upputalla,¹ Parikshit Thakur,¹ Naheed Ansari,¹ Anjali Acharya.¹ ¹Nephrology, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; ²Nephrology, Atlantic Dialysis, Queens, NY.

Background: Hemodialysis patients presenting to the emergency room are a vulnerable patient population. Majority of them have significant comorbid conditions. Delays in evaluation and institution of dialysis are common in busy emergency rooms. We undertook a project to improve quality of patient care as well as the patient experience with a goal to provide timely dialysis.

Methods: We analyzed baseline data from electronic medical record (EMR) pertaining to all hemodialysis patients presenting to the ER in a specified 8 week period. After brain storming within the team we identified a few factors that were seen as obstacles in providing timely dialysis. One of them was the time from patient triage to notification of the renal team. We instituted an educational program with the ER staff with focus on the timeliness of informing the renal team, establishing "triage to renal team notification time" of less than 30 minutes as a meaningful metric. Data was collected at pre and post intervention. The objective was to meet this goal >80% of the time over the 2 month intervention period.

Results: There was a positive impact on the triage to renal notification time. The percentage of timely notifications as defined, rose to >85% from a baseline of <25% and this effect was sustained over the 8 weeks. Most patient notifications happened within 10 minutes of triage.

Conclusions: A simple intervention on educating the ER staff made a significant impact on timely evaluation of dialysis patients presenting to the ER. There was an observable positive impact on patient experience. We view this as a simple first step in optimizing patient care and experience towards a seamless journey through the hospitalization. Simple innovative steps such as this could contribute to cost control by avoiding/minimizing dialysis treatments during off hours. In addition it could help mitigate staff fatigue and treatment errors thus improving patient safety.

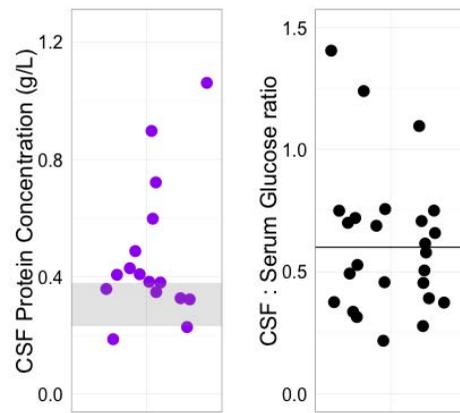
SA-PO184

Diagnostic Reference Values for Cerebrospinal Fluid May Not Be Useful in Haemodialysis Patients Suspected of Having Central Nervous System Infection Thomas Oates, Damien Ashby. Imperial NHS Trust, London, United Kingdom.

Background: Invasive investigations in haemodialysis (HD) patients can be associated with complications due to bleeding, and standard diagnostic tests, such as pleural fluid biochemistry, have been shown to be of limited value in this patient group. As a result, we examined the utility of cerebrospinal fluid (CSF) analysis in HD patients suspected of central nervous system (CNS) infection.

Methods: We used electronic records to retrospectively examine laboratory data from HD patients who had CSF analysis in a 5 year period. All patients were initially suspected of having a CNS infection but relevant culture and polymerase chain reaction tests ultimately proved negative for bacterial, mycobacterial, fungal or viral infections in all cases.

Results: 30 CSF samples from 29 patients were identified in the study period. CSF protein concentration was available for 16 samples (median 0.40g/L, range 0.19-1.06g/L, corrected for number of red cells in sample) and paired CSF and plasma glucose concentrations, allowing calculation of CSF:serum glucose ratio, for 25 samples (median ratio 0.58, range 0.21-1.40). Using the accepted normal CSF protein concentration of 0.23 to 0.38 g/L (see Figure shaded region), 8 out of 16 samples showed an elevated protein concentration suggesting CNS infection. Additionally, 13 out of 25 samples had a CSF:serum glucose ratio of less than the normal value of 0.6 (see Figure horizontal line) which is also suggestive of CNS infection.



Conclusions: CSF biochemistry is frequently used in the diagnosis of CNS infection. Our preliminary results suggest CSF protein and glucose concentrations should be interpreted with caution in HD patients and may not add diagnostic information in suspected CNS infection. We are currently investigating the hypothesis that CSF biochemistry may be influenced by duration of chronic kidney disease and HD vintage.

Funding: Clinical Revenue Support

SA-PO185

Continuous Renal Replacement Therapy (CRRT) and Hypoglycemia: A Retrospective Study on Patients Undergoing CRRT and Development of Hypoglycemia in Diabetic and Non-Diabetic Individuals Mamtha Balla,¹ Adam Lyons,¹ Mary C. Naglak,¹ Doron Schneider,¹ Robert A. Sirota.² ¹Internal Medicine, Abington Jefferson Health, WillowGrove, PA; ²HTN Nephrology Associates, Abington Jefferson Health, WillowGrove, PA.

Background: Hypoglycemia is a little known complication of CRRT. There are no studies available to evaluate the prevalence or intensity of hypoglycemia during CRRT. This study attempts to determine the frequency, timing, and severity of hypoglycemia as a complication of CRRT in diabetic and non-diabetic patients in the intensive care unit.

Methods: This was a retrospective observational study to assess the effect of CRRT on plasma glucose in diabetic and non-diabetic individuals who were admitted to Abington Jefferson Health. A chart review was used to complete a detailed data collection form for patients who underwent CRRT for several diagnosis (sepsis, medication overdose, acute renal failure) in 2013 and 2014 who met the selection criteria. Hypoglycemia is defined as Blood sugar less than 70mg/dl. Dialysate contained 100mg/dl glucose.

Results: After reviewing the charts for 218 CRRT events in 119 patients admitted to Abington Jefferson Health, 100 patients were studied based on selection criteria. The mean age of the study population was 66.3 + 15.3 years. Thirty-six of the 100 patients studied had hypoglycemia during CRRT. The number of episodes was as follows: 14/36 (38.9%) had one episode, 7/36 (19.4%) had two, 7/36 (19.4%) had three and 5/36 (13.9%) had five episodes (mean number of episodes was 2.7±1.9). Hypoglycemia occurred on average 9.9±6.1 hours from start of CRRT. Patients who had hypoglycemia during CRRT were more likely to have it again after CRRT (53%; 19/36) (p<0.0005). Of the 36 patients with hypoglycemia, 78% (28/36) had sepsis vs. 22% (8/36) who did not have sepsis but had hypoglycemia (p>0.05). No association was found between development of hypoglycemia and history of diabetes and CKD.

Conclusions: Our study showed that hypoglycemia is a frequent complication during CRRT. In order to prevent hypoglycemia from being under-recognized protocols including frequent blood glucose monitoring during CRRT should be in place.

SA-PO186

The Safety of Intravenous Hydration for the Prevention of Contrast Induced Nephropathy Yvonne R.P. de Waal,¹ Corinne E.A. Balemans,¹ Marc A.G.J. Ten Dam,² Louis J.M. Reichert,³ Jack F. Wetzels.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Nephrology, Canisius Wilhelmina Hospital, Nijmegen, Netherlands; ³Nephrology, Rijnstate Hospital, Arnhem, Netherlands.

Background: Contrast-induced nephropathy (CIN) is associated with marked morbidity and mortality. To prevent CIN, current guidelines advise intravenous hydration in high risk patients. Thus far, the possible side effects of hydration have received little attention. We evaluated the incidence of (serious) adverse events ((S)AEs) after intravenous hydration.

Methods: In a retrospective study we analyzed the incidence of (S)AEs after intravenous hydration in two Dutch hospitals. In one hospital (Rijnstate Hospital Arnhem) we evaluated all AEs related to hydration. In the other hospital (CWZ Nijmegen) the analysis was limited to SAEs, i.e. those necessitating prolonged hospital stay. Patient and outcome characteristics were retrieved from the hospital records.

Results: In the Rijnstate Hospital Arnhem we evaluated 233 records of patients hydrated in the period from February till July 2013. AEs occurred in 18 patients (8%). The most common AE was overhydration, which occurred in 11 patients (5%) and necessitated

prolonged hospitalisation in 4 (2%). Admission to the coronary care unit was needed in one patient. Almost all patients with overhydration (91%) had pre-existent cardiac disease and used diuretics. Infusion related AEs also occurred, like extravasation and phlebitis, in one case leading to *S. Aureus* bacteremia. In the CWZ Nijmegen we evaluated 257 medical records of patients hydrated from May 2013 till January 2014. Prolonged hospitalisation due to overhydration was necessary in 10 patients (4%).

Conclusions: Our study demonstrates that overhydration is a common adverse event after intravenous hydration and necessitates prolonged hospital stay in 2-4% of patients. These data provide arguments against routine hydration in patients with moderate increased risk of CIN. Patients with pre-existent cardiac disease are most prone to overhydration. However, these patients are also at highest risk for the development of CIN. Risk and benefits must be weighed when choosing strategies to prevent CIN.

SA-PO187

Cystatin C in Predicting Cardiorenal Syndrome Type 1 and Mortality in Patients with Acutely Decompensated Heart Failure with Preserved Renal Function Carlos Federico Varela,¹ Ivan Constantin,² Gustavo Cristian Greloni,¹ Griselda Bratti,¹ German Barrera Hugalde,¹ Cesar Belziti,² Rodolfo Pizarro,² Guillermo Javier Rosa diez,¹ ¹Nephrology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; ²Cardiology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background: Cardiorenal Syndrome type 1 (CRS 1) is defined as a worsening renal function that complicates acutely decompensated heart failure (ADHF). These patients experience higher mortality and morbidity. Serum creatinine (SC) is slow to reflect changes in kidney function. Cystatin C (Cys C) has emerged as a novel biomarker with a stronger correlation with cardiovascular disease than SC. The aim of our study was to evaluate Cys C in predicting CRS 1 and outcomes in patients admitted with ADHF and preserved renal function.

Methods: We conducted an observational and prospective study. We included patients above 18-years old with ADHF with preserved renal function defined as a SC below 1.3 mg/dL. We excluded patients with heart valvular disease and acute coronary syndrome. Cys C blood samples were collected on admission. We defined CRS 1 as a rise in creatinine by 0.3 mg/dL or more during five days.

Results: 166 patients aging 85 median (IQR 77-89) years old were enrolled. The incidence of CRS 1 was 29.7%, with an in-hospital mortality of 3.1%, and a total mortality (TM) of 24.4%. The median follow-up was 193 days. Cys C was significantly higher in patients with CRS 1 compared to those without (1.72±0.58 vs 1.51±0.41, p=0.03) and predict TM but did not predict in-hospital mortality (1.69± vs 1.57±0.48, p=0.58) or readmission (1.47±0.4 vs 1.6±0.5, p=0.58). In the multivariable analysis Cys C was an independent predictor of mortality (OR 3.31, IC1.38-7.93) while SC at admission was not (OR 0.48, IC 0.05-3.48). The area under the receiver-operating characteristic curve of Cys C for CRS 1 was 0.60 and for TM was 0.65. The best cutoff value was 1.6 mg/dL for both end points. It had a sensitivity and specificity of 61.2% and 60.3% for CRS 1, and 61.5% and 62% for TM, respectively.

Conclusions: Above a cut-off value of 1.6 mg/dL, Cys C predicts CRS 1 and mortality in patients admitted with ADHF with preserved renal function.

SA-PO188

Is Cystatin C a Better Biomarker of AKI in ICU to Compare NGAL? İtir Yegenaga, Fatih Kamis. Internal Medicine, Kocaeli Univ Medical School, Kocaeli, Izmit, Turkey.

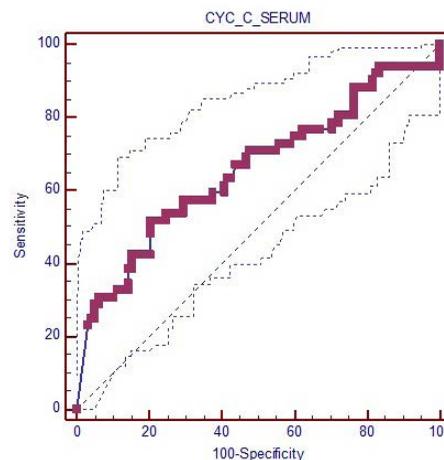
Background: Serum creatinine levels can be affected with many variable factors. We concluded that better bio-marker is needed to recognize AKI as early as possible. We studied Cystatin C (CysC) and Neutrophil Gelatinase Associated Lipocalin (NGAL) in ICU patients to determine which is more predictable.

Methods: Hundred and eighty three (85 male; mean age: 65) critically ill patient with no previous chronic renal failure history were included to this study. Clinical, laboratory evaluations were noted and blood was taken in 48 hours for CysC and NGAL and followed for 7 days, if they meet the RIFLE criteria.

Results: CysC and NGAL values for every stages RIFLE and serum CysC value were significant only for RIFLE-L stages (p=0.25) but not urinary CysC. NGAL in serum and also in urine were significantly different in RIFLE-I,F. Biomarkers were compared when fulfilled the RIFLE criteria in first 48 hour and following 3-7 days to non-AKI values.

	S-CysC mean± SD	U-CycC	S-NGAL Median(25-75)	U-NGAL Median(25-75)
(1) No-AKI N:122	30.42±/ 10.17*	7.38±/2.58	75.69(53.76-91.58)*	17.98(8.72-39.25)*
(2)AKI in 48 h N:14	32.23 ±/ 9.70	6.78±/1.65	95.28(67.98-110.90)	21.74(19.99-50.52)*
(3) AKI in 3-7 days N:15	31.40±/ 13.45	7.74±/2.42	123.68(90.89-166.31)	12.32(24.59-96.63)*
(4)AKI in 7days N:32	40.75 ±/13.38*	7.74±/1.82	136.38(117.96-220.54)*	66.06(59.39-75.17)*
	(1-4) P<0.001	p=0.714	(1-3) p=0.028 (1-4) p<0.001	(1-3) p=0.23 (1-4) p<0.001 (2-4) p=0.040

While sNGAL and u NGAL were significantly different between these two groups. Serum CysC level was related to mortality (figure 1)(AUC-ROC 0.68 CI; 0.575-0.733).



Conclusions: In our cohort NGAL obtained in 48 hours is more predictable biomarker than CysC for early AKI diagnosis following 7 days. But CysC levels were fairly predictive for mortality.

SA-PO189

The Effect of Point of Care (POC) Creatinine/eGFR Measurement on the Incidence of Contrast-Induced Acute Kidney Injury (CI-AKI) following Primary Percutaneous Coronary Intervention (PPCI) for the Treatment of ST Elevation Myocardial Infarction (STEMI) Firas Al-Janabi, Shah MohdNazri, John R. Davies, Thomas Roger Keeble, Ellie Gudde. Interventional Cardiology, Essex Cardiothoracic Centre, Basildon, Essex, United Kingdom.

Background: Contrast-induced acute kidney injury (CI-AKI) is a predictor of mortality, morbidity and length of hospital stay. During STEMI treatment with primary percutaneous coronary intervention (PPCI) there are a number of predictors of AKI including existing renal dysfunction (eGFR < 60) and contrast volume used.

Methods: A retrospective audit over 6 months at the Essex Cardiothoracic Centre identified 348 patients who had presented with STEMI and had PPCI. These patients formed the standard care control group. Prospectively 131 consecutive patients presenting with STEMI and under-going PPCI had a point of care creatinine measurement (STATSENSOR, Nova Biomedical). A comparison in rates of AKI was made between the two groups.

Results: In the standard care group, 9.7% of patients with normal renal function and 26.6% of patients with impaired renal function developed AKI. When creatinine was measured pre-PPCI, 8% of patients with normal renal function and 16.1% of patients with renal impairment developed AKI, a 39.5% reduction in AKI in those with renal dysfunction in the POC creatinine group. The average contrast volume in the standard care group was 159 ml, compared to 117.5ml when renal function was found to be impaired (eGFR < 60) pre-PPCI. 186ml was used on average in the POC group when creatinine was found to be normal.

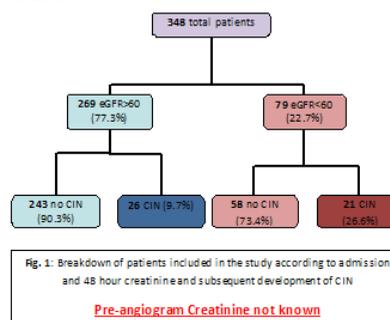


Fig. 1: Breakdown of patients included in the study according to admission and 48 hour creatinine and subsequent development of CIN

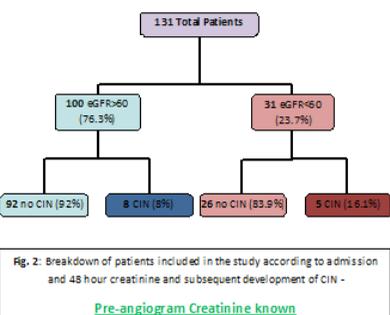


Fig. 2: Breakdown of patients included in the study according to admission and 48 hour creatinine and subsequent development of CIN -

Conclusions: Measuring the POC creatinine of 131 patients presenting with STEMI and undergoing PPCI reduces the rates of AKI by 39.5% in those with renal dysfunction. This appears to be mediated in part by a reduction in contrast volume in those patients identified with renal dysfunction (117.5ml) compared to normal renal function (186 ml).

Funding: Pharmaceutical Company Support - Nova Biomedical

SA-PO190

Serum Creatinine Variability Predicts Progression to CKD4
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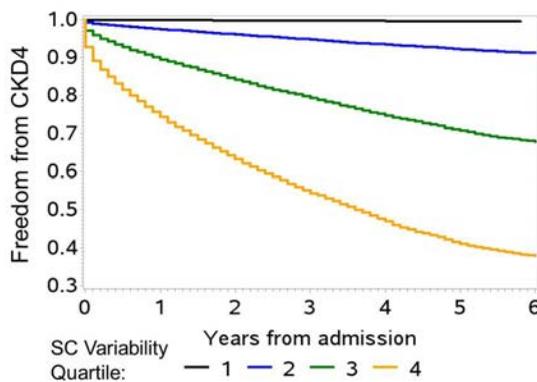
Background: Pre-dialysis patients have high serum creatinine (SC) variability. SC variability is associated with high death rates. We examined the association between SC variability and CKD progression in a large cohort of US veterans with a wide range of baseline eGFR.

Methods: VA patients admitted 10/1999 - 12/2005 with at least 4 months with SC and initial eGFR>30 ml/min/1.73 m² (using CKD-EPI) were selected. Autoregression-based slope was computed for each patient using monthly peak SC. SC variability was root mean-square residual of peak SC readings from the regression line. CKD4-date was the first date when eGFR permanently fell below 30 ml/min/1.73 m². Logistic regression was used to predict CKD4 using: initial eGFR, SC variability, SC slope, age, race, sex, months with SC readings, and comorbidities (DM, CAD, PNE, MI, angina, AKI, COPD, CHF). Kaplan-Meier (KM) analysis was used to examine time from first admission to entry into CKD4, stratified by SC variability quartile and baseline eGFR, and Cox regression was used to adjust survival estimates for the covariates above.

Results: Of 342,086 patients, 36,108 (10.6%) reached CKD4. The logistic model had strong prediction accuracy (c=.94) with sensitivity and specificity both .86. SC variability was strongly associated with entry into CKD4 (adjusted OR 3.79 [3.67-3.91], p<.001). Time to CKD4 differed by level of SC variability in KM (p<.0001; Figure) and Cox (HR 1.34 [1.31-1.36], p<.0001).

Conclusions: SC variability is strongly independently associated with rate of decline in renal function, at all baseline eGFR levels, after accounting for covariates, and is an important risk factor for entry into CKD4.

KM Estimated freedom from CKD4 by level of SC variability



Funding: Veterans Administration Support

SA-PO191

Assessment of Methods Used to Substitute for Missing Preadmission Creatinine Values in the Diagnosis and Staging of Acute Kidney Injury
 Amelie Bernier-Jean, Anatolie Duca, Francois Madore, Remi Goupil, Stephan Troyanov, Josee Bouchard. *Nephrology, Hopital du Sacre-Coeur de Montreal, Canada.*

Background: Missing preadmission serum creatinine values (SCr) are a common obstacle to the diagnosis and staging of acute kidney injury (AKI). As a workaround, the KDIGO guidelines suggest using a baseline SCr computed from the MDRD formula assuming a baseline estimated glomerular filtration rate (eGFR) of 75 ml/min per 1.73m². We hypothesized that surrogates for preadmission SCr will misclassify AKI incidence and severity when compared to a known preadmission SCr.

Methods: Over a 12-month period, we performed a retrospective single-center study of critically ill patients with known preadmission SCr to identify the most accurate method to estimate baseline SCr for AKI diagnosis and staging (KDIGO criteria). We assessed three surrogate methods: 1) the first hospital admission SCr, 2) the minimal SCr after ICU admission and 3) SCr computed for a eGFR of 75 ml/min per 1.73 m² using MDRD.

Results: Of 1001 randomly selected patients, a preadmission SCr was available for 498 and 14 were excluded for requiring acute renal replacement therapy. Median age was 67 (IQR 58-76), 60% were male and 98% were Caucasian or Asian. The median time between SCr measurement and admission was 116 (IQR 78-179) days. AKI incidence according to preadmission SCr was 24.8%. We reported in table 1 the AKI incidence, sensitivity, specificity and kappa values for each surrogate method.

	AKI incidence (%)	SEN	SPE	Kappa
N=484				
Known baseline creatinine	120 (24.8)	-	-	-
Hospital admission creatinine	93 (19.2)	75.0	99.2	0.80
Minimal creatinine	227 (46.9)	99.2	70.3	0.54
MDRD GFR 75ml/min/m2	131 (27.1)	91.7	94.2	0.83

For AKI staging, we found the following kappa values: 0.75 using the first SCr upon admission, 0.43 using the minimal SCr, and 0.66 using the computed MDRD eGFR of 75ml/min per 1.73m².

Conclusions: In our cohort, the MDRD computed SCr for a eGFR of 75 ml/min per 1.73m² was the best surrogate method for diagnosing AKI. Using the minimal SCr significantly overestimated the incidence of AKI. Concerning AKI staging, the first hospital admission SCr was the most accurate method.

SA-PO192

Fluid Balance and Oliguria in Early AKI Diagnosis After Liver Transplant
 Camila Lima,¹ Luciana Haddad,² Luiz M. Malbouisson,³ Luiz Augusto Carneiro D'Albuquerque,² Etienne Macedo.¹ ¹Nephrology, Univ of Sao Paulo, Brazil; ²Gastrointestinal Surgery, Univ of Sao Paulo, Brazil; ³Anesthesiology, Univ of Sao Paulo, Brazil.

Background: AKI is a frequent complication of liver transplant (LT), associated with increased morbidity and mortality. Early diagnosis can translate into secondary preventive measures and improve outcomes. We hypothesized that adjusting Scr for positive fluid balance (FB) and applying urine output(UO) criterion would improve timing of AKI diagnosis. In addition, we investigate whereas sequential assessment of urinary biochemistry after LT can improve prediction of early post-operative AKI development.

Methods: In a prospective cohort study, we recorded UO, FB and labs of patients undergoing LT. We assessed urine and blood biochemistry perioperative (before induction of anesthesia, after portal reperfusion, 6, 18, 24 hours after surgery). AKI diagnosis was based on UO and the sCr KDIGO criterion before and after correcting scr for FB (Scr adjusted), using the formula: ((weight*0.6)+(FB)/(weight*0.6)).

Results: Fifty-five patients >18 years undergoing LT from Jun13 to Oct14 were included in the analysis. twenty-seven percent (15) of patients developed AKI based on Scr criterion within 48h of surgery (early AKI). By adjusting Scr for fluid balance 38%(21) patients were classified as early AKI. Applying the UO criterion, 43patients were classified exclusively by this criterion as early AKI. All patient showed a decline in FeNa and the FeU after portal reperfusion. Patients developing early AKI had a higher decline and maintained lower levels for 24h. FeUrea values were significantly different 6 hours after surgery in early AKI patients. Patients with early AKI based on both criteria or exclusively by UO had a higher mortality and longer ICU and hospital stay than non-AKI patients.

Conclusions: Applying UO criteria and adjusting Scr for FB can help in the early identification of patients developing AKI after liver transplant. Tubular function assessment could be utilized along with biomarkers of kidney injury to identify patients with increased risk of developing AKI. Standardized approach for early AKI diagnosis in high-risk patients could improve outcomes.

Funding: Other U.S. Government Support

SA-PO193

Renal Angina Index a Practical Tool to Identify Patients at Increased Risk of Acute Kidney Injury
 Rolando Claire-Del Granado,¹ Andrea Pero,¹ Josee Bouchard,² Ravindra L. Mehta.³ ¹IIBISMED, Univ Mayor de San Simon, School of Medicine, Bolivia; ²Hospital du Sacre-Coer de Montreal, Canada; ³Univ of California San Diego Medical Center.

Background: Reliable prediction of acute kidney injury (AKI) has the potential to optimize treatment. Recently Goldstein SL et al. proposed an empiric clinical model of renal angina using patient demographic factors and early signs of injury to identify critically-ill children who would be at higher risk of AKI. We test the hypotheses that in a cohort of adult critically-ill patients, a modified renal angina index (RAI) will identify patients at high risk of developing AKI, and could be related to in-hospital mortality.

Methods: We included 124 consecutive patients admitted to our medical ICU. We measured serum creatinine (sCr) every 24 h for 7 consecutive days after ICU admission. RAI was calculated at ICU admission (day 1) and 24 h after (day 2) using the following formula: **Risk level** (vasopressors and invasive mechanical ventilation = 5; diabetes mellitus = 3; and sepsis = 1) X **Injury level** (decreases in eGFR: no change=1, 0-24.9%=2, 25-49.9%=4, and ≥50%=8). The composite range of the RAI is therefore: 1, 2, 3, 4, 5, 6, 8, 10, 12, 20, 24, and 40. We analyzed the value of a RAI score ≥8 to predict subsequent AKI (after 48 h, day 3) and survival.

Results: We identified 50(40.3%) patients with AKI (KDIGO guidelines sCr criteria), and 74(59.7%) patients who did not develop AKI. Patients with a RAI ≥8 were at higher risk of developing AKI within 7 days of follow-up (RR 1.64 95% CI 1.31-2.05; p<0.0001). A RAI ≥8 at ICU admission (day 1) and 24 h after admission (day 2) was able to identify individuals who developed AKI (day 3-7) with an AUC of 0.861 (95% CI 0.777-0.945); p<0.0001 and an AUC of 0.891 (95% CI 0.815-0.966); p<0.0001, respectively. No difference was found in terms of 28 day in-hospital mortality in patients with a RAI ≥8 vs a RAI ≤8.

Conclusions: The RAI provides a clinically feasible methodology to identify critically-ill patients at high risk of developing AKI before a rise in sCr occurs. This tool would permit the early identification of AKI to initiate preventive and treatment strategies minimizing extension of kidney injury.

SA-PO194

The Renal Angina Index Identifies Patients at High-Risk of Acute Kidney Injury – Analysis from AWARE: A Prospective Multinational Study of AKI in Critically Ill Children Rajit K. Basu,^{1,2} Ahmad Kaddourah,^{1,2} Stuart Goldstein,^{1,2} ¹*Pediatrics, Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH;* ²*On Behalf of the AWARE Study Investigators, Multinational Pediatric ICU.*

Background: We conducted a global, prospective observational study of critically ill children to study the epidemiology of pediatric acute kidney injury (AKI). We analyzed the discrimination of the renal angina index for prediction of AKI and patient outcomes.

Methods: Data from 32 centers (5 continents, data collection for 3 consecutive months in 2014) from children (aged 3 months to 25 years) admitted to a pediatric intensive care unit were analyzed. The renal angina index (RAI) was calculated on the day of admission (Day 0) as previously described. A cut-off of > 8 on Day 0 was used to determine fulfillment or absence of renal angina (RA+ vs. RA-). The primary outcome was the presence of severe AKI on Day 3, defined by change in serum creatinine from baseline using KDIGO stage 2-3 criteria (Day 3 AKI). Other patient outcomes were assessed at 28 days.

Results: 9.6% (501/5231) of children were RA+ on Day 0. The area-under-curve receiver operating characteristic of the Day 0 RAI for Day 3-AKI was 0.797 (95% confidence interval 0.759-0.836). RA+ was associated with a higher net fluid balance on Day 3 than RA- (p<0.001). Compared to RA-, Day 0 RA+ was associated with prolonged duration of mechanical ventilation, longer length of stay, increased use of extracorporeal therapies, and higher incidence of mortality.

Table 1. Outcome of Patients in AWARE Stratified by Day 0 Renal Angina

Outcome	RA (-)	RA (+)	p value
Day 3 AKI (%)	4.8	33.5	< 0.001, $\chi^2 = 156.4$
MV duration (days)	7.4 ± 7.0	8.5 ± 7.3	0.04
Length of Stay (days)*	7.2 ± 7.1	8.9 ± 6.9	<0.001
RRT use (%)	1.4	11.6	< 0.001, $\chi^2 = 100.2$
ECMO use (%)	0.8	2.8	0.002, $\chi^2 = 9.3$
Mortality (%)	3.6	11.0	< 0.001, $\chi^2 = 33.3$

*= patients who died within 48 hours were excluded
RRT = Renal Replacement Therapy
ECMO = Extracorporeal Renal Replacement Therapy

Conclusions: In AWARE, the largest prospective multi-center epidemiologic assessment of AKI in critically ill children, we demonstrate the ability of the renal angina index to identify patients at high risk of AKI, three days in advance. Fulfillment of renal angina early in the ICU course is associated with poor patient outcome.

SA-PO195

Phase Angle and Extracellular Hypervolemia, as a Prognostic Markers in Acute Kidney Injury Francisco Javier Lavilla, Maria Jose Molina Higuera, Diana Lopez Espinosa, Pelayo Moiron Fdez-Felechosa, Nuria Garcia-Fernandez, Paloma L. Martin Moreno, Pedro Errasti. *Nephrology, Clinica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: The bioelectrical impedance analysis (BIA) is a noninvasive and painless technique and easy to perform, which is used for determining body composition. Can offer information about membrane cell integrity, volemia and clinical status. We evaluate use of BIA and two bioelectrical parameters (Phase angle –PA-, and extracellular/intracellular water ratio –ECW/ICW-) as a prognostic markers in acute kidney injury (AKI).

Methods: We include a cohort of 83 patients (mean age 64 years SD 1.8, and male 72.3 %) with AKI and BIA. We evaluate clinical prognostic index (individual severity index –ISI-), inflammatory and protein metabolism analytical parameters (C-reactive protein, albumin, prealbumin) and chronic health index (Karnofsky –K-).

Results: Exitus 14.5%. PA and ECW/ICW was associated with prognosis in AKI.

	ISI	CRP	Alb	PreAlb	K
PA	r=-0.228, p=0.038	r=-0.250, p=0.027	r=-0.369, p=0.006	NS	r=-0.516, p<0.001
ECW/ICW	r=-0.271, p=0.001	r=-0.248, p=0.004	NS	r=-0.410, p=0.008	r=-0.253, p=0.003

PA: PHASE ANGLE ECW/ICW: EXTRACELLULAR/INTRACELLULAR WATER RATIO. ISI: INDIVIDUAL SEVERITY INDEX. CRP: C-REACTIVE PROTEIN. Alb: ALBUMIN. PreAlb: PREALBUMIN. K: KARNOFSKY.

PA was associated with protective risk mortality OR 0.425, p=0.007, CI 95% 0.229-0.780 and ECW/ICW with risk mortality OR 2.247 CI 95% 1.266-3.98. The AUC with PA was 0.770 (p=0.003, CI 95% 0.652-0.888) and with ECW/ICW was 0.778 (p=0.001, CI 95% 0.678- 0.879).

Conclusions: BIA is a useful technique to evaluate AKI. Lower PA and higher ECW/ICW are associated with worse prognosis in AKI. There are relation with inflammatory and protein metabolism status, and with health clinical status prior to the event.

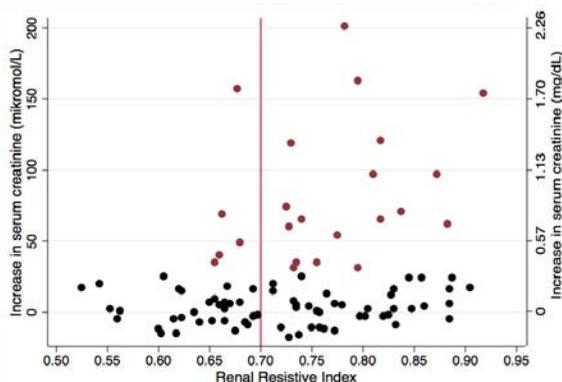
SA-PO196

Preoperative Renal Resistive Index Predicts the Risk of Acute Kidney Injury in Patients Undergoing Cardiac Surgery Daniel P. Olsson Hertzberg,¹ Ulrik Sartipy,² Martin Holzmann.¹ ¹*Dept of Medicine, Karolinska Inst, Stockholm, Sweden;* ²*Dept of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska Univ Hospital, Stockholm, Sweden;* ³*Dept of Molecular Medicine and Surgery, Karolinska Inst, Stockholm, Sweden.*

Background: Previous studies have indicated that Renal Resistive Index (RRI), an ultrasound-based measurement, can predict AKI in a variety of settings. To our knowledge, there are no studies investigating the predictive value of preoperative RRI and the risk of AKI in cardiac surgery patients. The aim of this study was to investigate whether an elevated preoperative RRI predicts AKI in a general cardiac surgery population.

Methods: Patients undergoing elective cardiac surgery were included prospectively between September 21, 2014 and April 22, 2015 at the Karolinska University Hospital. RRI was measured the day before surgery. An elevated RRI was defined as >0.7. The outcome AKI was defined as an absolute increase in post- compared to preoperative serum creatinine by 0.3 mg/dL (>26µmol/L) or a relative increase by >50%. The odds ratio for AKI was calculated by logistic regression in patients with a RRI >0.7 versus those with a RRI ≤ 0.7.

Results: 98 patients were included. In patients with a RRI ≤0.7, 6 (15%) patients developed AKI, compared to 19 (33%) in patients with a RRI >0.7. The mean increase in postoperative serum increase in patients with RRI ≤0.7 was 0.12 mg/dL (11 µmol/L) compared to 0.34 mg/dL (30 µmol/L) in those with RRI >0.7 (P=0.03). The odds ratio for developing AKI in patients with a RRI >0.7 compared to those with a RRI ≤0.7 was 2.76 (0.99-7.71).



Conclusions: We found that patients with an elevated RRI before cardiac surgery had an increased risk of developing AKI postoperatively. RRI might be a valuable tool for identifying patients with an increased risk of developing AKI connected to cardiac surgery.

SA-PO197

Development of a Postoperative Risk Stratification Tool via Bayesian Model Averaging for Acute Kidney Injury After Cardiac Surgery Allison Meisner,¹ Kathleen F. Kerr,¹ Heather Thiessen Philbrook,² Francis Perry Wilson,³ Amit X. Garg,² Michael Shlipak,⁴ Peter Kavsak,⁵ Richard P. Whitlock,⁵ Steven G. Coca,⁶ Chirag R. Parikh.³ ¹*Univ of Washington, Seattle, WA;* ²*Western Univ, ON, Canada;* ³*Yale School of Medicine, New Haven, CT;* ⁴*UCSF;* ⁵*McMaster Univ, ON, Canada;* ⁶*Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Acute kidney injury (AKI) is a frequent complication of cardiac surgery. We sought predictive combinations of biomarkers measured 0-6 hours after surgery, potentially in combination with cardiopulmonary bypass (CPB) time (to account for the degree of insult).

Methods: The primary endpoint was sustained mild AKI, defined as an increase of 50% or more in serum creatinine over preoperative levels lasting at least two days during the hospital stay. Severe AKI (secondary endpoint) was defined as a serum creatinine increase of 100% or more or dialysis during hospitalization. Data were from a cohort of 1219 adults undergoing cardiac surgery at 6 medical centers; among these, 117 developed sustained mild AKI and 60 developed severe AKI. We considered CPB time and 22 biomarkers as candidate predictors. We used Bayesian Model Averaging (BMA) methods to develop center-adjusted combinations for sustained mild AKI by (1) maximizing the posterior model probability and (2) retaining predictors with posterior variable probabilities above 0.5.

Results: The maximum posterior model probability combination included plasma NT-proBNP, plasma h-FABP and change in serum creatinine; the median probability combination additionally included plasma IL-6. The center-adjusted, optimism-corrected AUCs for these combinations were 0.80 (95% CI: 0.78, 0.88) and 0.81 (0.77, 0.88), respectively, for predicting sustained mild AKI, and were 0.81 (0.77, 0.90) and 0.83 (0.76, 0.90), respectively, for predicting severe AKI. For these data, the BMA methods yielded combinations with predictive capacity comparable to that achieved by standard frequentist methods but with smaller models.

Conclusions: Pending external validation, the identified combinations could be used to identify individuals at high risk of AKI immediately after cardiac surgery and could facilitate clinical trials of renoprotective agents.

Funding: Other NIH Support - RO1HL085757

SA-PO198

Low Pre-Operative Serum Bicarbonate Levels Predict Acute Kidney Injury After Cardiac Surgery Jong Hyun Jhee, Kyoung Sook Park, Hyung Jung Oh, Seung Hyeok Han, Tae-Hyun Yoo, Jung Tak Park. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Low serum bicarbonate levels are known to be risk factors for renal function deterioration in chronic kidney injury patients. However, it is not well known whether preoperative low serum bicarbonate levels are associated with the development of acute kidney injury (AKI) in patients who undergo cardiac surgery. Therefore, clinical implications of preoperative serum bicarbonate levels on AKI occurrence after cardiac surgery were evaluated.

Methods: The patients who underwent coronary artery bypass or valve surgery at Yonsei University Health System from January 2013 to December 2014 were enrolled. The patients were categorized into three groups according to pre-operative serum bicarbonate levels (group 1 <23 mEq/L, group 2 23-24 mEq/L, group 3 >24 mEq/L). Multivariate logistic regression analysis was performed to determine the effect of pre-operative serum bicarbonate levels on development of AKI at 48 hours after cardiac surgery.

Results: Among 452 patients, 228 patients (26.1%) developed AKI at 48 hours after cardiac surgery. Incidence of AKI was higher in group 1 (34.6%) than group 2 (26.3%) and group 3 (39.0%) (P <0.001). The duration of post-operative intensive care unit (ICU) stay was longer in AKI patients (AKI vs. non-AKI, 6.2 vs. 2.7 days, P<0.001). In addition, post-operative ICU stay was longer in the low pre-operative serum bicarbonate level groups [group 1 (4.4 days), group 2 (3.6 days), group 3 (3.3 days), P<0.001]. In multivariate logistic regression analysis, low pre-operative serum bicarbonate levels were significantly associated with post-operative AKI development even after adjusting for age, sex, hypertension, diabetes mellitus, operation type, hemoglobin, and glomerular filtration rate (group 3 as reference, odds ratio=2.36, 95% confidence interval=1.57-3.54, P<0.001).

Conclusions: Low serum bicarbonate levels were associated with higher incidence of AKI and prolonged ICU stay. Correction of low serum bicarbonate levels before cardiac surgery may reduce the risk of AKI development.

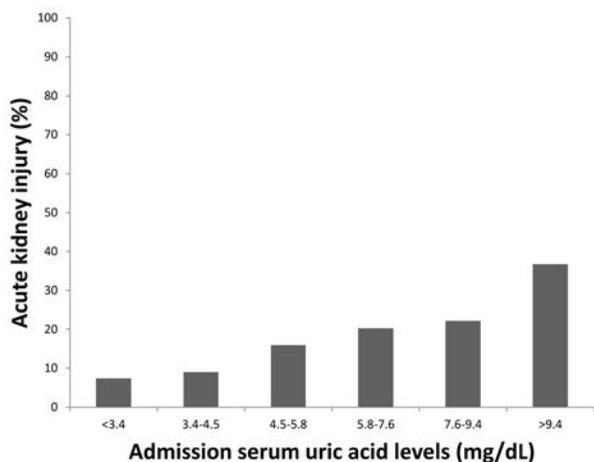
SA-PO199

Admission Hyperuricemia Increases the Risk of Acute Kidney Injury in Hospitalized Patients Wisit Cheungpasitporn,¹ Charat Thongprayoon,² Stephen B. Erickson.¹ ¹*Nephrology and Hypertension, Mayo Clinic, Rochester, MN;* ²*Internal Medicine, Bassett Medical Center, Cooperstown, NY.*

Background: The association between elevated admission serum uric acid and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of developing AKI in all hospitalized patients with various admission serum uric acid (SUA) levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission SUA available from January 2011 through December 2013 were analyzed in this study. Admission SUA was categorized based on its distribution into six groups (less than 3.4, 3.4 to 4.5, 4.5 to 5.8, 5.8 to 7.6, 7.6 to 9.4, and greater than 9.4 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI of various admission SUA levels using the most common SUA level reference range (5.8 to 7.6 mg/dL) as the reference group.

Results: Of 1,435 patients enrolled, AKI occurred in 263 patients (18%). The incidence of AKI and need for dialysis was increased in patients with higher admission SUA levels. After adjusting for potential confounders, SUA greater than 9.4 mg/dL was associated with an increased risk of developing AKI with odds ratios of 1.79 (95% CI 1.13-2.82). Conversely, admission SUA of less than 3.4 mg/dL and 3.4 to 4.5 mg/dL were associated with decreased risk of developing AKI with odds ratios of 0.38 (95% CI 0.17-0.75) and of 0.50 (95% CI 0.28-0.87) respectively.



Conclusions: Elevated admission SUA was associated with an increased risk for in-hospital AKI.

SA-PO200

Hypoalbuminemia Is a Strong Risk Factor for Acute Kidney Injury Progression in Elderly Patients in Intensive Care Unit Yu Kurata,¹ Keita Hirano,² Fumio Omata,³ Yasuhiro Komatsu.² ¹*Div of Nephrology, Mitsui Memorial Hospital, Chiyoda-ku, Tokyo, Japan;* ²*Div of Nephrology, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan;* ³*Center for Clinical Epidemiology, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan.*

Background: Population aging is a global issue; especially, Japan is experiencing rapid aging, at a faster speed than any other developed country, and those aged 65 or older comprised 25.9% of Japan's population as of September 2014. Previous studies showed elderly patients are at high risk for developing acute kidney injury (AKI). AKI is also a common clinical syndrome in the ICU setting, but its clinical presentation varies from mild to severe. Predicting whether AKI progress or not is difficult but can guide clinical decision making. The aim of the present study is to elucidate risk factors of AKI progression among elderly patients in ICU.

Methods: A retrospective study of patients age 65 and older developed AKI during ICU stay between January 2004 and September 2013. AKI was defined as increase in serum creatinine (sCr) of ³1.5 times baseline. The primary outcome was the progression to AKIN stage 3 (increase in sCr of 3 times over baseline or need for renal replacement therapy (RRT)) within 14 days after AKI development. Prerenal AKI, postrenal AKI, and AKIN Stage 3 at diagnosis of AKI are excluded; prerenal AKI is diagnosed when serum BUN-to-creatinine ratio is ≥ 20 and postrenal AKI is diagnosed based on clinical situation.

Results: 418 patients were included. The mean of age was 80.6 \pm 8.2 years, baseline sCr 0.89 \pm 0.40 mg/dl, and baseline eGFR 66.1 \pm 32.3 ml/min/1.73m². Among 418 patients, 77 (18.4%) experienced AKI progression and 83 (19.9%) died. Of the 77 patients with AKI progression, 25 (6.0%) patients received RRT. AKIN stage 2 at diagnosis (OR=2.33, 95%CI=1.23-4.36), RAS inhibitor use (OR=2.84, 95%CI=1.33-5.93), bacteremia (OR=1.69, 95%CI=0.89-3.14), hypoalbuminemia (OR=5.10, 95%CI=2.94-9.06) were risk factors for AKI progression.

Conclusions: Hypoalbuminemia is a strong risk factor for AKI progression in older patients in ICU. Further study is needed to evaluate whether correction of hypoalbuminemia could prevent AKI progression or not.

SA-PO201

Impact of Preexisting Serum Prealbumin on All-Cause Mortality in Community-Acquired and Post-Operative Acute Kidney Injury Patients Yanfeng Zou,¹ Dan Wen,¹ Jingyuan Xie,¹ Xiaonong Chen,¹ Wen Zhang,¹ Nan Chen.¹ ¹*Nephrology, Ruijin Hospital, Shanghai, China;* ²*Nephrology, Ruijin Hospital;* ³*Nephrology, Ruijin Hospital.*

Background: To explore the impact of pre-existing prealbumin concentration on all-cause mortality in AKI (acute kidney disease, AKI) patients.

Methods: From 2000 to 2010, 477 patients diagnosed with community-acquired AKI (CA-AKI) and treated in the Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University were enrolled in the CA-AKI group. 138 patients diagnosed with AKI after cardiac operations were enrolled in the post-operative AKI (PO-AKI) group. Data were collected at the time point of AKI onset and one year after the discharge.

Results: Patients with CA-AKI were younger than PO-AKI patients. Compared with PO-AKI patients, more patients in CA-AKI group suffered from chronic kidney disease, obesity and hyperlipidemia and less patients with cerebrovascular disease (CVD), anemia, shock, arrhythmia and so on. Risks for CA-AKI were atherosclerosis, CVD, arrhythmia, multiple organ dysfunction syndrome (MODS) and usage of vasoactive agents, and for PO-AKI were elderly age, arrhythmia and RRT (renal replacement therapy, RRT)-requiring. A higher level of preexisting serum prealbumin (PA) lead to better outcome in CA-AKI (HR 0.92, 95%CI 0.85-1.00) and PO-AKI group (0.91, 95%CI 0.84-0.99). In CA-AKI group, cumulative survival rate of patients in normal PA group (PA>20mg/dL) was higher than that in lower PA (PA \leq 20mg/dL) group (95.4% vs 88.3%, P=0.031). Similarly, in PO-AKI group, normal PA level was associated with a higher survival rate (74.1% vs 47.6%, P=0.019).

Conclusions: A significant difference was detected between CA-AKI group and PO-AKI in general characteristics, comorbidities, laboratory examinations, outcome, and risks. Patients with PA>20mg/dL showed better survival rate.

Funding: Government Support - Non-U.S.

SA-PO202

Usefulness of Serum Ischemia-Modified Albumin Levels to Predict Dialysis Requirement in Patients with Acute Renal Injury Mehmet Uzun, Harun Akar. *Internal Medicine, Izmir Tepecik Education and Research Hospital, Turkey.*

Background: Ischemia-modified albumin is a promising biomarker for early diagnosis of diseases related with ischemia. Ischemia leads to modification in albumin molecule by reducing its binding to cobalt. The aim of this study was to evaluate the levels of ischemia-modified albumin in patients with acute kidney injury (AKI).

Methods: Serum levels of ischemia-modified albumin were estimated in 51 patients with AKI.

Results: The mean age of 28 female and 23 male patients were 65.39 \pm 15.28 and 70.11 \pm 15.25, respectively. Levels of IMA were found to be high in 75.5% of the patients (>400) and were found to be normal in 25.5% of the patients (<400). Kaplan-Meier survival analysis showed that the survival was not different between IMA groups. Urine amounts were significantly different between IMA groups. The urine volume was lower in patients with higher IMA levels (>400).

Conclusions: In the present study, the levels of IMA were found to be significantly higher who needed hemodialysis treatment. IMA levels do not predict mortality. Taking these results together, serum IMA levels might give an idea about dialysis requirement in patients with AKI. More studies with larger sample groups may help to establish the role of IMA on decisions regarding dialysis initiation.

SA-PO203

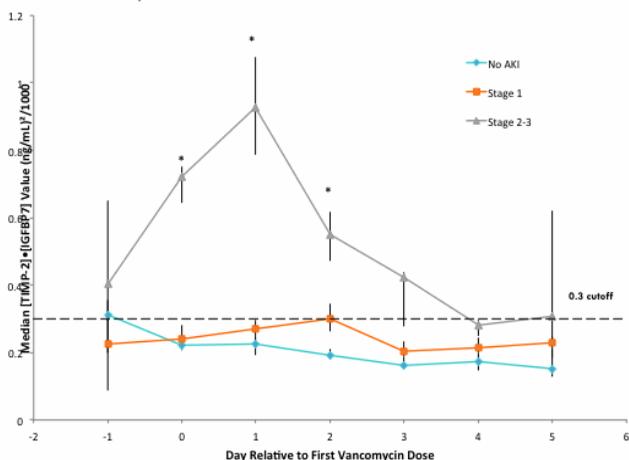
Urinary TIMP-2 and IGFBP7 Elevate Early After Vancomycin Administration in Critically Ill Patients Who Develop AKI Maria Ostermann,¹ Lui G. Forni,² Lakhmir S. Chawla,³ Jing Shi,⁴ Kianoush Banaei-Kashani,⁵ John A. Kellum,⁶ ¹King's College London, London; ²Royal Surrey County Hospital, Guildford; ³George Washington Univ, Washington; ⁴Walker Bioscience, Carlsbad; ⁵Mayo Clinic, Rochester; ⁶Univ of Pittsburgh, Pittsburgh.

Background: We previously validated a biomarker combination of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) for risk stratification of acute kidney injury (AKI).¹ A cutoff of 0.3 (ng/ml)²/1000 for [TIMP-2]•[IGFBP7] indicated AKI stage 2-3 at least 24h prior to serum creatinine.² We also showed that nephrotoxic drug use was common in patients developing AKI and that the [TIMP-2]•[IGFBP7] test could have identified patients earlier.³ In this sub-analysis of the Sapphire study¹, we examined the temporal changes in [TIMP-2]•[IGFBP7] following vancomycin.

Methods: We identified patients who received vancomycin and grouped them according to their maximum KDIGO AKI stage within 3 days of 1st dose of vancomycin. We calculated the median daily [TIMP-2]•[IGFBP7] value from day prior to 1st dose of vancomycin until 5 days after. A bootstrap analysis was used to calculate 1-sided p-values for comparison to the 0.3 (ng/ml)²/1000 cutoff.

Results: 249 patients received at least 1 dose of vancomycin. 137 (55%) developed AKI within 3 days [AKI 1 (n=81), AKI 2 (n=44), AKI 3 (n=12)]. In patients without AKI or with AKI 1, median [TIMP-2]•[IGFBP7] values were 0.3 (ng/ml)²/1000 for all time points.

Figure 1 Kinetics of urinary [TIMP-2]•[IGFBP7] in critically ill patients who received vancomycin.



In patients with AKI 2-3, median [TIMP-2]•[IGFBP7] values were significantly elevated on the day of the 1st vancomycin dose and remained elevated for the following 2 days.

Conclusions: In patients with AKI 2-3 after vancomycin administration, urinary [TIMP-2]•[IGFBP7] was significantly elevated on the first 2 days after the 1st dose. These biomarkers have the potential to improve management in patients receiving vancomycin.

Funding: Pharmaceutical Company Support - Astute Medical

SA-PO204

Peri-Operative Serum IL-33 Concentrations in Matched AKI and Non-AKI Patients Undergoing Cardiac Surgery Charles L. Edelstein,¹ Heather Thiessen Philbrook,² Jay L. Koyner,³ Michael Shlipak,⁴ Steven G. Coca,² Chirag R. Parikh,² ¹Univ Colorado Denver; ²Yale Univ; ³Univ Chicago; ⁴UCSF.

Background: Endothelial cell damage and death in the nephron is an early feature of AKI. Damage-associated molecular patterns (DAMPs) are endogenous molecules released by damaged cells including endothelial cells. IL-33, a DAMP, has been shown to be present in blood vessels in the kidney and released into the blood, but not the urine, in cisplatin-induced AKI in mice before the increase in serum creatinine. We sought to determine whether serum IL-33 levels are a biomarker of AKI in humans in a nested case-control study.

Methods: Perioperative plasma samples were obtained from patients enrolled in the TRIBE-AKI cohort. 35 cases of AKIN Stage 2 AKI or higher within the first 4 post-op days were matched to 70 controls with no AKI by pre-op GFR, age, sex, site and cohort. Blood samples were available pre-op, day 1 (0-6 hours), days 2 and 3. Serum IL-33 was measured by ELISA.

Results: The pre and post-operative levels of IL-33 are shown in Table 1. Using a mixed model accounting for the matching in the data, the first post-operative value of IL-33 was significantly different (p=0.005) between cases and controls after adjusting for pre-op values. There was a non-significant trend towards higher IL-33 levels on day 2.

Time point		Cases Mean (SD)	Cases Median (P25, P75)	Controls Mean (SD)	Controls Median (P25, P75)	P
Pre-op	Actual	1082 (2174)	155 (0,516)	1160 (2214)	58 (0, 641)	0.87
Day 1	Actual	1452(2131)	331 (71, 1922)	1172(2094)	72 (0,759)	0.048
Day 1	Delta from pre	355(926)	0 (-63, 202)	12(759)	-5 (-166, 0)	
Day 2	Actual	1591(2082)	315 (34, 2731)	1272(2236)	158 (0, 905)	0.08
Day 2	Delta from pre	456(1252)	0 (-97, 592)	111(1069)	0 (-163, 5)	
Day 3	Actual	1367(2098)	413 (12, 1391)	1383(2294)	135 (0, 1170)	0.38
Day 3	Delta from pre	282(1402)	0 (-152, 382)	222(1190)	0 (-82,30)	

Conclusions: Immediate post-operative serum IL-33 concentrations were higher in matched AKI cases compared to non-AKI controls. Further studies are needed to clarify the role of serum IL-33 in human AKI.

Funding: NIDDK Support SA-PO205

First Post-Operative Urinary Kidney Injury Biomarkers and Association with the Duration of AKI in the TRIBE-AKI Cohort Steven G. Coca, Girish N. Nadkarni, Amit X. Garg, Jay L. Koyner, Heather Thiessen Philbrook, Eric McArthur, Michael Shlipak, Chirag R. Parikh. *TRIBE-AKI Consortium.*

Background: We previously demonstrated AKI duration improves risk-stratification for AKI prognosis in addition to the magnitude of serum creatinine rise. We evaluated whether kidney injury biomarkers within 6 hours after cardiac surgery associate with post-operative AKI duration.

Methods: We included 1199 adults undergoing cardiac surgery in TRIBE-AKI cohort that survived to discharge and examined association between five urinary biomarkers: neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP) and albumin with duration of serum creatinine-based AKIN criteria for AKI (0 (no AKI), 1-2, 3-6, ≥7 days).

Results: Overall, 406 (34%) patients had AKI, of which 48 had stage 2/3 AKI. Of 358 with stage 1 AKI, 115 (32.1%) had AKI duration >3 days. An additional 41 (85%) with stage 2/3 AKI had duration of >3 days. Concentrations of all biomarkers increased with AKI duration and each log increase in biomarker was independently associated with greater odds of longer duration category (IL-18 OR 1.25, 95% CI 1.16-1.35; KIM-1: 1.36, 95%CI 1.21-1.52; albumin 1.21, 95% CI 1.10-1.33; L-FABP 1.14, 95% CI 1.07-1.21; NGAL 1.10, 95% CI 1.03-1.17).

Biomarkers at 0-6 hours	AKI Duration in days			
	0 (No AKI) (n=788)	1-2 (n=250)	3-6 (n=118)	≥7 (n=38)
Urine IL-18 (pg/mL)	9.3 (3.6-27.9)	15.8 (5.9-82.4)	23.1 (6.0-88.9)	45.9 (16.6-188.6)
Urine NGAL (ng/mL)	8.4 (3.3-32.8)	14.1 (5.2-79.9)	15.0 (5.6-86.3)	26.5 (10.3-418.3)
Urine KIM-1 (ng/mL)	0.4 (0.1-0.8)	0.5 (0.2-1.0)	0.7 (0.3-1.5)	1.0 (0.7-2.2)
Urine LFABP (ng/mL)	16.0 (3.3-79.0)	21.2 (6.4-178.7)	34.0 (6.6-183.3)	61.1 (13.9-371.9)
Urine Albumin (mg/L)	12.5 (6.4-30.8)	18.0 (7.9-53.7)	20.0 (9.0-61.3)	43.3 (19.0-70.4)

Conclusions: While most patients in the TRIBE-AKI Cohort experienced stage 1 AKI when classified by peak serum creatinine increase, one-third of those have duration of AKI of >3 days. Elevated urinary kidney injury biomarker within 6 hours of surgery may help in identifying of patients at risk for longer AKI duration, which may serve as a reliable metric for drug development trials.

Funding: Other NIH Support - NHLBI

SA-PO206

Urinary Biomarker Evaluation in Cancer Patients Receiving Cisplatin
 Blesy George,¹ Amandla Roque-Atilano,² Cara A. Chang,² Nickie L. Johnston,² Madeleine Gomez,² Lucas Ellison,² Xia Wen,¹ Lauren Aleksunes,¹ Daniel Bowles,² Cindy L. O'Bryant,² Melanie S. Joy.² ¹School of Pharmacy, Rutgers Univ, NJ; ²Schools of Pharmacy and Medicine, Univ of Colorado, CO.

Background: The study explored the time dependency of urinary biomarker changes and correlations between the biomarkers and traditional markers of kidney injury in a cohort of patients receiving cisplatin.

Methods: Urine was obtained at 1)baseline, 2)Day 3 and 3)Day 10 from patients (n=42) receiving cisplatin (25 mg/m²). Urinary kidney injury molecule-1 (Kim-1), calbindin, beta-2 microglobulin (B2M), clusterin, monocyte chemoattractant protein-1 (MCP-1), cystatin C, trefoil factor 3 (TFF3), tissue inhibitor of metalloproteinase 2 (TIMP2), and insulin growth factor binding protein 7 (IGFBP7) were measured with multiplex or ELISA.

Results:

Mean±SEM	Baseline	Day 3	Day 10
Kim-1 (ng/mL)	0.42±0.1 ^{A,B}	0.77±0.1	0.97±0.2
Calbindin (ng/mL)	59.0±13.8 ^B	70.1±12.2 ^C	544±163
B2M (ng/mL)	144±39.1 ^A	502±71.8 ^C	185±41.5
Clusterin (ng/mL)	42.0±23.5 ^B	27.7±8.5	52.9±16.1
MCP-1 (ng/mL)	0.62±0.2 ^B	0.45±0.1	1.0±0.23
Cystatin C (ng/mL)	39.5±7.7	77.3±22.8	64.9±19.0
TFF3 (ng/mL)	865±154 ^B	1441±202	1616±264
TIMP2 (ng/mL)	2.2±0.5	2.3±0.6	3.2±0.7
IGFBP7 (pg/mL)	2931±484	2357±514 ^C	4650±561
Albumin (ng/mL)	11,038±2067 ^B	15,958±2442	24,373±4232

A: baseline vs. Day 3 p<0.05, B: baseline vs. Day 10 p<0.05, C: Day 3 vs Day 10 p<0.05

The biomarker-GFR correlations were: TFF3 (r: -0.2590), B2M (r: -0.2017), Kim-1 (r: -0.1758), MCP-1 (r: -0.1390), cystatin C (r: -0.0936), IGFBP7 (r: -0.0764), clusterin (r: -0.0767), calbindin (r: -0.0647), and TIMP2 (r: -0.0619). The biomarker-albumin correlations were: calbindin (r: 0.7813), TFF3 (r: 0.5949), clusterin (r: 0.5869), Kim-1 (r: 0.3186), TIMP2 (r: 0.3016), MCP-1 (r: 0.2340), IGFBP7 (r: 0.2217), cystatin C (r: 0.1375), and B2M (r: 0.1149).

Conclusions: Urinary biomarkers display time dependent increases post cisplatin and exhibit variable degrees of correlation with GFR and urinary albumin. TFF3 had high concordance with both GFR and urinary albumin, which may be a favorable characteristic.

Funding: NIDDK Support

SA-PO207

Prediction of Long-Term Renal Outcomes in AKI Survivors by Urinary Biomarkers
 Rei Isshiki,¹ Kent Doi,² Maki Sumida,¹ Yoshifumi Hamasaki,¹ Naoki Yahagi,² Masaomi Nangaku,¹ Eisei Noiri.¹ ¹Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; ²Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: Although several epidemiological studies suggested that acute kidney injury (AKI) increases the risk of chronic kidney disease (CKD) development and progression, it is still unclear whether any AKI biomarker can predict long-term renal outcomes in AKI survivors. This study was aimed to evaluate the performance of urinary biomarkers for long-term renal outcome prediction.

Methods: We conducted an observational study examining the association of three urinary biomarkers measured at ICU admission [L-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl-β-D-glucosaminidase (NAG)] with CKD progression after discharge without major adverse kidney events (MAKE). MAKE were determined with death, incident dialysis dependency, or 50% reduction of eGFR at hospital discharge. Two different long-term renal outcomes were defined as follows; 30% reduction of eGFR or incident end-stage renal disease within two years after hospital discharge (*Outcome 1*) and halving of eGFR or incident end-stage renal disease in three years (*Outcome 2*).

Results: Among all the enrolled 495 patients, 393 patients discharged from the hospital without MAKE. Of them, 173 patients were followed up for two years after ICU discharge and 63 patients (36.4%) were positive for long-term renal outcomes (*Outcome 1*). A step-wise logistic regression analysis demonstrated that only urinary NGAL showed a significant association. For *Outcome 2*, 26 of 159 followed-up patients (16.4%) were positive and urinary L-FABP and NGAL were significantly associated with CKD progression in a univariate logistic regression analysis.

Conclusions: Urinary biomarkers measured at ICU admission were significantly associated with long-term renal outcomes after hospital discharge in MAKE-free AKI survivors.

SA-PO208

Significance of Serial Measurement of Acute Kidney Biomarker in Intensive Care Unit
 Rei Isshiki,¹ Kent Doi,² Maki Sumida,¹ Naoki Yahagi,² Masaomi Nangaku,¹ Eisei Noiri.¹ ¹Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; ²Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: AKI biomarkers have been developed with the concept of earlier detection of kidney damage than serum creatinine. However, single time point measurement appears not to provide sufficient information for detecting and predicting AKI in ICU patients who frequently suffer from multiple and transient/persistent renal insults. This study was aimed to evaluate whether serial measurement enables to predict AKI progression and recovery in these patients.

Methods: Serial measurements of AKI biomarkers including plasma and urinary NGAL, urinary L-FABP, and urinary NAG at ICU admission (day 1) and 24 hr after (day 2) were conducted in adult critically ill patients who were treated in a mixed ICU.

Results: Among the enrolled 272 patients, 33 were determined as newly developed AKI after ICU admission, 64 showed worsening of kidney function and 63 recovered from AKI. ROC analysis showed that biomarkers at day 2 showed no significantly additional benefit in predicting these three AKI outcomes compared with those measured at day 1. However, net reclassification improvement (NRI) analysis demonstrated adding AKI biomarkers at day 2 to the clinical model consisted of clinical variables and biomarker at day 1 significantly improved prediction of these AKI outcomes.

	Newly AKI		Worsening AKI		Recovery of AKI	
	AUC-ROC	Continuous NRI	AUC-ROC	Continuous NRI	AUC-ROC	Continuous NRI
Clinical model +D1uNGAL	0.89		0.86		0.78	
+D2uNGAL	0.92	0.92 (0.59 to 1.26)*	0.91	0.60 (0.33 to 0.88)*	0.80	0.39 (0.042 to 0.73)*
Clinical model +D1plNGAL	0.85		0.85		0.79	
+D2plNGAL	0.87	0.74 (0.39 to 1.092)*	0.87	0.61 (0.33 to 0.88)*	0.79	0.13 (-0.22 to 0.48)
Clinical model +D1uL-FABP	0.89		0.87		0.79	
+D2uL-FABP	0.89	0.63 (0.26 to 0.99)*	0.88	0.51 (0.23 to 0.79)*	0.82	0.42 (0.0077 to 0.076)*
Clinical model +D1uNAG	0.87		0.86		0.79	
+D2uNAG	0.89	0.85 (0.52 to 1.19)*	0.87	0.32 (0.0030 to 0.60)*	0.79	-0.031 (-0.38 to 0.32)

Conclusions: Serial measurement of AKI biomarkers involved in clinical models could contribute to prediction of AKI outcomes in a heterogeneous cohort of adult mixed ICU.

SA-PO209

Role of Carbonyl Stress Revisited in Pathogenesis of Tropical Acute Kidney Injury
 Pinaki Mukhopadhyay. Nephrology, NRS Medical College, Kolkata, West Bengal, India.

Background: Malaria and snake bite are two common causes of Acute Kidney Injury (AKI) in tropics with lot of morbidity and mortality. The aim of this study was to (I) evaluate the carbonyl and oxidative stress in these group and their pathogenesis link and (II) prognostic predictability of carbonyl and oxidative stress marker in this AKI.

Methods: All cases of falciparum malaria mediated AKI (FMAKI) (n=50), confirmed by antigen and/or in peripheral blood smear and snake bite mediated AKI (SAKI) (n=58) were included. AKI was calculated as per RIFLE criteria. Demographical, clinical and biochemical data were analysed and were followed from hospitalization to discharge/death. Oxidative and carbonyl stress markers [advanced oxidation protein product (AOPP), advanced glycation end product (AGE), pentosidine, dityrosine, thiobarbituric acid reactive substance (TBARS) and methyl glyoxal (MG)] were measured consecutively according to standard protocol. Predictive importance was assessed from trend analysis, receiver operated characteristic (ROC) curve analyses and multiple logistic regression with AKI as positive response.

Results: The Oxidative stress index (OSI) of FMAKI patients were 1.89 higher than controls. The TBARS, MG level were 6.49 and 5.56 times higher indicating a significant carbonyl stress in these patients. AOPP level was 2.33 times higher indicating proteins being highly insulted in FMAKI. Similarly in SAKI, significantly elevated total oxidant stress with decreased total antioxidant stress leads to net oxidative stress in SAKI patients depicted by increased OSI values (p<0.001). MG was increased by 3.48 times (p<0.001). Only AOPP (p=0.001) and MG (p=0.004) were found to be significantly elevated in expired patients than the survived indicating their predictive power for adverse outcome. At univariate level,

all parameters can differentiate between AKI and the non-AKI group. At multivariate level, methylglyoxal, AOPP and dityrosine appeared to be independent predictor of AKI in snake bite and malaria infected patients (p<0.05).

Conclusions: 1.MG,the carbonyl stress marker along with oxidative stress are significantly raised and possibly linked to the pathogenesis of AKI. 2.MG and AOPP can be used as a surrogate marker in these tropical AKI.

SA-PO210

Prediction of Short-Term and Long-Term Outcomes of AKI-Based on Plasma NGAL Karina Soto,^{1,3} Fernando Pereira,¹ Liliana Maria gonalves Cunha,¹ Iola Pinto,² Ana Luisa Papoila,³ Prasad Devarajan.⁴ ¹Nephrology, Hospital Fernando Fonseca; ²Inst Superior de Engenharia de Lisboa; ³Nova Medical School/FCM, Univ Nova de Lisboa, Portugal; ⁴Nephrology, Cincinnati Children's Hospital Medical Center, OH.

Background: We have previously shown a good performance of Plasma NGAL (pNGAL) as an AKI biomarker in emergency settings. Now we investigated a new AKI classification based on pNGAL for prediction of kidney dysfunction at discharge and at the end of follow-up.

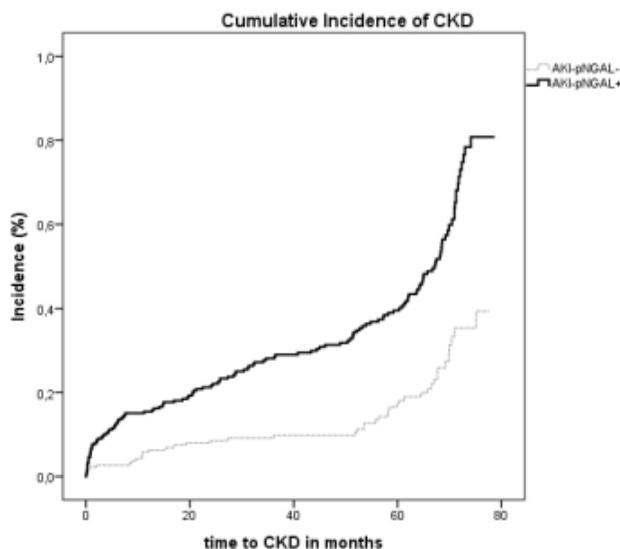
Methods: Patients from a previous study at ED were followed for >5y. During the index hospitalization, 21% were AKI (based on SCr), 26% transient azotemia, 51% normal function and 2.4% stable CKD. All patients had SCr and pNGAL measured at 0, 6,12, 24 and 48h of admission. A new AKI classification based on pNGAL levels (AKIpNGAL+) defined AKI as pNGAL=>110 ng/mL (cut-off by GAMS). A multivariable logistic and cox regression models were applied.

Results: Of 599 patients admitted, 97.8% were available at discharge and 54.4% at last follow-up. At admission 42.6% were reclassified as AKIpNGAL+ whereas only 21.7% were based on SCr. . All significant clinical variables were included in multivariable analysis at discharge.

Variables	OR	95% CI
AKIpNGAL+	4.2	2.3-7.6
Age	1.1	1.0-1.1
CVD	1.2	1.2-3.2
DM	1.5	1.5-4.0

p<0.001 all unless CVD=0.007

Having pNGAL>110 at ED corresponded to 4-fold increased odds for eGFR<60 mL/min (p<0.001 ROC-AUC 0.82). The cumulative incidence of CKD showed that most of AKIpNGAL+ developed CKD at 60 mo (the highest proportion 77%) (figure 1) HR for CKD: 2.4 for patients AKIpNGAL+ in long-term (p<0.001 ROC AUC 0.74) NRI 56.3 and IDI 0.03.



Conclusions: Patients who were AKIpNGAL+ had significant lost kidney function at discharge and more than 2-fold risk of developing CKD in long-term evolution. Plasma NGAL is a useful tool for CKD prediction, independent of serum creatinine.

SA-PO211

The Use of Novel Serum and Urinary Biomarkers to Predict the Development of Hepatorenal Syndrome in Patients with Advanced Cirrhosis Desmond Y.H. Yap,¹ Wai Kay Seto,¹ James Yy Fung,¹ See-Ching Chan,² Siu-Ho Chok,² Man-Fung Yuen,¹ Daniel Tak Mao Chan.¹ ¹Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong; ²Surgery, The Univ of Hong Kong, Hong Kong, Hong Kong.

Background: Hepatorenal syndrome (HRS) is associated with high mortality rates in advanced cirrhotic patients without liver transplantation. Prediction of the development of HRS remains difficult.

Methods: We prospectively recruited patients with Child's B or C cirrhosis and followed them at 2-week intervals 12 weeks or until HRS developed. Serum cystatin C (CysC), serum Neutrophil Gelatinase-Associated Lipocalin (NGAL), serum IL-18, urine kidney injury molecule-1 (KIM-1) and urine liver-type fatty acid binding protein (LFABP) were measured at recruitment (Baseline).

Results: 43 patients were included. 12 developed HRS at 7.3±5.1 weeks from Baseline. Patients who developed HRS had higher Baseline levels of serum CysC (1.42±0.51 mg/L vs. 1.07±0.50 mg/L, p=0.021), serum NGAL (129.10±68.66 ng/mL vs. 72.84±48.91 ng/mL, p=0.025), serum IL-18 (759.91±477.05 mIU/mL vs. 358.13±153.00 mIU/mL, p=0.001), urine KIM-1 and LFABP (3.64±3.34 ng/mL vs. 1.18±1.68 ng/mL and 10.17±8.37 ng/mL vs. 3.28±4.20 ng/mL, p=0.023 and 0.035 respectively) when compared to patients who did not develop HRS. The cut-off and positive and negative predictive values for HRS were shown in Table 1.

	Cut-off Value	AUC	95%CI	PPV (%)	NPV (%)	P-value
Baseline serum Cystatin C (mg/L)	0.899	0.748	0.572-0.924	52.4	90.9	0.021
Baseline serum NGAL (ng/mL)	90.47	0.756	0.592-0.939	72.7	75.0	0.025
Baseline serum IL-18 (mIU/mL)	442.84	0.858	0.708-1.000	73.3	92.9	0.001
Baseline urine KIM-1 (ng/mL)	1.499	0.785	0.607-0.963	75.0	84.2	0.008
Baseline urine LFABP (ng/mL)	3.398	0.765	0.578-0.949	54.5	86.7	0.035

Serum NGAL and IL-18 and urinary KIM-1 at Baseline were significantly associated with the development of HRS (OR 1.017, 95%CI 1.001-1.033, p=0.035; OR 1.007, 95%CI 1.002-1.013, p=0.012; OR 1.003, 95%CI 1.009-2.237, p=0.045, respectively).

Conclusions: Serum IL-18 and NGAL and urinary KIM-1 could serve as biomarkers to predict HRS in patients with advanced cirrhosis.

Funding: Private Foundation Support

SA-PO212

Robust Risk Assessment of Acute Kidney Injury After Acute Myocardial Infarction Using the Novel Biomarker C-Terminal Fragment of Agrin (CAF) Spyridon Arampatzis,¹ George Chalikias,² Vasileios Devetzis,¹ Stefan Hettwer,³ Dimitros Tziakas,² Uyen Huynh-do.¹ ¹Nephrology, Hypertension and Clinical Pharmacology, Uni. Hospital Bern, Inselspital, Switzerland; ²Cardiology, Democritus Univ of Thrace, Greece; ³Neurotune AG, Switzerland.

Background: Acute kidney injury (AKI) complicating acute myocardial infarction (AMI) increases subsequent morbidity and mortality. The objective of this study was to validate c-terminal fragment of agrin (CAF) as a novel AKI biomarker in patients with AMI.

Methods: 403 consecutive patients with AMI were enrolled, samples were collected at presentation for serum (sCAF), urine (uCAF) CAF, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18) and cystatin-C analysis. The presence of AKI was evaluated at 48 hours post admission and at discharge.

Results: The incidence of AKI was 6.7%-14.6% depending on time-point and criteria used and increased across quartiles of uCAF (x²:10.99, p<0.001). Both uCAF and sCAF significantly correlated with serum creatinine on admission (r=0.233, p<0.001 & r=0.175, p<0.001), at 48 hours (r=0.263, p<0.001 & r=0.226, p<0.001) and with peak creatinine as well (r=0.317, p<0.001 & r=0.225, p<0.001). The predictive accuracy for AKI of uCAF was good (AUC:0.630, 95%CI:0.552-0.708) and slightly better as that of urine NGAL (AUC:0.616, 95%CI:0.540-0.692, uCAF vs. uNGAL p=0.733), whereas that of sCAF was moderate (AUC:0.587, 95%CI:0.509-0.666). A uCAF value of 1033pM is suggested to have the best discriminating ability. The sensitivity of uCAF was 37% and the specificity 85% (NPV: 89%, PPV: 30%). Univariate analysis showed a strong association of uCAF with AKI incidence (OR:1.45, 95%CI:1.15-1.82, p=0.002) which remained significant even after adjustment for several confounders (OR:1.35, 95%CI:1.05-1.74).

Conclusions: Urine CAF analysis allows a robust risk stratification of AKI after AMI and thus optimized management in such patients.

Funding: Government Support - Non-U.S.

SA-PO213

At Myeloma Diagnosis, Age and Free Light Chain Level Predict Renal Function and These Factors with Free Light Chain Response Predict Renal Outcome Punit Yadav,^{1,2} Mark Trehane Drayson,^{1,2} Mark Cook,^{1,2} Jennifer H. Pinney,¹ Hannah V. Giles,² Yu sandar Aung,^{1,2} Paul Cockwell.^{1,2} ¹Univ Hospital Birmingham, UK; ²Univ of Birmingham, UK.

Background: Elevated involved immunoglobulin free light chain (FLC) is a major cause of renal impairment (RI) in myeloma. Relationships between presentation and post-induction (PI) renal function and serum FLC levels are not established.

Methods: We used central laboratory data from the MRC Myeloma IX trial which compared bisphosphonate and thalidomide-based therapies. Patients were divided into 3 eGFR categories: eGFR ≥ 60 ml/min, normal renal function; eGFR 30-59 ml/min, mild-moderate RI; eGFR < 30 ml/min, severe RI. Linear regression and Logistic regression modelling were used to explore independent determinants of renal function.

Results: 52.8% had an eGFR ≥ 60 ml/min; 37.3% had an eGFR 30-59 ml/min and 9.8% had an eGFR < 30 ml/min. Median eGFR in patients with involved λ FLC was significantly lower than those with κ FLC (58 [IQR 42-77] vs 63 [IQR 46-80]; $P=0.01$). Median eGFR for light chain only myeloma (LCO) was also significantly lower than those with IgG and IgA myeloma (49 [IQR 28-78] vs 62 [IQR 47-79] vs 63.5 [IQR 42.2-82.0] respectively; $P<0.0001$). Patients with a difference between involved and uninvolved FLC (dFLC) ≥ 500 mg/L had a lower eGFR compared to those with dFLC 100-499 mg/L and dFLC < 100 mg/L (52 [IQR 35-72] vs 66 [IQR 52.0- 82.2] vs 67 [IQR 54.2-82.0] respectively; $P<0.0001$). A dFLC level of 700 mg/L was the optimal cut-off value for prediction of severe RI, with an AUC of 0.80. Factors associated with eGFR at presentation were: age, \log_{10} dFLC, male gender and LCO myeloma. On censoring those with dFLC < 700 mg/L; age and \log_{10} dFLC were still associated with eGFR at presentation but not male gender and LCO myeloma. Factors that were independently associated with RI at PI were: age (odds ratio [OR] 1.033, $P=0.041$); presentation eGFR (OR 0.93, $P<0.0001$) and attainment of 3 VGPR (very good partial response) compared to $<$ PR (partial response) serum FLC response (OR 0.52, $P=0.005$).

Conclusions: Age and serum FLC level predict eGFR at presentation and age, presentation eGFR, and serum FLC response predict PI renal outcome.

SA-PO214

Urinary Biomarkers Improve the Prediction and Prognostic Assessment of Acute Kidney Injury in Critically Ill Patients Patrick T. Murray, Teresa Martin, Eoin J. Cotter. UCD Clinical Research Centre, School of Medicine, Univ College Dublin, Dublin, Ireland.

Background: Acute kidney injury (AKI) is common in intensive care unit (ICU) patients, and is diagnosed late by serum creatinine. New biomarkers may permit earlier detection and better management.

Methods: All patients admitted to the ICUs of two university hospitals were screened for this prospective cohort study. Clinical information and urine were collected on admission and daily for 7 days. Urine biomarkers analysed were neutrophil gelatinase-associated lipocalin (NGAL), α - and π - glutathione-S-transferases (GSTs), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), creatinine, and albumin. AKI was defined by modified KDIGO criteria, using ICU admission creatinine as reference. Values were compared between those who did or did not develop AKI or 30d adverse clinical outcomes (RRT or death). ROC curves were generated for prediction of AKI and outcomes by a clinical score (including age, gender, serum creatinine & urea, urine output) and urine biomarker values on admission. In patients developing AKI, ROC curves were similarly generated for the prediction of clinical outcomes with values obtained at time of AKI diagnosis.

Results: 659 patients were enrolled; 181 patients (27%) developed AKI within 7d of ICU admission. AKI stages at diagnosis were: Stg1 (n=81, 45%), Stg2 (n=17, 9%), Stg3 (n=83, 46%). On admission, addition of a panel of AKI biomarkers significantly but modestly improved prediction of AKI developing within the first 48h in ICU (AUC \pm SD: 0.79 \pm 0.12), compared to clinical score alone (0.77 \pm 0.11; $p=0.0001$). AKI biomarkers similarly improved the prediction of AKI developing within the first 7d (0.73 \pm 0.15), compared to clinical score alone (0.69 \pm 0.07; $p=0.0003$); and marginally improved the prediction of 30d RRT or death (0.7 \pm 0.1 vs 0.69 \pm 0.1; $p=0.05$). In patients developing AKI, AKI biomarkers at the time of diagnosis significantly improved prediction of 30d adverse clinical outcomes (RRT or death): 0.77 \pm 0.19, compared to clinical score alone (0.68 \pm 0.13; $p=0.01$).

Conclusions: Urinary biomarkers combined with standard clinical tests improved prediction of AKI and outcomes in ICU patients, on admission and at AKI diagnosis.

Funding: Pharmaceutical Company Support - Support-in-kind from Abbott Labs and Argutus/EKF Diagnostics (assay kits).

Irish Government support: Health Research Board and Dublin Centre for Clinical Research, Government Support - Non-U.S.

SA-PO215

Association of Growth Factor Biomarkers with Acute Kidney Injury and Long-Term Mortality in Adults following Cardiac Surgery William R. Zhang, Richard P. Whitlock, Heather Thiessen Philbrook, Eric McArthur, Amit X. Garg, Steven G. Coca, Peter Kavsak, Chirag R. Parikh. TRIBE-AKI Consortium.

Background: Following the structural damage and functional impairment from acute kidney injury (AKI), the kidney undergoes a coordinated process of repair involving regenerative growth factors. We conducted an ancillary analysis of a large, prospective study of adults undergoing cardiac surgery to investigate the utility of epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) in predicting kidney injury and mortality.

Methods: Patients undergoing cardiac surgery at high risk for AKI were enrolled at six academic centers. AKI was defined as a doubling in serum creatinine from baseline or receiving acute dialysis during the hospital stay. Postoperative plasma levels of EGF, VEGF, and a combination model of the two growth factors were evaluated for association with outcomes of AKI or long-term, all-cause mortality at a mean follow-up of 3 years.

Results: First postoperative and peak plasma EGF were not associated with AKI. Elevated peak plasma VEGF was independently associated with increased risk of AKI (adjusted odds ratio [OR] 7.4, 95% confidence interval [CI]: 1.1-47.9). Elevated first postoperative EGF was inversely associated with a lower risk of mortality (adjusted HR=0.67; 95% CI: 0.47-0.97). Elevated first postoperative VEGF was likewise associated with a lower risk of mortality (unadjusted HR=0.36; 95% CI: 0.16-0.82), though the association was attenuated following adjustment (adjusted HR=0.36; 95% CI: 0.15-1.04). When assessed conjointly, elevated levels of first postoperative EGF and VEGF together were independently associated with a lower risk of mortality (adjusted HR=0.28; 95% CI: 0.11-0.72).

Conclusions: Postoperatively, EGF and VEGF are released in response to AKI, and their concentrations were inversely associated with long-term mortality. These growth factors may serve as biomarkers of long-term outcomes in adults undergoing cardiac surgery.

Funding: Other NIH Support - R01HL085757

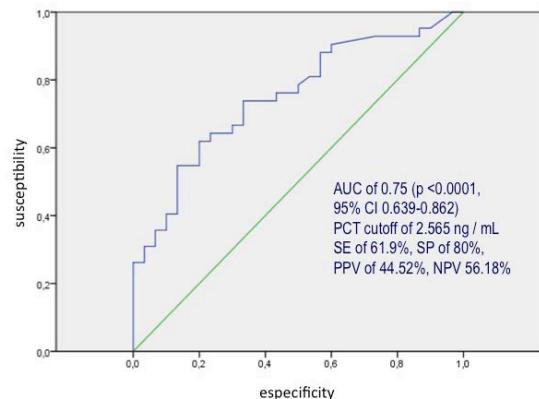
SA-PO216

Procalcitonin as a Predictor of AKI in Patients with Sepsis Jonathan Chavez,¹ Maria de la luz Alcantar Vallin,¹ Guillermo Garcia-Garcia,¹ Luis Arnoldo Muñoz,² ¹Nephrology Service, Hospital Civil de Guadalajara, Guadalajara, Mexico; ²Internal Medicine, Hospital Civil de Guadalajara, Guadalajara, Mexico.

Background: Sepsis is a common cause of AKI. Identifying patients at risk for AKI could improve clinical outcomes. Procalcitonin (PCT) reflects accurately the presence of sepsis and its severity. We evaluated the role of PCT as predictor of AKI in septic patients.

Methods: Cross-sectional study of 72 septic patients between January to December 2014. Patients with SCR ≥ 1.5 mg/dl before admission, ESRD patients and those with autoimmune comorbidity were excluded. PCT, Scr, urea, and WBC were measured on admission, and at 24 h and 48 h of hospitalization. X2 and t-test were used when appropriate. A ROC curve for PCT value on admission as well as the area under the curve (AUC), the standard AUC error, and sensitivity and specificity of PCT values were determined.

Results: Patients' mean age was 50.8 y (18-79); 37 (51.4%) were women. 18 (25%) patients had PCT value at < 0.5 ng / mL (negative) and 54 (75%) ≥ 0.5 ng / mL (positive) on admission. Forty-two (58.3%) patients developed AKI, 19 (45.2%) KDIGO 1, 12 (28.6%) KDIGO 2, and 11 (26.2%) KDIGO 3. Of the 42 patients who developed AKI, 37 (88.1%) had a positive value of PCT at admission ($p < 0.01$, OR 5.659, 95% CI 1.738 to 18.425). The ROC PCT presented an AUC of 0.75 ($p < 0.0001$, 95% CI 0.639 to 0.862). The cutoff of 2.565 ng / mL of PCT had the highest validity for predicting AKI with an SE of 61.9%, one SP of 80%, a PPV of 44.52%, 56.18% NPV, LR + LR of 0.80 and 0.77, respectively. Fig. 1



Conclusions: We found a significant association between levels of PCT and development of AKI in patients with sepsis. A cutoff PCT value of 2,565 ng / mL on admission had the highest validity for predicting AKI. Early recognition of septic patients at risk for AKI with PCT could improve clinical outcomes in this population.

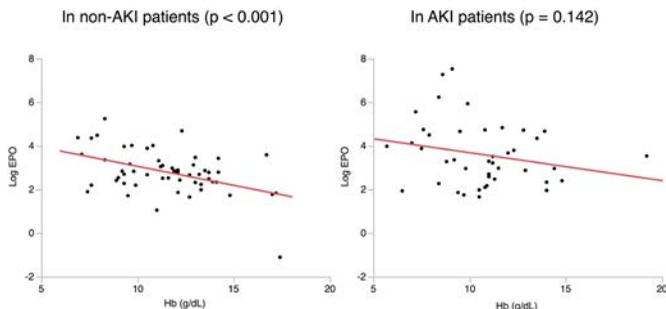
SA-PO217

Elevated Erythropoietin Concentration in AKI Is Associated with IGFBP-1 Rather Than Hemoglobin Tetsushi Yamashita, Eisei Noiri, Yoshifumi Hamasaki, Naoki Yahagi, Masaomi Nangaku, Kent Doi. *The Univ of Tokyo, Tokyo, Japan.*

Background: EPO expression will be increased by hypoxia in the kidney and hypoxic injury plays a crucial role in pathogenesis of AKI. However, little is known about blood EPO levels in critically ill patients complicated with AKI.

Methods: This study prospectively enrolled 98 adult critically ill patients who admitted to the adult mixed ICU. We measured plasma EPO and also measured plasma IGFBP-1 as a hypoxic marker, which is produced mainly by liver, and plasma NGAL and urinary NAG as renal damage biomarkers on ICU admission. This study was conducted to evaluate whether plasma EPO levels in AKI patients, was regulated by other factors than anemia.

Results: AKI occurred in 42 (42.9%) patients. Significantly higher plasma EPO in the AKI group was detected compared with the non-AKI group (16.13 [9.87–28.47] mIU/mL versus 27.81 [10.16–106.02] mIU/mL, p<0.05). Plasma EPO concentration was strongly and negatively correlated with hemoglobin in the non-AKI group but not in the AKI group.



In AKI group, plasma IGFBP-1 was strongly and positively correlated with plasma EPO. Multiple logistic regression analysis revealed plasma EPO in the AKI group was significantly associated only with plasma IGFBP-1 and complication of diabetes mellitus.

Conclusions: EPO production in AKI was enhanced by not anemia but systemic hypoxic stimuli evaluated by IGFBP-1, indicating unknown independent pathway of renal EPO production in AKI.

Funding: Government Support - Non-U.S.

SA-PO218

Predictive Value of Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) to Distinguish Prerenal AKI to Other Causes of AKI Chae Ho Lim, Young-Il Jo. *Div of Nephrology, Dept of Internal Medicine, Konkuk Univ Medical Center, Gwangjin-gu, Seoul, Republic of Korea; Div of Nephrology, Dept of Internal Medicine, Konkuk Univ Medical Center, Gwangjin-gu, Seoul, Republic of Korea.*

Background: Plasma Neutrophil gelatinase-associated lipocalin (NGAL) is a promising biomarker for acute kidney injury, but it's role for distinguishing prerenal AKI from other causes are not well known. The aim of this study was to evaluate the predictive value of plasma NGAL to distinguish prerenal AKI to other causes of AKI.

Methods: We reviewed all NGAL test from December 26, 2011 to February 28, 2015 in Konkuk University Medical center (Seoul, Republic of Korea) and subtract patients who taken fractional excretion of sodium (FENa) test at the same time. Patients were first grouped with Acute Kidney Injury Network (AKIN) stages and evaluated it's diagnostic role for AKI and second divided with prerenal AKI and other causes of AKI.

Results: Total 5814 NGAL test were done from December 26, 2011 to February 28, 2015 in Konkuk University Medical center, and 495 patients taken FENa test at the same time.

	No AKIN (n=226)	AKIN stage 1 (n=162)	AKIN stage 2 (n=60)	AKIN stage 3 (n=58)	p-value
Age (years)	65.7 (SD 15.4)	67.85 (SD 14.2)	60.5 (SD 15.9)	60.9 (SD 11.6)	No AKI vs Stage3 (**=0.01) S1 vs S2 (**=0.07) S1 vs S3 (**=0.001)
Male (%)	119(55%)	106(65%)	38(63%)	30(52%)	ns
BUN (mg/dL)	30.65 (SD 19.7)	39.2 (SD 19.2)	41.15 (SD 18.2)	52.7 (SD 24.2)	No AKI vs S1,2 (****=0.0001) S1 vs S3 (**=0.003)
Cr (mg/dL)	1.33 (SD 0.66)	1.99 (SD 1.07)	2.36 (SD 0.80)	3.72 (SD 2.02)	No AKI vs S1,2,3 (****=0.0001) S1 vs S3 (****=0.0001) S2 vs S3 (**=0.004)
DM (%)	36 (17%)	31 (19%)	8 (13%)	8 (14%)	ns
NGAL (ng/ml)	308.7 (SD 229.5)	489.9 (SD 392.4)	642.2 (SD 448.6)	767.9 (SD 388.6)	No AKI vs S1,2,3 (****=0.0001) S1 vs S3 (**=0.0002)

Table 1. Comparison according to AKIN stages.

	Prerenal AKI (N=128)	Other causes (N=152)	p-value
Age (years)	64.4 (SD 15.7)	65.1 (SD 13.3)	0.7118
Male (%)	81 (63%)	93(61%)	0.7197
BUN (mg/dL)	40.9 (SD 18.1)	43.7 (SD 22.7)	0.2567
Cr (mg/dL)	1.92 (SD 0.83)	2.77 (SD 1.72)	< 0.0001
DM (%)	21(16%)	27(18%)	0.5131
NGAL (ng/ml)	535.8 (SD 453.6)	616.7 (SD 425.6)	0.1142

Table 2. Comparison according to prerenal AKI and other causes of AKI.

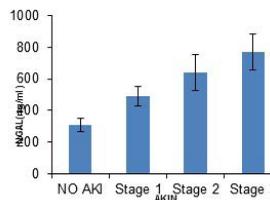


Figure 1. Plasma NGAL for AKI discrimination according to AKIN stages.

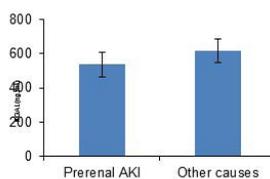


Figure 2. Plasma NGAL for discrimination according to prerenal AKI and other causes of AKI.

Conclusions: Plasma NGAL had a predictive value for diagnosing AKI but it itself had a limited value for distinguishing prerenal AKI from other causes of AKI.

SA-PO219

Neutrophil/Lymphocyte Ratio for Early Detection of Acute Kidney Injury (AKI) in Patients Admitted to the Emergency Room Mohsen Abu Alfeilat, Itzchak N. Slotki, Linda Shavit. *Adult Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel.*

Background: Neutrophil to lymphocyte ratio (NLR) is a readily available biomarker of systemic inflammation. Several studies have provided evidence of an association between elevated NLR and adverse outcomes in a variety of medical and surgical conditions, including CKD. In this study, we evaluated the predictive capacity of single Emergency Room (ER) measurement of NLR for early diagnosis of acute kidney injury (AKI).

Methods: We prospectively studied 294 patients aged 71.6 ± 17. NLR was measured at presentation to the ER. AKI was defined as a new-onset 1.5-fold or more increase in serum creatinine or a 25% decrease in estimated GFR sustained for at least 3 days despite volume resuscitation. The primary outcome was AKI. Secondary outcome was in-hospital mortality.

Results: 36 patients (12.2%) developed AKI and 26 (9%) died. Mean NLR was significantly higher in AKI compare to non-AKI patients (11.7 ± 15.2 vs 6.45 ± 7.19, p=0.048). A multivariate model adjusted for age, gender, blood pressure, and plasma albumin levels confirmed that NLR is higher in AKI patients (p=0.048). Receiver operating characteristics curve revealed AUC 0.715 (95% CI 0.63-0.8) sensitivity 0.78, specificity 0.65, OR 6.423 (CI, 2.659 to 16.026) for a cutoff value of NLR 5.5. The association between NLR and in hospital mortality was not statistically significant (p = 0.92).

Conclusions: Single ER measurement of NLR can be a useful tool for early diagnosis of AKI. This finding is particularly important in light of the widespread availability and low cost of NLR, especially compared with other biomarkers currently under study in the context of AKI.

SA-PO220

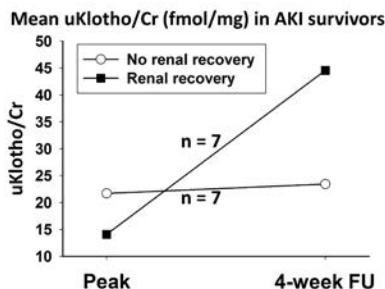
Urine Klotho in Human AKI Javier A. Neyra,¹ Xilong Li,² Beverley Adams-Huet,^{2,3} Carolina De La Flor,³ Ming Chang Hu,³ Robert D. Toto,^{1,2} Orson W. Moe.^{1,3} ¹Nephrology, UT Southwestern; ²Clinical Sciences, UT Southwestern; ³Mineral Metabolism, UT Southwestern, Dallas, TX.

Background: AKI is associated with increased morbidity and carries increased risk for subsequent CKD. Klotho deficiency has been observed in experimental AKI and low Klotho post-AKI is associated with progression to CKD in rodents. We report the first study of Klotho in human AKI.

Methods: We conducted a prospective study of 29 AKI patients and 29 controls without AKI in the ICU setting. We excluded patients with baseline eGFR<60 or kidney transplant. Urine samples were obtained within 24h of peak serum creatinine (SCR) or at RRT initiation

in AKI cases, and within 24h of ICU admission in frequency-matched controls. AKI was defined by KDIGO criteria. Longitudinal data from AKI cases were obtained throughout hospital stay. Renal recovery was defined as the ratio of follow-up SCr/baseline SCr ≤ 1.5 . Urine Klotho was measured by immunoprecipitation-immunoblot. Mixed-effects linear models were constructed to assess longitudinal trends of Klotho in AKI survivors.

Results: Mean (SD) age was 58 (17) years, 62% were men and 75% white. Patients with AKI had higher critical illness scores than controls without AKI. Five (17.2%) patients died and 8 (27.6%) required RRT in the AKI group. Only 3.5% patients died in the control group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 10 [IQR 4–20] vs 28 [14–52] fmol/mg, $p=0.003$. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited renal recovery ($n=7$, $\Delta+216\%$, $p=0.05$) but not in those that did not ($n=7$, $\Delta+8\%$, $p=0.91$), median follow-up 24 days.



Conclusions: uKlotho/Cr is significantly lower in patients with AKI when compared to ICU controls without AKI. uKlotho/Cr recovered only in patients that recovered kidney function. Klotho may serve as a prognostic marker for AKI recovery.

Funding: Other NIH Support - University of Texas Southwestern Medical Center O'Brien Kidney Research Core Center (NIH, P30 DK079328-06) and the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH, UL1TR001105).

SA-PO221

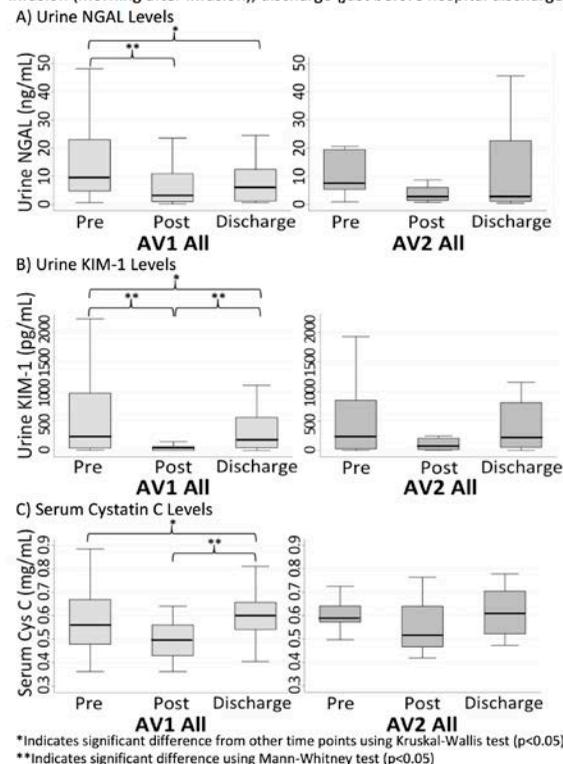
Biomarkers of Acute Kidney Injury in Children Treated with Cisplatin Kelly McMahon,¹ Shahrad Rod Rassekh,² Kirk Raymond Schultz,² Maury N. Pinsky,³ Tom D. Blydt-Hansen,² Cherry Mammen,² Ross T. Tsuyuki,³ Prasad Devarajan,⁴ Michael Zappitelli.¹ ¹McGill U, Montreal; ²U British Columbia, Vancouver; ³U Alberta, Edmonton, Canada; ⁴Cincinnati Children's Hosp, Cincinnati.

Background: Cisplatin(CisP) causes acute kidney injury(AKI) and may cause chronic kidney disease(CKD). Biomarkers(BioM) may allow early AKI diagnosis and treatment. Applying BioM to Long-Term Effects in Child/Adolescent Cancer Treatment(ABLE) is a Canadian study of cancer treatment toxicities, including nephrotoxicity. We study BioM of child CisP treatment for early and late renal outcome prediction. This analysis evaluates neutrophil gelatinase-associated lipocalin(NGAL), kidney injury molecule-1(KIM-1) and serum Cystatin C(CysC) with CisP therapy in the first 1/3 of subjects.

Methods: Ongoing, 8-site, prospective cohort of 150 children receiving CisP. Excluded: severe CKD. Protocol includes 2 "acute" visits[AV] around CisP infusion(pre, post, discharge urine/blood) for serum creatinine(SCr), CysC, urine NGAL, KIM-1. Outcomes: AKI (Kidney Disease Improving Global Outcomes[KDIGO] SCr criteria; AKI by National Cancer Institute(NCI) criteria(based on serum electrolytes).

Results: Data available in 44/60 (mean \pm SD age 7 \pm 6yrs; AV1/AV2 hospital stay 16 \pm 27/12 \pm 26 days; 55% male). AV1: 11% KDIGO AKI, 46% NCI AKI, 50% with either. AV2: 14% KDIGO AKI, 72% NCI AKI, 75% with either. BioM drop immediately post-CisP ($n=25$), followed by a rise at discharge.

Figure 1: BioM Levels During AV1 and 2 CisP Infusions. AV1 refers to first or second CisP cycle of treatment plan and AV2 refers to third or later CisP cycle of treatment plan. BioM collected at 3 time points: Pre-Infusion (just before infusion start), post-infusion (morning after infusion), discharge (just before hospital discharge).



A similar pattern is seen in AKI and non-AKI groups and when expressing BioM/urine creatinine(not shown).

Conclusions: This is a novel study of AKI BioM excretion in CisP-AKI. NCI-AKI is more common than SCr-AKI. The immediate BioM drop post-CisP may be related to injury protection from high fluid rate and/or urinary alkalization peri-CisP. Our larger sample size will allow to further characterize BioM excretion and evaluate BioM associations with AKI definition and outcomes.

Funding: Government Support - Non-U.S.

SA-PO222

Elevated Renal Injury Biomarkers Fall Transiently After Stenting in Human Atherosclerotic Renal Artery Stenosis (ARAS) Wei Wang,^{1,2} Ahmed Saad,¹ Sandra Herrmann,¹ Alfonso Eirin,¹ Hui Tang,¹ Lilach O. Lerman,¹ Stephen C. Textor.¹ ¹Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Nephrology, Dalian Municipal Central Hospital, Dalian, Liaoning, China.

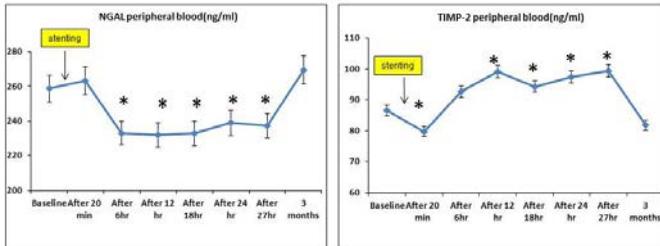
Background: ARAS reduces blood flow and perfusion pressures to the post-stenotic kidney (STK), ultimately producing inflammatory injury. The aim of our study was to identify and track renal injury biomarkers for 24 hours and 3 months after combined CT imaging and stent revascularization.

Methods: 12 patients with severe ARAS scheduled for revascularization for clinical indications were enrolled in a 3 day inpatient and restudied 3 months later. All subjects maintained ACE/ARB Rx and fixed Na⁺ intake, and were compared with Essential Hypertensives(EH) ($n=12$) undergoing the same biomarkers and imaging studies. Glomerular filtration rate (GFR) was measured by iothalamate clearance, blood flow and perfusion by Multidetector Computerized Tomography (MDCT) and NGAL, MCP-1, IL-10, TNF- α , KIM-1, IGFBP7 and TIMP-2 in renal vein and peripheral blood/IVC samples every 6 hours for 24 hours and after 3 months.

Results: Kidney perfusion, whole kidney blood flow, single kidney iothalamate GFR were reduced in the STKs compared to kidneys from EH and increased after stent revascularization.

	EH (n=12)	ARAS (n=12)		
		Baseline	20 minutes after stenting	3 months
Creatinine (mg/dl)	1.0±0.3	1.7±0.5		1.5±0.4
Cortical perfusion, mL/min per mL of tissue	3.61±1.26	2.36 ± 0.87*		2.65 ± 0.87
Cortical flow, mL/min	316±183	162 ± 84*		195 ± 80*
Single kidney GFR, mL/min per kidney	39±14	26± 14*		31 ± 19*
NGAL (renal vein)ng/ml	72±32	228± 63*	247 ±73	268 ± 74*
MCP-1(renal vein)ng/ml	153±78	663± 431*	403±252*	744±451

* P value < 0.05 vs EH. * P values < 0.05 vs baseline



Basal renal biomarkers were higher in EH. MCP-1 and IGFBP7 fell immediately then rose by 6 hours, while NGAL remained below baseline for 24 hours. All biomarkers rose to or above baseline by 3 months, despite increased STK GFR.

Conclusions: Renal biomarkers were universally elevated as compared to EH. Despite intense contrast exposure and renal artery stenting, our results demonstrate transient reductions during the 24 hours after revascularization in ARVD, before returning to sustained elevations by 3 months. These data reinforce ongoing inflammatory injury in ARVD despite restoration of blood flow to stenotic kidneys.

SA-PO223

Comparison of Urinary Angiotensinogen Level Between Septic and Dehydrated AKI Hiroyuki Suzuki, Eri Muso. Dept of Nephrology, Kitano Hospital, Osaka, Japan.

Background: Increasing evidences have suggested that urinary (U) angiotensinogen (ATG) is one of potential biomarkers related with severity of chronic kidney diseases (CKD). Recently, in addition to CKD, U-AGT has been reported to be a useful prognostic biomarker in acute kidney injury (AKI) especially after cardiac surgery, however, little is known about U-AGT in AKI due to other etiologies. In this study, we measured U-AGT in patients with pre-renal (dehydration) and renal (sepsis) AKI.

Methods: Fifteen patients who were hospitalized due to sepsis, and 6 patients who had AKI due to dehydration were included in the study. The patients included 13 women and 8 men with a mean age of 71.4 yr (range 41 to 94 yr). U-ATG levels were measured when sepsis or AKI was diagnosed and compared with clinical parameters and other known urinary renal injury biomarkers such as urinary liver-type fatty acid-binding protein (L-FABP), b2-microglobuline (MG), and NAG.

Results: Among 15 patients with sepsis, 7 were diagnosed as AKI. The number of cases in each AKIN stage from I, to III were 4, 1, and 2 in sepsis, and 3, 1, and 2 in dehydration, respectively. No patients have died from AKI. During AKI, peak Cre levels were 1.79mg/dl (238% increase) in sepsis group, and 2.88mg/dl (213%) in dehydration group. U-ATG in sepsis with AKI (84297±70397 ng AngI Eq/gCr) were significantly higher than in sepsis without AKI (12598 ±8916 ng AngI Eq/gCr) and dehydration group (14960±6771 ng AngI Eq/gCr). Among urinary markers, in sepsis group, U-ATG were strongly correlated with U-B2MG (r=0.914, p<0.01), U-NAG (r=0.552, p=0.033) and L-FABP (r=0.594, p=0.020) were also correlated with U-ATG. In contrast, in dehydration group, U-ATG were not correlated with U-B2MG, NAG, nor with L-FABP. In comparison with the severity of AKI and the levels of U-ATG, in sepsis group, ΔCre (peak – basal Cre) were positively correlated with U-ATG significantly (r=0.716, p=0.003). On the contrary, in dehydration group, U-ATG tended to decrease as maximum Cre increased.

Conclusions: Apparent difference of dynamism between in AKI due to sepsis and dehydration indicates that U-ATG could be a potent biomarker to distinguish renal from pre-renal AKI, before developing to CKD.

SA-PO224

AKI Development Upon SIRS Is Associated with Platelet Activation, Possibly Triggered by Mitochondrial DNA Derived from Damaged Cells Marcel Jansen,¹ Wilco P. Pulskens,² Diba Emal,¹ Sandrine Florquin,¹ Joris J. Roelofs,¹ Jaklien Leemans.¹ ¹Nephrology, Academic Medical Center, Amsterdam, Netherlands; ²Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Multiple inflammatory pathways are activated by non-infectious agents during Systemic inflammatory response syndrome (SIRS) leading to collateral damage, including the development of acute kidney injury (AKI). Pattern recognition receptors (PRRs) of the innate immune system sense Damage-Associated Molecular Patterns (DAMPs) leading to an immune response. Components of mitochondria e.g. unmethylated CpG-enriched mitochondrial DNA (mtDNA) that leak upon cell injury, are a source of DAMP. Platelets express several PRRs and play an important role in innate immunity. To

date, it is unclear which intrinsic factors trigger the onset of SIRS and associated AKI. We investigated the role of mtDNA during systemic inflammation and AKI and the role of platelets herein.

Methods: Human platelets were stimulated with mitochondrial DNA, genomic DNA or unmethylated CpG-enriched oligonucleotides (CpG ODN). Platelet activation was measured with FACS. In a single centre prospective observational study we included 37 patients diagnosed and classified for the onset of SIRS with or without the development of AKI that were admitted to the ICU. As a control we included (n=25) patients after elective major surgery without a diagnosis of either SIRS or AKI. Blood and urine samples were isolated and processed. Free circulating plasma and urinary mtDNA was determined by RT-PCR. Inflammatory mediators and PF4 in urine were measured using specific ELISA.

Results: Mitochondrial DNA, but not genomic DNA triggered platelet activation. Unmethylated CpG ODN, dose dependently stimulated platelet activation. Compared to ICU-controls, critically ill patients with SIRS demonstrated elevated levels of plasma and urinary mtDNA and proinflammatory cytokines. Compared to SIRS patients without AKI, the patients with AKI displayed elevated levels of urinary PF4—indicative of platelet activation.

Conclusions: The development of AKI in critically ill patients is associated with platelet activation, possibly triggered by mitochondrial DNA.

SA-PO225

Invaders in the Night: Sleep Apnea and Sub-Clinical Renal Injury Aaron A. Rampersad,¹ Shahab Bozorgmehri,¹ Areef Ishani,^{2,3} I. David Weiner,^{1,4} Satish P. Ramachandrarao,⁵ Rebecca Beyth,^{1,4} Muna T. Canales.^{1,4} ¹Univ of Florida, Gainesville, FL; ²Minneapolis VAMC; ³Univ of Minnesota, Minneapolis, MN; ⁴Malcom-Randall VAMC, Gainesville, FL; ⁵Univ of California, San Diego, CA.

Background: Sleep apnea is common in patients with CKD. We postulated that sleep apnea may cause renal injury through repeated ischemia-reperfusion. The current study correlated overnight changes in urinary excretion of renal injury biomarkers with severity of sleep apnea.

Methods: 39 consecutive participants in the SNORE Study, a longitudinal study of sleep apnea and kidney function decline, underwent overnight sleep study and provided spot urine samples before and after sleep. We measured urinary NGAL, L-FABP, KIM-1, and urinary cystatin-c levels, and correlated differences between AM and PM levels (AM-PM) with severity of sleep apnea or hypoxia. Sleep apnea was defined by the apnea-hypopnea index (AHI, events/hour); hypoxia was % total sleep time <90% SaO2 (%TST90). Data were log-transformed to normalize distribution.

Results: Patient characteristics: Mean age, 73.6±8.4 years; 90% male; 87% Caucasian, 13% black; BMI, 29.4±4.2 kg/m²; MDRD eGFR, 34.3±8.1 ml/min/1.73m²; Median urinary albumin/creatinine ratio, 46 mg/g Cr [IQR 9-357 mg/g Cr]. 69% had sleep apnea (AHI≥5); median AHI, 10 [IQR 2-23]; median %TST90, 15 [IQR3-22] with 34% %TST90<10%. Higher %TST90 was correlated with higher AM KIM-1 values (r=0.40, p=0.01) and greater increase in urinary KIM-1 (AM-PM) (r=0.32, p=0.04). None of the remaining biomarkers correlated with %TST90. Also, none of the overnight urinary biomarker changes correlated with AHI.

Conclusions: The correlation of KIM-1 with hypoxia suggests that SA may contribute to CKD through ischemic renal injury. Future studies with larger sample size and in non-CKD populations are needed to further test this hypothesis.

Funding: Other NIH Support - DK079337 UAB-UCSD O'Brien Center, Veterans Administration Support

SA-PO226

Body Mass Index and Acute Kidney Injury in Hospitalized Patients Yan Lun Allen Liu, Milind Nikam, Lee Ying Yeoh. Dept of Medicine, Khoo Teck Puat Hospital, Singapore.

Background: Acute kidney injury (AKI) is common in hospital settings. The association between AKI and Body Mass Index (BMI) in general hospitalized patients is not known. This study is to explore the incidence of AKI and the impact of BMI on AKI in hospitalized patients.

Methods: This was a single centre, retrospective, case-control study. All patients aged 21 or above under in-hospital care from January to December 2013 were recruited for analysis. We calculated the incidence of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria among different BMI groups (underweight [BMI < 18], normal [BMI 18-23], overweight [BMI 23-25] and obese [BMI > 25]), and then analyzed the risks of developing AKI within and between groups. Baseline creatinine was defined by the most recent value obtained in hospital up to 12 months before admission. If no previous serum creatinine was available, the lowest serum creatinine during hospitalization was used instead. If only one serum creatinine result was known during hospital stay, the baseline creatinine was estimated by the use of simplified Modification of Diet in Renal Disease (MDRD) formula (assuming a glomerular filtration rate [GFR] of 75 ml/min per 1.73 m²).

Results: A total of 12567 patients were recruited for analysis. Mean age was 62.5 ± 18.5 years. Male patients constituted 53.8% of the study population. 61.9% were Chinese ethnicity. There were 2656 patients suffered from AKI (21.1% of the whole study population), among which 10.7%, 6.1% and 4.4% had stage 1, 2 and 3 AKI respectively. Underweight patients (BMI < 18) had statistical significantly more stage 1 AKI than the rest of the population, while patients with BMI ≤ 25 had more stage 2 AKI (stage 1 AKI for underweight, normal, overweight and obese patients was 15%, 10.2%, 9.4% and 10.3% respectively; stage 2 AKI, 7.6%, 6.3%, 6.4% and 5.2% respectively). There was no difference in frequency of stage 3 AKI among different BMI groups.

Conclusions: Preliminary results revealed underweight hospitalized patients had increased risks of developing stage 1 AKI. Stage 2 AKI was more commonly seen in patients with BMI ≤ 25. BMI status was not associated with the development of severe AKI (stage 3).

SA-PO227

Hypermagnesemia as a Risk Factor for the Mortality in Intensive Care Unit Patients with Acute Kidney Injury Shunichi Shibazaki,¹ Makoto Araki,¹ Kohei Miura,¹ Daijo Inaguma.² ¹Dept of Nephrology, Suwa Central Hospital, Chino, Nagano, Japan; ²Dept of Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan.

Background: We need an easily measured biomarkers predicting for the mortality in acute kidney injury (AKI) because of high mortality rate. Therefore, we paid attention for serum magnesium (sMg) levels which reflects the renal tubular damage, and study the relationship sMg and prognosis in intensive care unit (ICU) patients with AKI.

Methods: A cohort study was conducted by collecting data from January to December 2014 in Nagoya Daini Red Cross Hospital. According to sMg at ICU 1st day, three groups were divided; low Mg group (sMg < 1.8mg/dL), normal Mg group (1.8mg/dL ≤ sMg < 2.6mg/dL), and high Mg group (sMg ≥ 2.6mg/dL). AKI was defined as serum creatinine (sCr) abrupt (within 7 days) increase to ≥ 1.5 times baseline or sCr increase by ≥ 0.3mg/dL. The primary endpoint was 28 days mortality after ICU admission. The secondary endpoint was the renal recovery rate, the renal replacement therapy (RRT) induction rate, and the transition rate to maintenance dialysis. Renal recovery was defined as an absence of AKI.

Results: Out of 1614 ICU patients, 200 patients were included. The number of each groups are following; low Mg group was 55, normal Mg group was 115, and high Mg group was 30. The mortality was higher in high Mg group than in other Mg group (p = 0.011). A multivariate analysis identified high Mg group as an independent risk factor for the mortality (p = 0.041). High Mg group had 2.39-fold increased odds of mortality against normal Mg group (95% CI 1.04 - 5.50). Kaplan-Meier curves showed the high Mg group was associated with higher mortality.

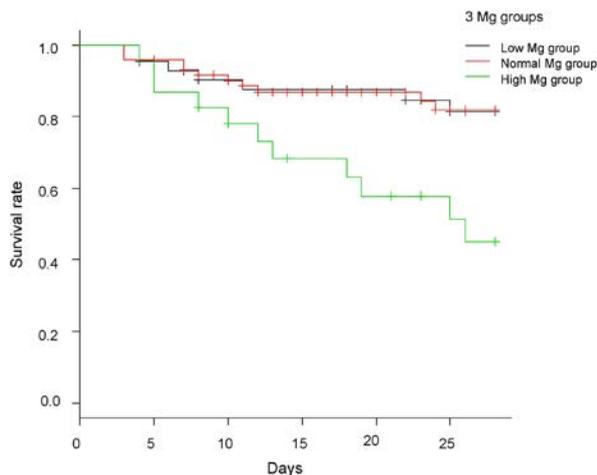


Figure 1: Kaplan-Meier curves for the mortality (p = 0.003)

There was no significant association between each groups and the secondary endpoints.

Conclusions: Hypermagnesemia is an independent risk factor for the mortality in ICU patients with AKI.

SA-PO228

Gemcitabine-Induced Thrombotic Microangiopathy (TMA): A Report from the French Pharmacovigilance Network Noemie Jourde-chiche,¹ Florence Daviet,¹ Frank Rouby,² Bertrand Gondouin,¹ Marion Sallée,¹ Julie Moussi-Frances,¹ Stephane Burtey,¹ Pascale Poullin,³ Bertrand Dussol,¹ Joelle Micallef.² ¹Nephrology, Aix-Marseille Univ, Marseille, France; ²Pharmacology and Pharmacovigilance, Aix-Marseille Univ, Marseille, France; ³Hemapheresis, Aix-Marseille Univ, Marseille, France.

Background: Gemcitabine is a chemotherapy which use can be limited by renal adverse events, in particular thrombotic microangiopathy (TMA). This study evaluated the occurrence of gemcitabine-induced TMA, and described therapeutic strategies and outcomes.

Methods: All spontaneous reports of TMA attributed to gemcitabine in the French Pharmacovigilance Network database, between January 2000 and May 2015, were reviewed using a standardized questionnaire.

Results: 81 cases of TMA were reported in 48 male (59%) and 33 female (41%), with a median age of 63.5 yrs (range 39-87). Gemcitabine was prescribed for pancreatic (58%), pulmonary (15%), breast (8%), biliary tract (6%), urinary tract (5%), uterine (3%), testicular (1%) or liver (1%) cancers, or T lymphoma (3%). TMA occurred after a median of 7 months (range 0.2-60), and a median cumulative dose of 21.8g (range 1.1-48.6). Main symptoms were hypertension (51%), diffuse edema and/or congestive heart failure (42%), acute renal failure (86%), thrombocytopenia (67%), hemolytic anemia (86%). Median

creatinine level was 1.8 mg/dL (range 0.8-17). In 6 patients, renal TMA was biopsy-proven. Renal replacement therapy was required in 10 (12%) patients, plasma exchanges (PEX) were performed in 17 (21%), 8 (10%) received fresh frozen plasma infusions, 9 (11%) corticosteroids, and 3 (4%) eculizumab (after PEX failure). Evolution data were available for 59 (73%) patients, among which the 17 treated with PEX. Hematological and renal remission was achieved in 35% with PEX versus 50% without, hematological remission without renal improvement in 18% with versus 26%, and no improvement was observed in 47% with versus 24% without PEX. Only one patient improved with eculizumab.

Conclusions: Gemcitabine treatment can be associated with TMA and severe renal adverse effects. The benefit of plasma exchange or eculizumab in this setting remains uncertain.

SA-PO229

Contribution of Drugs versus Risk Factors in Drug-Induced Renal Injury

Celina D. Cepeda,¹ Linda Awdishu,¹ Etienne Macedo,¹ Dinna Cruz,¹ Stuart Goldstein,² Jorge Cerda,³ David T. Selewski,⁴ Michael Zappitelli,⁵ Andrew J.P. Lewington,⁷ Ravindra L. Mehta.¹ ¹Nephrology, Univ of California San Diego, San Diego, CA; ²Nephrology, Univ of Cincinnati, Cincinnati, OH; ³Nephrology, Albany Medical College, Albany, NY; ⁴Nephrology, Univ of Michigan, Ann Arbor, MI; ⁵Nephrology, Univ of Montreal, Montreal, QC, Canada; ⁶Nephrology, Cares Hospital India, Hyderabad, India; ⁷Nephrology, St. James's Univ Hospital, Leeds, London, United Kingdom.

Background: Drug-induced renal injury (DIRI) is an increasing cause of acute kidney injury (AKI). Attribution of DIRI requires consideration of the drug exposure, the number of drugs involved and underlying or concomitant risk factors (RF). We hypothesized that underlying RF would influence attribution of DIRI.

Methods: The drug induced renal injury (DIRECT) study is an ongoing prospective multicenter study evaluating genetic determinants of DIRI. Each enrolled case was adjudicated for causality by two independent nephrologists. We analyzed the first consecutive 86 adult and pediatric AKI cases. We evaluated the percent agreement, kappa statistic, and contribution of each drug (in setting of multidrug injury) and AKI RF.

Results: Adjudicators agreed 87.2% (n=75) had DIRI. For non-DIRI cases, causality could not be established because of competing AKI RF. RF contributed to AKI in 86% of adults and 70% of children. Adjudicators disagreed on the percent attribution for each drug in 52%. For DIRI cases, inter-rater agreement on percentage attributed to drug 1 was 48% with kappa=0.239 (p=0.001). For non-DIRI cases, inter-rater agreement for drug 1 was 81.8% and RF attribution was 80%.

Percent Attribution of Drugs versus Risk Factors		
Percentage attributed to drug	Number of cases agreed upon	DIRI
		n=75
No agreement	39	30 (10-50)
0-25%	1	65 (60-65)
26-50%	20	40 (12.5-50)
51-75%	2	40
76-100%	13	0 (0-20)

Conclusions: Underlying RF are common in DIRI associated AKI. Causality assessment in DIRI is complex due to difficulty in determining the attribution of drug and RF. CAT for DIRI should incorporate AKI RF and their interaction with drugs.

Funding: Private Foundation Support

SA-PO230

Reduced Incidence of Post-Operative Acute Kidney Injury After Cardiovascular Surgery

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Background: Acute kidney injury (AKI) is a serious complication of cardiac surgery. The aim of this study was to examine time trends in incidence and survival of patients diagnosed with AKI following cardiac and thoracic aorta surgery.

Methods: This was a retrospective study of all heart and thoracic aorta operations performed on adults in Iceland from 2007 to 2014. AKI was diagnosed according to the KDIGO criteria based on serum creatinine values in the electronic database of the clinical laboratory at our institution. Survival status was verified at Statistics Iceland. The incidence of AKI and its outcome was compared between the first and second half of the 8 year study period using Chi squared and the Kaplan Meier method. Outcome between AKI and non-AKI patients was compared by propensity score matching (1:2, non-replacement matching).

Results: A total of 2224 patients underwent 2502 operations during the study period, of which 28.4% were acute operations. Median (range) age at operation was 67 (18-97) years and 70.7% of patients were men. AKI occurred after 417 operations (16.7%). Of these 302 (12.1%), 69 (2.8%) and 46 (1.8%) were of stage 1, 2 and 3, respectively. Incidence of AKI

decreased from 19.2% in the first period to 14.5% in the second period (p=0.002). Survival of AKI patients at 30 days and 1 year did not differ between time periods, being 82.6% vs 83.8% and 79.5% vs 76.8%, respectively (p>0.10). Survival was worse for patients with AKI compared with the propensity score matched control cohort, both at 30 days (86.1% vs. 96.5%, p=0.0001) and at 1 year postoperatively (81.2% vs. 91.5%, p=0.0001).

Conclusions: The incidence of AKI following cardiac and thoracic aorta surgery is decreasing. Nevertheless it still affects one in seven patients and even though most patients have mild AKI, it is associated with increased mortality which remains unchanged over the past decade. *Funding:* Private Foundation Support

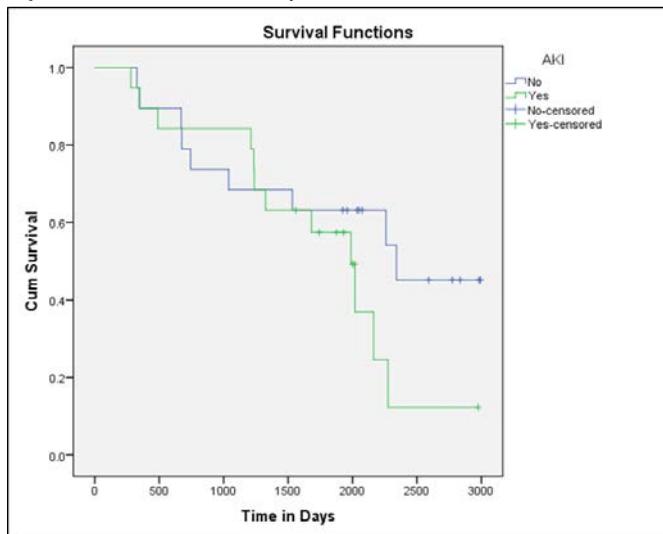
SA-PO231

Acute Kidney Injury in Patients with Chronic Kidney Disease: Aetiology and Survival Comparisons to Non-Acute Kidney Injury Chronic Kidney Disease Population Akib Khan,¹ James Ritchie,² Smeeta Sinha.³ ¹Senior House Officer, Imperial NHS Foundation Trust, London, United Kingdom; ²Renal Medicine, Univ of Manchester, Manchester, United Kingdom; ³Nephrology, Salford Royal Foundation Trust, Salford, United Kingdom.

Background: AKI, described by an acute (hours to days) fall in kidney function, is associated with significant morbidity and mortality. Poor outcomes exist when AKI is superimposed on CKD, a disease involving structural or functional renal abnormalities in a chronic setting (>3 months). We present a single-centre prospective observational study; retrospectively analysed. We determine the factors surrounding AKI on CKD. Aetiology, length of stay, specialist review and medication data were examined. We compare AKI on CKD patients' survival to matched non-AKI CKD patients.

Methods: CRISIS database CKD patients matching inclusion criteria treated at Salford Royal Foundation Trust were studied (n=542). A 2.0-3.0 and >3.0 times serum creatinine increase from last measurement was used to define Acute Kidney Injury Network stages 2 (n=17) and 3 (n=10) events respectively. Controls were matched by age, eGFR and blood pressure. Logistic Regression, Cox-Hazard Ratio and Kaplan-Meier Survival Plots were used.

Results: Aetiological factors associated with AKI included sepsis (48.1%), drug-induced (29.6%) and dehydration (25.9%). Septic-AKI had a 1.405 odds ratio (95%CI:0.099-19.936,p=0.801) of death compared to non-septic events. Hazard ratio for death due to AKI on CKD compared to non-AKI CKD was 1.77 (95%CI:0.72-4.33,p=0.207). Kaplan-Meier survival function clearly demonstrates this.



Conclusions: Aetiology of AKI in our patient group was similar to that seen in non-CKD studies. There was a clear trend towards increased all-cause mortality in patients with AKI on CKD in comparison to non-AKI CKD patients. Renal function decline rate following AKI on CKD should be explored in the future.

SA-PO232

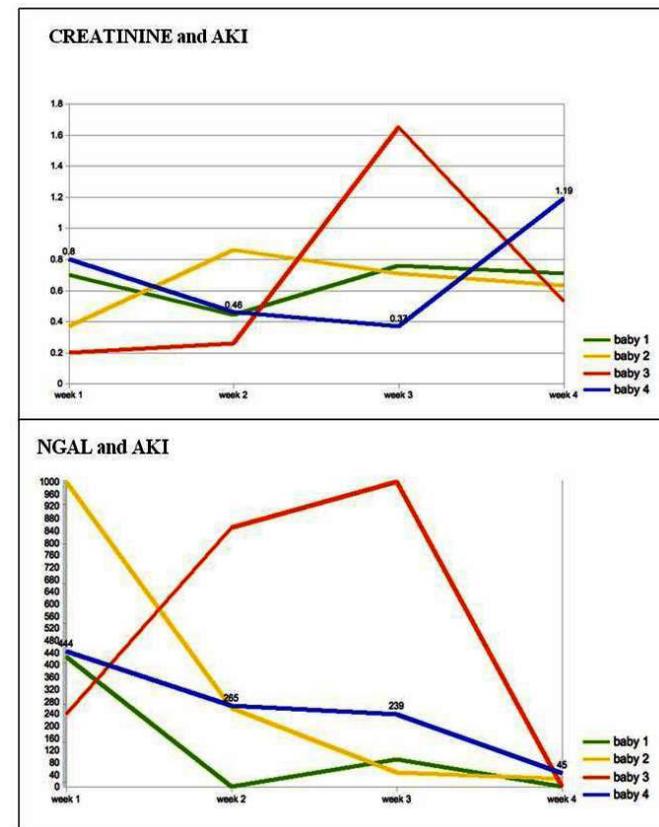
Prospective Study of Incidence and Early Detection of Acute Renal Failure in Preterm Babies in a Tertiary Center in South India Indira Agarwal, Nithya Ponmudi, Anil K. Kuruvilla, Vijayakumar Theophilus-Sunder. *Pediatric Nephrology, Christian Medical College, Vellore, Tamil Nadu, India; Neonatology, Christian Medical College, Vellore, Tamil Nadu, India; Nephrology, Christian Medical College, Vellore, Tamil Nadu, India.*

Background: Preterm babies are at risk for ischemia, hypovolemia and hypotension and thus vulnerable to Acute kidney injury (AKI). We aimed to study the incidence and predisposing factors for AKI in preterm babies and to assess the usefulness of urinary NGAL as a predictor of kidney injury.

Methods: Babies born < 32 weeks+6 weeks were recruited; those with abnormal antenatal renal scans and major congenital anomalies were excluded. Weekly monitoring of urine output, clinical progress, interventions, ventilation, unexpected events and use of nephrotoxic drugs was done. Serum creatinine and urine NGAL was collected at 72

hours of age and weekly thereafter. Descriptive statistics using mean+/- SD for continuous variables, ANOVA and chi square test / Fishers exact test for categorical variables and Risk factor analysis using log binomial was performed.

Results: Of the 4823 live births, 80 fulfilled inclusion criteria (10.14%). The incidence of AKI was 12.6%. The risk factors included oligoanuria, PDA, nephrotoxic drugs, low Apgar, mechanical ventilation, CPAP and abnormal antenatal scans. Urine NGAL was estimated in 31 babies. It rose earlier and was significantly elevated in those on mechanical ventilation by week 2 while Creatinine rose only by week 3.



NGAL was inversely proportionate to gestational age and birth-weight. Both NGAL rise and creatinine were higher in babies with AKI associated with NSAIDs, umbilical lines and asphyxia.

Conclusions: NGAL holds promise as an early marker of AKI and a non invasive test for serial monitoring of renal function in preterm babies. A study with a larger sample size is required to establish reference values for NGAL in preterm babies.

SA-PO233

Acute Kidney Injury Electronic Alerts in Primary Care Conor Patrick Moran,¹ Ying C. Kuan,¹ Patrick Lm Lynch,² Francis Mccarroll.¹ ¹Dept of Nephrology, Altnagelvin Hospital, Londonderry, United Kingdom; ²Dept of Clinical Chemistry, Altnagelvin Hospital, Londonderry, United Kingdom.

Background: Acute Kidney Injury, (AKI), is common with a variably reported mortality, (15-60%). A UK national audit reported that up to 30% of cases were avoidable and that as much as 43-61% of post-admission AKI experienced an unacceptable delay in recognition. AKI is regarded as the remit of Secondary Care and there have been few studies examining Community Acquired AKI, (CA-AKI). Guidelines have recommended the use of electronic alerts (e-alerts) for AKI detection in both Primary and Secondary care. We examined the incidence and mortality of CA-AKI.

Methods: We introduced AKI e-alerts with accompanying e-guidance in late October 2014 and prospectively collected data on the patients identified with severe AKI in Primary, (n=121), and Secondary care, (n=110), environments. Data collection was carried out for 3 months. The demographics of both cohorts were compared.

Results: Median age, (74.5 years vs. 75 years), gender distribution, (M:F: 48% / 52% vs. 44.5% / 55.5%), and median time to death, (8 days vs. 11 days), were comparable. 44 Alerts were from Primary Care and 77 from Emergency Department. Of the Primary Care Alerts, 20 patients were subsequently admitted. Of those who were not, 3 died within 30 days, (1. Died at 5 days, 2. Died at 8 days, 3. Died at 21 days). Despite this, Community-acquired AKI was associated with a 30-day mortality of 10.7%. Hospital-acquired AKI, (HA-AKI), was associated with a 28.2% 30-day mortality, (p<0.001). Sub-group analysis showed Primary care alert associated with 13.64% mortality and Primary Care alerts with 9.76%, (p<0.001). Median Age at Death; CA-AKI 80 years. Median time to death; CA-AKI 5 days, HA-AKI 11 days.

Conclusions: AKI is common and associated with a significant morbidity and mortality. CA-AKI is common opportunities at diagnosis and intervention are often missed with grave

consequences. Appropriate management of CA-AKI could help reduce the economic and physical burden associated with AKI and reduce the long-term burden of CKD. Further work is required to expand the role of AKI e-Alerts in Primary Care.

SA-PO234

Acute Kidney Injury Causes and Outcome: A Single Center Experience from Sudan Dalia Elrashid M Yousif,^{1,2} Maha Farah,² Len A. Usvyat,^{3,4} Roberto Pecoits-Filho,¹ Peter Kotanko.³ ¹PUCPR, Curitiba, PR, Brazil; ²Nephrology, SOBA Univ Hospital, Khartoum, Sudan; ³Renal Research Inst, New York, NY; ⁴Fresenius Medical Care, Bad Homburg, Germany.

Background: Acute kidney injury (AKI) is a challenging problem in Africa—a diverse continent with regards to population and financial and medical resources. There are no reliable statistics about the incidence of AKI in Africa. Based on sporadic regional publications the incidence has been estimated at 150 per million population. In addition to infectious diseases; toxins play a major etiologic role in AKI.

Methods: In this study we analyzed data from Omer Belail Renal Center in Soba University Hospital, Sudan, a tertiary referral center with a catchment area of 3 million citizens. All hemodialysis (HD) patients treated for AKI in the period between 1/1/2013 and 12/31/2014 were included in the study.

Results: Out of 520 hemodialysis patients we identified 69 patients with AKI; 39 (56.5%) were males. The mean±SD age was 40.5±17.4 years. Serum creatinine and blood urea levels on admission were 14.7±6.7 and 245±125 mg/dl, respectively. Serum creatinine and blood urea levels at discharge were 2.5±2.1 and 53±32 mg/dl, respectively. 29 patients (42%) experienced recovery of normal renal function; the recorded mortality was 13 %. AKI causes.

Acute tubular necrosis	15 (21.7%)
Obstructive uropathy	10 (14.5%)
Glomerulonephritis	7 (10.1%)
Acute interstitial nephritis	6 (8.7%)
Sepsis	6 (8.7%)
Snake bite	5 (7.2%)
Hair dye poisoning	4 (5.8%)
Hemolytic uremic syndrome	3 (4.3%)
Fluid depletion	1 (1.4%)
Others	12 (17.4%)

Conclusions: AKI has become increasingly prevalent in developing countries, and is associated with severe morbidity and mortality. Many causes of AKI can be prevented by interventions at the individual, community, and regional levels. Efforts should be directed to eradicate causes of AKI, expedite diagnosis, and aggressively manage pre-renal conditions and specific infections.

SA-PO235

Usefulness of Presepsin, Procalcitonin and IL6 as a Biomarkers of Adverse Renal Outcome and Mortality After Cardiac Surgery Alessandra Brocca, Grazia Maria Virzi, Maria Jimena Mucino-Bermejo, Davide Giavarina, Massimo de Cal, Claudio Ronco. *S Bortolo Hospital, Vicenza.*

Background: Cardiac surgery (CS) is now possible in increasingly high-risk patients (pts): accurate evaluation of surgical risk is crucial. Mortality and negative impact on distant organs must be evaluated. In a large number of clinical scenarios, biomarkers have been proven to be reliable tools in clinical settings either for single a single biomarker or a biomarker panels. Presepsin has been reported to be useful for stratifying mortality risk among septic pts in the ICU and thus it may also be helpful in many different clinical situations. Procalcitonin is related to the development of postoperative complications. IL6 is considered to be a major mediator of the acute phase response to cardiopulmonary bypass. The main aim of this study is to assess the usefulness of Presepsin, Procalcitonin and IL6 as a biomarkers in predicting mortality and negative renal outcome among CS pts.

Methods: Observational single center study that includes 122 adult CS pts. Blood samples were collected at the second day after surgery. Presepsin was tested by the PATHFAST Immunoanalyzer system, Procalcitonin by BRAHMS PCT sensitive KRYPTOR and IL6 by ELISA assay. A p-value of <0.05 was considered statistically significant.

Results: We observed that Presepsin and IL6 are better predictors of inhospital (AUC=0.831 and 0.819), 30-day (AUC=0.723 and 0.785) and global mortality (AUC=0.759 and 0.793) than Procalcitonin (p<0.05). Pts with worse renal outcome (defined as AKI, change on CKD stage or need for CRRT) have significantly higher Presepsin and Procalcitonin levels (p<0.05). IL6 is not significantly different in pts with adverse renal outcome compare whit those without.

Conclusions: Presepsin and IL6 levels correlate with the risk of death better than Procalcitonin. Higher Presepsin and Procalcitonin levels are associated with adverse renal outcomes in this population. It is possible that a combination of these three biomarker in an inflammatory multi-biomarker panel as opposed to a single biomarker should be taken as “add-value” rather than a “unique-predicting” data.

Funding: Private Foundation Support

SA-PO236

Allopurinol Attenuates Rhabdomyolysis-Induced Acute Kidney Injury: Renal and Muscular Protection Pedro H.F. Gois, Daniele Canale, Rildo A. Volpini, Daniela Ferreira, Mariana Veras, Maria H.M. Shimizu, Antonio C. Seguro. *Univ of São Paulo.*

Background: Myoglobinuric acute kidney injury (AKI) is the most severe complication of rhabdomyolysis. **Aim:** To evaluate the efficacy of allopurinol (Allo) on rhabdomyolysis-induced AKI.

Methods: Male Wistar rats were injected intramuscularly with 5ml/Kg body weight (BW) of either 50% glycerol (Gly) or 0.9% saline (S). Five groups were studied: S (n=5), S+Allo (n=6), Gly (n=7), Gly+Allo (n=7), Gly+ivAllo (n=7). S+Allo and Gly+Allo rats received Allo (300mg/L) in drinking water 7 days prior to and for 24h after Gly/S injection. Gly+ivAllo: intravenous Allo (50mg/Kg BW) 30' after Gly injection and 300mg/L in drinking water thereafter.

Results: Gly rats showed markedly reduced glomerular filtration rate (GFR, inulin clearance) associated with renal vasoconstriction, renal tubular damage, increased oxidative stress, apoptosis and inflammation. Allo treatment ameliorated all these alterations. Allo reduced muscular oxidative stress and accelerated its recovery.

	S	S+Allo	Gly	Gly+Allo
GFR (mL/min/100gBW)	1.12±0.03	1.02±0.05	0.49±0.04 ^{abc}	0.78±0.08 ^{af}
RBF (3h) mL/min	6.6±0.3	6.7±0.2	3.8±0.3 ^{abc}	5.3±0.5
Plasma TBARS (nmol/mL)	1.4±0.2	1.1±0.2	6.8±1.0 ^{abc}	3.7±0.8
Muscular TBARS	0.9±0.1	0.8±0.1	1.6±0.2 ^{abc}	0.8±0.1
Renal MnSOD (%)	100±2	113±27	311±55 ^{abc}	126±25
Renal Caspase-3 (%)	100±8	103±6	158±18 ^{abc}	67±5
CPK (3h) mg/dL	467±75	298±31	13.101±2.388 ^{abc}	11.265±2.100 ^{abc}
CPK (24h)	374±37	398±50	917±358 ^{abc}	358±45
TIS	0.06±0.01	0.22±0.05	1.48±0.13 ^{cd}	0.81±0.17 ^{ac}
Intrarenal Lymphocytes	7±1	6±1	27±2 ^{abc}	13±2 ^{bf}
Muscular Injury Score	0	0	2.2±0.2 ^{abc}	1.5±0.2 ^{ac}

^ap<0.001, ^bp<0.01 vs. SF, ^cp<0.001, ^dp<0.01 vs. Gly+Allo, ^ep<0.001, ^fp<0.01 vs. SF+Allo.

Therapeutic Allo also improved GFR (0.78±0.06), renal blood flow (RBF) (6.5±0.3), plasma TBARS (1.2±0.3) and tubular injury score (TIS) (0.89±0.17).

Conclusions: Prophylactic and therapeutic Allo attenuates Gly-induced AKI by reducing oxidative stress (systemic, muscular and renal), inflammation and apoptosis. It may represent a new therapeutic approach for rhabdomyolysis and myoglobinuric AKI. (FAPESP)

Funding: Government Support - Non-U.S.

SA-PO237

Cell Cycle Progression in the Early Phase of Septic Kidney Daisuke Nakano, Akira Nishiyama. *Dept of Pharmacology, Kagawa Univ, Kagawa, Japan.*

Background: The recovery of renal function after acute kidney injury (AKI) is likely controlled by proliferation of survived tubular cells in damaged nephrons containing cell death or sloughing. However, recent studies revealed that AKI concomitant with sepsis had significantly less tubular cell death than other forms of AKI, such as ischemic- and drug-induced AKI. It has not been examined whether septic AKI accelerates tubular cell proliferation in the condition with less cell death. In the present study, we examined the time-course changes in tubular cell proliferation after sepsis.

Methods: Lipopolysaccharide (LPS) and cecum ligation and puncture (CLP) model were used to induce sepsis in mice. Cell cycle progression was assessed by intravital imaging of Tg(FucciG1)#596Bsi (Fucci) mice, which express monomeric Kusabira-Orange2 in G1/0 phase cells, and immunohistochemistry for Ki67 or bromodeoxyuridine in young (8-12 weeks of age) and old (18-20 months of age) C57Bl/6 mice.

Results: Fucci mice (8 weeks of age) showed an increase in G1/0 to S transition of tubular cell cycle in the early phase of sepsis (within 2 hours in LPS and 4 hours in CLP). Ki67 and bromodeoxyuridine staining were increased only in young mice (Ki67⁺ cell number: 1.5±0.1 fold increase in both LPS and CLP mice compared to normal control), not in old mice (Ki67⁺ cell number: 0.8±0.1 fold in LPS mice and 1.0±0.1 fold in CLP mice compared to the control) at a similar time course observed in Fucci mice. Etoposide, an anti-cancer drug, abolished the cell proliferation after LPS injection in young mice. Importantly, old mice or etoposide-treated young mice showed much worse AKI as compared to young mice at 24h after sepsis. Moreover, mice lacking p21, a cyclin-dependent kinase inhibitor, showed a marked increase in Ki67⁺ cells after LPS (2.2±0.1 fold increase vs. WT mice).

Conclusions: These results indicate that sepsis induces tubular cell proliferation in the early-phase of septic kidney. This situation may be a compensatory mechanism against the development of AKI since the frequency of cell proliferation is inversely correlated with the severity of sepsis. Moreover, cell senescence may worsen this compensation leading to an increased risk of AKI.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

SA-PO238

Hepcidin Mitigates Endotoxin-Induced AKI Yogesh M. Scindia, Paromita Dey, Sundararaman Swaminathan. *Medicine, Univ of Virginia, Charlottesville, VA.*

Background: Sepsis is a common cause of acute kidney injury (AKI). Sepsis-associated inflammation induces hypoferrremia and thereby limits iron availability to pathogens. It has been shown that hepcidin-induced degradation of ferroportin and consequent iron restriction are key for this hypoferrremic state. Since, iron has been implicated in the pathogenesis of both sepsis and AKI, we hypothesized that hepcidin pretreatment would mitigate bacterial endotoxin-induced AKI.

Methods: C57BL/6 were treated with saline or 50 mg of hepcidin, 24 hours prior to LPS (*Escherichia coli O111:B4*) injection (6.5 mg/kg). Renal function, injury and inflammatory markers were examined up to 24 hours post LPS injection. Mouse glomerular endothelial cells (MGEC) were cultured with 100 ng/mL LPS for 6 hours after treating them with and without 1 mg/mL hepcidin for 12 hours.

Results: Kidney function (as measured by serum BUN) significantly declined 2 hours post LPS injection and progressively deteriorated for 24 hours. This was prevented by hepcidin treatment (BUN: LPS; 83.55 Vs Hepcidin + LPS; 32.33, $p < 0.001$). Renal NGAL expression paralleled the changes in BUN (NGAL: LPS; 6.74 Vs Hepcidin + LPS; 0.78, $p < 0.001$). Hepcidin treatment also reduced early systemic TNF alpha production following LPS injection (TNF alpha: LPS; 2266 Vs Hepcidin + LPS; 1248, $p < 0.01$). The ultra-structural morphology of the glomeruli revealed extensive loss of endothelial fenestrae and epithelial mitochondria in LPS treated mice, which was prevented by hepcidin treatment. However, MGEC cultures treated with or without hepcidin up-regulated endothelin gene to similar levels after stimulation with LPS.

Conclusions: Our results demonstrate a novel protective role of hepcidin in endotoxin-mediated AKI, which is largely exerted through down regulation of systemic cytokine production.

Funding: NIDDK Support

SA-PO239

ELK-B Peptide Prevents Renal Histological Damage and Mortality in Septic Mice Ana C. Souza,¹ Irina Baranova,² Jonathan Street,¹ Xuzhen Hu,¹ Peter S.T. Yuen,¹ Robert A. Star.¹ ¹*Kidney Diseases Branch, NIDDK, NIH, Bethesda, MD;* ²*Clinical Center, NIH, Bethesda, MD.*

Background: Targeting SR-BI/II and CD36 receptors with L-37pA, an antagonist peptide, reduced multi-organ failure, peritoneal bacterial counts, and increased survival from 6 to 27% in antibiotic-treated mice subjected to cecal ligation and puncture (CLP)-induced sepsis (J Immunol. 2012). We tested ELK-B, a peptide more specific to the CD36 receptor.

Methods: Because the free peptide was toxic, ELK-B was formulated with micellar 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine. For survival study, animals were randomized into two groups: CLP (N=16) and CLP+ELK-B (15 mg/kg, N=15). A blinded observer administered treatments every 12h until death or until euthanized per protocol. For acute studies, 10 mice/group were subjected to CLP+saline (CLP) or CLP+ELK-B; saline or ELK-B was administered IV 0 and 6h after CLP. 18h post-CLP mice were euthanized for peritoneal lavage, and blood/organs collection. Serum creatinine (Cr) was measured by HPLC, BUN by colorimetry, and AST, ALT by an autoanalyzer. PAS-stained kidney sections were scored for renal tubular damage. Peritoneal bacterial cell counts were expressed per mouse. Caspase-3 IHC was performed on spleens. Data were analyzed by ANOVA and log-rank test.

Results: ELK-B significantly increased survival: all CLP+vehicle mice died by 78h, whereas 31% of ELK-B treated mice were still alive at 7 days. The survival curves did not diverge until 36h. At 18h (before survival curves diverged), ELK-B did not alter Cr (sham, CLP, CLP+ELK-B= 0.07±0.01, 0.30±0.06, and 0.21±0.06 mg/dl); BUN, AST, or ALT. ELK-B significantly reduced tubular damage ($p < 0.001$ vs sham; $p < 0.01$ vs CLP+ELK-B). Spleen caspase-3⁺ cells were increased 18X in CLP and 6.8X in CLP+ELK-B but not statistically different. Log peritoneal bacterial counts were decreased 2X in CLP+ELK-B ($p < 0.05$).

Conclusions: ELK-B reduced 7 day mortality and 18h renal histological damage after sepsis. However, it did not alter other biochemical outcomes at 18h. This suggests that it may act late in sepsis, perhaps by increasing bacterial killing.

Funding: NIDDK Support

SA-PO240

Renal Ischemic Preconditioning Protects against Septic Acute Kidney Injury via miR-21 Ping Jia,¹ Yi Fang,¹ Mingyu Liang,² Xiaoliang Ding,¹ ¹*Dept of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China;* ²*Dept of Physiology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Septic acute kidney injury (AKI) is one of the most common and life-threatening complications in critically ill patients, and there is no approved effective treatment. We have shown ischemic preconditioning upregulates miR-21, provides renoprotection against subsequent ischemia reperfusion injury. Here we studied the effects of ischemic preconditioning on septic AKI and its mechanism.

Methods: Bilateral renal pedicles were clamped for 15 min in mice 24 h before the induction of septic AKI, and septic AKI was induced by intraperitoneal injection of lipopolysaccharide. The effects of renal ischemic preconditioning on LPS-induced AKI were investigated, including changes of renal function, histology, inflammation and apoptosis in kidneys. The role of microRNA, miR-21, in renal protection conferred by the ischemic preconditioning was examined using in vivo knockdown of miR-21 and miR-21 signaling pathways were analyzed.

Results: We observed that renal ischemic preconditioning provided morphological and functional renoprotection, characterized by attenuation of renal tubular damage, cell apoptosis, and a reduction in inflammation in circulation. Furthermore, we found that renal ischemic preconditioning significantly upregulated the expression of miR-21 in kidneys, suppressed proinflammatory factor PDCD4 expression and NF- κ B activity, increased IL-10 production. Meanwhile, renal ischemic preconditioning also suppressed the expression of PTEN which is a proapoptotic protein, activating Akt signaling pathway, subsequently increasing the expression of Bcl-2 and inhibiting Caspase-3. A locked nucleic acid-modified anti-miR-21, given before renal ischemic preconditioning, knocked down miR-21 effectively, and upregulated its target effector PTEN expression, resulting in increase of apoptosis, exacerbated LPS-induced AKI.

Conclusions: Our findings demonstrate that renal ischemic preconditioning protects against LPS-induced AKI, and miR-21 coordinates its downstream signaling to reducing cell apoptosis and circulatory inflammation, contributing to renal protection.

SA-PO241

Remote Ischemic Preconditioning Protects against Contrast-Induced Nephropathy via Renalase Induced by TNF α /NF κ B Pathway Feng Wang, Zeyuan Lu, Jianyong Yin, Guangyuan Zhang, Niansong Wang. *Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Renalase is a flavin adenine dinucleotide-dependent amine oxidase which has recently been suggested to be a reno-protective molecule. Herein we suggested that renalase expression induced by circulatory TNF- α which was evoked by remote ischemic preconditioning (rIPC) play a key role in contrast-induced nephropathy (CIN) protection.

Methods: CIN model was setup by Ioversol intravenous injection to SD rats. Limbs ischemic preconditioning was carried out 24 hours before CIN inducing. TNF- α blocking, NF- κ B blocking, HIF blocking and renalase blocking were performed respectively. TNF- α administration was also performed as rIPC mimic. Renal injury, kidney oxidative stress, renal function, renalase expression, and circulating TNF- α after IPC were assessed. HK2 exposure to TNF- α and its blocker were studied and renalase expression was assessed.

Results: Reduced tubular injury, decreased oxidative stress and improved renal function were observed in CIN rats following rIPC. The therapeutic effects could be neutralized by renalase blocking. Renalase expression was significantly up-regulated after rIPC. rIPC induced renalase expression could be abolished by TNF- α blocking or NF κ B blocking but not HIF blocking. Up-regulated renalase triggered by TNF- α could also be blocked by NF κ B both in vivo and in vitro.

Conclusions: Renalase expression which mediated by TNF α /NF κ B pathway played an essential role in reno-protection of rIPC for CIN.

Funding: Government Support - Non-U.S.

SA-PO242

DNA Methylation in Cisplatin-Induced Acute Kidney Injury Chunyuan Guo,^{1,2} Xiao Xiao,^{1,2} Qingqing Wei,^{1,2} Zheng Dong,^{1,2} ¹*Cellular Biology and Anatomy, Georgia Regents Univ, Augusta, GA;* ²*Charlie Norwood VA Medical Center, Augusta, GA.*

Background: DNA methylation is a major epigenetic modification, which plays an important role in regulating gene transcription without changing primary nucleotide sequence. DNA methylation has been implicated in major diseases, such as cancer. However, the changes of DNA methylation in kidney diseases, such as cisplatin-induced nephrotoxicity, remain unclear.

Methods: We determined the global DNA methylation changes in cisplatin-induced AKI by reduced representation bisulfite sequencing (RRBS) using kidney cortex from mice treated with cisplatin. We also established proximal tubule-specific DNMT1 (PT-DNMT1) knockout mice to determine the role of DNA methylation in cisplatin-induced AKI.

Results: Totally 1.5 and 1.9 millions of CpG sites were analyzed in the control and cisplatin treated kidney samples, respectively. Compared with control, cisplatin-treated samples showed aberrant DNA methylation changes, resulting in the identification of 236 differentially methylated regions (DMRs). Further analysis identified 15 genes that contained DMRs at 5' end regulatory promoter region or 5' UTR. To determine the pathological role of DNA methylation, we established the PT-DNMT1 model, in which the DNA methyltransferase 1 gene was specifically deleted from kidney proximal tubules. Compared with wide type mice, PT-DNMT1 knockout mice showed higher necrotic tubular damage at 4 day after cisplatin injection. Although BUN did not show difference between wide type and knockout mice, serum creatinine was increased in knockout mice treated with cisplatin.

Conclusions: Cisplatin induced significant changes in DNA methylation in kidney tissues, which may contribute to gene regulation and related kidney injury.

Funding: NIDDK Support, Veterans Administration Support

SA-PO243

Blockade of KCa3.1 Potassium Channels Protects against Cisplatin-Induced Acute Kidney Injury Cheng-Lung Chen,¹ Li-Heng Pao.^{1,2,3,4} ¹Graduate Inst of Life Sciences; ²School of Pharmacy, National Defense Medical Center, Taipei, Taiwan; ³Graduate Inst of Health-Industry Technology; ⁴Research Center for Industry of Human Ecology, Chang Gung Univ of Science and Technology, Taoyuan, Taiwan.

Background: Anti-tumor efficacy of cisplatin chemotherapy is mainly limited by its toxicity to normal tissues, particularly the kidney toxicity. Tubular apoptotic cell death significantly contributes to the pathogenesis of cisplatin-induced acute kidney injury (AKI). KCa3.1, a calcium-activated potassium channel, has been reported to participate in cell apoptosis. However, the involvement of KCa3.1 in cisplatin-induced AKI is unknown.

Methods: We examined KCa3.1 mediates cisplatin-induced tubular apoptotic cell death *in vitro*, as well as the development of cisplatin-induced AKI in KCa3.1^{-/-} and pharmacological blockade mouse models *in vivo*.

Results: Cisplatin treatment triggered an early induction in KCa3.1 expression, which is associated with apoptotic cell death in HK-2 cells, as well as with the development of renal tubular damage and cell apoptosis in mice. By treating with highly selective blocker TRAM-34, we found KCa3.1 inhibition suppressed cisplatin-induced apoptotic cell death in HK-2 cells. In the *in vivo* study, KCa3.1 deficiency reduced renal function loss, renal tubular damage and apoptotic marker caspase-3 induction in kidneys after cisplatin administration in KCa3.1^{-/-} mice. Pharmacological blockade of KCa3.1 by TRAM-34 similarly attenuated cisplatin-induced AKI in mice. Furthermore, we dissected the underlying mechanisms in which KCa3.1 blocking reduces cisplatin-induced apoptosis. We found KCa3.1 inhibition attenuated the cytochrome c release and the increase of intrinsic apoptotic mediator Bax, Bak and caspase-9 after cisplatin treatment. We also found KCa3.1 blocking inhibited cisplatin-induced the increase of ER stress mediator caspase-12, which is independent of calcium-dependent protease m-calpain activation.

Conclusions: Blockade of KCa3.1 protects against cisplatin-induced AKI through the attenuation of tubular apoptotic cell death by interference with intrinsic apoptotic and ER stress-related mediators, and that provides a potential target for the prevention of cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

SA-PO244

Bax Mimotope Therapy: Effective Treatment for Ischemic Acute Kidney Injury (AKI) Zhiyong Wang, Ryan M. Mulhern, Andrea Havasi, Ramon G. Bonogio, Steven C. Borkan. *Renal Section, Boston Univ Medical Center, Boston, MA.*

Background: Ischemic AKI causes renal cell death partly by Bax-mediated apoptosis. Recent studies show that Bax requires the chaperone nucleosphosmin (NPM) for mitochondrial targeting and apoptosis. We propose that a mimotope that interferes with Bax-NPM interaction is an effective treatment for ischemic AKI.

Methods: To assess mimotope efficacy, 2 mg control or therapeutic Bax mimotope was administered by a single tail vein injection in 6-week old B6 mice either before or after renal ischemia caused by 22 min of bilateral renal pedicle clamping, an insult that produces severe AKI. BUN/Cr, histologic injury score, caspase 3 activity, Bax activation and Bax-NPM interaction were compared in each experimental group at the above time points (n = 8 each group).

Results: Compared to control, Bax mimotope administration 15 min before or 15 min, 1, 2 or 3 hr after ischemia significantly improved renal function. No protection was observed if Bax mimotope exposure was delayed for 4 or more hours after ischemia. Although 12% of controls died of AKI, only 2% of animals died in the Bax mimotope groups. Despite equivalent Bax activation in both groups, the Bax mimotope improved histologic injury score, reduced caspase 3 activation and decreased Bax-NPM interaction as assessed by co-immunoprecipitation.

Conclusions: Selective interference of Bax-NPM interaction with a Bax mimotope within several hours of acute ischemia improves survival, significantly reduces the severity of AKI (lower BUN and Cr), decreases histologic injury score and inhibits Bax-mediated apoptosis downstream of Bax activation.

Funding: NIDDK Support

SA-PO245

Role of AMPK in Aristolochic Acid-Induced Acute Kidney Injury Anne-Emilie Declèves,¹ Inès Jadot,² Vanessa Colombaro,² Eric De prez,¹ Isabelle Habsch,² Kumar Sharma,³ Nathalie Caron,² Joelle L. Nortier.¹ ¹Free Univ of Brussels; ²Univ of Namur; ³Univ of California, San Diego.

Background: Experimental aristolochic Acid nephropathy (AAN) is a pertinent model of tubulo-interstitial nephritis characterized by an early phase of acute kidney injury (AKI) leading to progressive fibrosis and chronic kidney disease (CKD). Here, the present model was used to determine the role of AMPK in renal outcome and its involvement in the AKI-to-CKD transition.

Methods: C57BL/6J male mice were randomly subjected to i.p. injection of either sterile saline solution, AA, AA+AICAR (the specific AMPK activator) for 4 days. Mice were then euthanized either at day 5 or day 20.

Results: AA-treated mice displayed loss of renal function, as reflected by significant increases in plasma creatinine level and proteinuria at days 5 and 20. In addition, impairment of tubular cells was also observed by the significant increase in urinary excretion of lysosomal enzyme N-acetyl-β-D-glucosaminidase in AA-treated mice. These changes were

prevented by AICAR treatment. To further determine the role of AMPK in AA-induced oxidative stress, Nox1, 2 and 4 were investigated at the mRNA levels. No changes were observed for Nox1 and 4. However, Nox2 was significantly increased in AA-treated mice while this rise was prevented by AICAR treatment at day 5 but not at day 20. Moreover, the urinary hydrogen peroxide level, a stable product of ROS production, was significantly higher after AA intoxication and reduced with AICAR. Regarding inflammation, AA mice exhibited a significant increase in MCP-1 mRNA level. This rise was only prevented by AICAR at day 5. Finally, at day 5, there was no significant macrophage infiltration with AICAR while at day 20, this significant increase was not prevented by AICAR.

Conclusions: These findings show a beneficial effect of AMPK in AA-induced AKI. In view of these data, we suggest that chronic AICAR treatment is necessary for complete nephroprotection and recovery. The activation of AMPK represents a potential strategy to prevent the transition from AKI-to-CKD.

Funding: Government Support - Non-U.S.

SA-PO246

Nrf2 Activation in Tubular Cells Prevents Progression of AKI to CKD Masahiro Nezu,^{1,2,3} Tomokazu Souma,^{1,2,3} Sadayoshi Ito,² Norio Suzuki,³ Masayuki Yamamoto.¹ ¹Dept of Medical Biochemistry, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; ²Div of Nephrology, Endocrinology, and Vascular Medicine, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; ³Div of Interdisciplinary Medical Science, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Acute kidney injury (AKI) is one of the major risk factors for chronic kidney disease (CKD). Reactive oxygen species are generated by ischemia-reperfusion injury (IRI) during transition of AKI to CKD, and oxidative stress contributes to defects of renal tubular cells. Nrf2 is a master transcription factor for cellular defense against oxidative stress, and an E3 ubiquitin ligase subunit Keap1 negatively regulates Nrf2 activity. Here, we evaluated protective roles of the Keap1-Nrf2 system in AKI-to-CKD transition.

Methods: Unilateral ischemia reperfusion injury (UIRI) was performed to induce rodent model of AKI-to-CKD. Hypomorphic Keap1 knockdown mutant (KKD) and tubular-specific Keap1-null mutant (TKO) mice were used for genetic activation of Nrf2. A Keap1 inhibitor CDDO-Im was used for pharmacological activation of Nrf2.

Results: Remaining tubular areas at 14 days after UIRI were 64%, 51% and 34% in KKD, TKO and wild-type mice, respectively compared with their contralateral kidneys. CDDO-Im treatment after UIRI to wild type mice also protected against tubular defects (CDDO-Im, 63%). Nrf2-inducible antioxidant genes (*Nqo1*, *Hmx1*, *Gclc*, *Gclm*, and *Srxn1*) were transiently up-regulated in 3-6 hours after UIRI in wild-type kidneys, while both genetic and pharmacological activation of Nrf2 maintained expression of these genes at high levels throughout the observation period.

Conclusions: Activation of Nrf2 alleviates IRI-induced tubular loss through enhancing the antioxidant response system. Nrf2 inducers are one of prospective therapeutic candidates for preventing AKI-to-CKD transition.

Funding: Pharmaceutical Company Support - Chugai Pharmaceutical Co.

SA-PO247

Acute Kidney Injury in the Rat Is Prevented by Pirfenidone Ixchel Quetzalitzli Lima Posada,¹ Francesco Fontana,^{1,3} Nathan Berman,^{1,2} Gianni Cappelli,³ Norma Bobadilla.¹ ¹Inst de Investigaciones Biomédicas, UNAM e Inst Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico; ²Univ Panamericana, Mexico, Mexico; ³Univ degli studi di Modena e Reggio Emilia, Modena, Italy.

Background: Pirfenidone (PFN) is an orally active small molecule which acts mainly through an anti-fibrotic effect, but also possesses antioxidant and anti-inflammatory properties. This study was designed to evaluate the effect of the prophylactic treatment with PFN on acute kidney injury (AKI) due to bilateral renal ischemia (I/R) in the rat.

Methods: We studied three groups of rats: 1) sham operated (S) 2) rats undergone 20 min of ischemia and 24-h of reperfusion and, 3) rats treated with PFN (700 mg/kg), 24-h before ischemia (I/R+PFN). Serum creatinine, creatinine clearance (CrC) protein excretion, urinary levels of Hsp72 (UHsp72V) and nitrates and nitrites (UNO2/NO3V) were assessed. Mean arterial pressure (MAP) and renal blood flow (RBF) were recorded 24-h after surgery. Tubular injury (TI) was evaluated in fixed kidneys by counting the cast number and the number of injured tubules per field.

Results: As expected, the I/R group showed a reduction in CrCl (I/R 0.22 ± 0.04 vs. S 0.36 ± 0.06 ml/min/100 g BW; p<0.05), urinary output (I/R 20±9.5 vs. S 32.7±19.3 ml/day; p<0.05), RBF (I/R 1.08 ± 0.37 vs. S 1.53±0.17 ml/min/100 g BW; p<0.05), and a significant increase in UHsp72V assessed by Western blot. Extensive TI was evidenced by histological analysis. These alterations were associated with a decrease in UNO2/NO3V (I/R 3.1±1.3 vs. S 5.4±2.5 mmol/24-h). In contrast, I/R+PFN group showed restoration of CrCl (I 0.33±.04 ml/min/100g BW; p<0.05), urinary output (47.5 ± 5.7 ml/day; p<0.05), RBF (1.51±0.15 ml/min/100g weight; p<0.05). The levels of urinary Hsp72 were undetectable or very low and the histological signs of TI were significantly reduced. Interestingly, UNO₂/NO₃V was completely recovered (7.05±0.78 mmol/24-h; p<0.05).

Conclusions: Our results revealed that pre-treatment with PFN prevents AKI in the rat. Part of its renoprotective effects seems to be related with the restoration of NO production. These findings suggest that PFN could be a promising tool in the prevention of AKI.

Funding: Government Support - Non-U.S.

SA-PO248

HDAC8 Plays a Critical Role in the Epigenetic Activation of Fibroblasts and the Pathogenesis of Renal Fibrosis Scott R. Manson, Qisha Guo, Katelynn H. Moore, Paul F. Austin. *Dept of Surgery, Div of Urology, Washington Univ, St. Louis, MO.*

Background: The development of renal fibrosis is associated with changes in the expression of approximately 10% of the genome, suggesting widespread transcriptional dysregulation. Nonetheless, the roles of critical epigenetic pathways in disease progression remain poorly understood. Here, we examine the biological and therapeutic importance of histone deacetylases (HDACs) in the function of fibroblasts and the pathogenesis of renal fibrosis.

Methods: Renal fibrosis was modeled *in vitro* by treatment of NRK-49F fibroblasts with the pro-fibrotic cytokine TGF-β and *in vivo* in mice by unilateral ureteral obstruction (UO). The role of HDAC proteins was assessed by treatment with the broad spectrum HDAC inhibitor Trichostatin A (TSA) and the HDAC8-specific inhibitor PCI-34051. The translational relevance of these findings was assessed in patients who underwent a nephrectomy following UPJ obstruction.

Results: UO leads to a 6.1-fold increase in HDAC8 expression that localizes specifically to myofibroblasts. In NRK-49F cells, treatment with PCI-34051 promotes myofibroblast differentiation and apoptosis, but suppresses proliferation and matrix synthesis. These findings extend to the injured kidney *in vivo*, where HDAC inhibition results in a 41.6% decrease in *COL1A1* and a 61.6% decrease in *α-SMA*. Furthermore, there is a 77.9% decrease in the interstitial proliferative response, a 43.0% decrease in myofibroblast number, and a 31.1% decrease in renal fibrosis. Finally, the development of renal fibrosis in patients with obstructive kidney disease is associated with a 32.1% increase in the number of HDAC8-positive cells.

Conclusions: Together, these findings demonstrate that HDAC8 plays a critical role in regulating fibroblast activation. Treatment with HDAC inhibitors is also an effective therapeutic approach to reverse the epigenetic changes associated with the pathogenesis of renal fibrosis. Finally, since an increase in HDAC8 expression occurs in patients during disease progression, HDAC8-targeted therapies have therapeutic potential for the treatment of chronic kidney disease.

Funding: NIDDK Support, Private Foundation Support

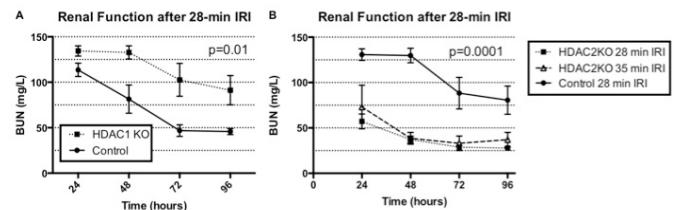
SA-PO249

Reciprocal Effects of HDAC1 and HDAC2 Deletion on Renal Ischemia-Reperfusion Injury David Dean Aufhauser,¹ Zhonglin Wang,¹ Guanghui Ge,¹ Tricia Bhatti,² Wayne W. Hancock,^{2,3} Matthew H. Levine.¹ *¹Surgery, Hospital of the Univ of Pennsylvania and the Children's Hospital of Philadelphia, Philadelphia, PA; ²Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA; ³Pathology and Laboratory Medicine, Hospital of the Univ of Pennsylvania, Philadelphia, PA.*

Background: Histone/protein deacetylases proteins (HDACs) have been implicated in renal ischemia-reperfusion injury (IRI). HDACs 1 and 2 are highly homologous Class I HDACs thought to have similar function.

Methods: This study included wild type C57BL/6 (B6) and inducible HDAC1- or 2- gene deleted mice (HDAC1KO and HDAC2KO). Renal-specific or extra-renal gene deletion was achieved with transplantation, native nephrectomy, and subsequent gene deletion. Warm IRI consisted of unilateral clamping of the renal pedicle and contralateral nephrectomy. Cold IRI was achieved through procurement, controlled interval of cold storage, and transplantation.

Results: HDAC1KO mice had impaired renal IRI tolerance compared to controls with higher BUN levels (p<0.01; Figure 1A) and increased fibrosis post-injury. HDAC2KO mice had improved early renal function (p<0.01; Figure 1B) and decreased fibrosis (p<0.01) compared to controls and tolerated extended periods of ischemia. In transplant models, renal-specific HDAC2KO mice had superior IRI tolerance with less renal impairment (p<0.01) and decreased fibrosis (p<0.01) compared to extra-renal HDAC2KO and controls. After transplantation with 18 hours of cold ischemia, HDAC2KO donor kidneys had improved BUN (p=0.02) and survival compared to controls.



Conclusions: HDAC1 and 2 have reciprocal effects on murine renal IRI tolerance, with HDAC1 deletion increasing vulnerability and HDAC2 deletion providing protection. The effect of HDAC2 deletion is profound, is intrinsic to the kidney, and extends to cold ischemia and renal transplantation.

Funding: NIDDK Support

SA-PO250

Renoprotective Effect of Long Acting Thioredoxin by Modulating Oxidative Stress and Macrophage Migration Inhibitory Factor against Rhabdomyolysis-Associated Acute Kidney Injury Hiroshi Watanabe,¹ Kento Nishida,¹ Masafumi Fukagawa,² Toru Maruyama.¹ *¹Dept of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto Univ, Kumamoto, Japan; ²Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Kanagawa, Japan.*

Background: Rhabdomyolysis-associated acute kidney injury (AKI) is a serious life-threatening condition. As such, more effective strategies are needed for its prevention and treatment. Although thioredoxin-1 (Trx) possesses superior biological activities, such as anti-oxidative and anti-inflammatory effect via the modulating macrophage migration inhibitory factor (MIF), its short blood retention limits the therapeutic application. To overcome this, we engineered long acting Trx by genetically fused with human serum albumin (HSA-Trx), and examined its renoprotective effect against glycerol-induced AKI.

Methods: HSA-Trx was prepared by using Pichia expression system. The mouse model of rhabdomyolysis-associated AKI was induced by the administration of a 50% glycerol solution.

Results: An intravenous HSA-Trx pre-treatment attenuated the glycerol-induced decline in renal function, compared to a PBS, HSA or Trx alone. HSA-Trx caused a reduction in the tubular injuries and in the number of apoptosis-positive tubular cells. Renal superoxide, 8-hydroxy deoxyguanosine, nitrotyrosine and the plasma Cys34-cysteinylated albumin were clearly suppressed by the HSA-Trx treatment. Prior to decreasing TNF-α and IL-6, HSA-Trx suppressed an increase of plasma MIF level. In LLC-PK1 cells, HSA-Trx decreased the level of reactive oxygen species and lactate dehydrogenase release induced by myoglobin. HSA-Trx treatment resulted in a threefold increase in the survival of lethal glycerol-treated mice. The post-administration of HSA-Trx at 1 and 3 hr after glycerol injection exerted a significant renoprotective effect.

Conclusions: HSA-Trx, a long acting Trx, has potential for use in the prevention and treatment of rhabdomyolysis-associated AKI via its extended effects of modulating oxidative stress and MIF.

SA-PO251

Selective Endothelin-A Receptor Antagonism Prevents the Progression of Acute Kidney Injury to Chronic Kidney Disease Neeraj Dhaun, *Queen's Medical Research Inst, Univ of Edinburgh, Edinburgh, United Kingdom.*

Background: AKI is common and associated with significant morbidity and mortality. AKI often progresses to CKD and endothelin-1 (ET-1) contributes to this. We hypothesized that therapeutic administration of selective ET_A receptor antagonism would protect from the transition of AKI to CKD.

Methods: 28 FVB mice underwent prolonged (50min) unilateral ischemia-reperfusion injury (IRI) with 28d recovery. 14 mice received daily selective ET_A antagonism (sitaxentan) starting 24h after IRI. We assessed blood pressure (BP) via telemetry, vascular function, renal injury and measures of the ET system.

Results: Systolic BP increased by ~5mmHg after IRI and was associated with vascular dysfunction in both resistance and conduit vessels. Sitaxentan partly prevented both of these. At 28d after IRI kidney weight was reduced (-55%) and associated with significant macrophage infiltration and fibrosis compared to the contralateral control kidney. Mice treated with sitaxentan had normal kidney weight, reduced macrophage infiltration and less fibrosis: IRI kidney vs. control kidney vs. IRI kidney with sitaxentan: F4/80 stain/high power field: 2.5vs.0.2vs.0.8%; picosirius red stain/high power field: 8.6vs.0.48vs.3.1%. For both macrophage infiltration and fibrosis, p<0.05 for IRIvs.control and for IRIvs.IRI with sitaxentan, p=ns for control vs. IRI with sitaxentan. Furthermore, an up-regulation of both the ET_A (28-fold) and ET_B (2-fold) receptors as well as pre-pro-ET-1 (10-fold) mRNA was seen in both the cortex and medulla of the IRI kidney relative to control. With sitaxentan treatment ET_A/ET_B receptor and pre-pro-ET-1 mRNA remained similar to baseline levels. Finally, renal ET-1 production increased following IRI and this was prevented by ET_A receptor antagonism (fractional excretion of ET-1: IRIvs.IRI with sitaxentan: 47vs.16%, p<0.05).

Conclusions: In an *in vivo* model of AKI progressing to CKD, ET_A receptor antagonism reduced BP and vascular dysfunction and prevented progression of renal injury and ET system activation after AKI. Therefore, selective ET_A receptor antagonism offers a potentially novel therapy for AKI. Translational studies are now warranted.

SA-PO252

Inhibition of Vascular Adhesion Protein-1 Suppresses Neutrophil Infiltration and Preserves Renal Function in the Rat Model of Renal Ischemia-Reperfusion Injury Shinji Tanaka, Tetsuhiro Tanaka, Reiko Inagi, Masaomi Nangaku. *Div of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan.*

Background: Vascular adhesion protein-1 (VAP-1) is an adhesin expressed in endothelial cells. With its unique properties as an ectoenzyme which catalyzes oxidative deamination of primary amines, VAP-1 plays a critical role in leukocyte trafficking. In light of a growing body of evidence that VAP-1 controls inflammation in various organs, such as the liver and the lung, we examined the effect of VAP-1 inhibition in the rat model of renal ischemia-reperfusion injury.

Methods: Rats were subjected to left renal ischemia for 45 min after right nephrectomy, followed by reperfusion for 48 h. A specific VAP-1 inhibitor, RTU-1096 (R-Tech Ueno, Tokyo, Japan), or vehicle was administered to rats since 7 days before the surgery (mixed with feed, 40 mg/kg/day).

Results: Immunofluorescence studies suggested that VAP-1 is expressed not only in endothelial cells of peritubular capillaries but also in interstitial cells of non-endothelial lineage. In vitro, higher mRNA expression of VAP-1 was confirmed in cultured pericytes. In vivo, VAP-1 enzyme activity in the whole kidney was unaffected by the surgery, but following VAP-1 inhibition by RTU-1096 (0.9 ± 0.1 vs. 7.0 ± 1.3 pmol/mg protein/min), renal function was significantly better preserved as compared to the vehicle group (BUN: 69 ± 6 vs. 139 ± 15 mg/dL, Cr: 1.4 ± 0.1 vs. 2.5 ± 0.2 mg/dL; $p < 0.01$), which was accompanied by amelioration in histological tubular injury and decreased KIM-1 mRNA levels. Immunohistochemical analysis revealed a significantly decreased number of neutrophils in the corticomedullary junction in the drug group, whereas the number of macrophages was similar. VAP-1 inhibition resulted in significantly lower mRNA levels of CXCL1 and CXCL2 in the kidney without affecting chemokines involved in macrophage recruitment, such as MCP-1, or major adhesion molecules, VCAM-1 and ICAM-1.

Conclusions: These data suggest that VAP-1 plays an important role in renal ischemia-reperfusion injuries by controlling neutrophil infiltration, and offer a promising view that its inhibition can be a novel therapeutic target in ischemic acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO253

Kim-1 Overexpressing Transgenic Zebrafish Identify mTOR as an Effector of Kim-1-Mediated Kidney Injury in Fish and Mice Wenqing Yin, Said Movahedi naini, Dirk M. Hentschel, Benjamin D. Humphreys, Joseph V. Bonventre. *Renal Div, Brigham and Women's Hospital, Boston, MA.*

Background: Mammalian kidney injury molecule 1 (KIM-1), an epithelial phagocytic receptor, is markedly upregulated in the proximal tubule in various forms of acute and chronic kidney injury in humans and many other species. Here, we characterized the zebrafish Kim family to consist of Kim-1, Kim-3 and Kim-4. By genetically expressing constitutive or tamoxifen-induced Kim-1 in zebrafish kidney tubules, we identified mTOR as an effector in Kim-1-mediated kidney injury. We then validated mTOR as a therapeutic target for kidney injury and fibrosis in KIM-1 overexpressing transgenic mice.

Methods: We created two transgenic zebrafish models of Kim-1 overexpression in nephrons employing the *cdh17* promoter. One model utilized a constitutively active promoter while the other utilized a tamoxifen-induced Cre-ERT2 recombinase to express Kim-1 in nephrons in a temporally-controlled manner. The role of mTOR signaling was evaluated using the inhibitor rapamycin. Zebrafish GFR was determined using the elimination rate of fluorescein-labeled dextran.

Results: Kim-1 was markedly upregulated after gentamicin-induced kidney injury and had conserved phagocytic activity in zebrafish. Both constitutive and tamoxifen-induced expression of Kim-1 in zebrafish kidney tubules resulted in shedding of the tubule brush border, reduced GFR, pericardial edema and increased mortality rate. Kim-1-induced kidney injury was associated with inhibition of growth of adult fish. Kim-1 expression led to mTOR pathway activation, and inhibition of this pathway with rapamycin increased survival. mTOR pathway inhibition in KIM-1 overexpressing transgenic mice also significantly reduced serum creatinine, proteinuria, tubular injury and kidney inflammation.

Conclusions: Persistent Kim-1 expression resulted in chronic kidney damage and growth impairment in zebrafish. Kim-1-mediated kidney tubular injury was mediated by the mTOR signaling pathway. This observation in zebrafish predicted the role of the mTOR pathway and therapeutic efficacy of rapamycin to protect the mouse kidney against KIM-1-mediated kidney injury and fibrosis.

Funding: NIDDK Support

SA-PO254

Treg and ILC2 Contribute to IL233 (a Novel Fusion Cytokine)-Mediated Protection in AKI Marta Stremaska,¹ Liping Huang,¹ Sheethal Jose,¹ Amandeep Bajwa,¹ Diane L. Rosin,^{1,2} Mark D. Okusa,¹ Rahul Sharma.¹ ¹CIIR, Univ of Virginia, Charlottesville, VA; ²Dept of Pharmacology, Univ of Virginia.

Background: Inflammation is an early event in AKI and studies have shown regulatory T cell (Treg)-mediated protection in inflammation driven injuries. Since we found that interleukin (IL)-2 upregulates IL-33 receptor-ST2 on CD4 T-cells, we hypothesized that IL-2 and IL-33 cooperate to expand endogenous Tregs. Indeed, a proportion of Tregs constitutively expressed ST2 and IL-33 contributed to promote Tregs. IL-2 and IL-33 in combination or as IL233 fusion cytokine, but not alone protected mice from IRI, with IL233 being more efficient than the combination.

Methods: We designed a fusion cytokine (IL233) containing the activities of IL-2 and IL-33 for better targeting of Tregs. The cytokines were expressed in *E. coli*, purified to homogeneity and tested in a mouse model of ischemia reperfusion injury (IRI). C57BL/6 male mice were pretreated (ip) with different doses of cytokines prior to 26 min of bilateral ischemia and 24 hours of reperfusion. Kidneys were characterized for function, acute tubular necrosis and the profile of infiltrating cells.

Results: IL-2 and IL-33 in combination or as IL233 fusion cytokine, but not alone protected mice from IRI, with IL233 being more efficient. Our data suggests that the IL233 treatment first increases splenic levels of Tregs followed by their mobilization. Since both IL-2 and IL-33 also promote Th2 response, an increase in IL-4 and IL-5, and a decrease in Th1 cytokines IFN γ and TNF α was seen, indicating a shift towards a protective Th2 response. Protected mice had a higher proportion of innate lymphoid cells 2 (ILC2) in the blood and the kidneys. Neutrophil infiltration in the kidneys was significantly lowered in IL233 treated mice. Treg adoptive transfer studies revealed higher degree of protection in

mice injected with Tregs obtained from mice pretreated with IL233. Adoptive transfer of ILC2, pretreated with IL233 also protected against IRI. In vitro experiments with IL233 pre-treated Tregs revealed their higher suppressive function.

Conclusions: Thus, IL233 cytokine attenuates kidney inflammation to protect from IRI and bears strong potential to be a therapeutic agent for AKI.

Funding: NIDDK Support

SA-PO255

Vagus Nerve Stimulation (VNS) Protects Kidneys from Ischemia-Reperfusion Injury Through Alpha 7 Nicotinic Acetylcholine Receptor ($\alpha 7$ nAChR) Expressing Splenocytes Tsuyoshi Inoue,¹ Chikara Abe,² Stefan Moscalu,¹ Liping Huang,¹ Hong Ye,¹ Diane L. Rosin,^{1,2} Patrice G. Guyenet,² Mark D. Okusa.¹ ¹Depts of Medicine, Univ of Virginia Health System; ²Depts of Pharmacology, Univ of Virginia Health System, Charlottesville, VA.

Background: The nervous and immune systems interact in complex ways to maintain homeostasis and respond to stress or injury. The inflammatory reflex referred to as the cholinergic anti-inflammatory pathway (CAP) modulates innate and adaptive immunity, and modulation of the reflex by VNS is effective in inflammatory disease models. The effect of VNS on AKI has never been examined. Experimental activation of vagal efferent fibers suppresses inflammation in a manner that depends on $\alpha 7$ nAChR in the CAP. However, the site of the essential $\alpha 7$ nAChR was not established.

Methods: We applied electrical VNS (5 Hz, 50 μ A for 10 min) 24 hr prior to kidney IRI and assessed kidney injury by evaluating plasma creatinine (PCr, mg/dl), kidney Kim-1 mRNA expression and histology (H&E). The effect of VNS on IRI was assessed by: a) prior splenectomy and b) adoptive transfer of splenocytes from VNS-stimulated mice to recipient mice subjected to IRI.

Results: VNS applied 24 hr prior to IRI markedly attenuated IRI. VNS reduced the IRI-induced increase in PCr by 65% ($P < 0.01$) and Kim-1 mRNA expression in whole kidney by $>70\%$ ($P < 0.01$). H&E-stained kidney sections confirmed the functional data. When splenectomy was performed 7 d before VNS and IRI, the protection by VNS was abolished. Adoptive transfer of splenocytes from VNS-treated mice to recipient mice subjected to IRI provided greater protection than splenocytes from mice who received sham VNS stimulation (PCr: 0.41 and 1.54 ($P < 0.001$) for VNS- and sham VNS-treated splenocytes, respectively). To evaluate the role of $\alpha 7$ nAChR, VNS was initiated 24 hr prior to IRI in $\alpha 7$ nAChR knock out ($\alpha 7$ KO) and WT mice. Compared to the protective effect of VNS on IRI in WT mice, no protection was observed in $\alpha 7$ KO mice. In addition, recipient mice were protected (PCr) from IRI if they received splenocytes from VNS-treated WT mice (0.41) but not from VNS-treated $\alpha 7$ KO mice (1.57, $P < 0.001$).

Conclusions: VNS-induced protection from IRI is consistent with activation of the CAP.

SA-PO256

Elevations of Intraglomerular Pressure Exacerbate Ischemia Reperfusion Injury-Induced Acute Kidney Injury Jie Zhang, Lei Wang, Shaohui Wang, Gensheng Zhang, Jin Wei, Ruisheng Liu, Kay-Pong D. Yip. *Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL.*

Background: The physiological and pathophysiological mechanisms of renal ischemia reperfusion (IR)-induced acute renal injury (AKI) are complex and have not been elucidated. We sought to determine whether intraglomerular hydrostatic pressure (Pg) during the ischemic phase plays a critical role in IR-induced AKI.

Methods: AKI was induced in three groups of C57BL/6J mice at 37 $^{\circ}$ C with IR by 18 min of bilateral clamping of renal arteries (RA), pedicles (RP), and pedicles plus pre-clamping of ureters 20 min before ischemia (PU). Free flow proximal tubular pressure (Pf) was measured with servo-nulling method during ischemia. Pf was used as an index of Pg.

Results: We found that mean Pf was higher in PU mice (48.9 ± 7.5 mmHg) than in RP mice (34.6 ± 3.6 mmHg). The RA mice had lower Pf (1.6 ± 1.2 mmHg) when compared to Sham operated mice (9.54 ± 2.2 mmHg). In separate experiments, the renal injury was determined 24 hours after IR in these mice. Plasma creatinine was significantly increased in all three groups compared with sham-operated group. The mean plasma creatinine were 2.1 ± 0.07 mg/dl, 1.85 ± 0.08 mg/dl, and 0.45 ± 0.7 mg/dl for PU, PR and RA, respectively. The mean plasma Kidney Injury Molecule-1 (KIM-1) levels were 2761 ± 493 pg/ml in PU, 1548 ± 220 pg/ml in RP and 734 ± 234 pg/ml in RA group, respectively. Histology by PAS staining showed that all AKI mice had a significant increase in renal tubular necrosis compared with sham-operated mice. However, there were more tubular necrosis in the cortex, medulla or cortex-medulla junction area in PU mice ($3.1 \pm 1.3\%$, $34.1 \pm 8.5\%$ and $54.4 \pm 6.9\%$) than in RP mice ($1.2 \pm 0.5\%$, $23.0 \pm 9.2\%$ and $50.1 \pm 12.7\%$). RA mice had the least tubular necrosis ($0.23 \pm 0.1\%$, $8.9 \pm 4.5\%$ and $31.7 \pm 10.2\%$).

Conclusions: We found that RA mice had lowest intraglomerular pressure and renal injury and that PU mice had highest intraglomerular pressure and most severe renal injury. These data indicate that elevations of intraglomerular and tubular pressure exacerbate IR-induced AKI. Intraglomerular and tubular pressure may be a novel therapeutic target for AKI.

SA-PO257

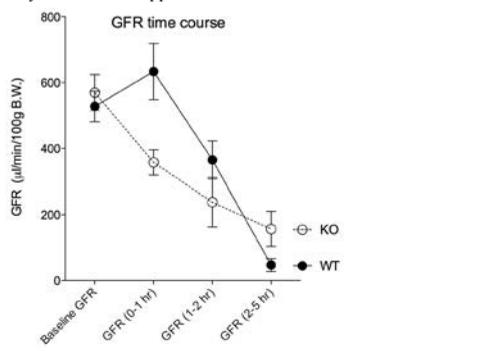
GFR in Conscious Mice After Sepsis: Role of Tubuloglomerular Feedback
Jonathan Street, Yuning George Huang, Peter S.T. Yuen, Robert A. Star. *NIDDK, Bethesda, MD.*

Background: Reabsorption of glomerular filtrate by the tubules is an energy intensive process. During sepsis the ability of the tubules to meet this energy demand may be impaired. To prevent renal salt wasting during sepsis it is hypothesized that activation of tubuloglomerular feedback reduces GFR and subsequently the metabolic demand on the tubules – “acute renal success”. Mice without tubuloglomerular feedback should maintain higher levels of GFR. In conscious mice we detected early changes in GFR using a novel transcutaneous measurement of a fluorescent filtration marker. Because adenosine 1a receptor (A1aR) signaling is required for tubuloglomerular feedback we directly measured GFR following sepsis in A1aR knockout mice.

Methods: Sepsis was induced in male A1aR knockout mice and littermate controls by cecal ligation and puncture. GFR was monitored in awake mice for 5 hours by plasma disappearance of FITC-Sinistrin, injected at 0 and 90 minutes after surgery, and its transcutaneous fluorescence measured by a miniaturized fluorimeter attached to the mouse back.

Results: The baseline GFR was similar in A1aR WT and KO mice. In WT mice, GFR was stable during the first hour following induction of sepsis. GFR slowly declined over hour two, and then fell rapidly to <10 % of normal and remained low for 5 hours. In contrast, the GFR was lower in KO mice than in WT mice in the first hour following sepsis (p=0.0226), then fell gradually to 27% of normal, with a smaller decrease observed after 2 hours compared to WT mice (p=0.0286).

Conclusions: In mice lacking tubuloglomerular feedback, unexpectedly, GFR begins to decrease earlier after sepsis suggesting impaired autoregulation. The sudden decrease in GFR in WT mice at 2 hours after induction of sepsis does not occur in A1aR KO mice. Tubuloglomerular feedback modestly supports, not suppresses, GFR in the first hour following sepsis, and only later acts to suppress GFR.



Funding: NIDDK Support

SA-PO258

Renal Functional Reserve May Be Inferred from Variation of Renal Resistive Index: Preliminary Evidence Sara Samoni,^{1,2} Federico Nalesso,² Gianluca Villa,² Silvia De Rosa,² Ilaria Petrucci,¹ Massimo de Cal,² Fiorenza Ferrari,² Alessandra Brendolan,² Mario Meola,¹ Claudio Ronco.² *¹Sant'Anna School of Advanced Studies, Pisa; ²IRRV, Vicenza.*

Background: The increase of glomerular filtration rate(GFR)after a protein load represents the renal functional reserve(RFR).Mechanical abdominal stress(MAS),through the compression of renal arteries and the consequent reduction of renal blood flow,can activate the autoregulation mechanism to maintain glomerular perfusion.Both phenomena are related to the afferent vasodilation,which can be displayed by the drop of renal resistive index(RI)measured by colorDoppler.We hypothesized that the variation of RI during MAS may predict the RFR.

Methods: In 15 healthy volunteers,MAS was performed through the application of a saline bag on abdominal wall.According to the performed dose-response curve,we used bags which weigh 10% of subject's BW.We recorded RI in mesorenal interlobar arteries each min for the 10 min of MAS.The RI reduction was defined by the difference between baseline RI and the lowest RI reached during MAS and expressed as percentage reduction(pDRI). RFR was measured through a standardized protein loading test.Spearman's correlation was applied to evaluate if pDRI correlates with RFR.

Results: We enrolled 9M and 6F with a median age of 30(24-57) yrs old.The median baseline CrCl was 99.2(70.3-132.8)ml/min/1.73m².The RFR ranged between 11.55%and 134.66%with a median value of 38.55%.The median baseline RI was 0.60(0.50-0.67)while pDRI ranged between 13.33%and 29.23%with a median value of 20%.The correlation between pDRI and RFR was 80.71%(p<0.001).According to physiology,RFR and pDRI may not be directly proportional;indeed,while ranges of RFR may widely broaden,pDRI should reach a plateau value.For this reason,we analyzed the linear regression model between pDRI and logarithm(ln)of RFR.According to this model,we found that an increase in pDRI was associated to an increase in the ln of RFR(coef0.10,p<0.001,95%CI:0.06;0.15,R²0.66).

Conclusions: Our results suggest that the variation of RI during MAS is an indirect measure of RFR,putting the bases for the development of a stress test that could be used for a rapid screen of RFR before potentially nephrotoxic procedures.

SA-PO259

5-Aminolevulinic Acid Attenuates Rhabdomyolysis-Induced Acute Kidney Injury in Mice Atsushi Uchida, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. *Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.*

Background: Rhabdomyolysis often occurs after severe skeletal muscle injury, and high mortality have been reported with the acute kidney injury (AKI) that develops subsequently. Thus, the establishment of effective prevention and treatment is a pressing problem. 5-Aminolevulinic acid (ALA) is the naturally occurring metabolic precursor of heme, and serves as protein material related to energy production. Previous study demonstrated that ALA has the potential to prevent cisplatin-induced AKI via the induction of heme oxygenase (HO)-1, and prevention of tubular apoptosis. We hypothesize that ALA plays a renoprotective role via the induction of HO-1 and anti-apoptotic pathway in rhabdomyolysis-induced AKI.

Methods: Male C57BL/6 mice were used.Rhabdomyolysis-induced AKI was induced by intramuscular injection of glycerol (50%) 5 ml/kg bw.ALA (30 mg/kg) was administered at 24 hr before or 24 hr after glycerol administration. These mice were sacrificed at 72 h after glycerol injection, and the blood and renal tissues were harvested. In vitro experiment, human proximal tubule cells were stimulated by 100 µM hemin to induce apoptosis. Cells were incubated for 24 hr with or without 1 mM ALA. Apoptotic cells were examined by TUNEL staining and caspase-3 expression.

Results: In vivo experiments, serum creatinine, blood urea nitrogen and urine NGAL excretion were increased in glycerol-injected group compared with saline-injected control group. ALA significantly reduced these changes in both pre and post treatment. ALA also ameliorated glycerol-induced morphological tubular damages. HO-1 level was increased in glycerol-injected group and further up-regulated by ALA treatment. ALA significantly attenuated macrophage infiltration and pro-inflammatory cytokine (IL-1beta and TNFα) expression. In vitro experiments, TUNEL-positive cells and caspase-3 expression were increased by hemin and were significantly reduced by ALA co-treatment.

Conclusions: ALA has renoprotective effects in glycerol-injected AKI. ALA is already used for tumor diagnosis in human. So the safety of the drug is proved in clinical use. ALA treatment may be a new therapeutic target in rhabdomyolysis-induced AKI.

SA-PO260

Ferroptosis as a Cause of Proximal Tubule Injury Joel M. Weinberg,^{1,2} Andreas Linkermann.³ *¹Nephrology, VA Healthcare System Ann Arbor, Ann Arbor, MI; ²Nephrology, Univ of Michigan, Ann Arbor, MI; ³Nephrology, Christian Albrechts Univ, Kiel, Germany.*

Background: ‘Ferroptosis’ has recently been described as a form of iron-dependent, lipid peroxidation-mediated cell death with a distinct injury pattern relative to other forms of necrosis and there is evidence that it contributes to AKI in vivo (PNAS 111:16835,2014, Nat. Cell Biol. 16:1180,2014). Here, we have refined approaches to study ferroptosis in freshly isolated proximal tubules (PT) and assessed new agents being developed to ameliorate it.

Methods: Freshly isolated rabbit (R) and mouse (M) PT were treated with either tert-butylhydroperoxide (tBHP, 5 mM) or hydroxyquinoline + ferrous ammonium sulfate (HQ+Fe, 10 µM each) followed by incubation for 120 min, then measurement of LDH release, malondialdehyde (MDA) production, mitochondrial membrane potential, and GSH.

Results: tBHP and HQ+Fe induced progressive LDH release that was more severe in M PTs (for HQ+Fe: R60'-35.5±6.8%, R120'-51.4±9.0%; M60'-72.1±2.6%, M120'-87.4±3.25%). These changes were accompanied by 5 fold increases of MDA levels and GSH depletion. LDH release and MDA production were iron and NAPH oxidase (Nox)-dependent since they were blocked by deferoxamine or the Nox1/4 inhibitor GKT 137831. Fer-1, the prototypical ferroptosis inhibitor that emerged from chemical library screening, strongly alleviated both forms of injury and associated MDA production at concentrations of 0.1 to 2 µM as did a panel of 23 other ferrostatin analogs with potencies similar to those seen in isolated non-renal cell systems. Interestingly, the lipophilic antioxidant, diphenyl-p-phenylenediamine (DPPD), was even more potent than the highly active ferrostatins. Ferrostatins were not effective against acute cell killing and energetic deficits induced by hypoxia/reoxygenation, indicating that the benefit seen during in vivo ischemia/reperfusion does not target that phase of injury.

Conclusions: Ferroptosis is strongly expressed in fully differentiated PTs, is suppressed by both newly developed ferrostatins and the classical lipophilic antioxidant, DPPD, and is an injury process that can be targeted to alleviate AKI.

Funding: Veterans Administration Support

SA-PO261

Identification and Characterization of IGFBP7 and TIMP2 Expression in Human Proximal and Distal Tubule Cells David R. Emlet,¹ Nuria M. Pastor-Soler,² Allison L. Marciszyn,² Xiaoyan Wen,¹ Jacob K. Volpe,¹ John A. Kellum.^{1,2} *¹Center for Critical Care Nephrology, Dept of Critical Care Medicine, Univ of Pittsburgh, Pittsburgh, PA; ²Renal Electrolyte Div, Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.*

Background: IGFBP7 and TIMP2 have been identified as biomarkers for Acute Kidney Injury (AKI), but little is known regarding any role in the pathogenesis of the disease. To study this question we established primary cell culture models of human proximal and distal tubule epithelial cells.

Methods: The cortex of human kidneys were dissociated and viable cells cultured. Proximal and distal tubule epithelial cells (PTECs and DTECs) were isolated with antibodies against CD13 and CD227 using the Dynabead pan-mouse IgG system. Isolated cells were cultured on transwell supports and characterized by immunoblot and immunofluorescence.

Results: CD13 isolated cells were positive for the PTEC markers Gamma Glutamyl Transpeptidase and Aquaporin-1. CD227 isolated cells were negative for GGT and AQP1 but positive for the distal tubule markers CD227 and E-cadherin. Microscopy demonstrated that both PTECs and DTECs formed tight junction monolayers with a low percentage of cells in cycle as identified by Ki-67. Analysis of conditioned media demonstrated that these cells can indeed express and secrete IGFBP7 and TIMP2. Importantly, we identified a preferential expression of IGFBP7 in PTECs and of TIMP2 in DTECs. Furthermore, we discovered evidence suggesting that TIMP2 is primarily secreted across the apical surface, while the majority of IGFBP7 is secreted across the basolateral surface. Despite this, we also found evidence to suggest that some IGFBP7 can be secreted apically, primarily in PTECs.

Conclusions: We have developed human cell culture model systems of PTECs and DTECs for the cellular/molecular analysis of AKI. We confirmed that IGFBP7 and TIMP2 can be expressed and secreted by these cells, and we have identified differential expression and secretion of these proteins across cell types and spatially within cells. These systems and knowledge will now allow for investigation of the potential role of these biomarkers in the molecular etiology of AKI.

Funding: Pharmaceutical Company Support - Astute Medical

SA-PO262

Klotho and S100A8/A9 as Discriminative Markers Between Pre-Renal and Intrinsic AKI Ji Yong Jung,¹ Ae Jin Kim,¹ Eul Sik Jung,¹ Byoungcho Choi,¹ Yun Jung Oh,² Chungsik Lee,² Han Ro,¹ Jae Hyun Chang,¹ Hyun Hee Lee,¹ Wookyoung Chung.¹ ¹Div of Nephrology, Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea; ²Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea.

Background: Early detection and accurate differentiation of the cause of acute kidney injury (AKI) may improve the prognosis of the patient. However, to date, there are few reliable biomarkers for the discrimination of pre-renal and intrinsic AKI. The purpose of this study was to determine whether AKI is associated with an altered level of klotho and S100A8/A9 (an endogenous toll-like receptor 4 ligand), and NGAL (neutrophil gelatinase-associated lipocalin) protein that may contribute to differentiate between pre-renal and intrinsic AKI.

Methods: Volume depleted pre-renal AKI model was induced by Male Sprague-Dawley rat were fed a low-salt diet (0.03%) without water 96hr before two times at intraperitoneal (IP) injection of furosemide (20 mg/kg) at 24hr intervals. In contrast, cisplatin-induced intrinsic AKI model were given by a single IP injection of cisplatin (5 mg/kg). All animals were euthanized 72hr after first IP injection. We also performed a proof of concept cross-sectional study to measure serum and urinary biomarkers in 77 hospitalized patients with established AKI.

Results: Compared with intrinsic AKI group, pre-renal AKI group caused a marked depression of urinary klotho level (13.21 ± 17.32 vs. 72.97 ± 17.96 pg/ml; P = 0.002). In addition, intrinsic AKI group caused a marked elevation of S100A8/A9 level than those of pre-renal AKI group (2629.97 ± 598.05 ng/ml vs. 685.09 ± 111.65 ng/ml; P = 0.002 in serum; 3361.11 ± 250.86 ng/ml vs. 741.72 ± 101.96 ng/ml; P = 0.003 in urine). Serum and urinary NGAL showed no difference between pre-renal and intrinsic AKI group. The proof of concept study with hospitalized AKI patients also demonstrated decreased urinary klotho in pre-renal AKI patients and increased urinary S100A8/A9 concentrations in intrinsic AKI patients.

Conclusions: The attenuation of urinary klotho and increment of urinary S100A8/A9 may contribute to discriminate the pre-renal AKI and intrinsic AKI.

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SA-PO263

Release of Extra Cellular DNA Contributes to Renal Ischemia Reperfusion Injury Through Platelet Activation and Formation of Neutrophil Extracellular Traps Marcel Jansen, Diba Emal, Sandrine Florquin, Joris J. Roelofs. Pathology, Academic Medical Center Amsterdam, Amsterdam, Noord-Holland, Netherlands.

Background: Renal ischemia reperfusion injury (I/R) results from a complex interplay between coagulation and inflammation, resulting in tissue damage. It has been shown that platelet inhibition protects from I/R. How platelets are activated upon renal I/R is not entirely known. In this study we investigate renal cell death, extracellular DNA release and neutrophil extracellular traps (NETs) as potential triggers for platelet activation and renal I/R injury.

Methods: We stimulated platelets with necrotic renal cells in presence or absence of deoxyribonuclease 1 (DNase1). Platelet activation and platelet-leukocyte formation were measured by FACS. We stimulated granulocytes with activated platelets and measured DNA release –indicative of NET formation. Vice versa we stimulated platelets with NETs and measured PF4 release. Mice were subjected to renal I/R and treated with DNase1 or vehicle, and sacrificed after 1 day. As marker for NET formation in tissue we stained renal tissue for citrullinated histone H3 and granulocyte marker Ly6G. In blood we measured Platelet Factor 4 (PF4), DNA, creatinine and urea.

Results: Supernatant from necrotic renal cells stimulated platelet activation and platelet-leukocyte complex formation and incubation with DNase1 reduced platelet activation. Activated platelets generated NETs in vitro and, vice versa, NETs stimulated platelet activation ex vivo. Mice subjected to renal I/R showed a significant increase of

extracellular DNA and PF4 levels in the circulation. Treatment with DNase1 improved renal function upon I/R. Immunostainings revealed presence of NETs in renal tissue after I/R. DNase1 treatment resulted in a trend towards fewer NETs and granulocytes in tissue.

Conclusions: Both DNA from necrotic kidney cells and NETs activate platelets, which in their turn cause further NET formation, leading to a vicious triad in the pathogenesis of I/R injury. Treatment with DNase1 may have therapeutic benefits in the context of renal I/R injury.

SA-PO264

The Role of Senescence of Bone Marrow Cells in Acute Kidney Injury Myung-Gyu Kim,¹ Sung Yoon Lim,¹ Jihyun Yang,¹ Young Ju Na,¹ So-Young Lee,² Sang-Kyung Jo,¹ Won-Yong Cho.¹ ¹Dept of Internal Medicine, Korea Univ Anam Hospital, Seoul, Republic of Korea; ²Dept of Internal Medicine, Eulji Univ Hospital, Seoul, Republic of Korea.

Background: There have been considerable growth in older population and age-related kidney disease in the world. It was demonstrated that the impairment in the potentiality to repair and regenerate of renal resident cells is a hallmark of biological processes associated with aging. However, the impact of senescence of bone marrow derived cells (BMDC) on kidney injury is not known. Here, we investigated the role of senescence of BMDC in the development and progression of ischemic acute kidney injury (AKI).

Methods: Seven wk-old female mice were sublethally irradiated and reconstituted with bone marrow from 12-mo-old (old-to-young, old BMT) or 7-wk-old (young to young, young BMT) mice. Then we performed renal ischemia reperfusion injury (IRI) in old or young BMT mice, and functional, histological kidney damage and inflammation were compared.

Results: The Y chromosome was detected in peripheral blood of BMT mice indicating successful reconstitution of female mice with male bone marrow. Although the population of immune cells in spleen between young and old BMT mice was not significantly different, old BMT mice showed less renal functional deterioration and histological damage after IRI. This was associated with less infiltration of F4/80 macrophages and lower level of tissue cytokine (IL-12). In vitro study with BMDCs also revealed that LPS-induced cytokine productions (IFN- γ , MCP-1 and IL-10) were significantly suppressed in old BM cells than young BM cells.

Conclusions: Our data shows that senescence of BMDC could affect susceptibility and response to renal ischemic injury possibly via immune modulatory effect. A better understanding of these processes may help us to develop new strategies that are specifically tailored for treatment of the elderly population.

SA-PO265

Optimal Transplantation Timing of Mesenchymal Stem Cell in Rat Model of Renal Ischemia Reperfusion Injury Xiaoyan Liu,¹ Xiaofang Yu,^{1,2} Jieru Cai,¹ Xiaoqiang Ding,^{1,2} ¹Kidney and Dialysis Inst of Shanghai, Shanghai, China; ²Div of Nephrology, Fudan Univ Zhongshan Hospital, Shanghai, China.

Background: To investigate whether timing of mesenchymal stem cells (MSCs) transplantation can determine the survival and therapeutic potential of MSCs in ischemic kidney.

Methods: The model of renal IRI was induced by the release of bilateral renal pedicle clamps following 60 min of occlusion. Six rats per group were sacrificed per time point, at 0h, 1h, 12h, 24h, 48h, 72h and 1 week post-I/R respectively. Passage 3 rat MSCs were cultured with different time points kidney homogenate supernatants. After reperfusion, CM-Dil-labeled MSCs or vehicles only were administered through the carotid artery of the animals 1h before reperfusion(-1h) and immediately(0h), 12h, 24h after reperfusion. The animals were sacrificed 48h after reperfusion and 24h after MSCs transplantation.

Results: The serum creatinine level peaked at 24h of reflow(470.6±41.65mmol/l, P<0.05) and NGAL peaked at 12h(7607±1066 pg/ml, P<0.05). The highest expression of inflammatory factor was in 12h and 24h groups, and the lower was in -1h, 0h and 1w groups. In vitro, there was lower cell apoptosis and higher proliferation in -1h and 0h groups compared with other groups. Significant kidney function and histological damage improvement was observed after the treatment of MSCs in -1h and 0h groups. Meanwhile, the expression of proinflammatory factor significantly decreased and anti-inflammatory factor significantly decreased in -1h and 0h groups compared with other point time groups and control group. In addition, we also observed more obvious inhibition of renal tubular cell apoptosis and promotion of proliferation in -1h and 0h groups compared with other groups. Consistent with the improvement above, the viability of implanted MSCs also increased in -1h and 0h groups.

Conclusions: MSCs transplantation 1h before reperfusion or immediately after reperfusion produces the most dramatic improvement in renal function and morphology in rat model of renal I/R injury. It is the optimal timing to transplant MSCs in IRI before the inflammatory response is established.

Funding: Government Support - Non-U.S.

SA-PO266

Reno-Protective Role of Par1b in Acute Kidney Injury Abhijeet Pal,¹ Natalie S. Uy,¹ James M. Pullman,² Zhongfang Du,¹ Kimberly J. Reidy.¹ ¹Pediatric Nephrology, Children's Hospital at Montefiore, Montefiore Medical Center/ Albert Einstein Medical College, Bronx, NY; ²Pathology, Montefiore Medical Center/ Albert Einstein Medical College, Bronx, NY. **Background:** Partitioning defective Par1 (aka MARK) is a member of the Par polarity protein family and that localizes to the basolateral aspect of renal tubular cells. Defects in apico-basal polarity and cell-cell adhesion occur in acute kidney injury (AKI). Mammalian homologues Par1a and 1b are serine threonine kinases that

are functionally redundant on kinase assays. We have identified a role for Par1a/1b in glomerular and proximal tubular development in mice associated with downregulation of Notch signaling. We hypothesized that Par1a/1b would contribute to renal epithelial repair in the setting of acute kidney injury.

Methods: Expression of Par1a/1b and Notch signaling was examined using western blotting and immunostaining in mouse models of tubular injury and human kidney tissue (leftover from clinically indicated renal biopsy). Proximal tubular injury was induced by in wild-type(WT) and Par1b knockout mice by injecting cisplatin (30mg/Kg, ip) or folic acid (250 mg/kg, ip). The degree of histological damage was assessed by light microscopy.

Results: Par1a/1b proteins are highly expressed in developing mouse kidneys and down regulated in the adult. Increased basolateral Par1a/b expression was observed after cisplatin/folic acid injury in the wild type mice compared to untreated controls. More severe dilated tubular injury was observed in the cisplatin and folic acid injured Par1b knockout vs WT mice. Preliminary data indicate that Notch ligand Jag1 expression was increased in cisplatin treated wild-type mice but not Par1b^{-/-} mice. In human biopsy samples, we identified tubular expression of Par1a and 1b.

Conclusions: Our data demonstrates that Par1 proteins has a reno-protective role in tubular injury. Further studies of the mechanisms of this effect and interaction with Notch signaling are ongoing.

Funding: NIDDK Support

SA-PO267

Small Heat Shock Protein Beta-1 (HSPB1) Is Upregulated and Regulates Mitophagy and Apoptosis of Renal Tubular Cells in Acute Kidney Injury Tatsuki Matsumoto, Kazu Hamada-Ode, Yoshiko Shimamura, Koji Ogata, Kosuke Inoue, Taro Horino, Yoshinori Taniguchi, Shimpei Fujimoto, Yoshio Terada. *Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Kochi, Japan.*

Background: Heat shock protein beta-1 (HSPB1, also known as HSP27) is a small heat shock protein involved in many cellular processes and reportedly protects cells against oxidative stress. Autophagy protects cells from many types of stress and is thought to play a key role in preventing stress in acute kidney injury (AKI). However, little is known about the role of HSPB1 in autophagy and apoptosis in the pathogenesis of AKI.

Methods: We used a rat ischemia/reperfusion AKI model and cultured renal tubular cells as an *in vitro* model. To elucidate the regulation of HSPB1, we evaluated the promoter activity and expression of HSPB1 in normal rat kidney (NRK)-52E cells in the presence of H₂O₂. To examine the regulation of autophagy by HSPB1, we established NRK-light chain 3 (NRK-LC3) cells that were stably transfected with a fusion protein of green fluorescent protein and LC3.

Results: The results of immunohistological examination showed that HSPB1 was expressed in proximal tubule cells after AKI. Real-time quantitative reverse transcription-polymerase chain reaction and western blot analysis showed that HSPB1 mRNA and protein expression were upregulated 6–72 h and 12–72 h, respectively, after ischemia/reperfusion injury. HSPB1 promoter activity as well as mRNA and protein expression indicated dose-dependent induction by H₂O₂. HSPB1 overexpression-induced autophagy in NRK-LC3 cells under normoxic conditions was confirmed with confocal microscopy, which revealed the presence of LC3-positive granules. Furthermore, H₂O₂-induced autophagy was inhibited by the transfection of small interfering RNAs for HSPB1. Overexpression of HSPB1 reduced BAX activation and H₂O₂-induced apoptosis, as measured by caspase 3 activity and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling assay.

Conclusions: These results indicate that HSPB1 upregulation plays a role in the pathophysiology of AKI.

SA-PO268

Developing a More Clinically Relevant Mouse Model of Cisplatin-Induced Acute Kidney Injury Cierra Sharp, Mark A. Doll, Tess Dupre, Deanna L. Siow, Parag P. Shah, Levi J. Beverly, Leah J. Siskind. *Univ of Louisville, Louisville, KY.*

Background: Cisplatin, a commonly used chemotherapeutic for the treatment of many solid cancers is known to induce acute kidney injury (AKI) in 30% of patients. Patients that develop cisplatin-induced kidney toxicity must either have the dose severely reduced or be switched to an alternative therapy to prevent long-term renal damage. In many cases the alternative therapy may be less effective at treating the tumor. Due to cisplatin's complex nephrotoxic mechanism of action, the development of renoprotective agents remains a challenge. Currently there are no FDA approved drugs for the protection of cisplatin-induced AKI. The standard mouse model of cisplatin-induced AKI is a single high dose of cisplatin (10-30 mg/kg), and animals are sacrificed 72h after injection. This model does not accurately represent the clinical dosing regimen, which involves repeated dosing of cisplatin.

Methods: In this study we compared the standard single dose model to a new multiple dose model where mice received lower doses of cisplatin once a week for 4 weeks. We measured and compared indicators of kidney function (KIM-1, NGAL, BUN, and Serum Creatinine) as well as inflammatory cytokines and chemokines (i.e. TNF α , IL6, CXCL1, MCP-1). Indicators of apoptosis and cell death were measured as well as indicators of fibrosis (i.e. TGF- β , CTGF, BMP-7, and Sirius Red staining).

Results: In comparing the results of the single and multiple dose models, BUN values were similar, suggesting a comparable loss of kidney function. However, KIM-1 and NGAL were reduced by roughly 10-fold and 100-fold, respectively. Inflammation was also decreased in this model with TNF α , IL6 and IL1- β reduced by 4, 10 and 5-fold, respectively. Fibrosis was nearly non-existent in the single dose model; however, the multiple dosing model showed a significant increase in fibrosis. Also, expression of PAI-1, a mediator of fibrosis was significantly increased in the multiple dosing model compared to the single dose model.

Conclusions: Taken together, we propose that the multiple dosing model is a more relevant model for the discovery of renoprotective agents in the prevention/treatment of cisplatin-induced AKI.

Funding: NIDDK Support

SA-PO269

Genetic Knock Out of CHOP Protects against Ischemia-Mediated Acute Kidney Injury Rachel Carlisle, Elise Brimble, Jeffrey G. Dickhout. *Nephrology, St. Joseph's Healthcare Hamilton and McMaster Univ, Hamilton, ON, Canada.*

Background: Acute kidney injury (AKI), a major cause of morbidity and mortality in North America, is characterized by a sudden increase in serum creatinine. Renal ischemia, a common cause of AKI, induces endoplasmic reticulum (ER) stress and activates the unfolded protein response. This leads to a subsequent upregulation in the expression of the pro-apoptotic gene, CHOP. Transgenic knock out of CHOP inhibits ER stress-mediated acute tubular necrosis, implicating CHOP in the pathogenesis of AKI.

Methods: Bilateral renal ischemia/reperfusion (I/R) was performed in mice, using atraumatic vessel clamps, and confirmed via colour change (red to dark purple) of the kidney. Surgeries were performed on C57BL/6 mice to determine the appropriate time point to cause significant renal damage. Various time points for renal ischemia were examined, between 25-55 mins, with 48-72 h of recovery. I/R surgeries were subsequently performed on C57BL/6 and CHOP knock out mice. Ischemia was induced for 55 mins, and mice recovered for 48 h. Plasma creatinine was measured using an enzymatic assay, and kidneys were stained to analyze renal damage. Imaging of the kidneys was focused on the juxtamedullary region, as this area is the most vulnerable to ischemic damage.

Results: Creatinine levels increased in response to I/R surgery in both wild type and CHOP knock out mice; however, creatinine levels from CHOP knock out mice were significantly lower than from wild type mice. Stained kidney sections confirm renal protection in CHOP knock out mice, demonstrating reduced cellular damage and vacuolization in kidneys from these animals.

Conclusions: These results suggest that CHOP plays a significant role in ischemia-mediated renal injury, and attenuating its expression may provide new therapeutic strategies to protect against AKI.

SA-PO270

The Protective Role of Doxycycline for Cisplatin-Induced AKI by Its Anti-Inflammatory and Anti-Oxidative Effects Terumasa Nakagawa¹, Yutaka Kakizoe¹, Yoshikazu Miyasato¹, Teruhiko Mizumoto¹, Manabu Hayata¹, Yuichiro Izumi¹, Takashige Kuwabara¹, Taku Miyoshi¹, Masataka Adachi¹, Kenichiro Kitamura², Masashi Mukoyama¹. ¹*Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan;* ²*Internal Medicine III, Univ of Yamanashi Faculty of Medicine, Yamanashi, Japan.*

Background: Cisplatin (CDDP) is a chemotherapeutic drug widely used for the treatment of solid tumors. However, its nephrotoxicity is the major dose-limiting factor. Doxycycline (Dox) is a tetracycline antibiotic commonly used in a variety of infections, but several other properties have been suggested such as an anticancer effect or the inhibition of matrix metalloproteinase (MMP). In this study, we investigated whether Dox exerts the protective effects on CDDP-induced acute kidney injury (AKI).

Methods: Ten-week-old male C57BL/6J mice were divided into following four groups: 1) Control, 2) Dox (2mg/ml in drinking water), 3) CDDP (25 mg/kg, intraperitoneally) and 4) CDDP+DOX. After 7 days pretreatment with Dox, CDDP was administrated, and animals were sacrificed 3 days later. BUN and serum creatinine (Cr) were measured and renal histological changes as well as, inflammation, and oxidative stress markers were evaluated. MMP and serine protease activities in the kidney tissue were accessed with zymography.

Results: No apparent adverse effects were observed in Dox group. Dox did not affect mRNA expression of transporters for CDDP (OCT-1, OCT-2 and MATE1) in the renal tubules. CDDP caused severe tubular damages along with elevated BUN and Cr levels. It also increased mRNA expression of inflammatory and profibrotic molecules, together with enhanced oxidative stress in the kidney. Dox alleviated significantly those detrimental changes (Cr: Control, 0.13 \pm 0.01; Dox, 0.13 \pm 0.03; CDDP, 1.04 \pm 0.20; and CDDP+Dox, 0.30 \pm 0.12 mg/dL). Moreover, Dox suppressed the activities of MMP-2 and 9 as well as serine proteases, which were enhanced by CDDP in the kidney tissue.

Conclusions: Dox mitigated CDDP-induced AKI through its pleiotropic effects, i.e., anti-inflammatory, anti-oxidative and enzyme-inhibiting effects. Our results suggest that Dox could become a new strategy for the prevention of CDDP-induced nephrotoxicity in humans.

Funding: Government Support - Non-U.S.

SA-PO271

Involvement of Indoxyl Sulfate in Exacerbated Susceptibility of Streptozotocin (STZ)-Induced Diabetic Rat Kidney to Ischemia/Reperfusion-Induced Acute Kidney Injury (AKI) Yuna Shimokawa,¹ Naoko Oyama,¹ Takashige Kuwabara,² Masashi Mukoyama,² Hirofumi Jono,^{1,3} Hideyuki Saito.^{1,3} ¹*Clinical Pharmaceutical Sciences, Kumamoto Univ School of Pharmacy, Kumamoto, Japan;* ²*Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Kumamoto, Japan;* ³*Pharmacy, Kumamoto Univ Hospital, Kumamoto, Japan.*

Background: Diabetes mellitus (DM) is one of the potential risk factors in progression of acute and chronic kidney failures. In patients with DM, AKI tends to be severer and the restoration delays compared to that in non-DM patients. However, the precise mechanism is unclear. Indoxyl sulfate (IS) is a representative oxidative stress-inducible uremic toxin and involved in the progression of renal failures. In this study, we examined the toxicological involvement of IS in ischemic AKI in DM rats.

Methods: STZ-induced DM rats and nondiabetic rats without STZ treatment (non-DM) were subjected to 20 min of renal ischemia/reperfusion (I/R), and the development of renal injury in DM and non-DM rats were compared. An oral indole adsorbent AST-120 was orally administered to rats (2.5 g/kg) at 24 h, 1 h before and 24 h after I/R. Serum and kidney tissues were collected at 48 h following I/R.

Results: In DM ischemic AKI group, serum creatinine (SCr) (4.3-fold vs non-DM ischemic rats) and BUN (7.0-fold) were increased. The kidney of DM rats with I/R exhibited severetubular injury compared to that of non-DM rats with I/R in association with a marked increase in serum Kim-1 level (25-fold). Hydroperoxide (1.7-fold) and IS levels in serum (14.7-fold) and kidney (5.8-fold) were also elevated. Immunoblot analysis revealed that renal expression of organic anion transporters rOAT1/rOAT3 mediating renal excretion of IS were significantly downregulated. AST-120 treatment prevented the increases in SCr and BUN, and renal tubular injury in DM rats with I/R, in association with the reduction of serum and renal IS levels. The downregulation of rOAT1/rOAT3 was restored by AST-120 treatment.

Conclusions: In conclusions, DM could be a pivotal factor in progression of ischemic AKI, and AST-120-removable uremic toxin(s) including IS could play a toxico-physiological role as a mediator in the DM-exacerbated ischemic AKI.

Funding: Government Support - Non-U.S.

SA-PO272

Discoidin Domain Receptor 1 Is a Key Mediator of the Ischemia-Reperfusion Induced Renal Injury Aude Dorison, Yi-chun Xu-dubois, Christos E. Chadjichristos, Eric Rondeau, Christos Chatziantoniou, Jean-claude Dussaule. *UMRS 1155, INSERM, Paris, France.*

Background: Discoidin Domain Receptor 1 (DDR1) is a non-integrin collagen receptor, expressed by different cell types in the kidney, which displays tyrosine-kinase activity.

We have previously demonstrated that a *de novo* expression of DDR1 in target cells was driving renal inflammation and fibrosis in different models of chronic kidney disease. The aim of our study was to investigate whether DDR1 participates in the pathophysiological mechanisms of ischemia/reperfusion (I/R), a model of acute renal injury.

Methods: To this end, male mice subjected to I/R were injected either with oligodeoxynucleotide (ODN) antisense sequences directed against DDR1 (AS, n=8) or with scrambled sequences (SCR, n=7). Mice were sacrificed after 24h and parameters of renal function, structure and inflammation were measured.

Results: DDR1 protein expression was strongly induced in proximal tubular cells after I/R and this expression was inhibited by the AS administration. Increased uremia (BUN) showed impaired renal function in SCR+I/R animals, whereas AS treatment lowered BUN levels. In addition, histological damage such as brush border alterations and tubular necrosis were significantly decreased and E-cadherin protein expression was preserved in AS+I/R mice. Kim-1, NGAL, vimentin and VCAM-1 mRNA expressions were increased in SCR+I/R compared to controls and significantly decreased in mice treated with AS. Moreover, the AS-induced inhibition of DDR1 was accompanied by decreased T-lymphocyte infiltration and mRNA expressions of TNF α , MCP1, IL-1 β , IL-6 and TGF β .

Interestingly, DDR1 staining performed on transplant patient biopsies with a delayed graft function showed a strong expression of DDR1 which was associated with the severity of tubular necrosis and vimentin expression.

Conclusions: DDR1 inhibition protects mice from the I/R-induced histological damage, inflammation and loss of renal function. DDR1 overexpression plays a deleterious role in this model of kidney injury, thus reinforcing the interest to develop agents capable of specifically blocking the function of this receptor.

Funding: Government Support - Non-U.S.

SA-PO273

Heat Shock Factor 1 and Crystallin- α B in Cisplatin-induced Renal Tubular Cell Apoptosis and Nephrotoxicity Qiang Lou,^{1,2} Zheng Dong.² ¹*Medical College of Henan Univ, Kaifeng, Henan, China;* ²*Dept of Cellular Biology and Anatomy, Georgia Regents Univ, Augusta, GA.*

Background: Cisplatin, a widely used chemotherapy drug, induces nephrotoxicity that is characterized by renal tubular cell death. In response to toxic stress, renal tubular cells may activate cytoprotective mechanisms, such as the expression of heat shock proteins. However, the heat shock response during cisplatin nephrotoxicity is largely unclear. The present study analyzed the heat shock response during cisplatin treatment of renal tubular cells in vitro and mice in vivo, and examined the relevant regulatory mechanisms.

Methods: For *in vivo* study, male C57BL/6 mice were given a single intraperitoneal injection of cisplatin. In vitro, cultured renal proximal tubular cells (RPTC) were incubated with cisplatin. To determine the role of heat shock factor 1 (HSF1), HSF1 was knocked down by stable transfection of specific shRNAs.

Results: In RPTC, cisplatin induced a rapid expression of HSF1 and specific heat shock proteins, including Hsp70, Hsp27, and Crystallin- α B. The induction of these proteins was transient and decreased at late time points of cisplatin treatment. Similar changes were verified in kidney tissues following cisplatin injection, whereas Hsp90 did not change significantly. Knockdown of HSF1 decreased Crystallin- α B expression and increased RPTC apoptosis. Interestingly, p38 activation was enhanced in these cells. Moreover, inhibition of p38 with SB203580 markedly inhibited cisplatin-induced apoptosis in HSF1-knockdown cells.

Conclusions: Induction of HSF1 is a cytoprotective response during cisplatin nephrotoxicity. Crystallin- α B appears to be a key heat shock protein induced by HSF1 for its protective effect. Heat shock response may regulate or co-operate with other signaling pathways, such as p38, to regulate tubular cell apoptosis.

Funding: NIDDK Support, Veterans Administration Support

SA-PO274

The Effect of the Cytoplasmic Domain of Tissue Factor in Contributing to Renal Ischemic Reperfusion Injury Is Both Protease Activated Receptor-1 (PAR-1) and Strain Dependent Jonathan H. Erlich,^{1,3} Sean E. Kennedy,^{1,2} Joseph J. Murphy,¹ Calum Wai Kit Chong.¹ ¹*Dept of Medicine, Univ of New South Wales, Randwick, Australia;* ²*Dept of Nephrology, Sydney Childrens Hospital, Randwick, NSW, Australia;* ³*Dept of Nephrology, Prince of Wales Hospital, Randwick, NSW, Australia.*

Background: The cytoplasmic domain of tissue factor plays a role in cell signaling and regulation of angiogenesis and inflammation. It may do this both by regulating intracellular signaling and via modulating protease activated receptor signaling. Previously we have shown that mice on a mixed genetic background deficient (MGB) in the cytoplasmic domain of tissue factor (TF^{defect/defect}) mice developed severe renal injury. TF^{defect/defect} have increased cytokine and PAR-1 expression. We further investigated the importance of increased PAR-1 signaling and the strain background of the mice.

Methods: Mice WT or TF^{defect/defect} on MGB or mice backcrossed onto CB7BL6 mice background underwent 25 min bilateral warm ischemia and 24 reperfusion. Renal function was assessed by serum creatinine and renal injury was further assessed by histology and expression of inflammatory mediators from renal tissue. The role of PAR-1 was assessed using the inhibitor SCH79797.

Results: TF^{defect/defect} mice on the MGB developed more severe injury at 24 than WT on a similar genetic background. These mice developed greater PAR-1 mRNA expression and treatment of these mice with the PAR-1 inhibitor reduced injury similar to PAR-1 deficient mice. In contrast the effect of TF cytoplasmic depletion was not seen in mice on C57BL6 background. These mice had similar PAR-1 induction to that observed in WT C57BL6. WT mice with a MGB had lesser renal injury and lower basal PAR-1 expression than WT C57BL6 mice. TF^{defect/defect} mice on MGB having similar basal PAR-1 expression and much greater inducible PAR-1 expression (5 fold compared to 2.8 fold for WT). TF^{defect/defect} on a C57BL6 background had similar renal injury and PAR-1 induction to WT mice.

Conclusions: The cytoplasmic domain of TF may contribute to renal IR injury by regulating PAR-1 expression. The role of the TF cytoplasmic domain in regulating renal injury is genetic background dependent.

SA-PO275

Protective Effects of Endonuclease Inhibitors on Cisplatin-Induced Acute Kidney Injury Dae Song Jang,¹ Tariq Fahmi,¹ Todd Fite,¹ Narsimha Reddy Penthalu,³ Dolapo Taiwo Odeniyi,¹ Alena Savenka,¹ Peter A. Crooks,³ Sudhir V. Shah,^{1,2} Alexei G. Basnakian.^{1,2} ¹*Univ of Arkansas for Medical Sciences, Dept of Pharmacology and Toxicology, Little Rock, AR;* ²*Central Arkansas Veterans Healthcare System, Div of Nephrology, Little Rock, AR;* ³*Univ of Arkansas for Medical Sciences, COP Pharmaceutical Science, Little Rock, AR.*

Background: Cisplatin is one of the most commonly used and the most nephrotoxic anticancer drugs. Acute kidney injury induced by cisplatin cannot be overcome and may lead to chronic kidney failure. Our previous studies showed that genetic inactivation of two kidney apoptotic endonucleases, DNase I and EndoG, was partially protective against tubular epithelial cell death induced by cisplatin. Until very recently, pharmacologically meaningful inhibitors of the endonucleases, which would be non-toxic and effective in vivo, were not available.

Methods: This study was aimed to determine if the two new endonuclease inhibitors recently identified by us, IG-17 (1,3-phenylene-bis-aminoguanidine hydrochloride) for DNase I and PNR-3-82 (5-((1-(2-naphthoyl)-5-methoxy-1H-indol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione) for EndoG, could ameliorate cisplatin toxicity to kidney tubular epithelial cells in vitro and in vivo.

Results: In vitro experiments using NRK-52E cells showed that the compounds are able to suppress endonuclease activity inside the cells provide partial protection against cisplatin toxicity measured using LDH release assay and TUNEL, and are non-toxic at the used concentrations. The inhibitors were found to markedly suppress the total-body endonuclease activity in mice at the dose of 5 mg/kg administered subcutaneously, and were non-toxic up to 25 mg/kg as measured using 14 blood plasma markers of organ toxicities.

Conclusions: Importantly, cisplatin-induced kidney injury was functionally (creatinine) and structurally (acute tubular necrosis, TUNEL) reduced by the administration of the inhibitors (5 mg/kg) in mice suggesting their potential therapeutic value.

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SA-PO276

Involvement of CYLD as a Regulatory Factor in Fibrotic Response of Ischemic AKI Kidney and Hypoxic HK-2 Cells Go Yoneda,¹ Naoki Suenaga,¹ Nozomi Yabuuchi,¹ Kazuhiko Nishi,² Hirofumi Jono,^{1,3} Hideyuki Saito.^{1,3} ¹Clinical Pharmaceutical Sciences, Kumamoto Univ Graduate School of Pharmaceutical Sciences, Kumamoto, Japan; ²Hemodialysis and Apheresis, Kumamoto Univ Hospital, Kumamoto, Japan; ³Pharmacy, Kumamoto Univ Hospital, Kumamoto, Japan.

Background: Cylindromatosis (CYLD), a tumor suppressor, regulates various signaling pathways by acting as a deubiquitinating enzyme. Recent studies have revealed that CYLD is associated with not only tumors, but also chronic inflammatory diseases, such as tissue fibrosis. It is well-documented that tissue fibrosis is common hallmark of chronic kidney disease (CKD), and CKD progresses toward end-stage renal disease through renal fibrosis. However, the molecular pathogenesis of renal fibrosis is not fully uncovered yet. In this study, we elucidated the roles of CYLD in renal fibrosis by using in vivo and in vitro models.

Methods: We generated model mice of ischemia/reperfusion (I/R)-induced acute kidney injury (AKI) and hypoxic human kidney (HK)-2 cells. CYLD expression in kidney tissue and HK-2 cells was determined by immunoblot analysis. Fibrosis gene expression of PAI-1, CTGF and COL1A1 were examined by RT-PCR.

Results: In I/R-induced AKI mice, serum creatinine (SCr) and BUN were elevated 2 days after I/R treatment, and renal fibrosis was induced 28 days after I/R treatment. In those kidney tissues of I/R-AKI mice, CYLD protein expression was markedly decreased (0.4-fold) in a time-dependent manner. Interestingly, fibrosis gene expression (PAI-1: 12-fold, CTGF: 2.5-fold, COL1A1: 4-fold) was significantly increased in response to the CYLD down-regulation. In HK-2 cells, siRNA knockdown of CYLD gene expression significantly increased the PAI-1 gene expression (12-fold). Moreover, CYLD mRNA expression was significantly suppressed (0.5-fold) under hypoxic condition, an important factor of CKD progression, whereas the PAI-1 gene expression (2-fold) was elevated in HK-2 cells. These results suggested that CYLD could play a pathological role in regulating renal fibrotic response.

Conclusions: In conclusion, CYLD may be a novel regulatory factor involved in renal fibrosis and its down-regulation may trigger fibrosis under ischemic and/or hypoxic conditions.

Funding: Government Support - Non-U.S.

SA-PO277

Attenuation of Renal Fibrosis After Unilateral Ischemia Reperfusion May Require a Multi-Target Approach Nathalie Le Clef,¹ Bruce L. Riser,² Patrick C. D'Haese,¹ Benjamin Arthur Vervaeke.¹ ¹Laboratory of Pathophysiology, Univ of Antwerp, Wilrijk, Antwerpen, Belgium; ²BLR Bio LLC, WI.

Background: Acute kidney injury (AKI) is an important risk factor of chronic kidney disease (CKD). We optimized a mouse model of AKI to CKD by unilateral ischemia-reperfusion (UIRI) with development of renal fibrosis. To validate this model for use in therapeutic intervention studies, 3 experimental treatments were tested: administration of 1) recombinant human CCN3 (CCN2/CTGF antagonist), 2) TGFβ1 neutralizing antibody (1D11) or 3) dexamethasone (corticosteroid).

Methods: Male C57Bl/6 mice underwent 21 min of unilateral ischemia-reperfusion (UIRI) at 36°C body temperature. 8 treatment groups (n>4/group, ip) were included: dexamethasone (10 mg/kg, daily), vehicle (PBS, daily), rhCCN3 (5 μg/kg, daily), vehicle (PBS, daily), antibody to TGFβ (0.5 mg/kg, every other day), vehicle (PBS, every other day), an untreated UIRI group and a sham group. Three weeks after UIRI renal fibrotic outcome was determined by gene expression analysis (qPCR) of collagen I, TGFβ, CTGF, CCN3, PAI-1 and TNFα.

Results: UIRI induced a ~40% reduction in renal mass. Treatment with rhCCN3, anti-TGFβ or dexamethasone did not attenuate this reduction. UIRI induces significant upregulation of the fibrosis-related genes. rhCCN3 treatment had no effect on gene expression. Anti-TGFβ antibody treatment induced significantly less upregulation of TGFβ and CCN3 gene expression, however, vehicle also reduced TGFβ expression. Dexamethasone treatment induced significantly less upregulation of collagen I and CCN2/CTGF gene expression and a trend towards higher CCN3 upregulation.

Conclusions: Despite the earlier proven benefits of TGFβ antagonism and CCN3 treatment on the development of fibrosis, neither treatment (at doses demonstrated to be effective in more mild injury models) showed effect in the UIRI model. Broad anti-inflammatory suppression by dexamethasone attenuated fibrotic gene expression. We speculate that the natural course of renal demise after UIRI is very robust and highly likely to require a multi-target approach. Whether some combination of the therapies tested here could have efficacy in this model remains to be determined.

Funding: Government Support - Non-U.S.

SA-PO278

The Effect of Oxygen and Hypothermic Therapy on the Prevention of Acute Kidney Injury Sang H. Woo,¹ Cholawat Pacharinsak,² ¹Medicine, Thomas Jefferson Univ, Philadelphia, PA; ²Dept of Comparative Medicine, Stanford Univ.

Background: There is no effective therapy for acute kidney injury. The effect of oxygen, hypothermic therapy delivered through urinary tract on the treatment of acute kidney injury has not been known. This pilot study was performed as a proof of concept of a catheter-based oxygen and hypothermic oxygen therapy in preventing and treating acute kidney injury.

Methods: Rats (n=6) were used for the experiment. Three rats were used to compare oxygen therapy and control. The other three rats were used to compare hypothermic oxygen therapy and control. Oxygen was cooled for hypothermic oxygen therapy before it was delivered to the kidney. Right kidneys received treatment (oxygen or hypothermic oxygen) and left kidneys were used for control. After a catheter was placed in a bladder, oxygen (or cooled oxygen) was delivered to the right kidney from the bladder through the catheter for five minutes for pretreatment before clamping. Both right and left renal arteries were clamped for 30-45 mins to induce acute kidney injury. Only right kidneys continued to receive oxygen or hypothermic oxygen during the clamping of renal arteries. The kidneys were extracted after the induction of acute kidney injury with the clamping. Gross examination of both kidneys during the clamping and after the extraction was performed.

Results: Gross examination of kidneys demonstrated less ischemic changes of kidneys treated with oxygen or hypothermic oxygen during and after the induction of acute kidney injury. As shown in Figure 1, right kidneys that received oxygen therapy or hypothermic oxygen therapy showed less ischemic changes on gross examination during the clamping and after extraction.

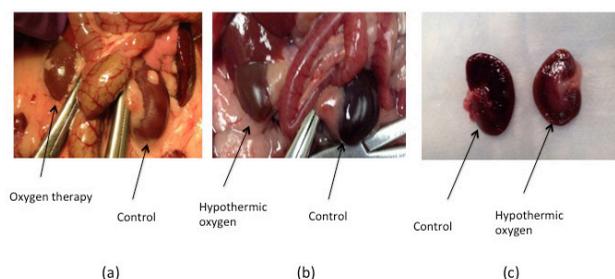


Figure 1

Conclusions: This pilot study shows novel methods for the prevention and treatment of acute kidney injury. Further study is necessary to investigate the benefits of catheter based oxygen and hypothermic therapy in the prevention and treatment of acute kidney injury.

SA-PO279

MicroRNA-17 Is Induced via P53 to Protect against Renal Ischemia-Reperfusion Injury by Targeting Death Receptor 6 Jielu Hao,^{1,2} Qingqing Wei,² Changlin Mei,¹ Zheng Dong.² ¹Nephrology, Shanghai Changzheng Hospital, Shanghai, China; ²Cellular Biology and Anatomy, Georgia Regents Univ, Augusta, GA.

Background: Ischemia-reperfusion injury is the critical cause of acute kidney injury (AKI) in clinical settings, which unavoidably develops into chronic kidney disease (CKD) due to lack of understanding of mechanism and effective therapies. In the present study, we investigated the role of microRNA-17 (miR-17) regulation in kidney against damage in ischemia-reperfusion injury.

Methods: Renal ischemia-reperfusion was induced in C57 mice by bilateral clamping of renal arteries, followed by releasing of the clamps. BUN and serum creatinine were measured to indicate the loss of renal function. In vitro, rat kidney proximal tubular cells (RPTC) were treated with hypoxia (1% oxygen). To test the effect of miR-17, anti-miR-17-LNA and miR-17 mimic were transfected before hypoxia. The change of p53 and DR6 were detected by Western blot. Pifithrin-α and dominant-negative p53 were used to determine the role of P53 in miR-17 expression.

Results: By real time PCR, we identified that miR-17 was significantly increased in kidney tissues after 30 minutes of bilateral renal ischemia and 12h-48h reperfusion. In the moderate injury model of 25 minutes of ischemia, miR-17 was induced at day 1 and the induction lasted for a week. In vitro, hypoxia also induced miR-17 in RPTC cells. Functionally, miR-17 mimic reduced apoptosis and caspase activation, whereas anti-miR-17-LNA increased apoptosis during hypoxia, suggesting a cytoprotective role of miR-17. Blockade of p53 with pifithrin-α or a dominant-negative mutant led to the suppression of miR-17 induction in hypoxia, supporting a role of p53 in this inductive response. Bioinformatics analysis predicted Death receptor 6 (DR6) as a target of miR-17. In line with this, we showed that the expression of DR6 was inhibited by miR-17 mimic, in contrast, increased by anti-miR-17-LNA.

Conclusions: MiR-17 is one of the microRNAs that are induced significantly during renal ischemia-reperfusion. MiR-17 induction is mediated by p53 and, upon induction, it may suppress downstream target genes, such as DR-6, to protect kidney cells and tissues from injury.

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SA-PO280

Proximal Tubule-Derived CSF-1 Mediates Expansion and Polarization of Renal Macrophages/Dendritic Cells and Recovery in Acute Kidney Injury

Yinquin Wang, Bing Yao, Raymond C. Harris, Ming-Zhi Zhang. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Colony-stimulating factor-1 (CSF-1)-mediated renal macrophage expansion and polarization play an essential role in recovery from acute kidney injury in ischemia/reperfusion (I/R)-injury and selective apoptotic proximal tubule injury in transgenic mice expressing the human diphtheria toxin receptor (DTR) and exposed to DT (DTR-AKI). In the kidney, a major site of CSF-1 production is in proximal tubular epithelial cells.

Methods: Male DTR mice with CSF-1^{fl/fl} (wild type) or with γ -GT-Cre:CSF-1^{fl/fl} (CSF-1 KO in renal proximal tubule) were used for DTR-AKI and for I/R injury (30 min of ischemia and contralateral nephrectomy).

Results: CSF-1 expression in the proximal tubule and its deletion in CSF-1 KO mice were confirmed with immunostaining. Six days after DTR-AKI, activation of the CSF-1 receptor (p-c-fms) was markedly attenuated in both renal tubules and interstitial cells, including macrophages (F4/80 and p-c-fms dual positive cells). Flow cytometry and qPCR indicated fewer renal macrophages/dendritic cells and reduced mRNA levels of M2 phenotype markers (CD206, IL-4R α , TGF- β and 15-LOX) in CSF-1 KO mice 6 days after DT injection. Although selective proximal tubule CSF-1 deletion did not affect the severity of kidney injury, it delayed renal functional recovery, in association with increased oxidative stress, increased secondary necrosis (HMGB1 expression) and severe tubulointerstitial fibrosis, with increased Picro-sirius red staining of fibrillary collagen and increased profibrotic and fibrotic components (α -SMA, CTGF, fibronectin, collagen I and IV). Selective proximal tubule CSF-1 deletion also led to delayed functional recovery after I/R injury, with decreased mRNA levels of M2 phenotype markers in isolated renal macrophages/dendritic cells and more severe renal fibrosis. In both I/R injury and DTR-AKI, selective proximal CSF-1 deletion had minimal effects on the expression of M1 phenotype markers.

Conclusions: These studies demonstrate that proximal tubule is a major source of CSF-1 that mediates the expansion and polarization of renal macrophages/dendritic cells that play an essential role in recovery following AKI.

Funding: NIDDK Support

SA-PO281

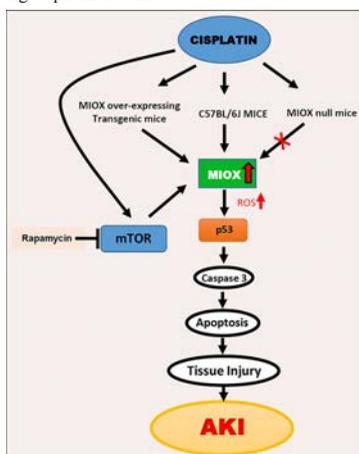
Ablation of Myo-Inositol Oxygenase Protects against Cisplatin-Induced Acute Kidney Injury by Inhibiting p53 Activation

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Background: MIOX is a renal tubular enzyme. Its role in the pathogenesis of diabetic nephropathy is currently being investigated. Conceivably, it modulates redox imbalance and apoptosis in tubular cells in diabetes via modulation of glucuronate-xylulose (G-X) pathway. However, its role in acute kidney injury (AKI) is unknown.

Methods: In this study we used both MIOX-over-expressing transgenic and MIOX null mice to elucidate its role in a model of cisplatin induced AKI.

Results: We observed severe cisplatin-induced proximal tubular injury in MIOX transgenic and protection in null mice compared to wild type mice. In transgenic mice an increased serum creatinine and urea levels, caspases-3 activity and tubular apoptosis along with marked deterioration of tubular morphology was observed. Renal injury was remarkably less in null mice compared to wild type mice. Cisplatin treatment led to p53 activation in wild type and MIOX transgenic mice, whereas minimal p53 activation was observed in MIOX null mice. Likewise, we noted that cisplatin induces mTOR pathway in both wild type and MIOX transgenic mice while such an effect was not observed in MIOX null mice. Treatment with mTOR inhibitor, rapamycin, prevented cisplatin-induced MIOX expression, p53 activation and deterioration of tubular morphology in control mice. In vitro studies revealed significantly high levels of ROS generation, caspases-3 activity and apoptosis in MIOX over-expressing cells compared to control cells transfected with empty vector following cisplatin treatment.



Conceivably, this was attributed to the accentuated induction of GX-pathway and its associated myriad enzyme system.

Conclusions: Overall this study suggest that MIOX is a mediator of cisplatin induced AKI via activation of G-X-ROS-p53 pathway, and genetic deletion of MIOX protects the kidney tubules from cisplatin induced renal injury.

Funding: NIDDK Support

SA-PO282

Precision Medicine for AKI: Novel RNA Labeling Technique Demonstrates Unique Transcriptional and Cellular Responses in Different Injury Models

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Background: The clarity brought to CKD patients by Precision Medicine has not been applied to AKI, which is currently defined by the rise of a single analyte, the Pcreatinine (Pcr).

Methods: To identify specific molecular responses we investigated 3 models: (i) ischemia (10min bilateral pedicle clamping), (ii) volume depletion (72 hr water deprivation which matched the Pcr of the ischemic model) and (iii) a model of cystitis (small volume UPEC inoculation). We generated a novel technique of cell and time-specific Cre mediated in-vivo RNA labeling to purify specific RNA species directly from the kidney.

Results: We analyzed RNA pools from the entire Collecting Duct (CD) and its subset Intercalated Cells (IC). We found a robust genetic response of CD to volume depletion (94.5% of the induced genes) but a limited genetic response to ischemia (3.2% of induced genes) with very little overlap (2.3%). In contrast, the IC subset demonstrated a greater response to ischemia (62% of the induced genes) compared to volume depletion (32% of induced genes) and only 6% of the genes were shared. Remarkably, the IC cell population demonstrated an overwhelming specific response to cystitis (95% of induced genes). Region specific laser capture microdissection validated the cellular distinctions: ischemia and volume depletion induced different transcriptional changes in different cells with limited overlap. Moreover, functional analyses demonstrated activation of different molecular pathways, and different secreted proteins. Testing the urine of 100 Emergency Department patients revealed five new candidate biomarkers that distinguished ischemia and volume depletion.

Conclusions: We found that despite identical Pcr, ischemia and volume depletion targeted different regions, cell types and genes with limited overlapping genetic responses: the CD responded robustly to volume depletion while the IC were unique sensors of ischemia and infection. These data demonstrate that while Pcr can not distinguish between models of injury, the specific responses of the nephron provide Precision AKI diagnoses.

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SA-PO283

Calcium Oxalate Crystal-Induced Acute Kidney Injury Involves Ripk3-Mlkl Mediated Tubular Cell Necroptosis

Hans J. Anders,¹ Jyaysi Desai,¹ Santhosh Kumar Vr,¹ Jonathan Nicodemus Eberhard,¹ Dana Thomasova,¹ Simone Romoli,¹ Andreas Linkermann,² Shrikant R. Mulay.¹ ¹Ludwig Maximilians Univ, Munich, Germany; ²Christian-Albrechts-Univ, Kiel, Germany.

Background: Crystalline nephropathy (CN) & nephro-/uroolithiasis involves crystal-induced renal inflammation via NLRP3 inflammasome (Mulay et al, JCI 2013), but the mode of direct crystal cytotoxicity remains elusive. The aim of the study was to investigate mechanisms of crystal cytotoxicity in kidney.

Methods: All *in vivo* experiments were approved by the local government authorities. Acute oxalate nephropathy (AON) was induced by i.p. injection of sodium oxalate (NaOx) (100mg/kg) and 3% NaOx in drinking water for 24hr. IHC, EM, RT-PCR, MTT assay, PI stain and multicolour FACS were used for data analysis.

Results: We found that crystals of calcium oxalate (CaOx), monosodium urate, calcium pyrophosphate dehydrate & cystine trigger caspase-independent necrosis of mouse tubular cells, human kidney cells & human renal progenitor cells. Pretreatment with RIPK1 inhibitor necrostatin-1 (Nec-1), MLKL inhibitor & RNA interference of RIPK3 or MLKL blocked crystal cytotoxicity. Consistently, deficiency of RIPK3 or MLKL protected mice from AON (e.g. plasma creatinine, BUN, tubular injury score, renal KIM-1 & π -GST mRNA expression, neutrophil count and TUNEL+ve cells) despite similar crystal deposition. I.p. injection of crystals induced neutrophil recruitment into peritoneal cavity, which was unaffected by Nec-1 as was crystal injection into air pouches at the back of mice. However, Nec-1 significantly reduced microvascular permeability & leukocyte extravasation from post-ischemic cremaster muscles. Thus RIPK1 signaling per se does not affect neutrophil recruitment. Next, we found that AON was significantly reduced in *Tnfr1*-deficient mice, with no additive effects with concomitant *Tnfr2* deficiency. Thus, TNFR1 signaling activates RIPK3-dependent necroptosis in this model. Finally, etanercept, TNFR inhibitor R-7050 & Nec-1 protected mice from AON.

Conclusions: Crystal-cytotoxicity involves TNFR1-RIPK1-RIPK3-MLKL pathway. All components of this pathway represent novel molecular targets for therapeutic interventions to limit CN.

SA-PO284

Allopurinol Protects against Rhabdomyolysis and Acute Kidney Injury Induced by a Membrane Protein (Lp25) from Pathogenic *Leptospires* Antonio C. Seguro,¹ Daniele Canale,¹ Patricia A. Abreu,² Denize Monaris,² Tatiana B. Gotti,² Larissa R. Matos,² Thales de Brito,¹ Pedro H F Gois,¹ Antonio J. Magaldi,¹ ¹Nephrology, Hospital das Clínicas FMUSP, São Paulo, Brazil; ²Lab. de Bacteriologia, Inst Butantan, São Paulo, Brazil.

Background: Acute kidney injury (AKI) in leptospirosis is frequently nonoliguric, hypo or normokalemic. Higher serum potassium levels, elevated creatine phosphokinase (CPK) associated with maximum serum creatinine level were observed in nonsurvivor patients suggesting that rhabdomyolysis contributes to more severe AKI in leptospirosis. Previous study from our group demonstrated that Lp25, a protein membrane from pathogenic *Leptospire*, was responsible for hyperkalemic AKI induced by rhabdomyolysis in guinea pig. Recent studies suggest that Allopurinol (Allo) protects individuals from exercise-induced rhabdomyolysis. The aim of this study was to evaluate the effect of Allo on guinea pigs injected with Lp25.

Methods: Three groups of guinea pigs were studied: 1- Sham (phosphate-buffered solution); 2- Lp25; 3- Lp25+Allo. One mL of PBS and Lp25 (400µg of Lp25/mL) were intraperitoneally injected for 4 days. Lp25+Allo received Allo (300mg/L) in drinking water during this time. On the 5th day, animals were placed in metabolic cages for 12 hour urine collection. We measured urinary volume (Ur V/12h), creatinine clearance (ml/min/100gBW), serum potassium (mEq/L), CPK (U/L), uric acid (mg/dL), phosphate (mg/dL). Data are mean±SEM.

Results: Lp25 induced hyperkalemia, rhabdomyolysis (elevated CPK, uric acid, phosphate) and oliguric AKI. Allo ameliorated CrCl, serum potassium, CPK and uric acid.

	Cr Cl	Ur V	K	CPK	Uric acid	P
Sham (n=7)	1.10± 0.18	25.1± 4.9	4.8± 0.3	897± 277	1.08± 0.19	6.9± 0.3
Lp25 (n=8)	0.48± 0.05 ^b	11.1± 1.8 ^a	6.8± 0.5 ^a	2852± 495 ^a	4.15± 0.48 ^b	9.3± 0.6 ^a
Lp25+ Allo (n=6)	0.91± 0.14 ^d	17.0± 3.7	5.1± 0.6 ^c	1331± 374 ^c	0.47± 0.07 ^d	8.4± 0.5

^a p<0.05, ^b p<0.01 vs. Sham; ^c p<0.05, ^d p<0.001 vs. Lp25

Conclusions: These data demonstrate that Allo attenuates rhabdomyolysis and AKI induced by Lp25 in guinea pigs. This may represent a new therapeutic approach for AKI in patients with leptospirosis. (CNPq, FAPESP).

SA-PO285

Conventional Autophagy Regulates the Degradation of AQP2 in Hypokalemia Wan-Young Kim,¹ Sun-ah Nam,¹ Yumi Kim,¹ Arum Choi,¹ Yongkyun Kim,² Jin Kim,¹ ¹Anatomy and Cell Death Disease Research Center, The Catholic Univ of Korea, Seoul, Korea; ²Internal Medicine and Cell Death Disease Research Center, The Catholic Univ of Korea, Bucheon, Korea.

Background: Autophagy is a catabolic pathway utilized to maintain a balance among the synthesis, degradation, and recycling of cellular component, thereby playing a role in homeostasis. Abundance of AQP2 is regulated through balance between production by translation and removal by degradation. Although AQP2 degradation is supposed to be occurred via lysosomal or proteasomal degradation, the precise mechanisms still remain unknown. It has been known that prolonged hypokalemia causes vasopressin-resistant polyuria and induces autophagy especially in principal cells (PC) of collecting duct.

Methods: To investigate the role of autophagy in the degradation of AQP2, we generated *AQP2-cre;Atg7^{fl/fl}* mice, in which *Atg7*, an essential gene for mammalian autophagy, was selectively inactivated in PCs. Hypokalemia was induced by K⁻-depleted diet for 2 weeks.

Results: In control *AQP2-cre;Atg7^{fl/fl}* mice, the distribution pattern of AQP2 was not different from *Atg7^{fl/fl}* mice. Immunolabeling of pS261-AQP2 was localized mostly subapical and punctate in appearance in the PCs. In contrast to pS261-AQP2, immunolabeling of pS256-AQP2 was localized mainly at the apical plasma membrane and subapical domains. In hypokalemic *Atg7^{fl/fl}* mice, the abundance of pS261-AQP2 was significantly reduced and redistributed to intracellular vesicles, and co-localized with LC3-positive vacuoles. In hypokalemic *AQP2-cre;Atg7^{fl/fl}* mice, there was a decrease of conversion of LC3-I to LC3-II and a marked accumulation of p62 selectively in PCs. Rab9 protein, an essential molecule for alternative autophagy pathway, and Rab9-positive vacuoles were markedly increased. Interestingly, pS261-AQP2 was distributed throughout the cytoplasm and not co-localized with Rab9- or LC3-positive vacuoles in the PCs of *AQP2-cre;Atg7^{fl/fl}* mice. There was no difference in localization of pS256-AQP2 at the plasma membrane from each genotype.

Conclusions: These results suggest that down regulation of AQP2 in hypokalemia could in part be caused by degradation of pS261-AQP2 in PCs through a LC3/Atg7-dependent conventional autophagy pathway.

Funding: Government Support - Non-U.S.

SA-PO286

Early Autophagy Precedes Angiotensin II-Induced Podocyte Apoptosis Tae-Sun Ha, *Pediatrics, Chungbuk National Univ, Cheongju, Chungbuk, Korea.*

Background: Autophagy is a highly regulated catabolic process that is involved in the turnover of unwanted cellular materials, on the other hand, apoptosis removes damaged or unwanted cells. Therefore, autophagy and apoptosis constitute the two processes through which injured/aged cells or organelles are eliminated. Angiotensin II (Ang II) induces podocyte injury resulting in apoptosis in vitro and in vivo. However, the relationship between autophagy and apoptosis in Ang II-induced podocytes is not elucidated and the role of Ang II-induced autophagy in podocyte survival remains unclear. We investigated the sequential relationship between autophagy and apoptosis in Ang II-induced podocytes.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times. The changes of podocyte autophagy and apoptosis were observed by electron microscopy, confocal imaging, Western blotting, and FACS assay according to the presence of Ang II. **Results:** Ang II-treated podocytes showed an increase in autophagosomes compared with control cells at early phase in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine, an inhibitor of PI3-kinase class III. Ang II also enhanced podocyte expression of autophagic proteins such as LC3-II and beclin-1. Atg5 siRNA further reduced the expression of LC3-II and cleaved caspase-3 suppressed by Ang II at 12 hrs. However, Atg5 siRNA did not affect the expression of Atg5, LC3-II, and cleaved caspase-3 in the presence of Ang II at 24 hrs. Thereafter, Ang II induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS assays. LY294002 and Atg5 siRNA further increased podocyte apoptosis induced by Ang II. Therefore, high concentrations of Ang II induced apoptosis, while autophagy response decreased, which implicated that autophagy preceded apoptosis for cytoprotection in angiotensin II-induced podocyte injury.

Conclusions: We suggest that Ang II induced autophagy in mouse podocytes prior to apoptosis as an early adaptive cytoprotective mechanism for podocyte survival after Ang II treatment and the imbalance between autophagy and apoptosis causes podocyte injury.

Funding: Government Support - Non-U.S.

SA-PO287

Emodin Ameliorates Cisplatin-Induced Renal Tubular Cell Apoptosis Through Activation of Autophagy Hong Liu,¹ Wei Sun,¹ Yigang Wan,² Liubao Gu,³ ¹Dept of Nephrology, Affiliated Hospital of Nanjing Univ of Chinese Medicine, Nanjing, China; ²Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing Univ Medical School, Nanjing, China; ³Center for Diabetes Care, Education and Research, Jiangsu Province Inst of Geriatrics, Nanjing, China.

Background: Autophagy plays a key role in regulating cell survival. Emodin can ameliorate cisplatin-related nephrotoxicity. Thus, we explored the effects and mechanisms of emodin on cisplatin-induced apoptosis in NRK-52E cells by activation of autophagy.

Methods: NRK-52E cells were treated with cisplatin with or without emodin, cell morphology and expressions of cleaved Caspase-3 and autophagy makers LC3 I/II, were detected. Red fluorescent protein-LC3 (RFP-LC3) plasmid was transiently transfected into NRK-52E cells, and changes of RFP-LC3 fluorescent particles were observed by fluorescence microscopy. The level of LC3 was tested after treated with Bafilomycin A1 and mTOR inhibitor rapamycin. Besides, morphological changes of apoptotic cells were observed and cell death was evaluated by FACS analysis. Finally, AMPK/mTOR signaling pathway related proteins were detected. Further, changes of cell morphology and the level of cleaved Caspase-3 were detected after the addition of compound C, which is an AMPK inhibitor.

Results: Emodin improved cisplatin-induced cell shape change, cell viability and caspase 3 cleavage. This protective effect of emodin was associated with increased LC3 conversion and occurrence of RFP-LC3 punctate structures. Further studies revealed that the suppressive effect of emodin on cisplatin-induced apoptosis could be abolished by suppression of autophagy with bafilomycin A1 and mimicked by activation of autophagy with rapamycin. Additionally, AMPK/mTOR signaling pathway was important for the induction of autophagy and inhibition of apoptosis.

Conclusions: Induction of autophagy could be an important mechanism by which emodin protected renal tubular cells against cisplatin-induced cell injury, and the potentially mechanism of emodin-induced autophagy may be attributed to the activation of AMPK and inhibiting mTOR signaling pathway. Emodin may have a therapeutic potential in the prevention of cisplatin-induced nephrotoxicity.

Funding: Government Support - Non-U.S.

SA-PO288

Autophagy in Renal Tubular Epithelial Cells Plays a Protective Role in Renal Fibrosis Yong Kyun Kim,¹ Sun-Ah Nam,² Wan-Young Kim,² Arum Choi,² Yumi Kim,² Ho Cheol Song,¹ Jin Kim,² ¹Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; ²Dept of Anatomy and Cell Death Disease Research Center, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Renal tubulointerstitial fibrosis (TIF) is the final common pathway of various renal injuries. Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell death or proliferation. Recent studies reported that autophagy has protective role in renal TIF. However, the mechanism of autophagy

regulating fibrosis is not fully understood. In this study, we investigated the proposed mechanisms of autophagy in renal TIF induced by UO by using conditional knockout mice in which Atg7 is genetically ablated specifically in tubular epithelial cell (TEC).

Methods: Atg7-floxed mice were crossed with Ksp-Cre mice to generate TEC-specific Atg7 knockout mice (Atg7^{fl/fl};Ksp-Cre⁺). Unilateral ureteral obstruction (UO) was performed. We examine the expression of epithelial-mesenchymal transition (EMT) markers. The expression of TGF- β , plasminogen activator inhibitor 1 (PAI-1) and p62 as the regulators of EMT were examined. We determined apoptosis and proliferation of TECs and the expression of c-Myc as a regulator of cell apoptosis and proliferation.

Results: In vitro, TGF- β treatment induced autophagy. In vivo, TEC-specific Atg7 deletion enhanced renal TIF after UO. TEC-specific Atg7 deletion increase expression of TGF- β and enhance tubular EMT (decrease E-cadherin and increase α -smooth muscle antibody and vimentin) after UO. In electron microscopy, TEC-specific Atg7 deletion results in ultrastructural alterations of TEC after UO. TEC-specific Atg7 deletion increase expression of PAI-1, P62 after UO. TEC-specific Atg7 deletion enhanced apoptosis and proliferation of TECs after UO. The expression of c-Myc was significantly increased mice with TEC-specific Atg7 deletion after UO.

Conclusions: Our data suggest that autophagy regulate EMT through TGF- β , PAI-1 and P62 during renal TIF. Autophagy also regulates apoptosis and proliferation of TECs through the expression of c-Myc during renal TIF. Autophagy could represent a therapeutic target for renal TIF.

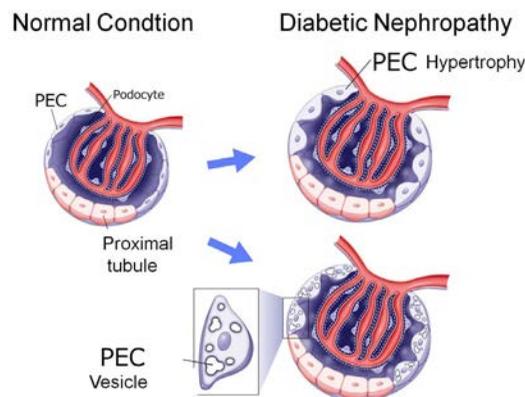
SA-PO289

Partial De-Differentiation of Parietal Epithelial Cells Caused by Reduced Expression of Sirt1 and Concomitant Increased Expression of p21 and CD133 in Diabetic Nephropathy Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. *Keio Univ.*

Background: We have previously reported the role of proximal tubular Sirt1 in diabetic nephropathy (DN). Parietal epithelial cells (PECs) and their cellular metabolism reportedly play a pivotal role in kidney. Sirt1 is a key energy sensor, whereas DN disrupts energy metabolism.

Methods: Thus, we examined the effect of Sirt1 expression in PECs on DN.

Results: In two DN murine models including streptozotocin-treated and db/db mice, expression of Sirt1 in proximal tubules and PECs was decreased at 8 weeks after the onset of DN, corresponding to the early stage of DN. Sirt1 expression was also downregulated in podocytes at 24 weeks. We further investigated the changes in PECs at 8 weeks. No change was found in the number of PECs. The morphology of all PECs showed hypertrophy, and some PECs contained autophagic vesicles, especially in the periphery or the border of the plasma membrane at basolateral sides.



HG treatment of cultured PECs resulted in significant reductions in cell proliferation and migration, while increasing the production of extracellular and basement membrane components such as type IV collagen. We performed DNA microarray, confirmatory real-time PCR, and immunofluorescence, revealing that an increase in Glut1 (glucose transporter) expression promoted influx of high amounts of glucose into PECs, which led to a reduction in Sirt1 expression and lysine acetylation-mediated activation of p21. Among the main molecular markers of precursor cells, including CD24, CD44, and CD133, only CD133 showed remarkable elevation, indicating that the decrease in Sirt1 expression caused the partial de-differentiation of PECs.

Conclusions: Sirt1 may be a promising target for protection against DN-induced de-differentiation of PECs, which would prevent not only hypertrophy of PECs but also the concomitant thickening of the basement membrane of Bowman's capsule.

SA-PO290

APOL1 Variants are Critical to Induce Vitamin D Receptor (VDR) Down Regulation in Dedifferentiated Podocytes Shabirul Haque,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,² Pravin C. Singhal.¹ ¹Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; ²Medicine, Rambam Health Care Campus, Haifa, Israel.

Background: African Americans carrying APOL1 variants (Vs) are prone to develop HIV-associated nephropathy (HIVAN). Recently, vitamin D receptor (VDR) has been reported to play a critical role in the development of HIVAN. We hypothesized that HIV-

induced dedifferentiation of podocytes is the first hit but to accelerate the injury a sustained second hit is needed and may be the sustained down regulation of VDR. Down regulation of VDR has been reported to activate renin angiotensin system in kidney cells. HIV-induced low VDR status in kidney cells has been shown to contribute to the progression of HIVAN. We asked whether APOL1 variants would be contributing to accelerate podocyte injury in HIV milieu through down regulation of VDR. In the present study, we evaluated the effect of APOL1 variants on podocyte VDR expression both in differentiated (DPs) and dedifferentiated podocytes (DDPs).

Methods: RNAs were extracted from human podocytes (both DPs and DDPs) stably expressing vector, G0, G1 and G2. cDNAs were amplified with a specific VDR primer specific. Vector, G0, G1 and G2 expressing DPs and DDPs were infected with HIV followed by Western blotting and probing for SNAIL (a transcription of VDR). Additionally, the effects of APOL1 variants were evaluated on glycosylation and methylation status of SNAIL.

Results: DDPs expressing G1 and G2 displayed moderate decrease in VDR mRNA expression, whereas, G0 expressing DDPs displayed only mild decrease in VDR expression. There was no alteration in VDR mRNA expression in DPs expressing either G0 or G1/G2. Vector-expressing DPs and DDPs did not reveal any expression of SNAIL. On the other hand, G0 and G1/G2 expressing DPs and DDPs displayed moderate expression of SNAIL. HIV further enhanced SNAIL expression by DPs and DDPs expressing G1/G2.

Conclusions: We conclude that APOL1 modulates VDR expression in DDPs only. Since HIVAN occurs in APOL1 variants only, presence of APOL1 variants seems to be critical to sustain HIV-induced podocyte injury.

SA-PO291

Post-Transcriptional and Post-Translation Status of APOL1 (G0) and Its Variants (G1 and G2) in Podocytes and 293T Cells Post-Transcriptional and Post-Translation Status of APOL1 (G0) and Its Variants (G1 and G2) in Podocytes and 293T Cells Shabirul Haque,¹ Xiqian Lan,¹ Gauri P. Patil,¹ Amrita Kaur Chawla,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,² Pravin C. Singhal.¹ ¹Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; ²Medicine, Rambam Health Care Campus, Haifa, Israel.

Background: APOL1 gene variants have been reported to contribute to higher prevalence of kidney diseases in African Americans. APOL1 gene is known to contribute to kidney cell injury but the mechanisms involved are not clear. Interestingly, renal biopsy specimens in kidney disease patients with APOL1 variants displayed lower podocyte expression of APOL1. However, the involved mechanism for lower APOL1 expression in these patients is not clear. Gene sequence alterations/mutations hamper either mRNA transcription stability or defects in protein translation. We hypothesized that mutation in APOL1 would lead to modulation of protein expression in podocytes.

Methods: Protein blots of human podocytes (HPs) stably expressing vector, APOL1G0, APOL1G1 and APOL1G2 were probed for APOL1 and reprobated for actin. RNAs were extracted with HPs expressing Vec, G0, G1 and G2 and cDNA were amplified with APOL1 specific primer. 293 T cells were transfected with equal amount of plasmids (vector, G0, G1, and G2) for 48 hours. Protein blots were probed for APOL1 and reprobated for actin. To evaluate stability/decay rate of APOL1 mRNA, APOL1/APOL1 variants expressing HPs were pulsed with actinomycinD and RNAs were harvested at different time points (0.0, 0.5, 1.0, 3.0, 8.0, and 24 hours) by Trizol method.

Results: APOL1 variants (G1/G2) expressing HPs displayed lower expression of APOL1 when compared APOL1G0. 293 T cells also displayed lower expression of G1 and G2. However, there was no difference in mRNA expression in APOL1G0 and APOL1G1/G2 expressing cells. Stability/decay kinetic assay revealed that variants (G1 and G2) of APOL1 mRNA decayed in an accelerated mode (more than 35%) during 1/2 to 24 hours after actinomycin D exposure.

Conclusions: These findings suggest that APOL1 variants protein instability may be related to loss/decay of variants APOL1 mRNA or to some extent defects in protein translation/stability.

Funding: NIDDK Support

SA-PO292

HIV Promotes NLRP3 Inflammasome Complex Activation in HIVAN Shabirul Haque, Xiqian Lan, Amrita Kaur Chawla, Rivka Lederman, Rabani Bharara, Ramachandra prasanna Bongu, Ashwani Malhotra, Pravin C. Singhal. *Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.*

Background: Dysregulated growth and loss of podocytes are important features of HIV-associated nephropathy (HIVAN). In a recent report, HIV induced programmed cell death in T cells has been implicated to pyroptosis as a consequence to inflammasome formation. We hypothesized HIV would also be promoting podocyte loss through the induction of pyroptosis. We evaluated the role of HIV in podocyte NOD-like receptor family, pyrin domain containing (NLRP) 3 protein complexes (inflammasomes) formation both *in vitro* and *in vivo*.

Methods: Renal cortical sections of control and Tg26 (HIVAN) mice (n=4) were labeled for inflammasome molecular markers (IMMs; NLRP3, ASC, cleaved caspase-1 and IL-1 β). Protein blots of renal tissues of control and Tg26 mice were also probed for IMMs and actin (n=11). Protein blots of empty vector (EV) - and NL4-3 (HIV)-transduced human podocytes (HPs) were probed for IMMs and actin (n=4). EV/HPs and HIV/HPs were evaluated for pyroptosis by PI staining under a fluorescence microscope as well as by FACS analysis. Effect of Tempol (SOD mimetic), caspase-1 inhibitors, and glyburide (an inhibitor of K⁺-efflux inhibitor was evaluated on HIV induced podocyte pyroptosis by morphologic assay and FACS analysis.

Results: Renal cortical sections of HIV-transgenic mice (Tg26) displayed increased podocyte expression IMMs. Renal tissues of Tg26 mice also displayed enhanced mRNA

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

expressions as well as protein expressions of IMMs. Serum from Tg26 mice showed higher levels of IL-1 β . HIV promoted pyroptosis in podocytes in a dose as well as time dependent manner. Since caspase-1 inhibitor not only attenuated podocyte expressions of caspase-1 and IL1 β in addition to protection against pyroptosis; this would confirm that HIV induced podocyte injury was mediated by caspase-1 activated complexes. Interestingly, HIV-induced podocyte pyroptosis could be partially inhibited by tempol as well as by glyburide.

Conclusions: These findings indicate that generation of reactive oxygen species and potassium efflux contributed to HIV-induced pyroptosis in podocytes.

SA-PO293

Urinary Cytochrome C (Cyto C) Detects Subliminal Injury and Correlates with Apoptosis in Acute (AKI) and Acute on Chronic Kidney Disease (A-CKD) Lena Succar,¹ Philip Peake,¹ Zoltan H. Endre.¹ ¹Prince of Wales Hospital and Clinical School, Univ of New South Wales, Sydney, NSW, Australia; ²Prince of Wales Hospital and Clinical School, Univ of New South Wales, Sydney, NSW, Australia; ³Prince of Wales Hospital and Clinical School, Univ of New South Wales, Sydney, NSW, Australia.

Background: Mitochondrial Cyto C is a potentially specific biomarker of apoptotic kidney injury in AKI. We investigated urinary Cyto C in detecting subliminal kidney injury (histological injury without an increase serum creatinine, sCr) in two models of A-CKD.

Methods: In male Sprague Dawley rats (i) adenine-CKD was induced by diet supplementation with 0.025% adenine, days (d) 0 to 28 and monitored until d56 (n=8). On d56, AKI was induced in rats by a subnephrotoxic (2mg/kg; n=8) or nephrotoxic (4mg/kg; n=8) cisplatin (Cis) dose ip and monitored to d63 (n=8 in matched controls). (ii) Aristolochic-acid nephropathy (AAN) induced by AA-1 (10m/kg) ip for five days and monitored to d21 (n=6) or d42 (n=6) then given 2mg/kg (n=6) or 4mg/kg (n=6) Cis and monitored to d28 and d49 respectively. Cyto C was measured by ELISA. Tubulointerstitial damage (TID) and TUNEL were quantified on d63.

Results: Cyto C levels increased in subliminal AAN (d1 to d7) and adenine-CKD (d3 to 21) without change in sCr, but increased in both CKD groups after 2mg/kg and 4mg/kg Cis dose in controls. In AAN, Cyto C levels increased progressively (d22 to d28) after Cis exceeding controls given 4mg/kg whereas Cyto C was lower after Cis on d42 to d49. Regardless of Ci dose, Cyto C increased in controls and adenine-CKD. A-CKD rats displayed diffuse medullary and cortical TID with positive TUNEL staining while injury in CKD alone was largely in outer medulla. In ANN peak Cyto C, 72 hours post Cis, correlated significantly with outer medullary (Spearman R=0.86*) and cortical apoptosis (R=0.81*). In adenine fed rats, Cyto C correlated only with medullary apoptosis (R=0.79*). sCr correlated only with severe diffuse cortical TID (R=0.94*) (*P<0.05).

Conclusions: Cyto C detected subliminal injury and correlated strongly with outer medullary apoptosis in A-CKD, which alone did not increase sCr. Cyto C is a useful biomarker for early detection of apoptotic kidney injury.

SA-PO294

Assessment of Graphene Toxicity to Kidney Tubular Epithelial Cells and Cell Spheroids Using DNase Activity Probe Tariq Fahmi,¹ Zeid A. Nima,² Julietta Sargsyan,¹ Alexandru S. Biris,² Alexei G. Basnakian.¹ ¹Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR; ²Univ of Arkansas at Little Rock, Center for Integrative Nanotechnology Sciences, Little Rock, AR.

Background: Recently invented nanomaterial, graphene, consists of monomolecular carbon sheets, which are extremely strong, light and flexible. It will be used widely because of its versatility. However, little is known about its potential for being a toxicant and environmental hazard, and methods to study graphene toxicity are not established. Kidney is one of the primary organs for the assessment of nanomaterial toxicity. We hypothesized that graphene induces nephrotoxicity mainly through DNA destruction, and measuring of DNase activity by using near infrared fluorescence (NIRF) DNase activity probe would be a reliable tool for assessing graphene cytotoxicity.

Methods: Non-modified graphene (50 μ g/ml) exposed with cultured rat kidney tubular epithelial NRK-52E cells induced TUNEL-type DNA fragmentation usually associated with cytotoxicity. Raman spectroscopy showed the TUNEL-positive cells have significantly higher graphene content than TUNEL-negative cells. DNase activity was quantified in live cells using the oligonucleotide-based NIRF probe. Quantitative immunocytochemistry (qICC) was then used to measure apoptotic DNases such as caspase-activated DNase (CAD), endonuclease G (EndoG), and DNase I, and the marker of oxidative stress, heme oxygenase-1 (HO-1).

Results: The NIRF fluorescence and all of the above qICC markers were induced in NRK-52E cells by graphene exposure. In addition, a 50% colocalization of HO-1 with DNase activity was observed suggesting a possible link between oxidative stress and the DNases. Furthermore, we developed kidney spheroids (mini-kidneys) model by culturing NRK-52E cells using 3D hanging drop method, and tested the graphene toxicity in this model by measuring the DNase activity using the NIRF probe. The result showed a strong dose-dependent increase of DNase activity induced by graphene.

Conclusions: Measuring of DNase activity by using NIRF probe in combination with TUNEL assay and qICC are appropriate tools for assessment of graphene toxicity.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

SA-PO295

Identification of a Novel Bidirectional Regulatory Mechanism Involving AKT/ β -Catenin and Anillin That Drives Podocyte Proliferation Gentzon Hall,^{1,3,4} Jose A. Gomez,¹ Brandon M. Lane,^{2,4} Guanghong Wu,⁴ Himani Vaidya,⁴ Robert F. Spurney,^{1,3} Rasheed A. Gbadegesin.^{2,3,4} ¹Internal Medicine, Duke Univ; ²Pediatrics, Duke Univ; ³Nephrology, Duke Univ; ⁴Duke Molecular Physiology Inst, Duke Univ.

Background: Mutations of the F-actin binding protein Anillin (ANLN) have been shown to cause familial FSGS. Although ANLN is a suspected modulator of phosphoinositol-3 kinase (PI-3K) signaling, specific interactions with PI-3K pathway intermediates and the role of these interactions in the pathogenesis of FSGS remains unknown.

Methods: siRNA-mediated gene knockdown studies, immunoblot and proliferation assays were performed by standard methods in conditionally immortalized human podocytes (CIHP) to examine the effects of ANLN depletion on PI-3K pathway signaling in podocytes. CIHP lines stably expressing tGFP-vector control or tGFP-ANLN_{WT} were established via lentiviral transduction to characterize the effects of ANLN overexpression on PI-3K signaling in podocytes.

Results: We evaluated the effect of ANLN overexpression and targeted ANLN knockdown (KD) on AKT activation in podocytes. Additionally, we explored the effects of pharmacologic inhibition of AKT on ANLN expression in podocytes. Finally, we examined the role of AKT-mediated activation of β -Catenin via the direct phosphorylation of serine 552 in podocyte ANLN expression. We determined that ANLN overexpression significantly attenuated AKT activation. Conversely, ANLN KD significantly enhanced AKT activation and upregulated AKT-mediated phosphorylation/activation of β -Catenin at serine 552. Pharmacologic inhibition of AKT also inhibited basal podocyte proliferation. Finally, we demonstrated that pharmacologic inhibition and targeted gene knock down of β -Catenin significantly attenuated podocyte ANLN expression.

Conclusions: These findings elucidate a novel mechanism of reciprocal regulation involving AKT/ β -Catenin signaling and ANLN which may provide valuable insights into the role of ANLN in the pathogenesis of FSGS and other proliferative podocytopathies.

SA-PO296

Akt Mediates Cell Survival in Proteinuric States Elif Erkan, Jian Gao, Sam Z. Coffey. *Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: The degree of proteinuria correlates with progression in association with tubulointerstitial injury in glomerulonephritis. High concentrations of albumin in the glomerular filtrate results in apoptosis. Protein kinase B (Akt) is a serine/threonine kinase involved in multiple signaling events including cell survival. We hypothesize that down regulation of survival protein, protein kinase B (Akt) triggers tubular apoptosis in proteinuric states.

Methods: We utilized *in-vitro* and *in-vivo* model of albumin overload. Human kidney proximal tubule epithelial cells (HKC-8) are exposed to 10mg/ml albumin for 24-hours to induce apoptosis. C57BL/6C mice are exposed to 10mg/g of intraperitoneal(ip) albumin injections for 6 weeks to induce albuminuria. Fluorometric caspase-3 assay and TUNEL staining were utilized to assess apoptosis. Protein expression was assessed by Western blotting and immunofluorescence. Kidney sections from bigenic (Fyn-/Cd2ap+/+) mice model of FSGS and patients with FSGS were evaluated for apoptosis and Akt expression.

Results: Albumin overload *in-vivo* and *in-vitro* resulted in proximal tubule epithelial cell apoptosis in association with down regulation of pser473 Akt and Thr-308 Akt expression. Furthermore mice model of FSGS and patient kidney biopsies confirmed down regulation of tubular pser473 Akt expression in association with apoptosis. Overexpression of Akt by a constitutively active mutant ameliorated the albumin induced apoptosis where as chemical inhibition of Akt by of MK2206 enhanced albumin induced apoptosis in HKC-8 cells. Phosphorylation of downstream targets of Akt, transcriptional factors forkhead family Foxo1 and 3 is inhibited in association with apoptosis in response to albumin overload.

Conclusions: Down regulation of Akt expression in proteinuric states results in tubular apoptosis which is a precursor to tubular atrophy. We postulate that decreased Akt phosphorylation of Foxo proteins allow them to translocate to nucleus and induce apoptotic gene expression. Therapeutic interventions directed to increase Akt expression in tubular epithelial cells can serve to prevent tubulointerstitial injury by inducing cell survival in proteinuric states.

Funding: NIDDK Support, Pharmaceutical Company Support - Malincrodt

SA-PO297

Altered Protein Kinase Signalling Causes Major Phenotypical Changes in Renal Cells from Patients with Nephropathic Cystinosis Ekaterina A. Ivanova,¹ Fanny Oliveira Arcolino,¹ Maria Pia Rastaldi,² Lambertus P.W.J. Van den Heuvel,¹ Elena N. Levchenko.¹ ¹Pediatric Nephrology, UZ Leuven, KU Leuven, Leuven, Belgium; ²IRCCS Policlinico, Milano, Italy.

Background: Cystinosis is caused by mutations affecting the lysosomal cystine transporter cystinosin and results in lysosomal cystine accumulation. Cystinosis causes proximal tubular dysfunction, but also glomerular damage, which is present starting from early age. Current therapy of cystinosis is based on cystine-lowering cysteamine treatment, which greatly improves the prognosis, but does not cure the Fanconi syndrome and fails to prevent kidney damage in the majority of patients. It is therefore likely that, apart from the transporter function, cystinosin is implicated in other important cellular processes. We have investigated the mTORC-Akt signalling cascade in cystinosin-deficient renal cells. Akt kinase lies at the crossroads of cellular signalling regulating cytoskeleton, motility,

response to stress and survival, and is a target of mTORC2 and an upstream activator of mTORC1. mTORC1 is the master regulator of autophagy and metabolism. mTORC1 and 2 are also implicated in the regulation of cytoskeleton and cell motility.

Methods: Using conditionally immortalized proximal tubular epithelial cells (PTECs) and podocytes originating from cystinosis patients and healthy donors, we performed biochemical and microscopic analysis of phosphorylation and activation of protein kinases in response to various stimuli.

Results: Phosphorylation of Akt1 and 2 was increased in cystinosis podocytes and PTEC in response to nutrient/growth factor replenishment and wounding of cellular monolayer. In podocytes, such increased phosphorylation, was associated with altered cytoskeleton, disturbed focal adhesion sites and increased motility. Treatment with specific Akt inhibitor demonstrated a prominent decrease of motility and Akt phosphorylation. mTORC1 activation in response to nutrient replenishment was delayed in cystinosis PTECs accompanied with abnormal subcellular distribution of the kinase complex, as revealed by antibody staining of mTOR.

Conclusions: We demonstrate that cystinosis dysfunction is associated with disturbed signalling of protein kinases mTORC1 and Akt1 and 2.

Funding: Private Foundation Support

SA-PO298

Interstitial Pericytes Decrease in Aged Mouse Kidneys Anna Maria Stefanska,¹ Diana G. Eng,¹ Natalya V. Kaverina,¹ Jeremy Stuart Duffield,² Jeffrey W. Pippin,¹ Stuart J. Shankland,¹ ¹*Div of Nephrology, Dept of Medicine, Univ of Washington, Seattle, WA;* ²*Biogen Idec, Cambridge, MA.*

Background: With increasing age, the kidney undergoes characteristic changes in the glomerular and tubule-interstitial compartments, which are ultimately accompanied by reduced kidney function. Studies have shown age-related loss of peritubular vessels. Normal peritubular vessel tone, function and survival depend on neighboring pericytes. Pericyte detachment leads to vascular damage, which can be accompanied by their differentiation to fibroblasts and myofibroblasts, a state that favors matrix production.

Methods: To better understand the fate of pericytes in the aged kidney, 27-month-old mice were studied. Picrosirius red staining was performed to evaluate kidney fibrosis. Histological sections were stained against endothelial antigen CD31 together with pericyte markers PDGFR β and NG2. Additionally, immunoreactivity of myofibroblast marker α SMA was assessed together with pericytes.

Results: Compared to 3 month-old young adult mice, aged kidneys showed a substantial decrease in capillaries, identified by CD31 staining, in both cortex and medulla. This was accompanied by a marked decrease in surrounding NG2⁺/PDGFR β ⁺ pericytes. This decrease was more pronounced in the medulla. Capillaries devoid of pericytes were typically dilated in aged mice. Aged kidneys were also characterized by interstitial fibrosis due to increased collagen-I and -III staining. This was accompanied by an increase in the number of pericytes that acquired a pro-fibrotic phenotype, identified by increased PDGFR β / α SMA⁺ staining.

Conclusions: These findings are consistent with the decline in kidney interstitial pericytes as a critical step in the development of changes to the peritubular vasculature with aging, and accompanying fibrosis.

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SA-PO299

Interactions of Urotensin II and Mitophagy in Diabetic Nephropathy and Its Implications on Drug Design Guan-Jong Chen, Fei Wu, Ai-hua Zhang. *Dept of Nephrology, Peking Univ Third Hospital, Beijing, China.*

Background: Urotensin II (UII), an important vasoactive neuropeptide, and the processes of mitophagy have been considered as possible therapeutic targets for treating diabetic nephropathy (DN). The present study is to define the interaction between UII and the process of mitophagy under the setting of DN.

Methods: Immunohistochemistry and western blot analysis were conducted on the protein extracts harvested from the kidney tissues of DN mice that were induced eighteen weeks after the injection of streptozotocin. For in-vitro cell experiment, HK-2 cells were cultured and treated with different concentrations of UII (10⁻⁷-10⁻⁹ mol/L) for 12 h and 3-MA treatment was used as a negative control. The cell protein extracts were then analyzed by western blot. For immunohistochemistry and western blot analysis, BNIP3 was used as a marker for mitophagy.

Results: Immunohistochemistry and western blot analysis results of the animal renal extracts show that the expressions of UII and BNIP3, marker of mitophagy, are upregulated for DN kidney compared to that of controls. In-vitro cell experiment results also demonstrate UII can upregulate BNIP3. Our data indicates that UII expression is positively associated with the expression of BNIP3.

Conclusions: Our results indicate that UII expression can upregulate mitophagy in DN. Past studies already demonstrate that mitophagy can have a therapeutic role in DN. Our study carries the implication that UII and its effect on the process of mitophagy presents potential opportunities for developing novel treatments for DN.

Funding: Government Support - Non-U.S.

SA-PO300

Reduction in CTGF Leads to Increased Proliferation Through Influences on Claudin-1 and Extracellular Matrix Protein Spondin 2 Leighton R. James, Yongxin Gao. *Medicine, Univ of Florida, Jacksonville, FL.*

Background: Accumulation of extracellular matrix is a characteristic feature of diabetic kidney disease. We have recently demonstrated that connective tissue growth factor (CTGF) mediate increases in extracellular matrix production, proteinuria and scarring in mice. In addition, CTGF may have anti-proliferative properties. In specific human neoplasm (breast, colon), increased CTGF have been linked to reduced proliferation, improved response to therapy and prognosis but data is not consistent. On the other hand, metastatic melanoma progression correlates with CTGF levels and inhibition of CTGF reduces invasion and migration.

Methods: To define a possible role for CTGF in proliferation, embryonic fibroblasts (MEF) generated from wild-type and a previously reported CTGF knock mice line were studied. Expression array (Illumina) was used to identify changes in gene expression in MEF. Protein expression was assessed by Immuno-blotting. Inhibitors of MAPK (SP600126, SB203580 and U0126) were used to assess role of MAPK in glucose-mediated CTGF expression by cultured MEF.

Results: CTGF gene disruption lead to enhanced proliferation (3-fold) in CTGF knockout cells compared with wildtype cells. Reduced CTGF led to 50% decreased expression of the gene for the extracellular protein, procollagen 4, alpha 2 (Col4a2; confirmed at protein level)) in association with 2.8-fold increased expression of claudin-1, a member of the tight junction proteins. In addition, there was a 3.2-fold increased expression of spondin-2 and a 1.6-fold increased expression of Secreted protein, acidic and rich in cysteine-like 1 (SPARCL1). Immunoblotting confirmed the observation for claudin 1. Glucose induced CTGF expression (2-3 fold) was attenuated by inhibitors of p38MAPK and JNK, but unaffected by inhibition of ERK (p42/44 MAPK).

Conclusions: In MEF, CTGF gene disruption leads to increased proliferation and altered matrix protein linked to increased expression of claudin 1 and other extracellular protein. Secondly, glucose-induced CTGF level is mediated by MAPK (p38 and JNK). Targeted alteration in CTGF along with one or more of these extracellular protein may offer new approaches to manage glomerulosclerosis.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO301

miR21 Upregulates YY1 to Increase Renal Cell Apoptosis in Diabetes Adam Kosti,^{1,2} Sitai Liang,^{1,2} Samy L. Habib,^{1,2} ¹*Geriatric Research, Education and Clinical CTR, South Texas Veterans Health System, San Antonio, TX;* ²*Cellular and Structural Biology, The Univ of Texas Health Science Center, San Antonio, TX.*

Background: The regulation of miRNAs in response to hyperglycemia that contributes to the pathogenesis of kidney disease has been underscored.

Methods: In the current study, we investigated the role of miR21 in regulation of cells apoptosis in human renal proximal tubular cells (Hk2) cells exposed to high glucose and in type II diabetes mouse model.

Results: Cells pretreated with either miR21 inhibitor or antisense before exposed to HG resulted in decrease YY1 expression and decrease cleavage of caspase 3. Nuclear extracts from Hk2 cells exposed to high glucose for 48hrs showed increase in binding of YY1 to the miR21 promoter element in nuclear extracts of cells by EMSA. On the other hand, pretreatment with miR21 inhibitor or antisense significantly decrease the binding of miR21 to YY1 in nuclear extracts of cells grown in NG or treated with HG. The DNA-protein complexes were significantly decreased in the presence of the YY1 antibody, indicating that YY1 is indeed a component of these complexes. Transfected the cells with promoter/reporter construct of miR21 showed significant increase in miR21 promoter activity in cells exposed to HG while cells pretreated with miR21 inhibitor reverse the effect of HG. In addition, significant increase in the percentage of TUNEL-positive tubular cells stained in the kidney sections of dbdb mice compared to kidney sections of the wild type mice. Quantitation of miR21 by real-time PCR showed significant increase miR21 levels in kidney of diabetic mice (db/db) compared to kidneys from wild type mice. Immunostaining analysis of miR21 showed that majority of miR21 staining within the tubular cells and glomerular compartments.

Conclusions: In summary, expose renal cells to HG and increase hyperglycemia in kidney of diabetic mice resulted in significant increase in miR21. Increase binding of YY1 to miR21 under HG condition suggesting the important role of miR21 in regulating YY1 to increase cell apoptosis. The data provide a novel role of miR21 as a target for controlling renal cell death that induced by hyperglycemia during diabetic nephropathy.

Funding: Veterans Administration Support

SA-PO302

The Role of miR-302 and Let7 in Macrophage Polarization Thomas K. Dodd, John Crean, Letizia De Chiara, Orina Belton. *Diabetic Complications and Renal Disease, Univ College Dublin, Dublin, Ireland.*

Background: Recent advances in the pathogenicity of renal injury highlighted the critical role of the immune system in the onset and resolution of disease. Monocytes canto differentiate along two pathways: pro-inflammatory (M1) due to the secretion of cytokines such as IL-6 and a pro-resolution attributable to the secretion of cytokines such as IL-10. Banerjee et al. have suggested that the ratio of M1 and M2 macrophages is controlled by

interplay between two micro RNAs, miR302 and Let7. We have recently shown that the silenced targets of miR302 and Let 7 are the TGF β type II and type I receptors respectively and hypothesize that this circuitry plays a critical role in macrophage differentiation.

Methods: The pro-resolving lipid mediator, conjugated linoleic acid (CLA), inhibits the acquisition of a pro-inflammatory macrophage phenotype by priming monocytes towards an anti-inflammatory M2 phenotype. To identify pathways associated with this phenotype we performed proteomic analysis of THP-1s treated with CLA. Exosomes were isolated from urine samples taken from patients with renal injury and analyzed for miRNA expression. Renal cells were transfected with miR-302 and let7 virus. TGF β receptor expression and signaling was analyzed by Western blot. Additionally, Thp-1 cells were transfected with miR302 and let7 and their effect on macrophage differentiation assessed for expression of CD68 and CD206.

Results: Bioinformatic and Western blot analysis revealed enrichment of the TGF β signaling pathway in THP-1 cells treated with CLA. miR302 expression was increased in the urine of patients compared to controls. Cells transfected with miR302 and Let7 displayed low levels of expression of the TGF β type 2 and type 1 receptors respectively and dampened Smad3 phosphorylation. miR302 and let7 prevented renal epithelial cell dedifferentiation. THP-1 cells transfected with both miRNAs demonstrated similarly enhanced plasticity.

Conclusions: miR302 and let7 have potential injury resolving roles in renal disease. Manipulation of this circuitry results in enhanced cell plasticity. In vitro studies suggest that this results in the generation of pro-resolution cellular phenotypes in both resident cells and macrophages.

SA-PO303

Dopamine D2 Receptor Regulates Wnt3/ β -Catenin Signaling and Apoptosis in Human Renal Proximal Tubule Cells Fei Han,¹ Prasad Konkalmatt,² Jianghua Chen,¹ Pedro A. Jose,² Ines Armando.² ¹Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China; ²Dept of Medicine, School of Medicine, Univ of Maryland, Baltimore, MD.

Background: Dopamine D2 receptor (D2R) in the kidney has a direct role in regulating renal inflammation and injury, and blood pressure. Some common single nucleotide polymorphisms (D2R SNPs; rs 6276, 6277, and 1800497) in the human *DRD2* gene are associated with decreased D2R expression and function.

Methods: We measured apoptosis and activation of Wnt3/ β -catenin signaling pathway in human renal proximal tubule cells (RPTC) carrying these D2R SNPs (RPTC-D2R SNPs), and in RPTC carrying D2R wild type (RPTC-D2R WT).

Results: RPTC-D2R SNPs showed increased apoptosis compared with RPTC-D2R WT (11 \pm 0.8% vs 2.3 \pm 0.4% TUNEL positive cells, P<0.01). We found that Wnt3 expression was increased in RPTC-D2R SNPs in comparison with RPTC-D2R WT (mRNA: 2.6 \pm 0.35 vs 1 \pm 0.11 fold; P<0.05; protein: 133 \pm 4% vs 100 \pm 5%; p<0.05). RPTC-D2R SNPs showed activated Wnt3/ β -catenin signaling pathway demonstrated by decreased β -catenin phosphorylation (64 \pm 4% vs 100 \pm 8%; P<0.05) and increased expression of downstream pro-apoptotic factors Bax (136 \pm 4.6% vs 100 \pm 5%, P<0.05) and FasL (128 \pm 5.6% vs 100 \pm 6.5%, P<0.05). Silencing D2R in RPTC-D2R WT increased Wnt3 expression, decreased β -catenin phosphorylation and increased expression of Bax and FasL. In contrast treatment of RPTC-D2R WT with a D2R agonist (quinpirole, 1 μ M, 24h) or transfection of RPTC-D2R SNPs with a *DRD2* which restored D2R expression decreased Wnt3 expression, increased β -catenin phosphorylation and decreased Bax and FasL expression. Moreover Wnt3 silencing in RPTC-D2R SNPs increased β -catenin phosphorylation (132 \pm 5% vs 100 \pm 9%, P<0.05), decreased Bax (68 \pm 2.5% vs 100 \pm 9%, P<0.05) and FasL (70 \pm 3% vs 100 \pm 9%, P<0.05) expression and reduced the number of apoptotic cells (6 \pm 1.0% vs 12 \pm 0.9% TUNEL positive cells, P<0.01).

Conclusions: D2R protect cells from apoptosis by regulating the Wnt3/ β -catenin pathway. These results may have clinical relevance for subjects bearing D2R SNPs.

SA-PO304

Effect of Omega-3 Fatty Acids on Nrf-2 Expression and Its Regulation in Cyclosporine Induced Rat Model Won Suk An,¹ Eu Gene Jeong,¹ Hansae Kim,² Dongyeol Lee,² Yun Jung Oh,³ Su Mi Lee,¹ Sung Hyun Son,⁴ Young Ki Son,¹ Seong Eun Kim.¹ ¹Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; ²Dept of Internal Medicine, Bong Seng Memorial Hospital, Busan, Republic of Korea; ³Dept of Internal Medicine, Cheju Halla General Hospital, Cheju, Republic of Korea; ⁴Dept of Internal Medicine, BHS Han Seo Hospital, Busan, Republic of Korea.

Background: Cyclosporine (CsA)-induced kidney injury is characterized by kidney dysfunction with inflammatory cell infiltrations, apoptosis, and fibrosis. Although Nrf-2 regulates antioxidant and anti-inflammatory process in kidney injury model, it is not clear omega-3 fatty acid (FA) role on Nrf-2 expression. The aim of this study is to investigate whether omega-3 FA affects the Nrf-2 expression and has anti-inflammatory, anti-apoptotic, and anti-fibrotic processes in CsA-induced nephropathy.

Methods: Male Sprague-Dawley rats fed a low-sodium diet were divided into three treatment groups: control (0.9% saline injection; n=5), CsA (15 mg/kg/day by subcutaneous injection; n=6), CsA with Omega-3 FA (300 mg/kg/day by gastric gavage; n=6). Kidney function was measured at the end of 4 weeks. The expression of Ik-b, ED-1, transforming growth factor- β 1 (TGF- β 1), α -smooth muscle actin (α -SMA), E-cadherin, Smads for inflammation and fibrosis, caspase-3, caspase-7, and BAX/Bcl-2 ratio for apoptosis, and Nrf-2 were examined by western blot analysis.

Results: Kidney function was decreased in CsA-treated rats compared with control. Compared with control, CsA group significantly upregulated ED-1 protein expression

and Ik-b. Omega-3 FA supplementation attenuated increased ED-1 expression and Ik-B. We found that caspase-3, caspase-7, Bax/Bcl2 ratio, TGF- β 1, Smad-2/3 and Smad-4 were activated in CsA group and that omega-3 FA prevented these activation related with apoptosis and fibrosis. The expression of Nrf-2 was decreased in CsA-treated rats but Nrf-2 was increased by omega-3 FA.

Conclusions: We suggest that Nrf-2 is one of potential mediator induced by omega-3 FA supplementation attenuating inflammatory pathway, fibrotic process and apoptosis. Further studies are necessary to elucidate cross-talks between Nrf2 expression and related signals of omega-3 FA.

SA-PO305

The Role of High Mobility Group Box 1 in Renal Epithelial Cell Survival During Hypertonic Stress Michael M. Yeboah,¹ Marla A. Chesnik,¹ Hayley Lund,² Kevin R. Regner,¹ David L. Mattson.² ¹Div of Nephrology, Medical College of Wisconsin, Milwaukee, WI; ²Dept of Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: High mobility group box 1 (HMGB1) is a ubiquitous and evolutionarily conserved, DNA-binding protein and is characterized as an alarmin or damage associated molecular pattern because of the ability of extracellular HMGB1 to trigger an inflammatory response when it binds to its putative receptors, including RAGE, TLR2 and TLR4. New and emerging evidence suggest that intracellular HMGB1 is involved with numerous cell survival functions. The aim of this study was to examine the functional role of HMGB1 in tubular epithelial cells during hypertonic stress.

Methods: In vivo, 2 groups of Dahl Salt sensitive rats were placed on high salt diet (4% NaCl, n=5/group) and were treated with either daily intraperitoneal injection of a HMGB1 inhibitor (glycyrrhizic acid) or a vehicle for 3 weeks while their blood pressure was monitored by telemetry. In vitro, NRK52E cells were incubated in control medium (332 mOsmol/kg) or hypertonic medium that contained NaCl (500 or 600 mOsmol/kg) for 6 hours in the presence or absence of the HMGB1 inhibitor. In other experiments, cells were transfected with scrambled siRNA or siRNA against HMGB1 and were exposed to control medium or hypertonic medium.

Results: Following exposure to a high salt diet, pharmacologic inhibition of HMGB1 resulted in more severe kidney damage as assessed by the percentage outer medullary area with tubular dilatation and protein casts, when compared with vehicle-treated rats. Inhibition of HMGB1 was associated with a significant increase in tubular cell apoptosis in comparison to vehicle treatment on TUNEL staining. Also, inhibition of HMGB1 led to significantly higher urinary albumin excretion and blood pressure at day 21 compared with vehicle treatment. Exposure of NRK52E cells to hypertonic medium resulted in increased expression and release of HMGB1 from the cells. Both pharmacologic inhibition and siRNA-mediated knock-down of HMGB1 led to reduced cell viability as determined by MTT assay.

Conclusions: HMGB1 plays an important role in renal tubular epithelial cell survival during hypertonic stress.

SA-PO306

KIM-1-Mediated Phagocytosis Defines a New Mechanistic Paradigm for Kidney Epithelial Cells, which Involves Autophagy and Anti-Inflammatory Antigen Presentation Craig R. Brooks, Melissa Y. Yeung, Takaharu Ichimura, Joseph V. Bonventre. Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: The expression of kidney injury molecule-1 (KIM-1), the protein most upregulated with proximal tubule cell (PTC) injury, transforms PTCs into semi-professional phagocytes. The processing of phagocytosed cells by the lysosomes can determine the immunogenicity of antigens derived from the phagosomal cargo. Here we compare the phagocytic processing of KIM-1-expressing PTCs to that of professional phagocytes and establish distinct mechanisms.

Methods: LLC-PK1 cells expressing KIM-1 were exposed to apoptotic cells. LC3 localization to the phagosome, phagosomal acidification and degradation were measured by live cell imaging, phagosome isolation and western blotting. NADPH oxidase (NOX) activity was blocked with diphenyleneiodonium and reactive oxygen species (ROS) were measured with fluorescent probes. MHC presentation was measured in primary PTCs directly using specific antibodies by flow cytometry. Functional implications were determined by activation of CD4+ and CD8+ T cells.

Results: KIM-1 binds to and induces phagocytosis of apoptotic cells within ~5-30 min, similar to professional phagocytes. Following uptake, however, PTCs process phagosomes more slowly than professional phagocytes, with delayed phagosomal acidification and phagosome degradation (4-12 hrs vs 1-2 hrs). Mechanistically, PTCs do not upregulate NOX-induced production of ROS, a process necessary for efficient acidification and degradation of the phagosome. LC3 associated phagocytosis (LAP), an important NOX-dependent feature of professional phagocytic function, is not observed in PTCs. PTCs instead induce canonical autophagy to clear phagocytosed debris. Delayed phagosomal processing and increased autophagy result in increased PTC antigen presentation and decreased T cell activation.

Conclusions: Autophagy plays a critical role in KIM-1-mediated phagocytosis in PTCs, distinguishing the epithelial cell process from the mechanism used by professional phagocytes. The PTC has evolved a distinct process which leads to anti-inflammatory antigen presentation which is beneficial in acute kidney injury.

Funding: NIDDK Support

SA-PO307

Apoptotic Cells Activate AMPK and Inhibit Proximal Tubular Cell (PTC) Growth without Change in Intracellular Energy Stores Philip Spiegel,¹ Snezana Vujicic,¹ Lanfei Feng,¹ Natalia O. Litbarg,¹ Vimal Patel,¹ Wilfried Lieberthal,² Jerrold S. Levine.¹ ¹*Nephrology, Univ of Illinois at Chicago, Chicago, IL;* ²*Nephrology, Stony Brook Univ Medical Center, Stony Brook, NY.*

Background: Apoptosis plays an indispensable role in the maintenance and development of tissues. We have shown that receptor-mediated recognition of apoptotic target cells by viable kidney PTCs inhibits the proliferation and survival of these viable PTCs. Here, we examined the effect of apoptotic target cells on PTC cell growth (cell size during G1 phase of cell cycle).

Methods: We used BU.MPT cells, a conditionally immortalized PTC line, as responder cells. BU.MPT cells, induced to undergo apoptosis in several ways, were used as apoptotic targets.

Results: Apoptotic cells potently activated AMP-activated protein kinase (AMPK), a highly sensitive sensor of intracellular energy stores. AMPK activation led to decreased activity of its downstream target, ribosomal protein p70 S6 kinase (p70S6K) and concomitant inhibition of cell growth. Importantly, these events occurred without detectable change in intracellular levels of AMP, ADP, or ATP. Inhibition of AMPK, either pharmacologically by compound C or molecularly by shRNA, diminished the effects of apoptotic targets, and largely restored p70S6K activity and cell size to normal levels. Apoptotic targets also inhibited Akt, a second signaling pathway regulating cell growth. Expression of a constitutively active Akt construct partially relieved cell growth inhibition, but was less effective than inhibition of AMPK. Inhibition of cell growth by apoptotic targets was dependent on physical interaction between apoptotic targets and PTCs, but independent of phagocytosis.

Conclusions: We conclude that receptor-mediated recognition of apoptotic targets mimics the effects of intracellular energy depletion, activating AMPK and inhibiting PTC cell growth. By acting as sentinels of environmental change, apoptotic death may enable nearby viable cells, especially non-migratory epithelial cells, to monitor and adapt to local stresses.

Funding: Clinical Revenue Support

SA-PO308

The Effect of Uremia on Cardiac Autophagy William White, Steven Michael Harwood, Petros Andrikopoulos, Muhammad M. Yaqoob. *William Harvey Research Inst, Barts & The London School of Medicine & Dentistry, Queen Mary Univ of London, London, United Kingdom.*

Background: Autophagy is the process by which cells remove and recycle unwanted structures, contributing to intracellular homeostasis and energy production. Cardiac autophagy has a role in ischemia protection and ventricular remodeling, and decreasing autophagy is central to aging. Evidence suggests these processes are disordered in CKD. We have previously demonstrated that autophagy may be down-regulated at a transcriptional level in uremic hearts, and now present data concerning cardiac autophagic-protein expression (LC3, p62) and senescence marker p53 in models of uremia.

Methods: *In Vitro* Rat cardiac myoblast cells (H9C2) were cultured in the presence of indoxyl sulphate (IS) to simulate a uremic milieu, for 24 or 48 h, with or without 25 mM chloroquine (CQ, a late-stage autophagy inhibitor) for the last 6h. Cells were lysed and underwent immunoblotting for LC3B and p62. *In Vivo* Rats were rendered uremic using an adenine diet (controls given normal feed), fasted for 24 h (to control for caloric intake) and given 10 mg/kg IP CQ prior to sacrifice. Cardiac tissues were homogenised and immunoblotted for LC3B, p62 and p53.

Results: *In Vitro* At 24 and 48 h the amount of LC3BII (a marker of autophagic flux) expressed increased with IS in a dose-dependent manner with and without CQ. At 48 h p62 expression decreased with IS in the absence of CQ, but increased in its presence. *In Vivo* setting LC3BII and p62 expression increased in the uremic hearts in line with the *in vitro* data. Interestingly p53 expression was increased in the uremic group.

Conclusions: Uremia appears to stimulate autophagy in cardiac tissues at the protein level, in contrast to our autophagy transcriptome data. Previous authors have found that changes in autophagic activity are not always mirrored at a transcriptional level. Interestingly p53 expression was greater in uremia, suggesting an increase in senescence, which we are currently investigating. Changes in autophagy activity and senescence in uremic hearts may contribute to the pathogenesis of uremic cardiomyopathy, and provide targets for therapy.

SA-PO309

Decorin Potentially Alleviates TGF- β 1 Induced Podocyte Injury by Inactivating mTORC1 and Increasing Autophagy Xing Mao, Zhigang Zhang, Huijuan Wu. *Dept of Pathology, Shanghai Medical College, Fudan Univ, Shanghai, China.*

Background: TGF- β 1 is the major factor mediating podocytes injury during mesangialproliferative glomerulonephritis (MsPGN), manifested by decreased autophagy, cytoskeleton relocation and increased apoptosis. Decorin (DCN), mainly secreted by mesangial cells (MCs) in glomeruli, is a natural antagonist of TGF- β 1 and has been shown to induce autophagy via Peg3 and Vps34. However, the mechanism underlying the aberrant autophagy in injured podocytes of MsPGN and the possible effect of DCN/TGF- β 1 axis on the crosstalk of MCs and podocytes are still not clear.

Methods: We used immunohistochemistry(IHC) to detect p-smad2 and LC3 in rat anti-Thy1.1 nephritis, and TGF- β 1 in human nephritis. Then we treated podocytes with TGF- β 1 or DCN and detected the expression of Vps34, p-S6K1(Thr389), TGF- β 1, p62 and LC3 by western blot.

Results: In this study, we firstly found increased p-smad2 and decreased LC3 by IHC in podocytes of rat anti-Thy1.1 nephritis with obvious proteinuria, and consistently, increased TGF- β 1 staining in human nephritis featured by MCs proliferation and proteinuria. Then we treated podocytes by TGF- β 1 (20ng/ml) for 1, 3, 6 and 12h, and found decreased protein expression of Vps34 and increased p-S6K1(Thr389) representing mTORC1 signaling, accompanied by increased P62 and decreased LC3II/Iratio. However, treatment of mouse soluble DCN (6.25nM or 100nM) for 1, 3, 6 and 12h on podocytes led to an increased protein expression of Peg3, decreased p-S6K1(Thr389), decreased P62 and increased LC3II/I ratio. Moreover, it also decreased TGF- β 1 in podocytes.

Conclusions: These results showed that TGF- β 1 evoked an activation of mTORC1 signaling and the abortion of macroautophagy in podocytes, whereas DCN downregulated TGF- β 1 protein expression, and thus inactivate mTORC1 signaling and induce autophagy on podocytes, indicating DCN may have a potential in alleviating TGF- β 1 induced podocyte injury in MsPGN.

Funding: Government Support - Non-U.S.

SA-PO310

Albumin Endocytosis in the Proximal Tubule Causes Accumulation of Dysfunctional Mitochondria Angela Nolin, Ryan M. Mulhern, Ramon G. Bonegio, Zhiyong Wang, Steven C. Borkan, John H. Schwartz, Andrea Havasi. *Renal, Boston Univ Medical Center, Boston, MA.*

Background: Proteinuria is a major risk factor for chronic kidney disease progression. Furthermore, exposure of proximal tubular epithelial cells (PTEC) to excess albumin promotes tubular atrophy and fibrosis, key predictors of progressive organ dysfunction. The mechanism by which protein exposure causes tubular cell injury is uncertain. We hypothesize that albumin endocytosis causes tubular cell injury by inhibiting autophagy, including mitophagy, resulting in an accumulation of dysfunctional mitochondria leading to enhanced ROS production, mitochondrial and cellular injury.

Methods: The effect of proteinuria was examined both *in vivo* and *in vitro* experiments. Proteinuria was induced in mice by injection of a sheep nephrotoxic serum that causes acute immune-complex glomerulonephritis with massive proteinuria by 24-48 hrs. *In Vitro*, to mimic nephrotic glomerular filtrate, PTECs were exposed to albumin. Autophagy was assessed in tissue samples from mice and primary PTECs. Steady state LC3-II, an autophagy marker was quantified by immunoblot. Autophagosomes (APs) were visualized in cell culture using fluorescent markers and in renal cortical tissue using immunohistochemistry. Mitochondrial respiration was measured in primary cells. Mitochondrial morphology and colocalization with autophagosomes were imaged using confocal microscopy. Reactive oxygen species production was measured using a 2',7'-dichlorofluorescein diacetate assay.

Results: Exposure to excess albumin induced defective autophagy and mitophagy *in vitro*. In renal cortices, proteinuria decreased both the number of LC3-II positive APs and the amount of LC3-II detected in cell lysates. Albumin-exposed cells accumulated damaged mitochondria with altered mitochondrial function and morphology. Albumin exposure caused mitochondrial dysfunction as evidenced by decreased oxygen consumption rate from coupled ATP production. Increasing albumin exposure time caused an increase in ROS production.

Conclusions: Dysfunctional autophagy caused by proteinuria likely contributes to tubular cell toxicity leading to renal progression.

Funding: NIDDK Support, Private Foundation Support

SA-PO311

Association Between a Marker of Aging and Cardiovascular Pathology in End-Stage Renal Disease Patients Karin Luttrupp,¹ Dagmar Mcguinness,² Abdul Rashid Tony Qureshi,³ Hannes Olsson,³ Annika Wernerson,³ Louise Nordfors,³ Jonaz Ripsveden,⁴ Peter F. Barany,³ Peter Stenvinkel.³ ¹*Dept of Molecular Medicine and Surgery, Karolinska Inst, Stockholm, Sweden;* ²*Inst of Cancer Sciences, Univ of Glasgow, Glasgow, United Kingdom;* ³*Dept of Clinical Science, Intervention and Technology, Div of Renal Medicine, Karolinska Inst, Stockholm, Sweden;* ⁴*Dept of Clinical Science, Intervention and Technology, Div of Radiology, Karolinska Inst, Stockholm, Sweden.*

Background: Patients with chronic kidney disease (CKD) display a progeric phenotype, with a high incidence of cardiovascular disease (CVD) and vascular calcification (VC). The process of VC is complex, and has been linked to apoptosis. A potential contributor to the calcification process is the pro-apoptotic factor cyclin-dependent kinase inhibitor 2A (CDKN2A). This study aims to investigate possible associations between CDKN2A expression, VC and CVD in a CKD population.

Methods: CDKN2A expression was determined in epigastric arteries (n=43) from patients with end-stage renal disease (ESRD) undergoing living donor renal transplantation (RTx). All arteries were scored for degree of calcification in percent. Coronary artery calcification (CAC) score was also obtained.

Results: The arterial expression of CDKN2A was significantly associated with VC (p=0.01, $\rho=0.4$), CVD (p=0.0002), CAC score (p=0.008, $\rho=0.5$) and diabetes mellitus (p<0.05). In addition, arterial CDKN2A expression was associated with MGP (p=0.007, $\rho=0.4$) and RUNX2 (p=0.046, $\rho=0.3$) expression in artery, both of which are involved in osteogenic transformation of vascular smooth muscle cells.

Conclusions: These findings provide evidence that cell senescence and apoptosis are important in the development of VEC and CVD in the uremic milieu, and further strengthen the hypothesis that comorbidities present in CKD could be caused by a premature ageing process. Attempts to ameliorate any progeric process in this patient group is therefore of great interest.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO312

Role of RTN1-A in Mediating Tubular Cell Injury Induced by Albumin Overload Ying Fan,¹ Wenzhen Xiao,² Peter Y. Chuang,² Kim Lee,² Niansong Wang,¹ John C. He.² ¹Dept of Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; ²Dept of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: We performed mRNA sequencing in the kidneys from the murine model of HIV-associated nephropathy and identified an association between the expression of an endoplasmic reticulum (ER)-associated protein reticulon-1, *RTN1*, and the severity of kidney disease. Of the three known *RTN1* isoforms, only *RTN1A* protein expression was increased in kidneys of multiple murine models and patients with kidney disease. Interestingly, both mRNA and protein expression of *RTN1-A* in the kidneys correlated inversely with estimated glomerular filtration rate (eGFR) in patients with diabetic kidney disease.

Methods: To determine how *RTN1-A* mediates the progression of kidney disease, we studied the role of *RTN1-A* in HK2 cells treated with or without human serum albumin (HSA) at different concentrations. Then, we studied the role of *RTN1-A* in vivo by generating a protein overload mouse model in both wild-type and *RTN1-A* knockdown mice.

Results: HSA induced both ER stress markers (GRP78 and CHOP) and apoptosis in HK2 cells. However, treatment with 4-PBA (inhibitor of ER stress) or knockdown of *RTN1-A* expression attenuated HSA-induced ER stress/apoptosis in HK2 cells. These data suggest that *RTN1-A* mediate HSA-induced ER stress and apoptosis of kidney tubular cells. To determine the effect of albumin overload on tubular injury in vivo, we generated tubular cell-specific *RTN1-A* shRNA knockdown mice, in which *RTN1-A* expression was reduced by 80%. Then, we inject BSA intraperitoneally in these *RTN1-A* knockdown mice and their control littermates to generate albumin overload mouse model. Mice with BSA injection developed significant proteinuria in both knockdown and wild-type mice. However, *RTN1-A* knockdown mice developed less tubulointerstitial injury than wild-type mice. Also, there was less apoptosis and lower expression of ER-stress markers in tubular cells of *RTN1-A* knockdown mice than wild-type mice.

Conclusions: These data suggest that *RTN1-A* likely mediates proteinuria-induced tubular cell injury and progression of kidney disease through ER stress and apoptosis.

Funding: NIDDK Support

SA-PO313

Inhibition of Caspase-1, but Not of Caspase-3, Ameliorates Diabetic Nephropathy: Does Apoptosis Play a Role in Diabetic Kidney Disease?

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Background: Glomerular apoptosis is thought to contribute to diabetic nephropathy (dNP), but insights into its pathogenetic relevance in dNP are incomplete.

Methods: Here we employed two partially distinct caspase inhibitors in db/db mice: M-920 (inhibiting caspases-1,-3,-4,-5,-6,-7) and CIX (inhibiting caspases-3,-6,-7,-8,-10). The nephromine database was interrogated for glomerular expression of apoptosis and inflammasome markers in human dNP. *In vitro* glucose stimulated podocytes were used. Findings were validated in caspase-1 and caspase-3 deficient mice.

Results: Both M-920 and CIX reduced glomerular cell death and caspase-3 and -7 activity, but only M-920 ameliorated dNP. Nephroprotection by M-920 was associated with reduced renal caspase-1 and inflammasome activity. Glomerular expression of inflammasome markers (NLRP3, CASP1, IL18, ASC), but not of apoptosis markers (CASP3, CASP7, PARP1), was significantly elevated in patients with dNP compared to non-diabetic controls. Markers of inflammasome activation (Nlrp3, caspase-1 cleavage) precede those of apoptosis activation (caspase-3, -7, and PARP cleavage) in glucose stressed podocytes *in vitro*. Finally, caspase-3 deficiency in mice does not protect from dNP, while both homozygous and hemizygous caspase-1 deficiency is protective.

Conclusions: Manifestation of diabetic nephropathy is independent of caspase-3 dependent cell death (apoptosis), but requires caspase-1 activation in mice. These data support a critical role of caspase-1 dependent inflammasome activation in dNP. Targeting the inflammasome may be superior to targeting apoptosis.

SA-PO314

Endothelial Autophagy Is Essential for Vascular Lipid Homeostasis

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Background: Cardiovascular disease is one of the common complications in chronic kidney diseases. It is known that autophagy plays a critical role in the course of kidney diseases. The resulting cardiovascular diseases are presumably regulated by autophagy. However the physiological role of autophagy in the vascular endothelial cells remains poorly understood.

Methods: Using human umbilical vein endothelial cells (HUVECs), induction of autophagy by ox-LDL, and uptake or transcytosis of LDL are analyzed. To inhibit autophagy pharmacologically, chloroquine is used. The essential autophagy gene, *Atg7* shRNA-mediated knockdown are performed to inhibit autophagy genetically. To assess an acute and chronic *in vivo* model of lipid exposure, we generated endothelial specific *Atg7* knockout in ApoE deficient mice (*Atg7^{endo}/ApoE KO*).

Results: Ox-LDL induced autophagosome formation in HUVECs. Moreover, native or ox-LDL appeared to be engulfed within autophagosomes by live cell imaging and electron microscopy. *Atg7* knockdown or pharmacological inhibition of autophagy resulted in higher accumulation of intracellular LDL, suggesting that in vascular endothelial cells, autophagy is one of the degradation machinery of excess lipids. As an acute model of lipid exposure *in vivo*, *Atg7^{endo}/ApoE* mice showed longer retention of ox-LDL within the retina after infusion of Dil ox-LDL. In a chronic model of lipid excess, we analyzed atherosclerosis in *ApoE KO* or *Atg7^{endo}/ApoE KO* mice. *Atg7^{endo}/ApoE KO* mice demonstrated markedly increased atherosclerosis.

Conclusions: In endothelial cells, autophagy appears to play a critical role in regulating excess intracellular lipids. Moreover, in both acute and chronic *in vivo* model, endothelial autophagy is essential to attenuate LDL accumulation within endothelial layer. Prevention of the decline in autophagy flux accompanied by kidney diseases pharmacologically might be beneficial to treat atherosclerotic diseases.

SA-PO315

Targeted Mutations at the p66 Locus Antagonize Stem Cell Aging and Delay Expression of Senescent Phenotypes in Diabetic Kidneys

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Background: Senescence has important implications for the biologic function of tissue stem cells, which maintain tissue homeostasis by replacement of old or dying cells and via the repair of tissue injury. The p66 longevity gene plays a key role in the activation of gene programs that induce senescent and apoptotic phenotypes. We hypothesize gene base strategies targeting p66 will delay or prevent stem cell senescence and premature aging phenotypes in diabetic kidneys.

Methods: Mesenchymal stem cells (MSCs) were isolated from kidneys of p66 KO mouse (p66 KO-MSCs) using established methods and plated in high glucose (HG) containing media. Microarray was used to profile secreted factors expressed by MSCs. p66 KO diabetic mice were generated to evaluate survival of MSCs in diabetic kidneys, glomerulosclerosis, interstitial fibrosis and tubular atrophy. Confocal imaging and immunofluorescent staining was used to identify MSCs, podocytes, renal tubular cells and to detect senescent protein p16^{INK4a} and proliferation marker Ki-67.

Results: Cultured p66 KO-MSCs at HG escape entry to senescent and apoptotic programs and display enhanced secretion of IGF-1, VEGF and HGF. Microarray detected unexpected cross talk between p66 and Wnt regulatory genes that antagonize senescence. Kidney sections from p66 KO diabetic mice show increased numbers of MSCs in glomeruli and tubules, with barely detectable histologic markers of aging and near normal urine albumin excretion. Kidney nuclei staining (+) for Ki-67 was upregulated, whereas p16^{INK4a} was downregulated.

Conclusions: These findings suggest a genetic link between p66 longevity gene, stem cell aging and senescent phenotype(s) in diabetic kidneys.

Funding: Private Foundation Support

SA-PO316

The Full Time Course and Localization of mTOR Activation in Compensatory Renal Hypertrophy

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Background: Previous studies documented an essential role for mTOR activation in mediating compensatory renal hypertrophy induced by unilateral nephrectomy (UNX) but the time course and localization of the mTOR activation are unclear.

Methods: 8-week-old male FVB/NJ mice were subjected to right UNX or sham surgery, followed by sacrifice at different time points to collect left kidney and determine the time course and localization of mTOR activation by immunoblotting and immunofluorescence staining for phospho-S6K1 and phospho-rpS6, along with nephron segment-specific markers.

Results: In this inbred mouse strain, UNX induced $8.27 \pm 0.93\%$ renal hypertrophy within 24 h. The hypertrophy continued to rise up to $12.74 \pm 3.32\%$, $39.78 \pm 7.06\%$, $45.56 \pm 7.72\%$, $45.92 \pm 2.80\%$, $49.13 \pm 2.09\%$, and $50.26 \pm 9.87\%$ by 48 hours, 1 week, 2 weeks, 1 month, 3 months, and 4-7 months, respectively. Thus, the hypertrophy is complete within 3-4 months, with ~50% hypertrophy on average. Immunoblotting indicated that UNX increased T389-phosphorylated S6K1 within 3 min, indicating mTOR activation, but had no effect on Akt, TSC2, AMPK, or ERK1 and ERK2 phosphorylation in the remaining kidney at any time points examined. The mTOR activity peaked at 24 h, remained at the plateau level even after 48 h, declined but still activated by 1 month, and returned to the basal level by 3 months after UNX. Immunofluorescence staining visualized the most prominent mTOR activation in the cytoplasm of LTL-positive tubules in response to UNX, although the basal mTOR activity in the kidney of sham-operated control mice was largely confined in THP-, calbindin-, and DBA-positive tubules, with very little in LTL-positive tubules. n=5-6 mice for each group and time point.

Conclusions: This is the first report on the full time course of dynamic mTOR activation and the first demonstration that UNX-induced mTOR activation is primarily localized in the proximal tubules of the remaining kidney. The present study also indicates that compensatory renal hypertrophy largely occurs within 1 week but is not complete until 3-4 months after UNX.

Funding: NIDDK Support

SA-PO317

EGF Dependent Regulation of VEGF-A Secretion by Proximal Tubule Cells Diana Zepeda-Orozco,¹ Hsiang M. Wen,¹ Nandita S. Raikwar,² Christie P. Thomas,² ¹*Pediatrics, Univ of Iowa, Iowa City, IA;* ²*Internal Medicine, Univ of Iowa, Iowa City, IA.*

Background: Vascular endothelial growth factor A (VEGF-A) plays a critical role in peritubular capillary development by promoting vasculogenesis and angiogenesis. It is now recognized that there is increased expression of VEGF-A by proximal tubular epithelial cells in ischemia reperfusion injury and in chronic tubulointerstitial injury. Although hypoxia is known to increase the expression of VEGF-A in proximal tubular epithelial cells *in vitro* and *in vivo*, the mechanisms regulating VEGF-A secretion by proximal tubule epithelial cells in normoxia has not been established.

Methods: We utilized HK2 cells, an immortalized human proximal tubule cell line, to characterize the epidermal growth factor (EGF)-dependent regulation of VEGF-A secretion by proximal tubular epithelial cells.

Results: EGF increases HIF1- α expression, stimulates VEGF-A secretion and promotes proliferation of HK2 cells under normoxic conditions. HIF1- α knockdown decreases EGF-dependent VEGF-A secretion indicating that the EGF effect is at least partly HIF1- α dependent even in normoxia. EGF stimulates HIF1- α and VEGF-A via activation of the EGF receptor and upregulation of mTOR and p42/44 MAPK pathways. P42/44 MAPK inhibition significantly downregulates HIF1- α dependent VEGF-A secretion and cell proliferation. Although mTOR inhibition reduces HIF1- α , it upregulates MAPK with a very modest reduction of VEGF-A secretion indicating that mTOR and p42/44 MAPK may act via parallel pathways in VEGF-A regulation. Finally, we demonstrate that the EGF-stimulated proliferation of HK2 cells is reduced by VEGF Receptor 2 (VEGFR2) blocker indicating that EGF stimulates proximal tubular cell proliferation via the secretion of VEGF and the activation of the VEGFR2 receptor.

Conclusions: EGF stimulates VEGF-A secretion via activation of the EGF receptor, and stimulation of HIF1- α . EGF stimulates proliferation of HK2 cells via the secretion of VEGF-A indicating that VEGF is an autocrine proximal tubular epithelial cell growth factor. The effects of EGF on HIF1- α , and VEGF-A in HK2 cells are modulated by complex crosstalk between p42/44 MAPK and mTOR pathways.

SA-PO318

Selective Regulation of a Novel Truncated CCN3 Protein by TGF β 1 in Human Tubule Epithelial Cells Matthew Pottle,¹ Bruce L. Riser,² Mark E. Dockrell,¹ ¹*SWT Inst for Renal Research, London, United Kingdom;* ²*BLR Bio, WI.*

Background: CCN3 is a member of the matricellular CCN family of proteins along with the structurally similar CCN2/CTGF, a powerful fibrotic agent, but recent work supports our hypothesis that CCN2 and 3 act in opposition to each other regulating fibrosis. In renal cell carcinoma tubular expression of CCN3 is reduced in patients with cancer. TGF β 1 has been shown to counter regulate the expression of CCN2 and CCN3 in the vertebral nucleus pulposus and in mesangial cells. We have previously characterised TGF β 1 induction of CCN2 in proximal tubule epithelial cells (PTEC); here we investigate the expression of CCN3 in primary human PTEC and its potential regulation by TGF β .

Methods: Primary human PTEC were cultured on collagen IV in supplemented medium. At 80% confluence cells were treated with TGF β -1 (0.25 -2.5 ng/ml) for 24 & 48h, medium was collected and cells lysed. Equal amounts of lysate were subjected to PAGE and Western blotting then probed with antibodies (Ab) to the C-terminal, N-terminal and hinge region of CCN3, as well as the hinge region of CCN2/CTGF.

Results: Under control conditions the anti-CCN3 hinge Ab revealed the expression in PTEC of the 51KDa full-length protein as well as a 39KDa isoform. The antibodies to the respective termini detected bands of approximately 23-28KDa. The C-terminal ab did not detect the 39KDa band. The antibody to the N-terminal detected proteins of approximately 45KDa as well as the 39KDa form. Treatment with TGF β for 24h had no effect on the 51KDa protein but significantly inhibited the expression of the 39KDa.

Conclusions: At a concentration that induces CCN2/CTGF expression in PTEC, TGF β does not regulate the expression of full length CCN3. However, it does reduce the expression of a truncated form apparently lacking the CT domain. The characteristics of

this smaller protein are not consistent with any known splice variants and may represent an intracellularly cleaved form regulated by TGF β 1. The lack of the CT domain would change the 3 dimensional conformation of the protein, inhibit its binding to various integrins and potentially remove the ability of the molecule to inhibit cell proliferation.

SA-PO319

Deletion of TGF-Beta Receptor in Renal Proximal Tubule Cells Impairs HGF Signaling Stelior Nlandu Khodo,² Leslie S. Gewin,^{1,2} ¹*Research, Tennessee Valley Veterans Affairs, Nashville, TN;* ²*Medicine, Div of Nephrology, Vanderbilt Univ, Nashville, TN.*

Background: The growth factors TGF-beta and HGF have antagonistic and synergistic interactions that govern renal development and response to injury. We previously showed that TGF-beta worsens the epithelial response to acute renal injury, so we postulated that epithelial TGF-beta signaling may inhibit responsiveness to HGF, a growth factor that mediates beneficial effects following epithelial injury.

Methods: To address how TGF-beta signaling alters epithelial responsiveness to HGF, we generated proximal tubule (PT) cells with the TGF-beta type 2 receptor, necessary for all signaling, either intact (TbRII^{fl/fl}) or deleted in vitro with adeno-Cre (TbRII^{-/-}). Responsiveness to HGF was assessed by receptor (cMet) phosphorylation, and the biological relevance of altered HGF signaling was determined by branching morphogenesis studies in 3D gels and migration assays.

Results: TbRII^{-/-} PT cells had increased tubular branching and impaired migration compared to cells with the receptor intact. Unexpectedly, PT cells lacking TbRII had impaired response to HGF in both branching morphogenesis and migration assays compared to TbRII^{fl/fl} cells. Consistent with this, TbRII^{-/-} PT cells had impaired cMet phosphorylation associated with reduced membrane expression of cMet and transcriptional downregulation of the HGF receptor. Notch signaling, a known inducer of cMet transcription, was increased in cells with TbRII intact, and Notch inhibition by gamma-secretase equalized the responses to HGF by PT cells with and without the receptor.

Conclusions: PT cells lacking TbRII have impaired responsiveness to HGF signaling, and this effect is due to reduced Notch-mediated cMet transcription. Thus, efforts to block TGF-beta signaling may inadvertently inhibit signaling pathways of other growth factors such as HGF.

Funding: Veterans Administration Support

SA-PO320

Enhancement of HGF-Induced Tubulogenesis by Endothelial Cell-Derived GDNF Masao Nakasatomi, Akito Maeshima, Shunsuke Takahashi, Hidekazu Ikeuchi, Toru Sakairi, Yoriaki Kaneko, Keiju Hiromura, Yoshihisa Nojima. *Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Maebashi, Gunma, Japan.*

Background: Renal proximal tubular epithelium can regenerate itself after a variety of insults. However, the microenvironment that regulates regeneration process of renal tubules after injury remains unclear. We previously established an *in vitro* 3D tubulogenesis assay which at least partly mimics *in vivo* regeneration processes of renal tubules after injury (Am J Physiol Renal Physiol: 301: F387-95, 2011). Utilizing this system, the endothelial cell-derived factors that regulate tubular formation was examined.

Methods: Human renal proximal tubular epithelial cells (RPTEC) were cultured in gels (type I collagen/matrigel mixture) in the presence of HGF with or without human umbilical vein endothelial cells (HUVEC) using Transwell filter system. The signaling pathways activated by co-culture with HUVEC in tubular structures were examined using phospho-receptor tyrosine kinase (RTK) array.

Results: HGF, a potent renotropic factor, induced aquaporin-1-positive tubular structures with microvilli, suggesting that these structures are morphologically equivalent to renal tubules *in vivo*. When co-cultured with HUVEC, HGF-induced tubular formation was significantly enhanced. Tubulogenic effect of HGF was also enhanced in the presence of HUVEC-conditioned media (HUVEC-CM), but not in the presence of VEGF, basic FGF or PDGF. Co-culture with HUVEC did not induce tubular structures in the absence of HGF. RTK array revealed that phosphorylation of RET (GDNF receptor) was markedly enhanced in tubular structures cultured with HUVEC-CM compared to those without HUVEC-CM. HUVEC produces GDNF and RPTEC expresses both RET and GFR alpha1 (co-receptor). HGF-induced tubular formation was significantly enhanced by addition of GDNF.

Conclusions: These data indicate that endothelial cell-derived GDNF potentiates tubulogenic action of HGF in a paracrine manner. GDNF-RET signaling may play a role in the crosstalk between renal tubules and surrounding endothelium during tubular regeneration after injury.

SA-PO321

Massive Formation of Ang(1-7) from AngII(1-8) Is Largely ACE2 Independent Peter Daniel Serfozo, Jan A. Wysocki, Minghao Ye, Daniel Batlle. *Div of Nephrology, Northwestern Univ - Feinberg School of Medicine, Chicago, IL.*

Background: AngII(1-8) degrading mechanisms are complex including cleavage by aminopeptidases that form AngIII and carboxypeptidases like ACE2 and Prolylcarboxypeptidase (PRCP) that cleave Phenylalanine to form Ang(1-7). The relative importance of these peptidases to the formation of Ang(1-7) is unknown but ACE2 has been assumed to be the main Ang(1-7) forming enzyme resulting from cleavage of AngII(1-8). We tested the hypothesis that Ang(1-7) formation largely occurs independently of ACE2.

Methods: After acute AngII(1-8) infusion to WT mice plasma concentrations of AngII(1-8), Ang(1-7) and Ang(1-5) were measured by LC-MS/MS. Additional measurements of Ang(1-7) by RIA and ELISA were performed for confirmatory purposes. Plasma ACE2 and PRCP activity in WT mice was measured using a fluorogenic substrate.

Results: Following AngII(1-8) infusion to WT mice plasma Ang(1-7) levels measured by MS were extremely high. Similarly high levels were also found when this peptide was measured by RIA and ELISA (Table).

	AngII(1-8)	Ang(1-7)
MS	244 ± 21 pg/ml	766 ± 199 pg/ml
RIA	n.a.	1527 ± 240 pg/ml
ELISA	1012 ± 223 pg/ml	1137 ± 394 pg/ml

In an ACE2 KO line there was no significant difference in Ang(1-7) levels as compared to WT mice and the levels of ACE2 activity in plasma of WT mice were low. Moreover, activity of PRCP, another Ang(1-7) forming enzyme is very low at the normal plasma pH. We therefore hypothesize that Ang(1-7) formation after AngII(1-8) infusion must be largely ACE2 and PRCP independent. To give further support for this hypothesis, we infused a different set of mice with AngII(1-8) in the presence of recombinant murine ACE2 or ACE2 + MLN, a specific inhibitor. Under all these conditions the levels of Ang(1-7) were massively increased and therefore unaccountable only by the conversion of AngII(1-8) to Ang(1-7) by ACE2 cleavage.

Conclusions: Formation of Ang(1-7) during AngII(1-8) infusion is massive and largely ACE2 independent. The increase in Ang(1-7) after AngII(1-8) infusion suggests the presence of unknown Ang(1-7) forming enzymes that are very active in plasma.

Funding: NIDDK Support

SA-PO322

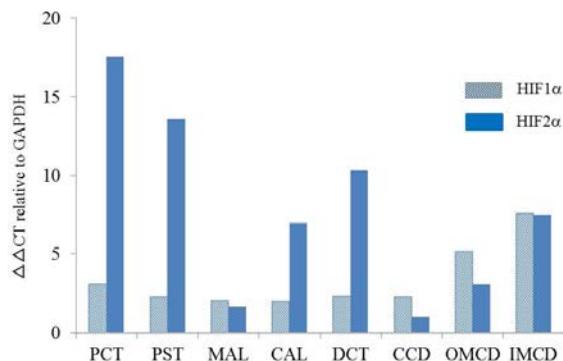
HIF1 α and HIF2-Induced Erythropoietin Production Along the Nephron Yuichiro Izumi,¹ Yukiko Yasuoka,² Yushi Nakayama,¹ Hideki Inoue,¹ Masashi Mukoyama,¹ Katsumasa Kawahara,² Hiroshi Nonoguchi.³ ¹*Nephrology, Kumamoto Univ Graduate School of Medical Science, Kumamoto, Japan;* ²*Physiology, Kitasato Univ School of Medicine, Sagamihara, Kanagawa, Japan;* ³*Internal Medicine, Kitasato Univ Medical Center, Kitamoto, Saitama, Japan.*

Background: Kidney peritubular interstitial cells produce erythropoietin (Epo) in response to hypoxia and/or anemia. By using in situ hybridization method, we have shown that Epo is also produced by the cortical nephron segments (mainly in PCT, DCT and CCD) in control and/or hypoxic conditions (Nagai, et al, 2014). The use of renin-angiotensin-aldosterone inhibitor has been suggested to exacerbate anemia in chronic kidney disease, suggesting aldosterone-regulated erythropoietin production.

Methods: To characterize the molecular machineries for Epo production in renal tubules, we examined the mRNA expressions of HIF1 α , HIF2 α , PHD2, mineralocorticoid receptor (MR) and EGF-receptor (EGFR) along the nephron in basal condition. Each nephron segment from SD rats was microdissected in the presence of ribonucleoside vanadyl complexes. After the extraction of RNA, mRNA expression was measured using RT-PCR and real-time PCR.

Results: Epo mRNA expression was confirmed in whole nephron segments by RT-PCR in basal condition. The expressions of HIF1 α , HIF 2 α and PHD2 mRNAs were detected in whole nephron segments both in RT-PCR and real time PCR. The largest expression of HIF2 α mRNA was observed in PCT. HIF2 α mRNA expression was larger than HIF1 α mRNA expression in most segments ($\Delta\Delta\text{CT}$ relative to GAPDH). MR and EGFR mRNAs expression was observed not only in distal but also in proximal tubules.

HIF1 α and HIF2 α mRNAs expression along the nephron in control rat



Conclusions: The results suggest the presence of HIF2 α induced-Epo production in renal tubules. The presence of MR in whole nephron segments suggest that aldosterone may have physiological effects for Epo production not only in distal but also in proximal tubules.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO323

Cytokine Response of Primary Human Mesangial Cells Is LPS Strain Dependent Margaret M. O'Neill, Carine Boustany, Steven S. Pullen. *CardioMetabolic Diseases Research, Boehringer Ingelheim Pharma, Inc, Ridgefield, CT.*

Background: LPS stimulation of Toll-like receptor 4 (TLR4) induces the release of proinflammatory cytokines which activate potent immune responses. LPS is an important structural component of the outer membrane of Gram-negative bacteria and consists of three parts: lipid A, a core oligosaccharide, and an O side chain. It has been studied extensively in models of inflammation with E.coli 0111:B4 most often referenced in the literature. The antigenicity of LPS varies from strain to strain depending on the composition its O side chain. A comparative study was designed to identify the optimal strain to be used for LPS-stimulated release of proinflammatory mediators from primary human mesangial cells (HMC).

Methods: HMC were stimulated with 7 strains of LPS and 24 hour supernatants were analyzed for production of inflammatory mediators (IL-1 β , IL-6, IL-8, TNF- α and MCP-1). Culture supernatants were assessed with MSD kits ProInflammatory 4-Plex II and MCP-1. TLR4 antagonists EX00076824 a small molecule and FHAN_2014062 an antibody were tested to evaluate inhibition of LPS activity in HMC using 3 LPS strains with most pronounced inflammatory effects.

Results: LPS induced strain-dependent increases in IL-6, IL-8, and MCP1 in HMC, while there was no effect on IL-1 β and TNF- α . When compared to controls, IL-6 production was significantly (p<0.05) increased: E.coli 0111:B4 (25X), LPS-EB (10X), E.coli K12 (44X), E.coli 055.B5 (8X), S.Minnesota (99X), S.typhosa (18X) and P.gingivitis (6X). All strains induced IL-8 and MCP-1 except for E.coli 055.B5 (no IL-8) and P.gingivitis (no IL-8 or MCP-1). Both TLR4 antagonists blocked LPS induced production of IL-6, IL-8, and MCP-1 in a dose dependent manner. IC₅₀ values for both inhibitors (EX00076824: 30-60nM; FHAN_2014062: 800-2700ng/ml) were consistent across LPS strains and analyte detected.

Conclusions: In this study we demonstrate that LPS-stimulated release of inflammatory mediators in HMC is strain dependent, and can be blocked using TLR4 antagonists. These data highlight the importance of identifying the most effective LPS strain in a cell type of interest, prior to initiating pharmacology studies.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals Inc.

SA-PO324

Effect of Angiotensin II Type 1 Receptor Blocker on 12-Lipoxygenase Activity and Slit Diaphragm Protein Nephron and P-Cadherin Expression in Type 2 Diabetic Rat Glomeruli Wan-ning Wang, Yuanyuan Zhang, Hongzhao Xu, Fu-zhe Ma, Tao Sun, Hang Yuan, Mindan Sun, Zhong-gao Xu. *Nephrology, The First Hospital of Jilin Univ, Changchun, Jilin, China.*

Background: 12-lipoxygenase (12-LO) and angiotensin II(Ang II) interaction plays an important role in the development of diabetic nephropathy (DN), in which proteinuria was thought to be associated with decreased expression of glomerular slit diaphragm protein nephrin and P-cadherin. However, it is unclear whether Ang II type 1 receptor blocker (ARB) regulates 12-LO activity and slit diaphragm protein expression in type 2 diabetic rat glomeruli and hence was investigated in this study.

Methods: Podocytes and glomeruli isolated from rats were used in this study. The 12-LO product 12(S)-HETE and Ang II were infused to rats by osmotic mini-pump. Rats fed high fat diet received low dose streptozotocin to make type 2 diabetes. Glomeruli were isolated with sieving method and classified into small glomeruli (SG, on the 75mm sieve) and large glomeruli (LG, on the 125mm sieve). ELISA, RT-PCR and Western blot for related targets were performed respectively.

Results: Ang II increased 12(S)-HETE levels in podocytes and glomeruli. Direct infusion of rats with 12(S)-HETE and Ang II significantly decreased LG nephrin, but increased SG nephrin expression compared to control. The glomerular P-cadherin expression was reduced after Ang II and 12(S)-HETE treatment and there was no difference between LG and SG. ARB did not affect blood glucose levels but completely attenuated increases in 12(S)-HETE content, AT1 expression and proteinuria induced by diabetes. Nephrin protein expression was significantly reduced in diabetic LG but increased in diabetic SG compared to control. P-cadherin expression was decreased in both diabetic LG and SG. These abnormalities were partially but significantly prevented by ARB treatment.

Conclusions: ARB could ameliorate the progression of DN via upregulation of glomerular nephrin and P-cadherin expression through inhibition of 12-LO activation in type 2 DN rat.

Funding: Government Support - Non-U.S.

SA-PO325

APOL1 Risk Variants and HIV Stimulate Induction of PDGF- β Receptor in Podocytes Xiqian Lan,¹ Hongxiu Wen,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,¹ Pravin C. Singhal.¹ ¹*Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY;* ²*Medicine, Rambam Health Care Campus, Haifa, Israel.*

Background: Clinical reports demonstrated that two coding sequence variants (G1 and G2) in the APOL1 gene are responsible for the higher percentage of kidney disease in African Americans. This disparity between patients with APOL1 variants versus wild type APOL1 increases by 10 fold for the development of HIVAN in patients of HIV infection who are not on antiviral therapy. Podocytes do not express platelet-derived growth factor (PDGF) receptors constitutively. Nonetheless, in experimental animal models, podocyte

upregulated expression of PDGFs manifested as progressive glomerulonephritis. We hypothesized that APOL1 risk variants and HIV carry potential for the induction of the activation of the PDGF pathway in podocytes.

Methods: To determine the effect of APOL1 and APOL1 variants expression, stably expressing Vector, APOL1G0, APL1G1, or APOL1G2 human podocyte (HP) cell lines were developed. To evaluate the effect of HIV expression, pseudo type HIV (NL4-3) or empty vector (control) virus was transduced into APOL1G0/HPs, APOL1G1/HPs and APOL1G2/HPs. After 48 h, RNAs were extracted. cDNAs were amplified with specific primers for PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFR β .

Results: HIV transduction significantly increased the expression of PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFR β in podocytes. G0/HPs, G1/HPs, and G2/HPs with or without HIV transduction did not display any change in the expression of PDGF-B, PDGF-C, or PDGF-D, when compared with vector; whereas, G2/HPs in HIV milieu displayed enhanced expression of PDGF-A. Interestingly, both G1/HPs and G2/HPs displayed 10 fold increase in PDGFR β expression when compared to vector/HPs or G0/HPs.

Conclusions: These findings indicate that PDGFs and their receptor PDGFR β can be induced by HIV and APOL1 risk variants. The present study could lead to new therapeutic targets for HIVAN.

Funding: NIDDK Support

SA-PO326

Assessment of Urinary Liver Type Fatty Acid Binding Protein in Patients of Type 2 Diabetes Mellitus with Early Chronic Kidney Disease Om Prakash Kalra,¹ Mohit Garg,¹ Ashok Kumar Tripathi,² Sunil Agarwal.¹ ¹Medicine, UCMS & GTB Hospital, Delhi, India; ²Biochemistry, UCMS & GTB Hospital, Delhi, India.

Background: Diabetes mellitus is the most common cause of chronic kidney disease (CKD) worldwide. Various markers are being identified which can detect nephropathy at an earlier stage. Both glomerular and tubular injury play an important role in etiopathogenesis of diabetic nephropathy (DN) and tubular damage precedes glomerular damage. Tubular markers like urinary neutrophil-gelatin associated lipocalin, urinary liver-type fatty acid binding protein (L-FABP) and kidney injury molecule-1 are newer markers for early kidney injury. In the present study, we assessed the role of urinary L-FABP as a tubular injury marker in DN.

Methods: This was a case control, cross sectional study. Eighty four subjects in the age group 30–60 years of either sex were taken and were divided into three groups: Group I: Healthy controls (n=28) Group II: Type 2 diabetes patients with normoalbuminuria (n=28) Group III: Type 2 diabetes patients with micro/macroalbuminuria (n=28). Detailed history, physical examination, liver and kidney function tests, urine albumin creatinine ratio (ACR) was done. Urinary L-FABP was measured by ELISA (CMIC, Tokyo).

Results: The urinary ACR levels were comparable in group I and II. Subjects in Group III had significantly elevated ACR values. Levels of urinary L-FABP were higher in subjects of group II and III when compared with group I. Values of L-FABP were also higher in group III compared to group II. There was a significant positive correlation found between urinary ACR and urinary L-FABP levels. A significant negative correlation was found between urinary L-FABP and eGFR.

Conclusions: Levels of urinary L-FABP are markedly increased in patients of diabetic nephropathy as compared to healthy controls. Levels were also increased in diabetes patients with normoalbuminuria suggesting early tubular injury in these patients. This suggests that urinary L-FABP may be a promising early marker for detection of diabetic nephropathy.

SA-PO327

Neuropilin1 Regulates Pericyte Behavior in Postnatal Kidney Monika Lucyna Wnuk, Regula Buegry, Werner A. Graber, Valentin Djonov. *Inst of Anatomy, Univ of Bern, Bern, Switzerland.*

Background: Neuropilin1 (Nrp1) is a transmembrane co-receptor implicated in the regulation of endothelial cell migration during angiogenesis. In the adult kidney, Nrp1 is however expressed not only by endothelium but also by pericytes including peritubular pericytes and mesangial cells.

Methods: In order to precisely address the role of Nrp1 in postnatal kidney, two complementary mouse models were used; in the first one, Nrp1 was deleted specifically in pericytes with tamoxifen-inducible NG2Cre line and in the second approach, Nrp1 was blocked with neutralizing antibody (Genentech). In both models, tamoxifen/antibody treatment started at P21.

Results: Mutant mice showed mild proteinuria and/or hematuria at 3 months of age with Nrp1 excision efficiency being around 30% based on colocalization level between Nrp1 and PDGFR β . Kidney histology revealed that it was primarily glomerular basement membrane (GBM) that was affected; mutant mice presented thickened, folded GBM with relatively intact podocyte foot process and endothelial fenestrations. The expression of genes encoding GBM proteins was examined and the deregulation of nidogen1 could be confirmed on protein level. Mutant mice showed additionally dilated capillaries with increased glomerular capillary surface area. Interestingly, these mice had also a tendency for fewer renin stained glomeruli as compared to Cre- controls. Furthermore, mutants had more BrdU-positive interstitial cells. Consistently, mice treated with anti-Nrp1 neutralizing antibody showed hematuria, mild mesangial expansion and GBM abnormalities including nidogen1 deregulation. Interestingly, in both models, male but not female mice were primarily affected. In vitro experiments with primary mesangial human and mouse cell lines showed increased cell proliferation, abnormal spreading and actin reorganization in Nrp1 knock down cells.

Conclusions: This study shows a novel role of Nrp1 in adult kidney pericytes. Future experiments with kidney challenge models and measurement of blood pressure will help to further clarify these interesting findings.

Funding: Government Support - Non-U.S.

SA-PO328

Development of a Spontaneous, Reproducible and Treatable Kidney Fibrosis Model Jessica Marie Overstreet, Ming-Zhi Zhang, Raymond C. Harris. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Kidney fibrosis in chronic kidney diseases causes gradual loss of kidney functionality. Currently, only a few kidney fibrotic models are available. New kidney fibrotic models are needed. Since our previous studies indicated that activation of epidermal growth factor receptor (EGFR) contributes to the development of renal fibrosis, we have developed a model with selective overactivation of proximal tubule EGFR.

Methods: B6D2 transgenic mice with selective overexpression of an EGFR ligand, human heparin-binding EGF (hHB-EGF) in renal proximal tubule, were generated. Male C57/BL6 homozygous hHB-EGF mice received vehicle (water) or erlotinib (80 mg/kg/day) by daily gastric gavage from 4 to 14 weeks of age.

Results: Kidney cortical hHB-EGF mRNA and protein levels were dramatically higher in homozygous hHB-EGF mice than in heterozygous mice. Profound renal interstitial fibrosis was found in both B6D2 and C57/BL6 homozygous hHB-EGF mice, but not in heterozygous mice, as indicated by histology and increased levels of the pro-fibrotic and fibrotic components (CTGF, α -SMA, collagen I and IV). Homozygous hHB-EGF mouse kidneys also exhibited increased oxidative stress and infiltration of both macrophages and T-lymphocytes. Interstitial fibrosis appeared as early as 4 weeks old. Homozygous hHB-EGF mice had increased kidney EGFR activation (increased phosphorylation of EGFR) and activation of downstream signaling, p-ERK and p-AKT. In addition, there was markedly increased p-Smad 2/3. p-EGFR, p-ERK, and p-Smad 2/3 were all primarily localized to proximal epithelial cells, indicating that hHB-EGF-mediated EGFR activation in proximal epithelial cells is the primary event in the development of interstitial fibrosis. Treatment with erlotinib, an inhibitor of EGFR tyrosine kinase activity, inhibited EGFR signaling and attenuated the development of renal interstitial fibrosis.

Conclusions: These studies suggest that ligand-mediated EGFR activation in renal proximal tubule epithelial cells leads to spontaneous, reproducible, and treatable renal interstitial fibrosis. Therefore, homozygous HB-EGF mice may be a useful renal fibrosis model to test the effectiveness of anti-fibrotic agents.

Funding: NIDDK Support

SA-PO329

LPA-LPA₁ Signaling Regulates Fibroblast Proliferation and Myofibroblast Differentiation Dependent on Epithelial Cell-Fibroblast Interaction Norihiko Sakai, Yasutaka Kamikawa, Akihiro Sagara, Yasuyuki Shinozaki, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Miho Shimizu, Kengo Furuichi, Takashi Wada. *Div of Nephrology, Kanazawa Univ, Kanazawa, Japan.*

Background: Renal fibrosis is a common pathway of progressive renal diseases, resulting in renal failure regardless of its cause. The accumulation of fibroblasts and myofibroblasts has been recognized as a hallmark of renal fibrosis. However, the precise mechanisms driving it remain to be determined. We have previously found the lipid mediator lysophosphatidic acid (LPA) and one of its receptors, LPA₁, stimulates peritoneal mesothelial cells to induce fibroblast proliferation through connective tissue growth factor (CTGF) production, suggesting the involvement of epithelial cell-fibroblast interaction regulated by LPA-LPA₁ signaling in the pathogenesis of organ fibrosis.

Methods: In this study, we focused on the effects of LPA-LPA₁ signaling on the interaction between renal tubular epithelial cells (RTEC) and renal fibroblasts (RFB).

Results: The stimulation with LPA induced CTGF expression in both RTEC and RFB in a time- and dose-dependent manner. The induction of CTGF in both cells was suppressed by the treatment with LPA₁ antagonist (AM095). In addition to that, LPA-induced CTGF expression in both cells was diminished by the treatment with Rho inhibitor (C3 toxin) and Rho kinase inhibitor (Y27632). In both cells, LPA enhanced the nuclear translocation of myocardin-related transcription factor (MRTF)-A/B and the transcriptional activity of MRTF-serum response factor (SRF), whereas Y27632 treatment inhibited those. The inhibition of MRTF-A/B-SRF pathway by the treatment with siRNA or a chemical inhibitor suppressed CTGF expression in response to LPA. Finally, CTGF derived from RTEC or RFB enhanced the proliferation of RFB and the expression of alpha smooth muscle actin in RFB.

Conclusions: In conclusion, LPA-LPA₁ signaling regulates epithelial cell-fibroblast interaction to induce fibroblast proliferation and differentiation into myofibroblasts through CTGF production dependent on Rho/Rho kinase/MRTF/SRF pathway.

Funding: Government Support - Non-U.S.

SA-PO330

TWEAK/Fn14 Signaling Promotes Kidney Disease by Driving Myofibroblast Activation, Inflammation and Vascular Instability Ivan G. Gomez,¹ Allie M. Roach,¹ Gamze Karaca,¹ Linda Burkly,¹ Jeremy Stuart Duffield.¹ ¹Research & Development, Biogen, Cambridge, MA; ²Medicine, Univ of Washington, Seattle, WA.

Background: We identified Fibroblast growth factor-inducible 14 (Fn14) as a receptor on pericytes, which is strongly upregulated as they differentiate into myofibroblasts *in vivo* in kidney disease. TNF-related weak inducer of apoptosis (TWEAK), a TNF-family

cytokine produced predominantly by myeloid leukocytes has been reported to activate NFκB signaling via Fn14. We discovered that NFκB signaling was activated in myofibroblasts *in vivo* and hypothesized that TWEAK/Fn14 signaling might be an important driver of pathological myofibroblasts in kidney disease.

Results: Fn14 deficiency ameliorates myofibroblast appearance, fibrosis and microvascular injury in the UUO model. TWEAK activates primary murine cultured kidney pericytes through Fn14, inducing proliferation, migration, myofibroblast differentiation and production of pro-inflammatory mediators. In addition, TWEAK/Fn14 signaling further activates established pathological myofibroblast cultures. Transcriptional profiling of TWEAK-stimulated myofibroblasts supports its multifaceted role and has identified TWEAK-response genes, including inflammatory, matrix pathways and vascular destabilizing pathways. TWEAK stimulates non-canonical NFκB pathway, an interferon response, as well as ERK signaling in myofibroblasts. Non-canonical NFκB downstream signaling plays a vital role in myofibroblast responses to TWEAK. The importance of TWEAK signaling in disease progression was evaluated in the mouse Alport model of chronic kidney disease. Anti-TWEAK antibodies preserve organ function and significantly attenuate disease progression.

Conclusions: These findings suggest that targeting the TNF superfamily TWEAK/Fn14 pathway is an approach to modulate myofibroblast activation and a novel way to block both inflammatory and fibrotic aspects of chronic kidney disease.

Funding: Pharmaceutical Company Support - Biogen

SA-PO331

Deregulation of Hippo-TAZ Pathway During Renal Injury Promotes Fibrotic Phenotype Rohan Samarakoon,¹ Lucas Falke,² Roel Goldschmeding,² Paul J. Higgins.¹ ¹Center for Cell Biology and Cancer Research, Albany Medical Center, Albany, NY; ²Dept of Pathology, Univ Medical Center Utrecht, Utrecht, Netherlands.

Background: Hippo pathway is the principal regulator of organ size. Transcriptional co-activator with PDZ-binding motif (TAZ), a nuclear transducer of Hippo pathway, is activated by loss of cellular polarity, tensional forces and soluble factors. TAZ has been implicated in the progression of lung fibrosis and cancer. However, role of Hippo-TAZ pathway in chronic kidney disease (CKD) is unknown.

Methods: We utilized three mouse models of renal injury [ureteral ligation (UUO), aristolochic acid nephropathy (AAN), streptozotocin (STZ)-driven diabetic nephropathy] and TAZ genetic manipulation in HK-2 tubular epithelial cells and NRK-49F renal fibroblasts to investigate role of TAZ in renal fibrosis.

Results: TAZ is activated [as evident by increased nuclear accumulation (4-fold) and expression (2.5-fold) at both in the tubular and interstitial cells and decreased TAZ^{Ser89} phosphorylation] in the UUO kidney compared to contralateral controls. TAZ expression is also upregulated in AAN and streptozotocin (STZ)-induced renal diabetic injury models. TAZ activation correlated with increased pSMAD3 in the fibrotic kidney. TGF-β1 and Angiotensin II stimulation, moreover, promoted TAZ and pSMAD3 nuclear entry in HK-2 cells suggesting that these cytokines likely disable core Hippo signaling. TAZ stable gene silencing in HK-2 cells, indeed, suppressed TGF-β1 and Angiotensin II induced CTGF, PAI-1 and fibronectin expression. Stable TAZ overexpression in HK-2 cells promoted epithelial dedifferentiation and proliferative arrest.

Conclusions: Activated during renal injury, TAZ is a novel profibrotic effector of TGF-β1 and Angiotensin II induced phenotypic responses. TAZ nuclear accumulation in response to TGF-β1 and Angiotensin II is suggestive of cross-talk among Hippo pathway and these cytokines.

Funding: Other NIH Support - GM057242

SA-PO332

Design and Characterisation of Novel BMP Agonists and Antagonists Daniel Crean, Satnam Surrae, Finian Martin, Catherine Godson. *UCD; UCD; UCD.*

Background: We have previously reported a role for the Bone Morphogenetic Protein [BMP] antagonist Gremlin as a driver of diabetic nephropathy and fibrosis in both kidney and lung. Bone Morphogenetic Proteins are integral regulators of bone and organ development. BMPs are secreted proteins and signal by associating with membrane bound receptors. The activity of BMP agonists is modulated by a family of secreted protein antagonists, including Noggin, Crossveinless-2 and Gremlin that limit BMP-receptor association by binding to the ligand and thereby inhibiting receptor binding.

Methods: We have analysed BMP-receptor and BMP-antagonist interactions using a newly designed automated pipeline, Protein Complex Tool (PCT). Co-crystal structures of the BMP-BMP receptor and the BMP-antagonist complexes were submitted to PCT and *in silico* alanine substitution scans were performed to calculate the free energy contribution of each BMP-2, or BMP-7, residue to the stability of the complexes with receptors, BMPRIa (BMP-2 only) and ActRIIa, and antagonists, Crossveinless-2 (BMP-2 only) and Noggin (BMP-7 only).

Results: The free energy calculations identified the key contributions of BMP residues to both binding events and suggested mutations that might generate super-agonist and dominant negative molecules. Further *in silico* analysis was performed by mutating each residue to each of the other 19 amino acids. From this we identified potential super-agonist and dominant negative mutations for both BMP-2: L51V and N102T (super-agonists) and S88G and L92D (dominant negatives), and BMP-7: E60T, D119I, I124A and K127E (super-agonists) and F117E and V122D (dominant negatives). The super-agonists will bind and activate receptor but will be resistant to binding by antagonist; in contrast, the dominant negatives, bind antagonist but not receptor.

Conclusions: Data will be presented from our investigations of these molecules as potential therapeutic leads for treating fibrotic diseases including DN.

Funding: Pharmaceutical Company Support - ROCHE

SA-PO333

Engineered Growth Factors to Treat Acute Kidney Injury Shawdeh Eshghi, Kris Kuchenbecker, Tim Stowe, Matt Onsum. *Silver Creek Pharmaceuticals, San Francisco, CA.*

Background: Acute kidney injury remains a major unmet medical need and economic burden. Currently there are no therapies that act directly on damaged kidney cells to promote survival. At Silver Creek Pharmaceuticals, we are engineering a new class of therapeutics called Smart Growth Factors that act selectively on damaged kidney cells to safely deliver pro-survival signals and restore kidney function.

Methods: We harness the potent pro-survival and mitogenic signaling of growth factors and engineer more desirable drug-like properties, including extended half-life and cell type-specific targeting. Our first SGF, designed to reduce cardiomyocyte death following acute myocardial infarction, has shown positive pre-clinical efficacy and is being prepared for an Investigational New Drug application. We are now designing an SGF to treat acute kidney injury, where apoptosis of proximal tubule cells is a leading mechanism of pathology. We developed an *in vitro* model of tubule cell apoptosis using hypoxia to screen wild type growth factors for the ability to restore cell viability and promote proliferation. We then used computational models to design SGFs that could maximize pro-survival signaling and targeting in damaged kidney tubule cells.

Results: SGF variants were built, expressed and purified in-house, and screened for their ability to activate pro-survival and proliferative signals selectively in damaged cells using the *in vitro* hypoxia model. SGFs with favorable rescue ability, selectivity and pharmacokinetics will be tested in a rodent AKI model using bilateral ischemia.

Conclusions: Smart growth factors have the potential to transform the treatment of acute kidney injury, but safely delivering potent pro-survival and mitogenic signals specifically to damaged cells, hopefully leading to better outcomes for this patient population.

SA-PO334

Loss of the Podocyte Glucocorticoid Receptor Exacerbates Proteinuria Julie Goodwin,¹ Xuefei Tian,² Shuta Ishibe.² ¹Pediatrics, Yale Univ School of Medicine, New Haven, CT; ²Internal Medicine, Yale Univ School of Medicine, New Haven, CT.

Background: Nephrotic syndrome is one of the most common renal diseases in children and podocyte foot process effacement is its histologic hallmark. Glucocorticoids (GC) are the mainstay of treatment. Podocytes express the glucocorticoid receptor (GR) and new evidence suggests that podocyte-specific GC effects may be central to controlling proteinuria.

Methods: Mice with knockout of GR in podocytes were generated by crossing GR fl/fl mice with podocin Cre mice. Proteinuria was induced using both a systemic stimulus (LPS) and a renal-specific insult (nephrotoxic serum (NTS)). Urine protein/creatinine ratios, serum albumin and GBM morphology were assessed in both controls and knockout animals. *In vitro*, wound healing assays and analysis of stress fiber formation after stimulation with LPS in the presence or absence of dexamethasone (DEX) were performed in primary podocytes isolated from animals of both genotypes.

Results: Podocyte GR knockout mice did not have a phenotype at baseline. Their weight, serum creatinine, serum albumin, urine protein/creatinine ratios and foot process diameter were similar to controls. When challenged with low-dose LPS (12.5 mg/kg, IP), knockout mice developed significantly more proteinuria (2.11 ± 0.77 vs. 0.60 ± 0.21, p<0.05, n=5/group) than did controls. Knockout mice also showed greater foot process effacement by EM after LPS (855 ± 157 nm vs. 466 ± 8 nm, p<0.05, n=5/group) compared to controls. When mice were treated with NTS, similar results were noted. *In vitro*, GR knockout podocytes showed fewer and more disorganized stress fiber formation and impaired wound healing after LPS treatment compared to control podocytes. Administration of DEX could rescue the *in vitro* phenotype in control, but not GR knockout, podocytes.

Conclusions: These results demonstrate that (1) loss of podocyte GR exacerbates proteinuria in two different models *in vivo*, (2) podocytes lacking GR are more intolerant to injury, and (3) DEX administration ameliorates cellular injury in control, but not GR-deficient, podocytes. We conclude that podocyte GR plays a key role in maintaining the integrity of the slit diaphragm after injury.

Funding: NIDDK Support

SA-PO335

Deletion of Inositol-Requiring Enzyme-1α in Podocytes Disrupts Glomerular Capillary Integrity and Autophagy Daniel Robert Kaufman,¹ Joan Papillon,² Takao Iwawaki,³ Andrey V. Cybulsky.^{1,2} ¹Physiology, McGill Univ, Montreal, QC, Canada; ²Medicine, McGill Univ, Montreal, QC, Canada; ³Medicine, Gunma Univ, Maebashi, Japan.

Background: Inositol-requiring enzyme-1α (IRE1α) is an endoplasmic reticulum (ER)-transmembrane endoribonuclease-kinase, which plays an essential function in extraembryonic tissues during normal development, and is activated during ER stress. IRE1α may be involved in upregulating genes associated with the unfolded protein response and

ER-associated degradation, as well as in the activation of c-Jun N-terminal kinase (JNK)-1, and induction of apoptosis and autophagy. In this study, we address the functional role of IRE1 α in podocytes.

Methods: Podocyte-specific IRE1 α knockout (KO) mice were produced by breeding mice with loxP sites surrounding exons 20-21 with podocin (NPHS2)-Cre mice. LoxP-mediated excision in glomeruli was confirmed with PCR.

Results: In male mice, deletion of IRE1 α in podocytes resulted in albuminuria beginning at 5 months of age, and worsening with time. Electron microscopy revealed focal podocyte foot process effacement in 9 month old male KO mice, as well as microvillous transformation of podocyte plasma membranes and cytosolic vacuolation. By light microscopy, glomerular cross-sectional area (an indicator of hypertrophy) was greater in KO males, compared with control, and capillary lumens occupied a higher fractional area of KO glomeruli, suggesting formation of aneurysms. By immunofluorescence microscopy, WT1-positive cells per glomerulus were comparable in KO and control males. Immunoblotting showed reduced LC3B-2 expression and JNK-1 phosphorylation in KO glomeruli, in keeping with reduced autophagy. There was also a reduction in nephrin maturation in KO glomeruli, suggesting impaired ER function. Finally, expression of IRE1 α or IRE1 α K599A (dominant inhibitor) in cultured COS-1 kidney cells did not affect ERAD, as monitored by the degradation of the CD3A ERAD reporter.

Conclusions: Podocyte-specific deletion of IRE1 α leads to albuminuria and morphologic evidence of podocyte injury. Thus, IRE1 α is essential to the maintenance of podocyte integrity as mice age. The mechanism may, at least in part, relate to disruption of autophagy in podocytes.

Funding: Government Support - Non-U.S.

SA-PO336

Consistent Downregulation of Autophagy Gene Atg12 Through MicroRNA-192 in Diabetic Nephropathy Supriya Deshpande,¹ Mitsuo Kato,¹ Mei Wang,¹ Rama Natarajan,¹ ¹City of Hope, ²City of Hope, ³City of Hope.

Background: Autophagy (Atg) plays a key role in the pathogenesis of kidney diseases, however its role in Diabetic Nephropathy (DN), and particularly in mesangial cells (MC) is not clear. TGF- β 1, a key player in the pathogenesis of DN, regulates expression of various microRNAs (miRs) including miR-192. Also, several miRs regulate expression of various Atg genes. We hypothesized that miR-192 plays an important role in Atg regulation in DN.

Methods: Atg gene expression was analyzed in type-2 diabetic (*db/db*) and in STZ-injected type-1 diabetic mice. To analyze the role of miR-192 in Atg regulation, STZ-injected mice were treated with control locked-nucleic-acid (LNA) oligonucleotides (oligos) or LNA oligos targeting miR-192 (anti-miR-192-LNA), and Atg gene expression was analyzed in kidneys. Atg gene expression was also analyzed in kidneys of WT and STZ-injected miR-192 knock-out (KO) mice. The effect of TGF- β 1 on Atg gene expression and GFP-RFP-LC3 puncta formation was analyzed using mouse MC (MMC).

Results: Expression of several Atg genes was decreased in kidneys of type-1 and type-2 diabetic mice compared to controls. Treatment with LNA-anti-miR-192 reversed the effect of diabetes on some of the Atg genes. Further, Atg gene expression was not affected in kidneys of diabetic miR-192-KO mice compared to controls. *In vitro* studies using MMC treated with TGF- β also showed a decrease in Atg gene expression compared to control. Transfection of MMC with miR-192 mimic oligos decreased expression of certain Atg genes. In addition, transfection of MMC with a GFP-RFP-LC3 plasmid decreased the average number of RFP-LC3 puncta/cell following TGF- β treatment, and this effect was reversed in MMC from miR-192-KO mice. Of all Atg genes analyzed, Atg12 expression was consistently decreased in these mouse models, and its decrease was reversed by anti-miR-192 LNA oligos as well as in miR-192-KO mice.

Conclusions: These results demonstrate that consistent downregulation of Atg12 through miR-192 contributes to an overall decrease in autophagy and subsequent increase in cellular hypertrophy in response to TGF- β 1 in MC and in glomeruli of diabetic mice leading to DN.

SA-PO337

mTOR Dependent Regulation of the Podocyte Metabolic Profile Tillmann Bork, Wei Liang, Tobias B. Huber. *Renal Div, Univ Hospital Freiburg, Freiburg, Baden-Wuerttemberg, Germany.*

Background: Podocytes play a critical role in the formation and maintenance of the kidney filtration barrier. Previously we have highlighted the role of mTOR signaling as regulator of podocyte adaption, differentiation and size-control. However, the eventual link between podocyte size control and the regulation of podocyte metabolism by mTOR remained elusive.

Methods: Mice models of mTOR hyperactivation (*Tsc1* P β CO) and mTOR loss of function (*Raptor* P β CO) were crossed to a Tomato/eGFP reporter line to efficiently isolate podocytes for primary cell culture studies. Mitochondrial respiration and ATP synthesis were assessed using Seahorse bioanalyzer with specific inhibitors of glycolysis and β -oxidation.

Results: Lipids are the main source for ATP synthesis due to oxidative phosphorylation in podocytes. Anaerobic glycolysis is the dominating pathway to use glucose. Active mTOR signaling pathway massively enhances basal metabolic activity and the capacity for oxidative phosphorylation as well as anaerobic glycolysis.

Conclusions: Podocyte metabolism relies on β -oxidation of lipids and anaerobic glycolysis. mTOR signaling regulates metabolic activity without affecting the preferences for the used metabolic pathways. Targeting the predominant metabolic pathways of podocytes might help to ameliorate diabetic nephropathy or podocyte ageing.

Funding: Government Support - Non-U.S.

SA-PO338

Derlin-2 Knockout Mice Unravel an Essential Role for Protein Dislocation in Podocytes Guohui Ren, Kwi Hye Koh, Jing Li, Changli Wei, Mehmet M. Altintas, Jochen Reiser. *Dept of Medicine, Rush Univ Medical Center, Chicago, IL.*

Background: Protein quality control represents a balance between chaperone-assisted folding and removal of misfolded proteins from the endoplasmic reticulum (ER). Disturbed balance results in ER stress in podocytes that is associated with cellular injury. Derlin-2, a component that nucleates cellular dislocation machinery, has been identified as an important element in skeletal and matrix producing cells.

Methods: Western blot and immunofluorescence staining were used for detection of protein expression. Derlin-2 knockdown or overexpression in podocytes was achieved with transduction of lentivirus containing shRNA or cDNA. Podocyte-specific Derlin-2 knockout mice were generated by crossing Derlin-2-floxed mice with podocin-Cre mice. Autophagy was detected with the conversion of LC3-I to LC3-II. Activation of caspase-12 was measured by cleavage of procaspase-12.

Results: Derlin-2 was expressed in both mouse and human podocytes. Derlin-2 deficiency in podocytes could be compensated for by inositol-requiring enzyme 1 (IRE1) induced autophagy at baseline conditions. However, in situations with induced ER stress owed to adriamycin (ADR) or other compounds, the compensatory response of autophagy was overwhelmed. Meanwhile, caspase-12 mediated apoptosis pathway was activated, and severe cellular injury ensued, leading to heavy proteinuria in podocyte-specific Derlin-2 knockout mice, as compared with wild type C57BL/6J control mice. In contrast, Derlin-2 overexpression *in vitro* attenuated podocyte injury. Derlin-2 expression was induced in podocytes of patients during focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy (DN) as well as in ADR nephropathy in BALB/cJ mice, streptozotocin (STZ)-induced diabetic mice and BTBR ob/ob DN mice.

Conclusions: Podocytes like osteocytes and chondrocytes emerge from mesenchyme and belong to a group of cells that employ Derlin-2 to guarantee protein quality and minimize ER stress for cellular homeostasis. Overexpression of Derlin-2 may be a mechanism to rescue damaged podocytes. Induction of Derlin-2 expression *in vivo* may have applications for prevention and therapy of glomerular diseases.

SA-PO339

Protein O-GlcNAcylation Is Essential for Normal Podocyte Structure and Function Shinya Ono,¹ Mako Yasuda,¹ Shinji Kume,¹ Osamu Sekine,¹ Jun Nakazawa,¹ Hisazumi Araki,¹ Masami Kanasaki,¹ Shin-ichi Araki,¹ Daisuke Koya,² Masakazu Haneda,³ Takashi Uzu,¹ Hiroshi Maegawa.¹ ¹Dept of Medicine, Shiga Univ of Medical Science, Otsu, Shiga, Japan; ²Div of Diabetology & Endocrinology, Kanazawa Medical Univ, Kahoku-Gun, Ishikawa, Japan; ³Div of Metabolism and Biosystemic Science, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan.

Background: Post-translational modification is essential for normal cell function. The addition of O-linked β -N-acetylglucosamine (O-GlcNAcylation) to proteins is a form of post-translational modification and serves as a nutrient/stress sensor for modulating cell functions. However, little is known about the role of O-GlcNAcylation in podocyte function.

Methods: O-GlcNAc transferase (OGT) is a critical enzyme for O-GlcNAcylation in mammals, and resides on the X chromosome. To examine the physiological role of O-GlcNAcylation in podocytes, we analyzed the renal phenotype of male podocyte-specific *Ogt*-knockout (Podo-OGTKO) mice, which were generated by crossbreeding *Ogt*-floxed mice with podocyte-specific *Cre* mice.

Results: O-GlcNAcylation was immunohistochemically observed in the nuclei of podocytes in wild-type mice, but was completely absent in Podo-OGTKO mice. Podo-OGTKO mice showed normal birth rate and growth up to 32 weeks of age. Proteinuria was first apparent at 8 weeks of age and increased with age up to 32 weeks. Scanning transmission electron microscopy showed disruption of podocyte foot processes in Podo-OGTKO mice after 8 weeks of age. Immunofluorescence showed podocin to have a punctate distribution in Podo-OGTKO podocytes and to be at a reduced level compared with wild-type mice. Furthermore, the numbers of podocytes in 16-week-old Podo-OGTKO mice were significantly decreased compared with wild-type mice. Finally, severe glomerular sclerosis with tubulointerstitial damage was observed in Podo-OGTKO mice at 32 weeks of age.

Conclusions: O-GlcNAcylation of intracellular proteins by OGT is necessary to maintain podocyte numbers and normal foot process structure. Our results provide new insight into podocyte biology.

SA-PO340

Identification of Novel Gene Products That Regulate Podocyte Function Daive Pietro Cina,^{1,2} Chengjin Li,³ Jason Moffat,⁴ Susan E. Quaggin.^{1,2} ¹Div of Nephrology, Northwestern Univ, Chicago, IL; ²Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; ³Tannenbaum-Lunenfeld Research Inst, Mount Sinai Hospital, Toronto, ON, Canada; ⁴Donnelly Centre and Banting and Best Dept of Medical Research, Univ of Toronto, Toronto, ON, Canada.

Background: Podocyte function is linked to the organization of its cytoskeleton and adhesion to the glomerular basement membrane. To identify genes that regulate podocyte function, we designed an *in vitro* genome-wide screen for factors involved in podocyte adhesion to fibronectin, an integrin mediated pathway, or sFLT1/Fc, a heparin sensitive pathway, using a pooled 90000 shRNA library.

Methods: A pool of knockdown podocytes was generated using this library and plated on both substrates for one hour followed by separation of the adherent and floating fractions and deconvolution by illumina sequencing. We developed a stringent method for statistical analysis and 'hit' determination and performed a small-scale validation of this method by interrogating top candidate genes individually. We also performed a larger scale validation using a secondary, focused pooled Cas9 mediated knockout screen.

Results: We identified 121 genes that increased adhesion to fibronectin and 145 genes that increased adhesion to sFLT1/Fc. We also identified 66 genes that decreased adhesion to fibronectin and 106 genes that decreased adhesion to sFLT1/Fc. *DPH1*, *DPH2*, *DPH3* and *DPH4* were in the top ten hits for increased adhesion to both fibronectin and sFLT1/Fc. Stable podocyte knockdown lines for these genes displayed increased adhesion to both substrates. We also generated Cas9 mediated podocyte knockout lines for *DPH1*, *DPH2* and *DPH3*, which displayed increased adhesion and a spreading defect.

Conclusions: We have developed a novel method for identifying genes that regulate podocyte function. Future work will investigate how *DPH1*, *DPH2* and *DPH3* regulate podocyte adhesion, and select novel candidate genes that decrease podocyte adhesion. This unbiased approach will yield a list of genes that broadens our understanding of podocyte physiology and the disease states that perturb this system resulting in kidney disease.

Funding: Government Support - Non-U.S.

SA-PO341

Targeted Deletion of Drp1 in Podocytes Mitigates Mitochondrial Remodeling and Progression of Diabetic Nephropathy Bernard A. Ayanga,¹ Yin Wang,¹ Shawn S. Badal,¹ Farhad R. Danesh.^{1,3} ¹Section of Nephrology, Univ of Texas MD Anderson Cancer Center, Houston, TX; ²Div of Nephrology, Baylor College of Medicine, Houston, TX; ³Dept of Pharmacology, Baylor College of Medicine, Houston, TX.

Background: Diabetic nephropathy (DN) is the most common cause of end-stage kidney disease in the United States. Recent evidence, from our lab and others, suggests that mitochondrial fission may be linked to the pathogenesis of DN and little is known on how mitochondrial fission contributes to the development of DN. Mitochondrial dynamics is regulated by at least three dynamin-related GTPases, including Opa1, mitofusin, and Drp1. Drp1 is an evolutionary conserved protein whose loss results in elongated mitochondria. We have previously reported that Rock1-mediated Drp1 activation leads to increased mitochondrial fragmentation and podocyte apoptosis. We hypothesized that attenuation of Drp1 expression and activity in podocytes may ameliorate features of DN.

Methods: To investigate the role of Drp1 in podocytes, we deployed a genetic and pharmacological approach using a model of Type 2 diabetes (*LepR^{fl}*). **First**, we crossed conditional Drp1 (db/m;*Drp1^{fl/fl}*) mice with a Podocyte-specific tamoxifen, inducible Cre recombinase to generate diabetic, db/db;Pod-*Drp1^{fl/fl}* mice. **Second**, we employed the Drp1 GTPase activity inhibitor, *Mdivi-1*, to pharmacologically assess the therapeutic potential of targeting Drp1 in diabetic mice.

Results: Both podocyte-specific, *Drp1^{-/-}* and pharmacological inhibition of Drp1 by *Mdivi-1* in diabetic mice exhibited significantly attenuated albuminuria, mesangial matrix expansion, increased podocyte numbers, reduced podocyte foot process effacement and attenuated glomerular basement membrane thickening. Ultrastructure analysis revealed significantly elongated mitochondria in *Drp1^{-/-}* diabetic mice compared to non-induced diabetic controls. Consistent with our *in vivo* observations, *Mdivi-1* treatment attenuated high glucose induced mitochondrial fission, apoptosis and mitochondrial ROS production in podocytes.

Conclusions: Our Data Suggest that Drp1 as a key regulator of mitochondrial dynamics in podocytes, and point to Drp1 as a potential therapeutic target in DN.

Funding: NIDDK Support

SA-PO342

A Lack of eNOS Leads to Mitochondrial Injury in the Podocytes Shuko Ueda,^{1,2} Shota Ozawa,^{1,3} Kiyoshi Mori,¹ Katsuhiko Asanuma,¹ Motoko Yanagita,^{1,4} Shunya Uchida,² Takahiko Nakagawa.¹ ¹TMK Project, Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; ²Teikyo Univ School of Medicine, Tokyo, Japan; ³Pharmacology Research Laboratories II, Mitsubishi Tanabe Pharma Corporation, Saitama, Japan; ⁴Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: Endothelial nitric oxide synthase deficiency was shown to accelerate the progression of glomerular injury in several types of renal disease, but the role of eNOS to podocyte integrity remains unclear.

Methods: In order to examine the role of eNOS in the podocytes, cell morphology and mitochondria were examined by using adult male eNOS knockout mice.

Results: A lack of eNOS caused the glomerular hypertrophy in occasionally accompany with mesangiolysis and glomerular sclerosis. Urinary albumin excretion was also significantly increased in the eNOS knockout mice compared to the wild type mice. Ultrastructural analysis showed that the injured podocytes exhibited the enlarged lysosomes, microvillus formation, pseudocysts and foot process effacement. An increase in oxidative stress was also associated with podocyte injury. With respect to mitochondria, its number was elevated while its size was reduced, suggesting that mitochondrial fragmentation was induced in the podocytes due to eNOS deficiency. While the expressions of several mitochondrial proteins were not altered, the D-17 mutation in mitochondrial DNA was significantly induced in the kidney of eNOSKO mice. Mitochondrial function was also likely impaired by eNOS deficiency as ATP level was significantly reduced in renal cortex of eNOSKO mice. Furthermore, the primary podocytes from eNOSKO mice exhibited the impairment of mitochondrial respiration. Consistently, conditioned medium derived from

cultured glomerular endothelial cells lacking NO caused a greater degree of mitochondrial fragmentation and an increase in mitochondrial oxidative stress in the cultured podocytes while such alterations was rescued by an NO donor.

Conclusions: These data suggest that eNOS may be necessary to maintain podocyte integrity, especially mitochondrial function.

SA-PO343

Cytosolic Phospholipase A2 Alpha Regulates G1 Progression Through Modulating Forkhead Box Protein O1 Activity Said Movahedi naini,¹ Gabriel Choukroun,² Dirk M. Hentschel,¹ Joseph V. Bonventre.¹ ¹Brigham and Women Hospital, Renal Division, Boston, MA; ²Amiens Southern Hospital, Renal Division, Amiens, Picardie, France.

Background: Mesangial cell (MC) proliferation is characteristic of a number of chronic progressive glomerular diseases. cPLA₂α is expressed in MCs and plays a role in cellular proliferation, however the mechanisms involved remain unclear. Here, we show for the first time a novel regulatory role for cPLA₂α in the regulation of G1 phase of the cell cycle that is conserved in zebrafish and mammals.

Methods: Mouse embryonic fibroblasts (MEFs) and MCs were derived from *cpla2a*^{-/-} mice. cPLA₂α was knocked down in zebrafish using morpholinos (MOs). Cell cycle progression was assessed by flow cytometry in zebrafish larvae and in G₀ synchronized cells after stimulation with PDGF. S phase population was assessed in zebrafish and MEFs by BrdU pulse studies. Analysis of the phosphorylation of proteins was carried out by western blot assays using phosphospecific antibodies.

Results: We identified two zebrafish *cpla2a* genes, termed *zcpla2a* and *zcpla2b*, with conserved phospholipase activity. In zebrafish and MCs cPLA₂α promotes G₁ progression via its phospholipase activity and through PGE₂ production. PGE₂ through the PI3⁻/K/AKT pathway, promotes FOXO1 phosphorylation and FOXO1 nuclear export. This, in turn, inactivates FOXO1 resulting in upregulation of cyclin D1 and downregulation of p27^{Kip1}, thus promoting G₁ progression. These data indicate an evolutionary conserved mechanism between lower vertebrates and mammals. Further, using pharmacological inhibitors, we show that cPLA₂α, RAF/MEK/ERK, and PI3⁻/K/AKT signaling pathways cooperatively regulate G₁ progression in response to mitogenic stimulation.

Conclusions: cPLA₂α is a critical effector of the G₁ phase of the cell cycle through its phospholipase activity. Pharmacological targeting of this enzyme may have important therapeutic benefits in disease mechanisms that involve excessive cell proliferation including progressive acute and chronic glomerulonephritis.

Funding: NIDDK Support

SA-PO344

Podocyte Specific Glycogen Synthase Kinase 3 Is Critical for Neonatal Survival and for Renal Function in Maturity Jenny Hurcombe,¹ Abigail Charlotte Lay,¹ Gavin Iain Welsh,¹ Peter W. Mathieson,¹ Satish Patel,² Susan E. Quaggin,³ James R. Woodgett,² Richard Coward.¹ ¹Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom; ²Samuel Lunenfeld Research Inst, Univ of Toronto, Toronto, ON, Canada; ³Feinburg School of Medicine, North Western Univ, Chicago, IL.

Background: GSK3 is a multi-functional serine/threonine kinase existing as two distinct but related isoforms: α and β. Knockout mouse models suggest that the GSK3 isoforms have different and cell type specific functions. This study aims to examine the importance of GSK3 in the podocyte.

Methods: We have used Cre/LoxP technology to generate mice with podocyte-specific ablation of GSK3α and/or GSK3β in development (using the podocin cre driver) and in maturity (using the doxycycline inducible podocin RfTA – tet-o-cre driver).

Results: Mice developmentally lacking either GSK3α or GSK3β specifically in the podocyte are viable with normal life span (up to 2 years) and normal renal histology. In contrast, mice null for both GSK3 isoforms, born at normal Mendelian frequency, die at 10-16 days with massive albuminuria and acidosis. These mice have vacuolated glomeruli and glomerulosclerosis. Knockout of GSK3α and β after full glomerular development, at 4 weeks of age, also results in significant renal disease which develops within 2 weeks of knockdown. It consists of significant albuminuria with renal failure in some mice. Furthermore, there is evidence of a crescentic proliferative glomerulopathy, together with massive fibrosis and glomerulosclerosis. Mechanistically the wnt signalling pathway is up-regulated and β-catenin activated throughout the kidney. Contemporaneous knockdown of β-catenin in the developmental model dramatically improves albuminuria and renal histology but not acidosis or survival indicating the involvement of other pathways. These are currently being investigated through a glomerular transcriptomic approach.

Conclusions: Podocyte specific GSK3 is critical for glomerular and renal function in development and full maturity. Loss of single isoforms can be compensated throughout life but loss of both is catastrophic.

Funding: Government Support - Non-U.S.

SA-PO345

Podocyte Oxidative Stress Coupled with Ubiquitin C-Terminal Hydrolase Deletion Exacerbates Renal Damage Naomi C. Read,^{1,2} Chet E. Holterman,² Douglas A. Gray,² Chris R. Kennedy,^{1,2} ¹*Cellular and Molecular Medicine, Univ of Ottawa, Ottawa, ON, Canada;* ²*Ottawa Hospital Research Inst, Ottawa, ON, Canada.*

Background: Ubiquitin C-terminal hydrolase L1 (UCHL1) may promote antioxidant by hydrolyzing ubiquitin-thioester bonds on glutathione (GSH) thereby protecting GSH from degradation. Podocyte UCHL1 is upregulated in diseased glomeruli where it may maintain redox balance. UCHL1-deleted mice overexpressing podocyte-specific NOX5 should exhibit exacerbated glomerular damage due to unregulated oxidative stress.

Methods: COS7 cells were infected with AdGFP or AdNOX5 and UCHL1 levels determined by immunoblot. UCHL1 mRNA was quantified by qPCR. UCHL1^{+/+} and NOX5^{pod+} mice were crossed to generate NOX5^{pod+/+}/UCHL1^{-/-} mice. Albuminuria (ACR) was measured by ELISA. Renal mass was normalized to tibia length. Glomerular filtration rate (GFR) was assessed by FITC-Inulin. Immunofluorescence with anti-PCNA and anti-renin was performed on renal sections. Blood pressure was determined by tail cuff plethysmography.

Results: UCHL1 protein increased 1.9-fold in COS7 cells infected with AdNOX5 vs. AdGFP-infected controls. Similarly, glomeruli from 12-week-old NOX5^{pod+} mice showed limited UCHL1 mRNA induction (1.5-fold). ACR increased in NOX5^{pod+/+}/UCHL1^{-/-} mice at 12 weeks (40ug/mg) but not in nonTG, UCHL1^{-/-} and NOX5^{pod+/+}/UCHL1^{-/-} mice (24, 28 and 25ug/mg). Renal mass was reduced by 10% in both UCHL1^{-/-} and NOX5^{pod+/+}/UCHL1^{-/-} mice as compared to nonTG mice. Interestingly, GFR was elevated in NOX5^{pod+/+}, UCHL1^{-/-} and NOX5^{pod+/+}/UCHL1^{-/-} mice (283, 362 and 352ul/min) vs. nonTG (198ul/min). In UCHL1^{-/-} mice regardless of NOX5 expression, hypercellularity was evident in the juxtaglomerular region. However, no differences were found in renin or PCNA expression, suggesting that the increased GFR is independent of the renin-angiotensin system. Blood pressure increased in NOX5^{pod+/+}/UCHL1^{-/-} mice (121mmHg vs. 113 and 109mmHg for nonTG and UCHL1^{-/-} mice), but was not different from NOX5^{pod+/+} mice (127mmHg) at 12 weeks.

Conclusions: UCHL1-null mice have altered renal function and mass. When intercrossed with NOX5^{pod+/+} mice, UCHL1 deletion combined with unchecked oxidative stress promotes filtration barrier damage.

Funding: Private Foundation Support

SA-PO346

Apolipoprotein L1 Has Diverse RNA and Protein Isoforms and APOL1-B3 Activates Pro-Inflammatory Signaling Hidefumi Wakashii, Jeffrey B. Kopp. *Kidney Disease Branch, NIDDK, NIH, Bethesda, MD.*

Background: Genetic variants apolipoprotein L1 (APOL1), present in individuals of recent African descent, are strongly associated with glomerular disease, but the molecular mechanisms have not been clarified. APOL1 mRNAs have seven exons, and produce splice variants which are predicted to code for distinct protein isoforms (A, B3 and C). However, it is unknown which isoforms drive glomerular disease.

Methods: We examined mRNA expression by TA cloning and determined protein localization using immunofluorescence (IF) of FLAG-tagged APOL1 in stably transfected cells. Mitochondrial fractions were isolated using a detergent-based method.

Results: Using RNA from human podocytes we cloned a new APOL1 splice variant (B3) that lacks exon 4, which contains the signal sequence of APOL1. APOL1-B3 was specifically recognized by APOL1-B antibody raised in rabbits immunized to exon 2. APOL1-B3 was absent from human serum, but was present in podocytes. Both endogenous and transfected APOL1-B3 partially co-localized with mitochondria in IF study and were detected in mitochondrial fractions by Western blot using either anti-FLAG antibody and APOL1-B antibody. By immunoprecipitation, APOL1-B3 was associated with NLRP12, which is a regulator of pro-inflammatory signaling. IL-1 receptor signaling was enhanced in APOL1-B3 stably transfected HeLa cells, and over-expressed NLRP12 overcame the enhancement of IL-1 receptor signaling by APOL1-B3.

Conclusions: APOL1 mRNA splicing produces multiple protein isoforms including A, B3 and C. APOL1-B3 was associated with NLRP12 and enhanced IL-1 receptor signaling. APOL1 nephropathies may be driven by podocyte inflammation and the TLR and IL-1 receptor signaling pathways may be therapeutic targets.

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TNF α Mediated NFAT Activation Causes Podocyte Cholesterol Accumulation in FSGS Christopher E. Pedigo,^{1,2} Farah Leclercq,^{1,2} Matthias Kretzler,³ Sebastian Martini,³ Alla Mitrofanova,^{1,2,4} Ximena A. Morales,^{1,2} Christian Faul,^{1,2} Alexis J. Sloan,^{1,2} George William Burke,⁴ Alessia Fornoni,^{1,2} Sandra M. Merscher,^{1,2} ¹*Nephrology, U of Miami;* ²*Katz Drug Discovery Center, U of Miami;* ³*U of Michigan;* ⁴*Surgery, U of Miami.*

Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common cause of glomerulonephritis in the US and podocyte injury is associated with the development of albuminuria. Tumor Necrosis Factor alpha (TNF α) levels are increased in a subset of patients with FSGS and TNF α alters ATP-Binding Cassette A1 (ABCA1) expression in association with altered cholesterol homeostasis. Treatment strategies for FSGS patients include cyclosporine A (CsA) which directly influences podocyte Nuclear Factor of Activated T-Cells (NFAT) activation. However a potential link between TNF α -NFAT-ABCA1-Cholesterol has not been established. We hypothesized that TNF α causes NFAT mediated lipid dependent podocyte apoptosis in FSGS.

Methods: Differentiated human podocytes were cultured in the presence of TNF α (100ng/ml). Caspase 3 activity was determined in human podocytes. Cyclodextrin (CD) was utilized to deplete cholesterol.

Results: FSGS sera treated podocytes demonstrated increased TNF α expression. Increased TNF α expression correlated with reduced ABCA1 expression in glomerular biopsies from FSGS patients. TNF α treatment of podocytes increased NFAT promoter luciferase activity and RCAN1 mRNA expression. Inhibition with CsA an upstream activator of NFAT prevented downregulation of ABCA1 and increased Caspase 3 activity. TNF α administration in mice caused glomerular NFAT activation and albuminuria that was prevented by CsA. Mice overexpressing podocyte specific constitutively active NFAT developed albuminuria and kidney cholesterol accumulation that was prevented by cholesterol depletion with CD.

Conclusions: TNF α expression is increased in glomeruli of patients with FSGS and in podocytes treated with sera from patients with FSGS. TNF α treatment of human podocytes causes NFAT activation leading to reduced ABCA1 expression and cholesterol accumulation in association with podocyte apoptosis. Our data suggest that treatments targeting the TNF α -NFAT-ABCA1-cholesterol axis may prevent podocyte injury in FSGS.

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Insulin Receptor Isoform A Is Implicated in Podocyte Injury in Diabetic Kidney Disease Alla Mitrofanova,^{1,2} Ximena A. Morales,¹ Mayrin Correa-Medina,¹ Christopher E. Pedigo,¹ Farah Leclercq,¹ George William Burke,² Sandra M. Merscher,¹ Alessia Fornoni,¹ ¹*Katz Family Drug Discovery Center, Div of Nephrology & Hypertension, Univ of Miami, FL;* ²*Dept of Surgery, Univ of Miami, FL.*

Background: Disruption of physiological insulin signaling occurs in podocytes in experimental diabetic kidney disease (DKD). Two isoforms of insulin receptor (IR) have been described that either lack (IRA) or contain (IRB) the 12 amino acids encoded by exon 11. IRA signals primarily through p70S6 kinase and IRB signals primarily through AKT. Podocytes are dependent on functional lipid rafts and associated protein caveolin-1 (Cav1) for proper signaling and survival. We have recently shown sphingomyelin-phosphodiesterase-acid-like-3b (SMPDL3b), which regulates the activity of acid-sphingomyelinase in podocyte lipid rafts, is upregulated in DKD and may contribute to podocyte injury. We tested the hypothesis that SMPDL3b overexpression suppresses IRB signaling and facilitates IRA signaling leading to podocyte hypertrophy and apoptosis.

Methods: Podocytes were treated with insulin (0.1 or 1 nM, 30 min) and samples were used for Western blot analysis. Co-immunoprecipitation experiments (Co-IP) were performed in HEK cells, transfected with 1ug of GFP- or FLAG-SMPDL3b, FLAG-IRA, FLAG-IRB, GFP-Cav1 plasmid. Apoptosis analysis was measured using Caspase-3 Fluorometric Assay kit. Cell surface area was measured by confocal microscopy (OPERA XL).

Results: Podocytes overexpressing SMPDL3b (OE) showed significant increase of IRB/IRA mRNA expression ratio compared to control podocytes (CT) (1.00 \pm 0.00 and 0.74 \pm 0.05, p<0.05). Co-IP demonstrated that both IRA and IRB interact with Cav1. SMPDL3b overexpression augmented IRA/Cav1 interaction and suppressed IRB/Cav1 interaction. OE podocytes showed bigger cell surface area compared to CT (2778.0 \pm 246.5 and 2171.0 \pm 54.7, p<0.05). Insulin stimulation had no effect on the caspase-3 activity in CT podocytes while it induced apoptosis in OE cells (1.19 \pm 0.08 and 2.14 \pm 0.32, p<0.05).

Conclusions: Our data suggest SMPDL3b overexpression in human podocytes impairs IRB signaling leading to increased apoptosis and augments IRA signaling resulting in cell hypertrophy.

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Cyclodextrin Improves Renal Function in Experimental Alport Syndrome Ximena A. Morales,^{1,2} Alla Mitrofanova,^{1,2,3} Christopher E. Pedigo,^{1,2} Judith T. Molina David,^{1,2} Mayrin Correa-Medina,^{1,2} Farah Leclercq,^{1,2} Javier T. Varona Santos,^{1,2} Gloria Michelle Ducasa,^{1,2} Sandra M. Merscher,^{1,2} Alessia Fornoni,^{1,2} ¹*Div of Nephrology and Hypertension, Dep of Medicine, Univ of Miami, Miami, FL;* ²*Peggy and Harold Katz Family Drug Discovery Center; Univ of Miami, Miami, FL;* ³*Dep of Surgery, Univ of Miami, Miami, FL.*

Background: Alport syndrome (AS) is an inherited disease caused by gene mutations involved in collagen type IV biosynthesis. No treatments are currently available for AS. 2-hydroxypropyl- β -cyclodextrin (CD) is a cholesterol depleting agent that is now in clinical trials for treating Niemann-Pick disease type C. We have recently reported that CD protects in experimental DKD by reducing cholesterol dependent podocyte damage. We hypothesized that CD improves renal function in an experimental model of AS.

Methods: Collagen Col4a3 knockout (KO) mice were used as a model for AS. Four-week-old Col4a3 (KO) and wild type (WT) female mice were injected subcutaneously with CD (4000 mg/kg) or vehicle (0.9% Saline solution), 3 times per week for 3 weeks. Four groups were analyzed: WT+vehicle (n=4), WT+CD (n=5), KO+vehicle (n=6), and KO+CD (n=4). Body weight and ACR (albumin/creatinine ratio) from urine were determined weekly. Serum creatinine and blood urea nitrogen (BUN) were analyzed by mass spectroscopy and ELISA respectively at treatment initiation and at sacrifice. Perfused kidneys and skin samples at the site of injection were collected for histological analysis (H&E, PAS) and for Oil Red O (ORO) Staining.

Results: H&E staining showed no toxicity at the site of CD injections. No body weight changes were observed during treatment. CD administration reduced glomerular

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

ORO staining and prevented the development of mesangial expansion in KO+CD group compared to KO+Vehicle. A significant reduction in ACR was observed after 3 weeks of CD treatment in KO+CD compared to KO+Vehicle mice ($p < 0.001$), accompanied by a trend in reduced serum creatinine. CD treatment did not affect ACR, renal function or mesangial expansion in WT mice.

Conclusions: Based on these results, we conclude that CD improves renal function in a mouse model for AS and could be a new therapeutic strategy for the treatment of AS patients.

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The Glomerular Matrisome in Alport Syndrome Is Altered prior to the Onset of Albuminuria Michael J. Randles,^{1,2} Sophie C. Collinson,¹ Jeffrey H. Miner,³ Rachel Lennon.^{1,2} ¹Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, Univ of Manchester, Manchester, United Kingdom; ²Inst of Human Development, Faculty of Medical & Human Sciences, Univ of Manchester, Manchester, United Kingdom; ³Renal Div, Washington Univ School of Medicine, St. Louis, MO.

Background: Alport Syndrome is caused by genetic defects in *COL4A3*, *COL4A4* or *COL4A5*, but despite this knowledge there are currently no targeted therapies. We aimed to build our basic understanding about the glomerular extracellular matrix (ECM) in Alport syndrome and performed global analysis of composition and ultrastructural imaging in the *Col4a3*^{-/-} mouse.

Methods: Cellular and extracellular matrix (ECM) fractions from wild type and *Col4a3*^{-/-} glomeruli at 6 and 16 weeks of age were analysed by mass spectrometry (MS) and imaged using serial block face-scanning electron microscopy (SBF-SEM).

Results: MS analysis revealed moderate changes in the composition of glomerular ECM at 6 weeks, even prior to the onset of barrier dysfunction. These included complete absence of type IV collagen $\alpha 3$, $\alpha 4$, $\alpha 5$ and upregulation of type IV collagen $\alpha 1$, $\alpha 2$, $\alpha 6$ and type VI collagen. At 16 weeks more dramatic changes were detected including elevated type IV collagen $\alpha 1$, $\alpha 2$, fibronectin, type I collagen, laminin $\alpha 2$ and fibrinogen chains. Global and pathway analysis of cellular fractions indicated changes in actin regulating proteins at 6 weeks and mitochondrial dysfunction at 16 weeks. SBFSEM demonstrated thickened and irregular glomerular basement membranes with evidence of podocyte protrusions into this ECM.

Conclusions: Our data demonstrate that Alport syndrome progresses with distinct early changes in ECM followed by more profound ECM accumulation, disruption and mitochondrial dysfunction. Enhanced understanding about the pathways that control podocyte cell-matrix adhesion may ultimately inform therapeutic strategies to correct or repair glomerular barrier function in Alport syndrome.

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Creation and Analysis of Mouse Models of Human Nephrotic Syndrome Caused by the Laminin b2 (LAMB2) S80R Mutation Steven Daniel Funk, Jeffrey H. Miner. Renal Div, Washington Univ School of Medicine, St. Louis, MO.

Background: Most cases of congenital nephrotic syndrome in the first year of life are caused by mutations in 4 genes expressed in podocytes: *NPHS1*, *NPHS2*, *WT1*, and *LAMB2*. *LAMB2* encodes laminin b2, a glomerular basement membrane component critical for glomerular filtration. We previously created transgenic mice using the nephrin promoter to study missense mutations discovered in patients with congenital nephrotic syndrome, including R246Q and C321R, which inhibit laminin-521 secretion and/or induce podocyte ER stress. Here we aimed to characterize a new mutation (S80R) in the *LAMB2* polymerization domain that was discovered in a delayed nephrotic syndrome patient; this delay suggests that chronic dysfunction in glomerular filtration may be the pathogenic mechanism.

Methods: In our first approach the S80R mutation was engineered into the rat laminin b2 cDNA and placed under the control of the nephrin promoter; this construct was used to make transgenic mice expressing *LAMB2*-S80R in podocytes on the *Lamb2*^{-/-} background. In a second approach, we utilized CRISPR/Cas9 and homologous recombination to "knock-in" the S80R point mutation into the endogenous *Lamb2* gene.

Results: Several transgenic mouse lines were characterized as very high, high, and low/mosaic *LAMB2*-S80R-expressing mouse lines. Surprisingly, high S80R expressors did not exhibit albuminuria up to 1 year of age. The low/mosaic expressors exhibited persistent, low level albuminuria that never progressed into the nephrotic range or overt kidney disease. These observations suggested to us that unregulated transgene expression may compensate for what could be only a mildly pathogenic mutation. We then used CRISPR/Cas9 technology in zygotes to generate *LAMB2*-S80R knock-in mice that will better mimic endogenous expression of the mutant protein, as in the patient. These are currently being bred for analysis.

Conclusions: The *LAMB2*-S80R mutation seems to be mild vs. other *LAMB2* mutations. S80 is in the laminin N-terminal (LN) domain important for laminin polymer formation. High transgene expression may compensate for S80R-induced polymerization defects, which will be avoided with CRISPR/Cas9-induced, S80R knock-in mutants.

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SA-PO352

Differential Roles of Cell Surface Proteoglycans in Podocyte-Glomerular Basement Membrane Adhesion Angela C. DiPoto-Brahmbhatt, Deborah J. McCarthy, Kevin J. McCarthy. Pathology and Translational Pathobiology, LSU Health Sciences Center-Shreveport, Shreveport, LA.

Background: Cell surface proteoglycans (PG), via their heparan sulfate (HS) chains, work in a cooperative fashion alongside integrins to mediate podocyte (POD)-glomerular basement membrane (GBM) interactions. Results of our previous studies have shown that complete loss of HS at the POD cell surface leads to the development of foot process effacement. Since POD have at least two cell surface HS PG's that are capable of mediating such interactions, the purpose of this study was to determine the effects of selective deletion of the cell surface PG, syndecan-1 (Sdc1) or syndecan-4 (Sdc4) on POD in vivo.

Methods: Frozen tissue sections of kidneys from wild-type (WT), Sdc1, or Sdc4 knockout (KO) mice were immunostained with antibodies against the core proteins of Sdc1 and Sdc4, HS (antibody HS4C3), synaptopodin (SYN), nephrin, and α -actinin-4. To determine the potential for loss of anionic charge associated with HS, 500 μ m sections of unfixed kidneys were labeled with polyethylenimine (PEI) followed by fixation and processing for transmission electron microscopy.

Results: TEM studies showed that the GBMs of both Sdc1 and 4 KO mice had GBM irregularities, the POD in Sdc4KO mice showing moderate foot process effacement. Immunostaining for HS did not show differences in staining intensity for HS between Sdc1 and Sdc4KO mice. However, PEI labeling showed that the GBMs in Sdc4 KO mice had larger aggregates of PEI than those found in the GBM of Sdc1KO mice. Immunostaining showed that a compensatory increase in Sdc4 expression in Sdc1KO glomeruli or Sdc1 expression in Sdc4KO glomeruli did not occur. The glomeruli of Sdc1 KO mice showed disruption of nephrin organization compared to Sdc4 and WT mice. Immunostaining for α -actinin-4 in both Sdc1KO and Sdc4KO glomeruli was also disrupted compared to control.

Conclusions: The data show that disruption of either Sdc1 or Sdc4 interactions with the GBM does affect the manner by which POD interact with the GBM. Although loss of Sdc4 was associated with the development of foot process effacement, the loss of either Sdc1 or Sdc4 have effects on POD cytoskeletal organization.

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ERM Protein Activation by CLIC4 in Glomerular Endothelial Cells Abass Almomany,¹ Mahtab Tavasoli,¹ Laiji Li,¹ John C. Edwards,² Barbara J. Ballermann.¹ ¹Medicine, Univ of Alberta, Edmonton, AB, Canada; ²Internal Medicine, St. Louis Univ, St. Louis, MO.

Background: We reported (J. Cell Sci. 2014, 127:5164) that the podocyte-predominant CLIC5A stimulates PI[4,5]P2 production and consequent ERM (ezrin, radixin, moesin) protein phosphorylation (pERM). Activated ERMs link membrane-spanning proteins to cortical actin, and inactive ERMs are unstable. CLIC4, homologous to CLIC5A, is expressed at high levels in glomerular and peritubular capillary endothelial cells (EC), and in proximal tubule brush border and basolateral membranes. CLIC4 deficient mice (CLIC4^{-/-}) have fewer glomeruli and a lower peritubular capillary density than wild-type mice (BMC Nephrology 2014, 15:54). Here, we explored whether CLIC4 regulates ERM protein activation, similar to CLIC5A.

Methods: Confocal immunofluorescence (cIF) microscopy was used to visualize CLIC4 and moesin kidney sections. Western blot analysis (WB) was used to study total and cytoskeletal fractions from isolated mouse glomeruli and cultured human glomerular EC cells. In cultured human glomerular EC, CLIC4 was silenced with CLIC4-specific siRNA \pm CLIC4 cDNA rescue.

Results: By cIF CLIC4 co-localized exquisitely with moesin in mouse glomerular EC. WB showed that CLIC4 is absent from CLIC4^{-/-} glomerular lysates, and that the ratio of pERM : tubulin is lower in CLIC4^{-/-} than in CLIC4^{+/+} glomeruli (1.28 \pm 0.11 vs. 2.26 \pm 0.30, respectively, $p < 0.01$, mean \pm SD, n=3). Total ERM protein was also reduced, and much less ERM protein was observed in the cytoskeletal fraction of CLIC4^{-/-}; compared to CLIC4^{+/+} glomeruli. In cultured human glomerular EC, CLIC4 siRNA reduced CLIC4 protein by >90% and resulted in ERM protein dephosphorylation and dissociation from the cytoskeleton, all rescued by over-expression of CLIC4. CLIC4-induced ERM phosphorylation was abolished by PLC activation with m-3M3FBS, indicating that PI[4,5]P2 dependence.

Conclusions: Hence, CLIC4 co-localizes with moesin in glomerular EC in vivo. Like CLIC5A, CLIC4 promotes ERM phosphorylation in a PI[4,5]P2-dependent fashion. We speculate that defective ERM phosphorylation may be responsible, in part, for the morphological and physiological abnormalities in CLIC4^{-/-} mice.

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Vascular Glycocalyx Syndecan (SDC) 4 Loss Coincides with Albuminuria in Diabetic Nephropathy (DN) Raina D. Ramnath, Amy Russell, Rebecca R. Foster, Gavin Iain Welsh, Andy Salmon, Simon C. Satchell. Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

Background: The endothelial glycocalyx is a critical determinant of vascular health and a key regulator of vascular permeability. Increasing evidence points to disruption of the endothelial glycocalyx as a contributor to development of albuminuria (albumin in the urine) and eventually DN. TNF α which is important in the development of microvascular disease in diabetes caused a disruption of the glomerular endothelial cells (GENC)

glycocalyx through shedding of SDC4 and heparan sulphate (HS). We seek to investigate the role of vascular endothelial glycocalyx in DN and determine the mechanisms involved in its disruption in DN.

Methods: DN was induced in DBA2J mice by giving daily intraperitoneal injection of streptozotocin (STZ) at 50mg/kg for 5 days. The mice became hyperglycemic at 2 weeks and significantly albuminuric at 8 weeks post STZ injection.

Results: In DN, SDC4 protein expression was significantly decreased in isolated glomeruli. This was accompanied by a corresponding increase in SDC4 in the circulation and in the urine, suggesting shedding of vascular glycocalyx SDC4. An increase in SDC4 shedding causes a positive feedback mechanism resulting in an increase in SDC4 mRNA synthesis in isolated glomeruli and GEnC. The glycocalyx SDC4 disruption coincides with albuminuria, strongly suggesting that vascular glycocalyx SDC4 damage is likely to contribute to albuminuria in DN. There was a significant elevation in gelatinase matrix metalloproteinase (MMP)2 in glomeruli in DN, suggesting that MMP2 could mediate SDC4 shedding. My in vitro data in human GEnC showed that gelatinase MMP9 was upregulated and resulted in the shedding of SDC4 and HS. This resulted in an increase in BSA permeability across the monolayer.

Conclusions: MMP2,9-mediated shedding of SDC4 is likely to contribute to vascular endothelial glycocalyx disruption and albuminuria observed in DN. Potential therapies targeted at glycocalyx protection will be of benefit not only in DN but also in ameliorating systemic vascular disease in diabetes.

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Blood Cell Velocities in Glomerular Capillaries Measured by 2-Photon In Vivo Microscopy Reveal Heterogeneous Blood-Flow Dejanira Pedoto,^{1,2} Eugenio Gutierrez,³ Luca Bordonì,¹ Sara Damiano,² Francesco Trepiccione,² Giovambattista Capasso,^{2,4} Sebastian Frische.¹ ¹Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark; ²Dept of Cardio-Thoracic and Respiratory Science, Second Univ of Naples, Napoli, Italy; ³Center for Functionally Integrative Neuroscience, Aarhus Univ, Aarhus, Denmark; ⁴Biogem, Ariano Irpino, Italy.

Background: Theoretical models have shown that the blood-flow within a glomerulus may be heterogeneous and that flow heterogeneity may affect the ultrafiltration coefficient and thus GFR. The aim of this study is to provide experimental data to test these model predictions by measuring glomerular capillary flow velocities by in vivo 2-photon microscopy.

Methods: Male Munich-Wistar rats were intubated, anesthetized with isoflurane, and mechanically ventilated. Blood pressure and heart-rate were monitored. The left kidney was externalized and the rat placed in the 2-photon microscope. Blood plasma was labeled by i.v. injection of 70 kD TexasRed-Dextran. Longitudinal lines in the lumen of capillaries in superficial glomeruli were scanned at a frequency of >700 Hz. The axial movement of single blood cells was measured. 308 different capillaries were analyzed in 17 glomeruli from 5 different rats.

Results: Blood cell velocity was 2.99 $\mu\text{m}/\text{ms}$ \pm 0.54. A Gaussian distribution and a Gamma-distribution were fitted to data from 13 glomeruli in which >12 capillaries were studied. C²-tests ($\alpha=0.05$) showed 5 of 13 datasets not to follow a Gaussian distribution and 1 of 13 not to follow a Gamma-distribution. The data from all 308 capillaries normalized to the mean of the respective glomerulus did not follow a Gaussian distribution ($P<0.05$). The Gamma-distribution allows an asymmetrical distribution around the mean and provided the best description.

Conclusions: This study provides experimental evidence of heterogeneity and an asymmetric distribution of blood cell velocity in glomerular capillaries. This new experimental evidence calls for refinement of current models of glomerular blood flow heterogeneity and invokes the possibility to investigate the potential regulatory control of the ultrafiltration coefficient by regulation of capillary flow heterogeneity, e.g. by the action of mesangial cells.

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Assessment of Exosomes Derived from Mesangial Cells Stimulated with High Glucose Antonio S. Novaes,¹ Fernanda Teixeira Borges,¹ Marcos Dias,² Mirian A. Boim.¹ ¹Medicine, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; ²CIPE - Centro Internacional de Pesquisa, A.C. Camargo Cancer Center, Sao Paulo, SP, Brazil.

Background: Exosomes and microvesicles (MV) are extracellular vesicles (EV) that play a key role in the intercellular communication and they have been recently involved in many physiological and pathological conditions. EV released by cells contains substances that can modify the function of other target cells. The content of these vesicles include proteins and nucleic acids such as microRNAs (miRNA). This study aimed to ascertain whether high glucose can modify the cargo of the human mesangial cell (HMC)-derived EV.

Methods: EV secreted from HMC were purified by ultracentrifugation serum-free medium and analyzed by electron microscopy. The vesicles size/concentration ratio was determined by the particle tracking using a nanoparticles analyzer (NanoSigh) and the characterization of the exosomes was performed by the presence of a specific marker CD63. Since mesangial cells are an important intrarenal source of the renin angiotensin system (RAS) components, we evaluated the presence angiotensinogen in the exosomes, by Western Blot. The exosomes obtained from control (C-Ex) and HG exposed HMC (HG-Ex) were used to evaluate whether they are able to modify the function of target control HMC. Exosomes were added to the culture medium and 24 hr after, the expression of fibronectin mRNA was estimated by real time PCR.

Results: The vesicles had a mean size of 140 nm and expressed the CD63, specific for exosomes. The amount and size of exosomes were not modified by stimulation with high glucose. It was observed the presence of angiotensinogen in the exosomes, and it was increased in the exosomes derived from HG stimulated HMC. Interestingly, the expression levels of fibronectin was higher in control HMC treated with HG-Ex compared with those treated with C-Ex, indicating that HG-Ex can modify the function of normal HMC.

Conclusions: In conclusion, the exosomes derived from HG stimulated HMC were able to induce fibronectin production in target control cells, and suggest that the intercellular communication through the exosomes may have pathophysiological implications in the diabetic kidney.

Funding: Government Support - Non-U.S.

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Axl Receptor Tyrosine Kinase Is Involved in Proliferation of Human Mesangial Cells Activated by PDGF Qi Bian,^{1,2} Joshua Charles Anderson,¹ Xianwen Zhang,¹ Zhi Qiang Huang,¹ Kerstin Ebeffors,⁴ Jenny C. Nyström,⁴ Stacy D. Hall,¹ Bruce A. Julian,¹ Christopher D. Willey,¹ Jan Novak.¹ ¹Univ of Alabama at Birmingham, Birmingham, AL; ²Changhai Hospital, Second Military Medical Univ, Shanghai, China; ³Univ of Gothenburg, Sweden.

Background: Proliferation of mesangial cells (MC) is an important feature in many glomerular diseases, including IgA nephropathy (IgAN). Platelet-derived growth factor (PDGF) is a potent stimulator of MC, activating multiple signaling pathways associated with proliferation of MC. Our global kinomic profiling revealed that activity of multiple kinases in MC increased after PDGF stimulation, including tyrosine kinase Axl. As there is limited information on the association of PDGF signaling and activation of Axl in human MC, we studied details of Axl involvement in human MC stimulated by PDGF.

Methods: MC were obtained from a commercial source or isolated from biopsy specimens of patients with IgAN or other glomerular diseases. Quiescent primary human MC were stimulated by PDGF AB in the presence or absence of different inhibitors. MC lysates were analyzed by global tyrosine-kinome profiling using PamStation@12 platform and Western blotting. MC proliferation was measured by BrdU incorporation. The expression and distribution of Axl in MC were assessed by immunofluorescence.

Results: Tyrosine-kinome profiling indicated that PDGF AB increased Tyro3, Abl, and Ltk kinase activities. Further data analyses predicted Axl as one of the key upstream kinases activated in PDGF-AB-stimulated MC. We found that Axl was expressed in all tested primary human MC. PDGF AB stimulated proliferation of MCs; this effect was inhibited by Axl-specific inhibitor R428. Signaling studies revealed that PDGF AB increased phosphorylation of multiple signaling proteins, including Axl, PDGFR- β , Akt1, and ERK1/2. R428 significantly inhibited phosphorylation of Axl and Akt1, and, to a lesser extent, also of ERK1/2 and PDGFR- β . MEK1/2 inhibitor U0126 and PI3K inhibitor LY294002 did not affect phosphorylation of Axl.

Conclusions: Axl is involved in PDGF-induced proliferation of cultured MC through multiple signaling pathways. Targeting Axl may provide a new therapeutic strategy for IgAN.

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Different Effects and Mechanisms of Prostaglandin E2 Receptor Subtypes EP2 and EP4 in TGF- β 1 Induced Mesangial Cell Injury Chen Xiao Lan,¹ Yuan Li.² ¹Affiliated Hospital of Nantong Univ; ²Affiliated Hospital of Nantong Univ.

Background: To study effects of prostaglandin E2 receptor subtypes 2 and 4 (EP2 and EP4) in mesangial cell injury by transforming growth factor - β 1 (TGF- β 1) and relevant signal pathways.

Methods: 1. The primary cultures of EP2 gene knockout (EP2^{-/-}), EP4 gene knockout (EP4^{flox/flox}) and wild type (WT) mice mesangial cells were established; 2. grouping: A: ① WT; ② WT +TGF- β 1; B: ③ EP2^{-/-}; ④ EP2^{-/-} + TGF- β 1; C: ⑤ EP4^{flox/flox} + AD-CRE (EP4KO); ⑥ EP4^{flox/flox} + AD-CRE (EP4KO) + TGF- β 1; Group ⑤ and ⑥ respectively take EP4^{flox/flox}+AD-GFP (EP4KO) and EP4^{flox/flox} + AD-GFP (EP4KO) +TGF- β 1 as control; 3. the level of PGE2, cAMP, the PKA activity of mesangial cell was tested; 4. PKA (H89) and ERK (PD98059) inhibitors were used to interdict PKA activity and ERK pathway in WT mesangial cell; EP2 or EP4 receptor agonist were used to pretreat WT MCs.

Results: 1. After TGF- β 1 stimulation, expression of FN and CTGF increased; the expression of FN and CTGF in Group EP2KO increased; the expression of FN and CTGF in EP4KO decreased; 3. after TGF- β 1 stimulation, the Smad3 phosphorylation level in EP2KO increased; while the Smad3 phosphorylation level markedly decreased in EP4KO; 4. the PGE2 level of WT mesangial cell increased at 12h after TGF- β 1 treatment; 5. the cAMP content in EP2KO was less than that of the control; PKA activity obviously declined; the cAMP content has no obvious changes in EP4KO; after stimulation with TGF- β 1, the PKA activity increased; 6. ERK inhibitor blocks the function caused by agonist EP4; while PKA inhibitor block the inhibition function of agonist EP2.

Conclusions: EP2 and EP4 have different regulating effects on injury and renal fibrosis of mesangial cells: EP2 receptor mediated PGE2 induced up-regulation of the level of cAMP and PKA activity, so as to inhibit transduction effects of TGF- β 1/Smad3 pathway and reduced the occurrence of injury and fibrosis of mesangial cell; while EP4 may coordinate the promotional effect of mesangial cell injury induced by TGF- β 1 by activating phosphorylation ERK pathway, resulting in regulating effects different from that of EP2.

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Mesenchymal Stem Cells in the Repair of the Damaged Mesangium: A Step by Step Ultrastructural Account of the Events Taking Place Jiamin Teng, Pathology and Transitional Pathobiology, Louisiana State Univ Health Sciences Center, Shreveport, LA.

Background: Not much is known about repairing the damaged mesangium. The use of mesenchymal stem cells (MSCs) to repair the injured mesangium is a rather novel concept. The present study aimed at analyzing the entire process using transmission electron microscopy in an effort to better understand the various steps involved.

Methods: Mesangial cells (MCs) cultured single layer in dish (2D) and on Matrigel (3D), MCs were first cultured to confluent and quiescent for 48 hours. Then they were incubated with glomerulopathic light chains (GLCs) (10 ug/ml) purified from the urine of patients with renal biopsy-proven light chain-related amyloidosis (AL-Am) (n=3) and light chain deposition disease (LCDD) (n=3) for 4 days and subsequently labeled MSCs were added. Samples were collected 10 days after the introduction of the MSCs (day 14) and processed for light and transmission electron microscopy.

Results: MCs revealed evidence of direct damage by the GLCs including apoptosis with apoptotic bodies released. MSCs identified and migrate to areas where cellular damage was present. When MSCs became activated they acquired a "macrophage" phenotype. They then became active in phagocytosing cell debris, apoptotic bodies damaged extracellular matrix and non-extracellular matrix material. Their process of cleaning the damaged mesangium resulted in MSCs full of cellular debris and eventually disposing of the internalized material. After performing this function, they proceeded to differentiate into mature MCs.

Conclusions: MSCs actively clean the injured mesangium by phagocytosing apoptotic cells and other material. They do so by transforming into a macrophage phenotype. Once the cleaning process is completed, they differentiate into MCs acquiring their characteristic smooth muscle morphology and functional properties. The entire sequence of events was documented by transmission electron microscopy providing an added dimension to the understanding of MSCs in the repair of the damaged mesangium.

Funding: Private Foundation Support

SA-PO360

Characterization of Circulating APOL1 Complexes and Their Kidney Distribution in African Americans Lijun Ma, Allison Weckerle, James A. Snipes, Dongmei Cheng, Abraham K. Gebre, Mariana Murea, Gregory A. Hawkins, John S. Parks, Barry I. Freedman. Wake Forest School of Medicine.

Background: The apolipoprotein L1 gene (*APOL1*) G1 and G2 renal-risk variants associate with non-diabetic nephropathy and cardiovascular disease in African Americans (AAs). Although substantial *APOL1* protein is present in the circulation, with enrichment in podocytes compared to other renal cells, little is known about circulating *APOL1* protein.

Methods: Total serum *APOL1* levels were examined by Western blot in a cohort of healthy AAs who had a 1st degree relative with kidney disease. *APOL1* protein complexes were isolated from fast protein liquid chromatography (FPLC) peak fractions and characterized by proteomic analyses. Results were subsequently verified by co-immunoprecipitation and Western blot.

Results: No significant differences were detected in serum *APOL1* protein concentration based on *APOL1* genotypes. However, serum *APOL1* protein binds to other protein complexes. Non-denaturing gradient gel electrophoresis and FPLC demonstrated that serum *APOL1* protein existed in two non-overlapping peaks (12.2nm and 20.0nm in diameter, respectively). The smaller complex was labeled complex A and the larger complex B. Density gradient ultracentrifugation and agarose gel electrophoresis confirmed that neither *APOL1* protein complex was associated with HDL or LDL cholesterol. The exposure of *APOL1* complex A surface epitopes appeared to be altered by G1/G2 renal-risk variants based on avidity to a specific monoclonal antibody from a non-G1/G2 associated immunogen (p=0.01). APOA1, haptoglobin-related protein (HPR), and complement C3 were present in *APOL1* complex A. APOA1, HPR, IgM, and fibronectin were present in *APOL1* complex B. In *APOL1* complex A, HPR- α was more abundant in those with G1 and G2 renal-risk variants, relative to G0 (GENMOD p=0.04, total N=12). Serum HPR- α was only present in *APOL1* complexes. Small amounts of HPR protein were detected in renal tubule cells but not glomeruli, whereas *HPR* mRNA was absent in the kidney.

Conclusions: Results provide unique insights on the composition of circulating *APOL1* complexes. The role of circulating *APOL1* in kidney and cardiovascular disease in AAs requires further investigation.

Funding: NIDDK Support

SA-PO361

Deep Mapping of the Native Mouse Podocyte Proteome Markus M. Rinschen,¹ Florian Grahmmer,² Tobias B. Huber,² Thomas Benzing,¹ ¹Internal Medicine, Univ Hospital Cologne, Cologne, Germany; ²Internal Medicine, Univ Hospital Freiburg, Freiburg, Germany.

Background: The entity of proteins expressed within a podocyte is still not known.

Methods: We performed mass spectrometry based absolute and relative quantification of the proteome of FACS-sorted native mouse podocytes.

Results: We resolved the podocyte proteome at a near-comprehensive resolution (more than 8000 identified proteins). Absolute copy numbers of proteins correlated with copy numbers obtained from deep-sequencing transcriptomic analysis. The dataset indicates agreement between transcriptome and proteome regarding expression of proteins which are mutated in hereditary forms of proteinuria and FSGS in humans. 541 proteins were enriched within podocytes at very high ratios and significance. This study suggests that

the podocyte is not only target to inflammatory stimuli such as TNF α and IFN γ , but also several unanticipated other stimuli. In addition, this study delineates podocyte enriched tyrosine kinases, a few of these are druggable. Protein domains significantly enriched in podocyte proteins comprise not only PDZ and Fn3 domains, but also i-set domain, an adhesion domain. The majority of podocyte specific proteins also stain positive for glomeruli in human samples, with a weak correlation between staining intensity and absolute protein abundance measured by MS/MS.

Conclusions: This initial, near comprehensive draft of the podocyte proteome reveals untapped molecules and mechanisms. This dataset will be of benefit to understand podocyte physiology, pathobiology and develop potential therapeutic strategies.

SA-PO362

Maternal Obesity Is a Significant Risk Factor for the Development of Diabetic Nephropathy Sarah J. Glastras,¹ Rachel Teh,¹ Michael Chi-Ho Tsang,² Hui Chen,² Amgad Sawiris,¹ Carol A. Pollock,¹ Sonia Saad,¹ ¹Dept of Medicine, Kolling Inst, Univ of Sydney; ²Univ of Technology, Sydney.

Background: Our previous studies have shown that maternal obesity is associated with increased renal injury in offspring. We hypothesised that a second-hit such as diabetes may further exacerbate diabetic nephropathy in offspring exposed to maternal obesity.

Methods: Female C57Bl6 mice were fed either normal or high-fat diet (HFD) for 6 weeks prior to pregnancy, during pregnancy and weaning and their offspring were weaned to chow diet or HFD. At Week 8, the male offspring were randomized to streptozotocin (STZ) 55mg/kg/day for five consecutive days, 100 mg/kg once only or placebo. Weight and glucose levels were tested fortnightly. 24 h urine collection was performed at Week 20 and 30. The kidneys were harvested at Week 32. The renal structure was observed. Gene expression levels of profibrotic, inflammatory and oxidative stress markers were measured by real time PCR and confirmed with protein quantification with Western blot and/or immunohistochemistry.

Results: Offspring of obese mothers had increased fat deposition. Diabetic offspring had reduced weight gain, hyperglycaemia, glycosuria and microalbuminuria. Urinary albumin measurements were highest in diabetic offspring of obese mothers exposed to 5 doses of STZ. The kidneys of the offspring exposed to maternal obesity and induced with diabetes had increased structural damage, renal fibrosis and increased inflammatory changes and markers of oxidative stress when compared to the kidneys of diabetic offspring of normal weight mothers. There was significant intrarenal lipid deposition in obese offspring, exacerbated by maternal obesity and diabetes.

Conclusions: Offspring exposure to maternal obesity accelerates the severity of damage to the kidney caused by diabetes. Fetal programming of renal inflammation and oxidative stress may be a key component to the accelerated risk. Offspring diet has a powerful effect on renal outcome.

Funding: Government Support - Non-U.S.

SA-PO363

Leucine-Rich Glycoprotein 1 : A Candidate Biomarker for Early Renal Function Decline in Type 2 Diabetes Sona Haku,^{1,2} Kouichi Tamura,¹ Jennifer W. Xu,² Carla Cavallin,² Hiromichi Wakui,¹ Kengo Azushima,¹ Kazushi Uneda,¹ Ryu Kobayashi,¹ Kotaro Haruhara,¹ Michael S. Simonson,² Satoshi Umemura,¹ ¹Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan; ²Dept of Medicine, Div of Nephrology and Hypertension, Univ Hospitals Case Medical Center and Case Western Reserve Univ School of Medicine, Cleveland, OH.

Background: Biomarkers that identify patients with type 2 diabetes and early renal function decline may improve our ability to intervene and slow progression to end-stage renal disease. In a Phase I preclinical exploratory study, we tested whether leucine rich glycoprotein-1 (LRG1), a candidate biomarker discovered in *db/db* mice, would identify patients with early decline in renal function.

Methods: Patients with type 2 diabetes were recruited into training (*n*=56) and independent, non-overlapping test (*n*=37) groups (median baseline eGFR = 80.3 ± 29.5 ml/min/1.73m²). LRG1 was measured in spot urine collections by ELISA, and performance was assessed as area under the receiver operating characteristic curve (AUC) with adjustment for clinical covariates of DKD.

Results: Urine LRG1 was associated inversely with eGFR (*r* = -0.546, *P* < 0.001) and positively with ACR (*r* = 0.283, *P* = 0.034). The AUC of LRG1 for identifying participants with baseline eGFR 90 – 60 was 0.815 ± 0.103; in contrast, the AUC of the albumin/creatinine ratio was 0.465 ± 0.093 (*P* < 0.01 versus LRG1). Adjustment for age, sex, race, duration of diabetes, and HbA_{1c} did not alter the AUC for LRG1, and these results were replicated in the test group. In participants with eGFR ≥ 60 ml/min/1.73m² at baseline, LRG1 predicted a 5-year outcome of eGFR < 60 or ESRD better than ACR (0.702 ± 0.085, *P* < 0.01 versus ACR, 0.520 ± 0.119).

Conclusions: Taken together, these results suggest LRG1 may identify patients with early renal function decline more accurately than ACR. Evaluation of LRG1 in prospective cohort studies of type 2 diabetes may lead to a better biomarker for identifying and monitoring DKD.

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SA-PO364

A Longitudinal Study on Kidney Function, Pathology, and Multiple Urinary Biomarkers in ZSF1 Rat Model of Type II Diabetic Nephropathy Zhi Su, Deborah Widomski, Marian T. Namovic, Diana L. Donnelly-Roberts, Laura Leys, Katherine Salte, Arthur L. Nikkel, Lauren Olson, Ji Ma, Timothy A. Esbenshade, Steve McGaraghty. *Renal Discovery, Abbvie, North Chicago, IL.*

Background: Obese ZSF1 rats display many clinical features of human type II diabetic nephropathy (DN). To further understand this model and to identify relevant biomarkers of disease progression, we followed the development of DN by measuring glomerular filtration rate (mGFR), histopathology, and a variety of urinary and tissue biomarkers over 24 weeks after uninephrectomy (Unx). Correlations between mGFR and individual urinary biomarkers were assessed.

Methods: Male rats (9-week old) underwent either a sham or Unx (right kidney) surgery and were fed a high carbohydrate diet. GFR was measured by transdermal clearance of FITC-sinistrin. Urine samples were collected once every 2-4 weeks for biomarker analysis, and renal tissue was examined for collagen deposition as well as for the levels of key inflammatory and fibrotic genes.

Results: Kidney hyperfiltration was observed (2-3 fold increase in mGFR) in obese rats 2-week after surgery lasting until week 4. The mGFR subsequently declined over time in these rats and was 2-fold lower than control rats by end of study. Compared to lean rats, obese rats also demonstrated time-dependent increases in urinary excretion of protein, KIM-1, L-FABP, NGAL, Cystatin C, Clusterin, Beta2-microglobulin, alpha1-acid glycoprotein, VEGF, MCP-1, TIMP-1, Collagen IV, TGF-b1, and TGF-b2. A significant correlation was found between mGFR and a number of urinary biomarkers (L-FABP, KIM-1, TIMP-1, Clusterin, Cystatin C, and TGF-b2). Kidney fibrosis was significantly elevated by week 12 post surgery and continued to expand in the following weeks. Unx increased the weight and glomerulosclerosis of the remaining kidney and accelerated the decline of mGFR in obese rats during late weeks of observation.

Conclusions: ZSF1 rats showed a progressive increase of fibrosis and loss of mGFR over the 24-week study. A number of urinary biomarkers demonstrated a strong inverse correlation with the time-dependent changes in mGFR. Additionally, Unx significantly increased glomerulosclerosis and loss of GFR in obese rats.

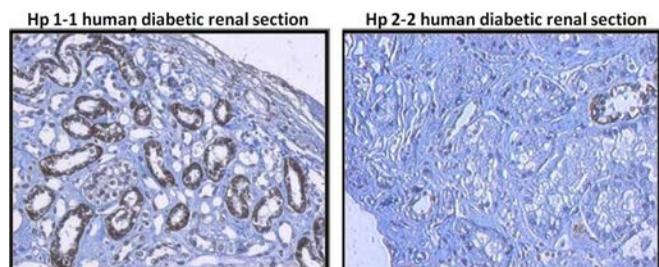
SA-PO365

Haptoglobin 2-2 Genotype Is Associated with Decreased Levels of Vitamin D Receptor (VDR), Klotho and Accelerated Renal Apoptosis in Mice and Humans Diabetic Nephropathy Farid M. Nakhoul,² Farber Evgeny,² Nadia Thawho,¹ Andy Levy,³ Inbal Dahan.¹ *¹Diabetic Nephropathy Lab, Baruch-Padeh Poriya M. Center, Lower Galilee, Israel; ²Nephrology, Faculty of Medicine In Galilee Bar Ilan Univ, Israel; ³Vascular Medicine, Technion, Haifa.*

Background: Haptoglobin (Hp) is an antioxidant protein by its ability to binds free hemoglobin (Hb) and prevents heme-iron mediated oxidation. Diabetic mice & humans with different Hp genotype (1-1, 2-2) have a different susceptibility to developed Diabetic Nephropathy (DN) due to impaired Hb clearance and increased iron deposits in the lysosomes of the kidney proximal tubules (PCT). This leading to increased renal oxidative stress and cell damage. Our study proposed a molecular mechanism explaining the influence of Hp genotype, klotho expression on 1-α hydroxylase and active vitamin D/VDR in DN patients.

Methods: Slides from kidney biopsies of DN patients and mice with different Hp genotype (1-1, 2-2) were subjected to Immunohistochemistry staining of iron modified with DAB method, klotho, active caspase 3, vitamin D receptor (VDR) and 1-α hydroxylase, using specific antibodies. Blood samples to Haptoglobin test and ELISA assays.

Results: There were significant increased in iron deposits in the renal PCT of Hp2-2 DN patients. In the PCT of Hp 2-2 mice and patients there was a significant increase expression of active caspase-3 staining that was accompanied with decrease renal expression of VDR, 1α hydroxylase and klotho levels.



Conclusions: Hp 2-2 genotype associated with increased iron deposits and high levels of PCT apoptosis. Decreased levels of the anti oxidant klotho and VDR in the renal PCT. We propose a molecular mechanism explaining the influence of Hp genotype and klotho expression on renal PCT apoptosis in DN patients. These results provide new insights into the role of Klotho and VDR expression on the pathogenesis of DN in patients with Hp2-2 genotype.

SA-PO366

Resistance Exercise Training Prevents Kidney Hypertrophy and Increases the Biogenesis Mitochondrial in Diabetic Rats Luciana Jorge,¹ Kleiton Augusto Santos Silva,¹ Rafael Luiz,¹ Rodolfo Rosseto Rampaso,¹ Janaina Paulini Aguiar,² Nestor Schor.¹ *¹Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil; ²Molecular Biology, Univ of Utah, Salt Lake City, UT.*

Background: Diabetic nephropathy(DN) is a progressive complication arising from diabetes. kidney cell response to injury includes cell division, cell hypertrophy and apoptosis. Increasing evidence indicates that the disruption of mitochondrial bioenergetics and structural change in the kidney may be important in the development and progression of DN. Therefore, is fundamental the understand of a non pharmacological intervention as exercise training to prevent those complications. We investigated the effect of resistance training(RT) on the DN pathogenesis.

Methods: Male Wistar rats were divided into: control(C), control trained(CT), diabetic(D) and diabetic trained (DT). DM was induced by STZ. Trained groups were submitted to a resistance exercise training on Ladder climb (8wk). Urinary volume and proteinuria were evaluated. Tissue weight/tibial length ratio was used as kidney hypertrophic index. Expression of P-Akt, P-Mtor, P-AMPK and MFN2 protein was evaluated by western blotting.

Results: RT improved renal parameters in DT group show a decreased urinary volume (D=160;DT=120;C=13;CT=14ml), proteinuria (D=45;DT=32;C=18;CT=7 mg/24h) (p<0.05). Diabetes resulted in increased hypertrophic index (50%) and RT prevented it. Renal expression of PAMPK and MFN2 was reduced in D group and RT normalized this expression (p<0.05). Moreover, the renal expression of PAKT and PmTOR were increased in the DM and the RT influence on it (p<0.05). Histological analysis showed glomerular hypertrophy in D and RT prevent this complication.

Conclusions: RT attenuated progression of diabetic nephropathy; Those improvements could be a result of increased AMPK/MFN2 pathway, an important pathway to biogenesis mitochondrial; and inhibition of AKT/mTOR pathway, responsible for hypertrophic response, demonstrating that those complications were prevented by exercise training. Ours findings demonstrated that RT is an important approach to avoid, both molecular and functional complications in diabetic kidney. Funds from FAPESP, CNPq and CAPES.

SA-PO367

Aerobic Exercise Training Improves Proteinuria and Renal Inflammatory Factors in Rats with Diabetic Nephropathy Rodolfo Rosseto Rampaso, Rafael Luiz, Kleiton Augusto Santos Silva, Luciana Jorge, Edson Andrade Pessoa, Mario Luis Ribeiro Cesaretti, Nestor Schor. *Nephrology, UNIFESP, SP, Brazil.*

Background: The objective of this study was to evaluate the effects of aerobic exercise training in controlling the progression of diabetic nephropathy, inflammatory factors, and its possible renoprotective effects.

Methods: Adult male Wistar rats/4 groups, n=8/group: Sedentary controls (C-SED), Diabetes+Sedentary (DM-SED), Diabetes+Exercise (DM-EXE) and control exercise (C-EXE). Diabetes was induced with STZ, 50 mg/kg iv. The exercise training were conducted on a treadmill 60min/day, 5 days/week/8 weeks. Weekly certain, maximal exercise test (set at 65-70% of MEtest). Glycemia after post 24 education (24 glycemiapt), MEtest, creatinine clearance/BW (CrCl/BW), arterial pressure (AP), proteinuria (uProt), renal inflammatory factors IL-6, IL-10 and TNF-α were measured. Data as mean ± SD.

Results:

	C-SED	DM-SED	DM-EXE	EXE
glycemiapt (mg/dl)	103±2.03	551±7.03*#	491±5.50*#	83±2.57
uProt (mg/24h)	17±0.88	46±2.05*#	18±0.72	16±0.99
CrCl/ (ml/min/BW)	5.65±0.66	5.02±0.43	4.19±0.37	4.21±0.29
AP (mmHg)	122±1.89	133.88±1.79*#	122±1.35	121±2.11
Weight (g)	455±6.00	236±14.41*#	324±9.34*#	387±8.71
MEtest (m/min)	23.2±0.49*#	19.5±0.57*#	35.1±0.97	37.5±0.57
IL-6 (pg/ml)	541±98	993±40*#	768±74*#	391±22
IL-10 (pg/ml)	545±86	876±34*#	654±31*#	453±28
TNF-α (pg/ml)	3.05±0.4	5.18±0.76*#	4.08±0.22*#	2.32±0.51
P<0.05; *VS C-SED #VS DM EXE & VS C- EXE				

Conclusions: Reductions in blood glucose and AP ~11% comparing DM-EXE vs DM-SED. The DM-EXE controlled weight loss ~40% compared to DM-SED, but did not prevent change in CrCl/BW with this protocol. However, the effect was surprisingly observed EXE reduction in both excretion through uProt ~60% and ~25% in MD-inflammatory factors comparing SED vs DM-EXE. Therefore, preliminary data suggests that aerobic exercise can reduce proteinuria and inflammatory factors in diabetic animals and hence reduce the potential effects caused by diabetic nephropathy and could reduce the progression of renal failure.

SA-PO368

Inhibition of miR-25 Processing Mediated by MeCP2 Phosphorylated by HIPK2 Can Upregulate NOX4 in Early Diabetic Nephropathy

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Background: Altered microRNA (miR) levels play key roles in the pathogenesis of diabetic nephropathy (DN), but it is unclear if miR processing is involved. Phosphorylated methyl-CpG binding protein2 (p-MeCP2), known to act as a transcriptional repressor, was recently reported to suppress the processing of several miRs. Homeo-domain interacting protein kinase2 (HIPK2) can bind to and phosphorylate MeCP2. However, it is not known if MeCP2 and HIPK2 are involved in processing and expression of candidate miRs involved in DN.

Methods: p-MeCP2 and HIPK2 staining in kidney sections from 4-week streptozotocin (STZ) injected diabetic and control mice, was studied by immunohistochemistry. Protein, mRNA and miR levels were examined by Western blotting (WB) or RT-qPCRs in TGF- β 1- or high glucose (HG)-treated mouse mesangial cells (MMCs).

Results: p-MeCP2 and HIPK2 immunostaining, and their protein levels were significantly higher in renal glomeruli (but not cortex) of STZ mice than control. Moreover, Seven in Absentia Homolog 1 (SIAH1), which mediates proteasomal degradation of HIPK2, was decreased in STZ mice compared with control. Among several regulated miRs, miR-25 and -93 levels were significantly decreased in STZ mice relative to control. The precursors of miR-25 and -93 were also significantly decreased in STZ mice, while conversely, NADPH oxidase4 (NOX4), a target of miR-25 that is associated with renal fibrosis and DN, was significantly increased in STZ mice. Protein levels of p-MeCP2 and HIPK2 were also increased in vitro in TGF- β 1- or HG-treated MMCs compared to control. Moreover, mRNA levels of the genes mentioned above in vivo were similarly regulated in MMCs in vitro, although only miR-25 and its precursor were significantly decreased in the treated MMCs.

Conclusions: NOX4, a target of miR-25, can be upregulated due to downregulation of miR-25. This occurs via impairment of miR-25 processing by p-MeCP2 phosphorylated by HIPK2 which is stabilized by decrease of SIAH1 in diabetes. These results reveal a novel mechanism for downregulation of key protective miRs during DN progression.

SA-PO369

Ursolic Acid Attenuated High Glucose Induced Podocyte Injury by Increasing Autophagy Level via Inhibition of miR-21 Expression and PTEN/Akt/mTOR Pathway

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Background: Autophagy played an important role in maintaining podocyte homeostasis. The defective autophagy might contributed to podocyte dysfunction under high glucose condition. In this study, we investigated the effects of ursolic acid (UA) on autophagy and injury of podocyte cultured with high glucose condition.

Methods: Conditionally immortalized murine podocyte were cultured in high glucose, the effect of PI3K inhibitor LY294002 and ursolic acid treatment would be observed. The autophagic inhibitor 3-MA was used to assess the effect of ursolic acid on autophagy in podocyte. The miR-21 expression was detected using RT-qPCR. The activation of PTEN-PI3K/Akt/mTOR pathway, expression of autophagy-associated protein and podocyte associated protein were determined by western blot. Immunofluorescence staining showed the expression of podocyte associated protein and endogenous accumulation of LC3. Autophagosomes were observed using electron microscopy.

Results: In the high glucose condition, high basal level of autophagy in podocyte became defective and defective autophagy facilitated the podocyte injury. miR-21 expression was upregulated, PTEN level was downregulated, PI3K/Akt/mTOR pathway was activated in podocyte cultured with high glucose. Ursolic acid and LY294002 can reduced podocyte injury by increasing autophagy level via inhibition of PI3K/Akt/mTOR pathway. However, LY294002 did not affect the expression of miR-21 and PTEN. Ursolic acid inhibited miR-21 expression and upregulated PTEN level. Downregulation of autophagy with 3-MA significantly suppressed the protective effect of ursolic acid on podocyte.

Conclusions: These data suggested that podocyte injury is associated with defective autophagy level under high glucose condition. Ursolic acid could reduce podocyte injury by increasing autophagy level via inhibition of miR-21 expression and PTEN/Akt/mTOR pathway.

SA-PO370

Hyperglycemic Memory in DN: Effects of Epigenetic Changes of SHP-1 in Podocytes

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Background: Previous animal and clinical observation suggested that disruption of normal insulin actions is a part of the etiology of diabetic nephropathy (DN). Although, intensive blood glucose control reduced the development of DN, the EDIC study showed that, if not started early, it is not sufficient to prevent DN progression. This hyperglycemic memory phenomenon can be explained by epigenetic changes. Our previous studies demonstrated that SHP-1, a protein tyrosine phosphatase, is elevated in renal cortex of type 1 diabetic mice (Akita) causing insulin unresponsiveness and DN. We hypothesize that epigenetics changes lead to persistent increase of SHP-1 expression despite systemic glucose normalization that triggers to hyperglycemic memory in DN.

Methods: The persistent expression of SHP-1 *in vivo* that contribute to hyperglycemic memory effect was evaluated using diabetic Akita (DM) mice treated with insulin implants

after 4 months of diabetes. Mouse podocytes were cultured in normal (5.6 mM; NG), high glucose concentrations (25 mM; HG) or HG prior returning glucose levels to NG for an addition 24-48h (HG+NG).

Results: Urinary albuminuria secretion, GFR, mesangial cell expansion and collagen IV expression were measured and were significantly increased by 2.3 fold, 64%, 58% and 40%, respectively in DM mice compared to non-DM mice and remained elevated despite glucose normalization with insulin implants. SHP-1 expression was increased by 2 fold in renal cortex of DM and DM mice treated with insulin implants. Elevated expression of SHP-1 mRNA, protein and phosphatase activity in HG conditions remained increased in spite returning glucose concentration to NG and associated with insulin actions inhibitions. Evaluation of histone modifications showed that monomethylation of the H3K4 (me1), which is associated with enhanced gene activity, in the promoter region of SHP-1 was increased in HG and remained elevated after returning to NG concentration.

Conclusions: In conclusion, hyperglycemia induces epigenetic changes on SHP-1 promoter causing persistent expression and elevated activity of SHP-1 leading to podocyte unresponsiveness to insulin and DN.

Funding: Government Support - Non-U.S.

SA-PO371

Targeting the Polycomb Repressive Complex Chromatin Remodeling Machinery for Therapeutic Benefit in Diabetic Nephropathy

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Background: Diabetic Nephropathy (DN) manifests as renal microvascular abnormalities, mesangial sclerosis and tubulointerstitial fibrosis as a result of longstanding hyperglycaemia. Emerging evidence indicates that multiple factors involved in the aetiology of diabetes can alter epigenetic mechanisms and regulate susceptibility to microvascular complications.

Methods: Immunoprecipitation, ChIP, Western Blot, miR302 overexpression, luciferase assay.

Results: We have previously identified SMAD3 and EZH2 as part of a context dependent switch enhancing complex that regulates cell fate during fibrotic processes. Here we describe the further characterisation of this interaction and delineate its potential pathogenic significance. Comparative analysis of gene expression data from patients, animals and cell models of diabetic kidney disease revealed a subset of genes that are potentially regulated by the interaction between Smad3 and EZH2, including critical regulators of epithelial fate such as E-Cadherin. Endogenous immunoprecipitation and luciferase assays performed in renal epithelial cells demonstrated that SMAD3 directly binds and recruits EZH2 to the E-Cadherin promoter causing its down-regulation during Epithelial to Mesenchymal Transition. We further demonstrated that this interaction is disrupted by mutating SMAD3 protein sequence. Perturbation of the interaction between SMAD3 and EZH2 was facilitated by viral overexpression of miR302. Human renal mesangial cells transduced with miR302 undergo profound changes in gene expression exhibiting de novo expression of SNAI1 and EZH2 and start to express de novo E-Cadherin.

Conclusions: Our results suggest that SMAD3 and EZH2 control the repression of E-Cadherin during DN, opening the possibility for therapeutic manipulation of this nexus during the progression of renal disease. Understanding the processes through which dynamic epigenetic silencing is controlled in adults cells will allow us to address the epigenetic state of acquired disease and whether original states, regenerative in nature, can be restored with therapy.

Funding: Government Support - Non-U.S.

SA-PO372

Effects of DPP4 Inhibitor versus Combined Treatment with DPP4 Inhibitor and ARB on Renal Function in Type 2 Diabetic Mice

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Background: Recent evidence has shown that DPP4 is involved in all steps leading to renal fibrosis, such as inflammatory response, cell apoptosis and fibrosis. The aim of our study was to investigate the mechanism and effects of DPP4 inhibitor (DA1229) alone and combined treatment with DPP4 inhibitor and ARB (LC158809) on renal injury in db/db mice.

Methods: The mice were divided into five groups as follows: non-diabetic db/m mice (control), untreated db/db mice, db/db mice treated with DA1229 (300mg/kg/d), db/db mice treated with LC158809 (1.5mg/kg/d) and db/db mice combined treatment with DA1229 and LC158809 for 12 weeks.

Results: 12week HbA1c level was significantly decreased in combined treatment group. Oxidative stress markers were not different from each other. Activity of serum DPP4 was significantly reduced with DA1229. 24h albuminuria significantly decreased with LC158809 treatment at 8 weeks and with DA1229 at 12 weeks in diabetic mice. However, no additive effect on albuminuria was observed with combined treatment. Administration of DA1229 or LC158809 significantly decreased accumulation of ECM protein, TLR4 and NOX4 expressions in glomeruli. No additive effects were observed in combined treatment group. Urinary excretion of nephrin was increased in diabetic mice and was decreased in combined treatment with DA1229 and LC158809. *In vitro*, DPP4 was expressed on the

podocyte membrane and its expression was activated by angiotensin-II. Nephron expression in cultured podocyte was attenuated by high glucose and angiotensin-II. This attenuation was recovered with DA1229 treatment, but not with other DPPIV inhibitors.

Conclusions: Our data suggest that renoprotective effects of DA1229 in experimental diabetic mice might be associated with protective effect of podocyte injury. DA1229 might be a potential therapeutic agent to slow the progression of diabetic nephropathy.

SA-PO373

PBI-4425, a Novel Anti-Inflammatory/Fibrotic Compound, Improves Kidney Function and Structure in the Diabetic db/db Mouse Model
Brigitte Grouix, Kathy Hince, François Sarra-Bournet, Liette Gervais, Alexandra Felton, Alexandre Laverdure, William Gagnon, Martin Leduc, Lilianne Geerts, Pierre Laurin, Lyne Gagnon. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: Kidney disease associated with diabetes mellitus is a major health problem worldwide. Glomerular injury plays a pivotal role in the development of diabetic nephropathy. PBI-4425 possesses a pleiotropic mechanism of action with anti-inflammatory, antioxidant and anti-fibrotic properties. The aim of this study was to investigate the protective effect of PBI-4425 on kidney function and structure in uninephrectomized (NX) diabetic (db/db) mice.

Methods: Total nephrectomy of the right kidney was performed on day 0 and animals were treated with vehicle or PBI-4425 (100 mg/kg, oral once a day) from day 1 through 105. Kidney function (GFR), kidney mesangial lesions, modulation of gene expression, and serum cytokines were investigated.

Results: GFR assessed by inulin clearance was significantly reduced in NX-db/db mice compared to NX-C57BL/6 negative control mice, and PBI-4425 treatment significantly improved GFR. As shown by PAS staining, NX-db/db mice had larger glomeruli with increased mesangial matrix. Mesangium lesions scores were significantly reduced by PBI-4425 treatment. Gene expression of inflammation, fibrosis, oxidative stress, and extracellular matrix remodeling markers were assessed. Kidney MCP-1, IL-6, Collagen I, iNOS, MMP2, and Timp1 mRNA expression were markedly increased in NX-db/db mice, and PBI-4425 treatment induced a significant decrease of these markers. Glomerular response to injury was accompanied by activation of kidney development-related genes, such as glomerular epithelial protein 1 (GLEPP1); expression of GLEPP1 was significantly increased in NX-db/db mice, and restored to the negative control level following treatment with PBI-4425. Moreover, PBI-4425 significantly reduced serum pro-inflammatory cytokines IL-1 β , IL-6, IL-12(p70), as well as TH9-type pro-inflammatory cytokine IL-9.

Conclusions: These results suggest that PBI-4425 offers the potential as a novel therapy for diabetic nephropathy by improving kidney function and structure, and reducing pro-inflammatory and pro-fibrotic markers.

SA-PO374

The Effect of Nox Inhibitor APX-15 on Diabetic Kidney Disease
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Background: Excess reactive oxygen species generated by NADPH oxidases (Nox) have been implicated in the inflammatory and fibrotic processes of chronic kidney disease. Recent studies have suggested the importance of renal Nox in the progression of diabetic nephropathy. Therefore, we investigated the effect of a novel NOX-inhibitor APX-15 on diabetic nephropathy in an experimental model of type 2 diabetic mice.

Methods: 8 to 10 week old db/db and db/db mice were treated with APX-15 for 12 weeks. APX-15 was administered by oral gavage at a dose of 60mg/kg/day. To compare the effects of APX-15 with a selective Nox inhibitor, db/db mice were treated with GKT136901 according to same protocol.

Results: APX-15 significantly improved insulin resistance in diabetic mice similar to GKT136901. Oxidative stress measured by plasma 8-isoprostane level was decreased in APX-15 group compared to diabetic control. All lipid profiles, both in plasma and tissues (kidney, fat, liver) improved with Nox inhibition. Nox mRNA expressions in adipose tissue (Nox1, Nox2) and in kidney tissue (Nox4) were downregulated and Nox protein expressions were decreased with APX-15. 24 hour urinary albumin excretion was reduced and creatinine clearance was preserved with APX-15. In diabetic kidney, structural changes were notably attenuated with APX-15. Importantly, mesangial expansion was significantly improved with APX-15, but not with GSK 136901. Kidney PAI-1 and TGF- β expressions were decreased and nephron expression increased in both APX-15 and GKT136901 groups compared to diabetic control. Additionally, F4/80 infiltrations in the adipose tissue and the kidney were decreased with APX-15.

Conclusions: Our findings suggest that APX-15 may have a better renoprotective effect compared to selective inhibitor GKT136901 in experimental animal model of diabetic nephropathy. Broad Nox inhibition with APX-15 might be a promising therapy for diabetic nephropathy.

SA-PO375

Metabolomics Reveals a Key Role for Fumarate in Mediating NOX4 Activity in Diabetic Kidney Disease
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Background: The NADPH oxidase isoform NOX4 has been linked with diabetic kidney disease (DKD), however a mechanistic understanding of the downstream effects of NOX4 remains to be established.

Methods: To clarify the role of increased NOX4, we examined the role of NOX4 in the podocyte-specific NOX4 transgenic mouse. We also treated F1 Akita (DBA/2J \times C57BL/6J-*Ins2^{AKita}*) mice with food pellets containing GKT137831, a NOX1/4 inhibitor from week 12 to week 28, and examined the effectiveness of treatment with the NOX1/4 inhibitor on the development of chronic kidney disease (CKD) and on the urine metabolome in a model of progressive DKD.

Results: Podocyte-specific induction of NOX4 in vivo was sufficient to recapitulate the characteristic glomerular changes noted with DKD, including glomerular hypertrophy, mesangial matrix accumulation, GBM thickening, albuminuria, and podocyte dropout. Intervention with a NOX1/4 inhibitor reduced albuminuria, glomerular hypertrophy, and mesangial matrix accumulation in the F1 Akita model of DKD. Metabolomic analysis from the mouse studies revealed that TCA related urinary metabolites were increased in DKD however fumarate levels were uniquely reduced by the NOX4 inhibitor. TCA cycle enzyme fumarate hydratase (FH) reduction has been linked to regulating urine fumarate and indeed, FH was reduced in the diabetic kidney (in mice and human tissue) and the Nox4 inhibitor increased FH levels. Induction of Nox4 both in vitro and in the podocyte-specific NOX4transgenic mouse led to reduced FH levels. The potential role of fumarate to DKD was demonstrated as fumarate was found to stimulate ER stress, matrix gene expression and regulate HIF-1 α and TGF- β .

Conclusions: Our data suggest that NOX4 is a major mediator of glomerular dysfunction with diabetes and renal FH is a key enzyme regulated in DKD and targeted by NOX4. Fumarate is a key link that connects metabolic pathways to DKD pathogenesis and may have application to monitor renal NOX4 activity.

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SA-PO376

The Prostaglandin E2 EP3 Receptor Regulates Diet Induced Obesity
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Background: Obesity is associated with a number of co-morbidities including diabetes, dyslipidemia and nonalcoholic fatty liver disease. Deletion of the PGE₂ E-prostanoid (EP) 3 receptor in mice has been shown to alter feeding patterns and increase food consumption.

Methods: To further characterize the effects PGE₂-EP3 signaling on diabetes in a setting of diet induced obesity, EP3^{-/-} mice were fed a high-fat diet (HFD; 45% calories from fat) or a control diet (10% calories from fat).

Results: Though no differences in body weight were observed in mice fed control diet, when fed a HFD, EP3^{-/-} mice became heavier relative to EP3^{+/+} mice (41.1 \pm 1.10 vs. 32.6 \pm 0.98 g; P<0.0001). EP3^{-/-} mice fed HFD had increased epididymal fat mass (1407 \pm 177 vs. 2401 \pm 167 mg; P<0.0001) and adipocyte size (6350 \pm 375 vs. 4330 \pm 469 μ m²; P=0.0005) compared to HFD fed EP3^{+/+} mice; paradoxically a relative decrease in both epididymal fat pad mass (P < 0.0001) and adipocyte size (P=0.0055) was observed in the heaviest EP3^{-/-} mice. EP3^{-/-} mice had increased macrophage infiltration (P<0.0001) and necrosis (P < 0.0001) in epididymal fat pads as compared to EP3^{+/+} mice. Adipocytes isolated from EP3^{-/-} mice lacked PGE₂-evoked inhibition of isoproterenol-stimulated lipolysis compared to EP3^{+/+} (1 nM ISO, \pm 100nM PGE₂; EP3^{+/+}: 10.2 \pm 1.14 vs. 4.4 \pm 1.84, P = 0.0036; EP3^{-/-}: 11.8 \pm 1.20 vs. 10.3 \pm 0.68 nmol glycerol/10,000 cells, P=0.9999). EP3^{-/-} mice fed HFD had ectopic lipid accumulation in skeletal muscle (7.5 \pm 1.24 vs. 17.7 \pm 1.82 mg triglyceride/mg; P<0.0001) and liver (14.6 \pm 2.83 vs. 78.5 \pm 13.0 mg triglyceride/mg; P<0.0001), with evidence of hepatic steatosis. When fed HFD, EP3^{-/-} mice became hyperglycemic (107 \pm 8.80 vs. 158 \pm 7.14 mg/dl; P<0.0001) and hyperinsulinemic (0.598 \pm 0.079 vs. 1.55 \pm 0.241 ng/ml; P<0.0001) when compared to EP3^{+/+} fed HFD, demonstrating a more severe insulin resistance phenotype in EP3^{-/-} (4.77 \pm 0.931 vs. 18.1 \pm 3.50 HOMA-IR; P<0.0001).

Conclusions: These results demonstrate that when fed a HFD, EP3^{-/-} mice have abnormal lipid distribution, developing excessive ectopic lipid accumulation and associated insulin resistance.

Funding: NIDDK Support, Veterans Administration Support

SA-PO377

Resveratrol Activates Renal Expressions of Adiponectin Receptor 1 and 2 in db/db Mice
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Background: Adiponectin is an adipocyte-derived adipokine that binds to adiponectin receptors (AdipoR) and exhibits antidiabetic effects via activation of AMPK and PPAR- α . Our previous study investigated the renoprotective role of resveratrol by decreasing lipotoxicity and inhibiting mesangial cell glucotoxicity in a manner dependent on the AMPK-SIRT1-PGC1 α axis in diabetic mouse model. The common pathway shared by both substances instigated us to explore the favorable effect of resveratrol on renal physiology through the activation of AdipoR.

Methods: Male *db/db* mice at 8 weeks of age were fed resveratrol (20 mg/kg/day) via gavage for 12 weeks. Serum, urine and renal tissue were obtained to analyze for changes in metabolic parameters, molecular levels and renal structure.

Results: Resveratrol treatment showed favorable effects on albuminuria, glomerular matrix expansion and inflammatory cell infiltration. Increased expressions of AdipoR1 and AdipoR2 were observed with increases in phosphorylated AMPK and PPAR- α level. It also ameliorated free fatty acid and triacylglycerol accumulation in the kidney which was related to increases in the phosphorylation of AMPK and the activation of SIRT1-PGC-1 α signaling and of the key downstream effectors, the PPAR- α -Forkhead box O (FoxO)1/FoxO3a-oestrogen-related receptor (ERR)-1 α -sterol regulatory element-binding protein 1 (SREBP1)/acetyl coenzyme A carboxylase (ACC). Furthermore, resveratrol increased eNOS phosphorylation and Bcl-2/Bax ratio which were associated with decreased apoptotic cells and oxidative stress as reflected by renal 8-hydroxy-deoxyguanosine (8-OH-dG) and urinary 8-OH-dG and isoprostane concentrations. Resveratrol prevented high-glucose-induced oxidative stress and apoptosis in cultured human glomerular endothelial cells (HGECS) through activation of both AdipoR and subsequent phosphorylation of AMPK and the downstream effectors.

Conclusions: In conclusion, our results suggest that resveratrol exerts its renoprotective effects through activation of both AdipoR which prevent lipotoxicity related apoptosis and oxidative stress in the kidney.

SA-PO378

Oral Treatment with PBI-4547, a Novel Anti-Diabetic and Anti-Fibrotic Compound, Ameliorates Kidney Function and Glomerular Integrity in the Diabetic *db/db* Mouse Model Martin Leduc, Brigitte Groulx, Kathy Hince, Alexandra Felton, François Sarra-Bournet, Liette Gervais, William Gagnon, Alexandre Laverdure, Mikael Tremblay, Marie-Pier Cloutier, Pierre Laurin, Lyne Gagnon. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: Diabetic nephropathy is the most common complication of longstanding diabetes affecting up to 30% of all diabetic patients, and is the main cause of end-stage kidney disease. This study examined the long-term nephroprotective effects of PBI-4547 in uninephrectomized (NX) diabetic (*db/db*) mice, a model of type 2 diabetes.

Methods: Total nephrectomy of the right kidney was performed on day 0 and animals were treated with vehicle or PBI-4547 (10 and 50 mg/kg, oral once a day) from day 1 through 105. Kidney function (GFR) and structure (mesangium lesions, glomerular integrity), regulation of pro-inflammatory/fibrotic gene expression in the kidney, as well as serum pro-inflammatory cytokine levels were examined.

Results: Kidney function assessed by GFR was significantly reduced in NX-*db/db* mice compared to NX-C57BL/6 negative control animals, and PBI-4547 treatment significantly improved GFR in NX-*db/db* mice. As shown by PAS staining, mesangial matrix accumulation/expansion was prominent in NX-*db/db* mice compared to the negative control, but was significantly suppressed in PBI-4547-treated NX-*db/db* mice. Moreover, qPCR analysis of the expression of MCP-1, IL-6, Collagen I, MMP2, Timp1, and iNOS showed that PBI-4547 downregulated diabetes-induced inflammation, fibrosis, oxidative stress, and extracellular matrix remodeling in the kidney. Expression of GLEPP1 was significantly increased in NX-*db/db* mice, and restored to the negative control level following treatment with PBI-4547. Serum levels of cytokines were measured (multiplex panel). Early/innate TNF- α , IL-1 β , and IL-6 cytokines were markedly reduced by PBI-4547, as well as TH1-type IL-12p70, IFN γ , IL-2 cytokines, and TH2-type IL-4, IL-5, IL-13 cytokines. TH9-type pro-inflammatory cytokine IL-9 was also decreased.

Conclusions: These results suggest that PBI-4547 is a potential novel therapy for diabetic nephropathy by improving kidney function and structure, and reducing pro-inflammatory and pro-fibrotic markers.

SA-PO379

Prostaglandin E2 Receptor 3 (EP3) Inhibits Vasopressin-Stimulated Water Reabsorption and Contributes to Diabetic Renal Dysfunction in Mice Ramzi Hassouneh, Rania Nasrallah, Joe A. Zimpelmann, Kevin D. Burns, Richard L. Hébert. *Kidney Research Centre, Cellular and Molecular Medicine, Univ of Ottawa, Ottawa, ON, Canada.*

Background: The early renal manifestations of diabetes are polyuria and reduced urine osmolality (Uosm), and when sustained long-term lead to nephropathy. We propose that these processes are mediated through the interaction of prostaglandin E2 (PGE2) acting via EP3 and the anti-diuretic hormone, vasopressin (VP).

Methods: Global EP3^{-/-} and wild-type (WT) 8wk male C57BL6 mice were injected with vehicle or streptozotocin (STZ) and analyzed after 12wks. Glomerular filtration rate (GFR) was measured by inulin clearance. Aquaporin (AQ) 1/2 and cyclooxygenase-2 (COX-2) were assessed by Western blotting. PAS stain was done to assess renal injury on paraffin sections. 24hr urinary VP excretion rate was quantified. Cortical collecting ducts (CCD) were microdissected for in vitro perfusion and stimulated with VP and sulprostone (SLP; EP3/1 agonist). 3H-inulin was used as a volume marker to measure net water reabsorption (Jv).

Results: EP3^{-/-} STZ show decreased polyuria, hyperfiltration, CCD injury, and VP levels compared to STZ. EP3^{-/-} STZ show increased Uosm compared to STZ. Cortex AQP2 and medulla AQP1/2 are decreased by 50% in STZ and restored to control levels in EP3^{-/-} STZ. Cortex and medulla COX-2 was increased up to 2-fold in STZ, and attenuated in EP3^{-/-} STZ (n=5, P<0.05). VP increased Jv in all groups, and SLP reversed this effect only in WT and STZ. See table.

	WT	EP3 ^{-/-}	STZ	EP3 ^{-/-} STZ
Blood Glucose (mM)	9.03 ± 1	7.79 ± 1	27.5 ± 4*	26.9 ± 4*
Urine Glucose (mM)	2.70 ± 0.2	2.14 ± 0.2	135 ± 0.1*	136 ± 0.1*
Kidney Wt./Tibia (mg/m)	9.56 ± 0.5	10.8 ± 0.4	11.8 ± 0.5*	11.0 ± 0.3
GFR (μ l/min)	211 ± 20	240 ± 10	332 ± 10*	269 ± 20**
Urine Volume (ml/24hr)	0.570 ± 0.06	0.760 ± 0.07	29.6 ± 2*	19.8 ± 2*
Urine Osmolality (Osm/kg)	1170 ± 90	1170 ± 70	458 ± 7*	536 ± 30**
VP Excretion (pg/24hr)	207 ± 80	184 ± 30	2920 ± 300*	1810 ± 300**
CCD Area (pixels x10 ³)	1.88 ± 0.1	1.74 ± 0.1	4.21 ± 0.2*	3.65 ± 0.2**
CCD Cysts (No/image)	0.0333±0.03	0.192 ± 0.1	7.97 ± 1*	5.36 ± 1**

Jv	WT	EP3 ^{-/-}	STZ	EP3 ^{-/-} STZ
Baseline	1	1	1	1
VP	1.62 ± 0.1 ^Δ	1.63 ± 0.2 ^Δ	1.65 ± 0.2 ^Δ	1.53 ± 0.1 ^Δ
SLP	1.20 ± 0.1**	1.53 ± 0.2 ^Δ	1.11 ± 0.5**	1.51 ± 0.2 ^Δ

*P<0.05 vs WT, †P<0.05 vs EP3^{-/-}, and ‡P<0.05 vs STZ using 1 way ANOVA with Tukey's post-test. Δ P<0.05 vs Baseline and **P<0.05 vs VP using t-test. N = 5 - 10.

Conclusions: Despite elevated VP levels in STZ, the CCD response to VP stimulation was no different than in WT, while SLP inhibited VP-induced Jv in both groups. In the absence of EP3, the VP-induced Jv was unchanged by SLP, confirming the importance of EP3 in this process. During diabetes, EP3 inhibition of VP-induced Jv may lead to polyuria and a sustained increase of VP, which may be injurious to the kidney.

Funding: Government Support - Non-U.S.

SA-PO380

Effects of Diuretics on SGLT2 Inhibitor-Induced Changes in Blood Pressure and Natriuresis in Obese Rats Suffering from the Metabolic Syndrome Akira Nishiyama, Daisuke Nakano, Wararat Kittikuluth. *Dept of Pharmacology, Kagawa Univ Medical School, Kagawa, Japan.*

Background: Experiments were carried out to investigate whether diuretics (hydrochlorothiazide + furosemide) impact on the effects of a sodium-dependent glucose co-transporter 2 (SGLT2) inhibitor on glucose metabolism, blood pressure and rate of urinary excretion of sodium in metabolic syndrome SHR/NDmcr-cp(+/+) rats (SHRcp).

Methods: Male 13-week-old SHRcp were treated with: (i) vehicle; (ii) the SGLT2 inhibitor luseogliflozin (10 mg/kg/day, p.o.); (iii) diuretics (hydrochlorothiazide; 10 mg/kg/day + furosemide; 5 mg/kg/day, p.o.); or (iv) luseogliflozin + diuretics for 5 weeks (n = 5-8 for each group). Blood pressure and glucose metabolism were evaluated by a telemetry system and oral glucose tolerance test, respectively.

Results: Vehicle-treated SHRcp developed non-dipper type hypertension (dark- vs. light-period mean arterial pressure (MAP): 148.6±0.7 and 148.0±0.7 mmHg, respectively, P=0.2) and insulin resistance. Compared with vehicle-treated animals, luseogliflozin-treated rats showed an approximately 4000-fold increase in urinary excretion of glucose and improved glucose metabolism. Luseogliflozin also significantly decreased blood pressure and converted the circadian rhythm of blood pressure from a non-dipper to dipper pattern (dark- vs. light-period MAP: 138.0±1.6 and 132.0±1.3 mmHg, respectively, P<0.01), which were associated with a significant increase in urinary excretion of sodium. Addition of diuretics did not influence luseogliflozin-induced improvement of glucose metabolism and circadian rhythm of blood pressure in SHRcp.

Conclusions: These data suggest that a SGLT2 inhibitor elicits its beneficial effects on glucose metabolism and hypertension in subjects with metabolic syndrome undergoing treatment with diuretics.

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SA-PO381

SGLT2 Inhibition Slows the Progression of Diabetic Nephropathy in the *db/db* Mice Li Tang, Yuan Yuan Wu, Yufeng Huang. *Fibrosis Research Laboratory, Div of Nephropathy, Univ of Utah, Salt Lake City, UT.*

Background: It has been shown that SGLT2 inhibitor not only enhanced renal glucose excretion and lowered blood glucose (BG) but also reduced albuminuria in patients with Type 2 diabetes (T2DM). However, the renoprotective effect of SGLT2 inhibition in diabetes has not fully established.

Methods: This study sought to determine whether dapagliflozin, a selective SGLT2 inhibitor, could slow the progression of glomerulosclerosis in the uninephrectomized *db/db* mouse, a model of T2DM.

Results: Untreated uninephrectomized *db/db* mice developed progressive albuminuria and glomerulosclerosis between wks 18 and 22, associated with increased renal expression of TGFB1, PAI-1, type IV collagen and fibronectin. Treatment with dapagliflozin (1mg/kg/d) via gel diet from wks 18 to 22 did not affect body weight but reduced BG (from 573.53±21.73 to 371.14±55.02 mg/dL, P<0.05) and HbA1c levels. Of note, treatment with dapagliflozin arrested the increases in albuminuria and markers of glomerulosclerosis seen in *db/db* mice between wks 18 to 22. Renal expressions of NF- κ Bp67, MCP-1, Nox4, Nox2, and p47phox and urine TBARS levels, the markers of renal inflammation and oxidative stress, were increased during disease progression in *db/db* mice. Treatment with dapagliflozin reduced these markers. In addition, *db/db* mice had markedly increased daily water intake, urine output, urinary sodium and potassium excretion but decreased urinary osmolality. Dapagliflozin had no effects on these measurements. Interestingly, dapagliflozin

ameliorated diabetes-induced glomerular hyperfiltration determined by elevated creatinine clearance rates (2.44±0.55 ml/min in treated db/db vs. 3.72±0.63 ml/min in db/db) and caused a significant reduction in renal RAS activity determined by urinary aldosterone levels (45.5±4.93 vs. 60.9±4.01, µg/24h, P<0.05).

Conclusions: These results suggest that SGLT2 inhibitor not only reduces albuminuria but also slows the progression of the glomerulosclerosis resulting from T2DM by improving hyperglycemia and renal inflammation and oxidative stress. Decreasing glomerular hyperfiltration and negatively regulating renal RAS activity by SGLT2 inhibitor may be also renoprotective.

Funding: Pharmaceutical Company Support - AstraZeneca R&D

SA-PO382

Effect of SGLT2 Inhibitor Ipragliflozin on Urinary Na Excretion and Body Fluid Volume Takahiro Masuda,¹ Yuko Watanabe,¹ Minami Watanabe,¹ Keiko Fukuda,¹ Akira Onishi,³ Hermann Koespell,² Volker Vallon,³ Daisuke Nagata,¹ ¹*Div of Nephrology, Department of Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan;* ²*Univ of Würzburg, Germany;* ³*Univ of California and VA San Diego Healthcare System, San Diego, CA.*

Background: Sodium-glucose cotransporter (SGLT) 2 inhibitors are new antidiabetic drugs that increase urinary glucose excretion (UGE) by inhibiting renal SGLT2. SGLT2 inhibitors may induce body fluid reduction due to the increase in urine volume and Na excretion, but the details remain unclear.

Methods: Spontaneously Diabetic Torii (DM) rat, a non-obese type 2 diabetic model was used in this study. At the onset of diabetes (blood glucose ≥ 250 mg/dl), DM rats and age-matched Sprague-Dawley (non-DM) rats were separated to vehicle (Veh) and 0.01% (in diet) Ipragliflozin (Ipra) group, respectively. After 8 weeks, bioimpedance spectroscopy (ImpediVet) for the assessment of total body water, urine collection and blood tests were performed.

Results: Renal membrane protein expression of SGLT2 was significantly higher in DM rats compared with non-DM rats. Ipra enhanced the expression of SGLT2 in non-DM rats, but not in DM rats. Ipra did not change plasma glucose in non-DM rats (Veh 172±11 vs. Ipra 158±5 mg/dl, P=0.12), but significantly decreased in DM rats (681±21 vs. 361±22 mg/dl, * P<0.05). Ipra increased fractional glucose excretion in non-DM rats (0.3±0.2 vs 31.3±2.1 %) and DM rats (31.5±1.7 vs. 52.9±3.2 %*). In non-DM rats, Ipra increased urine volume (36±7 vs. 61±5 ml/day*), UGE (0.03±0.01 vs. 4.8±0.2 g/day*), urinary Na excretion (3.0±0.4 vs. 4.2±0.3 mEq/day*), food intake (31±1 vs. 34±1 g/day*) and fluid intake (61±9 vs. 87±8 ml/day*). These parameters were higher in DM rats than in non-DM rats, but Ipra did not significantly change these parameters. Total body water (related to body weight) and fluid balance (fluid intake-urine volume) were similar among the 4 groups.

Conclusions: SGLT2 inhibition did not induce sustained changes in body fluid volume in DM or non-DM rats. In non-DM rats given Ipragliflozin, the increase in fluid intake might maintain fluid balance in response to the osmotic diuresis whereas the natriuresis is likely due to greater food intake.

Funding: Government Support - Non-U.S.

SA-PO383

Up-Regulated SglT2 Reduces Proximal Tubular Sirt1 and Augments Renal Gluconeogenesis in Early Stage Diabetic Nephropathy Hiroyuki Umino, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. *Keio Univ.*

Background: We previously reported that high glucose (HG) decreases proximal tubule (PT) Sirt1 prior to decreasing glomerular Sirt1, which leads to a disruption of tubule-podocyte communication in diabetic nephropathy (DN) (Nat Med 2013). Protein expression levels of SglT2 are elevated to compensate for the increased demand for glucose uptake in DN, which causes a rise in intracellular HG in PT. Here, we investigated whether SglT2-mediated HG down-regulates PT Sirt1.

Methods: Cultured PTs (HK2) were cultivated on a two-chamber-system consisting of an upper chamber equivalent to the ureteral lumen on the apical side of PTs and a lower chamber corresponding to the vascular lumen on the basolateral side of PTs. PTs were cultured with combinations of normal glucose (NG) or HG in each chamber to determine the polarity of HG that affects SglT2 and Sirt1 expression. We also administered a SglT2 inhibitor (canagliflozin) to 8-week-old db/db mice and analyzed the SglT2 and Sirt1 expression.

Results: HG in the lower chamber increased SglT2 and decreased Sirt1 expression, but HG in the upper chamber had no effect. Thus, high blood sugar (BS), but not glucosuria regulates SglT2 and Sirt1. Furthermore, in db/db mice, high BS also elevated SglT2 and lowered Sirt1 expression in PTs, as confirmed by immunofluorescence and immunoelectron microscopy, and reduced deacetylation of Foxa2, a Sirt1 target. Decreased Sirt1 expression led to an increase in Foxa2 acetylation, which induces gluconeogenesis. Results from DNA microarrays and confirmatory real-time PCR using laser-microdissected db/db PTs showed an increase in Pck1 and G6Pase in concert with SglT2 upregulation and Sirt1 downregulation. However, SglT2 inhibitors blocked these changes.

Conclusions: Increased SglT2 expression, already seen in the early stage of DN, forms a vicious cycle whereby both exogenous HG, mediated by a SglT2-induced influx of BS, and endogenous HG, generated by Foxa2-induced renal gluconeogenesis, reduce PT Sirt1 levels. Decreased Sirt1 acetylates and activates Foxa2, further promoting renal gluconeogenesis, which accelerates this cycle. However, SglT2 inhibitors can block the HG-induced reduction in Sirt1 levels and prevent DN progression.

SA-PO384

Characterization of Aged Mice Lacking SGLT2 Yiling Fu, Falk Bernhard Batz, Akira Onishi, Aleksandra Novikov, Panai Song, Volker Vallon. *Div of Nephrology, UC San Diego & VA San Diego Healthcare System, La Jolla, CA.*

Background: SGLT2 inhibitors have recently been approved in type 2 diabetes and long-term clinical trials are ongoing to further establish efficacy and safety. Humans with familial renal glycosuria due to mutations in SGLT2 do not show signs of general renal tubular dysfunction or other pathological changes, and they seem to have normal life expectancies. Here we compared the phenotype of non-diabetic aged male mice (at 24 months) that lack SGLT2 (*SglT2*^{-/-}) with their wild-type littermates (WT).

Methods: In awake mice, blood pressure (BP) and heart rate (HR) was measured by an automatic tail-cuff system and GFR by FITC-inulin plasma eliminations kinetics.

Results: Out of initially 11 *SglT2*^{-/-} and 14 WT, 2 mice per genotype died for unknown reasons before reaching an age of 24 months; thus 9 *SglT2*^{-/-} and 12 WT mice were analyzed. Consistent with results previously reported in young adult mice (3-5 months): aged *SglT2*^{-/-} and WT showed similar body weight (33.6±0.6 vs 32.1±0.9 g), blood glucose (105±6 vs 116±10 mg/dl), and GFR (329±36 vs. 370±20 µl/min); *SglT2*^{-/-} had higher urinary glucose excretion (381±71 vs 5±1 µmol/mg creatinine) associated with higher intake of food (3.8±0.1 vs 3.2±0.1 g/day) and fluid (8.9±0.2 vs 5.1±0.1 ml/day) and smaller adipocytes in subcutaneous and epididymal fat tissue (4790±446 vs 6348±130 and 8093±890 vs 11811±778 µm²/each P<0.01); urine pH was similar (6.2±0.1 vs 6.5±0.2) and no bacterial growth detected in bladder urine. Different from previous findings in young adult mice: aged *SglT2*^{-/-} had modestly higher kidney weight (15.4±0.9 vs 12.6±0.4 µg/g body wt), BP (105±2 vs 95±1 mm Hg) and HR (660±7 vs 625±9 1/min) than WT and lower hematocrit (38.1±1.0 vs 41.3±0.4% (each P<0.01)).

Conclusions: Aged *SglT2*^{-/-} mice show many of the expected phenotypes previously observed in young adult mice, and have preserved GFR and no evidence for ascending bacterial infections. An increase in kidney weight has previously been reported in 7.5 months old *SglT2*^{-/-} mice. Further analyses aim to better understand the latter findings and the observed modest changes in BP and hematocrit.

Funding: NIDDK Support

SA-PO385

Renal Secretion of the SGLT2 Inhibitor Empagliflozin and Rightward Shift in Its Glucosuric Response Curve in Mice Lacking OAT3 Yiling Fu,¹ Akira Onishi,¹ Panai Song,¹ Falk Bernhard Batz,¹ Eric W. Mayoux,² Volker Vallon.¹ ¹*Div of Nephrology, UC San Diego & VA San Diego Healthcare System, La Jolla, CA;* ²*Boehringer Ingelheim, Biberach, Germany.*

Background: SGLT2 inhibitors, like empagliflozin (EMPA), may reach their target in the brush border of the early proximal tubule through nephron filtration and tubular secretion. The organic anion transporter OAT3 in the basolateral membrane of the proximal tubule contributes to secretion.

Methods: Renal ³H-inulin clearance studies were performed in wild-type (WT) mice to characterize the renal handling of EMPA. EMPA was given in diet for 3 weeks (~30mg/[kg body wt x day]) ± i.p. bolus (10 mg/kg 1 hr before study). EMPA was determined by LC/MS/MS. Mean fractional protein binding of empagliflozin in mouse plasma is constant over a wide range (up to >=50µM) at 88.1 ±/− 0.5%. b) Metabolic cage studies were performed in mice lacking OAT3 and WT littermates; EMPA (0.3-30 mg/kg) or vehicle was applied i.p. together with an oral water load (30 ml/g bw) and the urine quantitatively collected over 3 hours to determine the glucosuric response.

Results: Comparing freely filtered and excreted amounts of EMPA revealed a fractional renal excretion of ~300-500 % for free plasma concentrations in the range of 1-2 nM (with chronic application in diet, which is close to the IC50 for mouse SGLT2) to 20-22 nM (with additional bolus application), indicating that 2/3 or more of the renal excretion of EMPA derived from renal secretion. B) OAT3^{-/-} showed a small but significant rightward shift in the glucosuria response curve to EMPA (ED50 ~6 vs. 3 mg/kg in WT; with significantly lower glucosuria at 1, 3, and 10 mg/kg (P<0.05), whereas vehicle/0.3 mg/kg and 30 mg/kg induced similar minimal and maximal glucosuria, respectively (n=9-19/dose).

Conclusions: The SGLT2 inhibitor empagliflozin is secreted by the kidney; this may involve OAT3 in the early proximal tubule whose activity is a determinant of the acute glucosuric effect of EMPA.

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SA-PO386

SGLT Inhibition Significantly Increases Oxygen Consumption of the Medullary Thick Ascending: A Modeling Study Anita T. Layton,¹ Volker Vallon,² Aurelie Edwards,³ ¹*Mathematics, Duke Univ, Durham, NC;* ²*Medicine and Pharmacology, Univ of California San Diego, La Jolla, CA;* ³*Centre National de la Recherche Scientifique, Paris, France.*

Background: The objective of this study was to investigate how changes in sodium reabsorption in the proximal tubule affect oxygen (O₂) consumption and the metabolic efficiency of the nephron.

Methods: To do so, we developed a detailed mathematical model of solute transport in a short-loop nephron of the rat kidney. Glucose is reabsorbed via sodium-glucose cotransporters (SGLTs) in the proximal tubule, which expresses the isoform SGLT2 in S1-S2 and the isoform SGLT1 in S3. We used the model to investigate the effect of inhibiting SGLT2, a novel treatment for reducing proximal tubule glucose uptake in diabetes, on renal Na⁺ transport and renal oxygen consumption (Q_{O₂}).

Results: Inhibiting SGLT2 shifts Na⁺ transport to downstream nephron segments, possibly increasing their Q₀₂. Of particular concerns are the S3 segment and medullary thick ascending limb (mTAL), which are at risk for hypoxic injury. Dual SGLT1-SGLT2 inhibition protects the S3 segment, but could further reduce mTAL oxygenation. Model simulations suggest that SGLT2 inhibition substantially increases S3 Q₀₂. Together with elevated membrane expression of Na-K-Cl cotransporter (NKCC2), SGLT2 inhibition also increases mTAL Q₀₂. Additionally, we used the model to determine the optimal combination of SGLT1 and SGLT2 inhibition, in terms of suppressing tubular glucose uptake and maintaining sufficiently low S3 and mTAL Q₀₂.

Conclusions: In conclusion, SGLT inhibition significantly increases oxygen consumption of the mTAL. This research was supported in part by NIH grant DK-89066.
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SA-PO387

SGLT2 Expression Is Increased in Human Diabetic Nephropathy: SGLT2 Inhibition Decreases Renal Lipid Metabolism, Inflammation and the Development of Nephropathy in Diabetic Mice Xiaoxin Wang,¹ Jonathan Levi,² Yuhuan Luo,¹ Evgenia Dobrinskikh,¹ Almut Grenz,¹ Michal Herman-Edelstein,³ Uzi Gafter,³ Avry Chagnac,³ Hermann Koepsell,⁴ Jeffrey B. Kopp,² A. Rosenberg,² Moshe Levi.¹ ¹Univ of Colorado Denver; ²NIDDK; ³Rabin Medical Center; ⁴Univ of Wurzburg.

Background: The renal sodium gradient dependent glucose transport protein SGLT2 expression is increased in renal biopsies from human subjects with diabetic nephropathy.

Methods: To determine the potential mechanisms of beneficial effects of SGLT2 inhibition in progression of diabetic renal disease we treated db/db mice with a selective SGLT2 inhibitor.

Results: We found that SGLT2 inhibition caused marked decreases in systolic blood pressure, kidney weight/body weight ratio, urinary albumin (745±36 mg/g in db/db vs. 207±5 mg/g in treated db/db, p<0.001) and urinary thiobarbituric acid-reacting substances (TBARS). SGLT2 inhibition also a) prevented renal lipid accumulation via inhibition of LPK, SCD-1 and DGAT1, key enzymes that mediate fatty acid and triglyceride synthesis, b) decreased inflammation via inhibition of CD68 macrophage accumulation, and expression of p65, TLR4, MCP-1 and OPN, and c) increased CD73 and decreased adenosine A receptors Adora1, Adora2a, and Adora2b mRNA. These effects were associated with prevention of mesangial expansion, accumulation of extracellular matrix proteins fibronectin and type IV collagen, as well as loss of podocyte markers WT1 and synaptopodin, as determined by quantitative immunofluorescence microscopy.

Conclusions: In summary, our study showed that SGLT2 inhibition modulates renal lipid metabolism and inflammation and prevents the development of nephropathy in db/db mice.

Funding: Pharmaceutical Company Support - J&J

SA-PO388

Loss of Angiotensin-Converting Enzyme 2 Alters Glomerular Structure in Non Obese Diabetic Mice Heleia Roca-Ho,¹ Marta Riera,¹ Marta Rebull,¹ Javier Gimeno,² Julio Pascual,¹ Maria Jose Soler.¹ ¹Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona; ²Pathology, Hospital del Mar, Barcelona.

Background: ACE2 has been shown to play an important role in diabetic nephropathy (DN). We studied renal morphology and kidney function in non-obese diabetic(NOD) female mice (with spontaneous autoimmune diabetes) carrying a deletion on ace2 gene(NOD.ACE2^{-/-} and NOD.ACE2^{+/-} after 30days of diabetes (DOD). Non obese resistant strain (NOR.ACE2^{-/-} and NOR.ACE2^{+/-}) was used as control mice.

Methods: To evaluate kidney function urinary excretion of albumin(UAE) and glomerular filtration rate(GFR) were calculated.UAE was determined on spot urine collections. GFR was measured using clearance kinetics of plasma FITC-inulin after 75min of a single bolus injection on conscious mice (N=6-13 animals/group). Paraffin embedded kidney sections were obtained. 20glomeruli were randomly selected for each animal. To assess renal morphology, PAS staining was performed. The extent of extracellular mesangial matrix was identified by PAS-positive material in the glomerulus and factored by the glomerular tuft area. Area calculations were performed using ImageJ software. To assess podocyte number in glomerular tuft, WT-1 staining was performed.

Results: NOD.ACE2^{-/-} mice showed glomerular area increase, mesangial matrix expansion and podocyte loss as compared to NOR.ACE2^{-/-} age matched mice. UAE was increased in both diabetic NOD mice, without differences among them. Interestingly, GRF was found decreased in NOD.ACE2^{-/-} showing a tendency for GFR decrease as compared to NOD.ACE2^{+/-}.

GROUP	UAE (µg Alb/mg Crea)	GFR (µL/min)	GLOMERULAR AREA (µm ²)	MESANGIAL AREA (µm ²)	PODCYTE NUMBER
NOR.ACE2 ^{+/-}	17.6±4.0	29.4±4.1	3213.6±226.6	975.3±78.2	12.1±0.5
NOR.ACE2 ^{-/-}	19.9±3.7	29.3±5.1	3220.3±145.7	877.2±47.1	13.8±0.4
NOD.ACE2 ^{+/-}	770.1±270.2 *	54.2±8.3 *	3713.1±107.3	1171.8±43.5 *	11.3±0.7
NOD.ACE2 ^{-/-}	512.0±288.3 **	36.3±6.4	3637.2±164.6 **	1178.0±48.8 **	10.2±1.0 **

* p≤0.05 vs. NOR.ACE2^{+/-}
** p≤0.05 vs. NOR.ACE2^{-/-}

Conclusions: Glomerular hypertrophy, mesangial matrix expansion and podocyte loss were found in female NOD.ACE2^{-/-} after30DOD.GFR values showed mild decrease in NOD.ACE2^{-/-} compared to NOD.ACE2^{+/-} mice. Our results suggest that ACE2 deletion worsens kidney injury in diabetic NOD mice.

SA-PO389

Ace2 Deficiency Accentuated AngII-Induced Hypertension and Albuminuria in Diabetic Mice Sergi Clotet-Freixas, Maria Jose Soler, Marta Rebull, Julio Pascual, Marta Riera. *Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain.*

Background: AngiotensinII (AngII) promote renal vasoconstriction, albuminuria, fibrosis, apoptosis and inflammation. ACE2 deficiency exacerbates hypertension in AngII-infused male mice. However, the effect of ACE2 deletion on diabetic and AngII-infused female mice has not been previously studied.

Methods: We evaluated the effect of AngII infusion in age matched C57BL/6 wild-type (WT) and ACE2KO streptozotocin(STZ)-induced female mice and their respective non-diabetic controls. At week 8 of follow-up, mice were anesthetized and minipumps for AngII infusion (ANGII) were surgically implanted. Sham-operated (SHAM) mice were used as control groups. Study groups: WT-Control(CONT) + SHAM, WT-CONT + ANGII, WT-Diabetic(DB) + SHAM, WT-DB + ANGII, ACE2KO-CONT + SHAM, ACE2KO-CONT + ANGII, ACE2KO-DB + SHAM, ACE2KO-DB + ANGII. Blood glucose, body weight, kidney weight/body weight (KW/BW), heart weight/body weight (HW/BW), systolic blood pressure (SBP) and urinary albumin excretion (UAE) were studied.

Results: Hyperglycemia and reduced BW were observed in all groups given STZ. ACE2 deletion and AngII infusion supposed a modest decrease in body weight in control and diabetic mice. Both, SHAM and AngII-infusedACE2KO diabetic mice showed higher KW/BW as compared to WT.AngII infusion significantly augmented HW/BW and SBP in control and diabetic ACE2KO mice as compared to non-infused mice. Diabetes and AngII infusion were accompanied by increased UAE in all groups. This increase was more pronounced in ACE2KO mice. Within AngII-infused groups, ACE2KO-CONT + ANGII and ACE2KO-DB + ANGII showed significantly higher HW/KW, SBP and UAE than WT-CONT + ANGII and WT-DB+ANGII.

Conclusions: Loss of ACE2 accentuated renal hypertrophy and AngII-induced hypertension, albuminuria and cardiac hypertrophy in diabetic female mice.

	BG (mg/dL)	BW (gr)	KW/BW (%)	HW/BW (%)	SBP (mmHg)	UAE (µgAlb/mgCrea)
WT-CONT + SHAM (n=10)	172.00 ± 7.61	25.87 ± 0.66	1.04 ± 0.05	0.49 ± 0.03	104.60 ± 1.59	11.56 ± 2.70
WT-CONT + ANGII (n=12)	175.17 ± 7.05	25.13 ± 0.92	0.95 ± 0.03	0.54 ± 0.02	108.52 ± 4.75	69.03 ± 36.12 *
WT-DB + SHAM (n=11)	306.55 ± 31.74 ⁵	21.24 ± 0.43 ⁵	1.13 ± 0.08	0.46 ± 0.02	102.04 ± 2.33	71.29 ± 12.00 ⁵
WT-DB + ANGII (n=11)	389.36 ± 44.05 ⁵	20.83 ± 0.27 ⁵	1.09 ± 0.07	0.49 ± 0.03	116.62 ± 4.68 *	186.66 ± 63.65 ⁵
ACE2KO-CONT + SHAM (n=10)	177.00 ± 11.77	24.40 ± 0.57	0.93 ± 0.06	0.50±0.02	107.56 ± 1.48	9.24 ± 1.72
ACE2KO-CONT + ANGII (n=10)	157.30 ± 8.07	23.28 ± 0.46	1.00 ± 0.04	0.65±0.03 [#]	133.31 ± 6.04 ^{#*}	436.00 ± 108.29 ^{#*}
ACE2KO-DB + SHAM (n=10)	354.30 ± 46.83 ⁵	20.24 ± 0.65 ⁵	1.34 ± 0.10 ^{5#}	0.50 ± 0.03	104.30 ± 2.11	98.04 ± 35.15 ⁵
ACE2KO-DB + ANGII (n=9)	436.78 ± 51.50 ⁵	19.82 ± 0.77 ⁵	1.31 ± 0.04 ^{5#}	0.60 ± 0.02 [#]	138.86 ± 7.36 ^{#*}	995.19 ± 321.35 ^{#*}

*P<0.05 vs SHAM, ⁵P<0.05 vs CONT, [#]P<0.05 vs WT.

Funding: Government Support - Non-U.S.

SA-PO390

Global ACE2 Deficiency Worsens Glomerular Cell Proliferation but Does Not Affect GFR in Diabetic Mice Jan A. Wysocki,¹ Minghao Ye,¹ Yashpal S. Kanwar,¹ Agnes B. Fogo,² Daniel Batlle.¹ ¹Northwestern Univ; ²Vanderbilt Univ.

Background: Alterations in ACE2 have been described in rodent models of diabetic kidney disease and in humans with type 2 diabetes where glomerular ACE2 expression has been found to be decreased similar to findings in diabetic db/db mice. At the tubular level however, ACE2 is increased. To examine the impact of ACE2 deficiency on kidney pathology we developed a model of type 2 diabetes with global ACE2 deficiency. The effect of STZ-induced diabetes on kidney pathology was also examined in ACE2KO mice with two different genetic backgrounds.

Methods: ACE2 deficient db/db mice were generated and backcrossed to the BLKS genetic background for at least 6 generations. The effect of ACE2-deficiency was also studied in WT and ACE2KO mice (C57BL6/J and FVB/N genetic backgrounds) that were rendered diabetic using STZ (2x150mg/kg).

Results: In ACE2 deficient db/db mice, there was a modest but significant reduction in podocyte count (10.3±0.2 vs. 11.1±0.1, p<0.05) and an increase in glomerular cellularity (1.81±0.13 vs. 1.06±0.11, p<0.001, respectively) but neither GFR (3.0±0.4 vs. 2.4±0.3ul/min/g) nor albumin excretion were significantly different from db/db WT controls. ACE2-deficient db/db mice also exhibited Lacis cell hyperplasia, increase in polar cells and foci of glomerular sclerosis. Glomerular cellularity was significantly increased also in mice with STZ-induced diabetes on the FVB/N but not in the C57BL6/J background as compared to their respective diabetic WT counterparts.

Conclusions: Genetic ACE2 ablation worsens glomerular hypercellularity in diabetic mice whereas GFR and ACR are not significantly altered and other markers of glomerular pathology are minimally affected.

Funding: NIDDK Support, Private Foundation Support

SA-PO391

Blood Pressure-Independent Amelioration of Glomerulosclerosis in Diabetic Rats Treated with Dual AT₁ Receptor-Nephrilysin Inhibition versus AT₁ Receptor Blockade Alone Lodi C.W. Roksnoer,¹ Richard Van Veghel,¹ Marian Clahsen - van Groningen,³ René De Vries,¹ Ingrid M. Garrelts,¹ Usha M. Bhaggoe,¹ Jeanette M. Van Gool,¹ Edith C.H. Friesema,¹ Frank P.J. Leijten,¹ Ewout J. Hoorn,² Alexander H. Danser,¹ Wendy W. Batenburg.¹ ¹Div. Pharmacology and Vascular Medicine, Dept Internal Medicine, Erasmus MC, Rotterdam, Netherlands; ²Div. Nephrology, Dept Internal Medicine, Erasmus MC, Rotterdam, Netherlands; ³Dept Pathology, Erasmus MC, Rotterdam, Netherlands.

Background: Dual AT₁ receptor-nephrilysin inhibition (ARNI) has recently been shown to exert beneficial effects on blood pressure (BP), NT-proBNP, and estimated GFR in heart failure patients, compared with AT₁ receptor blockade (ARB) alone. Nephrilysin is upregulated in epineural arterioles of diabetic rats. We hypothesized that ARNI improves cardiac and kidney parameters in diabetic TGR(mREN2)27 rats, a model displaying angiotensin II-mediated hypertension.

Methods: Rats were made diabetic with streptozotocin, for 5 or 12 weeks. In the final 3 weeks rats were treated with vehicle, the ARB irbesartan (15mg/kg.day) or irbesartan (15mg/kg.day) + the nephrilysin inhibitor thiorphan (0.1mg/kg.day; ARNI). BP was measured by telemetry in the 5-week group only.

Results: Baseline mean arterial BP (MAP) was 157±5mmHg. ARB and ARNI lowered MAP identically over the 3-week period, reaching a maximum reduction of ~50mmHg around day 7. Heart weight/tibia length ratio in 12-week diabetic rats was 17±9% lower after ARNI treatment vs. ARB treatment (P<0.05). Proteinuria and albuminuria were observed from 8 weeks of diabetes onwards. ARNI reduced proteinuria more strongly than ARB (-78% vs. -49%, P<0.05), and a similar trend was seen for albuminuria. Kidneys of ARNI-treated rats showed less focal segmental glomerulosclerosis than those of ARB-treated rats. At the end of the study, no differences between ARNI- and ARB-treated rats were found regarding diuresis, natriuresis, plasma endothelin-1, vascular reactivity (acetylcholine and endothelin-1 responses), or kidney sodium transporters.

Conclusions: ARNI reduces proteinuria, focal segmental glomerulosclerosis, and cardiac hypertrophy in diabetic TGR(mREN2)27 rats more strongly than ARB, and this occurs in a blood pressure-independent manner.

SA-PO392

Collateral Effects of Atrasentan on Renin-Angiotensin System Lidia Anguiano, Marta Riera, Marta Rebull, Julio Pascual, Maria Jose Soler. *Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain.*

Background: Endothelin-1 is a vasoconstrictor peptide that has been shown to be increased in diabetic kidney disease. In kidney cortex from obese diabetic mice ACE2 activity is increased whereas ACE activity is decreased. Objective: study the effect of atrasentan, an antagonist of type A endothelin receptor, on renin-angiotensin system (RAS) in obese diabetic mice(db/db) and its respective controls(db/m).

Methods: Diabetic groups: vehicle (VehDB), 10mg/kg/day atrasentan (10DB), 25mg/kg/day atrasentan (25DB), 50mg/kg/day atrasentan (50DB). Non-diabetic groups: vehicle (VehCONT), 10mg/kg/day atrasentan (10CONT). Animals were included in the study at 12weeks of life and treated for 16weeks. Systolic (SBP) and diastolic (DBP) blood pressure and ACE2 and ACE enzymatic activities in serum and kidney were analyzed.

Results: See table. Atrasentan therapy significantly decreased SBP and DBP in non-diabetic mice. Circulating and renal ACE2 activities were significantly increased in VehDB mice as compared to VehCONT. Atrasentan treatment at 25 and 50mg/kg/day reduced circulating and renal ACE2 activities. Circulating and renal ACE activities were decreased in VehDB as compared to VehCONT, with no modulation by atrasentan treatment.

	VehCONT	10CONT	VehDB	10DB	25DB	50DB
SBP(mmHg)	113.5±1.4 *	105.7±1.8 [§]	97.5±2.5	99.3±2.7	98.4±2.3	104.3±3.4
DBP(mmHg)	85.7±1.4 *	78.6±1.8 [§]	71.4±2.5	74.5±2.2	72.1±1.8	76.5±2.7
Serum ACE(RFU/μL)	68712.9±4081.5	75946.3±4113.2	35634.7±3595.4	34085.8±3239.6	32776.8±3146.4	34412.8±1738.2
Renal ACE(RFU/μg)	3818.6±416.5 *	3692.3±334.5	752.1±94.8	595.2±68.6	696.4±118.7	561.3±101.5
Serum ACE2(RFU/μL/h)	104.3±9.1 *	123.9±7.9	144.1±13.5	114.6±7.3	101.5±5.8 *	94.9±2.5 *
Renal ACE2(RFU/μg/h)	535.1±72.0 *	702.6±87.7	1126.9±130.8	816.8±119.6	837.2±65.8 *	837.2±184.8 *

*p<0.05 versus VehDB
[§]p<0.05 versus VehCONT

Conclusions: Atrasentan prevented the increase of circulating and renal ACE2 in diabetes, indicating a collateral effect by RAS modulation. These results suggest that the beneficial effect of atrasentan in diabetic nephropathy may be related with endothelin blockade and its effect in the non-classic RAS pathway.

SA-PO393

P16^{ink4a} Expression Is Increased via 12-Lipoxygenase in High Glucose-Stimulated Glomerular Mesangial Cells and Type 2 Diabetic Glomeruli Yuanyuan Zhang, Fu-zhe Ma, Tao Sun, Wan-ning Wang, Hang Yuan, Zhong-gao Xu. *Nephrology, The First Hospital of Jilin Univ, Changchun, Jilin, China.*

Background: Arachidonic acid-metabolizing enzyme 12-lipoxygenase (12-LO) is involved in glomerular hypertrophy of diabetic nephropathy (DN), in which cyclin-dependent kinase inhibitors (CKIs) play important roles. However, it is unclear whether 12-LO regulates the expression of the CKI p16^{ink4a} in DN.

Methods: Primary glomerular mesangial cells (MCs) and glomeruli isolated from rats were used in this study. The rats were fed a high-fat diet and given low-dose streptozotocin to induce type 2 diabetes. The 12-LO product 12(S)-hydroxyeicosatetraenoic acid [12(S)-HETE] was infused through an osmotic minipump. Enzyme-linked immunosorbent assay, Western blot, and morphometric analyses were performed.

Results: High glucose (HG) increased p16^{ink4a} protein expression in MCs, but this increase was prevented by the 12-LO inhibitor cinnamyl-3,4-dihydroxy-α-cyanocinnamate (CDC). The levels of p-p38MAPK and p16^{ink4a} in MCs were significantly elevated after 12(S)-HETE treatment, whereas the p38MAPK inhibitor SB203580 prevented these increments. Compared with levels in control MCs, marked increases in p38MAPK activation and p16^{ink4a} expression were observed in MCs plated on collagen IV, while CDC treatment prevented these changes. Subcutaneous injection of CDC did not affect glucose levels but completely attenuated the diabetes-related increases in 12(S)-HETE content, p16^{ink4a} expression, p-p38MAPK levels, glomerular volume, and kidney/body weight ratio. Compared with levels in controls, p16^{ink4a} and p-p38MAPK in the glomeruli derived from 12(S)-HETE-treated rats were significantly increased.

Conclusions: 12-LO-p38MAPK mediates the upregulation of p16^{ink4a} in HG-stimulated MCs and type 2 diabetic glomeruli, and new therapies aimed at 12-LO inhibition might be beneficial in ameliorating diabetes-induced glomerular hypertrophy.

SA-PO394

The Effect and Mechanism of Probulcol on Diabetic Nephropathy Tubulointerstitial Injury via Down-Regulating P66Shc Shi-kun Yang,¹ Xiaoxuan Xu,¹ Chun Hu,¹ Li Xiao,¹ Fuyou Liu,¹ Lin Sun.¹ ¹Dept of Nephrology, Kidney Inst of Central South Univ, Changsha, Hunan Province, China; ²Dept of Nephrology, Kidney Inst of Central South Univ, Changsha, Hunan Province, China.

Background: P66Shc induce mitochondrial ROS overproduction and lead to renal oxidative stress. Probulcol has the renal protective effect on the progression of DN. However, the mechanism remains poorly understood.

Methods: ICR mice were divided into control (n=10), DN (n=10), probulcol (10mg/kg/d) group (n=10), DMSO group (n=10). The DN model was induced by injection of STZ (40mg/kg body weight). Probulcol was intraperitoneally injected to the mice every other day for 12 weeks after the model was built. Renal lesions and the expression of SIRT1, P300, ACh3, P66Shc, FN were detected by HE, Masson staining, TUNEL, DHE, immunohistochemistry and western-blot respectively. In addition, HK-2 cells were incubated with different concentrations of D-glucose (5, 30mM) with or without probulcol, 1mM AICAR or 20uM Dorsomorphin or 1uM EX-527. The expression of P66Shc, SIRT1, P300, ACh3, AMPK, p-AMPK in HK-2 cells were detected by realtime-PCR, Western-blot and immunofluorescence assays. In addition, chromatin immunoprecipitation (ChIP) assay was used for determining the effect of probulcol on acetylation of histone of P66Shc gene.

Results: Compared to control, the reduced ECM protein and renal tubular damage were observed in DN mice after treated by probulcol. It also decreased the expressions of P300, P66Shc, FN in the kidney of DN mice. In addition, Probulcol can reduce the level of serum creatinine levels, attenuate renal ROS levels and apoptosis, while boost the expressions of p-AMPK and SIRT1. Furthermore, pretreatment with the selective AMPK inhibitor Dorsomorphin or SIRT1 inhibitor EX-527 could block the inhibitory efficiencies of probulcol. The ChIP analysis showed that probulcol treatment could decrease the acetylation of histone H3 in p66Shc gene promoter regions (-535 bp to -276 bp) in HK-2 cells induced by high glucose.

Conclusions: Probulcol could epigenetically suppress the expression of P66Shc through AMPK-SIRT1-ACh3 pathway, then ameliorate the apoptosis and oxidative injury in HK-2 cells induced by high glucose.

Funding: Government Support - Non-U.S.

SA-PO395

Macrophages in Type 2 Diabetic Nephropathy Celine Klessens, Malu Zandbergen, Ron Wolterbeek, Jan A. Bruijn, Ton J. Rabelink, Ingeborg M. Bajema, Daphne Thomas-ijpelaar. *Leiden Univ Medical Center.*

Background: Inflammation seems to play a role in type 2 diabetic nephropathy (DN). Therefore, novel therapies focus on inhibition of inflammation to inhibit renal failure in DN. Interstitial macrophages are present in progressive interstitial lesions, however, the role of glomerular macrophages in the development of diabetic glomerular damage remains incompletely understood. In this study we investigated the accumulation of macrophages in glomeruli and interstitium of humans with various stages of DN.

Methods: Kidney samples obtained at autopsy of type 2 diabetes patients (N=88) with histologically proven DN were stained with CD68 and CD163, as global and M2 macrophage markers. As controls, renal autopsy samples of 5 non-diabetic and 18 diabetic

patients without DN were used. Macrophages in 50 glomeruli per sample were counted. Interstitial macrophages were counted semi-quantitatively. Glomerular and interstitial macrophages were correlated to histological and clinical parameters.

Results: Glomerular CD68+ and CD163+ cells were present in all stages of DN according to the histopathological class and did not differ between classes, but the accumulation varied widely. The mean influx of glomerular CD68+ cells over the classes was 4.2 (range 0-19) and the mean influx of glomerular CD163+ cells was 2.1 (range 0-14.74). The mean ratio of CD163/68+ cells amounted 0.5. Glomerular macrophages were also present in the control groups. Renal function was associated with the number of CD68+ cells and CD163+ cells were significantly associated with histological lesions. Interstitial macrophages significantly correlated with clinical parameters like GFR stage and albuminuria.

Conclusions: We showed that macrophages (including anti-inflammatory CD163 + macrophages) are present in all stages of DN both in the glomerulus and interstitium. Correlation between clinical data and interstitial macrophages indicates that interstitial inflammation probably influences the progression of DN. In addition, presence of glomerular macrophages in early diabetic nephropathy suggests that they influence the glomerular diabetic damage as well. Therefore, therapies targeting macrophages might be a useful novel therapy in DN.

SA-PO396

Activation of CXCL16/CXCR6 Pathway by Inflammation Accelerates the Progression of Diabetic Nephropathy Zebo Hu, Kun Ling Ma, Yang Zhang, Wu Yu, Bi-Cheng Liu. *Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China.*

Background: Diabetic nephropathy(DN) was considered as a chronic inflammatory disease. Inflammation plays critical roles in the progression of DN. This study investigated the role of CXCL16/CXCR6 pathway in DN under inflammatory stress and explored its potential mechanisms modulated by purinergic receptor P2X ligand-gated ion channel 7 (P2RX7).

Methods: Diabetic db/db mice were randomly divided into two groups: db/db, and db/db+casein for eight weeks. Casein was subcutaneously injected to induce chronic inflammation. The morphological change of renal pathology and ultra-microstructure were checked by pathological staining and electron microscopy. Lipid accumulation in kidneys was observed by Filipin staining and quantitative assay of intracellular free cholesterol. The expression of CXCL16/CXCR6 pathway, inflammatory cytokine, and fibrotic index related molecules were detected by immunohistochemistry, immunofluorescent staining, and Western Blot.

Results: The 24-hour urinary protein, tubulointerstitial injury, inflammatory cell infiltration, and the protein expression of monocyte chemoattractant protein 1(MCP-1), tumor necrosis factor α (TNF α), CD68, α -Smooth muscle actin (α -SMA), and fibronectin (FN) in kidneys of db/db+casein mice were significantly increased compared with the db/db mice. Furthermore, there was significant lipid accumulation, increased protein expression of CXCL16 and CXCR6 and decreased disintegrin and metalloproteinase-10(ADAM10) expression in kidneys of db/db+casein mice compared with db/db mice, accompanied with increased P2X7R expression. Further analysis demonstrated that there was a positive correlation between P2X7R and CXCL16 expression.

Conclusions: Inflammation accelerates tubulointerstitial injury in DN partly through the activation of CXCL16/CXCR6 pathway, which may facilitate inflammation induction and lipid accumulation in cells. The P2X7R pathway may be involved in the activation of CXCL16/CXCR6 pathway.

SA-PO397

Albumin Glycation Induces Structural Changes That Reduce Proximal Tubule FcRn-Albumin Binding and Reclamation Mark C. Wagner,¹ Jered Myslinski,¹ Shiv Pratap Singh Yadav,³ George Rhodes,¹ Ruben M. Sandoval,¹ Sudhanshu Kumar,¹ Sarah E. Wean,¹ Fnu Ashish,³ Bruce A. Molitoris.^{1,2} *¹Nephrology Div, Dept of Medicine, Indiana Univ School of Medicine, Indianapolis, IN; ²Cellular & Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN; ³CSIR-Inst of Microbial Technology, Chandigarh, India.*

Background: Diabetic nephropathy remains the leading cause of chronic kidney disease (CKD) and ESRD. It results in increased albumin glycation and this is believed to be involved in proximal tubule cell injury and the pathophysiology of interstitial fibrosis and CKD progression.

Methods: To understand the mechanisms we have addressed specific in vitro albumin modifications and their impact on albumin-FcRn binding since proximal tubule FcRn is necessary for transcytosis and reclamation of filtered albumin.

Results: Those studies showed markedly reduced binding to FcRn when albumin was glycosylated proportional to the level of glycation. To address the mechanism for reduced binding we used SAXS analysis and molecular modeling to determine structural changes. SAXS data analysis revealed significant shape changes occur to albumin upon glycation which affected its binding affinity to FcRn. Our prediction would be that albumins with weaker FcRn binding would have more rapid serum clearance implying increased Pt catabolism via lysosomal degradation. Prior to evaluating modified albumin, control albumin was labeled with multiple fluorophores to determine conjugation ratios and dyes that retained normal pH dependent FcRn binding and would thus permit accurate serum clearance to be evaluated. The results agreed with our prediction and we are presently evaluating the serum clearance for the glycosylated albumins that have been conjugated to a fluorescent probe.

Conclusions: The data indicate modifications to albumin lead to structural alterations resulting in reduced pH dependent FcRn binding, which alters lysosomal catabolism leading to transcytosis and reclamation resulting in a shorter serum half life and may mediate the enhanced interstitial inflammation and fibrosis in diabetic nephropathy.

Funding: NIDDK Support

SA-PO398

The Effects of Glucagon-Like-Peptide-1 and Vitamin D on Inflammatory and Histological Changes of Diabetic Nephropathy in db/db Mice Yael Einbinder,^{1,2} Sydney Bencherit,^{1,2} Tali Zitman-Gal.¹ *¹Renal Physiology Laboratory, Dept of Nephrology and Hypertension, Meir Medical Center, Kfar Saba, Israel; ²Sackler Faculty of Medicine, Tel Aviv Univ, Tel Aviv, Israel.*

Background: Glucagon-like-peptide-1 is a gut incretin hormone that stimulates insulin secretion and may affect the inflammatory pathways involved in type 2 diabetes mellitus (DM). Calcitriol plays an important role in renal, endothelial, and cardiovascular protection. We evaluated the anti-inflammatory and histological effects of GLP-1 and calcitriol in a db/db mice diabetic model.

Methods: C57BL/6 (WT) and BKS.Cg-Dock7^m +/- Lepr^{db/db} (db/db) mice were randomized to: a) WT mice; b) db/db mice (diabetic control group); c) db/db mice+GLP-1 analog (100 nmol/kg); and d) db/db mice+GLP-1 analog +calcitriol (250 ng/kg). Blood glucose levels and weight were evaluated weekly. At the end of the 4-week treatment, kidneys were perfused and removed for protein analysis and histology.

Results: Blood glucose levels and weight were significantly higher in db/db mice compared to control WT mice. Blood glucose level was non-significantly lower in the db/db GLP-1 group compared to untreated db/db mice (460.5±83.2 mg/dl vs. 526.3±33.3 mg/dl). GLP-1 treatment significantly up-regulated eNOS protein expression and significantly down-regulated p65 protein expression compared to the db/db control group. Vitamin D did not further improve the beneficial effect observed on protein expression. Kidney VDR protein expression increased only in the vitamin D group compared to the db/db control group. Kidney histology demonstrated beneficial effect of GLP-1 treatment on glomerular hypertrophy in db/db mice at 26 weeks of age but had no significant effect on the severity of mesangial expansion.

Conclusions: In the experimental model of diabetic nephropathy (db/db mice), GLP-1 analog treatment improved the protein expression involved in the inflammatory response and significantly ameliorated the glomerular hypertrophy seen in the diabetic control group.

Funding: Private Foundation Support

SA-PO399

Mineral Metabolism and Interleukin-6: Predictive Risk Factors for Left Ventricular Hypertrophy in Patients with Diabetic Nephropathy Teresa M. Jeronimo,¹ André Fragoso,¹ Filipa Brito Mendes,¹ Ana Paula Silva,^{1,2} Ana Pocinho Pimentel,¹ Nelson Tavares,³ Pedro L. Neves.^{1,2} *¹Nephrology, Centro Hospitalar do Algarve, Faro, Portugal; ²Dept of Biomedical Sciences and Medicine, Univ of Algarve, Faro, Portugal; ³Cardiology, Centro Hospitalar do Algarve, Faro, Portugal.*

Background: Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular disease in patients with diabetic nephropathy (DN) and is an independent predictor of mortality in patients with chronic kidney disease (CKD). The aim of this study was to evaluate the predictive risk factors of LVH in a population of patients with DN.

Methods: The authors analysed the relationship of LVH with gender, body mass index (BMI), systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR), albumin, cholesterol, hemoglobin (Hb), calcium, phosphorus, parathyroid hormone (PTH), urine albumin-to-creatinine ratio (UACR), interleukin-6 (IL-6), hemoglobin A1c (HbA1c) and insulin resistance (HOMA-IR). Descriptive statistics, Student's t-test and logistic regression model were used.

Results: In a cross-sectional study were included 119 type 2 diabetic patients with CKD stages 3 and 4. Patients with LVH had significant lower values of eGFR and albumin, higher levels of UACR, HOMA-IR and IL-6. Phosphorus (odds ratio (OR) = 0.602 (1.075-4.414), p = 0.038), PTH (OR = 1.009 (1.098-3.000), p = 0.004) and IL-6 (OR = 1.264 (1.863-6.719), p = 0.0001) were independently related with LVH.

Variable	Adjusted OR (95% CI)	p-Value
Gender	-1.012 (0.064-2.076)	0.255
Age	0.032 (0.890-1.053)	0.455
BMI	0.170 (0.969-1.448)	0.098
SBP	-0.008 (0.944-1.043)	0.757
eGFR	-0.026 (0.930-1.021)	0.279
Albumin	-0.021 (0.137-7.012)	0.983
Hb	0.242 (0.770-2.106)	0.347
Phosphorus	0.602 (1.075-4.414)	0.038
iPTH	1.009 (1.098-3.000)	0.044
UACR	-0.001 (0.993-1.006)	0.865
HOMA-IR	0.422 (0.746-3.114)	0.247
IL-6	1.264 (1.863-6.719)	0.0001

Multivariate logistic regression model — risk factors of LVH.

Conclusions: Phosphorus, PTH and IL-6 were independent risk factors of LVH in our diabetic population with CKD stages 3 and 4.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

SA-PO400

Far-Infrared Therapy Retrieves Pancreatic Beta Cell Function and Survival in a Streptozotocin-Nicotinamide-Induced Type 2 Diabetic Mouse Model
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Background: In diabetes, the apoptotic cell death of insulin-producing beta cells leads to insulin deficiency. Recently, we found low-temperature far-infrared (FIR) irradiation increased proliferation and survival of human umbilical vein endothelial cells via promyelocytic leukaemia zinc finger protein (PLZF)-mediated PI3K/Akt activation.

Methods: In this study, we investigate the protective effects of FIR on pancreatic beta cell function and survival in the nicotinamide (NA) and streptozotocin (STZ)-induced type II diabetic mouse model. We used the PLZF siRNA transfection to inhibit the PLZF-mediated PI3K/Akt activation.

Results: The present study showed that FIR therapy decreased non-fasting blood glucose levels and increase blood insulin levels in diabetic mice in a dose-dependent manner. Immunohistochemistry staining revealed that FIR therapy retrieved insulin production of pancreatic beta cells in diabetic mice. But the influence of FIR on blood glucose and insulin levels was not found in NA/STZ-treated PLZF-knockout mice. We also used the insulin-secreting beta cell line RIN-m5f to investigate the protective effects of FIR *in vitro*. FIR irradiation promoted cell proliferation and inhibited STZ-induced apoptosis in RIN-m5f cells. FIR also induced PLZF nuclear translocation and increased PI3K expression and Akt phosphorylation in RIN-m5f cells. PLZF siRNA transfection inhibited the influence of FIR on RIN-m5f cells.

Conclusions: Our data suggest that FIR therapy retrieves pancreatic beta cell function and survival in diabetic mice via a PLZF-mediated pathway.

SA-PO401

Transgenic Mice Overexpressing Human CD39 (ENTPD1) Are Protected from High-Fat Diet-Induced Obesity and Insulin Resistance
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Background: CD39 is a vascular ecto-nucleotidase that sequentially hydrolyzes extracellular ATP to ADP and AMP, thus terminating P2 receptor signaling. Previously we reported that deletion of *Cd39* results in hepatic insulin resistance (IR). We also found that deletion of ATP/UTP activated P2Y₂-R confers significant protection against high-fat diet (HFD)-induced obesity and IR. Hence, we hypothesized that global overexpression of human CD39 (hCD39), which decreases the availability of extracellular nucleotides should attenuate development of HFD-induced obesity and IR.

Methods: Groups of age-matched adult wild type C57/Bl6 (WT) and syngeneic transgenic (TG) mice globally overexpressing hCD39 were fed regular diet (10% calories as fat; n = 5) or HFD (60% calories as fat; n = 7) with free access to food and water for 10 weeks. Body weights (BW), food and water consumption and urine output were monitored periodically. Glucose tolerance (GTT) and insulin sensitivity (IST) tests were conducted between 8 to 10 weeks.

Results: In response to HFD feeding, both genotypes showed significant increases in BW over the experimental period as compared to their counter parts fed regular diet. However, the gain in BW was significantly less in TG vs. WT mice (mean 21.5 ± 0.3 vs. 15.3 ± 2.0 g, n = 7, p = 0.005). There were no significant differences between the genotypes in the amount of food consumed, nor was there evidence of steatorrhea indicating malabsorption. Fasting blood glucose levels in HFD fed TG mice were 2-fold higher vs. WT mice (179 ± 12 vs. 88 ± 5 mg/dL, n = 7, p = 0.0001). When fed HFD, both genotypes exhibited glucose intolerance, but this was less severe in TG mice. In parallel, insulin sensitivity was significantly better in HFD-fed TG vs. WT mice.

Conclusions: Our results demonstrate that overexpression of hCD39 confers significant protection against the development of HFD-induced obesity and IR, and thus validating the proposition that dominantly deleterious roles are played by extracellular nucleotides in metabolic homeostasis.

Funding: Veterans Administration Support

SA-PO402

Mass Spectrometry Imaging Reveals a Role for Glomerular Sphingomyelin to Suppress AMPK Activity by Stimulating ATP Production in Mesangial Cells
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Background: We have recently shown that the ATP/AMP ratio is increased in the glomeruli in a mouse model of type 1 diabetes by matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) and may be the basis for reduced AMP-activated protein kinase (AMPK) in diabetic glomeruli. Here, we applied MALDI-MSI to identify a key molecule involved in the regulation of glomerular ATP.

Methods: For MALDI-MSI, 23 weeks-aged male diabetic Akita (C57BL/6J-Ins2^{Akita}) (A), wild type mice (W), and a normal human kidney (H) were used. For cell culture study, murine mesangial cells (MMCs) were treated with sphingomyelin(d18:1/16:0) (SM)-containing liposomes (SL), control liposomes (CL) and vehicle. For ATP measurements, MMCs were transfected with sphingomyelin synthase (SMS)1, 2 or control siRNA before treatment with liposomes.

Results: By MALDI-MSI, we found that SM(d18:1/16:0) was preferentially distributed in the glomeruli in W and H. Importantly, we found that SM is more abundant in glomeruli of A compared with W, and associated with increased SMS1 and 2 in the glomeruli (p<0.05). SL stimulated ATP production in MMCs compared with CL (p<0.01), and was inhibited by siRNA based inhibition of SMSs. AMPKα activity and PGC1α protein expression were significantly reduced by SL (p<0.05). In addition, SL increased glucose consumption and lactate production in high glucose conditions (p<0.05) suggesting a role for enhanced glycolysis.

Conclusions: We demonstrate using MALDI-MSI that the accumulation of glomerular SM in type 1 diabetic mice is associated with increased ATP in glomeruli and may contribute to reduced AMPK activity in diabetes. These findings suggest that reduction of SM may lead to novel therapeutic targets for the treatment of diabetic kidney disease.

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SA-PO403

Chronic Hyperglycemia Activates Autophagy Through an Increased Lysine-63 Linked Ubiquitination: A Candidate Mechanism in the Progression of Tubular Damage in Diabetic Nephropathy
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Background: Chronic hyperglycemia, a key pathogenic factor of diabetic nephropathy (DN), can alter autophagy whose role in tubular cells under hyperglycemic conditions (HG) remains unclear. We reported that lysine63-ubiquitination (K63-Ub) plays a key role in the progression of tubular damage in DN; moreover K63-Ub promotes protein autophagic clearance. Aim of our study was to: evaluate the HG effect in modulating autophagy in tubular cells (HK2); evaluate *in vivo* the autophagy state in patients with diabetes without renal damage and in different DN classes; investigate the K63-Ub role in the modulation of tubular cells autophagy.

Methods: K63-Ub was inhibited in HK2 under HG (30mM) by UBE2v1 silencing, E2 enzyme involved in K63-Ub, or by NSC697923 inhibitor. The expression of the autophagic factor LC3 was detected by western blotting and confocal microscopy. Immunohistochemistry (IHC) and immunofluorescence (IF) were performed on kidney biopsies of 3 control patients, 3 diabetic, 9 DN (classes IIb, III and IV).

Results: HK2 showed a significant increase in LC3 protein after 24h of HG. UBE2v1 silencing completely abolished LC3 induced protein expression after 24h of HG. Confocal microscopy showed the reduction of autophagic vesicles induced by HG in the presence of the K63-Ub inhibitor (NSC697923). IHC on kidney biopsies revealed an increased tubular expression of LC3 in diabetic patients vs controls, that persists in all DN classes and class IV patients showed cytoplasmic accumulation of fused-vesicles. The same tubules with activated autophagy, expressed K63-Ub proteins both in diabetic and in DN patients (IF).

Conclusions: In conclusion, our data demonstrate that chronic hyperglycemia induces an increase in autophagy, linked to the accumulation of K63 ubiquitinated proteins. However, uncontrolled autophagy levels could lead to tubular damage through the generation of intracellular vesicles, bringing to the progression of renal damage in DN patients.

SA-PO404

Abstract Withdrawn

SA-PO405

Complexome Profiling of Mitochondrial Respiratory Chain Proteins from Podocytes of Diabetic Mice
 Zengchun Ye, Shawn S. Badal, Daniel L. Galvan, Jianyin Long, Farhad R. Danesh. *Section of Nephrology, The Univ of Texas MD Anderson Cancer Center, Houston, TX.*

Background: Mitochondria play essential roles in many aspects of biology, and their dysfunction has been linked to diverse diseases, including diabetic nephropathy (DN). Central to proper mitochondrial function is oxidative phosphorylation (OXPHOS), coordinated by respiratory chain complexes encoded by both nuclear and mitochondrial genomes. Whether alterations in specific OXPHOS complex protein expression/activity contribute to mitochondrial dysfunction in DN remain largely unknown.

Methods: To assess complexome profiles, mitochondria were isolated from podocytes of 16-week-old diabetic (*db/db*) and nondiabetic (*db/m*) mice. Blue Native Gel Electrophoresis (BNE) was coupled with quantitative mass spectrometry (nano-HPLC/ESI/MS/MS) to identify known and unknown macromolecular protein complexes.

Results: We identified a total of 1216 mitochondrial proteins. Complexome profiling revealed mitochondrial complexes I and III to be markedly reduced in podocytes of *db/db* compared to controls. Consistent with MS results, Complex I activity was significantly reduced in podocytes of *db/db* mice compared to controls. Importantly, we found that the protein expression levels of Ndufb2, Ndufb3 and Ndufb8, all components of complex I, were significantly reduced in podocytes of *db/db* mice. We further validated

our initial results and found that the podocyte-derived mitochondria from diabetic db/db mice display markedly reduced message and protein expression levels of Ndufb8. These changes are coincident with significantly decreased Complex I activity from analogously isolated and processed mitochondria derived from db/db mice.

Conclusions: Our study uncovers a previously unrecognized role of complex I in the pathogenesis of DN. We propose that deficiencies in components of complex I may disrupt complex I assembly, eventually reducing mitochondrial oxidative metabolism of podocytes in diabetic kidney disease. Further genetic studies are currently underway in our laboratory to establish the value and limitations of using Ndufb8 transgenic mice in experimental models of diabetes as a model for targeting mitochondrial dysfunction in DN.

Funding: NIDDK Support

SA-PO406

Hyperglycemia and Hyperinsulinemia Increased Cell Proliferation and Regulated DNA Damage/Repair Pathways in Type II Diabetic (db/db) Mouse Samy L. Habib,^{1,2} Sitai Liang,^{1,2} ¹Geriatric Research, Education and Clinical CTR, South Texas Veterans Health System, San Antonio, TX; ²Cellular and Structural Biology, The Univ of Texas Health Science Center, San Antonio, TX.

Background: The mechanisms by which hyperglycemia and/or hyperinsulinemia activate cell proliferation to regulate the DNA damage/repair pathways and increase renal cell damage in diabetes remain unclear.

Methods: In the current study, we investigated the role of hyperglycemia and hyperinsulinemia in regulating cell survival and cell proliferation to regulate the DNA damage/repair pathways in the type II diabetic (db/db) mouse.

Results: Significant increase in proteinuria, albuminuria, creatinine in 24h urine as well as in serum insulin was detected in db/db mice compared to wild type mice. Cell proliferation was measured by Ki67 staining and PCNA expression in kidney sections of diabetic and wild type mice. Data showed significant increase of Ki67 staining and protein expression of PCNA in kidney of diabetic mice compared to wild type mice. The activity of survival kinase Akt (measured by phospho-Akt at Ser⁴⁷³) was significantly increased and associated with increased activation of mTORC1 (measured by phospho-p70S6K at Thr³⁸⁹) in kidney cortex of db/db mice compared to wild type mice by Western blot analysis. DNA repair OGG1 and the transcription factor regulates OGG1 (Nrf2) were significantly decreased and associated with increased in oxidative DNA damage (8-oxodG) in kidney homogenate from db/db mice compared to wild type mice. Gel shift analysis shows reduction of Nrf2 binding to OGG1 promoter in nuclear extracts of kidney homogenate of db/db mice compared to wild type mice. A portion of the DNA-protein complexes was significantly decreased in the presence of the Nrf2 antibody indicating that Nrf2 is indeed a component of these complexes.

Conclusions: In summary, our data provide a novel mechanism of increase renal cell damage through decrease binding of Nrf2 to the OGG1 promoter and consequence deficiency in DNA repair that lead to accumulate DNA damage and lead to renal complications under hyperglycemia and hyperinsulinemia condition in diabetic mice.

Funding: Veterans Administration Support

SA-PO407

Spleen Tyrosine Kinase Activation Promotes the Progression of Diabetic Nephropathy in the Early Stage Fei Liu, *Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.*

Background: Inflammation triggered by metabolic disorder has played an important role in the pathogenesis of diabetic nephropathy (DN) in the early stage. The inflammatory cytokines binding to immunoglobulin G Fc receptors (FcγRs) in the surface of cell contribute to the progression of inflammation. It was found in our previous study that there was an increased expression of FcγRs with an immunoreceptor tyrosine-based activation motif (ITAM-FcγRs) in the kidney of diabetic CRP-Tg mouse induced by streptozotocin (STZ). It was also observed that ITAM-FcγRs were increased and spleen tyrosine kinase (SYK) were activated in rat glomerular mesangial cells (GMC) cultured with high glucose. SYK is a cytoplasmic nonreceptor tyrosine kinase and plays critical role in intracellular signal transduction of ITAM-FcγRs. It has been established that activated SYK signal cascade leads to the pro-inflammatory cytokines production in antibody-dependent kidney disease. However, the role of SYK in the progression of DN remains unclear. The present study investigated the potential role of SYK activation in the early stage of DN.

Methods: Diabetes was induced by STZ in Sprague Dawley (SD) rats for assessment of kidney injury at 2, 4, 8 weeks by real-time PCR, immunohistochemistry and western blot analysis. In vitro, the pathogenic effect of SYK was observed.

Results: Compared with control, urinary albumin excretion significantly increased in diabetic SD rats at 2, 4 and 8 weeks after STZ injection. Renal inflammation has been developed with enhanced infiltration of macrophages and T cells, and upregulation of pro-inflammatory cytokines (IL-1β, TNFα) in diabetic rats. Enhanced renal inflammation in diabetic rats caused the increase of SYK phosphorylation and the over-activation of nuclear factor κB (NF-κB) signaling pathway. In vitro, high glucose significantly upregulated pro-inflammatory cytokines (IL-1β, TNFα) via SYK cascade, which further promoted high glucose-mediated renal inflammation.

Conclusions: These findings suggested that SYK may be as "signal switch" to activate NF-κB signaling pathway and promote the progression of renal injury in the early stage of DN.

Funding: Government Support - Non-U.S.

SA-PO408

Smooth Muscle Specific Heavy Chain Ferritin Knockout Mice as a Model of Obesity Vyvyca Walker, Bo Chen, Remy Joseph, Anupam Agarwal. *Nephrology Research and Training Center, Div of Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Ferritin, consisting of heavy (H) and light (L) chain subunits, is a highly conserved ubiquitous protein that safely sequesters iron in a non-toxic form. During the course of our studies to evaluate the role of heavy chain ferritin (FtH) in a model of vascular calcification in CKD, we generated a transgenic mouse using the cre-lox system with smooth muscle cell-specific deletion of FtH (FtH^{SM22-/-}). Serendipitously, we discovered the FtH^{SM22-/-} mice gained more weight compared to control "floxed" FtH mice and exhibited features resembling metabolic syndrome.

Methods: To characterize FtH^{SM22-/-} mice as a model of obesity, male FtH^{SM22-/-} mice and FtH^{SM22+/+} control mice were individually housed from 6-28 weeks of age to monitor weight, food intake, and body composition utilizing quantitative magnetic resonance (QMR) imaging. Protein analysis was performed on skeletal muscle and fat to determine expression levels of insulin signaling mediators and iron regulators. RNA analysis of inflammatory markers expressed in white fat was also performed.

Results: At 28 weeks old, FtH^{SM22-/-} mice gained more weight (30.58g ± 2.02 vs. 27.72g ± 1.06 controls) during the observation period and consumed significantly more food starting at 20 weeks of age than the controls. QMR studies revealed that FtH^{SM22-/-} mice had slightly more fat, lean and water mass compared to controls. Protein analyses of skeletal muscle and white fat revealed a loss of GLUT4 expression and iron trafficking proteins, respectively, in transgenic mice. Moreover, there was an increase in tissue iron concentration and gene expression of TNFα in the fat tissue of FtH^{SM22-/-} mice compared to controls. Interestingly, review of publically available microarray data sets (NCBI, GEO data set GDS3876) derived from human samples suggest a significant (~1.5 fold) increase in FtH gene expression in obese individuals compared to lean controls.

Conclusions: Over a third of the adults in the United States are obese. Obesity predisposes individuals to other health risks, including CKD, diabetes, stroke, and cardiovascular disease. Our studies provide a novel mouse model for obesity.

Funding: NIDDK Support, Veterans Administration Support

SA-PO409

The Induction and Role of p53 in Tubular Cell Apoptosis During High Glucose Treatment and Diabetes Lin Li,^{1,2} Zhengwei Ma,¹ Changlin Mei,² Zheng Dong,¹ ¹Dept of Cellular Biology and Anatomy, Georgia Regents Univ, Augusta, GA; ²Dept of Nephrology, Shanghai Changzheng Hospital, 2nd Military Medical University of PLA, Shanghai, China.

Background: p53, known as a tumor suppressor, plays a crucial role in the cellular response to various stresses. P53 has been implicated in diabetic kidney disease but its role remains unclear and controversial.

Methods: Kidneys from Akita mice and STZ-treated diabetic mice were collected for in vivo studies. In vitro, renal proximal tubular cells (RPTC) with or without p53 dominant negative (p53-DN) were cultured in medium containing 5.5 mM or 30 mM glucose. Apoptosis was evaluated by morphologic observation, TUNEL, and flow cytometric analysis. The cells were also fractionated to investigate the subcellular redistributions of Bax and cytochrome c. The expression of p53, phosphorylated-p53 and apoptosis-related proteins were examined by western blot, immunohistochemistry/immunocytochemistry and immunofluorescence.

Results: Apoptosis was detected in renal tubules within a few weeks of diabetes, which was accompanied by p53/p-p53 expression. In cultured RPTC cells, high glucose induced apoptosis and p53. In these cells, there were Bax translocation to the mitochondria and cytochrome c release. Interestingly, these changes and apoptosis were attenuated in p53-DN cells. Consistently, they were also suppressed by pifithrin-α, a pharmacological inhibitor of p53.

Conclusions: These results suggest that p53 may be an upstream mediator of tubular cell apoptosis during high glucose treatment and in diabetic kidneys. P53 is induced under these conditions and may activate the mitochondrial pathway of apoptosis.

Funding: NIDDK Support, Veterans Administration Support, Government Support - Non-U.S.

SA-PO410

Mechano-Growth Factor Regulates mTOR and Other Growth Factor Expression in Mouse Mesangial Cells, Enhancing Cell Proliferation and Extracellular Matrix Production: Implications for Diabetic Glomerulosclerosis Yongxin Gao, Leighton R. James, Charles W. Heilig. *Medicine, Univ of Florida College of Medicine-Jacksonville, Jacksonville, FL.*

Background: MGF-S mesangial cells (MC) overexpress Mechano-Growth Factor protein 13.2-fold, with increased GLUT1, glucose uptake, cell proliferation and extracellular matrix (ECM). Here we examined mTOR expression and downstream S6 kinase activation, VEGF and TGF beta1 in our MGF-EV empty vector control MC, MGF-S MC overexpressing MGF, and MGF-AS MC with suppressed MGF.

Methods: Western analyses for selected proteins in cultured MGF-EV, MGF-S and MGF-AS were performed with specific antibodies and band densities normalized to endogenous beta-tubulin. 3H2-Deoxyglucose (3H2-DOG) uptake rates were determined as we have previously published. P<.05 was considered significant in statistical analyses.

Results: MGF-S exhibited persistent stimulation of VEGF expression 1.6-fold the MGF-EV control. mTOR expression increased 7.7-fold vs MGF-EV, leading to activation

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

of S6 kinase (phospho-S6 kinase) protein 8.7-fold. This increase in mTOR and active S6 kinase correlated with an increased proliferation rate of MGF-S vs. MGF-EV. MGF-AS had suppressed mTOR by 69%, but suppressed active S6 kinase by an insignificant amount. VEGF expression was suppressed 60% in MGF-AS vs MGF-EV. TGF beta1 protein was increased 1.8-fold in MGF-S, and reduced 46% in MGF-AS. GLUT1 protein in MGF-S was increased 7.2-fold, with a 10.6-fold increased 3H2-DOG uptake rate. In contrast, 3H2-DOG uptake was suppressed 85% in MGF-AS vs. MGF-EV. In MGF-S, Type IV collagen (Col-IV) was increased 4.2-fold.

Conclusions: MGF-S MC demonstrate increased mTOR with S6 kinase activation, consistent with their enhanced proliferation rate, while the increased VEGF and TGF beta1 promote Col-IV protein expression. Overexpression of MGF in MC to mimic events in diabetic glomeruli recreates many features of high glucose-exposed MC. MGF-AS MC demonstrate a role for MGF in basal VEGF and TGF beta1 expression.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO411

High Fat and High Sucrose Diet Induce Steatohepatitis That Is Dependent on Fructokinase Takuji Ishimoto,¹ Miguel A. Lanasa,² Shoichi Maruyama,¹ Richard J. Johnson,² ¹Nephrology, Nagoya Univ of Graduate School of Medicine, Nagoya, Aichi, Japan; ²Renal Diseases and Hypertension, Univ of Colorado Denver, Aurora, CO.

Background: High fructose intake from added sugars, which are high in Western diet, correlates with the epidemic rise in obesity, metabolic syndrome, nonalcoholic fatty liver disease, and chronic kidney disease. However, the interaction of fructose with high fat intake, which is also rich in Western diet, remains unclear. Here we tested the interaction between fructose and fat, and determined whether if this was dependent on a primary enzyme in fructose metabolism, fructokinase.

Methods: Wild type mice and fructokinase knockout mice (C57BL/6J background, male) were assigned to one of three groups (n = 8-9) respectively, matching mean body weight among the groups. Mice had free access to tap water, and a low fat (11%, LFD), high fat (36%, HFD) or high fat (36%) and high sucrose (30%) diet (HFHSD) for 15 weeks. Urine samples were collected at 13 weeks using metabolic cages. At 15 week, blood was withdrawn, and tissues including kidney and liver were taken after 6 h fasting.

Results: Both wild type mice fed HFD and fructokinase knockout mice fed HFD developed obesity with mild hepatic steatosis without hepatic inflammation compared to mice fed LFD. In contrast, wild type mice fed HFHSD developed more severe hepatic steatosis and low grade inflammation and fibrosis in pathological analysis, but not in fructokinase knockout mice. Increased CD68, TNF-alpha, MCP-1, alpha-smooth muscle actin, and collagen I and TIMP1 expression were found in wild type mice fed HFHSD. These changes were prevented in the fructokinase knockout mice. Meanwhile, there was no significant change of urinary protein and urinary NGAL, and no apparent renal pathological change among groups.

Conclusions: This study demonstrated an additive effect of high fat and high sucrose diet on the development of hepatic fat accumulation. Furthermore, the combination of sucrose with high fat diet may induce steatohepatitis. These results indicates the important role of fructose in the development of fatty liver and nonalcoholic steatohepatitis.

Funding: NIDDK Support

SA-PO412

The Succinate Receptor 1 Contributes to Obesity-Induced Type II Diabetes and Chronic Kidney Disease Peter M.T. Deen,¹ Claudia Carmone,¹ Janna A. Van diepen,³ Joris Hubertus Robben,¹ Ana Carolina Ariza,¹ Olivier Devuyt,² Rinke Stienstra.³ ¹Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Physiology, Univ of Zürich, Zürich, Switzerland; ³Internal Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Cell stress-induced release of mitochondrial succinate and activation of its SUCNR1 receptor in the macula densa is essential for type I diabetes mellitus (T1DM)-related renin release and hypertension. Obesity-induced T2DM and Chronic Kidney Disease (CKD) are aggravated by hypertension and go with cell stress in adipose/kidney tissue and macrophages, which express SUCNR1. Here we tested the role of SUCNR1 in obesity-induced T2DM and CKD.

Methods: Wild-type (wt) and SUCNR1^{-/-} mice were fed a low fat diet (LFD; 10%) or high (H) FD (60%). At different weeks, mice were weighed, and subjected to metabolic cages (electrolyte measurements), glucose tolerance tests (GTT). Mice were sacrificed and blood and tissues collected.

Results: Blood succinate was increased in diabetic patients versus healthy controls. Isolated adipose tissue of wt and SUCNR1^{-/-} mice revealed increased succinate release with hypoxia or high glucose. 16 weeks LFD/HFD showed similar body, adipose tissue and kidneys weight gain for both HFD groups, but liver and heart weight gain was reduced in HFD SUCNR1^{-/-} versus wt mice. Starving glucose levels were similarly increased in both HFD groups, but SUCNR1^{-/-} mice had a better GTT response. Inflammatory signals and macrophage infiltration was higher in adipose tissue of wt than SUCNR1^{-/-} HFD mice. Bone marrow derived cells of SUCNR1^{-/-} mice migrated less efficient towards chemotactic signals from diabetic/hypoxic 3T3 cells. Blood sodium and urine volumes were similarly decreased and eGFR increased in both HFD groups versus LFD controls. However, only HFD wt mice showed albuminuria, elevated collagen IV expression, and some increase in inflammatory gene expression in the kidney.

Conclusions: SUCNR1-mediated chemotaxis of macrophages to affected adipose tissue and, possibly, increased SUCNR1-mediated hypertension, contributes to obesity-induced T2DM and CKD development. If similar in humans, the SUCNR1 may form a novel therapeutic target for T2DM and CKD.

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Fluoxetine Disrupts E-Cadherin-Mediated Cell Adhesion and Calcium Homeostasis in Pancreatic β Cells Yun-wen Chen,¹ Huang-Yu Chang.¹ ¹Pharmacology, National Cheng Kung Univ, Tainan, Taiwan; ²Pharmacology, National Cheng Kung Univ, Tainan, Taiwan.

Background: Major depressive disorder (MDD) is a common psychiatric illness and it affects as many as 840 million people. MDD and Type 2 diabetes (T2D) are disorders with mutual risk factors identified in prevalence study reports. Antidepressant treatment could be another critical factor affecting the bidirectional associations between MDD and T2D. Long-term use of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of antidepressants, is associated with an increased risk of developing T2D. E-cadherin mediated cell-cell adhesion has been linked to diseases such as cancer and diabetes. Loss of cell-cell adhesion in beta cells decreases insulin secretion.

Methods: Here we examine the effects of the SSRI fluoxetine (Prozac®) on beta cell function employing MIN6 cells, a mouse beta cell line, to elucidate the underlying molecular mechanisms.

Results: We showed that fluoxetine treatment significantly reduced glucose stimulated insulin secretion (GSIS). We found that fluoxetine has no effect on the total expression of E-cadherin, but decreased the surface of E-cadherin. Moreover, fluoxetine triggered E-cadherin accumulating in cytosol, mainly localized in Golgi, not in endoplasmic reticulum (ER). Our immunohistochemistry showed that reduction cell surface E-cadherin is due to increased endocytosis. Moreover, ER calcium release and the activation of store-operated calcium entry (SOCE) were suppressed by fluoxetine.

Conclusions: Taken together, the results suggested that the impairment of E-cadherin and calcium homeostasis may be underlying mechanisms by which fluoxetine caused the reduction of GSIS in pancreatic beta cells.

Funding: Government Support - Non-U.S.

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Involvement of Ischemic Condition in the Pathophysiology of Renal Damages in Obesity-Induced Kidney Injury Koji Futatsugi, Hirobumi Tokuyama, Makiko Naitoh, Shu Wakino, Hiroshi Itoh. *Internal Medicine, Keio Univ School of Medicine, Tokyo, Japan.*

Background: We have reported hypertrophic proximal tubules in obese mice which implies an inefficient oxygen supply in this area (Obesity Int, 2012). We examined whether hypoxic condition in proximal tubules are involved the pathogenesis of obesity-induced renal injury. We also test the hypothesis that this injury can be ameliorated by molecular intervention of prolyl hydroxylase domains (PHDs), sensors for tissue oxygen levels that is a crucial molecule for tissue response to hypoxia.

Methods: Tissue hypoxic conditions were assessed by pimonidazole immunostaining. Peritubular capillaries (PTCs) were evaluated by counting CD34 stained vessels. Tamoxifen (Tam)-inducible proximal tubules-specific PHD2 deficient mice were created by crossing PHD2^{lox/lox} mice and Tam-inducible *N-myc downstream-regulated gene-1-Cre* mice on C57BL/6J backgrounds. These inducible conditional knock out (CKO) mice and their wild-type littermates (WT) were fed a high fat diet (HFD) or a low fat diet (LFD) for 12 weeks. The expressions of PHD2 and VEGF were measured by real-time PCR and immunohistochemistry.

Results: The WT mice on HFD manifested renal histological changes, including cellular enlargement of proximal tubules and a rarefaction of PTCs, which were consistent with more hypoxic area in proximal tubules than in WT mice on LFD. Urinary albumin and NGAL excretion were higher in HFD-fed mice, indicating ischemic tissue damage in proximal tubular area. However, expression of either PHD2 or VEGF was unchanged in HFD-fed WT mice, suggesting the lack of hypoxic tissue response in HFD-fed WT. Injecting Tam to HFD-fed CKO mice downregulated PHD2 in proximal tubules, increased VEGF expression, increased the number of PTCs, decreased hypoxic area, and attenuated proximal tubular damages and albuminuria.

Conclusions: Hypoxic condition due to enlarged cell with vascular rarefaction is evident in the proximal tubular area of obese mice whereas tissue reaction to hypoxic damages failed to properly compensate. The early reduction of PHD2 specifically in the proximal tubules constitute a novel strategy against the progression process from an early stage of obesity-induced kidney injury.

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Herbal Mixture of Radix Puerariae and Fructus Crataegi Prevents Renal Injury in Type 2 Diabetes via Inhibition of AKT/PI3K Zhengyue Chen.^{1,2} ¹Runliang Diabetes Laboratory, Diabetes Research Center, School of Medicine, Ningbo Univ, Ningbo, China; ²Div of Nephrology, Ningbo Urology and Nephrology Hospital, School of Medicine, Ningbo Univ, Ningbo, China.

Background: It has been reported recently that radix puerariae (RP) is one of the best herbal medicines for metabolic diseases, as it has pronounced anti-oxidative effects and helps improving insulin resistance and lowering blood sugar and lipids levels. Fructus crataegi

(FC) also possesses strong antioxidant activity in vitro. The present study was designed to investigate whether RP and FC together (RPFC) can prevent renal injury through a diabetic rat model generated by a high-fat diet and a low-dose streptozotocin (STZ).

Methods: A Type 2 diabetic model was generated by feeding rats with high fat diet followed by injecting a low dose of STZ. Rats were randomly divided into five groups: normal, high fat diet, diabetes mellitus, high fat diet plus RPFC prevention, and diabetes mellitus plus RPFC prevention. RPFC was given to rats daily by intragastric gavage for 3 weeks. The rats were monitored for body weight, blood glucose, oral glucose tolerance, blood insulin and lipids, serum creatinine and urea nitrogen, urinary protein. Renal pathological changes were examined with hematoxylin and eosin staining, periodic acid schiff staining, and Masson trichrome staining. The mRNA and protein levels of α -smooth muscle actin (α -SMA) and collagen IV in the kidney were detected by RT-PCR, Western blot and immunohistochemical staining. The levels of PI3K and AKT were determined by Western blot.

Results: Rats treated with RPFC showed reduced 24 h urinary protein excretion and decreased blood glucose level compared with corresponding vehicle treated rats, but RPFC prevention did not affect blood lipids. Glomerulus mesangial matrix expansion, renal capsule constriction, and renal tubular epithelial cell edema were less severe following RPFC prevention. Moreover, RPFC prevention markedly reduced protein levels of PI3K, AKT, α -SMA and collagen IV in the kidney of diabetic rats.

Conclusions: Combined prevention with RPFC may inhibit the PI3K/AKT pathway in the kidney, thereby preventing renal injury in diabetic rats.

Funding: Private Foundation Support

SA-PO416

High Protein Diet Markedly Accelerates Diabetic Nephropathy Whilst Nephrectomy Has Minor Effects in the BTBR ob/ob Mouse Model
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Background: There is a need for better mouse models that resemble the features of diabetic nephropathy (DN). The obese diabetic BTBRob/ob mouse was recently shown to mimic key features of human DN including progressive proteinuria and glomerular lesions.

Methods: In an attempt to enhance the progression of renal disease further we challenged the model through unilateral nephrectomy (performed at 7 weeks of age) or supplementation with high protein content diet (40%, from 10 weeks of age).

Results: BTBRob/ob mice exhibited hyperinsulinemia and hyperglycemia with elevated HbA1c. The urinary albumin excretion rate (AER) was increased 33-fold in intact and 34-fold in nephrectomised BTBRob/ob at 20 weeks age whereas high protein diet increased AER 332-fold in BTBRob/ob at 18 weeks age compared with lean controls. Plasma creatinine level was lower in intact (median 3.2 μ M) and nephrectomised (median 2.9 μ M) BTBRob/ob compared with lean controls (median 7.2 μ M) at 20 weeks. At 18 weeks age high protein treated BTBRob/ob also had lower creatinine (median 3.2 μ M) indicative of hyperfiltration. Morphological assessment of glomeruli demonstrated notable mesangial matrix expansion in BTBRob/ob mice at 20 weeks, which was slightly increased by nephrectomy. High protein diet (up to 24 weeks of age) resulted in a significant aggravation of renal pathology, with increased mesangial expansion as well as subcapsular and interstitial fibrosis. Moreover, the high protein diet increased GBM thickness and decreased the number of podocyte slits per mm GBM.

Conclusions: In conclusion, the BTBRob/ob mouse demonstrated renal injury with marked albuminuria and glomerular morphological alterations. Disease progression was not significantly advanced by nephrectomy and maintained an intact capacity of filtration comparable to lean mice. Using high protein content diet appears to be a straightforward method to aggravate BTBR ob/ob pathology, which enables new end points for efficacy studies and shortens cycle times.

Funding: Pharmaceutical Company Support - AstraZeneca

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Insulin Stimulates Renal Proximal Tubule Sodium Transport in Overt Type 2 Diabetic Nephropathy
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Background: We have previously shown that the insulin receptor substrate (IRS) 2-dependent stimulatory effect of insulin on renal proximal tubule (PT) transport is preserved in insulin resistant humans without nephropathy, facilitating hypertension in metabolic syndrome (Kidney Int 87:535-42, 2015). Whether this stimulatory effect of insulin is preserved in type 2 diabetes (T2D) with overt nephropathy remains to be determined.

Methods: Cell pH measurement with BCECF was performed to estimate the activity of Na-HCO₃ cotransporter (NBCe1) in isolated PTs from 55 week-old OLETF rats. Compared to control LETO rats, OLETF rats showed extensive mesangial expansion (glomerular injury score 1.6 vs 3.3) and overt proteinuria (1.5 vs 34 mg/mg Creat). NBCe1 activity was also determined in a T2D patient with renal carcinoma who had decreased eGFR (39.2 ml/min/1.73m²), massive proteinuria (2.5 g/g Creat), and histological changes compatible with overt diabetic nephropathy.

Results: The basal NBCe1 activities of OLETF rats and the patient were comparable to those of respective non-diabetic control rats and humans. Furthermore, 10⁻⁸ M insulin markedly stimulated the NBCe1 activity by 65% and 104% in OLETF rats and the patient, respectively. While the expression of insulin receptor was moderately reduced by 15%,

the expression of IRS1 was severely reduced by 80% in kidney cortex of OLETF rats. However, the expression of IRS2 was completely preserved in kidney cortex of OLETF rats. Insulin-mediated Akt phosphorylation was also preserved in kidney cortex of OLETF rats.

Conclusions: These data indicate that insulin can induce sodium retention via its effect on PT transport even in T2D with overt nephropathy, which may at least partially explain increased cardiovascular risk and volume expansion occasionally associated with intensive glycemic control in T2D CKD patients. On the other hand, the reduced expression of IRS1 in PT could be relevant to enhanced renal gluconeogenesis in T2D.

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SA-PO418

Modulation of Akt/AS160 Phosphorylation Mediates Insulin Resistance in a Rat Model of Metabolic Syndrome
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Background: Insulin resistance is the underlying pathophysiologic hallmark of metabolic syndrome (MS) which is most often associated with obesity. While adipokines and inflammatory cytokines have been incriminated in the insulin resistance of MS, the exact underlying mechanisms and signaling processes have not been defined. The current study assessed the molecular mechanisms of insulin signaling in the skeletal muscle in ZSF1 rats which have leptin receptor mutation and phenotypically manifest MS.

Methods: Obese ZSF1 rats were maintained from the 8th week and sacrificed at 24 or 32 weeks and fed on high calorie high fat diet (Purina 5008) while control rats (lean ZSF and SD) were fed normal rat chow. Body weights and water intake were monitored weekly and blood and urine samples were obtained at 8 weeks and at the time of sacrifice for chemistry analysis. Skeletal muscle and fat tissue were also harvested and homogenates were examined for the expression of proteins involved in insulin signaling such as adiponectin and its receptor, insulin receptor substrate 1 (IRS1), Akt and AS160 by western blots.

Results: The obese ZSF1 rats showed full blown MS with obesity, hyperlipidemia, hypertension and hyperglycemia while the lean ZSF and SD rats were normoglycemic. The expression of GLUT 4 was decreased in both skeletal muscle and fat tissue of obese rats. Studies done previously in our lab demonstrated that compared to non-diabetic rats, plasma adiponectin levels were lower in obese ZSF rats and adiponectin expression was decreased in fat tissue but not in skeletal muscle. The expression of adiponectin receptor 1 and insulin substrate receptor 1 (IRS1) were similar in all rats. Furthermore, the expression of phosphorylated Akt and AS160 were reduced by 74% and 38% in diabetic obese ZSF1 rats compared to non-diabetic controls.

Conclusions: Our results demonstrate that while GLUT4 expression in insulin sensitive tissues is decreased in obesity mediated diabetes, several intermediary steps in insulin signaling are unaltered. However the most consistent finding was reduced phospho Akt/AS160, which could be a major determinant of insulin resistance in obesity.

Funding: Private Foundation Support

SA-PO419

Murine Recombinant ACE2 Reduces Renal Fibrosis in Experimental Alport Syndrome (AS)
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Background: ACE2 is a monocarboxypeptidase in the renin angiotensin system that catalyzes the breakdown of angiotensin II (AngII) to angiotensin-(1-7) (Ang1-7). We have reported that ACE2 expression and activity in kidney are reduced in experimental Alport Syndrome (AS) but the impact of this finding on disease progression has not been studied.

Methods: Accordingly, we evaluated the effects of murine recombinant ACE2 (mrACE2) treatment in *Col4A3*^{-/-} mice, a model of AS characterized by proteinuria and progressive renal injury. mrACE2 (0.5 mg/kg/day) was administered from 4 -7 weeks of age via osmotic mini-pump.

Results: Treatment with mrACE2 led to an increased urinary ACE2 excretion, reduced renal AngII level and a correspondingly increased Ang1-7 level in 7-week-old *Col4A3*^{-/-} mice. Pathological structural changes and albuminuria in the mutant mice were both attenuated by mrACE2 administration. mrACE2 ameliorated kidney fibrosis in *Col4A3*^{-/-} mice as shown by decreased expression of profibrotic genes, less accumulation of extracellular matrix proteins and inhibition of the TGF- β signaling activation. Further, the increases in proinflammatory cytokine expression, macrophage infiltration, inflammatory signaling pathway activation and heme oxygenase-1 (HO-1) level in *Col4A3*^{-/-} mice were also reduced by mrACE2 treatment. Lastly, mrACE2 influenced the turnover of renal ACE2, as it suppressed the expression of TNF- α converting enzyme (TACE), a negative regulator of ACE2.

Conclusions: In summary, treatment with mrACE2 alters angiotensin peptide metabolism in the kidneys of *Col4A3*^{-/-} mice and attenuates the progression of AS nephropathy.

SA-PO420

Blockade of CDK9 and Smad3/4 Signaling Reduces Renal Fibrosis in Mice with Unilateral Ureteral Obstruction Jinhua Li,¹ Xinli Qu,¹ Xiaoyun Jiang,² John F. Bertram,¹ David J. Nikolic-Paterson.³ ¹Dept of Anatomy and Developmental Biology, Monash Univ, Clayton, Vic, Australia; ²Dept of Pediatrics, The First Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, Guangdong, China; ³Dept of Medicine, Monash Medical Centre, Monash Univ, Clayton, Vic, Australia.

Background: TGF- β 1/Smad signalling plays a central role in the pathogenesis of renal fibrosis. Smad3 and Smad4 are pro-fibrotic, while Smad2 is anti-fibrotic. However, these Smads form heterogeneous complexes the functions of which are poorly understood. This study investigated Smad complexes in renal fibrosis in mouse unilateral ureteric obstruction (UO).

Methods: UO was established in wild type mice, mice heterozygous or homozygous for Smad3 and/or Smad4 (Smad3^{+/+}, Smad3^{+/-}, Smad4^{-/-}). siRNA was used to knock down CDK9. CDK9 activity and Smad3 c-terminal phosphorylation was inhibited by a specific CDK9 inhibitor or a Smad3 inhibitor in cultured mouse renal fibroblasts and in UO.

Results: Smad3^{+/+} mice exhibited substantial protection from renal fibrosis on day 7 UO, whereas Smad2^{+/+} or Smad2^{4/+} mice showed only modest protection. Formation of Smad3/Smad4/CDK9 complexes was an early event following UO in wild type mice, which involved nuclear phosphorylation of the linker regions of Smad3. Smad3 or Smad4 deficiency significantly decreased the formation of Smad4/CDK9 or Smad3/CDK9 complex, Smad3 linker phosphorylation as well as renal fibrosis but at different degrees. In vitro, TGF- β 1 stimulation of collagen 1 promoter activity involved formation of Smad3/Smad4/CDK9 complexes, and over-expression of each component gave additive increases in collagen promoter activity. A CDK9 inhibitor or CDK9 siRNA significantly reduced TGF- β 1-induced interaction between Smad3 and Smad4, Smad3 linker phosphorylation and fibrotic response in mouse renal fibroblasts. Co-administration of the CDK9 inhibitor and the specific Smad3 inhibitor achieved better protection from TGF- β 1-induced fibrotic response in vitro and renal interstitial fibrosis in UO.

Conclusions: Our studies suggest that the formation of Smad3/Smad4/CDK9 complex drive renal fibrosis in the UO model. Formation of this complex represents a novel target for anti-fibrotic therapies.

Funding: Government Support - Non-U.S.

SA-PO421

Genetic Activation of Nrf2 Signaling Protects against Chronic Kidney Disease Roderick J. Tan,¹ Dionysios V. Chartoumpakis,³ Dong Zhou,² Brittney M. Rush,¹ Haiyan Fu,² Thomas W. Kensler,³ Youhua Liu.² ¹Medicine, Univ of Pittsburgh, Pittsburgh, PA; ²Pathology, Univ of Pittsburgh, Pittsburgh, PA; ³Pharmacology, Univ of Pittsburgh, Pittsburgh, PA.

Background: The Keap1/Nrf2 pathway is upregulated in kidney injury, leading to the expression of an array of cytoprotective genes with antioxidant, anti-inflammatory, and detoxifying roles. Keap1 inhibits Nrf2 by sequestering it in the cytoplasm. During oxidative/electrophilic stress, Keap1 undergoes conformational change that renders it inactive and Nrf2 accumulates and enters the nucleus to upregulate target genes. Pharmacologic inducers of this pathway (e.g. CDDO-Me) have harmful off-target effects. Therefore, more specific study of the Keap1/Nrf2 pathway with genetic approaches is necessary to determine its therapeutic potential in chronic kidney disease (CKD).

Methods: Keap1 hypomorphic (HM) mice have lower Keap1 expression and increased Nrf2 activity. We subjected HM and wild-type (WT) mice to two models of CKD: unilateral ischemia followed by 10 days of reperfusion (IR); and unilateral ureteral obstruction (UO). Kidney injury was assessed with serum creatinine, histology, western blotting and quantitative real-time PCR (qPCR) for injury markers.

Results: Compared to WT, HM mice had increased expression of numerous Nrf2-regulated genes after injury. In IR injury, HM mice were significantly protected from developing CKD, demonstrating decreased serum creatinine and renal fibrotic lesions compared to WT mice. Furthermore, HM mice had lower levels of fibronectin, α -smooth muscle actin, and TGF- β . Inflammation was also suppressed in HM mice, as was pathologic β -catenin signaling, which is known to play a role in CKD progression. Similar results were obtained in the UO model.

Conclusions: Most studies on the Keap1/Nrf2 pathway examine acute kidney injury or utilize pharmacologic agents with off-target effects. We demonstrate here that genetic enhancement of the Nrf2 pathway is protective in two models of CKD in mice, due to increased expression of cytoprotective genes as well as downregulation of β -catenin signaling. These studies suggest that the Keap1/Nrf2 pathway should remain a promising target in CKD treatment.

Funding: NIDDK Support, Private Foundation Support

SA-PO422

Early and Late Treatment with PBI-4050, an Orally Active Anti-Fibrotic Agent, Reduces Fibrosis and Increases Survival of 5/6-Nephrectomized Rats Lyne Gagnon, François Sarra-Bournet, Lilianne Geerts, Brigitte Groulx, Jean-Simon Duceppe, Boulos Zacharie, Pierre Laurin. ProMetic BioSciences Inc., Laval, QC, Canada.

Background: PBI-4050, a first-in-class orally active compound which is currently in clinical phase Ib/II in CKD patients, displays anti-fibrotic activities via a novel mechanism of action. In a double-blind ascending dose (400 to 2400 mg) clinical phase I, PBI-4050

was found to be safe and well tolerated up to 2400 mg without any significant side effect. The aim of this study was to investigate the effect of early (Day 21) and late (Day 84) treatment of PBI-4050 on 5/6-nephrectomized rats.

Methods: Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4050 (200 mg/kg, once a day) or vehicle was initiated at day 21 or at day 84, following randomization based on their glomerular filtration rate (GFR) results. GFR was measured at day 21 or day 84 and assessed every 3 weeks up to day 190 (early) or day 128 (late).

Results: Early treatment with PBI-4050 resulted in a significant improvement (up to threefold relative to control) in GFR. It also significantly reduced proteinuria. Histological lesion scores of kidney were also significantly ($p < 0.05$) decreased in PBI-4050-treated rats (2.7 ± 1.5) compared to control (3.9 ± 1.4), as determined by HPE, PAS and Masson's trichrome staining. Early treatment with PBI-4050 induced a significant reduction of urine MCP-1 level. Furthermore, early treatment with PBI-4050 reduced the overexpression of fibrotic (TGF- β 1, collagen 1 and α -SMA), pro-fibrotic cytokines (IL-23p19 and IL-6), remodeling (MMP2, SPARC and fibronectin), and oxidative stress (iNOS) markers. Late treatment with PBI-4050 resulted in mild improvement of GFR and serum creatinine level (reduction of 50 mmol/L) but most importantly in an increase in survival (55% non-treated versus 80% with late treatment) at day 128.

Conclusions: These results suggest that PBI-4050 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and may potentially improve residual kidney function in patients with end-stage renal failure.

SA-PO423

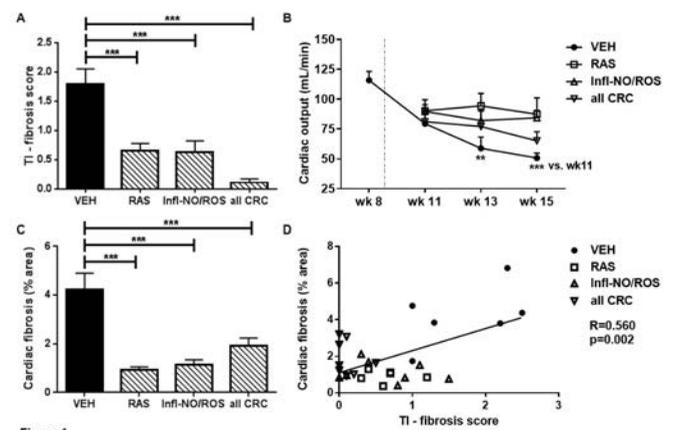
Targeting Cardiorenal Connectors Reduces Renal and Cardiac Fibrosis in Experimental Chronic Renocardiac Failure Nynke R. Oosterhuis,¹ Lennart G. Bongartz,¹ Branko Braam,³ Marianne C. Verhaar,¹ Roel Goldschmeding,¹ Carlo A. Gaillard,² Jaap A. Joles.¹ ¹UMC Utrecht, Netherlands; ²UMC Groningen, Netherlands; ³Univ of Alberta, Edmonton, Canada.

Background: Cardiorenal connectors (CRC) play a major role in progression of organ damage in renovascular failure (subtotal nephrectomy (SNX) followed by coronary ligation (CL)). We hypothesized that simultaneous inhibition of all CRC would be most effective in reducing cardiorenal fibrosis and functional decline.

Methods: In rats subtotal nephrectomy was followed by coronary ligation (wk 8) [Bongartz, AJP, 2012]. In wk 11 we administered losartan (RAS), or PDTC, tempol and molsidomine (Inflammation-NO/ROS) or all of these plus metoprolol (all-CRC) until wk 16.

Results: Tubulo-interstitial (TI) fibrosis decreased in all treated groups (fig 1A). However, renal function was not significantly affected by any treatment. Systolic dysfunction stabilized in all treated groups, but declined further in vehicle-treated rats (fig 1B). Cardiac fibrosis improved in all treated groups without significant additive effect of targeting all CRC (fig 1C). TI and cardiac fibrosis correlated (fig 1D). Only all-CRC reduced MAP. Diastolic hemodynamics and ventricular and cardiomyocyte size were not affected by any treatment. Reducing TI injury and renal and cardiac CTGF mRNA expression was most effective by targeting all CRC.

Conclusions: Pharmacological targeting of cardiorenal connectors in this model of chronic renovascular syndrome ameliorated the severity of cardiac and renal fibrosis and prevented further decline in systolic dysfunction.



SA-PO424

Fibroblast Growth Factor 23 Is Synthesised Locally by Renal Proximal Tubular Cells and May Be Pro-Fibrotic Edward Robert Smith,¹ Sven-Jean Tan,^{1,2} Stephen G. Holt,^{1,2} Tim Hewitson.^{1,2} ¹Dept of Nephrology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia; ²Dept of Medicine (RMH), The Univ of Melbourne, Melbourne, Victoria, Australia.

Background: Physiologically, FGF23 synthesis occurs predominantly in bone and regulates mineral handling in the kidney. In Chronic Kidney Disease, circulating levels become grossly elevated and are strongly predictive of disease progression, yet changes in FGF23 are not explained by increased osteocytic synthesis. Since extra-osseous FGF23

production is observed in diseased heart and vascular tissue, and is associated with the activation of pro-fibrotic cascades, the involvement of renal FGF23 synthesis and potential fibrogenic effects warranted investigation.

Methods: Kidneys were harvested from FVB mice at day 0 or after 3 or 9 days post-unilateral ureteric obstruction (UUO) (n=6). Paraffin-embedded sections were stained for FGF23 and with lectins to identify specific nephron segments. Total RNA was extracted from whole kidney tissue and laser-capture microdissected glomerular and tubular regions, and analysed by qPCR. Rat renal fibroblasts were cultured with exogenous recombinant human FGF23 and stained for α -smooth muscle actin (aSMA) to assess myofibroblast differentiation.

Results: Generalised low-level FGF23 protein staining was observed in proximal tubules at day 0, with more intense focal staining at days 3 and 9 post-UUO. Local FGF23 synthesis was confirmed by qPCR of whole kidney extracts, and specifically, in microdissected proximal tubular cells, but not glomeruli. Normalised FGF23 expression increased 11-fold in day 3 UUO relative to day 0 (both $p < 0.01$). Treatment of rat UUO fibroblasts with 10ng/mL FGF23 resulted in 4-fold increase in aSMA staining over 72h, equivalent to the effect of 1ng/ml transforming growth factor- β_1 (both $p < 0.01$).

Conclusions: Local renal FGF23 synthesis in proximal tubular cells is enhanced by tubulointerstitial injury and may augment myofibroblast differentiation.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO425

Quantitating Intracellular Oxygen Tension in Kidney by Phosphorescence Lifetime Measurement Yosuke Hirakawa,¹ Imari Mimura,¹ Toshitada Yoshihara,² Maso Kamiya,^{1,3} Yasuteru Urano,^{1,4,5} Seiji Tobita,² Masaomi Nangaku.¹ ¹Graduate School of Medicine, The Univ of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan; ²Dept of Chemistry and Chemical Biology, Gunma Univ, 1-5-1 Tenjincho, Kiryu, Gunma, Japan; ³PRESTO, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi, Saitama, Japan; ⁴Graduate School of Pharmaceutical Sciences, The Univ of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan; ⁵CREST, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi, Saitama, Japan.

Background: Hypoxia plays critical roles in the progression of chronic kidney disease, since intracellular reactions to hypoxia depend on intracellular oxygen (O_2) tension. However, existing techniques to detect intracellular hypoxia cannot quantify O_2 tension.

Methods: Phosphorescence lifetime (PL) measurement is reported to be useful to quantitate O_2 tension in vivo, however, most phosphorescent probes distribute extracellularly. Here we used BTPDM1, a lipophilic phosphorescent probe, to quantitate intracellular hypoxia in the kidney. We measured PL in Human Kidney 2 (HK-2) cells and murine kidney after BTPDM1 administration.

Results: We first made a calibration curve between PL and partial pressure of O_2 (pO_2) in HK-2 cells. Then we confirmed that BTPDM1 distributed in tubular cells *in vivo*. Next we measured PL of the murine kidney in normal condition, renal ischemia, hypoxemia and anemia. PL were calculated to be $1.8 \pm 0.2 \mu s$, $4.0 \pm 0.3 \mu s$, $2.8 \pm 0.2 \mu s$, $2.2 \pm 0.2 \mu s$, respectively. We also investigated chronic kidney damaged model mice of 7 days after 30 minutes unilateral ischemia-reperfusion (I/R) injury of kidney. PL of I/R injured kidney was longer than contralateral kidney ($2.2 \pm 0.2 \mu s$ vs $1.8 \pm 0.1 \mu s$). We also found an increase in pimonidazole adduct protein and a decrease in peritubular capillary density in I/R injured kidneys. We quantitated *in vivo* intracellular pO_2 by extrapolating the calibration curve in HK-2 cells. The intracellular pO_2 of normal kidney tubule was estimated to be 50mmHg, which was compatible with published value obtained by needle O_2 electrode.

Conclusions: Our novel technique allowed accurate estimation of intracellular O_2 tension of the normal and diseased kidney *in vivo* for the first time.

SA-PO426

Resveratrol Increases Expression of Heme Oxygenase-1 via Nrf2 Signaling to Ameliorate Renal Damage by Anti-Complement, Anti-Oxidative, and Anti-Apoptotic Effects in a Murine Model of Membranous Nephropathy Chia-chao Wu,^{1,2} Kuo-cheng Lu.³ ¹Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; ²Dept and Graduate Inst of Microbiology and Immunology, National Defense Medical Center, Taipei, Taiwan; ³Dept of Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic Univ, New Taipei City, Taiwan.

Background: Idiopathic membranous nephropathy (MN) is an autoimmune-mediated glomerulonephritis and a common cause of nephrotic syndrome in adults. There are limited available treatments for MN. We assessed the efficacy of resveratrol (RSV) therapy for treatment of MN in a murine model of this disease.

Methods: Murine MN was experimentally induced by cationic bovine serum albumin, with phosphate-buffered saline used in control mice. MN mice were untreated or given RSV. Disease severity and pathogenesis was assessed by determination of metabolic and histopathology profiles, lymphocyte subsets, immunoglobulin production, oxidative stress, apoptosis, production of heme oxygenase-1 (HO1) and signalings.

Results: MN mice given RSV had significantly reduced proteinuria and a marked amelioration of glomerular lesions. RSV also significantly attenuated immunofluorescent staining of C3 in the kidney. RSV treatment also reduced the production of reactive oxygen species, cell apoptosis, and upregulated heme oxygenase 1 (HO1). Inhibition of HO1 with tin protoporphyrin IX partially reversed the renoprotective effects of RSV. We show that concentration-dependent induction of HO-1 in E11 podocytes as RSV added. Nrf2 but not AMPK1/2 protein level can be upregulated by RSV. We find that an induction of Nrf2

exists at the HO-1 promoter regions segment #3 and #4 when RSV added. The Nrf2-specific siRNA attenuated the induction of HO1 mRNA by RSV. It suggests that increased Nrf2 at the HO1 promoter leads to elevated HO1 expression when RSV is exposed.

Conclusions: Our results show that RSV increased the expression of HO1 and ameliorated the effects of membranous nephropathy in a mouse model due to its anti-complement, anti-oxidative, and anti-apoptotic effects. RSV appears to have potential as a treatment for MN.

Funding: Government Support - Non-U.S.

SA-PO427

FVB Os/+ Mesangial Cells Exhibit Enhanced mTOR and Growth Factor Expression, Modeling the FVB Os/+ Glomerulosclerosis Mouse Yongxin Gao, Charles W. Heilig. *Medicine, Univ of Florida College of Medicine-Jacksonville, Jacksonville, FL.*

Background: We previously reported Fvb Os/+ mice which exhibit rapidly progressive glomerulosclerosis beginning within the first 2 weeks after birth. Here we examine primary culture mesangial cells (MC) from FVB Os/+ mice and FVB +/+ control mice to examine the phenotype of FVB Os/+ MC and identify cellular mechanisms which may contribute to glomerulosclerosis (GS) *in vivo*. FVB Os/+ MC have excess ECM production.

Methods: Primary culture MC were studied between passages 5-12. Western analyses were performed with specific antibodies against selected proteins to examine mTOR, phospho-S6 Kinase, and growth factor expression important to excess extracellular matrix (ECM) production. GLUT1 glucose transporter expression and 3H2-deoxyglucose uptake rates were also determined. $P < 0.05$ was considered significant for statistical analyses.

Results: GLUT1 and glucose uptake rate were both increased >2-fold in FVB Os/+ MC vs. FVB +/+ control MC, consistent with their increases in FVB Os/+ glomeruli. FVB Os/+ MC exhibited slowed proliferation consistent with the Os mutation. FVB Os/+ MC also had increased VEGF (1.6-fold) and TGF β 1 (2.7-fold), which likely contribute to the excess ECM production of these cells. The increased VEGF *in vitro* simulates increased VEGF in FVB Os/+ glomeruli *in vivo*. MGF was increased in FVB Os/+ MC (2.7-fold), mimicking increased glomerular MGF *in vivo*. We previously found MGF stimulates VEGF and TGF β 1 in MC. FVB Os/+ MC carry the Os mutation which impairs cell division, explaining their slow proliferation. Consistent with this, phospho-ERK1/2 was reduced 66%. In spite of increased mTOR (3.8-fold) and downstream phospho-S6 kinase (5.2-fold), the cells could not proliferate normally.

Conclusions: FVB Os/+ MC exhibit growth factor expression simulating glomerular growth factor expression *in vivo* in these mice. MGF expression is increased both in glomeruli *in vivo* and MC *in vitro*. MGF is a stimulus to VEGF and TGF β 1 expression as observed here. These growth factors are associated with excess ECM production in FVB Os/+ MC, despite suppressed Erk1/2, indicating another pathway is important to excessive ECM production.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO428

Role of Sodium-Glucose Linked Cotransporter-2 Inhibitor in the Kidneys of Salt Sensitive Hypertension Mikako Hisamichi,¹ Atsuko Ikemori,^{1,2} Takeshi Sugaya,¹ Kenjiro Kimura,³ Yugo Shibagaki.¹ ¹Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; ²Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; ³Dept of Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Sodium-glucose linked cotransporter-2 (SGLT2) is expressed in the apical side of the proximal tubules and can transport not only glucose but also sodium. Because salt is an aggravated factor for the salt sensitive hypertensive renal injury model, SGLT2 expression may be related to the progression of renal injury due to salt sensitive hypertension. The aim of this study is to reveal the role of SGLT2 inhibitor in angiotensin II (Ang II) induced renal injury.

Methods: Male C57/BL6 wild-type mice were divided into three groups: The Ang II group was systemically infused with Ang II for 16 days. The SGLT2 inhibitor (SGLT2-I) group was given an oral dose of the dapagliflozin SGLT2 inhibitor of 1mg/kg/daily in addition to an injection of Ang II. The control group was injected with a vehicle.

Results: In both the Ang II and the SGLT2-I groups, the degree of hypertension, the glycemic levels in blood and the body weight were similar. Renal gene expressions of angiotensinogen and SGLT2 significantly increased in both the Ang II and the SGLT2-I groups than the control group. Renal gene expression of the angiotensinogen in the SGLT2 inhibitor group tended to be lower than that in the Ang II group. The degree of macrophage infiltration and urinary albumin levels tended to be lower in the SGLT2-I group than in the Ang II group. These results suggested that SGLT2 inhibitor may attenuate the renal damage due to salt sensitive hypertension via inhibiting the activation of renal renin angiotensin system.

Conclusions: In conclusion, SGLT2 inhibitor may be a useful treatment of hypertensive renal disease.

SA-PO429

The Renoprotective Effect of Nuclear 1 Factor Related Factor 2 (Nrf2) Activator, Bardoxolone Methyl, in Aldosterone and High Salt-Induced Renal Injury Mikako Hisamichi,¹ Atsuko Ikemori,^{1,2} Takeshi Sugaya,¹ Kenjiro Kimura,³ Yugo Shibagaki.¹ ¹Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; ²Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; ³Dept of Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Activation of nuclear 1 factor related factor 2 (Nrf2) is reported to have anti-oxidant and anti-inflammatory effects. In the aldosterone (Ald) and high salt-induced renal injury model using mice, we previously reported that severe tubulointerstitial damage was provoked by oxidative stress. The aim of this study is to reveal the renoprotective effect of the Nrf2 activator in this model.

Methods: To evaluate the degree of tubulointerstitial damage using the urinary liver type fatty acid binding protein (L-FABP), known as a biomarker of the tubulointerstitial damage, we used human L-FABP chromosomal transgenic (L-FABP^{+/+}) mice. Male L-FABP^{+/+} mice were divided into three groups: The Ald group received systemic aldosterone infusions via an osmotic minipump and were given 1% NaCl water for 14 days. The Ald-Nrf2 group was given Bardoxolone Methyl of the Nrf2 activator intraperitoneally at a dose of 10mg/kg/daily in addition to an injection of aldosterone and salt. The control group was given only a vehicle.

Results: The gene expression of MCP-1, the gene expression of RANTES, the gene expression of collagen type I and III and the degree of macrophage infiltration were significantly greater in the kidneys of the Ald group compared to those in the control, and renal inflammatory reaction and renal fibrosis were significantly attenuated in the Ald-Nrf2 group. The degree of renal hL-FABP gene expression and urinary hL-FABP levels increased in the Ald group compared to the control and decreased in the Ald-Nrf2 group.

Conclusions: The Nrf2 activator, Bardoxolone Methyl, could attenuate renal oxidative stress induced by aldosterone and high salt, and consequently, renal inflammatory reaction and the production of renal collagen were prevented. Bardoxolone Methyl may be a useful treatment for renal disease.

SA-PO430

Detection of Mesangial Tissue Transglutaminase Activity in Human Kidney Biopsy Specimens Kazuo Takahashi,^{1,2,6} Tomohiro Mizuno,^{1,2} Takanori Onouchi,¹ Shin'ichi Akiyama,^{1,3} Hideki Tatsukawa,⁴ Mamoru Kusaka,¹ Tadashi Nagamatsu,² Yutaka Tsutsumi,¹ Shoichi Maruyama,³ Hiroshi Kitamura,⁵ Jan Novak,⁶ Kiyotaka Hitomi,⁴ Yukio Yuzawa.¹ ¹Fujita Health Univ School of Medicine, Toyoake, Aichi, Japan; ²Meijo Univ, Nagoya, Aichi, Japan; ³Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan; ⁴Nagoya Univ Graduate School of Pharmaceutical Sciences, Nagoya, Aichi, Japan; ⁵NHO Chiba-East Hospital, Chiba, Japan; ⁶Univ of Alabama at Birmingham, Birmingham, AL.

Background: Tissue transglutaminase (TG2) is a protein-cross-linking enzyme that plays an important role in tubulointerstitial fibrosis in animal models of chronic kidney disease and diabetic nephropathy. However, its pathological significance in human glomerular diseases remains unclear. TG2 transforms into catalytically active TG2 through conformational changes. Thus, it is crucial to detect catalytically active TG2 to assess the role of TG2 in human biopsy samples.

Methods: A total of 241 renal biopsy specimens obtained between January 2010 and December 2013 were assessed for TG2 activity by immunofluorescence microscopy with FITC-labeled highly reactive TG2 substrate peptides.

Results: Thirty-five of 65 (56%) patients with IgAN, 23 of 40 (58%) patients with lupus nephritis (LN), and 7 of 11 (64%) patients with secondary IgAN, including 8 IgA vasculitis patients, exhibited mesangial TG2 activity. In contrast, only 7 of 125 (6%) patients with other kidney diseases showed mesangial TG2 activity. IgAN patients with mesangial TG2 activity had higher levels of proteinuria (1.2 vs. 0.5 g/day, $P < 0.01$) and a higher mesangial score defined by the Oxford classification (0.53 vs. 0.38, $P = 0.03$) than those without mesangial TG2 activity. LN patients with mesangial TG2 activity showed higher presence of hematuria more than 20/hpf (39% vs. 0%, $P < 0.001$) and had histological evidence of active lesions more frequently than patients without mesangial TG2 activity (83% vs. 35%, $P < 0.001$).

Conclusions: Immune-complex mediated glomerulonephritis such as IgAN, LN, and IgA vasculitis frequently have the active form of TG2 in the mesangial area. This assay for mesangial TG2 activity may represent a useful new diagnostic test.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin Co., Otsuka Pharmaceutical Co., Baxter, Chugai Pharmaceutical Co., Mitsubishi Tanabe Pharmaceutical Co., Government Support - Non-U.S.

SA-PO431

Renoprotective Effect of Xanthine Oxidoreductase Inhibitor, Topiroxostat, in Hyperuricemic-Induced Renal Injury Atsuko Ikemori,^{1,2} Takeshi Sugaya,² Mikako Hisamichi,² Kenjiro Kimura,² Yugo Shibagaki.² ¹Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; ²Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; ³Dept of Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Hyperuricemia is known to be a risk factor of chronic kidney disease. The aim of this study is to reveal the effect of xanthine oxidoreductase inhibitor, Topiroxostat in a model of hyperuricemic renal disease provoked by adenine-containing diet.

Methods: To evaluate the degree of tubulointerstitial damage using urinary liver type fatty acid binding protein (L-FABP) known as a biomarker of the tubulointerstitial damage, we used human L-FABP chromosomal transgenic (Tg) mice. Male Tgmice (n=24) were fed a 0.2% w/w adenine-containing diet. Two weeks later from the start of the diet, renal dysfunction of these mice were confirmed and were divided into the four groups: the adenine group was given only the diet containing adenine. The Febuxostat (Feb) group and the Topiroxostat high (Top-H) or low (Top-L) groups were given the diet containing each Feb (3mg/kg), Top-H (3mg/kg), Top-L (1mg/kg) in addition to adenine for another 2 weeks. Thereafter, adenine-containing diet was stopped, only each medication was continued for additional 2 weeks and the kidneys in each group were removed.

Results: Renal dysfunction, the degree of macrophage infiltration, tubulointerstitial damage and renal fibrosis were significantly attenuated in the kidneys of the Feb, the Top-L and the Top-H groups compared to those in the adenine group. Serum uric acid levels and renal xanthine oxidoreductase activity in the Feb, the Top-L and the Top-H groups were significantly lower than those in the adenine group. Those levels in the Top-H group were significantly lower than those in the Feb group. Urinary excretion levels of L-FABP in both the Top-H and Top-L groups were significantly lower than those in both the adenine and Feb groups.

Conclusions: In conclusion, Topiroxostat attenuated the renal damage induced by hyperuricemia and may be a useful treatment for hyperuricemic renal damage.

Funding: Private Foundation Support

SA-PO432

Accumulation of Indoxyl Sulfate in Renal Tubular Cells Aggravates Kidney Injury in Rats with 5/6 Nephrectomy Ayano Konagai, Kaori Kikuchi, Ayako Fujieda, Sumie Goto, Hiroko Iijima, Yoshiharu Itoh. *Pharmaceuticals Division, Kureha Corporation, Tokyo, Japan.*

Background: Indoxyl sulfate (IS), a representative uremic toxin, is detected in renal tubular cells of CKD patients and 5/6 nephrectomized rats administered with IS. It has been suggested that the retention of IS is induced through organic anion transporters in the basolateral membrane of renal tubular epithelial cells and this retention leads to nephrotoxicity. However, the mechanism for IS accumulation in renal tubules remains unclear. To reveal the correlation between IS accumulation and renal dysfunction in 5/6 nephrectomized rats, we investigated the expression of transporters in the apical or basolateral membrane and of markers for renal injury, and a content of IS in renal tubular epithelial cells using a novel antibody against IS.

Methods: To study the serum concentration of IS, we used high-performance liquid chromatography (HPLC) and our newly developed enzyme-linked immunosorbent assay (ELISA). The renal sections from the rats were stained with the antibody for IS. The expression of the transporters in renal tubular cells and the markers for renal injury such as Kidney Injury Molecule-1 (KIM-1) were detected by immunohistochemistry.

Results: Serum level of IS was identified to be increased in the 5/6 nephrectomized rats compared to the normal rats by the newly ELISA. The new system could sensitively detect the low concentration of IS. The value determined by ELISA is in a good correlation with HPLC. Immunohistochemistry showed a significant IS staining in renal sections of the model rats. We found the presence of IS in hypertrophic tubular cells, where the expression of a transporter in the apical membrane mediating IS secretion was decreased, while the expression of a transporter in the basolateral membrane was retained. KIM-1, the marker for early kidney injury, was highly expressed in some tubules, but not in the IS positive cells.

Conclusions: Our findings suggest that IS is accumulated in renal tubular cells at the later stage of renal injury due to unbalance expression of transporters between in the apical membrane and in the basolateral membrane, and this accumulation aggravates kidney injury.

Funding: Pharmaceutical Company Support - KUREHA corporation

SA-PO433

IL-15 as a Potential New Therapeutic Treatment for Renal Fibrosis L. Lecru,¹ A. Devocelle,¹ V. Le coz,¹ C. Gallerne,¹ S. Ferlicot,² A. Durrbach,¹ P. Eid,¹ B. Azzarone,¹ H. Francois,¹ J. Giron-michel,¹ ¹UMRS Inserm 1197, Villejuif, France; ²Bicetre Hospital, Kremlin-Bicetre, France.

Background: The human epithelial cells of various tissues produce interleukine-15 (IL-15), which acts not only on immune cells, but also on epithelial cells, mainly via its anti-apoptotic action. Thus, human and mouse renal tubular epithelial cells (RPTEC) constitutively secrete IL-15. Our group recently reported that IL-15 preserves epithelial phenotype in human kidney tubular cells since IL-15 is sufficient to inhibit EMT commitment of RPTEC. Therefore, the goal of our study is to explore the renoprotective potential of IL-15 *in vitro* and *in vivo* in renal fibrosis.

Methods: Our study sought to examine if IL-15 could inhibit EMT in tubular epithelial cells *in vitro* and therefore ameliorate tubulointerstitial fibrosis using the unilateral ureteral obstruction model (UUO) in mice. We also analyzed IL-15 expression in various human nephropathies.

Results: IL-15 expression decreased in human renal disease and in mice during UUO ($p < 0.05$, $n = 19$). IL-15 treatment coupled with its soluble receptor (IL-15/IL-15R α), prevents interstitial fibrosis during UUO ($10.7 \pm 1.1\%$ in control group, vs $8.2 \pm 0.7\%$ in IL-15 treated mice and $6.4 \pm 0.6\%$ in IL-15/IL-15R α treated mice, $p < 0.01$, $n = 7$ mice/group), quantified by Sirius Red and Western Blot, through two different mechanisms. We first found a reduction of macrophages infiltration associated with a decrease of MCP1 expression in IL-15 and IL-15/IL-15R α treated mice ($p < 0.05$, $n = 7$ mice/group). IL-15 also reduced TGF β 1-induced EMT *in vitro* on RPTEC and tubular cell line (HK2) ($p < 0.05$). This protective effect of IL-15 acted through Snail inhibition and C-Jun activation ($p < 0.05$). Furthermore, we found a direct inhibition of IL-15 on collagen synthesis, in both HK2 (collagen IV) and myofibroblasts (collagen I and III).

Conclusions: In conclusion, IL-15 can attenuate TGF β 1-induced EMT by acting directly through a reduction of collagen synthesis, both on myofibroblast, the main effector of fibrosis, and tubular cell. IL-15 also modulates macrophages infiltration *in vivo* in UUO. Therefore IL-15 could be a novel therapeutic player in renal diseases.

SA-PO434

Loss of the Vascular Class 3 Semaphorin, Semaphorin 3G, Leads to Attenuated Fibrosis and Reduced Tubular Injury by Unilateral Ureteral Obstruction in Mice Kana Ide,¹ Yoshiro Maezawa,¹ Shintaro Ide,¹ Christer Betsholtz,² Minoru Takemoto,¹ Koutaro Yokote.¹ ¹*Clinical Cell Biology and Medicine, Chiba Univ Graduate School of Medicine, Chiba, Japan;* ²*Dept of Immunology, Genetics and Pathology, Uppsala Univ, Uppsala, Sweden.*

Background: Chronic kidney disease (CKD) is a large social health issue, affecting 10-16% of the adults worldwide. In advanced stage of CKD, tubulointerstitial fibrosis occurs and promotes renal failure. Although a number of cell types and secretory factors are known to be involved in the formation of renal fibrosis, its precise mechanisms are still unclear. Semaphorin 3G (Sema3G) belongs to a class 3 family of secreted semaphorin. Class 3 semaphorins binds to neuropilin receptors and plexin coreceptors, showing various biological functions in neural development, angiogenesis, immunological response, and tumorigenesis. In the kidney, Sema3G is expressed in podocytes and endothelial cells of extraglomerular blood vessels. However, its role in renal fibrosis is still unknown.

Methods: To understand the role of Sema3G in renal fibrosis, Sema3G knockout mice and control mice are subjected to unilateral ureteral obstruction (UUO).

Results: Histologically, UUO kidneys does not show obvious difference between controls and Sema3G KO. However, although mRNA expression of Tgfb and Snail, a key regulator of Tgfb-induced fibrosis, increases by UUO in controls, these increases are attenuated in Sema3G KO UUO kidneys (for Tgfb, 55% suppression compared to controls, $P < 0.01$). In addition, mRNA expression of Acta2 and Fibronectin, and serum BUN level tend to be reduced in Sema3G KO after UUO. Expressions of inflammatory markers do not show a consistent tendency. Interestingly, increase of a tubular injury marker, Kim-1, after UUO is largely suppressed in Sema3G KO mice (77% suppression compared to controls, $P < 0.05$ at day3, 95% suppression, $P < 0.01$ at day7), suggesting that Sema3G KO mice are protected from tubular injury.

Conclusions: Together, these data demonstrate that endothelial Sema3G acts on adjacent tubular/interstitial cells and promotes fibrosis by UUO. Identification of the mechanism of this interaction would provide new therapeutic targets for CKD and renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO435

Leukemia Inhibitory Factor Attenuates Tubulointerstitial Fibrosis in Unilateral Ureter Obstruction Sebastian Alexander Potthoff, Fabian Srugies, Lars C. Rump, Ivo Quack. *Nephrology, Medical Faculty - Heinrich Heine Univ Duesseldorf, Duesseldorf, Germany.*

Background: Tubulointerstitial fibrosis is common in chronic kidney disease which is often sustained by chronic inflammation. CD4+ T-cells play an important role in immune response in kidney disease. Leukemia inhibitory factor (LIF), a member of the Interleukin 6 family, and Interleukin 6 (IL-6) play a crucial role in regulating the balance between Th17- and regulatory T-cells (Treg): LIF augments expression of forkhead-box-P3 (Foxp3) leading to Treg. IL-6 induces RAR-related orphan receptor gamma (ROR γ) driving Th17 lineage development. Dysregulation or overproduction of Th17 cells result in sustained inflammation. Here, we investigate how LIF influences renal inflammation and tubulointerstitial fibrosis in unilateral ureter obstruction (UUO).

Methods: 6-8-week old male C57BL/6 mice were treated intraperitoneally daily either with LIF (10 μ g/kgBW; $n = 7$) or PBS (control; $n = 8$) starting 2 days prior to UUO. At day 10 after UUO, kidneys, spleen and paraaortal lymphnodes were extracted.

Results: qPCR from tissue lysates of obstructed kidneys (OB) revealed that NF κ B and RANTES as well as collagen1 and TGF- β were significantly downregulated in LIF treated mice. There was no significant difference between IL17a, IL-1b, MCP1, IL-6, TNF α , PAI1 and PDGFR1. Accordingly, expression of MCP1, NF κ B, RANTES and TNF α in the paraaortal lymphnodes were reduced by LIF. IL-1b and IL-6 expression tended to be reduced by LIF but failed to reach statistical significance. CD3+ cells accumulated in obstructed kidneys. LIF significantly reduced renal infiltration of CD3+ cells (OB vs. OB+LIF: 144 ± 6 vs. 115 ± 8 ; $p < 0.01$) and F4/80+ cells. LIF treatment significantly reduced

tubulointerstitial fibrosis in obstructed kidneys assessed by Sirius Red morphometry (OB vs. OB+LIF: 10.3 ± 2.4 vs. 5.1 ± 1.2 % area; $p < 0.05$) and collagen1 Western Blot analysis (OB vs. OB+LIF: 0.77 ± 0.12 vs. 0.32 ± 0.09 arbitrary units; $p < 0.01$).

Conclusions: These data confirm the critical role of inflammation in UUO. LIF treatment significantly attenuates tubulointerstitial fibrosis by inhibiting pro-inflammatory pathways and T-cell infiltration indicating a possible future treatment option.

Funding: Clinical Revenue Support

SA-PO436

Dendritic Cell-Specific Shp-1-Knockout Mice Spontaneously Develop Unique Glomerulo- and Tubulointerstitial Nephritis Mitsuharu Watanabe,¹ Keiju Hiromura,¹ Yoriaki Kaneko,¹ Masato Kinoshita,¹ Yuko Ohishi,¹ Toru Sakairi,¹ Hidekazu Ikeuchi,¹ Akito Maeshima,¹ Hiroshi Ohnishi,² Takashi Matozaki,³ Yoshihisa Nojima.¹ ¹*Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Japan;* ²*Dept of Laboratory Sciences, Gunma Univ Graduate School of Health Sciences, Japan;* ³*Div of Molecular and Cellular Signaling, Dept of Biochemistry and Molecular, Kobe Univ Graduate School of Medicine, Japan.*

Background: Src homology 2 domain-containing protein tyrosine phosphatase-1 (Shp-1) is a nonreceptor-type protein tyrosine phosphatase, which is highly expressed in hematopoietic cells. We have previously reported that dendritic cell (DC)-specific Shp-1 conditional knockout mice (CKO) spontaneously developed pneumonitis and nephritis at around 40 wks of age, together with anti-dsDNA antibody (J Immunol. 2012; 188, 5397). In the current study, we further characterize the renal lesions in the CKO mice.

Methods: CKO mice were generated by mating Shp-1-flox mice and CD11c-Cre mice. Mice were sacrificed at 8, 20, and 40 wks or later.

Results: Compared to control mice, CKO mice showed significantly higher serum creatinine at 40 wks or later. Anti-dsDNA antibody was detected at low levels at 8 wks and markedly elevated at 20 and 40 wks. At 40 wks, CKO mice showed severe proliferative glomerulonephritis and tubulointerstitial nephritis by light microscopy with mesangial IgG and C3 depositions by IF staining. Electron microscopy revealed electron dense depositions in mesangial area, but few in subendothelial or subepithelial area. Immunohistochemical staining showed marked accumulation of DCs (CD11c⁺), macrophages (F4/80⁺) and helper T cells (CD4⁺) at periglomerular and tubulointerstitial area. Infiltration of numerous DCs was also observed within glomeruli. Flow cytometric analysis of the CKO kidney showed the inflammatory cells increased with increasing age. Despite the prominent morphological changes, there was no significant increase of albuminuria, even at 40 wks.

Conclusions: The DC-specific ablation of Shp-1 in mice resulted in development of unique autoimmune glomerulo- and tubulointerstitial nephritis, which is distinct from typical lupus nephritis characterized by wire-loop lesions and heavy proteinuria.

Funding: Government Support - Non-U.S.

SA-PO437

TLR4 Mutant Mice Are Protected from Renal Fibrosis following Folic Acid Injection Ana C. Souza,¹ Irina Baranova,² Alexander V. Bocharov,² Jonathan Street,¹ Xuzhen Hu,¹ Kenneth J. Wilkins,¹ Peter S.T. Yuen,¹ Robert A. Star.¹ ¹*Kidney Diseases Branch, NIDDK, NIH, Bethesda, MD;* ²*Clinical Center, NIH, Bethesda, MD.*

Background: Local renal inflammation contributes to interstitial fibrosis (IF). Toll-like receptor 4 (TLR4) drives inflammation/ inflammasome and is expressed on renal epithelial cells (RECs). In the folic acid (FA) model of renal fibrosis there is an acute phase of acute tubular damage and a later phase of IF. To evaluate the role of TLR4 in renal inflammation-fibrosis, we analyzed the degree of inflammation that is dependent on TLR4 in RECs from WT or TLR4 mutant mice subjected to LPS. We further compared IF following FA injection in both strains.

Methods: Primary cultures of RECs isolated from WT or TLR4 mutant mice were incubated for 20h with increasing doses of LPS. Supernatant IL-6 was measured by ELISA. Total RNA was extracted, and RTqPCR performed for IL-6, IL-1 β , NLRP3, and GAPDH. Results were normalized by protein content. Exact stratified Wilcoxon test was used for differences. *In vivo*, FA (250 mg/kg IP) was given to 9 wk old TLR4 WT or mutant mice ($N = 16$ /group). Day 2 BUN was used as an AKI marker. Mice with [day 2:baseline BUN] ratio above 1.5 were included. At day 14, mice were euthanized and kidneys harvested for IF by Masson trichrome stain. Changes in IF (after adjusting for day 2 log BUN) were analyzed by regression analysis.

Results: LPS dose-dependently increased IL-6 secretion in TLR4 WT RECs, but TLR4 mutant RECs secreted very low levels of IL-6, and IL-6 mRNA expression was 7-fold lower than WT cells. TLR4 mutant RECs expressed less NLRP3 (2-fold), and IL-1 β (40-fold). Day2 log BUN was not different between the groups at day 2, and correlated with day 14 IF ($p < 0.01$). After adjustment for day2 log BUN, TLR4 mutant mice were protected from IF at day 14 ($p = 0.014$). Renal mRNA expression of IL-6, TNF- α , and TGF- β were not different between the strains at day 14.

Conclusions: *In vitro*, TLR4 signaling can stimulate inflammasomes and inflammatory cytokine production RECs. *In vivo*, although TLR4 is not required for the acute phase injury, the TLR4-mutant is protected from interstitial fibrosis, potentially via reduced sensitivity to DAMPs released after acute injury.

Funding: NIDDK Support

SA-PO438

A New Mouse Model of Glomerular Foam Cell Accumulation in Disease
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Background: Foam cells are lipid-laden cells of monocyte/macrophage origin which have a key role in the development of atherosclerosis. Similar foam cells are found in human kidney biopsies in various diseases (e.g. tip and cellular variants of focal segmental glomerulosclerosis (FSGS), diabetic nephropathy, and the interstitium in nephrotic states). The pathophysiologic significance of foam cells in the kidney is poorly understood, in part due to lack of good animal models. We sought to develop a robust animal model for foam cell accumulation in the kidney to test their pathogenic significance.

Methods: Six-week old apolipoprotein E (Apo E)-null C57BL/6 mice were divided into two groups. Group 1: Mice were gavaged daily with 1% hydropropyl methyl cellulose with 0.1% tween 80 (HPMC-Tween) (10ml/kg) for 30 days. Group 2: Untreated age-matched controls. Each organ including kidney was harvested for histologic evaluation. Immunohistochemical stains (IHC) for Mac2 were performed to quantify the state of monocyte/macrophage infiltration and urinalysis was conducted to calculate the urine albumin-creatinine ratio (ACR) and total albumin excretion.

Results: IHC for Mac2 revealed that 83.76% of glomeruli were infiltrated by foam cells in the HPMC-Tween treated group. Most showed several foam cells in each glomerulus. Neither FSGS nor mesangiolysis nor interstitial foam cell accumulation developed in the treated mice despite the prominent glomerular foam cells. Additionally, there was no significant difference in ACR between treated group and control group, although the treated mice revealed a trend of higher urine ACR, compared with pre-treatment urine.

Conclusions: Treated mice developed widespread glomerular foam cells. FSGS, mesangiolysis, or interstitial changes that are features of human renal foam cell injury did not develop within the limited 30 day observation period during which foam cells accumulated. We speculate affected mice may not have had sufficient time to develop sclerosis. Apo E null mice treated with HPMC-Tween has potential to be a good animal model for the studies of the tip and cellular variants of FSGS, for which no good mouse models currently exist.

Funding: Pharmaceutical Company Support - Genzyme

SA-PO439

Aberrant Methylated DNA Regions Lead to Low Activation of CD4⁺ T Cells with a Consequent Imbalance of the Th1/Th2 Polarization in IgA Nephropathy Patients
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Background: The immunoglobulin A nephropathy (IgAN) pathogenesis has a strong genetic component. In this setting, also the DNA methylation could be an important factor influencing the pathology. Aim of our study was the identification of abnormally methylated regions in CD4⁺T cells of IgAN patients.

Methods: A genome-wide screening of the DNA methylation CD4⁺T cells from 6 IgAN patients and 6 healthy subjects (HS) was performed. Differentially methylated regions have been validated on 40 samples of IgAN and HS by pyrosequencing and functional studies by 5-aza-2'-deoxycytidine and MSP-RT-PCR. The gene expression was verified by RT-PCR. Activation of CD4⁺T cells was studied by BrdU proliferation assays and IL2 and IL4 ELISA.

Results: We found 161 tiling regions, 12 promoters, 12 genes and 5 CpG islands differentially methylated. Three regions differentially methylated included genes involved in the response and proliferation of CD4⁺ T cells. In particular, we identified a hypermethylated region containing the gene coding for the miR-886 precursor and two hypomethylated regions containing TRIM27 and DUSP3 genes involved in the T cell receptor (TCR) signaling. We showed that these genes were dysregulated due to the aberrant methylation in IgAN patients. Moreover, we demonstrated that the hypermethylation of miR-886 precursor led to a decreased CD4⁺ T cell proliferation following TCR stimulation and to an over-expression of the TGFβ, also regulated by the miR-886 precursor.

Conclusions: We describe, for the first time, some DNA regions abnormally methylated in IgAN patients, some of which including genes involved in the TCR signalling and CD4⁺ T cell response and proliferation. These abnormalities led to a reduced activation of CD4⁺ T cells with a consequent T helper cell imbalance. These findings may play an important role in the pathogenesis of IgAN.

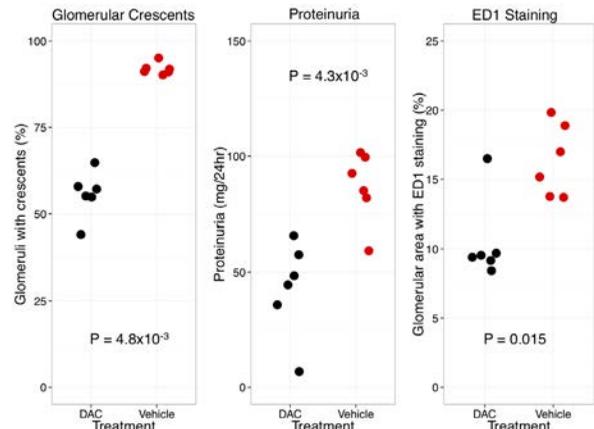
SA-PO440

5-Aza-2-Deoxycytidine Reduces Nephrotoxic Nephritis and DNA Cytosine Methylation in Nephritic Glomeruli and Macrophages In Vitro
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Background: Nephrotoxic nephritis (NTN) is a macrophage dependent rat model of crescentic glomerulonephritis (CRGN). We investigated whether DNA cytosine methylation could determine dysregulation of macrophage activity and contribute to CRGN susceptibility, by examining the effect of 5-aza-2'-deoxycytidine (DAC), an inhibitor of DNA methylation, on NTN phenotypes and DNA methylation in both nephritic glomeruli and bone marrow derived macrophages.

Methods: NTN was induced in male WKY rats. 6 rats were treated with intra peritoneal DAC and 6 controls with vehicle only. Treatment was given every three days prior to sacrifice at 10 days and then NTN phenotypes assayed. The effect of DAC on DNA methylation was examined by multiplexed PCR sequencing of bisulfite converted DNA in both nephritic glomeruli from NTN animals, and in WKY bone marrow derived macrophages treated *in vitro* with DAC.

Results: DAC treated animals had fewer glomerular crescents, less proteinuria and less glomerular macrophage infiltration (ED1 staining).



DNA methylation in nephritic glomeruli was decreased across 200 cytosine bases in DAC treated samples compared to controls ($P = 0.049$, Wilcoxon rank sum test). This decrease was driven by 39 cytosines that showed demethylation in DAC treated animals. *In vitro* sequencing in macrophages showed diverse methylation changes after DAC treatment depending on length of exposure and dose.

Conclusions: These experiments show that DAC treatment had a protective effect on NTN phenotypes in WKY rats with a reduction in DNA cytosine methylation in both nephritic glomeruli and macrophages. These results suggest that DNA methylation may be involved in the pathogenesis of CRGN and may represent a target for intervention.

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SA-PO441

Macrophages Present an Essential Source of Anti-Inflammatory Annexin A1 Signals During the Course of Acute Anti-Thy-1.1 Nephritis
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Background: Macrophage subpopulations exert distinctive effects during inflammatory kidney disease and may either aggravate kidney damage or foster renal repair. The anti-inflammatory protein annexin A1 (AnxA1) has been shown to shift macrophage polarization towards the anti-inflammatory M2 phenotype. Cellular sources and regulation of intrinsic AnxA1 signals during renal inflammation remain to be elucidated.

Methods: Adult Wistar rats were injected with anti-Thy-1.1 antibody to induce mesangioproliferative glomerulonephritis and examined after 24h (initiation phase), 5d (proliferation phase), and 15d (resolution phase). Regulation of AnxA1 was studied by qPCR and immunohistochemistry. AnxA1⁺ cells were characterized by triple labelling immunofluorescence using antibodies against CD68 for monocytes and macrophages, and CD206 for macrophages with M2 polarization. Quantification of immunoreactive cells was performed by cell counting on confocal micrographs.

Results: Induction of anti-Thy-1.1 nephritis caused a rapid increase of renal AnxA1 mRNA levels (24h: +92±16%; 5d: +128±19%; 15d: +78±33% relative to controls; $p < .05$). Quantitative image analysis revealed a pronounced interstitial accumulation of total, and CD206⁺ M2 macrophages at d5 (+150±40% and +260±29%; $p < .05$) and d15 (+378±43% and +600±100%; $p < .05$) as compared to controls. Triple labelling studies revealed elevated numbers of CD68⁺/CD206⁺/AnxA1⁺ interstitial M2 macrophages at d5 and d15 as compared to controls (+240±27% and +450±80%; $p < .05$). CD68⁺/CD206⁻/AnxA1⁺ macrophages were increased to a lesser extent (d15: +270±47% relative to controls; $p < .05$).

Conclusions: In conclusion, we have shown that AnxA1 expression and protein abundance are significantly increased during the course of anti-Thy-1.1 nephritis. Accumulation of CD206⁺/AnxA1⁺ and CD206⁻/AnxA1⁺ macrophages at d15 suggests that these cells present a relevant source for anti-inflammatory AnxA1 signals during the resolution phase of renal inflammation. Further studies are needed to establish the characteristics of these cells.

SA-PO442

Reduced Mitochondrial Energy Production in the Kidney Induces Focal Segmental Glomerulosclerosis in Low-Birth-Weight Rats at Adulthood Toshiyuki Imasawa. *Kidney Center, National Hospital Organization Chiba-East Hospital, Chiba-City, Chiba, Japan.*

Background: Intraglomerular hypertension has been linked with the pathogenesis of focal segmental glomerulosclerosis (FSGS) lesions in low-birth-weight (LBW) -related nephropathy, which is associated with a decreased number of nephrons. However, other mechanisms may participate in the pathogenesis of LBW-related nephropathy. Here, we investigated innate factors that could induce LBW-related nephropathy at adulthood.

Methods: LBW rats (N = 7) were obtained by intraperitoneally injecting pregnant rats with dexamethasone. Normal-birth-weight (NBW) rats (N = 7) were obtained by saline injection. At 4 weeks of age, the left kidney was removed and used for histological analysis and quantitative proteomics (label-free LC-MS). At 9 weeks of age, the right kidney was histologically analyzed.

Results: At 4 weeks of age, glomerular numbers in LBW rats were significantly lower than NBW rats (p < 0.01). However, there were no sclerotic lesions, and neither group showed any other pathological changes at this age. At 9 weeks of age, FSGS lesions were observed in 7.4% of glomeruli in LBW rats, but only 0.5% of glomeruli had lesions in NBW rats. The pathological changes in LBW rats at 9 weeks of age resembled that of human LBW-related nephropathy. Quantitative proteomics using the renal cortex from 4-week-old rats revealed that 685 proteins decreased in LBW rats compared with NBW rats, and among them, 97 proteins (14.2%) were mitochondrial proteins. In such reduced mitochondrial proteins, 12 subunits of OXPHOS, especially of complex III and V, and 15 enzymes of TCA cycle were significantly decreased in LBW rat cortices (p < 0.05). Western blotting revealed the reduced expression of p-AMPK, NRF-1, and TFAM, which are master regulators of mitochondrial biogenesis, in LBW rats at 4 weeks of age.

Conclusions: This is the first report to investigate the innate suppression of mitochondrial energy production in LBW animals. We have shown that in addition to intraglomerular hypertension, innate defects to mitochondrial energy production should induce the formation of FSGS lesions in LBW-related nephropathy at adulthood.

SA-PO443

Chronic Hypoxia Does Not Activate Innate Immunity Neither Promotes Kidney Injury in Normal Rats or Undergoing Renal Ablation 5/6 Lisienny C.T. Rempel, Gizely C.S. Moreira, Thalita F. Nascimento, Camilla Fanelli, Orestes Foresto-Neto, Simone C.A. Arias, Viviane D. Faustino, Claudia R. Sena, Vivian L. Viana, Victor F. Avila, Denise M. Malheiros, Niels O.S. Camara, Clarice K. Fujihara, Roberto Zatz. *Univ of Sao Paulo, Brazil.*

Background: Tissue hypoxia (Hyp) is thought to influence the pathogenesis of chronic kidney disease (CKD), but direct evidence that prolonged exposure to tissue Hyp initiates or aggravates CKD is lacking. We tested this hypothesis by chronically exposing to Hyp normal rats and rats with 5/6 nephrectomy (Nx). In addition, we investigated whether such effect of Hyp would involve activation of innate immunity.

Methods: Adult male Munich-Wistar rats underwent Nx (n=30) or sham surgery (S, n=19). Seven S (S_{norm}) and 13 Nx (Nx_{norm}) rats remained in normoxia, while 12 S rats (S_{hyp}) and 17 Nx rats (Nx_{hyp}) were kept in a normobaric Hyp chamber (12% O₂). Results at 8 weeks (BW, body weight, g; Hb, hemoglobin, g/dL; TCP, tail-cuff pressure, mmHg; Ualb/Ucr, urine albumin/creatinine; KW/BW, kidney/body weight; GSI, glomerulosclerosis index; %INT, % cortical interstitium; MØ, interstitial macrophages, cells/mm²; renal IL-1β (pg/g); and TLR-4 (2^{-ΔΔCt}).

Results:

	S _{norm}	S _{hyp}	Nx _{norm}	Nx _{hyp}
BW	307±8	285±7 ^b	280±6 ^a	271±6
Hb	15.6±0.2	18.1±0.6 ^b	14.1±0.4	16.6±0.5 ^b
TCP	143±2	139±3	195±7 ^a	182±5 ^a
Ualb/Ucr	0.2±0.1	0.2±0.1	4.9±1.3 ^a	3.7±0.6 ^a
KW/BW	0.5±0.0	0.4±0.0	0.5±0.0	0.4±0.0 ^b
GSI	0.3±0.3	0.3±0.1	9.9±4.9 ^a	3.3±0.9 ^{ab}
%INT	0.6±0.2	0.1±0.1	8.4±1.8 ^a	4.6±1.2 ^{ab}
MØ	9±3	11±2	76±6 ^a	38±7 ^{ab}
IL-1β	2.1±0.5	1.6±0.3	8.8±2.6 ^a	4.4±1.2 ^b
TLR-4	1.03±0.12	0.93±0.08	2.69±0.30 ^a	2.15±0.16 ^{ab}

Mean ± SE, *p < 0.05 vs. respective S, ^bp < 0.05 vs respective Nor.

Exposure to Hyp increased Hb in both S and Nx, but led to no injury or elevation of the renal content of IL-1β or TLR-4 in S. Unexpectedly, Hyp attenuated IL-1β, TLR-4, MØ, GSI and %INT in Nx.

Conclusions: We found no evidence that chronic Hyp initiates or worsens CKD. Chronic Hyp may be even renoprotective by unclear mechanisms, perhaps involving adaptive molecules. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

SA-PO444

Methylation Decreases Expression of Erythropoietin in Fibrosing Kidney Disease Ching-chin Yang,¹ Yu-ting Chang,¹ Szu Yu Pan,² Yu-hsiang Chou,¹ Yung-ming Chen,² Shuei-Liong Lin.^{1,2} ¹Physiology, National Taiwan Univ College of Medicine, Taipei, Taiwan; ²Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Renal erythropoietin-producing cells remain in atrophic kidneys and are capable of producing erythropoietin in dialysis patients who take the stabilizer of hypoxia-inducible factors. The mechanism of decreased response of renal erythropoietin-producing cells to anemic stimulation in chronic kidney disease remains unclear.

Methods: We use genetically modified mice who report pericytes/myofibroblasts and express pericyte-specific Cre recombinase to perform in vivo study. We also isolate pericytes/myofibroblasts from these mice for in vitro analysis of epigenetic modification and erythropoietin expression.

Results: Here we show that Foxd1+ progenitor-derived; Col1a1-GFP+; PDGFRβ+ kidney pericytes are erythropoietin-producing cells regulated by hypoxia-inducible factor 2 alpha but decrease such a function upon their transition to myofibroblasts in fibrosing kidney disease. Hypermethylation of erythropoietin 5'-untranslated region is demonstrated and associated with decreased expression of erythropoietin in kidney myofibroblasts. Demethylation with 5-azacytidine or knockdown of upregulated DNA methyltransferase 1 in kidney myofibroblasts is found to increase expression of erythropoietin in fibrosing kidney disease.

Conclusions: These studies demonstrate that epigenetic modifications may provide a molecular basis for decreased response of renal erythropoietin-producing cells to anemic stimulation in fibrosing kidney disease.

Funding: Government Support - Non-U.S.

SA-PO445

Multiparametric Magnetic Resonance Imaging for Assessing Renal Histopathology in a Mouse Model of CKD Gunnar Schley,¹ Jutta Janke,² Kai-Uwe Eckardt,¹ Tobias Bäuerle,² Carsten Willam.¹ ¹Nephrology and Hypertension, Univ of Erlangen-Nuremberg, Erlangen, Germany; ²Radiology, Univ of Erlangen-Nuremberg, Erlangen, Germany.

Background: Multiparametric magnetic resonance imaging (MRI) allows non-invasive assessment of renal pathologies, especially in patients with chronic kidney disease (CKD) as is does not require contrast agent administration. We aimed to establish an imaging protocol for multiparametric MRI in an experimental CKD mouse model and correlate radiological and histopathological parameters.

Methods: CKD was induced in male C57BL/6 mice (n=8) by feeding an adenine-supplemented diet for 3 weeks resulting in deposition of dihydroxyadenine crystals, tubular dilation, capillary loss, tubulointerstitial inflammation and fibrosis. Untreated animals (n=8) served as controls. Kidneys were fixed in paraformaldehyde and subjected to MRI in a 7-Tesla scanner ex vivo. Volumetry of renal cortex and medulla was performed on T2 weighted sequences. MRI parameters (apparent diffusion coefficient (ADC), fractional anisotropy (FA), T1, T2, T2* relaxation times) were determined for 3 regions of interest placed manually in the cortex and outer medulla, compared between CKD and controls kidneys and correlated with (immuno-)histological analyses for crystal density, tissue cellularity, tubular dilation, inflammatory infiltration, fibrosis, and vascularization.

Results: CKD resulted in significant volumetric augmentation of the medulla. T1 times did not differ in control and diseased kidneys, T2 and T2* times were significantly increased in both cortex and medulla, whereas ADC was increased only in the cortex of diseased kidneys in comparison to controls. In contrast, FA was significantly reduced in diseased cortex and medulla. T2 time correlated with the relative area of fibrosis (Spearman's rho 0.71 for cortex, 0.79 for medulla), infiltrated macrophages (0.69, 0.81), and tubular lumen (0.74).

Conclusions: Multiparametric MRI enabled characterization and diagnosis of chronic changes in the presented CKD model and showed correlation of T2 times with fibrosis, inflammatory infiltration, and tubular dilation. These results may help to broaden our understanding of MRI findings in CKD patients.

SA-PO446

Nuclear Magnetic Resonance Based Metabonomic Profiles Produced by Aristolochic Acids: Comparison with Well-Known Tubulotoxic Agents Marilyn Duquesne,^{1,2} Nordinn Rabai,¹ Anne-Emilie Declèves,² Coulon Françoise,³ Eric De prez,² Jean-Marie Colet,¹ Joelle L. Nortier.² ¹Lab Human Biology & Toxicology, UMONS; ²Lab Experimental Nephrology, ULB; ³Lab Histology, UMONS.

Background: Aristolochic acids (AA) are powerful nephrotoxic and carcinogenic products derived from Aristolochiaceae responsible for acute to chronic renal failure and urothelial cancer complications in countries using traditional herbal medicine. Early detection of renal tubular injury could be useful in individuals at risk of exposure to AA.

Methods: The Consortium of Metabonomic in Toxicology (COMET) has developed predictive models of renal toxicity based on the NMR-based metabonomic evaluation of urine and serum samples collected from rats acutely exposed to various well characterized nephrotoxics. Using this COMET protocol, we studied the metabonomic urine profile of rats exposed to one sc injection of AA I or II at different dosages (75, 100mg/kg). We then compared it to those obtained with 3 molecules known for their toxicity on the proximal tubule, i.e ifosfamide (Ifo: 7, 70mg/kg), gentamicin (Genta: 40, 400mg/kg) and cisplatin (Cis: 0.5, 5mg/kg), respectively.

Results: Metabonomic results obtained in AA rats demonstrated a urinary increase in metabolites involved in osmoregulation (taurine, betaine, glycine), cell death (lactate) and in reabsorptive capacity of the tubular epithelium (glucose), and a significant reduction of Krebs's cycle components (alpha-ketoglutarate, succinate, citrate), suggesting a mitochondrial injury. The comparison of these AA profiles with those obtained with Ifo, Genta and Cis revealed close similarities in 2D plots. However, the 3D modelization approach showed very close score plots shared by AA, Ifo and Cis and a different behaviour exhibited by Genta samples.

Conclusions: This metabonomic study confirms the mode of action of AA towards the proximal tubule and provides an original signature of induced mitochondrial insult. This approach could bring new insight in understanding the toxicity pathways of AA within the kidney. Moreover, it could be a useful tool of noninvasive screening in populations at risk of AA intoxication.

SA-PO447

Establishment of a 3-Step Method to Obtain the Absolute Number of Nephrons in Mice Xiaogang Chu, Jian-Kang Chen. *Depts of Cellular Biology & Anatomy and Medicine, Georgia Regents Univ, Augusta, GA.*

Background: Low nephron number is implicated in hypertension and kidney disease. Existing methods to determine nephron number have various limitations. While using the Cre reporter mice expressing membrane-Tomato/membrane-Green fluorescent protein (mT/mG) for other studies, we fortuitously noticed that the Tomato fluorescence remarkably visualized all glomeruli in the kidneys, which prompted us to establish a 3-step (Separate-Press-Count) method to obtain the exact nephron number in mice.

Methods: One homozygous mT/mG mouse (S232, available from the Jackson Laboratory, Stock Number: 007576) was bred with FVB/NJ mice. This produced ~11 heterozygous pups per litter. After the pups reached 6 weeks of age, they were weighed and euthanized. Each kidney was decapsulated, weighed, and bluntly separated into 35-45 pieces (1-2 mm² each) using forceps with non-serrated but blunted tips. Each piece was pressed between a microscope slide with grids and a coverslip, followed by counting of every single glomerulus under a fluorescence microscopy.

Results: The nephron number in male mice ranged from 10421 to 15577 (mean = 12977 ± 2136) for left kidney and 10374 to 15691 (mean = 13271 ± 2414) for right kidney (n=6) while that of female mice ranged from 13890 to 16277 (mean = 15184 ± 993) for left kidney and 14547 to 16165 (mean = 15555 ± 741) for right kidney (n=5). Thus, the mean total nephron number in male mice (25562 ± 4530) is lower than that of female mice (30739 ± 1443). This is still true when expressed as mean nephron number per gram of body weight (N/gBwt): male 1025 ± 179 vs. female 1362 ± 90; n=5-6, p<0.01). 5/6 nephrectomy (Nx) in male mice decreased N/gBwt down to 156 ± 17, increased blood pressure (BP) up to 142 ± 7 mmHg, elevated BUN level up to 292 ± 7 mg/dl, and caused 37.5% mice to die within 2 weeks while the remaining 5/6Nx mice with >241 N/gBwt had 130 ± 8 mmHg BP and 73 ± 25 mg/dl BUN and were still alive even 4 weeks after 5/6 Nx.

Conclusions: We have established a new simple method to count the absolute nephron number and are using it to define the minimum of nephrons per gram of body weight that can maintain the normal blood pressure and kidney function in mice.

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SA-PO448

New Aspects on the Difference in Permeability Between Proteins and Polysaccharides in the Glomerular Filtration Barrier Carl Mikael Öberg,¹ Joseph J. Groszek,² William Henry Fissell,² Bengt Rippe.¹ *¹Dept of Nephrology, Lund Univ, Lund, Skane, Sweden; ²Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN.*

Background: One of the many unresolved questions regarding the permeability of the glomerular filtration barrier (GFB) is the reason behind the marked difference in permeability between albumin and polysaccharide probe molecules such as Ficoll. The difference in sieving coefficients between albumin and a Ficoll molecule of the same molecular size (~36 Å) is ~2-3 orders of magnitude. Although this large difference in permeability has been attributed mainly to charge effects, we have previously shown that this would require a supraphysiological amount of charge on the filtration barrier, being about ~10 times more than the charge on the albumin molecule (~0.02 C/m²).

Methods: The classic heteroporous model by Deen, Bridges, Brenner and Myers (Deen et al. *AJP Renal Physiology*, 1985) was extended by introducing size distributions on the solute molecules, making them flexible in their conformation. Experimental sieving data for Ficoll, both from the rat glomerulus and from precision-made nanopore membranes, were analyzed using the model. The variation in solute size was quantified in terms of the geometric standard deviation (gSD) of the solute size distribution. The (mode) solute radius was assumed to be equal to the SE-radius and the pore size distribution gSD was set to unity.

Results: For the glomerulus (n=7), a gSD for the Ficoll size-distribution of 1.16 (± 0.01) was obtained, along with a small pore radius of 36.1 Å (± 0.5 Å) and a large pore radius of 152 Å (± 7 Å). For the nanopore membranes (n=16), a gSD of 1.24 (± 0.01) was found.

Conclusions: In the current study, we show, for the first time, that a variation of only ~15-17% in the size of the molecule is sufficient to explain the difference in permeability between albumin and Ficoll. In addition, we show that the effects of applying a size-distribution on the solute molecule are only evident when the molecular size is close to the size of the selective elements of the barrier. This is well in line with experimental data, both from the GFB and from synthetic membranes.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO449

Rapid MicroRNA Isothermal Amplification and Detection in Urine for Nephrotic Syndrome and Other Renal Disease Biomarker Discovery Kathrin Gassei, Chandramohan Ishwad, Jacqueline Ho, Abhay N. Vats. *Pediatrics, Childrens Hospital of Pittsburgh, Pittsburgh, PA.*

Background: MicroRNAs play an important role in renal development and are being explored as biomarkers for several renal diseases including nephrotic syndrome (NS). However, miRNA detection assays can be expensive, laborious, and time consuming. We have been developing a fast and reliable assay for microRNAs in urine and report a novel isothermal amplification method. We tested this method [called cross hybridization amplification (CHAMP)] for detection of miR-30a-5p in urine of patients with NS and controls.

Methods: We designed two 20-25 nt primers and a probe specific for miR-30a-5p. Primers were labeled with either Biotin or Digoxigenin on the 3'-end. Synthetic miR targets were developed for miR-30a, miR30b and Let7 microRNAs. Amplification required, Bst DNA polymerase enzyme, and incubation at 65°C for 30-60 min. Assay optimization was performed on urine samples spiked with synthetic miR constructs. Amplification and detection was performed with real-time PCR; gel electrophoresis and later flow devices.

Results: CHAMP was able to amplify and detect miR30a-5p in 60 minutes or less. The primers / probe were specific for miR30a and did not amplify mir30b or let7 microRNA. Appropriate melting curves were obtained for mir30a only. Amplicons were also detected by UV transillumination. The incorporation of Biotin and Digoxigenin in primers allowed the detection on lateral flow strips also. The presence of urine did not inhibit the reaction, and unprocessed urine could be used, without the need for RNA isolation. The de-identified urinary samples of 3 patients with steroid resistant NS had mir30a levels that were upto 200 fold higher than controls.

Conclusions: A novel isothermal amplification method (CHAMP) can be used for rapid microRNA detection in human urine. It allowed a rapid, sensitive, and highly specific amplification and detection of miRNA and is much easier and more cost effective than qPCR or microarray. CHAMP could detect miR-30a-5p, with sensitivity similar to qPCR, without the need for RNA isolation and could be used for biomarker discovery based on microRNA studies for NS and other renal diseases.

Funding: Other NIH Support - NIAID

SA-PO450

Dominant Negative Etv Expression in Metanephric Mesenchyme Reduces Nephron Endowment: A Model of Low Nephron Number CKD Susanne V. Fleig, Flavia G. Machado, Benjamin D. Humphreys. *Brigham and Women's Hospital, Boston.*

Background: The role of etv4 expression in the ureteric bud during kidney development has been established; however etv4 is also expressed in the metanephric mesenchyme. We asked what role Etv4 plays during nephrogenesis.

Methods: To inhibit etv4 function in the metanephric mesenchyme, we crossed mice with a loxP-flanked dominant-negative etv4 (R26-LoxP-DN-Etv4^{+/+}) with metanephric mesenchyme-specific six2-cre mice (Six2-TGC^{tg/tg}); cre-negative littermates served as control.

Results: Six2cre-DN-Etv4 mice express DN-etv4 in the nephron progenitor population starting dpc10.5. Cre-positive mice have lower body weight and fail to thrive. At four weeks, they have a reduced nephron number (24.4 ± 2.4 vs. 86.8 ± 6.9 glomeruli/section, p<0.0001). They develop kidney failure (at 4 weeks: BUN 103.8 ± 17.8 mg/dl vs. 14.1 ± 1.8 mg/dl, p < 0.001) and proteinuria (21.29 ± 7.23 g Albumin/g Creatinine vs. 0.14 ± 0.03 g Albumin/g Creatinine in urine, p<0.05). Their kidneys show all features of chronic kidney failure (protein casts, glomerulosclerosis, fibrosis) and they die at 3-5 weeks of kidney failure.

Conclusions: Etv4 expression in the metanephric mesenchyme is required for normal kidney development, and expression of DN-Etv4 in the six2+ population leads to defective kidney development with reduced nephron number and progressive chronic kidney failure at 3-5 weeks of age. Titration of DN-Etv4 expression in metanephric mesenchyme may provide a novel genetic model for low nephron endowment and progressive CKD.

Funding: NIDDK Support

SA-PO451

NO Depletion by L-NAME Causes Increases in Rat Glomerular Permeability In Vivo – Reversal with Tempol and L-Arginine, but Not with the Potent NO-Donor DEA-NONOate Bengt Rippe, Julia Dolinina, Kristinn Sverrisson, Anna Rippe. *Dept of Nephrology, Lund Univ, Lund, Sweden.*

Background: There is increasing evidence that the permeability of the glomerular filtration barrier (GFB) is regulated by a balance between the bioavailability of nitric oxide (NO) and the presence of reactive oxygen species (ROS). It has been postulated that normal or moderately elevated NO levels protect the GFB from permeability increases, while ROS, through reducing the bioavailability of NO, have the opposite effect.

Methods: In anaesthetized Wistar rats, the left ureter was cannulated for urine collection, while simultaneously blood access was achieved. To test the tentative antagonism between NO and ROS, rats were systemically infused with either L-NAME (6 mg/kg/min) or L-NAME together with the superoxide scavenger tempol (1 mg/kg/min), or L-NAME together with L-arginine (290 mg/kg/min). Furthermore, we tested whether the potent NO donor, DEA-NONOate, could reverse the permeability effects of L-NAME. To measure glomerular sieving coefficients (θ) to Ficoll, rats were infused with fluorescein

isothiocyanate (FITC)-Ficoll 70/400 (mol. radius 10-80Å). Plasma and urine samples were analyzed by high performance size exclusion chromatography (HPSEC) for determination of θ for Ficoll repeatedly during up to 2 hours.

Results: L-NAME increased θ for Ficoll_{70A} from 2.27 (\pm 1.30) \times 10⁻⁵ to 8.59 (\pm 2.06) \times 10⁻⁵ (n=6; p<0.05) in 15 min. Tempol (n=6) completely abrogated these increases in glomerular permeability, the θ Ficoll_{70A} being 7.0 (\pm 2.1) \times 10⁻⁶ at 15 min, which was also seen with L-arginine. However, DEA-NONOate did not reverse the permeability effects following L-NAME.

Conclusions: NO depletion *in vivo* by L-NAME caused increases in glomerular permeability, which could be reversed by either the ROS antagonist, tempol, or by L-arginine. By contrast, the potent NO-donor, DEA-NONOate, did not ameliorate the permeability effects of L-NAME. It is concluded that moderate levels of elevated NO production act to protect the permeability of the GFB, whereas very high levels of NO, as predicted following systemic DEA-NONOate infusion, may actually be detrimental to the GFB.

Funding: Government Support - Non-U.S.

SA-PO452

Down-Regulation Of Renal Tubular Wnt/ β -Catenin Signaling Induces Tubular Cell Death in Proteinuric Nephropathy Dickson W.L. Wong, Wai Han Yiu, Hao-Jia Wu, Ruixi Li, Kam Wa Chan, Joseph C.K. Leung, Loretta Y.Y. Chan, Kar Neng Lai, Sydney C.W. Tang. *Dept of Medicine, The Univ of Hong Kong/ Queen Mary Hospital, Hong Kong.*

Background: Persistent proteinuria from any causes is closely associated with chronic kidney disease (CKD) progression. Excessive transglomerular protein trafficking impacts on renal tubular cell injury by triggering tubular cell death. Studies on the role of Wnt/ β -catenin signalling in different forms of CKD have yielded discrepant results.

Methods: β -catenin expression was measured in control/ human serum albumin (HSA)-treated human kidney 2 (HK-2) cells and kidney cortical lysates of protein-overloaded mice given 4- or 8- week BSA injection by Western blotting and IHC staining. Genetic knockdown of β -catenin in HK-2 cells was achieved using siRNA transfection. Apoptotic phenotypes were evaluated by qPCR, Western blotting, IHC staining/ activity assay and TUNEL assay.

Results: Upon 4-day HSA stimulation, protein levels of active nuclear β -catenin in HK-2 cells declined by 67% \pm 0.04 (p<0.05) versus control. Simultaneously, Bax/Bcl-2 gene expression ratio increased significantly. HSA treatment with or without β -catenin siRNA transfection in HK-2 cells up-regulated Bax/Bcl-2 gene expression ratio by 116% \pm 0.2 (<0.05) and 52% \pm 0.2 (p<0.05), respectively. Similarly, TUNEL and caspase-3 activity was also increased by silencing β -catenin. In protein-overloaded mice, dynamic expression of tubular β -catenin was observed, with up-regulation (by 88% \pm 0.2 vs. control animals; p<0.05) at the early stage (4 weeks after BSA injection) and abrogation (24% \pm 0.2; p<0.05) in the late phase (8 weeks after BSA injection). UACR decreased during renal tubular β -catenin overexpression but increased thereafter as tubular β -catenin levels came down. Elevated apoptotic phenotypes were evident in the later phase and associated with up-regulation of NGAL and KIM-1 genetic expressions.

Conclusions: Protein-overload promotes renal tubular apoptosis via abrogation of Wnt/ β -catenin signalling *in vitro* and *in vivo*. *Funding:* supports: Hong Kong Society of Nephrology Research Grant (2013), and the National Basic Research Program of China 973 program no. 2012CB517600 (no. 2012CB517606).

SA-PO453

Endothelin-1 Induces Proteinuria by Heparanase-Mediated Disruption of the Endothelial Glycocalyx Marjolein Garsen,¹ Olivia Lenoir,² Angélique Rops,¹ Henry Dijkman,³ Brigtht Willemsen,³ Ton J. Rabelink,⁴ Jo H.M. Berden,¹ Pierre-Louis Tharaux,² Johan Van der Vlag.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Paris Cardiovascular Research Centre, Inst de la Santé et de la Recherche Médicale, Paris, France; ³Pathology, Radboud Univ Medical Center, Nijmegen, Netherlands; ⁴Nephrology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Diabetic nephropathy (DN) is the leading cause of chronic kidney disease in the Western world. Recently, endothelin receptor antagonists (ERAs) have emerged as a novel treatment for DN, but the mechanism underlying the protective effect of ERAs remains unknown. We previously showed that heparanase (HPSE), a heparan sulfate (HS)-specific endoglucuronidase, is essential for the development of DN. Loss of HS expression has been associated with the development of proteinuria. We hypothesize that endothelin-1 signals via HPSE.

Methods: In this study we evaluate the effects of endothelin-1 on HPSE expression and function *in vitro* and *in vivo*.

Results: Endothelin-1 induced HPSE expression in cultured mouse podocytes. Moreover, culture supernatant of endothelin-1-stimulated podocytes increased transendothelial albumin passage, which is HPSE-dependent. Experimental type 1 diabetes in wild type (WT) mice revealed proteinuria and renal damage, accompanied with an increased glomerular HPSE expression and a reduced glomerular HS expression. Proteinuria and renal damage were reduced in the diabetic podocyte-specific endothelin receptor knockout (podETRKO) mice, which showed a normal HPSE and HS expression. Importantly, glycocalyx thickness was reduced after induction of diabetes in the WT mice, but preserved in the diabetic podETRKO mice.

Conclusions: Our data show that endothelin-1 induces HPSE expression in the podocyte in experimental DN. Furthermore, these results suggest that HPSE cleaves HS in the endothelial glycocalyx, which results in a reduced glycocalyx thickness and the development of proteinuria.

SA-PO454

Endothelin-1 Increases Glomerular Permeability in Sick Cell Mice Malgorzata Kasztan,¹ Chiao-Wang Sun,² David M. Pollock.¹ ¹Cardia-Renal Physiology&Medicine, Univ of Alabama at Birmingham, Birmingham, AL; ²Biochemistry&Molecular Biology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Sickle cell disease (SCD) leads to nephropathy manifested by increased glomerular permeability (P_{alb}) and albuminuria/proteinuria. The endothelium-derived peptide, endothelin-1 (ET-1), with its powerful vasoconstrictor and pro-inflammatory effects mediated primarily through ET_A receptors, is elevated in SCD patients and may contribute to the development of sickle cell glomerulopathy. Therefore, the aim of the study was to determine whether ET-1 contributes to increased glomerular permeability to albumin in SCD and if ET_A receptors blockade ameliorates glomerular damage. Furthermore, because our preliminary studies showed sex differences in the vasoconstrictor response to ET-1 in sickle cell mice the study was designed to determine if sex differences exist in this response.

Methods: Experiments utilized 12 week old humanized sickle cell mice (HbSS) and genetic controls (HbAA) recently developed by the Townes' lab. Ambrisentan (ET_A antagonist), A-182086 (ET_{A/B} antagonist) or vehicle was administered via drinking water (10mg/kg/day) for 2 weeks. Glomeruli were isolated for direct permeability measurements as a volume response of glomerular capillaries to an oncotic medium generated by defined concentrations of albumin.

Results: P_{alb} was significantly higher in glomeruli from sickle mice (both in males and females) than control mice (0.50 \pm 0.07 and 0.47 \pm 0.06 vs. 0.13 \pm 0.02 and 0.10 \pm 0.2, respectively). Ambrisentan treatment significantly reduced the elevated P_{alb} in glomeruli from male (0.24 \pm 0.05 vs. 0.50 \pm 0.07) and female (0.20 \pm 0.03 vs. 0.47 \pm 0.06) HbSS mice. ET_{A/B} receptors antagonism with A-182086 also significantly decreased the P_{alb} in glomeruli from male (0.28 \pm 0.06 vs. 0.50 \pm 0.07) and female (0.24 \pm 0.03 vs. 0.47 \pm 0.06) HbSS mice. Treatment with both antagonists did not alter P_{alb} in HbAA mice.

Conclusions: These data support the hypothesis that ET-1 may play an important role in the development of sickle cell nephropathy and support the use of chronic ET_A antagonism as a prospective treatment for sickle cell nephropathy.

Funding: Other NIH Support - NIH/NHLBI (U01 HL117684-01)

SA-PO455

Longitudinal Transcutaneous Glomerular Filtration Rate (GFR) After Uninephrectomy (UNx) in Mice Hiroshi Kojima, Jonathan Street, Ana C. Souza, Peter S.T. Yuen, Robert A. Star. *Renal Diagnostics and Therapeutics Unit, NIDDK, NIH, Bethesda, MD.*

Background: Glomerular filtration rate is a universally accepted measure of global kidney function. Serum filtration markers such as serum creatinine, BUN, or cystatin C have confounding factors, and measuring clearance of "inert" markers requires blood and urine collection, which can be cumbersome in unstable, oliguric patients, and small animals. A new non-invasive method using fluorescently-labeled Sinistrin and a miniaturized fluorescence detector can non-invasively detect plasma disappearance in conscious mice. To determine if the assumptions for plasma disappearance are met, we tested the method in a classic mouse uninephrectomy model with a predictable change (50%) then slow recovery.

Methods: Young male CD-1 mice underwent left UNx at Day 0. Transcutaneous measurement of GFR was performed every 3-4 days until Day 18. Under isoflurane anesthesia, a depilatory was applied to the back, and a miniaturized fluorescence detector (NIC-Kidney; Mannheim Pharma & Diagnostics GmbH, Mannheim, Germany) was fixed on the exposed skin using a double-sided adhesive patch. After background signal was obtained, FITC-Sinistrin was injected intravenously. Data acquisition lasted 60 min. After removing injection artifacts, GFR was calculated using the half-life derived from the rate constant of the single exponential elimination phase of fluorescence-time curve.

Results: All fluorescence measurements decayed as a single exponential, consistent with a stable, single components model and a stable GFR during the time of measurement. Assuming that GFR declined 50% immediately after UNx, GFR gradually increased until 8 days post-UNx, when it plateaued at 75% of normal function.

Conclusions: FITC-Sinistrin plasma disappearance follows single component kinetics at baseline and after UNx, allowing calculation of GFR by single pool kinetics. This technology can easily detect renal hyperfiltration early after UNx.

Funding: NIDDK Support

SA-PO456

CHOP Deficiency Impedes Progressive CKD by Inhibiting Proteinuria Zahraa Mohammed-Ali,¹ Chao Lu,² Jeffrey G. Dickhout.^{1,2} ¹Medicine, McMaster Univ, Hamilton, ON, Canada; ²St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.

Background: Endoplasmic reticulum (ER) stress occurs due to the accumulation of misfolded proteins in the ER and is associated with proteinuria in chronic kidney disease (CKD). CHOP (GADD153/DDIT3) is a pro-apoptotic transcription factor that is upregulated during ER stress. Increased expression of CHOP has been shown in biopsies of patients with membranous nephropathy and membranoproliferative glomerulonephritis. CHOP deficiency protects against oxidative stress, albuminuria and inflammation in mouse models of acute kidney injury and diabetic nephropathy. Therefore, we hypothesized that CHOP deficiency would influence the development of CKD.

Methods: Our model of CKD combines a uninephrectomy and subcutaneous implantation of a slow release deoxycorticosterone acetate (DOCA) pellet and Angiotensin (Ang) II osmotic infusion pump in C57BL/6 male mice. Mice were also given 1% sodium

chloride in their drinking water. Mice with total CHOP knockdown were used to test the role of CHOP in CKD development. CKD was assessed using blood pressure and 24h total urinary protein and albumin measurements. On day 21 post-implantation, mice were sacrificed and PAS staining was used to evaluate renal intertubular cast formation and glomerular damage.

Results: In response to the CKD model, both CHOP^{-/-} and wild type (WT) mice experienced significant increases in systolic and diastolic blood pressure. However, CHOP^{-/-} mice showed significantly lower proteinuria and albuminuria. In addition, CHOP deficiency significantly decreased intertubular cast formation and glomerular damage in response to the model compared to WT.

Conclusions: CHOP deficiency resulted in a decrease in proteinuria and renal tissue damage. Along with inducing apoptosis, CHOP has been shown to interact with inflammatory pathways resulting in NF-κB activation. Further tests will evaluate the effect of CHOP deficiency on inflammatory, fibrotic and apoptotic response in our model. Our findings could lead to the development novel therapeutics to halt the progression of CKD.

Funding: Government Support – MOP-133484.

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SA-PO457

Caveolin-1 Is Crucial in the Pathogenesis and Progression of Light Chain Deposition Disease but Not in AL-Amyloidosis Jiamin Teng, Pathology and Transitional Pathobiology, Louisiana State Univ Health Sciences Center, Shreveport, LA.

Background: In-vitro models of glomerulopathic light chains (GLCs), including light chain deposition disease (LCDD) and light chain amyloidosis (AL-Am) have provided solid platforms to study the pathogenesis of these disorders and how initiation / progression takes place. C-fos and NF-κB have been found to be important signaling mechanisms in the initiation phase of these two disorders. The role of caveolin-1 in the initiation / progression phases was explored in this study using human and mouse caveolin-1 knock-out (KO) and wild type (WT) mesangial cells (MCs).

Methods: Human and Caveolin-1 KO and WT mouse MCs were grown on dishes (2D) and Matrigel (3D), and incubated with GLCs 10 μg/ml purified from the urine of renal biopsy-proven patients with LCDD and AL-Am. Downstream effects were tested by determining whether c-fos and NF-κB cytoplasmic to nuclear signal translocation occurred and analyzing the presence / absence and amounts of amyloid fibril formation in AL-Am and determining amounts of extracellular matrix production in LCDD.

Results: When LCDD GLCs were incubated with caveolin-1 KO cells, no c-fos or NF-κB cytoplasmic to nuclear migration occurred and there was no increase in the extracellular matrix. In contrast, normal translocation was observed with WT caveolin-1 MCs. In contrast, signal translocation for c-fos or NF-κB was unaffected and similar amounts of amyloid fibril formation occurred when WT and caveolin-1 KO MCs were incubated with AL-Am GLCs.

Conclusions: Caveolin-1 (through activation of c-fos and NF-κB) plays a crucial role in signaling in LCDD and subsequent downstream effects. The absence of caveolin-1 at the surface of MCs abolishes downstream effects in LCDD but not in AL-Am. While amyloid production still occurs when MCs are incubated with Am-AL GLCs, the production of excess extracellular matrix is abolished when LCDD GLCs are incubated with caveolin-1 KO MCs.

Funding: Private Foundation Support

SA-PO458

Inhibition of TRPC6 Channels Protects against Renal Fibrosis Yueh-lin Wu,^{1,2} Jian Xie,² Chou-Long Huang,² ¹Taipei Medical Univ Hospital, Taiwan; ²UT southwestern Medical Center, Dallas, TX.

Background: Fibrosis is an important process of tissue repair, yet excess leads to organ failure. Transformation of fibroblasts into myofibroblasts is a critical step in fibrosis and requires activation of multiple new genes. Ca²⁺-permeable TRPC3/6 channels contain NFAT response element in the promoter such that increased Ca²⁺ entry via TRPC3/6 may, by activating calcineurin/NFAT nuclear signaling cascade, lead to positive feedforward amplification and un-remitting gene expression. We test the hypothesis that TRPC6 is critical for fibroblast-myofibroblast transformation in kidney fibrosis and inhibition of TRPC6 may ameliorate fibrosis.

Methods: Wild type (WT) and Trpc6-null mice (129 SvJ) underwent unilateral ureteric obstruction (UUO) on left kidney and sham operation on contralateral kidney. Ten days after surgery, kidneys were harvested for histological analysis of fibrosis by trichrome staining and for measurement of mRNA expression by quantitative real-time PCR. In separate experiments, WT mice underwent UUO and received injection of TRPC3/6 inhibitor BTP2 (2 mg/kg daily by i.p.) or vehicle for 7 days.

Results: UUO induced a >20-fold increase in mRNA for Trpc6 in UUO kidney vs contralateral sham kidney in WT mice. mRNA for collagen-1, vimentin, cTGF, TGF-β1, and matrix metalloproteinases MMP-2 and MMP-9 as well as area for fibrosis measured by trichrome staining were also markedly increased in UUO vs sham kidney. Deletion of Trpc6 resulted in a significant reduction in fibrosis and blunted the increase in mRNA expression of collagen-1, vimentin, cTGF, TGF-β1, MMP-2, and MMP-9 in UUO kidney relative to those in WT mice. Trpc6 deletion did not alter the basal gene expression in sham kidney. Compared to vehicle-treated mice, BTP2 treatment also markedly decreased the measured area of fibrosis and attenuated the increase in expression of fibrosis and pro-fibrotic gene markers in UUO kidney. As in results from Trpc6 deletion, inhibition of TRPC6 by BTP2 had no effect on sham kidney.

Conclusions: Activation of TRPC6 may be critical for myofibroblast transformation in fibrosis. TRPC6 may be a new potential pharmacologic target in treating renal fibrosis.

SA-PO459

Histone Methyltransferase EZH2: A Novel Therapeutic Target for Renal Fibrosis Xiaoxu Zhou, Murugavel Ponnusamy, Evelyn Tolbert, George P. Bayliss, Shougang Zhuang. Dept of Medicine, Rhode Island Hospital and Alpert Medical School, Brown Univ, Providence, RI.

Background: EZH2 (Enhancer of Zeste Homolog 2) is a methyltransferase that induces histone H3 lysine 27 trimethylation (H3K27me3) and functions as an oncogenic factor in many cancer types. However, its role in renal fibrogenesis remains to be explored.

Methods: In this study, we studied the role EZH2 in the activation of cultured renal interstitial fibroblasts and development of renal fibrosis in a murine model of unilateral ureteral obstruction as well as mechanisms involved.

Results: Our results showed that EZH2 and H3K27me3 were highly expressed in the cultured renal fibroblasts and the fibrotic kidney from mice with unilateral ureteral obstruction. Pharmacological inhibition of EZH2 with 3-deazaneplanocin A (3-DZNeP) and GSK126, or silencing of EZH2 with its specific siRNA, inhibited serum- and TGFβ1-induced activation of renal interstitial fibroblasts in vitro. Administration of 3-DZNeP abrogated deposition of extracellular matrix proteins and expression of α-SMA in the obstructed kidney. Mechanistically, 3-DZNeP inhibited expression of type I TGFβ receptor and phosphorylation of Smad3, along with preservation of Smad-7 expression. 3-DZNeP was also effective in blocking phosphorylation of the EGF and PDGFR receptors, and suppressing activation of STAT3 and ERK1/2 signaling pathways in the injured kidney. Moreover, 3-DZNeP treatment abolished injury-induced renal expression of avb6 integrin, Notch1 and Notch3. Finally, EZH2 inhibition increased expression of PTEN, a protein tyrosine phosphatase associated with dephosphorylation of multiple tyrosine kinase receptors, in the kidney after ureteral ligation.

Conclusions: This study has identified EZH2 as an important epigenetic regulator of renal fibrosis and suggested that it could be a novel target for therapeutic interference in chronic kidney disease.

Funding: NIDDK Support

SA-PO460

Targeting PHD2 for the Treatment of Anemia and Interstitial Fibrosis in Chronic Kidney Disease Raechel Peralta, Xiaokun Xiao, Melanie Katz, Shuling Guo, Gene Hung, Sue Murray. Antisense Drug Discovery, Isis Pharmaceuticals, Inc., Carlsbad, CA.

Background: Anemia is a common manifestation of chronic kidney disease (CKD) and is associated with cardiovascular disease. The predominant cause of anemia in CKD is erythropoietin (EPO) deficiency. EPO is a hormone produced primarily by adult kidneys and is essential for the production of red blood cells. It has been shown in many animal models that EPO protects the kidney against interstitial fibrosis. Prolyl hydroxylase domain protein 2 (PHD2) is a primary regulator of hypoxia-inducible factors (HIFs) that regulate genes involved in cellular adaptation to reduced oxygen availability. When PHD2 is reduced, HIFα is stabilized and upregulates several genes to promote survival in low-oxygen conditions. Systemic PHD2 inactivation has been found to increase renal EPO production and stimulate red blood cell synthesis, which can improve anemia in CKD patients (Minamishima et al, Science 2010).

Results: Using antisense oligonucleotides (ASOs) designed against the PHD2 mRNA, we have demonstrated a 60% reduction of kidney PHD2 expression after 4 weeks of treatment (50 mpk/wk) compared to the saline group. In addition, we observed increases of EPO mRNA expression in the kidney interstitial fibroblasts by RT-PCR (~550-fold) and by in-situ analysis. We sought to demonstrate an improvement in anemia and renal fibrosis using our PHD2 ASO. We developed an adenine-induced mouse model of CKD that demonstrates severe anemia and interstitial fibrosis. After simultaneous administration of the 0.2% adenine diet and the PHD2 ASO (12 mpk/wk) for 12 weeks, we observed significant increases in kidney EPO mRNA (~35-fold) and plasma EPO levels (~12-fold) compared to the control ASO group. Histological analysis showed improved fibrosis based on reduced Sirius Red staining. There were also improvements in anemia based on whole blood analysis of hemoglobin and hematocrit levels.

Conclusions: These data indicate that reducing PHD2 with ASOs may be a viable option for treating CKD patients with severe anemia and renal fibrosis.

Funding: Pharmaceutical Company Support - Isis Pharmaceuticals, Inc.

SA-PO461

Fibronectin Assembly Mediates KIM-1 Induced TGFβ-Dependent Kidney Fibrosis Venkata Sabbiseti, Cuiyan Xin, Sandhya Padmanabhan, Bhargavi Chandrasekar, Akinwande A. Akinfolarin, Joseph V. Bonventre. Dept of Medicine, Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: Cell-extracellular matrix interactions play a crucial role in kidney fibrosis. Localized activation of TGFβ is critical for exertion of its cellular effects. Kidney Injury Molecule-1 (KIM-1) is upregulated in dedifferentiated proximal tubular cells (PTECs) following kidney injury and has been shown to induce kidney fibrosis *in vivo*. Here, we report that KIM-1 mediates fibrosis by up-regulating the critical components of the TGFβ activation machinery including fibronectin and corresponding integrin receptors. *In vivo*, blocking fibronectin assembly reduces kidney fibrosis.

Methods: Full-length KIM-1 or the KIM-1 mutant was overexpressed in LLC-PK1 and HEK cell lines and fibronectin and integrin levels were evaluated. Active TGFβ was measured using a bioassay. Mice were subjected to ischemia/reperfusion injury (IRI) or

unilateral ureteral obstruction (UO). In the UO model, mice were treated with fibronectin blocking peptide or control peptide to evaluate the effects of inhibition of fibronectin assembly on fibrosis.

Results: KIM-1 expressing PTECs produced significantly increased levels of fibronectin and fibronectin receptors. These increases were abrogated when phosphotyrosine-350 of KIM-1 was mutated or KIM-1 was deleted. KIM-1 expressing cells displayed higher levels of total and activated TGFβ as compared to control cells. In vivo, KIM-1 expressing tubular epithelial cells were characterized by high fibronectin staining after ischemia/reperfusion injury or UO. Blocking fibronectin assembly with a blocking peptide decreased fibrosis in the UO model.

Conclusions: KIM-1 induced localized activation of TGFβ through up-regulation of TGFβ, fibronectin and integrin receptors. Blocking fibronectin assembly reduced fibrosis in response to UO in vivo. This mechanism can contribute to the fibrosis associated with chronic expression of KIM-1 and may be a common feature of chronic kidney disease. Blocking fibronectin assembly may be therapeutically beneficial to prevent or reduce kidney fibrosis.

Funding: NIDDK Support

SA-PO462

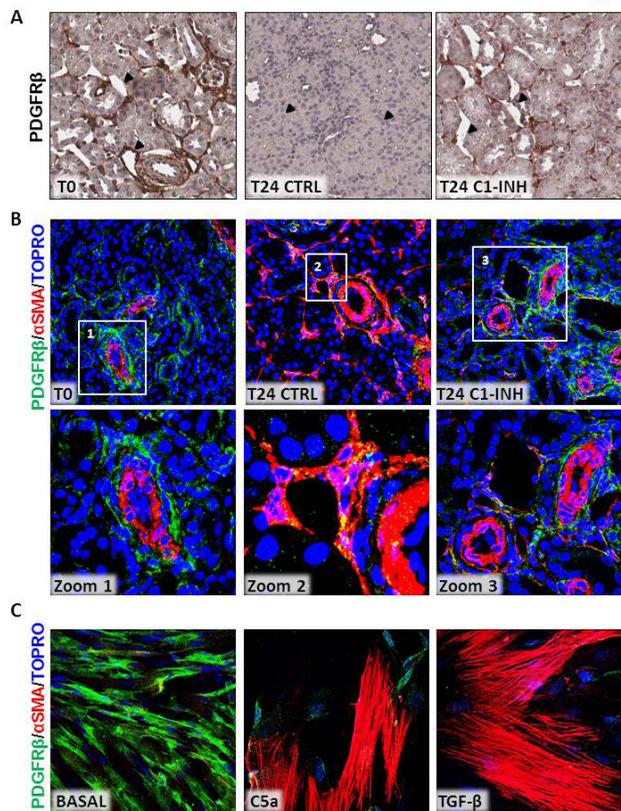
Complement Modulation by C1-Inhibitor Hampered Pericyte (PC) to Myofibroblast Trans-Differentiation (TDF) and Vascular Rarefaction in Ischemia/Reperfusion (I/R) Injury *Giuseppe Castellano,¹ Rossana Franzin,¹ Chiara Divella,¹ Alessandra Stasi,¹ Angelica Intini,¹ Margherita Gigante,¹ Marco Fiorentino,¹ G. Lucarelli,¹ M. Battaglia,¹ Giuseppe Grandaliano,² Loreto Gesualdo.¹* ¹*Nephrology and Urology Unit, Univ of Bari;* ²*Dept Medical and Surgical Science, Univ of Foggia, Italy.*

Background: Preservation of endothelium-Pericyte (PC) interaction is critical to counteract renal fibrosis during chronic kidney disease; no data are available on PC involvement in AKI. We investigated whether Complement might modulate PC activation in I/R.

Methods: Ten pigs underwent to 30 min of renal warm I, followed by 24h of R. Five pigs were treated with C1-Inhibitor (C1-Inh, 500U/Kg). Biopsies were analyzed by IHC and IF for PDGFRβ, Caspase3 and αSMA. FACS, AnnV-IP and IF were performed on human PC (PDGFRβ⁺ cells) stimulated with C5a (1x10⁻⁷M) for 24h in vitro.

Results: I/R injury induced PC to myofibroblasts TDF by reducing PDGFRβ without PC apoptosis (PDGFRβ/Caspase3) *in vivo*. TDF was accompanied by a significant decrease in capillary lumen area (**Fig1A** %T0:11.3±2.1;T24:3.9±2.3; p<0.05) and αSMA up regulation (**Fig1B**). C1-Inh preserved PDGFRβ expression in PC and restored peritubular capillary area (T24C1-Inh: 12.06±3.5 vs T24). In accordance, C5a induced PC proliferation and Collagen I production without apoptosis (Ann V) *in vitro*. C5a induced PC to myofibroblasts TDF, with PDGFRβ down-regulation (**Fig1C**. %Bas: 15.2±3.6; C5a:3.6±2.3; TGFβ:2.08±1.04,p<0.05) and remodeling of αSMA-stress fibers, with contractile phenotype. Finally, C5a significantly up-regulated Id2 factor in PC, which is pivotal for cellular de-differentiation.

Fig.1



Conclusions: Complement might contribute to PC to Myofibroblasts TDF in I/R injury, leading to vascular rarefaction and renal fibrosis. C1-Inh may be an effective strategy to prevent fibrosis development in transplanted kidney.

SA-PO463

Establishment of a Novel Mouse Strain to Trace Erythropoietin Producing Cells at Desired Time Points *Keiichi Kaneko, Motoko Yanagita. Nephrology, Kyoto Univ, Kyoto, Japan.*

Background: We previously reported that resident fibroblasts including Erythropoietin (Epo)-producing cells were lineage-labeled with myelin protein zero-Cre mouse strain and transdifferentiated into myofibroblasts during fibrosis with concomitant loss of Epo production. However, the previous method could not distinguish between Epo-producing cells and other resident fibroblasts and the behavior of Epo-producing cells remains unclear. Recently, Epo-Cre mice were generated which enabled the lineage tracing of the cells with the history of Epo production. Using the mouse strain, the transdifferentiation of Epo-Cre labeled cells into myofibroblasts during fibrosis has been demonstrated. Because Epo-Cre mice labeled the cells with the history of Epo production from fetal period to adult life, we tried to narrow down the period of labeling and to trace the certain cell population with the current Epo-producing ability at desired time points.

Methods: We generated a novel mouse strain in which inducible form of Cre is knocked-in at the locus of Epo gene (Epo-Cre^{ERT2} mice). Epo-Cre^{ERT2} mice were crossed with R26tdTomato mice. Tamoxifen was administered to activate inducible form of Cre, Cre^{ERT2}.

Results: Epo-Cre^{ERT2} labeled cells were located in the interstitium of the cortical and corticomedullary region of the kidney, and the numbers were increased with the induction of anemia. Epo-Cre^{ERT2} labeled cells expressed PDGFRβ and CD73, suggesting that Epo-Cre^{ERT2} labeled cells are resident fibroblasts and are likely to be Epo-producing cells. After unilateral ureteral obstruction (UO), Epo-Cre^{ERT2} labeled cells transdifferentiated into myofibroblasts. The ratio of Epo-Cre^{ERT2} labeled cells transdifferentiated into myofibroblasts was 68 % at day 3 and 86 % at day 5 of UO. The numbers of Epo-Cre^{ERT2} labeled cells were increased 1.9-fold at day 3 and 2.1-fold at day 5 of UO.

Conclusions: We generated a novel mouse strain and succeeded in labeling Epo-producing cells at desired time points. We demonstrated that Epo-producing cells transdifferentiated into myofibroblasts and were increased in fibrotic kidney. We aim to elucidate the mechanism of injury and repair of Epo-producing cells with this strain, Epo-Cre^{ERT2} mice.

SA-PO464

Role of PI3 Kinase γ in Recruitment of Bone Marrow-Derived Fibroblasts and Development of Renal Fibrosis *Yuanbo Wu, Hua Liang, William E. Mitch, Yanlin Wang. Medicine, Baylor College of Medicine, Houston, TX.*

Background: Renal fibrosis is a prominent pathological feature of chronic kidney disease leading to progressive loss of renal function. Although activated fibroblasts are responsible for the production and deposition of the extracellular matrix, the origin of activated fibroblasts mediating renal fibrosis remains debatable. Recent studies have shown bone marrow-derived fibroblasts contributed significantly to the pathogenesis of renal fibrosis. We have previously shown that CXCL16 plays a critical role in recruiting bone marrow-derived fibroblasts into kidney. However, the signaling mechanisms are not known. In the present study, we examined the role of PI3 kinase γ (PI3Kγ) in the recruitment of bone marrow-derived fibroblasts and development of renal fibrosis.

Methods: We examined the role of PI3Kγ in the recruitment of bone marrow-derived fibroblasts and the development of fibrosis using a mouse model of folic acid-induced nephropathy in wild-type (WT) and PI3Kγ-knockout (KO) mice in vivo and migration of cultured mouse monocyte treated with CXCL16 in vitro.

Results: Compared with WT mice, PI3Kγ-KO mice exhibited significant preservation of kidney function as measured by serum urea nitrogen and displayed significantly fewer bone marrow-derived fibroblasts dual positive for CD45 and PDGFR-β in the kidney 2 weeks after folic acid treatment. Furthermore, PI3Kγ-KO mice exhibited fewer α-smooth muscle actin (α-SMA) positive myofibroblasts and expressed less α-SMA protein in the kidney following folic acid treatment. Consistent with these findings, PI3Kγ deficiency significantly reduced total collagen deposition and suppressed expression of extracellular matrix proteins (collagen I and fibronectin). In cultured mouse monocytes, CXCL16 activated PI3Kγ and induced transwell migration, which was abolished in the absence of PI3Kγ.

Conclusions: These data indicate that PI3Kγ plays a pivotal role in recruiting bone marrow-derived fibroblasts into the kidney and developing renal fibrosis. Inhibition of PI3Kγ signaling may represent a novel therapeutic strategy for chronic kidney disease.

Funding: NIDDK Support

SA-PO465

Inhibition of K-Ras prior to Induction of Acute Kidney Reduces Long-Term Progression to Chronic Kidney Disease in a Murine Model of Aristolochic Acid Nephropathy *Sujit Kumar Saha, Bruce M. Hendry, Claire C. Sharpe. Dept of Renal Sciences, King's College London, London, United Kingdom.*

Background: Acute kidney injury (AKI) is recognised to be an early harbinger of chronic kidney disease (CKD). We have previously shown that K-Ras expression and activation are up-regulated in renal fibrosis and reducing K-Ras expression can prevent scarring. In this study our aim was to test whether transiently reducing K-Ras expression in the peri-AKI period can reduce progression to CKD.

Methods: CD1 mice received i.p. injections of either 3.5mg/kg Aristolochic Acid (AA) or normal saline on Day 1 and on Day 5. A treatment group were also given a single

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

subcutaneous injection of 100mg/kg of mouse K-Ras antisense oligonucleotide (ASO) 2 days prior to the first AA injection. A vehicle group was given a subcutaneous injection of saline 2 days prior to the first AA injection. Renal function at multiple time points was assessed through a blood urea nitrogen (BUN) assay. The degree of fibrosis was ascertained through Picrosirius Red (PSR) and Masson Trichrome (MT) staining to quantify collagen deposition. The expression of K-Ras was determined by Q-PCR.

Results: CD1 mice given AA suffered an AKI with a 4.6 fold rise in BUN at Day 12 that returned to baseline by Day 30. However by Day 80, the AA mice had a 57% higher BUN than control mice, demonstrating later onset CKD. AA mice treated with mouse K-Ras ASO pre-AKI suffered a similar AKI but BUN at Day 80 was 48% lower than untreated AA mice and was comparable with healthy controls. PSR and MT staining demonstrated a 5 fold increase in collagen deposition by Day 80 in AA mice which was reduced by 30% in ASO-treated animals. K-Ras expression was consistently unregulated in the untreated AA mice throughout the chronic phase but the transient treatment with ASO prior to the acute injury resulted in normalisation of K-Ras mRNA by Day 80.

Conclusions: Transiently reducing K-Ras expression in the peri-AKI period in a murine model of aristolochic acid nephropathy reduces downstream fibrosis and prevents the decline in renal excretory function. Targeting K-Ras may provide a future therapeutic option for preventing renal fibrosis and CKD following AKI.

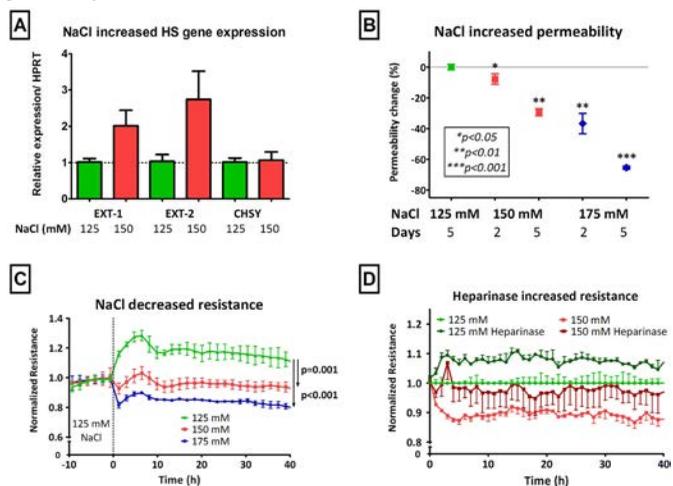
SA-PO466

Non-Osmotic Sodium Storage Affects Glomerular Endothelial Cell Permeability Rik Hg Olde Engberink,¹ Peter Ochodnický,² Simon C. Satchell,³ Ed van Bavel,⁴ Liffert Vogt.¹ ¹Nephrology, AMC, Amsterdam, Netherlands; ²Pathology, AMC, Amsterdam, Netherlands; ³Renal Unit, Univ of Bristol, Bristol, United Kingdom; ⁴Biomedical Engineering and Physics, AMC, Amsterdam, Netherlands.

Background: High dietary NaCl intake may affect glomerular permeability via pressure effects or via direct effects. In this respect, the Na⁺ buffering capacity of heparan sulfate glycosaminoglycans (HS-GAGs) in the endothelial surface layer (ESL) is of interest. The objective of this study is to investigate the interplay between Na⁺ and HS-GAGs and their effects on glomerular permeability.

Methods: Human glomerular endothelial cell (GEnCi) permeability to macromolecules was tested by measuring FITC-labeled albumin passage. Electrical resistance of a GEnCi monolayer, reflecting ESL Na⁺ content, was assessed with the ECIS® system at 4000 Hz. We studied the expression of gene coding enzymes involved in heparan sulfate (EXT-1, EXT-2) and chondroitin sulfate (CHSY) synthesis using real-time qPCR. Measurements were performed at different NaCl concentrations (125/150/175 mM ± HS degradation enzyme heparinase, 0.7 U/mL). We added mannitol to keep osmolality constant.

Results: Relative to 125 mM, EXT-1 and EXT-2 expression was higher after stimulation with 150 mM NaCl while CHSY expression remained unchanged (Fig A). Albumin permeability decreased after 2 and 5-d stimulation with 150 and 175 mM NaCl (Fig B). ECIS experiments showed that NaCl addition led to a concentration-dependent decrease in resistance (Fig C). NaCl did not alter resistance in the absence of cells. Heparinase increased resistance when added to 125 and 150 mM NaCl (Fig D). Mannitol did not alter permeability or resistance.



Conclusions: High NaCl stimulates HS-GAG synthesis of the glomerular endothelium, which may facilitate more Na⁺ binding. Subsequent higher ESL Na⁺ content may seal the glomerular barrier as suggested by both lower permeability and lower resistance.

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SA-PO467

Precision-Cut Human Kidney Slices as a Model to Elucidate the Pathogenesis of Renal Fibrosis Elisabeth G.D. Stribos,^{1,2} Theerut Luangmonkong,² Annemarie Leliveld,⁴ Igle J. de Jong,⁴ Willem Van Son,¹ Jan-luuk Hillebrands,³ Marc Maj Seelen,¹ Harry Van Goor,³ Peter Olinga,² Henricus A.M. Mutsaers.² ¹Dept of Internal Medicine, Div of Nephrology, Univ of Groningen, Univ Medical Center Groningen, Netherlands; ²Dept of Pharmaceutical Technology and Biopharmacy, Univ of Groningen, Netherlands; ³Dept of Pathology and Medical Biology, Div of Pathology, Univ of Groningen, Univ Medical Center Groningen, Netherlands; ⁴Dept of Urology, Univ of Groningen, Univ Medical Center Groningen, Netherlands.

Background: Renal fibrosis is a major problem in chronic kidney disease and chronic renal transplant failure. Unraveling the mechanisms underlying the initiation and progression of renal fibrosis is of key importance to identify new therapeutic targets. However, suitable human *ex vivo* models for renal fibrosis are lacking. Here, we explored precision-cut human kidney slices (PCKS) as a model for human renal disease.

Methods: PCKS were prepared from human cortical kidney tissue obtained from tumor-nephrectomies and cultured up to 96h. Morphology, cell viability (ATP levels, LDH leakage) and metabolic functionality (UDP-glucuronosyltransferase and transporter activity) were determined to assess PCKS integrity. Furthermore, inflammation- and fibrosis-related gene expression was characterized. To validate the model, renal fibrogenesis was induced using transforming-growth factor b1 (TGF-b1).

Results: Preparation of PCKS induced an inflammatory tissue response, while long-term incubation (96h) induced fibrogenesis as seen by increased expression of collagen type 1a1 (COL1A1) and fibronectin (FN1). Importantly, PCKS remained functional for more than 48h as evidenced by active glucuronidation and phenolsulfonphthalein uptake. Moreover, treatment with TGF-b1 augmented fibrosis, as illustrated by at least 1.8-fold increase of multiple fibrosis markers including COL1A1, FN1, plasminogen activator inhibitor-1 and α -smooth muscle actin.

Conclusions: After extensive characterization, PCKS appear to be an excellent model to investigate renal pathology *e.g.* renal fibrosis. Moreover, the human origin of PCKS makes this *ex vivo* model very suitable for translational research.

SA-PO468

Centrality of Bone Marrow-Derived Fibroblasts in Magnetic Resonance Imaging Contrast-Induced Systemic Fibrosis Viktor Drel,² Catherine Do,² Chunyan Tan,² Brent Wagner.^{1,2} ¹South Texas Veterans Health Care System, San Antonio, TX; ²Dept of Medicine, Univ of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: So-called “nephrogenic” systemic fibrosis is a ghastly sclerotic condition that occurs only in conditions of low renal function (acute kidney injury or severe chronic kidney disease) and gadolinium-based contrast exposure. Nothing is known about the pathobiology.

Methods: Experiments were designed to test if bone marrow from magnetic resonance imaging contrast-treated donors is stimulated to induce fibrosis, and to what degree these cells can be primed to home to affected organs. Male Fisher 344 rats that express human placental alkaline phosphatase (hPAP) were divided into two groups; one served as control, the other treated with pharmaceutical-grade gadodiamide (Omniscan, General Electric) 2.5 mol/kg IP daily, aiming for 20 doses over 4 weeks or evidence of systemic fibrosis. Rats with 5/6 nephrectomies were lethally-irradiated (900 Rad) followed by salvage bone marrow transplant from the control or contrast-treated donors. After an engraftment period, these recipients were divided into control and contrast-treated groups.

Results: Regardless of bone marrow source, contrast-treated recipients demonstrated severe skin fibrosis. Fibronectin was similarly increased by immunofluorescence and immunoblot, but a synergistic effect evident in recipients of contrast-treated animals. The fibroblast precursor (“fibrocyte”) markers, CD45RO and procollagen I, were increased in the contrast-treated recipients. Recipients of marrow from contrast-treated donors demonstrated greater dermal CD34 without histologic evidence of fibrosis.

Conclusions: Bone marrow from contrast-treated animals did not induce systemic fibrosis, therefore target organs (such as the skin) appear central to the process. However, given the synergistic effect, “primed” fibroblast precursors do have an increased affinity for diseased lesions. Clinically, this may explain why repeat administrations of gadolinium-based contrast correlate with chronicity.

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SA-PO469

SOCS2 Plays No Major Role in the Mouse Remnant Kidney Model of Fibrosis Yael Segev,¹ Muhamed Assadi,¹ Ralph Rabkin,^{2,3} Daniel Landau.^{1,4} ¹Microbiology and Immunology, Ben Gurion Univ, Beer Sheva, Israel; ²Research Inst, Veterans Administration Hospital, Palo Alto, CA; ³Medicine, Stanford Univ, CA; ⁴Pediatrics B, Schneider Children’s Medical Center, Petach Tikva, Israel.

Background: SOCS2, a key negative regulator of GH stimulated JAK/STAT5 signaling, is overexpressed in muscle, bone and liver of uremic rats and is presumably a cause of uremic GH resistance and growth retardation. SOCS2 deficient mice are GH sensitive, exhibit gigantism and accumulate collagen in skin, trachea and lungs (Reiser K et al, AJP 2004). Since GH overexpression in mice causes renal fibrosis, we tested whether SOCS2 deletion, by increasing GH sensitivity, accelerates remnant kidney fibrosis.

Methods: Four-week old SOCS2 deficient mice (high growth - HG strain) and normal wild-type mice (N) underwent 5/6 nephrectomy (CRF) or sham operation (SO), forming 4 groups: SO-N, SO-HG, CRF-N, CRF-HG. Mice were sacrificed after 3 weeks. IP bovine GH was given 30 min before sacrifice.

Results: Weight gain was reduced significantly in CRF-N versus SO-N. In contrast, growth of CRF-HG increased significantly versus both CRF-N and SO-N. Kidney SOCS2 mRNA, absent in HG mice, was significantly increased in CRF-N Vs SO-N. The degree of renal insufficiency was similar in CRF-N and CRF-HG mice. TGF- β and type IV collagen mRNA levels were increased to the same extent in SO-HG, CRF-HG and CRF-N Vs SO-N. Renal GH receptor mRNA levels were decreased in both CRF groups. GH stimulated STAT5 phosphorylation increased in SO-HG Vs SO-N, decreased in CRF-N Vs SO-N and increased in CRF-HG Vs CRF-N. IL6, SOCS3 mRNA and phospho-STAT3 levels increased similarly in both CRF groups Vs SO controls.

Conclusions: GH induced STAT5 signaling is depressed in remnant kidneys of CRF-N mice but is increased in non-uremic and uremic SOCS2 deficient mutants. Levels of fibrosis-related genes rose similarly in CRF-HG and CRF-N, despite absence of SOCS2 expression in CRF-HG mice. This suggests that SOCS2 does not play a central role in remnant kidney fibrosis. On the other hand, IL6 and its mediators phospho-STAT3 and SOCS3, were elevated in CRF-HG and CRF-N mice suggesting that inflammation may play a role in remnant kidney fibrosis.

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SA-PO470

β -arrestin2, Downstream of Angiotensin II Type 1 Receptor Biased Signaling Pathway, Plays an Important Role in Renal Fibrosis Yan-Dao Wang, Chen Yu. *Dept of Nephrology, Tongji Hospital, Tongji Univ, Shanghai, China.*

Background: Expect G protein signaling pathway, it is now considered that there is also a β -arrestin pathway in the downstream of G protein-coupled receptors (GPCRs); angiotensin II type 1 receptor (AT1R) belongs to GPCRs and angiotensin II (AngII) is a bi-stimulus to both G protein pathway and β -arrestin pathway; it is important to know which downstream pathway involving in AngII-AT1R-induced renal fibrosis. In this study, we used β -arrestin biased agonist SII ([1-sar, 4, 8-ile]-angiotensin II) to study β -arrestin pathway in renal fibrosis.

Methods: The model of unilateral ureteral obstruction (UUO) was used *in vivo*, and rat kidney fibroblast cell line (NRK-49F) was treated with SII *in vitro*.

Results: 1) SII induced the binding of β -arrestin2 with AT1R, not β -arrestin1. 2) SII increased the synthesis of collagen I and fibronectin in NRK-49F. Transfection of β -arrestin2 siRNA abolished the effect of SII on the accumulation of ECM. Overexpression of β -arrestin2 increased SII-induced ECM synthesis. 3) Candesartan pretreatment abolished collagen I and fibronectin up-regulation induced by SII in NRK-49F. 4) These effects were blocked in the presence of ERK1/2 blocker (PD98059). Transfection of siRNA targeting β -arrestin2 inhibited SII-induced ERK phosphorylation. Overexpression of β -arrestin2 enhanced SII-induced ERK1/2 phosphorylation. 5) The mRNA and protein levels of β -arrestin2 were significantly upregulated in the UUO model.

Conclusions: Our results suggested that AT1R downstream β -arrestin2 pathway, not β -arrestin1, might play a key role in renal fibrosis by forming complexes of β -arrestin2 and AT1R, inducing ERK1/2 phosphorylation and increasing ECM accumulation.

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SA-PO471

Deletion of ATR, a Master Molecule of DNA Damage Response, in the Proximal Tubule Exacerbates Kidney Injury and Increases Fibrosis Seiji Kishi,^{1,2} Takaharu Ichimura,^{1,2} Ryuji Morizane,^{1,2} Joseph V. Bonventre.^{1,2,3} *¹Renal Div, Dept of Medicine, Brigham and Women's Hospital, Boston, MA; ²Harvard Medical School, Boston, MA; ³Harvard Stem Cell Inst, Cambridge, MA.*

Background: Impaired response of cells to DNA damage can cause cellular senescence. We have previously implicated the DNA damage response of renal proximal tubule cell (RPTC) in progressive kidney injury and fibrosis. The purpose of this study was to investigate the role of Ataxia telangiectasia and Rad3-related (ATR), a master molecule of the DNA damage checkpoint, in kidney injury and fibrosis.

Methods: RPTC-specific conditional ATR knockout (ATR^{RPTC-/-}) mice were generated by crossing ATR floxed (ATR^{fl/fl}) mice, ATR^{-/-} mice and tamoxifen-inducible (SLC34a1-CreER²) mice. We evaluated the role of ATR in susceptibility to cisplatin nephrotoxicity, unilateral ureteral obstruction (UUO) and renal ischemia/reperfusion injury (IRI).

Results: Four days after cisplatin injection, ATR^{RPTC-/-} mice had increased kidney histological damage, increased Kidney Injury Molecule-1 (KIM-1) expression and decreased renal function compared with wild-type mice. Within the first 5 days, 34% of ATR^{RPTC-/-} mice died, while no WT mice died. Increased DNA damage and the number of apoptotic cells were also found in ATR^{RPTC-/-} mice. At 7 days after UUO, when compared with wild-type mice, ATR^{RPTC-/-} mice exhibited increased kidney histological damage, KIM-1 expression, DNA damage markers, and number of apoptotic cells. ATR deletion resulted in increased expression of fibrosis-related genes and increased kidney fibrosis. After IRI there was worse kidney function on day 3 and day 7 in ATR^{RPTC-/-} mice and increased interstitial fibrosis 4 weeks after IRI. Expression of p21, a marker of senescence, was significantly increased in ATR^{RPTC-/-} mice in each of the three models of injury.

Conclusions: ATR activation in the RPTC represents a protective response in acute and chronic kidney disease of various etiologies.

Funding: NIDDK Support

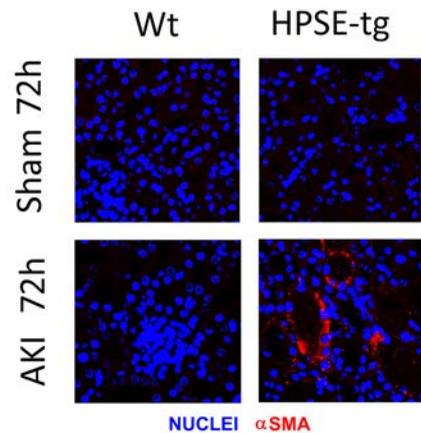
SA-PO472

Role of Heparanase in Renal Epithelial-Mesenchymal Transition Induced by Ischemia/Reperfusion Valentina Masola,¹ Gianluigi Zaza,¹ Giovanni Gambaro,² Maurizio Onisto,³ Gloria Bellini,¹ Gisella Vischini,² Iyad Khamaysi,⁴ Antonio Lupo,¹ Israel Vlodavsky,⁵ Zaid Abassi.⁵ *¹Renal Unit, Dept of Medicine, Verona, Italy; ²Columbus-Gemelli Hospital Catholic Univ, Roma, Italy; ³Univ of Padova, Padova, Italy; ⁴Rambam Medical Center, Israel; ⁵Technion, Israel.*

Background: Ischemia/reperfusion (I/R) activates epithelial-mesenchymal transition (EMT) of tubular cells, thus leading to organ fibrosis. Heparanase (HPSE) controls the EMT induced by FGF2 and TGF β . The aim of this study was to evaluate whether HPSE modulates the EMT induced by I/R.

Methods: Tubular cells (HK-2) wt and stably silenced for HPSE were subjected to 24h of hypoxia and 6h of reoxygenation. The cells were also treated with SST0001 (Sigma-Tau Research Switzerland SA), an inhibitor of HPSE. The I/R injury has been reproduced *in vivo* by clamping the renal arteries for 30 min in transgenic mice over-expressing HPSE (HPSE-tg) and their wt mice. Mice were sacrificed after 48 and 72 h. Gene and protein immunoreactivity of EMT markers (α -SMA, VIM, FN and TGF- β) were evaluated by real-time PCR, WB and IF; histology was assessed by PAS staining.

Results: *In vitro*; I/R increased the expression of EMT-markers in wt tubular cells but not in HPSE-silenced cells. Similarly, the inhibition of HPSE with SST0001 (Sigma-Tau Research Switzerland SA) in wt cells prevented the development of I/R induced EMT. *In vivo*; I/R induced acute tubular necrosis, which was more profound in HPSE-tg than their wt animals. In wt mice I/R-injury increased glomerular and tubular HPSE expression, but did not induce the EMT-markers. In contrast, I/R in HPSE-tg mice remarkably induced the expression of EMT-markers already after 72h.



Conclusions: HPSE is a crucial factor for the development of EMT induced by I/R. HPSE inhibition may therefore constitute a possible therapeutic approach for the prevention of fibrosis in organ transplantation.

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SA-PO473

Hydrogen Sulfide Deficiency in the Kidney and Brain in Aging Mice Hak Joo Lee,^{1,2} Kavitha lakshmi Satara natarajan,⁴ Meenalakshmi M. Mariappan,¹ Denis Feliers,¹ Jeffrey L. Barnes,^{1,2} Goutam Ghosh-Choudhury,^{1,2} Christopher G. Kevil,³ Balakuntalam S. Kasinath.^{1,2} *¹Medicine, MC7882, Univ of Texas Health Science Center, San Antonio, TX; ²Medicine, South Texas Veterans Health Care System, San Antonio, TX; ³Pathology, Louisiana State Univ, Shreveport, LA; ⁴Oklahoma Medical Research Foundation, Oklahoma City, OK.*

Background: Hydrogen sulfide (H2S) is constitutively synthesized by cystathionine γ lyase (CSE) and cystathionine β synthase (CBS). It regulates GFR and tubular transport in the kidney and NMDA receptors in the brain. H2S activates AMPK to inhibit mTORC1 and abrogate matrix protein increment in high glucose treated renal cells (Lee, JBC, 2012). Since mTORC1 is implicated in aging, we surveyed the status of H2S relative to mTORC1 in the organs of aging mice.

Methods: C57B6 mice, immunoblotting, H2S generation and content assays, histopathology, cell culture.

Results: The renal and cerebral CSE and CBS expression, H2S content and generation were reduced in old mice (26-32 mos old, n=6 mice) compared to young mice (4-6 mos old, n=8 mice); such changes were not seen in the heart or the skeletal muscle. Old mice showed increase in renal collagens I, III, fibronectin, parenchymal fibrosis, albuminuria, and rise in serum cystatin C. Signaling analysis showed that aging was associated with renal and cerebral activation of Akt, reduced phosphorylation of AMPK, and activation of mTORC1 manifest as increase in the phosphorylation of p70S6 kinase and 4E-BP1. Since insulin has been implicated in the aging process, we examined insulin regulation of CSE and CBS in renal proximal tubular epithelial (MCT) cells; insulin rapidly reduced CSE and CBS expression and decreased H2S generation. Insulin also promoted the synthesis of fibronectin matrix protein in MCT cells.

Conclusions: Our data show for the first time that the aging kidney and cerebrum share similar changes in H2S metabolism associated with reduced AMPK activity leading

to mTORC1 activation; these pathways could be related to age related changes including fibrosis. Insulin may mediate reduction in CBS, CSE and H2S and contribute to matrix accumulation in the aging kidney.

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SA-PO474

The Role of Ergothioneine/OCTN1 in CKD Yasuyuki Shinozaki,¹ Kengo Furuichi,¹ Shinji Kitajima,¹ Akinori Hara,¹ Yasunori Iwata,¹ Norihiko Sakai,¹ Miho Shimizu,¹ Takashi Wada.^{1,2} *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan; ²Dept of Laboratory Medicine, Kanazawa Univ, Kanazawa, Ishikawa, Japan.*

Background: Chronic kidney disease (CKD) is a strong risk factor for end stage kidney disease, and closely complicates with other organ damages. Organic cation transporter 1 (OCTN1) is known as a specific transporter for ergothioneine (ERGO). ERGO is reported to have a strong antioxidant effect. We hypothesized that OCTN1 function and the reduction of ERGO were closely related to the progression of CKD.

Methods: To evaluate the effects of OCTN1 function in CKD, everted sac method was used in CKD model or control mice. Furthermore, the pathological changes and oxidative stress in the kidney of OCTN1^{-/-} or OCTN1^{+/+} were evaluated in the CKD model mice. Moreover, the amount of ERGO in red blood cells of was measured in CKD patients.

Results: The uptake of ERGO in everted sac significantly decreased in CKD mice than control mice. Interstitial fibrosis, that evaluated by azan stain, sirius red stain, and the content of hydroxyproline of injured kidney, was significantly advanced in OCTN1^{-/-} CKD mice. Moreover, oxidative stress, that assessed by the number of 4-HNE stain positive cell, was exaggerated in OCTN1^{-/-} CKD mice (WT 26.4±9.7, KO 73.8±37.4/mm²), p<0.05). Correspondingly, the total antioxidant capacity decreased in OCTN1^{-/-} CKD mice. The concentration of ERGO in red blood cells decreased accompanied with CKD stage (G3b:30.0±4.4mg/mL, G4:25.8±5.6mg/mL, G5:14.8±8.1mg/mL, ESKD:5.1±3.9mg/mL).

Conclusions: The uptake of ERGO through OCTN1 decreased in CKD. The reduction of ERGO in CKD may participate in oxidative stress and progression of kidney injury.

SA-PO475

SIRT2-MDM2 Signaling Attributes to Fibroblasts Activation but Not Tubular Epithelial-Mesenchymal Transition During Tubulointerstitial Fibrosis Chun Zhang, Renyu You, Hua Su. *Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: Renal resident fibroblasts and tubular epithelial cells are the main sources for extracellular matrix producing myofibroblasts during tubulointerstitial fibrosis (TIF). Histone deacetylases (HDAC) inhibitors are shown to have an antifibrogenic effect in skin, liver and lung. Sirtuin 2 (SIRT2), belonging to class III HDAC, mediates p53 deacetylation and subsequently sensitizes the sequestration of p53 by MDM2, thereby resulting in a p53 reduction and cell cycle progression. Up to now it is unclear the role of SIRT2 and its association with MDM2 during renal fibrosis.

Methods: Unilateral Ureteral Obstruction (UUO) animal model was constructed on B57CL/6 mice. In vitro study cultured tubular epithelial cell line NRK-52E (TEC) and renal fibroblast cell line NRK-49F were employed. The expression of SIRT2 and MDM2 was regulated by its pharmacologic inhibitors or transfection of Lentiviral shRNA.

Results: It showed the protein level of SIRT2 was elevated markedly in UUO mice as well as the fibroblasts treated with TGF-β1. Nevertheless, in TECs the abundance of SIRT2 was not altered under TGF-β1 exposure. Additionally, AGK2, a specific SIRT2 inhibitor, attenuated the severity of TIF in UUO mice and the fibroblast activation triggered by TGF-β1. Next in fibroblast we found MDM2, a p53 inhibitor, was upregulated simultaneously under TGF-β1 stimulation. Interestingly, the increased MDM2 level can be minimized by pharmacologic or genetic blocking of SIRT2 which was not interfered by Nutlin-3 (an inhibitor of the interaction between MDM2 and p53). Thus, it indicated SIRT2 regulating MDM2 was p53 independent. Moreover, genetic deletion of MDM2 by shRNA transfection didn't affect the expression of SIRT2, although which could alleviate fibroblast activation.

Conclusions: Our current study suggests that besides p53, SIRT2 also could modulate MDM2 during fibroblasts activation, and targeting SIRT2-MDM2 signaling may be a potential strategy for the treatment of renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO476

The Role of cPLA₂ in Experimental Renal Fibrosis John Ross Montford, Allison M.B. Lehman, Raphael A. Nemenoff, Seth B. Furgeson. *Div of Renal Disease and Hypertension, UC Denver School of Medicine, Aurora, CO.*

Background: Chronic kidney disease (CKD) is characterized by progressive renal fibrosis involving poorly defined signaling events between renal epithelial cells, fibroblasts, and inflammatory cells. Cytosolic phospholipase A2 (cPLA2) is abundant in renal epithelium and inflammatory cells and serves as the rate-limiting enzyme in eicosanoid production. Since eicosanoids regulate many biological processes important in renal injury, we aimed to investigate the role of cPLA2 in the progression of renal fibrosis in a mouse model.

Methods: Wild type (WT) and cPLA2 globally deficient (KO) C57BL/6 mice were subjected to unilateral ureteral obstruction (UUO). In separate experiments WT mice were lethally irradiated and transplanted with either WT bone marrow or cPLA2-deficient bone

marrow. We then performed UUO 5-6 weeks after bone marrow transplantation. After UUO, we collected uninjured and injured kidneys for RNA, protein, flow cytometry, and histologic analysis, and preparation of single cell suspensions for flow cytometry.

Results: Compared with WT, cPLA2 KO animals had a 1.5-2.0 fold increase in histologic fibrosis at 14 days after UUO. In addition, the KO animals had elevated levels of mRNA for matrix proteins such as collagen and fibronectin, pro-fibrotic chemokines such as fractalkine, and inflammatory markers such as MCP-1 after UUO as compared with WT animals at 7 days. By flow cytometry, cPLA2 KO animals had significantly more infiltration of CD45+, CD11b positive-Ly6C negative cells than WT animals after UUO. Additionally, adoptive bone marrow transplant from cPLA2 KO mice into WT mice yielded worsening of histologic fibrosis after UUO as compared with transplants derived from WT animals.

Conclusions: Depletion of cPLA2 and/or its products, predominantly from circulating myeloid cells, contribute to the development of experimental fibrosis using a UUO model in mice.

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SA-PO477

Delayed Administration of Suramin Attenuates Peritoneal Fibrosis in Rats Chongxiang Xiong,¹ Na Liu,² Shougang Zhuang.¹ *¹Dept of Medicine, Rhode Island Hospital and Alpert Medical School, Providence, RI; ²Dept of Nephrology, Shanghai East Hospital, Tongji Univ School of Medicine, Shanghai, China.*

Background: Peritoneal fibrosis is one of the most serious complications in patients with peritoneal dialysis (PD) and lacks effective treatments. Our recent study showed that treatment with suramin, a compound that inhibits the interaction of multiple cytokines and growth factors with their receptors, attenuated the development of peritoneal fibrosis in a model of peritoneal fibrosis induced by chlorhexidine gluconate (CG). In the current study, we further assessed the therapeutic effect of suramin on the progression of peritoneal fibrosis in this model.

Methods: Rats were given a daily intraperitoneal injection of chlorhexidine gluconate (CG) for 3 weeks to induce peritoneal fibrosis followed by weekly administration of suramin at 20 mg/kg for an additional one or two weeks before kidneys were harvested.

Results: Delayed administration of suramin attenuated peritoneal membrane thickening and collagen fibril deposition occurred after CG exposure. Suramin was also effective in reducing CG-induced expression of α-smooth muscle actin, fibronectin and collagen I. Injury to the peritoneal membrane resulted in increased phosphorylation of Smad-3, a prominent mediator in transforming growth factor-β signaling, and epidermal growth factor receptor (EGFR), a key tyrosine kinase receptor associated with peritoneal fibrosis; suramin treatment blocked their phosphorylation. Similarly, suramin reduced CG-induced phosphorylation of transducer and activator of transcription-3 (STAT3) and extracellular signal-regulated kinase 1 and 2 (ERK1/2), two molecules that mediate profibrotic signal transduction. Moreover, delayed application of suramin suppressed CG-induced expression of several inflammatory cytokines in fibrotic peritoneum.

Conclusions: Our results indicate that suramin treatment inhibits the progression of peritoneal fibrosis via a mechanism involved in suppression of TGF-β1 and EGFR signaling pathways, and suggest that suramin holds a therapeutic potential for treatment of peritoneal fibrosis.

SA-PO478

MDM2 Mediates Tubulointerstitial Fibrosis and Fibroblasts Activation via p53-Independent Pathway Hua Su, Chen Ye, Chun Zhang. *Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: MDM2 is an E3 ubiquitin ligase which plays essential roles in podocytes and tubular epithelial cells injury or repair by regulating cell cycle and mediating inflammatory process. MDM2 exerts its pathophysiological effects via p53 dependent or independent pathway. However whether MDM2 is implicated in tubulointerstitial fibrosis (TIF) and fibroblasts activation is still unknown.

Methods: Patients with TIF (secondary glomerulonephritis and interstitial nephritis were excluded) were enrolled in this study and Unilateral Ureteral Obstruction (UUO) animal model was constructed on B57CL/6 mice. In vitro study cultured renal fibroblast cell line NRK-49F was employed. The expression of MDM2 and Notch1 was regulated by its pharmacologic inhibitors or transfection of Lentiviral shRNA. PYR-41 was used as an inhibitor of ubiquitin E1 activating enzyme.

Results: Here, we found the abundance of interstitial MDM2 was increased in patients with TIF as well as UUO mice. And interstitial MDM2 mainly originated from (myo) fibroblast. In vitro the expression of MDM2 was upregulated with fibroblasts activation under TGF-β1 stimulation, which was minimized by MDM2 knocking down but not by MDM2-p53 pathway inhibitor---Nutlin-3. Consistently, in UUO mice Nutlin-3 treatment cannot alleviate the interstitial fibrosis. Interestingly, we found Notch1, a molecule positively or negatively affecting the processes of proliferation, differentiation and apoptosis in a context-dependent manner, was reduced in cultured fibroblast treated with TGF-β1 which could be reversed by either genetic deletion of MDM2 or ubiquitin E1 activating enzyme inhibitor. Moreover, although pharmacologic or genetic blocking Notch1 signaling could trigger fibroblast activation it did not affect MDM2's abundance.

Conclusions: Our current study suggests that MDM2-Notch1 signaling pathway, not the classic MDM2-p53 pathway, is involved in fibroblast activation in an ubiquitination dependent manner during tubulointerstitial fibrosis.

Funding: Government Support - Non-U.S.

SA-PO479

Biomarkers of Collagen Type III and VI Turnover Can Predict Poor Recovery of Kidney Function in Kidney Transplant Recipients Daniel Guldager Kring Rasmussen,^{1,2} Signe Holm Nielsen,¹ Federica Genovese,¹ Morten Asser Karsdal,¹ Shengqiang Xia,² Martin Tepel.² ¹Nordic Bioscience, Denmark; ²Univ of Southern Denmark, Denmark.

Background: Allograft dysfunction is a common complication after renal transplantation (Tx). The turnover of extracellular matrix proteins, collagen type III and type VI, contributes to renal repair mechanisms which accompany allograft dysfunction. Distorted turnover may lead to progressive fibrosis and to loss of renal function. The objective of our study was to evaluate the role of specific collagen type III and type VI cleavage fragments for early allograft dysfunction after kidney Tx.

Methods: 171 incident patients, receiving a kidney allograft were enrolled at Odense University Hospital. Plasma and urine samples were collected at the first postoperative days. C3M and Pro-C6 were measured in samples using novel ELISAs. Early allograft dysfunction was defined as eGFR less than 30 mL per minute per 1.72m² 29 days after Tx. The relative change of plasma creatinine (RCPC) is the difference between plasma creatinine (pCrea) on the preoperative and first postoperative day divided by preoperative pCrea. Follow-up data on pCrea from a subset of patients was available at 6- and 12 months.

Results: Plasma Pro-C6 (pPro-C6) levels were significantly different in patients who received a deceased donor (DD), living donor (LD) and ABO incompatible (ABO) donor kidney (p<0.001). pPro-C6 had a negative correlation with eGFR 29 days post-Tx (p<0.0001, r=-0.35) and a positive correlation with pCrea at 6- (p=0.0001, r=0.31) and 12 months (p=0.0001, r=0.32). With a cut-off of 0.3 for the RCPC, ROC curves showed that plasma Pro-C6 predicted allograft dysfunction (p<0.0001, AUC=0.898). uC3M levels were not significantly different in patients receiving a DD, LD and ABO donor kidney. uC3M levels showed a negative correlation with plasma creatinine at 6- (p<0.0001, r=-0.37) and 12 months post-Tx (p<0.0001, r=-0.35). Plasma C3M was associated with plasma CRP (p<0.0001, r=0.62).

Conclusions: The study indicates that specific collagen type III and type VI cleavage fragments, i.e. C3M and Pro-C6, are both markers for early and late allograft dysfunction after kidney Tx, and reflect the underlying pathophysiology.

SA-PO480

Inhibitory Effect of Proximal Tubular Cells-Derived Neuropilin-1 in TGF Beta Signaling Pathway Rui Cheng, Xuemin He, Symon Ma, Jian-xing Ma. *Physiology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: Neuropilin-1 (NRP-1) is a co-receptor protein for multiple growth factors including class 3 smaphorins, VEGF, PDGF and TGF- β , and promotes signaling pathway involved in tumor growth, axonal chemorepellents, angiogenesis and liver fibrosis. In contrast, its function in the renal fibrosis has not been defined.

Methods: Primary renal proximal tubular cells (MRPTC) were cultured from *Nrp-1*^{fllox/fllox} mice. After infection of *Nrp-1*^{fllox/fllox} cells with adenovirus expressing Cre resulted in NRP1 Knock-out (*Nrp-1*^{-/-}) in the primary cells. Human proximal tubular cell line HKC-8, MEF cells and 3T3-L1 cells were used in this study. TGF- β -driven promoter transcriptional activity was measured by luciferase assay.

Results: NRP-1 was down-regulated by TGF- β in HKC8 and up-regulated in MEF cells and 3T3-L1 cells, suggesting the different regulation mechanisms and functions of NRP-1 between proximal tubular cells and fibroblasts. Over-expression of NRP-1 suppressed TGF- β -induced phosphorylation of Smad2/3 and expression levels of fibronectin. HKC-8 cells over-expressing NRP-1 showed significantly decreased levels of both TGF- β receptor I and receptor II. The *Nrp-1*^{-/-} cells showed higher TGF- β -induced Smad2/3 transcriptional activities and expression of fibronectin in *Nrp-1*^{fllox/fllox} MRPTCs, compared with control adenovirus-infected *Nrp-1*^{fllox/fllox} MRPTCs.

Conclusions: Proximal tubular cells-derived NRP1 inhibits the TGF beta signaling pathway. NRP1 functions are cell type-specific in the kidney.

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SA-PO481

The cAMP-epac Pathway Regulates Renal Fibrosis by Promoting Mitochondrial Biogenesis of Tubular Epithelial Cell Lei Jiang, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: As a universal second messenger, cAMP inhibits the formation of extracellular matrix in tissue fibrosis. Mitochondrial dysfunction is an early event in renal fibrosis, but how it leads to kidney fibrosis and how it is regulated is unclear. In this paper, we investigated the role of cAMP-epac pathway in mitochondrial biogenesis and renal fibrosis.

Methods: Animal models of renal fibrosis was induced by unilateral ureteral obstruction (UUO), chronic Ang II infusion and adriamycin administration. cAMP was given to CD1 mice under UUO by tail vein injection. Rolipram was injected intraperitoneally in CD-1 mice under UUO. A primary tubular epithelial cell (PTC) culture from normal CD-1 mice renal cortex was used. Rolipram, PKA activator, epac activator, PDE4b siRNA, epac siRNA were given to PTC respectively with TGF- β 1 stimulation. ATP kit and NAD⁺/NADH kit were used to evaluate the mitochondrial function. Real-time PCR was used to detect mitochondrial DNA (mtDNA) expression. The morphology of mitochondria was observed by electron microscope.

Results: 1. The level of cAMP was decreased in the fibrotic kidney; 2. PDE4b were upregulated obviously in the kidney under UUO, and the epac not PKA were responded to fibrosis; 3. Upregulation cAMP by giving PDE inhibitor (rolipram) or cAMP could

ameliorate the renal fibrosis and protect mitochondrial structure; 4. Rolipram could stabilize PGC-1 α expression and block the mitochondrial dysfunction induced by UUO; 5. TGF- β 1 could induce the downregulation of cAMP in PTC. Increasing the level of cAMP in PTC by rolipram, PDE 4b siRNA, epac activator or epac siRNA could reduce the damage of PTC under TGF- β 1 stimulation; 6. Rolipram could restore PGC-1 α expression, reduce the mtDNA damage and protect the mitochondrial function and structure of PTC under TGF- β 1 stimulation.

Conclusions: cAMP-epac pathway is involved in renal fibrosis. Increased cAMP level blocks the progress of renal fibrosis. cAMP promotes mitochondrial biogenesis and restores mitochondrial structure and function of tubular epithelial cell.

Funding: Government Support - Non-U.S.

SA-PO482

Endothelial Cell Thymosin β 4 Knock Down Ameliorates Kidney Fibrosis by Reducing Endothelial to Mesenchymal Transition (EndoMT) Jianyong Zhong,^{1,2} Haichun Yang,¹ Agnes B. Fogo.¹ ¹Dept of Pathology, Microbiology and Immunology, Vanderbilt Univ; ²Div of Pediatric Nephrology, Vanderbilt Univ, Nashville, TN.

Background: Thymosin β 4 (T β 4) is a G-actin sequestering protein with effects on angiogenesis, cell migration and matrix. Our previous data showed that exogenous T β 4 treatment ameliorated matrix accumulation at day 14 after unilateral ureteral obstruction (UUO). In this study, we investigated whether knockdown of T β 4 only on endothelial cells has effects on renal fibrosis.

Methods: We generated inducible endothelial cell T β 4 knockdown mouse (T β 4 KD) by mating T β 4 shRNA loxp mice with SCL Cre mice. SCL Cre negative mice were used as control (Cont). Tamoxifen was administered to induce T β 4 knockdown (\times 5, qod, from-8d). Mice were sacrificed at 14 days after UUO.

Results: Peritubular capillary density, assessed by CD31 staining, was significantly decreased in T β 4 KD mice (T β 4 KD 2.39 \pm 0.11 vs. Cont 3.20 \pm 0.08 %, P<0.001). Peritubular capillary permeability, measured by injecting Evans blue dye in vivo and assessing extravasated dye in the kidney, also was reduced in T β 4 KD mice (T β 4 KD 107.01 \pm 5.49 vs. Cont 161.85 \pm 16.32 mg/g KW, P<0.05). T β 4 KD had significantly decreased collagen I, accessed by IHC, vs Cont (T β 4 KD 15.24 \pm 0.57 vs. Cont 17.68 \pm 0.71 %, P<0.05), but no significant change in Sirius red positive area (T β 4 KD 0.91 \pm 0.03 vs. Cont 1.14 \pm 0.15 %) or total collagen (T β 4 KD 48.06 \pm 5.01 vs. Cont 53.50 \pm 2.34 mg/mg). T β 4 KD had less EndoMT (α -SMA⁺ and CD31⁺ double positive cells/high power: T β 4 KD 1.20 \pm 0.11 vs. Cont 1.74 \pm 0.17 P<0.05).

Conclusions: We conclude that endothelial cell thymosin β 4 knockdown results in impaired peritubular capillary number and function, with reduced collagen I protein in UUO. We speculate that T β 4 KD in endothelial cells may change endothelial function and modulate EndoMT.

Funding: NIDDK Support

SA-PO483

Endostatin and Transglutaminase 2 Are Geriatric Proteins Involved in Fibrosis of Aging Kidney Chi Hua Sarah Lin,¹ Jun Chen,¹ Gail V.W. Johnson,² Arthur J.I. Cooper,¹ Zhongtao Zhang,¹ Julianne Feola,² Jonathan Shein,¹ Heli Ruotsalainen,³ Taina Pihlajaniemi,³ Michael S. Goligorsky.¹ ¹New York Medical College; ²Univ of Rochester; ³Univ of Oulu, Finland.

Background: Endostatin (EST), the C-terminal fragment of collagen XVIII and a potent anti-angiogenic factor, is highly enriched in aging kidneys. It has also been described as an interactive partner of another profibrogenic factor, transglutaminase 2 (TG2), an enzyme cross-linking extracellular matrix proteins. We inquire the possible direct or auxiliary role they may play in the development of renal tubulointerstitial fibrosis of aging.

Methods: Studies were conducted in young and aging wild type mice, mice overexpressing EST and mice kidney of subcapsular injection of TG2 or EST.

Results: In wild type mice, aging kidneys exhibited 2-4-fold increase in TG2 paralleled by the increased cross-linking of extracellular matrix proteins and striped fibrosis. Ex vivo aortic rings embedded in matrigel supplemented with TG2 showed suppressed angiogenesis and proteolytic degradation. Injection of TG2 in the intact kidney produces increased cross-linking within 48h. Transgenic mice overexpressing EST showed renal interstitial fibrosis already at the young age, suggesting that EST may contribute to interstitial fibrosis in the aging kidney. Moreover, a month-long delivery of EST peptide via implanted minipumps to young mice also showed increased renal fibrosis, which became more robust when superimposed on the early "wound healing" phase of folic acid (FA)-induced nephropathy, a "second hit" model. Upregulation of TG2 and impaired renal function were also apparent in kidneys of mice with EST peptide delivery in combination with FA-induced nephropathy. Moreover, subcapsular injection of TG2 or EST increased the proportion of kidney-resident cells prematurely senescent.

Conclusions: These studies allow us to conclude that kidney fibrosis in aging may represent a natural outcome of deregulated EST and TG2, but more likely it appears to be a result of cumulative renal stresses occurring on the background of elevated geriatric proteins, EST and TG2.

Funding: NIDDK Support

SA-PO484

Angiopoietin-1 Deficiency Increases Tubulointerstitial Fibrosis

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Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in α SMA+ fibroblasts, myofibroblasts that produce collagen. Identification of factors that regulate the fibrotic response are excellent candidate targets for treatment of kidney diseases. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing and diabetic nephropathy. Angpt1 acts through the Tie2 tyrosine-kinase receptor expressed on endothelial cells and a subset of myeloid cells. Here, we test the hypothesis that loss of Angpt1-Tie2 signaling destabilizes endothelial cells and results in an increased fibrotic response.

Methods: To investigate the role of Angpt1 in renal fibrosis we utilized Angpt1 conditional knockout mice in experimental models of renal fibrosis, including unilateral ureter obstruction (UUO) and ischemia/reperfusion injury. Gene and protein regulation of fibrotic markers were investigated at different time points. We also performed lineage tagging experiments using Tie2-Cre and LysM-Cre to better understand the contribution of Tie2+ cells and macrophages to the myofibroblast population in UUO.

Results: Angpt1 deficient mice showed a significant ($p < 0.01$) increase in fibrotic area 3days after UUO, $9.7 \pm 0.45\%$, compared to controls, $7.9 \pm 0.24\%$. At the same time point, there was a trend (n.s) towards an increased number of myofibroblasts per field from 15.4 ± 1.8 in controls to 20.1 ± 4.1 in Angpt1 deficient mice. Ischemia/reperfusion experiments are ongoing. In our lineage tagging experiment we found that $18.5 \pm 0.03\%$ of myofibroblasts came from the Tie2-lineage whereas the LysM lineage contributed minimally, $2.4 \pm 0.005\%$.

Conclusions: Our results suggest that loss of Angpt1-Tie2 signaling increases tubulointerstitial fibrosis as seen by the increased expression of fibrosis markers in Angpt1 deficient mice. Ongoing work is designed to use other models of fibrosis and to elucidate the mechanism(s).

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SA-PO485

Inter-Alpha-Inhibitor Heavy Chain5 Interactions Control Fibroblast Myofibroblast Differentiation

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Background: Fibroblasts are central to CKD through their Transforming Growth Factor- β 1 (TGF- β 1)-triggered phenotypic transition into contractile, α -smooth muscle actin (α -sma)-positive myofibroblasts. Transition is dependent on an increase in the synthesis and accumulation of a pericellular matrix of hyaluronan (HA) and the HA-dependent co-localisation of CD44 with EGFR. Interactions of HA with hyaladherins, such as inter-alpha-inhibitor (I α I) and the protein product of Tumour necrosis factor-stimulated gene 6 (TSG-6) aid the assembly of this matrix and are also essential for the phenotypic activation of fibroblasts. The mechanisms controlling this effect, however, are not known and are the subject of this study.

Methods: Fibroblasts were incubated for 72 h with 10ng/ml TGF- β 1 to become myofibroblasts. RT-QPCR was used to assess mRNA, siRNA was used to knockdown mRNA expression, immunocytochemistry and SDS-PAGE/Western Blotting assessed protein levels.

Results: Following TGF- β 1 treatment, TSG-6 and α -sma, had different kinetics of induction. Using siCD44 or EGFR inhibitor AG1478 to interfere with the CD44/EGFR-dependent signal initiation prevented differentiation but had no effect on TSG6 expression. TSG-6, however, was essential for differentiation and using monoclonal antibody A38, HA-oligosaccharides, Cobalt, or siBikunin to interfere with the activity of TSG6, all prevented phenotypic change. These results suggested that it was the TSG6/I α I heavy chain (HC) interaction that was necessary for the effect. HC5 was shown to be the principal HC expressed in these cells. HC5 was released by hyaluronidase treatment of the fibroblast cell surface and siCD44, siTSG6 and siBikunin all inhibited the expression of HC5 protein. Finally, HC5 could be deleted on the cell by specific siRNA and this resulted in antagonism of phenotypic change, confirming its role in myofibroblast differentiation.

Conclusions: The mechanisms regulating TSG-6 and HA synthesis, during TGF- β 1-dependent induction of myofibroblasts are distinct. TSG-6, however, contributes to the pro-fibrotic response through its catalytic transfer of I α I HC5 to HA leading to the subsequent induction of phenotypic change.

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SA-PO486

Role of IL-4 Receptor α in Bone Marrow-Derived Fibroblast Activation and Renal Fibrosis

Hua Liang, Yuanbo Wu, Yanlin Wang. *Medicine, Baylor College of Medicine, Houston, TX.*

Background: Renal fibrosis is a common pathway leading to progression of chronic kidney diseases. We and others have shown that bone marrow-derived fibroblasts contribute significantly to the pathogenesis of renal fibrosis. However, the signaling mechanisms underlying the activation of bone marrow-derived fibroblasts in the kidney are incompletely understood. We have found that IL-4 and its receptor α (IL4R α) are induced in the kidney during the development of renal fibrosis. However, little is known about the role of IL-4R α in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis.

Methods: We examined the role of IL-4R α in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis using a mouse model of folic acid-induced nephropathy and cultured bone marrow monocytes treated with IL-4.

Results: Compared with wild-type (WT) mice, IL4R α -knockout (KO) mice exhibited significant preservation of kidney function as measured by serum urea nitrogen and accumulated significantly fewer bone marrow-derived fibroblasts dual positive for CD45 and PDGFR- β in the kidney 2 weeks after folic acid treatment. Furthermore, IL4R α -KO mice exhibited fewer α -smooth muscle actin (α -SMA) positive myofibroblasts and expressed less α -SMA protein in the kidney following folic acid treatment. Consistent with these findings, IL4R α deficiency significantly reduced total collagen deposition and suppressed expression of extracellular matrix proteins (collagen I and fibronectin). In cultured bone marrow monocytes, IL-4 activated STAT6 and induced expression of α -SMA and extracellular matrix proteins, which was abolished in the absence of IL4R α .

Conclusions: Our results have demonstrated that IL4R α plays an important role in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis. These results indicate that IL4R α signaling may represent a novel therapeutic target for chronic kidney disease.

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SA-PO487

Role of Scaffolding Protein JLP in Preventing Renal Fibrosis in Obstructive Nephropathy

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Background: Renal fibrosis is a common pathologic lesion in the end stage of various progressive kidney diseases, and is characterized by interstitial inflammation, proliferation of myofibroblasts, and progressive accumulation of extracellular matrix (ECM). The JNK-associated leucine zipper protein (JLP) is a crucial scaffolding protein in signals transduction and molecular trafficking. JLP has been found expressed in mouse tissues of brain, lung, spleen, testis, and kidney. We reported here, for the first time, the effects of JLP deficiency on the progression of renal fibrosis in mice model of unilateral ureteral obstruction (UUO).

Methods: *Jlp* Wild type (*Jlp*^{+/+}) and *Jlp* deficient (*Jlp*^{-/-}) mice were divided into four groups: *Jlp*^{+/+}- and *Jlp*^{-/-}-sham-operated groups, *Jlp*^{+/+}- and *Jlp*^{-/-}-unilateral ureteral obstruction (UUO)-operated groups (*Jlp*^{+/+}- UUO group and *Jlp*^{-/-}- UUO group). Mice were sacrificed at the days of 7 and 14 to evaluate the fibrosis by Masson and H&E staining. The expression of transforming growth factor- β 1 (TGF- β 1), α -smooth muscle actin (α -SMA), collagen I (COL-I), and collagen III (COL-III) were assayed by immunohistochemistry staining.

Results: One week after the surgery, more collagen deposition was observed in the renal interstitial area in *Jlp*^{-/-}- UUO group than in *Jlp*^{+/+}- UUO group. Similar to that, the expression of COL-I and COL-III were significantly increased in the kidney cortices in *Jlp*^{-/-}- UUO-operated groups. The expression of TGF- β 1 and α -SMA was also significantly higher in *Jlp*^{-/-}- UUO-operated group than in *Jlp*^{+/+}- UUO group.

Conclusions: Scaffolding protein JLP is critical in preventing renal fibrosis through the mechanism of inhibition TGF- β 1 expression and myo-fibroblast induction.

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SA-PO488

HGF-Producing Cell Sheet Suppress Renal Fibrosis Induced by Unilateral Ureteric Obstruction in a Rat

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Background: Tubulointerstitial fibrosis is a typical pathological finding in chronic kidney disease (CKD) and is associated with the progression of renal dysfunction. Recently several studies reported to suppress renal fibrosis by transplantation of cells expressing several growth factor, for example EGF, HGF. Cell sheet transplantation is a methodology of cell therapy for regenerative medicine. This technology demonstrated high effective therapy for diseases in other organs, such as cornea, periodontium, esophagus and heart. In this study, we performed to suppress renal fibrosis by local and sustained administration of hepatocyte growth factor (HGF) with HGF-producing cell sheet (HGF sheet) transplantation.

Methods: Human mesothelial cells transfected human HGF gene by lipofection were cultured on temperature-responsive dish for 4 days. When temperature reduced, these HGF-producing cells were detached from dishes as cell sheet without enzyme-treated. We performed unilateral ureteric obstruction (UUO) in nude rat and transplanted the HGF sheet immediately. To compare HGF sheet transplantation with intermittent administration of HGF protein, we also injected HGF protein from tail vein every 24 hours for UUO rat (HGF i.v.). The kidney volume after operation measured with CT every 7 days for 4 weeks.

Results: One week after operation, histologically the positive area of collagen and smooth muscle actin in kidney transplanted HGF sheet was significantly less compared to that in HGF i.v. kidney. Moreover, the kidney volume treated HGF sheet with UUO was significantly less compared to control 4 weeks after operation. And it maintained thick cortex tissues with a lot of glomeruli, tubules and microvessels in the kidney treated HGF sheet.

Conclusions: Local and sustained HGF administration with HGF sheet strongly suppressed renal fibrosis induced by UUO in a rat. Our results suggested that cell sheet therapy may be a promising strategy for renal disease.

Funding: Government Support - Non-U.S.

SA-PO489

Extracellular Matrix Modulates Macrophage Phenotype Profile Astgik Petrosyan,¹ Stefano Da Sacco,² Sargis Sedrakyan,² Giuseppe Orlando,³ Matthew Edward Thornton,¹ Brendan Grubbs,¹ Roger E. De Filippo,^{1,2} Laura Perin.^{1,2} ¹Univ of Southern California; ²Children's Hospital Los Angeles; ³Wake Forest School of Medicine.

Background: It is known that macrophages play an important role in kidney damage and resolution. An increase in macrophages phenotype type 1 (M1) is known to promote scar formation while an increase in macrophage phenotype type 2 (M2) leads to pro-healing processes. However little is known on how the extracellular matrix (ECM) can direct macrophages toward a specific phenotype acquisition during development, tissue homeostasis and disease.

Methods: Using established protocols we decellularized human adult healthy, adult diseased, and fetal kidneys; monocytes were seeded on the different ECMs and macrophage phenotype switch after 24hrs and 5 days was assessed. Macrophage maturation was tested by evaluating release of IL-10, IFN- γ , TNF- α and IL-4 in the culture media along with qRT-PCR and immunocytochemistry to evaluate expression of M1 (CD80 and CD86) and M2 (CD163, CD16, CD14 and CD200R) phenotypes.

Results: We observed that monocytes cultured on ECMs were able to mature into macrophages and present an increase in M1 marker (CD80) on diseased ECM, an increase in M2 markers (CD163, CD200R) on healthy ECM, and an increase in anti-inflammatory M2 marker (CD16) on fetal ECM, after 24hrs. After 5 days of co-culture there was an overall decrease in gene expression for all markers followed by an increase in media secretion of IL-10 on diseased ECM vs healthy and fetal ECM. Additionally after 5 days higher number of seeded monocytes appear to adhere onto the adult ECM vs the fetal ECM. IFN- γ , IL-4 or CD64 expression was not detected during 24hrs and 5 days. Monocytes capacity to mature into macrophages was confirmed *in vitro* by administration of phorbol myristate acetate (PMA) and 1,25-dihydroxy vitamin D3 with LPS.

Conclusions: This preliminary work suggests that the ECM has the capacity to modulate macrophage phenotype and might contribute to disease progression. Additionally, this model may be used to investigate mechanisms of ECM-dependent macrophage activation during renal disease and regeneration.

SA-PO490

High Salt Diet Induces Blood Pressure Independent Tubulointerstitial Remodeling and Lymphangiogenesis in Rat Kidney Ryanne S. Hijmans, Saleh Yazdani, Gerjan Navis, Jacob van den Born. *Nephrology, Univ Medical Center Groningen, Groningen, Netherlands.*

Background: In chronic kidney disease (CKD), proteinuria is an important cause of tubular activation and progressive tubulointerstitial damage. It has been shown that high salt (HS) intake can aggravate this renal damage. Although earlier studies mainly focused on the blood pressure dependent (BP) effects of sodium on the kidney, recent studies suggest there is a BP independent route as well. A HS diet has been shown to store Na⁺ in the skin and as a result of binding of Na⁺ to proteoglycans, the influx of macrophages stimulates the secretion of vascular endothelial growth factor C (VEGF-C). Macrophage-derived VEGF-C has been shown to induce lymphangiogenesis (LA) in the skin. As LA has a role in inflammatory remodeling, we hypothesize that HS diet exerts its BP independent effects on the kidney by inducing LA and renal tubulointerstitial (TI) remodeling. We tested this hypothesis in normal rats, to avoid interference with TI remodeling due to the primary renal disorder.

Methods: Male Wistar rats (n=15) were randomly assigned to one of three study groups. Two groups (both n=5) received a high salt diet of 8% salt, while the control group (n=5) had a normal rat diet. After 2 weeks, one of the two groups on a high salt diet was sacrificed, and the other groups were sacrificed at 4 weeks. The kidneys were stained and quantified for lymphangiogenic, fibrotic and inflammatory markers.

Results: Rats with HS intake showed an increased number of lymph vessels compared to their controls at week 4 (p<0.06). ED1+ macrophages also increased in the HS group at week 4 (p<0.06). There was a significant increase of myofibroblasts (α -SMA) after 4 weeks in the HS group (p<0.02). Except for week 1 (p<0.05), the HS groups showed no significant BP differences with their controls at 2, 3 and 4 weeks.

Conclusions: We showed that high salt intake induces tubulointerstitial lymphangiogenesis, inflammation and profibrotic changes in rat kidneys, even when the BP is not significantly different between the groups. This finding supports our hypothesis that HS intake has BP independent effects next to its well known BP dependent effects in CKD.

SA-PO491

Genetic and Epigenetic Analysis of the MicroRNA-200 Family for Association with End Stage Renal Disease Laura Jane Smyth,¹ Gareth J. McKay,¹ Alexander P. Maxwell,^{1,2} A.J. McKnight.¹ ¹Centre for Public Health, Queen's Univ of Belfast, Belfast, Northern Ireland, United Kingdom; ²Regional Nephrology Unit, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom.

Background: DNA methylation and miRNA profiles are associated with complex disease and are altered in uremic patients. We evaluated CpG sites, gene expression and SNPs of the miRNA-200 family and their target genes, including exploration of relevant methylation quantitative trait loci (meQTLs).

Methods: Quantitative DNA methylation was extracted from existing epigenome-wide association data (Illumina's 450K Methylation array) for individuals with and without

kidney disease (n=407). Following stringent quality control, a total of 14 significant CpG sites were identified within the miRNA-200 family, the most significant of which was cg23651812 (*MIR429*, P=4.1x10⁻⁴⁵). The top 20 predicted target genes were determined using miRDB for each miRNA (*MIR141*, *MIR200A*, *MIR200B*, *MIR200C* and *MIR429*). Target genes had 308 CpG sites with methylation data; the most significant for *MIR429* were cg11686204 in *ELL2* and cg19038462 in *ZEB1* (P=4.2x10⁻⁴⁸). RNA-Seq analysis was performed on renal transplant recipients and healthy controls using the Ion Proton™. RNA was selectively depleted for ribosomal RNA and up to 40 million reads were gained per sample. Differential methylation status was associated with expression of miRNA and their corresponding gene targets. Genome-wide SNP data (n=561,233 SNPs; 372 individuals) from the Illumina 660K array was analysed in PLINK with QTL methylation data from the individual miRNA (n=14) and their target genes (n=308) CpG sites.

Results: No genome-wide significant cis-meQTLs were identified for the miRNAs. Two cis-meQTLs were identified for *ZEB2* (rs10200550 and rs4347890), a target gene for *MIR429*. Genome-wide significant results (n=476 SNPs) were obtained for 67 target genes (maximum P=9.98x10⁻³²). These genes may influence miRNA regulation.

Conclusions: *CD36*, the top-ranked gene, has previously been linked to kidney disease where it is suggested that it has a prominent role in the development of renal fibrosis. We have provided a genomic map of the miRNA-200 family using novel data in order to assist in determining its association with ESRD.

Funding: Private Foundation Support

SA-PO492

A MicroRNA Signature of Epithelial-Mesenchymal Transition in Progression of Chronic Renal Disease Ali Ramezani,¹ Joseph M. Devaney,² Akshay Roy-Chaudhury,¹ Richard Scott,² Sara Karandish,¹ Susan Knoblauch,² Jeffrey B. Kopp,³ Dominic S. Raj.¹ ¹Div of Renal Diseases and Hypertension, George Washington Univ, Washington, DC; ²Center for Genetic Medicine Research, CNMC, Washington, DC; ³NIDDK, NIH, Bethesda, MD.

Background: Irrespective of the diverse initial causes, progression of CKD is characterized by increasing tubulointerstitial fibrosis. There is a great need for accurate, noninvasive biomarkers for early detection of fibrosis in the kidney and the progression of kidney disease. Recent evidence suggests that miRNAs participate in the fibrotic process in the kidney. The aim of this study was to examine the urinary and circulatory miRNA expression profiles regulating the EMT and whether they are reflected by parallel changes in the pro-fibrotic factors and the progression of kidney disease.

Methods: Blood and urine samples were obtained from 28 patients with CKD. Patients were divided into two groups according to their GFR: GFR<30 and GFR>30. Plasma and urinary levels of two biomarkers of fibrosis, collagens III (PIIINP) and IV, were measured. To analyze the involvement of miRNAs in kidney fibrosis, the plasma and urinary miRNA expression profiles of the patients were analyzed.

Results: Plasma and urine PIIINP and CIV levels were significantly increased in patients with GFR<30. Furthermore, miRNA expression profile of the patients showed 58 downregulated and 60 upregulated miRNAs in urine, and 51 downregulated and 61 upregulated miRNAs in the plasma of the patients with GFR<30 compared with GFR>30. A panel of 4 urine and 6 plasma miRNAs was identified which not only distinguished patients with GFR<30 from GFR>30, but their altered expression were also implicated in the phenotypic changes that occur during EMT and fibrosis. The altered expression levels of these miRNAs were validated in a tubular epithelial cell line, and studies are underway to validate their expression *in vivo*, in the Alb/TGF β mouse model.

Conclusions: Plasma and urinary miRNAs are reliable, noninvasive, and inexpensive markers for CKD fibrosis and progression. These miRNA panels warrant study in larger cohorts since plasma- and urine-based assays could provide a more feasible and safer screening compared to biopsy.

Funding: NIDDK Support

SA-PO493

The PR3 Receptor CD177 Is Controlled by Epigenetic Mechanisms Claudia Eulenberger,¹ Sylvia Bähring,¹ Friedrich C. Luft,¹ Ralph Kettritz,² ¹Charité-Buch, Experimental and Clinical Research Center, Berlin, Germany; ²Nephrology and Intensive Care Medicine, ECRC, Berlin, Germany.

Background: Proteinase 3 is the major ANCA antigen in granulomatosis with polyangiitis (GPA). PR3-ANCA binding to membrane-PR3 (mPR3) is a key event for neutrophil activation and vascular damage. The neutrophil-specific CD177 receptor enables mPR3^{high} expression on a neutrophil subset (CD177^{pos}/mPR3^{high}). ANCA patients show a higher percentage of CD177^{pos}/mPR3^{high} neutrophils compared to healthies, the higher the percentage, the worse the prognosis. We reported previously that CD177 protein and mRNA expression is restricted to CD177^{pos}/mPR3^{high} neutrophils with a random monoallelic mRNA expression pattern. We hypothesized that epigenetic mechanisms control CD177 gene expression.

Methods: Haplotype analysis, genome-wide methylation analysis, chromatin immunoprecipitation (ChIP) analysis and CD177 expression studies were performed in neutrophils and HeLa cells.

Results: Methylation analysis on CD177^{neg} and ^{pos} neutrophils revealed three CpGs in the potential CD177 promoter that were methylated in CD177^{neg}, but not in CD177^{pos} cells (p<0.001; n=6). ChIP identified an enrichment of the H3K4me3 mark (euchromatin) in the predicted CD177 promoter region in CD177^{pos} neutrophils (p<0.05; n=4). This putative promoter region contains a TATA box and binding sites for several transcription factors, including the AP1 family. We established a HeLa cell model that recapitulates the neutrophil situation. We observed CD177 mRNA in PMA-treated HeLa cells. HeLa cells also had euchromatin in the promoter region and CD177 mRNA followed a monoallelic expression

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

pattern. CD177 mRNA expression was upregulated when we transfected HeLa cells with the AP1 family members c-Jun, c-Fos and c-Ets1. The same AP1 family members bound the putative CD177 promoter region by ChIP experiments in HeLa and neutrophils. HeLa cell treatment with the demethylation agent 5-aza-2'-deoxycytidine led to a biallelic CD177 gene expression. Reporter assays in HeLa cells will further characterize the epigenetic and transcriptional CD177 regulation.

Conclusions: Our data strongly implicate epigenetic mechanisms that are responsible for the generation of distinct CD177/mPR3 subsets.

Funding: Government Support - Non-U.S.

SA-PO494

Application of Human Kidney RNA-seq Expression Quantitative Trait Loci in Chronic Kidney Disease Yi-An Ko, Frank S. Chinga, Nora Ledo, Katalin Susztak. *Renal Electrolyte and Hypertension Div, Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA.*

Background: There are more than 5 million sequence variants in humans. Some genetic variations influence transcript levels and therefore have the ability to interfere with cell and organ function. Such genetic variants are called expression quantitative trait loci (eQTL). The goal of our study was to identify such functionally important genetic variants at the genome-wide level.

Methods: This analysis requires the collection of large number of human tissue samples with genotype and transcript level data. Here we used 99 human kidney samples of Central European descents. RNAseq and genotype data was normalized and genotype data was imputed using 1,000 Genome reference data. The association between genotype and transcript levels was performed using Matrix eQTL software and was limited to *cis*-eQTLs where the genetic variant and transcript levels were within 2 megabases distance.

Results: We identified 164 significant target genes (we call these eGenes) and 7590 significant SNPs (eSNPs) that passed the threshold for statistical significance after multiple testing correction using adjusted *p*-values < 1.0E-10. Next we compared variants that influence gene expression in the kidney to those that have been published for other organs using the publicly available Genotype-Tissue Expression project (GTEx). Of the 164 eGenes, 103 were common between the kidney and other organs, indicating that there are cell type specific and cell type independent eGenes. Using kidney specific epigenome maps, we found that eSNPs were enriched on kidney specific regulatory elements, including promoters and enhancers. We also found a significantly greater overlap between kidney eGenes and polymorphisms that are associated with CKD development, compared to other traits (digestive, nervous, immune system diseases, hematological measurement, cardiovascular, and metabolic disease).

Conclusions: We identified transcript level changes associated with genotypic variations. These results can highlight kidney specific regulatory elements and may also help to identify target genes for polymorphisms associated with kidney function related traits.

Funding: Other NIH Support - NIH Roadmap Epigenomics Program 5R01DK087635-02

SA-PO495

RNA Sequencing Reveals Tumor Necrosis Factor α Inducible Protein 6 (TNFAIP6) as a Potential Single Gene Classifier of Renal Cell Carcinoma Oystein Solberg Eikrem,¹ Christian Beisland,¹ Andreas Scherer,² Arnar Flatberg,³ Trude Skogstrand,¹ Lea Landolt,¹ Sabine Leh,¹ Karin Margrethe Hjelle,¹ Vidar Beisvag,³ Hans-Peter Marti.¹ ¹Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; ²Spheromics, Kontiolahti, Finland; ³Dept of Cancer Research and Molecular Medicine, Univ of Science and Technology, Trondheim, Norway.

Background: The recent release of a new library preparation kit improved the cDNA library quality from formalin-fixed, paraffin-embedded (FFPE) tissues. In this study we demonstrate the feasibility of next generation sequencing (NGS) of mRNA obtained from FFPE tissues as compared with RNAlater® stored tissues.

Methods: Paired biopsies from tumorous and adjacent non-tumorous tissue of 16 patients with ccRCC were either FFPE or stored in RNAlater® (Qiagen) for 1 year. Total RNA was extracted utilizing the miRNeasy FFPE kit and the miRNeasy micro kit (Qiagen). Sequencing libraries were prepared using the TruSeq RNA Access Library Prep Kit® (Illumina).

Results: The average expression of detected transcripts in both FFPE and RNAlater® datasets correlated with $R^2=0.97$, and the log2 fold changes of the transcripts which are significantly altered in both datasets ($n=1106$) correlated with $R^2=0.94$. A classifier model with TNFAIP6 was developed for the FFPE dataset with a specificity of 100% and sensitivity of 94%; ROC AUC=0.99 (Fig. 1A); only one normal sample was misclassified due to a small admixture of cancer tissue. Classifier validation in an Affymetrix microarray dataset obtained from GEO (GSE53757) showed TNFAIP6 up-regulation in all tumor stages with both sensitivity and specificity of 94%; ROC AUC=0.98 (Fig. 1B).

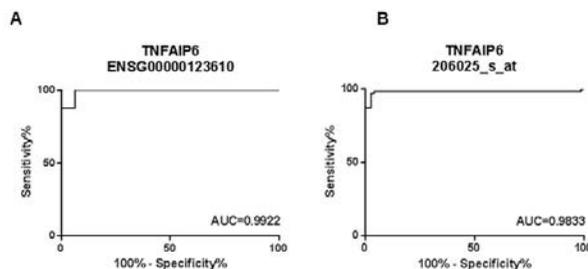


Figure 1: ROC of TNFAIP6. (A) present study, (B) validation in GSE53757 data set.

Conclusions: We describe a potential single gene classifier for ccRCC. Furthermore, NGS in FFPE tissues is feasible and correlates well with RNAlater® stored tissues. Thus, our studies open up novel diagnostic possibilities on archival renal biopsies.

Funding: Government Support - Non-U.S.

SA-PO496

Gene Expression Based Dissection of Chronic Kidney Disease Traits Pazit Beckerman, Katalin Susztak. *Renal, Electrolyte and Hypertension Dept, Univ of Pennsylvania, Philadelphia, PA.*

Background: Chronic kidney disease (CKD) is a progressive decline in kidney function. There are several manifestations of CKD including glomerular function change, albuminuria, glomerulosclerosis, tubulointerstitial fibrosis and metabolic changes. These traits are strongly correlated but the question remains whether they are driven by identical mechanisms.

Methods: We conducted genome wide transcript level analysis of 95 microdissected human kidney tubule samples. We used transcript level changes as quantitative traits to dissect underlying mechanisms. These samples included subjects with normal eGFR with or without diabetes (DM) or hypertension (HTN), and diseased kidney samples with low eGFR, fibrosis and sclerosis, with or without DM or HTN.

Results: We identified 1430 transcripts with significant linear correlation with eGFR. Pathway analysis indicated significant enrichment for inflammation and metabolism related pathways. Subgroup analysis indicated enrichment for TGF β and Wnt signaling and ECM receptor interactions only in earlier CKD stages. Our analysis identified 1606 transcripts that correlated with fibrosis and 1803 transcripts correlated with glomerulosclerosis. Similar to the clinical overlap between eGFR and fibrosis, we found that 78% of transcripts were identical. Transcripts that showed correlation with fibrosis but not with eGFR were enriched for inflammation related pathways. On the other hand, metabolism related genes correlated with eGFR but not with fibrosis. There were significant differences between male and female samples as well.

Conclusions: Our transcriptome-based dissection method highlights the relatedness of eGFR and kidney fibrosis, but also indicates potential differences in the underlying mechanisms of the two processes.

Funding: NIDDK Support

SA-PO497

Early-Onset, Severe Forms of Hypertension and Cardiovascular Complications Are Associated with APOL1 G1/G2 Susceptibility Alleles in African Americans Girish N. Nadkarni, Geneviève Galarneau, Stephen B. Ellis, Rajiv Nadukuru, Stuart Scott, Laura Rassmussen Torvik, Abel Kho, Geoffrey Hayes, Jennifer Pacheco, Rex L. Chisholm, Joshua C. Denny, Dan M. Roden, Eimear Kenny, Erwin P. Bottinger. *Electronic Medical Records and Genomics (eMERGE) Network.*

Background: Apolipoprotein L1 (APOL1) susceptibility alleles have been associated with kidney disease progression and ESRD in hypertensive African Ancestry (AA) populations. We explored whether these APOL1 alleles are associated with blood pressure-related traits in AA enrolled in the electronic medical records and genomics (eMERGE) Network.

Methods: Study populations included the Mount Sinai BioMe biobank discovery (dis) cohort ($n=5,213$) and three EMR-linked biobank replication (rep) cohorts, including Vanderbilt BioVU ($n=2,889$), Northwestern NUGene ($n=613$), and Mount Sinai BioMe ($n=1,655$). APOL1 single nucleotide polymorphisms (SNPs) rs73885319, rs71785313 and rs60910145 were genotyped in BioMe samples and imputed in BioVU and NUGene samples to determine APOL1 G1 and G2 risk alleles. Longitudinal phenotypic data were extracted from EMRs. Linear regression models & meta-analyses (METAL) were performed with age, sex, mean BMI, and eGFR as covariates.

Results: Compared with carriers of [0 or 1] APOL1 G1/G2 risk alleles, carriers of [2] risk alleles were diagnosed with hypertension a mean of 2.5 years (95%CI 1.9-2.9 yrs) earlier in life ($P_{dis}=0.04$, $P_{rep}=3 \times 10^{-4}$; Cox hazard); manifested 2-3 mmHg higher systolic BP (SBP) in younger AA (age 20-39) ($P_{dis}=0.07$, $P_{rep}=0.04$); and were exposed to more antihypertensive medication classes ($P_{dis}=0.11$; $P_{rep}=3 \times 10^{-4}$). Carriers of [2] risk alleles were more likely to manifest concentric left ventricular hypertrophy by echocardiogram (OR(95%CI)=1.52(1.14-2.02); $P<0.01$) and hemorrhagic cerebrovascular accidents (OR(95%CI)=2.42(1.01-5.97); $P=0.05$).

Conclusions: APOL1 G1/G2 susceptibility alleles are associated with early-onset, more severe form(s) of hypertension & with hypertensive complications hemorrhagic stroke

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

and concentric LVH independent of kidney function & BMI. These results may warrant a shift from kidney-intrinsic to systemic vascular pathomechanisms attributable to *APOL1* G1/G2 susceptibility alleles.

Funding: Other NIH Support - NHGRI

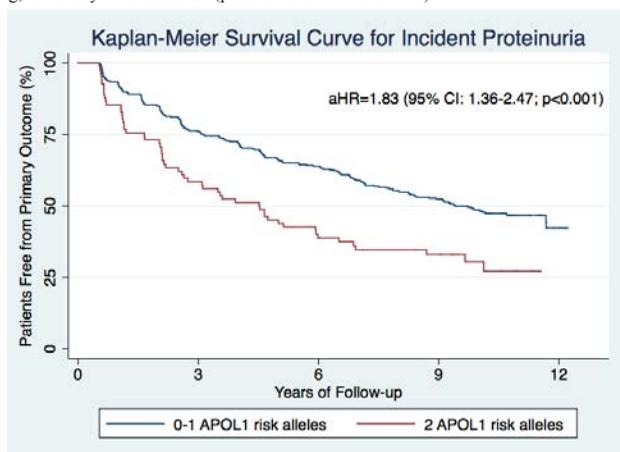
SA-PO498

Apolipoprotein L1 (*APOL1*) Gene Variants and Incident Proteinuria: Results from the African American Study of Kidney Disease and Hypertension (AASK) Teresa K. Chen,¹ Carmen A. Peralta,² Lawrence J. Appel,³ Michael J. Choi,¹ Michelle M. Estrella,¹ ¹Nephrology, Johns Hopkins Univ; ²Nephrology, Univ of California San Francisco; ³Medicine, Johns Hopkins Univ.

Background: *APOL1* gene variants are associated with kidney function decline. Whether these same gene variants are associated with incident proteinuria in the context of pre-existing chronic kidney disease (CKD) is unknown.

Methods: Using the trial and cohort phases of AASK (median follow-up of 6.8 years, maximum follow-up of 12.2 years), we evaluated participants who had hypertension-attributed CKD and who did not have proteinuria at baseline. Cox proportional hazards models were used to estimate the relative hazard of incident proteinuria (defined as a doubling of urine protein-to-creatinine ratio and UP/Cr ³0.22), comparing *APOL1* high-risk genotype (2 risk alleles) vs. low-risk genotypes (0-1 risk alleles). We adjusted for age, gender, baseline GFR, percentage of European ancestry, randomized blood pressure goal (usual vs. low), and randomized blood pressure drug (ramipril vs. metoprolol vs. amlodipine). Effect modification by randomized trial interventions and dietary sodium intake (as estimated by 24-hour urine sodium) was assessed.

Results: Of the 480 participants included in our study, 17% (n=82) had the *APOL1* high-risk genotype. Individuals with the *APOL1* high-risk genotype were 83% more likely to develop incident proteinuria compared to those with the low-risk genotypes (adjusted HR: 1.83; 95% CI: 1.36 to 2.47; p<0.001). The association between *APOL1* and incident proteinuria was not modified by randomized blood pressure goal, randomized blood pressure drug, or dietary sodium intake (p-interaction>0.05 for each).



Conclusions: Among African-Americans with CKD attributed to hypertension but without baseline proteinuria, high-risk variants of *APOL1* are associated with a greater risk of incident proteinuria.

Funding: NIDDK Support, Pharmaceutical Company Support - The AASK trial and cohort were also supported by the following pharmaceutical companies: King Pharmaceuticals, Pfizer, AstraZeneca, GlaxoSmithKline, Forest Laboratories, Pharmacia, and Upjohn.

SA-PO499

African Ancestry Specific Alleles Confer Chronic Kidney Disease Risk in U.S. Hispanics Nora Franceschini,¹ Adrienne M. Stilp,⁶ Michael F. Flessner,² Carmen A. Peralta,³ Sylvia E. Rosas,⁴ Cathy C. Laurie,⁶ Holly J. Kramer,⁵ ¹Epidemiology, Univ of North Carolina, Chapel Hill, NC; ²National Insts of Health, Bethesda, MD; ³Univ of San Francisco, San Francisco, CA; ⁴Harvard Univ, Boston, MA; ⁵Loyola Univ, Maywood, IL; ⁶Univ of Washington, Seattle, WA.

Background: Hispanics are a heterogeneous group with varying genetic ancestry. African ancestry can differ in Hispanics by country of origin, and its proportion relates to their risk of chronic kidney disease (CKD).

Methods: We examined the association of African ancestry population-specific risk alleles (*APOL1* and *HBB* rs334 related sickle cell anemia) with CKD in 11,921 Hispanics, aged 18-74 years, recruited in a community-based study in four US centers. *APOL1* G1/G2 alleles were genotyped and rs334 alleles were imputed (rsq=0.83). CKD was defined as an increased urine albumin to creatinine ratio (UACR) (≥ 17 mg/g in men and ≥25 mg/g in women), reduced estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² based on serum creatinine/cystatin C CKD-EPI equation, or presence of reduced eGFR or an

increased UACR. Analyses used generalized linear mixed models that accounted for the sampling strategy and family relatedness, age, sex, diabetes, systolic blood pressure and anti-hypertensive medications, and stratified by Hispanic background.

Results: There were 41% men, and mean age was 46 (SD =14). The prevalence of increased UACR was 14%, reduced eGFR was 4%, and combined CKD outcomes was 16%. Caribbean Hispanics (Cuban, Dominican, Puerto Rican, N=5348) had higher prevalence of 2 *APOL1* risk alleles (1% vs 0.1%) and rs334 allele (2% vs. 0.7%) compared to Mainland Hispanics (Central American, Mexican, South American, N=6,539). *APOL1* alleles were associated with increased UACR (p=10⁻⁴) and the composite CKD outcome (p=10⁻⁴), and rs334 was associated with same outcomes (UACR, p=10⁻⁷; CKD composite outcome, p=10⁻⁷) among Caribbeans only.

Conclusions: African-specific alleles are associated with CKD in Hispanics, but associations vary by Hispanic background. Medical care providers should be aware of the impact of these genetic variants for CKD risk in Hispanics.

Funding: Other NIH Support - R21HL123677, 1R01ES021367, 1R01HL118305-01A1

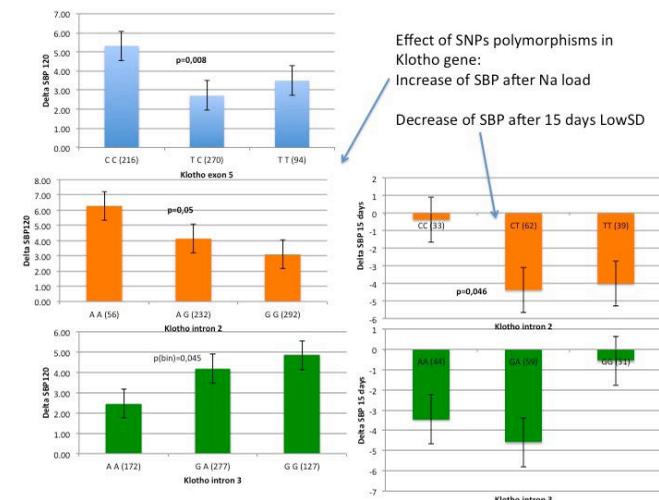
SA-PO500

Role of Klotho Genetic Polymorphisms in Salt-Sensitivity: A Link Between Salt and Aging? Chiara Lanzani, Lorena Citterio, Elena Brioni, Simona Delli Carpini, Marco Simonini, Guido Gatti, Elisabetta Messaggio, Paolo Manunta. Nephrology and Hypertension, San Raffaele Hospital, Milan, Italy.

Background: Previous data in transgenic mice showed that one-half klotho deficiency resulted in extensive premature aging, increased salt sensitivity and caused salt-sensitive hypertension. Recent gene expression study confirmed the expression of Klotho in renal distal tubular cells. The aim of this study is to evaluate the role of Klotho polymorphisms in salt sensitivity hypertension.

Methods: Design: study of pressure-natriuresis relationship in essential hypertensive patients, never treated before, naive (NHP) by Acute salt load (NaLoad: 310 mMol in 2 h iv) and low salt diet (Low SD: <100 mEq/die for 15 days). **Methods:** 580 NHP underwent NaLoad, whereas 137 NHP were compliant to lowSD protocol (of 324 enrolled).

Results: GWA analysis identified 32 SNPs in Klotho gene (restricted to 15 with tagging r²=0,80). Six of these resulted significantly associated to BP variation after NaLoad and LowSD. The effect of intron 2 and 3 SNPs genotype on SBP variation after NaLoad and LowSD are reported in the (figure 1) confirming the similar effect in the two manoeuvres.



Conclusions: These results are the first demonstration of the role of Klotho gene in salt homeostasis and hypertension development and suggest that Klotho polymorphisms affect sodium renal tubular excretion. If confirmed these results propose Klotho as key gene in salt sensitivity and aging.

Funding: Government Support - Non-U.S.

SA-PO501

Associations Between the Reticulon 1 Gene (*RTN1*) and End-Stage Kidney Disease Jason A. Bonomo,¹ Nicholette D. Palmer,¹ Ying Fan,² John C. He,² Donald W. Bowden,¹ Barry I. Freedman,³ ¹Center for Genomics & Personalized Medicine Research, Wake Forest School of Medicine; ²Dept of Internal Medicine, Section on Nephrology, Mount Sinai School of Medicine; ³Dept of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine.

Background: *RTN1* encodes endoplasmic reticulum stress proteins that have recently been associated with chronic kidney disease. We sought to determine if genetic variants within *RTN1* were associated with end-stage renal disease (ESRD) in African Americans (AAs) and European Americans (EAs) with diabetic (T2D-ESRD) and non-diabetic forms of ESRD.

Methods: We examined the *RTN1* gene region using a published AA T2D-ESRD genome-wide association study (Discovery study; n=922 cases, n=861 controls). Seven single nucleotide polymorphisms (SNPs) with p<0.05 were identified and genotyped in replication samples of AAs with T2D-ESRD (n=1,312) and controls (n=774), as well as

EAs with T2D-ESRD (n=604) and controls (n=1030). SNPs were also investigated in AAs with non-T2D ESRD (n=1,459 AA) and T2D in the absence of ESRD (n=500 AAs, n=620 EAs). Data were adjusted for age, gender, admixture, and the *APOL1* alleles, if applicable.

Results: The top *RTN1* SNPs from the Discovery study underwent replication testing in independent case-control samples of AAs with T2D-ESRD. Replication was observed with three variants and a combined T2D-ESRD analysis (Discovery + Replication study) in AAs yielded $p=0.015-3.0 \times 10^{-4}$ with $OR=0.67-0.77$ thus showing protection with the minor allele. One SNP, rs12434215, replicated association in EAs with T2D-ESRD ($p=0.019$, $OR=0.69$). Nominal associations were observed for SNPs rs12431381 and rs12434215 with non-T2D ESRD in AAs ($p=0.014-0.015$, $OR=0.77$). A combined AA all-cause ESRD analysis (n=3,800 cases, n=1,803 controls) demonstrated associations with rs12434215 ($p=6.7 \times 10^{-4}$, $OR=0.73$) and rs12431381 ($p=7.5 \times 10^{-4}$, $OR=0.75$). Minimal evidence of association between these three SNPs and T2D alone was observed in both AAs and EAs.

Conclusions: These data provides genetic evidence of association between *RTN1* and ESRD in AAs and EAs. Further studies are needed to clarify the signal.

Funding: NIDDK Support

SA-PO502

Interaction of Risk Alleles in Japanese Idiopathic Membranous Nephropathy Kenjiro Honda,¹ Myo Thiri,² Koji Okamoto,³ Kent Doi,¹ Hodaka Suzuki,⁴ Tsuyoshi Watanabe,⁴ Masaomi Nangaku,¹ Katsushi Tokunaga,² Eisei Noiri,¹ ¹Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; ²Dept of Human Genetics, Graduate School of Medicine, The Univ of Tokyo, Tokyo, Japan; ³Kidney Section, NIDDK/NIH, Bethesda, MD; ⁴Depts of Nephrology and Hypertension, Fukushima Medical Univ, Fukushima, Japan.

Background: Recent studies have reported the association of risk alleles of *PLA2R1* and *HLA-DQA1* with idiopathic membranous nephropathy (IMN) in the European and Chinese populations. However, both close association of the risk alleles and interaction between risk alleles of *PLA2R1* and *HLA* from high-resolution HLA typing among Japanese IMN patients has not been investigated.

Methods: Samples of Japanese biopsy-proven IMN patients (N = 183) and healthy control subjects (N = 620) were collected. Fifteen common variants were selected within *PLA2R1* gene. High-resolution association analysis of single nucleotide polymorphisms (SNPs) within *PLA2R1* and *HLA* alleles in *HLA-A, B, C, DRB1, DQB1* and *DPB1* was performed using 53 IMN cases and 420 controls. The significant associations discovered in the first sample set were validated by the second set that comprised of 130 IMN cases and 200 controls.

Results: The strong associations *HLA-DRB1*15:01* ($P=7.72 \times 10^{-5}$, $OR=2.9$) and *HLA-DQB1*06:02* ($P=5.12 \times 10^{-4}$, $OR=2.6$) were observed. Additionally, *HLA-Cw*07:04* and *HLA-DRB1*16:02* showed nominal association with IMN, while *HLA-B*07:02*, *HLA-DRB1*04:05* and *HLA-DQB1*04:01* were inversely associated with IMN. The associations did not remain significant after correction for multiple comparisons. In combined data analysis, *HLA-DRB1*15:01* and *HLA-DQB1*06:02* showed stronger association with IMN. In single locus analysis of *PLA2R1*, seven SNPs showed strong associations with IMN. Interaction analysis between *HLA* alleles and *PLA2R1* variants revealed high odds ratio for IMN with both risk alleles.

Conclusions: The associations of *PLA2R1* and *HLA* polymorphisms were identified in Japanese IMN patients. Moreover, *PLA2R1* risk alleles and *HLA* risk haplotype showed additive effects that were stronger than individual odds ratios, indicating the importance of interaction of these two genes in the development of IMN.

SA-PO503

Relationship Between rs3760106 Variation of *PRKCB1* Gene and End-Stage Renal Disease in Type 2 Diabetes Mellitus in Chinese Limei Liu,¹ Xiaoxu Ge,¹ Langen Zhuang,¹ Ming Li,¹ Rong Zhang,¹ Feng Wang,² Niansong Wang,² ¹Dept of Endocrinology and Metabolism, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital; ²Dept of Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.

Background: To explore the relationship between rs3760106 (C/T) variation of protein kinase C- β gene (*PRKCB1*) and end stage renal disease (ESRD) in type 2 Diabetes mellitus (T2DM) in Chinese.

Methods: 602 type 2 diabetes patients of Shanghai Han origin were recruited, which were divided into DN-ESRD group (n=274) with end-stage renal disease (ESRD) of diabetic nephropathy (DN) and DN-0 group (n=328) without diabetic nephropathy (DN-0). Taqman PCR assay was used to detect the genotypes of rs3760106 variation of *PRKCB1* gene. Genotypic and allelic frequencies and clinical characteristics were compared between two groups, including DN-0 and DN-ESRD groups as well as genotypic groups in DN-0 or DN-ESRD group.

Results: Three genotypes (CC, CT and TT) of rs3760106 were detected. The distribution of the three genotypes of type 2 diabetes patients was in accordance with Hardy-Weinberg equilibrium. There were significant differences in both genotypic and allelic frequencies between DN-0 and DN-ESRD groups ($p < 0.05$ for each). The frequencies of CT+TT genotype and T allele in DN-ESRD group were significantly higher than those in DN-0 group ($p < 0.05$ for each). Patients with risk allele T (i.e. CT and TT genotypes) were at significantly higher risk of developing ESRD ($OR = 2.14$, 95% CI, 1.18-3.87, $p < 0.05$). After adjusting for confounding variables, i.e., sex, onset age of diabetes and BMI with multi-factorial logistic regression model, this odds ratio (OR) remained significant [$OR=1.94$ (95% CI, 1.04-3.64)]. Moreover, compared with patients carrying CC genotype, those with CT+TT genotype had significantly higher fasting plasma glucose (FPG) level in DN-0 group ($p < 0.05$) or had an increasing tendency in DN-ESRD group ($p > 0.05$).

Conclusions: *PRKCB1* gene rs3760106 (C/T) is significantly associated with development of ESRD and T allele carriers are at higher risk of developing ESRD than those CC carriers in T2DM in Han Chinese of Shanghai.

Funding: Government Support - Non-U.S.

SA-PO504

The First Genome-Wide Association Study of Diabetic Nephropathy in Korean Type II Diabetes Patients Byeongwoo Kim,¹ Yeong Hoon Kim,¹ Sang Ho Lee,² Sunwook Kang,¹ ¹Dept of Nephrology, Inje Univ, Busan Paik Hospital, Busan, Korea; ²Dept of Nephrology, College of Medicine, Kyung Hee Univ, Seoul, Korea.

Background: It has been suggested that genetic susceptibility plays an important role in the pathogenesis of diabetic nephropathy. Recently, several genome wide association studies (GWAS) suggested that specific polymorphisms of candidate genes were associated with susceptibility to diabetic nephropathy. However, there was weak point in contents of GWAS DNA chip for GWAS. In fact, previous contents of GWAS DNA chip were fixed and did not cover SNPs in exon region and promoter region. In present study, we used the Axiom™ Genome-Wide Human Assay. The contents of assay are selected by researcher and useful to investigate association between several candidate SNPs and specific diseases.

Methods: To investigate whether specific polymorphisms are involved in the development of the diabetic nephropathy, 87 diabetic nephropathy patients and 104 diabetic controls in Korean with type II diabetes were studied. We firstly selected 47,777 genes of homo sapiens in NCBI gene database and searched the SNPs in dbSNP database. And the criteria for selection exonic SNPs, promoter SNPs, and intron SNPs in each gene were following: (1) SNPs with > 10% minor allele frequency (MAF), (2) >0.1 heterozygosity, (3) known genotype frequencies of SNPs in Asian population, (4) SNPs studied in previous study, and (5) unknown SNPs. Finally we selected 378,707 SNPs. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value. The analysis were analysis using Helixtree program.

Results: Among 378,707 SNPs, three SNPs (rs3214159 in *ABCC8* gene, rs3747636 in *PIK3C2B* gene, and rs3765156 in *PIK3C2B* gene) showed strongly significant association with diabetic nephropathy ($p < 0.00001$).

Conclusions: These results suggest that these significant SNPs may be useful to investigate the development of diabetic nephropathy.

Funding: Clinical Revenue Support

SA-PO505

An Efficient and Comprehensive Strategy for Genetic Diagnostics of All Hereditary Kidney Diseases Lisbeth Silva,¹ M. Lara Besada-Cerecedo,¹ Olaya Lamas-Gonzalez,¹ Patricia Regueiro Casuso,¹ Ana Barcia de la Iglesia,¹ Beatriz Sobrino,² Jorge Amigo,² Francisco Barros Angueira,² Angel Carracedo,² Candido Diaz Rodriguez,¹ Miguel A. Garcia-Gonzalez.¹ ¹Group of Genetics and Developmental Biology of Renal Diseases, Dept of Nephrology, Univ Hospital Complex and Health Research Inst of Santiago de Compostela (IDIS), Santiago de Compostela, A Coruña, Spain; ²Galician Public Foundation of Genomic Medicine, Santiago de Compostela, A Coruña, Spain.

Background: Sanger is a traditional and reliable method for sequencing, but next generation sequencing (NGS) has improved genetic diagnosis in a time and cost effective manner. We established and validated a NGS strategy for all hereditary kidney diseases, and compared it with traditional and NGS exome sequencing technologies.

Methods: Based in clinical classification and population prevalence, we generated four panels and test them in 318 patients with renal disease during 2 years of routine clinical assistance: (1) Panel for common cystic disease (8 genes, 129 patients); (2) Panel for common, rare and ultra-rare cystic diseases (72 genes, 48 patients); (3) Panel for glomerular disease (26 genes, 89 patients) and (4) Panel for tubule/interstitial disease (36 genes, 52 patients).

Results: This strategy has shown greater gene coverage, sensibility and specificity considering pseudogenes, compared to two independent NGS exome sequencing strategies (ampliseq n=2 and sureselect n=115). Also, we have developed a bioinformatics algorithm and generated an in-house database identifying a total of 6945 genomic variants (248 frameshift- and 66 nonframeshift- insertion/deletion/substitutions, 44 stopgain; 102 splicing, 807 nonsynonymous SNV, 592 synonymous SNV and 39326 non coding variants) that we have used to classify and re-classify considering every single genetic variant described into the literature. We have identify genetic interaction as the most common lack of positive genetic diagnosis and the major mechanism of phenotypic inter- and intra-familial variability.

Conclusions: Here we describe a novel strategy to anticipate disease and provide complete genetic information for clinical decision-making, in a time- and cost-efficient manner.

SA-PO506

Exome Sequencing as Diagnostic Tool in Daily Clinical Nephrology Practice Ilse M. Rood,^{1,2} Dorien Lugtenberg,^{1,2} Elisabeth A.M. Cornelissen,¹ Jeroen Schoots,¹ Nicole Van De Kar,¹ Michiel F. Schreuder,¹ Linda Koster-Kamphuis,¹ Jeroen Deegens,¹ Julia M. Hofstra,¹ Tom Nijenhuis,¹ Jack F. Wetzels,¹ Ronald Roepman,¹ Ernie M.H.F. Bongers.¹ ¹Radboud Center Renal Disorders, RadboudUMC, Nijmegen, Netherlands; ²Shared first author.

Background: Next generation sequencing, e.g. exome sequencing (ES), is currently the state of the art technique to identify mutations in genetic diseases. We developed a workflow for implication of ES in daily clinical practice for patients with a suspected hereditary kidney disease. The aim of this study was to analyze the diagnostic yield of this approach in clinical practice.

Methods: We developed a two-tier analysis, in which the first step is a kidney disease gene panel to screen for pathogenic variants in 187 genes, minimizing the change of coincidental findings. If causative mutations are not identified (first step), the complete exome data set was analyzed after additional written informed consent. We analyzed the diagnostic yield of this approach.

Results: From Jun. 2013 till Jan. 2015 we included 74 unrelated patients with kidney disease, defined as glomerular disease (n=34), cystic renal disease (n=16), electrolyte disorders (n=11), renal insufficiency of unknown cause (n=4) and other (n=9). The kidney disease gene panel revealed pathogenic mutations in 11 cases (15%), and likely pathogenic variants in 12 other cases (16%), necessitating follow-up studies. Further analysis of the complete exome data set in 19 patients, revealed candidate genes in 6 patients that are under investigation. In addition, copy number variation analysis revealed a pathogenic deletion in 2 patients (in one patient another pathogenic mutation was also identified in step one). There was 1 coincidental finding necessitating follow up for coloncarcinoma. In 23 patients open exome analysis is currently ongoing. Nine patients refused further analysis.

Conclusions: Currently, in 30 out of 74 patients (41%) (likely) causative mutations or new candidate genes were identified. We conclude that diagnostic exome sequencing is a powerful tool for detecting causative mutations in daily clinical practice without having the limitations of other gene testing approaches (single gene testing/targeted sequencing).

SA-PO507

Atypical Hemolytic Uremic Syndrome Targeted Re-Sequencing Study in a South Italian Cohort of Patients Matteo Accettura,¹ Anna Zito,¹ E.D. Stea,¹ Maddalena Gigante,² Paola Pontrelli,¹ S. Diella,² Giuseppe Castellano,¹ M. Giordano,³ L. Santangelo,³ Loreto Gesualdo.¹ ¹Emergency and Organ Transplants, Nephrology Unit, Univ of Bari, Italy; ²Medical and Surgical Sciences, Nephrology Unit, Univ of Foggia, Italy; ³Giovanni XXIII Hospital, Italy.

Background: Atypical hemolytic uremic syndrome (aHUS) is a multifactorial disease due to autoimmune or genetic factors leading to deregulated alternative complement pathway activation. At present 12 genes are associated to aHUS, however 30-50% of patients lack mutations in these genes resulting in still partially obscure genotype-phenotype correlations.

Methods: We enrolled 20 aHUS patients and 2 relatives from Apulia Region, Italy. We performed targeted parallel re-sequencing of the 12 known genes plus ADAMTS13, integrated in the panel for genetic diagnostic routine screening. We analyzed the genotypes, investigating the overlapping with other alternative complement pathway disorders, such as C3 glomerulopathy, Age-related Macular Degeneration (AMD) and drusen. We selected patients for their history of sporadic aHUS. Target enrichment was performed using an Illumina TruSeq Custom Amplicon panel. Sequencing was performed on Illumina MiSeq Desktop Sequencer. All variants were evaluated for their pathogenicity according to CADD, Sift and Polyphen algorithms.

Results: We identified 30 missense and one nonsense variants in known aHUS genes, plus seven missense variants in ADAMTS13. Several combined variants were identified which might explain the different phenotypic nuances of our patients, as well as, in some cases, their signs of other Complement-related diseases. We evidenced that different combination of variants together with different triggering factors result in a phenotypic spectrum encompassing all the Complement-related disease range. Additionally, in presence of some combinations, also other underlying pathologies can act as a triggering background for aHUS.

Conclusions: Our data suggest that (i) ADAMTS13 gene should be routinely sequenced for aHUS (ii) the overlapping with other complement-related diseases is considerable. Mutations should therefore be analyzed in combination, and the high-throughput strategy is the only feasible in this scenario.

SA-PO508

Whole Exome Sequencing (WES) Revealed Underlying Complexity in Genetic Studies of Familial IgA Nephropathy (fIgAN) Xuewen Song,¹ Nicole M. Roslin,² Meng Yi Xu,¹ Kairong Wang,¹ Jannel Liu,¹ Bushra Joarder,¹ Amirreza Haghighi,¹ Melody Ren,¹ Mitchell Li Cheong Man,¹ Joseph C.K. Leung,³ Sydney C.W. Tang,³ Kar Neng Lai,³ Andrew D. Paterson,² Florent Soubrier,⁴ York P. Pei.¹ ¹Div of Nephrology, Univ Health Network, Toronto, ON, Canada; ²Program in Genetics and Genomic Biology, Hospital for Sick Children, Toronto, ON, Canada; ³Div of Nephrology, The Univ of Hong Kong, Hong Kong, China; ⁴INSERM, Univ Pierre et Marie Curie Paris 06 (UPMC), Paris, France.

Background: Diagnosis of familial glomerular diseases may be confounded by non-specific clinical (i.e. hematuria and proteinuria) and/or pathological findings. Indeed, a recent study of familial focal segmental glomerulosclerosis (FSGS) has identified *COL4A3* and *COL4A4* mutations in ~10% of study families [Kidney Int 86:1253-59, 2014]. In the course of studying a cohort of fIgAN, we unexpectedly identified pathogenic mutations in 13 families with non-IgAN glomerular diseases.

Methods: We performed whole exome sequencing (WES) in 109 patients from 54 families all with at least 2 biopsy-proven cases.

Results: Our WES study identified heterozygous/hemizygous pathogenic *COL4A3* (c.1504+1G>A; p.G291R; p.G695R; p.G1054E; p.G1286R), *COL4A4* (p.Q970X; p.G1508A), and *COL4A5* (p.G48R; p.G325R) mutations in 9 families with fIgAN. These mutations occurred at the canonical splice junction or conserved glycine residues and segregated in all affected subjects within family. In two multiplex families, co-existence of thin basement membrane disease (TBMD) with fIgAN was also observed in the biopsied subjects in retrospect. Additionally, putative heterozygous pathogenic variants were found in 3 families in the known genes for FSGS (*ACTN4*, c.398-2A>G), CFHR5 nephropathy (*CFHR5*, p.C449fs), and membranous nephropathy (*PLA2R1*, p.C192G) and homozygous mutation in one family in another known gene for FSGS (*ADCK4*, p.S246N).

Conclusions: The presence of other glomerular diseases may confound the diagnosis of fIgAN in some putatively affected subjects ascertained based on urinary findings or even kidney biopsy. Due to its high prevalence in the general population, TBMD may be an important cause of phenocopy that can confound genetic linkage studies in fIgAN.

SA-PO509

Disease Gene Discovery for Familial IgA Nephropathy (fIgAN) by Whole Exome Sequencing (WES) Xuewen Song,¹ Nicole M. Roslin,² Meng Yi Xu,¹ Kairong Wang,¹ Jannel Liu,¹ Bushra Joarder,¹ Amirreza Haghighi,¹ Melody Ren,¹ Mitchell Li Cheong Man,¹ Joseph C.K. Leung,³ Sydney C.W. Tang,³ Kar Neng Lai,³ Andrew D. Paterson,² Florent Soubrier,⁴ York P. Pei.¹ ¹Div of Nephrology, Univ Health Network, Toronto, ON, Canada; ²Program in Genetics and Genomic Biology, Hospital for Sick Children, Toronto, ON, Canada; ³Div of Nephrology, The Univ of Hong Kong, Hong Kong, China; ⁴INSERM, Univ Pierre et Marie Curie Paris 06 (UPMC), Paris, France.

Background: IgAN is the most common primary glomerular disease worldwide. Genome-wide linkage scans have identified multiple susceptibility loci for fIgAN but no disease gene has yet been identified.

Methods: To identify susceptibility genes for fIgAN, we performed WES in 109 patients from 54 families all with >2 biopsy-proven cases and putatively affected members ascertained with persistent hematuria/proteinuria. In 3 multiplex families each with >5 affected cases, we also performed genome-wide linkage scans under a dominant model and focused WES on regions with suggestive linkage. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF<1%) deleterious variants of high (i.e. protein-truncating) and moderate (i.e. inframe indels and deleterious non-synonymous missense variants predicted by PolyPhen-2, Sift, Mutation Assessor, CADD_phred, PhyloP_Mam_avg, and PhyloPVert100_avg) impact.

Results: Overall, 99.8% of the targeted exome were covered with a mean depth of 100x. We examined 19 regions with LOD >1 in 3 multiplex families and ~3,000 immunologic candidate genes. We identified 26 candidate genes (i.e. *IFIH1*, *CD33*, *MSH6*, *ERAP2*, *FUT2*, *MMRN1*, *MINA*, *OAS1*, *TLR1*, *RNASEL*, *MARCO*, *THADA*, *BTNL1A1*, *PTPRK*, *REL1*, *ERCC1*, *ASB4*, *LCPI1*, *HK3*, *ASH1L*, *LTB*, *FES*, *MPO*, *GP1BA*, *BACH2*, and *EMP3*), each with rare deleterious variants affecting 2 or 3 unrelated families.

Conclusions: Our results suggest extensive genetic heterogeneity in fIgAN with many disease genes each contributing to a small proportion of cases. Future studies with expanded sample size will aid selection of the most promising candidate genes for functional studies. Identification of disease genes for fIgAN has the potential to improve diagnosis and treatment.

Funding: Government Support - Non-U.S.

SA-PO510

Discovery of New Risk Gene Loci in IgA Nephropathy: Genome-Wide Human Assay Kyung-Hwan Jeong, Tae Won Lee, Sang Ho Lee, Se Yun Kim, Jin Sug Kim, Shin Yeong Lee, Chun-Gyoo Ihm. *Internal Medicine, KyungHee Univ School of Medicine.*

Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis in Korea. The etiology of IgAN is complex with high genetic heterogeneity. Several genome wide association studies (GWAS) suggested that specific polymorphisms of candidate genes were associated with susceptibility to IgAN. However, previous contents of GWAS DNA chip were fixed and did not cover SNPs in exon region and promoter region.

Methods: We used the Axiom™ Genome-Wide Human Assay by Affymetrix. The contents of assay are useful to investigate association between several candidate SNPs and specific diseases. We firstly selected 47,777 genes of homo sapiens in NCBI gene database and searched the SNPs in dbSNP database. And the criteria for selection exonic, promoter, and intron SNPs in each gene were following: SNPs with >10% minor allele frequency, >0.1 heterozygosity, known genotype frequencies of SNPs in Asians, SNPs studied in previous study, and unknown SNPs. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value. The analysis was using Helix tree program.

Results: To investigate whether specific polymorphisms are involved in the development of the IgAN, 182 biopsy confirmed IgAN patients and 455 healthy controls were studied. We selected 378,707 SNPs. We carried out genome wide genotyping on customized Axiom™ Genome-Wide Human Assay Among 378,707 SNPs, 19 SNPs showed strongly significant association with IgAN ($p < 0.00001$). We identified at rs201580039, rs12219125 and rs5730189 that implicated the genes encoding KLF14 (Krueppel-like factor 14, 7q32.3, OR 8.04, $p = 4.95 \times 10^{-7}$), intergenic region at chromosome 10 (OR 0.24, $p = 1.72 \times 10^{-5}$) and unc-51 like autophagy activating kinase 2 (ULK2, 17p11.2, OR 8.44, $p = 3.61 \times 10^{-5}$) as susceptibility genes. To validate the previous reported susceptibility SNPs of IgAN, we selected and genotyped 19 SNPs. rs660895 of HLA-DRB1 and rs2856717 of HLA-DQB1 were significantly different between two groups.

Conclusions: These results suggest that these significant SNPs may be useful to investigate the development of IgAN.

SA-PO511

Mannan-Binding Lectin 2 Polymorphisms Were Associated with Progression of IgA Nephropathy Yan Ouyang, Jingyuan Xie, Meng Yang, Xiaoyan Zhang, Xiaoxia Pan, Weiming Wang, Nan Chen. *Nephrology Dept, Ruijin Hospital, Shanghai Jiao Tong Univ, School of Medicine, Shanghai, China.*

Background: Our aim is to evaluate whether MBL2 polymorphism associates with progression of IgA nephropathy (IgAN).

Methods: Patients with Primary IgAN were retrospectively recruited from 2009 to 2013. Renal specimen was semi-quantitative scored according to the Oxford scoring system. Whole coding and promoter regions of MBL2 were sequenced in 101 patients. Then 3 SNPs (rs11003125, rs7096206 and rs7095891) in promoter and 1 SNP (rs1800450) in exon1 of MBL2 were genotyped in other 185 patients by Sanger sequencing. The associations of the 4 SNPs with patients' clinical, pathological and prognostic parameters were analyzed. Serum MBL level was measured by ELISA.

Results: A total of 286 patients were enrolled, mean age at time of biopsy was 36.37 ± 12.1 years. ESRD was found in 29 patients (10.1%) after a mean follow-up time of 34.80 months. Among the 4 SNPs, only rs1800450, coding the 54th amino acid of MBL, significantly increased the risk of ESRD. More patients with rs1800450-AA (27.3%) progressed to ESRD compared to patients with GA genotype (15.5%) [$P = 0.326$] or GG genotype (6.8%) [$P = 0.015$]. Then all patients were divided into GG group (n=191), GA group (n = 84) and AA group (n=11) based upon genotypes of rs1800450. There were no differences of demographic, clinical and pathological parameters at time of biopsy, except for proteinuria ($P = 0.028$). Interestingly, serum MBL levels in patients with AA genotype (median 0ng/ml) were significant lower than GA genotype (median 243.28ng/ml) [$P < 0.001$] and GG genotype (median 1033.03ng/ml) [$P < 0.001$]. Kaplan-Meier survival analysis showed that mean survival time of AA group (38.90 ± 5.68 months) was significant shorter than GG group (66.01 ± 9.9 months) [$P = 0.173$] and GA group (56.37 ± 2.62 months) [$P < 0.001$]. Finally, AA independently increased the risk of ESRD (AA vs GG+GA, HR = 26.73, 95% CI 4.92-145.30, $P < 0.001$) after adjusted by sex, age and clinical indicators by COX regression analysis.

Conclusions: IgAN patients with rs1800450-A allele have a higher risk of disease progression probably as a result of lower MBL levels in these patients, which may increase the risk of infection.

SA-PO512

ARHGAP32 as a Candidate Gene for Primary Focal Segmental Glomerulosclerosis Guisen Li, Li Wang. *Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Focal and segmental glomerulosclerosis (FSGS) is one of common causes of end-stage renal disease worldwide. Previous studies showed that genetic factor played an important role in the pathogenesis of FSGS. The purpose of this study was to identify the candidate gene of FSGS in Chinese familial FSGS.

Methods: Total 21 individuals of a FSGS pedigree were involved in this study. Firstly, we screened the known causal mutations of *ACTN4*, *TRPC6*, and *INF2* gene in this pedigree. Then we conducted a genome wide scan for linkage study. And DNA of four members were assayed by whole exome sequencing. The data were filtered according to

the 1000 Genomes Project, ESP6500 and dbSNP information, and database with 69 exome sequencing project (without kidney diseases). By PCR sequencing methods, we detected candidate causal mutation. And then, we tested the mutation in other 97 sporadic FSGS patients and 96 normal controls.

Results: No mutation was detected from those exons of *INF2*, *ACTN4* and *TRPC6* in the FSGS pedigree. 8 loci suggested for linkage were identified, and the maximum two-point parametric LOD score of 1.69 was marked by D5S2115. A mutation (c.C1213G, p.L405V) of *ARHGAP32* gene was identified by combination with exome sequencing, genome-wide scan, function prediction of coding proteins. A new mutation (c.A3559G, p.T1187A) of *ARHGAP32* gene was detected in one sporadic FSGS patient from 97 cases and 96 controls. The *ARHGAP32* expression was detected in the glomeruli and tubule.

Conclusions: We found a candidate mutation of *ARHGAP32* gene for primary FSGS by combination with whole genome linkage analysis and whole exome sequencing.

SA-PO513

Targeted Sequencing in Adults with Focal Segmental Glomerulosclerosis Konstantinos Koutrotsos,¹ Jana Vandrovцова,² Thomas M. Connor,^{1,2} H. Terence Cook,² Marina Loucaidou,¹ Tim Aitman,³ ¹West London Renal and Transplant Centre, Imperial College NHS Trust, United Kingdom; ²Imperial College London, United Kingdom; ³Institute of Genetics & Molecular Medicine, Univ of Edinburgh, United Kingdom.

Background: Multiple genes underlying focal segmental glomerulosclerosis (FSGS) and/or steroid resistant nephrotic syndrome (SRNS) have been identified. We aimed to investigate the distribution of gene mutations in adult patients with FSGS by targeted sequencing.

Methods: 94 adults with familial or sporadic FSGS were recruited through a single renal unit in England. The mean age at diagnosis was 46.4, and 61 were male. Ethnicity: 42 Caucasian, 24 Afro-Caribbean, 24 South Asian. History of familial renal disease (14), recurrent FSGS in a renal transplant (21). DNA was extracted from whole blood or saliva using standard protocols. An Illumina TruSeq Custom Amplicon Targeted Next Generation sequencing (NGS) panel was designed covering 21 genes for FSGS. NGS sequencing was performed on the MiSeq v3 system. Data were analysed using our standard Mendelian disease pipeline and all variants were confirmed by Sanger sequencing.

Results: 19 rare, non-synonymous coding variants were identified, affecting 16 individuals, including 3 with a family history and 4 with recurrent disease. 14 variants were heterozygous dominant, 3 compound heterozygous, and 2 X-linked recessive. Known pathogenic mutations included *TRPC6* N143S and *NPHS2* R229Q. Control variants were accurately identified in *INF2* R214H, *NPHS2* V180M, and *MYH9* R1932fs. Other variants included *ACTN4* (1), *CD2AP* (4), *INF2* (1), *ITGB4* (3), *MYH9* (3), *NPHS2* (2), *NFX5* (2), *TRPC6* (2), and *WT1* (3); of these 13 were predicted to be pathogenic by SIFT and/or Polyphen2.

Conclusions: We have shown a high frequency of potentially pathogenic variants in our adult population with FSGS. We did not see enrichment for mutation carriers in those with a documented family history or recurrent disease. Targeted NGS allows rapid and inexpensive identification of these gene mutations.

Funding: Government Support - Non-U.S.

SA-PO514

Family Risk of Acute Kidney Injury Olafur S. Indridason,¹ Snaevur Sigurdsson,² Þórir E. Long,³ Gisli H. Sigurdsson,^{4,6} Martin I. Sigurdsson,^{4,5} ¹Div of Nephrology, Landspítali; ²Decode Genetics, Reykjavik; ³Dept of Medicine; ⁴Dept of Anesthesia, Landspítali - The National Univ Hospital of Iceland; ⁵Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland; ⁶Dept of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA.

Background: Previous studies indicate that certain genetic variants may predispose to acute kidney injury (AKI) in critically ill patients but global assessment of heritability and an unbiased genome-wide assessment of acute kidney injury is lacking. The purpose of this study was to assess the familiarity of AKI to support a common genetic background.

Methods: We used data from the clinical laboratory at Landspítali - The National University Hospital of Iceland to find all serum creatinine (Scr) measurements over 20 years. We identified each patient's highest Scr value and a baseline Scr within the preceding 6 months, defining AKI as a 50% increase in Scr compared to baseline (highest/baseline Scr > 1.5). Patients with ESRD and diseases known to result in AKI were excluded. To assess the familial relationship between individuals, we used the Icelandic Genealogy Database that contains reliable genealogy information on the entire Icelandic nation dating back to the year 1650. Familiarity of AKI was assessed by calculating the risk ratio of AKI in 1-5th degree relatives of AKI patients, and significance assessed by comparing the risk ratio to the risk ratio in 1000 randomly selected control groups.

Results: We identified 12,807 individuals with AKI. There was a significantly increased risk of AKI in the relatives of AKI patients with 1st-degree relative risk ratio (RR) of 1.26, 2nd-degree relative RR of 1.08, 3rd-degree relative RR of 1.12 ($p < 0.001$ for all). The risk ratio was even higher for the most severe AKI (highest/baseline Scr > 3.0), where 1st-degree relative RR was 1.36 ($p = 0.006$), 2nd-degree relative RR was 1.18 ($p = 0.067$) and 3rd-degree relative RR was 1.14 ($p = 0.06$).

Conclusions: Our results suggest a genetic component in the development of AKI and given the relationship between relative risk and the power to map disease genes by linkage analysis, GWAS studies might yield positive results.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

SA-PO515

Premature Death in First Degree Relatives of End Stage Renal Disease Patients Rannveig Skrunes,^{1,2} Einar Svarstad,^{1,2} Anna Reisaeter,³ Hans-Peter Marti,^{1,2} Bjorn Egil Vikse.^{2,4} ¹Dept of Medicine, Haukeland Univ Hospital, Bergen, Norway; ²Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; ³Dept of Transplantation Medicine, Rikshospitalet Oslo Univ Hospital, Oslo, Norway; ⁴Dept of Medicine, Haugesund Hospital, Haugesund, Norway.

Background: Increased risk of end stage renal disease (ESRD) and death in Norwegian living kidney donors has been reported. The majority of donors were related to the recipient. The present study investigates risk of death in first degree relatives of ESRD patients.

Methods: The Norwegian Population Registry has since 1960 registered all Norwegian Citizens. Sibling data are complete for most individuals since 1953. The National Cause of Death Registry has registered causes of death since 1969 and the Norwegian Renal Registry has registered all individuals with ESRD since 1980. The registries were linked. All citizens born in Norway with at least one registered first degree relative were included. A cohort-design was used. ESRD in a first degree relative was the main exposure variable and death and causes of death were the main outcome variables. Adjusted hazard ratios (aHR) were calculated using Cox regression analysis.

Results: 5,217,568 individuals were included, 27,650 had at least one relative with ESRD. 844,407 died during follow-up. aHR for death was 1.14 (95% CI 1.10-1.17) in individuals with a relative with ESRD compared to those without a relative with ESRD. Excluding known hereditary renal disease, aHR decreased to 1.12 (95% CI 1.09-1.16). Cardiovascular death aHR was 1.15 (95% CI 1.10-1.21), of which cerebrovascular death 1.34 (95% CI 1.22-1.47). aHR for death due to non-hereditary renal/ureteric disease was 2.32 (95% CI 1.84-2.94) with renal failure 1.80 (95% CI 1.26-2.56) and primary renal disease 5.88 (95% CI 4.04-8.56) as main contributors. Compared to individuals without a relative with ESRD, death occurred 9 years earlier in individuals who died before the age of 50 and 1 year earlier in individuals who died at age 70.

Conclusions: ESRD in first degree relatives was associated with premature death. Death due to cardiovascular- and non-hereditary renal diseases increased the most.

Funding: Government Support - Non-U.S.

SA-PO516

Identifying Genetic Predictors of Skin Cancer in Renal Transplant Populations Caragh P. Stapleton,¹ Mark McCormack,¹ Dervla M. Connaughton,² Paul J. Phelan,³ Gianpiero Cavalleri,¹ Peter J. Conlon.² ¹Dept of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin 2, Dublin, Ireland; ²Kidney Centre, Beaumont Hospital, Dublin 9, Dublin, Ireland; ³Dept of Nephrology, Royal Infirmary of Edinburgh, Edinburgh, NHS Lothian, United Kingdom.

Background: Renal-transplant recipients have a 33-fold increased risk of developing non-melanoma skin cancer relative to an age-matched non-transplanted individual. Some of this risk can be attributed to factors such as type of immunosuppressant treatment, however much of the risk remains unaccounted for. In this study we set out to map germline genetic variations influencing the development of skin cancer in our cohort of 325 renal-transplant recipients, using a genome-wide association study (GWAS) and candidate gene study design.

Methods: Both logistic regression and survival analysis was applied in our GWAS. Survival analysis was used in our candidate gene study. Multiple robust genetic loci for skin cancer in non-transplant populations have been identified via large GWAS. These genetic predictors of skin cancer (n=21) identified from non-transplant populations were examined to see if they have a higher effect size in renal-transplant recipients compared to the general population.

Results: For the candidate SNP analysis, a nominally significant association was found with a SNP in the *MC1R* gene (p=0.0157). The variant was found to have the same direction of affect as described in the original study and the odds ratio was higher. The presence of one or more copies of the minor allele caused a significant decrease in time to develop skin cancer post renal transplantation (hazard ratio = 2.06). We found a significant association in our GWAS between time to developing skin cancer post transplantation and a variant in *SPOCK1* (p = 4x10⁻⁸). We found that heterozygote individuals developed skin cancer 7 times faster than wild type homozygotes.

Conclusions: Associations were found between time to developing skin cancer post-transplantation and the genes *MC1R* and *SPOCK1*. We will be carrying out further testing in other cohorts for validation of results. This work is funded by Irish Research Council for Science, Engineering and Technology.

Funding: Government Support - Non-U.S.

SA-PO517

Genetic Variants in ANCA-Associated Vasculitis: A Meta-Analysis Chinah Rahmattulla,¹ Antien Mooyaart,¹ Daphne Van Hooven,¹ Jan W. Schoones,¹ Jan A. Bruijn,¹ Olaf Dekkers,^{1,2} European Vasculitis Genetics Consortium,³ Ingeborg M. Bajema.¹ ¹Leiden Univ Medical Center; ²Aarhus Univ Hospital.

Background: Genetic factors may influence the pathogenic pathways leading to anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). We performed a meta-analysis to determine the genetic variants most likely associated with AAV and investigated whether diagnostic and serological subtypes within AAV have distinct genetic backgrounds.

Methods: Studies investigating the association between genetic variants and AAV in humans were searched in PubMed, Embase, and Web of Science. All variants significantly associated with AAV in at least one study and investigated in at least two studies were included. Additionally, data on these genetic variants from the largest GWAS in AAV were included to increase the validity of this meta-analysis.

Results: The literature search yielded 5180 articles. Fifty-three articles investigating 55 genetic variants were included, 31 of which remained associated with AAV in a meta-analysis. These genetic variants were in or near the following genes: *SERPINA1*, *CD226*, *CTLA-4*, *HLA-B*, *HLA-DP*, *HLA-DQ*, *HLA-DR*, *HSD17B8*, *IRF5*, *PTPN22*, *RING1/RXR*, *RXR*, and *TLR9*. Moreover, we identified genetic distinctions between granulomatosis with polyangiitis and microscopic polyangiitis and between proteinase 3 ANCA vasculitis and myeloperoxidase ANCA vasculitis. In 79% of the genetic variants, subdivision based on ANCA serotype resulted in higher odds ratios than subdivision based on clinical diagnosis.

Conclusions: This meta-analysis identified 31 genetic variants associated with AAV, supporting a role for alpha-1-antitrypsin, the major histocompatibility complex system, and several distinct inflammatory processes in AAV pathogenesis. Our results indicate that subdivision of AAV based on ANCA serotype has a stronger genetic basis than subdivision based on clinical diagnosis.

SA-PO518

Meta-Analyses of Genetic Associations in New Onset Diabetes After Kidney Transplantation Katherine A. Benson,¹ A.J. McKnight,¹ Alexander P. Maxwell,^{1,2} ¹Centre for Public Health, Queen's Univ Belfast, Belfast, Northern Ireland, United Kingdom; ²Regional Nephrology Unit, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom.

Background: New-onset diabetes after transplantation (NODAT) is a serious complication following solid organ transplant. There is evidence of a genetic contribution to this disease and we have previously identified genetic risk factors associated with NODAT following kidney transplantation. These meta-analyses examine the pooled effect of genetic variants associated with NODAT in kidney transplant populations.

Methods: Relevant articles investigating the association between genetic markers and NODAT were identified by means of a database search of PubMed, Web of Science and Google Scholar from 1945 to 2015. Variants replicated in a minimum of three studies were included for analysis. Data was analysed using a random effects model in Review Manager 5.3. The association between identified variants and NODAT was calculated at the per-study allele level, where original studies were concordant with Hardy-Weinberg Equilibrium, to generate overall significance values and effect sizes.

Results: Our literature search returned 4,147 citations. Of the 36 eligible articles identified, 18 genetic variants from 13 genes were included for analysis. Of these, three were significantly associated with NODAT by meta-analysis at the 5% level of significance; *TCF7L2* rs7903146 p=0.01 OR=1.41, 95%CI=1.07-1.85 (n=2967 individuals), *CDKAL1* rs10946398 p=0.006 OR=1.43, 95% CI=1.11-1.85, (n=696 individuals), and *KCNQ1* rs2237892 p=0.0007 OR=0.70, 95% CI=0.54-0.91, (n=1270 individuals).

Conclusions: These meta-analyses identified three genetic variants statistically associated with NODAT. Ideally, these variants should be assessed in less heterogeneous studies with larger numbers of kidney transplant recipients with a carefully defined NODAT phenotype.

Funding: Private Foundation Support

SA-PO519

New Prioritization and Burden Analyses of Rare Variants in 208 Candidate Genes Are Questioning the Pathogenicity of Previously CAKUT-Associated Genetic Variants Nayia Nicolaou,¹ Sara L. Pulit,¹ Isaac J. Nijman,¹ Albertien M. van Eerde,¹ Ernie M.H.F. Bongers,² Rachel H. Giles,³ Nine V. Knoers,¹ Kirsten Y. Renkema.¹ ¹Medical Genetics, UMC Utrecht, Utrecht, Netherlands; ²Human Genetics, Radboudumc, Nijmegen, Netherlands; ³Nephrology and Hypertension, UMC Utrecht, Utrecht, Netherlands.

Background: The leading cause of end-stage renal disease in children is attributed to congenital anomalies of the kidney and urinary tract (CAKUT). Familial clustering and mouse models support the presence of monogenic causes. Genetic testing is insufficient as it mainly focuses on *HNF1B* and *PAX2* mutations that are thought to explain CAKUT in 5-15% of patients.

Methods: To identify novel, potentially pathogenic variants in additional genes, we designed a panel of genes identified from studies on familial forms of isolated or syndromic CAKUT and genes suggested by *in vitro* and *in vivo* CAKUT models. The coding exons of 208 genes were analyzed in 453 patients with CAKUT using next-generation sequencing. Rare truncating, splice-site variants and non-synonymous variants, predicted to be deleterious and conserved, were prioritized as the most promising variants to have an effect on CAKUT.

Results: Previously reported disease-causing mutations were detected. Five variants were fully penetrant causal mutations that improved diagnosis. We prioritized 148 candidate variants in 151 patients, found in 82 genes, for follow up studies. Using a burden test, we found no significant excess of rare variants in any of the genes in our cohort compared to controls.

Conclusions: Thus, in a study that represents the largest set of genes analyzed in CAKUT patients to date, the contribution of previously implicated genes to CAKUT risk is significantly smaller than expected and the disease may be more complex than previously assumed.

SA-PO520

Comparison of Genetic Associations with Different Definitions of CKD Progression in Children Matthias Wuttke,¹ Elke Wuehl,² Li Luo,³ Jayanta Gupta,⁴ Bradley Warady,⁵ Susan L. Furth,⁶ Anna Kottgen,¹ Franz S. Schaefer,² Craig S. Wong,³ ¹Freiburg Univ, Germany; ²Heidelberg Univ, Germany; ³Univ New Mexico; ⁴Texas Tech Univ; ⁵Children's Mercy, Kansas City; ⁶CHOP, Univ Pennsylvania.

Background: The PediGFR Consortium aims to identify genetic factors associated with pediatric chronic kidney disease (CKD) progression. The optimal definition of CKD progression for testing is unclear. To address this question, we performed genome-wide association studies (GWAS) of two different definitions of CKD progression, slope of the annual change in estimated GFR (eGFR) versus time-to-event (TTE).

Methods: There were >8 million genotyped and imputed markers from 1,122 patients. The calculation of slope was based on 2-41 eGFR values per patient. TTE was a combined primary endpoint of dialysis, transplant, 50% GFR loss or GFR <5 ml/min/1.73m². Respectively, cox proportional hazards and linear regressions were used for the GWAS of TTE and slope. Both analyses were adjusted for age, sex, principal components and baseline eGFR. For each definition, data were meta-analyzed from five study-/ancestry-specific groups in PediGFR.

Results: For TTE, follow-up time was 1.66-5.0 years (IQR) and an event rate of 34%. For slope, mean slope was -4.2 ml/min/1.73m². For comparison, we focused on SNPs present in all five groups with a minor allele frequency >0.05, and 12<50%. For TTE, 6 genomic regions contained one or more of such SNPs with p<1E-6, one of which reached genome-wide significance (p<5E-8). Hazard ratios per risk allele ranged from 1.58-1.97. For slope, there were 3 regions with p<1E-6, one of which reached genome-wide significance. All of the 6 TTE variants were nominally associated with slope (one-sided p<0.05), whereas 2 of the 3 slope variants were nominally associated with TTE. None of the loci with p<1E-6 overlapped between the two definitions.

Conclusions: Genetic variants associated with CKD progression differed based on the definition of the phenotype. GWAS of TTE identified more loci at p<1E-6 than slope and these were biologically more plausible based on current knowledge of kidney disease. However, the number of genome-wide significant loci was the same.

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SA-PO521

New Candidate Genetic Loci Associated with Pediatric Proteinuria in the CKiD Cohort Sophie Limou,¹ Derek Ng,² Kimberly J. Reidy,³ Robert Woroniecki,⁴ Susan L. Furth,⁵ Bradley Warady,⁶ Craig S. Wong,⁷ Jeffrey B. Kopp,⁸ Cheryl Ann Winkler,¹ Frederick J. Kaskel,³ ¹Leidos Biomedical Research, Inc / NCI-Frederick National Laboratory; ²Johns Hopkins Bloomberg School of Public Health; ³Children's Hospital at Montefiore/Albert Einstein College of Medicine; ⁴Stony Brook Univ Hospital; ⁵Children's Hospital of Pennsylvania; ⁶Children's Mercy Hospital; ⁷Univ of New Mexico; ⁸NIDDK, NIH.

Background: Proteinuria is an early marker for chronic kidney disease in adults and children. Here, we sought to identify genetic variants associated with baseline proteinuria in African American children diagnosed with chronic kidney disease from the CKiD cohort.

Methods: We genotyped 140 CKiD participants using the Illumina HumanExome beadchip v1.2 comprising over 250,000 markers, including putative functional exonic variants that were implicated in common metabolic disorders. 81,460 SNPs passed quality control and were tested for association with baseline proteinuria in 129 children with chronic kidney disease by linear regressions adjusted for age, gender, and the first five eigenvectors from the population stratification analysis.

Results: We identified several genetic loci that were significantly associated with proteinuria (P<10⁻⁸), as well as new candidate loci (10⁻⁵<P<10⁻⁸). Among the top hits, we notably revealed kidney-expressed genes that were previously associated with the TGF β pathway, renal homeostasis, IgA nephropathy, congenital kidney disease, and vascular integrity (e.g. *VAV3*, *STRA6*, and *HDAC7*).

Conclusions: Our study emphasizes the power of unbiased large genetic screenings to discover new factors associated with pediatric kidney conditions. These new results warrant independent replication and functional validation.

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SA-PO522

Genotype-Phenotype Analysis in Pediatric Patients with WT1 Glomerulopathy Eujin Park,¹ Yo Han Ahn,¹ Hee Gyung Kang,^{1,2} Hye Won Park,³ IL-Soo Ha,¹ Hae Il Cheong,^{1,2} ¹Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Korea; ²Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Korea; ³Dept of Pediatrics, Seoul National Univ Bundang Hospital, Seongnam, Korea.

Background: The *WT1* gene plays an essential role in urogenital and kidney development and its mutations manifest two different types of glomerulopathies, Denys-Drash syndrome (DDS) and Frasier syndrome (FS). In this multicenter retrospective cohort study, genotype-phenotype correlations in Korean pediatric patients with *WT1* mutations were analyzed.

Methods: During the period from 2001 to 2015, *WT1* mutations were detected in a total of 23 children by genetic screening.

Results: The patients were grouped into FS (n=10, having a mutation in intron 9) and DDS (n=13, having an exon mutation). Nine (69%) DDS patients presented as congenital

(CNS) or infantile nephrotic syndrome (INS), while 7 (70%) FS patients presented as steroid-resistant focal segmental glomerulosclerosis. Interestingly, monozygotic twin patients with DDS presented as end-stage renal disease (ESRD) without any previous history of glomerulopathy. Progression to ESRD was noted in 11 (85%) DDS patients at the median age of 0.22 (interquartile range [IQR], 0.07-1.65) years and in 5 (50%) FS patients at age 9.30 (3.25-16.50) years. Five (38%) DDS patients died at age 0.59 (0.27-2.29) years. Disorder of sexual development (DSD) was accompanied in 8 (62%) DDS and 7 (70%) FS patients. Three (13%) patients (2 with DDS and 1 with FS) had diaphragmatic defect/hernia. Five (22%) and six (26%) patients underwent prophylactic nephrectomy and gonadectomy, respectively. Among the rest of the patients, Wilms tumor and gonadoblastoma developed in 3 DDS patients and 1 FS patient, respectively.

Conclusions: The clinical manifestations and disease course of the Korean patients with *WT1* glomerulopathy were mostly same as those of previous reports. Of note, patients with *WT1* mutations may manifest atypically, i.e., chronic kidney disease without any preceding history of significant proteinuria and/or NS. DSD is common in both in FS and DDS and is a useful diagnostic clue. Prophylactic nephrectomy/gonadectomy is strongly recommended.

SA-PO523

Age of the NPHS2 p. V260E Mutation, a Cause of Childhood Steroid Resistant Focal Segmental Glomerulosclerosis, in the Ancestral Population of Black Africans in Durban, South Africa George W. Nelson,¹ Rajendra Bhimma,² Sophie Limou,¹ Jeffrey B. Kopp,³ Cheryl Ann Winkler,¹ ¹FNLCR, NCI, Frederick, MD; ²Univ of KwaZulu-Natal, Durban, South Africa; ³NIDDK, NIH.

Background: A study of 44 children with sporadic steroid resistant nephrotic syndrome (SRNS) with focal segmental glomerulosclerosis (FSGS) histology, in Durban, South Africa, revealed that 30% carried two copies of a missense mutation, p. V260E, in the podocin gene, *NPHS2*. This mutation has previously been reported as recessively associated with FSGS in consanguineous families in regions at one time in the Omani empire, suggesting spread with this empire. We speculated that the children in our study might be cryptically related from common descent from a recent ancestor.

Methods: Inheritance of the V260E mutation from two parents with a common ancestor will result in a region of homozygosity surrounding the locus, indicating the overlap of extended haplotypes preserved around the locus. To test for this we genotyped 10 individuals homozygous for the mutation, and 74 individuals homozygous for the wild type variant, with the Illumina exome chip. After QC, this chip provided 1674 markers within 20 megabases (Mb) of V260E. To predict the distribution of lengths of homozygous regions around the locus as a function of the number of generations between parents and their common ancestor carrying the mutation, we performed 10,000 coalescence simulations of recombination in each generation for n generations from 6 to 48.

Results: Plotting heterozygous and homozygous loci in the region surrounding V260E clearly showed regions of homozygosity around the locus. 8 of the 10 individuals had segments of homozygosity from 1.9 to 3.6 Mb. This distribution of lengths is inconsistent with a common ancestor within the last 20 generations.

Conclusions: Cryptic consanguinity does not explain the presence of homozygosity for NPHS2 V260E among Durban children with SR-FSGS. The indicated age of the mutation is inconsistent with introduction by the Omani Empire, which spread in East Africa beginning in the 1690s.

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SA-PO524

Genetic Markers Associated with Hemoglobin in the PediGFR Consortium Meredith A. Atkinson,¹ Anna Kottgen,² Elke Wuehl,³ Craig S. Wong,⁴ Matthias Wuttke,² Franz S. Schaefer,³ Bradley Warady,⁵ Susan L. Furth,⁶ ¹Johns Hopkins Univ; ²Univ of Freiburg; ³Heidelberg Univ; ⁴Univ of New Mexico; ⁵Univ of Missouri-Kansas City; ⁶Univ of Pennsylvania.

Background: Genome-wide association studies have identified genetic variants associated with erythrocyte traits, but associations in children with CKD have not been studied. Our goal was to identify whether single nucleotide polymorphisms (SNPs) are associated with hemoglobin (Hgb) decline in progressive CKD in children.

Methods: Longitudinal analysis of genotype and Hgb in 1,141 European (n=806) or Turkish (n=335) children in the Pediatric Investigation for Genetic Factors Linked to Renal Progression (PediGFR) consortium. With a candidate marker approach, linear mixed-effect modeling for Hgb regressed on time and genotype of 24 previously reported SNPs was performed, stratified by ethnicity. Bonferroni correction was used to account for multiple comparisons.

Results: In Europeans, a nominally significant association between SNPs on the RCL1 (p=0.03), BCL11A (p<0.001), RTBDN (p=0.006), and TFR2 (p=0.007) genes and increased risk for Hgb decline over time was noted. Among Turks, a significant association was seen with SNPs on the RCL1 (p=0.03), KIT (p=0.006), BCL11A (p<0.001), RTBDN (p=0.006), CD164 (p=0.031) and HBS1L/MYP (p=0.031) genes. The RCL1 gene has been associated with MCH. The TFR2 and HBS1L/MYP genes are associated with Hgb; TFR2 mediates cellular iron uptake and HBS1L/MYP is a quantitative trait locus controlling fetal Hgb. The KIT, BCL11A, RTBDN, and CD164 genes are associated with MCV, and have roles in hematopoiesis (KIT and CD164), persistence of fetal Hgb (BCL11A) and retinoid binding (RTBDN). After Bonferroni correction, only the SNP on BCL11A remained significantly associated with Hgb in Europeans and Turks, with marginal significance for SNPs on RTBDN and TFR2 in Europeans and on KIT and RTBDN in Turks.

Conclusions: We confirmed the association of selected genetic variants with decline in Hgb in children with progressive CKD, with differential effects by ethnicity at specific loci. Clarification of the genes involved in susceptibility to anemia has the potential to identify new therapeutic targets.

Funding: NIDDK Support

SA-PO525

Cell-Free Hemoglobin and HMOX1 in Sickle Cell Nephropathy
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Background: Chronic kidney disease (CKD) is observed in over 50% of adults with sickle cell disease (SCD) and hemoglobinuria, a consequence of intravascular hemolysis, is independently associated with CKD stage and its progression. In this study we investigate the mechanistic role of hemoglobinuria and HMOX1, the rate limiting enzyme for heme metabolism, in SCD nephropathy.

Methods: Urinary tubular (kidney injury molecule-1, KIM-1) and glomerular (nephrin) biomarkers of injury were measured in 32 SCD patients by ELISA from the University of Illinois at Chicago (UIC). We then cultured human kidney-2 (HK2) tubular cells with lyophilized hemoglobin (L-Hb) to determine biological responses and expression of candidate genes. We examined the association of CKD with 11 tag SNPs and the GT-repeat polymorphism in HMOX1 in 247 UIC SCD patients and in a separate replication cohort (Walk-PHaSST) of 482 SCD patients.

Results: Urine KIM-1 correlated with increasing urine cell-free hemoglobin concentration ($P=0.003$), while urine nephrin levels did not. HK2 culture studies showed increasing KIM-1 concentrations in the culture medium ($P=0.01$), decreasing HK2 cell viability ($P=0.01$), increased HMOX1 expression ($P=0.0001$) and protein concentration ($P<0.0001$) with incremental concentrations of L-Hb. We identified a SNP in HMOX1 (rs743811, MAF=0.14) that was significantly associated with CKD stage (OR 2.8, $P=0.0003$) and CKD stage ³ (OR 3.0, $P=0.02$) in the UIC cohort and with ESRD (OR 9.8, $P=0.0004$) and CKD stage ³ (OR 2.3, $P=0.04$) in our replication cohort. UIC SCD patients with ≥ 25 GT-repeats in the promoter region of HMOX1, known to be associated with increased HMOX1 inducibility and activity, had higher estimated glomerular filtration rate (eGFR) ($\beta=9.2$, $P=0.01$).

Conclusions: Cell-free hemoglobin contributes to sickle cell nephropathy through renal tubular injury. A tag-SNP in HMOX1, rs743811, was associated with kidney disease and the presence of shorter (GT)_n repeats correlated with increasing eGFR, raising the possibility that altered HMOX1 activity has a critical role in SCD-nephropathy.

SA-PO526

Telomere Attrition Is Associated with Renal Replacement Therapy and Immunosuppressive Treatment in End-Stage Renal Disease Patients
Karin Luttrupp,¹ Louise Nordfors,² Dagmara Mcguinness,³ Abdal Rashid Tony Qureshi,² Peter F. Barany,² Peter Stenvinkel.² ¹Dept of Molecular Medicine and Surgery, Karolinska Inst, Stockholm, Sweden; ²Dept of Clinical Science, Intervention and Technology, Karolinska Inst, Stockholm, Sweden; ³Inst of Cancer Sciences, Univ of Glasgow, Glasgow, United Kingdom.

Background: Telomere attrition is a feature of ageing and is accelerated by renal disease. The effects of renal replacement therapy (RRT) and immunosuppressants on telomere length and attrition are unknown. We therefore investigated changes in telomere length during 12 months of RRT and effects of immunosuppressants.

Methods: Telomere length was measured in whole blood DNA from 47 renal transplantation (RTx) and 49 dialysis patients. Data were collected at baseline and after 12 months of RRT. Telomere length determination was performed by qPCR using a Roche Light Cycler LC480. The relative T/S ratio (repeat copy number to single gene copy number) was determined in relation to the control DNA sample. Non-parametric statistical tests were used.

Results: RTx patients had a greater telomere attrition than dialysis patients ($p=0.008$), despite no significant differences in telomere length at baseline or after 12 months. RTx patients were divided into those receiving azathioprine ($n=11$) and those receiving mycophenolate ($n=32$). Mycophenolate-treated patients had greater telomere attrition than patients receiving azathioprine ($p=0.007$), although telomere length at baseline and after 12 months was not significantly different.

Conclusions: RTx patients have a greater telomere attrition than dialysis patients over the course of 12 months; this may reflect an increased stress associated with the transplantation procedure itself as opposed to dialysis treatment. This raises questions regarding the potential risk of accelerated ageing in RTx, which is commonly considered by be a superior form of RRT. In addition, mycophenolate-treated patients show greater telomere attrition than azathioprine-treated patients. This is currently being investigated further, as it could have clinical implications on the choice of treatment regimen.

Funding: Private Foundation Support, Government Support - Non-U.S.

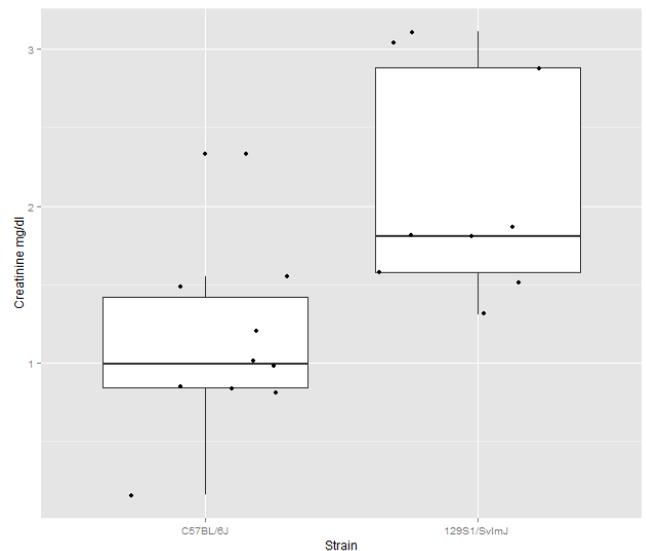
SA-PO527

Differences in Susceptibility to Cisplatin Nephrotoxicity Among 8 Mouse Strains
Gabor Bodonyi-Kovacs, Rosa Chan, Thu H. Le. Renal Div, Univ of Virginia, Charlottesville, VA.

Background: Cisplatin is a widely used chemotherapeutic agent with remarkable efficacy, but its use is limited by significant nephrotoxicity. Significant differences in susceptibility to nephrotoxicity among individual patients have been noted, but predicting those at risk remains a challenge. To begin to identify genes that play a role in susceptibility to cisplatin nephrotoxicity (CPN), we set out to determine differences in CPN among 8 genetically distinct founder mouse strains of the Collaborative Cross: A/J, C57BL/6J, 129S1/SvImJ, NOD/ShiLJ, NZO/HILtJ/CAST/EiJ, PWK/PhJ, and WSB/EiJ.

Methods: 10-14 week old male mice received ip. injection of 25 mg/kg cisplatin and serum was collected 72 hours later prior to sacrifice. Serum urea nitrogen (BUN) was measured for the 8 strains using a nonenzymatic, colorimetric kit (Arbor Assays) and analyzed by one way ANOVA and two sided t-test. Serum creatinine was measured using an enzymatic, colorimetric kit (Crystal Chem) and analyzed by a two sided t-test for the 2 strains that showed the largest difference in BUN.

Results: The 8 strains differed significantly in their serum BUN values ($p=0.042$). The number of animals in each group, and the mean and SD of BUN (mg/dl) were as follows: C57BL/6J ($n=4$) 188.6 \pm 9.2, CAST/EiJ ($n=3$) 207.9 \pm 32.7, NOD/ShiLJ ($n=5$) 236.7 \pm 93.0, PWK/PhJ ($n=4$) 240.9 \pm 27.2, WSB/EiJ ($n=5$) 254.1 \pm 51.6, A/J ($n=5$) 267.6 \pm 62.3, NZO/HILtJ ($n=5$) 290.0 \pm 50.7, 129S1/SvImJ ($n=4$) 319.5 \pm 28.3. The biggest differences were seen between the C57BL/6J and 129S1/SvImJ strains, ($p=0.0001$). In direct comparison the serum creatinine was significantly different between C57BL/6J ($n=10$) and 129S1/SvImJ ($n=9$) strains, ($p=0.0047$) (Figure 1).



Conclusions: Crosses from "susceptible" and "resistant" mouse strains may enable identification of novel genetic determinants governing individual susceptibility to CPN.

Funding: Other NIH Support - T32

SA-PO528

The PAX2-Related SNP rs1190739 Is Associated with Accelerated Loss of GFR in Diabetic Mellitus
Paul R. Goodyer,¹ Melanie Cosgrove,¹ James C. Engert.² ¹Pediatric Nephrology, Research Inst of McGill Univ Health Centre, Montreal, QC, Canada; ²Genetics, McGill Univ, Montreal, QC, Canada.

Background: In embryonic kidney, PAX2 is crucial for optimal branching of the ureteric bud and final nephron number. Previous studies show that common polymorphic variants of the PAX2 gene are associated with a 10% decrease in newborn kidney size. Brenner proposed that individuals with suboptimal nephron number might have accelerated loss of GFR in the setting of acquired renal disease in adulthood.

Methods: We used PLINK software to test for an association between PAX2 SNPs and reduced GFR among Caucasians (N=225) entered into the FIND ("Family Investigation of Nephropathy and Diabetes") cohort available through dbGaP. This cohort of adult diabetics consisted of 175 Afro-American, 225 European-American and 257 Mexican Americans with eGFR data 15-25 years after onset of diabetes. Association testing that incorporated a genomic inflation factor, as well as gender and duration as covariates was used. To test Brenner's hypothesis, we tested this PAX2 SNP for an additional association with subtle newborn renal hypoplasia among 225 healthy Caucasian newborns from Montreal. Kidney volume was measured by ultrasonography within the first 3 days of life.

Results: We identified a SNP (rs1190739) in the FIND cohort (MAF=6.5%) that was associated with a 15% decrease in GFR exclusively among European-American diabetics with one or more minor alleles ($p=0.022$). eGFR (ml/min/1.73m²) in European Americans was 70.71 for GG individuals, 61.64 for GT, and 41.9 for TT. No association was found between the rs1190739 SNP and eGFR among Afro-American and Mexican-American

subjects. Among healthy Montreal newborns, this same PAX2 SNP (rs11190739) was associated with a 10.2% decrease in newborn combined kidney volume in 14.6% of babies who were heterozygous for this common variant (p=0.036).

Conclusions: Our study provides the first evidence that a common PAX2 variant associated with newborn renal hypoplasia is also associated with decreased eGFR among Caucasians with diabetes mellitus for 15-25 years.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO529

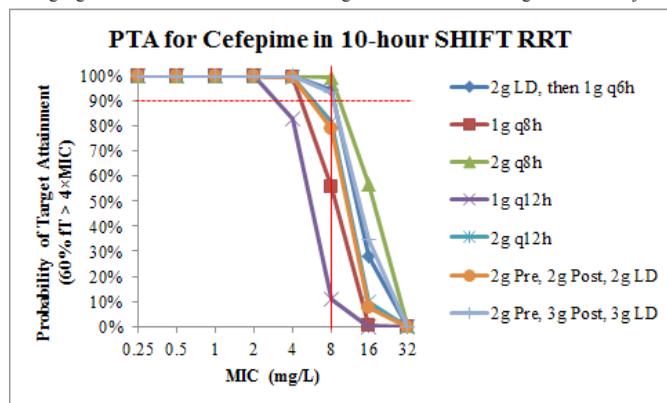
Cefepime Dosing in Modeled Critically Ill Patients Receiving SHIFT Hemofiltration or Hemodialysis Renal Replacement Therapies

Katherine N. Gharibian, Susan J. Lewis, Bruce A. Mueller. *College of Pharmacy, Univ of Michigan, Ann Arbor, MI.*

Background: Cefepime is an antibiotic commonly used in the ICU where acute kidney injury (AKI) is prevalent. SHIFT therapy, a 6-12 hour renal replacement therapy (RRT), also referred to as Prolonged Intermittent Renal Replacement Therapy (PIRRT) or Slow Low Efficiency Daily Dialysis (SLEDD), is increasingly utilized to help treat AKI. However, dosing information for cefepime in critically ill patients receiving SHIFT therapy is currently lacking.

Methods: Using previously-published pharmacokinetic (PK) data and a PK model developed for critically ill patients receiving SHIFT RRT, a series of 5000-subject Monte Carlo simulations were performed for 18 cefepime regimens in 8 scenarios with varying duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT relative to cefepime doses. Cefepime regimens were evaluated on the probability of attaining a free drug concentration equal to at least the minimum inhibitory concentration (MIC)×4 for ≥60% of the dosing interval during the first 48 hours of therapy. Optimal regimens yielded a probability of target attainment (PTA) ≥90% for MIC values ≤8 mg/L using the smallest total daily dose.

Results: Cefepime 1 g q6 hours with a 2 g loading dose was the only regimen to yield a PTA ≥90% in all 8 SHIFT settings while limiting the total daily maintenance dose to 4 g. This dosing regimen resulted in 48-hour mean trough concentrations >32 mg/L in most subjects.



Conclusions: In PK models of critically-ill subjects receiving 8 or 10 hours of SHIFT RRT, a cefepime dose of 1 g q6 hours with a 2 g loading dose yielded pharmacodynamic target attainment for >90% of the population.

Funding: Pharmaceutical Company Support - NxStage Medical, Inc.

SA-PO530

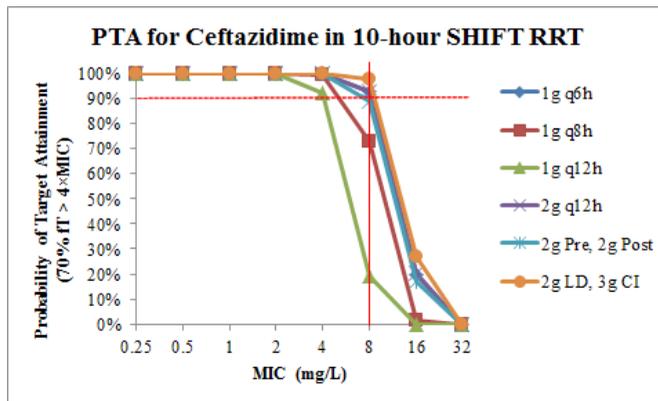
Identification of Optimal Ceftazidime Dosing Regimens in Modeled Critically Ill Patients Receiving SHIFT Renal Replacement Therapy

Katherine N. Gharibian, Susan J. Lewis, Bruce A. Mueller. *College of Pharmacy, Univ of Michigan, Ann Arbor, MI.*

Background: Ceftazidime is an antibiotic commonly used in critically ill patients. Ceftazidime doses of 2 g every 12 hours have been recommended for continuous renal replacement therapies (CRRT), however, no studies have evaluated the optimal dose in patients receiving SHIFT Therapy (NxStage Medical), a 6-12 hr RRT commonly referred to as Prolonged Intermittent Renal Replacement Therapy (PIRRT) or Slow Low Efficiency Daily Dialysis (SLEDD).

Methods: Pharmacokinetic (PK) data compiled from previously-published studies were used to develop models for critically ill patients receiving intermittent hemofiltration (HF) or hemodialysis (HD). Eight models were developed to account for the variability in settings including duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT relative to ceftazidime dose. Using a series of 5000-subject Monte Carlo simulations, 12 ceftazidime regimens were applied to each model and evaluated for the probability of attaining free drug concentrations equal to or greater than the minimum inhibitory concentration (MIC)×4 for ≥70% of the dosing interval during the first 48 hours of therapy. Optimal regimens yielded a probability of target attainment (PTA) ≥90% for MIC values ≤8 mg/L, the MIC for *Pseudomonas aeruginosa*.

Results: Ceftazidime administered in 4 g total daily doses (2 g q12 hours; 1 g q6 hours) yielded a PTA ≥90% in all 8 RRT models. Continuous infusion of the drug (3 g continuous infusion with a 2 g loading dose) achieved similar PTA values.



Conclusions: Published ceftazidime CRRT doses (2 g every 12 hours) yielded 90% PTA in modeled critically ill patients receiving 8 or 10 hours of SHIFT RRT. Future studies should validate these findings in the clinical setting.

Funding: Pharmaceutical Company Support - NxStage Medical, Inc.

SA-PO531

Use of Monte Carlo Simulation to Determine Optimal Meropenem Regimens in Patients Receiving SHIFT Renal Replacement Therapy

Susan J. Lewis, Katherine N. Gharibian, Bruce A. Mueller. *College of Pharmacy, Univ of Michigan, MI.*

Background: Current antibiotic dosing regimens often result in subtherapeutic concentrations in critically ill patients, but scant pharmacokinetic (PK) data exist to support antibiotic dosing. This study applied Monte Carlo simulations (MCS) to determine the initial meropenem regimen to treat critically ill patients receiving SHIFT Renal Replacement Therapy (RRT), a daily prolonged intermittent RRT.

Methods: Body weight & PK parameter [non-renal clearance, free fraction, volume of distribution & extraction coefficients] estimates with variability were obtained from relevant published studies. Values were randomly selected from the log-Gaussian distribution within the assigned limits to vary individual free meropenem concentration profiles. MCS were performed for 13 meropenem regimens including weight-based and pre- & post-SHIFT dosing, in 4 different SHIFT settings (4L/hour x 10 hours or 5L/hour x 8 hours in hemodialysis or hemofiltration) occurring either at the beginning of or 14-16 hours after meropenem infusion. Probability of target attainment (PTA) was evaluated using a pharmacodynamic target of ≥40% free meropenem concentrations above 4 times of the minimum inhibitor concentration (fT≥4xMIC) for *Pseudomonas aeruginosa* (2 µg/mL) for the first 48 hours of therapy. A ≥90% of PTA with the smallest daily dose was defined as optimal.

Results: Meropenem regimens using 32g/day attained ≥90% PTA. Meropenem 1g q12h and 1g given pre- & post-SHIFT were optimal regimens for all SHIFT settings. Weight-based regimens did not yield better target attainment than fixed-dose regimens.

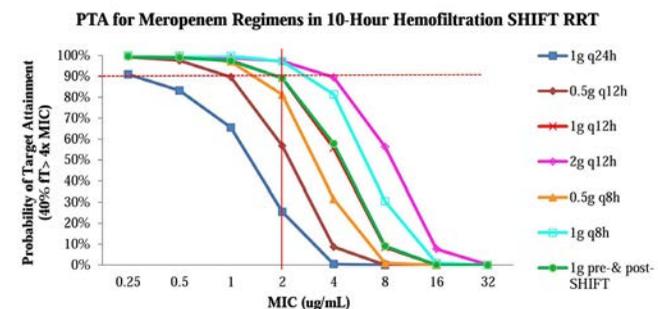


Figure. The horizontal red line indicates 90% PTA and the vertical red line the target MIC of 2 µg/mL. Meropenem regimens using 2g/day (green and red) were optimal in patients receiving 10 hour HF SHIFT

Conclusions: This simulation indicates that meropenem regimens using 2g/day should be used initially to treat critically ill patients receiving 8 or 10 hour SHIFT RRT. These results warrant clinical validation.

Funding: Pharmaceutical Company Support - NxStage Medical Inc.

SA-PO532

Evaluation of Piperacillin/Tazobactam Regimens in Patients with SHIFT Renal Replacement Therapy Susan J. Lewis,¹ Katherine N. Gharibian,¹ Ashita J. Tolwani,² William Henry Fissell,³ Bruce A. Mueller.¹ ¹College of Pharmacy, Univ of Michigan, MI; ²Univ of Alabama, AL; ³Vanderbilt Univ, TN.

Background: SHIFT Renal Replacement Therapy (RRT) is a prolonged intermittent RRT to treat critically ill patients with acute kidney injury, but lack of antibiotic pharmacokinetic (PK) data in this RRT limits its utility. This study evaluated probability of target attainment (PTA) of piperacillin/tazobactam regimens recommended in critically ill patients receiving SHIFT RRT, using Monte Carlo Simulations (MCS).

Methods: Mathematical PK models were constructed using literature-derived demographic/PK data with known variability. Four daily-SHIFT settings (hemofiltration or hemodialysis with effluent rates of 5L/hour x 8 hours or 4L/hour x 10 hours) occurring at 2 different times relative to drug dose were modeled. PTA of 13 piperacillin regimens (2-4g q6-8h) and 3 tazobactam regimens (0.5g q6h) with intermittent or prolonged infusion (4-hour or continuous) were evaluated. MCS generated free drug concentration profiles for each regimen in the 5,000 virtual patients. Pharmacodynamic targets were $\geq 50\%$ of time free piperacillin concentrations above 4x the minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* (16 µg/mL) and $\geq 50\%$ of time free tazobactam concentrations above corresponding threshold (4 µg/mL) for the initial 48 hour-therapy. The optimal regimen required $\geq 90\%$ of PTA for both agents.

Results: The attainment of $\geq 90\%$ of PTA required piperacillin 16g/day and tazobactam 2g/day in all SHIFT settings. Prolonged infusion was not superior to intermittent infusion to yield better PTA in patients receiving SHIFT RRT.

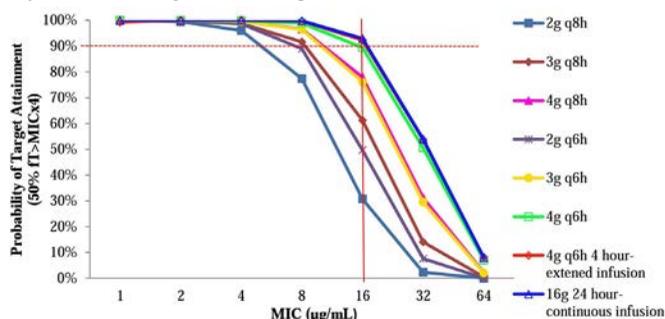


Figure. Predicted target attainment of piperacillin dosing regimens across MICs in patients receiving Daily-SHIFT for the initial 48 hours of antibiotic therapy. The horizontal red line indicates 90% of PTA and the vertical red line the target MIC of 16 µg/mL. A total of 16g/day with intermittent or prolonged infusion was required to attain the pharmacodynamic target successfully (green, red, and blue lines).

Conclusions: Piperacillin/tazobactam 4.5g q6h is recommended for critically ill patients receiving 8 or 10 hour SHIFT RRT. These PK simulation results need to be clinically validated.

Funding: Pharmaceutical Company Support - NxStage Medical Inc.

SA-PO533

Beta-Blocker Dialyzability in Chronic Hemodialysis Patients Alvin Tieu,¹ Thomas Velenosi,¹ Andrew S. Kucey,¹ Laura Elisabeth Mccuaig,¹ Matthew A. Weir,¹ Brad Urquhart.^{1,2} ¹Dept of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, London, ON, Canada; ²Dept of Medicine, Div of Nephrology, Western Univ, London, ON, Canada.

Background: There is a paucity of data available to describe beta-blocker dialyzability. Of the available information, most were obtained prior to implementation of high-flux dialysis membranes. This study aims to characterize the dialyzability of four of the most commonly prescribed beta-blockers in patients undergoing conventional high-flux hemodialysis (HD). Based on physicochemical properties, we hypothesize atenolol and metoprolol to be extensively removed by HD, while bisoprolol and carvedilol to be poorly dialyzed.

Methods: HD patients from the London Health Sciences Centre were recruited for a pharmacokinetic, crossover study. Atenolol (50mg), bisoprolol (5mg), carvedilol (6.25mg) and metoprolol (50mg) were administered separately to each patient over four hemodialysis sessions. Arterial and venous blood samples and total spent dialysate were collected. Beta-blocker concentrations were measured by mass spectrometry, and dialytic clearance was determined by the dialyzer and recovery clearance methods.

Results: Following dialysis, 6.78 mg of atenolol, 0.66 mg of bisoprolol, 0.02 mg of carvedilol, and 1.53 mg of metoprolol were recovered in spent dialysate. These amounts of dialyzed beta-blockers were applied in the recovery clearance method to produce dialytic clearance values of 124.0, 91.5, 1.3, and 150.2 mL/min for atenolol, bisoprolol, carvedilol, and metoprolol, respectively.

Conclusions: Beta-blocker efficacy can be hindered if substantial dialytic clearance occurs. Accordingly, atenolol and metoprolol were extensively cleared by HD, while carvedilol displayed low dialyzability. Contrary to previous literature, our data suggests moderate dialyzability for bisoprolol. With recent studies indicating heightened mortality risk in HD patients prescribed highly-dialyzable beta-blockers, drug dialyzability data is critically important to optimize pharmacotherapy in HD patients. Definitive characterization of beta-blocker dialyzability can allow for determination of post-dialysis supplemental drug doses, or alternative drug therapies.

Funding: Government Support - Non-U.S.

SA-PO534

Rituximab Exhibits Altered Pharmacokinetics in Patients with Membranous Nephropathy Uma R. Fogueri,¹ Wisit Cheungpasitporn,² David Bourne,¹ Fernando C. Fervenza,² Melanie S. Joy.¹ ¹Schools of Pharmacy and Medicine, Univ of Colorado, Aurora, CO; ²Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Rituximab (RTX) is an anti-CD20 antibody used in the treatment of glomerular diseases including membranous nephropathy (MN). There is little information about the pharmacokinetics of therapeutic proteins, including RTX in patients with glomerular diseases. The study evaluated rituximab pharmacokinetics in patients with MN from a pilot investigation (Fervenza et al, 2010).

Methods: Patients with MN (n=20) received 4 RTX weekly IV infusions (375mg/m²), with a repeat of the identical treatment at 6 months. Patient baseline characteristics were: gender (17M/3F), age (49±13 y), BSA (2.22±0.24 m²), urinary protein excretion (11.3±4.1 g/d), creatinine clearance (72±33 mL/min). Pharmacokinetic analysis was performed using rituximab plasma concentrations. Comparisons of pharmacokinetic parameters were made between the MN patients and published data from other populations.

Results: The MN population had a favorable reduction in urinary protein excretion 3 months after each RTX treatment course (7339±4114 mg/day and 4131±3441 mg/day, respectively), while creatinine clearance values were similar to baseline (72±31 mL/min and 82±37 mL/min, respectively). Patients with MN exhibited a shortened half-life (T_{1/2}), greater volume of distribution (V_d), and enhanced clearance of RTX vs. previous reports in other patient populations. These characteristics resulted in an exposure (AUC) that was significantly reduced in patients with MN.

	Membranous Nephropathy (N=20)	Follicular Lymphoma (N=22)	Autoimmune Disorders (N=14)
T _{1/2} (h)	231±143	513 (248-705)	484 (292-859)
Clearance(mL/hr)	29.6±9.5	11.2 (8.4-17.8)	14.5 (8.4-26.2)
V _d (mL)	9722±6877	3850 (3432-4686)	4642 (2266-5786)
AUC (mg h/mL)	31.4±12.7	73.6 (46.3-98.2)	56.9 (31.5-98.2)

Conclusions: The pharmacokinetics of RTX in patients with MN are significantly altered compared to published data from cancer and autoimmune populations. These results suggest shorter T_{1/2} and lower exposures to RTX in MN may necessitate higher doses and/or changes to dosing frequency in order to elicit an optimal therapeutic effect.

SA-PO535

Eculizumab Treatment Efficiently Prevents C5 Cleavage without C5a Generation In Vivo Elena Volokhina,¹ Grethe Bergseth,² Nicole Van De Kar,¹ Lambertus P.W.J. Van den Heuvel,¹ Tom Eirik Mollnes.² ¹Radboud Univ Medical Center, Nijmegen, Netherlands; ²Nordland Hospital, Bodø, Norway.

Background: The C5 inhibitor eculizumab has been successfully used to treat atypical hemolytic uremic syndrome (aHUS), however, available data on pharmacodynamics of this medication are limited. Recently, increased generation of C5a in a single patient with HELLP syndrome treated with eculizumab has been reported. Since this observation was unexpected, we aimed to reproduce these data and search for possible explanations for the findings.

Methods: Levels of C5a were analyzed in EDTA plasma samples of aHUS (n=3) patients using three commercial ELISA kits, one of the kits was also used in the HELLP study and other two kits were included as controls. The samples were collected before the first eculizumab dose and then at various time points during treatment.

Results: In line with the report on HELLP patient, the C5a values, measured by one of the commercial ELISA kits, increased significantly in all aHUS patients after the first eculizumab dose as compared to the values obtained before treatment (p=0.016). C5a remained elevated throughout the treatment period. Such increase could not be reproduced by using another two commonly available commercial kits. When eculizumab was added in vitro to normal human serum prior to activation, no generation of C5a was measured by all used kits.

Conclusions: Our data indicate that existing commercial assays require validation for specificity before being used to monitor effect of eculizumab, especially in clinical laboratory practice. This example illustrates how false conclusions can be drawn when based on results from one single commercial assay not satisfactorily validated for the purpose it is used.

Funding: Government Support - Non-U.S.

SA-PO536

Sensitive, Reliable and Easy-Performed Laboratory Monitoring of Eculizumab Therapy in Atypical Hemolytic Uremic Syndrome Elena Volokhina,¹ Nicole Van De Kar,¹ Grethe Bergseth,² Thea J. Van der velden,¹ Jack F. Wetzels,¹ Lambertus P.W.J. Van den Heuvel,¹ Tom Eirik Mollnes.² ¹Radboud Univ Medical Center, Nijmegen, Netherlands; ²Nordland Hospital, Bodø, Norway.

Background: Atypical hemolytic uremic syndrome is a severe renal illness caused by complement dysregulation. Treatment with the complement C5 inhibitor eculizumab is effective, but associated with high costs. Laboratory monitoring of these patients with

respect to complement function has not been standardized. The aim of this study was to evaluate novel complement functional assays for their application in routine follow-up of eculizumab-treated patients.

Methods: Complement activity in serum samples was analyzed using Wieslab® complement screen assay. The presence of eculizumab-C5 complexes in serum, EDTA plasma samples and in urine was measured using ELISA. Levels of sC5b-9 in urine were measured using electroluminescent epitope assay.

Results: First, we documented that the Wieslab® complement screen assay showed a sensitivity of 1-2% of C5 activity by adding purified C5 or normal human serum to a C5 deficient serum. Second, we found that all the patient samples obtained during the standard treatment course, were completely blocked for terminal complement pathway activity. Moreover, complement remained fully blocked when intervals between the eculizumab infusions were extended to four weeks. Levels of complexes between eculizumab and C5 were inversely correlated to the complement activity ($p=0.01$). Third, titrating serum from eculizumab-treated patients into normal serum, revealed that eculizumab was present in excess up to four weeks after infusion. Finally, we showed that increased urine sC5b-9 disappeared after eculizumab treatment.

Conclusions: We demonstrate sensitive, reliable and easy-performed assays to monitor eculizumab-treated patients, which can be used to design individual dosage regimens.

Funding: Government Support - Non-U.S.

SA-PO537

Dose Exposure Relationship of AKB-6548 Is Independent of the Level of Renal Function Akshay Buch, Bradley J. Maroni, Charlotte S. Hartman. *Akebia Therapeutics, Inc., Cambridge, MA.*

Background: AKB-6548 is a novel, once-daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) in development for the treatment of anemia in non-dialysis dependent (NDD) and dialysis dependent (DD) chronic kidney disease (CKD). Studies in NDD-CKD patients have shown AKB-6548 produces physiologic increases in erythropoietin, enhances iron mobilization, and produces a dose dependent increase in hemoglobin levels.

Methods: The pharmacokinetics (PK) of AKB-6548 have been evaluated in single and multiple dose studies in healthy volunteers and CKD patients (NDD-CKD and DD-CKD) over a broad range of dose levels. An analysis of results across studies was conducted to assess the potential impact of renal function on selecting the dose levels and dosing regimen in CKD patients. The analyses evaluated dose-linearity in drug exposure, clearance routes of AKB-6548 and its metabolites, as well as the impact of CKD severity and the hemodialysis procedure on drug disposition.

Results: In healthy volunteers, AKB-6548 demonstrated dose linearity and proportionality over single doses of 80-1200 mg and multiple doses of 500-900 mg/day. The PK parameters of AKB-6548 in healthy volunteers, NDD-CKD and DD-CKD patients were similar except for a slightly longer half-life with declining renal function (4.7 hr., 7.9 hr. and 9.1 hr., respectively). A mass balance study (using ¹⁴C- labeled drug) in healthy volunteers demonstrated both renal and fecal routes of parent drug and metabolite clearance, supporting use of AKB-6548 in CKD patients without significant differences in drug exposure. Moreover, AKB-6548 was minimally cleared by the hemodialysis procedure and the PK parameters were similar whether AKB-6548 was administered prior to or following dialysis.

Conclusions: The results demonstrate a linear dose-exposure relationship for AKB-6548 over a wide range of doses and support the utility of once-daily dosing and similar dose levels across the spectrum of CKD severity.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

SA-PO538

Nonclinical Pharmacokinetics and Toxicokinetics of RG-012, an Inhibitor of MicroRNA-21 Being Investigated for Treatment of Alport Syndrome John Stewart Grundy,¹ Kai Liu,¹ Steven Neben,¹ Cindy L. Berman,² Deidre Mackenna,¹ Neil W. Gibson.¹ *Regulus Therapeutics, San Diego, CA;* ²*Berman Consulting, Wayland, MA.*

Background: RG-012 is a single-stranded chemically modified oligonucleotide being developed to treat patients with Alport syndrome, which is characterized by loss of renal function associated with defects in specific collagen genes expressed in the kidney glomerular basement membrane. RG-012 inhibits miR-21, a microRNA target known to have increased expression in context of kidney stress and associated with renal dysfunction.

Methods: In vitro pharmacokinetic (PK) evaluations of RG-012 conducted during preclinical development included: plasma protein binding, metabolic stability in whole blood and liver lysates, and CYP450 inhibition/induction potential in cryopreserved human hepatocytes. In vivo PK and toxicokinetic (TK) properties of RG-012, and its major active metabolite (RG0005), were determined upon subcutaneous dosing of RG-012 in a set of nonclinical PK, pharmacology, and safety studies in CD-1, SV129, and COL4A3 mice (6.25-450 mg/kg/week) and cynomolgus monkeys (10-225 mg/kg/week).

Results: Both RG-012 and RG0005 were highly bound ($\geq 98\%$) to proteins in plasma from mice, monkeys, and humans. RG0005 was the only major degradation product seen in whole blood and liver lysates from all three species. RG-012 exhibited little to no potential to inhibit or induce CYP450 enzymes. Upon administration of RG-012, PK and TK properties of RG-012 and RG0005 were consistent across all nonclinical species and were characterized by rapid absorption, dose-dependent plasma exposure, rapid plasma clearance due mainly to extensive tissue distribution, and subsequent slow tissue elimination (half-lives in liver and kidney of ~2-3 weeks). Comparison of plasma and tissue exposure levels (RG-012+RG0005 combined) seen at the NOAEL in cynomolgus monkeys, the most

clinically relevant toxicological species, with those achieved at pharmacologically active dose regimens (ED₅₀ and ED₉₀) in a COL4A3 mutant mouse model, indicates a therapeutic index (TI) ranging from 3.4 to 25.4.

Conclusions: In conclusion, favorable nonclinical PK/TK properties and TI of RG-012 support initial clinical testing.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

SA-PO539

Novel Methodology for Assessing Inhibition of MicroRNA-21 by RG-012, a MicroRNA Therapeutic in Development for the Treatment of Kidney Dysfunction in Patients with Alport Syndrome John Rolf Androsavich, Xueqing Liu, Shweta Pandya, Deidre Mackenna. *Regulus Therapeutics, San Diego, CA.*

Background: microRNA-21 (miR-21) is upregulated in animals models with kidney dysfunction and also in patients with chronic kidney disease (CKD). RG-012 is a miR-21 inhibitor entering clinical development for treatment of CKD in Alport syndrome (AS) patients. RG-012 demonstrates activity both as a monotherapy and in combination with the ACE inhibitor ramipril in the Col4A3 deficient mutant mouse model of AS.

Methods: Two distinct methods have been developed to evaluate the ability of RG-012 to inhibit miR-21 in preclinical studies – the polysome shift assay (PSA) and alterations in the expression of miR-21 target mRNAs. The PSA measures direct target inhibition at the level of the physical interaction between microRNA and messenger RNA targets. C57Bl/6 mice were treated subcutaneously with RG-012 at doses ranging from 0.1 to 100 mg/kg. Tissue homogenates were separated using sucrose gradient ultracentrifugation, with microRNAs associating with messenger RNA targets in the heavier polysome fraction. The ability of RG-012 to displace the target miR-21 from the polysome containing fraction was used to assess direct target engagement.

Results: RG-012 demonstrated dose dependent displacement of miR-21 from polysomes in both liver and kidney with a maximum effect reached at dose levels that are efficacious in the Col4A3 mouse models. Loss of miR-21 from the polysomes was specific as levels of Let-7a, a control microRNA to which RG-012 has no complementarity, were unaffected. In the liver, target engagement was also assessed using mRNA derepression of a set of confirmed miR-21 target genes. Here, target gene derepression strongly correlated with polysome displacement. This comparison was not possible in kidney, however, because target genes are not regulated in kidneys in the absence of stress.

Conclusions: RG-012 directly and specifically inhibits miR-21 resulting in its displacement from actively translating polysome complexes and subsequent derepression of messenger RNA targets.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

SA-PO540

Tacrolimus Pharmacokinetics in Nephrotic Stage Mara Medeiros,¹ Saul Valverde,¹ Luis Velasquez-Jones,¹ Ana M. Hernández,¹ Gilberto Castañeda-Hernández,² Guido Filler.³ *¹Hospital Infantil de México Federico Gómez, Mexico;* *²CINVESTAV, IPN, Mexico;* *³Children's Hospital, Univ of Western Ontario, Canada.*

Background: While tacrolimus (Tac) therapy is not first-line therapy for childhood nephrotic syndrome, it is often used instead of cyclosporine to ameliorate the side effects. The pharmacokinetics of Tac can be influenced by many conditions, and it has a high plasma protein binding. The Tac pharmacokinetics during relapse and remission of childhood nephrotic syndrome have not been well described.

Methods: We performed 14 pharmacokinetic (PK) profiles (with measurements before and 0.5, 1, 2, 4 and 12 hours post intake) in 7 children with steroid-resistant nephrotic syndrome (SRNS) during relapse and in remission. These data were compared with historical PK data of 161 PK profiles in 87 pediatric renal transplant recipients with measurements before, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post intake. Tac levels were measured using the Abbott Tacro II assay. We used descriptive statistics to generate percentiles and compared these with the SRNS patients. We also compared the PK profiles during relapse and remission.

Results: Median age of SRNS patients was 3.2 years. Tacrolimus dose, biochemical values and pharmacokinetics parameters are shown in Table 1. Values as median and interquartile range.

	Baseline	Week 1	Week 16	P value*
Serum albumin (mg/dL)	2.1 (1.4, 2.9)	2.6 (2.4, 3.5)	3.7 (3.6, 3.7)	0.008
Proteinuria (mg/m ² /h)	54.5 (28.5, 168)	22 (5, 30)	4.5 (0.46, 30)	0.01
Cholesterol (mg/dL)	281 (229, 506)	286 (236, 383)	165 (137, 191)	0.0003
Triglycerides (mg/dL)	182 (115, 430)	173 (120, 276)	90 (49, 126)	0.02
eGFR (ml/min/1.73m ²)	114 (92, 349)	92 (91, 130)	85 (73, 120)	0.02
Tacrolimus dose mg/kg/day		0.11 (0.08, 0.12)	0.13 (0.08, 0.15)	0.81
Tacrolimus C0h (mg/dL)		7.9 (3.8, 10.2)	5.3 (3.6, 11.3)	1.0
AUC/Dose (ng*hr/ml/mg)		1858 (625, 3172)	3823 (1212, 4790)	0.07
Cmax/Dose [(ng/mL)/[mg/kg/d]		131 (93, 240)	188 (135, 330)	0.21
Tmax (h)		1 (1, 2)	0.5 (0.5, 2)	0.58
t ½ (h)		9.2 (6.1, 11.3)	8 (6, 12.8)	0.57

The PK profiles were well within the percentiles of the transplant children.

Conclusions: Tac PK profiles are not different in children with nephrotic syndrome during relapse and remission.

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SA-PO541

Clinical and Genetic Determinants of Longitudinal Dose-Corrected CNI Exposure in Children After Renal Transplantation Noel Knops,¹ Elena N. Levchenko,¹ Dirk R. Kuypers,² ¹*Pediatric Nephrology, Univ Hospitals Leuven, Leuven, Belgium;* ²*Nephrology, Univ Hospitals Leuven, Leuven, Belgium.*

Background: Calcineurin-inhibitors (CNI) have a narrow therapeutic index and dosing is difficult due to inter- and intra-individual variation in pharmacokinetics (PK). Polymorphisms in genes involved in drug metabolism can play a critical role in individual exposure. Data concerning long-term CNI exposure in relation to dose in children are scarce and in general based upon trough levels. We present the longitudinal follow up of 12-hour CNI PK in relation to dose, clinical and genetic factors in a cohort pediatric renal allograft recipients.

Methods: Retrospective single center study in subjects after renal transplantation (age 0-20 yrs) with annual PK assessments (6-point AUC0-12hr) for tacrolimus (Tac) or cyclosporine (CsA). Clinical and laboratory data were retrieved. Analysis of polymorphisms in *CYP3A4*, *CYP3A5*, *CYP3A7*, *POR* and *ABCB1* was performed.

Results: We collected 180 "full" AUCs for Tac, 56 for CsA in 51 kids. Mean age at Tx: 9.9 yrs(1-19); FU after Tx: 4.6 yrs (0-16). Dose-corr. exposure (AUC/ dose in mg/kg) increased with age: 854 (mean) in <5 yrs to 2702 (>15yrs); 817 to 1787 ng*hr/ml per mg/kg in Tac and CsA resp. (p< 0.01). Correction for dose per m² body surface (BS) demonstrated stable dose-corr. exposure for ages <15 yrs, and was higher only for >15 yrs (Tac: <5yrs-15 yrs: 44 (95%CI: 40-48) >15yrs: 73.4 ng hr/ml per mg/m²; CsA: 40 (CI 36-44) vs. 52. *CYP3A5* genotype was an important co-determinant of dose-corr. exposure for Tac (2.1 higher dose-req. in *1 vs *3/3), but not for CsA. *1 carriers had an attenuated increase in dose-corr.exposure into adulthood (27 vs. 39 in >15yrs; *3/3: 48 vs. 82 resp.)

Conclusions: Dose-corr exposure according to BS, in contrast to bodyweight, demonstrates stable CNI dose requirements in children <15 yrs. Polymorphisms in *CYP3A5* are important for individual Tac dose requirements and modify the effect of age. CsA is not affected by *CYP3A5*. Our data suggest that CNI dosing per m² in children after renal transplantation would be less prone to variation in exposure with age and thus preferred. *CYP3A5* genotype only aids in predicting Tac dose requirements.

Funding: Government Support - Non-U.S.

SA-PO542

Sex and Race Influences on Tacrolimus Pharmacokinetics in Renal Transplant Recipients Kathleen M. Tornatore,^{1,3} Calvin J. Meaney,¹ Joseph D. Consiglio,² Gregory E. Wilding,² Shirley Shwu-Shiow Chang,³ Rocco C. Venuto,³ ¹*NYS Center of Excellence in Bioinformatics & Life Science; Pharmacy, School of Pharmacy & Pharmaceutical Sciences;* ²*Biostatistics, School of Public Health;* ³*Medicine, School of Medicine & Biomedical Sciences; Univ at Buffalo, Buffalo, NY.*

Background: Tacrolimus (TAC) is the primary calcineurin inhibitor in immunosuppressive regimens for renal transplant recipients(RTR) and exhibits notable interpatient variability in pharmacokinetics(PK) necessitating therapeutic drug monitoring(TDM). There are limited data that characterize sex and race influences on TAC PK.

Methods: During a 12-hour PK study, we evaluated steady-state TAC trough (C₀), area under the concentration time curve 0-12 hours (AUC 0-12) normalized for dose, apparent clearance(CL) and total body weight(TBW) normalized CL using non-compartmental analysis. 65 stable African American (AA) and Caucasians (C) females(F) and males(M) who were greater than 6 months post-transplant and receiving TAC and mycophenolic

acid were enrolled. TAC dosage was adjusted using C₀ range of 4-9 ng/ml. TAC adverse effects(AE) were evaluated using standardized assessments to generate a cumulative AE score(CAE).

Results: The clinical and PK parameters are summarized below. Total and weight-normalized CL were most rapid with lower dose-normalized AUC in AAF compared to other RTR. Higher CAE was found in female RTR. No sex-race differences were noted for C₀ in spite of higher TAC doses in AA.

Mean(SD)	AAF[n=13]	AAM[n=20]	CF[n=16]	CM[n=16]	P Value
eGFR[ml/min/1.73m ²]	49.9(17.7)	57.4(13.4)	49.8(11.5)	64.4(16.2)	0.019
TAC dose[mg]	5.0(1.7)	3.7(1.6)	2.7(1.2)	2.2(0.7)	<0.001
TAC C ₀ [ng/ml]	7.2(1.8)	7.3(1.9)	6.7(1.7)	6.2(1.2)	NS
Apparent CL[L/hr]	40.0(16.8)	28.2(13.3)	22.2(8.9)	21.3(6.7)	0.0003
CL/TBW	0.47(0.23)	0.34(0.20)	0.32(0.15)	0.23(0.07)	0.005
AUC 0-12/ Dose[ng.hr/ml/mg]	29.6(12.5)	44.9(25.5)	54.6(25.9)	51.7(16.8)	0.001
CAE Score	0.21(0.06)	0.09(0.06)	0.16(0.09)	0.13(0.06)	<0.001

Conclusions: Sex-race differences in TAC PK contribute to differential dosing requirements in AA vs C. A more individualized approach to chronic TAC immunosuppression integrating sex-race with TDM and a standardized adverse effect assessment may benefit RTR.

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SA-PO543

Sex and ABCB1 Haplotype Associations with Tacrolimus Pharmacokinetics in Renal Transplant Recipients Kathleen M. Tornatore,^{1,3} Daniel Brazeau,² Calvin J. Meaney,¹ Louise M. Cooper,¹ Rocco C. Venuto,³ ¹*NYS Center of Excellence in Bioinformatics & Life Science; Pharmacy, School of Pharmacy & Pharmaceutical Sciences;* ²*GAP-Core Facility; Schools of Pharmacy & Medicine, Univ of New England, Portland, ME;* ³*Medicine, ECMC, School of Medicine; Univ at Buffalo, Buffalo, NY.*

Background: Tacrolimus (TAC) is the mainstay calcineurin inhibitor for immunosuppression in renal transplant recipients (RTR). TAC exhibits interpatient variability in pharmacokinetics (PK) attributed primarily to CYP 3A5 isoenzymes and P-glycoprotein (Pgp). Pgp is encoded by the *ABCB1* gene. The common single nucleotide polymorphisms (SNP): *1236C>T (rs1128503)*, *c.2677G>T/A (rs2032582)*, and *c.3435C>T (rs1045642)* have conflicting associations to TAC PK. This study objective evaluated these common SNP as haplotypes in relation to TAC PK.

Methods: During a 12-hr PK study, trough (C₀), apparent clearance (CL) and lean body weight (LBW) normalized CL were determined in 29 female and 36 male African American (AA) and Caucasian (C) stable RTR greater than 6 months post-transplant receiving TAC and mycophenolic acid. TAC dosage was adjusted to C₀ range of 4-9 ng/ml. The *ABCB1* SNPs: *c.1236C>T (rs1128503)*, *c.2677G>T/A (rs2032582)*, and *c.3435C>T (rs1045642)* were assessed. *ABCB1* haplotype associations comparing the primary variant TTT to CGC [wild-type (WT)] relative to TAC PK were computed using the THESIAS program with sex sub-analysis.

Results: TAC C₀ ranged from 5-10 ng/ml with no difference between groups in spite of higher doses in AA (P<0.0001). Significant associations of TTT to TAC dose, CL and CL/LBW were noted with sex sub-analysis and summarized as Phenotypic Mean with Confidence Interval (CI) of WT compared to variant in table. These data suggest RTR with TTT variant received lower doses and had slower TAC CL relative to sex.

Mean[SD]	CGC[WT] Phenotypic Mean[CI]	TTT- Phenotypic Mean[CI]	P Value
TAC Dose[mg]	2.4[1.7-3.2]	1.6[0.7-2.5]	0.029
Apparent CL[L/hr]	20.4[14.5-26.3]	13.9[7.9-20.1]	0.023
CL/LBW	0.48[0.37-0.60]	0.35[0.23-0.47]	0.022

Conclusions: The *ABCB1* haplotypes provide important insight into interpatient variability in TAC PK post renal transplant and the role of P-gp that is also influenced by sex.

Funding: NIDDK Support, Pharmaceutical Company Support - Astellas Scientific and Medical Affairs, INC

SA-PO544

Pharmacokinetics and Pharmacodynamics of Tacrolimus, and NFAT Regulated Gene Expression in Kidney Transplant Patients Frieder Keller, *Univ Hospital, Ulm, Germany.*

Background: Suppression of genes that are regulated by the nuclear factor of activated T-cells (NFAT) is an effect of calcineurin inhibitors. We correlated the pharmacodynamics to the pharmacokinetics of tacrolimus.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: This study was undertaken in the University Hospitals of Ulm (Frieder Keller) and Heidelberg (Claudia Sommerer, Thomas Giese, Martin Zeier). Tacrolimus trough concentrations (C_{trough}) and 1.5 – 2 hours later the peak concentrations (C_{peak}) were measured by LCMS. Simultaneously, the NFAT trough effect (E_{trough}) and the nadir effect (E_{nadir}) were determined. The pharmacokinetic half-life (T_{1/2}) was estimated from peak (C_{peak}) and trough concentrations (C_{trough}) considering the time distance between steady-state peak and troughs (10.5 – 10 hours). The pharmacodynamic concentration producing the half-maximum effect (CE₅₀) and the Hill coefficient (H) were estimated from trough effect (E_{trough}) at trough concentrations and from nadir effect (E_{nadir}) at peak concentrations. The two equations were solved by numerical iteration for an estimate of the two unknown parameters (CE₅₀, H).

Results: A total of 10 stable kidney transplant patients were included. The median age was 58 years and the median serum creatinine was 306 μmol/l. The pharmacokinetics of tacrolimus were estimated with T_{1/2} = 11 hours, Cl/F = 64 l/h and Vd/F = 480 l. The median value for NFAT was 89% (E_{trough}) of normal gene expression, and the nadir effect was 43% (E_{nadir}) representing the strongest immunosuppression of basal gene expression. The pharmacodynamics of tacrolimus were estimated with CE₅₀ = 7.7 ng/ml and the Hill coefficient with H = 4.6, respectively.

Pharmacodynamic Hill equation

$$CE_{50} = C_{trough} \cdot \left(\frac{E_{max}}{E_{trough} - 1} \right)^{\frac{1}{H}} = C_{peak} \cdot \left(\frac{E_{max}}{E_{nadir} - 1} \right)^{\frac{1}{H}}$$

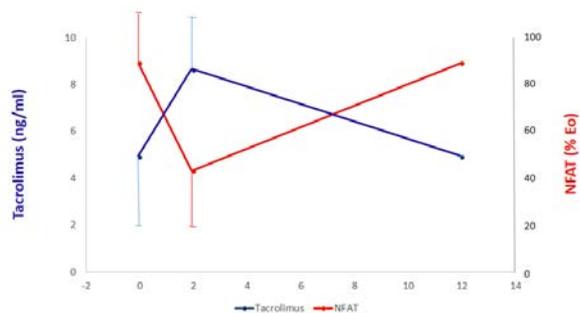


Figure 1: Tacrolimus pharmacokinetics (blue) and pharmacodynamics (red).

Conclusions: While on triple immunosuppression, the NFAT pharmacodynamics indicate a low concentration producing the half-maximum effect and a high Hill coefficient. These findings suggest a narrow trough-to-peak target concentration range of 4.0-to-9.5 ng/ml for tacrolimus.

SA-PO545

2-Sample Iohexol Plasma Clearance: The Clear Choice for Measuring Kidney Function in Rats Mandy E. Turner,¹ Kimberly J. Laverty,¹ Martin Kaufmann,¹ Glenville Jones,¹ Rachel M. Holden,² Michael A. Adams.¹ ¹Biomedical and Molecular Sciences, Queen's Univ, Kingston, ON, Canada; ²School of Medicine, Queen's Univ, Kingston, ON, Canada.

Background: The lack of simple and sensitive tools for longitudinal kidney function assessment in rodent models has impeded analysis of CKD onset and progression and the impact of interventions. This study evaluates 2-sample plasma clearance (pCl) of iohexol, a radio-contrast agent, compared to previously validated inulin pCl in rats to estimate GFR.

Methods: Progressive CKD was induced with a 0.25% adenine diet in male Sprague-Dawley rats (N=8). Following serial tail vein injections of iohexol (51.92 mg/kg) and FITC-inulin (2.5 μL/kg of 5% solution), 12 saphenous blood samples were taken from conscious rats over 5 hours, weekly (control, 5 weeks of adenine). Plasma creatinine was measured via the Jaffrey method, FITC-inulin via fluorometry, and iohexol via UPLC-MS. Two reference methods for pCl calculation were used: a 2-compartment model(2 COM) and trapezoidal approximation(TRA) of area under the curve.

Results: Reference methods of inulin pCl agreed well with iohexol pCl.

Reference Clearance	Comparative Clearance	R ²	%Bias/Precision	15% Accuracy
INU TRA	IHX 2-COM	0.86	6.0±16.9	62.6
	IHX TRA	0.93	3.9±10.9	81.4
	IHX 1-COM	0.93	6.8±13.3	69.8
	Cre	0.53		
INU 2-COM	IHX 2-COM	0.93	15.3±12.7	46.5
	IHX TRA	0.96	13.2±12.3	48.8
	IHX 1-COM	0.96	16.2±10.1	51.2
	Cre	0.58		

pCl of iohexol and inulin was significantly decreased, compared to baseline, after one week (p<0.005), whereas plasma creatinine concentration was not significantly elevated

until the third week (p=0.02). Characterization of a 1-compartment model using 2-samples was employed: samples at 30 and 90 min post injection yielded high agreement (R²=0.98) and no significant bias.

Conclusions: Iohexol pCl sensitively and accurately measures an early decline in kidney function, especially compared to creatinine. The 2-sample method for assessing kidney function is straightforward and is therefore suitable for large rat cohorts. This approach will both enable detection of early kidney disease and facilitate concise interpretation of results derived from pre-clinical studies.

Funding: Government Support - Non-U.S.

SA-PO546

Renal Nitrate Clearance in Chronic Kidney Disease Mark Gilchrist,¹ Jennifer Williams,² Richard D'Souza,² Miranda J. Smallwood,¹ Lindsay Hayman,¹ Angela C. Shore,¹ Paul G. Winyard,¹ Nigel Benjamin.³ ¹NHR Exeter Clinical Research Facility, Univ of Exeter, Exeter, United Kingdom; ²Renal Unit, Royal Devon and Exeter Hospital Foundation Trust, Exeter, United Kingdom; ³Horizon Inst, South Devon Healthcare Foundation Trust, Torquay, United Kingdom.

Background: Endogenously synthesised nitric oxide(NO) is rapidly oxidised to nitrite and nitrate. These oxidation products can be recycled back into nitric oxide via a complex entero-salivary pathway, thus preserving NO activity. It has previously been shown that 60% of circulating nitrate is excreted in the urine in 48 hours with the fate of the remainder unknown. 24hour urinary nitrate excretion is often used to estimate total body nitric oxide synthesis rates. It is not known what effect declining GFR has on renal nitrate clearance.

Methods: 27 subjects, 14M,13F, median age 70 (range 27-74years) with CKD-EPI eGFR between 9 and 89 were recruited. Following 24hrs low nitrate diet plasma nitrate concentration and 24 hour urinary nitrate excretion were measured to determine renal nitrate clearance using a microplate spectrophotometric method.

Results: There was a statistically significant correlation between renal nitrate clearance and eGFR: Pearson r = 0.748, p<0.0001. There was no relationship between plasma nitrate concentration and eGFR, p=0.239, or between plasma nitrate concentration and renal nitrate clearance, p=0.547.

Conclusions: As plasma nitrate concentration is unchanged despite diminished renal nitrate clearance at lower eGFRs, we suggest that non-renal clearance is responsible for a greater proportion of nitrate elimination as GFR falls. We conclude that 24 hour urinary nitrate excretion cannot be considered a reliable measure of total body nitric oxide synthesis in CKD. Elucidating the non-renal pathways of loss of the NO storage molecule, nitrate, may lead to novel therapeutic strategies in CKD and cardiovascular disease.

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The Pharmacodynamic Effect of Tenapanor Is Most Pronounced when Administered Before Food in Healthy Volunteers David P. Rosenbaum,¹ Mikael Knutsson,² Maria Leonsson Zachrisson,² Susanne Johansson.² ¹Ardelex Inc., Fremont, CA; ²AstraZeneca R&D, Mölndal, Sweden.

Background: Tenapanor (AZD1722), a small molecule with minimal systemic availability, is an inhibitor of the Na⁺/H⁺ exchanger NHE3. Tenapanor acts locally in the gut to reduce absorption of sodium (Na) and phosphate. This study evaluated the effect of food intake on the pharmacodynamics of tenapanor.

Methods: In this open-label, 3-way crossover study (NCT02226783), 18 healthy adults (mean age±SD, 35±11 years; 14 men) completed a randomized sequence of 4-day treatments with tenapanor hydrochloride 15 mg bid: before food (5–10 min before breakfast and dinner); after food (30 min after the start of breakfast and dinner); and at fasting (1 h before breakfast, and 3 h after dinner/1 h before an evening snack). There was a 2-day washout between treatments. All participants received the same meals on the same study days; diet was standardized for Na content.

Results: Stool Na content was higher for tenapanor taken before food than for after food or at fasting, with least-squares mean differences significant in both cases (Table). Differences in urinary Na were not significant. The difference in stool phosphorus (P) content was significant for tenapanor taken before food versus at fasting. The difference in urinary P was significant for administration before food or after food versus at fasting. Stool frequency and consistency were similar across treatments, and there were slightly higher stool weights for administration before or after food, compared with at fasting. There were no serious AEs or discontinuations due to AEs.

	Least-squares mean difference (90% CI) in excretion, mmol/day		
	Tenapanor		
	(Before food) – (after food) (n=18)	(After food) – (at fasting) (n=18)	(Before food) – (at fasting) (n=18)
Stool Na	8.8 (3.7, 14)	3.0 (-2.0, 8.1)	12 (6.8, 17)
Urinary Na	0.30 (-11, 11)	-6.8 (-18, 4.1)	-6.4 (-17, 4.5)
Stool P	1.6 (-1.2, 4.5)	3.3 (0.45, 6.1)	4.9 (2.1, 7.7)
Urinary P	-0.24 (-1.9, 1.5)	-3.7 (-5.4, -2.0)	-3.9 (-5.6, -2.2)

Conclusions: The pharmacodynamic effect of tenapanor, as judged by stool Na content, was greatest when tenapanor was taken before food. This supports taking tenapanor before meals in future trials.

Funding: Pharmaceutical Company Support - AstraZeneca

SA-PO548

Triferic Does Not Induce Non-Transferrin Bound Iron or Labile Plasma Iron: In-Vivo/In-Vitro Correlation Raymond D. Pratt,¹ Dorine W. Swinkels,² Carrie D. Guss,¹ Ajay Gupta.¹ ¹R&D, Rockwell Medical Inc., Wixom, MI; ²Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Triferic is a complex iron salt approved for administration via hemodialysate to maintain hemoglobin in patients with CKD 5HD. Triferic crosses the dialyzer membrane and binds to transferrin during hemodialysis replacing the obligatory iron losses in HD patients. Serum iron and transferrin saturation (TSAT) values rise after HD and return to the baseline by the start of the next dialysis session.

Methods: A pharmacokinetic (PK) study in healthy volunteers administered up to 10 mg of Triferic iron over 4 hours and up to 20 mg Triferic iron over 12 hours assessed the PK of serum total iron (sFe-total) and transferrin bound iron (TBI). An *in-vitro* study assessed labile plasma iron (LPI). Triferic iron was added to plasma like medium (40 mg/mL human serum albumin) at a concentration range of 0 to 112 mg/dL. In addition, Triferic was added to 5 different human plasma's (TSAT, range 10 - 46%; total iron binding capacity (TIBC), mean: 374 mg/dL, range: 342-446 mg/dL) across a concentration span up to and exceeding 100% TSAT. LPI was measured in the presence of 40 mM ascorbate using dihydrochlorodamine (DHR)-123 in the presence of 50 mM deferiprone (DFO) to detect iron-catalyzed radical generation.

Results: In the human PK study, sFe-total and TBI showed an identical PK profile. Non-transferrin bound iron (NTBI), calculated as the difference between sFe-total and TBI, showed no dose dependent increase up to a TSAT of 100%. In plasma like medium, LPI increased with increasing concentrations of Triferic iron. When Triferic was added to human plasma, there was a small increase in LPI observed when iron concentrations were less than 100% TSAT. The mean magnitude of LPI (expressed in concentration units) at approximately 100% TSAT was 5.35 mg/dL (mean 1.4% of the total iron concentration). Once 100% TSAT was exceeded, the LPI increased rapidly.

Conclusions: Triferic rapidly donates iron to transferrin *in vivo* and *in vitro*. In vivo, at TSAT less than 100%, NTBI was minimal. In vitro, the LPI results confirm the lack of redox active iron in plasma until the plasma TIBC is exceeded.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO549

Impact of Tubular Luminal H⁺/Organic Cation Antiporter, MATE, on Imatinib-Induced Fluid Retention Moto Kajiwara,^{1,2} Satoshi Masuda.¹ ¹Dept of Pharmacy, Kyushu Univ Hospital, Fukuoka, Japan; ²Dept of Research and Development of Next Generation Medicine, Kyushu Univ, Fukuoka, Japan.

Background: A tyrosine kinase inhibitor, imatinib (IMA) is the first class agent against chronic myeloid leukemia. Although little is known about mechanism involved, more than 50% of imatinib-treated patients suffering from edema. *In vitro* study reported that clinical blood level of IMA inhibits multidrug and toxin extrusion (MATE, SLC47A)-mediated transport of metformine, a hypoglycemic drug. MATE is highly expressed in the brush border membrane of proximal tubular cells mediating the efflux of organic cations, such as metformin, monoamines. The renal dopaminergic system is likely responsible for regulating >50% of net renal salt and water excretion when salt intake increases. In this study, we test a hypothesized that IMA prevents natriuresis by inhibiting MATE-mediated dopamine (DA) secretion into tubule lumen and consequently causes edema.

Methods: C57BL/6 wild type mice (WT) and Mate1 knockout mice (KO) were used. Sodium levels in the urine of mice were measured using an ion-selective electrode. Urinary DA concentration was measured with a liquid chromatography-tandem mass spectrometry.

Results: To determine whether IMA inhibits dopamine uptake by MATE, we examined [³H]DA uptake in HEK293 cells transiently expressed human (h) MATE1, hMATE2-K, and mouse (m) MATE1 in the presence of various concentration of IMA. Uptakes of [³H] DA by those cells were inhibited by IMA in a concentration dependent manner with IC₅₀ values (μM) of 1.1, 13.8, and 100.6, respectively. *In vivo* acute saline-loading experiments were performed to examine inhibitory effect of IMA on urinary DA secretion in WT. In IMA-treated WT, the amount of urinary DA and urinary sodium were decreased to 42% and 27% of that observed in vehicle-treated WT, respectively. Consistently, urinary dopamine was almost undetectable in KO. Furthermore, fraction water weight in mice body was significantly increased in IMA-treated WT compared to vehicle-treated WT (P<0.05).

Conclusions: IMA prevents natriuresis by inhibiting MATE-mediated DA secretion into tubule lumen and consequently causes edema.

Funding: Government Support - Non-U.S.

SA-PO550

Optimizing Between-Patient Variability in Response to Renoprotective Drugs: Meta-Analysis of Rotation Trials Sergei Petrykiv,¹ Dick de Zeeuw,¹ Frederik I. Persson,² Peter Rossing,^{2,3} Hans-Henrik Parving,³ Gozewijn Dirk Laverman,¹ Hidde Jan Lambers Heerspink.¹ ¹Univ Medical Center, Groningen, Netherlands; ²Steno Diabetes Center, Gentofte, Denmark; ³Univ Copenhagen, Denmark.

Background: Individual response to albuminuria lowering intervention is highly variable between patients. To investigate whether uptitrating the dose of drug, changing the mode of intervention (with similar or different drug classes), or lowering dietary sodium intake improves individual response variability, we meta-analyzed individual responses to different modes of anti-albuminuric intervention in non-diabetic and diabetic patients.

Methods: Randomized rotation trials were analyzed to assess correlation of patient-specific responses (n=216 patients) to anti-albuminuric interventions. Included studies (N=20) compared the anti-albuminuric effect of uptitrating the dose of intervention in the RAS (RASi) (N=10 comparisons) and NSAIDs (N=1), rotation within the same class of RASi (e.g. ACEi to ARB; N=5) or NSAIDs (N=1), rotation between RASi and NSAIDs (N=2), and rotation from high to low sodium intake during RASi (N=1). A two stage meta-analysis was performed. First, deemed reversion was conducted in each study to assess correlation in response. Individual study results were then meta-analyzed. Albuminuria was measured in 24-hr urine samples.

Results: The albuminuria response to one dose of RASi or NSAID positively correlated with the response to a higher dose of RASi or NSAID, rotation within the same class of RASi or NSAIDs, rotation between RASi and NSAIDs, and rotation from high to low salt intake. Correlations were consistent in diabetic and non-diabetic patients.

	Correlation	P-value
Uptitration dose of RASi or NSAID	0.73	<0.01
Rotation within class of RASi or NSAID	0.54	<0.01
Rotation between RASi and NSAIDs	0.44	<0.01
Rotation high to low salt intake	0.48	<0.01

Conclusions: The correlations observed in this study indicate that patients poorly responding to one dose or mode of albuminuria lowering intervention also respond poorly to other doses or modes of intervention in the RAS. Whether other drugs targeting pathways beyond the RAS improve individual response variability requires further study.

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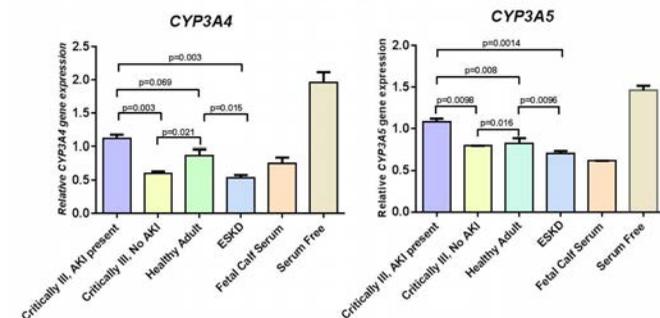
Acute Kidney Injury Serum Upregulates Hepatic Transcription of Cytochrome P450 3A4 and 3A5 Katie Lane,¹ John Dixon,¹ Ekram Nabi,² Barbara J. Philips,¹ Iain Macphree,³ Mark E. Dockrell.² ¹Critical Care, St. George's Univ of London, United Kingdom; ²South West Thames Inst for Renal Research, United Kingdom; ³Renal Medicine, St. George's Univ of London, United Kingdom.

Background: Hepatic drug metabolism by cytochrome P450 3A (CYP) is reduced in end stage kidney disease (ESKD) and acute kidney injury (AKI). The underlying mechanisms are uncertain. Previously we reported suppression of CYP3A4 mRNA transcription when human hepatocytes (HepG2) were exposed to serum from ESKD patients compared to healthy adults. CYP3A4 and 5 protein concentrations were unchanged. We now investigate whether serum from patients with AKI elicits similar results.

Methods: Serum was collected from critically ill adults with varying AKI severity. Sera from KDIGO 0 (n=15) and KDIGO 3 (n=16) AKI patients were applied individually to HepG2s for 24 h, when cells were lysed. CYP3A4 and 3A5 gene expression was examined by RT-qPCR. CYP3A4 and CYP3A5 protein expression was examined by Western blotting. The sera were also applied to HepG2 in a pooled fashion, alongside pooled sera from adults with ESKD prior to hemodialysis (n=10) and healthy adults (n=6), to allow comparison with previous data.

Results: AKI serum exposure doubled CYP3A4 gene expression compared to No AKI serum (p=0.0055 individual and p=0.003 pooled). AKI serum CYP3A5 mRNA increased approx. 25% compared to No AKI serum (p=0.11 individual and p=0.0098 pooled).

Comparison of Pooled Serum (10%) Effects on HepG2 CYP3A4 and CYP3A5 gene expression



CYP3A4 and 3A5 protein concentrations did not differ after exposure to AKI or No AKI sera ($p=0.35$, $p=0.43$).

Conclusions: In contrast to ESKD, hepatocyte exposure to AKI serum upregulates *CYP3A4* and *CYP3A5* transcription compared to No AKI serum. *CYP3A4* and *3A5* protein concentrations were unchanged. Further serum analysis will determine whether differences in inflammatory profiles may be responsible. The results underscore the need to view drug metabolism in AKI as distinct from that in ESKD.

Funding: Private Foundation Support

SA-PO552

The Effect of Gut-Derived Uremic Toxins on the Expression of Hepatic Drug Metabolizing Enzymes in Chronic Kidney Disease Thomas Velenosi, Alvin Tieu, Andrew S. Kucey, David A. Feere, Brad Urquhart. *Physiology and Pharmacology, Univ of Western Ontario, London, ON, Canada.*

Background: Hepatic drug metabolism is altered in patients with chronic kidney disease (CKD). Previous studies suggest that uremic toxins affect drug metabolizing enzymes in CKD. We hypothesize that gut-derived uremic toxins are involved in the downregulation of hepatic drug metabolizing enzymes and that removal of gut-derived uremic toxins by AST-120 will recover hepatic CYP3A and CYP2C enzyme function and expression in rats with CKD.

Methods: Huh7 human hepatoma cells were treated with various uremic toxins as well as a cocktail of all uremic toxins. Chronic kidney disease was induced in male Wistar rats using 0.5% adenine supplemented into rat chow. Control rats were pair-fed to CKD animals. After 5 weeks, control and CKD animals were further divided and received 8% AST-120 or a control diet. Rats were sacrificed 8 weeks after initiation of the study and plasma and liver tissue were obtained.

Results: Indoxyl sulfate caused a concentration-dependent decrease in Huh7 CYP3A4 expression with an IC50 value of 179.8 ± 20.1 μ M. In CKD rats, gut-derived uremic toxins: indoxyl sulfate, p-cresyl sulfate and hippuric acid were significantly increased 4.8-fold, 11.8-fold and 3-fold; respectively, compared to controls. Animals with CKD treated with AST-120 had indoxyl sulfate, p-cresyl sulfate and hippuric acid levels significantly lower than CKD animals and similar to control animals. Hepatic CYP3A2 mRNA expression was significantly decreased by 90% in rats with CKD ($P<0.05$); however, rats with CKD given AST-120 had a 25% recovery in CYP3A2 mRNA expression. Rats with CKD had decreased hepatic CYP2C11 mRNA expression that was not recovered by AST-120.

Conclusions: Uremic concentrations of indoxyl sulfate decreased CYP3A4 mRNA expression in Huh7 cells. AST-120 given to rats with CKD reduced indoxyl sulfate, p-cresyl sulfate and hippuric acid levels similar to control levels. Hepatic CYP3A2 mRNA expression was decreased in CKD and partially recovered by AST-120. AST-120 did not affect the downregulation of CYP2C11 in rats with CKD. Therefore, gut-derived uremic toxins may partially mediate the downregulation of hepatic CYP3A in CKD.

SA-PO553

The Effect of AST-120 on Hepatic and Intestinal Drug Transporter Expression in Chronic Kidney Disease Andrew S. Kucey,¹ Thomas Velenosi,¹ Alvin Tieu,¹ Stephanie E. Nevison,¹ Brad Urquhart,^{1,2} *Dept of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, London, ON, Canada;* ²*Lawson Health Research Inst, London, ON, Canada.*

Background: Chronic kidney disease (CKD) is the progressive decline in renal function over time. There is a marked reduction in both renal and non-renal drug clearance in CKD. AST-120 is an oral adsorbent that promotes the elimination of gut-derived toxins that accumulate in CKD due to impaired clearance. It is hypothesized that there will be a reduction in the expression of drug transporters in CKD conditions. AST-120 will help recover drug transporter expression in CKD by decreasing uremic toxins that accumulate in CKD.

Methods: In vivo: CKD was induced in Wistar rats by treatment with adenine (0.7%) in standard rodent chow for 7 weeks. Treatment groups received AST-120 in the final 3 weeks to decrease the concentration of uremic toxins. Expression of hepatic and intestinal transporters were determined by real-time PCR. In vitro: Using the human hepatoma cell line Huh7, specific uremic toxins (e.g. indoxyl sulfate, p-cresyl sulfate, CMPF) will be tested to see if they directly impair rosuvastatin transport. Rosuvastatin uptake will be measured with ultra-performance liquid chromatography coupled to mass spectrometry.

Results: Preliminary results have shown that OATP2 expression is decreased by 25% in CKD rat livers compared to control. Treatment with AST-120 causes a significant reduction in the plasma concentration of the uremic toxins indoxyl sulfate and p-cresyl sulfate. AST-120 treatment restores OATP2 expression to control levels.

Conclusions: Decreased hepatic OATP2 expression in CKD will result in reduced clearance of substrate drugs. This could lead to toxicity if a lowered dose is not administered. On average a CKD patient will be co-prescribed 10 different drugs. Clarifying the impact of CKD on drug transporter expression and activity will help guide dosing in this patient population.

SA-PO554

Patient Characteristics and Genetics Contribute to Kidney Function After Cisplatin Therapy Cara A. Chang,¹ Nickie L. Johnston,¹ Madeleine Gomez,¹ Lucas Ellison,¹ Lauren Aleksunes,² Steven R. Kleeberger,³ Daniel Bowles,¹ Cindy L. O'Bryant,¹ Melanie S. Joy,¹ *¹Skaggs Schools of Pharmacy and Medicine, Univ of Colorado, Aurora, CO;* *²Ernest Mario School of Pharmacy, Rutgers Univ, NJ;* *³NIEHS.*

Background: It is known that kidney function can decline after a single dose of cisplatin necessitating alternate chemotherapeutic regimens. The current study explored the contribution of patient characteristics and polymorphisms in drug metabolism and transport genes relevant to cisplatin kidney disposition on changes to renal function.

Methods: Blood (5mL) was obtained from patients (n=206) who received cisplatin. Genotyping assessments included candidate SNPs in kidney uptake and efflux transporters (*SLC22A2*, *ABCC2*, *SLC47A1*) and metabolism pathways (*GSTA1*, *GSTP1*, *GGT1*). Genotyping was performed using QuantStudio multiplex assays and coded [0(wt/wt), 1(wt/var), or 2(var/var)]. Glomerular filtration rate (GFR, mL/min/1.73m²) and changes from pre-cisplatin to the time just prior to the second dose were calculated. Univariate and multivariate analyses were performed using patient characteristics and genotyping results.

Results: Patient demographics (mean \pm sd) included: age 53 \pm 14 y, weight 80 \pm 20 kg, BSA 1.9 \pm 0.3, Caucasian 90%, gender (50%M/50%F), and cisplatin dose (65 \pm 23 mg/m²). Specific patient characteristics that significantly ($p<0.05$) contributed to a beneficial effect on GFR were non-Caucasian race, baseline GFR, and non-fractionated cisplatin dosing. Genetic variant in *GSTP1*/GST pi-1 variant (rs1695) and wildtypes in *SLC22A2*/OCT2 (rs2279463 and rs3127573) significantly ($p<0.05$) contributed to a beneficial effect on GFR. Variables retained in the final model (R^2 25.25%, $P<0.0001$) were: Change in GFR = $38.983 - 0.1714$ (weight) - 0.3685 (baseline GFR) + 5.893 (*GSTP1*; rs1695).

Conclusions: The results from this study demonstrate the combined role of patient characteristics and genetic variants in drug disposition genes on changes to GFR secondary to cisplatin. Appropriate risk stratification based on patient characteristics and genetics may be used to apply precision medicine to reduce the risk of kidney injury from cisplatin and potentially other nephrotoxins.

Funding: NIDDK Support

SA-PO555

Influence of Genetic Variations in Fcγ Receptors (FcγR) and Cytochrome P450 (CYP450) Enzymes on Treatment Outcomes in ANCA-Associated Vasculitis (AAV) Divya Indrakanti,¹ Rodrigo Cartin-cesa,² Gary S. Hoffman,³ Cees Kallenberg,⁴ Carol Langford,³ Peter A. Merkel,⁵ Paul Monach,⁶ Robert Spiera,⁷ E. William St. Clair,⁸ Ulrich Specks,² John H. Stone,⁹ Daniel J. Birmingham,¹ Brad H. Rovin.¹ *¹The Ohio State Univ Wexner Medical Center, Columbus, OH;* *²Mayo Clinic and Foundation;* *³Cleveland Clinic Foundation;* *⁴Univ of Groningen, Netherlands;* *⁵Univ of Pennsylvania;* *⁶Boston Univ School of Medicine;* *⁷Hospital for Special Surgery;* *⁸Duke Univ Medical Center;* *⁹Massachusetts General Hospital.*

Background: The Rituximab in AAV (RAVE) trial compared rituximab (RTX) to cyclophosphamide (CYC) for the treatment of AAV. Using the RAVE cohort we investigated whether known single nucleotide polymorphisms (SNPs) in FcγR or CYP450 enzyme genes were associated with the response to RTX and CYC treatment, respectively.

Methods: SNPs for FcγR (FcγRIIA 491G>A, FcγRIIB 695T>C, FcγRIIIA 559T>G) and CYP450 (CYP2B6 1459C>T, CYP2C19 681G>A) were analyzed by direct sequencing of PCR-amplified genomic DNA. Each SNP was tested as a predictor of the primary outcome, complete remission at 6 months, using logistic regression including the covariates baseline BVAS/WG, ANCA type, and new versus relapsing disease. The association of these SNPs with the trial's secondary outcomes, including time to complete remission, time to relapse, and time to B-cell reconstitution, were analyzed by Kaplan-Meier and Cox proportional hazard ratios.

Results: No significant associations were identified between FcγRIIA, FcγRIIB, FcγRIIIA, CYP2B6 or CYP2C19 SNPs and the primary outcome. However, the 491AA genotype of FcγRIIA was associated with a shorter time to complete remission (183 \pm 47 versus 241 \pm 114 days) to complete remission (n=52, $p<0.001$) in the entire cohort.

Conclusions: None of the SNPs tested influenced response to treatment with RTX or CYC in AAV. The finding that FcγRIIA 491G>A was associated with a shorter time to complete with both RTX and CYC implies FcγRIIA may be involved in disease pathogenesis and response to therapy.

Funding: Pharmaceutical Company Support - Genentech

SA-PO556

The *GSTA1* Polymorphism and Cyclophosphamide Therapy Outcomes in Lupus Nephritis Patients Na Hong Wang, Jun Xue. *Nephrology, Nephrology, Shanghai, China.*

Background: Pulsed low-dose cyclophosphamide (CTX) therapy has become the most effective approaches in improving the clinical outcomes of lupus nephritis (LN) patients. However, variations in CTX therapeutic outcomes in LN patients are incompletely understood.

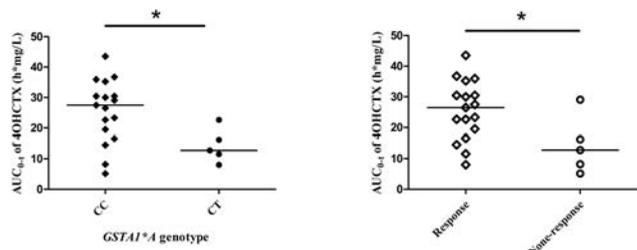
Methods: We investigated the contributions of known allelic variants in *CYP2B6*, *CYP2C19*, *CYP3A5*, *GSTA1*, *GSTP1*, *ABCC1* and *ABCC4* genes to CTX therapy outcomes

in LN patients. Pharmacokinetics of CTX and 4-hydroxycyclophosphamide (4OHCTX) were obtained from 22 patients randomly enrolled from 77 LN patients and applied to explore the mechanism.

Results: GSTA1, one of detoxification enzymes to CTX, gene polymorphism could greatly influence the therapeutic outcome to CTX treatment in these 77 LN patients. LN patients with a GSTA1*A mutation (CT heterozygous) had a risk of none-response ($P=0.005$).

Genotype	No. of patients response	No. of patients none-response	P
CYP2B6*4 AA(n=38) GA/GG(n=39)	33 29	5 10	0.25
CYP2C19 GG(n=31) GA/AA(n=46)	24 38	7 8	0.57
CYP3A5 GA/AA (n=40) GG(n=37)	35 27	5 10	0.15
ABCC1/MRP1 CT/TT(n=63) CC(n=14)	50 12	13 2	0.73
ABCC1/MRP1 GG(n=67) GT(n=10)	52 10	15 0	0.20
ABCC4/MRP4 GG(n=35) GT/TT(n=42)	28 34	7 8	1
GSTA1*A CC(n=59) CT(n=18)	52 10	7 8	0.005**
GSTA1*B GG(n=60) GA/AA(n=17)	50 12	10 5	0.30
GSTP1 AA(n=45) GA/GG(n=32)	38 24	7 8	0.39

Pharmacokinetics data indicated that patients with a GSTA1*A heterozygous variant had a lower exposure to 4OHCTX compared to wild-type patients (12.8(9.8, 19.5) h*mg/L vs. 27.5 (18.1, 32.8) h*mg/L, $P=0.023$), but not CTX. And clinical efficacy was significantly related to higher exposure to 4OHCTX, $P=0.038$.



Conclusions: LN patients with GSTA1*A heterozygous genotypes had poor CTX treatment response due to less exposure to activated 4OHCTX. A pharmacogenomic approach using the GSTA1 SNP may be useful for predicting clinical efficacy to CTX therapy in LN patients, and facilitating individualized therapy.

SA-PO557

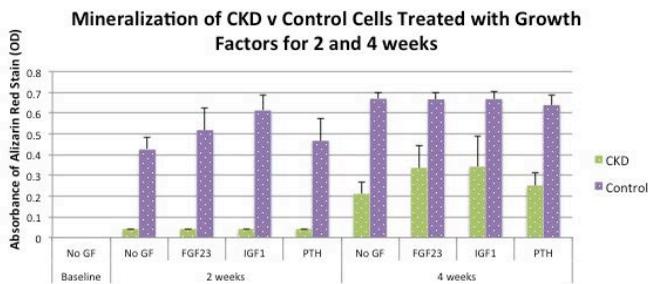
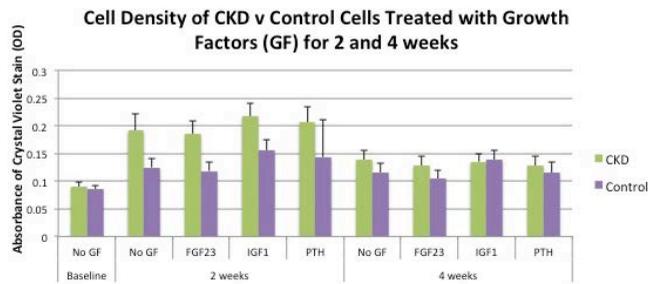
Effect of Growth Factors on Bone Mineralization in Health and CKD
Nadine Khouzam,¹ Renata C. Pereira,¹ Isidro B. Salusky,¹ Richard E. Bowen,² Katherine Wesseling-Perry.¹ ¹Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; ²Orthopedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, United Kingdom.

Background: Children with chronic kidney disease (CKD) develop unexplained resistance to PTH and GH. Moreover, bone expression of FGF23 is very high in CKD. Data suggest that FGF23 may directly suppress osteoblast maturation and mineralization in mice (Weng JBMR 2009); however, it is not known whether excess expression of this hormone has direct effects on bone cells in CKD. We have previously demonstrated that primary osteoblasts isolated from patients with CKD have defects in maturation and mineralization, even when removed from the uremic milieu. We thus hypothesized that CKD-mediated alterations in osteoblast maturation may contribute to a blunted response to growth factors in pediatric CKD.

Methods: Human osteoblasts isolated from 3 patients with CKD and 3 normal controls were grown to confluence and induced to mineralize. Cells were treated twice weekly with fresh media and 100 nm of PTH, 200ng/mL of IGF1 or 10ng/mL of FGF23 for 0, 2 and 4 weeks. Cell density and mineralization were assessed by staining parallel wells with crystal violet and alizarin red respectively and quantified using spectrophotometry.

Results were expressed as the mean (+ SE) in optic density. A mixed model was used to test differences in proliferation between CKD cells and healthy controls and between hormone dosages over time.

Results: Cells from CKD patients mineralized at a slower rate than cells from normal controls ($p<0.05$). The addition of growth factors did not have a significant effect on the rate of mineralization for the sample size used.



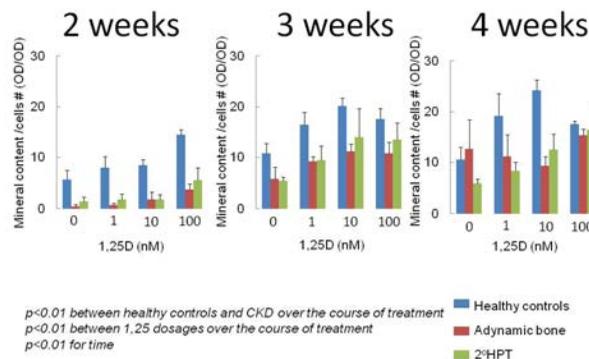
Conclusions: Diminished mineralization is present in CKD; as previously demonstrated in pediatric patients. Further studies are required to assess whether PTH, IGF1 and FGF23 have an effect on mineralization of human osteoblasts.

SA-PO558

CKD Induces Intrinsic Alterations in Osteoblast Response to 1,25D
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Background: Skeletal mineralization defects are common in pediatric CKD patients. In vivo 1,25(OH)₂vitamin D (1,25D), the only currently approved therapy for the treatment of 2°HPT in children, fails to normalize skeletal mineralization in these patients. We have recently demonstrated that primary osteoblasts obtained from patients with CKD have altered proliferation, differentiation and mineralization characteristics, suggesting that CKD results in intrinsic changes to osteoblast biology, independent of circulating mineral ion and hormone concentrations.

Methods: To evaluate the interaction between CKD and 1,25D therapy on osteoblast maturation and mineralization, primary human osteoblasts from 3 healthy controls, 3 pediatric dialysis patients with low bone turnover (adynamic bone) and 3 pediatric patients with high bone turnover (2°HPT) were cultured under pro-mineralizing conditions consisting of 10mM β-glycerolphosphate and 100 ug/ml ascorbic acid in the presence of 1,25D at 1, 10, and 100 nM. After 2, 3, and 4 weeks of growth under mineralizing conditions, cells were washed with PBS, fixed with 10% formalin, and stained with 2% Alizarin Red S. The amount of mineral content was assessed by measuring absorption of acetic acid-extracted Alizarin Red S dye (at 405 nm) normalized by live cell concentration (as assessed by absorption (at 570 nm) of methanol-extracted Crystal Violet staining obtained from parallel cultures).



Results: 1,25D treatment decreased proliferation and increased mineralization; however, high concentrations were required in cells from CKD patients (Figure).

Conclusions: CKD induces osteoblast resistance to 1,25D.
Funding: NIDDK Support, Private Foundation Support

SA-PO559

Fourier Transform Infrared Spectroscopy Crystallinity Indices in Bone from Patients with ADPKD Renata C. Pereira,¹ Berenice Y. Gitomer,² Isidro B. Salusky,¹ Diana George,² Jason W. Stoneback,³ Karen B. King,³ Myles S. Wolf,⁴ Michel Chonchol.² ¹*Pediatrics, UCLA, Los Angeles, CA;* ²*Medicine, Univ of Colorado, Aurora, CO;* ³*Orthopaedics, Univ of Colorado, Aurora, CO;* ⁴*Nephrology, Northwestern Univ, Chicago, IL.*

Background: We have previously shown that patients with autosomal dominant polycystic kidney disease (ADPKD) and normal kidney function have a low bone turnover state. This is coupled with increased expression of fibroblast growth factor 23, dentin matrix protein 1 and osteopontin in bone compared to healthy controls. To further characterize the bone defect in ADPKD Fourier transform infrared (FTIR) spectroscopy was undertaken.

Methods: ADPKD patients with an average eGFR 111 mL/min/1.73m² and normal parathyroid hormone levels underwent standard tetracycline double labeling prior to transiliac crest bone biopsy. FTIR imaging was performed on bone sections from 6 ADPKD patients and 6 age and sex matched healthy historical controls.

Results: The mean (SD) age and eGFR of ADPKD patients were 29±4 yrs and 115 mL/min/1.73m², respectively. The sex distribution was 5 males and 1 female. Crystallinity a measure of the size of mineral crystals and the degree of order within the crystals was obtained by FTIR and differed significantly between ADPKD and control samples. The differences were more pronounced in the cortices (1.22 vs. 1.19; p = 0.03) than in the trabeculae (1.19 vs. 1.17; p= 0.48). There were no significant differences in heterogeneity of crystallinity, mineral/matrix, carbonate/mineral, collagen maturity (cross links) or acid phosphate substitution between ADPKD and historical control samples.

Conclusions: We describe for the first time a significant difference in the chemical composition of cortical bone measured by FTIR in patients with ADPKD when compared to historical control bone samples. Bone crystallinity has been associated with bone strength and stiffness, it is thus intriguing to hypothesize that the observed changes may impact bone quality and expression of bone proteins in ADPKD. Future studies that also assess bone strength and elasticity will be required to more fully investigate bone quality in ADPKD.

Funding: NIDDK Support

SA-PO560

Late Onset Avascular Osteonecrosis in Renal Transplant Recipients Spyridon Arampatzis, Anita Maurer, Vasileios Devetzi, Uyen Huynh-do. *Nephrology, Hypertension and Clinical Pharmacology, Uni. Hospital Bern, Nelspital, Bern, Switzerland.*

Background: Avascular osteonecrosis (AO) after renal transplantation (RT) is a debilitating skeletal complication. In most studies patients with AO presented within the first 24 months after RT. In order to determine the prevalence and therapeutic outcome of late onset AO (>24 months after RT) we conducted a single-center retrospective study based on radiological/histological confirmed cases.

Methods: We conducted a single-center retrospective study among our RTR with a clinical diagnosis of AO over the past two decades. We evaluated 70 cases with a AO. In 46 patients AO was radiological/histological confirmed and all relevant clinical, radiological and laboratory data were extracted and analyzed.

Results: The average follow-up time was 14 (±8) years after the first RT. The prevalence of AO was 5.4%. Overall, 41 patients showed AO of the femoral head, 23 bilateral AO of the femoral head, 5 of the knee and 5 of other locations, while 43 patients were symptomatic at time of diagnosis. In our cohort 71% presented late onset (>24 months) AO after RT. On average, AO was diagnosed 90 months after RT (SD±78). Furthermore, RTR with late onset were younger at the time of first RT (39±15 years, p<0.01) than the ones with early onset (53±14). A considerably higher cumulative dose of prednisone was administered to patients with late onset of AO prior to their first AO (21±11g vs. early onset 4±1g, p-value <0.001) and a higher percentage of late onset RTR received corticosteroids even prior to their first RT (48%) compared to the group of early onset (15%; p=0.038). Overall, 34% of the patients presented with an advanced stage of AO Ficat III or IV at first diagnosis of AO and 57% needed total hip arthroplasty.

Conclusions: Late onset avascular necrosis represent a corticosteroid related complication, with a particularly high prevalence among young RTR and is associated with significant morbidity. The majority of AO patients have a bilateral manifestation and present with advance structural femur failure resulting in hip replacement.

SA-PO561

Indoxyl Sulfate Exacerbates Low Bone Turnover Induced by Parathyroidectomy in Rats Junya Hirata,¹ Kazuya Hirai,¹ Hirobumi Asai,¹ Masaki Inada,² Chisato Miyaura,² Hideyuki Yamato,¹ Mie Watanabe-Akanuma.¹ ¹*Kureha Corporation, Tokyo, Japan;* ²*Tokyo Univ of Agriculture and Technology, Tokyo, Japan.*

Background: Low-turnover bone disease is one of the bone abnormalities observed in chronic kidney disease (CKD) patients and recognized to be associated with low serum parathyroid hormone (PTH) level and skeletal resistance to PTH. Indoxyl sulfate (IS) is a representative uremic toxin that accumulates in the blood as renal dysfunction progresses in CKD patients. In order to examine whether IS exacerbates low bone turnover, we produced rats with low bone turnover by parathyroidectomy (PTX) and fed these rats a diet containing indole, a precursor of IS, to elevate blood IS level from indole metabolism.

Methods: Male SD rats were underwent PTX. From 2 weeks after PTX, the rats were fed a diet containing 0.5% indole (w/w) for 4 weeks. Serum IS levels and bone

metabolism related markers were examined periodically. After the end of indole treatment, histomorphometric analyses in the secondary spongiosa of the femur and measurement of bone mineral density of the tibia were performed.

Results: Histomorphometric analyses revealed significant decreases in both bone formation-related parameters (mineralized surface/ bone surface, bone formation rate/ bone surface) and bone resorption-related parameters (eroded surface/ bone surface, osteoclast surface/ bone surface) in PTX rats. In indole-treated PTX rats, further decreases in bone formation-related parameters were observed. On the other hand, there were no decreases in bone resorption-related parameters in indole-treated PTX rats when compared to the PTX rats. Serum IS levels in indole-treated PTX rats were elevated during the indole treatment period and the levels were similar to those in CKD and dialysis patients.

Conclusions: IS exacerbates low bone turnover through inhibition of bone formation by mechanisms unrelated to skeletal resistance to PTH in rats. Our data suggest that IS may be one of the uremic toxins that contribute to progression of low-turnover bone disease in patients with CKD or on dialysis whose serum IS levels are elevated because of renal dysfunction.

SA-PO562

Changes of Marrow Adipocyte Away from Bone Surface After Parathyroidectomy in Patients with Secondary Hyperparathyroidism Aiji Yajima, Ken Tsuchiya, Kosaku Nitta. *Medicine, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: We've already reported that marrow adipocytes proliferated around bone surface after parathyroidectomy for secondary hyperparathyroidism. However, fibrous volume was reduced near bone surface where adipocytes proliferated after the surgery. In addition, adipocytes may be associated with bone remodeling, because adipocytes suppress the function of osteoblasts. Therefore, the parameters of marrow adipocyte, which are away from bone surface were histomorphometrically measured before and after parathyroidectomy for secondary hyperparathyroidism.

Methods: Sixteen hemodialysis (HD) patients suffering from secondary hyperparathyroidism (Age: 58.4 ± 8.4 years, HD duration; 14.3 ± 6.8 years) were treated by total parathyroidectomy with immediate autotransplantation (parathyroidectomy) and received iliac bone biopsies before and at 1 week (n=4) and at 4 weeks (n=10) after parathyroidectomy. Adipocyte volume per marrow volume (Fa.V/Ma.V:%), adipocyte number per marrow volume (N.Fa/Ma.V:/mm²), and mean adipocyte volume (Fa.V/N.Fa (×10⁻³ mm²/N) were obtained in the area away from bone surface. If there are so many artifacts in bone marrow, the bone samples were excluded from this research.

Results: Serum intact parathyroid hormone (i-PTH) level was decreased from 1268.8 ± 459.6 to 18.5 ± 7.9 pg/mL. Fa.V/Ma.V was significantly increased from 22.4 ± 6.3 to 30.9 ± 8.1 % (P<0.001), N.Fa/Ma.V was also increased from 183.3 ± 48.1 to 217.7 ± 47.1 N/mm² (P<0.001), and Fa.V/N.Fa was not changed (1626.9 ± 418.5 to 1668.7 ± 548.1 (×10⁻³ mm²/N) after parathyroidectomy.

Conclusions: The facts substantiate that an acute reduction of PTH induced an increase of adipogenesis. As reported previously, osteoblast surface transiently increased at 1 week after parathyroidectomy, but it acutely decreased at 4 weeks after the surgery. These findings mean that undifferentiated stem cells went to the adipogenesis after the acute reduction of PTH in patients receiving HD.

Funding: Private Foundation Support

SA-PO563

Evaluation of Marrow Adiposity in Patients Pre and Post-Kidney Transplantation: Comparison Between Bone Histomorphometry Mariel Jose Hernandez,¹ Luciene dos Reis,² Igor Marques,² Fellype C. Barreto,³ Elias David-Neto,⁴ Rosa M.A. Moyses,^{2,5} Ezequiel R. Bellorin-Font,¹ Vanda Jorgetti.² ¹*Nephrology Div, Univ Central de Venezuela, Caracas, Venezuela;* ²*Nephrology Div, Univ de Sao Paulo, Sao Paulo, Brazil;* ³*Medical School, Pontificia Univ Católica, Curitiba, Brazil;* ⁴*Urology Div, Univ de Sao Paulo, Sao Paulo, Brazil;* ⁵*UNINOVE.*

Background: The osteoblasts (Obs) and adipocytes (Ads) derive from the mesenchymal cells (MSCs). An imbalance in the differentiation of Obs and Ads could be decisive to preserve the integrity of bone. We analyzed bone histomorphometry and marrow adiposity in bone biopsies from patients before and after kidney transplantation (KT).

Methods: We compared biochemical parameters and bone histomorphometry data from 23 patients, before and one year after KT, under standard immunosuppressive therapy including glucocorticoids. Adipocytes area (Ad.Ar/T.Ar,%), number (N.Ad/B.Pm,n/mm), and the ratio adipocytes/active osteoblasts (N.Ad/N.AcOb), and adipocytes/total osteoblasts (N.Ad/N.TOb) indexes were measured.

Results: Our patients were young (42.3±2.6 years) and mostly male (14). One year after KT, PTH levels (515.6±424.1 vs. 96± 137.1), bone alkaline phosphatase (98.2±63.9 vs. 37.4± 26.6) and sclerostin (1.1±0.8 vs. 0.5± 0.1) decreased significantly. A significant increase in Ad.Ar/T.Ar (24.3±11.6 vs. 30.6±10.5), N.Ad/B.Pm (37.3±20.6 vs. 47.9±25), N.Ad/N.AcOb (240.4±657.6 vs. 674.6±1192.4) and N.Ad/N.TOb (128.2±362.3 vs. 230.5±642.4) and a decreased osteoblast number/tissue area (22.8±21.9 vs. 5.3±2.8) was observed. In the post-transplant biopsies significant correlation was found between N.Ad/N.TOb and PTH (r=-0.48), trabecular number -Tb.N (r=-0.29) and mineral apposition rate (r=-0.23); as well as between Ad.Ar/T.Ar and bone volume (r=-0.36) and between N.Ad/B.Pm and Tb.N (r=-0.72).

Conclusions: KT improved biochemical findings related to bone mineral disease, however, this condition is also clearly associated with an inverse relationship of the bone

mass and osteogenic cellularity with marrow adiposity, compromising dynamic parameters. MSCs differentiation is competitively balanced; mechanisms that promote one cell fate actively suppress mechanisms that induce the alternative.

SA-PO564

High Marrow Adiposity Is Associated with Low Turnover Bone Disease in Peritoneal Dialysis Patients Felype C. Barreto,¹ Rodrigo Azevedo de Oliveira,⁵ Mariel Jose Hernandez,⁶ Ana Clara Simões Flório Almeida,¹ Luciene dos Reis,² Aluizio B. Carvalho,³ Vanda Jorgetti,² Rosa M.A. Moyses,^{2,4} ¹Pontificia Univ Católica do Paraná; ²Univ de São Paulo; ³Univ Federal de São Paulo; ⁴Univ Nove de Julho, UNINOVE; ⁵Univ Federal do Rio Grande do Norte; ⁶Univ de Caracas.

Background: Marrow adiposity has been implicated in the pathogenesis of bone disorders, such as osteoporosis and bone fragility. We sought to investigate the relationship between marrow adiposity and renal osteodystrophy in peritoneal dialysis patients.

Methods: We analyzed transiliac bone biopsy specimens from 41 peritoneal dialysis patients (age: 50.3±10.2 yrs) by quantitative histomorphometry to assess bone and marrow adipocyte parameters. Selected biochemical parameters, such as serum markers of bone turnover and sclerostin, were measured.

Results: Adipocyte area (Ad.Ar), perimeter (Ad.Pm) and percentage of adipocyte volume per marrow volume (Ad.V/Ma.V) correlated positively with age. Diabetic patients had higher marrow adiposity than non diabetic patients (Ad.V/Ma.V = 50±14 vs 39±12%; P=0.009; Ad.Ar=0.19±0.06 vs 0.15±0.05 mm²; P=0.02). Ad.V/Ma.V demonstrated inverse association with bone specific alkaline phosphatase (r = -0.32; P=0.04) and direct relationship with sclerostin (r=0.38; P=0.01). No association was found between marrow adiposity and dynamic bone histomorphometric parameters. Interestingly, patients with Ad.V/Ma.V > 41% (median) presented higher percentage of low turnover bone disease (P=0.04) as well as significantly lower bone specific alkaline phosphatase (39.5±27.3 vs 65.3± 28.9 U/L; P=0.006) and higher sclerostin (2.3±0.97 vs 1.6±0.97 ng/mL ;P=0.02) levels than patients below the median.

Conclusions: Increased marrow adiposity seems to be associated to lower osteoblast activity and to low turnover bone disease in peritoneal dialysis patients. The higher marrow fat in diabetic and aged patients might expose them to an increased risk for fracture. Further studies are required to understand the possible contribution of marrow adiposity to the pathogenesis of renal osteodystrophy.

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SA-PO565

Role of Wnt10b Signaling in Cinacalcet-Induced Bone Anabolic Effects Cai-Mei Zheng,^{1,2} Yung-Ho Hsu,^{1,2} Yuh-feng Lin,^{1,2} Jia-Fwu Shyu,^{1,3} Kuo-cheng Lu.^{1,4} ¹Graduate Inst of Clinical Medicine, Taipei Medical Univ, Taipei City, Taiwan; ²Dept of Nephrology, Shuang Ho Hospital, New Taipei City, Taiwan; ³Biology and Anatomy, National Defense Medical Center, Taipei City, Taiwan; ⁴Dept of Medicine, Cardinal-Tien Hospital, New Taipei City, Taiwan.

Background: Chronic kidney disease-mineral bone disorders (CKD-MBD) is important for osteoporosis and bone fractures in CKD patients. Since calcium receptor plays an important role in osteoclast differentiation, we assume that calcimimetic agents (cinacalcet) might have a role in bone remodeling.

Methods: Bone marrow mononuclear cells isolated from rat femur and tibia were induced into osteoclasts by M-CSF and RANKL treatments. Osteoclasts were treated with different doses of cinacalcet. Untreated osteoclasts used as control. The release of Clastokine Wnt10b was measured by ELISA and Western blot. Alizarin red staining was used to evaluate mineralization of osteoblasts co-cultured with osteoclasts. Fluo-4 AM stain was used to determine intracellular calcium changes. Cinacalcet treated and untreated CKD animal models (5/6 nephrectomy) were used to analyse the changes in clastokines and bone mineral density.

Results: In osteoclasts, cinacalcet decrease the TRAP stain reaction. However, ELISA analysis showed increases of Wnt10b expression in supernatant collected from the cinacalcet-treated osteoclasts. Pretreatment of Wnt10b secretion inhibitor, C-59, blocked the increase of Wnt10b induced by cinacalcet. Western blot analysis showed an increase intracellular Wnt10b in the cinacalcet-treated osteoclasts. Culture of osteoblasts with the cinacalcet-treated osteoclasts supernatant showed an increase of mineralization as indicated by alizarin red staining. Intracellular calcium staining is increased in cinacalcet-treated osteoclasts, which demonstrated its effect on osteoclast Wnt 10b release is through intracellular calcium oscillation. Clastokines and bone mineral density (BMD) changes are also noted in CKD rats before and after cinacalcet treatment.

Conclusions: Cinacalcet decrease osteoclastic activity, but increase the secretion of Wnt10b through intracellular calcium oscillation. Cinacalcet also related with certain clastokine and BMD changes in CKD animals.

SA-PO566

Changes of Osteocyte Number in Micropetrosis Area After Treatment of Secondary Hyperparathyroidism Aiji Yajima, Ken Tsuchiya, Kosaku Nitta. *Medicine, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Osteocyte number decreased after total parathyroidectomy with immediate autotransplantation (parathyroidectomy) for secondary hyperparathyroidism in hemodialysis (HD) patients (JBMR 2010). Osteocyte number in micropetrosis area and in the other area was measured before and after parathyroidectomy and treatment with cinacalcet hydrochloride (HCL).

Methods: Thirteen HD patients received parathyroidectomy and transiliac bone biopsies before and at 3-9 weeks after parathyroidectomy (Group I). And eight HD patients with secondary hyperparathyroidism were treated by cinacalcet HCL and received bone biopsies before and at 1 year after the treatment (Group II). Osteocyte number in micropetrosis area (N.Ot/Mp.V;N/mm²) and in the other area (N.Ot/(BV-Mp.V);N/mm²) were measured before and after the treatment.

Results: Serum intact parathyroid hormone (i-PTH) levels decrease from 1186.5 ± 768.3 to 24.8 ± 8.1 pg/ml after parathyroidectomy. N.Ot/Mp.V was decreased from 159.8 ± 71.2 to 110.1 ± 87.3 N/mm² (P<0.001), and N.Ot/(BV-Mp.V) was not changed (from 236.1 ± 69.3 to 262.2 ± 79.3 N/mm²) after parathyroidectomy (Group I). Serum i-PTH levels decrease from 903.6 ± 503.0 to 212.7 ± 98.1 pg/ml after the treatment with cinacalcet HCL. N.Ot/Mp.V was not changed in both micropetrosis area (100.1 ± 68.2 to 99.6 ± 76.1 N/mm²) and in the other area (from 240.1 ± 56.3 to 279.6 ± 88.6 N/mm²) after the treatment (Group II).

Conclusions: Cinacalcet HCL did not reduce osteocyte number in both micropetrosis area and in the other area, suggesting that this agent improves bone quality by maintaining osteocytic perilacunar/canalicular system. Parathyroidectomy reduces osteocyte number in only the micropetrosis area.

Funding: Private Foundation Support

SA-PO567

Trabecular Bone Score in Kidney Transplant Recipients Kyla Lynn Naylor,¹ Lisa M. Lix,² Didier Hans,³ Amit X. Garg,^{1,4,5} David N. Rush,² William Leslie.² ¹Western Univ; ²Univ of Manitoba; ³Lausanne Univ Hospital; ⁴London Health Sciences Centre; ⁵Inst for Clinical Evaluative Sciences.

Background: Kidney transplant recipients have altered bone mineral metabolism and are at a higher risk of fracture compared to the general population. There is conflicting evidence regarding the ability of bone mineral density (BMD) to accurately predict fracture. Trabecular bone score (TBS) is a texture measure derived from dual energy x-ray absorptiometry (DXA) lumbar spine images which provides information independent of BMD. We assessed TBS in kidney transplant recipients.

Methods: We included 327 kidney transplant recipients from Manitoba, Canada, who received a post-transplant DXA (median 106 days post-transplant). We matched each kidney transplant recipient (mean age 45 years, 39% men) to three controls from the general population (matched on age, sex, and date of DXA). Lumbar spine (L1-L4) DXA images were used to derive TBS. Non-traumatic incident fracture (excluding hand, foot, and craniofacial) (n=31) were assessed during a mean follow-up of 6.6 years. We used logistic regression to determine predictors of TBS and hazard ratios per standard deviation decrease in TBS to express the gradient of risk for fracture prediction using Cox proportional hazards regression.

Results: Compared to the general population, kidney transplant recipients had a significantly lower lumbar spine TBS (1.41 ± 0.13 versus 1.37 ± 0.13, p<0.001). Multiple logistic regression revealed reduced TBS (lowest versus highest tertile) in kidney transplant recipients compared to the general population (adjusted odds ratio, 2.13 95% confidence interval [CI] 1.47-3.07). TBS predicted fractures in kidney transplant recipients independent of the Fracture Risk Assessment (FRAX) score and spine BMD (adjusted hazard ratio per standard deviation decrease in TBS 1.57, 95% CI 1.07-2.29).

Conclusions: Kidney transplant recipients had abnormal bone texture as assessed by TBS. Lumbar spine TBS was able to predict incident fractures in kidney transplant recipients and may provide novel insights into skeletal fragility in this unique population.

SA-PO568

Low Bone Turnover Disease Is Prevalent 1 Year After Successful Renal Transplantation: A Cross-Sectional Bone Biopsy Study Pieter Evenepoel,¹ Patrick C. D'Haese,² Liesbeth Viaene,¹ Geert J. Behets.² ¹Nephrology, Univ Hospitals Leuven, Leuven, Belgium; ²Pathophysiology, Univ of Antwerp, Antwerp, Belgium.

Background: Studies evaluating bone histomorphometry in renal transplant recipients are scanty and so far hampered by small sample size and heterogeneity.

Methods: We evaluated bone histomorphometry (according to TMV classification), laboratory parameters of mineral metabolism (including biPTH, FGF23, sclerostin, OPG, sRANKL), biomarkers of bone formation (bsAP) and bone resorption (TRAP5b, NTX), and inflammation (IL6) in an unselected cohort of 60 renal transplant recipients (44 males, age 56±12 yrs) 1 year after successful transplantation (NCT01886950). Standard immunosuppressive regimen consisted of steroids, a calcineurin inhibitor and mycophenolate mofetil. Mean cumulative methylprednisolone dose at 1 year was 1.7 g/d.

Results: Sixty-five % of the patients presented with disturbances in at least one of the TMV parameters. High, normal and low bone turnover disease were observed in 1.7, 45.0, and 53.3 % of renal transplant recipients, respectively. Mineralization was delayed in 17.0 % and bone volume was low in 15.0 %. Patients with persistent

hypercalcemic hyperparathyroidism (n=4, 7%) showed either low or normal bone turnover. Hypophosphatemia was present in 11%. Vitamin D stores were sufficient in 52% (median HydroxyvitaminD 32 ng/ml). Spearman correlation revealed significant correlations between bone formation rate and biomarkers of bone formation & resorption (direct: bsAP: r:0.36, p<0.01; TRAP5b: r:0.40, p<0.01; NTX: r:0.38, p<0.01) and inflammation (inverse: IL6: r:-0.51, p<0.001), but not with mineral metabolism hormones (PTH, FGF23, sclerostin).

Conclusions: Low bone turnover disease is the most prevalent bone disease in renal transplant recipients 1 year after successful renal transplantation. Additional studies are required to clarify underlying pathophysiological mechanisms. PTH, FGF23 and sclerostin do not correlate with histomorphometric parameters and circulating biomarkers of bone turnover.

SA-PO569

Sclerostin Bone Expression and Blood Levels in Patients with Chronic Kidney Disease Stages 2-5 Florence Lima, Marie-Claude M. Faugere, Hanna W. Mawad, Hartmut H. Malluche. *Div of Nephrology, Bone & Mineral Metabolism, Univ of Kentucky, Lexington, KY.*

Background: Sclerostin (Scl) produced by osteocytes (ocy) was found to be increased in blood in early stages of CKD patients (pts) with renal osteodystrophy (ROD). The aim of this study was to establish when blood scl levels and bone expression are increased and how they progress with worsening CKD.

Methods: Fifty pts underwent anterior iliac crest biopsies and blood was drawn at time of biopsy. Kidney function was determined by creatinine clearance using MDRD calculation. There were: 11 CKD-2, 16 CKD-3, 9 CKD 4-5 pts, and 14 healthy aged-matched controls. Scl concentrations in blood were determined by ELISA and scl expression in bone was determined in undecalcified bone sections by measuring number of ocy exhibiting positive scl immunostaining. Measurements were done separately in cortical and cancellous bone. Bone sections were also evaluated by histomorphometry for turnover, mineralization and volume.

Results: Blood scl levels were significantly greater in CKD compared to controls with no differences between stages (P<0.01).

Bone scl expression was significantly higher in cortex of CKD 2-5 pts compared to controls (P<0.01). Scl expression was significantly greater in cortical than in cancellous bone in CKD. In cancellous bone scl expression was higher in CKD; this reached significance in CKD-3 (Figure 1).

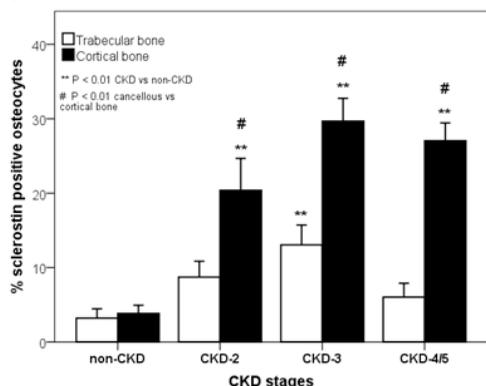


Figure 1. Sclerostin positive ocy per total ocy number in cancellous and cortical bone (mean ± SE).

Scl expression in cortical and cancellous bone correlated with serum scl (rho=0.30, 0.40, rsp; P<0.05). Serum scl correlated negatively with bone formation, activation frequency and osteoblast number (rho=-0.33, -0.38, -0.43, rsp; P<0.05). Scl in bone correlated negatively with trabecular thickness (rho=-0.51; P<0.05), osteoblast and osteoclast surface, and erosion depth (rho=-0.50, -0.52, -0.55, rsp; P<0.01).

Conclusions: These findings ascribe a potential role to scl in the pathogenesis and management of ROD.

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SA-PO570

Single Timepoint and Longitudinal Serum Sclerostin Levels as Mortality Predictors in Prevalent Dialysis Patients Lotte Lips,¹ Camiel L.M. de Roij van Zijdewijn,¹ Marc G. Vervloet,¹ Peter J. Blankestijn,² Denis Fouque,⁴ Solenne Pelletier,⁴ Pieter M. Ter Wee,¹ Menso Jan Nubé,¹ Muriel P. Grooteman.¹ *¹Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; ²Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands; ³Internal Medicine, Maasstad Hospital, Rotterdam, Netherlands; ⁴Nephrology, Centre Hospitalier Univ de Lyon, Pierre Benite, France.*

Background: Currently, data are conflicting whether high serum Sclerostin (sScl) levels, a 22kDa-sized glycoprotein inhibiting bone formation, are positively or negatively associated with mortality. Its concentration may change over time. Therefore, we investigated whether longitudinal sScl levels predict mortality better than a single measurement.

Methods: A post-hoc analysis on data from the CONTRAST study was performed, a RCT comparing online postdilution hemodiafiltration to hemodialysis in prevalent dialysis patients. sScl was measured in a subset of patients. Patients were eligible for analysis if a baseline (T0) and a 6 months (T6) sScl value were available. Hazard ratios (HRs) were calculated within quartiles for sScl level at T0, T6 and for DsScl. All-cause mortality was used as end point. As the interaction between dialysis modality and DsScl was non-significant (p>0.1), pooled estimates are reported. To correct for multiple testing, a two-sided p-value <0.01 was considered statistically significant.

Results: Out of 714 patients, 341 were available for analysis. Baseline characteristics between these groups did not differ. Median sScl at T0, T6 and DsScl was 136.3 pmol/L (interquartile range [IQR] 98.7-186.1), 134.0 pmol/L (IQR 100.4-183.0) and 0 pmol/L (IQR -25 to 15), respectively. sScl values at baseline and T6 were negatively associated with mortality (adjusted HRs highest versus lowest quartile 0.49 [95% CI 0.30-0.81] and 0.48 [95% CI 0.29-0.82], respectively). However, we found no association between DsScl and mortality.

Conclusions: A single timepoint sScl is inversely associated with mortality in our cohort of dialysis patients. sScl change over a six month period does not predict mortality.

SA-PO571

Variation of PTH and Bone Biomarkers in Hemodialysis Patients Pierre Delanaye,¹ Xavier Warling,¹ Martial Moonen,¹ Nicole Simone Smelten,¹ Hans Pottel,² Jean-marie H. Krzesinski,¹ Etienne Cavalier.¹ *¹Univ of Liège, Belgium; ²Univ of Leuven, KULAK.*

Background: Bone turnover must be monitored in dialysis patients. KDIGO guidelines suggest to measure and follow-up both parathormone (PTH) and bone-specific alkaline phosphatase (b-ALP). Also underlined by the KDIGO, clinical decision should be based on variations (or slopes) (Δ, in%) of these biomarkers, more than on isolated concentrations. In this work, we studied the correlation between DPTH and Δ of different bone biomarkers: PINP, CTX, TRAP-5b, osteocalcin and sclerostin. Δ were studied at different timings, namely 6 weeks (T6W), 6 months (T6M) and 1 year (T1Y).

Methods: We have prospectively followed the variations of these biomarkers over one year in patients from 3 independent dialysis centers at T6W (n=123), T6M (n=108) and T1Y (n=93). We analyzed DPTH with Δ of bone biomarkers by univariate linear regression. We also categorized patients according to variations reaching the critical difference of the biomarkers at one year. These results were analyzed by Mantel-Haenszel c² test.

Results: At T6W, a significant correlation was only found between DPTH and ΔCTX (r=0.38, p<0.0001). At 6M, a significant correlation was found between DPTH and ΔCTX (r=0.38, p<0.0001) and Dosteocalcin (r=0.27, p=0.0049). At T1Y, a significant correlation was found between DPTH and ΔCTX (r=0.47, p<0.0001), DP1NP (r=0.4, p<0.0001), Db-ALP (r=0.29, p=0.0054) and Dosteocalcin (r=0.36, p=0.0004). No correlation was found at T1Y neither between DPTH and DTRAP-5b nor Dsclerostin. The same conclusions were reached when variations reaching the critical differences were considered. Correlations between DPTH and Dbone biomarkers were particularly poor in patients with low PTH levels (as defined by the KDIGO) at baseline. Conclusions remained the same if analysis was restricted to the 93 patients who completed the study.

Conclusions: A concordance between variations of PTH on one hand and variations of CTX, b-ALP, osteocalcin and PINP on the other hand can be observed in dialysis patients, but only after a long follow-up (at least one year). Variation of bone biomarkers need repeated measures and must not be analyzed on a too short period.

SA-PO572

Interleukin-1 Inhibition, Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), and Physical Function Kristen L. Nowak,¹ Adriana Hung,^{2,3} Talat Alp Ikizler,² Heather Farmer,¹ Natjalie Salas,² Rafia I. Chaudhry,² Andrew N. Hoofnagle,⁴ Gerard John Smits,¹ Michel Chonchol.¹ *¹Univ of Colorado Denver; ²Vanderbilt Univ; ³VA Tennessee Valley Healthcare System; ⁴Univ of Washington.*

Background: Epidemiologic studies have suggested a possible link of chronic systemic inflammation with vitamin D deficiency, intact parathyroid hormone (iPTH), and fibroblast growth factor 23 (FGF23) excess, which are a central features of CKD-MBD. Declining renal function is also associated with worsening physical function, which may be explained by systemic inflammation, CKD-MBD, or both. We hypothesized that inhibiting inflammation with an interleukin-1 (IL-1) trap would improve vitamin D deficiency, iPTH and FGF23 excess, as well as physical function in patients with moderate-to-severe CKD.

Methods: In a two-site, double-blind trial, 42 patients with stage 3-4 CKD were randomized to receive either the IL-1 trap rilonacept (160 mg/week) or placebo for 12 weeks. The following CKD-MBD markers were assessed in serum before and after the intervention: calcium, phosphorus, 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)₂D), iPTH, and iFGF23. A battery of tests was also administered in a sub-group (n=22) to assess multiple domains of physical function (endurance, locomotion, dexterity, balance, strength, and fatigue).

Results: Participants were 63±11 years of age, 24% female, 29% Hispanic, mean eGFR 38±13 ml/min/1.73m², and mean high sensitivity C-reactive protein (hsCRP) 4.7±4.2 mg/L. Rilonacept effectively reduced systemic inflammation, as evidenced by reduced hsCRP levels (p<0.01). There was no change in serum calcium, phosphorus, 25(OH)D, 1,25(OH)₂D, iPTH, or FGF23 levels (p>0.41) with IL-1 inhibition. Similarly, rilonacept did not alter locomotion, dexterity, balance, strength, or fatigue (p>0.22). However, endurance (400m walk time) tended to be reduced in the rilonacept (-29 sec) as compared to placebo (-6 sec; p=0.059).

Conclusions: 12 weeks of IL-1 inhibition did not improve circulating markers of CKD-MBD or physical function (although it tended to improve endurance). These results support that inflammation does not directly mediate CKD-MBD or select domains of physical function.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Regeneron Pharmaceuticals, Inc., Private Foundation Support

SA-PO573

Serum Metabolomic Profiling and CKD-MBD: A New Tool for Bone Turnover Evaluation Aline Lourenco Baptista,¹ Kallyandra Padilha,² Pamela Araujo Malagrino,³ Gabriela Venturini,² Ana Carolina de Mattos Zeri,³ Janaina Silva Martins,⁴ Rodrigo Azevedo de Oliveira,⁵ Geuza Dutra,⁶ Luciene dos Reis,¹ Vanda Jorgetti,¹ Alexandre Costa Pereira,² Rosa M.A. Moyses.^{1,6} ¹Nephrology, USP; ²Molecular Cardiology, INCOR, USP; ³LN Bio, CNPEM; ⁴UEM; ⁵UFRRN; ⁶Master Degree Program, UNINOVE, Brazil.

Background: Bone biopsy still is the gold standard to assess bone turnover in CKD patients and serum biomarkers are not able to replace histomorphometry. Recently, metabolomics has emerged as a new technique that could potentially improve disease diagnoses and the understanding of pathophysiology. However, as this approach has never been tested in the CKD-MBD scenario we investigated whether a serum metabolomic profile could help us to better predict bone turnover in CKD patients.

Methods: Serum and bone histomorphometry data from hemodialysis (HD, n=51) and peritoneal dialysis patients (PD, n=40) were analyzed. They were classified as high (HT, 49.4%) or low turnover (LT). Metabolomic analysis was done through MRI spectroscopy, followed by identification and quantification of metabolites and PLS-DA. As HD had a completely different metabolome of PD group, we analyzed them separately. In addition, we selected the main metabolites found in each group and searched for the metabolic pathways involved.

Results: The difference between LT and HT was explained by 12 metabolites in HD and 8 in PD (p = 0.03 and 0.01, respectively). ROC curve analysis showed that parathormone and alkaline phosphatase were the best predictors for HT, whereas glycerol and glucose were the best predictors for LT in HD and PD, respectively. The main canonical pathways involved were glycine degradation, tyrosine biosynthesis IV and phenylalanine degradation I in HD and creatine-phosphate biosynthesis, pyruvate fermentation to lactate and AMPK signaling in PD group.

Conclusions: In this preliminary analysis, we identified new metabolites that might be used as biomarkers of bone turnover. Moreover, the differences in metabolome between the two dialysis modalities and the different metabolic pathways suggest that the pathophysiological mechanisms involved in the modulation of bone turnover in these patients might be different.

Funding: Government Support - Non-U.S.

SA-PO574

Deletion of the Gene Encoding the Transient Receptor Potential Canonical Type 1 (TRPC1) Channel Produces Hyperparathyroidism, Low Calcitonin (CaT), Hypercalcemia, but Hypocalciuria and Enhanced Bone Mass: Evidence for the Role of TRPC1 in Regulating Intracellular Ca ([Ca²⁺]_i) in Target Cells Bonnie Eby,¹ Alexander Lau,¹ Lindsay J. Barron,¹ Marybeth Humphrey,¹ Leonidas Tsiokas,² Kai Lau.^{1,3} ¹Medicine, Univ of Oklahoma, Oklahoma City, OK; ²Cell Biology, Univ of Oklahoma, Oklahoma City, OK; ³Medicine, VA Medical Center, Oklahoma City, OK.

Background: We recently showed that TRPC1 deficiency impairs store-operated Ca entry (SOCE), reduces [Ca²⁺]_i, stimulates PTH and causes hypercalcemia. We here evaluated the potential mechanism & consequence.

Methods: We studied male TRPC1 wild-type & null mice by metabolic, clearance (Cl), & micro-CT techniques. PTH, 1,25 di(OH) vit D (1, 25 D), & CaT were measured by mouse ELISA. We analyzed Ca & P (by published methods) & creatinine (Cre) by HPLC.

Results: Hypercalcemia in null mice emerged at 2 mon & lasted through 21 mon, when last checked. Serum Ca was high in fed & fasted null mice (10.1 vs. 9.4 mg%), excluding gut hyperabsorption. In pg/ml, [PTH] was higher in the null (598 vs. 402), [1,25 D] (301 vs. 308) similar & CaT lower (2.2 vs 2.8). P (6.6 vs. 6.5 mg%) was similar. At 7 mon, femur (105 vs. 84 mg) & hind limb (189 vs. 151 mg) were heavier, but the latter was shorter (34.5 vs. 35.7 mm), implying higher bone density in the null. Urine Ca (1.2 vs 2.2 mg/d), CaCl (14 vs. 26 ml/min) & urine Ca:Cre (1.8 vs. 3.1) were reduced. At 16 mon, urine OH-proline, absolute (400 vs. 734 mg/d) or ratioed to Cre (0.54 vs 0.96), was reduced. At 19 mon, on micro-CT, proximal tibia of null mice had 80 % more bone volume to tissue volume, 37% more trabecular number, 25 % less trabecular spacing, & 3-fold increase in trabecular connectivity density.

Conclusions: 1. TRPC1 deficiency impairs SOCE, reduces [Ca²⁺]_i, stimulates PTH, and inhibits calcitonin in their respective glands, producing hypercalcemia independent of 1,25 D or P. 2. Lack of TRPC1 channels produces hypocalciuria in the kidney & reduced bone resorption and skeletal PTH resistance in osteoclasts. 3. Our data support the critical role of TRPC1 channels in regulating [Ca²⁺]_i in the many cells where it is ubiquitously expressed.

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SA-PO575

Role of the Sodium/Calcium Exchanger NCX1 in Osteoclasts Giuseppe Albano,^{1,3,4} Candice Stoudmann,^{2,4} Willy Hofstetter,³ Olivier Bonny,^{2,4} Daniel G. Fuster.^{1,3,4} ¹Div of Nephrology, Hypertension and Clinical Pharmacology, Univ of Bern, Bern, Switzerland; ²Inst of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; ³Dept of Clinical Research, Univ of Bern, Bern, Switzerland; ⁴NCCR Kidney.CH, Univ of Zürich, Zürich, Switzerland.

Background: Previous studies demonstrated that inhibition or siRNA-mediated knock-down of sodium/calcium exchanger 1 (NCX1) in osteoclasts decreases bone resorption in vitro, indicating a critical role of NCX1 in osteoclast-mediated bone resorption.

Methods: To test the role of NCX1 in osteoclasts in vivo, we generated mice with osteoclast-specific deletion of NCX1 (NCX1^{DOC/DOC}). For this purpose, mice with a floxed exon 11 of NCX1 were crossed with mice expressing Cre-recombinase under the influence of the osteoclast specific cathepsin K promoter.

Results: Osteoclasts differentiated from NCX1^{DOC/DOC} mice displayed an 80-90 % reduction of NCX1 protein compared to wild-type mice. NCX1 expression was unaltered in extrasosseous tissues in NCX1^{DOC/DOC} mice. NCX2 and NCX3 were present at low levels in wild-type osteoclasts and not upregulated in NCX1^{DOC/DOC} osteoclasts. In vitro RANKL stimulation of bone marrow cells isolated from wild-type and NCX1^{DOC/DOC} mice yielded no differences in osteoclast development and resorptive activity. In addition, at 3 months of age, structural parameters of bone, quantified by high-resolution microcomputed tomography, were not different in NCX1^{DOC/DOC} mice compared to wild-type littermates. To stimulate osteoclast-mediated bone resorption, we performed surgical ovariectomy (OVX) in 12 week old female mice, but OVX-induced bone loss over 12 weeks was similar in WT and NCX1^{DOC/DOC} mice.

Interestingly, however, at 6 months of age, female NCX1^{DOC/DOC} mice had significantly higher bone volume whereas male NCX1^{DOC/DOC} mice displayed reduced bone volume compared to wild-type mice.

Conclusions: Our data indicate that genetically induced deficiency of NCX1 in osteoclast-precursors and mature osteoclasts does not affect osteoclast differentiation and bone resorption in vitro. However, NCX1^{DOC/DOC} mice display an age- and sex-specific phenotype. Additional studies are needed to unveil the underlying mechanisms.

Funding: Government Support - Non-U.S.

SA-PO576

The Impact of a Previously Created AV-Fistula on Radial Bone Mineral Density Measurements in Renal Transplant Recipients Spyridon Arampatzis, Vasileios Devetzis, Uyen Huynh-do. *Nephrology, Hypertension and Clinical Pharmacology, Uni. Hospital of Bern, Inselspital, Bern, Switzerland.*

Background: The arteriovenous-fistula (AVF) of the distal radius often remain patent after transplantation. Distal radius is the typical site for peripheral DXA measurements in renal transplant recipients (RTR). Since no data exist concerning the impact of a previously created AVF on peripheral bone characteristics in RTR we evaluated the effect of AVF on bone mineral density (BMD) as mirrored by contralateral differences between forearms and explored the densitometric correlation of distal radius with the tibia as an alternative peripheral measurement site.

Methods: This cross sectional study included 40 renal transplant recipients (RTR) and 40 chronic kidney disease (CKD) patients matched for age, gender and BMI. In addition to relevant demographic, biochemical and clinical aspects we assessed bone characteristics of both forearms, femoral neck and tibia by DXA.

Results: The CKD patients without any AVF, displayed no significant discrepancies concerning BMD in both forearms. In RTR BMD was significantly lower in the AVF forearm in comparison to the contralateral non AVF forearm. This observation was evident at all measured subregions of the AVF radius sides, i.e. at the 1/3 radius (0.710±0.103 vs. 0.727±0.104, p=0.003), ultradistal radius (0.424±0.085 vs. 0.444±0.080, p=0.007) and total radius (0.571±0.090 vs. 0.589±0.090, p=0.001) as well. This significant side-to-side difference was 7.5% at the 1/3 radius, 7.2% at the total radius, and 7.0% at the ultradistal radius, respectively. The BMD intersite analysis between radius and distal tibia showed a strong and highly significant correlation (r = 0.7346-0.875) between corresponding peripheral sites.

Conclusions: In conclusion, a previously placed AVF in RTR exerts a negative impact on the ipsilateral radius resulting in significant side-to-side BMD differences. A strong densitometric association exist between peripheral sites and thus DXA measurements at the tibia can be considered as a valuable alternative site to radius. Longitudinal studies are needed in order to replicated these findings by incorporating methods with higher bone density definition.

SA-PO577

Cortical Bone Analysis in Pre-Dialysis Patients: A Comparison with a Dialysis Population Catarina Carvalho,¹ Juliana Magalhães,¹ Ricardo Neto,¹ Luciano Pereira,¹ Teresa Adrago,² Joao M. Frazao.¹ ¹Nephrology and Infectiology Research and Development Group, INEB, Porto, Portugal; ²Nephrology, Hospital Santa Cruz, Lisboa, Portugal.

Background: ROD presents early in CKD pts. Bone biopsy is the gold-standard diagnostic tool. Cortical bone represents 80% of human bone and is the major determinant of bone strength.

Methods: We evaluated cortical bone histomorphometry in 13 CKD stage 3 and 4 pts. (9 male, age 65.1±10.4, eGFR 23.3±8.3ml/min/m², who underwent trans-iliac bone biopsy and compared them to 13 dialysis pts (9 male, 11 on HD, age 52.15±10.2, 55.3±17.6 mo in RRT).

Results: Biochemical values and external cortical bone parameters of both groups shown in table

	Pre-dialysis	Dialysis	p value
PTHi (pg/ml)	157.8±85.9	283.2±187.5	0.038
Ca (mg/dL)	9.6±0.4	9.0±0.6	0.009
Pi (mg/dL)	3.6±0.8	4.8±2.2	0.087
External Cortical			
Po (%)	12.5±7.9	12.6±6.6	0.973
CtTh (µm)	635.6±323.2	384.6±170.5	0.023
OnMS/BS (%)	3.0±5.6	4.1±4.3	0.593
OnBFR/BS (µm ³ /µm ² /y)	1.8±2.4	15.0±15.4	0.025
OnOS/BS (%)	23.5±9.4	26.2±10.0	0.506
OnES/BS (%)	9.2±4.5	7.0±8.8	0.463
OnOTh (µm)	6.8±2.3	9.9±5.0	0.067
OnAjAR (µm ³ /µm ² /day)	0.02±0.03	0.15±0.15	0.023

Dialysis pts compared to the pre-dialysis population showed more deranged cortical bone, with decreased cortical thickness, increased osteonal bone formation rate and adjusted apposition rate. In this pre-dialysis population, external cortical porosity positively correlated with both trabecular bone volume and osteoid volume (respectively, r=0.70 and 0.76, p=0.016 and p=0.006). External cortical osteonal BFR correlated negatively with S-calcium (r=-0.88, p=0.021) and positively with trabecular thickness (r=0.88, p=0.021). These findings were not observed in internal cortical suggesting that this is more stable to PTH effects.

Conclusions: In pre-dialysis pts, our findings support that PTH has a modulating effect on both trabecular and cortical bone. As renal disease progresses cortical thinning is more pronounced, eventually contributing to the higher fracture rate. Understanding cortical abnormalities may have implications in the treatment of CKD-MBD.

SA-PO578

Chronic Kidney Disease Severity Is Independently Associated with Deficient Bone Mineralization, Hip Fracture and Post-Fracture Mortality Farsad Afshinnia,¹ Robert J. Ackermann,¹ Ka kit Wong,¹ Baskaran Sundaram,² Panduranga S. Rao,¹ Subramaniam Pennathur.¹ ¹Univ of Michigan; ²Thomas Jefferson Univ.

Background: While decreased bone mineral density (BMD) is associated with fracture in non-chronic kidney disease (CKD) subjects, its utility in CKD has been questioned because of associated renal osteodystrophy. In this study, we aim (a) to estimate prevalence of decreased BMD by CKD severity in a large tertiary care academic medical center (b) test whether CKD severity is independently associated with hip fracture and decreased hip BMD, and (c) ascertain if CKD increases mortality following hip fracture.

Methods: This study is a retrospective cohort of 25109 patients with bone densitometry, clinical and lab values from 2001 to 2013 at the University of Michigan. Deficient mineralization (DM) is defined as BMD±2.5 standard deviation (SD) below the mean peak bone mass of young, healthy adults. Clinical outcomes are all-cause mortality and hip fracture. Logistic regression was used to assess the risk associated with fracture. Cox survival model was used to assess risk of all-cause mortality by stage of CKD in hip fracture.

Results: Mean age was 61 years (SD=14). There were 4700 males (18.7%) and 23215 (92.5%) were Caucasian. There were 20507, 4226, 293, and 83 patients with eGFR≥60, 30-59, 15-29, and <15 mL/min, respectively. There was a graded increase in prevalence of DM at total hip from 6.4% in eGFR≥60 to 27.7% in eGFR<15 mL/min (P<0.001). Hip fracture was observed in 544 patients of which 122 (22.4%) died during follow up. Hip fracture ranged from 1.9% in eGFR≥60 to 9.6% in eGFR<15 mL/min (P<0.001). CKD stage 4 and 5 was independently associated with 2.2 folds higher odds of DM (95% CI: 1.6-3.0, P<0.001) and 1.7 folds higher odds of hip fracture (95% CI: 1.0%-2.7%, P=0.044) as compared to eGFR≥60. In an age and co-morbidity adjusted Cox model, risk of mortality following hip fracture was 6.5-fold (95% CI: 1.8-23.3, P=0.004) higher in eGFR<15 compared to eGFR>60 mL/min.

Conclusions: This study highlights utility of BMD to predict fracture in CKD, underscores the burden of DM on outcomes, and reveals independent higher mortality after hip fracture in end stage kidney disease.

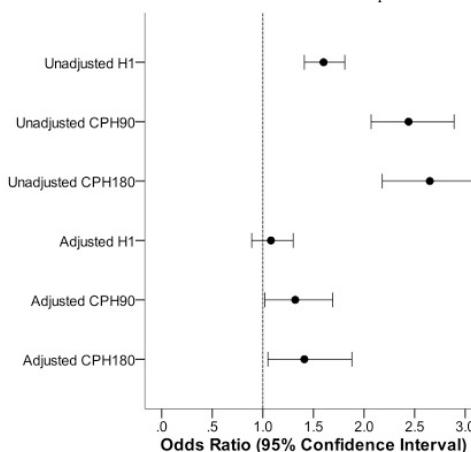
SA-PO579

Chronic Hyponatremia Is a Novel Risk Factor for Hip Fracture in Chronic Kidney Disease-Mineral Bone Disease Sagar U. Nigwekar,¹ Andrew S. Allegretti,¹ Julia Beth Wenger,¹ Juan Carlos Ayus,² Ravi I. Thadhani,¹ Ishir Bhan.¹ ¹Massachusetts General Hospital; ²Renal Consultants of Houston.

Background: Risk factors that make skeleton more fragile in chronic kidney disease (CKD) are uncertain. Considering recently reported direct effects of sodium depletion on bone health, we investigated chronic persistent hyponatremia (CPH) as a novel risk factor for hip fractures caused by CKD-mineral bone disease (CKD-MBD).

Methods: Cases for this multi-center case-control study were elderly (>65 years) patients with CKD (eGFR <60 ml/min) with a new hip fracture. Controls (CKD patients with no hip fracture) were matched to cases on age, sex, race and comparative health. Primary exposure was serum sodium <135 mEq/L on at least 2 occasions ≥ 90 days apart within one year preceding hip fracture for cases and within the first year of study entry for controls (CPH90). Secondary exposure definitions were hyponatremia on at least 1 occasion (H1) and hyponatremia on at least 2 occasions ≥ 180 days apart (CPH180). Variables for multivariable logistic regression analyses were identified using stepwise selection.

Results: We analyzed 1,236 cases and 4,515 controls. Mean age of all patients was 84 ± 9 years, 87% were whites, and 39% were females. Serum calcium, phosphate, parathyroid hormone and 25-hydroxy vitamin D levels were similar between cases and controls. Prevalence of CPH90 (21.2 vs. 9.9%, P<0.001), CPH180 (15.5 vs. 6.5%, P<0.001) and H1 (52.7 vs. 41.1%, P<0.001) were higher in cases compared to controls. In analyses adjusted for falls, tobacco use, osteoporosis, eGFR, body mass index, heart failure and medications, CPH90 and CPH180 were associated with increased risk of hip fracture but H1 was not.



Conclusions: CPH is a risk factor for hip fractures caused by CKD-MBD. Mechanistic studies are needed to investigate the effects of CPH on bone turnover, mineralization and volume in CKD.

Funding: Private Foundation Support

SA-PO580

Follicle Stimulating Hormone Is Associated with Low Bone Mineral Density in Women in Hemodialysis Priscila Preciado, Enrique Rojas-Campos, Alfonso M. Cueto-Manzano, Benjamin Gomez-Navarro. *Unidad Investigación Médica en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico.*

Background: CKD-BMD associated to sexual hormonal status have not been well evaluated. **Aim:** Assess the association between female hormones (FSH and estradiol) and bone mineral density (BMD) in women in hemodialysis (HD).

Methods: Cross-sectional study in 46 women (20-60 years), at least 3 months in HD in a tertiary care setting between Jan-Jul 2014. Pregnant patients or with steroid medication were excluded. Physical examination and blood markers of sexual hormonal and mineral-bone status were done. A bone densitometry of lumbar spine and non-dominant femur was performed; the results were classified as *normal*, *osteopenia* and *osteoporosis*.

Results: 5 had osteoporosis and 5 had osteopenia in the lumbar spine. In the femur, 2 had osteoporosis and 18 had osteopenia. Comparisons are shown in Table. BMD in lumbar spine was associated to FSH (R² 0.27; P<0.0001), FSH (OR -0.52 [-0.02 - -0.008]; p<0.0001), on the other hand BMD in femur (R² 0.30; p=0.001), FSH (OR -0.34 [-0.01 - -0.001]; p=0.02), and CRP were significantly associated (OR -0.32 [-0.02 - -0.001]; P=0.03)

LI - LA	Normal (N 36)	Abnormal (N 10)	p value
Age (years)	30 ± 8	44 ± 12	<0.0001
Phosphorus (mg/dl)	5.9(4.9-7.7)	5.6 (5.3-5.9)	0.53
Calcium (mg/dl)	9.1 (8.0-9.6)	9.3 (9.0-9.6)	0.40
Alkaline phosphatase (U/l)	233 (121-435)	131 (93-232)	0.16
PTHi (pg/ml)	795 (446-1064)	164 (112-456)	0.001
Estradiol (pg/ml)	114 (79-244.4)	71 (54 -98)	0.03
FSH (pg/ml)	4.8 (4-8.5)	66.07 (7.3-136.4)	0.001
C Reactive protein (mg/l)	4.0 (3-9.4)	6.3 (3.0-33.3)	0.62
FEMUR	Normal (26)	Abnormal (20)	p value
Age (years)	31.0 ± 8.4	35.7 ± 12.6	0.18
Phosphorus (mg/dl)	6.2 (4.87-7.7)	5.4 (5.24-6.3)	0.29
Calcium (mg/dl)	8.9 (8-9.4)	9.4 (9-9.62)	0.03
Alkaline phosphatase (U/l)	163 (97-316)	223.5 (109-509)	0.38
PTHi (pg/ml)	756 (349-958)	591 (166-1011)	0.67
Estradiol (pg/ml)	133.9 (92.2-244.4)	82.6 (57.4-178.8)	0.14
FSH (pg/ml)	4.78 (4.03-9.13)	7.01 (4.46-5.50)	0.20
C Reactive protein (mg/l)	3.1 (3-7.0)	7.8 (3-32.1)	0.02

Conclusions: In women in HD, the higher levels of FSH predicts lower BMD in the lumbar spine, while in the femoral region higher FSH and CRP predicts lower BMD.

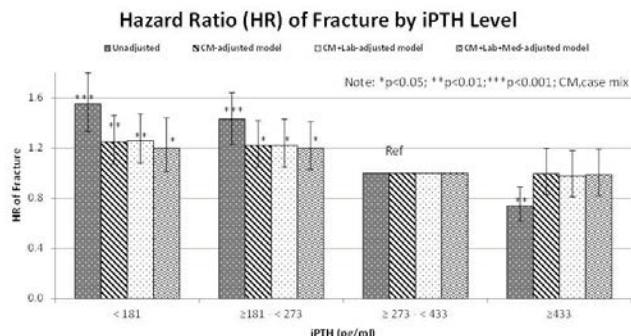
SA-PO581

Time Averaged Intact Parathyroid Hormone Concentration as a Risk Factor For Hip Fractures in Patients on Dialysis Steven Fishbane,¹ Azzour Hazzan,¹ Kenar D. Jhaveri,¹ Lin Ma,² Eduardo K. Lacson.² ¹Div of Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY; ²Fresenius Medical Care, North America, Waltham, MA.

Background: Recent studies found the incidence of hip fractures has increased greatly in patients on dialysis. Most of the increase occurred in patients with characteristics typical of bone frailty, where oversuppression of intact parathyroid hormone (iPTH) could be harmful. Since recent studies have not addressed clinical risk factors, we studied time-averaged iPTH as a risk factor for hip fractures.

Methods: 142,407 prevalent patients of Fresenius Medical Care had hip fractures identified by ICD-9 codes. Four cohorts were constructed: observation periods 2001-2003, 2004-2006, 2007-2009, 2010-2012. For each, the prior year was used to measure exposure. Risks for fractures were analyzed for each cohort and for the combined cohorts. Three models for risk adjustment were created: Case Mix CM-adjusted: age, gender, race, dialysis vintage, and diabetic status, CM+Lab adjusted and CM+Lab+Med adjusted.

Results: For the combined cohorts, unadjusted analyses indicated higher hip fracture risk with lower iPTH (p<0.0001), lower calcium (p=0.003), lower phosphate (p<0.0001) and lower IV vitamin D (p<0.0001). In the fully adjusted model the two lowest iPTH quartiles were significantly associated with greater risk of fractures (HR 1.2, 95% CI 1.01-1.44, p=0.03 for lowest quartile, iPTH < 181 pg/ml). Similarly the lowest quartile for calcium was associated with greater risk (< 8.7 mg/dl, HR 1.00-1.37, p=0.04). Serum phosphate and iv vitamin D were no longer associated with risk in the fully adjusted model.



Conclusions: In conclusion, we found that that lower time-averaged iPTH and calcium were associated with a greater risk for hip fracture in dialysis patients.

Funding: Clinical Revenue Support

SA-PO582

The Discriminative Ability of Three Fracture Risk Assessment Tools in Hemodialysis Patients Ying Qian, An jin Chang, Xiaonong Chen, Nan Chen. Dept of Nephrology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ School of Medicine, Shanghai, China.

Background: The present study aimed to explore factors associated with fractures among hemodialysis patients, and assess the ability of the World Health Organization's fracture risk assessment tool (FRAX) compared with bone mineral density (BMD) and OSTA to discriminate fracture status.

Methods: We enrolled 118 hemodialysis patients in this cross-sectional study. Parameters including serum calcium, phosphate, intact parathyroid hormone, 25 hydroxy vitamin D, alkaline phosphatase were analyzed. Clinical characteristics were also collected. BMD values were tested using dual-energy X-ray absorptiometry at the lumbar spine and hip region. OSTA and FRAX scores were calculated using formula or through the FRAX website. Factors associated with fractures were examined. Discriminative ability of BMD, OSTA and FRAX (non-BMD model and BMD model) in fracture status was assessed with receiver operator characteristic curves (ROC) analysis.

Results: There were 16 (13.56%) fractures in 118 hemodialysis patients. Patients with fractures were significantly older and more osteoporosis. All BMD parameters at hip region (including femoral neck, femoral shaft, and total hip) were notably lower in fracture group than in non-fracture group (0.74 (0.65~0.87) vs 0.82 (0.74~0.96); 0.88 (0.77~1.01) vs 0.99 (0.86~1.14); 0.80 (0.66~0.88) vs 0.88 (0.78~1.00)). There was no difference in clinical characteristics or blood biochemistry levels between the two groups. Areas under ROC curves of BMD, OSTA, FRAX1 (non-BMD model) and FRAX2 (BMD model) were 0.692 (95% CI: 0.600 to 0.774), 0.654 (95% CI: 0.561 to 0.739), 0.917 (95% CI:0.851 to 0.960), and 0.851 (95% CI:0.773 to 0.910), respectively. Either FRAX1 or FRAX2 performed better than BMD and OSTA at identifying patients with fractures (P < 0.05). But FRAX2 performed no better than FRAX1 (P>0.05). The best cutoff values were 0.91, <3, 7.2%, 3.4%.

Conclusions: Among hemodialysis patients, age and BMD at hip are associated with fracture. FRAX performs better than BMD and OSTA in discriminating fracture status, suggesting its usefulness of fracture risk prediction in hemodialysis patients.

Funding: Government Support - Non-U.S.

SA-PO583

Teriparatide for Low Bone Mass in Hemodialysis Patients Rikako Hiramatsu, Yoshifumi Ubara, Junichi Hoshino, Kenmei Takaichi. Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: Fracture rates in dialysis patients are extremely higher than general population. Recently the prevalence of low turnover has greatly increased in dialysis population. Teriparatide would be also beneficial for low turnover dialysis patients with low bone mass. However, there have been only a few reports describing the use of teriparatide in dialysis patients.

Methods: Design This was a prospective, single-center, observational study. Hemodialysis patients with low iPTH (iPTH<60 pg/mL) coexisting low bone mass determined by lumbar spine (LS) or /and femoral neck (FN) T-score<-2.5 with DXA were eligible and subcutaneous recombinant human PTH₁₋₃₄ (20 µg teriparatide; Forteo) was injected 3 times per week at the end of each hemodialysis sessions. We analyzed the following parameters, including serum Ca, P, albumin, ALP, iPTH and bone metabolic makers including iPINP, BAP, OC, and TRACP-5b at baseline and following teriparatide. BMD at LS and FN were measured at baseline, 6, 18 months after treatment. **Pharmacokinetics** After the 24th administration of teriparatide, we measured the serum teriparatide acetate concentrations.

Results: Five patients (median age; 72 years old, median hemodialysis periods; 24 years) were included. After teriparatide injection, BMD of LS as well as FN at 6 months significantly increased from 0.67±0.18 to 0.68±0.19 g/cm² and from 0.44±0.08 to 0.48±0.07 g/cm², respectively. Corrected Ca levels significantly decreased at 3 and 6 months with increases in endogenous iPTH in response to lowering of serum Ca. As for bone metabolic markers, percent changes of serum BAP and serum iPINP levels significantly increased at 3 and 6 months. Conversely, serum TRACP-5b decreased after injection. Throughout this study, there were no fractures. Pharmacokinetics result is shown in Figure 1. There was a peak at 30 minutes at 157.2 pg/mL, and then it rapidly decreased to undetectable level at 240 minutes.

Conclusions: In conclusion, treatment with teriparatide, the dose was 20 µg 3 times/ week, which is smaller than the suggested dose for non dialysis patients, led to increase of BMD at LS and FN. Our data on pharmacokinetic of teriparatide suggested that we can use this agent in normal dose in dialysis patients.

SA-PO584

Restless Leg Syndrome in Hemodialysis Patients: Possible Relationship with Mineral and Bone Metabolism Precil Diego Miranda de Menezes Neves,¹ Ramaiane Aparecida Bridi,¹ Rosa M.A. Moyses,^{1,2} Rosilene M. Elias,¹ ¹Nephrology Div, Univ of São Paulo, São Paulo, Brazil; ²Nephrology Div, Univ Nove de Julho - UNINOVE, São Paulo, Brazil.

Background: Restless legs syndrome (RLS) is a movement sleep disorder that is common among patients on hemodialysis (HD) and is associated with cardiovascular morbidity and mortality. The physiopathology of this syndrome is not completely understood, and CKD-MBD may be implicated. We aimed to evaluate the prevalence of RLS in patients on hemodialysis, testing the relationship with CKD-MBD markers.

Methods: Prevalence and severity of RLS were assessed using the International RLS Study Group (IRLSSG) rating scale.

Results: Of the 101 patients (53.5% women) included, RLS was observed in 29 patients (28.7%), with mild, moderate, severe and very severe presentation in 1, 12, 13 and 3 patients, respectively. RLS was more frequent among women (62% vs 38%, $p=0.04$), and was associated to high phosphate-P (6.0 ± 1.7 vs 5.2 ± 1.7 mg/dl, 0.048), lower transferrin saturation-TS ($32 \pm 16\%$ vs $46 \pm 29\%$, $p=0.019$) and a tendency toward high parathyroid hormone-PTH [529 (190, 1017) pg/ml vs. 305 (143, 546) pg/ml, $p=0.054$]. Logistic regression showed that female gender (HR=2.8, $p=0.039$), P (HR=1.4, $p=0.042$) and TS (HR=0.9, $p=0.033$) were independently associated to RLS. As 22.8% of patients were already submitted to parathyroidectomy, we further categorized PTH as \geq or <500 pg/ml. This new variable was modeled in another regression model, which came out independently associated to a high risk of RLS (HR 3.0, $p=0.027$). We also compared patients with RLS severe/very severe to those with RLS mild/moderate. The first group presented higher P, and lower serum albumin, iron, and ionic calcium. Finally, multivariable regression showed that severity score was dependent on P and vit D insufficiency ($r^2=0.37$).

Conclusions: Besides all traditional risk factor for RLS already described in the general population, CKD-MBD seems to play a role in the pathophysiology of this syndrome in HD patients. It is plausible that the relationship between RLS and CKD-MBD contribute to the increased mortality risk observed in these patients.

SA-PO585

Vascular Smooth Muscle Cells from CKD Rats Have Increased Intracellular Calcium Chad A. Zarse,¹ Mikaela Lee Mckenney,² Stacey L. Dineen,² Rebecca S. Bruning,² Michael Sturek,² Neal X. Chen,¹ Sharon M. Moe.^{1,3} ¹Nephrology, IU School of Medicine; ²Physiology, IU School of Medicine; ³Roudebush VAMC, Indianapolis, IN.

Background: CKD vascular smooth muscle cells (VSMC) exhibit phenotypic plasticity which promotes calcification and increases cardiovascular risk. Changes in intracellular calcium (iCa) as CKD progresses may regulate transcription of genes requisite for this process. This study examined iCa homeostasis in early and advanced CKD.

Methods: We studied VSMC freshly isolated from 10 week normal Sprague Dawley (SD) and CKD Cy/+ rats and 35 week normal SD, CKD Cy/+ (~15% nl function), and CKD rats treated with 3% calcium gluconate. (n=6-8 per group). Intracellular calcium was measured with Fura-2 using a ratiometric approach (F360/F380 nm). Basal iCa, sarcoplasmic reticulum (SR) store release, and store-operated calcium entry (SOCE) was assessed. Expression of common calcium regulatory proteins NCX1 and SERCA2a was examined by Western Blot. Results were compared by ANOVA.

Results: Basal iCa levels were lower in 10 week CKD VSMCs compared to NL (0.76 ± 0.02 vs. 0.66 ± 0.02 , $p < 0.05$) however increased 1.5-fold by 35 weeks to become greater than NL (0.98 ± 0.01 CKD, 0.81 ± 0.02 NL, 0.90 ± 0.04 CKD+Ca, $p < 0.05$). SR store release was greater in CKD VSMCs at both 10 weeks (0.45 ± 0.02 vs. 0.37 ± 0.02 , $p < 0.05$) and 35 weeks (0.62 ± 0.02 CKD, 0.44 ± 0.03 NL, 0.50 ± 0.03 CKD+Ca, $p < 0.05$). At 10 weeks, SERCA2a expression was greater in CKD rats in part explaining the lower basal iCa levels, however, at 35 weeks SERCA2a and NCX1 were both decreased in CKD rats, consistent with higher iCa levels. There was no difference in SOCE at 10 weeks but by 35 weeks was increased in the CKD+Ca cohort ($p < 0.05$) with a trend toward significance in the CKD cohort ($p = 0.08$), also consistent with higher observed basal iCa levels.

Conclusions: Basal iCa, SR store release, and SOCE increases with progressive CKD at least in part due to changes in expression of the common calcium regulatory proteins SERCA2a and NCX1. The increase in iCa is likely a key mechanism in our previous observations that CKD VSMCs display an osteogenic phenotype, which is known to worsen cardiovascular outcomes.

Funding: Other NIH Support - NIAMS, NHLBI, Veterans Administration Support, Pharmaceutical Company Support - 2013-2014 Sanofi Nephrology Fellowship Award

SA-PO586

The Role and Mechanism of Nrf2/HO-1 Pathway in Oxidative Stress-Induced Vascular Calcification in End-Stage Renal Disease In Vitro Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.

Background: To investigate the mechanism of Nrf2/HO-1 pathway in oxidative stress(OS)-induced vascular calcification in end-stage renal disease(ESRD) in vitro, and to explore a new target for the intervention of vascular calcification in ESRD.

Methods: 1. Rat aortic vascular smooth muscle cells(RASMCs) were cultured and divided into 4 groups: the complete medium cultured group, the calcification medium cultured group, the group of complete medium cultured for 42h and then sulforaphane (SFN) cultured for 6h, the group of complete medium cultured for 46h and then H₂O₂ cultured for 2h. Detect nuclear Nrf2 expression in each group by western blot. 2. 4 groups of RASMCs were cultured: the calcification medium cultured group, the group of H₂O₂ pretreated for 2h and then calcification medium cultured, the group of SFN pretreated for 6h and then calcification medium cultured, the group of SFN pretreated for 6h and H₂O₂ pretreated for another 2h, and then calcification medium cultured. Detect the expression of intracellular reactive oxygen species (ROS) by using DCFH-DA probe, and the expression of Nrf2, Heme Oxygenase (HO-1), Runx-related transcription factor 2(Runx2) by western blot.

Results: 1. Nrf2 expression in nuclear was enhanced after SFN and H₂O₂ stimulation. 2. The expression of Nrf2, Runx2 and ROS, but not HO-1, were induced by calcification medium in a time-dependent manner. 3. ROS was significantly reduced after H₂O₂, SFN, SFN + H₂O₂ pretreated, and decreased gradually with incubation time ($P < 0.05$). 4. The expression of Nrf2 and HO-1 were induced by SFN, and the expression of Runx2 was

inhibited in calcification medium. 5. The expression of Nrf2, HO-1, Runx2 could be induced by H₂O₂, but the expression of Runx2-induced calcification medium decreased gradually within incubation time after H₂O₂ or SFN + H₂O₂ pretreated.

Conclusions: The calcification in RASMCs is associated with the overexpression of endogenous ROS. Overexpression of Runx2 induced by endogenous ROS, but not exogenous ROS, may be inhibited or attenuated by the activated Nrf2/HO-1 pathway.

SA-PO587

Matrix Vesicles from Calcifying Vascular Smooth Muscle Cells (VSMC) Have Different MicroRNA (miRNA) Expression from Non-Calcifying VSMC Neal X. Chen,¹ Sarath Chandra Janga,² Kalisha O'Neill,¹ Manjunath Siddappa,² Jeanette N. McClintick,³ Sharon M. Moe.^{1,4} ¹Nephrology; ²Biohealth Informatics; ³Medical and Molecular Genetics, Indiana Univ; ⁴Roudebush VAMC, Indianapolis.

Background: Treating VSMC with high phosphorus induces the production of calcifying matrix vesicles (CaMV) that initiate mineralization within the extracellular matrix of VSMC. MV are similar to exosomes which are known to contain miRNA important in cell-cell communication. We hypothesized that the miRNA expression profile in calcifying MVs (CaMV) would differ from non-calcifying MV (CTLMV) isolated from CKD rats.

Methods: VSMC from CKD rats (n=3) were incubated with control media or high-phosphorus (calcifying media) and MV isolated. Total RNA was isolated from CaMV or CTLMV, miRNA quantified, and MiRNA array was performed using GeneChip miRNA 3.0 Array. We analyzed the miRNA on array that changed at least 2 fold in the comparison groups with a p value of < 0.01 and false discovery rate of $< 20\%$. Bioinformatic target gene prediction was performed using Targetscan and Miranda. CTLMV or calcifying MV were also co-cultured with VSMC to assess the change in calcification.

Results: CaMV increase calcification when added to VSMC compared to CTLMV. The arrays demonstrated 33 increased miRNAs and 17 decreased miRNAs in CaMV vs CTLMV. Real time PCR confirmed the miR-30c expression, known to regulate vascular calcification, is increased in CaMV vs CTLMV. Additional regulatory miRNA identified via target prediction analysis followed by functional enrichment yielded multiple miRNA-mRNA networks. Narrowing the analyses to only those RNA controlled by at least 3 miRNAs identified important miRNAs, including cell signaling pathways known to be involved in vascular calcification: Decreased expression of miRNAs (Ca vs CTL) that would upregulate target genes involved in PI3 kinase signaling. In contrast, increased miRNA expression in CaMV vs. CTLMV would lead to downregulation of several signaling pathways including MAPK, RAS, mTOR and FOXO.

Conclusions: Calcifying MV contain different miRNAs compared to CTLMV. MiRNAs contained in calcifying MV may be transferred to other VSMC and regulate signaling pathways involved in vascular calcification.

Funding: Other NIH Support - NIH R01AR058005, Veterans Administration Support

SA-PO588

The Precedence of the Reduced Osteopontin Expression and the Increased Calcium Phosphate Nanoparticle to the Calcification by Phosphate Load with Normal Fasting Glucose in Human Vascular Smooth Muscle Cells Masanori Tokumoto,¹ Shunsuke Yamada,^{1,2} Kazuhiko Tsuruya,³ Takamari Kitazono,² Hiroaki Ooboshi.¹ ¹Div of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; ²Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ³Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: It is well-known that vascular calcification (VC) develops in diabetes mellitus patients. On the other hand, malnutrition is also reported to induce VC. Thus, we examined how glucose load affects phosphate (P)-induced calcification in human vascular smooth muscle cells (hVSMC).

Methods: We added P of 1, 1.5, or 2.0 mM in the culture media (DMEM) of hVSMC with normal fasting or high glucose (HG) (100 or 450 mg/dl), although hVSMC are usually cultured with HG. The degree of calcification, the content of calcium P nanoparticle (CPP) in the media, and the expression of both the intrinsic calcification inhibitors and the chondro-osteogenic differentiation markers were examined at Day 1, 7, and 14.

Results: Regardless of P load amount, the degree of calcification was severer with normal fasting glucose at Day 7 and 14. At Day 7, the mRNA expression of Sox9, a chondrogenic differentiation marker, increased by P load and was higher with normal fasting glucose. The content of calcification correlated significantly with the SOX9 mRNA expression at Day 7. At Day 1, the content of CPP increased by P load, and was higher with normal fasting glucose. The SOX9 mRNA expression at Day 7 correlated significantly with the content of CPP at Day 1. At Day 1, the mRNA expression of osteopontin (OPN), a calcification inhibitor, decreased by P load and was less with normal fasting glucose. Moreover, it negatively correlated with the content of CPP at Day 1 and the correlation was more intensive with normal fasting glucose. There was no significant change in the mRNA expression of chondro-osteogenic differentiation markers at Day 1.

Conclusions: In conclusion, P load with normal fasting glucose reduced OPN expression and induced the formation of CPP, followed by the chondrogenic differentiation and calcification in hVSMC.

Funding: Pharmaceutical Company Support - Kyowa Hokko Kirin, Government Support - Non-U.S.

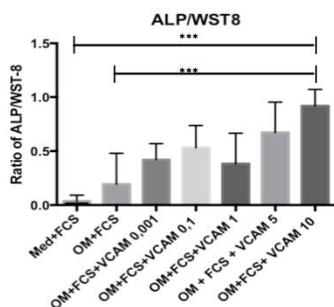
SA-PO589

VCAM - 1 and TNF Alpha Induce Vascular Calcification In Vitro
 Kevin Willy, Ralf Schindler, Daniel Zickler. *Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin.*

Background: VCAM, TNF alpha and soluble TNF alpha receptor 1 (sTNFR1) are elevated in patients with chronic kidney disease (CKD). In previous clinical trials with high cut-off dialysis plasma levels of these molecules and *in vitro* vascular calcification were lowered. Here we assessed the role of sTNFR1 and VCAM on *in vitro* calcification.

Methods: In human vascular smooth muscle cells (VSMCs) vascular calcification was induced by osteogenic medium (OM). VCAM, TNF- α and sTNFR1 were added. Calcification was quantified by alkaline phosphatase staining and alizarin red staining. Calcification was then normalized to WST - 8.

Results: VCAM enhances vascular calcification *in vitro* in a dose-dependent manner (p<0,0001). TNF- α -induced calcification was effectively inhibited by sTNFR1 (50% reduction of the initial level; p<0,0001). sTNFR1 alone does not promote vascular calcification.



VCAM concentration: 0,001 - 10 µg/mL.

Conclusions: VCAM and TNF alpha promote vascular calcification *in vitro*. Their elimination with high cut-off dialysis or their pharmacological blockade may be advantageous in regard to vascular calcification in CKD.

Funding: Pharmaceutical Company Support - Gambro GmbH, Government Support - Non-U.S.

SA-PO590

The Triplehelical Collagen Analog (GPO)₁₀ Affects Calcifications of Vascular Smooth Muscle Cells in a Concentration Dependent Manner
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Background: Extensive remodeling of the extracellular matrix and the trans-differentiation of vascular smooth muscle cells (VSMC) contribute to the pathogenesis of vascular calcifications in patients with chronic kidney disease (CKD). Matrix metalloproteinases (MMPs) are proteolytic enzymes that impact on both of these processes and, thus, represent potential therapeutic targets. We have previously shown that the synthetic collagen analog (Gly-Pro-Hyp)₁₀ - (GPO)₁₀ - impacts the substrate binding and the enzymatic activity/stability of the gelatinases MMP-2 and -9 in a concentration dependent manner [1]. Aim of this study was therefore to investigate potential regulatory functions of (GPO)₁₀ in an *in vitro* model of arteriosclerotic VSMC calcification.

Methods: Calcifications of murine VSMC were induced by a calcification medium (CM) containing elevated concentrations of calcium and phosphorus with or without the presence of different (GPO)₁₀-concentrations. VSMC calcifications were quantified by measuring calcium depositions and ALP-release in the cultures. Effects on MMP-activities were determined by specific substrate assays.

Results: CM-treated VSMC exhibit strong calcifications compared to control. Low (GPO)₁₀ concentrations (50-70 nM) massively enhanced calcifications of VSMC and were accompanied by elevated gelatinase activities in VSMC supernatants. In contrast, higher concentrations of (GPO)₁₀ (680 nM) blocked CM-induced calcifications of VSMC and reduced gelatinolytic activities in culture supernatants.

Conclusions: Considering the important function of MMP-2 and -9 in VSMC calcification [2], the collagen peptide (GPO)₁₀ on the one hand indirectly impacts the VSMC calcification by modulating MMP activities. On the other hand, direct effects of (GPO)₁₀ e.g. by interaction with collagen receptors might simulate a "healthy" vessel matrix, which will be investigated in future studies. [1] Ruelh, M., et al., *Fibrogenesis Tissue Repair*, 2011. 4(1): p. 1. [2] *JASN* 25: 2014 (SA-OR062, p.95A; TH-PO555, p.233A; FR-PO833, p.562A).

Funding: Private Foundation Support

SA-PO591

Protective Effects of Epigallocatechin Gallate (EGCG) on Vascular Calcification In Vitro and In Vivo
 Uwe Querfeld,^{1,2} Karoline Websky,² Christian Freise,² Kerstin Sommer,² Ursula Schulz,² Veronika Bobb.² *¹Pediatric Nephrology, Charité, Berlin, Germany; ²Center for Cardiovascular Research, Charité, Berlin, Germany.*

Background: Vascular calcifications are common in patients with chronic kidney disease (CKD). Our preliminary studies indicate that inhibition of matrix metalloproteinases (MMP)-2 and -9 suppresses the development of arterial calcification in uremic rats. Epigallocatechin gallate (EGCG), a polyphenol ingredient of green tea, has strong antiinflammatory properties and inhibitory effects on MMPs. We therefore investigated potential protective effects of EGCG on calcium uptake of vascular smooth muscle cells (VSMC) *in vitro* and in an animal model of uremia-associated arteriosclerosis *in vivo*.

Methods: *In vitro*, calcifications of murine VSMCs were induced by a high phosphate (HP)-medium and cells were treated with different EGCG-concentrations (20-100µg/ml). VSMC calcifications were quantified using the ortho-cresolphthalein-method and proteolytic activities of MMP-2 and -9 in VSMC supernatants were determined by gelatin zymographies. C57BL/6 mice were 5/6-nephrectomized and arterial calcifications were induced by calcitriol (1µg/kg body weight) and a HP-diet (2% phosphate). One cohort (n=10) was additionally administrated 0.02% EGCG in drinking water. Animals were sacrificed after 2 weeks of treatment and aortic calcifications were quantified after von Kossa-staining.

Results: *In vitro*, EGCG provoked a dose-dependent decrease of HP-induced calcification (up to 85%) of VSMCs and of proteolytic MMP-2 and -9 activities. *In vivo*, all calcitriol-treated mice had severe arterial calcifications, involving 50% of the arterial wall after only 2 weeks of treatment. EGCG had no significant inhibitory effect on the development of vascular calcifications.

Conclusions: In this "negative experimental trial", EGCG had no beneficial effect in the chosen animal model, which (considering the rapid development of calcifications) may have been too aggressive, thus overriding potential protective effects of EGCG. Encouraged by the positive *in vitro* results, the effects of EGCG and other polyphenols should nonetheless be further investigated in other animal models of uremia-associated arteriosclerosis.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO592

Mechanism of Calcification by Iron Stimulation in Vascular Smooth Muscle Cells
 Sayuri Kawada,¹ Yasuyuki Nagasawa,¹ Mutsuki Kawabe,² Aritoshi Kida,¹ Mana Yahiro,¹ Tomoko Kimura,¹ Kiyoko Yamamoto,¹ Masayoshi Nanami,¹ Yukiko Hasuie,¹ Takahiro Kuragano,¹ Keiji Nakasho,² Hideki Ohyama,² Takeshi Nakanishi.¹ *¹Dept of Internal Medicine, Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; ²Dept of Pathology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.*

Background: In CKD patients, atherosclerosis is one of important key factors which determine their prognosis. It was reported the calcification induced by TNF-alpha was related with iron in HUVEC cells by our group. To reveal the relationship between calcification in vascular media and iron stimulation using vascular smooth muscle cells.

Methods: The aorta smooth muscle cells were cultured for three weeks. At day 0, we changed the usual culture medium to calcification medium, and TNF-alpha and iron were added to the calcification medium. Calcification in each condition was confirmed by Alizarin staining. And to reveal early mechanism to enhance the calcification by iron and TNF-alpha stimulation, we compared the gene expression profile between each condition in day 1 and day 3 using microarray analysis. We confirmed gene expression of cytokine which had increased in microarray analysis by real-time PCR.

Results: We confirmed both iron and TNF-alpha stimulation enhanced calcification by Alizarin Staining. Moreover, both iron and TNF-alpha stimulation at the same time enhanced calcification more strongly than single stimulation. We picked up a cytokine which had increased with both iron and TNF-alpha stimulation in the microarray analysis as similar as the Alizarin Staining result had shown. We confirmed gene expression of this cytokine by real-time PCR. Gene expression was increased at day1 by stimulation of iron (5.8±3.0 fold change vs control), TNF-alpha (7.8±1.9 fold change vs control), and both stimulation (53.1±27.1 fold change vs control), synergistically.

Conclusions: Iron stimulation enhanced calcification in vascular smooth muscle cells along with TNF-alpha stimulation. The possibility was suggested that this gene change from the early stage participated in the mechanism that iron promoted blood vessel media calcification.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

SA-PO593

Kidney Injury/Repair Stimulates Vascular Disease Through Activin and Systemic Wnt Inhibition
 Matthew James Williams, Olga A. Agapova, Yifu Fang, Toshifumi Sugatani, Carmen M. Halabi, Keith A. Hruska. *Pediatrics, Nephrology, Washington Univ School of Medicine, Saint Louis, MO.*

Background: We show that the vascular effects of CKD are an interplay of Wnt inhibition and activin induced modulation of Activin receptor (ActRIIA) function resulting in a stimulation of atherosclerosis and vascular calcification.

Methods: CKD with elevated activin and Wnt inhibitors, especially Dkk1, was induced in the mouse models for vascular calcification, lineage tracing, and Alport's. Activin, Dkk1, ActRIIA, psmad 2/3, aklotho and collagen levels were measured by Elisa, RT-PCR and westerns. Vascular smooth muscle cell (VSMC) function was measured by pressure

induced arterial dilatation *in situ*. Cell lineage tracing was performed in Rosa-tdT mice bred to endothelial specific Tie2-Cre mice. Mice harboring Rosa-tdT express tomato red in cells harboring Cre recombinase.

Results: Circulating activin and Dkk1 levels were increased while aklotho levels were decreased by CKD. In diseased kidneys, activin was expressed in myofibroblasts, and activin receptor, ActRIIA, signaling through Smad 3 was increased. An ActRIIA ligand trap, RAP-011, inhibited renal pSmad 3, ColA1 expression, urinary protein levels, and Dkk1 levels, and increased tubular epithelial klotho levels. In the vasculature, CKD decreased VSMC ActRIIA protein levels, and ActRIIA signaling was decreased along with decreased VSMC differentiation and function. The ActRIIA ligand trap increased VSMC differentiation and inhibited osteoblastic transition and atherosclerotic calcification. In the circulation, the ActRIIA ligand trap decreased Dkk1 levels. CKD induced expression of tomato red in cells of the adventitia after two weeks of femoral artery injury in Tek-Cre/Rosa-tdT CKD mice compared to Tek-Cre/Rosa-tdT mice with normal kidney function.

Conclusions: CKD increased circulating free activin levels, decreased VSMC function, stimulated aortic osteoblastic transition and atherosclerotic calcification. Decreasing effects of elevated activin in CKD with an ActRIIA ligand trap, inhibited Smad dependent renal fibrosis, blocked aortic osteoblastic transition, increased VSMC differentiation and decreased vascular calcification.

Funding: NIDDK Support, Pharmaceutical Company Support - Celgene

SA-PO594

Transient Azotemic Episode Exacerbates Vascular Calcification in Adenine-Induced Uremic Rats Daisuke Mori,¹ Isao Matsui,¹ Akihiro Shimomura,² Yasuo Kusunoki,¹ Sayoko Yonemoto,¹ Masamitsu Senda,¹ Yusuke Sakaguchi,¹ Takayuki Hamano,² Yoshitaka Isaka,¹ Hiromi Rakugi,¹ ¹*Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Japan;* ²*Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Japan.*

Background: Urea, the final metabolite of amino acids in the body, can carbamylate proteins at lysine residues, and thereby modifies characteristics of proteins irreversibly. Several studies have revealed that functions of proteins are impaired by carbamylation. Acute kidney injury (AKI) is a representative pathological condition that elevates serum urea temporarily. Although AKI is not a perpetual condition, it is well-known that AKI increases subsequent risk of cardiovascular diseases through yet-unknown mechanisms.

Methods: We evaluated the effects of transiently elevated serum urea on vascular calcification (VC). Male Sprague-Dawley rats at age 9 weeks were divided randomly into two groups: cellulose-pretreated + adenine diet (group C+A) and urea-pretreated + adenine diet (group U+A). Urea-pretreated group received 10% urea diet from 9 to 13 weeks of age. Cellulose served as a control for urea. After one week of urea-washout period, all rats received 0.75% adenine-containing diet up to 19 weeks of age.

Results: Serum urea levels were 15.87 ± 2.96 mg/dL in cellulose-pretreated group and 39.20 ± 3.74 mg/dL in urea-pretreated group at the end of the pretreatment period. Serum urea levels in urea-pretreated group were normalized to 14.73 ± 1.28 mg/dL during the washout period. At age 19 weeks, rats in group U+A developed severer VC in comparison with the rats in group C+A. Serum creatinine, urea nitrogen, calcium, phosphate, magnesium, albumin, and body weight were not different between the two groups at age 19 weeks. Western blot analysis of the aorta revealed that dietary pretreatment of urea increased carbamylated protein.

Conclusions: Pretreatment of urea exacerbated VC in adenine-induced uremic rats. Protein carbamylation might link urea-pretreatment to VC.

SA-PO595

SNF472 Inhibits Cardiovascular Calcification in Uremic Rats Joan Perelló,^{1,2} Carolina Salcedo,¹ Ellen Neven,³ Geert J. Behets,³ Pieter H. Joubert,¹ Patrick C. D'Haese,³ Miquel D. Ferrer,¹ ¹*R&D Dept, Laboratoris Sanifit, Palma, Illes Balears, Spain;* ²*Laboratory of Renal Lithiasis Research, Univ of Balearic Islands, Palma, Illes Balears, Spain;* ³*Laboratory of Pathophysiology, Univ of Antwerp, Antwerp, Belgium.*

Background: SNF472, an intravenous (i.v.) formulation of phytate, has been shown to inhibit cardiovascular calcification (CVC) in non-uremic conditions. We investigated the pharmacokinetics (PK) and efficacy (inhibition of CVC) of i.v. SNF472 in control and uremic rats.

Methods: The first part of the study was performed with 10 male Wistar rats in which uremia was induced by 10 daily oral (p.o.) administrations of 600 mg/kg adenine followed by p.o. administrations of 300 ng/kg α-calcidol on days 11 and 13. Ten animals received 10 mg/kg and ten animals 50 mg/kg of SNF472 daily as 4-hour i.v. infusions. Blood was collected at days 1 (controls) and 14 (uremic) and plasma SNF472 concentrations were measured at different time points. In an efficacy study uremia was induced as above whilst α-calcidol was administered 3 times/week from day 11 to day 19. Twelve rats received daily 4-hour i.v. infusions of 50 mg/kg SNF472 and twelve rats received saline from day 0 to day 19. At day 19 all surviving animals were sacrificed and blood and tissue samples were collected to measure SNF472 plasma levels as well as calcium content in aorta and heart.

Results: Steady state was reached at 60 minutes in control animals receiving 50 mg/kg SNF472 but not in those receiving 10 mg/kg. Steady state was reached in uremic animals, but with exposures between 3 and 7 times lower than in controls. All the animals in the efficacy study developed uremia as a consequence of the high-dose adenine administration. The exposure to SNF472 in uremic animals was distinctly lower (5-fold for Cmax). SNF472 treatment resulted in a significant reduction in CVC of 80 and 88% in aorta and heart, respectively.

Conclusions: Daily SNF472 4 hour infusions of 50 mg/kg inhibit the development of CVC by up to 88% in a rat adenine model of uremia. These results support further investigation of SNF472 in the treatment of CVC in patients with calcification-related disorders such as calciphylaxis and ESRD patients.

Funding: Pharmaceutical Company Support - Laboratoris Sanifit S.L.

SA-PO596

Enzyme Therapy for Vascular Calcification W. Charles O'Neill,¹ Kelly E. Manning,¹ Koba A. Lomashvili,¹ Nelson Hsia,² Pechii Lee,² Francis T. Danahy,² Kim L. Askew,² Anthony G. Quinn,² ¹*Renal Div, Emory Univ School of Medicine, Atlanta, GA;* ²*Synageva Biopharma, Lexington, MA.*

Background: Pyrophosphate (PPi) is a key endogenous inhibitor of hydroxyapatite formation that circulates at levels sufficient to prevent vascular calcification. PPi is produced from extracellular ATP by the ectoenzyme, nucleotide pyrophosphatase pyrophosphorylase 1 (NPP1) and deficiency of this enzyme produces severe fatal medial arterial calcification in humans. Mice lacking NPP1 have undetectable plasma PPi and also develop arterial calcification. We examined whether exogenous NPP1 can increase plasma PPi and prevent vascular calcification in these mice.

Methods: Recombinant proteins containing the extracellular portion of human ENPP1 fused to human IgG1 Fc (ENPP1-Fc) were created and injected into two mouse models of NPP1 deficiency (Enpp1^{-/-} and Enpp1^{asj/asj}). NPP1 activity was measured by conversion of [³²P]ATP to ³²PPi with separation by thin-layer chromatography. Plasma PPi was measured by a radiometric enzyme assay using UDP-[¹⁴C]glucose and UDP-glucose pyrophosphorylase.

Results: Intravenous injection of NPP1-Fc (6 mg/kg) into Enpp1^{-/-} mice increased plasma NPP1 activity to a peak of 160 ± 10% of normal at 4 hours with a decline to 70 ± 5% of normal by 72 hours. There was no increase in aortic NPP1. Plasma PPi followed a similar pattern, with a peak of 2.2 ± 0.6 uM at 4 hours declining to 0.21 ± 0.04 uM at 72 hours (normal: 2.18 ± 0.33 uM). With subcutaneous injection, plasma NPP1 was 110 ± 13% of normal and plasma [PPi] was 0.38 ± 0.14 uM after 48 hours. Subcutaneous injection every 48 hr reduced aortic calcium content 86 ± 5% (p<0.001) after 18 days in Enpp1^{-/-} mice fed a high phosphorus diet, and improved survival at 10 weeks from 15% to 50% (p<0.001) in Enpp1^{asj/asj} mice fed a high phosphorus, low magnesium diet.

Conclusions: Administration of NPP1 in NPP1-deficient mice produces an increase in circulating PPi that is sufficient to prevent vascular calcification and increase survival. The ability of Enpp1 fusion proteins to raise PPi levels and inhibit tissue calcification supports the potential to reduce vascular calcification in other calcification-prone states.

Funding: Pharmaceutical Company Support - Synageva Biopharma

SA-PO597

The Risk of Medial Arterial Calcification in Early Chronic Kidney Disease W. Charles O'Neill,^{1,2} Kum Hyun Han,^{1,2} Arshad Ali,¹ Ansley O'Neill,¹ Kelly E. Manning,¹ ¹*Renal Div, Emory Univ, Atlanta, GA;* ²*Internal Medicine, Dept of Internal Medicine, Inje Univ College of Medicine, Ilsan Paik Hospital, Goyang, Korea.*

Background: Medial arterial calcification is common in advanced chronic kidney disease (CKD) but whether this risk begins in early CKD is unknown. There is also concern that possible benefits of vitamin D and calcium in this group may be offset by potential induction of vascular calcification. We have previously shown that breast arterial calcification is a readily available and specific marker of medial arterial calcification and that its prevalence is increased in advanced CKD.

Methods: From a computerized search of medical records, 446 women with CKD and mammograms were randomly selected. After exclusion of women with renal transplants or other stages of CKD, history of warfarin use, or non-screening mammograms, 333 women with CKD 3 (MDRD formula) were identified and individually matched by age and diabetes status to women with an estimated GFR >90 ml/min/1.73 m². Digital mammograms were visually inspected for arterial calcification.

Results: Mean age was 69.5 ± 0.6 (range: 44-91), mean eGFR was 49.5 ± 0.4 ml/min/1.73 m², 20.1% had diabetes, 31.5% were receiving calcium supplements, 31.3% were receiving vitamin D (> 1000 units/d), and 1.8% were receiving an active form of vitamin D. Controls had a mean eGFR of 104.1 ± 0.7 ml/min/1.73 m². The prevalence of arterial calcification was the same in CKD 3 patients (35.1%) and controls (33.3%). Dividing the CKD 3 patients by different thresholds of serum creatinine yielded similar results. There was no difference in calcification between patients taking or not taking calcium supplements (36.2% vs. 34.6%), vitamin D (36.2% vs. 34.6%), or both (30% vs. 32.5% with neither). In a logistic regression, only age was a significant determinant of arterial calcification (p<0.0001).

Conclusions: The prevalence of medial arterial calcification is not increased in women with stage 3 CKD, indicating that the risk begins at stage 4 CKD. Supplementation of calcium or vitamin D does not increase the risk of medial arterial calcification in these patients.

Funding: Clinical Revenue Support

SA-PO598

Deoxycholic Acid (DCA), a Metabolite of Circulating Bile Acids, and Coronary Vascular Calcifications in Chronic Kidney Disease (CKD) Makoto Miyazaki,¹ Shinobu Miyazaki-anzai,¹ Audrey L. Keenan,¹ Kristen L. Nowak,¹ Jessica B. Kendrick,¹ Geoffrey A. Block,² Michel Chonchol.¹ ¹Univ of Colorado Denver; ²Denver Nephrology.

Background: Our group has previously shown that DCA, a metabolite of circulating cholic acid, induces vascular mineralization and osteogenic differentiation in animal models and that circulating levels of DCA are elevated in patients with CKD. We investigated whether increased DCA serum levels are associated with an increase risk for higher coronary artery calcification (CAC) volumes and lower lumbar bone mineral density (BMD) in CKD patients.

Methods: We used stored baseline serum samples in 112 patients with moderate to advanced CKD (eGFR=20-45 mL/min/1.73m²) who participated in a randomized-controlled study to examine the effects of phosphate binders on vascular calcification. Circulating DCA levels were assayed using liquid-chromatography-tandem mass spectrometry (LC-MS/MS). CAC volume was obtained using GE-Imatron C150 scanner and lumbar BMD was determined using abdominal computed tomography scans with a calibrated phantom of known density. Linear regression models were used to examine the cross-sectional association between DCA with CAC volume and lumbar BMD.

Results: Participant characteristics were as follows: mean age, 68±11 years; 50% women; 10% black; mean eGFR, 32±8 mL/min/1.73m²; and median DCA 58.4 (IQR 29-112) ng/mL. After adjusting for demographics, co-existing illness, body mass index, eGFR and circulating markers of CKD-MBD including serum calcium, phosphorus, vitamin D, parathyroid hormone and fibroblast growth factor 23, an increase serum DCA level > 58 ng/mL positively associate with CAC volume (B: 494.84 ± 238.82; p=0.03) and negatively associated with BMD (B: -20.35±9.56; p=0.03).

Conclusions: Higher serum levels of DCA in patients with stage III and IV CKD is independently associated with higher CAC volume and lower lumbar BMD. Larger cohort studies are needed to confirm these findings.

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SA-PO599

Fibroblast Growth Factor 23 and Fetuin A Levels in Pre-Dialysis Stage 4-5 Chronic Kidney Disease Patients with Aortic Calcification: A Case Control Study Vijayakumar Theophilus-Sunder, Anna T. Valson, Vinoo George David, Santosh Varughese, Tamilarasi Veerasamy. *Dept of Nephrology, Christian Medical College, Vellore, Tamil Nadu, India.*

Background: Vascular calcification (VC) contributes to the increased cardiovascular mortality seen in CKD. However, not everyone with advanced CKD develops VC, indicating that circulating levels of factors that modulate VC may play a role in determining individual susceptibility towards VC. We aimed to examine this hypothesis by measuring the levels of FGF-23 and Fetuin-A in a group of pre-dialysis CKD Stage 4-5 patients who had documented abdominal aortic calcification (AAC) and an age, gender and eGFR matched group of patients who did not have AAC.

Methods: Out of a pre-existing cohort of 710 patients with CKD Stage 4-5, 28 patients with AAC (Group 1, cases) were compared with an equal number of age, gender and eGFR matched patients without AAC (Group 2, controls) with respect to their demographic and biochemical parameters, including FGF-23 and Fetuin-A. AAC was assessed by lateral abdominal X ray, while Fetuin-A and intact FGF-23 were estimated by ELISA in serum.

Results: Groups 1 and 2 were matched for age (mean age 57.7 and 57.8 years respectively, p = 0.938), gender (84.6% males in both groups) and eGFR (median eGFR 14.5 and 13.1 respectively, p = 0.826), and were not significantly different with respect to risk factors for AAC such as presence and duration of diabetes, hypertension, smoking and obesity. Levels of calcium, phosphorus, PTH, 25 (OH) vitamin D, serum cholesterol, triglycerides, HDL and LDL were also comparable between the two groups. However, median FGF23 levels were significantly higher in Group 1 [25.2, (Q1= 14, Q3=34.2)] compared to Group 2 [12.1 (Q1 = 6.6, Q3 = 14.1), n = < 0.001]. Median Fetuin-A levels were also significantly higher in Group 1 [5.5 (Q1=4.4, Q3=6.5)] compared to Group 2 [4.1 (Q1 = 3.6, Q3 = 5.7, n = 0.034).

Conclusions: Pre-dialysis patients with Stage 4-5 CKD with AAC, had higher FGF-23 and Fetuin-A levels compared to age, gender and eGFR matched patients who did not have AAC. The nature and mechanism of this association between elevated FGF23 and Fetuin-A levels and AAC requires further exploration.

SA-PO600

Lack of Association Between Serum Osteoprotegerin, Osteopontin and Fetuin-A Levels and the Longitudinal Changes in Arterial Stiffness in CKD Patients Undergoing Renin-Angiotensin System Blockade Cecilie Lyngso,¹ Marie Frimodt-Moller,² Marianne Rix,² Anne-Lise Kamper,² Svend Strandgaard,¹ Arne Hoj Nielsen,¹ Allan Flyvbjerg,³ Mette Bjerre.³ ¹Dept of Nephrology, Herlev Hospital, Herlev, Copenhagen, Denmark; ²Dept of Nephrology, Rigshospitalet, Copenhagen, Denmark; ³The Medical Research Laboratory, Dept of Clinical Medicine, Aarhus Univ, Aarhus, Denmark.

Background: Osteoprotegerin (OPG), osteopontin (OPN) and fetuin-A, have been suggested to participate in the accelerated development of arteriosclerosis seen in patients with chronic kidney disease (CKD). We have previously shown that measures of vascular stiffness were significantly reduced after 24 weeks of treatment with renin-angiotensin

system (RAS) blocking agents. The aim of this longitudinal post hoc study was to investigate whether serum levels of OPG, OPN and fetuin-A were associated with these same changes in markers of arterial stiffness found in CKD patients treated with RAS blocking agents.

Methods: Serum OPG, OPN and fetuin-A levels were measured in 57 patients with CKD stage 3-5, mean eGFR 29 ml/min, as a post hoc analysis of data acquired during a 24-week controlled trial in which patients were randomized to treatment with 16 weeks of monotherapy with either enalapril or candesartan followed by 8 weeks of dual blockade. Serum levels were obtained upon study entry and after 16 and 24 weeks of RAS blocking therapy and compared to aortic pulse-wave velocity and augmentation index.

Results: Except for a significant correlation between OPG and central pulse pressure (p < 0.05), serum levels of OPG, OPN and fetuin-A did not correlate to markers of vascular stiffness. There were no significant changes in serum levels of OPG, OPN and fetuin-A when monotherapy with enalapril or candesartan was compared to dual blockade.

Conclusions: The present results do not corroborate the use of OPG, OPN and fetuin-A as surrogate markers for vascular stiffness in patients with CKD.

SA-PO601

Hyperuricemia Is Significantly Associated with Coronary Artery Calcification and Vascular Stiffness in Asymptomatic Subjects Undergoing General Health Examination Ah Ran Choi, Hae Yeul Park, Seok-Hyung Kim, Hoon Young Choi, Sung-Kyu Ha, Hyeong Cheon Park. *Nephrology, Gangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Recent studies suggest that hyperuricemia may be associated with increased adverse cardiovascular events even in healthy subjects. Quantity of coronary artery calcium (CAC) correlates with atherosclerotic plaque burden and increased cardiovascular events. This study aimed to determine the relationship between serum uric acid level (sUA) and brachial-ankle pulse wave velocity (ba-PWV), coronary artery calcium score (CACS) as well as other traditional cardiovascular risk factors in asymptomatic subjects.

Methods: We consecutively enrolled 4,703 asymptomatic subjects who underwent ba-PWV and coronary CT angiography as part of a general health examination. A high ba-PWV group, those having increased vascular stiffness, was defined as ba-PWV greater than 1497.5 cm/s (75th percentile). The subjects were stratified into four groups according to sUA.

Results: Mean age of enrolled subject was 52.8 ± 9.4 years, 61 % of the study participants were male. Eight point four percent of the study participants showed CACS greater than 100. The adjusted odds ratio (OR, 95% confidence interval) for the presence of high ba-PWV in the second to fourth sUA quartile vs. first sUA quartile was 1.45 (1.137-1.840, P<0.003), 1.42 (1.081-1.866 P<0.012), 1.66 (1.246-2.218, P<0.001), respectively after adjusting for age, gender, diabetes, hypertension, smoking, body mass index (BMI), estimated glomerular filtration (eGFR), fasting blood sugar (FBS) and calculated LDL. Moreover, subjects with CACS greater than 100 also showed that fourth quartile of sUA was associated with high ba-PWV compared with the first quartile of sUA [OR 2.4, (1.65-3.47, P<0.001)]. Multivariate linear regression analysis demonstrated that old age, male, hypertension, diabetes, BMI, FBS, eGFR and sUA were significantly associated with mean ba-PWV and log transformed CACS.

Conclusions: Our results show that sUA is an independent risk factor for increased vascular stiffness and coronary atherosclerosis in asymptomatic adults undergoing health examination.

SA-PO602

Abdominal Aortic Calcification Score on Plain Radiograph as a Predictor of Coronary Artery Calcification Score on Computed Tomography and T-Score on BMD in Dialysis Patients Eu Gene Jeong,¹ Su Mi Lee,¹ Young Ki Son,¹ Dongyeol Lee,² Hansae Kim,² Sung Hyun Son.³ ¹Dept of Internal Medicine, Dong A Univ Hospital, Busan, Republic of Korea; ²Dept of Internal Medicine, Bong Seng Memorial Hospital, Busan, Republic of Korea; ³Dept of Internal Medicine, BHS Han Seo Hospital, Busan, Republic of Korea.

Background: Not only coronary artery calcification scores (CACS) on computed tomography (CT) but also several VC scores on plain radiographs can predict cardiovascular events. However, there is no study about the correlation between CACS on CT and VC scores of several sites on plain radiographs. Therefore, we evaluated which VC scores among several VC scores on plain radiographs are a predictor of CACS on CT in dialysis patients. We also investigated the association between VC scores and bone mineral density (BMD).

Methods: We conducted this single center cross-sectional study from March 2013 to September 2014. We checked the plain radiographs of the feet, hands, pelvis, and lateral lumbar spine and estimated the VC scores. CACS on CT and BMD were evaluated. We defined severe CACS as CACS > 1000. FGF-23, fetuin-A, osteoprotegerin (OPG) and receptor activator of NF-κB ligand (RANKL) were analyzed with ELISA.

Results: The mean ages of 61 patients including 38 hemodialysis(HD) and 23 peritoneal dialysis(PD) patients were 58.6±10.2 years. The prevalence rate of significant VC was 75.4% and prevalence rate of severe CACS was 26.2%. The OPG levels were higher in patients with severe CACS(p=0.019) and significant VC(p=0.009). Patients with AAC score≥5 had lower T score of wrist and hip than patients with AAC score<5. CACS is positively correlated with AAC score(r=0.639, p<0.001), VC score of the hands and pelvis (r=0.494, p<0.001). AAC score is negatively correlated with T score of wrist(right: r=-0.286, p=0.027) and hip(right: r=-0.259, p=0.045)on BMD. AAC score(B=59.4, C.I.=18.3-100.6, p=0.006) and VC score of the hands and pelvis(B=225.8, C.I.=69.7-381.8, p=0.006)on plain radiographs were independently associated with CACS on CT.

Conclusions: AAC score among several VC scores on plain radiographs is the most reliable predictor of CACS on CT and T score on BMD in dialysis patients.

SA-PO603

Total Body Multislice Computed Tomography as a Gold Standard of Vascular Calcification

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Background: Vascular calcification (VC) is a marker of cardiovascular risk in CKD patients. Imbalance of calcium-phosphate parameters and secondary hyperparathyroidism (sHP) has been proposed as inductors of VC. Traditionally VC has been evaluated with Kauppila, Adragao and coronary Agatston scores but they are limited to restricted body areas and may underestimate total VC. We proposed a new method to assess VC in CKD patients with mild sHP based on total body multislice computed tomography (MSCT) without contrast.

Methods: Multicenter transversal study which included incident dialysis patients with mild sHP (PTH >150pg/dL) after signed informed consent. Kauppila and Adragao scores were determinate on abdominal and pelvis/hand X-ray, respectively. Total body area calcification (cm²) was measured by MSCT. Patients with a total calcified area of >150 cm² were considered calcified. Sensibility and specificity of Kauppila and Adragao scores were calculated considering total calcified body area > 150 cm² as reference.

Results: We enrolled 22 patients (13 hemodialysis / 9 peritoneal dialysis), 45% diabetics, 62±15 years old. Mean±SD were: phosphorus 4.6±1.5mg/dl, calcium 9.21±0.44mg/dL and parathyroid hormone 278±132pg/dL. They presented mean Kauppila score of 6.9±6.9, Adragao score of 2±3.7 and total calcified area of 112.6±196.7cm². 77% patients were calcified, considering positive if overall calcified area was >150cm². Diabetics and those with previous cardiovascular events had higher total body calcified area, whereas gender and type of dialysis didn't demonstrate any influence on calcification. Sensibility of Kauppila and Adragao scores were 70% and 30% respectively, whereas specificity of both of them was 100%.

Conclusions: It is possible to evaluate the overall body calcified area in patients with ESRD by multislice computed tomography, which could be considered as a potential gold standard of global vascular calcification in those patients.

SA-PO604

Comparison of Mineral Metabolic Markers and Therapy in Chronic Hemodialysis Patients with Different Degree of Abdominal Aortic Calcification Score

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Background: The correlations of vascular calcifications with different markers of CKD-MBD and also its therapy are not always consistent across the studies and cross-sectional associations are favoured over long-term analyses. We therefore aimed to evaluate laboratory markers and therapy load over a longer period in chronic hemodialysis patients with different severity of abdominal aortic calcification (AAC).

Methods: In hemodialysis patients AAC was determined by lateral lumbar radiography and quantified by Kauppila score. Patients were divided in two groups according to median AAC score of the whole group. Mean active vitamin D and cinacalcet intake for last 4 years and calcium carbonate for last 10 years (or whole dialysis vintage for those on dialysis for shorter time) and mean mineral metabolism markers (Ca, P, iPTH, CaxP product and alkaline phosphatase (AF) for last 4 years) were compared between the groups.

Results: 20 patients with high AAC score were significantly older (72±9 vs. 59±15 years, p=0.003) and more often diabetic (15% vs. 2%, p=0.04) compared to 19 patients with low score, but there was no difference in dialysis vintage (6.4±4.8 vs. 5.3±4.2 years, p=0.44) or presence of cardiovascular disease. We found no difference in mean calcium carbonate dose (4.1±1.6 vs. 4.4±1.9 g/day, p=0.59) or mean cinacalcet dose (21±26 vs. 12±17 mg/day, p=0.18), but significantly higher mean calcitriol-equivalent dose of active vitamin D (1.7±0.8 vs. 0.9±0.8 mg/week, p=0.03). There was no significant difference in Ca, CaxP product, iPTH or AF, but P was significantly higher (1.6±0.2 vs. 1.4±0.3 mmol/l, p=0.03) in group with high AAC score.

Conclusions: In patients with higher AAC score higher mean active vitamin D dose and higher phosphate levels over a long period of time were found in addition to older age and more diabetes. We find this retrospective analysis important because treatment and laboratory values were evaluated over a prolonged period.

SA-PO605

Influence of the Bone Mineral Disorder on Vascular Calcification Occurrence and Progression in Hemodialysis Patients

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Background: Cardiovascular disease is the main cause of death in hemodialysis patients; vascular calcification (VC) is common among them. The main objective of this study was to evaluate the influence of bone mineral disorders in VC and its progression in a prospective cohort of patients. Secondly, we intend to identify clinical, laboratory and nutritional predictors of the presence and progression of VC.

Methods: Adult patients undergoing HD for ≥90 days were included. At the beginning of and after 12 months Kauppila and Adragao methods were used to determine the VC score

(VCS); and clinical, hormonal, inflammatory, biochemical, and nutritional markers were measured. Bone biopsy and histomorphometric analysis were performed at the beginning of follow up.

Results: Sixty patients completed the study; of them 41.7% were male, 43.4% diabetic, and the mean age was 56. 7±13.8 years. At the beginning of the follow-up, 75% of the patients exhibited VC. Age > 60 years (Odds ratio=50.2, 95%CI= 4.1-618.4, p=0.002), FGF23 levels > 3000 Ru/ml (Odds ratio=5.7, 95%CI= 1.00-329, p=0.05), and serum fetuin A >673 g/l (Odds ratio=7.34, 95%CI= 1.26-43.7, p=0.03) were independent predictors of VC. Regarding VC progression age > 60 years (Odds ratio=4.3, 95%CI= 1.003-18.5, p=0.049), serum fetuin A >673 g/l (Odds ratio=6.4, 95% CI= 1.47-27.9, p=0.01), no use of statins (Odds ratio=5.6, 95%CI= 1.13-28.1, p=0.03) were the only independent predictors. Bone turnover and histomorphometric findings were not associate with VC and its progression.

Conclusions: The present study reinforces the role of age, FGF23 levels, use of statins on the VC process and arises a paradoxical effect of serum fetuinA on VC and its progression, which deserves new and more specific investigations.

SA-PO606

Low Bone Mineral Density of Lower Extremities Associates with Coronary Calcification Score in End-Stage Renal Disease Patients

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Background: Kidney transplantation (Rtx) corrects many abnormalities in uremia but mineral and bone disorders and cardiovascular disease often persevere. We investigated associations between low bone mineral density (BMD) and coronary artery calcification (CAC) in patients (pts) with end stage renal disease (ESRD) undergoing living donor Rtx.

Methods: In 40 pts (aged 44 ± 13 years; 60% male) undergoing living donor Rtx, BMD measurements were made before (n=19), close to (n=40) and after (n=13) Rtx and CAC measurements (n=34) were also made close to Rtx. BMD was assessed by dual-energy X-ray absorptiometry (DXA) and CAC by computed tomography. We investigated the associations between BMD and CAC (measured at the same time). Logistic regression models were adjusted for age, gender and diabetes.

Results: Altogether 32% (11/34) pts had CAC Agatston score ≥ 100. CAC associated with age (rho = 0.46, p < 0.01) and diabetes (rho = 0.57, p < 0.001). At baseline, there were significant associations between CAC and BMD of upper extremities (rho = -0.49, p < 0.01), BMD of lower extremities (rho = -0.66, p < 0.001) and BMD of femoral neck (rho = -0.58, p < 0.001). In multivariate analysis adjusted for age, gender and diabetes, BMD of lower extremities remained as significantly lower in pts with CAC scores ≥ 100 (p < 0.05). No significant differences were seen between values of BMD obtained -2.0 [-4.4, -1.1] years before Rtx (n=19) as compared to BMD obtained close to Rtx at -0.1 [-0.7, 0.6] years (n=40) or 2.1 [1.1, 3.3] years after (n=13) Rtx. Sex-stratified analyses also showed no significant differences in BMD before, close to and after Rtx.

Conclusions: BMD of lower extremities is associated with CAC in ESRD pts undergoing living donor Rtx. No significant changes in BMD were found when comparing values before, close to and after Rtx. Further studies are required to elucidate the mechanism(s) linking BMD to CAC score in ESRD pts.

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SA-PO607

Association of Vascular Calcification Biomarkers with Peripheral Arterial Disease in Hemodialysis Patients

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Background: Vascular calcification is common in ESRD patients. We evaluated whether the vascular calcification biomarkers, namely osteoprotegerin (OPG), fetuin A, and matrix Gla protein (MGP) are associated with PAD among incident hemodialysis (HD) patients in the Predictors of Arrhythmia and Cardiovascular Events (PACE) study.

Methods: We performed a cross-sectional analysis among 402 participants in whom these biomarkers were measured at baseline. We defined PAD as ABI <0.9 or >1.4 and/or a documentation in the medical record at study entry. Using multivariable logistic regression we evaluated the association of OPG, fetuin A and MGP with prevalent PAD. Sensitivity analysis was performed in persons who had PAD defined only by medical records.

Results: PAD was prevalent in 28% (n=111) of the cohort. Mean age was 55 years, 72% were black. 60% were ever smokers, 58% had diabetes, 37% had coronary artery disease, and 69% hypercholesterolemia. The median OPG and MGP levels were 10.1 pmol/L and 1412 pM, respectively; the mean fetuin A level was 0.51 g/L. Adjusting for age, gender, race, Charlson co-morbidity index, smoking, diastolic blood pressure, mean serum phosphate, and mean dialysate calcium concentration, 1 pmol/L higher OPG was associated with 1.07-fold increased odds of PAD. There was no association of fetuin A or MGP with PAD. In sensitivity analysis, the association of OPG and odds of PAD was similar to the main results.

Association of Vascular Calcification Biomarkers with Odds of PAD		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
OPG, per 1 pmol/L higher	1.06 (1.02-1.11)	1.07 (1.01-1.13)
Fetuin A, per 1 g/L higher	0.88 (0.24-3.26)	1.25 (0.27-5.81)
MGP, per 1-log pM higher	0.98 (0.75-1.28)	0.91 (0.66-1.25)

Conclusions: In this population of incident HD patients at high risk of PAD, OPG was significantly associated with odds of PAD. Whether the elevation of OPG is causal to the development of PAD or whether it serves as a marker of disease severity needs to be explored.

Funding: NIDDK Support

SA-PO608

Association of Metabolic Syndrome with Aortic Arch Calcification and Outcome in Non-Diabetic Peritoneal Dialysis Patients Cheng Chia Lee,^{1,2} Kun-Hua Tu,^{1,2} Ya-chung Tian,^{1,2} Ming-Yang Chang,^{1,2} Chih-Wei Yang.^{1,2} ¹Dept of Nephrology, Kidney Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan; ²Chang Gung Univ, College of Medicine, Taoyuan, Taiwan.

Background: Vascular calcification (VC) is now recognized as an important risk factor for mortality in dialysis patients. Previous studies have shown conflicting results regarding the association of the metabolic syndrome (MetS) and mortality in patients on peritoneal dialysis (PD). Despite the controversial definition of MetS in PD patients, the association between MetS and the presence and severity of VC in the non-diabetic PD patients remained unknown.

Methods: We enrolled 277 non-diabetic PD patients into this study. Posterior-anterior chest X-ray were assessed for the aortic arch calcification (AoAC). Frequency of different components and their constellation as MetS were determined according to the modified Adult Treatment Panel III criteria. Using multinomial logistic regression, the factors determine baseline AoAC were analyzed. We used Kaplan Meier analysis to assess the impact of MetS on both mortality and technique failure.

Results: Mean age was 48.4 ± 13 years and 43.1% (n=118) had metabolic syndrome. 179 patients were classified as no visible calcification (AoAC grade 0), 51 patients as mild calcification (AoAC grade 1), and 47 patients as moderate to severe calcification (AoAC grade 2+3). The adjusted odds ratio for AoAC grade 1 was 3.03 (95% CI: 1.34-6.84) and for AoAC grade 2+3 was 6.25 (95% CI: 2.26-17.27) among patients with MetS as compared with those without MetS. Multivariate linear regression analysis showed that MetS (P < 0.001) was independent risk factor for higher inflammation, as denoted by high sensitivity C-reactive protein. Over a mean of 45.9 months of follow-up, 34 patients died. Kaplan Meier analysis demonstrated that the incidence of mortality and technique failure does not differ in patients with and without MetS.

Conclusions: MetS was independently associated with the presence and severity of AoAC but cannot predict mortality or technique failure in non-diabetic PD patients. Nevertheless, non-diabetic PD Patients with MetS warrant more aggressive risk factor management to reduce the risk of VC.

SA-PO609

Increased Peripheral Arterial Calcification in Patients Receiving Warfarin Kum Hyun Han,² W. Charles O'Neill.¹ ¹Renal Div, Emory Univ, Atlanta, GA; ²Internal Medicine, Inje Univ College of Medicine, Ilsan Paik Hospital, Gyeong, Korea.

Background: Matrix gla-protein is a vitamin K-dependent inhibitor of vascular calcification, and genetic deficiency or inhibition with warfarin produces medial vascular calcification in animals, raising concerns that warfarin may promote vascular calcification in humans. We recently showed that warfarin use is associated with increased breast arterial calcification but whether this is reflective of other arteries or occurs in men as well is unclear. Therefore, we compared the prevalence of calcification in peripheral arteries in patients with and without warfarin therapy.

Methods: A random sample from a computerized search of medical records yielded 430 patients with x-rays performed during or after warfarin therapy. Each was matched to a patient without warfarin exposure based on age and diabetes. Patients with warfarin exposure < 1 month, history of ESRD, or serum creatinine > 2.0 were excluded. X-rays were reviewed visually for arterial calcification.

Results: Mean age was 66.9 ± 0.8, 41% were males, and 34% had diabetes. The indication for warfarin was atrial fibrillation in 45% and venous thrombosis or embolism in 44%, and mean duration of warfarin was 4.8 yrs (range: 1 month to 38 yrs). 68% were on warfarin at the time of the x-ray and the remainder had been off warfarin for a mean of 2.4 yrs (range: 1 day to 25 yrs). Serum calcium was slightly lower (9.04 ± 0.03 vs. 9.17 ± 0.03, p=0.0005) in the warfarin patient but serum creatinine and phosphorus did not differ. Prevalence of arterial calcification was 44% greater in warfarin patients (30.2% vs. 20.9%, p=0.0023) but not on x-rays performed prior to warfarin (26.4% vs. 22.4%, n=156), indicating that the increase was due specifically to the warfarin and not to underlying disease or other patient characteristics. The increase in calcification was seen only after > 5 yrs of warfarin and only in the ankle and foot. It was similar in men and women and greatest (2.4-fold) in patients under age 60 (15% vs. 6.3%, p=0.04).

Conclusions: Warfarin use is associated with lower extremity arterial calcification in both men and women independent of age, diabetes, and other patient characteristics.

Funding: Clinical Revenue Support

SA-PO610

Matrix Gla Protein and Vascular Calcification in Patients with End Stage Renal Disease Hannes Olauson,¹ Christian L. Meuwese,¹ Karin Luttrupp,¹ Annika Wernerson,¹ Peter F. Barany,¹ Cees Vermeer,² Peter Stenvinkel.¹ ¹CLINTEC, Karolinska Inst, Sweden; ²VitaK, Maastricht Univ, Netherlands.

Background: Vascular calcification (VC) is a common and severe consequence of end-stage renal disease (ESRD). Matrix Gla protein (MGP) is a calcification inhibitor expressed by the vasculature that counteracts the development of VC.

Methods: In 84 ESRD patients undergoing LD-Tx at Karolinska University Hospital, biopsies from the inferior epigastric artery were obtained during surgery. Vascular calcification was assessed by von Kossa staining both by manual scoring (0-3) and by semi-automated analysis (%). Total uncarboxylated MGP (t-ucMGP) and dephospho-uncarboxylated MGP (dp-ucMGP) were measured in plasma. Tissue MGP expression was quantified in arterial biopsies by TaqMan rtPCR. DNA methylation of the MGP gene was assessed in peripheral blood from 12 ESRD patients and 12 healthy controls.

Results: 50 patients (59.5%) had low VC scores (0 and 1) and 34 (40.5%) patients high VC scores (2 and 3). Plasma levels of dp-ucMGP were higher in patients with high VC scores compared to patients with low VC scores (2214 [1413-2995] vs. 1701 [1275-2233] pmol/L, p<0.05) and also associated with calcification (%) (Fig 1A: β [95%CI]: 26 [7 to 45] p<0.01). Additionally, calcification (%) associated with arterial expression of MGP (Fig 1B: β [95%CI]: 0.04 [0.02 to 0.06] p<0.0001). t-ucMGP levels were not associated with measures of VC. DNA methylation of the MGP gene was significantly lower in patients with ESRD compared to healthy controls (adjusted p<0.01).

Figure 1

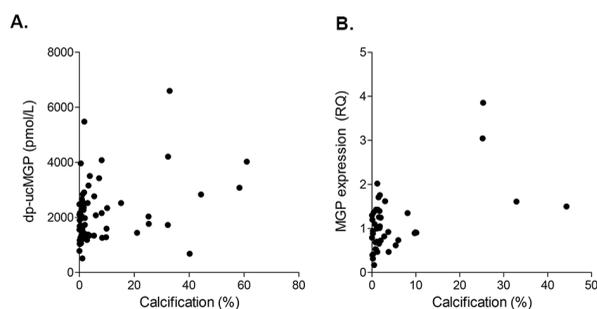


Figure 1. The association between calcification % (as assessed by semi-automated analysis) and A) plasma dp-ucMGP levels, and B) tissue MGP expression.

Conclusions: Tissue and plasma levels of dp-ucMGP were higher in patients with VC versus those without, possibly indicating a compensatory up-regulation of MGP to prevent further progress. The observation that the methylation of the MGP gene was lower in ESRD than in controls suggests that the altered expression could be due to epigenetic regulation.

Funding: Government Support - Non-U.S.

SA-PO611

A Nationally Representative Case Control Study of Calciphylaxis Risk Factors Sagar U. Nigwekar,¹ Sophia Zhao,^{1,2} Julia Beth Wenger,¹ Franklin W. Maddux,² Jeffrey L. Hymes,² Ravi I. Thadhani,¹ Kevin Chan.^{1,2} ¹MGH; ²Fresenius Medical Care North America.

Background: Prior studies evaluating calciphylaxis risk factors suffer from sample size limitations and none examine whether characteristics at dialysis initiation predict calciphylaxis risk.

Methods: Data for this matched case control study were derived from hemodialysis (HD) population at the Fresenius Medical Care North America (FMCNA). Cases were identified from FMCNA calciphylaxis prospective database. Controls (HD patients without calciphylaxis) were matched to cases on age, sex, and race. Data on variables at HD initiation were abstracted. Variables for multivariable logistic regression analyses were identified using stepwise selection.

Results: We analyzed 1,025 calciphylaxis cases (52% biopsy-confirmed) and 2,050 controls. Body mass index, diabetes mellitus (DM), serum parathyroid hormone (PTH) level, use of warfarin and phosphate binders were higher whereas serum calcium and active vitamin D use were lower at HD initiation in cases compared to controls.

	Cases (n=1,025)	Controls (n=2,050)	P value
Age, years	54±14	54±14	NA
Sex, female %	67	67	NA
Race, white %	49	49	NA
BMI, kg/m ²	36.3±9.9	30.3±8.5	<0.001
DM, %	61.2	44.4	<0.001
Albumin-corrected calcium, mg/dL	8.6±1.3	8.8±1.0	<0.001
Phosphorous, mg/dL	5.1±2.3	4.9±1.7	0.18
PTH, pg/mL (median, IQR)	339 (153, 658)	288 (129, 523)	<0.001
Albumin, g/dL	3.3±0.8	3.5±0.6	<0.001
Warfarin, %	23.3	7.4	<0.001
Active vitamin D, %	70.8	80.9	<0.001
Cinacalcet, %	7.2	4.3	0.06
Phosphate binder, %	65.5	58.5	0.04
Statin, %	44.3	38.0	0.67
Insulin injections, %	25.6	15.5	<0.001

No significant differences were noted for serum phosphorous, dialysate calcium, use of statins and cinacalcet. In DM subgroup, insulin injection use was more common in cases. In multivariable analyses, obesity (OR: 2.55, 95% CI: 1.82-3.59), DM (OR: 2.63, 95% CI: 1.88-3.69), use of warfarin (OR: 3.60, 95% CI: 2.40-5.41) and insulin injections (OR: 1.29, 95% CI: 1.07-1.89) were associated with higher risk. Similar results were noted in analyses restricted to biopsy-confirmed cases.

Conclusions: Obese, diabetic HD patients treated with insulin injections or warfarin are at high risk for calciphylaxis.

Funding: Private Foundation Support

SA-PO612

Calciphylaxis Quality Improvement Project and Case Series Rohan V. Mehta, Jean Luc Franck, Jason Cobb. *Renal Div, Emory Univ, Atlanta, GA.*

Background: Calciphylaxis (Calcific Uremic Arteriolopathy) is a serious condition characterized by extended length of stays and multiple hospital admissions. The treatment of calciphylaxis can become a burden on the healthcare system especially with the demands on hospital systems to become more efficient. The lengths of stay & 30-day readmission rates are becoming a measure of hospital quality. We developed a multidisciplinary team including nephrologists, hospitalists, dermatologists, hospital administration, nurses, wound care staff, social workers, dieticians, and palliative care. The purpose of the team is to improve the quality of care of our calciphylaxis patients. In development of this quality improvement project we began by examining our baseline patient population. We are reporting our baseline data as a case-series.

Methods: Retrospective chart review of calciphylaxis patients from 2001-2014 in our single center hospital which includes academic and community physicians. Baseline data reported included age, calcium, phosphorus, PTH, albumin, hemoglobin, creatinine, BUN, and the use of warfarin. Treatment options, the length of stay, and number of admissions were reported.

Results: In 20 reported patients, 19 were African-American. Average age was 61 years old. Average calcium levels of 8.8 mg/dl and phosphorus of 5.5 mg/dl. The average PTH was 573, albumin 2.75 gm/dl, hemoglobin of 10.4 gm/dl BUN of 42, and creatinine 6.5 md/dl. 13 patients received hyperbaric oxygen treatment, 9 patients received sodium thiosulfate infusions, and 6 patients received cinacalcet. 11 patients were using warfarin for medical conditions including atrial fibrillation and deep venous thrombosis. The average length of stay was 45 days and 3 admissions per patient.

Conclusions: We reported one of the largest single center and predominant African-American calciphylaxis case series. In comparison to other reported calciphylaxis series our average PTH was lower and a high percentage of our patients were using warfarin at time of diagnosis. Future tasks include testing if the multidisciplinary quality improvement team interventions can improve our patient quality of care and hospital goals such as reductions in length of stay and 30-day readmission rates.

SA-PO613

Calciphylaxis – A Multi-Interventional Treatment Regimen Including Vitamin K Supplementation Might Reduce Mortality in Chronic Kidney Disease Patients Daniel A. Hochfellner,¹ Barbara Binder,² Werner Ribitsch,¹ Alexander R. Rosenkranz,¹ Gernot Schilcher.¹ ¹Clinical Div of Nephrology, Dept of Internal Medicine, Medical Univ of Graz, Graz, Austria; ²Dept of Dermatology, Medical Univ of Graz, Graz, Austria.

Background: Calciphylaxis is a rare disease predominantly affecting patients with chronic kidney disease (CKD) with a high mortality mainly due to wound infection. Recently, multimodal therapy schemes including sodium thiosulfate (STS) have been established. The role of a standardized Vitamin K supplementation remains unclear.

Methods: In a retrospective study we evaluated the impact of a standardized, multi-interventional treatment regimen on the mortality of calciphylaxis patients treated at the Clinical Department of Nephrology, Medical University of Graz, Austria between January 2009 and February 2014. Patients were treated with STS, dermatological wound management and high dose supplementation of vitamin K1 (Phytomenadion 30mg/week). The primary endpoint was mortality compared to the present literature. Secondary endpoints included gender distribution, number of biopsy proven cases, analysis of triggering events and time from event to diagnosis. Data were collected from medical records.

Results: 20 patients with newly diagnosed Calciphylaxis at different CKD stages (CKD 5, n= 15; CKD 4, n= 3; CKD 3, n= 1; no CKD, n= 1.) were included. The mortality was 25% versus 52% compared to recent literature. Gender distribution and amount of biopsy proven cases were comparable to other retrospective studies. 12 patients (60%) had a known preceding event such as trauma possibly having triggered development of calciphylaxis. The period from event to diagnosis was 103±94 days. 19 patients (95%) received STS. In contrast to other multimodal therapeutic concepts 95% (19) of our patients additionally received high dose vitamin K supplementation.

Conclusions: In our cohort calciphylaxis was associated with a markedly reduced mortality as compared to published outcome data. We hypothesize that supraphysiological supplementation of vitamin K in addition to thiosulfate therapy and our multi-interventional treatment regimen play an important role in the treatment of calciphylaxis.

SA-PO614

The German Calciphylaxis Registry Vincent Brandenburg,¹ Jürgen Floege,² Joanna Korbil,¹ Markus Ketteler.³ ¹Cardiology, RWTH Aachen Univ Hospital, Aachen, Germany; ²Nephrology, RWTH Aachen Univ Hospital, Aachen, Germany; ³Nephrology, Klinikum Coburg, Coburg, Germany.

Background: Calciphylaxis (CUA) is a rare disease and for patients a devastating condition associated with high morbidity and mortality. CUA is characterised by painful, ischemic, partly necrotic skin ulcerations. Pathomorphologically, media calcification of cutaneous arterioles and extracellular matrix remodelling are the hallmarks of CUA. Epidemiology and risk factors are incompletely understood. Referring patients to specialized units is limited due to high disease burden.

Methods: Therefore, we established an internet-based observational registry in 2006 (www.calciphylaxie.de) to allow online notification for pts with CUA. The registry includes a comprehensive data base with 71 parameters concerning patient and laboratory data, clinical background and presentation as well as therapeutic strategies. The diagnosis of CUA is made on clinical and/or histological grounds by the referring physician.

Results: Until Febr 2015 n=253 patients with CUA have been recorded (~ 30 pts/year at constant rate) with a median delay of 28 days after onset: 99% Caucasians, 60% females; 76% HD and 10% PD patients; median age 66 (IQR 61-76) years. Co-medication at the time of diagnosis: 75% ESA, 51% vitamin K antagonists (VKA). Skin biopsy was done in 45%, prior PTex in 12%; major skin lesion in 80% at the legs. Median lab data upon diagnosis of CUA: Alk Phos 113 U/L (IQR 86 - 167); PTH 173 ng/L (IQR 73-390), total calcium 2.20 mmol/L (IQR 2.04-2.36), phosphorus 1.62 mmol/L (IQR 1.28-2.00). Among the most frequently recorded therapeutic procedures were: surgical necrosectomy (plus antibiotics), intensifying dialysis modality, reduction of calcium supply, i.v. sodium-thiosulfate application. Survival was analyzed in a subgroup of 91 pts: Median survival time was 516 days after online notification.

Conclusions: CUA is a rare disease among ESRD pts with high mortality. Therapeutic strategies vary significantly among centers; EBM guidelines are absent. VKA usage appears to be risk factor for CUA in ESRD pts. The German CUA registry is a valuable tool to collect data and may become a basis for a European registry (EuCalNet).

Funding: Pharmaceutical Company Support - Sanofi, Amgen

SA-PO615

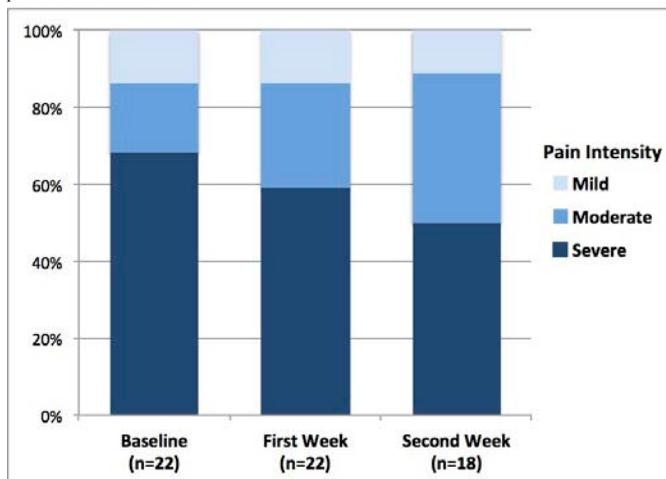
Evaluation of the Effects of Sodium Thiosulfate Treatment on Calciphylaxis Pain Guillermo Ortiz, Joshua Wibecan, Julia Beth Wenger, Ravi I. Thadhani, Sagar U. Nigwekar. *Nephrology Div, Massachusetts General Hospital, Boston, MA.*

Background: Intravenous sodium thiosulfate (STS) is commonly prescribed to treat calciphylaxis, a highly fatal disease that presents with excruciating painful skin lesions. Anecdotal reports suggest that STS may improve calciphylaxis associated pain (CAP) within 2 weeks of initiation; however, systematic evaluation of effects of STS on CAP is lacking.

Methods: This observational study included 22 patients with biopsy-confirmed calciphylaxis who were hospitalized at our center for ≥ 2 weeks during 2012-2014 for newly diagnosed calciphylaxis and were treated with STS. Medical records were reviewed to abstract clinical data including CAP severity (0-10 scale) and analgesic use. CAP scores at baseline, 1-week, and 2-week time-points were noted and classified into mild (1-3),

moderate (4-6), and severe (7-10) categories. Responders were patients who reported $\geq 30\%$ improvement in CAP severity score from baseline during the first 2 weeks of treatment. Predictors of response and association between CAP response during the first 2 weeks of STS treatment and 6-month outcomes (skin lesion status, mortality) were examined in univariate logistic regression analyses.

Results: Median age was 60 years (Range: 52-67), 59% were males, 95% were whites, 55% were on dialysis, 36% had chronic kidney disease not requiring dialysis, and 9% had normal kidney function. Median duration between lesion appearance and STS initiation was 12 weeks (Range: 6-19). There was a trend toward decrease in severe CAP from baseline to 2-weeks (figure 1) despite steady doses of opiate medications. No significant predictors of CAP response were observed and CAP improvement at 2-weeks did not predict 6-month outcomes.



Conclusions: A large prospective trial is needed to ascertain the effects of STS on CAP.

SA-PO616

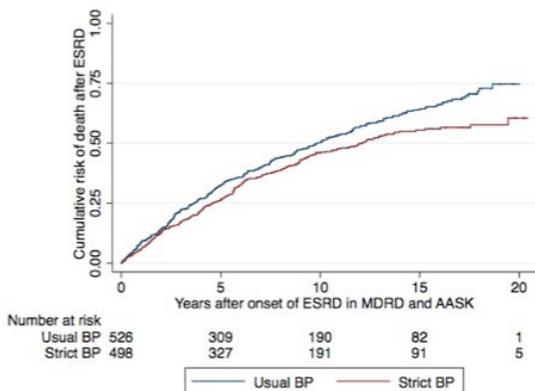
Long-Term Impact of Strict Blood Pressure Control During CKD on Mortality Risk After ESRD Elaine Ku,¹ Lawrence J. Appel,² Jennifer J. Gassman,² Miroslaw Smogorzewski,² Mark J. Sarnak,³ David V. Glidden,¹ Chi-yuan Hsu.¹ ¹UCSF; ²AASK; ³Tufts.

Background: In extended follow-up of the Modification of Diet in Renal Disease (MDRD) study, we reported that strict BP control did not lower risk of ESRD but associated with lower mortality risk after ESRD (HR 0.72 [95% CI 0.58-0.89]) (Ku KI 2015). To further address this issue, we conducted parallel analyses in the African American Study of Kidney Disease (AASK) and *post-hoc* pooled analyses of AASK and MDRD.

Methods: AASK randomized 1094 persons with CKD attributed to hypertension to strict (mean arterial pressure [MAP] <92) versus usual BP control (MAP <102-107 mmHg) between 1995-2001. We ascertained death and ESRD status through 6/2012 via US Renal Data System (USRDS) and Social Security Death Index for 1067 enrollees with non-missing identifiers.

Results: In extended AASK follow-up, 397 cases of ESRD and 475 deaths (208 after ESRD) occurred. The risk for ESRD was 0.94 (95% confidence interval [CI] 0.77-1.14), overall mortality risk was 0.92 (95% CI 0.77-1.10), and risk for death after ESRD onset was 0.92 (95% CI 0.70-1.20) comparing strict versus usual BP arms. Thus, the CI for death after ESRD was wider and included the prior MDRD estimate. In pooled MDRD/AASK analysis (N=1907), the corresponding risk for ESRD (1024 cases) was 0.90 (95% CI 0.80-1.02), overall mortality (N=920) was 0.87 (0.76-0.99), and risk for death after ESRD (N=532) was 0.78 (95% CI 0.75-0.92).

Mortality Risk after ESRD during Long-term Follow-up



Conclusions: Although AASK analyses did not achieve conventional statistical significance for outcomes of interest, potentially due to inadequate power, pooled results

demonstrated a continued association between strict BP control and lower mortality risk after ESRD. These data provide the most persuasive evidence to date that aggressive management of BP prior to ESRD may have a persistent benefit after ESRD onset.

Funding: NIDDK Support

SA-PO617

Obesity, Renin-Angiotensin System Blockade, and Chronic Kidney Disease: A Population-Based Cohort Study Jordana B. Cohen, Alisa J. Stephens-Shields, Michelle Denburg, Amanda Hyre Anderson, Raymond R. Townsend, Peter P. Reese. *Univ of Pennsylvania, Philadelphia, PA.*

Background: Obesity substantially increases the risk of the development and progression of chronic kidney disease. Adipose tissue expresses all of the components of the renin-angiotensin system (RAS), which is an important contributing factor to the high prevalence of hypertension in obese patients, and drives renal hyperfiltration and subsequent glomerular injury.

Methods: We performed a retrospective cohort study using The Health Improvement Network, a primary care database with comprehensive demographic, laboratory, and pharmacologic data from patients in the United Kingdom. We evaluated the effect of time-updated exposure to RAS blockade versus all other antihypertensive medications in obese, hypertensive, non-diabetic patients with normal or mildly reduced kidney function using a Cox proportional hazards model as estimated by pooled logistic regression to assess the hazards of developing a 50% reduction in estimated glomerular filtration rate (eGFR) or end stage renal disease. In addition to adjusting for baseline comorbidities including age, gender, socioeconomic status, cardiovascular disease, and body mass index (BMI), we adjusted for time-varying covariates including systolic blood pressure (SBP), number of antihypertensive medications, use of mineralocorticoid antagonists, and eGFR.

Results: There were 219,701 patients that met inclusion criteria, with a median 4.9 years of follow-up. Median baseline eGFR was 72.6 mL/min/1.73m², median SBP was 146 mmHg, and median BMI was 32.8 kg/m². 59% of patients were on RAS blockade at baseline, and 69% of patients were on it for at least half the duration of follow-up. Taking into account time-updated exposure, there was a significantly reduced hazard of adverse renal outcomes in patients treated with RAS blockade compared to those treated with other antihypertensive medications (HR 0.93, p<0.01).

Conclusions: This study, conducted in a large real-world cohort of patients with detailed and time-updated data about blood pressure treatment, provides important evidence that RAS blockade may protect against deterioration in renal function among obese, hypertensive, non-diabetic patients.

Funding: NIDDK Support

SA-PO618

Distribution and Prognostic Value of Central Blood Pressure in Chronic Kidney Disease Yun Jung Oh,¹ Su Mi Lee,² Ji Yong Jung,³ So Mi Kim,⁴ Chungsik Lee.¹ ¹Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea; ²Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; ³Dept of Internal Medicine, Gacheon Univ Gil Hospital, Incheon, Republic of Korea; ⁴Dept of Internal Medicine, Jeju National Univ Hospital, Jeju, Republic of Korea.

Background: Central blood pressure (CBP) has been shown to be a better predictor for cardiovascular events and target organ damages than brachial blood pressure. However, little is known about comparative values of CBP and brachial BP in chronic kidney disease (CKD) population. We investigated the distribution of CBP and evaluated the comparative values of CBP and brachial BP for the prediction of renal progression in both CKD and non-CKD population.

Methods: We conduct this study using data from 868 subjects who underwent CBP measurement by the radial artery tonometric method between 2009 and 2013. Demographic and clinical characteristics were obtained from a review of the medical records at the time of CBP measurement. The outcome was renal progression defined as decline of estimated glomerular filtration rate greater than 30% of baseline during the follow-up.

Results: In overall, estimated central systolic BP (cSBP) was higher than brachial systolic BP (bSBP). The cSBP was significantly increased with age in non-CKD group, but such a correlation was not observed in CKD group. In CKD population, high cSBP group with greater than mean cSBP value (¹150mmHg) had significantly increased probability of renal progression (P=0.016), while high bSBP (¹140mmHg) group did not predict the outcome (P=0.370). In contrast, the predictor of renal progression was high bSBP not cSBP in non-CKD population. In Cox analysis adjusted for covariates, high cSBP remained a predictor of renal progression in CKD population (HR 5.408; 95% CI 1.008-29.030; P=0.049), whereas high bSBP was not a significant predictor in non-CKD population (HR 2.893; 95% CI 0.786-10.650; P=0.110).

Conclusions: The CBP had different correlation with age and clinical significance according to presence or absence of CKD, and the high cSBP was strong independent predictor of kidney disease progression in CKD patients.

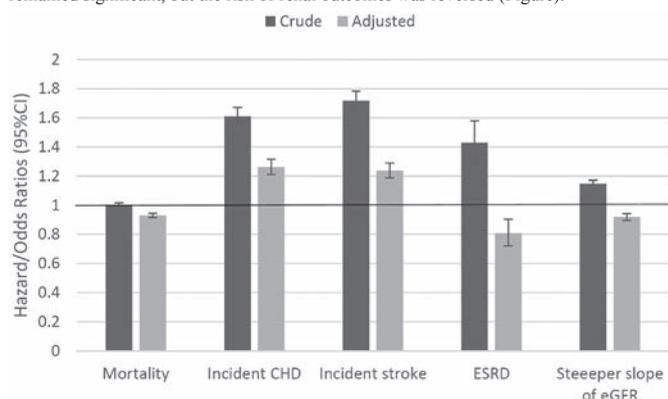
SA-PO619

Clinical Characteristics and Outcomes Associated with Resistant Hypertension in a Large Cohort of U.S. Veterans Csaba P. Kovacsdy,^{1,2} Miklos Zsolt Molnar,² Adriana Hung,³ Jun Ling Lu,² John J. Sim,⁴ Robert B. Canada,² Elvira Gosmanova,² Fridtjof Thomas,² Kamyar Kalantar-Zadeh.⁵ ¹VA Medical Center, Memphis, TN; ²Univ of Tennessee Health Science Center, Memphis, TN; ³VA Medical Center, Nashville, TN; ⁴Kaiser Permanente, CA; ⁵Univ of California, Irvine, CA.

Background: The prevalence of true resistant hypertension (RH), the characteristics of patients with RH and its association with clinical outcomes is unclear.

Methods: From 2,398,778 patients with essential HTN, we identified 95,334 (4%) with RH, defined as: Failure to achieve BP<140/90 mmHg with >=3 antihypertensives (one being a thiazide diuretic) or success with >=4 drugs; excluding measurements when pain score was >5, when interfering medications were prescribed and excluding those with confounding conditions (CKD, secondary HTN, sleep apnea, urinary obstruction, adrenal, thyroid and parathyroid over-activity). We examined associations with mortality, incident CKD, ESRD, steeper slopes of eGFR, incident coronary heart disease (CHD) and stroke in Cox models and logistic regression models adjusted for demographic and socioeconomic factors, comorbidities, BP, and antihypertensives.

Results: The mean SBP/DBP in RH and non-RH patients were 148±22/81±14 vs. 137±19/78±12 mmHg. Compared to non-RH, patients with RH were older (64±11 vs. 62±13), more likely to be black (25 vs. 17%) and had a higher prevalence of DM and CVD. Crude mortality was similar and the incidence of the renal and cardiovascular end points was higher in RH. After full adjustment the risk of CHD and stroke associated with RH remained significant, but the risk of renal outcomes was reversed (Figure).



Conclusions: RH is relatively infrequent (4%) among patients with essential HTN, and is associated with older age and a higher comorbidity burden. Patients with RH have a higher risk of incident CHD and stroke.

Funding: NIDDK Support, Veterans Administration Support

SA-PO620

Association of Components of Body Mass Index with Treatment-Resistant Hypertension in Men and Women with Chronic Kidney Disease Toshiyuki Aoki,¹ Yasushi Ohashi,¹ Reibin Tai,¹ Kiyoto Koibuchi,² Atsushi Aikawa,¹ Ken Sakai.¹ ¹Nephrology, Toho Univ School of Medicine, Ohta-ku, Tokyo, Japan; ²Nephrology, Saiseikai Eastern Hospital, Yokohama, Kanagawa, Japan.

Background: Treatment-resistant hypertension is a risk for cardiovascular disease and end-stage renal disease. However, the appropriate clinical management strategies remain unclear in patients with CKD. Our objective is to investigate the association of components of body mass index (BMI) with treatment-resistant hypertension in patients with CKD.

Methods: Body fluid composition was measured in 310 patients with CKD from 2005 to 2014, and BMI was separated into 3 components – (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW), and (c) extracellular water (ECW). Treatment-resistant hypertension was defined as an office BP of ≥130/80 mmHg, despite receiving ≥3 antihypertensives including diuretics, or ≥4 drugs usage. The main outcomes were adverse renal outcomes, as defined by a decline of 50% or more from baseline GFR or initiation of renal replacement therapy and cardiovascular events.

Results: The prevalence of treatment-resistant hypertension were 69 male patients (35.4%) and 19 females (16.5%). Patients with treatment-resistant hypertension were more likely to be diabetic, have a higher BMI, GFR, and proteinuria, and to be older especially in women. In the components of BMI, those in men and women tended to have higher ECW content and free water mass, respectively. Higher ECW contents in men and diabetes in relation to higher free water mass in women were independently caused treatment-resistant hypertension. Compared with patients with no treatment-resistant hypertension during a median 743-day follow-up, those with treatment-resistant hypertension had worse adverse renal outcomes (16.2 vs. 6.1 per 100 patient-years, P < 0.001) and cardiovascular events (5.0 vs. 1.6 per 100 patient-years, P < 0.001).

Conclusions: Treatment-resistant hypertension is associated with diabetes in relation to higher free water mass in women and higher ECW in men, which exhibits adverse renal outcomes and cardiovascular events. These findings emphasize the importance of adequate weight and volume status.

SA-PO621

Adherence Assessment in Resistant Hypertension: A Comparison Between Pill Count and Direct Method of High Performance Liquid Chromatography Analysis in Urine Patricia Cardoso Alarcon Hori, Silvana de Barros, Indira Fernandes Braga Azam, Andrea Pio de Abreu, Andrea Cassia Perreira Sforsini, Vanusa Barbosa Pinto, Decio Mion Junior, Giovanio Vieira da Silva. Nephrology and Pharmacy, General Hospital of Sao Paulo Univ, Sao Paulo, Brazil.

Background: Poor adherence to antihypertensive therapy is one of possible causes of resistant hypertension. Pill count is currently considered the standard for assessing drug adherence, but as an indirect method, it is inaccurate. The aim of this study was to compare the pill count with the direct method of toxicological urine screening in patients with resistant hypertension.

Methods: Patients with resistant hypertension criteria were included: office blood pressure (BP) above goal (systolic BP> 140mmHg and/or diastolic BP> 90mmHg) taking 3 or more antihypertensive agents of different classes, one of them diuretic, or office BP below goal taking 4 or more classes. Adherence was assessed by direct method of high performance liquid chromatography analysis for antihypertensive drugs or their metabolites in 4 different urine samples, with 30-day interval between them. Simultaneously, pill count was also performed. Patient was considered adherent by direct method if it was found every prescribed agents in at least 3 urine samples. Regarding pill count, patient was considered adherent if he consumed at least 90% of prescribed agents.

Results: 18 patients were selected: 78% women, age 57.5 ± 5.7 years, body mass index 29.3 ± 3.6 kg/m², office mean BP 151/88 ± 20/15 mmHg and 24 hours mean BP by ambulatory blood pressure monitoring 132/85 ± 21/12 mmHg. The average number of antihypertensive agents prescribed was 4.8 ± 0.8 classes per patient. 3 (17%) and 2 (11%) patients were considered adherent by direct method and pill count, respectively. However, the agreement between methods was poor (Kappa correlation coefficient -0.15).

Conclusions: Adherence to therapy in patients with resistant hypertension was very low in both methods. There was no agreement between pill count and direct method. The best method to assess adherence in resistant hypertension is yet to be determined. Supported by FAPESP, CNPq.

Funding: Government Support - Non-U.S.

SA-PO622

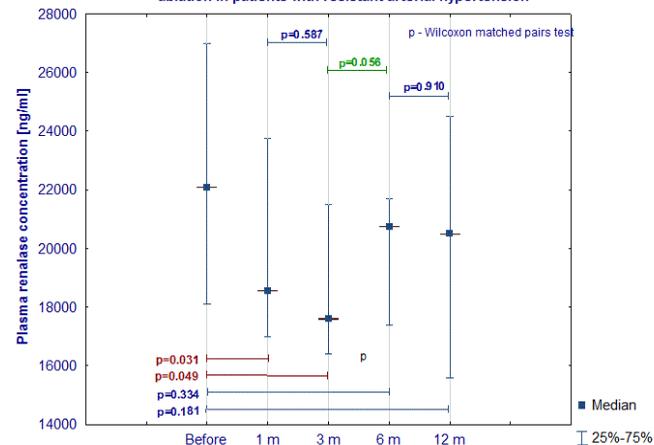
Plasma Renalase Concentration Before and After Radiofrequency Renal Denervation in Patients with Resistant Hypertension: Preliminary Results Marcin Adamczak,¹ Beata Czerwińska,¹ Maciej T. Wybraniec,² Michal Lelek,² Katarzyna T. Mizia-Steć,² Andrzej Wiecek.¹ ¹Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland; ²1st Dept of Cardiology, Medical Univ of Silesia, Katowice, Poland.

Background: Renalase is a catecholamine-metabolizing enzyme produced by proximal tubular cells in kidney which is supposed to be involved in blood pressure regulation. The aim of the study was to evaluate plasma renalase concentration after radiofrequency renal denervation (RDN) in patients with resistant arterial hypertension (HTN).

Methods: 19 patients (10 men; median age 56 (48; 57) years; BMI 30.9±4.4 kg/m² and eGFR 89±17.7 ml/min/1.73 m²) with resistant HTN were enrolled in the study. In all patient plasma renalase concentration was measured before and 1, 3, 6 and 12 months after RDN by ELISA method (Cloud-Clone Corp, Houston, USA).

Results: A significant decrease of both office systolic and diastolic blood pressure 6 months after RDN was found (192 ± 31 vs. 177 ± 28 mmHg, p=0.03; 113 ± 23 vs. 99 ± 21 mmHg, p=0.002, respectively). One and 3 months after RDN plasma renalase concentration decreased significantly, with a subsequent return to values comparable with baseline at 6- and 12-month follow-up (median of 22100 vs. 18550 vs. 17600 vs. 20750 vs. 20500 ng/ml respectively; Friedman analysis of variance p=0.054).

Median of plasma renalase concentration before and 1, 3, 6, and 12 months after renal artery ablation in patients with resistant arterial hypertension



Conclusions: 1. RDN leads to the temporary decrease of plasma reninase concentration in patients with HTN. 2. Lower plasma reninase concentrations seems to be a counteract reaction to the antihypertensive effects of RDN.

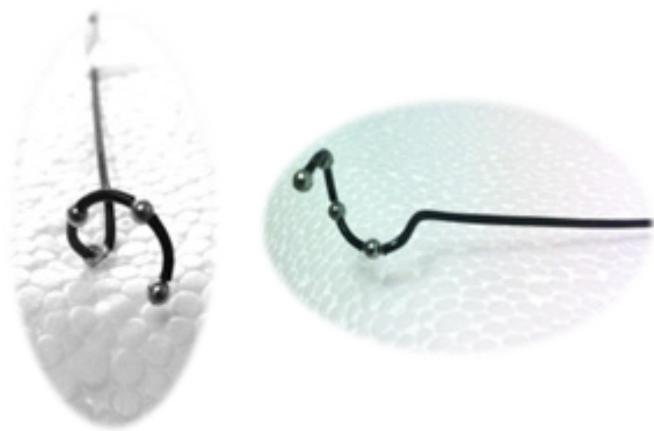
Funding: Government Support - Non-U.S.

SA-PO623

A Non-Vascular Treatment for Resistant Hypertension Richard R. Heuser,¹ Adam Gold,² ¹Cardiology, St. Luke's Medical Center, Phoenix, AZ; ²Verve Medical, Scottsdale, AZ.

Background: Systematic arterial hypertension remains the most common and important risk factor for cardiovascular and renal disease. A safe and effective medical device effecting a significant and immediate fall in arterial BP addresses an unmet clinical need. Early clinical experience with the Verve non-vascular device causes an immediate BP drop in patients with resistant hypertension.

Methods: In humans, there is a greater abundance of efferent compared with afferent nerve fibers and the afferent nerves are much less abundant in general and are much less abundant as one goes away from the aorta. In contrast to the widespread distribution of EFFERENT Sympathetic nerve fibers in the kidney, the majority of the AFFERENT Renal Sensory nerves are located in the renal pelvic area. With our first generation device, we treated patients with resistant hypertension. Four patients with resistant hypertension were treated. They had immediate blood pressure drop (Systolic Mean 44mmHg, Diastolic Mean 13mmHg), which was maintained for 3 months. Because of the possibility of calyceal damage noted in follow-up in our animal model, we have redesigned the probe and shortened the duration of therapy.



Results: In over two dozen animals, it appears that we get a similar histopathologic results with our first generation probe without late pelvic or calyceal damage. In our first clinical application of this helical probe, there also is an immediate blood pressure drop.

Conclusions: Unlike other renal denervation treatments, the Verve natural orifice approach appears to treat the afferent nerves and results in an immediate blood pressure drop. More patients will need to undergo treatment to confirm these encouraging results. We will present our first series of resistant hypertensive patients treated with the helical device.

SA-PO624

Microparticles Cause Preeclampsia and Kidney Injury by Activation of Inflammasome in the Placenta Shrey Kohli, Berend Heinrich Isermann. *Inst of Clinical Chemistry and Pathobiochemistry, Otto Von Guericke Univ, Magdeburg, Germany.*

Background: Preeclampsia is a hypertensive disorder of pregnancy associated with high morbidity and mortality. Hallmarks of preeclampsia are endothelial damage and functional (e.g. proteinuria) and morphological renal aberrations. The only known remedy against this is the delivery of the placenta. Cell derived microparticles (MP) of different origins are elevated in preeclampsia but their mechanistic relevance is unknown. Preeclampsia is also associated with a pro-inflammatory condition but there are meager mechanistic insights into this as well.

Methods: To address these questions MP (endothelial or platelet derived) were injected into C57/Bl6 pregnant mice and the pregnancy outcome (embryonic survival and growth, placenta morphology) was studied. Morphology of the kidney was studied using PAS staining and electron microscopy. Proteinuria was studied as a measure of renal dysfunction. To address mechanistic questions, inflammasome activation by MP in placenta and trophoblast cells was studied using western blotting and immunohistochemistry. Human trophoblast derived cells and placentas from pregnancies complicated with pre-eclampsia were also studied for activation of inflammasome. NLRP3 and Casp-1 KO mice were used to rescue the mice from disease conditions and establish causality of the mechanism.

Results: MP caused preeclampsia associated with fetal loss and embryonic growth restriction in mice. This was associated with renal damage indicated by proteinuria, glomerular enlargement, thickness of glomerular basement membrane, and podocyte effacement in the kidney. Human and mouse placenta analysis indicated inflammasome activation seen by elevated expression of NLRP3, cleaved casp-1 and IL-1 β . The pregnancy outcome and renal function was rescued in NLRP3 and Casp-1 KO mice.

Conclusions: Our results establish that MP are causative of preeclampsia, fetal death, embryonic growth restriction, and renal injury. These pathogenic effects of MP are mechanistically linked with inflammasome activation in the placenta.

Funding: Government Support - Non-U.S.

SA-PO625

Short Term Sequela of Preeclampsia Michael Yannik Girsberger,¹ Irene Mathilde Hoesli,² Michael Dickenmann.¹ ¹Clinic for Transplantation Immunology and Nephrology, Univ Hospital Basel, Basel, Baselstadt, Switzerland; ²Dept of Gynaecology and Obstetrics, Univ Hospital Basel, Basel, Baselstadt, Switzerland.

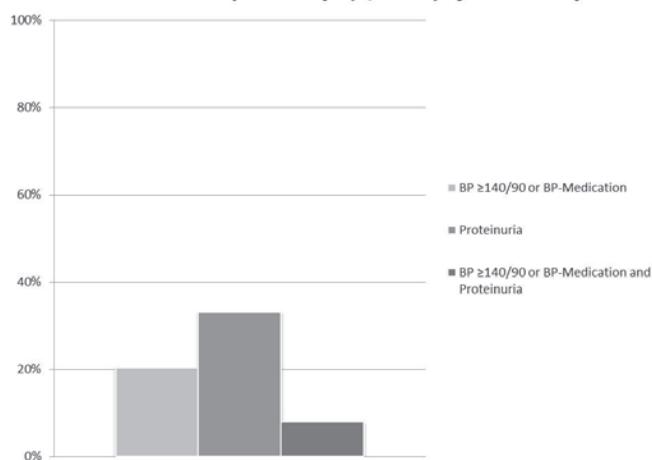
Background: Data on sequela in the first year after preeclampsia are scarce. We investigated kidney function, blood pressure, proteinuria and urine sediment in women with preeclampsia six month after delivery.

Methods: From January 2007 to July 2014 all women with preeclampsia and 6-months follow up at the university hospital Basel were prospectively analysed. Preeclampsia was defined as new onset of hypertension ($\geq 140/90$ mmHg) or worsening hypertension and either proteinuria or signs of end-organ dysfunction. Hypertension was defined as a blood pressure (BP) $\geq 140/90$ or the use of antihypertensive medication. Proteinuria was defined as a protein-to-creatinine ratio in a spot urine > 11 mg/mmol. Urine sediment was evaluated by a nephrologist.

Results: 202 women were included. Baseline characteristics are shown in Table 1 and follow up data are shown in Figure 1. The mean time of the follow up visit was 172 days (+/- 39.6) after delivery. The mean blood pressure at follow up was 124/76 mmHg (+/- 14/11, range 116-182/63-110) and the mean serum-creatinine was 61.8 μ mol/l (+/- 11.6). Mean estimated glomerular filtration rate (CKD-EPI) was 110.7 ml/min/1.73m² (range 59.7-142.4 ml/min/1.73m²). No active urine sediment (e.g. signs of glomerulonephritis) was observed.

Onset Gestational Week	36+1.75 (+/- 3.9)
Gravida	1.75 (+/- 1.16)
Para	1.41 (+/- 0.78)
Multiple pregnancy (twins, triplets) (27/202)	13.4%
Diabetes before pregnancy (4/201)	1.99%
Gestational diabetes (19/202)	9.4%
Previous hypertension (16/202)	7.9%
HELLP (40/198)	20.2%
Eclampsia (4/198)	2.0%
Severe Preeclampsia (132/197)	67%
Acute Kidney Injury (17/197)	8.6%
Chronic kidney disease (4/201)	1.99%

Mean Follow up 172 days (+/- 39.6) after delivery



Conclusions: The findings stress the importance of a close follow up to identify those women who need further care.

SA-PO626

Preeclampsia: Long-Term Effects on Pediatric Neurologic Disability

Alberto Tejedor Jorge, Clara Nicolas, Patrocinio Rodríguez Benítez, Olga Arroyo, María Silva, Laura Matesanz, Carmela Mercurio, Manuel Sánchez Luna. *Hospital General Univ Gregorio Marañón.*

Background: Preeclampsia affects up to 10% of pregnancies worldwide and is one of the main causes of fetal morbidity and mortality. Although it has been linked to developmental delay, its long-term effects on neurologic development in children have yet to be sufficiently quantified. Our aim is to evaluate whether the preeclampsia's severity and the therapeutic options used to manage it correlate to the degree of developmental delay in these infants.

Methods: This is an observational and descriptive study performed on a population of 96 women who were diagnosed with preeclampsia at Hospital General Universitario Gregorio Marañón between 2007 and 2014, and their 111 children. To evaluate the mother, we gathered data pertaining to her medical history, renal function markers, and medical management of the preeclampsia. To assess the children, we collected fetal growth measurements, acute fetal distress markers and main diagnoses at birth. We used the Pediatric Disability Inventory in its computerized adaptive test version (PEDI-CAT) to study neurologic development, and the TNO-AZL Preschool children Quality of Life (TAPQOL) to estimate health-related quality of life.

Results: Early-onset and more severe preeclampsias were associated with higher preterm birth and perinatal mortality rates. Preeclampsias with a greater impact on maternal organ function showed a clear correlation to higher periventricular-intraventricular hemorrhage rates in the newborn. In terms of neurologic development, PEDI-CAT percentiles were consistently lower in the Social/Cognitive domain than in other areas. Lower Social/Cognitive percentiles were associated to both lower maternal IgG levels and presence of necrotizing enterocolitis during the neonatal period.

Conclusions: Early-onset preeclampsias have a greater negative impact on both maternal renal function and fetal morbimortality. A connection between preeclampsia and poor social/cognitive outcomes exists that warrants further research, as does the possible link between between preeclampsia, immunity, and autistic features.

SA-PO627

Do Hypertension Providers Inquire About Hypertension in Pregnancy?

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Background: Hypertensive pregnancy disorders are increasingly recognized as a risk factor for future hypertension and cardiovascular disease. However, knowledge of this risk may be inadequate among internal medicine providers.

Methods: We reviewed all new consults in a 2-month period in a hypertension subspecialty clinic. We determined the frequency with which providers documented a reproductive history, a history of hypertension in pregnancy and known cardiovascular risk factors. We also studied whether there were differences according to gender and level of training of the provider (consultants vs. residents/fellows) using the chi-square test.

Results: There were 102 consults for hypertension in the study period. The majority of consults were by consultants, 55/102 (53.9%), and 23/102 (22.6%) were by female providers. A reproductive history, including number of pregnancies, infertility and/or intent of pregnancy, were documented in 37/102 (36.3%) of notes. Chart review revealed that 85/102 (83.3%) of women had live births, but it was documented in only 31 (36.5%) of notes. Female providers were more likely to document pregnancies (57.9% vs. 30.3%, p=0.03). Of the women who had live births, 15/85 (17.7%) of providers inquired about hypertension in pregnancy and 12/85 (14.1%) inquired about preeclampsia. Other hypertension and cardiovascular risk factor documentation by level of training are shown below.

Risk Factor, n(%)	Resident/Fellow (n=47)	Consultant (n=55)	P-value
Dietary issues	29 (62%)	32 (58%)	0.72
Alcohol Use	37 (79%)	36 (55%)	0.94
Illicit Drug Use	16 (34%)	2 (4%)	<0.0001
Smoking	41 (87%)	47 (85%)	0.79
Exercise	27 (58%)	29 (53%)	0.71
Medication-related effects	32 (68%)	31(56%)	0.23
Family History of Hypertension	43 (92%)	38 (69%)	0.005
Renal Disease	44 (94%)	41 (75%)	0.01
Dyslipidemia	17 (36%)	25 (46%)	0.34
Diabetes	22 (47%)	25 (46%)	0.89
Obstructive Sleep Apnea	22 (47%)	21 (38%)	0.38
Hypertension in Pregnancy*	5/36 (14%)	10/49 (20%)	0.44
Preeclampsia*	5/36 (14%)	7/49 (14%)	0.96

*Only in women with live births

Conclusions: Hypertension specialists rarely document a reproductive history or a history of hypertension in pregnancy, irrespective of level of training. Female providers were more likely to document pregnancies.

SA-PO628

Accuracy of a Spot Urine Protein-to-Creatinine Ratio in Preeclampsia

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Background: Correlation between a 24 hour urinary protein excretion with a spot urine protein-creatinine (SP/Cr) ratio in patients with preeclampsia is unclear. Moreover, urinary creatinine excretion is greater in populations such as Africans and non-white Hispanics. We studied the correlation of the SP/Cr ratio with a 24 hour urine protein measurement in this minority population.

Methods: ICD-9 codes of 642.4, 642.5, 642.6, 642.7 representing mild pre-eclampsia to eclampsia were used for data collection. Only 110 women with both 24 urinary protein collection and (SP/Cr) were included in the analysis. Correlation between SP/Cr and 24-hour protein excretion was assessed by Spearman correlation coefficient. The sensitivity and specificity of the SP/Cr ratio at various cut-offs for the prediction of significant proteinuria were estimated with a 95% confidence interval, using the 24-hour urine collection as gold standard. Receiver operating characteristic (ROC) curve analysis was used to determine the best discriminator values of the (SP/Cr) to predict proteinuria above 300 mg/ 24 hr. A P value of 0.05 or < was significant.

Results: The median SP/Cr ratio was 0.30 (interquartile range (IQR) 0.3) while the median 24 hour urine protein was 316.5 mg (IQR 286.8). The overall Spearman correlation was 0.48 (P= .0001). and 0.63 (P=0.05), 0.59 (P= .01), and 0.45 (P= .0001) for the 1st, 2nd, and 3rd trimesters respectively. At the cut-off value of 0.15 for SP/Cr, the sensitivity and specificity were 91.8% and 75.5% respectively. The cut-off SP/Cr ratio 0.25 was identified as the best threshold to detect a 24 hour protein excretion of 300 mg with a sensitivity and specificity of 75% and 59% respectively. The area under the curve (AUC) by the ROC curve analysis was found to be 0.69.

Conclusions: Even in a minority, inner city population we found significant correlation between the 24 hour protein excretion and the SP/Cr ratio, especially in the 2nd and 3rd trimesters of preeclampsias. Our findings are in line with the literature despite a minority patient population.

SA-PO629

Thiazide Diuretics for Hypertension in Kidney Transplant Recipients Using Tacrolimus

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Background: Hypertension after kidney transplantation is common and associated with poorer graft and recipient outcomes. Recently, we and others showed that tacrolimus activates the thiazide-sensitive sodium chloride cotransporter to cause hypertension. This suggests that thiazide diuretics may be especially effective drugs in this context, but prospective data are lacking.

Methods: We conducted a non-inferiority crossover trial to compare chlorthalidone (CT, 12.5-25 mg) with amlodipine (AML, 5-10 mg). Patients were invited for ambulatory blood pressure measurement (ABPM) if office BP >140/90 mmHg. Other criteria included eGFR >30 ml/min, proteinuria < 1 g, and no use of glucocorticoids. The treatment periods were randomized, lasted 8 weeks (allowing dose titration after 2 weeks), and were separated by a 2-week wash-out. Background anti-hypertensive drugs were allowed except for other diuretics.

Results: 71 patients underwent initial ABPM of whom 45 patients (63%) with average wake SBP >140 mmHg were enrolled (median 2.6 years after transplantation). 38 patients completed the study (5 patients stopped during CT mainly due to electrolyte disorders vs. 2 during AML, p=0.4). CT and AML both markedly reduced ABPM after 8 weeks (151/85 ± 11/9 to 141/81 ± 12/9 mmHg vs. 151/84 ± 13/9 to 138/79 ± 14/7 mmHg). There was no statistical difference in blood pressure response between the two drugs (p=0.3 by 2-way ANOVA). Dose titration rates were similar (42% for CT vs. 37% for AML, p=0.8). CT decreased eGFR (53 ± 17 to 46 ± 15 ml/min), whereas amlodipine increased it (50 ± 16 to 53 ± 17 ml/min, P<0.001). The first post-CT eGFR returned to baseline (51 ± 17 ml/min). Treatment with CT resulted in less proteinuria (median 14 vs. 19 mg/mmol, p=0.03) and less edema (8 vs. 31%, p=0.02). Regression analysis showed that a higher aldosterone to renin ratio, lower baseline serum potassium, and higher baseline serum bicarbonate predicted a better anti-hypertensive response to CT.

Conclusions: Thiazide diuretics effectively lower blood pressure in kidney transplant recipients using tacrolimus. Thiazides were especially effective in patients with more aldosterone effect.

SA-PO630

The Detrimental Effects of Beta-Blockers on Central Hemodynamic Parameters: A Propensity Score Analysis

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Background: Central blood pressure (BP) and aortic stiffness are better predictors of the cardiovascular burden than peripheral BP. Beta-blockers (BB) are known to reduce central BP to a lesser extent than peripheral BP, a hypothesized consequence of heart rate (HR) reduction. Therefore, the association between BB use, HR and central hemodynamic indices were studied in the treated hypertensive participants of the CARTaGENE study.

Methods: Using propensity score analyses, BB users (n=605) were matched to controls having similar clinical characteristics with (Model 1) and without (Model 2) adjustment for HR. This resulted in 457 and 510 pairs with adequate balance, except for a different HR in Model 2 (62.5 ± 10.5 vs. 70.4 ± 11.5 bpm, p<0.001).

Results: In Model 1, the difference between peripheral and central systolic BP (DSBP) was 8.3 mmHg (IQR 5.8, 11.6) with BB compared to 9.7 mmHg (7.1, 13.5) without (p<0.001), indicating that for any given peripheral BP, BB use resulted in higher central systolic BP. Pulse pressure amplification, augmentation index and augmented pressure were also less favorable with the use of BB. The different HR in Model 2 further increased the detrimental DSBP observed with BB to 7.9 (5.6, 11.0) vs. 10.6 (8.1, 14.3) without (p<0.001) and was associated with a higher central pulse pressure (46.5 ± 13.0 vs. 43.3 ± 11.3, p<0.001).

Parameters	Model 1			Model 2		
	No beta-blocker	Beta-blocker	p-value	No beta-blocker	Beta-blocker	p-value
Central SBP	120 ± 15	121 ± 16	0.67	118 ± 15	121 ± 17	0.006
ΔSBP	9.7 (7.1-13.5)	8.3 (5.8-11.6)	<0.001	10.6 (8.1-14.3)	7.9 (5.6-11.0)	<0.001
Central PP	45 ± 11	46 ± 13	0.45	43 ± 11	47 ± 13	<0.001
PP amplification	1.3 (1.2-1.3)	1.2 (1.1-1.3)	<0.001	1.3 (1.2-1.4)	1.2 (1.1-1.3)	<0.001
Augmentation Index	29 ± 11	31 ± 11	0.005	27 ± 11	31 ± 10	<0.001
Augmented pressure	13 (9-17)	13 (9-19)	<0.001	11 (7-16)	14 (9-20)	<0.001

Conclusions: This study shows that the unfavorable central hemodynamic profile of BB has both a HR-dependent and a HR-independent component.

Funding: Government Support - Non-U.S.

SA-PO631

Risk of Development of Dementia During Treatment of Hypertension with Different Calcium Channel Blockers

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Background: Arterial hypertension (HTN) is proved to be a risk factor for development of dementia. Medical treatment of HTN may decrease the risk of dementia. Experimental study pointed to the possibility of difference between different calcium channel blockers (CCB) in their neuro-protective effect. The aim of our study was to evaluate the risk of dementia during treatment of HTN with one of three different CCBs.

Methods: This is a retrospective cohort study based on electronic database of Clalit Health Services, Central District. Study period was 11 years (2002-2012). Inclusion criteria: age 40-75, diagnosis of HTN without diagnosis of "Dementia" at the starting point, minimal duration of treatment > 30 months with single specific CCB. New diagnosis of dementia was established according to appearance of its diagnostic code in the chronic diseases register or prescription of medication for its treatment – whatever occurred first.

Results: 15,664 patients were included in the study; 3,884 were treated with amlodipine, 2,062 - with nifedipine, 609 – with lercanidipine and 9,109 never received CCBs. The mean age was 60.7 years, 52.9% were females and the mean baseline creatinine was 1.0 mg/dL. 13.4% of patients died during the study period. Dementia developed in 765 (4.9%) patients. Adjusted HR of dementia in patients treated with amlodipine, nifedipine and lercanidipine was 0.60 (p<0.001), 0.89 (NS) and 0.90 (NS).

Conclusions: Treatment of arterial hypertension with amlodipine may be associated with decreased risk of development of dementia in comparison to treatment without CCBs.

SA-PO632

The Association Between Antihypertensive Agents and Postural Blood Pressure Response Using Beat-to-Beat Data: Results from the Irish Longitudinal Study on Ageing

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Background: Beat-to-beat blood pressure (BP) measurements provide a dynamic picture of BP behavior during postural change. Impaired BP stabilization after standing is associated with substantial morbidity and mortality. We aimed to define the relationship between class of antihypertensive drug and BP stabilization during an active stand.

Methods: Cross-sectional analysis from The Irish Longitudinal Study on Ageing, a nationally representative cohort study of 8175 adults ≥50 years. Beat-to-beat BP was recorded in participants undergoing an active stand test. We defined grade 1 hypertension according to European Society of Cardiology criteria (systolic BP [SBP] 140-159mmHg ± diastolic BP [DBP] 90-99mmHg). Orthostatic hypotension (OH) was defined as a drop in SBP ≥20mmHg ± DBP ≥10mmHg. Outcomes were sustained OH (OH throughout the test) and impaired BP stabilization (OH at each 10-second (s) interval during the test [total 110s]). Outcomes were assessed using logistic regression models adjusted for potential confounding variables.

Results: A total of 536 participants with self-report hypertension were receiving monotherapy with a renin-angiotensin-aldosterone-system inhibitor (317), betablocker (89), calcium channel blocker (89) or diuretic (41). Betablockers were associated with increased odds of sustained OH vs untreated grade 1 hypertension (OR 3.4, 95% CI 1.9-6.0). This was evident from 20s (OR 2.3, 95% CI 1.4-3.7) and remained statistically significant at 110s (OR 2.8, 95% CI 1.6-4.9). Multivariable adjustment did not attenuate the association. No significant association was detected among the other drug classes.

Conclusions: In older hypertensive adults betablocker monotherapy was associated with a >3-fold increased odds of OH compared to subjects with untreated grade 1 hypertension. The effect was evident from 20s after standing and was sustained. This should inform decision-making regarding appropriate choice of antihypertensive agent in older adults.

SA-PO633

Effect of Vitamin D on 24 Hour Ambulatory Blood Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Background: Lower levels of 25-hydroxyvitamin D (25[OH]D) have been associated with an increased risk of hypertension in prospective cohort studies, suggesting that vitamin D might be a modifiable target for the prevention of hypertension. Vitamin D supplementation has also been shown to decrease clinic blood pressure (BP) in some studies.

Methods: We performed a randomized, double-blind, placebo-controlled trial of nonhypertensive participants with body mass index ²⁵, and 25[OH]D ≤20ng/mL; subjects were randomized to receive either ergocalciferol 50,000 units or placebo, once a week for 8 weeks. Mean 24 hour BP was measured using 24 hour ABPM at baseline and 8 weeks after starting the study.

Results: By the end of the trial, 29 and 27 participants randomized to receive vitamin D and placebo, respectively, had adequate 24 hour ABPM at both baseline and at 8 weeks. Mean vitamin D levels increased from 14.9 to 30.3 ng/mL in the intervention group and from 14.4 to 17.4 ng/mL in the placebo group. Vitamin D supplementation did not lower BP at 8 weeks; 24 hour systolic BP changed from 120±10 to 122±8 mmHg in the intervention group (p-value=0.29), and from 124±8 to 125±10mmHg in the placebo group (p-value=0.38), with a treatment effect p-value of 0.92.

Conclusions: In this randomized, double-blind, placebo-controlled trial of overweight/obese normotensive individuals, there was no improvement in mean 24 hour blood pressure after repletion of vitamin D. These findings are not consistent with vitamin D being a modifiable target for prevention of hypertension.

Funding: NIDDK Support

SA-PO634

Effect of Uric Acid Lowering on Intrinsic Renal and Systemic Renin Angiotensin System Activity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Background: Higher levels of uric acid have been associated with an increased activity of the renin angiotensin system (RAS) in animal models of hypertension and kidney disease. Similarly, individuals with high levels of circulating uric acid have increased renal specific RAS activity measured using renal plasma flow (RPF). However, the effect of lowering serum uric acid on RAS activity in humans is unknown.

Methods: We performed a randomized, double-blind, placebo-controlled trial analyzing the Modifiable Effectors of Renin System Activation Treatment Evaluation (MODERATE). Normotensive individuals with body mass index (BMI) ²⁵ and uric acid level ≥ 5.0 mg/

dL were randomized to receive either allopurinol 300/600mg, probenecid 500/1000mg, or placebo daily for 8 weeks. Renal specific and systemic RAS activity was measured at baseline and 8 weeks after starting the study.

Results: By the end of the trial, 36, 30 and 41 participants randomized to receive probenecid, allopurinol and placebo, had RAS measurements at baseline and 8 weeks, respectively. Uric acid levels changed from a mean of 5.9, 5.6 and 5.6 mg/dL to 3.9, 3.9 and 5.7 mg/dL in the probenecid, allopurinol and placebo groups, respectively. Renal specific RAS, measured by change in RPF to captopril in high sodium balance, was not improved after uric acid lowering: RPF response to captopril changed from 42.6±38.8 at baseline to 45.3±43.9 mL/min at 8 weeks with probenecid (p-value=0.26), from 40.5±34.9 to 35.1±29.8 mL/min with allopurinol (p-value=0.23), and 37.3±46.9 to 35.9±26.2 mL/min with placebo (p-value=0.70). Similarly, changes in plasma renin activity and plasma angiotensin II levels did not significant change with treatment.

Conclusions: In contrast to animal experiments and observational studies, this randomized, double-blind, placebo-controlled trial found that lowering uric acid had no effect on renal specific or systemic RAS activity.

Funding: NIDDK Support

SA-PO635

Effect of Vitamin D Supplementation on Intrinsic Renal and Systemic Renin Angiotensin System Activity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial *Ciaran Joseph McMullan,¹ Lea Borgi,¹ Gary C. Curhan,¹ Naomi D.L. Fisher,² John P. Forman.¹* ¹Renal Div, Brigham and Women's Hospital, Boston, MA; ²Endocrine Div, Brigham and Women's Hospital, Boston, MA.

Background: Disruption of vitamin D signalling in rodents causes activation of the renin angiotensin system (RAS). In humans lower circulating 25[OH]D is associated with increased renal specific RAS activity (measured using renal plasma flow [RPF]); in addition, a small, open label, uncontrolled study found that vitamin D supplementation decreased renal specific RAS activity. However, the effect of vitamin D supplementation on the RAS in humans with vitamin D deficiency has never been examined in a rigorous manner.

Methods: We performed a randomized, double-blind, placebo-controlled trial of normotensive individuals with body mass index ²⁵ and vitamin D deficiency (25[OH]D ≤ 20 ng/mL); subjects were assigned to receive either ergocalciferol 50,000 units or placebo, once a week for 8 weeks. Renal specific (assessed by RPF response to captopril in high sodium balance) and systemic RAS activity (plasma renin activity [PRA] and angiotensin II levels [AngII]) were measured at baseline and 8 weeks after starting the study.

Results: By the end of the trial, 43 and 41 participants allocated to receive vitamin D and placebo, completed the study with measurement of renal and systemic RAS activity. Mean vitamin D levels increased from 14.9 to 30.3 ng/mL in the ergocalciferol group and from 14.4 to 17.4 ng/mL in the placebo group. Renal specific RAS did not significantly change after vitamin D repletion: the RPF response to captopril was 33.9±56.1 mL/min at baseline and 35.7±47.7 mL/min at 8 weeks in the ergocalciferol group (p-value=0.26); and was 37.3±46.9 mL/min at baseline and 35.9±26.2 mL/min at 8 weeks in the placebo group (p-value=0.70), with a treatment effect p-value of 0.27. Similarly, vitamin D supplementation had no effect on PRA or AngII levels.

Conclusions: In contrast to animal experiments, observational studies, and open-label uncontrolled interventions, this randomized, double-blind, placebo-controlled trial found no effect of vitamin D supplementation on RAS activity in vitamin D deficient individuals.

Funding: NIDDK Support

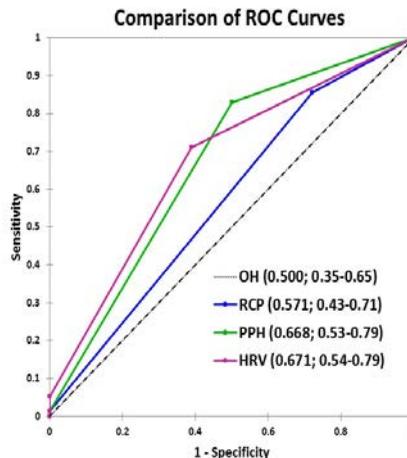
SA-PO636

Comparison of Office Orthostatic Blood Pressure and 24-Hour Ambulatory Blood Pressure Measurements in the Prediction of Autonomic Dysfunction *Girish Singhania, Rajesh Mohandas, Kawther Farouk Alquadan, Abhilash Koratala, A. Ahsan Ejaz.* *Nephrology, Univ of Florida, Gainesville, FL.*

Background: Evaluation of orthostatic hypotension (OH) may involve office orthostatic blood pressure (BP_{OH}) measurements, 24-hour ambulatory BP (ABP) and autonomic reflex screen (ARS). We investigated the predictive performance of BP_{OH} and the variables of ABP, i.e., reversal of circadian pattern (RCP), postprandial hypotension (PPH) and noncompensatory heart rate variability (HRV), to predict autonomic dysfunction as measured by the AUC of the ROC curves.

Methods: Data from previously published study were analyzed. Ninety-four patients were included for analysis. BP_{OH}, RCP, PPH, HRV were investigated for the presence or absence of autonomic dysfunction. Autonomic dysfunction was defined as a CASS (composite autonomic scoring system) score of ³. Comparisons of the AUCs of the ROC curves of the candidate parameters were performed.

Results: ROCs of candidate parameters are shown in Fig. 1.



The diagnostic performance to predict autonomic dysfunction for HRV was superior to PPH. Both were superior to RCP. RCP was a better predictor of autonomic dysfunction than office BP_{OH}.

Conclusions: Our data suggests that ABP is a reliable, simple and inexpensive predictor of autonomic dysfunction in routine clinical practice.

SA-PO637

Factors Predicting Long Term Renal Prognosis in Malignant Nephrosclerosis *Peng Xia, Jiabin Lang, Yubin Wen, Mingxi Li, Hang Li, Xuemei Li, Xuewang Li, Limeng Chen.* *Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: This study investigated correlations between kidney pathology and Renin-Angiotensin System(RAS) activation, RAS inhibitor response and prognosis of malignant hypertensive nephrosclerosis(MHN) patients.

Methods: This retrospective cohort study included 82 essential MHN patients from Jan.2003 to Oct.2014 with renal biopsy followed up to May2015. Pathology were evaluated by two pathologists independently. Localized renin expression and peritubular capillaries(PTC) area were evaluated by IHC staining of renin and CD34. Renal replacement therapy, kidney transplant and death were defined as the primary end point.

Results: 87.8% of patients were male with mean age of 34.7±8.8ys. Clinical data showed highest blood pressure(BP)226.6±25.7/152.2±22.0mmHg, serum creatinine(Scr)5.31±3.79mg/dl, proteinuria2.06±1.83g/d(n=68) and mean eGFR21.3±15.1ml/min.1.73m². Glomerular Sclerosis Index, tubular atrophy and interstitial fibrosis were 1.51±0.51, 63.7±18.3% and64.0±18.3%. MHN patients has a lower PTC proportion (2.27±0.74%(n=35),3.75±0.79%(n=17), P<0.001) and a higher renin-positive juxtaglomerular apparatus ratio(35.1±17.8%,(n=35),21.2±15.0%(n=17), P=0.008) comparing with glomerular minimal lesion patients. Tubularinterstitial lesions correlated with Scr(r=0.547,P<0.001), eGFR(r=-0.574,P<0.001) and proteinuria(r=0.447,P<0.001). PTC area correlated with Scr(r=-0.675,P<0.001,n=35) and eGFR(r=0.648,P<0.001,n=35). 90.4%patients received RAS inhibitors which was associated with improvements in BP (136.7±9.9/86.8±8.2mmHg,P<0.001),Scr(4.06±2.74mg/dL,P<0.001) and proteinuria (2.26±1.89vs.1.26±0.86g/d,n=45,P<0.001). After 54.1±36.6 months follow up, 1-year and 5-year cumulative renal survival rates were 93%and 65%. RAS inhibitors, BP control and eGFR over 30ml/min·1.73m² correlated with longer renal survival by Kaplan-Meier analysis. Cox regression identified RAS inhibitors(RR=0.24,95%CI(0.09,0.62),P=0.004) and CKD stages(RR=4.72,95%CI(1.71,13.03),P=0.003) as independent factors predicting renal outcome.

Conclusions: MHN patients had localized activation of renin and less PTC area. RAS inhibitors benefited patients in BP control, eGFR improvements and long-term renal outcome.

Funding: Government Support - Non-U.S.

SA-PO638

Office Blood Pressure Monitoring: A Novel Tool for Evaluating Blood Pressure in Children (and Adults) *Gianluigi Ardissino,¹ Paolo Marchetto,¹ Francesca Tel,¹ Sara Testa,¹ Ilaria Possenti,¹ Michela Perrone,¹ Luciano Sangaletti,¹ Amelia Ballarino,¹ Stefani Rotondo,¹ Silvia Ghiglia,¹ Franco De luca,² Patrizia Salice.¹* ¹Pediatric Nephrology and Cardiology, Fondazione IRCCS Ca'Granda Policlinico, Milan, Italy; ²Pediatric Cardiology, Policlinico Univ, Messina, Italy.

Background: Blood pressure measurement (BPM) is a common procedure in clinical practice but in children (C) obtaining reliable values can be challenging. Casual office BPM, the standard of care, is all but accurate and ABPM may be difficult to perform or even misleading.

Methods: Office Blood Pressure Monitoring (OBPM) was developed at our Center in 2010 for evaluating BP in C with serial and automated BPM (³10 in at least 30 min)

with a standard oscillometric device. BP values are uploaded in a software to calculate the coefficient of variation (CV) after having excluded outlier values (<5th and >95th centile of the recorded values).

Results: Since 2010 a total of 402 OBPMs have been performed but only the 282 in 110 C (59% Males) aged <18 yrs old (IQR 4.8-12.1) with a CV <10% for both syst and diast BP were considered for the analysis. The table compares BP as measured by OBPM with a single BPM (1st and 3rd) and with the mean of the 3 initial measurements (*: p<0.01 vs. others BPMs with student's t test for paired data and c²).

	Systolic	Diastolic	Patient BP class No. (%)		
	Mean Z score ± sd		Normotensive	Border-line	Hypertensive
1 st BP	1.92±1.40	1.62±1.27	70 (24.8)	26 (9.2)	186 (66.0)
2 nd BP	1.75±1.40	1.51±1.20	72 (25.5)	36 (12.8)	174 (61.7)
1 st , 2 nd and 3 rd BP (mean)	1.81±1.31	1.55±1.15	75 (26.6)	30 (10.6)	177 (62.8)
OBPM	1.69±1.30*	1.48±1.12*	88 (31.2)	37 (13.1)	157 (55.7)*

Conclusions: OBPM provides significantly lower BP values, leading to a diagnosis of poor BP control in a smaller number of patients (-10%). Given the lack of a gold standard, the present analysis doesn't demonstrate that OBPM is more reliable than standard procedures however serial BPM have the potential of reducing measurement biases and white coat effect. We recommend the routine use of OBPM for measuring BP in C at risk of hypertension rather than relying upon few measurements.

SA-PO639

A Simple Prediction Score for Incident Hypertension in a Korean Population
 Jong-Hwan Jung, Sung Kwang Park, Won Kim, Kyung Pyo Kang, Sik Lee.
Dept of Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Republic of Korea.

Background: We aimed to develop a simple prediction model for incident hypertension that could help to prevent or delay the onset of hypertension for some patients who did not experience hypertension yet.

Methods: The Korean Genome and Epidemiology Study was used for the model development (n=3533) and internal validation (n=1698). Hypertension was defined when either the systolic and diastolic blood pressures (SBP, DBP) were 140 and 90 mmHg or higher or being treated with antihypertensive medications.

Results: SBP, age and DBP, parental hypertension, obesity, high density lipoprotein (HDL), current smoking and fasting glucose were significantly associated with incident hypertension. Integer scores were assigned to variables based on the magnitude of associations SBP (-2 to 5), age and DBP (-2 to 5), parental hypertension (2), obesity (2), low HDL (2), current smoking (2) and high fasting glucose (2).

	b (se)	Adjusted OR (95% CI)	Assigned score
Systolic blood pressure			
SBP <110	-0.6 (0.2)	0.55 (0.36-0.85)	-2
110 ≤ SBP < 115		1	0
115 ≤ SBP < 120	0.6 (0.2)	1.87 (1.25-2.81)	2
120 ≤ SBP < 125	0.9 (0.2)	2.43 (1.61-3.67)	3
125 ≤ SBP < 130	1.1 (0.2)	2.87 (1.85-4.44)	4
130 ≤ SBP	1.3 (0.2)	3.64 (2.32-5.71)	5
Age and Diastolic blood pressure			
age 40-50 and DBP ≤ 70	-0.8 (0.3)	0.45 (0.27-0.75)	-2
age 50-60 and DBP 70-80		1	0
age 60-70 and (DBP ≤ 70 or DBP 70-80)	0.4 (0.2)	1.44 (1.03-2.00)	2
age 40-50 and DBP ≥ 80	0.9 (0.2)	2.51 (1.65-3.81)	3
age 50-60 and DBP ≥ 80	1.1 (0.2)	3.10 (1.94-4.95)	4
age 60-70 and DBP ≥ 80	1.3 (0.3)	3.53 (2.12-5.88)	5
Parental hypertension			
	0.4 (0.2)	1.41 (1.05-1.89)	2
Obesity			
	0.4 (0.1)	1.46 (1.13-1.89)	2
HDL < 40mg/dl			
	0.2 (0.1)	1.29 (1.01-1.66)	2
Fasting glucose ≥ 126mg/dl			
	0.6 (0.3)	1.84 (1.03-3.28)	2
Smoking			
	0.4 (0.1)	1.54 (1.14-2.09)	2

Based on the Youden index, 5 or greater defined a high risk with 76% sensitivity, 72% specificity, 27% positive predictive value and 96% negative predictive value.

Conclusions: This prediction algorithm, weighted towards common modifiable variables, showed good performance characteristics in a Korean population.

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Hemodynamics and Cardiovascular Autonomic Efficiency During Blood Pressure Variations in Hemodialysis Dan Sapoznikov, Rebecca Backenroth, Dvora Rubinger. *Nephrology and Hypertension Services, Hadassah Univ Medical Center, Jerusalem, Israel.*

Background: Chronic hemodialysis (HD) is associated with hemodynamic instability and with reduced cardiovascular autonomic efficiency (CaE).

Methods: To define hemodynamic changes associated with intradialytic blood pressure variations, beat-to-beat systolic blood pressure (SBP) and interbeat interval (IBI) monitoring using Finometer device and Beatscope software was performed during HD sessions in 69 non-diabetic patients (Pts), age 56±15 y. Cardiac output (CO) and total peripheral resistance (TPR) were calculated using the Modelflow simulation method. Differences in variability indices during SBP periods, 10% above (high) or below (low) the mean SBP were considered representative of CaE.

Results: During low to high SBP periods, two patterns of changes were noted: increased CO and decreased TPR (18 Pts, TPR↓), and relatively stable CO with increased TPR (51 Pts, TPR↑). Low frequency (LF) range variability of SBP and IBI, CO and TPR (median and interquartile ranges) were:

	TPR↓		TPR↑	
	Low-high SBP	p	Low-high SBP	p
SBP (mmHg)	109(33)-146(28)	0.001	114(25)-159(31)	0.001
IBI (ms)	830(235)-844(226)	NS	808 (158)-827(177)	NS
sd IBI (ms)^	26(14)-22(10)	NS	23 (17)-24(22)	NS
LF SBP (mmHg/Hz)	132(140)-146(102)	NS	127(123)-99(160)	NS
LF IBI (ms ² /Hz)	1706(1894)-1118(1593)	NS	1014(2480)-1589(3757)	NS
CO (L/min)	4.20(1.64)-5.95(2.81)	0.001	6.19 (1.90)-6.32(1.41)	NS
TPR(mmHg.s/ml)	1.160(0.359)-0.922(0.412)	0.001	0.808 (0.196)-1.046(0.443)	0.001

^sd: standard deviation

The proportion of Pts with intradialytic hypotension (56%) was significantly higher in TPR↓ than in TPR↑ (28%, p=0.036), while TPR changes were directly correlated with post dialysis SBP (r=0.453, p=0.001) and with sd IBI (r=0.357, p=0.003) in all Pts. There were no differences between groups in other variables.

Conclusions: 1.CaE resetting during HD may be associated with predominant CO and/or TPR variations; the latter are significantly correlated to sd IBI, a strong marker of autonomic activity. 2.Intradialytic hemodynamics may be different in hypotension-prone Pts. These observations are relevant to the pathogenesis of intradialytic hemodynamic instability and of postdialysis hypertension.

SA-PO641

Antihypertensive Medications and Blood Pressure Control in Chronic Kidney Disease: A Cross-Sectional Analysis from the German Chronic Kidney Disease (GCKD) Study Karl F. Hilgers,¹ Matthias Schmid,² Silvia Huebner,¹ Martin Busch,³ Seema Baid-Agrawal,⁴ Anna Kottgen,⁵ Georg Schlieper,⁶ Claudia Sommerer,⁷ Gunter B. Wolf, MHBA,³ Kai-Uwe Eckardt.¹
¹Univ Hospital Erlangen; ²Univ of Bonn; ³Univ Hospital Jena; ⁴Charite Medical Univ; ⁵Univ of Freiburg; ⁶RWTH Univ Hospital; ⁷Univ Hospital Heidelberg, Germany.

Background: We reported low rates of blood pressure (BP) control in a large German cohort of patients with chronic kidney disease (CKD). Here, we analyzed the antihypertensive drug therapy to assess the prevalence of resistant hypertension, and to determine associations with control of BP.

Methods: The German Chronic Kidney Disease (GCKD) study is a prospective observational cohort study which enrolled 5217 patients with CKD in Germany. Inclusion criteria were an estimated glomerular filtration rate (eGFR) of 30-60 mL/min×1.73 m² or overt proteinuria. At enrollment, office BP was measured by trained study nurses, and information on medications was collected from patients.

Results: Office BP was obtained from 5181 participants, 4958 (95 %) were classified as hypertensive (≥ 140/90 mmHg or use of antihypertensive medication). In 2410 (49 %) hypertensive patients, BP was controlled (defined as < 140/90 mmHg). Inhibitors of the renin-angiotensin system (RAS; ACE inhibitors, sartans and aliskiren) were the most frequently used antihypertensives (87.4 % of participants), followed by diuretics (61.6 %), beta-blockers (57.7 %) and calcium channel blockers (39.6 %). 81.4 % of hypertensive participants received 2 or more different antihypertensive substances. Of the patients with uncontrolled hypertension, 49.9 % met the definition of resistant hypertension (uncontrolled despite 3 or more antihypertensive substances, including a diuretic). In multivariate analysis, RAS inhibitors were associated with better control of BP (odds ratio 1.48, p<0.001), as were diuretics (odds ratio 1.16, p=0.036).

Conclusions: Resistant hypertension was present in 49.9% of CKD patients whose BP was not controlled. RAS inhibitors were widely used and associated with better odds for controlled BP whereas the use of diuretics was less frequent than expected.

Funding: Private Foundation Support, Government Support - Non-U.S.

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Associations Between Cystatin C Based eGFR, Ambulatory Blood Pressure Parameters, and in-Clinic versus Ambulatory Blood Pressure Agreement in Older Community-Living Adults Tyler Woodell, Jan M. Hughes-Austin, Tiffany Tran, Atul Malhotra, Joseph A. Abdelmalek, Dena E. Rifkin. UC San Diego.

Background: Although CKD IV-V has been associated with abnormal ambulatory blood pressure (ABPM) patterns, the associations with milder CKD have not been determined. We examined the relationship between mild chronic kidney disease (measured by cystatin C-based eGFR) and abnormal ABPM (including nocturnal dipping) in healthy older adults. Further, we assessed agreement between clinic and ambulatory blood pressure monitoring.

Methods: 334 older community-living adults had clinic BP and 24-hour ABPM measured. Serum cystatin C levels were used to calculate eGFR_{Cr} using the CKD-EPI equation. Multiple linear regression was performed to examine associations between eGFR < 60 ml/min/1.73m² (CKDcys) and ABPM parameters. Bland-Altman analysis was performed to evaluate agreement between clinic and ambulatory measurements.

Results: Average age was 72. Average eGFR_{Cr} was 78 ± 20, and 60 individuals with CKDcys. Compared to those without CKDcys, individuals with CKDcys were older, more likely to have clinic-based hypertension and less likely to be dippers. After multivariate analysis, the presence of CKDcys was significantly associated with lower mean ambulatory diastolic blood pressure (DBP) (-2 mm Hg, p = 0.048), but not with nocturnal dipping or other ABPM parameters. Analyses using creatinine-based eGFR yielded similar results. Clinic systolic blood pressure (SBP) significantly overestimated mean wake time ambulatory SBP; mean difference was 11 mmHg for those without CKDcys (95% limits of agreement -14 to 35 mmHg) and 14 mmHg for those with CKDcys (95% limits of agreement -13 to 41 mmHg); there was no statistically significant effect modification by CKD status.

Conclusions: In older community-living adults, mild CKD as detected by cystatin C was associated with lower ambulatory DBP, but not with dipping status. This result is in contrast to findings with more advanced CKD in other studies and suggests that abnormal ABPM may only emerge at more advanced stages of CKD. The presence of CKD did not affect interpretation of clinic vs. ABPM pressures, although accuracy of clinic SBP was poor in this older cohort.

Funding: NIDDK Support

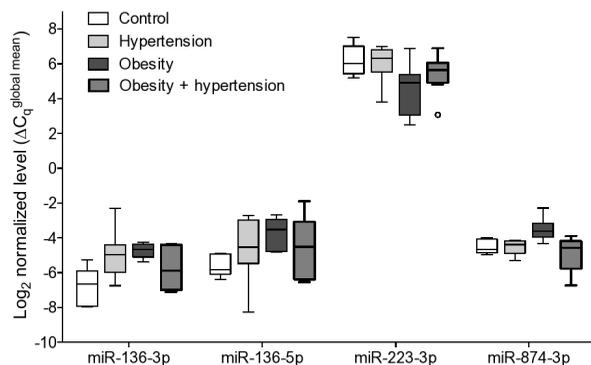
SA-PO643

Serum MicroRNA Biomarkers for Obese Children with Hypertension Scott Saint-Amour,¹ Santosh Kumar Patnaik,² Sudha Garimella,¹ ¹Pediatric Nephrology, Univ at Buffalo, Buffalo, NY; ²Cardiothoracic Lab, RPCI, Buffalo, NY.

Background: Childhood obesity is a major health problem and 30% of obese children may develop hypertension. There is no clinical method to identify high risk obese children before they develop hypertension. MicroRNAs are non-coding RNAs that are implicated in pathways of inflammation and vascular injury. There has been no characterization of miRNA profiles of obese children with hypertension. This study aims to characterize miRNA profiles as a first step toward evaluating miRNAs as biomarkers for obesity-related hypertension.

Methods: 39 patients ages 3-21 were placed in four cohorts based on presence or absence of obesity and hypertension. Total serum RNA was isolated using miRCURYBiofluids kit Exiqon®, and examined for miRNAs by RT-PCR. C_q values were normalized by the global mean method. Rates of false discovery (FDR) arising from multiple testing were assessed from P values with the Benjamini-Hochberg method.

Results: 69 of 179 examined miRNAs were detected in all samples. MiRNA measurements were globally reduced in sera of obese normotensive Vs. controls. Four miRNAs were identified as differentially expressed between these two groups at FDR <10%, whereas no miRNA was identified as differentially expressed between controls and hypertensive obese. Tukey plots of miRNAs in the cohorts are shown.



Conclusions: Serum levels of four miRNAs appear to be reduced in patients with obesity alone, but not in those with obesity and hypertension. While it is possible that serum miRNA differences were because of variables such as serum lipid content and medications, our study suggests that serum miRNAs have utility in detecting hypertension

risk in obese children. This should be validated in a larger study, and the biomarker value of the serum miRNAs correlated with ambulatory blood pressure monitoring data as well as left ventricular hypertrophy.

Funding: Pharmaceutical Company Support - Roswell Park Cancer Institute Support to Dr. Sai Yendamuri in the Cardiothoracic Lab at RPCI was used for this study.

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Effect of Prenatal and Childhood Lead Exposure on Blood Pressure at 4 Years of Age Alison P. Sanders,¹ Katherine Svensson,¹ Chitra Amarasiriwardena,¹ Priyanka Basnet,¹ Ivan Pantic,² Adriana Mercado-Garcia,³ Lourdes Schnaas,² Andrea A. Baccarelli,⁴ Martha M. Tellez-Rojo,³ Chris Gennings,¹ Lisa M. Satlin,¹ Robert O. Wright.¹ ¹Icahn School of Medicine at Mount Sinai; ²National Inst of Perinatology; ³National Inst of Public Health; ⁴Harvard T.H. Chan School of Public Health.

Background: Prenatal lead (Pb) exposure occurs during a susceptible period of renal development and may program later life cardiovascular and renal disease.

Methods: Systolic and diastolic blood pressure (SBP and DBP) was obtained using an automated oscillometer from 397 children at 4 years of age in the PROGRESS cohort located in Mexico City. Maternal blood samples were previously collected at the 2nd trimester (2T), 3rd trimester (3T), and at delivery and children's blood samples were collected at birth (cord blood), 1 year, and 2 years of age. Blood lead levels (BLLs) were analyzed via inductively coupled plasma-mass spectrometry. We performed linear regression to examine the associations between longitudinal BLLs and children's SBP, DBP, and pulse pressure (mSBP-μDBP) adjusting for child's age, sex, body mass index, maternal education and environmental tobacco smoke.

Results: Maternal 2T BLLs ranged between 0.7 and 18.8 mg/dL, and 89 (22%) prenatal BLLs were above the CDC guideline level of 5 mg/dL. Increased 2T and 3T BLLs were associated with decreased pulse pressure (p<0.05) and modestly associated with increased DBP (p=0.1).

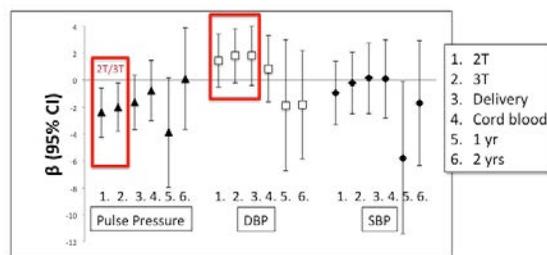


Figure 1. The effect of longitudinal lead exposure on childhood blood pressure at 4 yrs. Estimates (β) and 95% confidence intervals (CIs) were adjusted for child's age, sex, body mass index, as well as maternal education and environmental tobacco smoke.

No significant associations were observed for childhood BLLs and BP. Stratification by sex showed that the effect of prenatal Pb (2T and 3T) on decreased pulse pressure was significant only among females.

Conclusions: Prenatal Pb exposure may contribute to subclinical changes in the developing kidney or cardiovascular system leading to elevated BP in childhood. Future studies will assess if the contributions of early life Pb exposure to BP outcomes persist at later life stages.

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Smoking, Microalbuminuria and Renal Function in Essential Never Treated Hypertensive Patients Dimitrios Petras,¹ Vanessa Tzamouris,³ Athanasios Bramos,⁴ Panagiota E. Giannou,¹ Stella-Maria Kyvelou,³ Eva Karpanou,² Gregory Vyssoulis.³ ¹Nephrology Dept, Hippokraton Hospital, Athens, Greece; ²1st Cardiology Clinic, Onassis Cardiac Surgery Center, Athens, Greece; ³Hypertensive Unit, 1st Cardiology Clinic, Univ of Athens, Hippokraton Hospital, Athens, Greece; ⁴Microbiology Dept, Hippokraton Hospital, Athens, Greece.

Background: The aim of the present study was to identify possible differences depending on patient's individual smoking history with renal function and microalbuminuria in essential never treated hypertensive patients.

Methods: The study included 6100 consecutive patients with essential hypertension. In each patient the smoking status has been assessed by means of a standard questionnaire. Each patient had renal profile work up including microalbumin levels, albumin creatinine ratio in 24h urine collection (ACR) and 24h creatinine clearance.

Results: The study population was divided according to the smoking status in three groups: Smokers (n=2350), Ex-smokers (n=663) and Non-smokers (n=3121). Microalbumin and ACR were significantly higher in smokers compared to ex-smokers and non-smokers [(26.3±24.3 vs 23.6±21.7 vs 22.0±20.0, p<0.0001), (31.5±30.2 vs 28.8±29.3 vs 27.4±27.2, p<0.0001), respectively]. There was no significant difference in creatinine clearance among the three groups of smokers (p=NS)

Parameters	Smokers (n=2350)	Ex Smokers (n=663)	Non Smokers (n=3121)	p
Microralbumin (mg/dl)	26.3±24.3	23.6±21.7	22.0±20.0	0.0001
ACR	31.5±30.2	28.8±29.3	27.4±27.2	0.0001
24h creatinine clearance	122±37.8	121.4±37.1	121.4±36.8	0.914
SBP (mmHg)	162.7±10.3	164.4±9.7	162.4±10.6	0.0001
DPB (mmHg)	101.6±7.2	100.1±8.3	99.6±7.9	0.0001
Age (years)	51.3±12.7	57.1±12.8	55.1±14.2	0.0001
N (males)	1321	437	1506	0.0001

Conclusions: In conclusion, in this retrospective large cohort study of essential never treated hypertensive patients there is a clear association that active smoking is associated with higher microalbumin and ACR levels in these patients.

SA-PO646

Comparison of Salt Taste Thresholds and Salty Usage Behaviors Between Myanmar and Korean Adults Hyungjin Cho.¹ *Div of Nephrology, Dept of Internal Medicine, College of Medicine, Univ of Ulsan, Asan Medical Center, Seoul, Republic of Korea;* ²*Div of Nephrology, Dept of Internal Medicine, Jeju National Univ Hospital, Jeju, Republic of Korea.*

Background: Excessive oral salt intake can induce hypertension. According to previous studies, prevalence of hypertension is higher in Myanmar than Korea. We postulated that Myanmar adult had higher salt taste thresholds and eat much saltier food. The aim of this study is comparing of salt taste thresholds and salt usage behavior scores between Myanmar and Korean adults.

Methods: This cross sectional study enrolled the patients who visited volunteer medical service clinic at Ansung in Korea and Hlegu and Bago in Myanmar in August 2014. We measured vital signs, height and weight of each patient and evaluate detection threshold, recognition threshold, salt preference. All patients took urinalysis and checked spot urine Na. They also filled up the salt usage behavior questionnaire.

Results: Total 131 patients were enrolled and 64 of them were Myanmar and 67 were Koreans. Blood pressure was significantly higher in Myanmar adults than Koreans. Detection threshold, recognition threshold, salt preference, spot urine sodium and salt usage behavior score was also higher in Myanmar than Koreans.

	Myanmar (n=64)	Korea (n=67)
Detection threshold (%)***	0.102±0.108	0.046±0.026
Recognition threshold (%)**	0.174±0.163	0.103±0.115
Salt preference (%)**	0.44±0.16	0.37±0.10
Spot urine sodium (mg/dL)**	157.7±84.3	117.0±62.1
Salt usage behavior score*	11.4±2.5	10.4±2.4

*p<0.05, **p<0.01, ***p<0.001

We calculated correlation coefficient between spot urine Na and other parameters that related to salt intake. The salt preference, salt usage behavior score and detection threshold significantly correlated with the spot UNa.

Conclusions: All parameters related to salt intake, such as detection thresholds, the recognition thresholds, salt preference, salt usage behavior score and spot urine sodium concentration, of Myanmar were significantly higher than those of Korean.

SA-PO647

Relationship Between Circadian Rhythm of Blood Pressure and Intrarenal Arteriosclerosis Keiji Kono, Hideki Fujii, Kentaro Nakai, Shunsuke Goto, Shinichi Nishi. *Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan.*

Background: Hypertension (HT) is a common complication in chronic kidney disease (CKD) patients. CKD patients often have circadian rhythm disorder of blood pressure (BP). However, the relationship between circadian BP pattern and intrarenal damage remains unclear.

Methods: Ninety patients with glomerulonephritis were included in this study. Patients with diabetes mellitus and prescription for antihypertensive agents were excluded. Clinic BP (CBP) and 24-h ambulatory BP (ABP) measurements were performed in all the study patients, and who were divided into the following four groups; normotension (NT), white coat hypertension (WHT), masked HT (MHT) and sustained HT (SHT). As renal histopathological assessments, we evaluated the percents of sclerotic glomeruli (SG) and interstitial fibrosis (IF), and classified the degrees of intimal thickening of intra-lobular arteries (ILA) and arteriolar hyalinosis (AH) into four grades (none, mild, moderate, severe) in each biopsy specimen.

Results: The prevalence of NT, WHT, MHT and SHT was 60.0%, 3.3%, 23.3% and 13.4%, respectively. In comparison of circadian BP pattern, all-day HT was most prevalent in the SHT group, and nocturnal HT was most prevalent in the MHT group. SG and IF were significantly severe in the SHT group compared to the NT group. As for intrarenal vascular lesions, the MHT and SHT groups had more severe AH compared to the NT and

WHT groups, whereas ILA was comparable between all the four groups. Furthermore, we investigated the relationship between intrarenal vascular lesions and clinical characteristics. ILA was significantly correlated with age and renal function, whereas AH was significantly correlated with age, sex, smoking, total cholesterol, HT based on ABP (ABPHT) and HT based on CBP (CBPHT). In multivariate analysis, ILA was significantly correlated with only age, and AH was significantly correlated with age and ABPHT.

Conclusions: Our findings suggest that intrarenal AH was markedly severe not only in the SHT group, but also in the MHT group. Careful ABP monitoring should be recommended in patients with glomerulonephritis.

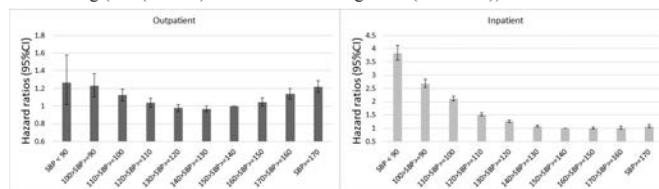
SA-PO648

Association of Inpatient versus Outpatient Systolic Blood Pressure with All-Cause Mortality in Patients with Normal Estimated Glomerular Filtration Rate Osita W. Okechukwu,¹ Miklos Zsolt Molnar,¹ Praveen Kumar Potukuchi,¹ Jun Ling Lu,¹ Fridtjof Thomas,¹ Kamyar Kalantar-Zadeh,² Csaba P. Kovacs.^{1,3} ¹*Univ of Tennessee Health Science Center, Memphis, TN;* ²*Univ of California, Irvine, CA;* ³*VA Medical Center, Memphis, TN.*

Background: Hypertension is associated with worse outcomes, and its treatment of improves mortality and cardiovascular disease. Hospitalized patients undergo frequent BP measurements, and hence hospitalization is an opportunity to diagnose and treat hypertension. However, it is unclear if BP measured as inpatient is associated with outcomes.

Methods: From 3,499,271 US veterans with normal eGFR, we identified 1,113,515 patients with inpatient and outpatient SBP recordings. We examined the association of baseline outpatient SBP, and baseline inpatient SBP (defined as the SBP obtained on the first day of the first hospitalization following cohort entry) with all-cause mortality in Cox proportional hazards analyses. Models included both in- and outpatient SBP and their interaction terms, and were adjusted for age, gender, race, eGFR, comorbidities, socio-economic factors, and antihypertensives.

Results: Low SBP was associated with higher mortality in both settings, but much more so inpatients (Figure). Outpatient SBP >140-149 mmHg was associated with linearly higher mortality (hazard ratio (95%CI) for SBP ³170 mmHg: 1.22 (1.16-1.29), p<0.001), but with less increase in mortality in the inpatient setting, which was only present for SBP ³170 mmHg (HR (95%CI) for SBP ³170 mmHg: 1.08 (1.02-1.14)).



Conclusions: SBP shows markedly different associations in the outpatient vs inpatient setting, with higher blood pressures in the inpatient setting conferring less mortality risk compared to the outpatient setting. Until randomized controlled clinical trials are done, caution is warranted when treating hypertension in hospitalized patients.

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SA-PO649

Fibroblast Growth Factor 23 and Sodium-Volume Regulation: FGF23-Response to Sodium Restriction in Essential Hypertensive Subjects and to Long Term Extracellular Volume Reduction in Hemodialysis Patients Francesca Mallamaci, Patrizia Pizzini, Daniela Leonardi, Sebastiano Cutrupi, Rocco Tripepi, Giovanni Tripepi, Carmine Zoccali. *Clin. Epid. and Physiopath. of Renal Dis. and Hypert. & Nephrology, Dialysis, and Transplantation Unit, CNR-IFC & Azienda Ospedaliera, Reggio Calabria, Italy.*

Background: Dietary sodium load causes volume expansion and hypertension in mouse models of FGF23 and α Klotho deficiency. FGF23 also associates with ultrafiltration volume in cross-sectional analyses in hemodialysis (HD) patients (pts) further implicating this bone hormone in extracellular volume regulation.

Methods: 32 uncomplicated essential hypertensives were randomized to a 2-weeks high sodium diet (200mmol/day) or to a 2-weeks low sodium diet (10-20 mmol/day). After 1 week wash out, these treatments were crossed-over. At the end of each diet-period, pts underwent 24h urine sodium, 24h ABPM and serum intact FGF23 measurements. The FGF23 response to UF intensification was assessed in 52 hypertensive HD pts. FGF23 and standardized BP measurements were performed at baseline and after 6 months of UF intensification.

Results: In essential hypertensives, PRA and aldosterone (P<0.01) rose during low sodium. However, FGF23 remained unmodified [low sodium: median 36.2 pg/mL, inter-quartile range (IQR):32.4-44.0; high sodium:33.9 pg/mL, IQR:29.5-41.0; P=0.18]. Changes in FGF23 were unrelated to systolic and diastolic ABPM, heart rate, PRA and aldosterone changes. In hypertensive HD pts, baseline FGF23 was 4062 pg/ml (IQR: 1381-12571). BP during the longitudinal study fell from 144 to 139 mmHg (P=0.02) along with a parallel decline in dry body weight (BW)(from 63.7 to 62.8 Kg) but FGF23 remained unchanged (3688 pg/mL, IQR: 1372-14117, P=0.30). Changes in FGF23 were unrelated (P=0.90) with ongoing changes in dry BW.

Conclusions: Changes in sodium intake that potently activate the renin-aldosterone system do not alter FGF23 in essential hypertensives. Similarly, extracellular volume

reduction by UF intensification does not materially influence FGF23 in hypertensive HD pts. These findings suggest that FGF23 is unlikely to play a role in the response to changes in sodium intake in human hypertension.

Funding: Government Support - Non-U.S.

SA-PO650

Association of Urinary Albumin Excretion and Salt-Sensitivity of Blood Pressure: Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study Jing Chen,^{1,2} L. Lee Hamm,¹ Chung-shiuan Chen,² Kevin K. Wu,² L. Gabriel Navar,¹ Jiang He.^{2,1} ¹*Medicine, Tulane School of Medicine, New Orleans, LA;* ²*Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, LA.*

Background: Albuminuria is a marker of early kidney injury and associated with risk of hypertension, cardiovascular disease, end-stage renal disease, and premature death. However, it is unknown whether urinary albumin excretion is associated with salt- and potassium-sensitivity.

Methods: We investigated the association between urinary albumin excretion and salt- and potassium-sensitivity of blood pressure (BP) among GenSalt study participants. The GenSalt dietary intervention consisted of a 7-day low sodium diet (51.3 mmol sodium/day), 7-day high-sodium diet (307.8 mmol sodium/day), and 7-day high-sodium diet with potassium supplementation (307.8 mmol sodium/day and 60 mmol potassium/day). Twenty-four hour urinary albumin excretion was estimated at baseline and at the end of each intervention from 100 randomly selected GenSalt participants.

Results: Urinary albumin-to-creatinine ratio (ACR, mg/g) was significantly reduced during low-sodium and potassium-supplementation interventions to 2.26 (1.11, 4.61) and 2.10 (1.46, 4.26), respectively, from a baseline ratio of 2.97 (1.20, 6.40) and increased during the high-sodium intervention to 3.23 (2.15, 5.73) with P for group difference=0.005. One standard deviation higher of baseline log-transformed ACR (2.23 mg/g) was significantly associated with 1.5 (95% CI 0.3, 2.7) mm Hg higher in mean arterial BP (P=0.01) from low-sodium to high-sodium intervention (salt-sensitivity) but not statistically significantly associated with potassium-sensitivity after adjusting for confounding factors.

Conclusions: These data indicate that urinary albumin excretion may be associated with BP salt-sensitivity.

SA-PO651

Effects of Nephrectomy on Blood Pressure and Its Circadian Rhythm Naro Ohashi,¹ Sayaka Ishigaki,¹ Shinsuke Isobe,¹ Takayuki Tsuji,¹ Akihiko Kato,² Hideo Yasuda.¹ ¹*Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Japan;* ²*Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Japan.*

Background: Intrarenal renin-angiotensin system (RAS) activation causes disturbance of sodium excretion from the kidney by increasing sodium reabsorption in the tubulus, with resultant blood pressure (BP) elevation and nocturnal hypertension. However, the effects of nephrectomy on BP and its circadian rhythm have not been clarified in the patients who have various renal functions.

Methods: We investigated 25 nephrectomized patients [17 men and 8 women, age: 61.3±14.7 years, chronic kidney disease stage 1 in 3 patients, stage 2 in 7, stage 3 in 5, stage 4 in 1 and stage 5 in 9 (hemodialysis in 8 and peritoneal dialysis in 1)]. Body weight (BW), circulating RAS [plasma renin activity (PRA) and plasma angiotensin II (AngII)] and 24-h ambulatory BP monitoring (ABPM) were examined before and after nephrectomy. We divided the daytime and nighttime for 24-h ABPM using sleep and waking times. Renal function [estimated glomerular filtration rate (eGFR)] was evaluated in non-dialysis patients.

Results: In non-dialysis patients, eGFR after nephrectomy was significantly decreased compared with that before nephrectomy (before nephrectomy, 67.8±23.1 ml/min/1.73m² and after nephrectomy, 47.9±16.5 ml/min/1.73m²; p<0.01). There were no significant differences in the levels of BW, BPs during daytime, nighttime and 24-h periods, and circulating RAS before and after nephrectomy. However, night-to-day (N/D) ratio of systolic BP (SBP) was significantly increased after nephrectomy compared with that before nephrectomy (before nephrectomy, 93.0±6.7% and after nephrectomy, 97.4±7.5%; p=0.032), and the patterns of circadian BP rhythm were also significantly changed before and after nephrectomy (p=0.021). Namely, dipper pattern decreased and nondipper and riser patterns increased after nephrectomy. On the other hand, no significant findings were found in N/D ratio of SBP and the patterns of circadian BP rhythm in dialysis patients before and after nephrectomy.

Conclusions: Nephrectomy has effects on nocturnal hypertension due to the decrease of renal sodium filtration ability, but not absolute values of BP.

Funding: Government Support - Non-U.S.

SA-PO652

Association of Urinary Dopamine and Norepinephrine Excretion with Salt- and Potassium-Sensitivity of Blood Pressure Jing Chen,^{1,2} L. Lee Hamm,¹ Chung-shiuan Chen,² Kevin K. Wu,² L. Gabriel Navar,¹ Jiang He.^{2,1} ¹*Medicine, Tulane School of Medicine, New Orleans, LA;* ²*Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, LA.*

Background: Dopamine and norepinephrine may play an important role in regulating sodium and potassium reabsorption in the proximal tubules. It is unknown, however, if urinary dopamine and norepinephrine excretion are associated with salt- and potassium-sensitivity of blood pressure (BP).

Methods: We investigated the association of urinary dopamine and norepinephrine with BP salt- and potassium-sensitivity among Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study participants. The GenSalt dietary intervention consisted of a 7-day low sodium diet (51.3 mmol sodium/day), 7-day high-sodium diet (307.8 mmol sodium/day), and 7-day high-sodium diet with potassium supplementation (307.8 mmol sodium/day and 60 mmol potassium/day). Twenty-four hour urinary dopamine and norepinephrine were estimated at baseline and at the end of each intervention in 100 randomly selected GenSalt participants.

Results: Urinary dopamine (µg/24-h) was significantly (p=0.01) reduced from baseline (191.5±124.2) during high-sodium (157.2±143.2) and high-sodium and potassium-supplementation (149.9±139.7) interventions. Likewise, urinary norepinephrine (µg/24-h) was significantly (p<0.0001) reduced from baseline (38.6±24.3) during high-sodium (24.5±21.4) and high-sodium and potassium supplementation (24.6±24.1) interventions. In addition, one standard deviation higher in urinary dopamine concentration (124.2 µg/24-h) was associated with 1.5 (-2.5, -0.6) mm Hg of mean arterial BP reduction from high-sodium to high-sodium plus potassium supplementation (p=0.001). One standard deviation higher in urinary norepinephrine concentration (24.3 µg/24-h) was associated with 1.4 (0.2, 2.6) mm Hg mean arterial BP increase from low-sodium to high-sodium (p=0.02) and 2.2 (-3.1, -1.3) mm Hg mean arterial BP reduction from high-sodium to high-sodium plus potassium supplementation (p<0.0001).

Conclusions: These data indicate that urinary excretion of dopamine and norepinephrine may play a role in BP salt- and potassium-sensitivity.

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SA-PO653

Difference of Impact on Cardio-Ankle Vascular Index Among Various Blood Pressure Indexes in Patients with Non-Diabetic Chronic Kidney Disease Hideo Okonogi, Tetsuya Kawamura, Akira Fukui, Shinya Yokote, Nobuo Tsuboi, Yoichi Miyazaki, Makoto Ogura, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Several studies reported that pulse pressure (PP) is the predictor of heart and kidney risks. On the other hand, arterial stiffness negatively correlates with renal function, and is the predictor of all causes mortality and mainly cardiovascular events in chronic kidney disease (CKD). Cardio-ankle vascular index (CAVI) is a non-invasive indicator of arterial stiffness, and is not influenced by the blood pressure (BP) at the time of examination. Therefore, we examined the relationship between various BP indexes and CAVI in patients with non-diabetic CKD.

Methods: Fifty-nine patients with non-diabetic CKD, who were diagnosed by first time biopsy, were included. Relationships between various BP indexes and CAVI were analyzed. Then receiver-operating characteristic (ROC) analysis for diagnosis of the presence of high arterial stiffness (CAVI≥9, suggesting the presence of arterial sclerosis) were analyzed.

Results: As a result, systolic BP (SBP) and PP significantly correlated with CAVI (r=0.433, p<0.01 and r=0.624, p<0.01, respectively), while diastolic BP (DBP) and mean BP (MBP) did not correlate with CAVI. The ROC curves for diagnosis of the presence of high arterial stiffness by each BP index showed that SBP, DBP, MBP and PP had an area under the ROC curve (AUC) value of 0.786 (p<0.01), 0.425, 0.614 and 0.906 (p<0.01), respectively. Then, by two-graph ROC analysis, the threshold values of SBP and PP were obtained as 132.4mmHg (sensitivity 71%, specificity 71%) and 55.5mmHg (sensitivity 82%, specificity 82%), respectively.

Conclusions: These results indicated that PP has the most strong impact on arterial stiffness among various BP indexes. PP may affect renal function and cardiovascular risk via increase in arterial stiffness.

SA-PO654

Uric Acid Levels Are Associated with Peripheral but Not Central Blood Pressure Parameters in Normotensive Individuals Pierre-Luc Lavoie, Stephan Troyanov, Francois Madore, Remi Goupil. *Nephrology, Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada.*

Background: Uric acid is increasingly recognised as a risk factor for cardiovascular disease. Whether this could be explained by changes in peripheral or central blood pressure (BP) profiles remains controversial. The aim of this study was to assess the association of uric acid levels with peripheral and central hemodynamic parameters in untreated normotensive individuals.

Methods: Of 20,004 CARTaGENE participants, 8,420 were normotensive individuals not treated for hyperuricemia or hypertension with valid pulse wave analysis (46.9% male, 52.6 yo). The associations between uric acid levels and peripheral systolic BP (SBP), pulse pressure (PP) central systolic BP (cSBP), central PP (cPP), pulse pressure amplification (PPA), augmentation index (AIx) and augmented pressure (AP) were tested with linear regressions.

Results: In univariate analyses, uric acid levels were significantly associated with all parameters. In contrast, in multivariate analyses, only SBP and cSBP remained independently associated with uric acid levels. As cSBP is usually highly dependent of SBP, it was further adjusted for peripheral BP, where it was not independently associated with uric acid levels (β coefficient -0.003, p=0.51).

Parameters ^b	Univariate		Multivariate ^a	
	β coefficient ^c	p-value	β coefficient ^c	p-value
SBP	0.260	<0.001	0.062	<0.001
PP	0.108	<0.001	-0.004	0.77
cSBP	0.167	<0.001	0.068	<0.001
cPP	-0.027	0.013	0.002	0.89
PPA	0.236	<0.001	-0.005	0.65
Alx	-0.272	<0.001	0.002	0.85
AP	-0.210	<0.001	0.006	0.60

^a adjusted for gender, age, BMI, diabetes, cardiovascular disease, smoking history, eGFR, fasting glucose, total cholesterol, HDL, TSH, and heart rate.
^b PPA expressed in 0.01 unit and Alx in %. All others in mmHg.
^c expressed per 10 umol/L of serum uric acid.

Conclusions: In normotensive individuals, uric acid levels were independently associated with SBP, but not with other hemodynamic parameters. Whether the increased risks associated with uric acid levels are explained by these parameters remains uncertain and needs further study.

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SA-PO655

Blood Pressure Trajectory and Events in the Cardiovascular Health Study
 Christopher C. Smitson,¹ Rebecca Scherzer,¹ Michael Shlipak,¹ Mark J. Sarnak,² Michelle Odden,³ Carmen A. Peralta.¹ ¹UCSF; ²Tufts; ³OSU.

Background: The association of blood pressure (BP) trajectories with clinical events in elders is not well established. The importance of integrating trajectories of systolic (SBP) and diastolic (DBP) is not known.

Methods: Among 4,067 participants in the Cardiovascular Health Study, we used repeated measures from the first 7 years to identify discrete trajectories of SBP, DBP and joint SBP/DBP by latent class analysis. We evaluated independent associations of BP trajectory with all-cause mortality, incident CVD (myocardial infarction, cardiac arrest, stroke or CVD death), and heart failure using multivariable Cox models with follow up beginning after 7th year (median follow-up 9.3 years).

Results: Mean age at 7th year was 78. Considering SBP or DBP separately, trajectory groups were primarily determined by baseline BP, and these were not independently associated with outcomes (all p>0.05). In contrast, three distinct groups were identified using joint SBP/DBP: (1) concordant increasing, (2) discordant (stable SBP and decreasing DBP), and (3) concordant decreasing. Compared with a concordant increasing, a concordant decreasing and discordant trajectory had increased risk of death. Concordant decreasing was also associated with increased risk for incident CVD and HF, compared with concordant increasing. Findings did not differ when we stratified by use of antihypertensives.

	Event Rate per 1000 PY	Multivariable Analysis HR (95% CI)
Mortality		
Concordant Increasing (n=1838)	60.6 (57.1, 64.4)	1 [reference]
Discordant (n=1109)	62.2 (57.6, 67.2)	1.16 (1.03, 1.31)
Concordant Decreasing (n=1120)	83.9 (78.2, 90.1)	1.20 (1.06, 1.36)
Incident CVD		
Concordant Increasing (n=1332)	24.0 (21.4, 26.9)	1 [reference]
Discordant (n=779)	25.2 (21.8, 29.2)	1.16 (0.93, 1.44)
Concordant Decreasing (n=726)	30.6 (26.5, 35.4)	1.26 (1.01, 1.58)
Incident HF		
Concordant Increasing (n=1689)	32.3 (29.5, 35.3)	1 [reference]
Discordant (n=998)	32.6 (29.0, 36.7)	1.00 (0.84, 1.20)
Concordant Decreasing (n=946)	42.2 (37.7, 47.3)	1.18 (0.99, 1.42)

Conclusions: Among community-dwelling elders, distinct BP trajectories were identified integrating SBP and DBP. Decreasing BP is associated with higher risk for adverse outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO656

Serum Uric Acid and Vascular Stiffness in African Americans with Hypertension
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Background: Elevated serum uric acid levels as well as vascular stiffness is associated with hypertension and cardiovascular (CV) disease. However, how uric acid affects vascular stiffness is not known. We examined the relationship between uric acid and vascular stiffness in a cohort of African American men and women with well-controlled hypertension.

Methods: 120 African-Americans with controlled hypertension were randomized in a double-blind, placebo controlled study to allopurinol (300mg/dl) or placebo for 4 weeks. Vascular stiffness was assessed by augmentation index at baseline and at 4 weeks after allopurinol therapy. Uric acid was characterized as low or high (>7 mg/dL in men and > 6 mg/dL in women).

Results: The mean age was 48.7 ± 8.73 years and majority of the participants were women (71%). Augmentation index was negatively correlated with uric acid at baseline (R= -0.24 p=0.009). The high uric group as compared to the low uric acid group, had a lower augmentation index (9.07 ± 5.52 vs. 11.22 ± 5.23 p=0.03) while the mean BP (119 /75 vs 118/75), age (48.7 vs 48.6), and endothelial function as measured by endoPAT (2.2 vs. 2.2) were similar. With allopurinol therapy there was a drop in uric acid by 2.23 ± 1.4 mg/dl as compared to placebo -0.15 ± 0.9 mg/dl but there were no significant changes in vascular stiffness or endothelial function.

Conclusions: In African Americans with hypertension uric acid is negatively associated with vascular stiffness and short-term therapy with allopurinol does not alter vascular stiffness. These changes are not explained by endothelial function. The mechanistic basis of how uric acid may be protective against vascular stiffness may explain the many conflicting studies on the contribution of uric acid to cardiovascular risk and merits further investigation.

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SA-PO657

The Impact of Renin-Angiotensin System Blockers on Renal Sodium Handling: An Analysis of CARTaGENE
 Catherine Delmas-Frenette, Stephan Troyanov, Josee Bouchard, Francois Madore, Remi Goupil. *Nephrology, Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada.*

Background: Renin-angiotensin system blockers (RASB) reduce the effects of angiotensin II, and subsequently aldosterone, leading to vasodilation and natriuresis. The magnitude of the RASB-induced natriuresis compared to diuretics and other anti-hypertensive agents remains uncertain.

Methods: We identified patients treated for hypertension from the prospective CARTaGENE cohort, a random sample of the Quebec population aged 40 to 69, who had available urinary sodium levels. We compared the fractional excretion of sodium (FeNa) between patients on beta-blockers or calcium channel blockers without diuretics (Group 1), on RASB without diuretics (Group 2) and on diuretics (Group 3) with ANOVA and a general linear model adjusting for age, gender, estimated glomerular filtration rate (eGFR), diabetes and peripheral mean arterial pressure (pMAP).

Results: Of the 3828 individuals with treated self-declared hypertension, 155 had urinary measurements. Of these 61% were male, their mean age was 59±8 years, 23% had diabetes and the eGFR and pMAP were 85±14 ml/min/1.73m² and 93±11 mmHg. Groups 1, 2 and 3 included 42, 72 and 41 patients, respectively. In unadjusted analyses, patients in Group 1 (0.67±0.33) had lower FeNa than Group 2 (1.02±0.51, p=0.001) and Group 3 (1.25±0.70, p<0.001), while Group 2 had lower FeNa compared to Group 3 (p=0.029). In the adjusted analysis, Group 2 still had higher FeNa than Group 1, but the results were similar to Group 3.

Treatment	Adjusted FeNa (95% CI)	p-value (vs Group 1)	p-value (vs Group 2)
Group 1 (beta-blockers and calcium channel blockers)	0.75 (0.59-0.92)	-	-
Group 2 (RASB)	1.01 (0.88-1.13)	0.049	-
Group 3 (diuretics)	1.19 (1.03-1.36)	0.001	0.22

Conclusions: After adjustment for important covariables, RASB therapy is associated with a natriuresis similar to diuretics and greater than other antihypertensive drugs in hypertensive patients. Whether the degree of natriuresis parallels the blood pressure response to these agents remains to be determined.

Funding: Government Support - Non-U.S.

SA-PO658

Urine Mitochondrial-DNA Copy Number Identifies Renal Injury in Severe Renovascular Disease Alfonso Eirin,¹ Ahmed Saad,¹ Sandra Herrmann,¹ Hui Tang,¹ Amir Lerman,² Stephen C. Textor,¹ Lilach O. Lerman.^{1,2} ¹*Divs of Nephrology and Hypertension, Mayo Clinic; ²Cardiovascular Diseases, Mayo Clinic, Rochester, MN.*

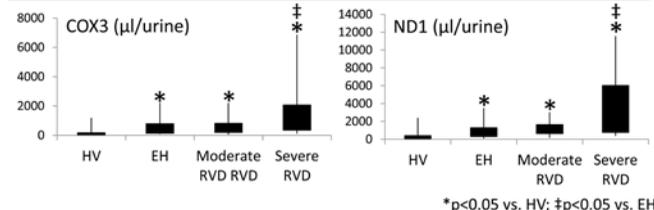
Background: We have previously demonstrated that mitochondrial injury contributes to renal dysfunction in swine renovascular disease (RVD), but its implications in human RVD remain unknown. Fragments of the mitochondrial genome released from dying cells are considered surrogate markers of mitochondrial injury. We hypothesized that RVD would be associated with increased urine mitochondrial DNA (mtDNA) copy numbers.

Methods: We prospectively measured urinary copy numbers of the mtDNA genes COX3 and ND1 by quantitative real-time PCR in essential hypertensive (EH), moderate RVD, and severe RVD patients (based on ultrasound criteria and evident loss of functional tissue), during constant sodium intake and anti-hypertensive regimens, and compared them with healthy volunteers (HV). Systemic levels of the kidney injury molecule neutrophil gelatinase-associated lipocalin (NGAL) were measured by ELISA.

Results: Blood pressure was similarly elevated in EH and RVD, yet serum creatinine and NGAL were higher and estimated glomerular filtration rate (eGFR) lower in RVD versus HV and EH (Table). Urinary COX3 and ND1 were higher in EH and moderate RVD compared to HV, and further elevated in patients with severe RVD (Figure). In RVD patients, urinary COX3 and ND1 directly correlated with NGAL (R²=0.18, p=0.02 and R²=0.37, p<0.001), proteinuria (R²=0.33, p<0.001 and R²=0.53, p<0.001), and serum creatinine (R²=0.27, p=0.002 and R²=0.16, p<0.02) levels, and inversely with eGFR (R²=-0.11, p=0.05 and R²=-0.13, p<0.04, respectively).

Conclusions: We found progressive increments in urinary mitochondrial injury markers with increased severity of RVD, implicating mitochondrial injury in kidney damage in human RVD. Mitochondria might represent a novel therapeutic target in RVD.

	HV (n=22)	EH (n=25)	Moderate RVD (n=20)	Severe RVD (n=14)
Age (years)	66.0±9.4	60.8±17.5	69.3±7.2	69.9±8.2
Gender (F/M)	12/11	10/15	12/8	3/11
BMI (kg/m ²)	26.8±4.2	27.2±4.5	26.8±4.2	28.1±3.4
Mean arterial pressure (mmHg)	87.7±8.1	93.3±10.5*	90.3±9.2*	98.8±11.9*
Antihypertensive drugs (number)	0.0±0.0	2.9±1.2*	2.6±1.4*	3.6±1.2*
Serum creatinine (mg/dl)	0.95±0.16	0.97±0.29	1.18±0.34**	1.59±0.37**
eGFR CKD-EPI (ml/min/1.73m ²)	76.2±11.9	79.4±21.4	57.6±20.4**	44.5±17.8**
NGAL (ng/ml)	65.3±23.5	71.9±36.1	147.9±55.6*‡	158.1±90.7*‡
Proteinuria (mg/24h)	84.0±82.6	77.4±56.21	90.6±62.2	208.2±401.7



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SA-PO659

Association Between Urinary Big Angiotensin-25 and Microalbuminuria in Hypertensive Patients Yasuhiro Yamashita,¹ Sayaka Nagata,¹ Yuji Sato,² Kazuo Kitamura,¹ Shouchi Fujimoto.³ ¹*Div of Circulatory and Body Fluid Regulation, Dept of Internal Medicine, Faculty of Medicine, Univ of Miyazaki, Miyazaki, Japan; ²Dialysis Div, Univ of Miyazaki Hospital, Miyazaki, Japan; ³Dept of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, Univ of Miyazaki, Miyazaki, Japan.*

Background: In hypertensive patients, albuminuria is a predictive factor for cardiovascular events. Recently, a newly glycosylated angiotensin-related peptide, Big angiotensin-25 (Bang-25), was isolated from human urine (Nagata et al. *Biochem Biophys Res Commun* 2013), and it was localized to podocytes in kidney tissue. Bang-25 may be involved in the renin-independent pathway for localized angiotensin II generation, and can contribute to diagnosis in organ disorders. Using cross-sectional data, we investigated the relationship between urinary Bang-25 and albuminuria in hypertensive patients.

Methods: We examined the data of 408 hypertensive patients (male 50.5%; mean age 70±10 years, BMI 25±3.7 kg/m², diabetes mellitus 38.0%, and eGFR 72±17 ml/min/1.73m²). We evaluated urinary albumin/creatinine ratio (ACR) and we measured urinary Bang-25 by specific AlphaLISA immunoassay. The association between urinary Bang-25/creatinine ratio and microalbuminuria was analyzed by a multivariate logistic method.

Results: Thirty patients were excluded because of macroalbuminuria (ACR>300 mg/gCr). Of 378 patients, 96 had microalbuminuria (30≤ACR<300 mg/gCr). Patients were then divided by quartiles of Bang-25/creatinine ratio. Older patients, females, lower hemoglobin, lower uric acid, and higher HDL were more prominent in higher Bang-25/creatinine quartiles. After adjusting for age, sex, eGFR, and presence of diabetes, the odds

ratios (95% confidence intervals) for microalbuminuria per quartile, calculated using multivariate logistic analysis, were as follows: Q1, reference; Q2, 0.72 (0.33-1.54); Q3, 0.99 (0.49-2.01); and Q4, 2.05 (1.01-4.14).

Conclusions: Higher urinary Bang-25/creatinine quartile was significantly associated with microalbuminuria in hypertensive patients. As Bang-25 is localized to podocytes, it may play some role in the development of albuminuria.

SA-PO660

Independent Association of Vitamin D on Endothelial Function: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Lea Borgi,¹ Ciaran Joseph McMullan,¹ Gary C. Curhan,¹ Naomi D.L. Fisher,² John P. Forman.¹ ¹*Nephrology, Brigham and Women's Hospital, Boston, MA; ²Endocrinology, Brigham and Women's Hospital, Boston, MA.*

Background: In nonhypertensive individuals, lower levels of 25-hydroxyvitamin D (25[OH]D) have been associated with an increased risk of hypertension, and vitamin D deficiency has been associated with endothelial dysfunction in such individuals. However, the effect of vitamin D supplementation on endothelial dysfunction in nonhypertensive individuals has not been examined in a rigorous fashion.

Methods: In this randomized, double-blind, placebo-controlled trial of nonhypertensive, nondiabetic overweight or obese individuals with vitamin D deficiency (body mass index [BMI] ≥25 and 25[OH]D<20ng/mL), we assigned subjects to receive either ergocalciferol (50,000 units) or matching placebo, once a week for 8 weeks. Our primary outcome was endothelial-dependent vasodilation (EDV) measured by brachial artery ultrasound at baseline and 8 weeks post-randomization.

Results: By the end of the trial, 46 and 47 participants were allocated to receive ergocalciferol and placebo, respectively. Mean 25(OH)D levels increased from 14.9 to 30.3 in the vitamin D group and 14.4 to 17.4 in the placebo. EDV did not change significantly with either vitamin D repletion (from 6.3±3.6% at baseline to 6.1±4.6% at 8 weeks; p-value=0.78) or placebo (7.9±4.7% to 6.8±4.7%; p=0.17). The treatment effect p-value (comparing the 8-week change with ergocalciferol to the change with placebo) was 0.35.

Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (measured as EDV) after repletion of vitamin D in overweight/obese non-hypertensive individuals.

Funding: NIDDK Support

SA-PO661

Secondary Hypertension, Primary Hyperaldosteronism, and Renal Cell Carcinoma Nicole Piero,¹ Krishnanath Gaitonde,^{1,2} Charuhas V. Thakar.^{1,2} ¹*Cincinnati VA Medical Center; ²Univ of Cincinnati.*

Background: Primary hyperaldosteronism (PH) is the most common cause of secondary hypertension. Renal cell carcinoma (RCC) can cause secondary hypertension, but as a renin-mediated process. We describe 5 cases referred for evaluation of PH (uncontrolled hypertension and hypokalemia), incidentally diagnosed with RCC, and the potential role of RCC as a renin-independent mechanism for hypertension.

Methods: At the initial renal visit, average blood pressure (BP) was 167/87 mmHg, with an average of 4 BP meds (no aldosterone blockers). Average serum levels of potassium, sodium and bicarbonate were 3.1, 143 and 30 mmol/L respectively. Average plasma renin activity (PRA) was 0.12 ng/ml/hr, average serum aldosterone (sAldo) was 16.6 ng/dL, with a mean sAldo:PRA of 143.6. In 24-hour urine analysis, aldosterone ranged from 11.8 to 30.2 ng/dL and sodium ranged 82-226 mmol/24 hours. All patients required 1 or 2 aldosterone blocking agents to achieve an average BP of 134/75 mmHg. Upon imaging, 4/5 had adrenal adenomas and all 5 patients had incidental solid renal masses with radiological characteristics of RCC. To date, 3/5 have had renal masses treated with partial/total nephrectomy or cryotherapy; all have confirmed pathology of RCC. All those undergoing RCC treatment were had improved BP with 2/3 having reduced therapy. At presentation these 3 patients had an average BP of 159/87 mmHg and were on an average of 4.6 BP meds; between 5 and 9 months after RCC treatment BP was 133/75 mmHg on average of 4 BP meds; 2/3 able to eliminate aldosterone blockade. 2/3 patients treated for RCC had follow-up biochemical assessment. sAldo:PRA normalized in the patient with partial nephrectomy; whereas it remained elevated in patient treated with cryotherapy.

Conclusions: To our knowledge this is the first case series describing a possible renin-independent, aldosterone-mediated mechanism for secondary hypertension associated with RCC. Although presence of adrenal and renal tumors has been reported, this series describes a physiological link between the two. Whether RCC leads to maladaptive steroid pathways leading to an aldosterone-like action in mediating hypertension requires detailed analysis of RCC tumors.

SA-PO662

Effect of Uric Acid Lowering Agents on Endothelial Function: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Lea Borgi,¹ Ciaran Joseph McMullan,¹ Gary C. Curhan,¹ Naomi D.L. Fisher,² John P. Forman.¹ ¹*Nephrology, Brigham and Women's Hospital, Boston, MA; ²Endocrinology, Brigham and Women's Hospital, Boston, MA.*

Background: In nonhypertensive individuals, higher levels of serum uric acid have been associated with an increased risk of hypertension, and elevated serum uric acid has been associated with endothelial dysfunction in such individuals. However, the effect of lowering serum uric acid on endothelial dysfunction in nonhypertensive individuals has not been examined thoroughly.

Methods: In this randomized, double-blind, placebo-controlled trial of nonhypertensive, nondiabetic overweight or obese individuals with elevated serum uric acid (body mass index [BMI] ≥ 25 and serum uric acid ≥ 5 mg/dL), we assigned subjects to receive one of the following: allopurinol 300mg daily for 4 weeks followed by 600mg daily for 4 weeks; probenecid 500mg daily for 4 weeks then 1000mg daily for 4 weeks; or matching placebo. Our primary outcome was endothelial-dependent vasodilation (EDV) measured by brachial artery ultrasound at baseline and 8 weeks post-randomization.

Results: By the end of the trial, 43, 44 and 47 participants were allocated to receive probenecid, allopurinol and placebo, respectively. Mean serum uric acid levels decreased from 5.9 to 3.6 mg/dL in the probenecid group, from 5.6 to 2.9 mg/dL in the allopurinol group, and were unchanged in the placebo group (5.6 to 5.7 mg/dL). EDV did not change significantly with either probenecid (from 7.6 \pm 5.1% at baseline to 8.4 \pm 5.2% at 8 weeks; p-value=0.39), allopurinol (from 7.4 \pm 6.0% at baseline to 5.9 \pm 4.6% at 8 weeks; p-value=0.09) or placebo (6.8 \pm 3.8% to 7.1 \pm 4.9%; p=0.66).

Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (measured as EDV) after lowering serum uric acid in overweight/obese non-hypertensive individuals.

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SA-PO663

Azelnidipine Can Restore the Deceleration Capacity of Heart Rate Variability (DC) In CKD Patients with Preceding Treatment with ARB
 Michio Fukuda,¹ Toshiyuki Miura,¹ Yoshiaki Ogiyama,¹ Ryo Sato,¹ Daisuke Fuwa,¹ Hiroyuki Ito,¹ Tetsuhei Matsuoka,¹ Yukako Isobe-Sasaki,¹ Ken Kiyono,² Yoshiharu Yamamoto,³ Junichiro Hayano,¹ Nobuyuki Ohte.¹ ¹Nagoya City Univ; ²Osaka Univ; ³Tokyo Univ.

Background: Recently, we have hypothesized that DC, novel measure of cardiac vagal modulations, is also attributable to sympathetic nerve activities. Azelnidipine was reported to decrease non-Gaussianity index of HRV ($I_{25\%}$), which can serve as a marker of sympathetic cardiac overdrive.

Methods: In 43 hypertensive patients with CKD under treatment with an angiotensin receptor blocker (ARB), we tested whether 8-week add-on administration of azelnidipine can increase DC. DC was calculated by Bauer's signal processing technique of phase-rectified signal averaging. For reference, the power of high frequency (HF, 0.15–0.40 Hz) obtained from frequency measure of HRV was examined as a conventional indicator of vagal activity.

Results: DC increased (6.17 \pm 1.84 to 6.55 \pm 1.85, p=0.002) and $I_{25\%}$ decreased (0.56 \pm 0.15 to 0.50 \pm 0.12, p=0.001), while no significant changes were observed in other HR variability measures including HF (p=0.9). Change in DC correlated inversely with the change in $I_{25\%}$ decreased (r=-0.38, p=0.01), but not with the change in HF (p=0.8).

Conclusions: Our findings are consistent with the thesis that DC is not a simple measure of vagal activity but a product of complex interplay between sympathetic and vagal nerve activities.

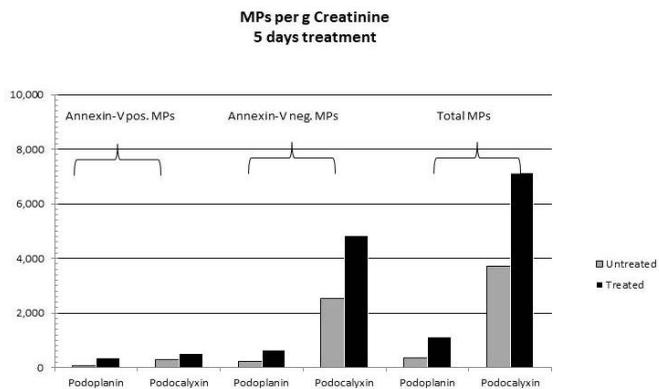
SA-PO664

Elevated Levels of Podocyte Derived Urinary Microparticles in Angiotensin II Induced Hypertension
 Uta Erdbruegger, Christine Rudy, Sylvia Cechova, Rosa Chan, Joseph C. Gigliotti, Thu H. Le. *Div of Nephrology and HTN, Univ of Virginia Health System, Charlottesville.*

Background: Early and non-invasive biomarkers of kidney damage are needed to identify hypertensive patients at risk for kidney damage. Urinary microparticles (uMPs) have gained significant attention as potential novel biomarkers for kidney damage, and have already been identified in pre-albuminuric diabetic glomerular injury. These vesicles are less than 1 micron in size and carry markers of the parent cell. We hypothesized that podocyte derived uMPs are elevated in angiotensin II-induced hypertension (HTN).

Methods: Wild-type mice were treated with AII (400ng/kg/min) via mini-osmotic pumps. Untreated WT mice served as controls. Blood pressure was measured with tail-cuff manometry. 24 hour urines were collected after 5 days of AII treatment. Enumeration and phenotyping of MPs was done of podocyte culture supernatant and urine. UMP levels were normalized to urinary creatinine concentration. Podocalyxin (Pcal), podoplanin (Ppla) and annexin 5 (AV) were used as surface markers.

Results: Pcal and Ppla positive MPs as well as AV positive and negative MPs were detectable in supernatant from primary podocyte cultures. Compared to untreated controls (n=3), AII treated mice (n=2) had an increase in systolic blood pressure (SBP) by 33 mmHG (p=0.02). Despite similar urinary albumin/creatinine ratios between groups, there was a trend of higher levels of total numbers of Pcal and Ppla positive MPs in hypertensive mice compared to untreated (see Figure1). In addition, AV negative but Ppla and Pcal positive MPs were also numerically higher in hypertensive mice compared to AV positive uMPs.



Conclusions: In conclusion, podocyte derived urinary MPs are detectable in AII HTN. These findings need to be confirmed in a larger group of animals. Urinary MPs can be potential marker for kidney end-organ damage in HTN.

Funding: Clinical Revenue Support

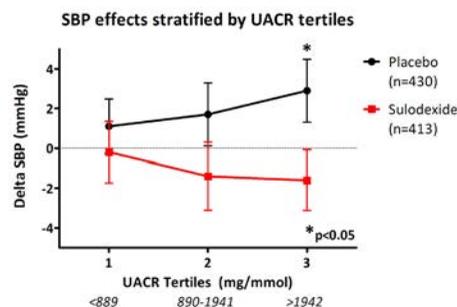
SA-PO665

Blood Pressure Lowering Effects of Sulodexide Depend on Albuminuria Severity
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Background: Diabetic patients have a thinner endothelial surface layer (ESL), especially when macroalbuminuria is present. Sulodexide, a mixture of glycosaminoglycans (GAGs), increases ESL thickness. Previous data indicate that the ESL is pivotal for BP regulation. In this study, we assessed whether the BP reducing effect of sulodexide is modified by albuminuria severity (a surrogate for the ESL) in type 2 diabetic patients.

Methods: In a post-hoc analysis of the randomized, double-blind, placebo-controlled Sun-MACRO trial, including type 2 diabetic patients with macroalbuminuria and maximal angiotensin II receptor blocker therapy, we studied the BP effects of sulodexide 200 mg/d. We stratified patients in baseline urinary albumin-creatinine ratio (UACR) tertiles. We used ANCOVA to study whether baseline UACR modified the 3-month SBP changes of sulodexide.

Results: Data of 843 patients were available for analysis. Baseline BP was 138/73 mmHg. At 3 months, mean (SEM) SBP change was -0.9 (\pm 0.9) and +1.7 (\pm 0.9) mmHg in the sulodexide and placebo arm, respectively (p=0.037). The SBP reduction was most pronounced in the highest UACR tertile (-1.6 (\pm 1.5) vs 2.9 (\pm 1.6) mmHg; p=0.042). Treatment (p=0.015), baseline SBP (p<0.001), heart rate (p=0.007) and UACR (p=0.007) were associated with SBP change. We found an interaction between treatment and UACR (p=0.047), indicating that sulodexide and placebo differently affected SBP at various UACR levels. Age, eGFR, BMI, Hba1c and lipid profile (i.e., factors influencing ESL thickness) did not modify the treatment effect. The BP differences persisted during the first year of follow-up (p=0.047).



Conclusions: The BP reducing potency of sulodexide is modified by albuminuria severity in type 2 diabetes, indicating that ESL restoration may represent a new target for BP treatment in these patients.

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SA-PO666

Under-Diagnosis of Hypertension in a Large Cohort of Overweight/Obese Adolescents
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Background: The obesity epidemic in children is strongly associated with increasing prevalence of childhood hypertension (htn) along with heightened risk for cardiovascular morbidity and mortality in adulthood. Therefore we assessed the identification of htn in overweight/obese adolescents cared for by a large healthcare system utilizing an EMR system.

Methods: We performed a retrospective study of patients (pts) in the Nemours Health Care System, aged 12-17 years, with a BMI > 85%ile, and >3 documented BPs > 120/80 in the outpatient setting, between 1/2010 and 12/2014. Pts with established diagnosis of htn (ICD-9 codes 401.XX - 405.XX), renal or heart disease were excluded.

Results: Of the 6604 distinct pts identified, only 255 (3.8%) received a diagnosis of htn during the study period, while 6,349 (96.2%) were undiagnosed. Pts who were undiagnosed had lower BMIs and BPs and were less likely to be African American or have Medicaid and were seen less by Nephrology, Cardiology or Weight management subspecialties compared with those diagnosed with htn (table). Additionally undiagnosed pts had fewer abnormal BPs and had a longer interval between their 1st and 3rd abnormal BP compared with those diagnosed with htn.

	Diagnosed HTN (n=255)	Undiagnosed HTN (n=6349)	P-value
Age (years)	13.9±1.6	13.9±1.5	NS
BMI (Z-Score)	2.17 (1.77,2.49)	1.88 (1.47,2.26)	<0.001
SBP (mmHg)	128 (122,134)	126 (122,131)	<0.002
DBP (mmHg)	74 (68,80)	70(65,76)	<0.001
African American (%)	38.0	25.4	<0.001
Medicaid (%)	37.2	29.9	<0.01
Seen by Nephrology (%)	30.1	9.6	<0.001
Seen by Cardiology (%)	53.3	13.8	<0.001
Seen by Weight Management (%)	25.1	8.1	<0.001
Abnormal BPs (n)	6 (4,10)	4 (3,6)	<0.001
Median time between 1 st & 3 rd BP (days)	251 (110,480)	364 (182,623)	<0.001

Data is presented as Mean±SD or Median (Interquartile range)

Conclusions: In this large cohort of overweight/obese adolescents with htn, the vast majority of pts were undiagnosed and not referred to subspecialists who manage BP monitoring and treatment. Thus it is crucial that future efforts focus on improving detection and early recognition of htn in order to reduce cardiovascular morbidity and mortality in this at-risk population.

SA-PO667

Multidisciplinary Selection of Angioplasty Indications in Atheromatous Renal Artery Stenosis Leads to an Improvement in Blood Pressure, Drug Sensitivity and Renal Function Thomas Fournier,¹ Florence Sens,¹ Olivier Rouviere,² Antoine Millon,³ Laurent Juillard.¹ ¹Nephrology, Hôpital E.Herriot, Hospices Civils de Lyon, Lyon, France; ²Radiology, Hôpital E.Herriot, Hospices Civils de Lyon, Lyon, France; ³Vascular Surgery, Hôpital E.Herriot, Hospices Civils de Lyon, Lyon, France.

Background: Angioplasty as treatment of atheromatous renal artery stenosis (ARAS) is controversial since 3 large randomised trials (CORAL, ASTRAL, STAR) failed to prove the superiority of percutaneous renal artery angioplasty and stenting (PTRAS) over medical treatment alone (MT). However, since population selection was questionable among other bias, the extrapolation of these results in clinical practice is uncertain.

Methods: ARAS cases were discussed during bi-monthly multidisciplinary meetings gathering nephrologists, radiologists and vascular surgeons from April 2013 to February 2015. For every patient, we compiled clinical, biological and radiological data. We then recorded blood pressure (BP), renal function and treatment evolution after a one-year follow-up.

Results: During 23 months, 52 cases were discussed. Mean age was 69 years. Two thirds of patients had at least 3 cardiovascular risk factors. Mean BP was 161/77 mmHg, despite the use of 2.5 ± 1.1 anti-hypertensive drugs. CKD-EPI was 53mL/min/1.73m². 31% of patients had a history of pulmonary edema. Collective decisions were PTRAS for 21 patients (40%), MT for 28 patients (54%) and surgery for 3 patients (6%). PTRAS and MT groups were initially comparable (blood pressure, renal function, treatment, comorbidities). In the PTRAS group, a significant improvement at 1 year was observed for BP control (systolic -22.6 +/- 29.3 mmHg; diastolic -10.1 +/- 12.9 mmHg), antihypertensive drug number (-0.8 +/- 0.94) and creatinin (-18.3 +/- 35.4 µmol/L). In the MT group, these improvements were not observed.

Conclusions: The significant improvement observed in the PTRAS could be explained by a better selection of patients who could benefit from PTRAS, based on radiologic data analysis and systematic multidisciplinary approach. Multidisciplinary identification of PTRAS indications leads to a better BP control, a reduction in anti-hypertensive drugs use and an improvement in renal function.

SA-PO668

Comparison of Control Rates Among Recommended Drug Selection Strategies for Initial Therapy of Hypertension Kamel A. Gharraibeh,¹ Stephen T. Turner,¹ Arlene B. Chapman,³ Rhonda M. Cooper-DeHoff,² Julie A. Johnson,² Gary L. Schwartz.¹ ¹Nephrology and Hypertension, Mayo Clinic, MN; ²College of Pharmacy, Univ of Florida, FL; ³Nephrology, Univ of Chicago, IL.

Background: Thiazide diuretics (TD) are recommended for initial therapy of hypertension (HTN). In addition to this TD for all, other recommended strategies for initial drug selection are based on age/race (A/R) criteria or on measures of plasma renin activity (PRA). It is uncertain which of these 3 strategies achieves the highest control rate with monotherapy in stage-I HTN.

Methods: Blood pressure (BP) responses from the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study were used to estimate control rates for each of the 3 strategies: (i) TD (hydrochlorothiazide) for all, (ii) TD for all black subjects and for white subjects aged ≥50 years and a renin-angiotensin system (RAS) blocker (atenolol) for whites aged <50 years (A/R strategy) or (iii) TD for suppressed PRA < 0.6 ng/ml/h and a

RAS blocker for non-suppressed PRA ≥ 0.6ng/ml/h regardless of age or race (PRA strategy). In PEAR, adults with stage 1 HTN were treated with either hydrochlorothiazide (n=148 black and 218 white subjects) or with atenolol (n=146 black and 221 white subjects). BP response was assessed in the clinic and by 24-hour ambulatory BP (ABP).

Results: Overall, the PRA strategy was associated with the highest control rate compared to the other strategies: **clinic BP:** 48.9% with PRA strategy, 40.8% with A/R strategy (P=0.0004) and 31.7% with the TD strategy (P<0.0001); **ABP:** 61.3% with PRA strategy, 51.6% with A/R strategy (P<0.0001) and 43.9% with TD strategy (P<0.0001). This was also true for each racial subgroup: **clinic BP:** in whites: 50.3% with PRA strategy, 40.6% with A/R strategy, P=0.002 and 25.4% with the TD strategy P<0.0001; in blacks: 46.7% with PRA strategy, and 41.1% for the other 2 strategies, P=0.08, **ABP:** in whites 63.5% with PRA strategy, 50.9% with A/R strategy, P<0.0001 and 38.2% with TD strategy, P<0.0001; in blacks 57.9% with the PRA strategy, and 52.6% with the other 2 strategies P=0.099.

Conclusions: Compared to TD or A/R, the PRA strategy for initial drug selection in stage I HTN was associated with the highest control rate.

Funding: Other NIH Support - PEAR was supported by the National Institute of Health Pharmacogenomic Research Network grant (U01 GM074492) and the National Center for Advancing Translational Sciences under the award number UL1 TR000064 (University of Florida), UL1 TR000454 (Emory University), and UL1 TR000135 (Mayo Clinic). PEAR was also supported by funds from the Mayo Foundation

SA-PO669

Primary Hyperaldosteronism: An Inner City Hypertension Clinic Experience! Ewalola A. Ijaduola, Srijan Shrestha, Islamiyat J. Babs animashaun, Jeffrey D. Wallach, Sudhanshu Jain. *Nephrology, Harlem Hospital Center, New York, NY.*

Background: Primary Hyperaldosteronism (PA) has historically been regarded as a rare disorder. Recent studies have shown a widely variable prevalence. We screened for PA in the Hypertension(HTN) Clinic at Harlem Hospital in patients with predominantly African-American and Hispanic ethnicities.

Methods: Retrospective cross-sectional study of patients seen at Harlem HTN Clinic between January 2008 to November 2013. The inclusion criteria were patients seen with completed aldosterone and renin levels. The exclusion criteria were patients on spironolactone prior to the laboratory studies or with incomplete data. Prevalence was measured as number of patients with both an Aldosterone/Renin ratio >20 and an Aldosterone level >15ng/dl as a ratio of total number of patients tested.

Results: A total of 268 patients who had plasma aldosterone and renin activity obtained was reviewed. Of these, 8 patients had incomplete data and were excluded. 220 of the remaining 260 patients in the study were black, while 40 patients were Hispanic. Notably, 43/260, or 16.5% of the patients were found to have met biochemical criteria for PA. About half, 22/43 or 51% of the patients had CAT Scans showing adrenal adenomas. Additionally, one patient had bilateral enlarged adrenal glands consistent with adrenal hyperplasia, 10 had CAT scans with no evidence of an adrenal mass, while the remaining 10 patients had no abdominal imaging. In the 43 patients who met biochemical criteria for PA, 34 patients were black, 16 of which (47%) had CT evidence of adrenal adenoma while 1 patient had bilateral hyperplasia. Of the 9 Hispanic patients, 6 (67%) had CT evidence of adrenal adenoma. Overall, the prevalence of PA was 34/220 (15.4%) in African-American patients and 9/40 (22.5%) in Hispanic patients.

Conclusions: Our study suggests a higher than anticipated prevalence of PA in African-American and Hispanic patients in Harlem, NYC, based on selective screening with plasma aldosterone and plasma renin activity. In addition adrenal adenomas were present by CT scan in at least 50% of cases, potentially treatable with surgery. Thus,adequate screening of patients for PA is essential, especially in minorities.

SA-PO670

HIV-2 and Chronic Kidney Diseases (French HIV-2 Cohort ANRS CO5) Jerome Turet,^{3,4} Aissatou Paye,¹ Marine Naudin,¹ Roland Tubiana,^{3,4,5} Philippe Genet,⁶ Diane Descamps,^{2,7,8} Françoise Brun-Vezinet,² Catherine Fagard,¹ Genevieve Chene,¹ Sophie Matheron,^{2,7,8} The french ANRS co5 cohort.¹ ¹INSERM U897, Univ Bordeaux, France; ²AP-HP Hôpital Bichat, France; ³AP-HP Hôpital Pitié Salpêtrière, France; ⁴UPMC, Univ Paris 06, France; ⁵INSERM UMR 1136, France; ⁶Hôpital Argenteuil, France; ⁷Univ Paris Diderot, France; ⁸IAME, INSERM UMR 1137, France.

Background: The link between HIV-2 and chronic kidney diseases (CKD) has not been studied. We describe the prevalence of CKD and their risk factors in people living with HIV-2.

Methods: All patients included in the HIV-2 French national cohort with 2 creatinine measurements at least 3 months apart were included. Glomerular filtration rate was estimated by MDRD formula and used to categorize CKD according to the NKF classification. Risk factors were determined by uni and multivariate analyses using a Cox model which included the main known risk factors for CKD and the main characteristics of HIV infection.

Results: Out of 1048 patients, 737 had 2 creatinine measurements. Their characteristics did not significantly differ from those of the total cohort: mean age (SD) was 50 (11) years, 62% of the patients were females, and 80.1% originated from sub-Saharan countries. On average, HIV-2 infection was diagnosed 12.8 (6.8) years before last creatinine measurement. Prevalence of CKD stage ≥2 was 39.8% and that of chronic kidney failure (stage ≥3) was 7.2%. Univariate analysis revealed that age (HR=1.06, p<10⁻⁴), HIV stage (HR=3.1, p<10⁻⁴ for CDC stage C), HIV-2 plasma viral load (HR=1.9 for each increment of log₁₀(copies/ml), p<10⁻³), and CD4 count (HR=3.12, p<10⁻² if <100/mm³) were risk factors for chronic

kidney failure. HIV stage A (HR=0.3, p<10⁻⁴) had a protective effect. Multivariate analysis revealed that age (HR=1.05, p=0.002) and CDC stage A (HR=0.35, p=0.01) were risk and protecting factors, respectively.

Conclusions: The prevalence of CKD in this very large cohort of people living with HIV-2 seems to be comparable to what is known in literature for people living with HIV-1. HIV-2 infection parameters determine most of the kidney risk. The role of ARV exposition remains to be taken into account.

Funding: Government Support - Non-U.S.

SA-PO671

Effect of Nephropathy on the Frequency of Cardiac Dysautonomia in HIV Patients Syed Rizwan Bokhari,¹ Syed Hunain Riaz,² Qurrat-ul-ain Abid,² Hafiz I. Ahmad,¹ Muhammad Zaman Khan Assir,² Fahmina Ashfaq,² Kashif Saleem.²
¹Dept of Nephrology, Allama Iqbal Medical College/ Jinnah Hospital, Lahore, Pakistan; ²HIV Clinic, Jinnah Hospital, Lahore, Pakistan.

Background: Dysfunction of autonomic nervous system including Cardiac Dysautonomia (CD) is seen in a variety of conditions like diabetes mellitus, adrenal insufficiency and renal failure. CD is well documented in patients with renal dysfunction/CKD. Prevalence of renal dysfunction (HIV Nephropathy) is high in our population of HIV positive patients, but the effect of HIV nephropathy on the frequency of CD has not been previously studied. We conducted this study to determine the effect of HIV Nephropathy on the frequency of CD.

Methods: This cross sectional study was conducted at HIV Clinic in collaboration with the Department of Nephrology Jinnah Hospital Lahore. A total of 47 HIV positive patients were enrolled; 13 (28%) with nephropathy and 34 (72%) without nephropathy. Patients underwent 5 tests for cardiac autonomic dysfunction including resting tachycardia, abnormal heart rate response to deep breathing, abnormal Valsalva ratio, abnormal 30:15 ratio and postural hypotension. Patients with 2 or more abnormal tests were considered positive for CD.

Results: Of 47 patients, 39(83%) were male, 5(11%) female and 3(6%) were transgender with median age of 31 years (range 19-56 years). The median CD4 count was 339 (range 39-797) and 96% (n=45) patients were on highly active anti-retroviral therapy (HAART). The median duration of HIV was 12 months (range 1-56) and median duration of HAART was 11 months (range 0-49). CD was seen in 42 (89%) patients. Seventeen (36.2%) patients had 2, 18(38.3%) had 3, 6 (12.8%) had 4 and 1 (2%) had 5 abnormal tests. The frequency of CD was comparable among patients with and without nephropathy [92% (12 out of 13) vs 88% (30 out of 34), respectively; p value=1]. The presence of CD had no correlation with CD4 count, degree of renal impairment, treatment regimen and duration on HAART.

Conclusions: There was high frequency of CD in our population of HIV patients and it was independent of presence or absence of nephropathy, CD4 count and duration of anti-retroviral therapy.

SA-PO672

Glomerular Filtration Rate Estimating Equations Using Beta-Trace Protein and Beta-2 Microglobulin in Chronic Kidney Disease Lesley Inker, Hocine Tighiouart, Josef Coresh, Meredith C. Foster, Amanda Hyre Anderson, Gerald J. Beck, Gabriel Contreras, Tom Greene, Amy Karger, John W. Kusek, James P. Lash, Julia Lewis, Jeffrey R. Schelling, Sankar D. Navaneethan, James H. Sondheimer, Tariq Shafi, Andrew S. Levey. *Chronic Kidney Disease Biomarkers Consortium*.

Background: Beta-trace protein (BTP) and beta-2-microglobulin (B2M), like cystatin C (Cys), are novel serum filtration markers that have stronger associations with adverse outcomes than serum creatinine (Cr). However, comparisons of BTP and B2M to Cr and Cys as filtration markers are limited by the absence of rigorously developed GFR estimating equations.

Methods: Using a pooled database of three populations with CKD (N=3551, mean measured GFR using iothalamate [mGFR] 48 ml/min/1.73m²), we developed equations to estimate mGFR using Cr, Cys, BTP or B2M. Equations were developed in 2/3 of the population and tested in the remaining 1/3.

Results: The table shows the coefficients included in each equation and the performance of the equations in the validation dataset compared to established CKD-EPI Cr-Cys equations.

Performance of GFR estimating equations in the validation dataset		
Description	IQR(95%CI)	1-P ₃₀ (%)(95%CI)
BTP age, sex*	15.0 (14.1, 15.9)	23.6 (21.3, 26.1)
B2M*	12.9 (12.2, 13.8)	18.4 (16.2, 20.8)
BTP-B2M*	12.1 (11.4, 13.0)	15.5 (13.3, 17.7)
CKD-EPI Cr age, sex, race*	11.6 (10.9, 12.4)	16.4 (14.2, 18.6)
CKD-EPI Cys age, sex*	11.4 (10.6, 12.4)	16.9 (14.9, 19.1)
CKD-EPI Cr-Cys age, sex, race	9.3 (8.7, 10.1)	11.3 (9.5, 13.2)
Average of CKD-EPI Cr-Cys + BTP-B2M	10.2 (9.5, 11.0)	9.6 (8.0, 11.4)

IQR, interquartile range of mGFR-eGFR. 1-P₃₀% of estimates >30% of mGFR. Bias is not shown as it is expected to be near zero, since both the development and the validation dataset are random samples of the total dataset. *p<0.001 for difference of 1-P₃₀ from CKD-EPI Cr-Cys equation

Conclusions: BTP and B2M are less influenced by age, sex and race than Cr or Cys but did not improve precision (IQR) or errors (1-P₃₀), even when averaged with Cr-Cys equation. CKD-EPI BTP and B2M equations provide tools for future study in their associations with mGFR and risk and adverse outcomes, but further study is required before clinical use.

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SA-PO673

Estimation of Glomerular Filtration Rate P.C. Pham,¹ Ruchika Bhasin,¹ Afsaneh Haftbaradaran,¹ Eileen C. McCann,¹ Solomon C. Huang,¹ Saman Sarani,¹ Anita Kamarzarian,¹ Golriz Jafari,¹ P.T. T. Pham.² ¹Div of Nephrology and Hypertension, Olive View-UCLA Medical Center, Sylmar, CA; ²Kidney Transplant, UCLA Medical Center, Los Angeles, CA.

Background: Estimations of glomerular filtration rates (GFR) based on routine 24 hour urine collections have been replaced by relatively accurate equations derived from large epidemiological studies. Nonetheless, equations including Modification Diet in Renal disease-4 and 6 variables (MDRD-4, -6) and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) are known to have wider variations in predicting GFR among patients with relatively good kidney function. As renal clearance of any solute is dependent on its presence in the plasma and not whole blood, we suspect that varying hemoglobin/hematocrit (Hct) may play an important role in the actual clearance of solutes. We aim to determine if adding the plasma factor PF (1 - Hct/100) to MDRD-4, -6, or CKD-EPI equations can improve the accuracy of determining actual GFR.

Methods: This is a retrospective pilot study where the most recent 200 existing 24-hour urine collections obtained with creatinine concentrations as recorded by the Olive View-UCLA Medical laboratory are collected for analysis. Only 24-hour urine collections with concurrent measurements of complete blood count and chemistry 7 are included. To minimize poor 24 hour collections, only samples with urine creatinine ranging between 15-25 mg/kg body weight/day are used. PF is added as an inverse multiplication factor to MDRD-4 and 6-variables and CKD-EPI equations to assess for variations when correlated with actual 24 hour urine collections.

Results: 90 out of 200 samples met inclusion criteria. Albeit small, when each of the aforementioned equation was adjusted for PF, R² variation improved. MDRD-4: unadjusted R²=0.836 to adjusted R²=0.853, MDRD-6, R²=0.811 to 0.813, CKD-epi, R²=0.746 to 0.747.

Conclusions: Adding PF to MDRD-4, MDRD-6, and CKD-EPI equations reduced variations when correlated to 24 hour urine collections. Of interest, PF appears to improve MDRD (derived for CKD patients where anemia is prevalent) variations better than CKD-EPI. Large-scale reevaluation of eGFR estimates with consideration for PF is warranted.

SA-PO674

Interest of Cystatin C in the Evaluation of Glomerular Filtration Rate in Type 2 Cardio-Renal Syndrome *Delphine Kervella,^{1,3} Sandrine Lemoine,^{2,3} Florence Sens,^{1,3} Eric Pouliquen,^{1,3} Laurence Dubourg,^{2,3} Fitsum Guebre-egziabher,^{1,3} Laurent Juillard.^{1,3}* ¹Nephrology, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; ²Renal Function, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; ³Univ Claude Bernard Lyon 1, Lyon, France.

Background: In patients suffering from type 2 cardio-renal syndrome (CRS2), glomerular filtration rate (GFR) is overestimated with creatinine based formulae, leading to the misclassification of these patients in chronic kidney disease stages. As cystatin C is less dependent from muscle mass than creatinine, the aim of this study was to determine if estimation of GFR based on cystatin C offers a better evaluation of renal function than creatinine-based estimations in patients with CRS2.

Methods: GFR measured by Inulin clearance (measured GFR, mGFR) in 50 patients with CRS2 was compared to estimations of GFR (eGFR) with CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) formulae based on creatinine (CKD EPI), cystatin (CKD EPI_{CYST}) and cystatin and creatinine (CKD EPI_{CYST-CREAT}). We calculated absolute bias (eGFR-mGFR) and accuracy 30% for each formula.

Results: Mean mGFR is 26.5±11.5 mL/min/1.73 m². eGFR are 41.5±20, 32±15 and 35±14.5 mL/min/1.73 m² with CKD EPI, CKDEPI_{CYST} and CKD EPI_{CYST-CREAT} respectively.

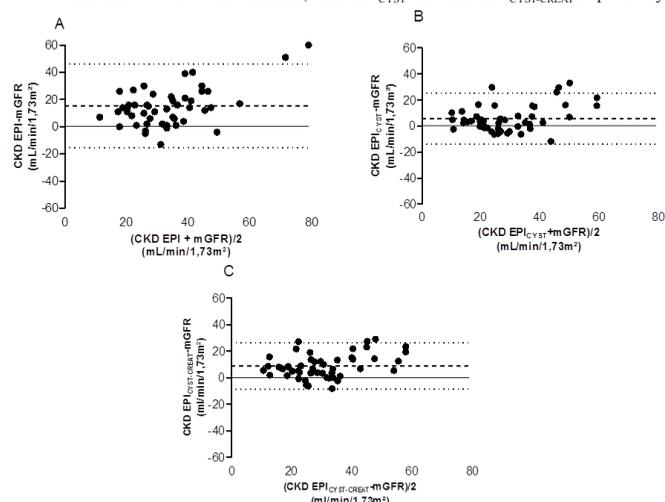


Figure 1. Bland and Altman plots of CKD EPI (A), CKD EPI_{CYST} (B), and CKD EPI_{CYST-CREAT} (C).

Thick dashed line represents mean bias between eGFR and mGFR, thin dashed lines represent limits of agreement 95% of mean bias.

These values of eGFR are significantly different from mGFR. Mean absolute bias are 15.4, 5.7 and 8.8 mL/min/1.73 m² and accuracies 30% are 30%, 68% and 48% respectively. The accuracy of CKD EPI_{CYST} is significantly higher than the accuracy of CKD EPI.

Conclusions: Glomerular filtration rate is strongly overestimated with creatinine-based CKD EPI formula in CRS2 patients as previously described. CKD EPI formula based on cystatin C offers a better evaluation of GFR in this population. The high prevalence of malnutrition in this population can explain these results.

SA-PO675

Creatinine Level in Capillary Blood: A New Tool for Instant Estimation of Glomerular Filtration Rate *Maurice Laville,¹ Solenne Pelletier,² Denis Fouque.¹* ¹Nephrologie, Univ de Lyon, Pierre Benite, France; ²Nephrologie, Hospices Civils de Lyon, Pierre Benite, France.

Background: Serum creatinine is the most used endogenous marker to estimate glomerular filtration rate (eGFR) in clinical practice. A handheld device (StatSensor®, Nova Biomedicals) allows to measure creatinine level in capillary blood. The aim of the study was to assess the accuracy of GFR values (eGFR) estimated from capillary blood creatinine level (CBCr), as compared with GFR values simultaneously measured by a gold standard method (mGFR) in patients with CKD.

Methods: The study included 79 adult patients (36 men, 43 women) who underwent renal function tests. The consent form contained information on the procedure and on the later use of the information for research. Inulin clearance was performed using a continuous infusion of inulin, and urine collections by periods of 30 min. Blood tests were done in the middle of each period of urine collection. Measurements of polyfructosan concentrations were performed using an enzymatic method. Inulin clearance was calculated in each period to obtain the average, and normalized to 1.73 m² body surface area. A drop of capillary

blood was collected from a finger simultaneous to the first and the last blood sampling for inulin measurement. The drops were deposited on a test strip including enzyme reagents and inserted into the SatSensor® device. Reading was done at 30 sec. eGFR was calculated from CBCr with the CKD-EPI equation and the average of the 2 values was taken as eGFR. To assess the performance of CBCr-derived eGFR, the mean absolute bias (eGFR - mGFR) and the correlation coefficient (R²) were calculated.

Results: Mean age was 54 ± 17 years, and mean BMI was 25 ± 5 kg/m². Mean value of mGFR was 61 ± 27 mL/min/1.73 m². Mean bias was -5.2 mL/min/1.73 m². On correlation analysis, there was no significant difference between the 2 methods (correlation coefficient 0.86 [0.7;1.0]).

Conclusions: Estimation of GFR using instant measurement of capillary blood creatinine level and CKD-EPI formula provides consistent results as compared with a gold standard method for GFR measurement, and could be used for screening and self-assessment purposes.

Funding: Clinical Revenue Support

SA-PO676

Renal Function Estimated with Different Formulae and Mortality in the INCIPE Cohort: Results After 8 Years Follow-up *Pietro Manuel Ferraro,¹ Antonio Lupo,² Giovanni Gambaro.¹* ¹Div of Nephrology, Catholic Univ of the Sacred Heart, Rome, Italy; ²Div of Nephrology, Univ of Verona, Verona, Italy.

Background: Chronic kidney disease is a known risk factor for adverse outcomes. Its presence and severity is usually ascertained with formulae to estimate renal function based on serum creatinine and/or cystatin C. We analyzed whether renal function estimated with different formulae has a differential association with mortality.

Methods: The INCIPE cohort is a sample of the Italian population enrolled in 2006-07, with follow-up data available up to 2014. CKD stages were defined as GFR ≥90, 89-60, 59-45 and <45 mL/min based on the following formulae: Cockcroft-Gault (CG), Cockcroft-Gault normalized to body surface area (nCG), abbreviated MDRD (MDRD), 6-variables MDRD (MDRD-6), CKD-EPI calculated with serum creatinine (EPI-Cr), with serum cystatin C (EPI-Cys), and with both serum creatinine and cystatin C (EPI-CrCys). CKD stage was then included in a Cox proportional hazards model together with age, body mass index, sex, high blood pressure, diabetes, dyslipidemia, previous cardiovascular disease, smoking status and albuminuria. Harrell's c statistics with 95% confidence intervals (CI) were then calculated and compared for each formula.

Results: The final sample included 2,916 participants, all caucasians, 47.4% males, with an average age at enrollment of 59.9±11.4 years. Participants contributed a total of 22,514 person-years of follow-up (median follow-up 7.9 years) during which 198 death events occurred. Overall, the models were highly predictive of mortality

	Harrell's c	95% CI
CG	0.818	0.788, 0.848
nCG	0.818	0.788, 0.848
MDRD	0.820	0.791, 0.849
MDRD-6	0.819	0.789, 0.848
EPI-Cr	0.818	0.789, 0.848
EPI-Cys	0.826	0.797, 0.856
EPI-CrCys	0.821	0.791, 0.850

The GFR-Cys model performed significantly better than MDRD-6 (difference in c-statistics of 0.008, 95% CI 0.001, 0.015; p=0.034), whereas all the other models performed similarly.

Conclusions: Our study suggests that CKD defined with the CKD-EPI cystatin C formula shows a better prediction of mortality after accounting for a large number of potential risk factors.

SA-PO677

Do the BIS Equations Better Predict Death in Older Women? *Muna T. Canales,^{1,2} Terri L. Blackwell,³ Areef Ishani,^{4,5} Brent C. Taylor,⁴ Allyson Hart,⁶ Rebecca Beyth,^{1,2} Kristine E. Ensrud.^{4,5}* ¹Malcom-Randall VAMC; ²Univ of Florida; ³California Pacific Medical Center; ⁴Minneapolis VA Health Care System; ⁵Univ of Minnesota; ⁶Hennepin County Medical Center, Minneapolis, MN.

Background: KDIGO 2012 guidelines recommend use of the CKD-EPI equations to estimate GFR except when there are alternate equations that may perform better for certain populations such as older adults. The BIS equations were specifically developed in an aged population, but their performance when compared to the CKD-EPI equations to predict mortality in older adults is unclear.

Methods: We conducted a prospective study of 1289 community-dwelling elderly women (≥72 years old) enrolled in the Study of Osteoporotic Fractures (SOF) who had both serum cystatin-C (cysc) and creatinine (SCR) measured at Year 10 (1992-1994). We used Cox proportional hazards regression and net reclassification improvement (NRI) to compare the ability of the BIS2 (cysc & SCR-based), CKD-EPI_{cr,cysc}, BIS1 (SCR-based), and CKD-EPI_{cr}, expressed as 4 eGFR categories (≥75, 60-74, 45-59, <45) to predict death. For NRI analyses, reference equations were CKD-EPI_{cr,cysc} for BIS2 and CKD-EPI_{cr} for BIS1.

Results: The mean age was 79.5±4.6 years; 89% were white. Mean BMI was 27±5 kg/m². Mean follow-up time was 9±4 years. % eGFR<60 was: CKD-EPI_{cr,yscr} 33%, BIS2 48%, CKD-EPI_{cr} 24% and BIS1 49%. When compared to eGFR≥75 and after adjustment for age, race, BMI, HTN & DM, eGFR<45 by BIS2 was associated with a 2.1-fold greater risk of death (95% CI 1.5-3.0) vs 1.9-fold for eGFR<45 by CKD-EPI_{cr,yscr} (95%CI 1.5-2.5); BIS1 eGFR<45 was associated with a 1.6-fold greater risk of death (95% CI 1.1-2.1) vs 1.8-fold for eGFR<45 by CKD-EPI_{cr} (95% CI 1.4,2.4; p trend <0.001 across categories for each equation). In category-based NRI analyses neither of the BIS definitions materially changed discrimination of mortality risk when compared to CKD-EPI equations.

Conclusions: In this cohort of older community-dwelling women, the BIS equations identified a greater proportion of participants as having CKD. With respect to mortality risk prediction, the BIS equations did not perform better than current CKD-EPI equations recommended by KDIGO 2012.

Funding: Other NIH Support - NIA, Veterans Administration Support

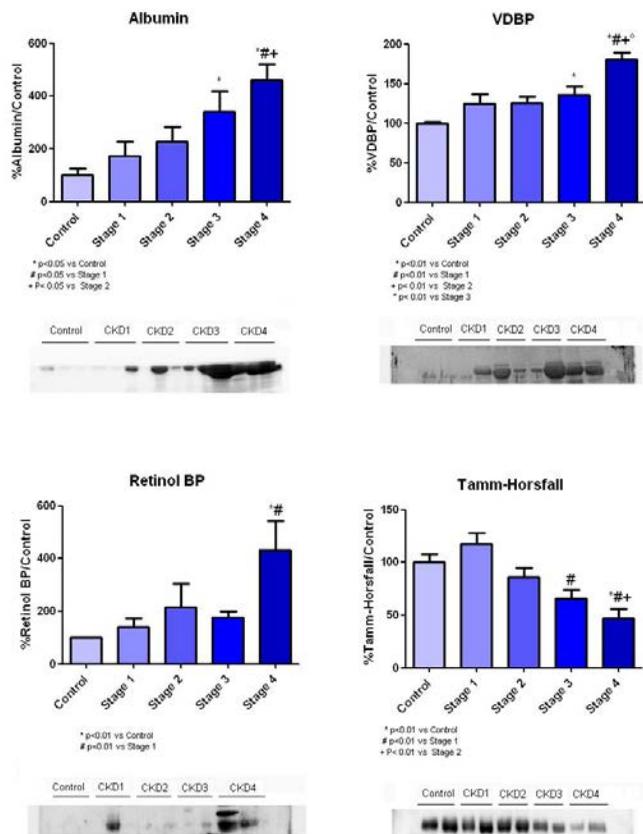
SA-PO678

Canine Chronic Kidney Disease: New Protein Biomarkers and Treatment with Human Umbilical Cord Mesenchymal Stem Cells
 Camila Eleuterio Rodrigues,¹ Jose Manuel Condor Capcha,¹ Talita R. Sanches,¹ Douglas Caragelasco,² Cinthia Martorelli,² Fernanda Chacar,² Priscila Queiroz Gouveia,¹ Irene L. Noronha,¹ Marcia Kogika,² Lucia Andrade.¹ ¹Div of Nephrology, School of Medicine; ²Dept of Veterinary Internal Medicine, Univ of Sao Paulo, Brazil.

Background: There are few strategies to prevent the progression of renal disease in humans or animals. In canine chronic kidney disease (cCKD), as in human CKD, proteinuria correlates with CKD progression, although there are no established urinary protein biomarkers. cCKD has become more common, dogs routinely being euthanized upon reaching the advanced stages. Mesenchymal stem cells (MSCs) have proven renoprotective in rodent CKD models. Here, we aim to characterize the roles that urinary excretion of albumin (Alb), Tamm-Horsfall protein (THP), vitamin D-binding protein (VDBP) and retinol-binding protein (RBP) play in cCKD and to determine whether human umbilical cord MSC (huMSC) administration slows its progression.

Methods: We performed Western blotting for urinary exosomal expression of Alb, THP, VDBP and RBP in cCKD stage 1-4 dogs (n=10/stage) and control dogs (n=10). We evaluated huMSC phenotypes with flow cytometry and immunocytochemistry. We randomized CKD stage 3 dogs to receive i.v.-injected placebo (n=5) or 10⁶ huMSC/kg (n=6). We measured serum creatinine (SCr), serum urea (SUr) and the urinary protein:creatinine ratio (UPC) monthly for a year.

Results: Alb, THP, VDBP and RBP correlated significantly with cCKD progression.



Over the study period, UPC decreased in treated dogs (2 excluded for external causes) and increased in control dogs (-25.46±29.63 vs. 81.93±25.56%, p<0.05); SCr and SUr did not differ between the groups (183.6±236.2 vs. 32.02±68.69 and 48.3±31.7 vs. 45.3±62.2%, respectively); treated dogs presented less proteinuria.

Conclusions: Our findings broaden perspectives for CKD treatment. Supported by FAPESP.

SA-PO679

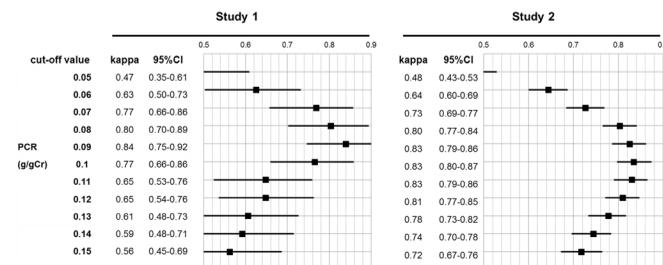
Validation of the Urine Total Protein-To-Creatinine Ratio-Based Chronic Kidney Disease Risk Classification: A Secondary Analysis
 Hiroyuki Yamamoto,¹ Kyoko Yamamoto,^{1,2} Yutaro Nishi,¹ Kyoko Takeda,¹ Hiroko Izumo,¹ Yasuhiro Komatsu.¹ ¹St. Luke's Int'l Hospital, Tokyo, Japan; ²Tohoku Univ Graduate School of Medicine, Sendai, Japan.

Background: The most recent Japanese chronic kidney disease (CKD) guideline states that patients without diabetes should be classified using the total urine protein-to-creatinine ratio (PCR) instead of the urine albumin-to-creatinine ratio (ACR); however, validation of the PCR is still required. This study was conducted to validate the PCR-based CKD risk classification compared with the ACR-based classification and to explore more accurate methods for classification, focusing on relatively early CKD patients.

Methods: We conducted a secondary analysis using two previous datasets with diabetic or cardiovascular patients who were classified into CKD stages A1-A2 and G1-G3b. We assessed the CKD stage and risk classification of each patient according to the estimated glomerular filtration rate and the ACR- or PCR-based classification method. Then, various candidate PCR values were utilized as the cut-off values between stages A1 and A2. Cohen's kappa statistics were calculated to evaluate the agreement between each classification method.

Results: In total, 860 patients (131 from the diabetic clinic and 729 from the cardiovascular clinic) were enrolled. Using the cut-off value recommended in the current guideline (PCR 0.15 g/gCr), the misclassification rates in these populations were 26.0% and 16.6%, respectively; the misclassifications were primarily caused by underestimation. The kappa statistics achieved 0.56 (95% confidence interval, 0.45-0.69) and 0.72 (0.67-0.76), respectively. Using PCR values of 0.08-0.10 g/gCr as the cut-off value improved the misclassification rates and kappa values.

Conclusions: Current PCR-based CKD classification method leads to underestimation of risk classification in outpatient setting.



Funding: Private Foundation Support

SA-PO680

Beta-Trace Protein as Renal Marker in Older Adults – Results from the Berlin Initiative Study
 Natalie Ebert,¹ Olga Jakob,² Jan Bartel,³ Markus van der Giet,¹ Mirjam Schuchardt,¹ Christine A. White,⁴ Elke Schaeffner.¹ ¹Nephrology, Charité, Berlin, Germany; ²Epidemiology and Biostatistics, Charité, Berlin, Germany; ³Labor Limbach, Heidelberg, Germany; ⁴Nephrology, Queen's Hospital, Kingston, ON, Canada.

Background: It has been shown that GFR estimation based on b-Trace Protein (BTP), a relatively novel biomarker, is reliable and might serve as an alternative in kidney transplant recipients. Whether BTP-based eGFR equations can be applied in older adults is not known.

Methods: BTP has been analysed by immunonephelometry with N-Latex® bTP Assay on a BN ProSpec® System, Siemens, Germany. Analysis was done in 570 participants of the Berlin Initiative Study (mean age: 78.5 yrs) who underwent iohexol clearance measurement (mean mGFR: 60.3 mL/min/1.73m²). The following 3 currently available eGFR equations were used: Pöge (BTP): GFR = 47.17 × BTP^{-0.7933}; Pöge (BTP/Crea): GFR = 974.31 × BTP^{-0.2594} × creatinine^{-0.647} and White (BTP/Crea): GFR=167.8 × BTP^{-0.758} × creatinine^{-0.204} × (0.871 if female). Comparison of BTP estimating equations with mGFR was done for determination of bias (mGFR-eGFR), precision (SD) and accuracy (P10, P30).

Results: The boxplot includes median and eGFR range calculated with the 3 GFR-equations. Mean eGFR was 100,3 for Pöge (BTP), 62,7 for Pöge (BTP/Crea) and 86,2ml/min/1.73m² for White (BTP/Crea).

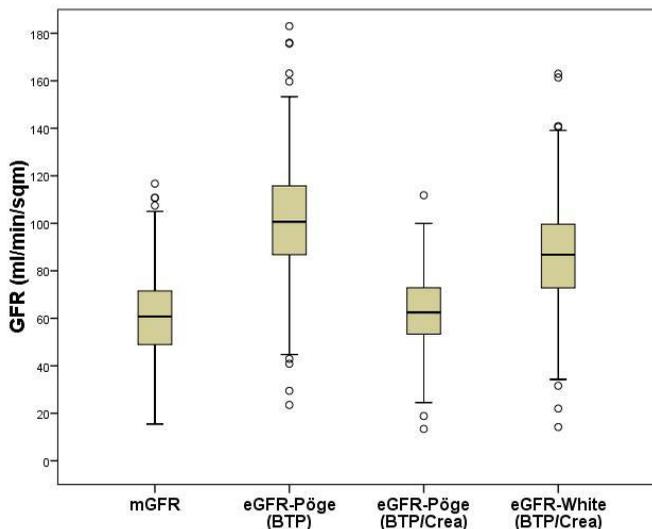


Table 1 shows bias, precision and accuracy for all 3 equations compared to mGFR.

	Mean Bias (ml/min/1.73m ²)	SD of Differences	Mean Percentage Bias (%)	SD of perc. Bias	P10 (%)	P30 (%)
Pöge, BTP	40.0	15.5	71.4	32.4	1.2	5.8
Pöge, BTP/Crea	2.40	10.4	6.68	18.6	45.0	87.9
White, BTP/Crea	25.9	13.0	46.0	24.4	3.3	25.7

Conclusions: Currently available eGFR equations that were developed for adult kidney transplant recipients are not applicable in non-transplanted elderly patients. Further research is necessary to evaluate whether BTP is a useful renal marker for older adults.

Funding: Private Foundation Support

SA-PO681

Galectin-3, Possible Useful Biomarker in Predicting Chronic Kidney Disease in Hepatitis C Positive Patients Hany Refaat, Haitham Ezzat, Amr Mohab. *Nephrology Dept, Ain Shams Univ, Cairo, Egypt.*

Background: Galectin-3, a profibrotic mediator, is involved in mechanisms of tubulointerstitial fibrosis and CKD progression. Data regarding its predictive value of CKD development in Hepatitis C patients is scarce.

Methods: In this Cohort study, we measured the level of Galectin-3 in the sera of 80 Hepatitis C positive patients. Patients were stratified into two groups: Forty hepatitis C positive patients with normal kidney function (Group I), and 40 hepatitis C positive patients with CKD (Group II). Galectin-3 concentration was also measured in 10 healthy individuals, as a control group (Group III). Other laboratory investigations were done which included hemoglobin level, serum creatinine, eGFR by MDRD equation, ALT, AST, INR, serum albumin, serum bilirubin and CRP titre. We correlated galectin-3 concentrations with demographic and biochemical parameters in all groups.

Results: 30 females (33.3%) and 60 males (66.7%) were included in the study with mean age 47.6±5.3 years. Plasma levels of Galectin-3 were highest in group II (22.1±5 ng/ml) when compared to group I (15 ±2.4 ng/ml) and group III (9.7±2.5 ng/ml) (p<0.001). Also CRP titre was highest in group II (10.1±1.5 mg/L), when compared to group I and III (2.5±0.9 mg/L and 2.3±1.1 mg/L respectively) (p<0.001). There was positive correlation between Galectin-3 level and CRP titre in both group I and II (p<0.001). Moreover, in group II, Galectin-3 level was positively correlated with serum creatinine (p<0.001), while inversely correlated with eGFR (p<0.001). There was no correlation between serum Galectin-3 level, and INR, ALT, AST and serum albumin in both group I and II.

Conclusions: In hepatitis C positive patients, galectin-3 concentrations increased with progressive renal impairment. Galectin-3 levels were not correlated with liver functions, suggesting the predictive value of galectin-3 for CKD development in hepatitis C positive patients.

SA-PO682

Chronic Kidney Disease: Long Term Prevalence Trends and Influence of Modifiable Risk Factors Stein I. Hallan,¹ Marius Altern Øvrehus,² Solfred Romundstad,² Dena E. Rifkin,¹ Arnulf Langhammer,² Joachim H. Ix.¹ *¹UCSD, La Jolla, CA; ²Faculty of Medicine, NTNU, Trondheim, Norway.*

Background: Prevalence of chronic kidney disease (CKD) is high worldwide, and it has been increasing in the US. However, less strict treatment goals for hypertension have recently been suggested despite increasing prevalence of obesity and diabetes. We aimed to determine whether CKD prevalence is increasing in Norway, evaluating the influence of changing prevalence of CKD risk factors on CKD prevalence, and compared findings to corresponding US data.

Methods: We included general population based participants from the Nord-Trøndelag Health Studies (HUNT), Norway: 65237 from HUNT2 (1994-96) and 50586 from HUNT3 (2006-08). eGFR and u-ACR based on fresh blood and 3 urine samples were used to diagnose CKD. Thorough quality-control and comparisons of methods over time excluded analytical drift. We used attendance weights used to avoid responder bias.

Results: Total CKD prevalence remained stable in Norway 1996-2007 (11.3%-11.1%, p=0.42) but increased in subjects >75 years (36.6%-39.3%, p=0.014). eGFR <60 ml/min/1.73m² increased (4.5%-4.8%, p=0.033) while albuminuria >30mg/g decreased (7.9%-7.4%, p=0.034). The most important contributors were a strong blood pressure decline during this 10 years period, more physical activity and lower cholesterol; without these improvements 2.8, 0.7 and 0.6 percentage-point higher CKD prevalence would have been expected, respectively. In contrast, the prevalence of diabetes and obesity increased moderately, but diabetics received more intensive preventive therapy, and the proportion of diabetic patients with CKD decreased substantially (33.4%-28.6%, p=0.002). In contrast, published US data indicate a stronger increase in obesity and diabetes, and physical activity was low and not improving. Access to effective care was also suboptimal for a substantial group of the population.

Conclusions: In contrast to the US where CKD prevalence has been increasing, it remained stable over a 10 year period in Norway, likely due to substantial improvements in blood pressure, lipids and physical activity despite modestly increasing diabetes and obesity.

Funding: NIDDK Support

SA-PO683

Natural Progression of Chronic Kidney Disease in Optimally Managed Patients on the Maximum Conservative Management Pathway Suzanne H. Forbes, Kieran Mccafferty, Muhammad M. Yaqoob. *Nephrology, Royal London Hospital.*

Background: The natural progression of advanced chronic kidney disease (CKD)/ end-stage renal disease (ESRD) managed in a specialist palliative care nephrology clinic setting is unknown.

Methods: We conducted an observational study of all patients with advanced CKD undergoing predialysis counselling between 2009-2014 in a single UK center. All patients who opted for conservative management were followed up prospectively in a specialist conservative care clinic and their clinical phenotype and renal outcomes recorded. Change in eGFR was noted in those patients whose eGFR was <10, with 2 or more serum creatinine estimations taken more than 2 months apart.

Results: We prospectively studied 354 patients with median length of follow-up 452 days (165-769). Median eGFR at referral was 8ml/min (7-9). Demographics are shown.

Age	78 (73-84)
Gender	M - 62% F - 38%
Diabetes	Yes - 62% No - 38%
Ethnicity	Caucasian - 39% South Asian - 37% Black - 14% Other - 10%
Cause of CKD	Diabetes - 38% Renovascular (including hypertension) - 24% Urological - 9% GN - 5% Other - 4% Unknown - 20%
Previous Modality	Nephrology/Low Clearance Clinic - 92% Failing Transplant - 2% Unknown to Service - 6%
Death (n)	209
Cause of Death n (%)	Cardiac - 16 (8) Sepsis - 13 (6) Stroke - 2 (1) Unknown - 38 (18) Other - 12 (6)
Age at Death	80 (75 - 85)
Time to Death (days)	276 (103 - 555)

Fall in eGFR in ml/min/year was 3.9 (1.8-8). Neither baseline eGFR (p=0.13) nor presence of diabetes (p=0.72) affected this rate of decline. Time to death from eGFR 10ml/min was 276 days.

Conclusions: In this first longitudinal study of conservatively treated patients with advanced CKD, variable rate of decline of eGFR ranging between 1.8-8ml/year led to death of 55% of the cohort within the median follow up period of 15 months. Reassuringly the majority of patients died at their preferred place of terminal care (home/hospice) and were registered as deaths due to ESRD. Over 50% of patient's eGFR decline was less than 4 ml/min per year which could translate into a life expectancy of >1 year without dialysis in these exceedingly frail individuals. Prospective study is ongoing to determine the quality of life of these patients treated conservatively.

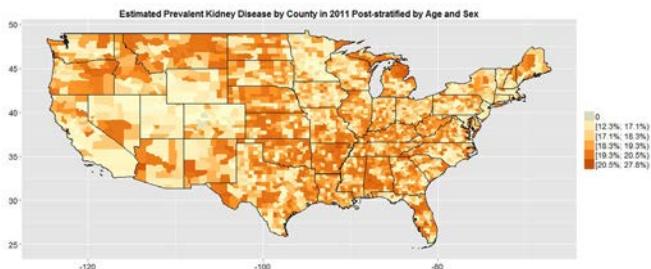
SA-PO684

Estimating County-Level Prevalence of Chronic Kidney Disease (CKD) in the United States Sai Hurrish Dharmarajan,¹ Jennifer L. Bragg-Gresham,¹ Hal Morgenstern,¹ Yi Li,¹ Neil R. Powe,² Delphine S. Tuot,² Deborah Rolka,³ Sharon Saydah,³ Rajiv Saran.¹ ¹Univ of Michigan, Ann Arbor, MI; ²Univ of California, San Francisco, CA; ³Centers for Disease Control and Prevention, Atlanta, GA.

Background: The prevalence of adult CKD in the US, estimated from 2005-2012 national survey data, is about 13%; however, those surveys are not designed to provide estimates for small regions. Applying a Bayesian multi-level model (BMLM), we estimated adult CKD prevalence in US counties using national and state surveys.

Methods: Data on self-reported CKD and risk-factors were obtained from (i) the National Health and Nutrition Examination Survey (NHANES 2005-2012; n=20,831), and (ii) the Behavior Risk Factor Surveillance System (BRFSS 2011; n=506,467); NHANES also provided CKD laboratory data. CKD was defined as estimated glomerular filtration rate 15-60 ml/min/1.73m² or urinary albumin-to-creatinine ratio >30mg/g. As BRFSS does not include laboratory data, CKD for each person in the BRFSS was multiply imputed using a logistic regression model trained on NHANES data. A BMLM that effectively borrows information from neighboring counties was then fit to each imputed dataset to produce 10 sets of county-level estimates of CKD prevalence. These estimates were combined to obtain a final prevalence estimate for each county.

Results: Estimated county-level prevalence of CKD ranged from 12.3 to 27.8% (median: 18.8%) in 2011 (see map).



The standard deviation of these estimates ranged from 0.8 to 7%, and the coefficient of variation ranged from 5 to 32% of the estimate, suggesting good statistical precision.

Conclusions: We believe this is the first attempt to estimate CKD prevalence in U.S. counties. Our approach yields estimates with improved statistical precision for small counties, and is being used to study geographic variation in CKD burden across the U.S.

Funding: Other U.S. Government Support

SA-PO685

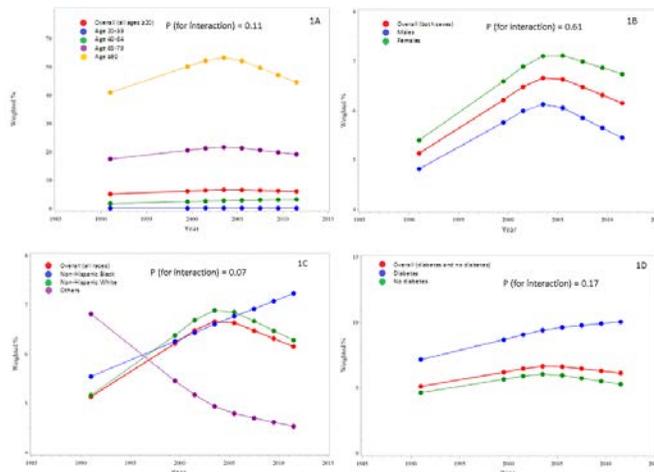
Overall CKD Prevalence in the U.S. Has Stabilized in Recent Years

Daniel P. Murphy,¹ Charles E. McCulloch,¹ Feng Lin,¹ Tanushree Banerjee,¹ Jennifer L. Bragg-Gresham,² Mark Eberhardt,³ Meda E. Pavkov,³ Rajiv Saran,² Neil R. Powe,¹ Chi-yuan Hsu.¹ ¹UCSF [Drs. CY Hsu and NR Powe are Co-Senior Authors]; ²Univ of Michigan; ³CDC.

Background: ESRD incidence rates in the U.S. have stabilized recently. We sought to better understand trends in CKD prevalence since 2003-2004.

Methods: We examined data on adults from the National Health and Nutrition Examination Surveys from 1988 through 2012. We determined prevalence of stage 3-4 CKD (CKD-EPI equation eGFR 15-59 mL/min/1.73m²) overall and by age, sex, race, and diabetes strata. We examined crude prevalence and adjusted prevalence for age, sex, race, and diabetes mellitus (diagnosed and undiagnosed). Restricted cubic splines were used to model trends. The years 2003-4 (last years with published literature) were compared to 2011-12 (most recent years of available data).

Results: Consistent with the published literature, we saw a rise in CKD prevalence from the late 1990s to the early 2000s. But since around 2003-4, adjusted and unadjusted prevalence of CKD have stabilized (Figure). This temporal trend was observed across age (p for interaction=0.11), sex (p=0.61) and racial-ethnic subgroups (p=0.07; although the trend in non-Hispanic blacks appeared to differ); and did not differ by diabetes status (p=0.17). There was no difference in overall stage 3-4 CKD prevalence comparing 2003-4 and 2011-12 (p=0.25). Similar trends were seen with an expanded definition of CKD to include persons with higher eGFRs but albuminuria or used the MDRD equation.



Conclusions: Over the last decade in the U.S., there has been stabilization in the overall prevalence of stage 3-4 CKD, with a possible exception in blacks. This is contrast to what has been reported by prior studies analyzing older data but consistent with the observed stabilization of overall ESRD incidence. Efforts should be continued to implement reno-protective measures, especially in blacks.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

SA-PO686

Global Prevalence of Chronic Kidney Disease Categories 3-5 – A Systematic Review Tazeen H. Jafar,¹ Pryseley Nkouibert Assam,^{1,2} Fahad Javaid Siddiqui,¹ Shreyasee S. Pradhan,¹ Edwin S.Y. Chan.² ¹Duke-NUS Graduate Medical School, Singapore; ²Singapore Clinical Research Inst.

Background: Chronic kidney disease (CKD) has become a leading contributor to the global burden of disease. We performed a systematic review of published studies to estimate the global prevalence of CKD categories 3-5 defined by estimated glomerular filtration rate (eGFR) less than 60 ml/min/m².

Methods: PubMed, EMBASE and Scopus were searched for studies published in English from 2003 to 2013 reporting prevalence of CKD categories 3-5 in the general population. Studies were included if they (1) sampled from the general adult population, (2) assessed CKD using CKD-EPI or MDRD Study equations; (3) not on renal replacement therapy.

Results: A total of 13,081 studies were considered, of which 566 studies from 54 countries assessed prevalence of CKD, and 284 studies were in unselected general population. The global prevalence of CKD accounting for clustering among all adults aged 20 years or older are shown in table below

CKD Category (C)	Countries	Studies	CKD Prevalence (95% CI)	Expected Number of Individuals with CKD (Millions) (95% CI)
C 3 to 5 (eGFR <60 ml/min/1.73m ²)	41	264	7.0 (5.2 to 9.3)	335.0 (249.0 to 446.0)
C 3 to 5 (20 to 65 yrs)	29	66	3.9 (2.1 to 7.2)	154.4 (80.0 to 289.0)
C 3 to 5 (65+ yrs)	25	58	28.9 (19.3 to 41.1)	229.6 (154.4 to 328.0)
C 3 only (eGFR 30-59 ml/min/1.73m ²)	27	86	6.2 (4.2 to 9.3)	332.8 (220.9 to 446.0)
C 4 only (eGFR 15-29 ml/min/1.73m ²)	18	50	0.3 (0.2 to 0.4)	14.4 (11.5 to 17.2)
C 5 only (eGFR <15 ml/min/1.73m ²)	15	29	0.1 (0.1 to 0.2)	5.2 (3.8 to 7.2)

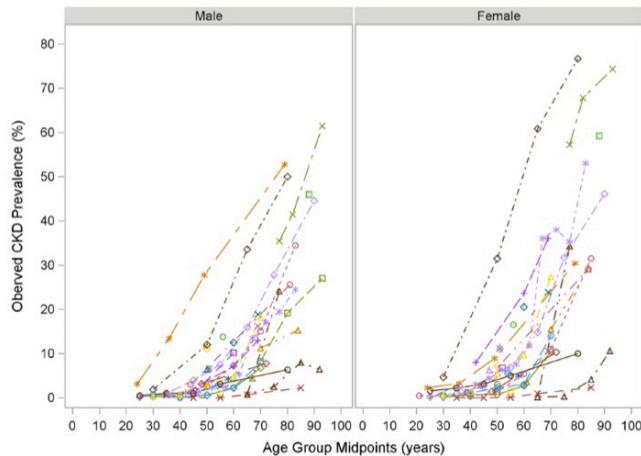


Figure shows the association of age with CKD categories 3-5. Sensitivity analysis revealed consistent CKD prevalence (6.9%) for all 566 studies.

Conclusions: Clinically significant CKD is high both in younger and older adults globally. Our findings call for institution of urgent public health efforts for CKD prevention and management.

SA-PO687

Prevalence of Chronic Kidney Disease with Diabetes and Glomerulonephritis in China Luxia Zhang, Jinwei Wang, Ming Hui Zhao. *Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.*

Background: Diabetes is the leading cause of end stage kidney disease worldwide, while glomerulonephritis is thought to be the predominant cause in developing countries. However, the surging prevalence of diabetes in developing countries such as China may have substantial impact on the spectrum of chronic kidney disease.

Methods: A national in-patient database involving 19.5 million patient-records was used. Diagnoses of chronic kidney disease with diabetes (DM-CKD) as well as with glomerulonephritis (GN-CKD) were extracted from International Classification of Diseases-10 codes of the discharge diagnoses. Furthermore, a general population-based, national representative sample of 47 204 participants was used. Identification of DM-CKD and GN-CKD was based on laboratory tests and the questionnaire inquiring about medical history. Then the prevalence of DM-CKD and GN-CKD was compared among both hospitalized population and general population.

Results: Among 19.5 million hospitalized patients, 1.19% and 0.79% were identified as with DM-CKD and with GN-CKD, respectively. Compared with GN-CKD, DM-CKD was associated with 7.2% (95% confidence interval [CI] 6.4-8.0%), 5.4% (95%CI 4.7-6.0%) and 59% (95%CI 46-73%) increase of costs, length-of-stay and in-hospital mortality, respectively. For general population, the prevalence of GN-CKD is also exceeded by that of DM-CKD at 0.84% (95%CI 0.68-1.00%) and 1.23% (95% CI 1.06-1.41%), respectively. The estimated number of DM-CKD patients in China was 20.1 million.

Conclusions: Our study indicates that DM-CKD surpassed GN-CKD in both hospitalized population and general population, which marked a transition of kidney disease spectrum in China. Furthermore, DM-CKD is associated with substantial increased healthcare resources utilization and increased risk of in-hospital mortality.

Funding: Government Support - Non-U.S.

SA-PO688

Prevalence of Chronic Kidney Disease on the U.S.-Mexico Border: Role of Acculturation Jonathan Michael Starkey,¹ Kristina Vatcheva,² Susan P. Fisher-Hoch,² Joseph B. McCormick.² *¹Inst for Translational Sciences, Univ of Texas Medical Branch, Galveston, TX; ²Univ of Texas School of Public Health, Houston, TX.*

Background: Mexican-Americans are the dominant Hispanic group in the US and face significant health disparities, including end-stage renal disease, diabetes and obesity. We characterize the quantity and associations of chronic kidney disease (CKD) in Cameron County, TX where almost 90% of the population is Hispanic and is predominantly zero or first generation Mexican-American.

Methods: The Cameron County Hispanic Cohort (CCHC) is a random sample of the Hispanic population on the southernmost point along the US-Mexico border. 1,777 participants with baseline serum creatinine measurements from 2003-2014 are included in this cross-sectional study. The glomerular filtration rate (eGFR) is estimated from serum creatinine and CKD is defined as eGFR < 60 mL/min/1.73 m². The weighted prevalence of CKD is estimated. A multivariate model of factors associated with CKD outcome.

Results: The prevalence of CKD is 6.0% in the CCHC and estimates the prevalence in Cameron County, TX. Stratified by gender, the prevalence in men and women is 6.9% and 4.9%, respectively. Multivariate analysis reveals significant associations of country of birth (OR 2.14, 95% CI [1.02, 4.46] for those born in the US), hypertriglyceridemia (OR

2.72, 95% CI [1.41, 5.239]) and granulocyte count (OR 1.345, 95% CI [1.058, 1.708]) with CKD status after adjusting for age, gender, diabetes status, cardiovascular disease history, hypertension, smoking history, obesity, LDL and statin use.

Conclusions: The prevalence of CKD in the CCHC is higher than previous national estimates in Hispanics or Mexican-Americans. The data suggest that acculturation, triglycerides and inflammation are associated with CKD in Hispanics living on the US-Mexico border. More research is needed in Mexican-Americans to investigate CKD in this growing minority population.

Funding: Other NIH Support - K22 LM011869-01A1, National Library of Medicine (NLM) Starkey, Jonathan M (PI)

MD000170 P20 funded from the National Center on Minority Health and Health Disparities (NCMHD) McCormick, Joseph (PI), and the Centers for Clinical and Translational Science Award ULI TR000371 from the National Center for Advancing Translational Science (NCATS)

Clinical and Translational Science Award (UL1TR000071)

SA-PO689

Validation of the Kidney Failure Risk Equation in Manitoba Reid Whitlock,^{1,2} Paul Komenda,^{1,2,3} Claudio Rigatto,^{1,2,3} Allison Dart,^{1,3,4} Joe A. Bueti,^{3,4} Randy Walld,¹ Navdeep Tangri.^{1,2,3} *¹Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; ²Nephrology, Seven Oaks Hospital, Winnipeg, MB, Canada; ³Medicine, Univ of Manitoba, Winnipeg, MB, Canada; ⁴Nephrology, Health Science Centre, Winnipeg, MB, Canada.*

Background: Patients with chronic kidney disease (CKD) are at risk for progression to kidney failure. We previously developed the Kidney Failure Risk Equation (KFRE) to predict the progression of CKD to kidney failure in patients referred to nephrologists. This study aims to validate the KFRE in an unreferred population in Manitoba, and to determine risk thresholds for clinical decision-making.

Methods: We included patients from the Diagnostic Services of Manitoba database with an eGFR < 60 mL/min/1.73 m² and a urinary albumin creatinine ratio measured between October 1, 2006 – March 31, 2007. Five year kidney failure risk was predicted using the 4-variable KFRE and compared with treated kidney failure events from the Manitoba Renal Program database. Sensitivity and specificity for KFRE thresholds (3% and 10% over 5 years) were then compared to eGFR thresholds (30 and 45 mL/min/1.73m²).

Results: 1,512 patients were included and 151 developed kidney failure over the 5-year follow-up period. The 4-variable KFRE more accurately predicted kidney failure when compared to eGFR alone (AUROCs 0.90 [95% confidence interval (CI) 0.88-0.92] for KFRE vs. 0.78 [95% CI 0.74-0.83] for eGFR). At a risk threshold of 3% over 5 years, the KFRE had a sensitivity of 97% and a specificity of 62%.

Conclusions: The KFRE is highly accurate at predicting 5-year risk of kidney failure in a population based sample of Manitobans with CKD Stages 3 to 5. Integration of the 4-variable KFRE into laboratory information systems should be considered.

Funding: Private Foundation Support

SA-PO690

A Risk Prediction Model of End-Stage Renal Disease in Type 1 Diabetes Using Urine MCP-1 as an Alternative Biomarker of ACR Masayuki Yamanouchi, Monika A. Niewczas, Natalia Z. Nowak, Andrzej S. Krolewski. *Genetics & Epidemiology, Joslin Diabetes Center, Boston, MA.*

Background: There is a great need to develop risk prediction models to recruit patients at high risk of end-stage renal disease (ESRD) for clinical trials in patients with type 1 diabetes. We developed two models to predict progression of CKD 3 and 4 to ESRD in 5 years in patients with type 1 diabetes: "ACR model" that consists of patient's age, eGFR, HbA1c and ACR, and "Urine MCP-1 model" that consists of the same markers but replacing ACR with urine MCP-1.

Methods: We identified 285 patients with type 1 diabetes and impaired renal function (eGFR: 15-60 mL/min/1.73m²) from Joslin Proteinuria Cohort that was followed for 7 to 18 years to ascertain ESRD. We focused on the events within 5 years from enrollment. For the ACR model, the Cox model identified four baseline variables: age, eGFR, ACR, and HbA1c for the final model. For the urine MCP-1 model, urine MCP-1, age, eGFR and HbA1c were identified by the Cox model. Assigned point scores corresponded to each coefficient.

Results: 5-year risk of ESRD in the study group was 40.5%. In the ACR model, the variable with highest magnitude was eGFR<30, 4 points; followed by ACR>300, 2 points; HbA1c >7.5, 1 point; and age <45 years, 1 point, while in the urine MCP-1 model, the variable with highest magnitude was eGFR<30, 2 points; followed by urine MCP-1 >545, 1 point; HbA1c >7.5, 1 point; and age <45 years, 1 point. The model with urine MCP-1 performed almost equal to the model with ACR (C statistic of 0.702 (0.556-0.831) vs. 0.719 (0.574-0.845)). Although the number of patients who developed ESRD in the high risk group in the urine MCP-1 model is smaller than in the ACR model, the incident rate of ESRD in the high risk group in the urine MCP-1 model was much higher than in the ACR model (291/1000 vs. 196/1000, p<0.001).

Conclusions: Using the risk score with urine MCP-1, we can identify a subgroup of patients at very high risk of ESRD.

SA-PO691

A Reliable Formula to Estimate 24-h Urine Sodium Excretion from Morning Fasting Urine in Patients with Chronic Kidney Disease Se Yun Kim,¹ Ho Jun Chin,² Sejoong Kim,² Dong Ki Kim,³ Suhnggwon Kim,³ Jung Hwan Park,⁴ Sung Joon Shin,⁵ Bum Soon Choi,⁶ Chun Soo Lim,⁷ Sang Ho Lee.¹ ¹Kyung Hee Univ Hospital, Seoul, Korea; ²Seoul National Univ Bundang Hospital, Seong-Nam, Korea; ³Seoul National Univ Hospital, Seoul, Korea; ⁴KonKuk Univ Hospital, Seoul, Korea; ⁵Dongguk Univ Ilsan Hospital, Goyang, Korea; ⁶Seoul St. Mary's Hospital, Seoul, Korea; ⁷Seoul National Univ Baramae Medical Center, Seoul, Korea.

Background: Estimated 24 hour urine sodium excretion based on spot urine has been proposed to replace 24 hour urine collection in epidemiologic studies. However, estimated sodium excretion has not been verified whether it is useful in patients with chronic kidney disease (CKD) as well as in interventional study. The aim is to evaluate the estimated sodium excretion in prospective low salt diet education study (ESPECIAL) cohort.

Methods: New formula was developed from baseline data of 228 CKD patients of ESPECIAL cohort using a multivariate linear regression and compared with previous three formulas from healthy population (Kawasaki, INTERSALT, Tanaka) and one from CKD patients (Nerbass) for the prediction of 24 hour sodium excretion after ARB treatment and low salt diet education.

Results: Among previous reported formulas, the estimation by Tanaka's formula showed the smallest bias (estimated 144.3±46.5 vs. measured 154.1±69.6 mEq/day), but weak correlation (r=0.34). We developed new formula with improved bias (estimated 154.0±39.7 mEq/day) and correlation (r=0.56). New formula also showed the best correlation (r=0.57) with smallest bias (estimated ± mEq/day) even after ARB treatment, which did not showed significant change of measured sodium excretion (156.3±70.6 mEq/day). Intensive low salt diet education elicited the significant decrease of measured sodium excretion (121.2±59.4 mEq/day). Although new formula also showed best correlation, any of formulas did not predict the amount of the decrease of measured sodium excretion.

Conclusions: We developed more reliable formula for estimating urine sodium excretion for CKD patients. However, our data suggests estimated sodium excretion could be applied for epidemiological study rather than low salt intervention study.

SA-PO692

Evaluation of Glycated Albumin for Glycemic Monitoring in Diabetic Nephropathy Yang Fei, Ying Fan, Yumei Liu, Niansong Wang. Dept of Nephrology and Rheumatology, Shanghai Jiaotong Univ Affiliated the Sixth Hospital, Shanghai, China.

Background: Glycated albumin(GA) has been now widely used for the evaluation of blood glucose in diabetic nephropathy(DN) patients. However, the effect of proteinuria on GA should be taken into account, especially in patients with advanced DN.

Methods: A total of 621 diabetic nephropathy patients from year 2009 to 2014 were enrolled in the study. According to the 24h urinary protein(UP) output, subjects were divided into 3 groups defined as (1) microalbuminuria: UP=30-300mg/24h, (2) moderate albuminuria: UP=300-1000mg/24h, (3) macroalbuminuria: UP>1000mg/24h.

Results: In all DN patients, the related factors of GA were fasting blood glucose(FBG), postprandial blood glucose(PBG), body mass index (BMI) and 24h UP. The multivariate regression equation was GA = 0.254FBG + 0.347PBG-0.341 BMI-1.306UP, (R2=0.375). There was no correlation between GA and 24h UP in DN patients with micro or moderate albuminuria. However, GA was found to be much lower and negatively correlated with 24h UP in DN patients with macroalbuminuria. Therefore, adjusted GA (adjGA) was applied for those subjects, taking 24h UP, serum albumin (SA) and the ratio of normal albumin metabolism days to total albumin metabolism days into account. adjGA=mGA×(1+3.75×UP/SA). As a result, GA value was increased after adjustment in DN macroalbuminuria group. The adjGA was also found only correlated with FBG and PBG, and had no relation with 24h UP and SA.

Conclusions: In diabetic nephropathy patients, blood glucose, serum albumin and 24h urinary protein output may serve as important factors for the evaluation of GA on glycemic level. GA tended to be underestimated in DN patients with macroalbuminuria. The adjGA may be a better way to objectively evaluate glycemic status in patients with advanced DN.

SA-PO693

Fat Mass, Lean Body Mass and Serum Filtration Markers in Adults in the United States: The National Health and Nutrition Examination Survey (NHANES) Meredith C. Foster,¹ Julie K. Bower,² Josef Coresh,³ Roger A. Fielding,³ Lesley Inker,¹ Andrew S. Levey.¹ ¹Tufts Medical Center; ²The Ohio State Univ; ³Johns Hopkins Univ; ⁴Tufts Univ.

Background: Established serum filtration markers are influenced by body composition (creatinine by muscle mass, cystatin C by fat mass) but limited data exist evaluating associations of these markers with body composition assessed using a gold-standard measurement approach. Our aim was to examine the association of body composition quantified using dual energy X-ray absorptiometry (DXA) with serum creatinine and cystatin C in US adults.

Methods: We conducted a cross-sectional analysis in 4378 adults age 18+ years from NHANES 1999-2002. Body composition included total lean mass and total fat mass; body mass index (BMI, kg/m²) was included for comparison. Associations of natural log-

transformed creatinine and cystatin C with body composition measures were evaluated using multivariable linear regression, stratified by age. Analyses were weighted to account for the NHANES design with multiple imputation for missing DXA data.

Results: Lean mass was associated with higher serum creatinine in all age groups whereas higher fat mass was associated with higher creatinine in adults age 65+ (Table). Lean mass and fat mass were associated with higher serum cystatin C across all age groups; associations of lean mass with cystatin C were not significant with additional adjustment for fat mass.

Table: Association of body composition with serum creatinine and cystatin C by age group, NHANES 1999-2002

	Ln(Creatinine)		Ln(Cystatin C)	
	Beta	p-value	Beta	p-value
Age 18-39 (48% women; mean age 29 yrs, lean mass 50.9kg, fat mass 25.4kg, BMI 26.8kg/m ²)				
Fat Mass (per 5 kg)	-0.006	0.08	0.014	<0.001
Lean Mass (per 5 kg)	0.010	0.03	0.017	<0.001
BMI (per 5 kg/m ²)	-0.007	0.3	0.027	<0.001
Age 40-64 Years (52% women; mean age 50 yrs, lean mass 51.5kg, fat mass 29.5kg, BMI 28.7kg/m ²)				
Fat Mass (per 5 kg)	-0.002	0.6	0.025	<0.001
Lean Mass (per 5 kg)	0.009	0.02	0.024	<0.001
BMI (per 5 kg/m ²)	-0.003	0.7	0.043	<0.001
Age 65+ Years (58% women; mean age 74 yrs, lean mass 45.5kg, fat mass 28.4kg, BMI 27.7kg/m ²)				
Fat Mass (per 5 kg)	0.009	0.05	0.024	<0.001
Lean Mass (per 5 kg)	0.021	0.002	0.022	0.002
BMI (per 5 kg/m ²)	0.024	0.006	0.048	<0.001

Note: Models adjusted for age, sex, and race/ethnicity. Abbreviations: BMI, body mass index; SE, standard error. Unweighted N by age group: 18-39, N=953; 40-64, N=1435; 65+ N=1990

Conclusions: Fat mass and lean mass are differentially associated with creatinine and cystatin C in US adults. Findings in younger adults suggest that observed associations may reflect the impact of body composition rather than kidney function on serum marker levels. Further work is needed to determine how the observed associations are influenced by GFR and body composition simultaneously and the impact of fat and lean mass on CKD prevalence estimates.

Funding: Private Foundation Support

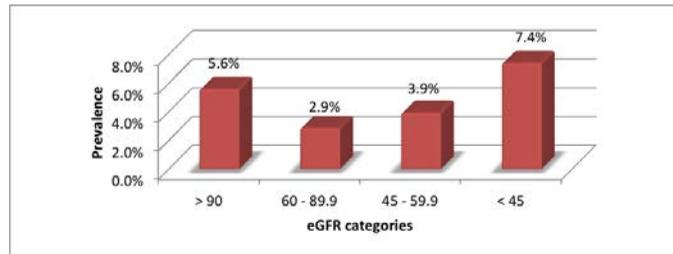
SA-PO694

Associations of the Levels of Kidney Function with Protein-Energy Wasting Syndrome Are Independent of Serum CRP and Bicarbonate Xiaorui Chen,¹ G. Wei,¹ Robert E. Boucher,¹ Dominique Ferranti,¹ Michel Chonchol,³ Kalani L. Raphael,¹ Srini Beddhu.^{1,2} ¹U of Utah; ²VA SLC; ³UC Denver.

Background: Inflammation and metabolic acidosis are putative causative factors of protein-energy wasting (PEW) in CKD. Therefore, we examined whether serum CRP and bicarbonate levels attenuate the associations of CKD with PEW in 11,834 adult (age > 20 yrs) participants in the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: PEW syndrome was defined as the presence of at least one criterion in two out of three categories: serum chemistry (albumin < 3.25 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 20 kg/m² or unintentional wt loss > 10% over 1 yr), and muscle mass (body fat % < 10% or MAMC < 10% of 50th percentile of reference population). Using eGFR 60 to 89 ml/min/1.73 m² as the reference, the odds of PEW in ≥ 90, 45-59 and < 45 ml/min/1.73 m² groups were examined in logistic regression models using svy suite in STATA 13.

Results: Mean age was 46.0 yrs, 50.3% were male, 9.5% were black. The prevalence of PEW syndrome had a U shaped association with the level of kidney function.



Compared to the reference group, both eGFR ≥ 90 and < 45 groups had nearly two-fold increased odds of PEW. This was not attenuated after adjusting for serum CRP or bicarbonate.

eGFR (ml/min/1.73m ²)	PEW syndrome OR (95% CI)	
	Model 1*	Model 2 [§]
60 - 89.9	Ref	Ref
≥ 90	1.95 (1.41, 2.68)	1.86 (1.36, 2.55)
45 - 59.9	1.11 (0.70, 1.76)	1.17 (0.72, 1.90)
<45	2.09 (1.05, 4.13)	2.33 (1.10, 4.97)

* adjusted for age, gender, race, education, smoking, alcohol use, MI, CHF, stroke, diabetes, lung disease and cancer

[§] Above + serum CRP and serum bicarbonate

Conclusions: PEW syndrome is highly prevalent in those with lower kidney function. This appears independent of inflammation and serum bicarbonate. Further studies are warranted to determine the mechanism of PEW syndrome in the CKD population.

Funding: NIDDK Support

SA-PO695

Awareness and Perceived Risk of CKD Among African American Patients with CKD Raquel C. Greer,¹ Yang Liu,¹ Jessica M. Ameling,¹ Deidra C. Crews,¹ Patti Ephraim,¹ Lisa A. Cooper,¹ L. Ebony Boulware.² ¹Johns Hopkins Univ; ²Duke Univ.

Background: African Americans (AAs) are disproportionately affected by CKD with greater prevalence of advanced disease and poorer control of CKD risk factors. Patients' awareness of CKD may facilitate engagement in self-management behaviors to modify CKD risks.

Methods: As part of a baseline assessment for a randomized controlled trial, we characterized CKD awareness and perceived risk of CKD among AAs with uncontrolled hypertension and CKD (eGFR 15-60 ml/min/1.73m² or UACR³30mg/g). We assessed patients' self-reported CKD awareness ("Do you have a kidney problem or chronic kidney disease?"; yes or no response) and degree of perceived likelihood ("How likely do you think it is that you could develop kidney problems or kidney failure in the next 10 years?"; not likely versus slightly, moderately, or very likely response) and perceived concern of developing CKD ("How concerned are you about developing kidney problems in the next 10 years?"; not concerned versus slightly, moderately, or very concerned response). We constructed multivariable models to assess patient characteristics independently associated with patients' CKD awareness and perceived CKD risks.

Results: Among 52 AA patients with CKD, the mean age was 58 years, 67% were female, 67% had diabetes, 15% had coronary artery disease, 40% had eGFR<60 and 60% had albuminuria alone. The majority (n=37, 71%) of patients were not aware of their CKD. Among these, 27% (n=10) considered themselves unlikely to develop CKD and 19% (n=7) were not concerned about developing CKD. CKD awareness was greater among patients with an eGFR<60 (vs. eGFR≥60) (adjusted percentages (AP) [95% CI]: 50% [19-81%] and 19% [reference], respectively; p=0.05. Conversely, patients with diabetes reported less CKD awareness than those without diabetes (AP [95% CI]: 53% [reference] and 10% [2-38%], respectively; p=0.008). Perceived risk of CKD did not vary by patient characteristics.

Conclusions: Among AA patients with uncontrolled hypertension and CKD, awareness of CKD was low, with some patients unconcerned about developing CKD in the future. Strategies to improve recognition of CKD risks among AAs at high CKD risk are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO696

Discussions About CKD Between African Americans with High CKD Risks and Their Primary Care Physicians Raquel C. Greer,¹ Debra L. Roter,¹ Yang Liu,¹ Jessica M. Ameling,¹ Deidra C. Crews,¹ Patti Ephraim,¹ Lisa A. Cooper,¹ L. Ebony Boulware.² ¹Johns Hopkins Univ; ²Duke Univ.

Background: Routine primary care visits provide an important opportunity for primary care physicians (PCPs) to discuss CKD risk modification with patients at high risk, but the frequency of patient-physician discussions about CKD is unknown.

Methods: In a randomized controlled trial of African American (AA) patients with uncontrolled hypertension, we analyzed audio-recorded encounters between patients and their PCPs using the Roter Interaction Analysis System to characterize the occurrence of CKD discussions (e.g., discussion of kidney disease, eGFR, creatinine, or albuminuria) and patient-physician communication patterns (e.g., patient-centeredness, the degree to which the discussion focused on the patient's psychosocial and lifestyle context) during routine primary care visits. In multivariable logistic regression models, we assessed patient, visit, and communication characteristics independently associated with the presence of CKD discussions among all patients and among those with CKD (eGFR<60ml/min/1.73m² or UACR³30mg/g).

Results: Among 124 patients, the mean age was 58 years, 69% were female, 48% had diabetes, 35% had CKD (mean eGFR 83). The average visit length was 22 minutes. Patients and PCPs discussed CKD in 47% of visits and discussions more frequently occurred among patients with CKD (vs. without CKD) (66% and 36% respectively, p=0.002). Discussions were less common [Odds Ratio (95% CI)] in visits of patients ≥ age 60 (vs. <60) [0.3 (0.1-0.8)] or with higher eGFR [0.96 (0.95-0.98), per ml/min/1.73m²], and more common when visits were more (vs. less) patient-centered [2.4 (1.0-5.8)] or when diabetes was (vs. was not) discussed [3.7 (1.5-9.4)]. Patient gender, comorbid disease, and visit length did not predict discussions. Among patients with CKD (n=44), CKD discussions were also less common among patients ≥ age 60 [0.1 (0.2-0.9)] or with higher eGFR [0.96 (0.92-1.0)].

Conclusions: AA patients at high risk of CKD and their PCPs discussed CKD in fewer than half of routine primary care visits. Efforts to improve the occurrence of CKD discussions during routine primary care encounters are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO697

Primary Care Utilization Is Associated with Reduced Mortality Among Older Adults With CKD Raquel C. Greer,¹ Hsien-Yen Chang,¹ Gerard Fenton Anderson,¹ Bernard G. Jaar,¹ Craig Pollack,¹ Nae-Yuh Wang,¹ Lawrence J. Appel,¹ L. Ebony Boulware.² ¹Johns Hopkins Univ; ²Duke Univ.

Background: Routine primary care visits provide opportunities to identify and manage patients' CKD risk factors and to provide preventative care. It is unclear how primary care utilization impacts clinical outcomes among older adults with CKD.

Methods: We quantified the association between primary care utilization and ESRD incidence or mortality among older US adults with CKD (in 2005-2006) using Medicare claims. We assessed (in 2006) patients' primary care utilization (no visit vs. at least one), other care utilization (nephrology care [no visit vs. at least one]), the total number of ambulatory evaluation and management (E & M) visits with any type of provider), and patients' comorbid conditions and sociodemographics. We used standard and cause-specific (accounting for competing risk of death) Cox proportional hazard models overall and stratified by age (65-74, 75-84, or ≥ 85 years) to estimate hazard ratios (HRs) for ESRD or mortality.

Results: Among 106,765 patients, most (79%) had at least one primary care visit in 2006, and 21% had at least one nephrology visit. The median number of ambulatory E&M visits was 10. Compared to patients with no primary care visits, patients with at least one visit were younger (78 vs. 80 mean years, p<0.001), less likely African American (10 vs. 14%, p<0.001), and had a greater prevalence of diabetes (46 vs. 42%, p<0.001), hypertension (88 vs. 78%, p<0.001), or coronary artery disease (74 vs. 72%, p<0.001). Over 4 years of follow-up, 4,264 patients developed ESRD and 45,059 died. Primary care utilization was not associated with ESRD incidence. However, compared to patients with no primary care visits, patients with at least one visit had a lower risk of death [HR (95%CI): 0.73 (0.72-0.75)] overall and in age stratified models.

Conclusions: Primary care utilization was not associated with lower ESRD risk, but it was associated with a lower risk of death among older adults with CKD. Efforts to improve the engagement of primary care providers in the care of patients with CKD represent an important strategy to improve the health of this high risk population.

Funding: NIDDK Support

SA-PO698

Routine Use of Health Care Among High-Risk African Americans at Risk of CKD Clarissa Jonas Diamantidis,¹ Nrupen Anjan Bhavsar,¹ Julia J. Scialla,¹ Cleomantina A. Davenport,¹ Rasheeda K. Hall,¹ Crystal C. Tyson,¹ Mario Sims,³ Tara Smith Strigo,¹ Neil R. Powe,² L. Ebony Boulware.¹ ¹Medicine, Duke Univ, Durham, NC; ²Medicine, UCSF, San Francisco, CA; ³Medicine, Univ of Mississippi Medical Center, Jackson, MS.

Background: Engagement in routine health care (RHC) is a key strategy to decrease health inequities among African Americans (AAs) at high risk of developing CKD or CKD complications. We examined demographic, attitudinal and socio-cultural factors associated with RHC among high-risk AAs at risk of CKD incidence or progression.

Methods: We quantified the prevalence of RHC (physical exam <1 year prior) use among AA Jackson Heart Study (JHS) baseline participants (from 2000-2004) with hypertension (HTN) or diabetes. We identified demographic, attitudinal (e.g., perceived discrimination, anger and hostility, stress, trust in health providers) and educational (i.e., CKD awareness) factors independently associated with RHC use. Those missing demographic or attitudinal data were excluded.

Results: Of 5301 JHS participants, 1152 met inclusion criteria. Most (n=909, 79%) reported RHC use. Rates of RHC were similar in those with and without CKD (22% vs. 23%). Participants not using RHC (vs. using) were more likely to be < 55 years of age (51% vs 37%), male (43% vs. 30%), without HTN (9% vs. 5%), tobacco users (38% vs. 29%), and uninsured (14% vs. 9%), all p<0.05. Participants not using RHC less frequently reported trust in their health provider (80% vs. 95%), more frequently reported difficulty obtaining health services (17% vs. 8%), and less frequently reported provider satisfaction (91% vs. 98%), all p<0.05. In multivariable models, not using RHC was associated with age <55 (OR 1.75 [95% CI 1.25-2.5]), male sex (OR 1.55 [1.12-2.16]), < HS diploma (OR 1.63 [1.12-2.34]), no HTN (OR 2.14 [1.13-4.1]), lower provider trust (OR 3.27, [1.61-6.65]) and less anger and hostility (OR 1.53, [1.1-2.1]).

Conclusions: Among high-risk AAs in the JHS, younger participants and males were less likely to use RHC. Those with low trust were also less likely to use RHC. Efforts to address health risks among high-risk AAs should target those using less RHC and consider attitudinal barriers to RHC.

SA-PO699

Development of a Question Prompt Sheet for Patients with Chronic Kidney Disease Swati Lederer,^{1,2} Michael J. Fischer,^{1,2} Howard S. Gordon,^{1,2} Anuradha Wadhwa,² Subhash Popli,² Elisa J. Gordon.^{2,3} ¹Jesse Brown VAMC and Univ of Illinois, Chicago, IL; ²Hines VA Hospital, Hines, IL; ³Northwestern Univ, Chicago, IL.

Background: Patients with chronic kidney disease (CKD) commonly have unmet information needs. Greater patient participation in healthcare discussions can address these needs, and is associated with improved health outcomes. A question prompt sheet (QPS), a list of questions to prompt discussion, has been shown to increase patient participation in other chronic disease discussions; however, no QPS has been developed for CKD patients.

Methods: We conducted a 2-phase cross-sectional study involving semi-structured telephone interviews to develop a QPS targeted to patients with moderate CKD. Patients with an estimated glomerular filtration rate $<60\text{ml/min/1.73m}^2$, on dialysis, or with a transplant were recruited from a single VA nephrology clinic. Phase 1 interviews included 17 open-ended questions assessing patients' CKD information needs. Responses were qualitatively analyzed to generate an initial 67-item QPS. Phase 2 participants reviewed a pre-mailed QPS to rate the importance of asking each question on a 5-point Likert scale, provide open-ended feedback, and rate their willingness to use a CKD-QPS. Question item responses were analyzed to refine and reduce QPS questions.

Results: A total of 76 patients completed interviews (phase 1: $n=32$, phase 2: $n=44$). Most were male (96%), non-Hispanic white (68%), and mean age was 66 years. Patients desired more information about CKD, particularly regarding self-care techniques, dialysis/transplant, and CKD complications. The final QPS tool included 37-questions divided into 10 CKD subtopics (i.e., CKD definitions, causes, impact, monitoring, labs, self-care, treatment, dialysis, transplant, managing comorbid conditions). Most patients (91%) reported being 'completely' or 'very' willing to use a CKD-QPS in future doctor visits.

Conclusions: CKD patients have unmet information needs and wish to use a CKD-QPS. Further research is needed to assess whether our CKD-QPS effectively addresses patients' information needs, enhances doctor-patient communication, and improves health outcomes.

Funding: Veterans Administration Support

SA-PO700

Medication Burden and Safety in Veterans with Chronic Kidney Disease Swati Lederer,^{1,2} Michael J. Fischer,^{1,2} Zhiping Huo,² Katie Suda,² Kevin Stroupe,² ¹Jesse Brown VAMC and Univ of Illinois Hospital, Chicago, IL; ²Hines VA Hospital, Hines, IL.

Background: Veterans are at exceptionally high risk for chronic kidney disease (CKD) and other chronic health conditions. Pharmacologic treatments are a core aspect of CKD disease management. We characterized medication burden and safety and their relationship to CKD severity among elderly Veterans.

Methods: Using national VA databases, we included all female and a random 10% sample of male VA healthcare users who were >65 years old. We characterized the average number of medications, frequency of contraindicated medications, and occurrence of concerning drug-drug interactions. CKD was defined by estimated glomerular filtration rate (eGFR) in 2008 and classified according to conventional eGFR-based severity groups. A non-CKD comparison was used ($\text{eGFR} \geq 60\text{ ml/min/1.73m}^2$). Medications were identified in calendar year 2009 from VA utilization data and Medicare Part D claims.

Results: Among a final cohort of 96,317 Veterans, 47% had CKD (mean age=79.8, male=81%, non-black=93%, hypertensive=90%, diabetic=33%). Mean medication number increased with CKD severity: 8.5 (eGFR ≥ 60), 9.6 (eGFR 30-59), 11.7 (eGFR 15-29), 12.5 (eGFR <15). After adjusting for demographic characteristics, CKD stage 3, 4, and 5 took 1.3, 3, and 3.6 more medications, respectively, compared to the non-CKD group ($p\text{-value} < 0.0001$). Contraindicated medications were often prescribed to patients with an $\text{eGFR} < 30\text{ml/min/1.73m}^2$ and included bisphosphonates (5%) and nonsteroidal anti-inflammatory drugs (4%). Concerning drug-drug interactions with an $\text{eGFR} < 60\text{ml/min/1.73m}^2$ included: sedatives-opioids (3.8%), ace inhibitor-angiotensin receptor blocker (1.6%), statins-diltiazem or verapamil (5.1%).

Conclusions: Greater severity of CKD was independently associated with an increasing number of medications among elderly Veterans. Medications that were contraindicated in CKD and concerning drug-drug interactions were commonly prescribed. Increased awareness and interventions are needed to improve medication management and safety in Veterans with CKD.

Funding: Veterans Administration Support

SA-PO701

Illicit Drug Use and Chronic Kidney Disease in an Urban Population Tessa Kimberly Novick,¹ Anika Alvanzo,¹ Yang Liu,¹ Alan B. Zonderman,² Deidra C. Crews,¹ ¹Johns Hopkins Univ, Baltimore, MD; ²National Inst on Aging, NIH, Baltimore, MD.

Background: Opioid and cocaine use have been associated with risk of ESRD in retrospective studies, however, the association of illicit drug use with chronic kidney disease (CKD) has not been well-examined in prospective studies. Our objective was to determine the association of illicit drug use with reduced kidney function, albuminuria and rapid kidney function decline (KFD) among a cohort of urban-dwelling adults.

Methods: Our study included 2,286 Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study participants who are community-dwelling African American and white adults from 12 neighborhoods in Baltimore MD. We used logistic regression to examine whether opioid or cocaine use (defined as ≥ 5 lifetime uses of either drug) was associated with baseline reduced eGFR ($<60\text{ ml/min/1.73m}^2$ by CKD-EPI), baseline albuminuria (albumin-to-creatinine ratio $>30\text{mg/g}$) or rapid KFD (eGFR decline of $>3\%$ per year over a median of 4.7 years of follow up).

Results: Participants' mean age was 48 years, 57% were African American, 15% reported opioid use, and 22% reported cocaine use. Those reporting illicit drug use (opioid or cocaine) were more likely to be male, African American, living in poverty and/or uninsured; and tobacco use, problem drinking, and hepatitis B and/or C infection were more prevalent among illicit drug users than non-users ($P < 0.01$ for all variables). Our adjusted models included those variables above, and age, diabetes and hypertension. A total of 5.3% of illicit drug users had reduced eGFR compared to 5.0% of non-users (NS). A total of 5.9% of illicit drug users died during follow-up compared to 3.8% of non-users ($P 0.03$).

Outcome	N for analysis	N events	Opioid Users vs Non Opioid Users Adjusted Odds Ratio (95% CI)	Cocaine Users vs Non Cocaine Users Adjusted Odds Ratio (95% CI)
Reduced eGFR	2286	115	2.7 (1.5, 4.9)	1.4 (0.9, 2.3)
Albuminuria	1652	190	1.2 (0.8, 1.7)	1.8 (1.3, 2.5)
Rapid KFD	1665	245	0.9 (0.6, 1.3)	0.9 (0.7, 1.3)

Conclusions: Illicit drug use was associated with prevalent reduced eGFR and albuminuria, but not rapid KFD. Illicit drug use may be an important risk factor for CKD in urban populations.

Funding: NIDDK Support, Other NIH Support - Intramural study of the National Institute on Aging

SA-PO702

A Tailored, Interactive Mobile Health Communication Application for Patients with Chronic Kidney Disease: Development and Feasibility Assessment Yali Cao. *Nephrology, China-Japan Friendship Hospital, Beijing, China.*

Background: Chronic kidney disease (CKD) is an increasingly common chronic condition whose prognosis can be improved by patient involvement and self-management. Patient involvement can be fostered by web-based Interactive Mobile Health Communication Applications (IMHCAs) combining health information with decision support, social support and/or behavior change support. Tailoring content and tone of IMHCAs to the individual patient's needs might improve their effectiveness.

Methods: A tailored, IMHCAs was developed by collaborative profession (nephrologist, nurse, research fellow, web developer). The effectiveness and usage of the tailored IMHCA were tested against the control arm without access to this IHCA in a small-scale single-blinded randomized trial. The content covers information on CKD, its complications and sequelae, and its treatment options including health behavior and dietary guidance. In the intervention group the content is delivered in dialogue form, tailored to relevant patient characteristics (the stage of CKD and the Etiology). Eighty patients (forty patients at each arm) with stage 3-5 CKD were enrolled in the study. The data were collected directly after the first visit, and at 3-month follow-up.

Results: There were no difference between the two groups as to the age, gender, CKD stage and blood pressure. Three months after system use, participants using the tailored system displayed significantly more knowledge ($P=0.001$), better blood pressure compliance rate ($P=0.02$) and improved dietary behavior, mainly regarding low protein and enough calories ($P=0.003$).

Conclusions: This is the first tailored IMHCAs in China. Our data demonstrated that implementation of IMHCAs into standard practice is feasible. Suggested developments will augment reported strengths to inform ongoing testing in the wider China network of units.

Funding: Government Support - Non-U.S.

SA-PO703

Evaluation of Clinical Pharmacy Services in the Management of Kidney Disease Calantha K. Yon, Chai L. Low. *Pharmacy, Veterans Affairs San Diego Healthcare System, San Diego, CA.*

Background: Chronic kidney disease (CKD) and end stage renal disease (ESRD) place a significant burden on healthcare systems and is the focus of national health initiatives. Management of CKD requires a multidisciplinary approach to maximize outcomes. Studies support the impact of clinical pharmacists (CP) in medication management, but studies demonstrating the significance of a CP as part of a multidisciplinary approach to management of AKI and CKD/ESRD are lacking. This study evaluates the effectiveness of pharmacy services in the setting of a multidisciplinary approach to the management of AKI and CKD/ESRD.

Methods: Interventions by a CP in the inpatient setting were collected from 12/1/2010 to 11/1/2011 as part of Nephrology Consults. Interventions were categorized as: drug interaction, dose/frequency adjustment, untreated diagnosis, adverse reactions, duplication of therapy, and other. Cost avoidance from these interventions were calculated. Outpatient pharmacy patient encounters were monitored from 1/1/2008 to 12/31/2014 as patient visits or interventions in hemodialysis (HD), peritoneal dialysis (PD), erythropoietin stimulating agent (ESA) clinic, and renal access clinic. CPs were involved in the management of anemia, hypertension, immunizations, mineral bone disease, transplant, dialysis related infections, pharmacokinetic drug monitoring, medication reconciliation and patient counseling.

Results: Most of the 440 inpatient interventions were dose adjustments for renal function and medication therapy for untreated diagnoses during AKI. Inpatient interventions by a CP resulted in \$706,911 in cost avoidance. HD and PD encounters by a CP increased from 241 in 2008 to over 1,400 since 2011. Patient visits in the ESA/anemia clinic increased from 185 in 2008 to near 300 in 2014. Encounters in the renal access clinic increased from 19 in 2008 to near 300 in 2014.

Conclusions: The expansion of pharmacy services in nephrology at Veterans Affairs San Diego Healthcare System has resulted in the improvement in the quality of care provided to patients with AKI, CKD or ESRD with significant cost avoidance. Clinical pharmacists play a significant role in the multidisciplinary approach to the management of CKD/ESRD.

SA-PO704

Views and Practice Patterns of Dialysis Medical Directors Towards End-of-Life Decision Making for Patients with End-Stage Renal Disease

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Background: Nephrologists frequently engage in end-of-life decision making for patients with end-stage renal disease (ESRD). Patients with ESRD report infrequent end-of-life discussions and nephrology trainees report feeling unprepared for end-of-life decision making, but the views of dialysis medical directors have not been studied. Our objective is to understand dialysis medical directors' views and practice patterns on end-of-life decision making for patients with ESRD.

Methods: We administered questionnaires to dialysis medical directors during medical director meetings of three different dialysis organizations in 2013. Survey questions corresponded to recommendations from the Renal Physicians Association clinical practice guidelines on initiation and withdrawal of dialysis.

Results: There were 121 medical director respondents from 28 states. The majority of respondents felt "very prepared" (66%) or "somewhat prepared" (29%) to participate in end-of-life decisions and most (80%) endorsed a model of shared decision-making. If asked to do so, 70% of the respondents provided prognostic information "often" or "nearly always". For patients with a poor prognosis, 36% of respondents would offer a time-limited trial of dialysis "often" or "nearly always", while 56% of respondents would suggest withdrawal from dialysis "often" or "nearly always" for those with a poor prognosis currently receiving dialysis therapy. Patient resistance and fear of taking away hope were the most commonly cited barriers to end-of-life discussions.

Conclusions: Views and reported practice patterns of medical directors are consistent with clinical practice guidelines for end-of-life decision making for patients with ESRD but inconsistent with patient perceptions.

Funding: NIDDK Support

SA-PO705

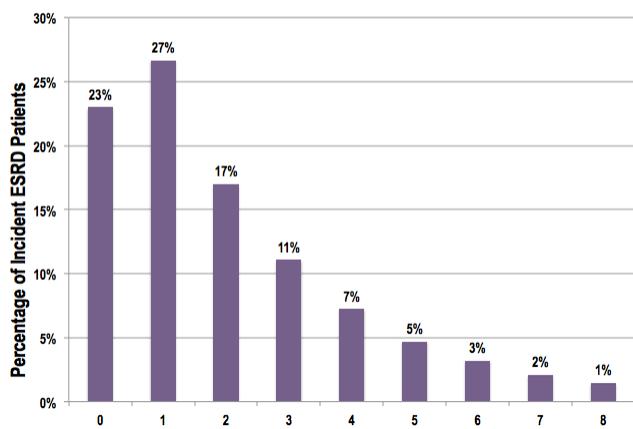
Emergency Department Utilization Among United States ESRD Patients

Brendan P. Lovasik, Rebecca H. Zhang, Taylor A. Melanson, Stephen O. Pastan, Rachel E. Patzer. *Emory Univ, Atlanta, GA.*

Background: Single center studies suggest that ESRD patients have a high rate of emergency department (ED) utilization, with 0.9-2.4 ED visits/patient-year. Prior studies show that ESRD is a stronger risk factor for ED use than heart failure, lung disease, or cancer. However, ED utilization among a national ESRD patient population has not been examined.

Methods: We examined a cohort of 788,162 incident adult ESRD patients in the United States Renal Data System from 2005-2011. ED utilization was identified using CPT codes 99281-5 (Severity Levels 1-5) and 99291 (Critical Care) by American College of Emergency Physicians guidelines. ED and hospital admission, diagnosis, and procedures were obtained from the USRDS and Medicare Physician/Supplier and Inpatient databases for Medicare Part A/B claims.

Results: In the first year of ESRD diagnosis, 1,143,372 ED visits were observed for 480,176 unique ESRD patients. 77% of ESRD patients used the ED within the first ESRD year at an average of 2.69 ED visits/patient-year. The national range was 1 to 172 ED visits per year with median 2 visits (interquartile range 1-4 visits) and 95th percentile 8 visits.



The top 5% of patients accounted for 80.4% of ED visits, and 7 patients utilized the ED over 100 times in their first ESRD year. Nearly half (46.0%) of ED visits were coded as a Severity Level 5, with 9.6% coded as Critical Care emergencies. 15.4% of ESRD patients in the ED were admitted to the hospital, with vascular access infection, pneumonia, and congestive heart failure as most common indications.

Conclusions: This study is the first to our knowledge to describe ED utilization in a national sample of ESRD patients. Compared to the national average, ESRD patients have higher ED use (2.69 vs. 0.4) and hospital admission rates (15.4 vs. 11.9%). Comprehensive understanding of ED utilization will aid development of outpatient and ED interventions.

SA-PO706

Impact of Evidence-Based Clinical Care on Major Adverse Clinical Events in Patients with Clinically Significant Proteinuria: A Population-Based Retrospective Cohort Study Julius Oluoch Okel,¹ Bilal Qarni,¹ Timothy Olusegun Olanrewaju,² Aminu K. Bello.¹ ¹Univ of Alberta; ²Univ of Ilorin, Nigeria.

Background: Proteinuria is an important prognostic marker for cardiovascular (CV) and renal events. Most studies of quality of care (QoC) in chronic kidney disease (CKD) have focused on other markers for risk stratification and outcomes. We hypothesized that in proteinuric CKD, markers of good quality care will be associated with lower risk of adverse clinical outcomes (all-cause mortality, all-cause hospitalization, CV and renal outcomes).

Methods: We used a population-based cohort of patients with significant proteinuria (albumin:creatinine ratio (ACR) ≥60 mg/mmol, protein:creatinine ratio (PCR) ≥100 mg/mmol or protein ≥3+ on dipstick) to evaluate current patterns of evidence-based care and association with outcomes. Markers of good quality care were defined as nephrology referral, relevant laboratory testing and appropriate medication use (ACEi/ARBs; statins). Participants were followed from their index date until March 2009 for outcomes of all-cause mortality, hospitalization, CV and renal events. The associations between quality of care markers and outcomes were estimated using Cox proportional hazards models.

Results: Of the 71,660 with at least 1 or 2 proteinuria measurements, 16,204 (22.6%) had significant proteinuria. At follow-up, receipt of good quality care [1] timely referral, 2)HbA1c testing, 3)use of ACEi/ARBs and 4) use of statins] was associated with reduced risk of mortality: 0.67 (0.59-0.75), 0.52 (0.46-0.59), 0.68 (0.62-0.74), and 0.63 (0.57-0.69), and all-cause hospitalization: 0.85 (0.69-0.93), 0.65 (0.59-0.72), 0.93 (0.87-0.99), and 0.82 (0.77-0.88) respectively. There were no statistically significant associations with the risk of CV and renal events.

Conclusions: This study examined the link between evidence-based treatment and clinical outcomes in an especially high-risk population with CKD. Good quality care impact on mortality risk and reduced risk of hospitalization. The impact of QoC on renal and cardiovascular events is less clear. The findings would justify future interventions to increase uptake of such treatments in patients with proteinuric CKD.

SA-PO707

APOL1 Risk Alleles and Risks of Cardiovascular Disease in Children with Focal Segmental Glomerulosclerosis (FSGS) Robert Woroniecki,¹ Derek Ng,² Sophie Limou,³ Cheryl Ann Winkler,³ Kimberly J. Reidy,⁴ Mark Mitsnefes,⁵ Craig S. Wong,⁶ Bradley Warady,⁷ Susan L. Furth,⁸ Jeffrey B. Kopp,⁹ Frederick J. Kaskel.⁴ ¹Stony Brook Children's Hospital, Stony Brook, NY; ²Johns Hopkins Bloomberg School of Public Health, Baltimore, NY; ³NCI, NIH, FNL, Frederick, MD; ⁴Einstein/Children's Hospital at Montefiore, Bronx, NY; ⁵Cincinnati Children's Hospital, Cincinnati, OH; ⁶Univ of New Mexico, Albuquerque, NM; ⁷Children's Mercy Hospital, Kansas City, MO; ⁸Univ of Pennsylvania, Philadelphia, PA; ⁹NIDDK, NIH, Bethesda, MD.

Background: APOL1 renal risk alleles are a major cause of glomerular disease in African Americans (AA). It is controversial as to whether individuals with high risk (HR) APOL1 genotypes (2 risk alleles) are at risk for atherosclerotic heart disease, and association with left ventricular hypertrophy (LVH) has not been explored. It is unclear whether children with focal segmental glomerulosclerosis (FSGS) and HR APOL1 are at increased cardiovascular risk.

Methods: Self-identified AA children with FSGS in CKiD study cohort were genotyped for APOL1 renal risk variants: G1 (rs73885319, S342G) and G2 (rs171785313, NY388-389 deletion), and compared to non-AA children with FSGS; none with HR.

Results: Of 79 children with FSGS, 36 were non-AA, and 25 were AA with HR APOL1. Compared to non-AA, children with HR APOL1 developed FSGS at a later age, 11.5 (IQR: 9.5, 12.5) vs 6 (IQR: 2.5, 11) years, p=0.005. There were no differences in GFR, hemoglobin, iPTH, calcium-phosphate product, or CRP. HR APOL1 subjects had a higher prevalence of uncontrolled hypertension (52% vs 28%, p=0.06) and a lower prevalence of nephrotic range proteinuria (13% vs 43%, p=0.02). Subjects with HR APOL1 had higher left ventricular mass index (41 [28, 53] vs 30 [27, 33] g/m^{2.7}, p=0.01) and a higher prevalence of LVH (53% vs 12%, p=0.009) compared to non-AA children with FSGS.

Conclusions: Children with FSGS and HR APOL1 have later onset kidney disease and are at higher risk for cardiovascular disease than non-AA.

Funding: NIDDK Support, Private Foundation Support

SA-PO708

Trends in Burden of Out-of-Pocket Expenses in United States Adults with Kidney Disease from 2002-2011 Mukoso N. Ozieh,¹ Kinfe Gebreegziabher Bishu,² Clara E. Dismuke,² Leonard Egede.² ¹Nephrology, MUSC; ²Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: High out-of-pocket (OOP) burden negatively impacts healthcare access and outcomes. Studies examining high OOP burden in the general population exists however no studies has examined OOP healthcare burden in people with kidney disease (KD). This study examined trends in high OOP healthcare in people with KD while concurrently evaluating the impact of insurance status and income category on high OOP burden.

Methods: We analyzed 2,966 adults aged 18-64 years with kidney disease using the Medical Expenditure Panel Survey-MEPS. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute and unspecified renal failure; 158 - chronic renal failure; 160 - calculus or urinary tract and; 161

- other diseases of kidney and ureters. OOP burden was calculated by dividing total family OOP spending on healthcare in a given year by the family's self-reported pretax income for that year. A person with KD is considered to have high OOP burden if the family total OOP spending on healthcare exceeds 10% of the family income. We used t-test to examine the mean changes from the bench mark year (2002/2003) to the subsequent time periods.

Results: Mean annual total family OOP spending was highest for prescription drugs over the years. Compared to the privately and publicly insured, uninsured status in people with KD was associated with high mean annual total family OOP spending. Of the 2,966 adults with KD, 19% faced a high OOP burden from 2002-2011. Overall, the proportion of people with high OOP fell by 10 percentage points from 2002/2003 to 2010/2010. The proportion of poor/near poor people and uninsured with high OOP was as high as 52% and 30% respectively in 2002/2003 but fell to about 25% and 27% respectively in 2010/2011.

Conclusions: Trends in high OOP burden in people with KD has decreased over time however people with kidney disease in the US still experience high OOP burden. Policies to reduce high OOP in people with KD could significantly impact KD outcomes.

SA-PO709

Health Disparities and Increased Risk of Developing End Stage Renal Disease in Patients with Chronic Kidney Disease Alejandro Pepon Romero, Ritika Sharma, Candace D. Grant, Ronak Patel, Monika Wadhvani, Vladimir Liberman, Shanza Mujeeb, Sairah Sharif, Shayan Shirazian, Nobuyuki (Bill) Miyawaki, Joseph Mattana. *Medicine, Winthrop-Univ Hospital, Mineola, NY.*

Background: Health disparities occur in groups of people that experience suboptimal health care based on their social, economic, and/or environmental disadvantage. Identifying how these disparities affect the risk of chronic kidney disease (CKD) progression to end stage renal disease (ESRD) can hopefully lead to a reduction in these health inequities and improve clinical outcomes for all CKD patients. We examined health disparities and the risk of ESRD using patient-specific and community-specific variables.

Methods: We studied a cross-section of 623 patients with stage 3 and 4 CKD and estimated their 2- and 5-year risk of ESRD using the method of Tangri et al. (JAMA 2011; 305:1553-1559). The U.S. Census Bureau Community Survey was used to obtain patient zip code-specific data including percent foreign born, percent below the poverty level, median household income, and percentage graduating high school. We did a multivariable generalized linear analysis on the outcome variables of the 2 and 5 year risk of ESRD.

Results: Lower household income was associated with a higher risk of ESRD at 2 and 5 years (p<0.05). There was a trend towards a higher risk of ESRD amongst patients from zip codes with higher poverty rates and lower education levels. Being single, including by divorce and separation but not by being widowed, was associated with a significantly higher risk of ESRD. We also found that patients on Medicaid and patients with private insurance or self pay had a significantly higher ESRD risk compared to those on Medicare.

Conclusions: Our findings suggest that there are substantial health disparities related to CKD and the risk of ESRD. Some of these disparities are patient-specific but others appear to be related to variables associated with the community where they reside. This suggests that evaluation of patient-specific as well as community-specific variables might help to better individualize CKD care and improve our ability to identify and treat the patient at increased risk of developing ESRD.

SA-PO710

Impact of Timely AV Fistula Placement on Resource Utilization After Initiation of Dialysis Edwin J. Anand,¹ Kabir Jalal,³ Laura L. Argauer,² Brian M. Murray,¹ Pradeep Arora,⁴ Rocco C. Venuto.¹ ¹Medicine, SUNY at Buffalo, Buffalo, NY; ²Computer Task Group, Buffalo, NY; ³Epidemiology, SUNY at Buffalo, Buffalo, NY; ⁴Medicine, VA Medical Center, Buffalo, NY.

Background: Maintenance dialysis is ideally initiated in the outpatient setting with a permanent access. This requires advance planning and of care between nephrologists, and access surgeons. The costs associated with 'crash' initiation of dialysis is anticipated to be high. In this observational study, we studied the hospitalization rates and costs of care in the 12 months following dialysis initiation between patients who started dialysis in an ideal manner versus sub optimally.

Methods: Claims and laboratory data from a large, regional insurance company covering half a million patients between January 2001 and May 2014 were reviewed. 32,121 patients were identified to have CKD (at least one eGFR <60 ml/min/1.73 m²). Of these, 422 patients developed ESRD during the observed period. We defined a 'crash' if the first instance of dialysis was in an inpatient setting, provided they had at least one eGFR value indicative of CKD before their first dialysis. Univariate and multivariate analyses were performed to analyze the effect of 'crash' on hospitalization and costs for 12 months following initial dialysis.

Results: 422 patients were started on dialysis in the above period. 257 patients (61%) had a crash start of dialysis. 86 patients (20%) had a fistula prior to dialysis. Compared to patients who did not crash, patients who crashed were older (p <0.0001), had a higher hospitalization rate in the one year period (p=0.0089). Multivariate analysis confirmed that patients who crashed had a significantly higher hospitalization rate in the one year following dialysis (p=0.0067). Patients with a fistula in place prior to dialysis experienced fewer hospitalizations (p=0.0377). Cost in the first year was also higher in patients who had a 'crash' without a fistula (p=0.0181). The cost advantage of having a fistula decreased with increasing age (0.0402).

Conclusions: Dialysis 'crash' results in increased morbidity and resource utilization. Coordination of care and timely access creation should reduce hospitalization and costs.

SA-PO711

DASH Diet Accordant Foods in the Homes of Urban African Americans at Risk for CKD Deidra C. Crews,¹ Yang Liu,¹ Edgar R. Miller,¹ Patti Ephraim,¹ Jessica M. Ameling,¹ Kimberly Gudzone,¹ Lisa A. Cooper,¹ L. Ebony Boulware.^{1,2} ¹Johns Hopkins U., Baltimore, MD; ²Duke U., Baltimore, MD.

Background: The Dietary Approaches to Stop Hypertension (DASH) diet is recommended for the treatment of hypertension, especially among African Americans (AAs). Many barriers may hinder urban AAs from following the DASH diet, putting them at increased risk of poor health outcomes, including CKD.

Methods: In a randomized trial of urban AAs with uncontrolled hypertension, we assessed (via interview and home inspection) the presence of DASH diet accordant foods and full-sized kitchen appliances needed to prepare DASH meals. We examined factors associated with having DASH diet accordant foods or needed appliances using logistic models adjusted for age, sex, food insecurity (skipping meals due to lack of money), income, literacy, diabetes, obesity, CKD (eGFR <60 or albuminuria) and comorbid disease (Charlson Index).

Results: Among 159 participants, mean age was 57 yrs and 74% were female. Only 14.5% had 5 of the DASH food categories in their homes (fruits, vegetables, low fat dairy, whole grains, plant proteins). Over 80% had full-sized ovens and refrigerators.

DASH Accordant Foods in Home	N (%) Participants
Fresh or frozen vegetables	131 (82%)
Fresh or frozen fruits	93 (58%)
Low fat dairy	48 (30%)
Whole grains	102 (64%)
Plant proteins	129 (81%)

Participants with CKD (vs without) had lower odds of having fresh fruits (adjusted odds ratio, 95% confidence interval: 0.40, 0.18-0.86). Younger age (yr increments) and annual income <\$30K (vs ≥\$30K) were associated with lower odds of having whole grains (0.96, 0.93-0.99 and 0.28, 0.11-0.72, respectively). Younger age was associated with lower odds of having plant proteins (0.94, 0.90-0.99). Persons with low literacy (<3rd grade level versus higher) had lower odds of having an oven (0.15, 0.04-0.52) and lower odds of a full-sized refrigerator in their homes (0.12, 0.02-0.59).

Conclusions: The homes of urban AAs at high risk for CKD were often lacking either foods or needed appliances required for DASH meals. The lack of these items was associated with CKD, younger age, low income and/or low literacy. Interventions to improve DASH adherence in this high-risk group should consider these factors.

Funding: NIDDK Support, Other NIH Support - NHLBI

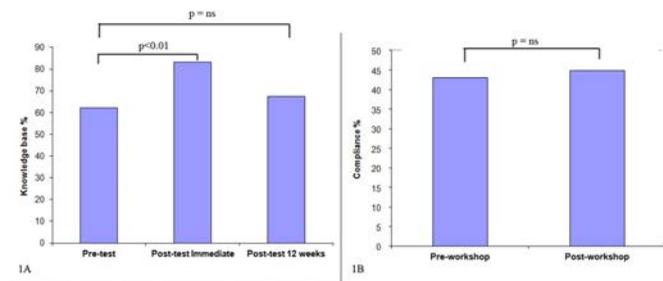
SA-PO712

ABCD of CKD Management Among Internal Medicine Residents: Are Interactive Workshops and Web-Based Tools Useful? Swati Arora, Richard J. Marcus, Khaled Nashar, Bhavna Chopra, Jia Zhang, Gargi Davda, Emad Sedki, James B. Reilly, Kalathil K. Sureshkumar. *Nephrology and Hypertension, Allegheny General Hospital, Pittsburgh, PA.*

Background: Chronic Kidney Disease (CKD) is under-recognized and suboptimally managed especially in primary care setting. We aimed to evaluate the impact of interactive workshops and web-based tools in improving CKD management among internal medicine residents.

Methods: A pre-test assessed knowledge in areas of CKD diagnosis, anemia (A), bone-mineral disease (B), control of BP (C) and degree of proteinuria (D). Interactive workshop on ABCD of CKD lasting 90-minutes was conducted over 5 weeks along with access to self-developed online CKD management resource (www.nephromania.com). Post-test was conducted at workshop conclusion and 12 weeks later. Assessment for post-intervention CKD care improvement was done through chart review.

Results: Among 98 participating residents, 25% utilized the online resource and 62% found it very helpful with majority bookmarking it on smart phones. KDOQI guidelines awareness, recognition of CKD diagnosis and complications were respectively 22%, 70% and 75% on pre-test, 98%, 93% and 90% on immediate post-test (P<0.001), declining to 86%, 77% and 74% at 12-weeks. Aggregate scores are shown in Figure 1A. Practice patterns measured through chart-review (n=94) to assess compliance with CKD guidelines over next 3 months failed to show change (figure 1B).



Conclusions: Our study showed effectiveness of targeted interactive workshops to improve recognition of CKD and its complications. Intellectualizing the taught concepts by residents did not translate to improved patient care. Declining retention of core concepts at 12-week testing indicates the need for ongoing reinforcement sessions. Continued education including online resources utilization is warranted as opposed to annual core-lectures provided by most training programs.

SA-PO713

Evaluating Progress of Healthy People 2020 Chronic Kidney Disease Objectives: Are We There Yet? Aseel Ryskulova,¹ Lawrence Agodoa,² Paul W. Eggers,² Kevin C. Abbott.² ¹NCHS, CDC; ²NIDDK, NIH.

Background: Chronic Kidney Disease (CKD) is a significant public health problem in the U.S. and a major source of disability, poor quality of life, and premature death for those afflicted. CKD and End-Stage Renal Disease (ESRD), the final stage of the CKD, exact a high economic price. In 2012 ESRD costs exceeded \$49 billion dollars including 34 billion (about 20%) of total Medicare expenditures. An estimated 11.5% of adults ages 20 or older had physiological evidence of CKD determined from data collected through the 2001-06 National Health and Nutrition Examination Survey (NHANES). Each year in the United States, more than 115,000 people are diagnosed with ESRD.

Methods: Reflecting the importance of CKD, 24 CKD objectives area were included in the Healthy People 2020 (HP2020) national health goals to reduce new cases of CKD and related complications, disability, death, and economic costs. CKD objectives are focused on improving cardiovascular care in patients with CKD; increasing the proportion of patients with CKD and diabetes who received recommended evaluation and treatment; reducing death rate and percentage of U.S. population with CKD; and increasing CKD awareness in persons with impaired renal function. All CKD objectives are measurable, having at least one data point from national data systems including the NHANES, National Death Index, and U.S. Renal Data System.

Results: In 2015, 14 objectives had met their target (n=9) or showed improvement (n=5). Six objectives showed little or no significant change. Two objectives: increase the proportion of persons with diabetes and CKD who received recommended medical treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and increase the proportion of patients receiving a kidney transplant within 3 years of ESRD, moved away from the target. The remaining 2 objectives were not evaluated as they were informational with no target set. Disparities persisted by sex, race/ethnicity, and SES status.

Conclusions: The presentation will cover the most recent national and state data for selected CKD objectives and provide an overview of the HP2020 and data search using the HP2020 website.

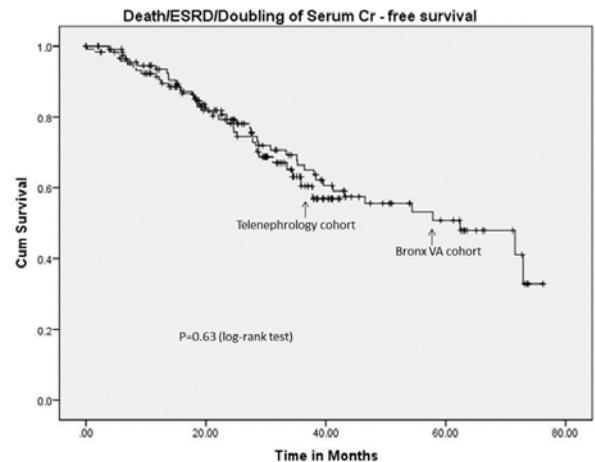
SA-PO714

Telenephrology for the Remote Management of Chronic Kidney Disease (CKD): A Retrospective Cohort Study Rajeev Rohatgi,^{1,2} Judy K. Tan,² Anita Mehrotra.² ¹Medicine, James J. Peters VAMC, Bronx, NY; ²Medicine, Icahn School of Medicine, New York, NY.

Background: Veterans with CKD who live in the Hudson Valley Veterans Affairs Medical Center (HVAMC) catchment area travel to the Bronx VAMC for nephrology care. Analysis of the no-show and cancellation frequencies for these renal appointments exceeded 50%, likely due to the distance between HVAMC and the Bronx (60 miles).

Methods: We hypothesized that patients managed via a telenephrology service, where patients visit their local VA and are evaluated remotely via videoconference by a Bronx VA nephrologist, would exhibit comparable clinical outcomes and visit compliance as in-person renal care. In a retrospective observational study, the clinical outcomes of CKD patients enrolled in telenephrology (n=117) and the Bronx VA nephrology clinic (n=121) from 2008-14 were compared.

Results: Characteristics of the groups were similar (initial creatinine [Cr], eGFR, distribution of CKD stage, urine protein) except for race and probable cause of CKD. Prior to the telenephrology service, 53.1% of scheduled visits of HVAMC patients to the Bronx VAMC renal clinic were either cancelled or "no-shows" and this was reduced to nearly half (29.2%) after instituting telenephrology (p<0.001). Moreover, the frequency of attending appointments was greater in the telenephrology (70.8%) vs. Bronx VA cohort (61.8%) which was driven by a greater frequency of cancelled visits in the Bronx VA (27.9%) vs. the telenephrology group (15.8%). The incidence of a composite outcome of doubling of Cr, ESRD and/or death was similar between both groups (Figure 1). The change in blood pressure and eGFR from baseline to 1 year was also similar.



Conclusions: Telenephrology is not inferior to in-person care for the management of CKD and may be superior for visit compliance. Application of this technology is a promising method to deliver care to CKD patients.

Funding: Veterans Administration Support

SA-PO715

Engaging Urban African Americans at Risk for CKD in Discussions About Their Diet Deidra C. Crews,¹ Debra L. Roter,¹ Raquel C. Greer,¹ Yang Liu,¹ Patti Ephraim,¹ Jessica M. Ameling,¹ Kimberly Gudzone,¹ Lisa A. Cooper,¹ L. Ebony Boulware.^{1,2} ¹Johns Hopkins U., Baltimore, MD; ²Duke U., Durham, NC.

Background: Patient-physician discussions about diet are recommended in primary care to decrease patients' health risks, including CKD. However, little is known about the frequency of diet discussions or factors influencing them among African Americans (AAs) at increased CKD risk.

Methods: In a randomized trial of urban AAs with uncontrolled hypertension, we audio-recorded patients' routine visits with their primary care physicians (PCPs) at the first visit following enrollment. We transcribed audio recordings, and quantified the frequency of patient-physician discussions about diet during visits. We marked transcripts for discussions of 36 dietary terms (e.g. sodium, weight, sweets). We also assessed patterns of patient-physician communication, including patient centeredness (degree to which the discussion focused on the patient's psychosocial and lifestyle context), during each encounter using the Roter Interaction Analysis System. We identified factors independently associated with discussions of diet using logistic regression.

Results: Among 127 participants, mean age was 58 years and 70% were female. Average PCP visit lasted 25 minutes. Diet was discussed in 73% of visits, but only included discussion of the Dietary Approaches to Stop Hypertension (DASH) diet in 12%, weight/obesity in 36%, and cholesterol in 39% of visits. Independent predictors of diet discussions (odds ratio, 95% confidence interval) were patient centeredness score ratio (7.5, 1.3-41.9), annual income (3.8, 1.4-10.5 comparing ≥\$10k vs <\$10k), and visit length (1.07, 1.02-1.1 for each minute increment). Patient age, gender, literacy, comorbid disease burden, obesity, diabetes nor CKD status predicted discussions.

Conclusions: Discussions of diet in primary care were frequent, and they were more likely to occur when visits were longer, were centered on patient priorities, and were attended by patients with incomes ≥\$10k. Diet discussions focused on various topics, but infrequently on the recommended DASH diet or other key aspects of dietary modification. Improvements in the content of diet discussions among African Americans at risk for CKD may be needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO716

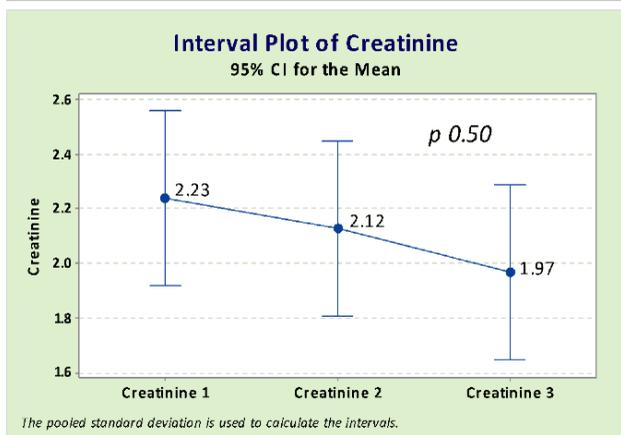
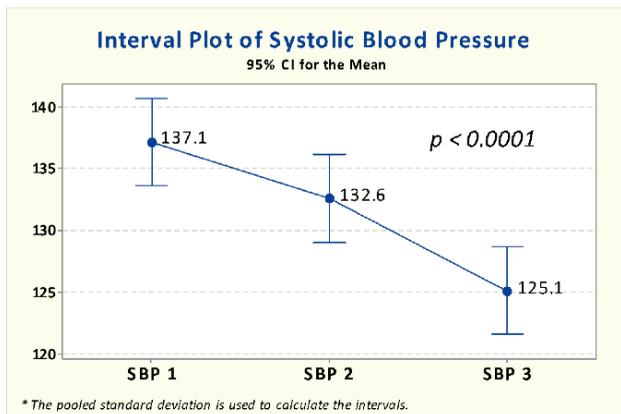
Tele-Nephrolog: A Feasible Way to Improve Access to Care for Patients with Kidney Disease Who Reside in Underserved Areas Marco A. Ladino Avellaneda, Desiree Garcia, Joslyn Wiley, Jose M. Cardona-Guzman, Alejandro Valdes, Alberto J. Sabucedo, Roberto J. Echeverri. Dept of Medicine/Div of Nephrology, Miami VAMC/Univ of Miami, Miami, FL.

Background: The Miami VA Healthcare System serves veterans in three South Florida counties: Miami-Dade, Broward and Monroe, with an estimated veteran population of 175,000. To overcome geographical barriers and facilitate the access to nephrology evaluations, we implemented Provider-Patient Tele-Nephrology using secured videoconferencing.

Methods: A retrospective and descriptive study design was used to evaluate the effect of the Tele-Nephrology clinic intervention. Multiple clinical indicators were included in the analysis: blood pressure control, stabilization of the renal function and electrolyte/metabolic control. 101 patients that were evaluated in the clinic between 2013-2015 were included and the indicators were collected retrospectively.

Results: 101 patients were included, 95% male (n=96) and 5% female (n=5). The mean age was 65.5 years. 50 patients had Chronic Kidney Disease (CKD) stage III (49.5%), 14 patients had CKD stage IV (13%), 8 patients had CKD stage II (7.9%). A one-way analysis of variance analysis (ANOVA) between subjects was conducted and showed that the effect

of the Tele-Nephrology clinic intervention on reducing blood pressure was statistically significant (systolic blood pressure P-value <0.0001). Renal function stabilized but the creatinine changes over time were not statistically significant (P-value: 0.50).



The potassium showed a significant improvement in this sample (P-value: 0.0076). Phosphorous and bicarbonate did not show a statistically significant improvement (p-value 0.79 and 0.91).

Conclusions: With the tele-nephrology clinic intervention we were able to effectively improve blood pressure and stabilize renal function in patients with kidney disease who reside in underserved areas.

SA-PO717

Impact of Exercise Counseling on Physical Function in Chronic Kidney Disease Clara Bohm,¹ Mara McAdams-DeMarco,² Navdeep Tangri,¹ Brett M. Hiebert,¹ Leroy J. Storsley,¹ Lawrence J. Cheskin,² Claudio Rigatto.¹ ¹Univ of Manitoba; ²Johns Hopkins Univ.

Background: Few studies have investigated the effect of exercise counseling on physical function (PF) in chronic kidney disease (CKD). Using retrospective, quasi-experimental pretest-posttest non-equivalent control group design, this study investigated the effect of attending a real-world exercise counseling clinic (ECC) on PF in individuals with CKD.

Methods: Individuals with any stage of CKD registered with the Manitoba Renal Program from Jan. 1, 2011 to Dec 1, 2014 were eligible for inclusion. The exposed group (EC) included individuals who attended ECC. The control group (CG) included individuals who did not attend ECC, but participated in an observational frailty study. **Primary Outcome:** Change in Short Physical Performance Battery score (SPPB) at 1 year. Ranging from 0-12, lower SPPB represents worse PF. **Secondary Outcomes:** Change in health-related quality of life (HRQOL) at 1 year using EQ5D-3L; 2. Change in physical activity (PA) at 1 year using HAP and PASE. **Analysis:** Mann Whitney U, Independent T and Chi-square tests used for group comparisons.

Results: Of 194 individuals in EC and 216 in CG eligible for 1-year follow-up, 73 (37%) in EC and 72 (33%) in CG were assessed. At baseline, mean age was lower in EC (60 years) as compared to CG (68 years); p<0.01. Median SPPB scores at baseline and follow-up were significantly different between groups, but change in SPPB over time was not.

Group	N	Baseline SPPB (IQR)	Follow-up SPPB (IQR)	Mean Change in SPPB (SD)
EC	73	11 (9-12)	11 (9-12)	-0.2 (2.0)
CG	72	10 (8-11)	9 (6-11)	-0.6 (2.2)
P-value		p = 0.01	p = 0.01	p = 0.32

Subgroup analysis of individuals with eGFR < 30 ml/min or on dialysis reduced the differences in age and SPPB between groups, but demonstrated no significant difference to change in SPPB over time. HRQOL did not change significantly between groups. Proportion of individuals with improved PA over 1-year was 36% and 38% in EC and CG, respectively (p=0.82).

Conclusions: In this study, an exercise counseling clinic had no significant effect physical function as measured by SPPB at 1-year, suggesting that exercise counseling alone is inadequate to improve physical function in CKD.

SA-PO718

Ideal and Actual Support of Renal Replacement Therapy Modality Selection Patients with Chronic Kidney Disease: A Nationwide Survey in Japan Shiho Kosaka,¹ Shinichi Nishi,² Yugo Shibagaki,³ Junichi Hoshino,⁴ Kazuo Takahashi,⁵ Yukiko Katagiri,¹ Chika Murayama,¹ Yuka Funaki.¹ ¹Sophia Univ, Tokyo, Japan; ²Kobe Univ Graduate School of Medicine, Kobe, Japan; ³St. Marianna Univ Hospital, Kawasaki, Japan; ⁴Toranomon Hospital, Tokyo, Japan; ⁵Fujita Health Univ School of Medicine, Toyoake, Japan.

Background: Optimal renal replacement therapy (RRT) selection supports for chronic kidney disease (CKD) patients are essential to improving post-therapy outcomes. We aimed to investigate how and when modality selection supports for patients with CKD are used by nephrologists in Japan, through a nationwide questionnaire survey of nephrologists.

Methods: A questionnaire was mailed to 1903 board-certified nephrologists of Japanese Society of Nephrology. Questionnaire items targeting support for modality selection examined the following points: establishment of an RRT modality selection (RRT-MS) clinic, ideal and actual disease stage at which RRT-MS explanation is discussed, timing of RRT initiation, and type of specialist discussing RRT-MS with patients.

Results: The valid response rate was 12.3% (234/1903). Ninety-four out of 234 responding nephrologists (40.9%) had clinics dedicated to RRT-MS. Modality selection was most frequently discussed at CKD stage 4 (53.0%), stage 3b (22.8%), and stage 3a (13.4%). Nephrologists considered stage 3b (32.5%), stage 3a (19.5%), most ideal for discussing RRT-MS; a significant difference was therefore found between ideal and actual timing of RRT-MS discussion. Timing (by eGFR) of access placement of hemodialysis (HD) and peritoneal dialysis (PD) was significantly earlier in patients of RRT-MS clinics than in those of conventional clinics (HD, 12.3/14.1; PD, 12.6/14.9 mL/min/1.73 m²). Regarding types of specialists, nurses most frequently supported patients in RRT-MS (67.1%); however, this may be partly explained by the fact that nephrologists are required to commit more specialiststo supporting patients for RRT-MS.

Conclusions: A gap between ideal and actual timing of discussion of RRT-MS with patients in Japan was identified. To promote appropriate timing of RRT-MS among CKD patients, early and multidisciplinary support systems should be structured.

Funding: Government Support - Non-U.S.

SA-PO719

Primary Care Physicians' Perceived Barriers and Facilitators to Care of Older Adults with Kidney Failure Not on Dialysis Helen Tam-Tham, Brenda Hemmelgarn, Chandra Mary Thomas, Karen Fruetel, Robert R. Quinn, Kathryn M. King-Shier. Univ of Calgary, AB, Canada.

Background: Primary care physicians are important care providers for older adults with kidney failure, but how they perceive and practice conservative (non-dialysis) care has not been studied. We undertook a qualitative study to describe barriers, facilitators, and possible enhancements of conservative care in the community for these older adults.

Methods: Semi-structured telephone interviews were conducted with primary care physicians from southern Alberta, Canada. Participants were identified by a snowball sampling strategy and purposively sampled based on sex, age, and rural/urban location of clinical practice. All participants managed at least 1 patient ≥75 years with kidney failure (eGFR <15ml/min/1.73m² for at least 3 months, not on dialysis) over the past year. Transcripts were analyzed thematically by conventional content analysis.

Results: Twenty-seven primary care physicians participated in this study (55.6% of participants were male, 55.6% of participants were aged 40 to 60 years, and 51.9% of participants practiced in the primary care setting for greater than 20 years). Perceived barriers to conservative care included: managing expectations of kidney failure for patients and their families, optimizing medical management of conservative care, and negotiating provider roles and responsibilities of co-management. Facilitators for care included: establishing patient and their family expectations of care early, preserving continuity of care, and utilizing a multidisciplinary team approach. Primary care physicians also identified suggestions for enhancement of conservative care in the community, including direct telephone access by primary care physicians to conservative care clinicians, treatment decision aids for patients and their families, and a conservative care clinical pathway for primary care providers.

Conclusions: We found important barriers and facilitators to conservative care by primary care physicians in the community. Further investigation of potential strategies that remove barriers and enable facilitators is required to improve the quality of conservative care in the community.

Funding: Government Support - Non-U.S.

SA-PO720

Asking Patients If They Are Aware of Their Chronic Kidney Disease: Does the Question Matter? Delphine S. Tuot, Yunnuo Zhu, Alexandra Velasquez, Juan Maciel Espinoza, Celia Mendez, Tanushree Banerjee, Chi-yuan Hsu, Neil R. Powe. *Univ of California San Francisco.*

Background: Awareness of chronic kidney disease (CKD) is low, even among patients with advanced disease. Increasing awareness to 11.7% is a Healthy People 2020 goal. The National Health and Nutrition Examination Survey (NHANES) measures CKD awareness using the question “Have you ever been told by a doctor or other health professional that you had weak or failing kidneys (excluding kidney stones, bladder infections, or incontinence)?” The framing of this question may influence responses. We sought to compare its sensitivity/specificity to different questions as well as to awareness of other chronic conditions.

Methods: We administered a questionnaire to 220 English, Spanish and Cantonese-speaking adults who received primary care in a public healthcare delivery system. We obtained demographic data, screened for health literacy and ascertained patient awareness about chronic health conditions, including CKD, diabetes, hypertension and hyperlipidemia. CKD awareness was measured using the NHANES question and additional ones, asking if patients had been told about “kidney disease”, “protein in the urine”, “kidney problem”, or “kidney damage”. Health conditions were verified by medical record review.

Results: In our diverse study population (9.6% White, 40.5% Black, 36.4% Hispanic, 12.0% Asian), mean age was 58, mean eGFR was 47 ml/min/1.73m² and 47% had low health literacy. Sensitivities of each CKD awareness question were: 26.7% for “kidney damage”, 28.0% for “kidney disease”, 33.5% weak or failing kidneys” (NAHNES), 36.2% for “protein in the urine” and 40.6% for “kidney problem”. Specificities ranged from 88.2% to 97.7%. Combining all 5 questions yielded a sensitivity of 61.1% and a specificity of 79.6%. This was comparable to awareness of hyperlipidemia (68.8%) but was lower than awareness for hypertension and diabetes (89.6% and 94.3% respectively). Sensitivities were lower in patients with low health literacy.

Conclusions: CKD awareness is low compared to other chronic diseases. Nevertheless, by using more sensitive combinations of questions to ascertain CKD awareness, we have likely reached the Healthy People 2020 goal.

Funding: NIDDK Support

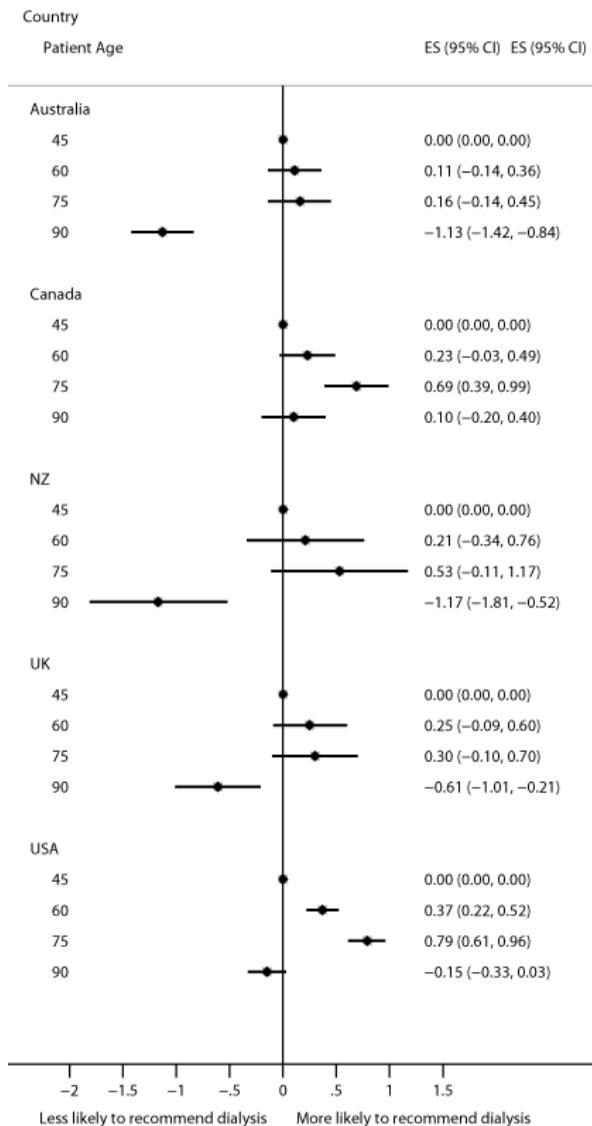
SA-PO721

The Effects of Age and Symptoms on Recommendations to Initiate Dialysis Michael Walsh, Rajnish Mehrotra, Carmel M. Hawley, Marcello Tonelli, Clare I. Castledine, Stephen P. McDonald, Peter Margetts, Darin Treleaven, Vicki Levidiotis, K. Scott Brimble. *McMaster Univ.*

Background: The extent to which patient characteristics influence Nephrologists’ recommendations regarding initiation is unclear. We conducted an international survey to examine the effect of country on recommendations to initiate dialysis.

Methods: Nephrologists from Australia, Canada, New Zealand, the UK and the US were surveyed by email. The survey included clinical vignettes that varied patient characteristics. The recipient scored the likelihood they would recommend initiating dialysis on an 8-point modified Likert scale anchored at 1 (definitely would not) and 8 (definitely would). Results were analysed using mixed-effects regression.

Results: 771 nephrologists were included. The degree to which patient age was associated with recommending dialysis varied by country (p<0.001 for interaction) (Figure 1). For a given level of GFR, only nephrologists from Canada (p<0.001) and the US (p<0.001) were more likely to recommend dialysis for patients age 75 than those aged 45. Conversely, nephrologists from Australia (p<0.001), New Zealand (p<0.001) and the UK (p=0.003) were less likely to recommend dialysis for patients aged 90 than those age 45. All nephrologists were more likely to recommend dialysis as symptoms increased but this association was less pronounced in the US and Australia (p<0.001 for interaction). Patient comorbidities, nephrologists’ years in practice, and practice type were not associated with recommendations.



Conclusions: For patients at a given eGFR, other characteristics such as age and symptom burden influence nephrologists’ recommendations to initiate dialysis but the extent of this influence differed substantially between nephrologists in different countries. Further research is required to understand the effect of these differences on patients and health systems.

SA-PO722

The Association of Community Health Indicators with Late Nephrology Referral in Patients Reaching End-Stage Renal Disease in the U.S. Jung-Im Shin, Mari Palta, Micah R. Chan, Brad C. Astor. *Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: Late nephrology referral in patients reaching end-stage renal disease (ESRD) is associated with inadequate preparation for dialysis and poorer clinical outcomes after renal replacement therapy (RRT). Previous studies have focused on individual-level factors to identify patients at higher risk of late nephrology referral. Environmental and socioeconomic conditions of communities in which patients live may also impact nephrology referral patterns.

Methods: We assessed the association of community health indicators with late nephrology referral in 587,574 patients reaching ESRD, using the data from United States Renal Data System (USRDS) from 2005-2012. An overall community health risk score was calculated using 35 community-level factors based on 1) health outcomes, 2) health behaviors, 3) access and quality of care, 4) socioeconomic factors, and 5) physical environment, using County Health Rankings data from University of Wisconsin Population Health Institute. Late nephrology referral was defined as the first encounter with a nephrologist occurring < 6 months before RRT initiation. Multilevel logistic regression models adjusted for individual characteristics, including demographics, cause of ESRD, body mass index, comorbidities, and insurance and employment status.

Results: The prevalence of late nephrology referral was 47.8%. A significant dose-response relationship of community risk score with late nephrology referral was found, with an adjusted odds ratio of 1.52 (95% CI: 1.36-1.71) for the highest versus lowest risk communities.

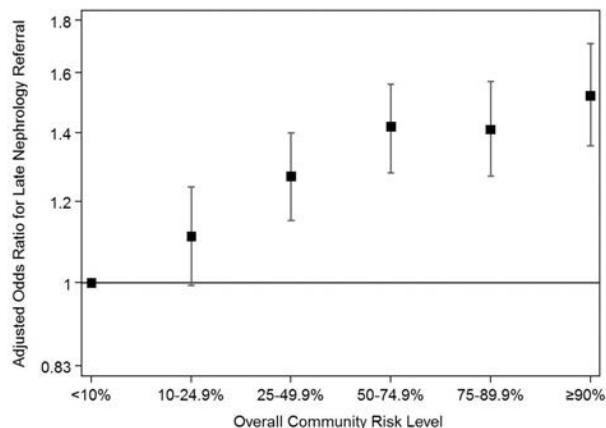


Figure 1. Adjusted odds ratio for late nephrology referral, by overall community risk level.

Conclusions: Higher community risk is significantly associated with late nephrology referral, independent of individual-level factors. Community risk may be an important consideration for developing interventions to improve access to pre-ESRD nephrology care.

SA-PO723

Assessment of Quality of Care Received by Patients with Predialytic Chronic Kidney Disease Seen at a Philippine General Medicine Out-Patient Clinic – Experience at a Government Training Hospital *Rizza Ann B. Lio, Section of Nephrology, Univ of the Philippines-Philippine General Hospital, Manila, Philippines.*

Background: In a country with limited access to dialysis and transplantation such as the Philippines, it is imperative to recognize patients with early stage CKD and aggressively intervene in a timely fashion to prevent ESRD and death. The objective of this study is to evaluate the quality of care (QoC) of patients with predialytic CKD seen at a general medicine clinic.

Methods: This was a retrospective study which reviewed the medical records of 276 patients with CKD Stages 3-4 who have at least 1 year of consult. Patients who were admitted for critical illness, and are on dialysis were excluded. For each QoC parameter, percentage of patients who received the appropriate care were reported. For the QoC correlates, Mann-Whitney U Test, Kruskal-Wallis Test or regression analysis was done.

Results: The mean QoC score for this study is 58.36% (± 23.7%) and the average annual GFR decline is 3.92 mL/min/1.73m².

	Percentage Achieved
CKD Monitoring	
Diagnosis	72.83
Staging	39.13
Monitoring of GFR	97.10
Monitoring of Proteinuria	54.35
Cardiovascular Care	
BP Control	70.29
Glycemic Control	69.6
Dietary Modification	
Salt Restriction	82.25
Protein Restriction	30.43
Anemia Monitoring	51.81
Metabolic Bone Disease	
Baseline Calcium	66.67
Baseline Phosphate	44.93
Baseline Alkaline Phosphatase	10.51
Acidosis	70
Drug Safety	83.33
Nephrology Referral	55.47
TOTAL	58.36

In majority of patients, physicians failed to deliver CKD-specific management strategies such as proteinuria monitoring, protein restriction, anemia and metabolic bone disease recognition. Nephrology comanagement is associated with a better quality of care (85.9 vs. 48.6, p <0.001) and a lower GFR decline (1.64 vs. 4.7 mL/min/1.73m²; p <0.001).

Conclusions: The study confirmed that there are significant gaps and challenges as well as opportunities for improvement in the delivery of quality health care to our patients. There is a need for education to improve the knowledge of primary care physicians in CKD management in consideration to the limited number of nephrologists in the country.

SA-PO724

Chronic Kidney Disease (CKD) Patients’ Understanding of Renal Replacement Therapy (RRT) Options: Early Findings from the U.S. CKD Outcomes and Practice Patterns Study (CKDopps) *Laura H. Mariani,^{1,2} Charlotte Tu,¹ Brian Bieber,¹ Elodie Speyer,¹ Jarcy Zee,¹ Hal Morgenstern,² Benedicte Stengel,³ Bruce M. Robinson,¹ Francesca Tentori.^{1,4}* *¹Arbor Research Collaborative for Health, Ann Arbor, MI; ²Univ of Michigan, Ann Arbor, MI; ³Inserm UMR1018, France; ⁴Vanderbilt Univ, Nashville, TN.*

Background: Current KDIGO guidelines indicate that kidney failure patients should receive information on all RRT modalities, including conservative management. Even when education is provided, patients’ understanding of such a complex topic may be limited. We report the perspective of US participants in the first year of CKDopps.

Methods: CKDopps is a new international prospective cohort study that enrolls adult advanced CKD patients in national samples of nephrology clinics in the US, Brazil, France, and Germany and follows patients through the dialysis transition period. As of early 2015, 245 US participants with eGFR <30 mL/min/1.73m² completed a self-administered questionnaire including their understanding of, education on, and preferences for RRT options.

Results: The median age of patients was 71; 43% were male and 57% had diabetes. 66% of patients reported they received no education about treatment options for kidney failure; 20% said they received one-on-one education; and 14% participated in a class. 34% recalled that in-center hemodialysis (HD) was discussed as a treatment option, and less than 25% recalled their doctor discussing peritoneal dialysis, home HD, conservative management, or transplantation. 58% of participants reported they did not know if transplantation was an option for them. Nearly 3 out of 5 participants did not know what RRT option they would choose if their kidneys failed.

Conclusions: Understanding of RRT options was poor among CKDopps participants in the US. Though the responses may not necessarily reflect information that was actually provided by their nephrology clinic teams, our results indicate that current educational strategies fail to adequately communicate key messages on RRT.

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SA-PO725

Statin Prescribing Among U.S. Ambulatory Outpatient Visits for Patients with CKD *William A. Janes,¹ Talar Markossian,¹ David J. Leehey,² Benjamin Ling,¹ Nicholas Burge,² Vinod K. Bansal,¹ Julia Koval,¹ Ivan Pacold,¹ Kevin Stroupe,² Holly J. Kramer.¹* *¹Loyola Univ Chicago; ²Hines VA Medical Center.*

Background: Approximately 1 in 3 adults with CKD is at high risk of developing cardiovascular disease (CVD). Recent lipid management guidelines agree that statins alone should be used for CVD prevention via lipid lowering. However, lack of congruent recommendations for statin use in adults with CKD may lead to low utilization of statins in this population at high risk for CVD.

Methods: Outpatient visit data during years 2006 to 2010 were obtained from the National Ambulatory Medical Care Survey to determine the frequency of statin prescriptions among outpatient visits for adults age ≥50 years with non-dialysis stage 1-5 CKD based on ICD9 codes. Drug type (particular statin or other cholesterol lowering drugs type) was determined by the generic code recorded in the survey data. The analysis accounted for the complex survey design and utilized the sampling weight, cluster and strata statements so that results are generalizable to US outpatient ambulatory visits during years 2006-2010.

Results: A total of 2262 visits were included with patients being 48% white, 54% male and mean age of 69.6 years. 52% visits were covered by Medicare. Overall, 43% and 31.5% of visits for non dialysis CKD stage 3-5 and stages 1-2, respectively, included a statin prescription with simvastatin being the most commonly prescribed statin. Table 1 shows the prevalence of statin prescription in all patients with non-dialysis dependent CKD by provider type for the outpatient visit.

Clinician Type	% Visits (standard error) with Statin Prescribing for Adults age ≥50 years with non-dialysis CKD by prescriber type
Internal Medicine/Family Practice	35.6 (0.05)
Cardiology	46.8 (0.10)
Nephrology	45.4 (0.13)
Advanced Nurse Practitioner	40.6 (0.16)
Physician Assistant	7.7 (0.04)

Conclusions: These results suggest that the rate of prescription of statins in CKD patients is suboptimal and differs by the provider who cares for the patient with CKD. Lack of CVD preventive care may impact overall CVD risk in patients with non-dialysis dependent CKD.

SA-PO726

Patients' Knowledge of Their Chronic Kidney Disease Stage and Education About Kidney Failure Prevention – The CKD-REIN Cohort Benedicte Stengel,¹ Celine Lange,² Briançon Serge,² Luc Frimat,³ Denis Fouque,⁴ Maurice Laville,⁴ Christian Jacquelinet,² Bruce M. Robinson,⁵ Ziad Massy,^{1,6} Christian Combe.⁷ ¹Inserm U1018-CESP UVSQ, Villejuif; ²Agence Biomedecine; ³CHU Nancy; ⁴CHU Lyon; ⁵Arbor Research Collaborative for Health, Ann Arbor; ⁶A.Paré - APHP; ⁷CHU Bordeaux, France.

Background: Patient knowledge about their CKD stage and how to prevent kidney failure is important to reduce ERSD risk through better adherence to treatment and lifestyle changes. We report primary findings about CKD knowledge among patients seen by nephrologists in France.

Methods: We used baseline data from the CKD-REIN study, a prospective cohort of patients with CKD stage 3 and 4 in a national sample of 40 nephrology clinics. Information was collected from patient interview and self-administered questionnaire. Comparisons between stages were adjusted for age and gender.

Results: Median age was 68[60-76] and 56% were men. About 80% reported knowledge that their kidney function was low. Patients were more likely to know their creatinine level (~40%) than GFR or CKD stage. For each question, knowledge increased slightly from stage 3 to stage 4. Education about how to prevent kidney failure was uncommon (€10%)

	Answers	Stage 3 n=1,107	Stage 4 n=925	p
Patient Interview				
Has a doctor ever told you your kidney fonction was low?	Yes	77%	82%	0.002
Do you know your creatinine level ?	Yes	39%	43%	0.04
Do you know your GFR level ?	Yes	18%	27%	<0.001
Do you know your CKD stage ?	Yes	32%	34%	0.1
Patient questionnaire				
Have you attended a class or received one-on-one education about the prevention of kidney failure?	Yes, a class Yes, one-on-one	4% 4%	10% 9%	<0.001
During the past year, how many times have you see the nephrologist ?	None 1 or 2 ≥3 times	2% 72% 26%	2% 48% 50%	<0.001

Conclusions: Most CKD patients seen by nephrologists are aware that they have low kidney function, but their knowledge of disease severity is low. Very few received education about prevention of kidney failure. While the precise impact of these gaps in knowledge on CKD outcomes requires further investigation, the findings highlight the need to more effectively educate CKD patients about its potentially serious consequences.

Funding: Pharmaceutical Company Support - Amgen, Baxter, Fresenius, GSK, Lilly, MSD, Sanofi, Government Support - Non-U.S.

SA-PO727

The Cost-Effectiveness of Primary Screening for Chronic Kidney Disease in Rural and Remote First Nations Thomas W. Ferguson,¹ Navdeep Tangri,^{1,2} Matthew T. James,³ Zhi Tan,³ Claudio Rigatto,^{1,2} Paul Komenda.^{1,2} ¹Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; ²Medicine, Univ of Manitoba, Winnipeg, MB, Canada; ³Medicine, Univ of Calgary, Calgary, AL, Canada.

Background: Chronic Kidney Disease (CKD) is a risk factor for cardiovascular disease, early mortality, and kidney failure. We have shown that the burden of CKD in First Nations (FN) populations in Manitoba is similar to that in diabetic and hypertensive populations. The cost-effectiveness of screening for CKD and subsequent treatment in FN or other high-risk indigenous populations has not yet been described.

Methods: We constructed a Markov model comparing screening in adult FN (age 18+) for CKD by both proteinuria and estimated glomerular filtration rate (eGFR) to usual care from the perspective of the publicly funded Canadian health care payer. Patients were assigned an initial risk classification based on urine albumin-to-creatinine ratio and eGFR using the Kidney Disease Improving Global Outcomes (KDIGO) heat map. We obtained screening tests results on 1346 adult participants from the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) initiative. Our analysis was further stratified into communities accessible by road and communities accessed by air travel. Our primary outcome of interest was the incremental cost per quality-adjusted life-year (QALY).

Results: Overall crude prevalence of CKD in FN was 26.7%. Screening for CKD was associated with an ICER of \$33,500/QALY in comparison to usual care. Restricting the model to screening in the remotest air access communities (prevalence of CKD 36.0%), this ratio fell to an ICER of \$16,180/QALY. In less remote road access communities (CKD prevalence 18.4%) this ICER was \$63,780/QALY. Primary model drivers included the cost of dialysis, assumed treatment effectiveness, and rates of progression towards kidney failure.

Conclusions: Targeted screening for CKD in rural and remote First Nations is likely cost-effective (< \$50,000/QALY). These findings may be translatable to other high-risk indigenous groups with elevated rates of CKD and kidney failure and warrant further research.

SA-PO728

Getting a Diagnosis of Chronic Kidney Disease: Despite Fears, Patients Want to Know Early Julie A. Wright Nunes,¹ Meghan Roney,² Eve Kerr,³ Akinlolu O. Ojo,¹ Angela Fagerlin.^{1,2,3} ¹Internal Medicine, Univ of Michigan, Ann Arbor, MI; ²Center for Bioethics and Social Sciences in Medicine, Univ of Michigan, Ann Arbor, MI; ³Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI.

Background: Little is known about patient perspectives related to getting a diagnosis of chronic kidney disease (CKD). This information could help providers optimize diagnosis messaging at the point of care.

Methods: Using root/cause analysis and quality function deployment we conducted semi-structured patient interviews. Adult patients with established non-dialysis CKD were interviewed between January-October 2014. Interviews were audiotaped and transcribed. Content analysis was done with Dedoose, a qualitative software package.

Results: 49 patients completed interviews. Mean (SD) age was 63 (14) years, 50% were male, 80% were Caucasian and 84% had CKD Stage 3-5. Key themes emerged from a total of 786 statements: 1) Reaction to diagnosis (160 statements) 2) Barriers to accepting diagnosis (61 statements) and 3) Expectations of diagnosis communication (122 statements). 45% of patients felt fearful after getting a CKD diagnosis - most often related to perceived threats of future dialysis and death. Barriers to diagnosis acceptance included disbelief because of lack of symptoms and lack of prior familiarity with CKD. Despite fear and denial the majority of patients (63%) desired early diagnosis communication by their providers, i.e. at earliest stages of identification. Consistent terminology and disease explanations by providers across the care continuum were perceived as critical to effective communication and diagnosis delivery, yet patients expressed frustration at inconsistent terminology/explanations.

Conclusions: Our findings emphasize that patients learning of a CKD diagnosis can experience fear, but they also prefer early communication of diagnosis. More work is needed to set uniform diagnosis terminology for patients with CKD across the care continuum.

Funding: NIDDK Support

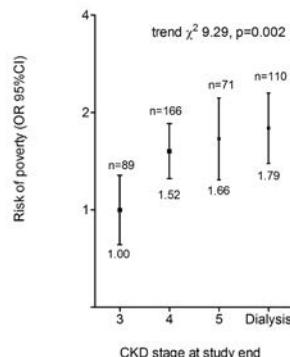
SA-PO729

The Impact of Chronic Kidney Disease on Household Income: Does Health Affect Wealth? Rachael L. Morton,^{1,3} Alan Cass,² Borislava N. Mihaylova.³ ¹Univ Sydney, Australia; ²Charles Darwin Univ, Australia; ³Univ Oxford, United Kingdom; ⁴On behalf of SHARP Collaborators.

Background: The impact of progressive chronic kidney disease (CKD) on household income is unclear. We sought to determine whether CKD severity and non-fatal adverse events were associated with a fall into poverty.

Methods: Prospective cohort study among participants with moderate-to-severe CKD randomized into the Study of Heart and Renal Protection (SHARP) with information on household income at study entry and study end (median follow-up 5 years). Household income recorded as: High (> twice the participating country median); Medium-high (> the median, but < twice the median); Medium-low (< the median, but > half the median); and Low (< half the median income, i.e. poverty). Logistic regression models with socio-demographic factors, smoking, prior diseases, severity of CKD, income category at entry and incident non-fatal events (myocardial infarction, stroke, incident cancer, initiation of dialysis, kidney transplantation) were used to determine a fall into poverty, defined as a move into the lowest household income category.

Results: 2914 SHARP participants were included in the analysis; 933 of these were in poverty at screening and a further 436 (22% of the remaining) moved into poverty by study end. In addition to black ethnicity, low educational attainment, single adult household and low income category at baseline, CKD severity was a significant predictor of a fall into poverty.



Those who received kidney transplant were less likely to fall into poverty (OR 0.48, 95%CI 0.31-0.72). Non-fatal adverse events were not significantly associated with a fall into poverty.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Patients in advanced stages of CKD are at an increased risk of falling into financial hardship. Kidney transplantation may have a role in reducing the risks of household poverty due to CKD.

Funding: Government Support - Non-U.S.

SA-PO730

Healthcare Expenditures for Non-Dialysis Dependent Kidney Disease Compared to Other Chronic Diseases *Christina Small,¹ Holly J. Kramer,¹ Karen A. Griffin,¹ David J. Leehey,¹ Vinod K. Bansal,¹ Kavitha Vellanki,¹ Talar Markossian.¹* ¹Loyola Univ Chicago; ²Hines VA Medical Center.

Background: There is a paucity of literature comparing the expenditures of kidney disease with other common costly chronic diseases in the United States. Our study compares the U.S. healthcare expenditures of non-dialysis dependent kidney diseases to several other chronic conditions.

Methods: This study used the 2012 Medical Conditions and Consolidated Data files from the Medical Expenditure Panel Survey administered by the Agency for Healthcare Research and Quality. Analyses included adults age ≥ 21 years with one of the following conditions: kidney disease, stroke, cancer, or a combination of the three (multichronic). Non-dialysis dependent kidney disease included any ICD9 code for kidney related conditions while chronic kidney disease (CKD) included only ICD9 code “585”. Analyses of calculated healthcare expenditures accounted for the complex survey design and incorporated the sampling weights so that estimates represent healthcare expenditures for the 2012 adult U.S. population (~313.4 million). Out of pocket healthcare expenditure burden was defined as the ratio of out of pocket healthcare expenditure to total person-level income for the year 2012.

Results: The mean age for non-dialysis dependent kidney disease and CKD was 56.5 and 65.9 years, respectively. Table 1 shows the median total and out of pocket healthcare expenditure values and mean out of pocket healthcare expenditure burden for kidney disease, CKD and other chronic conditions.

Chronic Condition	Median Out of Pocket Expenditures, \$ (range)	Median Total Expenditures \$(range)	Mean Out of Pocket Expenditures Burden %
CKD	862 (38-13,915)	22, 919 (1,782-189,893)	9.5
Any kidney disease	795 (0-42,034)	6,351 (0-262,189)	5.0
Cancer	760 (0-54,698)	8, 528 (0-147,533)	5.2
Stroke	790 (0-79, 313)	7,606 (0-212, 886)	5.2
Multiple Chronic Conditions	824 (2-5,711)	16, 323 (992-276, 047)	6.0

Conclusions: Healthcare expenditures including out of pocket costs are higher for non-dialysis dependent CKD compared to other chronic medical conditions. Policy efforts should focus on reducing the healthcare cost burden for patients with kidney disease.

SA-PO731

Smartphone-Based Self-Management System for Chronic Kidney Disease: Results from a Single Centre Prospective Trial *Stephanie W. Ong,^{1,2} Sarbjit Vanita Jassal,¹ Akib Uddin,³ Kelly Min,¹ Joseph A. Cafazzo,³ Alexander G. Logan.¹* ¹Nephrology, Univ Health Network, Toronto, ON, Canada; ²Pharmacy, Univ Health Network, Toronto, ON, Canada; ³Centre of Global eHealth Innovation, Univ Health Network, Toronto, ON, Canada.

Background: Following user-centric design principles we developed a smartphone-based self-management support system for patients with advanced CKD. The patient interface focuses on 4 behavioral elements over which they have direct control: monitoring BP at home, self-assessment of symptoms, managing medications and tracking laboratory results. The main objectives of this 6-month prospective study were to determine acceptability, measured by system adoption and adherence, and assess effectiveness by measuring pre and post changes in BP, medications, labs and self-management behaviors.

Methods: We tested the mobile app system in 10 renal clinics at a single academic renal center in Toronto. The 47 enrolled patients were instructed at a regular clinic visit on the use of the mobile app. The clinical team independently received information on the mobile app system’s operation.

Results: 61% of participants were non-smartphone owners. All had more than one chronic condition and on average were on 10 to 15 medications. Most were over the age of 50 with the greatest representation in the age group 55-64. >80% of the users achieved more than the recommended 80% adherence rate to mobile app use. 27% with normal clinic BP readings were discovered to have ‘masked’ hypertension on home BP monitoring. By the end of the study the SBP fell by 6.8 ± 20.4 mm Hg (p<0.05) and DBP, by 0.9 ± 9.1 mmHg. Out of 250 medication reviews, 49% required intervention from the clinical team, such as altering drug dosing. Due to the short study duration and infrequency of lab testing, there were no changes in pre and post laboratory test results. On exit, patients and clinicians felt the mobile app helped engage and empower patients in their CKD care.

Conclusions: The mobile app was acceptable and suggests improvements in BP management and medication error prevention. This offers early evidence to supporting innovative use of mobile technology in CKD management and strongly support evaluating its use in a larger clinical.

SA-PO732

Potentially Preventable Hospitalization Among Patients with Chronic Kidney Disease and High Inpatient Use *Paul E. Ronksley, Braden J. Manns, Marcello Tonelli, James Wick, Brenda Hemmelgarn.* *Univ of Calgary, Calgary, AB, Canada.*

Background: While prior studies have observed high rates of hospitalization among patients with chronic kidney disease (CKD), little attention has been given to those with high inpatient use. We explored clinical characteristics, patterns of hospital use, and potentially preventable acute care encounters among hospitalized patients with CKD.

Methods: We identified all adults (≥18 years) with an eGFR<60 mL/min/1.73m2 in Alberta, Canada between Jan 1 and Dec 31, 2009, excluding those with prior kidney failure. Patients with CKD were linked to administrative data to capture clinical characteristics and frequency of hospital encounters, and followed until death or end of study (Dec 31, 2012). Patients with 1 or more hospital encounters were categorized into 3 groups: persistent high use (upper 5% of inpatient use (≥3 encounters/yr) in 2 or more years), episodic high use (upper 5% in 1 year only), or non-high use (lower 95% in all years). Within each group we described patient characteristics and calculated the proportion of potentially preventable hospitalizations as defined by 4 CKD-specific ambulatory care sensitive conditions (ACSC); heart failure, hyperkalemia, volume overload, malignant hypertension.

Results: During a median follow-up of 3 years, 57007 patients had 118671 hospitalizations of which 1.7% of patients were persistent high users of hospital services, 12.3% episodic high users, and 86.0% non-high users. Persistent high users were often younger, male, First Nations, living in rural areas, and had higher levels of comorbidity compared to episodic and non-high use groups. Overall, 24804 (20.9%) CKD-related ACSC encounters were observed in the cohort. The proportion of ACSC encounters were higher in persistent high users (29.1%) compared to episodic (27.3%) and non-high users (17.3%) (p<0.01). The majority of the encounters were attributed to heart failure and hyperkalemia in all groups.

Conclusions: A substantial proportion of hospitalizations among patients with CKD and high inpatient use are ACSC-related. These findings suggest opportunities to reduce inpatient use and cost by focusing on strategies to improve community-based care for this subset of patients.

SA-PO733

Effect of Increased Blood Pressure Variability on Neurocognition in Children with Chronic Kidney Disease *Marc Lande,¹ Susan R. Mendley,² Matthew Matheson,² S. Shinnar,² Arlene C. Gerson,² Joshua A. Samuels,² Bradley Warady,² Susan L. Furth,² Stephen R. Hooper.²* ¹Univ of Rochester; ²CKiD Investigators.

Background: Increased blood pressure variability (BPV) is associated with lower neurocognitive test (NCT) performance in adults. We previously studied children with chronic kidney disease (CKD), who are at risk for cognitive dysfunction and increased BPV. However, little is known about the impact of increased BPV on cognition in children with CKD.

Methods: Children 6-18 years enrolled in the prospective NIH-sponsored Chronic Kidney Disease in Children (CKiD) study had NCT including WASI Matrix Reasoning, parent BRIEF, CPT-II, Digit Span, and Verbal Fluency. Casual BP visit-to-visit BPV was assessed by SD (BPV-SD) and average real variability (ARV), and 24-hour ambulatory BP monitoring by SD of wake and sleep periods. For unadjusted analyses, test scores of the subjects with BPV in the upper tertile were compared to that of subjects in the lower tertile. Multiple linear regressions were used to evaluate the relation between BPV and NCT scores, adjusting for BP index, sex, age, maternal education, race, BMI %ile, estimated GFR, % of life with CKD, nephrotic proteinuria, and low birth weight.

Results: Depending on the task, 121- 511 subjects had both BP and NCT results available. In unadjusted analysis, subjects with increased visit-to-visit systolic BPV scored lower on Verbal Category Switching (3rd vs 1st tertile of BPV-SD, 8.4 ± 2.7 vs 9.8 ± 3.0, p = 0.004; of ARV, 8.6 ± 3.0 vs 9.7 ± 2.5, p = 0.009). There was no effect of increased visit-to-visit BPV or ambulatory BPV on any other task. In adjusted analyses, increased visit-to-visit systolic BPV remained significantly associated with lower Verbal Category Switching scores for BPV-SD (β=-0.28, 95% CI:-1.34, -0.15) and there was a trend for ARV (β =-5.7, 95%CI:-1.16, 0.03).

Conclusions: Increased visit-to-visit systolic BPV was independently associated with decreased Verbal Category Switching scores in children with CKD. These results suggest that children with CKD may have difficulties with set shifting that are related, in part, to increased BPV. Further study is needed to determine the significance of this isolated result.

Funding: Other NIH Support - NHLBI

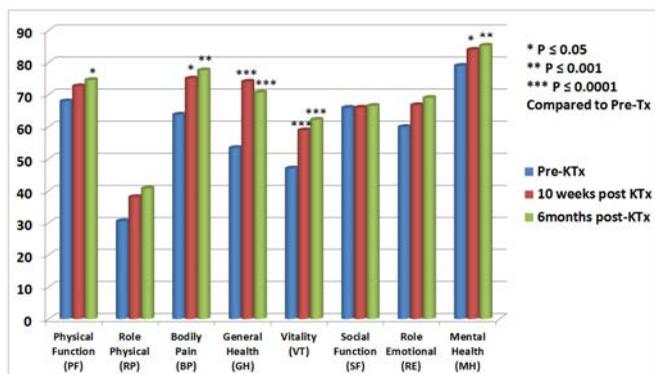
SA-PO734

Rapid Post-Transplant Improvement of HRQOL in Older Kidney Recipients Kristian Heldal,^{1,2} Kjersti Lønning,^{2,3} Tomm Bernklev,^{2,4} Nanna von der Lippe,² Anna Reisaeter,³ Anders Hartmann,^{2,3} Marit helen Andersen,³ Karsten Midtvedt.³ ¹Clinic of Internal Medicine, Telemark Hospital, Skien, Norway; ²Inst of Clinical Medicine, Faculty of Medicine, Univ of Oslo, Oslo, Norway; ³Clinic of Cancer, Surgery and Transplantation, Oslo Univ Hospital, Rikshospitalet, Oslo, Norway; ⁴Research Unit, Telemark Hospital, Skien, Norway.

Background: It is widely accepted that health-related quality of life (HRQOL) is significantly compromised in patients with ESRD. In adults, kidney transplantation (KTx) is known to improve HRQOL. In older recipients there is a lack of studies measuring the effect of KTx on HRQOL. The aim of this study was to measure HRQOL longitudinally in enlisted patients >65 years of age, from pre-transplant and until 6 months after KTx.

Methods: Patients >65 years listed for transplantation at our centre were asked to complete the SF36 questionnaire at enlisting and thereafter every 6 months until KTx. Post transplant, the patients received a new SF36 form after 10 weeks and 6 months.

Results: A total of 180 patients have been included from Jan 2013. Mean age at enlisting was 70.6 years (65.0-81.8) and 68% were male. By the end of May 2015, 100 patients were transplanted and 59 of them had completed both pre- and post-transplant questionnaires. Mean time from completing the first pre-tx questionnaire to transplantation was five months. When comparing the scores for the last SF36 pre-tx with 6 months post-tx, there was a statistical significant increase of the mean scores for GH (53-71), PF (68-74), BP (64-78), VT (53-71) and MH (79-85). There was also a tendency towards improved scores for RP and RE, while the SF score was unchanged.



Conclusions: Our preliminary findings indicate that older patients report a significant improved HRQOL measured by SF36 already 10 weeks after KTx and the status remains stable after 6 months. Longer follow-up is warranted.

Funding: Government Support - Non-U.S.

SA-PO735

L-Carnitine Improves Cognitive and Renal Functions in a Rat Model of Chronic Kidney Disease Zaher Anis Armaly,² Adel Rafik Jabbour,¹ Avi Avital.³ ¹Dept of Nephrology, Bar Ilan Univ, E.M.M.S. Hospital, Nazareth, Israel; ²Dept of Biochemical Laboratory, E.M.M.S. Hospital, Nazareth, Israel; ³Behavioral Neuroscience Lab, Dept of Physiology, Rappaport Faculty of Medicine, Technion and The Emek Medical Center, Haifa, Israel.

Background: Over the past decade, the prevalence of chronic kidney disease (CKD) has reached epidemic proportions. L-Carnitine, considered as the "gatekeeper" responsible for admitting long chain fatty acids into mitochondria. L-Carnitine synthesis and turnover are regulated mainly by the kidney and its levels inversely correlate with serum creatinine (Scr) of normal subjects and CKD patients. Previous studies showed that L-Carnitine administration to elderly improves and preserves cognitive function. Yet, there are no clinical intervention studies that investigated the effect of L-Carnitine administration on cognitive impairment evidenced in CKD patients. Thus, we investigated the effects of L-Carnitine treatment on renal function and cognitive performance in a rat model of progressive CKD.

Methods: Animals were subjected to right unilateral nephrectomy combined with 2/3 of left kidney ligation. Sham operated rats served as controls. Following 14-days recovery period, animals were randomly assigned into two treatment conditions: treatment with saline (sham n=7; CKD n=9) or L-Carnitine (250 mg/kg) (sham+car n=7; CKD+car n=8) by daily intraperitoneal injections, for 8 consecutive weeks. Then all rats were sacrificed, blood samples and remnant kidney were collected, for biochemical and histological analysis, respectively. Two way shuttle avoidance test was used to assess the effects of CKD and L-Carnitine treatment on cognitive-related behavior.

Results: We found that all CKD animals exhibited renal dysfunction, as indicated by elevated sScr, BUN, and histopathological abnormalities. L-Carnitine treatment of CKD rats significantly reduced Scr and BUN, attenuated renal hypertrophy and decreased renal tissue damage. In addition, in the two way shuttle avoidance learning, CKD animals showed cognitive impairment which recovered by the administration of L-Carnitine.

Conclusions: Administration of L-Carnitine in a rat model of CKD, significantly improved cognitive and renal functions.

SA-PO736

Being a Relative to Patients with Chronic Kidney Disease – Experiences of Participation in Care and Treatment Hanne Agnholt,¹ Jette Kristiansen,² Mona Kyndi Pedersen.³ ¹Dept of Nephrology, Aalborg Univ Hospital, Aalborg, Denmark; ²Univ College of Northern Denmark, Aalborg, Denmark; ³Clinic for Internal Medicine, Aalborg Univ Hospital, Aalborg, Denmark.

Background: Studies concerning the lives of patients with chronic kidney disease have focused on the patients, and not the relatives. However, relatives share and are affected by the same consequences as the patient with regard to changes in everyday life, roles in the family and mutual relationship. The purpose of the study was to gain insight into and understanding of the needs of the relatives of patients with chronic kidney disease with regard to their ability to provide support in everyday life, and the expectations of the relatives of participation in care and treatment.

Methods: A qualitative study based on four focus group interviews with four to eight relatives in each group (in total 27 relatives). The groups were formed according to the age and gender of the relatives as well as their relation to the adult patient with chronic kidney disease.

Results: The study demonstrated how relatives provide substantial support to the patient both in everyday life and in care and treatment. In relation to the patient, it was a constant challenge for relatives to find the balance between supporting and taking over. They expressed a need for recognition by both the close relations and the health care professionals as well as a need for sharing their experiences with other relatives in the same situation. The analysis identified six themes: 1. Different needs and possibilities for support and participation. 2. Finding balance between disease and everyday life. 3. Emotional pressure. 4. The importance of recognition. 5. Need for regaining energy, and 6. Collaborating with health care professionals.

Conclusions: When collaborating with the relatives with regard to care for patients with chronic kidney disease, the health care professionals should actively recognize the patient support that the relatives already provide in everyday life. Initiatives of participation in care and treatment should be based on collaboration and the needs, expectations and possibilities of both the patient and the relatives.

SA-PO737

CKD(3-5) Affects Endurance, Strength, Balance and Fine Motor Skills which Are Not Detectable by Questionnaire Naomi D. Clyne,¹ Matthias Hellberg,¹ Peter Hoglund.² ¹Clinical Sciences Lund, Nephrology, Lund Univ, Lund, Sweden; ²Laboratory Medicine, Clinical Pharmacology, Lund Univ, Lund, Sweden.

Background: Physical functions are impaired in dialysis patients. It is unclear which functions are affected and how they decline in the course of CKD. This study investigated the effects of declining GFR (CKD 3-5) on measured physical functions, self perceived physical functioning and well-being.

Methods: In this cross sectional analysis 101 patients (40 women, 61 men; mean age: 67±13 years, median GFR: 21 (9-41) ml/min/1.73m²) were tested with 6 Minutes Walk (6-MWT), Isometric Quadriceps Strength (IQS), Functional Reach (FR) and Picking-up (PUT). Self perceived physical functioning and well-being were assessed by KDQOL-SF™. GFR was measured with Iohexolclearance and comorbidity by Davies' index. Multivariable linear regression analyses were employed including the following explanatory variables: GFR, age, sex, comorbidity and the interaction between sex and age.

Results: Significant associations were found between decline in GFR and endurance (6-MWT; p=0.039), strength (IQS; p=0.035), balance (FR; p=0.024) and fine motor skills (PUT; p=0.015) as well as by the patients' perceived domains in the KDQOL-SF™ of effects- (p=0.023) and burden (p=0.016) of kidney disease and social support (p=0.006) after having taken the explanatory variables into account. There were significant associations between the KDQOL-SF™ domains role physical and emotional well-being and 6-MWT (p=0.018; p=0.018, respectively) and IQS (p=0.005; p=0.045, respectively), but these were dependent on age, sex and comorbidity and not driven by GFR.

Conclusions: Physical functions comprising endurance, strength and fine motor skills were impaired relatively early in the course of CKD (3b-5), seemed to progress with declining GFR and could be detected by easy to perform physical function tests. The relationship between self perceived physical functioning and well being, respectively, with measured endurance and strength, respectively, were driven by age, sex and comorbidity but not by decline in GFR. The only domains that discriminated for GFR associated influence were effects- and burden of kidney disease and social support.

SA-PO738

The Prevalence of Cognitive Impairment in Chinese Peritoneal Dialysis Patients Chi-bon Leung, Cheuk-Chun Szeto. Dept of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong.

Background: Cognitive impairment is common amongst patients with chronic kidney disease and may be associated with excessive morbidity in dialysis patients. This study determines the prevalence and risk factors of cognitive impairment in Chinese peritoneal dialysis (PD) patients.

Methods: We studied 178 prevalence PD patients (103 males). Cognitive impairment was screened by the 10-item Abbreviated Mental Test (AMT) questionnaire. We also determined patients' comorbidity load, dialysis adequacy, residual renal function, nutritional status, and degree of frailty.

Results: The mean age was 60.7 ± 11.7 years; vintage of dialysis 42.5 ± 44.1 months. Average AMT score was 9.3 ± 1.3. The AMT score is closely associated with age (r =

-0.398, $p < 0.0001$). AMT score also has a modest but significant correlation with Charlson's comorbidity index ($r = -0.192$, $p = 0.010$), subjective global assessment score ($r = 0.153$, $p = 0.041$), malnutrition inflammation score ($r = -0.212$, $p = 0.004$), serum albumin level ($r = 0.184$, $p = 0.024$), and frailty index ($r = -0.199$, $p = 0.008$), but not with vintage of PD, dialysis adequacy, or residual renal function. When defined as a AMT score < 7 , 14 patients (7.9%) had cognitive impairment.

Conclusions: Cognitive impairment is not uncommon amongst Chinese PD patients. Frailty and malnutrition are the major risk factors of cognitive impairment in our cohort, while comorbidity load and dialysis adequacy have little effect.

Funding: Government Support - Non-U.S.

SA-PO739

Neurocognitive Functioning and Association with Clinical Outcomes in Adults with End-Stage Kidney Disease: The COGNITIVE-HD Study Giovanni F.M. Strippoli,^{1,2,3,4} ¹On behalf of the COGNITIVE-HD Study Investigators*; ²Diaverum Medical Scientific Office; ³Univ of Bari; ⁴Univ of Sydney.

Background: Cognitive impairment and neurocognitive disorder have been associated with increased mortality in the general population. Whether dialysis patients have specific patterns of cognitive dysfunction, or whether cognitive function is associated with activities of daily living and durability of dialysis treatment remain poorly understood.

Methods: The COGNITIVE-HD study will provide detailed neuropsychological assessments of cognitive function among hemodialysis patients to characterize age- and education-adjusted prevalence and patterns of cognitive impairment and the associations with physical and social functioning and clinical outcomes including cardiovascular events at 12 months. The COGNITIVE-HD study is a prospective, longitudinal, population study of 751 adults conducted in 20 dialysis centers in Italy. A detailed battery of comprehensive testing for executive function, visuospatial function, language, learning and memory, personality traits, and complex attention has been carried out by a trained psychologist at baseline to assess for presence of cognitive impairment and to evaluate the pattern of cognitive deficits, and any association between cognitive impairment and activities of daily living.

Results: Preliminary analyses have been conducted on the Mini Mental State Examination (MMSE) evaluation of cognitive function among 702 participants (mean age 68.2 years, 60% men). 50% had normal cognitive function (MMSE score 27-30), 22% had mild cognitive impairment (score 26-24). 198 patients (28%) had MMSE results compatible with dementia (score < 24), of whom 51%, 48% and 1% had mild, moderate and severe impairment respectively.

Conclusions: The COGNITIVE-HD is a population-based study of cognitive function involving dialysis patients that has the potential to inform candidate interventions for treatment trials of cognitive impairment in the setting of advanced kidney disease. *List of study investigators: S Palmer, M Ruospo, A Iurillo, V Saglimbene, P Natale, O Barulli, L Gargano, AM Murgio, C Loy, JC Craig, DW Johnson, M Tonelli, J Hegbrant, C Wellheim, G Logroscino and GFM Strippoli.

SA-PO740

Lower Renal Function Predicts Poorer Performance in Specific Domains of Neurocognitive Function in Older Hypertensive Men Stephen L. Seliger,^{1,2} Jason Kissler,³ Jamie Giffuni,² Leslie I. Katzel,^{1,2} Shari R. Waldstein,³ ¹Medicine, U Maryland Sch Medicine; ²GRECC, VA Maryland Healthcare System; ³Psychology, U Maryland Baltimore Co.

Background: CKD has been associated with lower cognitive performance, especially in older adults. However, the specific pattern of functional deficits is uncertain, and many prior reports have not accounted for common vascular risk factors of ageing such as hypertension.

Methods: We tested neurocognitive functions using a multi-item test battery among older (60+) community-dwelling hypertensive males with stage 2-4 CKD (n=108) and without CKD (n=68). Subjects were free of stroke and dementia. GFR was estimated using the MDRD equation. Multiple linear regression was used to compare those with and without CKD, and to estimate associations of eGFR and proteinuria with cognitive functions, adjusting for demographics and potential confounders (education, depression, blood pressure, hemoglobin, fasting glucose, smoking, alcohol use, and BMI).

Results: Mean age was 69.1±7.4 years, mean SBP 134±18 mm Hg, and 47% were African-American; mean eGFR was 42.9±14.5cc/min/1.73m² among those with CKD. Among all subjects, lower eGFR was linearly associated with worse performance on tests of attention, non-verbal memory, visuospatial ability, manual dexterity, and language fluency after multivariable adjustment (Table). In contrast, those with stage 2-4 CKD as a group did not differ from controls in cognitive performance after adjustment for confounders, nor was proteinuria correlated with cognitive test performance.

Adjusted associations (β) of estimated GFR with neurocognitive function

Cognitive Test	Functional Domains	Standardized β	p-value
Logical Memory Immediate	Verbal Memory & Learning	0.07	0.388
Logical Memory Delayed	Verbal Memory	0.048	0.56
Visual Reproductions Immediate	Non-verbal Learning & Memory	0.175	0.019
Visual Reproductions Delayed	Non-Verbal Memory	0.13	0.099
Grooved Pegboard (dominant)	Motor Speed, Manual Dexterity	-0.161	0.039
Grooved Pegboard (non-dominant)	Motor Speed, Manual Dexterity	0.005	0.948
Digit Span, Forwards	Simple attention	0.179	0.029
Digits Span, Backwards	Concentration, Working Memory	-0.041	0.591
Trails A	Psychomotor Speed,	-0.119	0.076
Trails B	Complex attention, set-shifting	-0.039	0.574
Stroop Color Word	Response Inhibition	0.104	0.234
Judgment of Line Orientation	Visuospatial Ability	0.144	0.05
Symbol Digit Substitution	Psychomotor Speed	0.099	0.179
Verbal Fluency	Language Fluency	0.168	0.038
Category Fluency – Animals	Language Fluency	-0.009	0.913
Category Fluency – Supermarket	Language Fluency	0.138	0.106

Conclusions: Among older men, those with primarily mild-moderate CKD and HTN do not have lower cognitive function compared to hypertensive controls after accounting for common cognitive risk factors. However, across a range of GFR, lower renal function is associated with worse performance in specific domains of cognitive function.

Funding: NIDDK Support, Veterans Administration Support

SA-PO741

Neurocognitive Function and Psychiatric Disorder in Children with Chronic Kidney Disease from the KNOW-Ped CKD Cohort Study (Korean Cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease) Kyoung Hee Han,¹ Eujin Park,² Yo Han Ahn,² Seong Heon Kim,³ Joo Hoon Lee,⁴ Young Seo Park,⁴ Hee Gyung Kang,² Hae Il Cheong,² Curie Ahn,⁵ Il-Soo Ha,² ¹Dept of Pediatrics, Jeju National Univ School of Medicine, Jeju, Republic of Korea; ²Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Republic of Korea; ³Dept of Pediatrics, Pusan National Univ Children's Hospital, Yangsan, Republic of Korea; ⁴Dept of Pediatrics, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea; ⁵Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: We determined whether pediatric chronic kidney disease (CKD) is associated with neurocognitive impairment and psychiatric disorder from the KNOW-PedCKD cohort study in Korea.

Methods: A total of 322 children (M:F 218:104) enrolled from seven major pediatric nephrology centers of Korea from July 2010 to December 2013 were the subject of this study. Neurocognitive function and psychiatric status of pediatric CKD patients were evaluated using Wechsler intelligence scale for children, Child Behavior Checklist, ADHD Rating Scale-IV, State-Trait Anxiety Inventory, Child Depression Inventory and Parental bonding instrument-Korean version.

Results: Verbal, performance and full scale IQ were lower in younger age and congenital anomalies of the kidney and urinary tract as a cause of CKD. More than 10 percent of school-age children with CKD presented significant emotional distress including somatization (15%), attention problems (15%) and anxiety (12%). Impact of progression of CKD on their neurocognitive function and psychiatric status will be investigated in KNOW-PedCKD as follow-up study.

Conclusions: In young patients with CKD and those with multiple congenital problems in addition to CKD suffer from low intelligence and psychiatric disorder. Pediatric CKD patients with low intelligence and psychiatric disorder need close attention and developmental training techniques. **Acknowledgement.** This work was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (2013E3301600, 2013E33081601).

Funding: Government Support - Non-U.S.

SA-PO742

Awareness of Kidney Disease Is Associated with Depressive Symptoms: NHANES 2005-2010 Shayan Shirazian, Robert Diep, Joseph Mattana, Ritika Sharma, Rose Calixte. Winthrop Univ Hospital.

Background: Depressive symptoms are common in patients with chronic kidney disease (CKD). The purpose of this study was to define variables associated with depressive symptoms in patients with CKD including awareness of CKD diagnosis.

Methods: We used data from the National Health and Nutrition Examination Surveys (NHANES) 2005-2010. Non-pregnant subjects age > 20 with CKD stage 1-4, who completed both an awareness of kidney disease questionnaire and a Patient Health Questionnaire (PHQ-9) were included. Three outcome groups were defined: 1) minimal depressive symptoms (PHQ-9 score 0-4), subthreshold depressive symptoms (PHQ-9 score 5-14) and severe depressive symptoms (PHQ-9 score > 14). All analyses were performed with appropriate

weighting. Chi-square and unpaired t-tests defined significant differences between outcome groups. Multivariable logistic regression defined variables independently associated with subthreshold depressive symptoms. Significance was defined as $p \leq 0.05$.

Results: Of the 2500 subjects with CKD that met study criteria, 21.8% had subthreshold depressive symptoms and 3.3% had severe depressive symptoms. Multivariable predictors of subthreshold depressive symptoms included female gender, lower education, lower income, single marital status, Mexican and Black race, diabetes, elevated diastolic blood pressure, smoking, cardiovascular comorbidity and awareness of kidney disease. 6.4% of subjects were aware they had CKD. CKD awareness was significantly associated with subthreshold, but not severe, depressive symptoms in univariable analysis (OR 1.76, CI 1.10-2.80). In multivariable analysis, the association between awareness of CKD and subthreshold depressive symptoms remained significant ($p=0.05$). There was a significant interaction between awareness and stage 1 CKD on subthreshold depressive symptoms (OR 8.25, CI 2.24-30.63), and between awareness and female gender on subthreshold depressive symptoms (OR 2.19, CI 1.09-4.38).

Conclusions: Awareness of kidney disease is significantly associated with subthreshold depressive symptoms. This association is possibly mediated by distress caused by CKD diagnosis. Increased psychosocial support, especially in early stages of CKD, may be warranted.

SA-PO743

Vitamin D Deficiency Is Significantly Associated with Depression in Chronic Kidney Disease Patients Jong Hyun Jhee, Sul A. Lee, Hyung Jung Oh, Jung Tak Park, Seung Hyeok Han, Shin-Wook Kang, Tae-Hyun Yoo. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Recent studies have reported significant associations between vitamin D deficiency and depression in the general population. Although both vitamin D deficiency and depression are common features in chronic kidney disease (CKD) patients, the association between these two prevalent factors in this patient population remains poorly elucidated. Therefore, the association between vitamin D deficiency and depression in CKD patients was investigated.

Methods: The data from the Korean National Health and Nutritional Examination Survey between 2010 and 2012 were used. A total of 495 patients with estimated glomerular filtration rate ≤ 60 mL/min/1.73m² were enrolled. Vitamin D deficiency was defined as 25-hydroxyvitamin D3 [25(OH)D3] levels ≤ 10 ng/mL. Patients were dichotomized by the presence of vitamin D deficiency. Depression was determined by the EuroQOL-5D (EQ5D) questionnaire. Independent association between vitamin D deficiency and depression was evaluated by multivariate logistic regression analysis.

Results: The mean age was 71.2 ± 9.3 years, and 257 patients (51.9%) were female. The median 25(OH)D3 levels were 17.9 (13.9-22.7) ng/mL. The prevalence of depression in CKD patients was higher compared to the general population (14.3% vs. 11.1%, $P=0.031$). In addition, the prevalence of depression was significantly higher in patients with vitamin D deficiency than those without vitamin D deficiency (27.0% vs. 13.3%, $P=0.022$). Multivariate logistic regression analysis showed that vitamin D deficiency was a significantly independent predictor of depression after adjusting for age, sex, alcohol, body mass index, hypertension, diabetes mellitus, anemia, suicidal idea, EQ5D index, and serum parathyroid hormone levels (odds ratio=6.27, 95% confidence interval=1.57-25.05, $P=0.009$).

Conclusions: Depression was highly prevalent in CKD patients. Vitamin D deficiency was a significantly independent predictor of depression in CKD patients. Therefore, determining vitamin D levels might be helpful to predict depression in these patients.

SA-PO744

Comparison of Prevalence and Predictors of Fatigue in Advanced Chronic Kidney Disease and Cancer Patients Manisha Jhamb,¹ Sanah Parvez,² Khaled Abdel-Kader,³ Mark L. Unruh,² Jennifer L. Steel.¹ ¹Univ of Pittsburgh; ²Univ of New Mexico; ³Vanderbilt Univ.

Background: Although >50% of patients with advanced CKD report fatigue, its presence, predictors and consequences are under-appreciated by renal providers. We compared the symptom burden among CKD/ESRD patients to those with advanced hepatobiliary cancer (CA).

Methods: In 237 patients with advanced kidney disease (35% CKD stage 4-5, 65% ESRD) and 606 with advanced CA, patient-reported symptoms and health-related quality of life (HRQOL) were assessed using validated fatigue, pain, sleep quality, depression and HRQOL questionnaires. Chi-square and ANOVA were used to test between group differences and linear regression was employed to test predictors of fatigue.

Results: In unadjusted analyses, CKD patients reported statistically (but not clinically) less fatigue, similarly poor sleep quality, and significantly lower prevalence of depression and pain as compared to CA patients. Lower levels of fatigue were strongly associated with higher HRQOL in both groups ($r=0.80$, $p<0.001$ in CKD; $r=0.67$, $p<0.001$ in CA). Depression was significantly associated with higher levels of fatigue for both groups ($p<0.001$ for both). Poor sleep quality was associated with higher fatigue in both groups ($r=-0.40$, $p<0.001$ in CKD; $r=-0.27$, $p<0.001$ in CA). Similarly, in both groups, more pain was associated with higher fatigue ($r=0.41$, $p<0.001$ for MOS SF-36 pain score in CKD; $r=-0.48$, $p<0.001$ for BPI in CA). Using linear regression, and including those factors significantly associated with fatigue, 29% of the variance in CKD and 31% in CA cohort was explained by depression, sleep and pain.

	CKD/ESRD (n=237)	Cancer (n=606)	p-value
Age (yrs)	54.7 ± 14.9	61.6 ± 10.9	<0.001
Males	152 (64.2%)	391 (64.6%)	0.91
FACT-F score	34.5 ± 11.2	32.7 ± 12.1	0.05
Clinical levels of depression*	61 (25.7%)	242 (41.7%)	<0.001
PSQI Sleep Quality score	7.7 ± 4.3	7.3 ± 4.1	0.32
Clinical Levels of Pain**	47 (18.7%)	157 (31%)	<0.001

questionnaires used - Functional Assessment of Chronic Illness Therapy - Fatigue (FACT-F), Brief Pain Inventory or the Medical Outcomes Short-Form 36 pain subscale, Pittsburgh Sleep Quality Index, Center for Epidemiological Studies-Depression scale or the Patient Health Questionnaire-9 or Beck Depression Inventory, MOS SF-36 or FACT-Hepatobiliary.
 § presented as Mean ± SD for continuous and n(%) for categorical variables
 *based on clinical cut offs for BDI, PHQ, and CES-D
 **one SD below or above the mean for SF 36 Pain or BPI respectively

Conclusions: Patients with advanced CKD experienced similar levels of fatigue and poor sleep quality as those with advanced CA. Sleep, depression, and pain were significant predictors of fatigue in these chronically ill patients.

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SA-PO745

Urinary Incontinence Is Common Among Adults with Chronic Kidney Disease (CKD) and May Impact Patient Compliance with Diuretics Mitul Natu Patel, David J. Leehey, Kavitha Vellanki, Vinod K. Bansal, Julia Koval, Linda Brubaker, Neelam Balasubramanian, Jasmin Sandhu, Anuradha Wadhwa, Holly J. Kramer. *Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Background: Urgency urinary incontinence (UUI) is a stigmatized condition that may be common among adults with CKD due to the older age and high prevalence of comorbidities (obesity and diabetes) that increase risk for UUI in this population. Diuretics, which are commonly used for hypertension management, may exacerbate UUI symptoms. However, the impact of UUI on diuretic compliance has not been previously assessed in adults with CKD.

Methods: This pilot study recruited 89 adults with non-dialysis dependent stage 3-5 CKD who are prescribed diuretics for hypertension management. All participants provided written informed consent. Study participants completed the Morisky Medication Adherence Scale (MMAS), a validated questionnaire for hypertension medication compliance with scores ranging from 0 (poor adherence) to 11 (excellent adherence). Participants were asked "Do you ever avoid taking the diuretic (water pill) because it increases the urge to urinate or because it makes you urinate before reaching the toilet?" Information on UUI prevalence and nocturia was collected using standardized, validated questions for urinary symptoms.

Results: The mean age of the participants was 71 years, 54% were male and 71% were white. Overall, UUI was present in 44%, and 93% reported nocturia (waking at night to urinate) and 33% reported severe nocturia (waking 3 or more times to urinate). Overall 17% reported ever not taking their diuretic due to urinary urgency and this was significantly more frequent among those with UUI vs. those without UUI (32% vs. 6%; $P=0.002$). Compared to patients who do not avoid diuretics, patients who reported ever avoiding diuretics showed significantly lower median values of medication adherence scores (7.0 vs. 10.0; $P<0.001$) and were less likely to have a blood pressure $<140/90$ mmHg at the clinic visit (53% vs. 72%; $P<0.05$).

Conclusions: UUI is common among older adults with CKD and may negatively impact compliance with diuretics and blood pressure management.

SA-PO746

Validation of a Patient-Perceived Symptom Score for Chronic Kidney Disease Stephanie A. Brown,¹ Freya Tyrer,² Amy L. Clarke,¹ Laetitia H. Lloyd-Davies,¹ Andrew G. Stein,³ Carolyn Tarrant,² Alice C. Smith.¹ ¹Leicester Kidney Exercise Team, Univ of Leicester; Leicester, United Kingdom; ²Dept of Health Sciences, Univ of Leicester; United Kingdom; ³Univ Hospitals of Coventry and Warwickshire, United Kingdom.

Background: Chronic Kidney Disease (CKD) is associated with a range of symptoms, even at relatively early stages. There is increasing recognition of the importance of the patient symptom experience for clinical management and quality of life, but validated symptom scores are lacking. We have refined and validated an existing draft CKD symptom questionnaire listing 11 common renal symptoms plus lines for additional symptoms not included in the list.

Methods: Validation was undertaken in 4 phases. In Phase 1, 219 patients with CKD1-5 not requiring renal replacement completed the draft questionnaire to identify the most common symptoms in this population. Phase 2 explored cognitive validity via semi-structured interviews with 11 patients, after which the draft questionnaire was refined. Phase 3 was a focus group with 5 patients, to review and further refine the updated questionnaire. Phase 4 was content validity testing: the questionnaire was sent to 16 external expert clinicians for assessment of relevance, clarity and comprehensiveness.

Results: Phase 1 identified 13 common symptoms, and Phases 2 and 3 confirmed symptom selection and refined the wording used to describe them. The symptom descriptions finalised were: itching, sleep disturbance/insomnia, loss of appetite, feeling tired, pain in bones/joints, poor concentration/mental alertness, loss of libido/erectile dysfunction, loss of muscle strength/power, shortness of breath, cramp/muscle stiffness, restless legs/difficulty keeping legs still, need to urinate more often, feeling cold. In Phase 4, 14 of 16 experts responded (87.5%). 10 of the 13 symptoms had “excellent” or “good” evaluation scores, and the content validity index of the whole questionnaire was 0.81, falling within the recommended threshold.

Conclusions: This work has provided a new, validated symptom score for the early/pre-dialysis CKD population, which can be used as a patient reported outcome measure in both clinical management and research.

Funding: Private Foundation Support

SA-PO747

Impact of Psychosocial Factors in Advanced Chronic Kidney Disease on Wait-Listing for Transplantation Sanjeev Akkina, James P. Lash, Jason Roy, Boyang Chai, Michael J. Fischer, L. Lee Hamm, Peter D. Hart, Chi-yuan Hsu, Yonghong Huan, Anne M. Huml, Radhakrishna Reddy Kalleem, Manjula Kurella Tamura, Anna C. Porter, Ana C. Ricardo, Sylvia E. Rosas, Raymond R. Townsend, Peter P. Reese, Meera Nair Harhay. *CRIC Study Group Investigators.*

Background: Transplantation (Tx) is generally regarded as the best option for renal replacement therapy. However, few patients with CKD are listed for Tx when eligible. We examined the association between psychosocial factors in patients with advanced CKD and wait-listing for kidney Tx.

Methods: The study population includes 803 individuals with an eGFR of less than or equal to 20mL/min/1.73m² (advanced CKD) in the Chronic Renal Insufficiency Cohort study. The primary predictors were health related quality of life (HRQOL) and depressive symptoms assessed within 24 months prior to reaching the eGFR inclusion criteria using the Kidney Disease QOL (KDQOL)-36 survey and the Beck Depression Inventory (BDI), respectively. The primary composite outcome was wait-listing or transplantation (WLT). Cox proportional hazards models were used to examine the association between low HRQOL (¹ SD below the cohort mean) and BDI (¹¹) with WLT.

Results: Of the 803 subjects, 380 (47%) were wait-listed including 120 that proceeded to Tx. Compared to individuals who were not WLT, those in the WLT group were more likely to be younger, male, have no history of cardiovascular disease, and have proteinuria > 300mg/day (p < 0.01). After adjustment for demographic and clinical variables, a low Mental Component Summary (MCS) score was associated with a lower likelihood of WLT (Table). There was no association between the BDI or other QOL measures with WLT.

Predictor	Adjusted Model (HR, 95% CI)
BDI ≥ 11	0.88 (0.69-1.12)
KDQOL (≥1 SD below the cohort mean)	
-Mental Component Summary	0.73 (0.56-0.95)
-Physical Component Summary	0.92 (0.69-1.24)
-Symptoms/Problems	0.97 (0.71-1.32)
-Burden of Kidney Disease	0.82 (0.61-1.09)
-Effect of Kidney Disease on Daily Life	0.94 (0.69-1.28)

Conclusions: Lower MCS scores were associated with lower likelihood of WLT. Further work is needed to evaluate the impact of poor mental QOL in advanced CKD and how it might influence wait-listing.

Funding: NIDDK Support

SA-PO748

Perspectives on Pregnancy in Women with Chronic Kidney Disease Allison Tong,¹ Mark A. Brown,² Wolfgang C. Winkelmayr,³ Jonathan C. Craig,¹ Shilpa Jesudason,⁴ ¹The Univ of Sydney; ²St. George Hospital; ³Baylor College of Medicine; ⁴Royal Adelaide Hospital.

Background: Women with chronic kidney disease (CKD) often have difficulty achieving pregnancy, and are at increased risk of adverse pregnancy outcomes. Given the medical, ethical and emotional complexities of pregnancy in CKD, the clinical approach should involve explicit consideration of women’s values; of which there are sparse data. We aimed to describe the beliefs, values, and experiences of pregnancy in women with CKD, to inform pre-pregnancy counseling and pregnancy care.

Methods: Semi-structured interviews were conducted with 41 women aged 22-56 years with advanced chronic kidney disease, from two renal units in Australia. Transcripts were analyzed thematically.

Results: Six themes were identified: bodily failure (conscious of fragility, noxious self, critical timing, suspended in limbo); devastating loss (denied motherhood, disempowered by medical catastrophizing, resolving grief, barriers to parenthood alternatives, social jealousy); intransigent guilt (disappointing partners, fear of genetic transmission, respecting donor sacrifice, medical judgment); rationalizing consequential risks (choosing survival, avoiding fetal harm, responding to family protectiveness, compromising health, decisional

ownership, unjustifiable gamble); strengthening resolve (hope and opportunity, medical assurance, resolute determination, reticent hope); and reorientating focus (valuing life, gratitude in hindsight).

Conclusions: Decisions surrounding pregnancy in the context of chronic kidney disease require women to confront uncertainties about their own survival, disease progression, guilt towards their family and kidney donor, the outcomes of their offspring, and genetic transmission. Communicating the medical risks of pregnancy to women with chronic kidney disease must be carefully balanced with their values of autonomy, hope, security and family. Informed and shared decision making that is sensitive to women’s priorities as identified in this study can contribute to improved pregnancy, health and psychosocial outcomes in this vulnerable population.

SA-PO749

Nrf2 Activator, Resveratrol, Ameliorates Aging-Related Progressive Renal Injury Eun Nim Kim, In-Ae Jang, Ji Hee Lim, Min Young Kim, Byung Ha Chung, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim, Yoonsik Chang, Bum Soon Choi. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: The senescence markers of kidney have been shown to cause many changes in the energy metabolism. Two important issues in aging kidney are mitochondria dysfunction and oxidative stress. Nrf2 activator, Resveratrol may prevent inflammation and oxidative stress by activating SIRT1 and Nrf2. We examined that Resveratrol can potentially ameliorates the cellular condition, such as renal injury due to cell oxidative stress and mitochondria dysfunction caused by aging.

Methods: Male 19-month-old C57/BL6 mice were used in this study. Resveratrol (0.04%) was provided to old mice for 6month. We compared histological change, oxidative stress, and aging-related protein expression in the kidneys between Resveratrol treated old-mice group (RSV) and vehicle old-mice group (VH).

Results: In our study, expression of Nrf2 in nuclear (1 ± 0.1 fold vs. 2 ± 0.4 fold; p < 0.01 vs. VH) was increased in RSV. Expression of SIRT1 (1 ± 0.2 fold vs. 1.31 ± 0.11 fold; p < 0.05 vs. VH) was increased in RSV. p-AMPK/Total AMPK ratio expression (1 ± 0.1 fold vs. 1.79 ± 0.2 fold; p < 0.01 vs. VH) was increased in RSV compared with VH. RSV group displayed decreased albuminuria and Creatinine clearance increased with RSV. There were decreases in mesangial volume, tubulointerstitial fibrosis and collagen IV in RSV. Immunohistochemistry of F4/80 expression in glomerulus and tubule were decreased in RSV compared with VH. Also, TGF-β was decreased in RSV. Urine isoprostane and 8-OHdG excretion decreased with aging. Antioxidant enzyme, HO-1 (1 ± 0.08 fold vs. 1.6 ± 0.1 fold; p < 0.001 vs. VH) and NQO-1 (1 ± 0.06 fold vs. 1.3 ± 0.1 fold; p < 0.01 vs. VH) were increased in RSV compared with VH.

Conclusions: These results suggest that activation of Nrf2 may benefit aging-related renal injury related with SIRT1 and AMPK activation by reducing oxidative stress. Pharmacologically targeting Nrf2 signaling molecules may reduce the pathologic changes of aging in the kidney.

SA-PO750

Dual Agonist of Nuclear Hormone Receptor Farnesoid X Receptor and G Protein Coupled Receptor TGR5 Exhibits Calorie Restriction Mimetic Effects in Aging Mice Xiaoxin Wang,¹ Evgenia Dobrinskikh,¹ Yuhuan Luo,¹ Luciano Adorini,² Moshe Levi.¹ ¹Univ of Colorado Denver; ²Intercept Pharmaceutical Company.

Background: Previous studies have shown that calorie restriction (CR) in mice and in rats prevent age-related proteinuria and glomerulosclerosis. We have observed an age-related decrease in renal nuclear hormone receptor farnesoid X receptor (FXR; NR1H4), and G protein-coupled receptor TGR5 (GPBAR1 or GPR131) expression. In contrast, renal FXR and TGR5 expression are increased by CR in the aging mice. FXR and TGR5 expression are also increased in the long-lived Ames dwarf mouse. The purpose of the present study was to determine if activation of FXR and TGR5 in the kidneys of ad lib fed aging mice have similar effects to CR.

Methods: We studied 5 month old ad lib fed, 24 month old ad lib fed, 22 months old ad lib fed mice treated with the dual FXR/TGR5 agonist INT-767 for 2 months, and compared them to lifelong 24 month old CR mice.

Results: Treatment of 22 month old ad lib fed aging mice with FXR/TGR5 dual agonist INT-767 for 2 months decreases albuminuria, TGF-β expression, and fibronectin accumulation in aging mice. INT-767 stimulates mitochondrial biogenesis, increases mitochondrial DNA content, and mitochondrial transcription factors Nrf-1 and Tfam in the aging kidney. INT-767 also increases the expression of SIRT1, PGC-1α, and ERRO mRNA, as well as PGC-1α and SIRT3 protein abundance. INT-767 activation of the mitochondrial NAD-dependent deacetylase SIRT3 restores its targets MCAD and acetyl-IDH2 to normal levels, which are important for regulation of mitochondrial fatty acid β-oxidation as well as mitochondrial redox status. Furthermore, INT-767 increased expression of NAMPT and Nrk1, enzymes involved in synthesis of sirtuins substrate NAD.

Conclusions: Our results therefore indicate that activation of FXR and TGR5 in the aging kidney reverses most of the age-related changes and the effects of FXR and TGR5 are similar to beneficial effects achieved by lifelong CR.

Funding: NIDDK Support

SA-PO751

ESRD in Nonagenarians in the United States, 1995 Through 2010
 Donal J. Sexton, Scott Reule, Robert N. Foley. *Medicine, Univ of Minnesota, Minneapolis, MN.*

Background: Patients in their 90's are increasingly being considered for maintenance dialysis, comprehensive epidemiological data could help with decision making.

Methods: We used US census data and data for patients who initiated maintenance dialysis between 1995 and 2010 (N=1,557,117) to examine trends in ESRD for those aged 90 to 99 years (N=14,289).

Results: The rate of ESRD in 1995-1996 was 0.6 per million per year in those aged 90-99 years respectively. Standardized incidence ratios (SIRs) rose between 1995 and 2010 both overall (SIR 2.8), and individually in males (2.89), females (2.7) white (3.1) African American (1.93) and other races (2.43). Median survival was 10.7 months. "Unspecified renal failure" was the most common reported cause of ESRD (62.6%), followed by "diabetes mellitus type 2" (15.89%), "ATN without recovery" 3.47%, "GN (not histologically examined)" 3.18%, "renal artery stenosis" 2.44% and other 12.44%. Causes of death included; Cardiac deaths 42.4%, Infection 12.07%, Withdrawal of dialysis/Uremia 10.16%, Stroke/Intracranial Hemorrhage 3%, Cachexia 2.99%, Cancer 2.45%, Other 12.03% and Unknown 14.89%. Mortality fell over time, AHR (95% CI) 0.79 (0.72, 0.87) in 2009-2010 vs 1995-1996. Factors associated with a higher likelihood of death included; ischemic heart disease (AHR 1.13), AV graft (AHR 1.36 vs AV fistula), or venous catheter for hemodialysis vascular access (AHR 1.7 vs AV fistula), shorter pre-dialysis nephrology care (AHR 1.37), higher eGFR at dialysis initiation (AHR 1.13), serum albumin < 3.5 g/dl (AHR 1.34), cerebrovascular disease (AHR 1.21), peripheral vascular disease (AHR 1.14), cancer (AHR 1.08), inability to ambulate (1.43) or transfer (1.59), "ATN without recovery" as primary cause of ESRD (AHR 1.11 vs "renal failure not specified").

Conclusions: ESRD in nonagenarians has risen over the period of observation in the United States. Rising prevalence may be attributable not only to rising incidence but to falling mortality also.

SA-PO752

Impact of Geriatric Multi-Morbidity Versus Medical Multi-Morbidity on Quality of Life in Older CKD Patients
 Christine Liu,^{1,2} Jamie Giffuni,³ Kieran Reid,² Leslie I. Katzel,³ Stephen L. Seliger,³ Daniel E. Weiner,² Roger A. Fielding.² ¹Boston Univ, Boston, MA; ²Tufts Univ, Boston, MA; ³Univ of Maryland, Baltimore, MD.

Background: Geriatric conditions are constellations of signs and symptoms not always linked to a disease, such as cognitive impairment and fatigue; geriatric conditions are associated with worse quality of life (QoL). Older adults with CKD are likely to have geriatric multi-morbidity (GM), defined as ² geriatric conditions. Medical multi-morbidity (MM) is also common in this population and affects QoL. We compared the impact of GM to MM on QoL in older CKD patients.

Methods: We used baseline data from an ongoing trial of exercise in persons ⁵⁵ years with stage 3b-4 CKD. For GM, persons were defined with 1) cognitive impairment if Montreal Cognitive Assessment <26; 2) poor physical function if Short Physical Performance Battery \leq 7; 3) dizziness as reported by Memorial Symptom Assessment Scale; 4) fatigue if responded \geq "good bit of time" to feeling worn out on Short Form-36 (SF-36); and 5) chronic pain if \geq "moderate" pain on SF-36. For MM, hypertension, diabetes, CAD, and COPD were self-reported, and depression was defined as Beck Depression Inventory ¹⁵. QoL was measured with the SF-36. Linear regression adjusting for age, sex, race, site, BMI, and eGFR was utilized.

Results: Of 72 persons (31% women, mean age 68.6 \pm 7.8 years, mean eGFR 33.3 \pm 9.8 ml/min/1.73m²), 49% (35) had GM and 76% (55) had MM. GM was associated with lower scores in all SF-36 subdomains (all p<0.05). MM was associated with lower scores in two SF-36 subdomains (both p<0.05).

Conclusions: In older adults with CKD, geriatric multi-morbidity is common and likely affects QoL.

Standardized β s of the associations of geriatric multi-morbidity and medical multi-morbidity with SF-36				
SF-36 subdomain	Geriatric multi-morbidity	P value	Medical multi-morbidity	P value
Physical functioning	-0.519	<0.001	-0.185	0.09
Role-physical	-0.489	<0.001	-0.060	0.61
Bodily pain	-0.650	<0.001	-0.025	0.81
General health	-0.451	<0.001	-0.259	0.02
Vitality	-0.524	<0.001	-0.136	0.25
Social functioning	-0.503	<0.001	-0.077	0.49
Role-emotional	-0.289	0.02	-0.257	0.05
Mental health	-0.353	0.07	-0.106	0.41

Funding: Private Foundation Support

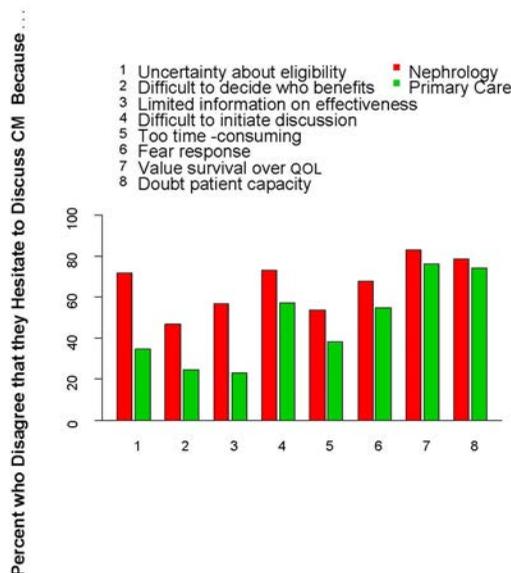
SA-PO753

A Survey of Provider Knowledge, Attitude, and Practices Surrounding Conservative Management for Patients with Advanced Chronic Kidney Disease
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Background: Despite the potential benefits of conservative management (CM), discussing CM as a viable treatment option rarely occurs. Several factors might contribute to this but no studies in the U.S. have described them. The purpose of this survey was to describe nephrologists' (NEPHs) and primary care providers' (PCPs) knowledge, attitudes, and practices of CM for patients with advanced CKD.

Methods: We developed a survey based on the relevant literature to include items assessing knowledge, attitudes, and self-reported practices of CM for patients with advanced CKD. We then conducted a web-based cross sectional survey between April and May 2015. We used the American Medical Association's Physician Masterfile to identify NEPH and PCPs practicing in the U.S.

Results: 431 (67.6% NEPHs, 32.4% PCPs) providers completed the survey. The respondents were, on average, white, predominantly male, and in their 30s and 40s. A majority of both PCP (83.5%) and NEPH respondents (78.2%) reported that they were likely to discuss CM with their older advanced CKD patients. Self-reported number of patients managed conservatively was at least >11 patients for 30.6% NEPHs and 49.2% of PCPs. As shown in the figure where a higher percent demonstrates a lower barrier, the major barriers to CM discussions identified by NEPHs and PCPs significantly differed.



There were significant differences in knowledge across the groups with PCPs reporting significantly more uncertainty about survival rates with CM.

Conclusions: Both NEPH and PCP are comfortable with discussing CM with their patients. PCPs have less certainty regarding patient selection for CM and report feeling less informed about outcomes of CM.

Funding: Pharmaceutical Company Support - DCI Inc

SA-PO754

Which Therapeutic Project for Elderly Reaching ESRD? Patient's Characteristics and Outcomes
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Background: The KDIGO guidelines recommend referral for planning RRT in people at risk of kidney failure. Treatment without dialysis in ESRD patient is another therapeutic option especially in elderly. The objective of our study is to describe the therapeutic projects declared by nephrologist and associated patient's characteristics and outcomes in a prospective design.

Methods: 573 patients over 75 y/o (82 \pm 5 y/o) with eGFR below 20 (14 \pm 4) were included by nephrologists in 2009 and followed 4 yrs (Moranne et al 2012). At baseline, we recorded social, clinical characteristics and therapeutic project declared by nephrologist. The first project was considered at the second visit as Postponed decision about dialysis (STAB), decision to start Dialysis when required (DIAL), Non-dialysis made by nephrologist (NDne) or at patient's request (NDpt). During follow-up, we evaluated the dialysis start and death before dialysis and compared patient's characteristics and incidence of these events according to the therapeutic projects.

Results: The therapeutic project was STAB in 234 patients (41%), DIAL in 216 pts (38%), NDne in 66 (12%) and NDpt in 55 (10%). Patients were older in ND group, with more women for NDpt and more comorbidities for NDne (dementia, active malignancy,

CVD, less physical autonomy). After 4 yrs follow-up, the number of death before dialysis and dialysis start were 10%/85% for DIAL, 42%/34% for STAB, 67%/20% for NDpt and 95%/2% for NDne respectively. There was significantly more emergency start for the NDpt group starting nevertheless dialysis. In all groups, the main reasons declared by nephrologist to start dialysis were: eGFR level, fluid overload and weight lost.

Conclusions: In this population, we observed many patients with stable conditions and high risk mortality which anyway raises the issue of dialysis options and care organization. Although some patients expressed their willingness not to start dialysis at one point or another, it could nonetheless occur but with worst condition. On the contrary, if the dialysis option isn't retain by the nephrologists, it will not occur.

Funding: Pharmaceutical Company Support - Roche, Baxter, Amgen, Fresenius, MSD, Shire

Agence de Biomedecine; Société Francophone de Dialyse, Government Support - Non-U.S.

SA-PO755

Specific Prognosis Factors of Death and Dialysis Start for Elderly Patients Reaching ESRD in the Prospective PSPA Cohort Study Coraline Fafin,¹ Cécile Couchoud,² Cecile M. Vigneau,³ Olivier Moranne.¹ ¹Nephrology, CHU Nice, Nice, France; ²Agence de Biomedecine, REIN, St Denis de la Plaine, France; ³Nephrology, CHU Pontchaillon, Rennes, France.

Background: The death before dialysis start is high in elderly patients reaching ESRD and the treatment without dialysis is another option. We need to better predict the outcomes of this specific population and identify prognosis factors to improve strategies of care. The objective of our study is the identification of prognosis factors of dialysis start or death before dialysis in a multicenter prospective cohort of elderly reaching ESRD.

Methods: 573 patients over 75 y/o (82±5 y/o) and with eGFR below 20 (eGFR 14 ± 4 mL/min/1.73m²) were included by nephrologist in 2009-10 (Moranne et al 2012). At baseline, we recorded social and clinical characteristics, laboratory test and medications. Information about death or dialysis status is available for all patients after 4 years follow-up. Prognosis factors for dialysis start or death before dialysis were quantified with subdistribution hazard ratios using proportional hazard regression models constructed according to Fine and Gray to take account competing risks.

Results: After 4 yrs follow-up, 274 patients (48%) started dialysis and 223 (39%) died. Compared to patient still alive without dialysis, the variables independently associated with higher risk of death prior to dialysis are: higher age, male, diabetes, lower eGFR, behavioural disorder, less mobility, cerebrovascular disease, cardiac heart failure, active malignancy and anemia. The variables associated to higher probability of dialysis start are: lower age, male, lower eGFR, high blood pressure, hyperphosphatemia, higher proteinuria, chronic respiratory disease, cerebrovascular disease and less behavioural disorder or active malignancy.

Conclusions: We observed a higher probability of dialysis start than death before dialysis in this population of elders included by nephrologists. We identified specific prognosis factors that could discriminate the risk of starting dialysis or died before dialysis to help organisation of the CKD 5 care in elderly patients.

Funding: Pharmaceutical Company Support - roche baxter amgen fresenius msd shire

SA-PO756

Ageing and Decreased GFR: A 1,249,388 Elderly Population-Based Study Regina C.R.M. Abdulkader,¹ Emmanuel A. Burdman,¹ Yeda Aparecida Oliveira Duarte,² Maria Lucia Lebrão,³ Dirce M.T. Zanetta.² ¹Div of Nephrology, Univ of Sao Paulo Medical School, Sao Paulo, SP, Brazil; ²Epidemiology, School of Public Health of the Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: GFR decreases with ageing and so a low GFR in old people might occur due to a physiologic process instead of being a mark of disease. However, comorbidities can superimpose on this process, and reduce GFR by a pathologic course. This study aims to assess the frequency of isolated low GFR without coincident diseases in a geriatric population in a developing country megalopolis.

Methods: A multistage cluster sampling (1,353 inhabitants) was used in order to obtain a sample representative of the elderly population of São Paulo megalopolis (1,249,388 inhabitants aged ≥60 years). Participants answered a survey on socio-demographic factors and health and had urine and blood samples collected. GFR < 60 mL/min/1.73m² (estimated by the abbreviated MDRD equation) was defined as low and presence of hematuria or proteinuria as kidney damage. Data are presented as weighted proportion or means and standard errors. Comparisons were made by chi-square with Rao-Scott correction or t-test.

Results: Individuals with GFR < 60 (19.8%) were older (75 ± 1 vs. 69 ± 1 y, p<0.001), had lower education level, more hypertension, diabetes and cardio-vascular disease and more kidney damage (35% vs 15%, p<0.001), when compared with the group with GFR ≥ 60. In the low GFR group only 25% of the individuals had no simultaneous diseases and no kidney damage.

Conclusions: Low GFR was associated with kidney damage and/or coincident chronic diseases that might affect the kidneys in this population. These data strongly suggest that in this group of geriatric individuals low GFR is indicative of renal disease. **Funding:** Government Support - Non-U.S (FAPESP, Ministério da Saúde, Brasil).

Funding: Government Support - Non-U.S.

SA-PO757

Indoxyl Sulfate, a Representative Uremic Toxin, Suppresses Myogenic Differentiation: Implication in Uremic Sarcopenia Chih-Kang Chiang,^{1,2} Un Iong Ao,¹ Yuan-Siao Chen,^{1,2} Shing-Hwa Liu.¹ ¹Inst of Toxicology, College of Medicine, National Taiwan Univ, Taipei, Taiwan; ²Depts of Integrated Diagnostics and Therapeutics and Internal Medicine, College of Medicine, National Taiwan Univ, Taipei, Taiwan.

Background: Sarcopenia (or muscle wasting) is a common feature of the uremic phenotype and predisposes this vulnerable patient population to increased risk of comorbid complications, poor quality of life, frailty and premature death. Accumulation of uremic toxin would be the most significant difference between health and uremic subjects. We hypothesized that indoxyl sulfate (IS), a representative protein-bound uremic toxin, might disturb skeletal myotube differentiation and contribute to sarcopenia in uremic patients.

Methods: The mouse myoblast cell line C2C12 was applied to evaluate myotube differentiation and signaling. Cell viability evaluated by MTT assay. Cell morphology was observed by microscope. Hematoxylin and eosin staining morphologically analyzed the multinucleated myotube formation. The expressions of myogenic differentiation markers and related signaling proteins were determined by Western blotting.

Results: We first investigated the non-lethal concentration of IS by MTT assay, and found IS level less than 1mM without significant cellular toxicity as compared with control group. In order to development the protocol, we confirmed myotubes were visibly formed throughout 4 days of differentiation first. IS significantly attenuated the number of myotubes and the percentage of mature myotubes. Furthermore, IS significantly and dose-dependently decreased the expression of MyoD, Myogenin and myosin heavy chain, which is the representative markers of slow and fast myofiber phenotype, both in translational and transcriptional level. The molecular signals of myotube differentiation were also disturbed by IS treatment.

Conclusions: These findings suggest that IS, a uremic toxin, dysregulates myotube differentiation in C2C12 cells. This is the first time to provide additional evidence that IS might contribute to the development of sarcopenia in uremic patients. Further explore would give the light to provide potential therapeutics in uremic sarcopenia.

Funding: Other NIH Support - MOST in Taiwan

SA-PO758

Attitudes, Experiences and Perspectives of Elderly Kidney Transplant Recipients: Thematic Synthesis of Qualitative Research Jule Pinter,¹ Camilla Sara Hanson,¹ Jonathan C. Craig,¹ Jeremy R. Chapman,¹ Klemens Budde,² Fabian Halleck,² Allison Tong.¹ ¹Univ of Sydney; ²Charité - Universitätsmedizin Berlin.

Background: Kidney transplantation offers improved survival and quality of life in an increasing number of elderly patients with end-stage kidney disease. However, elderly kidney transplant recipients may face unique challenges due to a higher burden of comorbidity, greater cumulative risk of immunosuppression-related complications, and increasing frailty. We aimed to describe the perspectives of elderly kidney transplant recipients.

Methods: Electronic databases were searched to April 2015. Thematic synthesis was used to analyze the findings.

Results: 41 studies involving more than 120 kidney transplant recipients aged 60 yrs and over were included (29 studies did not specify number of patients aged ≥ 60 yrs). We identified 6 themes. *Regaining strength and vitality* meant valuing the marked physical and psychosocial improvements in daily functioning and life participation. *Extending life* was the willingness to accept an organ, including an extended criteria kidney, to prolong survival. *Debt of gratitude* entailed a need to be consciously appreciative towards their donor whilst knowing they were unable to repay their sacrifice. *Moral responsibility of maintaining health* motivated adherence to medication and lifestyle recommendations out of an ethical duty to protect their gift and prolong graft survival. *Disillusionment with transplant* reflected disappointment and exasperation at having to contend with *side effects and adverse events* such as cancer, and residual physical limitations. *Finality of treatment option* reflected an acute awareness that their current transplant may be their last and some would not return to dialysis if the transplant failed.

Conclusions: Kidney transplantation reverses deterioration of functioning and well-being that patients experienced whilst on dialysis. However, elderly transplant recipients may have anxieties about debilitating adverse events, comorbidities, and a sense of vulnerability that the current transplant may be their last. Addressing these concerns in the care of elderly kidney transplant recipients may improve treatment outcomes in this growing population.

SA-PO759

New Perspectives on the Evolution of Quality of Life and Depression Among Hemodialysis Patients Christiane Hegedus Karam, Nadia Guimaraes-Souza, Adriano Luiz Ammirati, Maria C.C. Andreoli, Thais Nemoto Matsui, Fabiana Dias Carneiro, Rosana Cardoso, Ana Merzel Kernkraut, Bento C. Santos. Nephrology, Hospital Albert Einstein, São Paulo, Brazil.

Background: Hemodialysis is the most common treatment for patients with chronic kidney disease. Five to 22% of those also have a psychiatric condition. The objective of this study was to evaluate the quality of live perception and depression symptoms in three groups of age (<65, 65-75, e >65 y.o.).

Methods: This was a retrospective observational study. Clinical and social demographic data were collected from clinical records. The Kidney Disease Quality of Life and Beck depression inventory were used to assess quality of life and depression symptoms.

Results: 104 patients were included. 68.3% were man, 71.2% married, 91.3% Caucasian and 44.2% were in productive life period. A relation between quality of life-score and time in dialysis was observed (p=0.0118, CI -0.0023; 0.0003). Patients younger than 65 y.o. showed more favorable results, such as general health perceptions, emotional well-being, energy/fatigue, pain and dialysis staff encouragement. Patients between 65 to 75 y.o. showed lower energy/fatigue index (11.98; CI -22.93; -1.02) and a reduction of 18.97-points (IC -33.97; -3.98) for emotional well-being. A 15.04-point (CI -27.21; -2.87) and a 14.78-point (-26.46; -3.10) reduction, for patients between 65-75 y.o. and for older than 75 years, respectively, was observed in physical function. Burden of kidney disease had a reduction of 13.29 (-25.40; -1.18) and sexual function reduced 69% (27%; 87%) in 65-75 y.o. patients. Patients older than 75 years had a significant increase in quality of social interaction (17%; CI: 1%;36%) and an increase of 16% (CI 3% -30%) in social support. Depression correlated with time in hemodialysis (p = 0.0007; CI 0.14%; 0.55%). For each month an increase of 0.35% on depression symptoms was found.

Conclusions: For patients younger than 65 years hemodialysis treatment represents a rehabilitation possibility. Patients over 75 years had significant increase on social support and social interaction. Patients 65 to 75 y.o. had worse perception of quality of life.

SA-PO760

Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults: The Cardiovascular Health Study Kristen L. Nowak,¹ Traci M. Bartz,² Lorien S. Dalrymple,³ Joachim H. Ix,⁴ Ian H. De Boer,² Bryan R. Kestenbaum,² Michael Shlipak,⁵ Pranav S. Garimella,⁶ Michel Chonchol.¹ ¹Univ of Colorado Denver; ²Univ of Washington; ³Univ of California Davis; ⁴Univ of California San Diego; ⁵Univ of California San Francisco; ⁶Tufts Medical Center.

Background: Fibroblast growth factor 23 (FGF23) may inhibit 25-hydroxyvitamin-D-1 α -hydroxylase (CYP27B1) in monocytes. We hypothesized that higher circulating FGF23 would lead to an increase in serious infection risk because FGF23 decreases the intracrine production of 1,25-dihydroxyvitamin D (1,25(OH)₂D), which consequently reduces production of cathelicidins.

Methods: Plasma C-terminal FGF23 concentrations were measured in 3141 Cardiovascular Health Study participants. Cox proportional-hazards models were used to examine the association between FGF23 levels and the first infection-related hospitalization (multivariable models adjusted for demographics, co-existing illnesses, body mass index, tobacco use, albumin, estimated glomerular filtration rate, urine albumin creatinine ratio, C-reactive protein, and IL-6). We tested whether associations differed by the presence of chronic kidney disease (CKD) (eGFR; >60 [n=2309] or ≤60 ml/min/1.73m² [n=832]).

Results: Participants were 78±5 years, 60% females, and the median serum FGF23 level was 70 [IQR 53, 99] pg/mL. During a median follow-up of 15.7 years, 1162 (37%) had an infection-related hospitalization. In the adjusted models, participants in the highest quartile of FGF23 (compared to the lowest) had a higher risk of infection (hazard ratio [HR] 1.33; 95% confidence interval [95% CI], 1.10-1.60). The association was stronger for those participants with CKD (HR 1.27; 95% CI 1.11-1.46 per doubling of FGF23) than in those without CKD (HR 1.07; 95% CI 0.98-1.17 per doubling of FGF23; p-value for interaction: 0.06). The addition of serum calcium, phosphorus, vitamin D and PTH into the statistical models did not attenuate these associations.

Conclusions: In ambulatory elders, higher serum FGF23 levels were independently associated with the risk of first infection-related hospitalization. This association appeared stronger in the setting of CKD.

SA-PO761

Characteristic of the Elderly Patients in the Chronic Renal Insufficiency Standards Implementation Study (CRISIS) Cohort Compared to Their Younger Cohort A Descriptive Analysis Maharajan Raman, Darren Green, James Ritchie, Thilini Nishani Abeygunaratne, Smeeta Sinha, Philip A. Kalra. *Renal Medicine, Salford Royal NHS Foundation Trust, Salford, Manchester, United Kingdom.*

Background: CKD in the Elderly is associated with high mortality and slower rate of progression to ESRD. Identifying the characteristics of this phenotype and modifying their risk may reduce the burden of death but this can be challenging due to the heterogeneity of the disease in this group.

Methods: The CRISIS cohort of 2706 participants was divided into four groups based on their age. Descriptive statistical analysis was performed using SPSS and in between group significance was calculated using one way ANOVA or Chi-Square test.

Results: Essential characteristics of the cohort are shown in the table below.

	<55years	55- <65years	65- <75years	>75years	P value
Number	644	507	823	732	
Age*(years)	43.2± 8.9	60.5± 2.8	70± 2.8	80.2± 3.7	0.000
Male(%)	56.4	63.9	64	64.5	-
Current Smoker(%)	19.7	15	12.2	5.2	-
Systolic Blood Pressure*	131.6± 22.9	138.2± 22.4	141.2± 23.6	141.59± 25.7	0.000
eGFR(ml/min/1.73m²)*	35.9± 19.0	34± 17.7	32± 16.4	28.7± 13.2	0.000
Urine PCR(mg/mmol)*	119.4± 201.5	89.8± 189.4	70.3± 147	55.7± 113.8	0.000
Primary Renal Disease(%)					
Hypertension	5.3	10.1	14.1	19.9	
ARVD	3	7.5	14.8	21	
Diabetes	14.8	20.1	19.9	13.3	
Obstructive Uropathy	0.8	1.4	1.3	2	
Glomerulonephritis	25.8	20.7	12.4	7.5	
Pyelonephritis	12	4.7	4	2.9	
APKD	12.6	5.1	2.6	1.1	
Other	17.4	17.9	15.9	11.7	
Unknown	8.2	12.4	14.8	20.5	
Medications(%)					
1. RAS Blockade					
Dual	9.6	9.5	4.9	3.4	
Single	61	54.6	57.1	50	
None	27	34.7	37.7	45.6	
2. Beta Blocker	31.8	36.5	42.3	40	
3. Calcium Channel Blocker	45	56.4	56.5	54.2	
4. Statin	44.6	62.1	70.2	61.6	
5. No Blood Thinners	71.4	52.5	41.2	32.9	
Renal Replacement Therapy(%)	32.1	20.8	14.3	6.6	0.000
Death(%)	11.1	21.8	42.2	52.5	0.000
Co-Morbidity(%)					
>1 Vascular co-morbidity	3.3	12.2	19.8	22.6	0.000
>1 Non-Vascular co-morbidity	2.8	7	5.5	7.7	0.001
Diabetes	19.2	37.2	39	33.2	0.000

*mean±SD

Conclusions: The group aged >75 years had the highest incidence of death and accumulation of co-morbidities. We aim to develop a risk prediction model to identify the characteristics of this phenotype, which may help in modifying their risk.

SA-PO762

Muscle Strength Rather Than Muscle Mass Is More Important in Evaluating Physical Function in Elderly Patients with Predialysis Chronic Kidney Disease Yasuhiro Taki,¹ Koji Hiraki,² Keita Uehara,¹ Hiroo Kawarazaki,¹ Tsutomu Sakurada,¹ Yugo Shibagaki.¹ ¹Dept of Nephrology and Hypertension, St. Marianna School of Medicine, Kawasaki, Kanagawa, Japan; ²Dept of Rehabilitation Medicine, St. Marianna School of Medicine, Kawasaki, Kanagawa, Japan.

Background: Recently, physical function has been reported to be strongly associated with prognosis of patients with chronic kidney disease (CKD). Sarcopenia is well described in CKD patients on dialysis especially of the elderly and is known to be associated with reduced physical function, but whether this is the case in elderly predialysis CKD is undetermined.

Methods: We enrolled consecutive 85 elderly patients (age over 60) with predialysis CKD (estimated GFR:eGFR < 60 ml/min/1.73m²) in outpatient nephrology clinic at St Marianna University Hospital. We evaluated kidney functional parameters, muscle mass by bioimpedance, muscle strength by dynamometer (hand grip, knee extension) and 4-meter walking speed in these participants.

Results: Average age was 74 years old, 76% were men, 33% had diabetes mellitus (DM) and average eGFR was 28.6ml/min/1.73m². Patients were divided into those with eGFR<30 or >30. After adjustment for age, gender and history of DM, hand grip strength (-4.36, 95%CI:-0.85--7.85), knee extension strength (-5.62, 95%CI:-2.28--8.97) and 4-meter walking speed (-0.12, 95%CI:-0.02--0.22) were significantly reduced in those with eGFR<30. However, there was no difference in muscle mass (-0.23, 95%CI:-0.68--0.23).

Conclusions: In conclusion, muscle strength and walking speed but not muscle mass declined along with progression of CKD. Thus, it seemed more important to check muscle strength and walking speed rather than muscle mass when evaluating physical function in elderly patients with predialysis CKD.

SA-PO763

Lower Muscle Endurance, Strength and Quality Are Associated with Greater Risk of Functional Limitations in Older Adults with CKD Baback Roshanravan,¹ Kushang V. Patel,³ Linda F. Fried,² Ian H. De Boer,¹ Cassianne Robinson-Cohen,¹ Anne B. Newman,² Bryan R. Kestenbaum.¹
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Background: Chronic kidney disease is associated with inflammation and insulin resistance contributing to fatigue and muscle weakness. The association of muscle endurance, strength, and quality with functional limitation among persons with CKD is unknown.

Methods: We studied 186 participants with eGFR_{creys}<60 at the year 3 Health ABC visit. Participants were excluded if unable to complete >90% of quadriceps isokinetic fatigue testing. Quadriceps endurance was defined by total work using isokinetic dynamometer. Quadriceps strength was measured by isometric torque. Leg lean mass (leglm) was measured using DXA. Muscle quality was defined by specific work (work/leglm) and specific torque (torque/leglm). Outcome was incident persistent severe lower extremity limitation (PSLL) based on 2 consecutive reports of having a lot of difficulty or inability to walk 1/4 mile or climb 10 steps without resting. We used competing risks regression.

Results: Participants had a mean age 76.2 ±3yrs, eGFR_{creys} of 49.2 ±10. None had mobility disability. There were 82 PSLL events over a median 6 years. After adjustment each 1-SD lower quadriceps isokinetic work and isometric maximal torque were associated with a 1.38 fold (95% CI 1.04, 1.85, P=0.028) and 1.43 fold (95% CI 1.01, 2.03 P=0.045) greater risk of PSLL, respectively. Leg lean mass was not associated with PSLL (P=0.12).

	Unadjusted SHR	Adjusted SHR
Isokinetic Work (Joules)	1.26 (0.99, 1.61)	1.38 (1.04, 1.85)*
Specific work (Joules/kg)	1.32 (1.06, 1.64)*	1.38 (1.09, 1.76)*
Isometric Torque (N*m)	1.37 (1.04, 1.79)*	1.43 (1.01, 2.03)*
Specific Torque (N*m/kg)	1.46 (1.10, 1.94)*	1.42 (1.04, 1.93)*
Per 1-SD difference Adjusted for demographics, comorbidity, activity, cognitive function, statins & bicarbonate, ±leg lean mass *P<0.05, +P<0.01		

Conclusions: Among older adults with CKD free of mobility disability, lower muscle endurance, strength, and quality are independently associated with greater risk of severe lower extremity limitation.

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SA-PO764

Efficacy and Safety of Exercise Training in Patients with Predialysis Chronic Kidney Disease Yugo Shibagaki,¹ Koji Hiraki,² Takashi Yasuda,¹ Kenjiro Kimura.¹ ¹Div of Nephrology and Hypertension, St. Marianna Univ; ²Div of Rehabilitation, St. Marianna Univ.

Background: Efficacy and safety of exercise training has not been well studied in patients with predialysis chronic kidney disease (CKD). Since we have reported in elderly patients with predialysis CKD that there was a significant reduction in muscle strength and short-term exercise did not damage kidney, we conducted a randomized controlled trial to elucidate the long-term efficacy and safety of exercise in this population.

Methods: Study design was a randomized controlled trial. Thirty six male elderly patients with CKD stage 3-4 seen at the outpatient nephrology clinic at St. Marianna University Hospital agreed to participate in the study with written informed consent. We randomly divided them into intervention (I) group and control (C) group. Patients with I group were advised to walk fast for 30 minutes a day or 10,000 foot steps a day and was trained to do muscle training for upper/lower extremities at every clinic visit for 12 months. Patients with C group did not received exercise advice. Both groups received conventional drug therapy for CKD and were checked the daily foot steps by pedometer. Primary outcome was the change in estimated glomerular filtration rate (eGFR) and secondary outcomes were the changes in muscle strengths by dynamometer (hand grip and knee extension).

Results: There were no difference in baseline characteristics (demographic, kidney functional parameter, hemoglobin and serum albumin level) with average age of 68.7±6.8 years and eGFR of 39.0±11.6 ml/min/1.73m². Change in eGFR were not different at 12 months among both groups. Muscle strength in knee extension increased in I group (0.65±0.17kgf to 0.70±0.17kgf in knee extension) but not in C group (0.66±0.15 to 0.62±0.13kgf) (0.65±0.17kgf to 0.70±0.17kgf in knee extension) but not in C group (0.66±0.15 to 0.62±0.13kgf), which showed statistically significant difference. Change in muscle strength in hand grip also showed the difference between the groups.

Conclusions: Only the advise on exercise training could increase the physical activity and muscle strength without compromising kidney function in the elderly patients with predialysis CKD.

SA-PO765

Determinants of Impaired Cardiorespiratory Fitness in Older Adults with CKD Stephen L. Seliger,^{1,2} Jamie Giffuni,² Roger A. Fielding,³ Eamon F. Fleming,³ Christine Liu,^{4,6} Leslie I. Katzel,^{1,2} Kieran Reid,³ Sushrut S. Waikar,⁵ Andrew M. Well,⁶ Daniel E. Weiner.³ ¹Medicine, U Maryland Sch of Medicine; ²GRECC, VA Maryland Healthcare System; ³Tufts Univ Sch of Medicine; ⁴Boston Univ Sch of Medicine; ⁵Brigham and Women's Hospital; ⁶Emory Univ School of Medicine.

Background: Chronic Kidney Disease (CKD) may be associated with impaired cardiorespiratory fitness (CRF). We examined methods of estimating CRF in CKD and identified factors associated with CRF.

Methods: We measured peak aerobic capacity (VO₂peak) using a modified Graded Exercise Treadmill Test (GXT) in 71 older adults with CKD stage 3b-4 in an ongoing exercise clinical trial. GFR was estimated with the CKD-Epi equation. Linear regression was used to examine factors associated with VO₂peak. Resting VO₂ was measured prior to GXT in seated position. Metabolic Equivalents of Task (MET, oxygen consumption during exercise relative to rest) was estimated at peak exercise based on GXT stage and compared to actual achieved METS.

Results: Mean age was 68.4±7.7 years, with 61% African-Americans, 30% women; mean eGFR was 33±11 ml/min/1.73m² and mean Hb 12.3±1.6 g/dL. Mean VO₂peak was 17.4±5.4 ml/kg/min, which was 31±17% lower than expected based on normative values (p<0.001). In a multivariate model including demographics and co-morbidity, lower hemoglobin - but not GFR - was associated with lower VO₂peak (Table). Albuminuria did not correlate with VO₂peak.

Covariate	Standardized β	p-value
Age	-0.25	0.005
African-American	0.08	0.3
Male	0.41	<.001
Diabetes	0.01	0.9
Cardiac Disease	-0.25	.002
Body Mass Index	-0.47	<.001
GFR	0.09	0.3
Hemoglobin	0.19	0.025

Estimated METS: Mean achieved METS was 5.6±1.8. Although there was low bias for estimated vs. achieved METS (mean difference, -0.45), precision and accuracy were poor, with only 35% of predicted values within 1 MET of achieved values, and nearly one third of estimated values >30% different from achieved.

Conclusions: Among older adults with CKD stage, CRF as reflected by VO₂peak is markedly impaired. Lower hemoglobin, obesity, and prevalent cardiac disease are associated with worse aerobic capacity. The use of estimated METS during treadmill testing poorly estimates actual aerobic capacity.

Funding: NIDDK Support, Veterans Administration Support

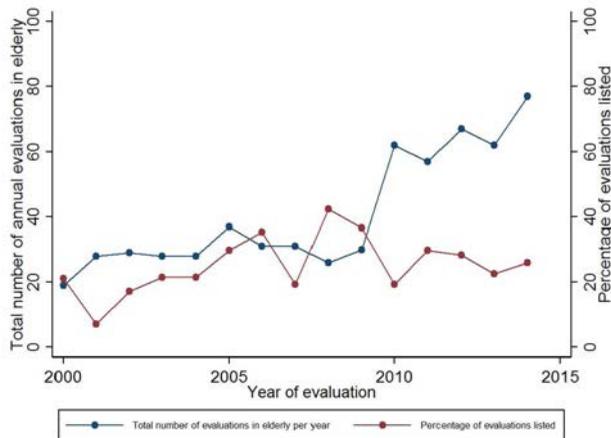
SA-PO766

Access to Kidney Transplantation and Outcomes of Those Listed for Kidney Transplant in Elderly Pritika Shrivastava, Ankit Sakhuja, Diane M. Cibrik, Abhijit S. Naik. Div of Transplant Nephrology, U Michigan, Ann Arbor, MI.

Background: Data suggests that patients above 70 years of age (>70 y.o.) with ESRD derive a benefit from kidney transplant (KT). We report our single center experience of access to transplant and outcomes for those >70 y.o. listed for KT. We used the number of evaluations in a year and rate of acceptance after evaluation as surrogate markers for KT access in elderly.

Methods: We assessed the rate of acceptance for KT and its trends over the years for those >70 y. o. between 2000-2014. Linear regression was used to assess trends over time. Differences in rates of listing stratified by diabetes status, KT rates among those approved for listing by diabetes status and mortality among those transplanted vs waitlisted was assessed.

Results: Over 15 year period, we evaluated 612 elderly patients (pts). 25.3% of those evaluated were approved to be listed for transplant. There were 9 patients who were evaluated twice of those 5 were approved for listing the second time and two got transplanted. There was 300% increase in annual evaluation of the elderly from year 2000 to 2014 and trend towards increased acceptance rate of those evaluated (slope=+0.82, p=0.12).



The acceptance rate was lower in diabetics compared to non-diabetics (18.2% vs 32.0%; p=0.001). 38.0% of listed pts have been transplanted and the rate of transplant did not differ by diabetes status. Of those transplanted 59.3% had living donors. Mortality among those transplanted was 64.4% in comparison to 87.3% of those waitlisted (p=0.001).

Conclusions: Only a fourth of those >70 evaluated for KT were accepted for listing, though there has been some improvement in the acceptance rate for listing over time. Acceptance rate was significantly lower among elderly diabetics. Mortality though improved remained significantly high for transplant vs waitlisted patients.

SA-PO767

P-Cystatin C Improves GFR Estimation in Older People Karin Werner,¹ Anders G. Christensson,² Mats Pihlgård,¹ Sölve Elmståhl.¹ ¹Dept of Geriatrics, Lund Univ, Malmö, Sweden; ²Dept of Nephrology and Transplantation, Lund Univ, Malmö, Sweden.

Background: There is a need for validation of commonly used cystatin C and creatinine based formulas for eGFR (estimated glomerular filtration rate) in the older segment of the general population for all levels of kidney function.

Methods: Markers used for eGFR estimation were P-Cystatin C and P-Creatinine. Measured GFR (mGFR) adjusted to body surface area was performed by a single sample iohexol clearance in 112 participants, aged 70-100 years old from the population-based cohort "Good Aging in Skåne". The participants were selected to cover a wide range of kidney function and to obtain an even distribution regarding sex and age. The timing of the sample depended on eGFR (eGFR >50, 25-50, and <25 at 4, 7, and 24 hours respectively). Formulas using both markers (CKD EPI combined, Lund-Malmö combined, BIS2), only creatinine (CKD EPI creatinine, MDRD) and only cystatin C (CKD EPI cystatin C) were compared. The analysis included bias (median difference: mGFR-eGFR), precision (IQR: interquartile range of the differences), accuracy (P30: percentage of estimates ±30% of mGFR) as well as accuracy (P30) above and below mGFR 45.

Results: There were 57 women and 55 men. Mean age was 82 years and mean GFR 55 ml/min per 1.73m². Results are presented in the table.

eGFR	CKD-EPI comb	Lund-Malmö	BIS2	CKD-EPI creatinine	MDRD	CKD-EPI cystatin C
Median difference (ml/min per 1.73m ²)	3.3	4.2	6.1	-0.5	2.9	6.1
IQR (ml/min per 1.73m ²)	7.9	8.4	12.6	10.5	11.6	8.8
% P30	96	95	94	86	84	93
% P30 mGFR>45	99	96	93	92	91	92
% P30 mGFR<45	92	92	95	73	70	95

Conclusions: All the formulas that include cystatin C performed well in this Swedish cohort with a mean age above 80. This confirms that it is safe to use either of those formulas in our older patients across a wide spectrum of kidney function. However, the formulas based solely on creatinine are not reliable enough below GFR 45. Further sub-analysis can demonstrate detailed performance for males and females respectively, for all CKD-stages and for smaller age-intervals.

Funding: Government Support - Non-U.S.

SA-PO768

Factors Associated with Early Death After Dialysis Initiation Among Elderly CKD Patients Fahad Saeed, Susana Arrigain, Jesse D. Schold, Joseph V. Nally, Sankar D. Navaneethan. *Nephrology, Cleveland Clinic.*

Background: There are limited studies examining prognosis for elderly CKD patients following dialysis initiation. Herein, we evaluated the factors associated with poor one year survival after dialysis initiation among elderly CKD patients at our institution.

Methods: We studied 621 CKD patients ≥65 years from an EMR based CKD registry linked to the USRDS data. We retrospectively analyzed factors associated with one year mortality after dialysis initiation including: age, sex, race, presence of diabetes, hypertension, BMI, stroke, CHF, COPD, malignancy, peripheral vascular disease, depression, alcohol use, smoking, presence of AVF, pre-dialysis serum albumin and potassium.

Results: In our study, 224 (36%) patients died within the first year of dialysis initiation. Results from the Cox proportional model showed that older age and CHF were associated with early deaths, while higher albumin, presence of AVF and HTN were associated with a lower hazard of early death.

Conclusions: CHF and older age in the pre-dialysis setting are associated with higher 1-year mortality after dialysis initiation. These prognostic data need to be presented to geriatric CKD patients while discussing renal replacement therapy options.

Table. Multivariable Cox model of 1 year mortality among elderly CKD patients

Parameter	Hazard Ratio (95%CI)
Age per 1 year increase	1.05 (1.03, 1.07)
Male sex vs. female	1.16 (0.87, 1.55)
African American vs. not	0.82 (0.58, 1.16)
Smoke	
no	Ref
Yes	1.15 (0.64, 2.07)
Missing	1.26 (0.67, 2.36)
BMI	
<18.5 kg/m ²	2.22 (0.85, 5.76)
18.5-25 kg/m ²	Ref
25-29.9 kg/m ²	0.74 (0.52, 1.06)
30+ kg/m ²	0.87 (0.60, 1.27)
Missing BMI	0.44 (0.22, 0.88)
Diabetes mellitus	1.18 (0.86, 1.63)
Hypertension	0.71 (0.45, 1.11)
Cerebrovascular disease	0.96 (0.64, 1.42)
COPD	0.82 (0.44, 1.53)
CHF	1.76 (1.27, 2.45)
CAD	1.00 (0.72, 1.39)
Malignancy	1.20 (0.86, 1.67)
PVD	0.65 (0.32, 1.29)
Alcohol use	
No	Ref
Yes	0.73 (0.52, 1.04)
Missing	0.98 (0.57, 1.69)
Depression	0.69 (0.37, 1.30)
Albumin (g/dl) per 1 unit increase	0.75 (0.59, 0.96)
Potassium (meq/l) per 1 unit increase	0.92 (0.74, 1.13)
AVF access	
No AVF	Ref
AVF present	0.35 (0.20, 0.61)
Missing	0.72 (0.45, 1.16)

SA-PO769

Differential Significance of Prognostic Factors for 6-Month and 3-Year Mortality in Elderly Patients on Hemodialysis Koji Harada,¹ Azusa Izumiya,¹ Tomohiro Kawamura,¹ Juri Tsukahara,¹ Koichi Sumida,¹ Yukinari Yamaguchi,¹ Yasuhiro Akai.² ¹Dept of Nephrology, Rakuwakai-Otowa Hospital, Yamashina, Kyoto, Japan; ²Center for Postgraduate Training, Nara Medical Univ, Kashihara, Nara, Japan.

Background: As the population of elderly people has been growing, the number of older chronic kidney disease patients commencing renal replacement therapy (RRT) is increasing. The survival advantage of RRT may be counterbalanced by the burden of treatment and its negative effect on quality of life in the elderly, and old age is no longer seen as a contraindication to RRT. Therefore, it is important to evaluate survival factors in this population. We conducted this study to investigate prognostic factors for mortality in elderly patients starting hemodialysis (HD) for end-stage renal disease (ESRD).

Methods: This is a single-center, retrospective cohort study from January 2009 to December 2014. In total, 90 ESRD patients commencing HD were enrolled. All the patients were aged 65 years or older. Six-month and 3-year survival rates and prognostic factors for mortality were evaluated.

Results: The mean follow-up period was 21.7±18.3 months. The 6-month and 3-year survival rate were 94.0% and 66.9%, respectively. Age, unplanned initiation of HD, presence of heart failure, high value of estimated GFR on starting HD, Charlson comorbidity index (CCI), and Eastern Cooperative Oncology Group Performance Status scale (ECOG-PS) were associated with 3-year mortality, whereas only the presence of heart failure and ECOG-PS were significant predictors of 6-month mortality. There was no significant difference in 6-month mortality rate between patients aged ≥ 80 and < 80. On the other hand, 3-year mortality rate of ≥ 80 year-old patients was significantly higher than that of < 80 (≥ 80: 53.3% vs < 80: 14.2%, p = 0.0004).

Conclusions: There is a variation of significance among different prognostic factors according to the duration of life after starting hemodialysis. The presence of heart failure and ECOG-PS predicted short-term mortality among elderly ESRD patients starting HD. These results might help clinical decision making when nephrologists consider commencing HD for elderly ESRD patients.

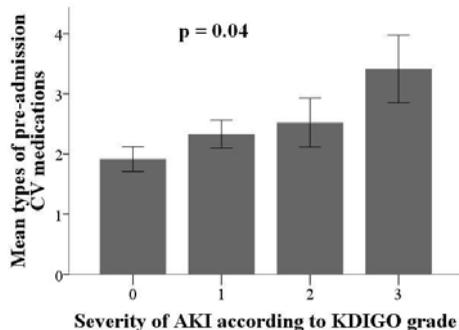
SA-PO770

Cumulative Cardiovascular Polypharmacy Is Associated with the Risk of Geriatric Acute Kidney Injury Chia-Ter Chao,¹ Hung-Bin Tsai.² ¹Dept of Medicine, National Taiwan Univ Hospital Jin-Shan Branch, New Taipei City, Taiwan; ²Dept of Traumatology, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Polypharmacy is common in the elderly due to multiple morbidities. However, the effect of polypharmacy on renal outcomes is rarely recognized. We investigated the effect of cardiovascular polypharmacy on acute kidney injury (AKI) in elderly patients.

Methods: We used the Taiwan National Health Insurance PharmaCloud system to investigate the relationship between cumulative cardiovascular medications in the 3 months prior to admission and risk of AKI in the elderly at admission to general wards. Community-dwelling elderly patients (>60 years) were prospectively enrolled and classified according to the number of pre-admission cardiovascular medications. Cardiovascular polypharmacy was defined as use of 2 or more relevant medications.

Results: We enrolled 152 patients, 48% with AKI (based upon Kidney Disease Improving Global Outcomes [KDIGO] classification) and 64% with cardiovascular polypharmacy. The incidence of AKI was higher in patients taking more cardiovascular medications (0 drugs: 33%; 1 drug: 50%; 2 drugs: 57%; 3 or more: 60%; p = 0.048). Patients with higher KDIGO grades also took more cardiovascular medications (p = 0.04).



Multiple regression analysis showed that patients who used 1 or more cardiovascular medications had increased risk of AKI at admission (1 drug: odds ratio [OR] = 1.63, p = 0.2; 2 drugs: OR = 4.74, p = 0.03; 3 or more drugs: OR = 5.92, p = 0.02), and that cardiovascular polypharmacy increased the risk of AKI (OR 2.58; p = 0.02). Each additional cardiovascular medication increased the risk for AKI by 30%.

Conclusions: We found that elderly patients taking more cardiovascular medications had increased risk for adverse renal events. Interventions that reduce polypharmacy may be able to reduce the incidence of geriatric AKI.

SA-PO771

Low Bicarbonate Associates with Higher Mortality Independent of pH in Healthy Older Individuals: The Health, Aging, and Body Composition Study Kalani L. Raphael,¹ Rachel A. Murphy,² Michael Shlipak,³ Suzanne Satterfield,⁴ Hunter K. Huston,¹ Anthony Sebastian,³ Deborah Sellmeyer,⁵ Kushang V. Patel,⁶ Anne B. Newman,⁷ Mark J. Sarnak,⁸ Joachim H. Ix,⁹ Linda F. Fried.¹ ¹Univ of Utah; ²Univ of British Columbia; ³Univ of California San Francisco; ⁴Univ of Tennessee; ⁵Johns Hopkins Univ; ⁶Univ of Washington; ⁷Univ of Pittsburgh; ⁸Tufts Medical Center; ⁹Univ of California San Diego.

Background: Low serum [HCO₃⁻] associates with higher mortality in CKD. The purpose of this study is to determine if [HCO₃⁻] associates with all-cause mortality independent of systemic pH in healthy older persons.

Methods: Data were analyzed from the Health, Aging, and Body Composition Study, an observational study of black and white adults aged 70-79 years followed from 1997-2014. Arterialized venous blood gas measurements were obtained in 2,287 individuals. Participants were grouped into one of 3 [HCO₃⁻] categories: <23.0 (low), 23.0-27.9 (reference group),

and ≥28.0 mEq/L (high). Mortality hazard ratios (HR) in the low and high [HCO₃⁻] groups were compared to the reference group using Cox models adjusted for demographics, eGFR, albuminuria, COPD, smoking, and pH. Multiplicative interaction terms tested whether CKD status modified the relationship between [HCO₃⁻] categories and mortality.

Results: The mean age was 76 years, 51% were female, and 38% were black. The mean pH was 7.41, mean [HCO₃⁻] was 25.1 mEq/L, 11% had low and 10% had high [HCO₃⁻]. The mean eGFR was 82.1 ml/min/1.73m²; 12% had CKD. During follow-up (mean 10.3 years), 1,326 (58%) participants died. The adjusted all-cause mortality HR was 1.24 (95% CI, 1.02-1.49) in the low [HCO₃⁻] category and 1.03 (95% CI, 0.84-1.26) in the high [HCO₃⁻] category compared to the reference group. CKD status did not modify the association between [HCO₃⁻] and mortality (p=0.74).

Conclusions: Healthy older persons with low [HCO₃⁻] have higher mortality risk than those with normal [HCO₃⁻] independent of pH and potential confounders. High [HCO₃⁻] does not associate with higher mortality. The potential health benefits of normalizing low [HCO₃⁻] in generally healthy older persons should be investigated.

Funding: Other NIH Support - National Institutes on Aging and National Institute of Nursing Research, Veterans Administration Support, Private Foundation Support

SA-PO772

Low Urinary Creatinine Excretion Is a Valid Surrogate for Frailty in Patients with Advanced Chronic Kidney Disease Harmke Polinder-Bos,¹ Hakan Nacak,² Friedo W. Dekker,² Stephan J.L. Bakker,¹ Carlo A. Gaillard,¹ Ron T. Gansevoort.¹ ¹Internal Medicine, Univ Medical Center Groningen, Groningen, Netherlands; ²Epidemiology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Muscle wasting is a key component of frailty, which is highly prevalent in advanced stages of chronic kidney disease (CKD). Whether low urinary creatinine excretion (UCrE), a marker of low muscle mass, is a valid surrogate for frailty in this population is unknown. We studied cross-sectional associations between frailty and a low UCrE in patients with CKD stages 4 and 5 (not on dialysis).

Methods: 2748 healthy individuals of the general population were included to define low UCrE. Low UCrE was defined as height-indexed UCrE below the age- and sex-specific 5th percentile. In a CKD population including 320 and 967 participants of the resp. PREPARE-2 and NECOSAD studies, associations of frailty, the individual components that define frailty, and frailty-associated variables with low UCrE were evaluated using multivariate logistic and linear regression models. Frailty was defined as a composite construct including self-reported poor physical functioning, exhaustion, low physical activity, and underweight.

Results: In the general population with a median age of 46 years, median UCrE was 9.8 mmol/day for women and 14.3 mmol/day for men, compared to 7.0 mmol/day and 9.5 mmol/day in CKD patients, respectively. In the CKD patients with a median age of 63 years, low UCrE was found in 38%. Frailty, and the individual components that define frailty, were associated with a low UCrE, independent of comorbidities (OR frailty = 2.19 [1.28-3.77], p=0.005). Of the frailty-associated variables, lower hemoglobin and albumin levels, and higher parathyroid hormone levels were associated with low UCrE. Adjustment for GFR attenuated the associations of frailty, and the individual components that define frailty with low UCrE, except for underweight.

Conclusions: Low UCrE is a valid surrogate for frailty, independent of comorbidities. Low UCrE is strongly determined by a lower kidney function, suggesting that reduced kidney function induces changes in muscle mass and performance leading to frailty.

SA-PO773

Oral Anticoagulation and Kidney Function in Elderly Antonios Douros,¹ Elke Schaeffner,² Olga Jakob,³ Reinhold Kreutz,¹ Natalie Ebert.² ¹Clinical Pharmacology, Charité; ²Nephrology, Charité; ³Clinical Epidemiology, Charité.

Background: In the past years new oral anticoagulants (NOACs) were approved expanding our pharmacological arsenal. Data on their utilization in elderly compared to vitamin K antagonists (VKA) are scarce and the impact of kidney function (KF) on NOAC use in a population with declining glomerular filtration rate (GFR) is of great interest. The present study investigates anticoagulant use and KF in people ≥ 70 years.

Methods: Individuals included in the analysis were participants of the Berlin Initiative Study (BIS). BIS is a population-based prospective cohort study initiated in 2009 in Berlin, Germany, to evaluate KF in people ≥ 70 years. Medication was assessed through personal interviews and coded using the Anatomical Therapeutic Chemical Classification System. For GFR estimation we used the CKD-EPIcr equation. Predictor analysis was conducted via logistic regression.

Results: Figure 1 illustrates the percentage of drug use for the three NOACs and phenprocoumon, the most common VKA in Germany, over the course of 4 years.

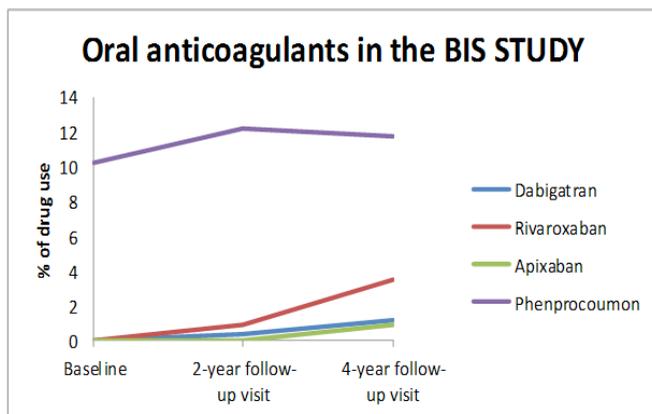


Table 1 shows the characteristics of patients for each oral anticoagulant group during the 4-year follow-up visit (01/2014-04/2015).

	Phenprocoumon (n=153)	Dabigatran (n=14)	Rivaroxaban (n=46)	Apixaban (n=12)
Age mean±SD (years)	84±6	87±4	84±5	85±5
Female sex n (%)	62 (41)	4 (29)	24 (52)	9 (75)
eGFR _{CKD-EPI} < 60ml/min/1.73m ² n (%)	64 (42)	3 (21)	16 (35)	5 (42)
Myocardial infarction n (%)	27 (18)	3 (21)	8 (18)	1 (9)
Stroke n (%)	17 (11)	3 (21)	0 (0)	2 (17)

The probability of dabigatran use rose with increasing age (+12%), and the probability of phenprocoumon use rose in case of eGFR < 60 ml/min/1.73m² (+54%) or male sex (+82%).

Conclusions: Our data show that also in the elderly NOAC use increased over the past years. Characteristics such as age, sex or KF had an impact on the choice of oral anticoagulation.

Funding: Other NIH Support - Kuratorium für Dialyse und Nierentransplantation (KfH Foundation of Preventive Medicine)

SA-PO774

Can Morbidity Predict Mortality in Dialysis Patients? Kathryn Ducharlet,¹ Vijaya Sundararajan,² Nuala Barker,¹ Jodie L. Burchell,² Robyn G. Langham.¹ ¹Dept of Nephrology, St. Vincent's Hospital, Fitzroy, Victoria, Australia; ²Dept of Medicine, Melbourne Univ, Fitzroy, Victoria, Australia.

Background: Symptom management and quality of life (QOL) in dialysis patients is increasingly important in determining treatment approach and outcome research. This study identified symptoms, QOL, functional status in dialysis patients, determining if symptom burden had an impact on mortality.

Methods: A single-centre cross-sectional study was undertaken in dialysis patients with median follow up time 10 months. Patients completed surveys incorporating POS-S renal, WHOQOL-BREF and Karnofsky Performance scale. A Log rank test determined the risk of death based on symptom severity.

Results: 112 patients were recruited; 67 hemodialysis, 10 home/nocturnal hemodialysis and 35 peritoneal dialysis patients, average age 66 years, 66% male. Patients had high symptom burden (median POS-S score 13 (inter-quartile range (IQR) 9, 22)) and reduced total QOL 4 (IQR 3,4), health satisfaction 3 (IQR 2,4) and performance status 60 (IQR 50,70). A log rank analysis was performed on 104 POS-S renal responses with 8 deaths during the study. A significant impact of pain, shortness of breath, nausea, mouth problems, drowsiness, poor mobility and skin changes on survival was found.

Symptom	Number (%) n = 112	Log rank test (Chi ²) n=104
Pain	82 (73%)	10.56*
Shortness of breath	72 (64%)	8.18*
Weakness	98 (88%)	1.62
Nausea	44 (39%)	9.54*
Vomiting	25 (22%)	9.49*
Poor appetite	58 (52%)	3.53
Constipation	62 (55%)	3.06
Mouth problems	38 (34%)	16.29**
Drowsiness	68 (61%)	8.22*
Poor mobility	76 (68%)	12.28*
Itching	70 (63%)	3.95
Difficult sleeping	89 (79%)	9.02
Restless legs	57 (51%)	8.05
Feeling anxious	62 (55%)	6.01
Feeling depressed	52 (46%)	3.13
Diarrhoea	68 (61%)	3.40
Skin Changes	28 (25%)	60.37***

*P<0.05, **P<0.01 ***P<0.001

Conclusions: This study demonstrated high symptom burden, reduced functional status and QOL in dialysis patients. Patients with severe pain, weakness, shortness of breath, nausea, mouth problems, drowsiness, poor mobility and skin changes were more likely associated with higher mortality risk. Symptom identification and management may help predict and improve patient QOL outcomes in dialysis patients.

SA-PO775

Outcomes of Cardiopulmonary Resuscitation in Maintenance Dialysis Patients Based on CPR Characteristics Haris Farooq Murad, Fahad Saeed. Cleveland Clinic Foundation.

Background: Cardiopulmonary resuscitation (CPR) is associated with high rates of mortality, especially in patients with end stage renal disease (ESRD). Previous studies have reported an in-hospital mortality rate of up to 75% in ESRD patients undergoing CPR. There are no large studies to date on how individual CPR characteristics relate to the long term outcomes in these patients. Herein, we aimed to answer this question.

Methods: By an EMR inquiry, we identified all the adult patients (>18years) who had underwent CPR from January 2006 to December 2014, and then selected patients who were on maintenance dialysis. We conducted a chart review of CPR characteristics and its association with the hospital discharge survival. We studied following variables: initial rhythm, duration of CPR, in-hospital versus out of hospital CPR and the use of hypothermia protocol.

Results: We studied a total of 497 ESRD who had undergone CPR. Sixty eight percent of our patients had expired in the hospital post-CPR. Pulseless electrical activity (PEA) was the most common initial rhythm (51.4%), followed by ventricular arrhythmias (19.6%) and asystole (19.2%). In-hospital mortality was the highest (76.8%) for patients with asystole. Mortality rates at the time of discharge were 73.3% for PEA and 57.7% for patients with ventricular arrhythmias respectively. Fifty six percent of patients who underwent therapeutic hypothermia died in the hospital as compared to 68.9% of those who did not undergo a cooling protocol. CPR duration of greater than 10 minutes was associated with higher in-hospital mortality (76.1%) as compared to patients who had CPR for less than 10 minutes (40.9%). Patients who had undergone out of hospital CPR (by paramedics or bystanders), 72.2% died before discharge; while 68.9% of patients who underwent CPR in the hospital expired during the same hospitalization. The average length of stay for patients who were alive at discharge was 17 days.

Conclusions: CPR in dialysis patients is associated with high mortality rates. It is possible to predict hospital discharge survival of patients with cardio-pulmonary arrest based on the CPR characteristics.

SA-PO776

End of Life Care Preferences in Maintenance Dialysis Patients Haris Farooq Murad,¹ Muhammad Adil Sardar,¹ Syed Zamrak Khan,¹ Sara N. Davison,² Fahad Saeed.¹ ¹Cleveland Clinic Foundation; ²Univ of Alberta.

Background: Dialysis patients have an annual mortality rate of 20-25%. A previous Canadian study comprising mainly of Caucasian patients has shown that patients are interested in active involvement in end of life care discussions and majority would want to know their prognosis on dialysis. In this Caucasian predominant cohort, approximately 50% chose to be DNR. It is not known if patients' preferences on end of life care are any different in a racially more diverse cohort of patients in the U.S.

Methods: We collected data on 423 out of 440 dialysis patients from 7 dialysis facilities in the U.S. using self-reported questionnaires.

Results: Our study included 28.1% Caucasian and 66.7% African American patients. Eighty three percent of the patients felt that their QOL was an important determinant in guiding their future care plans, and 72.3% of patients reported that they need to have frequent discussions about their QOL with their nephrologist. Only 35.4% of patients actually get information about their health and well-being from their nephrologists. Only 8.6% of patients had a discussion with any Physician, nurse or social worker regarding end of life care during the past 12 months. Notably, 74.2% of our participants reported that they would like to have such discussions with their health care providers. Sixty seven percent of the patients wished to be full code. Fifty six percent of the patients preferred to die at home versus 20.4% wanted to die in a hospice facility and 13.4% in a hospital. Only 23.6% of patients knew about palliative care.

Conclusions: There is a need to have more dialogue between patients and their nephrologists regarding end of life care preferences, and it is necessary to develop policies and practices that would help address this need.

SA-PO777

“So I had No Choice”: Perceptions of Dialysis Decision-Making Among Older Adults Keren Ladin,¹ Daniel E. Weiner.² ¹Occupational Therapy, Tufts Univ, Medford, MA; ²Medicine, Tufts Univ Medical School, Boston, MA.

Background: Multiple treatments are available to older patients with advanced chronic kidney disease. However, poor communication about available treatment options may result in a mismatch between patient preferences and treatment choice.

Methods: Semi-structured in-depth interviews were conducted with a purposive sample of 26 dialysis patients aged 65 and older at two dialysis clinics in the Greater Boston area. Trained researchers conducted, audiotaped and transcribed interviews. Applying grounded theory, interviews were analyzed in an iterative process to identify emergent codes. Codes were discussed using consensus and organized into themes.

Results: Twenty-six patients participated in the interview. Mean age was 77±9 years; 50% were men, 19% African American and 58% diabetic. Median vintage was 28 (17, 39) months. Four major themes with associated subthemes were identified. The first, “Deciding to start dialysis” revealed that only two patients conceptualized dialysis initiation as a choice. Patients were seldom informed of conservative management, and many had unanswered concerns about trade-offs among treatment choices. The second theme, “Experience with dialysis”, included positive and negative physical, emotional, and social consequences of dialysis and logistics of care. While many reported greater than anticipated levels of pain, fatigue, and frustration over transportation costs and time spent, others reported substantial benefits, including increased longevity and the ability to achieve life goals. The third theme, “Patient Role”, revealed patients tied self-worth to meeting clinical goals. Finally, “End-of-life (EOL) preferences and conversations” revealed that most patients had not discussed EOL with their clinical team and/or with loved ones.

Conclusions: Many older patients who treated with dialysis do not perceive that they had a choice when making their dialysis decision. Initiating dialysis may contradict patients’ EOL preferences, and many desire greater information and more discussions with clinicians. Older adults’ preferences and experiences with dialysis vary, underscoring the importance of patient involvement in decision-making.

SA-PO778

Improving Advance Care Planning in Elderly Outpatients with Chronic Kidney Disease – A Quality Improvement Initiative Ritu K. Soni,¹ Jane O. Schell.^{1,2} ¹Section of Palliative Care and Medical Ethics, Univ of Pittsburgh Medical Center, Pittsburgh, PA; ²Renal-Electrolyte Div, Univ of Pittsburgh Medical Center, Pittsburgh, PA.

Background: Despite a high annual mortality rate in patients with advanced chronic kidney disease (CKD), advance care planning (ACP) is underutilized. A minority of dialysis patients complete advance directives (AD). Timely ACP ensures that patients’ preferences for future care are respected and is associated with less intensive care at end of life. We sought to introduce ACP and increase documentation of AD in older outpatient CKD patients.

Methods: This quality improvement study was conducted over 15 weeks in older outpatients at the University of Pittsburgh Kidney Clinic. The intervention included training and supporting the CKD nurse educator to introduce and encourage ACP completion. Inclusion criteria were age older than 65 years and referral to the CKD education session. The CKD nurse educator was assigned the role of asking whether each patient had AD and a designated healthcare power of attorney (HPOA). The nurse additionally offered every eligible patient the *Five Wishes* AD form and documented their responses.

Results: Of the 110 patients who underwent CKD education over a period of 15 weeks, 52 (47.2%) were eligible. Thirty-one of 52 (59.6%) patients already had AD and 32 of 52 (61.5%) had a HPOA. Thirteen of 52 (25%) were interested in reviewing the *Five Wishes* AD form although 2 of them had already completed an AD. The AD and HPOA screening information was documented by the nurse educator in 59.6% and 61.5% patients respectively. One patient had an AD scanned in the electronic records and one patient requested referral to the Renal Supportive Care clinic for continuation of ACP discussions.

Conclusions: We report a successful nurse educator based quality improvement initiative to increase AD documentation in older nephrology outpatients. Our data suggest that although many of these patients have previously completed AD, these preferences are not documented in the medical chart. A nurse educator based intervention is effective in improving documentation rates of AD.

SA-PO779

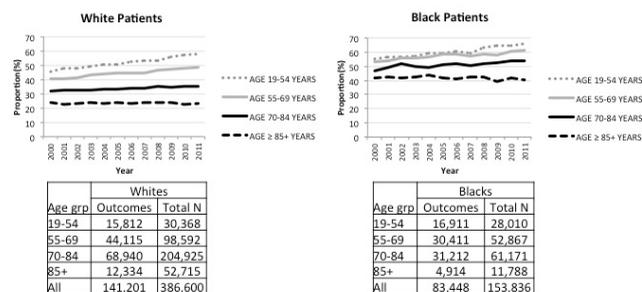
Trends in Inpatient Intensive Procedures in the Last Six Months of Life Among Medicare Beneficiaries Treated with Maintenance Dialysis, 2000-2011 Nwamaka Denise Eneanya,¹ Susan M. Hailpern,² Ann M. O’Hare,² Manjula Kurella Tamura,³ Ronit Katz,² Yoshio N. Hall.² ¹Div of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ²Kidney Research Inst, Univ of Washington, Seattle, WA; ³Geriatric Research and Education Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA.

Background: Many US dialysis patients undergo intensive procedures intended to prolong life such as mechanical ventilation, cardiopulmonary resuscitation or feeding tube placement at the very end of life. Little is known about trends over time in use of intensive procedures in this population.

Methods: We examined temporal trends in receipt of inpatient intensive procedures in the last 6 months of life by age and race among 601,942 adult Medicare beneficiaries treated with maintenance dialysis who died between January 1, 2000 and December 31, 2011.

Results: From 2000 to 2011, inpatient admissions during the last six months of life increased slightly from 89% to 90%. Among those admitted, there was a marked increase in the use of intensive procedures ranging from 38% in 2000 to 44% in 2011. Intensive procedures at the end of life were more common among black vs. white patients (50% to 57% vs. 34% to 39%) and among younger vs. older patients (50% to 61% for those < 55 years vs. 27% to 26% for those 85+ years).

Proportion of hospitalized decedents receiving an intensive procedure in the last 6 months of life during 2000-2011.



In adjusted analyses, racial differences in receipt of intensive procedures were most pronounced at older ages (black vs. white aOR [95% CI]: 1.38 [1.33-1.42] in patients < 55 years, 2.48 [2.38-2.59] in patients 85+ years).

Conclusions: From 2000 to 2011, a growing number of Medicare beneficiaries treated with maintenance dialysis received intensive procedures during the final months of life. These procedures were most common and increased most dramatically in younger patients while racial differences were most pronounced in older patients.

Funding: NIDDK Support

SA-PO780

Will Nephrologists Implement an Advance Directives Program in Their Patients? (Quality Improvement Program) Ali Mohammed Habeeb, Sheldon W. Tobe. Nephrology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

Background: Mortality remains high among patients on dialysis. Advanced age and multiple co-morbidities are the majors predictors for increasing mortality. ADs extend patients’ autonomy and are the best tool to inform about a patient’s preferences for health care decisions when they become unable to make such decisions. Chronic dialysis patients have been shown to want to discuss ADs in the past.

Methods: We reviewed 215 chronic in-center hemodialysis patients at Sunnybrook Health Sciences Centre from March to April 2015 by the dialysis unit social workers for any documents related to ADs (like Living wills, Substitute Decision Maker (SDM) and CPR forms). Only 2 patients had ADs in their charts (1.0%). When this data has presented to the Nephrologists they agreed that ADs should be discussed with their patients and that this was a quality improvement issue. Will the staff nephrologists change their practice behaviour and begin to ask their hemodialysis patients about ADs and document the discussion?

Results: As part of the process to discuss ADs, the unit’s social workers distributed a pamphlet for the patients with simple and explicit definitions and advantages of AD and also provided explanations about the contents of the pamphlets. The Staff Nephrologists were educated about the importance and advantages of ADs in their patients and were asked to start discussing the issues with their patients. The Nephrologists will also be educated about how an AD discussion might go and how to document the results of the discussion. In 3 months, a review of the patients’ charts will again look for any documented ADs. We will also study the response of individual dialysis staff and their participation in completing and discussing the ADs. We will assess the potential barriers for not completing ADs by the dialysis unit staff and by patients and attempt to address these barriers.

Conclusions: Expected Outcome: Based on the Prochaska model we are anticipating the dialysis staff are now in the contemplation stage and we are aiming to observe the progression in their behavior to more advanced stages of behavior and try to find out what are the barriers that prevent the progression.

SA-PO781

Current Practice of Advance Care Planning in Australia and New Zealand
 Rachael L. Morton,¹ Lucy Spencer,² Allison Tong,¹ Carol A. Pollock,^{1,2} Karen M. Detering,⁴ Josephine M. Clayton,^{1,3} ¹The Univ of Sydney, Australia; ²Royal North Shore Hospital, Australia; ³HammondCare Palliative Care Service, Australia; ⁴Austin Health, Australia; ⁵On behalf of Univ of Technology Sydney Collaborators.

Background: Recent guidelines emphasise the need to improve advance care planning (ACP) for patients with chronic kidney disease (CKD). Little is known about current ACP practice in Australian/New Zealand renal centres. We aimed to describe current practice and barriers to ACP from the perspective of renal clinicians.

Methods: A cross-sectional survey was administered online to nephrology nurses, nephrologists and social workers between May 2014 and January 2015. Survey questions covered the topics of experience, skills, comfort and knowledge regarding ACP, workplace policies and procedures concerning ACP, perceived barriers and facilitators to ACP, and perceived need for new CKD-specific ACP programs and materials.

Results: 375 participants completed the survey, mean age 48 years, from renal centers in all Australian states and territories and New Zealand. 57% indicated that ACP was performed in their workplace on an ad-hoc basis; 22% reported that there was a formal program; 13% reported that ACP hardly ever occurred; and 8% were unsure. 61% reported that ACP was done poorly, 32% well, and 7% were unsure. Perceived barriers to ACP included patient/family discomfort with the topic (84% of respondents), difficulty engaging families and lack of clinician expertise (83% each), lack of clinician time (82%), health professional discomfort (72%), cultural/language barriers (65%), environmental problems such as lack of space (61%) and lack of formal policy/procedures (60%). Whilst discouragement from colleagues or managers was identified as a barrier in only 19% of cases, narrative comments on the survey emphasised the gate-keeping role played by nephrologists.

Conclusions: ACP in Australian/New Zealand renal centres is subject to health system, provider and patient related barriers. Given the volunteer effect associated with online surveys, our study may underestimate the need for ACP support. Targeted interventions are needed to improve ACP in Australian and New Zealand renal centres.

Funding: Private Foundation Support

SA-PO782

Nephrology Leadership Required to Address Unmet Palliative Care Needs in Dialysis Centers
 Alvin H. Moss,¹ Stacey Culp,¹ Dale Lupu,² Cheryl Arenella,² Nancy C. Armistead,³ ¹Medicine, West Virginia Univ School of Medicine, Morgantown, WV; ²Daleview Associates, Silver Spring, VA; ³Mid-Atlantic Renal Coalition, Richmond, VA.

Background: Because of high symptom burden, numerous comorbidities, and shortened life expectancy, dialysis patients are increasingly recognized as appropriate candidates for early and continuous palliative care.

Methods: In 2013 the Coalition for Supportive Care of Kidney Patients conducted an online survey of dialysis professionals and administrators using ESRD Network and Renal Physicians Association email lists to determine perceptions about how well patient palliative care needs are met. Differences among disciplines were assessed by chi-squared testing and one-way ANOVA.

Results: The 487 respondents included 41 nephrologists, 152 nurses/physician assistants, 199 social workers, and 95 dialysis center administrators. There was a significant difference by discipline in reported unmet palliative care needs for symptom management, care coordination, and family bereavement support, with administrators least likely to view each need as unmet (all $p < .02$). In rating possible barriers to providing high quality palliative care in their centers, mean scores differed by discipline for 7 items, and nephrologists were most likely and administrators least likely to perceive them as barriers (all $p < .05$). "Guidelines to help with decision-making in seriously ill patients" was selected as the top priority for change by each discipline (37% overall, $p = .47$ by discipline). Nephrologists were most likely to be aware that a dialysis guideline already existed and to have used it (43.9% vs 3.3% RN/PA vs 10.6% MSW vs 8.5% administrator, $p < .001$).

Conclusions: Nephrologists report more unmet palliative care needs, barriers, and resources than the administrators who oversee dialysis centers. Because the respondents were self-selected, a study limitation, the results likely underestimate unmet palliative care needs. To better address palliative care needs, nephrologists need to lead interdisciplinary collaborations, including administrators, to implement palliative care pathways already established in evidence-based clinical practice guidelines.

SA-PO783

Hospice and Race for End-of-Life Care in U.S. Dialysis Patients
 Robert N. Foley,¹ Scott Reule,¹ Donal J. Sexton,² ¹Div of Nephrology, Univ of Minnesota, Minneapolis, MN; ²Div of Medicine, National Univ of Ireland, Galway.

Background: While hospice use is increasingly used for end-of-life care in dialysis patients, we hypothesized that important racial disparities may be present.

Methods: To address this hypothesis, we examined USRDS files to characterize end-of-life care for deaths occurring between 2006 and 2011.

Results: During this 5-year period, the proportion of deaths in hospice increased from 14.7% to 24.2%; grouped by age at death, the following trends were observed: < 65 years-11.5% to 15.0%; 65 to 79 years-19.1% to 26.1%; 80-89 years-24.9% to 34.3%; ≥ 90 years-25.9% to 39.6%. As shown in the accompanying Table, associations of hospice use

among decedents included more recent calendar year, older age and female sex. Hospice use varied substantially with race: compared to whites, adjusted odds ratios of hospice use were 0.56, 0.56 and 0.57, respectively, in patients of African American, Native American and Asian race.

Conclusions: While end-of-life care in hospice settings is growing rapidly in the US, substantial, unexplained racial disparities exist.

Candidate Variable	Comparator	Adjusted Odds Ratio
Death in 2008	2006	1.18
Death in 2009	2006	1.27
Death in 2010	2006	1.39
Death in 2011	2006	1.51
Age 65-80	< 65	1.80
Age 81-90	< 65	2.52
Age ≥ 90	< 65	3.03
> 1 year on RRT	≤ 1	0.98
Female	Male	1.12
Asian	White	0.57
African American	White	0.56
Native American	White	0.56

SA-PO784

Palliative Care Perspectives of Latinos with End-Stage Renal Disease
 Lilia Cervantes,^{1,2} Stuart L. Linas,^{1,2} Stacy M. Fischer.¹ ¹Dept of Medicine, Univ of Colorado, Denver, CO; ²Dept of Medicine, Denver Health and Hospital, Denver, CO.

Background: Latinos are the fastest growing minority and have a nearly 2-fold faster progression from chronic kidney disease to end-stage renal disease (ESRD). Despite the high symptom burden and mortality suffered by patients with ESRD, there is limited palliative care research and Latinos are underrepresented in existing palliative care studies. The purpose of our study is to provide the first description of the Latino palliative care perspective.

Methods: Observational descriptive survey of adult English and Spanish speaking Latinos with ESRD from a safety-net hospital and two private dialysis centers. We modified Davison's 2010 End of Life Care Preferences and Needs Survey to include known barriers to palliative care in the Latino community. The survey was translated to 3rd grade Spanish and then back-translated to English.

Results: Participants (n=61) had a mean age of 59 years ± 12, mean Charlson Comorbidity Index of 6.5 ± 2.5, and a dialysis vintage mean of 43.3 months ± 44.8. The majority (77%) spoke Spanish and reported limited understanding of hospice and palliative care. We found that 60 (98%) want to be informed about their prognosis and 55 (90%) want to be prepared and plan ahead; however, only 16 (26%) had discussed prognosis and only 10 (16%) had discussed end-of-life care with their nephrologist. The majority of participants stated that it was their doctor's choice (68.8%) to start dialysis; however, few (14.7%) regret the decision to start dialysis. Participants reported a preference to have advance care planning conversations on a routine basis (86.8%), after starting dialysis but before becoming ill (85.2%), and while receiving dialysis (47.5%) or at home (37.7%). Participants want their family have a central role in medical decision-making (93.4%) and care-giving (95%).

Conclusions: Our findings provide the first description of the palliative care perspectives of a predominantly Mexican Latino population with ESRD. By understanding the palliative care perspectives and barriers experienced by Latino patients with ESRD, we can move toward a value-based and patient-centered model of palliative care.

Funding: Private Foundation Support

SA-PO785

Symptom Burden Amongst Latinos with End-Stage Renal Disease
 Lilia Cervantes,^{1,2} Stuart L. Linas,^{1,2} Stacy M. Fischer.¹ ¹Dept of Medicine, Univ of Colorado, Denver, CO; ²Dept of Medicine, Denver Health and Hospital, Denver, CO.

Background: All patients with end-stage renal disease (ESRD) experience a high symptom burden. Although Latinos represent 19% of the US ESRD community, little research is available on their symptom burden. The purpose of our study was to provide the first description of symptom burden prevalence and severity amongst Latinos with ESRD.

Methods: Observational descriptive survey of adult English and Spanish speaking Latinos with ESRD from a safety-net hospital and two private dialysis centers. We used Davison's ESAS-r: Renal tool which measures physical and psychological symptom distress and contains 11 symptom items on a Likert scale of 0-10. Moderate = 4-6 and severe = 7-10. We asked three questions about symptom treatment preferences.

Results: Participants (n=61) had a mean age of 59 ± 12 years, mean Charlson Comorbidity Index of 6.5 ± 2.5, and a dialysis vintage mean of 43.3 ± 44.8 months. The majority were born in Mexico (90.2%), spoke Spanish only (77%), and had a less than high school education (72.2%). Overall, Latinos experience a substantial symptom burden with a mean of 6.8 ± 2.9 symptoms of which 5.1 ± 2.8 are moderate or severe symptoms. Tiredness

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

was experienced by 83.5% of patients and reported as moderate or severe by 67.2%. Pain was present in 65.6% and moderate or severe in 49.1%. Depression was reported by 55.7% and anxiety by 49.1% and moderate or severe in 49.2% and 39.3%, respectively. The majority (78.6%) of patients reported lack of well-being and feeling drowsy (70.5%). With respect to medication preferences, our cohort prefers Western Medicine (77.1%) over traditional curandero (22.9%) medicine and is agreeable (77.1%) to taking a few more medications if it meant all symptoms could be controlled. Our Latino cohort prefers (88.5%) to have their physical symptoms (e.g. pain, nausea) treated by nephrology staff.

Conclusions: Latinos with ESRD suffer from a debilitating symptom burden and over half of the symptoms are amenable to symptom directed therapy. Our findings support the early identification and treatment of physical symptoms by nephrology staff.

Funding: Private Foundation Support

SA-PO786

Care of the ‘Failing HD Patient’: Role of a Supportive Care Register *Tracy Maryan, Maria Da Silva-Gane, Suresh Mathavakkannan. Renal Unit, Lister Hospital, Stevenage, Hertfordshire, United Kingdom.*

Background: Older dialysis patients (>70) often have significant comorbidities, that worsen with duration on HD. Continuation of dialysis often occurs at the expense of frequent illness episodes. There is a progressive decline in cognitive and physical function that exacerbates dialysis. We had introduced a Supportive Care Register (SCR) in 2012 to identify ‘failing dialysis patients’ based on their physical performance scores. We attempted to understand whether being on the SCR enabled better patient care when these patients were admitted with inter-current illnesses.

Methods: Data was collected from Patient Administration System (PAS) and Renal IT database in a large Tertiary (non-transplanting) Renal Unit serving a catchment population of 1.2 million. Data maintained in the SCR was reviewed. Total number of HD patient admissions to the acute renal service in 2013 were obtained with analysis of demographics, length of stay (LoS) and outcomes at discharge. Patients who were admitted were checked against the SCR entries.

Results: 287 out of the 409 total HD patients were admitted (123 F, median age 68 years, 590 episodes) with 137 of these patients being admitted more than once. The LoS was 9 days. 49 patients died in 2013 (28M; 76±16 yr; vintage 60 m; LoS 18±12 p<0.05). 28 patients died in hospital or at home/hospice following withdrawal of dialysis and institution of palliative care. 16 patients had died following severe acute illness. Five patients died at home. 18/28 patients were on the SCR and had discussions relating to ongoing and future dialysis therapy and advanced and preferred place of care planning prior to their last admission in the clinic setting. Seven patients had proceeded to discussions regarding resuscitation.

Conclusions: In conclusion, establishment of a SCR for dialysis patients with declining functional capacity and significant comorbidities allows for an early identification of patients at risk of physical and functional decompensation. Once identified, establishing a dialogue in the OP dialysis setting about future care needs and expectations allows for a more integrated care approach when patients decompensate to the point of being unable to continue dialysis.

Funding: Government Support - Non-U.S.

SA-PO787

A Descriptive Study of Home Palliative Service Utilization and Care Trajectory Among Patients Dying on Dialysis *Gihad E. Nesrallah,¹ Stephanie Dixon,² Marnie MacKinnon,³ Sarah E. Bota,² Jade S. Hayward,² Erin Arthurs,² Peter G. Blake,³ Amit X. Garg,² Sara N. Davison.⁵ ¹Nephrology Program, Humber River Hospital, Toronto, ON, Canada; ²Inst for Clinical Evaluative Sciences, London, ON, Canada; ³Ontario Renal Network, Toronto, ON, Canada; ⁴Ottawa Health Research Inst, Ottawa, ON, Canada; ⁵Faculty of Medicine, Univ of Alberta, Edmonton, AB, Canada.*

Background: Palliative care service use and outcomes among Ontario’s dialysis recipients remain uncharacterized.

Methods: We conducted a descriptive, retrospective, cohort study of 5,507 patients who died while receiving or withdrawing from chronic dialysis (hemodialysis or peritoneal dialysis) in Ontario, between January 1, 2010 and December 31, 2012. Data sources included the Ontario Renal Reporting System, the Canadian Organ Replacement Register, the Home Care database, and other linked administrative health datasets. The date of death served as the index date, and we examined patterns of service use in the prior 365 days. We present selected measures of health service use and outcomes.

Results: Cohort characteristics at death, expressed as median (IQR) or percent of cohort included: 75 (16) yrs old, 3.0 (5) yrs on dialysis, 42% female, 65% had diabetes, 14 (4) Johns Hopkins ACG (comorbidity score). Final dialysis modality was 85% centre HD, 1% home HD, 4% PD, 10% missing. During the last year of life, 11.3% received at least one palliative care service in the home, and 17.5% withdrew from dialysis in the last 30 days of life. In the last 14 days of life, 44% of patients had an emergency department (ED) visit and 36% had an ICU visit. ED and ICU visits were less frequent among patients who had received home palliative services in the last year of life. Place of death was ICU in 33%, and acute care hospital (without ICU) in 32%, while only 3.6% of patients died at home. Patients with home palliative care services in the last year of life had a greater frequency of death at home (15 vs. 2%) compared with those who did not.

Conclusions: Home palliative care services may not be used optimally by dialysis patients in Ontario. Further studies are needed to understand barriers to accessing palliative care services and to improve service planning and delivery.

SA-PO788

Ventilator Dependent Dialysis Patients *Jack Rubin. Los Amaios.*

Background: We have started treating ventilator dependent patients at our dialysis unit and wish to share our results.

Methods: Chart review was done on all ventilator dependent patients treated at our unit.

Results: All data are shown mean ± sd. To date we have treated 19 patients (8F/11M) aged 71 ± 14 years with a mean time on dialysis of 90 ± 102 days. These patients were on dialysis prior to coming to us a mean 741 ± 1046 days. Seven were started within 2 months of their catastrophic event. Mean last available KT/V 1.5 ± 0.3, weight 152 ± 41 pounds, dialysis time 194 ± 21 minutes, bun 90 ± 20, creatinine 4.5 ± 1.5 Hemoglobin 9 ± 1 g%, albumin 3 ± 0.5 g%, pre-albumin 18 ± 9 mg%, calcium 9.2 ± 0.6 mg% and phosphorus 3.4 ± 1.3 mg%. Four patients were transferred a mean of 71 ± 54 days because of insurance issues. 7 are on dialysis 97 ± 137 days and 8 have died after 94 ± 95 days on dialysis. There were no apparent differences in the parameters listed above between those transferred for insurance reasons, those who died and those still receiving treatment. 7 patients were non communicative, 7 were diabetic, 2 had a fistula and the rest catheters, 3 had atrial fibrillation and all a history of hypertension and congestive heart failure. Deaths were caused by gastrointestinal bleeding (1) and sepsis (7).

Conclusions: These non verbal non communicative patients are receiving aggressive end-of-life care fostered in some cases by unrealistic family expectations and in other instances by state conservators who prefer treatment until death so that outpatient withdrawal of dialysis and comfort care is not a realistic option. There are two groups - vintage patients and new to dialysis patients with a catastrophic event. The goal should be to educate families on the consequences of dialysis for the patient so that they do not start or allow withdrawal of dialysis after a defined trial. Upon taking on treatment of this group of patients the dialysis unit should anticipate a lower star rating in the benchmarks as most are on catheters and are frequently admitted for infection, bedsores or pulmonary complications. To sustain these selected patients requires a dedicated staff of nurses, respiratory technicians and ambulance services.

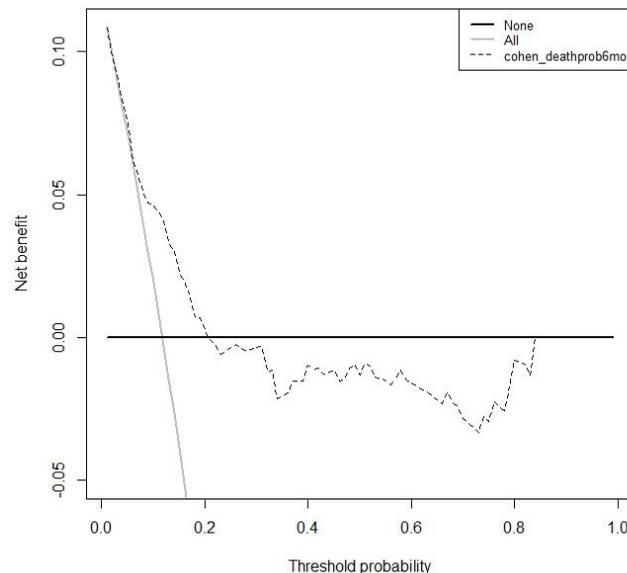
SA-PO789

External Validation of a Prediction Model for 6-Months Mortality Risk (MR) in Patients on Hemodialysis *Adeera Levin,^{1,2} Brian Forzley,¹ Helen Chiu,² Lee Er,² Ognjenka Djurdjev,² Mohamud A. Karim,¹ Rachel C. Carson,¹ Gaylene M. Hargrove,¹ Dan J. Martinusen.³ ¹Dept of Medicine, Faculty of Medicine, UBC; ²BC Provincial Renal Agency; ³Island Health Authority, BC, Canada.*

Background: End-Stage Renal Disease (ESRD) is associated with poor prognosis. Clinicians must be prepared to address end-of-life issues; hence, identifying patients at higher MR is recommended. We aimed to validate a 6-month MR prediction model for prevalent hemodialysis patients derived by Cohen et al. (2010) in a Canadian cohort and assess its clinical utility.

Methods: 375 prevalent dialysis patients in two regions of BC, Canada, were followed for 6 months. Data including serum albumin (ALB), age, peripheral vascular disease and dementia captured when the surprise question (SQ) was asked were used to validate the 6-month MR model. Model performance was evaluated through discrimination, calibration and decision-curve analysis.

Results: The observed mortality was 13.3% at 6-months. The model had reasonable discrimination (c-stat=0.70) but poor calibration (slope=0.46 [95% CI: 0.24, 0.69]) in our data. Decision curve showed added value of the model for threshold probabilities of 8%-20% (= 12-42% fewer false-positive death), but no more beneficial to “treat-all” for probability <8% and “treat-none” for probability >20%.



Exploratory analysis showed that only SQ (OR=2.3, 95% CI 1.05, 4.97) and ALB (OR=0.22, 95% CI 0.10, 0.46) were associated with 6-month MR. Simpler models appeared to perform equally well.

Conclusions: The existing prediction model by Cohen et al. has reasonable discrimination but over-estimated the number of deaths and may require recalibration of model coefficients. The model may guide advance care planning conversations, but caution is required when applying this model in clinical decisions. A simpler model may enhance feasibility for use. Further research is needed prior to utilizing the model to predict death.

Funding: Government Support - Non-U.S.

SA-PO790

Identifying Advanced Chronic Kidney Disease Patients with Same Survival Under Conservative Care versus Dialysis Csaba P. Kovcsdy,^{1,2} Miklos Zsolt Molnar,¹ Jennie Jing,³ Melissa Soohoo,³ Jun Ling Lu,¹ Elani Streja,³ Lawrence Agodoa,⁴ Kevin C. Abbott,⁴ Paul W. Eggers,⁴ Kamyar Kalantar-Zadeh.³ ¹Univ of Tennessee Health Science Center, Memphis, TN; ²VA Medical Center, Memphis, TN; ³Univ of California, Irvine, CA; ⁴NIH/NIDDK, Bethesda, MD.

Background: It is unclear if dialysis offers advantages over conservative care in certain patients with advanced CKD who do not have rapidly deteriorating kidney function.

Methods: From 659,546 US veterans with CKD we identified 9,273 who transitioned to dialysis, and 6,136 who reached eGFR<15 ml/min/1.73m², but did not start dialysis. We matched these groups for their eGFR slope and for the last eGFR prior to ESRD, and restricted analyses to patients with no rapid pre-ESRD progression (defined as a slope of -5 to <0) and pre-ESRD eGFR of 10 to 14.9. We examined all-cause mortality using time-stratified Cox models (by 1-year increments) to account for non-proportionality of hazards.

Results: Of 1,026 veterans included in the analysis, 651 patients did not, and 375 patients did initiate dialysis. Baseline age, gender, race, eGFR slope and last eGFR, and comorbidities were similar in the dialysis vs. no dialysis groups. Overall, 624 patients died over a median follow-up of 1.5 years. Patients on dialysis experienced lower mortality in the first year (HR, 95%CI: 0.25, 0.17-0.36, p<0.001) and in year 2 (0.67, 0.52-0.87, p=0.003). Among patients who survived at least 2 years (28% of the original cohort), the risk of death associated with dialysis was 28% higher but not statistically significant (1.28, 0.94-1.75, p=0.12) during the subsequent time period. In this latter group baseline slopes were flatter (-2.1(1.3) vs. -1.9(1.2)), but their other characteristics were similar to the overall cohort.

Conclusions: Among patients with eGFR 10-15 ml/min/1.73m² and no rapid loss of kidney function, transition to dialysis was associated with survival advantage over a two year time period. However, in 28% of the patients conservative management was not associated with worse mortality. Better characterization of patients who may benefit from conservative management warrants additional studies.

Funding: NIDDK Support, Veterans Administration Support

SA-PO791

Enteric Dialysis – Stabilization of the Gut Microbiome using Probiotics and Prebiotics (Gut-Kidney Connection) Natarajan Ranganathan,¹ Eli A. Friedman.² ¹Research and Development, Kibow Biotech Inc, Newtown Square, PA; ²Downstate Medical Center, State Univ of New York, Brooklyn, NY.

Background: Recent scientific evidence from the human microbiome project has revealed that the trillions of gut microbiome exceed the human microbiome by a factor of 10. There are just 23,000 human genes as against the 3.3 million genes coded by the gut microbiome. This complex microbiome has a major role to play in health and diseases. Scientific evidence has shown that the imbalance in the ratio of this complex microbial community leads to dysbiosis a cause for various diseases. The use of beneficial microbes-probiotics and prebiotics is generally well recognized towards digestive, gut and immune health. However, novel and niche application of probiotics and prebiotics as a dietary supplement in stabilization of Gut Microbiome towards Chronic Kidney Disease (CKD) is relatively new. Many independent reviews in various scientific journals have reflected on various topics such as gut Microbiome, its dysbiosis, impact of the altered intestinal characteristics including small bowel bacterial overgrowth, newer uremic toxins, adsorbent drugs and several observational small scale clinical studies from Kibow and many others.

Methods: “Renadyl” a synbiotic dietary supplement was studied in randomized clinical trials in CKD 3 and 4 and ESRD patients. Other oral therapies for removal of uremic toxins include the use of keto acids and charcoal sorbents.

Results: Our studies using Renadyl for “Enteric Dialysis” showed reduction in levels of various uremic toxins like urea and indoxyl glucuronide. Levels of CRP also decreased with improved quality of life. This demonstrates the potential restoration of the gut microbiome dysbiosis with the use of specific strains of probiotics.

Conclusions: The use of a well-researched, clinically documented and safe probiotic/prebiotic dietary supplement formulation has the potential to safely perform continuous 24h/7d uremic toxin removal and thus stabilize the gut Microbiome and its dysbiosis. Hence, the concept of “Enteric Dialysis” with continuous removal of uremic toxins may be the future key to providing an alternative HOPE for renal failure population.

Funding: NIDDK Support

SA-PO792

Charcoal Hemoperfusion in the Treatment of Pruritus in Cholestatic Liver Disease Wonnarn Kittanamongkolchai, Ziad El-Zoghby, Nelson Leung. *Nephrology, Mayo Clinic, Rochester, MN.*

Background: Pruritus is a distressing symptom in a considerable proportion of cholestatic patients and few of them do not respond to conventional treatment. Charcoal hemoperfusion (CH) is an extracorporeal technique to eliminate albumin-bound substances that are accumulated during cholestasis by the passage of blood through a column containing activated charcoal. Several case reports have shown significant reduction of bilirubin in mechanical jaundice and neonatal hemolytic jaundice. However, the published data of CH for the treatment of resistant pruritus in cholestatic patients is scarce.

Methods: Procedure code “Charcoal hemoperfusion” was used to identify patients who received charcoal hemoperfusion at Mayo Clinic, Rochester from 1/1/2000 to 5/1/2015.

Results: Thirteen patients were identified. All patients had failed conservative treatment and 2 of them had not responded to plasmapheresis. A median of 5(1-9) sessions for a total of 20(1-33) hours were performed. CH resulted in a significant decrease of pruritus in 9 patients (69%). 2 patients did not have significant relief and 2 patients did not pursue further treatments after having adverse reaction during the first session. Median pruritic score significantly decreased from 9/10 (9-10) to 4/10 (0-9) posttreatment (p=0.004). Duration of symptom free period ranged from 8 to 46 days (median 18 days) in 6 patients who returned for follow up. 6 patients (46%) experienced adverse reactions described in Table 1.

Table 1.

Sex (M/F)	4/9		
Age	53 (12-68)		
Diagnosis			
Primary sclerosing cholangitis	5		
Failed liver transplant	3		
Primary biliary cirrhosis	1		
Cirrhosis	2		
Others	2		
AST (U/L)	125 (47-267)		
ALT (U/L)	121 (38-357)		
ALP (U/L)	457 (126-1544)		
Number of sessions	5 (1-9)		
Total treatment hours	20 (1-33)		
Duration of symptom free (days)	18 (8-46)		
Complications			
Fever and rigor	2		
Pain (head, chest, back)	4		
Bleeding	2		
Nausea	1		
Hypotension	1		
Lightheadedness	1		
	Pre-treatment	Post-treatment	p-value
Pruritic score (0-10)	9 (9-10)	4 (0-9)	0.004
Total bilirubin (mg/dL)	2.9 (0.6-13.5)	2.9 (0.5-13.8)	0.3
Hemoglobin (g/dL)	11.5 (8.6-13.3)	11.1 (8.8-13.4)	0.3
Leukocyte (x10 ⁹ /L)	6.9 (2.2-18.3)	6.7 (1-16.4)	0.8
Platelet (X10 ⁹ /L)	237 (64-522)	148 (25-380)	0.004

*Data represented in median(min-max)

Conclusions: Charcoal hemoperfusion is an effective therapy for refractory cholestatic pruritus. However, the improvement is not sustainable and the short benefit should be balanced with the invasive nature of the therapy and the relatively common adverse reactions.

SA-PO793

Strict Adherence to Medicaid InterQual® Criteria Increases Adverse Events and Health Care Utilization in Undocumented Dialysis Patients S. Jawad Sher, Melissa D. Anderson, Ranjani N. Moorthi, Sharon M. Moe, Michael T. Eadon. *Medicine, Indiana Univ, Indianapolis, IN.*

Background: Current estimates suggest there are 6000 undocumented ESRD patients in the US that may be ineligible for scheduled hemodialysis. To meet emergency Medicaid requirements, hospitals have sought creative ways to treat undocumented patients. We present data from an undocumented cohort as it progressed through a succession of three periods with different dialysis criterion.

Methods: This is a retrospective evaluation of a prospective cohort of 20 undocumented ESRD patients. The patients were followed over 3 consecutive periods (P1, P2, P3) each of 2 months duration. In P1, patients received twice weekly dialysis. In P2, patients were dialyzed based on strict emergent InterQual® Criteria. In P3, emergent criteria included long interdialytic interval as an additional justification. Adverse outcomes, utilization, and dialysis adequacy in P2 and P3 were compared to P1.

Results: The mean age of the cohort was 35.9 y, 30% were female, 45% were employed, and none were US citizens. Emergent dialysis (P2&P3) was associated with increased biochemical abnormalities (peak K+, mean BUN and serum bicarbonate) as compared to P1 scheduled dialysis (P < 0.05). Emergent dialysis (P2&P3) was associated with an increase in nights hospitalized and ICU days (Fig1). Strict adherence to InterQual® Criteria (P2) was

associated with increased adverse events with a composite OR for intubation, bacteremia, NSTEMI, ICU admit, and death of 48 (5.9-391.2) compared to P1. P2 charge estimates increased from P1 (\$357,501 v \$202,326 per person per year, P<0.001).

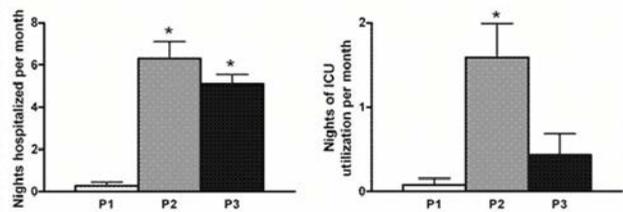


Fig. 1 – Hospital utilization per patient per month. * = P < 0.05.

Conclusions: Strict adherence to InterQual® Criteria increases adverse events and healthcare cost per patient. We must determine better alternatives to emergent dialysis which minimize cost, while maintaining dignity, safety, and quality of life.

SA-PO794

Factors Associated with Withdrawal of Care (WOC) in Maintenance Dialysis Patients Fahad Saeed, Robert Butler, Jesse D. Schold. *Nephrology, Cleveland Clinic.*

Background: There is paucity of data on factors leading to WOC in dialysis patients. We studied this question by using the NIS dataset, 2005-2011.

Methods: We studied the following six major primary diagnoses: MI, cardiogenic shock, sepsis, stroke, CPR and coma. Effect of age, sex, race, hospitals' profit status and comorbidities were assessed on WOC status. We studied 836563 dialysis patients' admissions, and WOC occurred in 68152 patients.

Results: Male sex, African American and Latino races, smoking, obesity, psychosis and anemia carried lower odds of WOC. Primary diagnoses of CPR, coma, MI, cardiogenic shock, and sepsis; and co-morbidities such as CHF, dementia, HTN, CA, liver disease, paralysis, chronic lung disease, DM, weight loss were associated with higher odds of WOC. Odds of WOC were increased by approximately 6 % per year of patient age. Teaching hospitals had higher odds while private hospitals carried lower odds of WOC status.

Conclusions: Age, non-profit hospital status, coma, metastatic malignancy and weight loss are the most significant factors associated with WOC among dialysis patients. These prognostic data should be considered while treating such patients.

Odds Ratio Estimates			
Effect	Point Estimate	95 % CI	P-Value
Male vs. Female	0.892	0.860-0.926	<.0001
Black vs. White	0.494	0.445-0.548	<.0001
Hispanic vs. White	0.445	0.355-0.557	<.0001
Other vs. White	0.582	0.507-0.668	<.0001
Tracheostomy	0.670	0.564-0.796	<.0001
G-tube	0.785	0.671-0.918	0.0025
CPR	1.624	1.400-1.884	<.0001
GI Bleed	1.225	1.134-1.323	<.0001
Cardiac shock	2.311	2.002-2.668	<.0001
MI	1.365	1.258-1.481	<.0001
Coma	4.850	4.025-5.843	<.0001
Sepsis	2.130	1.964-2.311	<.0001
Stroke	1.544	1.419-1.680	<.0001
Smoking	0.565	0.498-0.642	<.0001
Malnutrition	0.682	0.593-0.784	<.0001
Dementia	1.966	1.736-2.227	<.0001
Alcohol abuse	1.239	1.092-1.406	0.0009
Anemia	0.874	0.808-0.945	0.0008
CHF	1.225	1.163-1.291	<.0001
DM	0.614	0.575-0.656	<.0001
HTN	0.673	0.634-0.714	<.0001
Liver disease	1.430	1.279-1.599	<.0001
Metastatic cancer	3.334	2.988-3.719	<.0001
Obesity	0.777	0.708-0.851	<.0001
Paralysis	1.214	1.096-1.346	0.0002
Psychosis	0.863	0.763-0.976	0.0191
Cancer	2.323	2.095-2.576	<.0001
Weight loss	2.154	1.819-2.551	<.0001
Teaching hospital status	1.263	1.048-1.522	0.0140

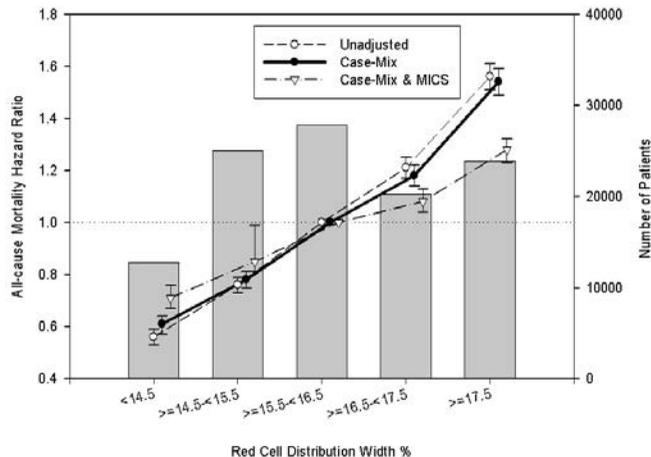
SA-PO795

Red Cell Distribution Width and Mortality in Incident Hemodialysis Patients Tania Vashistha,¹ Elani Streja,¹ Miklos Zsolt Molnar,² Connie Rhee,¹ Steven M. Brunelli,³ Hamid Moradi,¹ Tae Hee Kim,¹ Vanessa A. Ravel,¹ Melissa Soohoo,¹ Csaba P. Kovcsy,² Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC; ³DaVita Clinical Research.

Background: Red cell distribution width (RDW) is a measure of red blood cell size and variability that is often used as an indicator of iron-deficiency anemia. Although RDW has recently been found to be associated with mortality in the general population, few studies have examined this association in hemodialysis (HD) patients.

Methods: We examined the association of RDW with all-cause mortality in a cohort of 109,675 incident HD patients from a large dialysis organization during 2007-2011 using Cox proportional hazards regression with adjustment for case-mix (demographics, comorbidities covariates) and markers of malnutrition and inflammation (MICS). RDW was divided into 5 categories <14.5, 14.5-<15.5, 15.5-<16.5, 16.5-<17.5, and ≥17.5 %.

Results: The mean age (mean±SD) of the cohort was 63±15 years old and included 44% females, 58% diabetics, and 31% African Americans. Higher baseline RDW was linearly associated with higher all-cause mortality risk in both unadjusted and fully adjusted models.



Conclusions: Higher RDW is associated with higher mortality risk in HD patients. It is unclear whether RDW is a risk factor for mortality or an epiphenomenon of underlying biological and metabolic imbalances across RDW categories. Further studies are needed to confirm the findings generated from our study and to determine the mechanisms underlying the RDW-mortality association.

Funding: NIDDK Support

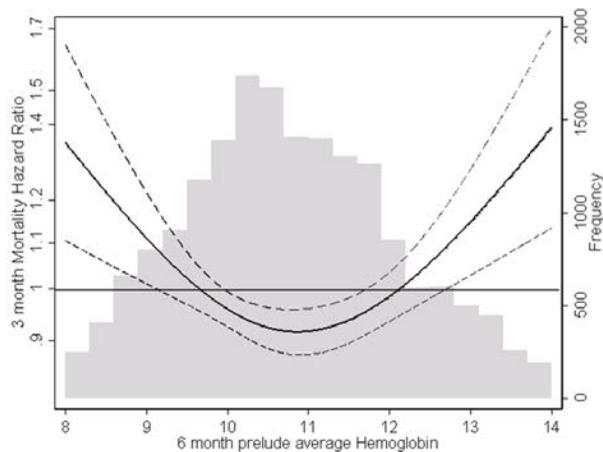
SA-PO796

Association of Pre-ESRD Hemoglobin with Early Post-ESRD Mortality Among U.S. Veterans: A Transition of Care in CKD Study Melissa Soohoo,¹ Connie Rhee,¹ Vanessa A. Ravel,¹ Elani Streja,¹ Jennie Jing,¹ Danh V. Nguyen,¹ Csaba P. Kovcsy,² Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC.

Background: Patients with chronic kidney disease (CKD) are often afflicted with anemia. Previous studies have shown that low hemoglobin (HGB) is associated with pre-dialysis mortality in non-dialysis dependent CKD patients, yet the association of HGB levels in the immediate period preceding dialysis (prelude) and early post-dialysis mortality remains unknown. We hypothesized that lower HGB levels are associated with higher post-transition survival in comparison to higher HGB levels.

Methods: We investigated 18,555 US veterans who initiated dialysis between 10/2007-9/2011 and had at least 1 HGB measurement during the 6 month prelude period before dialysis transition. 6 month averaged HGB was used as a continuous predictor of early post dialysis all-cause mortality occurring in the first 3 months after initiation using restricted cubic spline models and Cox proportional hazard regressions. The models were adjusted for age, gender, race, ethnicity, region and primary cause of ESRD.

Results: The analytic cohort was a mean±SD age of 68±11 yrs, among whom 30% were African-American, 7% Hispanic and 50% had diabetes as the cause of ESRD. The 6 month prelude HGB average was 10.9±1.6 g/dL. Prelude HGB exhibited a U-shaped association with 3-month post-ESRD all-cause mortality; patients with a 6 month prelude HGB average between 10-11.5 g/dL had better survival, whereas patients with HGB measurements <9 g/dL or >13 g/dL had higher mortality (Figure).



Conclusions: HGB during the 6 month prelude period prior to dialysis initiation exhibited a U-shaped association with all-cause mortality in the immediate interval post-dialysis with the best survival when HGB was between 9 and 11 g/dL. These results confirm the findings of earlier clinical trials, and support current therapeutic paradigms for management of pre-ESRD anemia.

Funding: NIDDK Support

SA-PO797

Higher Serum Ferritin Levels are Associated with Better Survival in the HEMO Study Anna Jeanette Jovanovich,^{1,2} Eugene J. Nuccio,² Alfred K. Cheung,^{3,4} Tom Greene,⁴ Michel Chonchol.² ¹Denver VA Medical Center; ²Univ of Colorado Denver; ³VA Salt Lake City; ⁴Univ of Utah.

Background: Ferritin is an important indicator of total body iron stores and has been shown to prevent ox-LDL-induced oxidative injury in endothelial cells. Studies regarding the relationship between serum ferritin levels and all-cause mortality in chronic hemodialysis patients are conflicting. The purpose of this study was to determine the relationship between higher serum ferritin levels and death among participants in the Effect of Dialysis and Membrane Flux in Maintenance Hemodialysis (HEMO) trial.

Methods: We studied the association of serum ferritin and iron levels with all-cause mortality among 1799 subjects from the HEMO trial. Cox regression models adjusted for important confounding variables including demographics, comorbidities, treatment assignment, smoking, and albumin.

Results: Mean age was 58±14 years, 56% were female, and 63% were black. Median (IQR) ferritin and iron levels were 249 (2-497) ng/mL and 50 (5-78) µg/dL, respectively. Over a mean follow-up of 2.84 years, there were 582 deaths. Among subjects with levels in the highest quartile compared to the lowest quartile, both ferritin and iron were significantly associated with reduced all-cause mortality in adjusted analyses, odds ratio (OR) 0.67 (95% CI, 0.46-0.97) and OR 0.60 (95% CI, 0.42-0.85), respectively.

Conclusions: Among subjects participating in the HEMO trial higher serum ferritin and iron levels were associated with reduced mortality. We hypothesize that ferritin may play an important role in protecting the endothelium from oxidative stress-induced damage.

Funding: NIDDK Support, Veterans Administration Support

SA-PO798

Anemia in Chronic Kidney Disease Patients Could Be Linked to Indoxyl Sulfate Levels Denise Mafra,¹ Natalia Alvarenga Borges,¹ Milena Barcza Stockler-Pinto,² Amanda F. Barros.² ¹Medical Sciences Graduate Program, Federal Univ Fluminense, Brazil; ²Cardiovascular Sciences Graduate Program, Federal Univ Fluminense, Brazil.

Background: Indoxyl sulfate (IS) is a uremic toxin derived from the action of colon bacteria in dietary tryptophan. This toxin is related to many complications for chronic kidney disease (CKD) patients, including anemia. The aim of this study was to verify the relationship between IS plasma levels and anemia in hemodialysis (HD) patients.

Methods: This transversal study included 18 HD patients (50% men, 54.2 ± 11.6 yrs, BMI 26.3 ± 4.7kg/m², time on dialysis 51 (30-52) months, all patients received the same dose erythropoietin per week). Routine laboratory parameters were measured, the total IS plasma levels were quantified with high-performance liquid chromatography (HPLC) and protein C reactive (CRP) levels analyzed by Immunoenzymatic Assay. Statistical analyzes were performed with SPSS version 19.0.

Results: The mean of hemoglobin was 11.0 ± 1.28 g/dL and hematocrit of 34.2 ± 3.0%. The mean of IS plasma levels was 23.9 (10.3 - 100.9) mg/L and CRP 3.1 (1.3 - 8.6) mg/dL. Multivariate linear regression analysis adjusted for age, sex, time on HD, albumin, BMI, CRP revealed that serum hemoglobin (β = -0.62; p = 0.01) was independently and negatively associated with IS levels.

Conclusions: This study provided evidence that IS seems be associate with anemia in HD patients and therapeutic strategies in the clinical care to reduce uremic toxins levels may be effective to management of anemia in HD patients.

Funding: Government Support - Non-U.S.

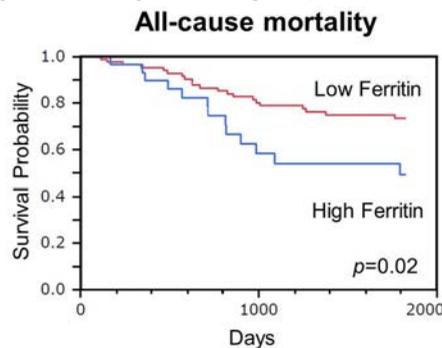
SA-PO799

High Ferritin Level Above 100 Ng/ml Is Associated with Poor Clinical Outcomes in Maintenance Hemodialysis Patients Raku Son,¹ Takuya Fujimaru,² Takeshi Kimura,³ Masataka Hasegawa,² Yuki Heath,² Fumika Taki,² Miyuki Futatsuyama,² Masahiko Nagahama,² Yasuhiro Komatsu.² ¹Internal Medicine, St. Luke's International Hospital, Tokyo, Japan; ²Nephrology, St. Luke's International Hospital, Tokyo, Japan; ³Center for Clinical Epidemiology, St. Luke's International Univ, Tokyo, Japan.

Background: Ferritin is a well-known marker of iron deficiency anemia, but the target ferritin level in maintenance hemodialysis (MHD) patients still remains controversial among countries. This study is to examine the association of baseline ferritin level and clinical outcomes.

Methods: We retrospectively collected data of 116 patients on MHD at St Luke's International Hospital for 60 months. Ferritin level above 100 ng/ml was defined as high ferritin (HF) group and the rest as low ferritin (LF). The primary end point was all-cause mortality. The secondary endpoints included cardiovascular events and positive blood cultures. Cox proportional hazard analysis was performed as multivariate analysis.

Results: Of the 116 patients (age 65.3±13.4, 70% of males), 29 patients belonged to HF and 87 to LF. During the follow-up (median 60 months, IQR 24.1-60 months), 22 patients (18.9%, 13 in HF and 9 in LF) died. In Kaplan-Meier survival curves, HF showed significantly poor survival compared with LF (p=0.02).



After adjusting age, sex, vintage of hemodialysis and past medical history of diabetes mellitus, hazard ratio (HR) of HF was 2.60 (95% confidence interval 1.25-5.24, p=0.01). The multivariate analysis for cardiovascular events revealed a similar result with statistical significance (HR 2.65, 95% confidence interval 1.07-6.31, p=0.04). For positive blood cultures, HR of HF was 1.81, although not statistically significant (p=0.17).

Conclusions: In MHD patients, ferritin level above 100 ng/ml increases all-cause mortality and cardiovascular events.

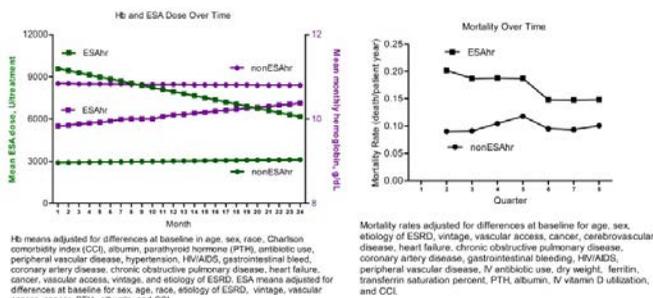
SA-PO800

Erythropoietin-Stimulating Agent (ESA) Hyporesponse (ESAhr) Is Associated with Persistently Elevated Mortality Among Hemodialysis (HD) Patients Jiacong Luo,¹ Donna E. Jensen,¹ Sarb Shergill,² Bradley J. Maroni,² Steven M. Brunelli.¹ ¹DaVita Clinical Research, Minneapolis, MN; ²Akebia Therapeutics, Cambridge, MA.

Background: Prior studies have examined the association between ESAhr and outcomes among HD patients. However, none has been conducted using contemporary data nor with a definition of ESAhr that is relevant in contemporary practice, specifically following 2011 changes to the US ESA labels and reimbursement policy.

Methods: We retrospectively studied a cohort of prevalent (vintage >6 months) HD patients from a single large provider (N=98,972) for 24 months (2012-2013). ESAhr was defined as 2 consecutive bimonthly hemoglobin (Hb) measures <10 g/dL with erythropoietin dose >7700 U/treatment. Patients were categorized as of 1Q2012 and followed longitudinally. Associations between ESAhr and mortality were determined using generalized estimating equations adjusting for baseline characteristics.

Results: At baseline, 12,361 (12.5%) patients qualified as having an ESAhr. Mean ESA dose was initially 3-fold greater in ESAhr than control patients and remained 2-fold greater by the end of study.



Hb means adjusted for differences at baseline in age, sex, race, Charlson comorbidity index (CCI), albumin, parathyroid hormone (PTH), antibiotic use, peripheral vascular disease, hypertension, HIV/AIDS, gastrointestinal bleed, coronary artery disease, chronic obstructive pulmonary disease, heart failure, cancer, vascular access, vintage, and etiology of ESRD. ESA means adjusted for differences at baseline for sex, age, race, etiology of ESRD, vintage, vascular access, cancer, PTH, albumin, and CCI.

Initially, mean Hb level was approximately 1 g/dL lower among ESAhr patients and remained 0.4 g/dL lower through the end of study. During follow-up, ESAhr was associated with a greater adjusted risk of mortality vs nonESAhr (control referent). Incidence rate ratios (95% confidence interval) ranged from 2.24 (1.93-2.60) in the 2nd quarter to 1.48 (1.18-1.84) in the 8th quarter.

Conclusions: Using a contemporarily relevant definition, ESAhr at a single point in time is potentially and persistently associated with greater ESA utilization, lower Hb levels, and higher mortality risk.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

SA-PO801

Impact of ESAs and Iron on Survival in Hemodialysis Patients: Which Is the Best, Which Is the Worth? Jacques B. Rottembourg,¹ Alain Guerin.²
¹Dept of Nephrology, Hôpital de la Pitié, Paris, France; ²Hemodialysis Units, Diaverum, Paris, France.

Background: Appropriate anemia management for Hemodialysis (HD) patients (Pts) is still challenging. Intravenous (IV) iron and erythropoiesis-stimulating agents (ESAs) are the main thérapies, with conflicting outcomes. In the unit, pts were treated over the last seven years, cumulative doses of ESAs (darbepoetin alfa [DA]), converted in µg per session, and IV iron (iron-sucrose [IS]), converted in mg per session, were exactly constantly reported. Survival depending on the cumulative dose of each product and both products together was calculated using the Kaplan Meier methodology.

Methods: 300 incident HD pts (67% male) mean[M] (SD) age at start 59.7(16.3) years, were treated for 100,430 dialysis sessions [S], receiving all over 1,192,250 µg of DA, and 1,794,050 mg of IS. M Hb level was 11.55(0.77) g/dL, M TSAT 37.1(8.5)%, and M ferritin 562(322) µg/L. The M DA dose injected was 12.91(9.90) µg per S. The M IS dose injected was 20.91(11.57) mg per S. Expressing the separate doses of DA and IS received by the pts in three categories for each product, we obtained 9 categories of pts, depending on whether they received low, middle, or high doses of ESA and IS per S: M doses were [5.4(2.6), 10.8(3.3), 25.1(14.8)µg] for ESA, [12.5(4.5), 18.4(3.4), 32.3(11.9) mg] for IV iron respectively.

Results: Survival was expressed at 1000, 2000, and 3000 days (d):

	ESA-Low	p	ESA-Middle	p	ESA-High
Iron-Low	50 Pts	p<0.012	39 Pts	p=NS	36 Pts
	1000 d : 100%		1000 d : 91%		1000 d : 92%
	2000 d : 96%		2000 d : 74%		2000 d : 61%
	3000 d : 70%		3000 d : 35%		3000 d : 40%
	p=NS		p=NS		p=NS
Iron-Middle	39 Pts	p<0.001	49 Pts	p=NS	31 Pts
	1000 d : 100%		1000 d : 96%		1000 d : 88%
	2000 d : 90%		2000 d : 57%		2000 d : 46%
	3000 d : 77%		3000 d : 24%		3000 d : 33%
	p=NS		p<0.05		p<0.001
Iron-High	29 Pts	p<0.004	41 Pts	p=NS	53 Pts
	1000 d : 95%		1000 d : 93%		1000 d : 67%
	2000 d : 79%		2000 d : 10%		2000 d : 31%
	3000 d : 75%		3000 d : 0%		3000 d : 0%

The better survival was obtained in the group of low ESA and low IV iron, the worth was high ESA and high IV iron. Survival is better with low ESA, whatever is the IV iron dose injected. High ESA dose, whatever IV iron dose is injected, seems to be worth.

Conclusions: Because the majority of patients on HD receives ESA and IV iron, rigorously conducted and adequately powered clinical trials studying the cumulative doses of ESA and IV iron, reflective of present-day practice, are greatly needed.

SA-PO802

Relationship Between Statin Prescription and Erythropoietin Stimulating Agent (ESA) Hyporesponsiveness in Hemodialysis (HD) Patients: Results from the Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS) Takeshi Hasegawa,^{1,3} Junhui Zhao,² Douglas S. Fuller,² Brian Bieber,² Yun Li,³ Jarzy Zee,² Hal Morgenstern,³ Masaomi Nangaku,^{4,5} Bruce M. Robinson,² Norio Hanafusa.^{4,5} ¹Fukushima Medical Univ Hospital, Fukushima City, Fukushima, Japan; ²Arbor Research Collaborative for Health, Ann Arbor, MI; ³Univ of Michigan, Ann Arbor, MI; ⁴The Univ of Tokyo, Tokyo, Japan; ⁵Anemia Working Group of JDOPPS, Japan.

Background: Statins are widely used in HD patients and have pleiotropic anti-inflammatory and anti-oxidative effects, but the latest guideline is advising against starting its use in this population. Hypothesizing that statins could be used as adjuvant treatment for renal anemia, we examined the association between statin prescription (Rx) and ESA hyporesponsiveness (ESAHYPO) in Japanese HD patients (pts) prescribed ESAs.

Methods: We included 3,208 pts in 178 HD facilities dialyzed 3x/week for ≥4 months from JDOPPS phases 3-5. Statin Rx was reported at baseline. ESAHYPO was defined in the next 4 months as a binary indicator (mean hemoglobin (hgb) <10 g/dL and mean ESA

dose >7,500 units/wk) and separately as ESA resistance index (ERI, mean ESA dose/[post-dialysis body weight*mean Hgb]). We used adjusted logistic and linear regressions to evaluate the associations.

Results: 16.1% of pts reported statin Rx at study entry; 8.8% were classified as ESAHYPO during follow-up. Compared to pts without statin Rx, pts with statin Rx had lower odds of ESAHYPO. Similarly, ERI was lower for statin Rx vs. no statin Rx (adjusted mean ratio [95%CI] = 0.93[0.88, 1.00] in model 3).

Table: Association of statin prescription with subsequent ESA hyporesponsiveness

Statin Rx	N Pts	N Events	Odds Ratio of Hgb < 10, ESA > 7500 for Statin Users vs. Non-Users (95% CI)*		
			Model 1 ^b	Model 2 ^c	Model 3 ^d
+	516	35	0.71(0.49,1.02)	0.66(0.45,0.97)	0.70(0.47,1.03)
-	2692	246			

- a. ESA and Hgb are averaged over the four months after baseline.
 - b. Model 1: Adjusted for DOPPS phase
 - c. Model 2: Adjusted for model 1 + age, gender, vintage, 11 summary comorbidities and post dialysis weight
 - d. Model 3: Adjusted for model 2 + Kt/V, treatment time, hospitalization within 3 months, IV iron prescription, CRP, albumin, TSAT, ferritin
- A ratio of 1: 200 was used to convert darbepoetin to the equivalent epoetin dose.

Conclusions: Our results suggest that statins may reduce ESAHYPO in HD pts. Causal inference is limited by the observational design and unmeasured compliance with statin Rx. The applicability of this finding to non-Japanese populations merits further study, as reported statin Rx is low in JDOPPS.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

SA-PO803

25(OH)D Deficiency Contributes to the Erythropoietin Hyporesponsiveness in Patients on Maintenance Hemodialysis Pu Lei, Daqing Hong, Fei Deng, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.

Background: The aim of this study was to identify the factors that contribute to erythropoietin hyporesponsiveness in patients on maintenance hemodialysis (MHD).

Methods: demographic data , hemoglobin, dose of erythropoetin, biochemical indicators and other related indicators of 80 MHD patients were collected and analyzed retrospectively. They were followed up for 12 moths. Erythropoietin resistance index (ERI) was used to evaluate the response to erythropoietin in patients on MHD. The ERI was calculated dividing the weekly weight-adjusted (kg) dose of ESA (IU) by the hemoglobin level (g/dL). Logistic regression study was used to determine the key variables which might be independently associated with erythropoietin hyporesponsiveness in MHD patients.

Results: Mean erythropoietin resistance index (ERI) for the entire study population was 16 U/kg/week/g/dl. 26% patients were erythropoietin hyporesponsive. Patients were divided into two groups according to ERI: ERI<25IU/week/kg/g/dl and ≥25IU/week/kg/g/dl. In ERI≥25 U/kg/week/g/dl cases, the proportion of female gender was higher, hemoglobin and 25(OH)D were significantly lower than that of patients with ERI<25 U/kg/week/g/dl. In addition, comparing with ERI<25 U/kg/week/g/dl patients, body mass index (BMI) and serum cholesterol were slightly lower in ERI≥25 U/kg/week/g/dl patients(p=0.05). Logistic regression study adjusted gender, dialysis periods, BMI, Kt/v, serum cholesterol, serum albumin, and alkaline phosphatase, indicating an independent association between 25(OH) D deficiency and the erythropoietin hyporesponsiveness(HR:4.590, 95%CI:1.277~16.503).

Conclusions: Erythropoietin hyporesponsiveness is prevalent among MHD patients. Female gender and malnutrition are associated with erythropoietin hyporesponsiveness. 25(OH)D deficiency is the main risk factor for erythropoietin hyporesponsiveness. Improving 25(OH)D deficiency and malnutrition may increase the response to erythropoietin treatment in MHD patients.

SA-PO804

Incidental Findings on 15 Fluorodeoxyglucose Positron Emission Tomography Along with Low Dose Computerized Tomography (FDG PET CT) Scans Among Clinically Stable Haemodialysis with Erythropoietin Stimulating Agent (ESA) Hypo Responsiveness (ESA-R) Tarun Kaushik, Stanley Fan, Neringa Vilimiene, Muhammad M. Yaqoob. Nephrology (*Contributed equally), Barts Health Cardiovascular Biological Research Unit and Barts Health NHS Trust, United Kingdom.

Background: Burden of comorbidities is high among hemodialysis (HD) patient. Underlying infective focus or occult malignancy is always of concern when clinically stable patients have ESA-R (ESA resistance index of ≥6.5 U/kg body weight/Hb gm/dl per week).

Methods: Patients with similar characteristics were recruited as a part of an on-going clinical trial, which also included whole body FDG PET CT scan at baseline and at six month. Any clinically significant finding was reported to clinical team for further action. We were therefore in a unique position to report incidental findings in this cohort of patients.

Results: Out of total 111 scans 31% showed pathological tracer uptake including suspected malignancy. 2 patients with confirmed malignancy had to be suspended from on going living donor kidney transplant work up. 4 patients needed antibiotics and 1 had anti TB therapy. 7 patients needed appropriate invasive investigations for confirmatory diagnosis. There was no association between elevated CRP around time of scan and pathological tracer uptake (P=0.468)

Imaging	Initial	Follow up	Total
Number of scans	62	49	111
Pathological tracer uptake	20	15	35
Suspected malignancy	9	1 (new)	10
Lung nodule	0	1	
Inflammatory / infective lymphadenopathy	4	1 (old)	
Colonic polyp (non malignant)	1		
Infected renal cyst	1		
Infected sebaceous cyst	1		
Renal cell carcinoma	1		
Papillary carcinoma of thyroid	1		
Confirmed malignancy (new)	2	2 (old)	2
Pathological uptake (other)	11	11	22
Arthropathy	2	2	
Sialadenitis	2	1	
Access related infection	1	1	
Gastric mucosal uptake	2	3	
Lung changes	3	2	
Lymphadenopathy	0	1	
Other	1	1	

Conclusions: This observation confirms occult disease burden among this study group which otherwise would have been undetected and may have seriously impacted patient outcome. We recommend that HD patients with ESA-R should be regarded as high risk and further work is needed to devise easily accessible monitoring tools as part of their management.

SA-PO805

Serial Hepcidin Concentrations in Incident and Prevalent Hemodialysis Subjects Relating to ESA Response Michael E. Brier,¹ Michael Merchant,¹ Xiaolan Zhang,² Jonathan Himmelfarb,³ Brad H. Rovin,² Jon B. Klein.^{1,4} ¹Medicine, Univ of Louisville, Louisville, KY; ²Medicine, Ohio State Univ, Columbus, OH; ³Medicine, Univ of Washington, Seattle, WA; ⁴Robley Rex VA Medical Center, Louisville, KY.

Background: Hepcidin is a key regulator of iron metabolism and alterations in levels may contribute to an apparent erythropoietin (EPO) resistance. The purpose of the current study was to determine the effect of incident vs. prevalent subjects on hepcidin concentrations at a single point in time and serially up to 6 months.

Methods: We collected blood for hepcidin measurement in 257 prevalent and 33 incident hemodialysis subjects from 2 locations (Louisville and Washington). Repeated blood samples were collected for up to 6 months in 66 prevalent and 33 incident subjects. A total of 752 hepcidin measurements were performed. Additionally we collected EPO dose, hemoglobin (Hb), TSAT, and Ferritin. Hepcidin-25 peptide was measured by EIA (Bachem Group) and values are reported as ng/ml.

Results: Hepcidin concentrations in Incident subjects were higher (191±141) vs. Prevalent subjects (151±102, p=0.043) and in Females (n=93, 169±109) vs. Males (n=151, 140±97, p=0.015). There was no difference by Race p=0.948 (African American n=132, 150±106; Caucasian n=95, 151±101; Asian n=10, 154±78; Other n=7, 173±96). Forty five prevalent and 11 incident subjects did not require EPO (EPO naive) for anemia for 6 months prior to Hepcidin measurement. ANOVA of hepcidin by Incident (p=0.018) and EPO naive (p=0.006) showed significant differences (Incident EPO Naive 156±96; Incident EPO 206±161; Prevalent EPO Naive 97±86; Prevalent EPO 164±101). Hepcidin concentrations remained constant in Incident subjects for the first 6 months of dialysis (p=0.913). (Month 1-6; 190, 153, 180, 178, 176, 166).

Conclusions: Differences in Hepcidin concentration exist between Incident and Prevalent hemodialysis subjects as well as Males and Females. Increased Hepcidin concentrations in Incident subjects are maintained for at least the first 6 months in dialysis. Those subjects that are naive to EPO have the lowest Hepcidin concentrations and may provide evidence for the usefulness of Hepcidin as a therapeutic target.

Funding: NIDDK Support

SA-PO806

Female Gender Is Associated with Higher Degree of Erythropoietin Hyporesponsiveness in Maintenance Hemodialysis Patients Daqing Hong, Fei Deng, Li Wang. *Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: To investigate the difference of erythropoietin hyporesponsiveness between female and male patients.

Methods: 310 MHD patients (163 male and 147 female) were enrolled with their demographic information, comorbidities, erythropoietin dosage, hemoglobin, dry body

weight, ferritin and Kt/V collected between Jan, 2014 and Mar, 2014. ERI was calculated to study the response to erythropoietin treatment. Covariates were analyzed to compare the relationship between gender and erythropoietin hyporesponsiveness.

Results: The ERI index was higher in female patients than male patients (28.8±16.0 vs. 20.2±12.3 U/kg/week/g/dl, P<0.05). Hb was lower and Kt/V was higher in female patients than in male patients (P<0.05). There were no difference in age, ferritin, and PTH between male and female patients (P<0.05). The mean dosage of erythropoietin was higher in female than in male patients (14934±6927U vs. 13353±7554U, P>0.05). Patients were divided into 3 groups according to the tertiles of ERI and no difference was found in PTH, ferritin, Kt/V and age among the three groups.

Conclusions: Female hemodialysis patients are associated with higher degree of erythropoietin hyporesponsiveness. Special attention must be paid to them when treatment strategy is made to treat anemia.

SA-PO807

Oral Vitamin C Supplementation Reduces Erythropoietin Requirement in Hemodialysis Patients with Functional Iron Deficiency Tanjim Sultana, Maria V. DeVita, Michael F. Michelis. *Medicine, Lenox Hill Hospital, New York, NY.*

Background: Functional iron deficiency (FID) is a major cause of erythropoietin (Epo) hyporesponsiveness and persistent anemia in dialysis patients. Vitamin C acts as a reducing agent and enhances mobilization of the ferrous form of iron to transferrin thus increasing its bioavailability. High dose intravenous vitamin C has been shown to decrease the Epo requirement and improve hemoglobin levels in previous studies. This route has its downside regarding difficulty of use, higher cost and associations with increased oxalate levels and inflammatory markers. Use of oral vitamin C has been limited due to the concerns of low bioavailability and patients compliance to medication. This study assessed the effect of low dose oral vitamin C on Epo dose requirements in stable hemodialysis patients with functional iron deficiency.

Methods: This prospective study included 22 stable hemodialysis patients with functional iron deficiency defined as transferrin saturation (Tsat) <30% and ferritin levels of >100 mcg/L with Epo requirement of ≥ 4000 u/HD. Patients received oral vitamin C 250 mg daily for three months. Epo dose was adjusted according to unit protocol depending on the hemoglobin level. Hemoglobin, iron and Tsat levels were recorded monthly. None of these participants received iron or renal vitamin supplementation during the study period.

Results: The mean Epo dose was reduced in fifteen participants by 867±1356u/HD (p=0.03). In seven responders there was 33% reduction in Epo dose from their base line. No ill effects of oral vitamin C were observed. Despite adjustment of Epo dose, hemoglobin level was significantly increased from 10.1±0.6 mg/dL to 10.7±0.6 mg/dL (p=0.03). There were no significant change in Tsat and ferritin levels.

Conclusions: Daily low dose oral vitamin C supplementation reduced Epo dose requirements in hemodialysis patients with functional iron deficiency. Despite concerns regarding oral vitamin C absorption in dialysis patients this study indicates Vitamin C is well tolerated and effective.

SA-PO808

The Greatly Misunderstood Erythropoietin Resistance Index Yossi Chait,¹ Sahir Kalim,³ Joseph Horowitz,¹ Christopher V. Hollot,¹ Elizabeth D. Ankers,³ Michael J. Germain,² Ravi I. Thadhani.³ ¹UMass; ²WNE Renal & Transplant Assoc; ³MGH.

Background: The use of erythropoiesis stimulating agents (ESAs) to treat anemia in end stage renal disease remains controversial due to reported associations with adverse events. Many studies introduce so-called ESA resistance indices (ERIs) to characterize a patient's resistance to ESA.

Methods: We use retrospective data from a cohort study of incident hemodialysis patients (n=8924). ERI is defined as average weekly erythropoietin (EPO) dose (IU) per kg body weight (EPOwt) per average hemoglobin (Hgb) (g/dl) over a 3-month period. Linear regression was used to describe the relationship between ERI and EPOwt. Logistic (Cox proportional hazards) regression modelled the relationship between 1-year mortality (survival time) and albumin, age, and either ERI or EPOwt.

Results: ERIs were strongly linearly related with EPOwt (r=0.98) but weakly correlated with 1/Hgb (r=0.44). Associations between covariates and mortality based on two logistic regression models differing only by a single covariate, EPOwt or ERI, were almost identical (figure 1); the same was found for Cox proportional hazards models (Table 2).

Table 1: Logistic regression of death on covariates albumin, age, and X, where X = log(ERI) (Model A) or X = log(EPOwt) (Model B). OR: odds ratio, Sens: sensitivity, Spec: specificity.

	Model A		Model B	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Albumin	0.320 (0.278-0.369)	< 2e-16	0.312 (0.270-0.359)	< 2e-16
Age	1.035 (1.029-1.040)	< 2e-16	1.034 (1.029-1.040)	< 2e-16
X	1.380 (1.239-1.536)	4.22e-09	1.330 (1.188-1.489)	7.2e-07
	AUC=0.72, Sens=0.65, Spec=0.67		AUC=0.72, Sens=0.64, Spec 0.68	

Table 2: Cox proportional hazard regression results with covariates albumin, age, and X = log(ERI) (Model A) or X = log(EPOwt) (Model B). HR: hazard ratio.

	Model A		Model B	
	HR (CI) (P-value)	P-value	HR (CI) (P-value)	P-value
Albumin	0.357 (0.317-0.403)	< 2e-16	0.348 (0.309-0.392)	< 2e-16
Age	1.032 (1.027-1.037)	< 2e-16	1.032 (1.027-1.037)	< 2e-16
X	1.343 (1.219-1.479)	2.17e-09	1.301 (1.175-1.441)	4.29e-07

The area under the ROC curve (AUC) was changed by <1% when covariates ERI or EPOwt were removed from the logistic regression model (AUC = 0.71, sensitivity = 0.66, specificity = 0.65).

Conclusions: ERIs are strongly linearly related to weight-adjusted EPO doses by a "universal" (i.e., not patient specific) formula, hence are merely surrogates of EPO dose. Because true resistance must depend on both the input, (EPO) and its effect (Hgb increase over endogenous Hgb level), ERI appears to be a poor marker of resistance. EPO dose itself, even though a statistically significant covariate, does not substantially strengthen the association between mortality and albumin and age as assessed by logistic or Cox regression.

Funding: NIDDK Support

SA-PO809

Evaluation of Iron Deposition by MRI in the Heart and Liver in End Stage Renal Disease Patients on Hemodialysis Rhea Bhargava,¹ Ibrahim Saeed,³ Joseph S. Soltys,⁴ Omkar U. Vaidya.² ¹Dept of Internal Medicine, Univ of Missouri- Kansas City, Kansas City, MO; ²Dept of Nephrology and Hypertension, Univ of Missouri- Kansas City, Kansas City, MO; ³Dept of Cardiovascular Diseases, Mid America Heart Inst, Saint Luke's Hospital, Kansas City, MO; ⁴Dept of Cardiovascular Imaging, Cardiovascular Imaging Technologies, LLC, Kansas City, MO.

Background: Anemia is highly prevalent in patients with chronic kidney disease and its management is one of the key components of treatment in this population. 2011 introduced the bundling system which led to increased use of parenteral iron to treat anemia in this population. There has been significant controversy regarding our current model of iron and whether this leads to iron overload and increased mortality.

Methods: Retrospective evaluation of patients with end-stage renal disease on hemodialysis who had a cardiac MRI for clinical reasons to evaluate for iron deposition in the heart and liver. Exclusion criteria: Porphyria cutanea tarda, chronic liver disease, hemochromatosis, sideroblastic anemia, thalassemia. Inclusion criteria: End stage renal disease and received a cardiac MRI after 3-5 years of hemodialysis.

Results: Average total dose of venofer dose before cardiac MRI was 3500 mg. Average ferritin level :695 ng/ml. Average iron saturation : 34%. All patients receiving IV iron had hepatic iron deposition. No correlation was seen between ferritin or iron saturation and hepatic iron deposition. A weak relationship was noted between the total iron dose and hepatic iron deposition.

Conclusions: These data suggest that even though we still use iron markers like ferritin and iron saturation for treatment of anemia in ESRD patients, this may not have a correlation with iron deposition in the liver. Significant iron deposition was not noted in the myocardium. MRI can be a useful modality to evaluate iron overload in this population. Larger studies are needed to evaluate this issue and to formulate an ideal way of intravenous iron dosing in ESRD patient on hemodialysis.

SA-PO810

Achieved Iron Stores and Clinical Safety in a Trial of Ferric Citrate as a Phosphate Binder Kausik Umanath,¹ Barbara A. Greco,² Molly Mcfadden,³ Diana I. Jalal,⁴ Sean D. Barry,⁵ Simin Goral,⁶ Mohammed Sika,⁷ Robert M. Niecestro,⁸ Mark Koury,⁷ Julia Lewis,⁷ Tom Greene,³ Jamie P. Dwyer,⁷ The Collaborative study group.⁸ ¹Henry Ford Hosp; ²Baystate Med Ctr; ³U of Utah; ⁴U of Colo; ⁵LSU Health; ⁶U of PA; ⁷Vanderbilt; ⁸CSG.

Background: Adequate Fe stores are needed for hematopoiesis in ESRD pts on ESA, but optimal Fe stores assuring efficacy/safety are unknown. PO Fe preparations have been unable to do this. In a multicenter phase 3 RCT we showed ferric citrate (FC) as a Phos binder ↑Fe stores and ↓IV iron/ESA use. We studied subjects' safety in this trial based on achieved Fe stores.

Methods: 441 subjects randomized 2:1 to FC or non-Fe-containing active control were followed for 52 wks. IV iron use was at a site's discretion while ferritin <1000 ng/mL and TSAT <30%. Serious adverse events (SAE), ferritin and TSAT were studied using time-dependent Cox regression, relating trailing 3-mo running means of ferritin/TSAT to subsequent SAE. 1° outcome was composite of CV, ID, GI and Hepatobiliary SAE. Clinical classes of ferritin/TSAT were used, adjusted for age, sex, black race, DKD and prior CVD.

Results: 437 subjects were analyzable. No baseline Δ among groups existed. TSAT 30-50% protected against future SAE, Table 1, but not so for any ferritin category, Table 2. Hazard ratio (HR) for 1° outcome per 10 unit Δ in TSAT was 0.81 (0.66-0.99, p=0.045) with adjustment for ferritin, and HR per 400 unit Δ in ferritin was 1.16 (0.9-1.48, p=0.23) with adjustment for TSAT. Sensitivity analyses, adjusted for baseline Alb and Phos, and introducing a 1-mo lag to address confounding by ferritin as acute phase reactant, showed no Δ in result.

Table 1. TSAT<30% is referent.

TSAT, %	HR	95% CI	p
30-50	0.56	0.37-0.86	0.007
>50	0.9	0.46-1.75	0.76
Adjusted for Ferritin			
30-50	0.58	0.37-0.88	0.012
>50	0.91	0.45-1.86	0.8

Table 2. Ferritin< 500 ng/mL is referent.

Ferritin, ng/mL	HR	95% CI	p
500-1000	0.8	0.52-1.23	0.3
>1000	0.85	0.47-1.55	0.6
Adjusted for TSAT			
500-1000	0.87	0.56-1.34	0.53
>1000	0.94	0.5-1.79	0.86

Conclusions: TSAT 30-50% appears to be protective vs <30%. No TSAT upper limit was evident. There were no SAEs at ferritin. Fe stores across the range studied did not risk at levels, and TSAT associated with ↑ risk of ID, CV and GI SAEs.

Funding: Other U.S. Government Support, Pharmaceutical Company Support - Keryx Biopharmaceuticals, Inc.

SA-PO811

Paricalcitol, Klotho and Renal Anemia in Hemodialysis Patients Miguel Uriol Rivera,¹ Sheila Cabello Pelegrin,¹ Gonzalo Gómez Marqués,¹ Manuel Luque-Ramírez,² ¹Nephrology, Son Espases Univ Hospital, Palma de Mallorca, Islas Baleares, Spain; ²Endocrinology, Ramón y Cajal Univ Hospital, Madrid, Spain.

Background: Low Klotho levels, a protein linked to aging, is associated with an increase in the erythropoiesis process (programmed red-cell death). Chronic Kidney Disease is considered as a state of Klotho deficiency. We evaluate the association between plasma sKlotho levels with iron and hematologic parameters, and the influence of paricalcitol on their changes.

Methods: Data were obtained from the MIR-EPO study (EudraCT: 2009-015511-40). Chronic hemodialysis patients were stratified as a function of paricalcitol use (Group A) or not (Group B). Erythropoietin-stimulating agents (ESA) and iron supplementation were administered in order to maintain hemoglobin (Hb) between 10.5 and 12.0 g/dl and transferrin saturation (TSAT) ≥ 20%. After a 3-month titration period, sKlotho was measured (month 3 and 6 of follow-up) by ELISA. The changes in sKlotho from month 3 to 6 (Δ) and their associations with iron metabolism and hematologic parameters as a function of paricalcitol use were assessed.

Results: A total of 31 patients were evaluated (Group A: 23; Group B: 8). Intact parathyroid hormone (iPTH) levels and ESA doses did not change during the study. Mean sKlotho levels decreased at month 6 compared to month 3 in the whole group of patients (527 vs 474 pg/ml; P=0.001). After adjustment for iPTH and globular sedimentation rate, mean sKlotho levels in the Group A were higher than those observed in the Group B throughout the study (537 versus 401 pg/ml, P=0.005). Δ sKlotho correlated with Δ serum iron (r: 0.42, P=0.020) in the Group A of patients. A cubic regression model showed that Δ sKlotho strongly explained Δ serum iron in these subjects (F: 9.5, R²: 0.64, P=0.001). Δ sKlotho were also associated with changes in iron supplementation (r: -0.47, P=0.030) in the Group A of patients. In the Group B, a direct correlation between Δ sKlotho and Δ red blood cell count was found (r: 0.73, P=0.030).

Conclusions: Soluble Klotho is associated with iron metabolism in hemodialysis patients. Higher soluble Klotho levels may be a novel beneficial effect of paricalcitol use on renal anemia.

Funding: Private Foundation Support

SA-PO812

Influence of the Paricalcitol on Iron Metabolism in Hemodialysis Patients Miguel Uriol Rivera,¹ Juan Rey Valeriano,¹ Aina Obrador,¹ Manuel Luque-Ramírez,² ¹Nephrology, Son Espases Univ Hospital, Palma de Mallorca, Islas Baleares, Spain; ²Endocrinology, Ramón y Cajal Univ Hospital, Madrid.

Background: Interleukin-6 (IL-6) and hepcidin may play a role in the pathogenesis of iron functional deficiency (IFD). The influence of the Paricalcitol in IFD is not known.

Methods: Data were obtained from the MIR-EPO study (EudraCT: 2009-015511-40). Chronic hemodialysis patients were stratified as a function of paricalcitol use (Group A) or not (Group B). Erythropoiesis-stimulating agents (ESA) and iron supplements were administered in order to maintain hemoglobin (Hb) between 10.5 and 12.0 g/dl and transferrin saturation (TSAT) ≥ 20%. After a 3-month titration period, plasma IL-6 and hepcidin were measured (month 3 and 6 of follow-up) by ELISA. The changes in IL-6 and hepcidin levels from month 3 to 6 (Δ) and their associations with iron metabolism and hematologic parameters as a function of paricalcitol use were assessed.

Results: A total of 31 patients were evaluated (Group A: 23; Group B: 8). Intact parathyroid hormone (iPTH) and ESA doses did not change throughout the study. We found no correlation between Δ IL-6 and Δ hepcidin (r: -0.10, P=0.640). However, Δ IL-6 correlated with Δ TSAT (r: -0.40, P=0.030). After adjustment for iPTH and globular sedimentation rate, mean IL-6 levels in Group A were lower than in Group B (8 versus 22 pg/ml, P=0.010). IL-6 levels decreased in the whole group of patients throughout the study, but these changes correlated with an increase in serum iron and TSAT only in the Group A. Hepcidin decreased in the whole group of patients throughout the study as well. Correlation between Δ hepcidin

and ΔHb ($r:-0.49, P=0.010$) was found in the whole group of patients. Interestingly, mean hepcidin levels were higher in Group A than in Group B (992 vs 494 pg/ml, $P=0.050$) during the study. In the Group A, $\Delta\text{Hepcidin}$ correlated with ΔHb ($r:-0.55, P=0.030$).

Conclusions: IL-6 and hepcidin are likely related to different iron pools (functional and storage, respectively) since no correlations between their changes were found. Paricalcitol therapy showed an unexpected increase in iron availability for erythropoiesis that might be associated with changes in IL-6 and hepcidin levels.

Funding: Private Foundation Support

SA-PO813

48 Week Open Label Safety Extension Study with Ferric Citrate Demonstrates Favorable Safety Profile in Subjects Not on Intravenous Iron: A Post-Hoc Analysis Bryce Foote, Lisa Loram, Luke S. Acree, Adam Schayowitz. *Keryx Biopharmaceuticals, Boston, MA.*

Background: Ferric citrate (FC) is an iron-based phosphate binder approved for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. The Phase 3 pivotal trial in subjects with ESRD demonstrated FC to effectively control serum phosphorus but also significantly increased serum iron parameters. This 48-week open label extension study to the Phase 3 pivotal trial was conducted to demonstrate long-term safety of ferric citrate. The primary data have been reported previously.

Methods: Subjects from the pivotal FC RCT (NCT01191255) who completed the active control period and, if eligible, the placebo control period were eligible to enroll in the safety extension trial. 79% had a time lag between participation in the RCT and this trial. The primary outcome was safety as assessed by lab data and adverse events (AE). 168 subjects enrolled. 166 received a dose of FC. The data presented are a post-hoc analysis of 98 of the 166 subjects that did not receive IV iron for the duration of the 48-week trial. Safety data regarding changes in serum iron parameters and treatment emergent AEs by system organ class are presented.

Results: Of the 98 subjects included in this analysis, 71 subjects were randomized to FC in the previous Phase 3 trial and 27 to the AC group. Table below shows the changes in TSAT and serum ferritin over the 48 wk period. Data presented as mean (SD).

Time (wk)	TSAT (%)	Serum ferritin (ng/mL)
0	34.5 (14.1)	772 (378)
12	37.9 (16)	891 (458)
24	38.1 (15.9)	904 (450)
36	41.7 (19.1)	961 (517)
48	40.9 (19)	872 (417)

83% of subjects experienced at least one treatment emergent adverse event with the most common being gastrointestinal disorders (40%) and infections and infestations (37%).

Conclusions: Subjects receiving ferric citrate and no IV iron demonstrated serum phosphorus control over the 48 wk study period, and an increase in TSAT and serum ferritin. The increase in TSAT did not exceed 45% in subjects receiving ferric citrate and no IV iron, which might suggest that ferric citrate is absorbed but the risk of excessive iron absorption is low.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

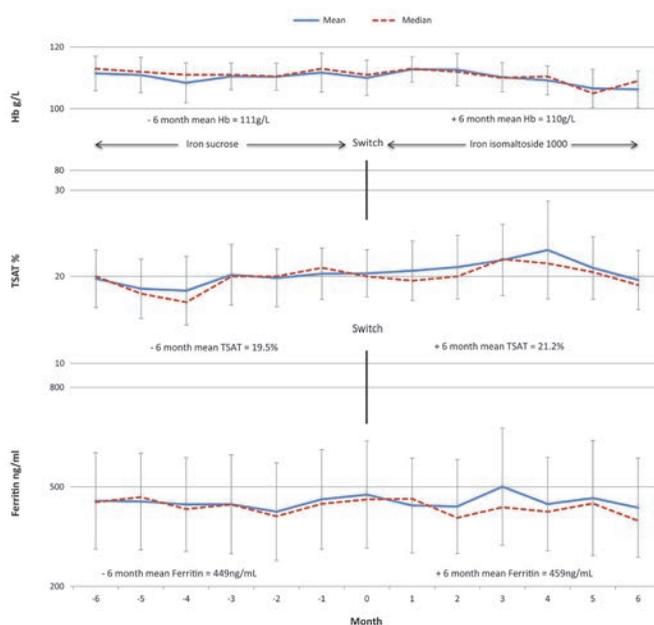
SA-PO814

Iron Isomaltoiside: A Novel Intravenous Iron Preparation for Hemodialysis David Jackson, Christopher Brown, Grant Sugiura, Rachel S. Ashcroft, Ashraf I. Mikhail. *Nephrology, ABM Univ Health Board, United Kingdom.*

Background: Diafer® (iron isomaltoiside) is newly licensed in Europe for iron deficiency anaemia in CKD patients on dialysis. It is thought the controlled-release matrix minimises free iron; possibly reducing side effects. Little is known about the efficacy & safety of Diafer in clinical practice. This study aims to assess the impact of this novel formulation on anemia parameters in prevalent hemodialysis (HD) patients previously maintained on iron sucrose.

Methods: Data was collected for 13 months; 6 month pre-switch (iron sucrose), 1 month crossover, & 6 month post-switch (iron isomaltoiside). All patients received dialysis for ≥ 3 months before evaluation, excluding potential bias of iron loading doses. For both preparations, patients received intradialytic bolus doses of 100mg at frequencies dependant on individual requirements as per current practice.

Results:



Parameter	Iron Sucrose		Switch	Iron Isomaltoiside		Sig
	Mth -6 to -1		Mth 0	Mth +1 to +6		
	Mean	Median	Mean	Mean	Median	
Hb (g/l)	111	112	110	110	111	N
Ferritin (ng/ml)	449	447	477	459	435	N
TSAT (%)	19.5	19.0	20.4	21.2	20.0	Y
ESA (U/wk)	7868	6000	7980	7053	6000	Y
Iron (mg/mth)	202	200	186	168	200	Y
CRP (mg/l)	14	7	15	18	8	Y

The percentage of patients maintaining Hb target (100-120g/L) was 71% with iron sucrose & 70% with iron isomaltoiside. No adverse drug reactions were observed. No metallic tastes were reported with Diafer administration. The CRP rise during months 1-6 was imparted by 2 infections & 1 amputation.

Conclusions: Iron isomaltoiside maintains Hb stability & adequate iron status in HD patients when incorporated into current practice. While these data suggest Diafer may reduce ESA & iron requirements, further analyses are necessary to validate these findings. Whether the potential to reduce labile iron with iron isomaltoiside impacts on clinical outcomes is yet to be determined.

Funding: Government Support - Non-U.S.

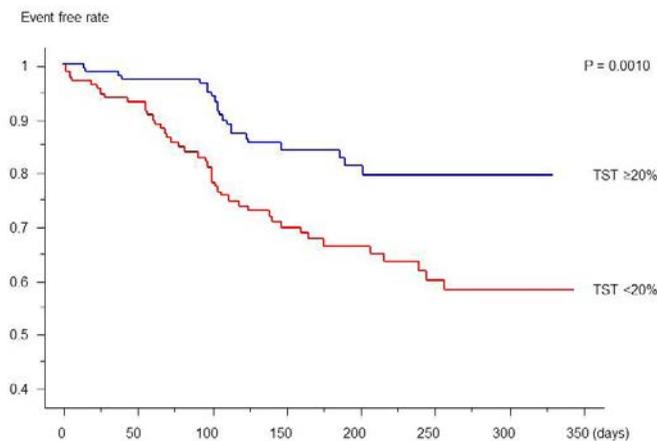
SA-PO815

Low Iron Availability May Influence on Second Patency Rates of Vascular Access in Patients on Hemodialysis Yukiko Hasuike, Wataru Fukao, Takeshi Nakanishi. *Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.*

Background: Vascular access (VA) is essential for the patients on HD. However, VA failure is often occurred even after percutaneous-transluminal angioplasty (PTA). Iron is important for normal vascular physiology, and insufficient iron availability can lead to various vascular dysfunction. The purpose of this study was to examine the factors affecting VA patency after PTA, including iron availability and oxidative stress.

Methods: Blood samples were taken from 281 HD patients at the PTA. Routine blood chemistries and factors related to iron metabolism (transferrin saturation rate (TST), ferritin), oxidative stress (advanced oxidation protein products (AOPP), 8OHdG, GSH/GSSG), and inflammation (high-sensitive CRP, interleukin-6, tumor necrosis factor- α , pentraxin-3) were measured. The end point of study was the re-vascularization or re-operation of VA during the observational period after PTA. Cox proportional hazards models for the end point was used.

Results: 133 patients (47.3%) had native arteriovenous fistula. During follow-up period, re-vascularization was performed in 34 patients and re-operation in 31 patients. The patients with VA failure had higher numbers of leukocytes and platelet, significantly lower TST, and a tendency of higher AOPP compared with the patients without VA failure. There was no significant difference in other factors between the patients with and without VA failure. The Kaplan-Meier analysis showed lower TST (<20%) was associated with VA failure ($p=0.0010$, (figure 1)).



Cox regression analysis also revealed that lower TST (hazard ratio 2.316, 95% confidence interval 1.385-3.873, p=0.0014) was related to VA failure.

Conclusions: TST <20% was associated with the poorest event-free patency of VA after PTA. Low Iron availability might affect the second patency rates of VA.

SA-PO816

Triferic Has a Safety Profile Similar to Placebo: An Integrated Safety Analysis of Phase 2 and 3 Studies Yivian H. Lin, Raymond D. Pratt, Carrie D. Guss, Ajay Gupta. *R&D, Rockwell Medical Inc, Wixom, MI.*

Background: Triferic is a novel soluble iron compound delivered via the dialysate to prevent iron deficiency and maintain hemoglobin in CKD-HD patients.

Methods: The Triferic clinical program included 3 large placebo-controlled efficacy studies lasting 36 to 48 weeks (Controlled Studies), one large placebo-controlled short-term safety study, 3 open-label (OL) safety studies of up to 48 weeks, and 3 small controlled early Phase 2 studies. Patients randomized to Triferic in the 2 pivotal controlled studies who completed the randomized treatment and transitioned to the OL study received Triferic for up to 72 weeks.

Results: Exposure-adjusted most frequent adverse event rates (AE) are presented in the table below.

Adverse Events	Controlled Studies		All Studies
	Triferic	Placebo	All Triferic
Subjects (N)	346	345	1411
PYE (Patient Year)	159	161	780
Total TEAE (N)	2089	2081	10766
	Events/100 Patient-Years of Exposure		
Procedural hypotension	291.5	290.6	226.6
AVF Site Complication	35.3	39.1	39.7
Headache	34.6	21.1	33.2
Nausea	29.6	34.8	36.4
Dizziness	28.3	20.5	28.0
HD-induced Symptom	27.7	25.5	68.1
Cough	26.4	18.0	17.2
Diarrhea	25.8	31.1	33.0
Muscle Spasms	22.7	26.7	19.6

Discontinuations and exposure-adjusted AE were similar to placebo in the controlled studies with no increase in the OL studies. The exposure-adjusted mortality rate in the Controlled Triferic group was 7.9/100 PYE, compared to 7.2/100 PYE in placebo. The mortality rate in the All Triferic group was 6.5/100 PYE. No deaths occurred during Triferic administration and none were attributed to Triferic. There were no reports of anaphylaxis in over 100,000 individual doses of Triferic. Suspected hypersensitivity reactions, vascular access thrombotic events, composite cardiovascular events and systemic or serious infections were also similar between the Triferic and placebo groups.

Conclusions: Triferic was well tolerated in long-term controlled and OL studies. Triferic, administered at each treatment, maintained Hgb and iron balance compared to placebo. The safety profile in short and long-term studies supports a favorable benefit-risk profile for use as a maintenance iron therapy for CKD-HD patients.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO817

Structural, Physical and Functional Characterization of Ferric Pyrophosphate Citrate (FPC, Triferic), A Novel Iron Compound for Pharmaceutical Applications Ajay Gupta,¹ Garry J. Handelman,² Raymond D. Pratt,¹ ¹R&D, Rockwell Medical Inc., Wixom, MI; ²Univ Massachusettes, Lowell, MA.

Background: Ferric pyrophosphate citrate (FPC) is the first iron compound approved for parenteral administration that is not an iron-carbohydrate complex. FPC has a molecular mass of about 1313 Da, and high solubility of FPC in aqueous solutions allows its administration via the dialysate.

Methods: FPC is a complex iron salt in which Fe³⁺ is bound to pyrophosphate (PPi) and citrate by coordinate covalent bonds. Extended X-ray absorption fine structure (EXAFS) spectroscopy showed that the Fe in FPC is in the ferric (Fe³⁺) state and does not complex with sulfate. EXAFS analysis demonstrated that Fe forms a stable complex with 6 O atoms at 2.02 Å in the first coordination sphere and with 2 P and 4 C atoms at 3.22 Å and 2.98 Å, respectively, in the second coordination sphere. FPC demonstrates stability in both the solid and solution forms.

Results: The uptake rate of FPC iron by human apo-transferrin was measured *in vitro* by monitoring absorbance at 471 nm. At an identical set of conditions we observed 75% Tf saturation in <10, 15, and >9 x 10⁴ sec for Fe(NTA), FPC and Fe(citrate), respectively. We conclude that Tf loading from FPC is rapid and of similar magnitude to that from ferric nitriloacetic acid, but over four orders of magnitude faster than from ferric citrate. The observed rapid binding kinetics allows for facile Fe³⁺ uptake by transferrin for transport to the bone marrow for hemoglobin synthesis. Pharmacokinetic studies of FPC administered IV to healthy volunteers demonstrate dose-proportional kinetics with a t_{1/2} of approximately 1.4 hours. No non-transferrin bound iron has been detected at TSAT levels of up to 100%.

Conclusions: FPC is a novel iron compound that is ideally suited as a maintenance treatment for CKD 5HD patients. FPC replaces ongoing iron losses and maintains hemoglobin. The small doses of iron and the lack of a carbohydrate shell contribute to the favorable safety profile. FPC represents a new paradigm for rational iron replacement in patients on chronic hemodialysis.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO818

Proton Pump Inhibitors and CYP2C19 Are Associated with Iron-Deficiency Anemia in Hemodialysis Patients: A Cross-Sectional Study Akio Nakashima,¹ Ichiro Ohkido,¹ Keitaro Yokoyama,¹ Mitsuyoshi Urushima,² Takashi Yokoo.¹ ¹Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan; ²Div of Molecular Epidemiology, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Hyporesponsiveness to erythropoiesis stimulating agents (ESA) is an important phenomenon in dialysis patients. As chronic proton pump inhibitor (PPI) use reduces gastric acid secretion, it seems possible that chronic PPI use might lead to iron malabsorption and anemia. In addition, PPI is mainly metabolized by cytochrome P₄₅₀ (CYP) enzymes, particularly CYP2C19, in the liver. The genotypes of CYP2C19 affect the pharmacokinetics and pharmacodynamics of PPI. However, there is no study investigating the relationship between PPI use and anemia status that includes the effect of CYP2C19 genotype in hemodialysis patients.

Methods: This cross-sectional cohort study analyzed 1350 hemodialysis patients. DNA was isolated from leukocytes in peripheral blood. We used polymerase chain reactions and direct sequencing to analyze CYP2C19 genotypes. We analyzed anemia status with and without PPI usage, including the association with CYP2C19 genotypes.

Results: PPI use was associated with a significantly lower mean serum hemoglobin concentration. Iron and TSAT were also lower in PPI users. ESA dosage was significantly higher in patients receiving PPIs (mean [SD] PPI: 3685 [3288] IU/week; non-PPI: 2899 [2734] IU/week; P<0.001), and multiple regression analysis indicated a significant relationship between PPI use and ESA dosage (β: 494.1 P=0.011). CYP2C19 genotypes were significantly associated with iron status and anemia. Multiple regression analysis demonstrated that CYP2C19 poor metabolizer (PM) type was significantly associated with ESA dosage in PPI users (β: 901.1 P=0.036).

Conclusions: In this study, we found that PPI use is associated with iron status and anemia in hemodialysis patients. Among the dialysis patients receiving PPIs, CYP2C19 genotype was associated with hemoglobin levels, ESA dosage, and iron status.

SA-PO819

A 4-Week Dose Response Study of the Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 in Japanese Anemic Hemodialysis Subjects Yukihiro Endo,¹ Tomoko Kohno,¹ Yukiko Imai,¹ Natsumi Kawase,¹ Katsutoshi Hara,¹ John J. Lepore,² Alexander Ralph Cobitz,² ¹GlaxoSmithKline, Tokyo, Japan; ²GlaxoSmithKline, King of Prussia, PA.

Background: Hypoxia inducible factor (HIF)-prolyl hydroxylase inhibitors, such as GSK1278863, are an emerging class of oral agents for treatment of anemia associated with chronic kidney disease (CKD). Dose response of GSK1278863 for anemia correction in Japanese hemodialysis-dependent (HDD) subjects is reported.

Methods: We evaluated the relationship between GSK1278863 dose and hemoglobin (Hgb) response in Japanese HDD subjects with anemia of CKD in a 4-week, randomized, double-blind, placebo-controlled study (funded by GlaxoSmithKline). Subjects on thrice weekly hemodialysis for at least 8 weeks and with Hgb of 8.5-10.5 g/dL after stopping their

erythropoiesis stimulating agent for at least 2 weeks were randomized to placebo or to 4 mg, 6 mg, 8 mg or 10 mg of GSK1278863 once daily. The primary endpoint was Hgb change from baseline at Week 4. Other endpoints included circulating levels of erythropoietin (EPO), vascular endothelial growth factor (VEGF) and hepcidin.

Results: A total of 97 subjects were randomized, and 86 subjects completed the study. Mean Hgb at baseline ranged from 9.68 g/dL to 9.92 g/dL across the treatment groups. After 4-week treatment, GSK1278863 produced dose-dependent increases in mean Hgb from baseline (placebo: -1.41 g/dL; 4 mg: -0.28 g/dL; 6 mg: -0.01 g/dL; 8 mg: 0.54 g/dL; 10 mg: 0.97 g/dL). A posterior distribution from Bayesian four parameter Emax model estimated that 2.0 mg, 3.9 mg and 8.7 mg doses would, on average, lead to achieve placebo corrected increases in Hgb over 4 weeks of 0.5 g/dL, 1.0 g/dL and 2.0 g/dL, respectively. Dose-dependent increases in EPO and decreases in hepcidin were observed across the GSK1278863 groups, while no trends of increase in VEGF were observed in any groups. All AEs were reported as single instances in any treatment groups except nasopharyngitis, and no trends in AEs were noted. There were no deaths in the study.

Conclusions: This study demonstrated that GSK1278863 produced dose-dependent elevations in Hgb concentration in Japanese HDD subjects across the dose range tested.

SA-PO820

A Three-Year Study of an ESA Treatment Algorithm for Patients with Renal Anemia: Stable Hb Levels Obtained with Twice-Monthly Administration of CERA (Second Report) Teruhiko Maeba, Shigeru Owada. Internal Medicine, Asao Kidney Clinic, Kawasaki, Japan.

Background: Treatment of renal anemia in hemodialysis(HD) patients requires an adequate ESA dosage to maintain stable Hb levels. Guidelines in Japan recommend determining ESA dosage based on Hb levels measured twice a month. An algorithm for the administration of continuous erythropoietin receptor activator (CERA) has been prepared and implemented to treat patients on HD. The 2-year study results were previously reported during the ASN Kidney Week 2014 (TH-PO 820).

Methods: Based on the algorithm, CERA was administered for 1 year to 102 HD patients being treated with rHuEPO. After the 1st year, the algorithm was reviewed, and some cases of fluctuating Hb levels because of terminating and restarting CERA administration were found. Therefore, the algorithm was revised. Consequently, CERA administration was continued for another 2 years. The target Hb level was 10.5–11.0 g/dl, and Hb levels, CERA dosage, Erythropoietin Resistance Index (ERI), and iron dosage were investigated. CERA was administered once every 2 weeks, and the dosages were changed within a range of 25 mg/dose based on Hb levels. The standard iron dosage was not changed during the evaluation period.

Results: Hb levels at the baseline and 1, 2, and 3 years after the baseline measurement were 10.9 and 11.1, 11.2, and 11.2 g/dl, respectively. The corresponding CERA dosages, administered every 2 weeks, were 62 ± 16, 38 ± 25, 36 ± 23, and 33 ± 21 mg, respectively, and ERI values were 0.11 ± 0.04, 0.06 ± 0.05, 0.06 ± 0.04, and 0.06 ± 0.04, respectively. To reduce fluctuations in Hb levels to a possible extent, terminating CERA administration was avoided. Serum ferritin levels gradually decreased from 147.9 ± 122.1 at the baseline to 112 ± 95, 88 ± 67, and 67 ± 47 ng/ml in the 1st, 2nd and 3rd years, respectively, and weekly iron dosage decreased from 13 ± 1.5 at the baseline to 11 ± 2.6 and 11 ± 2.4 mg in the 2nd and 3rd years, respectively.

Conclusions: Three years of twice-monthly CERA administration, based on the algorithm, could maintain stable Hb levels, improve ERI, and reduce iron dosage. Twice-monthly CERA administration based on the algorithm effectively controlled anemia in HD patients.

SA-PO821

Continuous Erythropoiesis Receptor Activator (CERA) for the Anemia of Chronic Kidney Disease (CKD): A Meta-Analysis of Randomized Controlled Trials Valeria M. Saglimbene,¹ Suetonia Palmer,^{2,3} Giovanni F.M. Strippoli.^{1,3} ¹Diaverum Medical Scientific Office; ²Univ of Otago Christchurch; ³Cochrane Kidney and Transplant.

Background: Targeting high hemoglobin levels with erythropoiesis-stimulating agents (ESA) leads to adverse effects in people with chronic kidney disease (CKD). Whether there are treatment differences between different ESA agents is uncertain.

Methods: We did a systematic review of randomized controlled trials evaluating treatment effects of CERA compared with other epoetins (darbepoetin alfa and epoetin alfa or beta) or placebo/no treatment, in people with any stage of CKD. We systematically searched Cochrane databases. Results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference and 95% CI for continuous outcomes using random-effects meta-analysis.

Results: 17 studies involving 5397 participants were eligible. Studies compared CERA with epoetin (n=8 studies), darbepoetin (n=5), differing frequency (n=2) and dose (n=4). Compared to epoetin and darbepoetin CERA had similar effects on mortality, hypertension, need for blood transfusion and iron therapy.

Outcome	Relative Risk (95% CI)	
	CERA vs epoetin	CERA vs darbepoetin
Mortality	1.06 (0.72-1.55)	1.10 (0.73-1.65)
Hypertension	1.01 (0.86-1.18)	1.00 (0.73-1.36)
Need for blood transfusion	0.94 (0.68-1.30)	0.64 (0.30-1.37)
Iron therapy	1.03 (0.91-1.15)	0.99 (0.95-1.03)

In two studies of low-moderate risk of bias, CERA significantly improved quality of life as measured by SF36. Data were sparse for differing frequency of administration and dose. Evidence for treatment effects of CERA was absent among children and particularly limited for kidney transplant recipients. Studies included in this review were generally at high or unclear risk of bias.

Conclusions: There is no evidence that CERA has different effects on patients-centered outcomes compared to epoetin or darbepoetin among adults with CKD. CERA may improve health-related quality of life, but further high quality trials are needed. Its effects in children with CKD and kidney transplant recipients remains poorly understood.

SA-PO822

Risks of Long-Term Management for Anemia, Cardiovascular Disease (CVD) Death and Risk Factors for Heart Failure in Maintenance Hemodialysis Hajime Hirano,¹ Haruhito Azuma,¹ Hideaki Shima.² ¹Blood Purification Center, Osaka Medical Collage, Takatsuki, Japan; ²Nephrology, Osaka Medical Collage, Takatsuki, Japan.

Background: In this study, to evaluate the various outcome factors, the effects of improvement in anemia in patients treated with hemodialysis on the vital prognosis were evaluated focusing on changes after enrollment.

Methods: This retrospective study was conducted with 201 outpatients with hemodialysis at our Blood Purification Therapy Center and our other related hemodialysis facilities from March 2005 to February 2007 (24 months, 136 males and 65 females, age: male: 59.4 years old, female: 59.8 years old, overall: 59.5 years old). Using CVD death and hospitalization due to heart failure as outcomes, 2-year risk of CVD death was analyzed by logistic regression model with surviving patients. In addition, to assess anemia, changes over a long time after start of observation were evaluated.

Results: The multivariate analysis revealed 3 factors for CVD death risk including smoking history (OR: 9.06 [95%CI: 1.86–44.0, p=0.006]), history of ischemic heart disease (OR: 3.82 [95%CI: 1.19–12.25, p=0.024]) and hypercalcemia. (OR: 1.77 [95%CI: 1.00–3.13, p=0.049]). Similarly, the risk factors for heart failure were smoking (OR: 3.11 [95%CI: 0.78–12.36, p=0.101]) and history of ischemic heart disease (OR: 5.03 [95%CI: 1.46–17.33, p=0.010]), and history of ischemic heart disease was the only significant variable in the final step.

Conclusions: The factors that influence the risk of CVD death included smoking, history of ischemic heart disease and hypercalcemia. The risk factors occurring heart failure included history of IHD, and it was shown that the effects of smoking and history of IHD on prognosis were stronger than the effects of anemia. The evaluation of changes in Hb over time revealed that the low Hb sustained for a long time would increase the risk. In addition, the risk of death was high in the high-dose rHuEPO group suggesting the risk in the low rHuEPO response patients.

SA-PO823

Anemia Management in ESRD Patients Admitted to the Hospital Priyanka Govindan, Arjun V. Sharma. Dept of Nephrology, Univ of Washington Medical Center, Seattle, WA.

Background: Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. Anemia can be managed successfully with appropriate investigations and therapy in the ESRD population. The aim of the study was to see how appropriate the management of anemia was in our hospital in patients on dialysis and to identify areas for improvement.

Methods: Selected patients were those with ESRD on hemodialysis and peritoneal dialysis that underwent in-hospital dialysis at the University of Washington Medical Center from July 1st 2014 to Sep 30th 2014. The patients who had been undergoing dialysis for less than 12 weeks were considered to have AKI and were excluded from the analysis. In addition, the patients who underwent dialysis only in the Intensive Care units were excluded. The data was collected from the electronic medical records of the individual patient charts. Gender, Age, Anemia status, Lowest Hemoglobin, Iron panel, Reticulocyte count were noted in addition to treatment with iron, blood transfusions and ESA.

Results: A total 145 dialysis patients were identified and 65 of them had both ESRD and anemia. 73.86% of these patients were found to be anemic by KDIGO. Patients in the 60-69 age range had the largest number of anemia with a total of 20 falling in this category. 18 patients had a Hemoglobin between 7.0-7.9. Among the anemic patients 48.5% did not have an iron panel checked and 86.4% did not have a reticulocyte count checked. 40% of those with a Hb < 6 mg/dl had an iron panel checked. In patients with Hemoglobin of less than 11.31% were treated with ESA at least once during their hospital stay. 36.36% received transfusions. 50% of the patients who received blood transfusions did not have an iron panel.

Conclusions: Routine investigations for the management of anemia are being missed regularly. Worse anemia was associated with fewer investigations. We suspect that the management of anemia in patients with ESRD can be improved with more comprehensive labs and therapy. • We intend to follow up with an intervention involving the EMR making it easier to work up anemia in the hospital.

SA-PO824

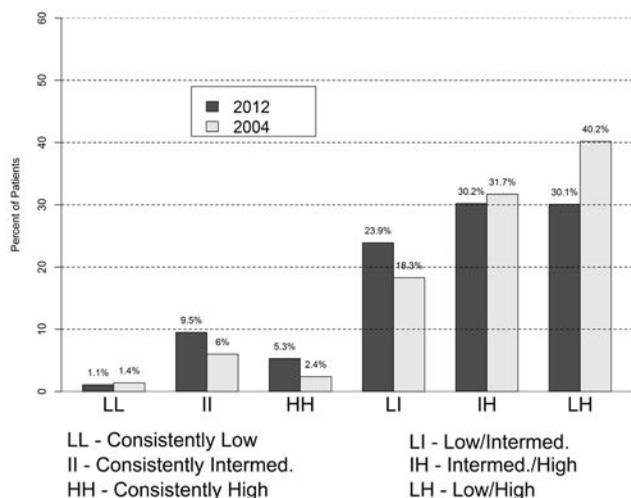
Variability in Hemoglobin (Hb) Levels in Hemodialysis (HD) Patients in the Current Era David T. Gilbertson,¹ Yan Hu,¹ Yi Peng,¹ Sarb Shergill,² Bradley J. Maroni,² ¹CDRG/MMRF; ²Akebia Therapeutics, Inc.

Background: Hb variability in dialysis patients has been characterized using a number of methods. The majority of this work occurred prior to the 2011 change in CMS reimbursement policy and ESA labels. We therefore examined Hb variability and patient demographics from current data and compared the results to those obtained prior to implementation of these policy changes.

Methods: We used CMS ESRD data to define a cohort of chronic HD patients who were alive from Apr 1 through Dec 31, 2012. Using a method from Ebben et al. (CJASN 1:1205-1210, 2006), monthly Hb values were categorized as low (L), intermediate (I), and high (H), where L and H were based on monthly Hb values below or above the 25th and 75th percentiles, respectively. Variability was then classified based on the Hb categories during a 6-month period, resulting in 6 categories of variability (see figure legend).

Results: The figure compares the percentage (%) of patients in each Hb variability group in 2004 compared to 2012. The 25th and 75th percentiles in the 2012 data were 10.2 and 11.5. Corresponding 2004 values were 11 and 12.5. Similar % of patients were observed in 2004 and 2012 for the LL and IH categories. A higher % of patients was consistently intermediate (II) in 2012 than 2004 (9.5% vs. 6.0%), whereas a larger % was observed for LI and a smaller % for LH. Compared to the overall 2012 cohort, II patients were older (mean=65.2), and LL or HH patients were younger (mean=58.2 and 57.8). LL had the highest % who were black (48.8%).

Conclusions: While Hb levels have decreased during the last few years, Hb variability is still present. The lower % of patients in the LH group is consistent with a narrowing of the overall Hb distribution. Further studies are needed to assess the association of variability with outcomes in the current era.



Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

SA-PO825

Prevalence and Predictors of Naturally Occurring Normal Hemoglobin Concentration in Hemodialysis Patients Zakaria Abdulnabi, Veeda O. Landaras, Shalini Bumb, Abdulah Alrifai, Jay B. Wish, Peter B. De Ore, Thomas H. Hostetter, Mirela A. Dobro. Case Western Reserve Univ, Cleveland, OH.

Background: Epidemiological data and clinical observations suggest that erythropoietin producing cells exist even in ESRD kidneys. A small subset of ESRD patients have naturally occurring normal hemoglobin levels, without the use of blood transfusions or erythropoietin stimulating agents (ESA), but limited data exists in this field. The aim of this study was to evaluate the prevalence and predictors of naturally occurring hemoglobin concentration ≥ 12 mg/dl in hemodialysis patients.

Methods: This analysis is a retrospective chart review of ESRD patients receiving hemodialysis at Centers for Dialysis Care in East Cleveland, OH, from April-September 2013. Data collected included demographics, cause of renal disease, co-morbidities, duration of ESRD, dialysis access, indices of dialysis adequacy, systolic blood pressure, hemoglobin level, PTH, albumin, calcium, phosphorus. Multivariable regression models were used to identify independent associations with the outcome of interest.

Results: In this cohort of 449 community dialysis patients, the prevalence of naturally occurring hemoglobin level ≥ 12 mg/dL, without the use of ESA, was 5.3%, slightly higher than previous reports of around 2%. In unadjusted analyses, compared to ESRD patients with a hemoglobin level ≥ 10 mg/dL maintained with the use of ESA, the patients with naturally occurring hemoglobin ≥ 12 mg/dL were more likely to be younger, male, with an arteriovenous fistula, longer dialysis vintage, lower systolic blood pressure and higher serum albumin level. In adjusted analyses, male sex, serum albumin and systolic blood pressure remained statistically significantly associated with naturally occurring hemoglobin concentration ≥ 12 mg/dL (OR 3.66(95%CI 1.11-12.06); 14.10(2.21-90.11); and 0.98(0.96-0.99), respectively).

Conclusions: In this sample of community dialysis patients, male sex, serum albumin and systolic blood pressure were the strongest predictors of naturally occurring higher hemoglobin concentration. Further studies to evaluate the mechanisms underlying these associations, including factors stimulating sites of extrarenal erythropoiesis are warranted. Funding: NIDDK Support

SA-PO826

Estimation of Pre-Dialysis Hemoglobin Concentration Using the Crit-Line® Monitor Stephan Thijssen, Hanjie Zhang, Doris H. Fuertinger, Peter Kotanko. Renal Research Inst, New York, NY.

Background: Pre-dialysis laboratory measurements of hemoglobin (Hb) are generally used for anemia management. In some clinics, bi-weekly or even weekly Hb measurements are performed for this purpose. The Crit-Line® Monitor (CLM) provides Hb non-invasively and continuously during hemodialysis (HD), but initial readings early during HD are systematically lower than pre-HD laboratory values due to hemodilution caused by the priming fluid. We present a method of correcting CLM Hb for hemodilution.

Methods: Pre-HD reference Hb (Hb_Spec) was measured by Spectra East Laboratories. Hb obtained by CLM (Hb_CLM) was averaged between minutes 4 and 6 after start of the HD treatment. The difference between the two (Hb_Spec - Hb_CLM) was estimated as $\Delta Hb = (V_{sal} * 0.5^{(t_{CLM}/t_{1/2_sal})} - V_{UF}) * Hb_{CLM}/BV$, with V_{sal} = amount of priming fluid (saline) infused at start of HD, t_{crit} = time point of Hb_CLM measurement (5 min into HD), $t_{1/2_sal}$ = plasma half life of infused saline (20 min, adapted from ATC Consensus Statement, 2004), V_{UF} = cumulative ultrafiltration volume up until t_{crit} , and BV = pre-HD blood volume (obtained by estimating post-HD BV via Nadler equation (using post-HD weight, sex, height), then dividing by end-HD relative blood volume and subtracting V_{sal}). Corrected Hb_CLM was calculated as $Hb_{corr} = Hb_{CLM} + \Delta Hb$.

Results: 5,731 HD treatments from 952 chronic HD patients in the USA were analyzed. Without correction, Hb_CLM was found to be systematically lower than Hb_Spec by on average 0.425 g/dL (SD 0.59 g/dL). After correction for hemodilution, the difference (Hb_corr - Hb_Spec) was reduced to -0.068 g/dL (SD 0.59 g/dL).

Conclusions: When applying a correction for the hemodilution caused by infusion of the priming fluid at the start of HD, the corrected Crit-Line® Hb is nearly identical on average to the pre-HD Hb measured by a reference laboratory. More and more clinics are employing Crit-Line® Monitors for fluid and anemia management. Crit-Line® Hb corrected in this way may be used for anemia management, which could reduce blood draws and costs.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO827

Hemodialysis (HD) Patients Who Can Maintain Fair Hb Level (>10g/dl) without Iron or Erythropoietin (Epo) Administration Showed Higher Serum Soluble Transferrin Receptor(sTfR) and Normal Epo, Vitamin C (VC) Levels Noriko Saito,¹ Kazuhide Saito,² Tetsuo Morioka,¹ Hisaki Shimada,¹ Kojo Ikarashi,¹ Yutaka Tsubata,¹ Shunsuke Sakai,¹ Shigeru Miyazaki,¹ ¹Nephrology, Shinraku-en Hospital, Niigata, Japan; ²Urology, Niigata Univ, Niigata, Japan.

Background: HD patients have severe anemia and their Hb levels were recommended to be maintained at greater than 10g/dl using iron and Epo supplementation. Certain HD patients showed Hb levels over 10g/dl without iron or Epo. This time, we studied erythropoiesis and iron metabolism markers in these patients in order to analyze the background mechanism.

Methods: 21 HD patients who could maintain Hb level at 10g/dl and greater without iron or Epo for more than 3 months(G1) were enrolled in this study. 23 HD patients with Hb level less than 10g/dl without iron or Epo for more than 2 months(G2) and 30 healthy volunteer(GN) were also enrolled as control. Blood samples were collected before HD and Epo, hepcidin(HPC), sTfR, VC and standard hematological parameters were examined. The data are indicated as median(interquartile range).

Results: 1. In G1, ferritin(20(14-36) ng/ml), transferrin saturation(14(8-19)%), HPC(0.7(0.2-4.5)ng/ml) were significantly lower than those in both GN and G2, respectively. The percentage of hypochromic RBCs(%HypoHe)(2.7(1.5-4.8)%) was higher than those of GN and G2. 2. MCV values were not significantly different in all three groups. 3. sTfR level, a marker of erythropoietic activity, of G1(30.0(22.1-36.5)nmol/L) was significantly higher than those of GN and G2. 4. Epo level(7.3(5.1-15.2)mIU/mL), reticulocytes(12(9-15)%) and VC(6.8(2.8-23.4)µg/mL) of G1 were not significantly different from those of GN, whereas significantly higher than those of G2, respectively. 5. In G1, negative correlation was revealed between VC and %HypoHe($r = -0.437, p = 0.048$), whereas positive correlation between %HypoHe and sTfR($r = 0.816, p < 0.001$). By multivariate analysis, %HypoHe was the predictor of sTfR($\beta = 0.834, p < 0.001$).

Conclusions: HD patients with fair Hb level revealed higher sTfR, %HypoHe and normal Epo, MCV, VC and low HPC levels. These results indicated that iron utilization of these patients was upregulated and this may participate in the maintenance of erythropoiesis.

Funding: Private Foundation Support

SA-PO828

Acute Effects of Erythropoietin Administration on Blood Pressure in Dialysis Patients Nawf Hamad Al-Gublan, Kristin M. Corapi, Ishir Bhan. *Nephrology, Massachusetts General Hospital, Boston, MA.*

Background: Erythropoiesis-stimulating agent (ESA) doses are often held in patients with end stage renal disease (ESRD) because of hypertension. However, missed doses may exacerbate anemia of chronic disease. The acute effects of ESA on blood pressure are unknown. We hypothesized that ESA administration during dialysis would not be associated with a significant change in blood pressure.

Methods: With institutional review board approval, we retrospectively reviewed the medical records of 100 hemodialysis patients who were admitted to our hospital between 1/2013-4/2015. All patients in this study were prescribed, and received, ESA's during dialysis. Patients were excluded if dialyzed in the ICU, received vasopressors, were treated for hypertensive urgency (>180/110 mmHg), initiated on hemodialysis, or only underwent ultrafiltration without dialysis. Blood pressure just prior to and 2 hours after ESA were compared using a paired t-test.

Results: The mean age was 61.6 years (±12.8), 42% were male, 66% were Caucasian, 16% African-American, and 10% Asian. Mean change in blood pressures immediately prior to ESA administration and 2 hours after are summarized.

	Pre-Dialysis	Just Prior to ESA	2 Hours Post ESA	Mean Change (95% CI)	
SBP	136±25	132±27	128±25	-4.5 (1.74)	p=0.008
DBP	68±11	67±10	66±11	-1.2 (0.25)	p=0.18

No statistically significant increase in SBP or DBP was noted. In fact, we observed a significantly lower SBP 2 hours after ESA dosing. In a subgroup analysis of patients with an SBP > 160 immediately prior to ESA administration, an even greater decrease in SBP was noted 2 hours after ESA compared to a subgroup with an SBP < 160 (p=0.004). No significant relationship existed between dose of ESA and effect on blood pressure (SBP, p=0.52; DBP, p=0.95).

Conclusions: We demonstrated a decrease in systolic blood pressure 2 hours after ESA administration with no significant change in diastolic blood pressure. Withholding EPO during dialysis due to hypertension may be unnecessary.

SA-PO829

Serum Ferritin Predicts Mortality Regardless of Inflammatory and Nutritional Status in Incident Peritoneal Dialysis Patients Meiyuan Wu,¹ Kyoung Sook Park,² Hyung Jung Oh,² Jung Tak Park,² Seung Hyeok Han,² Tae-Hyun Yoo,² Shin-Wook Kang.^{1,2} ¹Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea; ²Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Serum ferritin levels have been proposed as a prognostic factor in hemodialysis (HD) patients, due to its close relationship with inflammation and malnutrition. Since iron supplementation methods and factors affecting nutritional status are somewhat different from those of HD patients, the impact of serum ferritin on clinical outcomes was investigated in incident peritoneal dialysis (PD) patients.

Methods: A prospective cohort of 408 PD patients from the Clinical Research Center for End-Stage Renal Disease was selected. Patients were divided into three groups according to tertiles of Ln ferritin concentrations (group 1: <4.69 ng/mL, group 2: 4.69-5.58 ng/mL, group 3: >5.58 ng/mL). Cox proportional hazard analysis was performed to determine the independent prognostic value of serum ferritin levels for all-cause mortality.

Results: The mean age was 51.2±13.2 years and 236 (57.8%) were male. During a median follow-up of 25 months, 46 (11.3%) patients died. Univariate Cox analysis revealed that the mortality risk was significantly higher in group 2 [hazard ratio (HR)=2.65, 95% confidence interval (CI)=1.11-6.34, P=0.029] and group 3 (HR=3.16, 95% CI=1.33-7.48, P=0.009) compared to group 1. Moreover, multivariate Cox proportional hazard models revealed that Ln ferritin was independently associated with an increased risk of all-cause mortality (per 1 ng/mL increase, HR=1.94, 95% CI=1.31-2.88, P=0.001), even after adjustment for variables representing inflammatory and nutritional status.

Conclusions: Higher serum ferritin level was a significant independent risk factor for all-cause mortality regardless of systemic inflammation and nutritional status. Therefore, determining serum ferritin levels could be a useful marker to predict clinical outcomes in incident PD patients.

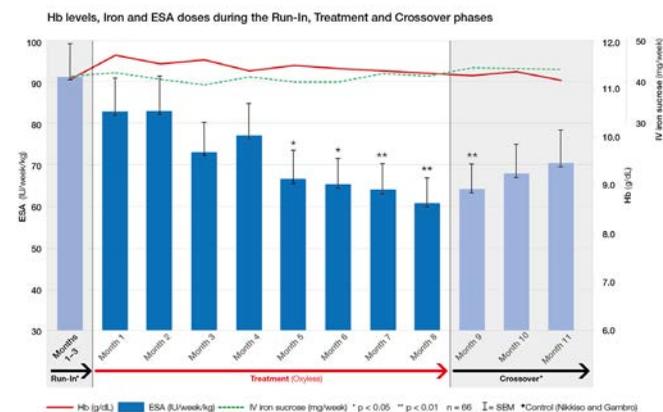
SA-PO830

Improving Anemia Therapy in Hemodialysis Patients: Interim Results of a Clinical Audit Iain C. Macdougall,¹ Antonio Sousa,² Carlos Andrade,² Erika Schumann,³ Thomas Ryzlewicz,⁴ Franz Ferdinand Becker,⁴ Amelia Fairburn-Beech,⁴ William Kilgallon.⁴ ¹Renal Unit, King's College Hospital, London, United Kingdom; ²Fundação Renal Portuguesa, Portalegre, Portugal; ³Via Medis, Riesa, Germany; ⁴Oxylless Ltd, London, United Kingdom.

Background: An earlier pilot audit (ASN 2013, PUB200) suggested that the use of a novel bloodline (Oxylless), which reduces the contact between blood and air, could improve the efficiency of Erythropoietin Stimulating Agent (ESA) therapy by prolonging red cell survival. The aim of this investigation was to explore this effect in a larger population.

Methods: Patients (n=110; >18 years, HD ≥ 3 months via AV fistulae) were entered into a 16-month open label, single crossover audit following a 3 month Run-In. Patients reverted to control bloodlines (Nikkiso/Gambro) in the Crossover phase after treatment with Oxylless. Hemoglobin (Hb) levels, IV iron sucrose and ESA doses were reported.

Results: Data analysis was conducted on 66 patients from two clinics. Twenty six patients dropped out due to transplantation and intercurrent events, death (n=14) and clinic transfers (n=4). Hb was maintained over the Treatment phase (11.22-11.34 g/dL). Mean ESA doses reduced by 34% (p<0.01) at month 8, equal to 1,909 IU/week/patient. IV iron dose did not change significantly during the audit.



Patients of a shorter dialysis vintage (<4 years, n=35) showed a greater reduction in ESA usage (-42%, p<0.01) compared with those of a longer vintage (>4 years, n=31, -23%). By month 11 (Crossover) ESA doses increased by 9.7 IU/week/kg; 32% of the reduction seen during Treatment.

Conclusions: The reduction in ESA doses observed during Treatment, and the initial reversal in the Crossover, suggest that this novel bloodline can improve anemia therapy in HD patients. The audit design increases the confidence in the data validity. These results could have clinical and financial benefits for HD service delivery.

Funding: Pharmaceutical Company Support - Oxylless Ltd

SA-PO831

First in Human Feasibility Study Assessing the Tablo Hemodialysis System Luis E. Morales-Buenrostro,¹ Jose Antonio Nino-Cruz,¹ Javier Zúñiga-Varga,¹ Juan M. Ardivin Ituarte,¹ May L. Yau,² Luis Alvarez.³ ¹Dialysis Dept, Nefros Investigacion SC, Mexico City, DF, Mexico; ²Outset Medical Inc, San Jose, CA; ³Palo Alto Medical Foundation, Menlo Park, CA.

Background: Self-care, at home or in-center, is a must for patients who want more independence and control, or have geographical or mobility constraints. Widespread adoption of this modality requires an easy to use dialysis machine with real-time water treatment capabilities. We conducted a first in human feasibility study to assess the safety and performance of the TABLO™ Hemodialysis System, that may meet these requirements.

Methods: We enrolled 5 patients receiving hemodialysis 3 times/week, with a well-functioning fistula or high-flow catheter. Primary outcomes of measure were Kt/V and adverse events.

Results: A total of 27 treatments in 5 patients were analyzed. Patients had the following characteristics: 40% female (n=2), mean age of 50 years, weighed 66 kg, height of 160 cm, 40% (n=2) fistula, 60% (n=3) high-flow catheter, average treatment time of 183 minutes, average fluid removal of 0.57 L, 80% (n=4) had an unknown etiology of ESRD, and 20% (n=1) had hypertension. Heparin was administered in 52% of treatments. The average single pool Kt/V was 1.4. One patient had only one treatment and was withdrawn from the study due to commute issues. Subjects were monitored during dialysis treatment by in-center staff, per institutional protocol. Only one interdialytic event, mild headache, was reported. In total, 3 subjects reported cramping (n=6/27 treatments) and 1 had hypotension (n=1/27 treatment). There were no unanticipated adverse events, serious adverse events or deaths in the study.

Conclusions: The TABLO™ Hemodialysis system was safe and showed good performance during treatments with shorter times, minimal fluid removal and heparin utilization. The standards of conventional dialysis were maintained without serious adverse events related to the device. The incorporation of an integrated water treatment module and touchscreen with animated step by step instructions was extremely easy to use. This system will allow self-care access, both in-center and at home, in a larger number of patients.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

SA-PO832

The Big Red Kidney Bus: Mobile Holiday Dialysis Peter G. Kerr,¹ Lesley Ross,¹ Jo M. Fairbairn,² Anne C. Wilson.² ¹Nephrology, Monash Health, Clayton, Vic, Australia; ²Kidney Health Australia, South Melbourne, Vic, Australia.

Background: The availability of hospital based hemodialysis for those wishing to travel is scarce and often results in restricted opportunities for patients on dialysis to have a holiday. The Kidney Health Australia (KHA) and Monash Health (MH) Big Red Kidney Bus Project (BRKB) offers patients the ability to dialyse on the BRKB whilst on holiday at one of a range of Victorian tourist destinations.

Methods: The aim of the BRKB Project is to provide safe, fully staffed mobile haemodialysis care, to enable people, their families and carers to take a break. KHA owns the bus, manages the bookings and markets the BRKB nationally. MH, a regional health care provider oversees the clinical assessment and treatment and provides medical supervision, dialysis nurses and renal technicians.

The BRKB is a modified bus accommodating 3 hemodialysis machines, dialysis chairs and complete water treatment. Typically, holiday dialysis on the BRKB operates across 2 sessions per day, 6 days per week duplicating the dialysis parameters of the patients' home unit. The bus is driven to and parked at caravan parks around Victoria for 6-week periods, during which time patients may book in for dialysis sessions. Their accommodation is up to them to decide on – with the option of using cabins in the parks or local motels (or their own caravans).

Results: Since its inaugural visit in October 2014, 148 different patients have taken advantage of the BRKB. The bus has visited 6 sites around the State and has site bookings for the next 10 months. Participating holidaymakers were overwhelmingly positive about the service. They found the booking system easy to use. The dialysis service on the bus was delivered to the standard of care experienced at their home units. The professionalism of the nursing staff and friendliness was commended and all participants would recommend the service to others in need of hemodialysis. Most had actively recommended the service to others.

Conclusions: The BRKB is a unique project that provides patients with the opportunity to dialyse on the bus while taking a much-needed holiday.

Funding: Private Foundation Support

SA-PO833

Patient and Caregiver Values, Beliefs and Experiences when Considering Home Dialysis as a Treatment Option: A Semi-Structured Interview Study Rachael C. Walker,¹ Kirsten Howard,⁴ Rachael L. Morton,¹ Suetonia Palmer,² Mark R. Marshall,³ Allison Tong.¹ ¹Univ of Sydney; ²Univ of Otago; ³Middlemore Hospital, New Zealand; ⁴Univ of South Australia.

Background: Home dialysis is associated with higher quality of life and economic benefits to health care systems compared with facility dialysis. However, little is known about the decision-making process of patients when considering home dialysis as a treatment option.

Methods: This semi-structured interview study aimed to describe patient and caregiver values, beliefs and experiences when considering home dialysis, to inform policy and practice strategies that align with patient preferences. We conducted semi-structured interviews with adults with CKD Stage 4-5D (on dialysis <1 year) and their caregivers, treated in 3 nephrology centers in New Zealand. Transcripts were analyzed thematically.

Results: 43 patients (18 pre-dialysis, 13 peritoneal dialysis, 4 home hemodialysis and 9 facility hemodialysis) and 9 caregivers participated. We identified 5 themes related to decision-making when considering home dialysis; lacking decisional power (complexity of information, limited exposure to home dialysis, feeling disempowered, deprived of choice, pressure to choose); sustaining relationships (maintaining cultural involvement, family influence, trusting clinicians, minimizing social isolation); reducing lifestyle disruption (sustaining employment, avoiding relocation, considering additional expenses, seeking flexible schedules, creating free time); gaining confidence in choice (guarantee of safety, depending on professional certainty, reassurance of peers, overcoming fears); and maximizing survival.

Conclusions: Patients feel disempowered when choosing home dialysis and make decisions that sustain their relationships, maintain lifestyle values and maximize survival. Confidence in their modality decision is gained by medical professional and peer support combined with overcoming safety concerns. Pre-dialysis programs that address these patient experiences may support home dialysis as a treatment option.

Funding: Pharmaceutical Company Support - Baxter Clinical Evidence Council research program

SA-PO834

Patient Experiences of Training and Transition to Home Hemodialysis: A Longitudinal Mixed Methods Study Camilla Sara Hanson,^{1,2} Jeremy R. Chapman,³ Jonathan C. Craig,^{1,2} David C. Harris,^{3,4} Lukas K. Kairaitis,⁴ Mary ann Nicdao,⁴ Mary Mikhael,⁴ Allison Tong.^{1,2} ¹School of Public Health, The Univ of Sydney, Sydney, NSW, Australia; ²Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW, Australia; ³Centre for Transplant and Renal Research, Westmead Hospital, Sydney, NSW, Australia; ⁴Dept of Renal Medicine, Westmead Hospital, Sydney, NSW, Australia.

Background: Home hemodialysis (HD) can offer better survival and quality of life outcomes compared with in-centre HD. However, psychosocial barriers such as fears of needles and medical isolation may limit home HD uptake. This study aims to describe patients' perspectives on training and transition to home HD; to inform strategies to optimize home HD programs.

Methods: Three semi-structured interviews were conducted prospectively with 20 patients before, during and after home HD training at an Australian renal unit. The CHOICE satisfaction survey was administered during the first and final interview. Transcripts were analyzed thematically.

Results: We identified six themes: persevering despite trepidations (intimidation of machinery, acquiescing to fatal risks, reconciling cannulation fears, dispelling concerns of neglect, tolerating concessions); optimizing learning pathway (practicing problem solving, learning from mistakes, grasping technical complexity, minimizing cognitive overload); developing confidence (believing in own abilities, depending on caregiver partnership, faith in crisis support); interrupted transition momentum (lacking individual attention, language barriers, installation delays, illness and complications, acclimatizing to new conditions); noticing immediate gains (reclaiming normality, satisfying self-sufficiency, personalizing treatment regime); depleting resources and energy (exhaustion, draining financial reserves, imposing caregiver burden). There was no significant change in satisfaction with care after commencing home HD.

Conclusions: Individualized home HD training fosters confidence and competency in patients; however patients may face anxiety and exhaustion with medical responsibilities. Ensuring access to respite, medical assistance, and psychosocial support may alleviate treatment burdens for patients commencing home HD.

Funding: Private Foundation Support

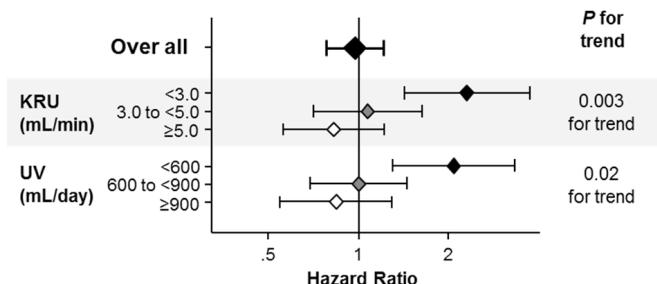
SA-PO835

Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Hemodialysis Patients Yoshitsugu Obi,¹ Elani Streja,¹ Connie Rhee,¹ Vanessa A. Ravel,¹ Alpesh Amin,¹ Csaba P. Kovcsdy,² Rajnish Mehrotra,³ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UTHSC; ³UW.

Background: We have previously reported that an incremental hemodialysis regimen (e.g., dialysis initiation at twice weekly) was associated with more preserved residual kidney function over a year of dialysis therapy (WCN 2015, Cape Town). Here, we compared survival between the incremental vs. conventional regimen.

Methods: In a longitudinal cohort of 33,277 patients who initiated maintenance hemodialysis over four years (1/2007-12/2010) and survived the first year, 364 patients treated with the incremental regimen were matched to 4,797 patients treated with the conventional regimen on age, gender, race, the use of central venous catheter as blood access, and a history of congestive heart failure at the initiation of dialysis. The incremental hemodialysis regimen was associated with ~20% higher residual renal urea clearance (KRU) and 24-hr urine volume (UV) after 1 year of dialysis initiation. We then examined survival after the first year.

Results: Patients were 69±12 years old, 39% female, 13% non-Hispanic Black, and 64% diabetic. Median KRU and UV were 4.74 (IQR, 3.23-6.65) mL/min/1.73m² and 1,150 (IQR, 800-1,650) mL/day, respectively. Baseline KRU and UV modified the association between the incremental regimen and mortality; the incremental regimen was associated with higher mortality in patients with KRU <3.0 mL/min/1.73m² or UV <600 mL/day, but not in those with higher levels of KRU and UV.



Conclusions: Among incident hemodialysis patients with substantial RKF, incremental hemodialysis may be a safe transitioning regimen associated with greater preservation of RKF, whereas in patients without substantial RKF it should be avoided.

Funding: NIDDK Support

SA-PO836

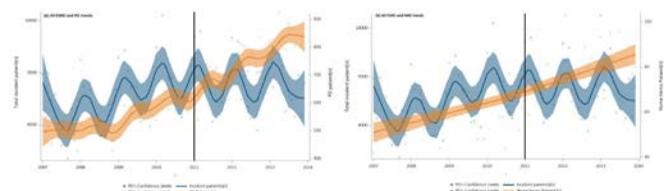
Seasonal Trends in Dialysis Initiation and Rising Home Dialysis: Results from the USRDS Hui Liu,¹ Yang Jiao,² Douglas Lehmann,² Richard Hirth,³ Yi Li,² Rajiv Saran.¹ ¹Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI; ²Dept of Biostatistics, Univ of Michigan, Ann Arbor, MI; ³Dept of Health Management and Policy, Univ of Michigan, Ann Arbor, MI.

Background: Motivated by increasing interest in home dialysis and incentive for it in the bundled payment system, we examined incident trends in home dialysis use in the United States Renal Data System (USRDS).

Methods: Using USRDS data (2007-2013), monthly counts of all new ESRD cases in the US, as well as incident home hemodialysis (HHD) and incident peritoneal dialysis (PD) patients were tracked. Incident HHD patients were those who started HHD within 90 days of entry into an ESRD program and incident PD patients those who started PD as their initial modality.

Results: In 2013, over 55% of US facilities offered only in-center HD, 24.7% both HD and PD and 13.5% offered HD, PD and HHD. Figure 1 shows trends in monthly ESRD and PD utilization in the US during 2007-2013. The incidence rate of ESRD has been stable since 2010, but the number of new PD starts has risen steadily since 2009 and has somewhat further accelerated since 2011. Figure 1 also shows a seasonal trend for new ESRD and PD starts: incident ESRD cases tend to peak in the first 3 months of the year, while new PD starts tend to peak by mid-year. Rising HHD use is evident since 2007, without seasonal variation. A substantial variation in the annual growth rate of PD is notable across the states.

Comparison of monthly trends in counts of all new ESRD patients with incident peritoneal dialysis (PD) and home hemodialysis (HHD) patients, 2007-2013



Conclusions: We report steadily rising home dialysis use in the US, both HHD and PD, since 2007 and 2009, respectively. This rise predates the implementation of the bundled payment system in 2011, although PD use seems to be rising faster since 2011. Research into this seasonality in ESRD incidence and the impact of rising home dialysis use are warranted.

Funding: NIDDK Support SA-PO837

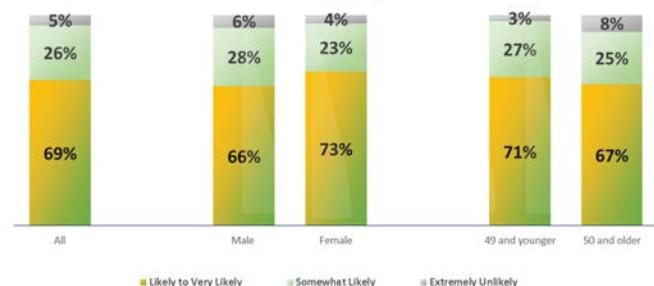
Understanding Barriers to Home-Based and Self-Care In-Center Hemodialysis May L. Yau,¹ Luis Alvarez,² Michelle Carver,¹ Geoffrey A. Block,³ Glenn Matthew Chertow.⁴ ¹Outset Medical, Inc, San Jose, CA; ²Sutter Health, Menlo Park, CA; ³Denver Nephrology, Denver, CO; ⁴Stanford School of Medicine, Palo Alto, CA.

Background: Despite superior outcomes and lower associated costs, few patients with end stage renal disease undergo selfcare (SC) or home hemodialysis (HHD). Few studies have examined patient and physician barriers to SC and HHD and the degree which innovative technology might facilitate adoption.

Methods: We surveyed 250 in-center patients (pts) receiving hemodialysis and 51 board-certified nephrologists to identify key barriers to adoption of SC and HHD.

Results: Overall, 172 (69%) pts reported that they were “likely” or “very likely” (figure 1) to consider SC hemodialysis if they were properly trained on a new hemodialysis system designed for SC.

Patients that would consider performing self-care on a novel, patient centered hemodialysis system



Nephrologists believed that pts were capable of performing dialysis-relevant tasks, including: weighing themselves (98%), wiping down the chair and machine (84%), clearing alarms during treatment (53%), taking vital signs (46%), and cannulating vascular access (41%), but thought that patients would not be willing to do the same.

Description of tasks	% of patients CAPABLE to be more involved	% of patients WILLING to be more involved
Weigh themselves	98%	69%
Wipe chair/machine after treatment	84%	34%
Clear alarms during treatment	53%	31%
Take/record vitals	45%	29%
Document/monitor treatment	43%	27%
Collect supplies	41%	27%
Cannulate their access	41%	16%
Set up machine	35%	19%
Administer medications	31%	26%
Take down machine	22%	21%

Reasons that nephrologists believe pts are hesitant to pursue SC do not correspond to reasons reported by patients.

Conclusions: SC and HHD offer several advantages to patients and dialysis providers. Overcoming real and perceived barriers with new technology, and education will be required for these modalities to gain traction in the coming years.

Funding: Pharmaceutical Company Support - Outset Medical, Inc

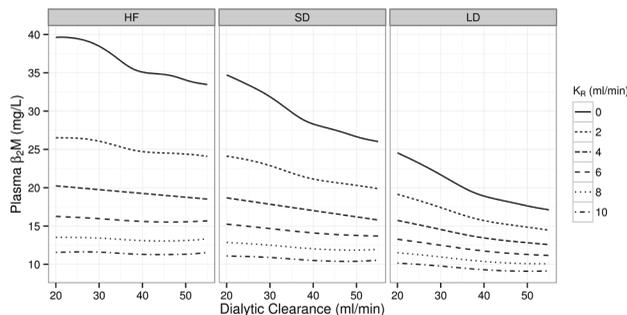
SA-PO838

Dialyzer Clearance, Residual Renal Function and Middle Molecule Levels in Daily Dialysis Christos Argropoulos, Maria-Eleni Roumelioti, Mark L. Unruh. *Internal Medicine, Div of Nephrology, UNM-HSC, Albuquerque, NM.*

Background: Beta 2 Microglobulin (B2M) has emerged as a predictor of cardiovascular morbidity, mortality and LVH in patients with CKD and ESRD. Daily dialysis leads to higher B2M removal and has been associated with improvements in LVH and mortality in randomized trials. It is not known how B2M levels vary with dialysis membrane clearance (Kd) in daily dialysis regimens.

Methods: We adopted a population kinetic model (PKM) for the intraindividual variability in the generation, distribution and extrarenal removal of B2M (ASN 2014, SA-PO969). We used the PKM to simulate B2M concentrations in patients dialyzed with HF membranes in thrice weekly or daily sessions. For the latter we applied the intervention protocols for Short (SD) and Long Daily (LD) dialysis utilized in the FHN trials. The impact of Kd relative to residual renal function (RRF) on B2M was examined across the three dialysis modalities.

Results: B2M was lower in SD or LD relative to thrice weekly HF dialysis irrespective of RRF; the highest differences from HF (Δ , 95%CI) were obtained in anuric pts: 7.5, 7.4-7.62 (SD) and LD 17.2, 17-17.4 mg/dl. The modelled average B2M relative to Kd is shown:



There were significant interactions ($p < 0.001$) between modality and RRF, as well as modality and Kd. A Kd of 60 ml/min resulted in lower B2M in LD and SD v.s. HF patients.

Modality	RRF (ml/min)	Δ B2M (mg/l) KD (60 vs 20 ml/min)	LCI	UCI
HF	0	6.8	6.7	7.6
SD	0	8.2	7.5	8.9
LD	0	8.6	7.8	9.2

The differences between lower and higher dialyzer clearances were minimal (< 1.1 mg/dl) at higher RRF irrespective of modality.

Conclusions: In simulations, higher dialyzer clearance is associated with lower plasma B2M in patients on daily dialysis, especially at lower levels of RRF. Whether these differences translate to improved cardiovascular outcomes should be confirmed in clinical studies.

SA-PO839

Wessex Kidney Centre Experience of Nocturnal Home Haemodialysis Using the NxStage System One Venkat Gangaram, Amanda Jane Laird, Laura Hignell, Natalie L. Borman. *Renal Medicine, Wessex Kidney Centre, Queen Alexandra Hospital, Portsmouth, United Kingdom.*

Background: Wessex Kidney Centre (WKC) Portsmouth established Home Haemodialysis (HHD) programme in 2009. In the absence of an in-house technician and limited capital the programme was set up using NxStage system one (NSO). WKC has now established a rapidly growing HHD programme using exclusively NSO, trained 97 patients to date includes nocturnal therapy.

Results: A total of 18 patients have received NHHD with mean time of 12.3 months (range 1 to 31). All patients dialyse alternate nights processing 40-60 litres using dual needling access and a single bolus of Enoxaparin Sodium. Patients have regular transonic monitoring of their access and home visits. Two NHHD patients successfully dialyse alone. The mean age is 47.7 years (range 26 to 80), 78% male, 94% Caucasian with mean BMI 26.9. The Access used was AV fistula 56%, AV graft 22% and CVC 22% of patients. 14 patients changed from short daily HHD (SDHHD), 3 patients from in centre Haemodialysis and 1 from Peritoneal dialysis. Laboratory parameters have been favourable as shown below.

	C.Ca mmol/L	PO4 mmol/L	K mmol/L	Hb g/l	Alb g/l	Ca-PO4 mmol ² /L ²	sKt/V
Pre-NHHD (N=18)	2.4	1.6	4.9	11.3	35	3.8	2.44
6 months (N=14)	2.4	1.4	4.7	12.3	36	3.3	2.57
12 months (N=10)	2.4	1.36	4.6	12.3	36	3.0	2.50

Retention has been excellent with one patient returning to in-centre HD after 25 months of HHD. Two patients switched to SD HHD as it more suited to their lifestyle and five patients have been transplanted. Pill burden has reduced, with less or no phosphate binders (mean number of binders reduced from 6 to 2) and a 40 % reduction in antihypertensive medications after 12 months. Patients experience has been excellent with self reported improvements in quality of life including facilitating return to employment. A number of patients have successfully travelled taking their NSO both within UK and abroad.

Conclusions: In Conclusion, NHHD using NSO is a viable alternative for HHD patients with our data suggesting good clinical outcomes. Patients have improved quality of life and with less pill burden, flexibility and more opportunity to engage in social activities.

SA-PO840

Current and Future Training of Home Haemodialysis Nurses Ruth Silverton,¹ Philippa Catherine Brown,¹ Paul Laboi,¹ Nicola Thomas.³ ¹Dept of Renal Medicine, York Hospital, United Kingdom; ²School of Health and Social Care, London South Bank Univ, United Kingdom.

Background: The UK National Institute for Health and Care Excellence recommend that >10% of dialysis patients be treated by home haemodialysis (HHD), however only 4.1% of patients in the UK are undergoing this modality. Success with HHD can be attributed to a supportive health policy, formal infrastructure, committed individuals and home dialysis experience; providing a patient-centred approach. Lack of nursing expertise is reported as a barrier to home dialysis for 30% of units. A 2010 survey by the Australian HOME network revealed insufficient resources in dialysis units to provide support and education to patients. A potential barrier to HHD in the UK is specific training for renal nurses on the facilitation of shared or self-care.

Methods: The extent of current training provision for dialysis nurses in order to educate patients in home therapies/shared care was evaluated via an online survey. A link to the survey was sent to the British Renal Society database and the survey was available online for 1 month. There were 63 respondents.

Results: Over 76% of respondents (n=48) had worked in renal care for >10 years, with a third (n=21) receiving more than 5 days of structured training in how to teach self care. The majority of this training (51%) was as part of an 'in-service programme', with just over half (53%) of all nurses surveyed feeling adequately prepared for educating patients. The preferred mode of further training was face to face at a national event (38%), with a quarter (n=14) citing e-learning as the preferred option.

Conclusions: Data from the survey highlights a lack of adequate, standardised training for HHD nurses, demonstrating the need for a structured programme that ensures up-to-date best practice. As a result, we plan to pilot a specific HHD training scheme that involves patients and carers in curriculum planning and delivery, with content including; assessment of patients' learning styles, how to facilitate shared decision-making with patients, and how to evaluate effectiveness of the HHD programme.

SA-PO841

Daily Hemodialysis in France: Patient's Characteristics, Trajectories, and Treatment Modalities Adelaide Pladys,^{1,2} Sahar Bayat,¹ Cécile Couchoud,³ Cecile M. Vigneau.^{1,4} ¹French School of Public Health, Rennes, France; ²Univ Rennes 1, Rennes, France; ³French Biomedecine Agency, Saint Denis La Plaine, France; ⁴CHU Pontchaillou, Rennes, France.

Background: Increased weekly frequency of hemodialysis (HD) sessions should have positive effects on the control of several biological data of end stage renal disease patients. However, a recent study observed contradicting results in terms of survival compared to previous ones. Patients included in this study came mainly from France where knowledge about daily hemodialysis (DHD) practices is poor. In this context, the aim of this study was to describe the characteristics of French patients in DHD, the treatment modalities and the individual trajectory before starting such a program.

Methods: Were included all patients ³18 y/o who started DHD between 2003 and 2012 in France. Biochemical and treatment characteristics were extracted from the French Renal Epidemiology and Information Network (REIN registry) then described and compared by groups using Chi-square tests.

Results: 753 patients were included in the study. According to the median age (64 years), two groups of patients were distinguished: old group (≥64 years) characterized by lots of comorbidities such as diabetes (48% vs 29%, p<0.0001), active malignancy (17% vs 10%, p<0.0001), ³1 cardio-vascular disease (80% vs 41%, p<0.0001) compared to the younger one (<64 years). At the 31/12/2013, 30.4% of the young patients underwent renal transplantation and 69% of the old ones were died. The main regimen observed was HD 6x/week with sessions' duration of 3 hours. Among these patients, 496 started with other dialysis modality before switching to DHD (sDHD) and 257 started directly with DHD (dDHD). Before starting DHD, 81% of sDHD patients were in HD 3x/week and 5.4% had ³1 modality change. dDHD patients initiated DHD in urgent condition for 57% of them and 92.6% underwent DHD in centre.

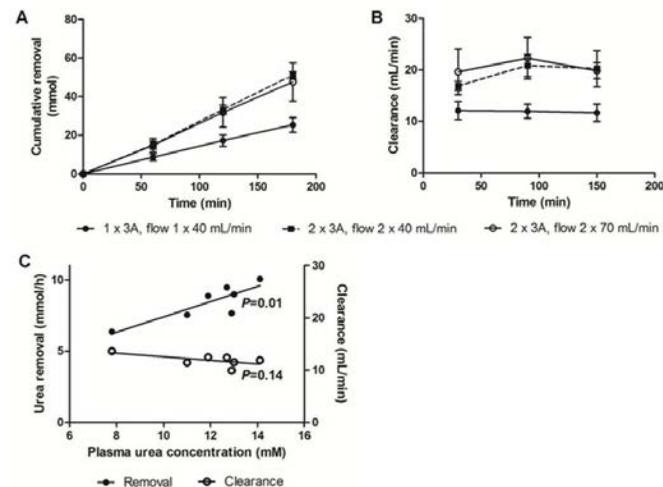
Conclusions: DHD in France is addressed both to old patients with lots of comorbidities who died rapidly and to young patients in better medical conditions who accessed more to renal transplantation. DHD regimens are various and depend of patients' characteristics and previous trajectories.

SA-PO842

In Vivo Urea Removal by Electro-Oxidation in a Wearable Dialysis Device Maarten Wester,¹ Frank Simonis,² Diënty Hazenbrink,¹ Jaap A. Joles,¹ Karin G. Gerritsen.¹ ¹Nephrology and Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands; ²Nanodialysis BV, Oirschot, Netherlands.

Background: In EU consortium NEPHRON+ a wearable dialysis device is being developed that can offer prolonged dialysis by continuous regeneration of a small volume of dialysate. A major challenge is the removal of urea, since the daily urea production is high and removal by adsorption difficult. Electro-oxidation (EO) seems attractive since electrodes are durable, small and inexpensive. Here, we studied in vivo urea removal by EO in a hemodialysis model in goats.

Methods: An EO-unit containing 10 graphite electrodes for EO and sorbent beads for K+ and PO43- removal was incorporated in a dialysate circuit in series with activated carbon (AC:25g/unit). 3 Ampère (A) was applied using 1 EO-unit (1x3A;N=7) or 2 EO-units in parallel (2x3A;N=7). Healthy goats were instrumented with a CVC, heparinized blood was pumped (110mL/min) during 3hrs over a 0.2m2 Polyflux dialyzer and dialysate was recirculated over the EO unit in counter current direction (40mL/min for 1x3A; 2x40mL/min and 2x70mL/min for 2x3A; total dialysate volume 100mL (1 EO-unit) or 150mL (2 EO-units)). Urea was infused to achieve higher urea concentrations.



Results: Urea removal and clearance were 8.4±1.5mmol/h and 11.9±1.6 mL/min, respectively, using 1 EO unit (Fig. A,B) and remained stable during consecutive hours. Use of 2 units in parallel doubled the removal of urea and caused a 1.6-fold increase in urea

clearance. Increase of the dialysate flow did not further increase urea removal. Urea removal was dependent on urea plasma concentrations (Fig.1C). Limited release of ammonia/-um was observed (0.16±0.03 mole per removed mole of urea).

Conclusions: EO by graphite electrodes combined with AC shows promising urea removal in vivo. Research aimed at increasing the efficacy and biocompatibility testing is warranted.

SA-PO843

Unplanned “Crash” Home Dialysis Starts: Single Center Experience from a University Hospital in the United States Kristen P. Tamura,¹ Jose A. Morfin,² ¹Nephrology, UC Davis Medical Center, Sacramento, CA; ²Nephrology, UC Davis Medical Center, Sacramento, CA.

Background: There is a high incidence of starting dialysis from the hospital to the in-center unit, and frequently these starts are unplanned and unexpected (“crash”). To this end, we sought to implement an educational program to identify patients suitable for a home dialysis modality, unplanned home hemodialysis (UHHD) and unplanned peritoneal dialysis (UPD).

Methods: We performed a retrospective observational analyses on patients who were started on dialysis from January 2013 to April 2015 in a diverse patient population admitted to UC Davis Medical Center in Sacramento, CA. We devised a systematic and comprehensive screening educational program to provide all modality options. We identified patients suitable UHHD, and UPD, both which were transitioned to a home dialysis training program upon discharge. Clinical characteristics and outcomes were compared to groups who had a standard start home dialysis (SHHD, SPD) during the study period. Our measured outcomes include the following: average training days, interval of technique failure rate (patient drop out), access status and complications, infections, hospitalizations and mortality in the first 90 days.

Results: Preliminary results reveal the groups tended to have similar demographic profiles with the average age for patients starting an unplanned home dialysis 51.5 years of age, 60% non-white race, but with a trend toward more males at 59% compared to standard starts.

Group	# Subject	Training Days Mean	90 Days Drop Out Number	180 Day Drop out Number	% Retention at 12 months
U HHD	9	19.6*	1	02	77.7*
S HHD	27	21.8	3	2	75.7
U PD	10	9.2+	3	0	70.0+
S PD	28	10.5	6	2	71.4

*not statistically sig.between UHHD vs SHHD
+not statistically sig.between UPD vs SPD

Conclusions: In this small representative sample, UHHD and UPD was a viable option for programs to consider for the transition of new dialysis patients from the hospital to the outpatient setting. We found similar outcomes in comparison to patients starting home dialysis training in a traditional standard way. Education and screening of home dialysis therapies should be promoted in the hospital setting.

SA-PO844

Quality of Life After 1 Year of Nocturnal Home Hemodialysis Is Comparable to Quality of Life After Renal Transplantation Anna A. Bonenkamp,¹ Franka E. Van reekum,¹ Marianne C. Verhaar,¹ Brigit C. van Jaarsveld,² ¹Nephrology & Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands; ²Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

Background: Quality of life (QOL) is an important outcome measure for pts with ESRD. Several studies found improved QOL in Nocturnal Home Hemodialysis (NHHD) compared to conventional HD (CHD). There are no studies comparing QOL in NHHD vs Tx. Therefore, some pts on NHHD hesitate whether or not to apply for a place on the renal transplant (Tx) waiting list. The aim of this study is to assess the difference in QOL between NHHD and Tx after 1 yr of follow up.

Methods: Data were obtained from the ongoing NOCTX-study, which evaluates the 3-yr progression of coronary atherosclerosis in pts treated with CHD, PD, NHHD and Tx. In this study, QOL was measured with the Kidney Disease QOL-SF questionnaire at baseline (<3 mo after start) and after 1 yr in NHHD (n=22; 5-7x/wk, 6-8 hr HD; all Tx-waitlisted) and Tx (n=30). Composite scores (Physical = PCS, Mental = MCS) and disease related domains were used. One yr results were analyzed with an unpaired t-test.

Results: Pts (n=52) were 50±12 yr, 67% male and median duration of RRT was 37±31mo. Baseline characteristics were comparable between the groups. PCS was 46±9 in NHHD and 44±8 in Tx group at baseline; follow up PCS was 44±7 and 47±9 respectively (p=0.13). MCS at baseline was 53±9 vs 53±8 and 50±12 vs 52±9 after 1 yr (NS). Compared to NHHD, Tx-pts scored better on the domain ‘Effects of kidney disease’ (75±18 vs 86±14 p=0.01). Sexual function had a remarkably good response rate (90%) and equal scores between NHHD and Tx (69±34 and 75±27 p=0.55). In other KDQOL domains no significance was observed.

Conclusions: This is the first study to compare QOL between Tx-pts and wait-listed NHHD-pts. Physical and Mental Composite Scores were similar. In disease specific domains, Tx and NHHD scored not significantly different except for the domain ‘Effects’. These data support an important role for NHHD as an alternative to renal transplantation.

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SA-PO845

Association of Vascular Access Type with Mortality, Hospitalization, and Transfer to In-Center Hemodialysis in Patients Undergoing Home Hemodialysis Matthew B. Rivara,¹ Melissa Soohoo,² Elani Streja,² Miklos Zsolt Molnar,³ Alfred K. Cheung,⁴ Ronit Katz,¹ Onyebuchi A. Arah,⁵ Allen R. Nissenson,^{6,7} Jonathan Himmelfarb,¹ Kamyar Kalantar-Zadeh,² Rajnish Mehrotra,¹ ¹Kidney Research institute, Seattle, WA; ²Harold Simmons Ctr for Kidney Dis Research & Epidemiology, Univ of California Irvine Med Ctr, Irvine, CA; ³Div of Nephrology, Univ of Tenn Health Science Ctr, Memphis, TN; ⁴Div of Nephrology, Univ of Utah, Salt Lake City, UT; ⁵Epidemiology, Fielding School of Pub Health, Los Angeles, CA; ⁶DaVita, Inc., El Segundo, CA; ⁷David Geffen Sch of Med at UCLA, Los Angeles, CA.

Background: In individuals undergoing in-center hemodialysis (HD), use of central venous catheters (CVCs) is associated with worse clinical outcomes compared to use of arteriovenous access. However, it is unclear whether a similar difference in vascular access type risk is present in patients undergoing home HD, as these patients have higher dialysis treatment frequency and lower rates of exposure to sources of nosocomial infection.

Methods: We examined the associations of vascular access type with all-cause mortality, hospitalization, and transfer to in-center HD in patients who started home HD from 2007-2011 in 464 facilities in 43 states in the United States. We analyzed the data using competing-risks hazards regression with vascular access type at the start of home HD as the primary exposure in a propensity score-matched cohort (1052 patients; 526 with CVC, 526 with arteriovenous access).

Results: Compared to arteriovenous access use, CVC use was associated with increased risk for mortality (hazard ratio [HR] 1.78; 95% confidence interval [95% CI] 1.21 to 2.61) and hospitalization (HR 1.38; 95% CI 1.19 to 1.59). CVC use was not associated with increased risk for transfer to in-center HD (HR 1.07; 95% CI 0.81 to 1.40). The results of analyses in the entire unmatched cohort (2481 patients), with vascular access type modeled as baseline exposure at start of home HD or as a time-varying exposure, were similar.

Conclusions: In a large nationally representative cohort of home HD patients, CVC use was associated with increased risk for mortality and hospitalization.

Funding: NIDDK Support

SA-PO846

Time to Transplant Associates with Home Dialysis Modality Rita Suri,^{1,3} Gihad E. Nesrallah,² Lihua Li,³ Lakshman Gunaratnam,³ ¹Centre de Recherche, Centre Hospitalier de l’Univ de Montréal, Univ of Montreal, Montreal, QC, Canada; ²Humber River Hospital, Toronto, ON, Canada; ³Nephrology Div, Western Univ, London, ON, Canada.

Background: We recently showed that prevalent end-stage renal disease patients starting home daily hemodialysis (DHD) have reduced cardiovascular and infection-related hospitalization risk compared to those starting peritoneal dialysis (PD). As current hospitalization precludes being active on the transplant wait-list, we investigated whether DHD patients receiving home DHD would be more likely to be transplanted than those receiving PD.

Methods: We matched 2997 adults starting home daily hemodialysis (DHD) in a single US dialysis provider’s facilities from 2004-2011, to 2997 contemporaneous USRDS patients starting PD by US state and propensity-scores. Demographics, comorbidities (form 2728 and hospitalization codes), and outcomes were ascertained from USRDS. We used Cox regression stratified on matched sets censoring for death, and competing risk analysis using Fine’s approach for stratified data, to compare times to transplantation between groups.

Results: Baseline variables were balanced between groups after matching, with standardized differences <10%. During 12,558 years of follow-up (mean 2.1±1.4 yrs), 514 DHD and 428 PD patients were transplanted. DHD patients were 19% more likely to be transplanted than PD patients (DHD 8.2 vs PD 6.8 per 100 patient-yrs; HR 1.19, 95%CI 1.05-1.35, p=0.012). Competing risk analysis accounting for death and follow-up losses yielded a HR of 1.18 (95%CI 1.04-1.33, p=0.010). Time to wait-listing did not differ between groups (HR 0.97, 95% CI 0.90-1.06, p=0.54), but once waitlisted, PD patients were significantly more likely to be permanently removed from the wait-list (PD 14.2% vs. DHD 10.2%, RR 1.39 (95%CI 1.09-1.78), p=0.008).

Conclusions: In this prevalent cohort, home DHD patients were more likely to be transplanted than matched PD patients, and less likely to be permanently removed from the wait-list during follow-up. Mean times to wait-listing were similar, suggesting that the groups were well-matched at baseline. Further study is needed on the factors responsible for the differential transplantation rates observed in home DHD and PD patients.

Funding: Private Foundation Support

SA-PO847

Spectrum of Mutations in PKD1 and PKD2 Genes in 100 Unrelated Italian Pedigrees with ADPKD – Sanger Sequencing versus Next Generation Sequencing (NGS) Maddalena Gigante,¹ S. Diella,¹ Matteo Accetturo,² Paola Pontrelli,² Giovanni Stallone,¹ Giuseppe Grandaliano,¹ Loreto Gesualdo,² ¹Univ of Foggia, Foggia, Italy; ²DETO, Univ of Bari, Bari, Italy.

Background: ADPKD is caused by mutations in PKD1 or PKD2 genes. Although, clinical studies and case reports describing one or few ADPKD families have been reported in Italian population, to date a comprehensive molecular study is still lacking.

Methods: PKD1 and PKD2 genes were analyzed in 150 Italian ADPKD patients from 100 unrelated pedigree - the largest Italian cohort analyzed to date in a single study - using Sanger sequencing and NGS. The potential pathogenicity of the newly identified variants was evaluated by combining different *in silico* methods.

Results: We identified the largest number of definitively and probable pathogenic mutations (n=78) reported in a single study in Italian population, achieving an overall detection rate of 90%. 55 mutations (52 PKD1 and 3 PKD2) have not been previously described, expanding the spectrum of known ADPKD mutations. We identified 12 *de novo* PKD1 mutations in sporadic patients without family history, providing a definitive diagnosis of ADPKD. We found the largest number of *de novo* mutations reported in a single study (15%) demonstrating, for the first time, that the prevalence of PKD1 *de novo* mutations may be underestimated. 4/32 PKD1 mutations were found in 32 unrelated Italian patients, a sign of founder effect. 20 patients were analyzed by NGS: we confirm the presence of a nonsense PKD1 mutation and the lacking of clear pathogenic mutations in 3 patients previously analyzed by Sanger, and the presence of definitively/probable pathogenic mutations in the 17 not previously genotyped patients. All NGS results have been confirmed by Sanger sequencing, achieving sensitivity and specificity of 100%.

Conclusions: Our data provide important new advances in the molecular diagnostics of ADPKD: (i) describe for the first time new potential founder mutations in Italy; (ii) report the largest number of *de novo* mutations identified in a single study and (iii) provide a new NGS method with a detection rate comparable to Sanger sequencing but with significantly lower cost and reduced turnaround time.

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SA-PO848

The Use of Screening MR Angiography in Patient with ADPKD Claudine Christiaens, Ruben Poesens, Dirk R. Kuypers, Bert Bammens, Bjorn Meijers. *Nephrology, Univ Hospitals Leuven, Belgium.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with the development of intracranial aneurysms and an elevated risk of hemorrhagic stroke (HS). It is suggested that screening MR angiography reduces the incidence of hemorrhagic stroke. Current screening criteria include positive aneurysmal history in relatives, neurological symptoms and planned major surgery. The efficacy of these screening criteria has, however, not been fully evaluated.

Methods: We performed a single-center retrospective analysis of all ADPKD patients followed at the University Hospitals Leuven, between January 1990 (date of the first MR angiography) and August 2014. Baseline demographics and occurrence of screening criteria, screening MR angiography, intracranial aneurysm and hemorrhagic stroke were evaluated.

Results: We identified 865 patients with ADPKD. Those who were seen at least three times (n=627, median age 51y, 49% males) were included for analysis. Mean duration of follow up was 11.6 years. In this cohort, current screening criteria were met in 183 ADPKD patients (29.2%). Of these, 136 (74.3%) had screening MR angiography. In patients with no MR angiography, presence of screening criteria was associated with an elevated risk of hemorrhagic stroke (12.8% vs. 4.0%, P 0.02). Use of MR angiography in patients with screening criteria was related with a lower risk of hemorrhagic stroke during follow-up (2.2% vs. 12.8%, P 0.01).

Conclusions: In patients with ADPKD, current screening criteria for intracranial aneurysm are associated with an 3-fold elevated risk for future hemorrhagic stroke and performing MR angiography seems effective in reducing this risk.

SA-PO849

Influence of Genotype on ADPKD Progression in the HALT PKD Cohort Christina M. Heyer,¹ Kaleab Z. Abebe,² Vicente E. Torres,¹ Ronald D. Perrone,⁴ Marie C. Hogan,¹ William E. Braun,⁵ Godela M. Brosnahan,³ Peter G. Czarnecki,⁶ Charity G. Moore,⁷ Peter C. Harris,¹ Dana Miskulin,⁴ The HALT PKD Investigators.⁸ ¹Mayo Clinic, Rochester, MN; ²U of Pittsburgh, Pittsburgh, PA; ³U of Colorado, Denver, CO; ⁴Tufts, Boston, MA; ⁵Cleveland Clinic, Cleveland, OH; ⁶Brigham and Women's Hospital, Boston, MA; ⁷Carolina's Health Care System, Charlotte, NC; ⁸7 Sites.

Background: We assayed here the influence of the ADPKD disease gene (PKD1 or PKD2) or PKD1 mutation type (truncating or non-truncating) on the rates of renal disease progression over 5 years in the HALT PKD cohort.

Methods: PKD1 mutation type was divided into strength groups: truncating (MSG1), and more or less penetrant non-truncating (MSG2 and MSG3). Correlations were made between gene type/MSG and changes in eGFR or height adjusted total kidney volume (htTKV).

Results: PKD1 patients had a faster eGFR decline than PKD2 (3.3 vs. 1.87 ml/min/1.73m²/yr; P<0.0001) but the rate of htTKV increase did not differ (6.44 vs. 6.81%/yr; P=0.42). Baseline PKD1 htTKV was larger than PKD2 (733, 557ml/m; P=0.0001) and

so PKD1 kidneys expanded to a greater extent (268, 217ml/m/5yr; P=0.0001). Rates of change in eGFR or htTKV did not differ between PKD1 MSG3 and MSG1 (P=0.15 and 0.70), but MSG3 baseline kidneys were smaller relative to MSG1 and MSG2 (611, 753, 777ml/m; P=0.004) and so the volume increase was less (221, 262, 277ml/m; P=0.004). PKD2 patients were less likely to reach a study endpoint (death, ESRD or 50% eGFR decline; P=0.0003), but there was no difference between PKD1 MSG1, 2, 3 (P=0.61). Patients with no mutation detected, had a slower increase in htTKV (4.84%/yr; P=0.008 vs. PKD1). The study showed a difference in TKV increase between the low and standard blood pressure groups (5.6 vs. 6.6%/yr; P=0.006). The magnitude of difference was similar when restricted to PKD1 MSG1 (5.7 vs. 6.7%/yr; P=0.0518) or PKD1 MSG1 and 2 (5.8 vs. 6.6%/yr; P=0.0543), but not significant in the smaller populations.

Conclusions: PKD1 MSG3 kidneys are smaller but not because they grow more slowly; possibly because they have less early cysts, similar to PKD2 vs. PKD1. Since genetic and allelic effects do not alter progression rates, restricting analysis by genetic factors did not improve significance.

Funding: NIDDK Support

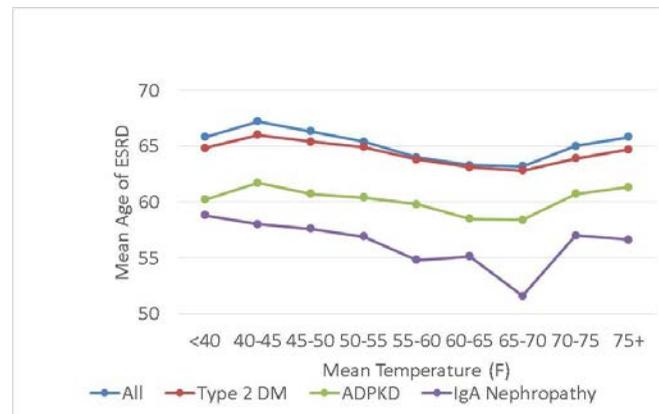
SA-PO850

Climate Temperature Affects the Age of End-Stage Kidney Disease in Autosomal Dominant Polycystic Kidney Disease (PKD) Marwan M. Abbas,¹ Michael E. Bleyer,¹ Elizabeth Swain,¹ Kendrah O. Kidd,¹ Gregory B. Russell,² Anthony J. Bleyer.¹ ¹Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; ²Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC.

Background: Vasopressin receptor 2 antagonists decrease cyst size in PKD. We postulated that patients in hotter climates would have more concentrated urine, and this would affect the age of ESRD in PKD.

Methods: We obtained demographic data and cause of ESRD on 1,332,402 individuals who had their first occurrence of ESRD between ages 30 and 90 between 1971 and 2012 from the US Renal Data system (USRDS). We obtained annual mean temperatures from 1990 to 2010 for US weather stations and linked a participant's zip code to the nearest weather center. We correlated the mean age of onset of ESRD for PKD and other causes of ESRD with 5 degree temperature intervals. We created a multivariate model for PKD patients, with the dependent variable age of ESRD and independent variables race, gender, year starting dialysis, residual GFR at start of ESRD, annual median income by patient zip code, and temperature as discrete variables in 5 degree intervals.

Results: Figure 1 shows the mean age of onset of ESRD by disease. Cold and warm temperature extremes were associated with increasing age of ESRD for PKD, but also other diseases.



Variable	Type III SS	F value	p value
Temperature	11156	8	<0.0001
Gender	3076	18	<0.0001
Race	30783	45	<0.0001
Median income by zip code	25287	150	<0.0001
GFR at start of ESRD	79568	472	<0.0001
Year starting ESRD	82317	488	<0.0001

The multivariate model showed that temperature had a minimal effect on age of ESRD compared to other variables in the model.

Conclusions: There was a U-shaped relationship for age of ESRD according to temperature that was present in PKD and other diseases. However, in a multivariate model, climate temperature had a minimal effect on age of ESRD in PKD.

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SA-PO851

Urinary Biomarkers and Prediction of Disease Progression in Autosomal Dominant Polycystic Kidney Disease

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Background: The variable disease course of ADPKD underlines the importance of predicting disease progression especially since therapeutic options are now available. Conventional risk markers (age, gender, GFR, total kidney volume (TKV)) lack sensitivity, are expensive or time consuming to measure. We therefore investigated whether easy to measure urinary markers can predict disease progression and have additional value to conventional risk markers.

Methods: At baseline tubular damage and inflammatory markers were measured in 24-hr urine; albumin, IgG, KIM1, NAG, b2MG, H-FABP, MIF, NGAL and MCP-1. Kidney function was estimated (eGFR by CKD-EPI) and measured (mGFR by ¹²⁵I-iothalamate), and TKV by MRI. Disease progression was expressed as annual change in eGFR, mGFR, and height-adjusted (ht)TKV. Multivariate linear regression was used to assess the predictive ability of the markers above conventional risk markers.

Results: Included were 104 ADPKD patients, 40±11yrs, 39% female, eGFR 77±30, mGFR 79±29 ml/min/1.73m² and htTKV 852 (510-1243) mL/m. During a follow-up of 3.8±1.2 yrs, annual change in eGFR was -3.2±3.0, in mGFR -3.0±3.0 mL/min/1.73m² and in htTKV 6.2±5.9%. b2MG and MCP-1 were associated with annual change in eGFR (St. β=-0.23, p=0.02; St. β=-0.38, p<0.001 resp.) and mGFR (St. β=-0.24, p=0.03; St. β=-0.24, p=0.03 resp.), even when adjusted for conventional risk markers, but not with annual change in htTKV. Similar results were obtained when patients with an eGFR≥60 mL/min/1.73m² were selected. Combined b2MG and MCP-1 had an added predictive ability for annual change in eGFR (R²=0.178 vs. 0.324, p=0.008) and in mGFR (R²=0.134 vs 0.217, p=0.07). The best predictive model for annual change in eGFR included age, htTKV, MIF, b2MG and MCP-1 (R²=0.343, p=0.025), and for annual change in mGFR, gender, b2MG, NGAL and MCP-1 (R²=0.211, p=0.5).

Conclusions: b2MG and MCP-1 both predict disease progression, and had an added predictive value on top of conventional risk markers. These markers have therefore potential to serve as a predictive tool for clinical practice.

SA-PO852

The Novel Surrogate Marker of Autosomal Dominant Polycystic Kidney Disease (ADPKD) – Urinary Copeptin

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Background: Experimental studies suggest a detrimental role for Arginine vasopressin (AVP) in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). Copeptin consists of the C-terminal portion of Pro-AVP and has been shown to be a reliable and stable substitute for circulating AVP concentration. In contrast to serum or plasma, urinary proteins do not undergo detectable degradation by endogenous proteases after voiding. It is unknown, however, whether urinary copeptin concentration are associated with disease severity in patients with ADPKD.

Methods: Serum and Urinary copeptin concentration were measured by immunoassay in ADPKD patients with CKD stage ≤ 4. We compared our measurements with clinical parameters including estimated Glomerular Filtration Rate (eGFR), Total Kidney Volume (TKV), and height-adjusted TKV (htTKV). Logarithmic transformation of all variables was performed to fulfill the requirement of equal distribution of the residuals.

Results: We included 50 patients in this study (24 females and 26 males; mean age: 49.3 years). The median eGFR and TKV were 53.2 ml/min/1.73 m² (interquartile range: IQR; 29.4 - 68.45) and 1138.1 ml (IQR; 814.7 - 2065.0), respectively. The median urinary copeptin level was 12.19 (IQR; 6.91 - 22.32) ng/ml. We could show the positive-correlation between u-copeptin and plasma copeptin but without significant relationship (p = 0.198). Although there are no significant correlations between plasma copeptin and eGFR (R = -0.245, p = 0.227), there are significant correlations between plasma copeptin and htTKV (R = 0.458, p = 0.019) and TKV (R = 0.465, p = 0.017). On the other hand, Urinary copeptin/u-Cr was statistically associated with the various markers of disease severity in ADPKD (positively with TKV (R = 0.351, p = 0.014), htTKV (R = 0.383, p = 0.008) and negatively with eGFR (R = -0.304, p = 0.036).

Conclusions: In ADPKD subjects, a higher urinary copeptin concentration is associated with disease progression, suggesting that urinary copeptin may be a surrogate marker to detect disease severity renal prognosis in ADPKD.

SA-PO853

The Burden of Tolvaptan Treatment for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Last year, Japan became the first country in the world to approve tolvaptan for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Because tolvaptan has powerful diuretic effect, patients have to take huge amount of water to prevent dehydration. We evaluated the burden of tolvaptan treatment on patients with ADPKD.

Methods: This study targeted Japanese patients with ADPKD on tolvaptan. An initial dose of tolvaptan was 60 mg. Estimated glomerular function rate (eGFR) and total kidney volume (TKV) were measured at regular intervals. The burden of tolvaptan treatment was evaluated by visual analog scales. Statistical analysis was performed using analysis of variance.

Results: We included 40 patients (male: 28, female: 12). The median age was 46.5 years (interquartile range: IQR 24 - 69 yr.). The median baseline eGFR was 43.4 ml/min/1.73m² (IQR: 26.9 - 58.8) and the median baseline TKV was 1,917 ml (IQR: 1,378 - 2,905). The median starting dosage of tolvaptan was 60 mg (IQR: 30 - 60) and the median treatment period was 8 months (IQR: 6 - 11). We observed no statistical variations in eGFR (p = 0.787) and TKV (p = 0.561) during treatment. There were no significant changes in VAS scores for general fatigue (p = 0.817), anorexia (p = 0.393), back pain (p = 0.682), and abdominal distention (p = 0.607) during treatment. Although analysis of variance demonstrated that aquaretic burden including thirst and dry skin were significantly increased after Tolvaptan treatment (p = 0.003), 35 % (n = 14) of patients did not completely sense thirst at all during treatment, and 42 % (n = 17) of patients spontaneously improved without any additional treatment or tolvaptan withdrawal.

Conclusions: Although analysis of variance demonstrated that aquaretic burden including thirst and dry skin were significantly increased after Tolvaptan treatment, almost third of the patients did not completely sense thirst at all from beginning of Tolvaptan treatment, and the remaining third part of patients spontaneously improved.

SA-PO854

Adapted PKDOC Disease Predicts Actual Progression of Autosomal Dominant Polycystic Kidney Disease in TEMPO3:4

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Background: The Polycystic Kidney Disease Outcomes Consortium (PKDOC) has submitted for FDA and EMA concurrence, the use of total kidney volume (TKV) as a prognostic biomarker to enrich autosomal dominant polycystic kidney disease (ADPKD) trials for patients likely to display progressive decline in renal function and progression to end-stage renal disease (ESRD). A disease progression model linking TKV growth (with baseline covariates of age and eGFR) to longitudinal eGFR was constructed using a combination of PKDOC datasets including ADPKD patients with TKV data collected over 30 years of follow-up.

Methods: This report uses baseline data for placebo subjects from the TEMPO 3:4 ADPKD clinical trial to support this approach to disease progression modelling by comparing model predicted and observed TKV and eGFR. Simulations were performed by utilizing the PKDOC model with subject-specific baseline TKV and eGFR measurements from subjects enrolled in TEMPO 3:4.

Results: Bias (mean of the relative error) and precision (square mean of relative error) of TKV and eGFR were derived to assess the predictive performance of the PKDOC model. The model resulted in very robust predictions of TKV and eGFR with mean (95% CI) bias values of 2.98% (1.1-5.1) and 3.03% (1.4-4.7), respectively. Mean (95% CI) precision on TKV and eGFR were 42.9% (19.1-68.7) and 37.9% (34.0-43.4), respectively. The coefficient of determination (r²) for observed and model predicted TKV and eGFR data were 0.957 and 0.877, respectively.

Conclusions: The disease progression model developed with PKDOC data and applied to the TEMPO placebo dataset demonstrated excellent predictive power for TKV and eGFR. This demonstrates the utility of the disease model in prognosis and potential for evaluation treatment effects.

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SA-PO855

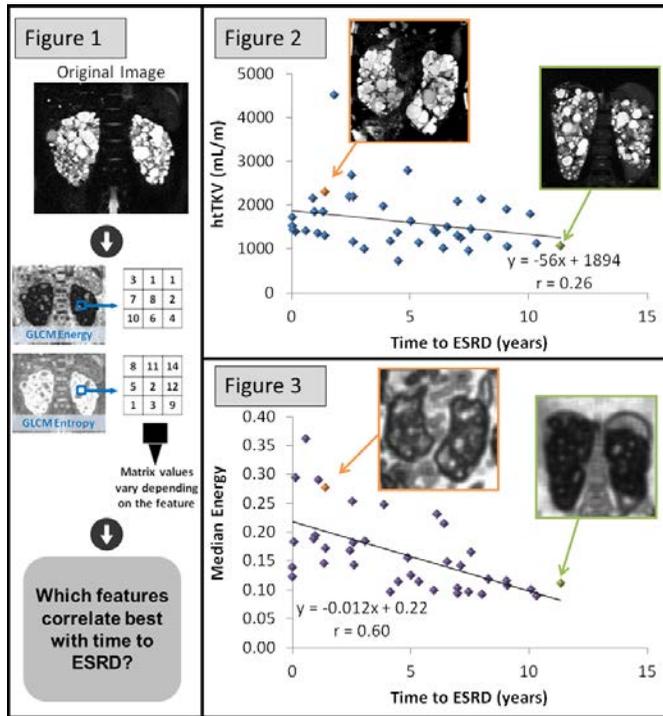
Polycystic Kidney Disease Imaging Biomarkers – The Texture of Things to Come

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Background: Medical imaging is essential for polycystic kidney disease (PKD) diagnosis, monitoring, and outcome prediction. Research studies use total kidney volume (TKV) as an imaging biomarker to follow the progression of PKD. However, TKV overlooks underlying structural and functional complexities of the kidneys. We hypothesize that texture analysis may provide quantifiable measurements of renal tissue structure to improve patient outcome prediction.

Methods: A retrospective cohort of 20 patients (38 exams) was identified who had imaging prior to reaching end-stage renal disease (ESRD). Image texture features were generated from the baseline MR images and analysis of the correlation to known time-to-ESRD was performed. A total of 18 texture features were computed for each MRI scan. The analysis workflow is shown in Fig. 1.

Results: Texture features were well correlated to time-to-ESRD and many individual texture features outperformed height-adjusted TKV (htTKV) as shown in Figs. 2 and 3. Example T2 MRIs and their corresponding energy image feature (measure of heterogeneity) for two different patients with markedly different times-to-ESRD are also shown for comparison. In addition, entropy (measure of image randomness) and gray-level non-uniformity (measure of neighboring pixel similarities) were also found to be well correlated (r-values of 0.66 and 0.73, respectively).



Conclusions: We present the first use of texture analysis for PKD assessment. Results are promising in terms of identifying new imaging biomarkers that correlate with disease progression. This approach could function as a surrogate to more difficult imaging methods (e.g., quantitative MRI) and costly analysis (e.g., cyst segmentation). It is likely that combining texture analysis with other patient data will allow for substantial improvements to PKD prognosis.

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SA-PO856

Accuracy of Traditional and Novel Renal Filtration Markers for Estimating GFR in ADPKD Patients Stephen L. Seliger,¹ Charalett E. Diggs, MSN,¹ Thomas C. Dowling,² Robert Christenson,³ Terry J. Watnick.¹ ¹Medicine, U Maryland Sch Medicine, Baltimore; ²Ferris State Univ; ³Pathology, U Maryland Sch Medicine, Baltimore.

Background: The best method for estimating GFR in ADPKD is unclear. Changes in tubular handling of filtration markers may affect estimating equation accuracy.

Methods: Among 51 adults with ADPKD and eGFR >20 cc/min/1.73m², we measured GFR using iohexol plasma clearance (iGFR), serum creatinine (Scr, IDMS-traceable assay), Cystatin C (CysC, Dimension VISTA assay) and beta-trace protein (BTP, immunonephelometric assay, Siemens). We estimated GFR (eGFR) using validated equations based on Scr (CKD-Epi_{Cr}, MDRD), Cystatin-C (CKD-Epi_{CysC}), both CysC and Scr (CKD-Epi_{Cr+CysC}) or Scr and BTP (White equation). We compared the bias, precision, overall accuracy, and classification (for iGFR <60 cc/min/1.73m²) of each estimating equation.

Results: Mean age was 51±12 years, 71% were female, 84% Caucasian, and mean iGFR was 68.4±/-34.2 cc/min/1.73m². Of the 5 equations, the CKD-Epi_{CysC} had the highest bias (overestimating GFR), lowest precision and accuracy, and was least sensitive for detection of low iGFR (Table). The CKD-Epi_{Cr} and BTP/Scr-based White equations had least bias and highest precision. Sensitivity and specificity were not significantly different between the Scr- and BTP-based estimating equations. (Table)

Performance Characteristic	Bias	Precision	Accuracy		Sensitivity	Specificity
			P30 ¹	RMSE ²		
Statistic	Mean Difference	Inter-quartile range of Difference	for iGFR <60			
CKD-Epi _{Cr}	0.8 (-4.5, 6.0)	-9.2, 9.3	76.5%	18.7	84%	88%
MDRD	5.6 (-11.0, -0.2)	-19.5, 4.6	76.5%	19.5	88%	85%
CKD-Epi _{CysC}	17.7 (12.2, 23.2)	2.2, 27.8	51.0%	19.1	52%	100%
CKD-Epi _{Cr+CysC}	9.0 (4.1, 13.9)	-3.9, 18.2	74.5%	17.1	68%	96%
White _{BTP+Cr}	-0.5 (-5.8, 4.9)	-9.3, 12.3	70.6%	18.4	80%	88%

1. P30 represents proportion with of GFR estimates that are within 30% of measured GFR.
2. Smaller values indicate higher accuracy

Conclusions: In ADPKD patients, cystatin-based GFR equations may over-estimate true GFR, in contrast to the lower bias observed in the general CKD population. The Scr-based CKD-Epi equation performed best overall among 5 equations. The utility of equations utilizing beta-trace protein deserves further investigation.

Funding: NIDDK Support

SA-PO857

Statins, ADPKD Severity and Progression in the TEMPO 3:4 ADPKD Clinical Trial Vicente E. Torres,¹ Ron T. Gansevoort,² Ronald D. Perrone,³ Olivier Devuyst,⁴ Arlene B. Chapman,⁵ Eiji Higashihara,⁶ Wen Zhou,⁷ John Ouyang,⁷ Jaime Blais,⁷ Frank S. Czerwiec.⁷ ¹Mayo; ²U Groningen; ³Tufts U; ⁴U Zurich; ⁵U Chicago; ⁶Kyorin U; ⁷Otsuka.

Background: In ADPKD, low HDL and high LDL cholesterol are associated with faster total kidney volume (TKV) increase and eGFR decline. A randomized controlled trial (RCT) of pravastatin in children showed lower TKV expansion without effect on renal function.

Methods: Exploratory post-hoc analysis of TEMPO 3:4 (3-year RCT of tolvaptan in relatively early but progressive ADPKD, age 18-50 yrs, TKV ≥750 ml, eCrCl ≥60 ml per minute) to examine whether use of statins might have affected ADPKD progression. Linear mixed-effect models that adjust for gender, age and baseline TKV and eGFR were used to compare TKV and eGFR slopes between groups.

Results: Patients randomized to placebo using statins were older, had larger TKV and lower eGFR at baseline, and their TKV and eGFR slopes were steeper compared to statin nonusers (Table). Similarly, patients randomized to tolvaptan using statins were older and had lower eGFR, with a non-significant trend to larger TKV compared to statin non-users; however, there was no difference between TKV and eGFR slopes of statin users and nonusers randomized to tolvaptan. Statin use did not affect a composite end point of clinically relevant ADPKD events in the placebo (HR=1.013, P=0.91) or tolvaptan (HR=0.954, P=0.65) group.

	Placebo (n=484)			Tolvaptan (n=961)		
	No	Yes	P	No	Yes	P
Statin use						
N	416	68	---	827	134	---
Sex (% male)	51.0	57.4	0.33	49.7	62.7	0.005
Baseline age (yrs)	38.5	40.9	<0.001	38.0	41.8	0.025
Baseline eGFR (ml/min/1.73 m ²)	83.5	73.9	<0.001	82.4	74.8	0.003
Baseline TKV (ml)	1638	1848	0.039	1678	1867	0.067
eGFR slope (ml/min/1.73 m ² /yr)	3.57	4.54	0.058	-2.74	-2.64	0.76
TKV slope (%/yr)	5.76	7.10	0.033	3.90	4.29	0.42

Conclusions: Older patients with more advanced and/or severe ADPKD are more likely to be treated with statins. Placebo patients using statins progressed faster; tolvaptan slowed progression and annulled the difference between statin users and nonusers.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical

SA-PO858

Systems Biology of Polycystic Kidney Disease Kelly A. George,^{1,2} Herve Husson,³ Ramya Kalyana Kumar,² Vishal S. Vaidya,^{1,2} Oxana Beskrovnaya,³ Jagesh V. Shah.^{1,2} ¹Laboratory of Systems Pharmacology, Harvard Medical School, Boston, MA; ²Renal Div, Brigham and Women's Hospital, Boston, MA; ³Genzyme Corp, Framingham, MA.

Background: Polycystic kidney disease (PKD) is a group of hereditary disease states characterized by cystic kidneys and often accompanied by other manifestations such as cystic liver and hypertension. PKD occurs in 1 in 500 people, usually resulting from a dominant mutation in one of two genes, PKD1 or PKD2. There are no treatments for PKD and it is the leading genetic cause of renal failure. Numerous studies have identified pathways that are misregulated in PKD but targeting these individual pathways has not led to a successful therapeutic intervention or molecular biomarker.

Methods: To identify potential biomarkers and develop a systems-level understanding of PKD, we are using transcriptomics, and quantitative proteomics and phospho-proteomics to evaluate the state of cystic and normal kidneys in a mouse model of PKD. Kidney cysts also induce injury to the surrounding tissues, confounding any analysis of the "cystic state". In an effort to separate the injury signature from the cystic signature, we are also evaluating the state of the injured kidney using a folate model of acute kidney injury and fibrosis. The multi-kinase inhibitor Roscovitine has been shown to prevent cystogenesis in mouse models of PKD but its mechanism of action remains unknown. To gain insight into the mechanism(s) of Roscovitine and to identify biomarkers that change with treatment, we are also using the above "omic" strategies using kidneys from mice following treatment.

Results: From the transcriptomic experiments, we have a list of potential biomarker candidates that are currently being tested by qPCR in mouse tissue at various stages of disease progression. Phosphorylation at motifs for CDKs, CK1, CaMK, and others are reduced in kidneys treated with Roscovitine. The primary transcription factor family found to be suppressed with Roscovitine treatment is the E2Fs, likely a result in the loss of CDK signaling.

Conclusions: These experiments will not only provide candidate biomarkers for PKD progression, but will also yield a deeper understanding of the state of the cystic kidney.

Funding: Pharmaceutical Company Support - Sanofi Genzyme, Private Foundation Support

SA-PO859

Prognostic Enrichment Strategies in the TEMPO 3:4 ADPKD Clinical Trial
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Background: An image classification of ADPKD based on diffuse (class 1) vs asymmetric (class 2) cyst distribution along with estimated cyst growth determined by age and height-adjusted total kidney volume (htTKV, subclass A-E) has been proposed for prognostic enrichment by excluding patients with a lesser risk for progression (classes 1A-B and 2).

Methods: This enrichment strategy was compared, post-hoc, to exclusion criteria used for TEMPO3:4 to examine tolvaptan effects on ADPKD progression in patients with early but progressive renal disease (18-50 year-old, TKV ≥750 ml, eCrCl ≥60 ml/min).

Results: 1436 TEMPO 3:4 subjects with baseline MRIs were classified, finding only 10% class 2 or 1B and no 1A subjects. TEMPO3:4 enriched categories 1C-E (90%) compared to the published cohorts (62%, Irazabal 2014 JASN). TKV and eGFR slopes steepened from class 1B to 1E (both P<0.001, Table).

Class: N (%)	2: 42 (3.1)		1B: 96 (7.4)		1C: 474 (37)		1D: 441 (34)		1E: 220 (18)	
	TKV	eGFR	TKV	eGFR	TKV	eGFR	TKV	eGFR	TKV	eGFR
Placebo	2.48	-1.66	3.25	-2.10	5.12	-3.59	6.62	-3.89	7.75	-4.93
Tolvaptan	2.27	-1.34	1.23	-1.79	1.79	-2.32	3.03	-2.99	4.96	-3.46
P-value	0.88	0.75	0.023	0.64	< 0.001	< 0.001	< 0.001	0.007	< 0.001	< 0.001

Tolvaptan effects on TKV and eGFR slopes was greater in classes 1C to E. Originally, tolvaptan blunted TKV and eGFR slopes from 5.51% to 2.80% and from -3.70 to -2.78 ml/min/1.73m² per year (both P<0.001), and lowered the risk for a composite endpoint (CE) of clinical progression events (hazard ratio [HR] 0.87, p=0.0095, Torres 2012 NEJM). Removing class 1A-B and class 2 patients from the trial, marginally improved estimates of tolvaptan effects on TKV and eGFR slopes 5.78% to 2.91% and -3.93 to -2.82 ml/min/1.73 m² per year (both P<0.001), and the CE endpoint (HR 0.84, p=0.0032).

Conclusions: Prognostic enrichment strategies using kidney morphology can enhance ADPKD trials for rapidly progressing patients, increasing power and reducing costs. Refinements of imaging criteria can improve the probability of success of future clinical trials.

Funding: NIDDK Support

SA-PO860

Prognostic Enrichment Design in Clinical Trials for ADPKD: The HALT PKD A Trial
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Background: Patients with mild ADPKD phenotype are less likely to be informative in clinical trials. An image classification into typical (diffuse cyst distribution) class 1A → E (determined by age and height adjusted total kidney volume, (TKV) and atypical (asymmetric cyst distribution) class 2 has been proposed for prognostic enrichment design in clinical trials with recommendations to exclude class 1A and 2 and follow-up class 1B patients to more precisely define their risk for progression.

Methods: Post-hoc analysis of HALT-PKD A, (RCT of rigorous vs standard BP control on TKV increase and eGFR decline; eGFR>60 ml/min/1.73 m²) to investigate the performance of this classification for prognostic enrichment design.

Results: 551 participants were classified by 2 raters (98.2% agreement) into class 1A (6.2%), 1B (20.3%), 1C (34.1%), 1D (22.1%), 1E (11.8%), and 2 (5.4%). TKV increase and eGFR decline became steeper from class 1A → 1E (both P<0.0001). HALT PKD A had shown slower TKV increase, faster eGFR decline in the first four months (F0-5) and marginally slower eGFR thereafter (F5-80), without a significant overall (F0-80) effect with rigorous BP control. To ascertain the ability to detect an effect of rigorous BP control in imaging classes of increasing severity, we grouped classes 1A and 2 (lowest severity), 1B and 1C (intermediate severity), and 1D and 1E (highest severity). Beneficial effects on TKV increase and eGFR decline were detected only in class 1D and 1E.

	Class 1A & 2 (n=64)			Class 1B & 1C (n=300)			Class 1D & 1E (n=187)		
BP	TKV %/yr	F0-80 eGFR ml/min/yr	F5-80 eGFR ml/min/yr	TKV %/yr	F0-80 eGFR ml/min/yr	F5-80 eGFR ml/min/yr	TKV %/yr	F0-80 eGFR ml/min/yr	F5-80 eGFR ml/min/yr
Standard	4.61	-1.16	-1.39	6.20	-2.47	-2.63	7.80	-4.37	-4.44
Low	4.20	-1.20	-0.98	5.47	-2.84	-2.67	6.44	-3.57	-3.36
P-value	0.64	0.94	0.44	0.11	0.15	0.88	0.033	0.051	0.011

Conclusions: Strategies for prognostic enrichment such as the image classification should be used in the design of RCTs for ADPKD to increase their power and reduce their cost.

Funding: NIDDK Support

SA-PO861

Long-Term Safety Profile of Tolvaptan in Japanese ADPKD Patients
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Background: Tolvaptan was first approved in Japan for autosomal dominant polycystic kidney disease (ADPKD) based on results of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 trial (TEMPO) to evaluate 3-year efficacy and safety. **Purpose:** Examine adverse drug reactions (ADRs) of tolvaptan for up to extended 3 years after TEMPO in Japanese ADPKD patients.

Methods: This open-label study was conducted in 135 patients participating in the preceding TEMPO. Doses of tolvaptan were adjusted from 60 to 120 mg/day.

Results: Main ADRs, thirst (77%), pollakiuria (57%), polyuria (38%), and hyperuricemia (15%) were noted during up to 3 years. In TEMPO, hepatic function-related ADRs were observed more frequently for tolvaptan than for placebo early during treatment. In this study, 8 patients (6%) experienced >3-fold increases above upper limits of normal serum ALT or AST 3 to 9 months after tolvaptan initiation, but all recovered after tolvaptan cessation. Of these 8 patients, 7 had been allocated to placebo in TEMPO. However, the residual one patient allocated to tolvaptan similarly had shown increased serum ALT in TEMPO. None of the 8 patients met Hy's Law criteria. No ADRs besides those seen in TEMPO were newly observed in this study.

Conclusions: Hepatic function-related ADRs occurred early during treatment and were reversible. Tolvaptan was thus indicated to be a promising drug for treatment of ADPKD for up to 6 years while carefully monitoring ADRs including hepatic function abnormalities.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Co., Ltd.

SA-PO862

Pregnancy Outcome in Articipants in the HALT PKD Clinical Trials
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Background: ADPKD is the most common hereditary disease. Fertility rates are not impaired in ADPKD women, however, preexisting hypertension and proteinuria associate with increased maternal and fetal complications. In the HALT PKD trials, 38 pregnancies occurred despite counseling and review with participants. We now present maternal and fetal outcomes from these pregnancies.

Methods: In a secondary analysis, data regarding maternal and fetal outcomes and complications of reported pregnancies were obtained including spontaneous abortions, delivery types and still births. Data collection relied on completion of protocol case report forms, followup of hospital discharge summaries and patient based reports if available.

Results: In HALT A and B, 203 and 89 women were premenopausal. In all pregnancies, study medications were stopped immediately or before the pregnancy began. 36 pregnancies occurred in 30 women with 6 experiencing 2 pregnancies. 26 women experienced 32 pregnancies in Study A (12.8%) and 4 occurred in 4 women in Study B (4.5%). In Study A baseline TKV was 871.5±502.9 mls, and GFR was 104.3±17.5 mL/min. In Study B, baseline GFR was 51.6 9.3 ml/min. Information on pregnancy outcome was not available in 3 pregnancies (2 LTFU and 1 pregnant at the end of study). In 33 pregnancies, 58% resulted in a live birth (100% in HALT B). In the remainder, 7 spontaneous and 2 therapeutic abortions, 1 ectopic and 1 stillbirth occurred. Two C-sections, one for pre-eclampsia and one pre-term delivery were reported.

Conclusions: In this secondary analysis of HALT Study A and B, 10.3% of premenopausal women became pregnant despite ongoing counseling and informed consent regarding the need to avoid becoming pregnant. A high spontaneous abortion rate was noted with a conservative live birth rate estimate of 58%. Pre-eclampsia, preterm delivery and ectopic pregnancy, all known to associate with ADPKD, occurred in 9% of pregnancies. No direct evidence for fetal injury due to telmisartan or lisinopril exposure was noted.

Funding: NIDDK Support

SA-PO863

Renal Concentrating Capacity and Copeptin Concentration in Patients with ADPKD and IgA Nephropathy with Impaired Renal Function
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Background: ADPKD patients have an impaired maximal urine concentrating capacity (Umax). Whether this is an specific effect of renal function impairment, or specific for ADPKD is yet unknown. We hypothesized that ADPKD patients have a more severely impaired Umax in comparison with non-ADPKD renal disease patients, which leads to an exaggerated vasopressin (AVP) response that may be damaging to the kidney.

Methods: 15 ADPKD (eGFR<60) and 15 IgAN patients, matched for age, sex and eGFR, underwent a water deprivation test to determine Umax. Urine and plasma osmolality (Uosm and Posm), albuminuria (ACR) and plasma copeptin (surrogate marker for AVP in pmol/L), were measured at baseline and after water deprivation (average 17 hours). Height adjusted total kidney volume (htTKV) was measured by MRI.

Results: Umax was lower in ADPKD compared with IgAN patients. Upon water deprivation Posm increased in ADPKD (p=0.003), but not in IgAN (p=0.1), whereas copeptin increased in both groups similarly (ADPKD: p=0.001; IgAN: p=0.02). Copeptin after water deprivation was negatively associated with Umax in both groups (ADPKD: R=-0.72, p=0.002; IgAN: R=-0.70, p=0.004). In ADPKD, copeptin and albuminuria were correlated after water deprivation (R=0.71, p=0.003), independently of eGFR or htTKV. Furthermore, htTKV in ADPKD was associated after water deprivation with Posm (R=0.52, p=0.048), copeptin (R=0.58, p=0.03) and Umax (R=-0.54, p=0.04).

	ADPKD	IgAN	p-value
Baseline			
eGFR	43±9	44±14	0.74
Posm	289±5	294±10	0.14
Uosm	378±157	498±144	0.04
Copeptin	14.0 (6.6-29.1)	11.9 (7.3-26.1)	0.98
Umax			
Posm	293±6	295±10	0.51
Uosm	533±138	642±148	0.046
Copeptin	26.6 (12.8-43.0)	20.7 (10.3-43.0)	0.84

Conclusions: ADPKD patients have a lower Umax compared with IgAN patients with similar renal function. Remarkably, this is not accompanied with an exaggerated increase in AVP. Notwithstanding, ADPKD severity was associated with stronger increases in Posm, copeptin and albuminuria during water deprivation. This suggests that in ADPKD water deprivation may be deleterious and should be avoided.

Funding: Government Support - Non-U.S.

SA-PO864

Total Abdominal Organ Volume Is a Major Risk Factor for Malnutrition in Ambulatory Patients with Autosomal Dominant Polycystic Kidney Disease
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Background: In Autosomal dominant polycystic kidney disease (ADPKD), malnutrition may develop as renal function decreases and abdominal organ volume enlarged. In this study, we evaluated the nutritional status of outpatient ADPKD patients by using subjective global assessment (SGA) and investigated the risk factors for malnutrition.

Methods: In this single center, cross sectional study, anthropometric and laboratory data including serum creatinine (sCr), albumin, and cholesterol were collected, and total kidney and liver volume were measured. Total abdominal organ volume was defined as the sum of total kidney and liver volume and adjusted by height (htTAV).

Results: A total of 288 patients (47.9%) were included and mean age was 48.3±12.2 years. Mean estimated glomerular filtration rate (eGFR) was 65.3 ± 25.3 mL/min/1.73m². Mean SGA score was 6.6±0.6. 168 patients (58.3%) were in chronic kidney disease stage 1 or 2, 99 (34.4%) stage 3 and 21(7.3%) stage 4. Total 21 patients (7.3%) were mild to moderately malnourished (SGA 4-5) and 63 patients(21.7%) were at risk of malnutrition (SGA 6). There was no difference in SGA score distribution with sex. Physical scores related to nutritional status in total and male were age, height, weight and body mass index. However none of these parameters were related in female. Lower hemoglobin level and poor renal function were related with low SGA score in total and male but only decreased renal function was related in female. In contrast, higher htTAV was consistently correlated with lower SGA score, even in subjects with eGFR ≥ 45 mL/min/1.73m². Subjects with htTAV ≥2,340 ml/m showed 8.7-fold higher risk of having malnutrition, after adjusting for sex, age, hemoglobin, albumin and sCr.

Conclusions: Nutritional risk was detected in 30% of ambulatory patients with ADPKD and relatively preserved renal function. Intraabdominal organ growth in ADPKD may affect the nutritional status independently from the renal deterioration.

SA-PO865

Tyrosine Kinase Inhibitor Tesevatinib for Patients with Autosomal Dominant Polycystic Kidney Disease
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Background: Tesevatinib (formerly KD019) inhibits both epidermal growth factor receptor (EGFR) and SRC. It decreases cyst growth and slows the decline in renal function in BPK mouse & PCK rat PKD models. In oncology trials the most common adverse events (AEs) were EGFR inhibitor AEs of acneiform rash and diarrhea. The 1/2-life of approx. 60 hrs allows for schedules other than daily dosing.

Methods: This study evaluated the safety and tolerability of tesevatinib at several doses and schedules. Eligibility used Ravine criteria for autosomal dominant polycystic kidney disease (ADPKD) in patients (pts) aged 18-55 years with eGFR ≥ 50 mL/min/1.73 m².

Results: 46 ADPKD pts were enrolled into 5 dose/schedule cohorts. At 150 mg/day, 3/5 pts had moderate rash occurring during the first 28 days that was not tolerated and led to study discontinuation for 2. The tolerability of intermittent dosing schedules using 150 mg (Mon, Wed, Fri or Mon, Thu) was improved over 150 mg/day, but 1 case of severe rash occurred. QTc prolongation to ≥485 ms occurred in 2 pts on 100 mg/day, and 1 pt on 150 mg MWF. The most common AEs overall in preliminary safety data were diarrhea (36%), rash (33%), nausea (29%), and asymptomatic CPK increase (24%). Other AEs included asymptomatic mild amylase elevations (21%).

Dose/Schedule	No. Pts	Gender (M)	Median Age (Yrs)	Median TKV (mL)
50 mg/day	9	3	39	1308
100 mg/day	8	5	37	1525
150 mg/day	5	2	41	1094
150 mg MWF	14	4	36	1344
150 mg MT	10	4	37	795
Total	46	18	38 (19-55)	1138 (411-3873)

Conclusions: Tesevatinib 150 mg in various schedules was associated with skin rash that was not well tolerated. A rate of QTc prolongation not acceptable for chronic use was associated with tesevatinib 100 mg/day. Tesevatinib 50 mg/day appears to be a well tolerated dose in patients with ADPKD, although some acneiform rash occurs. In order to confirm the safety profile at 50 mg/day, an additional 20 pts are being enrolled.

Funding: Pharmaceutical Company Support - Kadmon Corporation

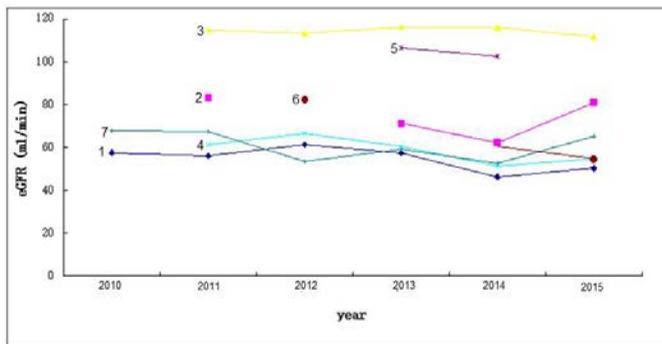
SA-PO866

Retrospective Analysis of Changes in Renal Function in Patients with PKD and Diabetes on Metformin
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Background: Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 600,000 Americans. The cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel participates in secretion of cystic fluid whereas the mammalian target of rapamycin (mTOR) pathway drives proliferation of cyst-lining epithelial cells. CFTR and mTOR are both negatively regulated by AMP activated protein kinase (AMPK). Metformin, a commonly used diabetes medication, activates AMPK. In two mouse ADPKD models, metformin produced a significant decrease in kidney cystic index relative to controls. Therefore, metformin may provide clinical benefit in PKD patients.

Methods: IRB-approved data collection of patients with PKD and diabetes from office visits between 3/1/2010 and 2/28/2015 were analyzed. Estimated GFR (eGFR) was calculated by using CKD-EPI formula. The ACEI/ARB usage was also recorded.

Results: One-hundred forty-nine patients with PKD were identified during a 5-year period. Of these patients, 13 also had a diagnosis of diabetes. Of these 13 patients, 1 patient was lost to follow up. Four patients have had a kidney transplant with the development of diabetes following transplantation. Eight patients had both PKD and diabetes – 7 were on metformin at some time whereas 1 had never. Regarding this group of PKD patients on metformin, we present data on renal function trend measured by eGFR.



eGFR trend in 7 patients with PKD and diabetes who took metformin

Time on metformin:		
1. 2012-2015	4. 2012-2015	7. 2012-2015
2. 2013-2015	5. 2014	
3. 2011-2015	6. 2014-2015	
Time on ACEI/ARB:		
1. 2011-2015	4. 2015	7. 2011-2015
2. 2014	5. 2015	
3. 2011-2015	6. 2014-2015	

Conclusions: Renal function did not change significantly during the period that patients were on metformin. We will continue to observe these patients and accumulate more patients with PKD and diabetes but not on metformin to see if metformin is beneficial in PKD patients.

SA-PO867

11β-Dichloro Inhibits Cyst Progression in an Adult ADPKD Model Sorin V. Fedeles,¹ Bogdan I. Fedeles,³ Yasunobu Ishikawa,¹ Rachel Gallagher,¹ John M. Essigmann,³ Stefan Somlo.^{1,2} ¹Dept of Internal Medicine, Yale School of Medicine, New Haven, CT; ²Dept of Genetics, Yale School of Medicine, New Haven, CT; ³Dept of Chemistry, M.I.T., Cambridge, MA.

Background: ADPKD is the most common monogenic disorder for which no effective therapy exists. We have previously shown that the novel antitumor agent 11β-dichloro specifically induced apoptosis in *Pkd1* null cells (ASN 2013 FR-OR100). Administration of 11β-dichloro resulted in amelioration of cystic disease in the *Pkd1*^{fl/fl}; *Pkhd1*-Cre neonatal ADPKD model. In the current work we explored the pathways involved in the pro-apoptotic effect of 11β-dichloro and investigated whether the beneficial effect seen in the early model is also present in an adult inducible *Pax8*^{Cre}; *TetO-cre*; *Pkd1*^{fl/fl} model which is more akin to the human disease.

Methods: *Pax8*^{Cre}; *TetO-cre*; *Pkd1*^{fl/fl} mice were induced with doxycycline for 2 weeks beginning at P28. 11β-dichloro was administered by IP injection at a dose of 10 mg/kg, 3 times a week for 12 weeks beginning from P42; At the end of treatment the kidneys were harvested for analysis.

Results: 11β-dichloro treated adult mice resulted in a decrease in KW/BW ratio as compared to vehicle injected controls (2.6±0.1 vs. 6.1±0.4); There was no difference in body weight between treated and control. These changes were accompanied by a decrease in the cystic index (29%±1.5 vs. 49%±1.4), BUN (41±2.4 vs. 83±2.7), and creatinine (0.18±0.007 vs. 0.37±0.02). 11β-dichloro specifically increased apoptosis in cyst-lining cells but not in wild-type. UPR and ROS have been implicated as potential drivers of the 11β-dichloro-dependent pro-apoptotic phenotype. We found that upregulation of the UPR marker XBP1s and its transcriptional targets *Bip* and *Erdj4* was specific to the *Pkd1* null cells compared with wild-type, *in vitro* and *in vivo*. Treatment with 11β-dichloro increased mRNA levels of the antioxidant genes catalase and *SOD1* specifically in the *Pkd1* cystic kidneys and not in vehicle-treated kidneys.

Conclusions: 11β-dichloro specifically induces UPR, ROS, and apoptosis in cystic vs. wild-type kidneys. In an adult inducible cystic model, the compound ameliorates polycystic disease progression and improves kidney function.

Funding: Other U.S. Government Support, Private Foundation Support

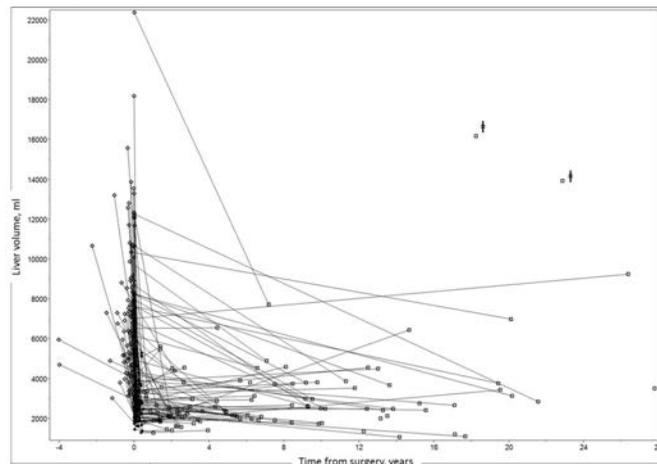
SA-PO868

Outcomes of Combined Partial Hepatectomy and Cyst Fenestration for Massive Polycystic Liver Disease Fouad T. Chebib,¹ Amber Harmon,¹ Maria V. Irazabal,¹ Yeon Soon Jung,¹ Marie C. Hogan,¹ Patrick S. Kamath,¹ Vicente E. Torres,¹ David M. Nagorney.² ¹Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Dept of Surgery, Mayo Clinic.

Background: Partial hepatectomy and cyst fenestration (PHCF) selectively provides clinical benefit in highly symptomatic patients Polycystic Liver Disease (PLD). This study aims to ascertain whether the reduction in liver volume achieved by PHCF is sustained long-term.

Methods: Clinical data was retrieved from the electronic records in all PLD patients who underwent PHCF between 1985 and 2014. Preoperative Liver volumes (LV1), postoperative (LV2) and late follow up (LV3) were measured from MR or CT images.

Results: Among 186 patients who underwent PHCF, 91% were Caucasian women with ADPKD with a mean age of 49 years. Major peri-operative complications (Clavien III/IV) occurred in 24% of the patients. Operative mortality (<90 days) was 2.7% with one death from liver failure. Overall survival was 95%, 90%, 76.5% and 59% at 1, 5, 10 and 15 years respectively. Imaging records for volumetry were unavailable in 37 patients. Of the remaining 149 patients, 30 patients had imaging for one LV, 65 for two LV and 54 for all three LV. Median LV was 6812 ml preoperatively and 2502 ml after PHCF leading to a median postoperative liver volume reduction of 61%.



Two patients without available LV1 and LV2 images had marked recurrent hepatomegaly 23 and 26 years after PHCF

At follow-up (mean 7.8 years), median LV was 2500 ml. Interestingly, 29 out of 61 patients with available LV2 and LV3 showed further regression in LV upon follow up (median -14.8%); while the rest showed mild growth of 9.5%. Overall volumetric comparison of preoperative to follow-up liver imaging showed sustained liver volume reduction (median 60%).

Conclusions: Sustained long-term reductions in LV after PHCF can be achieved in selected patients with severe, highly symptomatic PLD. In our experience, liver-related death and subsequent liver transplantation are infrequent after PHCF.

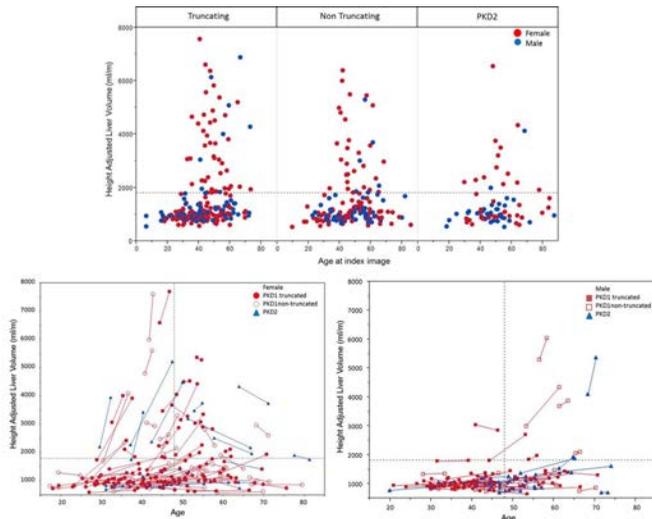
SA-PO869

Effect of Genotype on the Severity and Volume Progression of Polycystic Liver Disease (PLD) in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Fouad T. Chebib,¹ Yeon Soon Jung,² Christina M. Heyer,¹ Maria V. Irazabal,¹ Marie C. Hogan,¹ Peter C. Harris,¹ Vicente E. Torres,¹ Ziad El-Zoghby.¹ ¹Div of Nephrology, Mayo Clinic, Rochester, MN; ²Kosin U.

Background: PLD is the most common extrarenal manifestation in pts with ADPKD. Here we analyzed the influence of genotype and gender on the severity of PLD.

Methods: Clinical data was retrieved from electronic records in a large cohort of pts who were mutation screened, determined to be PKD1 or PKD2 and had available CT or MR liver imaging during 2000-2014 at the Mayo Clinic (n=445). Liver volumes (LV) were measured by stereology on axial images and adjusted to height (HtLV).

Results: Among the 445 pts, 220 (49.5%) had truncating *PKD1*, 153 (34.4%) nontruncating *PKD1* and 72 (16.1%) *PKD2* mutations. Compared to nontruncating *PKD1* and *PKD2*, pts with truncating *PKD1* were younger at time of first imaging (43.6 vs 47.6 and 50.4; p<.001), had lower median survival time to ESRD (62.4 vs 66.9 and 81.4; p<.001, Log-Rank), and larger kidney volumes (785 vs 614 and 548 ml/m; p<.001). LV in pts with *PKD1* truncating, *PKD1* nontruncating and *PKD2* were not different (HtLV 1039, 1076 and 1058 ml/m, respectively; p=.53). Female pts had larger HtLV compared to males (1104 vs 1019 ml/m; p<.001). Annualized median liver growth rates were 1.65, 1.74 and 1.2% for truncating *PKD1*, nontruncating *PKD1* and *PKD2*, respectively (p=.75). Females younger than 48 had higher annualized median growth rates compared to those older than 48 (2.65 vs 0.09%; p<.001). When adjusting for age, gender and baseline LV, growth rate remained unaffected by the ADPKD genotype.



Conclusions: In contrast to the renal phenotype, ADPKD gene type or *PKD1* mutation type were not significantly associated with the severity or growth rate of PLD in ADPKD pts. This finding, along with the demonstrated gender influence, indicate that modifiers beyond the disease gene significantly influence this phenotype.

SA-PO870

Eligibility for Renal Transcatheter Arterial Embolization in Patients with Autosomal Dominant Polycystic Kidney Disease Tatsuya Suwabe, Yoshifumi Ubara, Junichi Hoshino, Rikako Hiramatsu, Kenmei Takaichi. *Dept of Nephrology, Toranomon Hospital, Tokyo, Japan.*

Background: In patients with ADPKD, massive renal enlargement is a serious problem. Renal transcatheter arterial embolization (TAE) is effective for reducing renal volume, but there is large variation of its effectiveness and the reasons remain unclear. We investigated factors influencing the renal volume reduction rate (RVRR) for one year after TAE.

Methods: All patients with ADPKD who received renal TAE at Toranomon Hospital from 2006 to 2013 were enrolled. We calculated RVRR by the calculation formula (1 - renal volume at each time after TAE / renal volume before TAE)*100, and analyzed factors affecting RVRR. We also compared sequential change of large cysts (>5cm), by classified them into four groups as cysts with wall thickening (>4mm), cysts with acute hemorrhage, normal cysts, and the others.

Results: 449 patients (228 men, 221 women, mean age; 57.0 ± 9.1 years) were enrolled. The RVRR at 1 year after TAE ranged from 3.9 to 84.8%, and the least squares mean RVRR calculated using mixed model was 45.73% (95% confidence interval [95% CI]; 44.36 to 47.10%). Multivariate analysis using mixed model revealed that large cysts with wall thickening (regression coefficient: -5.830, 95% CI: -9.140 to -2.520, p=0.0006), age/(5years) (-0.847, -1.073 to -0.621, p<0.0001), dialysis duration/(12months) (-0.115, -0.193 to -0.037, p=0.0039), systolic blood pressure/(10mmHg) (0.283, 0.065 to 0.501, p=0.0109), and number of microcoils used for renal TAE (1.333, 0.784 to 1.882, p<0.0001) had a significant influence on the RVRR. Among large cysts, only cysts with wall thickening did not decrease in volume. Significantly more microcoils were needed to achieve complete renal artery occlusion in patients with younger age and less dialysis duration.

Conclusions: Cyst wall thickening had an important influence on cyst volume reduction. Renal TAE was more effective in patients who were younger, had shorter dialysis duration, or had hypertension, parameters that might be associated with cyst wall stiffness. Renal artery narrowing may occur in older patients or those on longer dialysis, which might contribute to renal TAE being less effective in these patients.

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SA-PO871

Patient Reported Health Related Quality of Life in ADPKD: Analysis from OVERTURE Dorothee Oberdhan,¹ Arlene B. Chapman,² Ronald D. Perrone,³ Andreas L. Serra,⁴ Jason C. Cole,⁵ Wen Zhou,¹ Holly Krasa,¹ Jaime Blais,¹ Frank S. Czerwiec.¹ ¹Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD; ²Univ of Chicago, Chicago, IL; ³Tufts, Boston, MA; ⁴Univ of Zürich, Zürich, Switzerland; ⁵PPD, San Diego, CA.

Background: ADPKD imposes a burden on health-related quality of life (HRQoL). Few studies have systematically examined the impact of renal and extra-renal symptomatology on patient's HRQoL. The purpose of this analysis was to capture disease specific burden across all disease stages while determining specificity and sensitivity of existing and new HRQoL instruments.

Methods: The impact of disease progression on HRQoL in 3,409 ADPKD subjects involved in the OVERTURE observational study were evaluated by patient report outcomes (PRO) questionnaires, including the ADPKD-IS, ADPKD-UIS, BPI, EQ-5D, and SF-12v2. HRQoL was assessed by comparing subjects in CKD2-5 to subjects in CKD1 at baseline.

Magnitude of change of 0.2, 0.5 and 0.8 standard deviations (SD) represent small, moderate and large effects on HRQoL. Other measures of disease severity, including TKV, were assessed independently.

Results: HRQoL in ADPKD was impacted at different disease stages depending on the sensitivity and specificity of the PRO used. The disease-specific ADPKD-IS scale distinguished physical, emotional and fatigue related burden as early as CKD3. Similarly, the SF-12 PCS scale was able to distinguish burden by CKD3. The SF-12 MCS and EQ5D were not sensitive to disease progression until CKD5. The impact of disease burden prior to ESRD was driven by specific questions focused on physical activity, anxiety, and exhaustion. Subjects reported being bothered by the shape of their abdomen in an independent question as early as CKD3 which associated with larger kidney volumes (htTKV > 635ml/m).

Conclusions: Studies to date have had limited success in their attempt to characterize HRQoL in ADPKD patients by using general health surveys. Disease specific instruments better capture the burden experienced by patients in earlier stages of ADPKD prior to gross kidney enlargement and effects associated with ESRD and dialysis.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

SA-PO872

Fibroblast Growth Factor 23, Renal Progression and Death in Patients with Autosomal Dominant Polycystic Kidney Disease Michel Chonchol, Berenice Y. Gitomer, Xuan Cai, Tamara Isakova, Isidro B. Salusky, Renata C. Pereira, Myles S. Wolf. *Div of Renal Diseases and Hypertension, Univ of Colorado Denver.*

Background: No prospective studies examined fibroblast growth factor 23 (FGF23) and clinical outcomes among individuals with autosomal dominant polycystic kidney disease (ADPKD). We tested the hypotheses that higher serum FGF23 is a risk factor for kidney disease progression and mortality in adults with ADPKD.

Methods: We measured intact FGF23 levels (Kainos) in stored baseline serum samples in 1,002 patients who participated in the HALT-PKD randomized controlled trial of two different blood pressure control strategies. We used Cox proportional-hazards models to examine the associations between continuous levels and quartiles of iFGF23 and the primary composite endpoint of time to a 50% reduction in estimated glomerular filtration rate (eGFR) from baseline, end stage renal disease (ESRD) or death.

Results: At baseline, participants had a mean age of 42 ± 10 years, mean eGFR of 71.4 ± 26.4 mL/min/1.73m², mean serum phosphate of 3.4 ± 0.5 mg/dL, and median (IQR) iFGF23 of 52.6 (38.6 – 73.7) pg/mL. During a median follow-up of 5.6 years, 226 patients (22.6%) reached the composite endpoint. After adjusting for demographic factors, traditional cardiovascular risk factors, baseline eGFR, and randomized treatment group in Cox proportional hazards models, ascending quartiles of FGF23 were associated with a stepwise increased risk for the composite endpoint (HR 1.0 [reference], 1.54 [95% CI, 0.69 - 3.47], 2.92 [CI, 1.38 - 6.19], and 3.41 [CI, 1.61 - 7.22]). Similar results were obtained when FGF23 was examined on a continuous scale (HR 1.94 [95% CI, 1.39 - 2.69] per 1 SD lnFGF23 increase).

Conclusions: Higher serum FGF23 is an independent predictor of kidney disease progression and death in adults with ADPKD. Further studies are required to determine the mechanisms underlying these relationships and to test whether interventions that reduce FGF23 levels might be renoprotective.

Funding: NIDDK Support

SA-PO873

Natural History of Polycystic Liver Disease in the HALT ADPKD Cohort Marie C. Hogan,¹ Kaleab Z. Abebe,² Susan Spillane,² Frederic F. Rahbari-Oskoui,³ Godela M. Brosnahan,⁴ Charity G. Moore,² Vicente E. Torres.¹ ¹Mayo C for the HALT PKD Study Group; ²UPitt; ³Emory; ⁴U Col.

Background: Although hepatomegaly in polycystic liver disease (PLD) is common, few studies have evaluated natural history & factors associated with progression. **Goal:** Examine change in height adjusted liver volume (htLV) & factors influencing progression in participants in HALT-PKD-A randomized clinical trial.

Methods: Baseline PLD group (mild (htLV<1000ml;n=240) moderate (1000-1800ml; n=271) & severe (>1800ml; n=28; 81% female)) & follow up htLVs, quality of life (QOL:SF36), influence of telmisartan (T) vs placebo (P) on progression were assessed (n=558, age 15-49y, eGFR > 60 ml/min). We assessed factors influencing htLVs such as treatment group, age, gender, genotype (in separate models) & factors influencing progression over time were examined using linear mixed models.

Results: Annual htLV growth rates were 0.76, 0.91, & 1.08% (P=NS) in the mild, moderate, & severe groups, respectively (figure 1). Neither baseline age or genotype associated with annual htLV increase. There were strong negative relationships of eGFR (p=.02) & serum albumin (p=.0003) with htLV. Prior pregnancy & higher parity (both age adjusted) associated with htLV but not with progression over time. Increases in htLV were associated with increased rates of fatigue/weakness (p=0.003) and declines in SF-36 physical functioning over time (p=0.02). Progression was independent of drug assignment (T 0.89% vs P 1.07% p.a.;p=NS) & BP target (low 0.81 vs std. 1.15% p.a. p=NS).

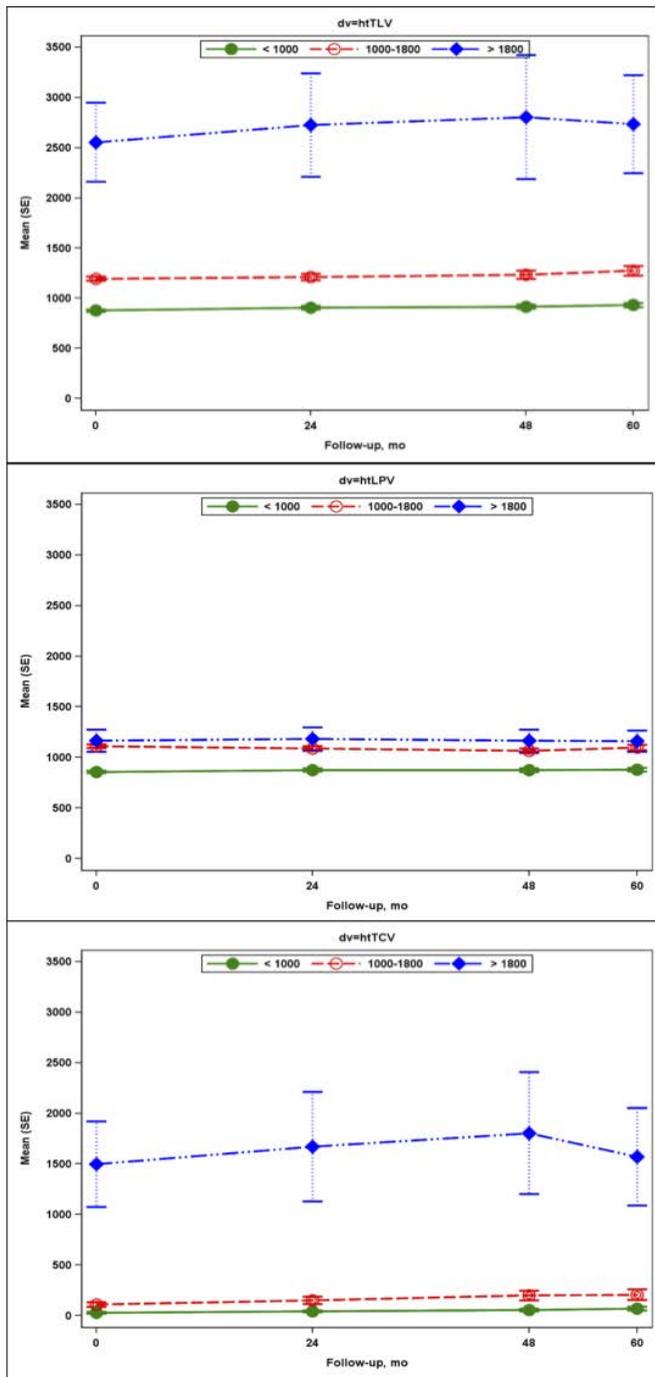


Figure 1: Mean (±SE) htTLV, parenchymal volume (htLPV) & total liver cyst volume (htTCV) at month in study by baseline htTLV group (<1000, 1000-1800, >1800ml).

Conclusions: HTLVs increased in HALT-A participants over time, correlated with fatigue/ weakness and were associated with measurable continued declines in SF36 QOL subdomains.

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SA-PO874

Towards Personalised Medicine – Treating a Renal Ciliopathy Shalabh Srivastava,¹ Simon Ramsbottom,¹ Sophie Saunier,² Colin Miles,¹ John Andrew Sayer.¹ ¹Nephrology, Inst of Genetic Medicine, Newcastle Univ, Newcastle upon Tyne, United Kingdom; ²Laboratory of Inherited Kidney Diseases, Imagine Inst, Paris, France.

Background: Renal ciliopathies are genetic disorders presenting with nephronophthisis, cystic kidneys or cystic dysplasia. Pathogenesis of ciliopathies may include altered signalling or defective DNA damage response. Due to the huge genetic/phenotypic variability in ciliopathies it is pertinent to explore the most important contributor to individual phenotypes. We investigated disease mechanisms of a patient with Joubert Syndrome aiming to provide a personalised medicine approach to treatment.

Methods: We identified a family with 2 affected siblings with a ciliopathy phenotype. Ciliopathy gene panel sequencing followed by Sanger sequencing and segregation analysis was undertaken to provide a molecular genetic diagnosis. We established Human Urine derived Renal Epithelial Cell (HUREC) cultures from one sibling and a control. Cultured cells where characterised and their response to therapeutic agents quantified.

Results: The siblings exhibited a cerebro-retinal-renal phenotype with renal corticomedullary cyst formation and progressive renal failure. Panel sequencing followed by Sanger sequencing confirmed biallelic mutations in *CEP290* (c.2817G>T, p.Q939N; c.2848insC, p.Q950Pfs*6) in both affected patients. The c.2817G>T is located in the last base of exon 25 and is predicted to lead to a splicing defect. There was no difference in mitosis or centriole numbers in control and proband's cells. Control cells formed spheroids in 3D culture (100%) whilst the proband's cells showed a defect in spheroid forming index (17%) and absent primary cilia. In the proband cells there was a rescue of spheroid forming index in response to treatment with hedgehog agonists SAG(smoothened agonist) (67%) and purmorphamine (75%) and a rescue of primary cilia.

Conclusions: In a family with a ciliopathy we have confirmed a molecular genetic defect in *CEP290*. Using HURECS we have characterised, at a personalised medicine scale, the cellular defect. This data suggests that renal ciliopathies may have potential therapeutic targets and investigation through individual HUREC based model is an exciting new development.

SA-PO875

Effect of Metformin on the Progression of Autosomal Dominant Polycystic Kidney Disease Godela M. Brosnahan,¹ Michel Chonchol,¹ John R. Holmen,² Eugene J. Nuccio,¹ Berenice Y. Gitomer.¹ ¹Univ of Colorado; ²Intermountain Healthcare, Salt Lake City, UT.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder resulting in end-stage renal disease (ESRD), without an approved treatment. In an animal model of ADPKD metformin therapy resulted in amelioration of cystic renal growth. We sought to determine whether patients with ADPKD and type 2 diabetes treated with metformin had slower progression to ESRD than similar patients treated with other antidiabetic drugs.

Methods: We conducted a population-based cohort study of adult patients with ADPKD and type 2 diabetes between January 1/2000 and December 31/2014. We identified 322 adults with ADPKD and type 2 diabetes, of whom 119 were treated with metformin only and 203 with other antidiabetic agents. Among these we identified 31 subjects treated with metformin only who could be matched for age, sex, race, history of hypertension and coronary artery disease, and baseline renal function to 31 subjects not treated with metformin. The primary outcomes were incident ESRD and all-cause mortality.

Results: The median age of the enrolled participants was 61 years, 45% were women. Approximately 74% and 26% had a history of hypertension and myocardial infarction, respectively. The baseline MDRD-eGFR in participants receiving and not receiving metformin was 49±12 and 47±14 mL/min/1.73m² (p=0.70). After a median follow-up of 4.5 years, incident ESRD occurred in 29% and 16% of those not exposed and exposed to metformin, respectively, with a OR of 2.13 (95% CI 1.10-3.46; p=0.02). Deaths occurred in 32% and 26% of those not exposed and exposed to metformin, with a OR of 1.37 (95% CI 0.5-2.47; p=0.60).

Conclusions: Metformin therapy may slow progression to ESRD in ADPKD adults with type 2 diabetes compared to other antidiabetic drugs. Because metformin has an excellent safety record, a trial to slow the progression of ADPKD in the absence of diabetes is warranted.

Funding: NIDDK Support

SA-PO876

Frequency and Reasons for Hospitalization Among ADPKD Patients with GFR >25 mls/min Dana Miskulin,¹ Kaleab Z. Abebe,⁵ Ronald D. Perrone,¹ Marie C. Hogan,² Frederic F. Rahbari-Oskoui,³ Peter G. Czarnecki,⁴ Susan Spillane,⁵ Arlene B. Chapman,⁶ Robert W. Schrier,⁷ Vicente E. Torres,² Charity G. Moore.⁵ ¹Tufts Medical Center, Boston; ²Mayo Clinic, Rochester; ³Emory Univ, Atlanta; ⁴Brigham and Women's Hospital, Boston; ⁵Univ of Pittsburgh; ⁶Univ of Chicago; ⁷Univ of Colorado.

Background: There is a paucity of data about the frequency and causes of hospitalization in Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Methods: Information about hospitalizations was prospectively collected in the HALT-PKD Studies, 2 multi-center trials involving people with ADPKD and GFR>60 ml/min (Study A) and GFR 25-60 ml/min (Study B). The primary diagnosis was designated after review of discharge summaries and independently adjudicated by a committee.

Results: Total patient years (ptyrs) of follow-up in the 558 Study A patients and 486 Study B patients were 3147 and 2506. The incidence rate (IR) of all-cause hospitalization in Study A and B, respectively, was 67.7 and 123.3 per 1000 ptyrs, which compares to 80.3 and 118.0, in respective age-matched general populations (CDC/NHDS National Hospital Discharge Survey, 2010). The IRs in Study A and B, respectively, for cardiovascular-related hospitalization were 7.0 and 18.1 per 1000 ptyrs, and for ADPKD-related hospitalization (primary diagnosis kidney or liver cyst pain, infection or hemorrhage, pyelonephritis, kidney stones or cerebral aneurysm) were 12.7 and 26.7 per 1000 ptyrs. The most common primary diagnoses are listed in the table.

Table 1: Most Common Reasons for Hospital Admission*

Study A (eGFR >60 ml/min)		Study B (eGFR 25-60 ml/min)	
Primary Diagnosis	IR/1000ptyrs	Primary Diagnosis	IR/1000ptyrs
Acute pyelonephritis/Cyst infection	3.18	Abdominal Pain	9.58
Abdominal Pain (undisclosed/unspecified)	2.86	Kidney Cyst Hemorrhage	5.99
Chest Pain	2.54	Chest Pain	5.59
Kidney Cyst Pain (w/o hemorrhage, infar)	2.54	Kidney Cyst Pain (w/o hemorrhage)	5.19
Kidney Cyst Hemorrhage	2.22	Acute Pyelonephritis/Cyst	4.79
Nephrolithiasis	2.22	AKI All Causes	4.79
Suicide Ideation/Attempt	2.22	Liver Cyst Pain	3.99
Atrial Fibrillation	1.91	Nephrolithiasis	3.99
Liver Cyst Pain	1.91	Osteoarthritis Lower Leg	3.19
Acute Appendicitis	1.59	Fever Undetermined Origin	3.19

*Excluding Pregnancy. Abbreviations: IR, Incidence Rate; AKI, Acute Kidney Injury; w/o, without; infar, infarction; ptys, patient-years.

Conclusions: As compared with the respective age-matched general US populations, hospitalization rates were lower in ADPKD patients with GFR>60mls/min and higher in patients with GFR 25-60 mls/min. PKD-related complications were more common than cardiovascular related diagnoses as the primary reason for hospitalization in both Study A and B.

Funding: NIDDK Support, Private Foundation Support

SA-PO877

Effect of Statins on the Progression of Autosomal Dominant Polycystic Kidney Disease (the HALT PKD Investigators) Godela M. Brosnahan,¹ Kaleab Z. Abebe,² Frederic F. Rahbari-Oskoui,³ Charity G. Moore,² Kyongtae Ty Bae,² Robert W. Schrier,¹ Jared J. Grantham.⁴ ¹Univ of Colorado; ²Univ of Pittsburgh; ³Emory Univ; ⁴Univ of Kansas.

Background: ADPKD is the most common hereditary disease resulting in end-stage renal failure (ESRD), without an approved treatment. In a small randomized trial comparing pravastatin for 3 years (y) with placebo in 110 patients age 8-22 y, the statin group experienced a slower rate of renal enlargement. No large trial has tested the effect of statins in ADPKD adults.

Methods: We performed a secondary analysis of the HALT PKD trials, categorizing participants into 3 groups based on statin use: 1) never users, 2) less than 3 y, and 3) at least 3 y of use. For subjects in Study A (n=558, age 15-49 y, eGFR > 60 ml/min/1.73m²) we compared the percent change in height-adjusted total kidney volume (htTKV), in height-adjusted total liver volume (htTLV) and the rate of decline in eGFR between the 3 statin use groups. For participants in Study B (n=486, age 18-64 y, eGFR 25-60 ml/min/1.73m²) we compared time to composite endpoint of death, ESRD or 50% decline in eGFR. Follow-up was 5-8 y.

Results: In HALT Study A only 59 subjects used statins for > 3y and 37 for < 3y. There was no difference in the rate of annual htTKV increase (6.41%, 7.11%, 5.97%; p=NS) or htTLV growth (1.02%, 1.15%, 0.65%; p=NS) between the 3 groups, after controlling for sex, age, and treatment arms. The rate of eGFR decline was faster in group 2 (4.07 ml/min/y) than in groups 1 and 3 (2.93 and 2.82 ml/min/y; p=0.015), after adjusting for the more favorable baseline characteristics of group 1 (more females, younger age, higher baseline eGFR). In Study B 118 subjects used statins for > 3y and 76 for < 3y. There was no difference in time to endpoint between the 3 groups.

Conclusions: In this secondary analysis of the HALT PKD trials, statin therapy for 3 years did not slow the rate of renal or liver enlargement or of eGFR decline in ADPKD adults, but these results are limited by the small numbers of statin users in Study A, different statin drugs and doses, and non-randomized allocation to groups.

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SA-PO878

Assessment of a Dosage-Sensitive Mutational Network for PKD in a Large Cohort of Patients with Early and Severe Forms of Polycystic Kidney Disease Carsten Bergmann,^{1,2} John Devane,² Steffen Neuber,¹ Eva Decker,¹ Uyen Tran,³ Oliver Wessely,³ Elisabeth B. Ott.² ¹Center for Human Genetics, Bioscientia, Ingelheim, Germany; ²Renal Div, Univ Hospital, Freiburg, Germany; ³Cellular & Molecular Medicine, Cleveland Clinic.

Background: ADPKD patients with early and severe disease manifestations only make up a minor proportion, but are crucial for a better understanding of PKD. Affected families have a high recurrence risk for babies with a severe clinical course often resulting in perinatal death. Especially in prenatal cases the diagnostic distinction between different forms of PKD and other ciliopathies can be difficult and illustrates the need for more comprehensive genetic testing.

Methods: An accurate genetic diagnosis is crucial for genetic counselling, prenatal diagnostics and the clinical management of patients. To this end, we established a sequence capture based NGS approach targeting 95 genes for cystic and polycystic kidney disease. This includes *PKD1*, which - due to the presence of pseudogenes - is difficult to test. As an additional advantage over conventional Sanger sequencing we were able to detect copy number variations. The biological significance of some of the detected alleles were subsequently tested by *in vitro* and *in vivo* studies using a range of animal models including zebrafish, *Xenopus* and mice.

Results: We analysed a cohort of 309 patients exhibiting early and severe PKD. In a considerable percentage of patients we did not detect just one single mutated gene/allele, but additional mutations *in trans*. Notably, this proportion increased, the more severely the patients were affected. The affected genes were not limited only *PKD1*, *PKD2* or *PKHD1*. In particular, a subgroup of patients with non-syndromic disease harboured mutations in genes typically related to ciliopathies such as nephrophthisis, Joubert, Meckel, and Bardet-Biedl syndrome. Finally, we used zebrafish, *Xenopus* and mice to validate some of our findings in terms of a functionally proven dosage-sensitive network.

Conclusions: This study is the most comprehensive analysis performed so far and points towards a general and underestimated concept for the modification of disease gene expression.

SA-PO879

Determinants of Progression in Early Autosomal Dominant Polycystic Kidney Disease - Is It Blood Pressure or Renin-Angiotensin-System Blockade? The HALT PKD Trial Godela M. Brosnahan,¹ Kaleab Z. Abebe,² Charity G. Moore,² Theodore I. Steinman,³ Frederic F. Rahbari-Oskoui,⁴ Susan Spillane,² Kyongtae Ty Bae,² Robert W. Schrier.¹ ¹Univ of Colorado; ²Univ of Pittsburgh; ³Beth Israel Deaconess; ⁴Emory Univ.

Background: The HALT PKD Study A (558 subjects age 15-49 years, eGFR > 60 ml/min/1.73m²) showed that intensive control of systolic blood pressure (SBP) to 95-110 mmHg was associated with a slower rate of kidney volume growth compared to standard control (SBP 120-130 mmHg). It is unclear whether this result was due to lower BP per se or to greater blockade of the renin-angiotensin-aldosterone system (RAAS) by allowing higher drug doses in the low BP group.

Methods: We performed a secondary analysis of HALT PKD Study A categorizing participants into 3 groups based on lisinopril (L) and telmisartan (T) dosage at 4 months, after initial dose titration: 1) high, defined as L 40 mg + T 80 mg daily, 2) middle (everyone not high or low) and 3) low, defined as L < 20 mg + T < 40 mg daily. We compared the percent change in height-adjusted total kidney volume (htTKV) and the rate of eGFR decline between the 3 groups during follow-up for 5-8 years.

Results: Participants in the high dose group (n=51) were more likely male and assigned to the low BP arm; they had higher baseline BP and lower eGFR at 4 months than subjects in the mid- (n=272) and low-dose (n=165) groups. After adjustment for age, sex, genotype, target BP (low or standard), and eGFR at 4 months, there was no significant difference in the rate of kidney growth (5.63, 6.40 and 5.83%/yr) or eGFR decline (3.00, 2.94 and 3.29 ml/min/yr) between the low, middle and high dosage groups.

Conclusions: In this secondary analysis of HALT Study A in young ADPKD adults, a higher dosage of RAAS blocking drugs was not associated with a slower rate of htTKV growth or of eGFR decline, after adjustment for allocation to intensive BP control. Low BP appears to be the main determinant for reducing kidney volume growth.

Funding: NIDDK Support, Other NIH Support - cooperative agreements (grants DK62408, DK62401, DK62410, DK62402, and DK62411, DK082230) with the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, the National Center for Research Resources General Clinical Research Centers (RR000039 Emory University, RR00585 Mayo Clinic, RR000054 Tufts University, RR000051 University of Colorado, RR23940 Kansas University, and RR024296 Beth Israel Deaconess Medical Center), and the Centers for Translational Science Activities at the participating institutions (RR025008 Emory University, RR024150 Mayo Clinic, RR025752 Tufts University, RR025780 University of Colorado, and RR024989 Cleveland Clinic), Pharmaceutical Company Support - Boehringer Ingelheim Inc donated telmisartan and matched placebo. Merck & Co Inc donated lisinopril., Private Foundation Support

SA-PO880

The Short Term Effect of Tolvaptan for CKD Stage4 Autosomal Dominant Polycystic Kidney Disease Haruna Kawano,^{1,2} Satoru Muto,^{2,3} Shigeo Horie.^{1,2}
¹Urology, Juntendo Univ Graduate School of Medicine, Tokyo, Japan; ²Urology, Teikyo Univ, Tokyo, Japan; ³Endowed Course for the Study of Polycystic Kidney Disease, Juntendo Univ Graduate School of Medicine, Tokyo, Japan.

Background: In Japan, the treatment of tolvaptan, a V2 receptor antagonist, started from March 2014. Indication criteria of tolvaptan for ADPKD treatment in Japan is adult patient with more than 750ml total kidney volume (TKV) and more than about 5%/year increasing rate of TKV. It is contraindication to use tolvaptan for patients with eGFR<15ml/min/1.73m². It is recommended to reduce dose of tolvaptan for patients with CCR<30ml/min. However, the treatment effect for patients with CKD stage 4 is still unknown. So, we evaluated the short time efficacy of tolvaptan treatment for patients with CKD stage 4.

Methods: Thirteen patients (5 females and 8 males, mean age; 52.5 years) with ADPKD who started tolvaptan at our hospitals from April 2014 to April 2015 were analyzed in this study. Although our standard starting dose of tolvaptan for patients with good renal function is 60mg/day, we administered 15mg/day for patients with eGFR<25ml/min/1.73m² patients. Patients were measured eGFR and TKV at the commencement of treatment and at 1.5 and 6 months later.

Results: The baseline median eGFR and TKV were 21.8 ml/min/1.73m² (range; 17.1-28.9) and 2,810ml (range; 1,031-5,847), respectively. The change of median eGFR from baseline at 1.5 months and at 6 months were -0.36 ml/min/1.73m² (p=0.39) and -1.80 ml/min/1.73m² (p=0.04), respectively. The change of median TKV from baseline at 1.5 months and at 6 months were -132ml (p=0.39) and +12ml (p=0.93), respectively. One female patient and one male patient temporarily stopped their treatment at 3 months and at 6 months because of their eGFR decreased to lower than 15 ml/min/1.73m². Hepatic toxicity, hypernatremia, and the other severe adverse events were not detected.

Conclusions: No severe adverse events were occurred and 85% of CKD stage4 patients could keep treatment for 6 months without CKD progression. Tolvaptan was safe and tolerable for ADPKD patients with CKD stage 4 in lower dose.

Funding: Pharmaceutical Company Support - Otsuka pharmaceutical Co., Ltd., Government Support - Non-U.S.

SA-PO881

Estimation of Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease Edwin M. Spithoven,¹ Maatje D.A. van Gastel,¹ A. Lianne Messchendorp,¹ Niek F. Casteleijn,¹ Ron T. Gansevoort.¹ ¹Internal Medicine, Nephrology, UMC Groningen; ²On behalf of the DIPAK Consortium, Netherlands.

Background: Measuring total kidney volume (TKV) in autosomal dominant polycystic kidney disease (ADPKD) by magnetic resonance image (MRI) and manual tracing is time consuming. Two alternative MRI methods have recently been proposed to estimate TKV (eTKV_{ELLIPSOID} and eTKV_{PANK}) which require less time.

Methods: ADPKD patients with a wide range of kidney function were included, if they had an approved T2 weighted MRI. A test set of 10 MRIs was used for assessing reproducibility, 220 for cross-sectional analyses and 48 for longitudinal analyses with a follow-up of three years. mTKV was used to assess Irazabal risk categories, reclassification was calculated for eTKV_{ELLIPSOID} and eTKV_{PANK}. Measured TKV (mTKV) was manually traced. eTKV_{ELLIPSOID} was calculated as advised in literature as $\pi/6 * (\text{length}_{\text{coronal}} + \text{length}_{\text{sagittal}})/2 * \text{width} * \text{depth}/1000$ and eTKV_{PANK} as $\text{midslice} * \text{number of slices covering the kidney} * 0.624$ or 0.637 for the left and right kidney, respectively.

Results: In the test set, intra- and inter-coefficients of variation were low; mTKV 1.8% and 2.3%, eTKV_{ELLIPSOID} 3.9% and 6.3%, and eTKV_{PANK} 3.0% and 3.4%. Duration of analyses were respectively 55, 5 and 15 minutes. In cross-sectional analyses baseline kidney volumes (liters) were 1.96 (1.28-2.82) for mTKV, 1.93 (1.25-2.82) for eTKV_{ELLIPSOID} and 1.81 (1.17-2.62) for eTKV_{PANK}, the latter both significantly different from mTKV (p=0.004 and p<0.001 respectively). Bias was low and precision high for repeated mTKV (0.2%±3.2%), eTKV_{ELLIPSOID} (1.4%±9.2%) as well as eTKV_{PANK} (4.6±7.6%). In longitudinal analyses, no significant differences were observed between percentage change in mTKV (16.7±17.1%) compared to change in eTKV_{ELLIPSOID} (19.3±16.1%) and eTKV_{PANK} (17.8±16.1%). Both methods resulted in limited reclassification in Irazabal risk categories; 6.7% for eTKV_{ELLIPSOID} and 9.8% for eTKV_{PANK}.

Conclusions: Both methods to estimate TKV perform relatively well compared to mTKV, and detect similar changes in TKV over time. Since eTKV_{ELLIPSOID} requires less time than eTKV_{PANK}, we suggest this method should be preferred in clinical care.

Funding: Private Foundation Support

SA-PO882

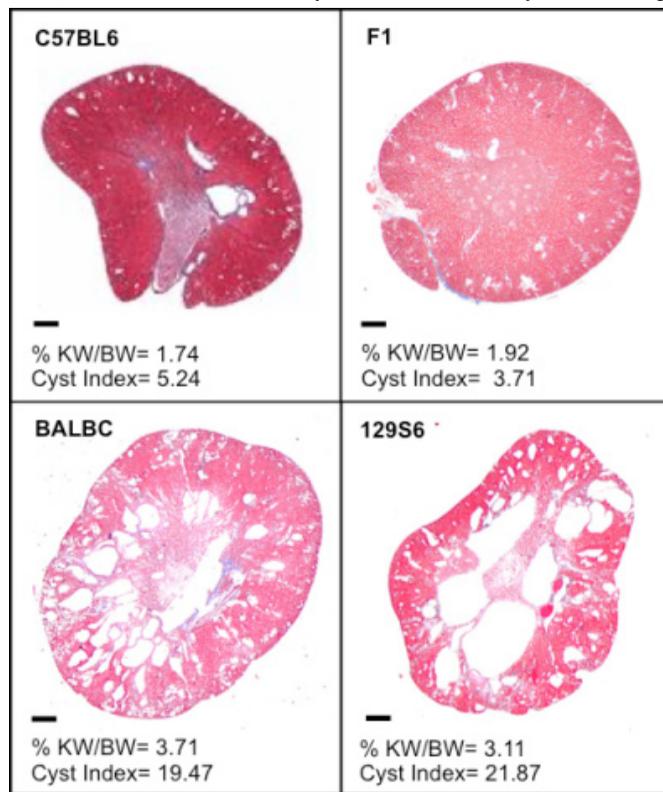
Genetic Background Radically Alters Disease Progression in the Pkd1^{RC/RC} Model Diana L. Escobar, Katharina Hopp, Cynthia J. Sieben, Peter C. Harris. Mayo Clinic, Rochester, MN.

Background: Studies in ADPKD patients and PKD mouse models have shown that genetic background influences the disease phenotype. Here, we evaluated the phenotype of the homozygous Pkd1: p.R3277C (RC) model in three new backgrounds: BalbC, 129S6, and F1 (C57BL6 X BalbC) and compared them to C57BL6.

Methods: To characterize the cystic disease burden, Pkd1^{RC/RC} animals were inbred into three different strains and aged to 3 months (m). At this time point %Kidney Weight/Body W, BUN levels, kidney cyst index were used to compare disease severity.

Results: Already at this early stage of cyst progression (3m) genetic background significantly affects the severity of the disease in the Pkd1^{RC/RC} model with %KW/BW significantly higher in the BalbC (3.31) and 129S6 (3.12) backgrounds compared with F1 (1.92; P<0.0001, <0.001) or C57BL6 (1.74; both P<0.0001). However, BUN levels did not deviate from the physiological norm at this early stage of the disease in any of the backgrounds. In respect to cyst index, 129S6 (21.87%) and BalbC (19.47%) animals had a greater disease burden compared to F1 (3.71%; both P<0.0001) and C57BL6 (5.24%; both P<0.0001) animals. No significant difference was found between 129S6 and BalbC mice (P=0.47). Histological analysis showed a distribution of variously sized cysts in the medulla and cortex in BalbC and large cysts mainly in the medulla in 129S6, which contrasted with small cysts mainly in the cortex in F1 and C57BL6 (figure 1). Immunofluorescence at 3m in all backgrounds showed the majority of cyst had a collecting duct (CD) origin, however some cysts were negative for the nephron markers LTA-AQP1 (PT), AQP2-DBA (CD).

Conclusions: This study highlights the role of genetic background in cystic disease progression in the Pkd1^{RC/RC} model. Due to the more rapid progression and severe cystic burden, the BalbC and 129S6 models may be more suitable for PKD pre-clinical testing.



Funding: NIDDK Support

SA-PO883

Influence of Kidney Volume on Progression to Advanced Stages of Chronic Kidney Disease in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Alan S.L. Yu,¹ Jared J. Grantham,¹ Arlene B. Chapman,³ Kyongtae Ty Bae,² Doug Landsittel,² Chengli Shen,² Vicente E. Torres,⁴ Michal Mrug,⁵ Peter C. Harris,⁴ Frederic F. Rahbari-Oskoui,⁶ Michael F. Flessner,⁷ William M. Bennett.⁸ ¹U Kansas; ²U Pittsburgh; ³U Chicago; ⁴Mayo Clinic; ⁵UAB Birmingham; ⁶Emory U; ⁷NIH; ⁸Legacy Good Samaritan Med Ctr.

Background: The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease III (CRISP III) is the continuation of a longitudinal cohort study of patients with ADPKD designed to identify predictors of CKD progression and kidney failure. Cyst enlargement and hence increase in kidney volume is believed to be on the causative pathway that leads to decline in GFR and kidney failure.

Methods: In 241 patients, height-adjusted total kidney volume (htTKV) was determined by MRI at baseline, and serial GFR determined by corrected iothalamate clearance and serum creatinine estimating equations.

Results: After a mean follow-up of 11.1 years, 59.8%, 32.1% and 21.6% of subjects reached CKD stage 3, 4 and 5. In multivariable logistic regression analysis, baseline htTKV was an independent predictor for the development of CKD stages 3, 4 and 5 by the final visit, after correction for age, sex, race, BMI, and baseline GFR. Similar results were obtained whether CKD stage was determined using iothalamate clearance, MDRD eGFR, or CKD-Epi eGFR. The estimated htTKV at age 18 yr was also predictive of subsequent CKD stage 3.

Endpoint ^a	htTKV at baseline ^b		htTKV at age 18 yr ^b	
	OR (95% CI)	p value	OR (95% CI)	p value
CKD stage 3	1.35 (1.20, 1.53)	< 0.001	1.16 (1.01, 1.32)	0.026
CKD stage 4	1.33 (1.18, 1.51)	< 0.001	1.05 (0.86, 1.27)	0.86
CKD stage 5	1.41 (1.23, 1.63)	< 0.001	1.02 (0.81, 1.27)	0.87

Conclusions: Kidney volume measured by MRI at a single timepoint is a powerful predictor for the development of advanced stages of CKD over the ensuing 11 years. Consistent with prior analyses, greater kidney volume is strongly associated with higher rates of CKD progression, further supporting the notion that cyst enlargement is the primary cause of GFR loss and kidney failure.

Funding: NIDDK Support

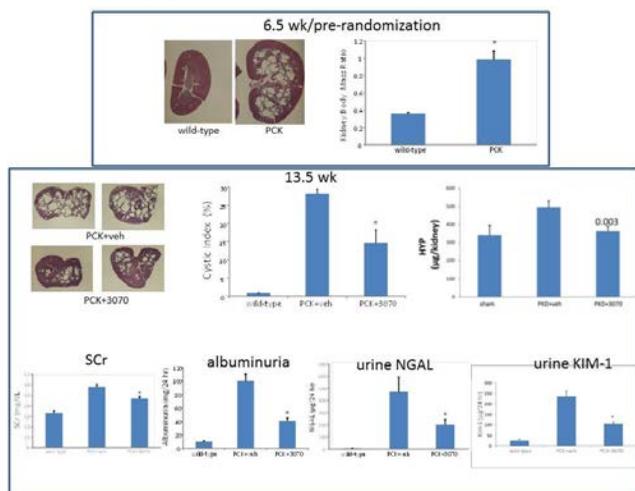
SA-PO884

Therapeutic Effects of the Fibrokinase Inhibitor ANG3070 in Polycystic Kidney Disease Prakash Narayan, Liming Zhang, Bin Duan, Jingsong Li, Ping Zhou, Siobhan McCormack, Latha Paka, Itzhak D. Goldberg. *Angion Biomedica Corp.*

Background: Aberrant receptor tyrosine kinase signaling has been implicated in cyst expansion, renal interstitial fibrosis, increased kidney volume and reduced renal function in polycystic kidney disease (PKD). We investigated the effects of a novel, orally bioavailable, small molecule fibrokinase inhibitor, ANG3070, in experimental PKD.

Methods: Male PCK rats (PCK/CrljCrl-pkhd1pck/Crl) were rats were randomized to vehicle or ANG3070 (25 mg/kg, BID, PO) at 6.5 weeks of age following confirmation of frank disease and sacrificed at 13.5 weeks. Age-matched male Sprague-Dawley rats served as wild-type controls.

Results: ANG3070 has no effect on mean arterial pressure. In PCK rats with diseased kidneys (figure1), randomization to ANG3070 treatment was therapeutic, reducing cystic index, renal interstitial fibrosis (hydroxyproline (HYP), albuminuria and other urine biomarkers of renal injury and serum creatinine (* p<0.05).



Conclusions: With ongoing investigational new drug enabling toxicology studies suggesting a large safety index, these data support the continuing development of ANG3070 for PKD, a disease currently without cure. Supported by PR130909 and AR058041-02.

Funding: Other NIH Support - AR058041-02, Other U.S. Government Support

SA-PO885

Extended Follow-Up of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP III): The Predictive Value of Height Corrected Total Kidney Volume (htTKV) for the Future Development of CKD Stages 3a, 3b, 4 and 5 After Ten Years Follow-Up in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Arlene B. Chapman,¹ Chengli Shen,² Alan S.L. Yu,³ Michal Mrug,⁴ Frederic F. Rahbari-Oskoui,⁵ Vicente E. Torres,⁶ Jared J. Grantham,³ Michael F. Flessner,⁸ Kyongtae Ty Bae,² Doug Landsittel,² Peter C. Harris,⁶ William M. Bennett.⁹ ¹*U of Chicago*; ²*U of Pittsburgh*; ³*U of Kansas*; ⁴*Univ of Alabama Birmingham*; ⁵*Emory Univ*; ⁶*Mayo Clinic*; ⁷*National Insts of Health*; ⁸*Legacy Good Samaritan Hospital*.

Background: CRISP III is a longitudinal observational cohort study of 241 ADPKD individuals now extending beyond 10 years. Measures of cyst burden by magnetic resonance imaging (MR) provide an accurate assessment through measures of htTKV. We have shown previously that baseline htTKV predicts CKD stage 3 after 8 years. We now evaluate whether baseline htTKV can predict CKD Stage 3a,3b, 4 and 5 after 10 years of followup.

Methods: Participants underwent protocol visits including MR imaging, iohalamate clearance and serum creatinine measurements. Baseline htTKV was evaluated in its capacity to predict later CKD stages both individually and in a multivariable model that includes age, race, gender, and baseline iohalamate clearance. Receiver operator characteristic area under the curves (AUROC) were developed for reaching CKD stage 3a, 3b, 4 or 5 after a minimum of 10 years of followup.

Results: At 10 years, 59.8%, 32.1% and 21.6% of patients had reached CKD stage 3, 4 or 5. Baseline htTKV alone predicts CKD stage 3 in 10 years with a ROC of 0.85 and an optimal TKV cut point of 470 ml/m. Multivariable analysis assessing future CKD Stage 3a, 3b, 4 and 5 at 10 years demonstrated a ROC of 0.89, 0.87, 0.90, and 0.89 respectively.

Conclusions: HtTKV is a powerful predictor of the development of all advanced stages of CKD within 10 years with an optimal htTKV of 470 ml/m for CKD Stage 3.

Funding: NIDDK Support

SA-PO886

Alterations in Renal Oxylinp in Models of Polycystic Kidney Disease: Potential for Cyclooxygenase Inhibition for Disease Treatment Harold M. Aukema,^{1,2} Jessay Gopuran Devassy,^{1,2} Md Monirujjaman,^{1,2} Tamio Yamaguchi,^{1,2} Amir Ravandi.³ ¹*Human Nutritional Sciences, Univ of Manitoba, Winnipeg, MB, Canada*; ²*CCARM, St. Boniface Research Hospital Research Centre, Winnipeg, MB, Canada*; ³*Inst for Cardiovascular Sciences, St. Boniface Research Hospital Research Centre, Winnipeg, MB, Canada*.

Background: In both the Han:SPRD-Cy rat and the *pcy* mouse, prostanoids formed via the cyclooxygenase (COX) pathway are elevated, while oxylinps produced via the lipoygenase (LOX) and cytochrome P450 (CYP) pathways are reduced. Importantly, inhibiting the formation of the elevated COX oxylinps with selective (NS-398) or unselective (aspirin) COX inhibitors reduces the progression of disease in the Han:SPRD-Cy rat, suggesting their potential use in the treatment of nephronophthisis. It is not known, however, whether renal oxylinps are altered in orthologous models of human polycystic kidney disease (PKD).

Methods: Renal oxylinps were examined in orthologous models of autosomal dominant (AD) and autosomal recessive (AR) PKD. *Mx1Cre-Pkd1^{fllox/fllox}* mice (ADPKD1) were injected with saline or pI:pC at 5 weeks of age, and control and diseased kidneys were obtained at 21 weeks of age. Control and diseased kidneys from *Pkd2^{WS25/-}* mice (ADPKD2) and PCK (ARPKD) rats were obtained at 16 weeks of age. Over 100 oxylinps were analyzed by LC/MS/MS.

Results: In *Mx1Cre-Pkd1^{fllox/fllox}* mice with disease, renal levels of the COX metabolites, prostaglandin (PGE)₂ and 6-keto-PGF_{1α} were elevated by 35 and 59%, respectively. In *Pkd2^{WS25/-}* mice, PGE₂, 11β-PGE₂, PGF_{2α}, PGD₂, and 6-keto-PGF_{1α} were elevated in diseased kidneys by 43, 49, 46, 67 and 136%, respectively. In the PCK rat model of ARPKD, PGE₂ and 6-keto-PGF_{1α} were elevated by 38 and 50%, respectively. In all three models, although not as consistent as the COX oxylinp changes, LOX and CYP oxylinps were generally lower, which is similar to findings in the Han:SPRD-Cy rat and *pcy* mouse.

Conclusions: The elevated renal COX oxylinps in these PKD models are consistent with other cystic kidney disease models. This suggests that COX inhibition with common drugs such as aspirin or selective COX inhibitors may be beneficial in PKD, as it is in other models of cystic kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO887

Hepatorenal Fibrocystic Diseases in Children Eujin Park,¹ Yo Han Ahn,¹ Hee Gyung Kang,^{1,2} Hye Won Park,³ IL-Soo Ha,¹ Hae Il Cheong.^{1,2} ¹*Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Korea*; ²*Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Korea*; ³*Dept of Pediatrics, Seoul National Univ Bundang Hospital, Seongnam, Korea*.

Background: Hepatorenal fibrocystic diseases (HRFCDs) are a group of monogenic disorders characterized by developmental abnormalities involving the liver and kidney. In this study, we performed genotype and phenotype analyses of children with HRFCDs to determine the distribution of underlying diseases.

Methods: A total of 36 children with HRFCDs were recruited, with genetic tests performed in 22 patients and 14 patients diagnosed clinically as having autosomal recessive polycystic kidney disease (ARPKD).

Results: In children with HRFCDs, ARPKD was the most common disease (16/36, 44.4%) followed by nephronophthisis 13 (NPHP13, 11/36, 30.6%) and Meckel-Gruber syndrome type 3 (MKS3, 4/36, 11.1%). Renal function deteriorated faster in children with NPHP13. The main hepatic pathology was Caroli disease in the NPHP13 patients, while most other patients had Caroli syndrome or congenital hepatic fibrosis. Of note, three of four MKS3 patients had an accompanying choledochal cyst. No ARPKD patients had other organ involvement, while several NPHP13 patients had ocular and/or neurodevelopmental involvement. In contrast, all MKS3 patients had severe ocular and neurodevelopmental involvement.

Conclusions: NPHP13 is a major disease belonging to HRFCDs, and thorough evaluation of its clinical features, including kidney, liver and other organ involvement, may aid in the differential diagnosis of HRFCD.

SA-PO888

Identifying Genetic Modifiers in Severe Polycystic Liver Disease (PLD) by Whole Exome Sequencing (WES) Amirreza Haghghi,¹ Young-Hwan Hwang,² Ning He,¹ Kairong Wang,¹ Winnie Y. Chan,¹ Xuewen Song,¹ Joost P.H. Drenth,³ York P. Pei.¹ ¹Div of Nephrology, Univ of Toronto, Toronto, Canada; ²Div of Nephrology, Eulji Univ College of Medicine, Seoul, Korea; ³Dept of Gastroenterology and Hepatology, Radboud Univ, Nijmegen, Netherlands.

Background: Severe PLD (sPLD) is a rare and poorly understood phenotype seen in ADPKD and ADPLD. Mutations of *PRKCSH* or *SEC63* in ADPLD reduce functional polycystin-1 dosage by decreasing endoplasmic reticulum (ER) protein-processing and aggravates cystic disease severity in-vivo (Nat Genet 43: 639-647, 2011). We hypothesize that rare mutations in ER pathway genes may modify PLD.

Methods: We performed WES using Illumina HiSeq2000/2500 with SSV4/5 capture kit in 88 patients (24 affected discordant sib-pairs and 7 affected concordant sib-pairs for sPLD and 27 sporadic cases). All sPLD patients had a liver span >25 cm by CT/MRI or >3x normal liver volume. In addition to genome-wide analysis, we performed focused analysis on 168 ER genes. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare deleterious variants of high and moderate impact as predicted by PolyPhen-2, Sift, Mutation Assessor, Mammalian and Vertebrate nucleotide-level conservation, and Combined Annotation Dependent Depletion.

Results: Overall, we achieved a mean target coverage of 108X with 90% of targeted exomes having >30X read depth. We identified 4,696 rare deleterious variants that segregated with PLD disease severity in at least one family. From them, we found 7 non ER genes (*TTN*, *DNAH10*, *DNAH14*, *HMCN2*, *NEB*, *OBSCN* and *ADAMTS8*) with rare variants that segregate in 4 to 6 families each and 8 ER genes (*WFS1*, *UGGT1*, *UGGT2*, *SEC24D*, *SEC23B*, *EIF2AK4*, *ATF6B* and *RPN1*) with rare variants that segregate in at least one family and 3-4 sporadic sPLD cases.

Conclusions: Our results suggest extensive genetic heterogeneity with no one single gene accounting for a large proportion of sPLD cases. Future studies with expanded sample size will help to identify promising candidate genes for follow-up functional studies. Identification of genetic modifiers of sPLD has the potential to improve risk prediction and treatment of this unusual complication.

Funding: Private Foundation Support

SA-PO889

TOSCA – TuberOus SCLerosis Registry to Increase Disease Awareness: Renal Manifestations of Tuberous Sclerosis Complex John C. Kingswood,¹ Anna C. Jansen,² ¹Sussex Kidney Unit, Royal Sussex County Hospital, Brighton, United Kingdom; ²Pediatric Neurology Unit, UZ Brussel, Brussel, Belgium.

Background: Renal manifestations are the most common cause of morbidity and mortality in adult patients with tuberous sclerosis complex (TSC). The aim of the TuberOus Sclerosis registry to increase disease Awareness (TOSCA) is to understand the various manifestations of TSC. The baseline data of renal manifestations in the overall TOSCA cohort are presented here.

Methods: Patients diagnosed with TSC were enrolled in TOSCA from 170 sites across 31 countries worldwide. Patients will be followed up for up to 5 years with interim analysis performed every year.

Results: Baseline core data from 2093 patients were entered in the registry as of September 30, 2014 (cut-off date for the 2nd interim analysis). Median age at consent was 13 years (0-71). Renal angiomyolipomas were reported in 987 (47.2%) patients. Median age at diagnosis of angiomyolipoma was 13 years (0-67). Of the 946 (95.8%) patients with ongoing renal angiomyolipomas, 396 (41.9%) had multiple and bilateral lesions, 329 (34.8%) had lesions > 3 cm, and 204 (21.6%) had growing lesions. Symptoms/signs associated with renal angiomyolipomas, reported either individually or in combination with others, were elevated blood pressure (48 [5.1%]), microscopic hematuria (35 [3.7%]), hemorrhage (47 [5.0%]), impaired renal function (36 [3.8%]), and pain (51 [5.4%]). Renal angiomyolipomas were treated in 274 (27.8%) patients; major treatment modalities included embolization in 98 (35.8%) and mammalian target of rapamycin (mTOR) inhibitors in 78 (28.5%) patients. Other renal features reported were renal malignancy (24 [1.1%]), multiple renal cysts (477 [22.8%]), polycystic kidneys (73 [3.5%]), and impaired renal function (43 [2.1%]).

Conclusions: The prevalence of renal angiomyolipomas of 47.2% in our cohort compared to 80-85% in the literature probably reflects their young mean age. Despite this the intervention rate was high, emphasizing the need for active surveillance. This is the largest cohort of patients with TSC ever reported, thus TOSCA is a powerful tool to delineate the natural history of TSC.

Funding: Pharmaceutical Company Support - Novartis Pharma AG

SA-PO890

Sirolimus Reduces Fundamentally the Vascular and/or Muscular Components of Angiomyolipomas and Can Be Neoadjuvant to Partial Nephrectomy in Tuberous Sclerosis Complex Patients with Multiple and Large Tumors Associated with Surgical Risk Elieser H. Watanabe,¹ Fernando I. Yamauchi,² Hilton M. Leao-Filho,² William C. Nahas,³ Luiz F. Onuchic.¹ ¹Nephrology, Univ of Sao Paulo, Sao Paulo, SP, Brazil; ²Radiology, Univ SP, Sao Paulo, SP, Brazil; ³Nephrology, Univ SP, Sao Paulo, SP, Brazil.

Background: Renal angiomyolipomas (AMLs) are commonly associated with tuberous sclerosis complex (TSC). Because AMLs may complicate with lethal hemorrhage, invasive intervention is preozonized for high-risk lesions. These procedures, however, imply in

potential loss of functional renal mass and operative risk, particularly in TSC patients with multiple and bilateral involvement. Since AML pathogenesis is based on the loss of mTOR inhibition, clinical trials have evaluated and shown efficacy of mTOR inhibitors (mTORi) to reduce tumor size. Such studies, however, were not capable of proving mTORi long-term benefit. Given that tumor size is an independent predictor of renal function decline after partial nephrectomy, we hypothesized that pre-surgical treatment with mTORi might be beneficial.

Methods: In this retrospective study we report the effects of neoadjuvant therapy with the mTORi sirolimus in TSC patients with multiple/large AMLs undergoing nephron sparing surgery (NSS).

Results: As expected, sirolimus decreased tumor volume (-32.9±30.8%, n=22 from 9 patients, serum level of 10.4±1.3 ng/mL; p<0.001). This reduction occurred essentially due to the non-fatty compartment decrease (-56.2±33.1%; p<0,001) while the fatty component showed no significant variation. A lower rate of early operative complications was found in the treated compared to the non-treated group (0%, n=7 vs 43%, n=6; p<0,05). Such complications included mostly intraoperative bleeding (75%). Long-term complication rates did not differ between the groups. Sirolimus was well tolerated and no serious adverse event was reported.

Conclusions: Our data indicate that sirolimus acts fundamentally at the vascular-containing compartment, suggesting that it may decrease the bleeding risk. In addition to its potential benefit as neoadjuvant therapy for large/multiple AMLs undergoing NSS, our findings revealed that the use of sirolimus was safe and reduced surgical complications.

Funding: Government Support - Non-U.S.

SA-PO891

The ARegPKD Registry Study – Initial Clinical Characterization of an International ARPKD Cohort Kathrin Eber,¹ Gema Ariceta,² Carsten Bergmann,^{3,4} Heiko Billing,⁵ Reinhard Buettner,¹ Ali Duzova,⁶ Heike Goebel,¹ Dieter Haefner,⁷ Thomas Illig,⁷ Augustina Jankauskiene,⁸ Djalila Mekahli,⁹ Bruno Ranchin,¹⁰ Anja Christine Sander,¹¹ Sara Testa,¹² Lutz Thorsten Weber,¹ Dorota Wicher,¹³ Elke Wuehl,¹⁴ Franz S. Schaefer,¹⁴ Max Liebau.¹ ¹Univ Hospital of Cologne, Germany; ²Univ Hospital Vall d'Hebron, Barcelona, Spain; ³Bioscientia Center for Human Genetics, Ingelheim, Germany; ⁴Univ Hospital of Freiburg, Germany; ⁵Univ Hospital of Tuebingen, Germany; ⁶Hacettepe Univ, Ankara, Turkey; ⁷Hannover Medical School, Germany; ⁸Center for Pediatrics, Univ Hospital of Vilnius, Lithuania; ⁹Univ Hospital of Leuven, Belgium; ¹⁰IRCCS de Lyon, Bron, France; ¹¹Univ of Heidelberg, Germany; ¹²Fondazione IRCCS Ca Granda Ospedale Maggiore Polic, Milano, Italy; ¹³The Children's Memorial Health Inst, Warsaw, Poland; ¹⁴Univ Hospital of Heidelberg, Heidelberg, Germany.

Background: Autosomal recessive polycystic kidney disease (ARPKD) is the rare form of polycystic kidney disease presenting in early childhood. There is unexplained phenotypic heterogeneity. Current therapeutic approaches continue to be largely opinion-based and symptomatic.

Methods: ARegPKD is an international, mostly European, pro- and retrospective, observational study in both pediatric and adult ARPKD patients to generate a deeply-characterized ARPKD cohort. Using web-based questionnaires regarding patients' clinical data in combination with associated biobanking and reference histology ARegPKD will characterize long-term ARPKD courses and set roots for future translational research.

Results: In June 2015 63 centers have registered and more than 130 patients have been included (57,6 % male; median age at inclusion 7,6 years; number of follow-up visits up to 17). Here we present data on general patient characteristics, genetic testing, renal and hepatic phenotype putting a special focus on the peri- and postnatal period (prenatal findings, ventilation modalities, sonographical findings, laboratory values).

Conclusions: ARegPKD aims to deeply characterize ARPKD patients in order to provide evidence base for clinical treatment decisions and contribute to the understanding of this severe renal disorder of early childhood.

Funding: Private Foundation Support

SA-PO892

The Effect of Sodium Nitrite on Central and Peripheral Hemodynamics, Vasoactive Hormones, GFR and Sodium Excretion in Healthy Subjects Jeppe B. Rosenbaek, Safa Al Therwani, Janni Majgaard Jensen, Frank H. Mose, Erling B. Pedersen, Jesper N. Bech. Univ Clinic in Nephrology and Hypertension, Holstebro Hospital and Aarhus Univ, Denmark.

Background: Recent research has shown that sodium nitrite is readily converted to nitric oxide (NO) by enzymes in vivo and exerts vasodilation. Previous studies based on nitric oxide synthase inhibition indicates a natriuretic effect of nitric oxide. The purpose of the present study was to examine the effects of sodium nitrite on central and peripheral blood pressure, heart rate, fractional sodium excretion and GFR.

Methods: In a single blinded, crossover, placebo controlled dose-response study 12 healthy subjects were treated, in a randomized order, with placebo (isotonic NaCl) or one of three doses of sodium nitrite 40, 120 or 240 mg/kg/hour for two hours. Each examination was preceded by 4 days standardized diet. Subjects were supine and water loaded throughout the day. Before, during and after sodium nitrite administration we measured diastolic, systolic and mean arterial blood pressure (DBP, SBP and MAP), heart rate, plasma renin, angiotensin II and aldosterone, GFR by chrome-EDTA clearance, fractional sodium excretion and urinary excretion rate of nitrite and nitrate (NO₃).

Results: Fractional sodium excretion were reduced by 0.25% 95%CI (0.02;0.47) by the lowest dose, 0.24% (-0.12;0.59) by the intermediate dose and 0.32% (0.06;0.59) by the highest dose compared to placebo. The highest dose of sodium nitrite reduced SBP by 4.5 mmHg (0.5;8.5), DBP by 3.8 mmHg (0.9;6.7), MAP by 4.0 mmHg (1.2;6.8) and increased P-renin concentration by 17.6% (2.9;32.2), P-angiotensin II by 21.8% (4.6;38.9) and urinary excretion rate of NO_x by 95% (59;132) compared to placebo. There was no effect on heart rate, GFR or aldosterone.

Conclusions: In supine, water loaded subjects a two hour infusion of 240 mg/kg/hour sodium nitrite exerts an antinatriuretic and BP lowering effect. The rise in urinary excretion rate of NO_x suggests an increased bioavailability. The activation of the renin-angiotensin-aldosterone system (RAAS) could either be mediated directly by nitrite/NO or by baroreceptor reflex. The antinatriuretic effect might, at least partially, be mediated by the RAAS.

Funding: Government Support - Non-U.S.

SA-PO893

The Spatial Distribution of Metabolites Determined by Imaging Mass Spectrometry in the Kidneys of Rats Treated with Furosemide
Hyu-jeong Choi, Euijung Park, Tae-Hwan Kwon. *Dept of Biochem and Cell Biol, Sch of Med, Kyungpook Natl Univ, Taegu, Korea.*

Background: In the kidney, metabolic processes vary among the cortex (COR), outer medulla (OM), and inner medulla (IM), and the concentrations of metabolites are different according to the kidney zones. We aimed to examine the regional differences of the significantly changed metabolites in the kidneys of rats treated with loop diuretics by exploiting the matrix-assisted laser desorption/ionization (MALDI) and imaging mass spectrometry (IMS).

Methods: Osmotic minipumps were implanted in male Sprague-Dawley rats to deliver 12 mg/day of furosemide (s.c.). Vehicle-treated control rats (n = 14) and furosemide-treated rats (furosemide rats, n = 15) were maintained in metabolic cages for 6 d on a fixed daily amount of rat chow (15 g/220 g bw/rat) with free access to water intake.

Results: At day 6, higher urine output (32 ± 4 vs. 9 ± 1 ml/day) and lower urine osmolality (546 ± 44 vs. 1,677 ± 104 mOsm/KgH₂O) were observed in furosemide rats. Extracts of COR, OM, and IM were analyzed by UPLC/Q-TOF MS. The filtered peaks in UPLC/Q-TOF MS were subjected to multivariate analysis, revealing a clear differentiation between the two groups. UPLC-QTOF-MS identified significant changes of metabolites, including acetyl carnitine, betaine, carnitine, choline, dehydrocarnitine, and glycerophosphorylcholine (GPC). Next, significant changes of metabolites were also identified by IMS and MALDI-TOF/TOF, including choline compounds (choline, phosphocholine, phosphocholine derivatives and GPC), carnitine compounds (carnitine, dehydrocarnitine, acetyl carnitine and acyl carnitine) and betaine. Importantly, the spatial distribution and relative quantitation of identified metabolites were analyzed by IMS. Choline compounds were increased in COR and OM, but decreased in IM from furosemide rats. Carnitine compounds were increased in COR and IM in furosemide rats. Betaine and GPC were decreased in OM and IM in furosemide rats.

Conclusions: Taken together, IMS applied to the kidney sections successfully provides the spatial distribution and relative quantitation of significantly changed metabolites in the kidneys of furosemide rats.

Funding: Government Support - Non-U.S.

SA-PO894

Bicarbonate Supplementation Improves Vascular Function in Patients with Chronic Kidney Disease: A Pilot Study Jessica B. Kendrick,^{1,2} Emily Decker,¹ Kristen L. Nowak,¹ Michel Chonchol.¹ *¹Univ of Colorado Denver, Aurora, CO; ²Denver Health Medical Center, Denver, CO.*

Background: Metabolic acidosis, as reflected by a low serum bicarbonate level, is associated with increased risks of endothelial dysfunction, hypertension and death. Metabolic acidosis induces inflammation and endothelin-1, both of which contribute to vascular dysfunction. Whether alkali therapy improves vascular function in patients with chronic kidney disease (CKD) is unknown.

Methods: Seven subjects (5 men and 2 women) with stage III/IV CKD and serum bicarbonate level: 16-22 mEq/L completed a pilot, prospective, open-label, crossover study of 14 weeks duration examining the effect of oral sodium bicarbonate supplementation on endothelial function. The primary endpoint was change in brachial artery flow mediated dilation between treatment and control conditions. Each period was 6 weeks in duration with a two-week washout period in between. Patients were treated with oral sodium bicarbonate tablets two to three times per day for goal serum bicarbonate of ≥ 23 mEq/L.

Results: The mean (SE) age and eGFR was 59 (3.3) years and 21.9 (2.6) ml/min/1.73m², respectively. The mean (SE) serum bicarbonate level increased after sodium bicarbonate administration from 18.4 (0.7) mEq/L to 23.7 (0.9) mEq/L. The mean (SE) serum bicarbonate level did not change in the control arm. Blood pressure control was similar between the two conditions. Brachial artery flow-mediated dilation was 42% higher after 6 weeks of sodium bicarbonate replacement (3.78 ± 1.58 to 5.35 ± 1.31%) whereas it decreased by 14% during control conditions (3.51 ± 0.53 to 3.01 ± 0.91%).

Conclusions: Bicarbonate supplementation in patients with CKD and low serum bicarbonate levels results in improved vascular function. Large randomized trials need to be performed to determine if treatment with alkali therapy can reduce cardiovascular disease in patients with CKD.

Funding: NIDDK Support

SA-PO895

Tenofovir-Related Distal Tubular Acidosis in HIV Infected Patients
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Background: Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor extensively used worldwide and is now the most prescribed drug on Highly Active Antiretroviral Therapy (HAART). TDF toxicity is mainly targeted at the proximal tubule, and in severe cases can cause Fanconi Syndrome or acute kidney injury. Despite this, there are no studies evaluating other types of tubular toxicity. This study evaluated the presence of distal renal tubular acidosis (dRTA) in HIV patients on HAART.

Methods: Sixty one HIV patients older than 18 years on treatment with HAART for more than 6 months and GFR estimated by CKD-EPI equation greater than 45 ml/min/1.73m² were evaluated. They were divided into two groups: 31 used HAART that included TDF and 30 used HAART with no current or previous use of TDF. They were submitted to fluid restriction for 12 hours and received 40mg of furosemide and 0.1mg of hydrocortisone, following the acidification test proposed by Walsh *et al* (2007). We measured serum bicarbonate and the following parameters: hourly urinary pH (0h to 4h) by potentiometry, urinary ammonium (uNH₄⁺) by spectrophotometry and urinary titratable acidity (uTA) by NaOH (0h and 4h). The diagnosis of dRTA was established when the urinary pH was higher than 5.3 in all measurements.

Results: There was no significant difference between the groups in terms of age, gender, ethnicity, CD4 count or eGFR. The prevalence of dRTA was 6% in the group without TDF and 26% in TDF group (p=0.04). In both groups, patients without dRTA showed increase in uNH₄⁺ (p=0.05 and p=0.009, respectively) and in uTA (p=0.04 and p=0.05, respectively), unlike patients diagnosed with dRTA that showed no significant increase neither in uNH₄⁺ (p=0.44 and p=0.34, respectively) nor in uTA (p=0.52 and p=0.11, respectively). In all cases with dRTA, the serum bicarbonate was normal, featuring an incomplete presentation.

Conclusions: The prevalence of incomplete dRTA in patients using TDF was significantly higher than the group not using the drug. This is the first study suggesting a possible association between TDF and dRTA. Subsequent studies will be necessary to corroborate this hypothesis.

SA-PO896

Comparison of Acid-Base Disorder Between Patients Undergoing Ileal Neobladder and Ileal Conduit Jung-woo Noh,¹ Eunjung Kim,¹ Ja-Ryong Koo.¹ *¹Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym Kidney Research Inst, Seoul, Korea; ²Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym Kidney Research Inst, Seoul, Korea; ³Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym Kidney Research Inst, Seoul, Korea.*

Background: Since the 1980s, the orthotopic ileal neobladder (INB) has been as a new option by eliminating the need for a cutaneous stoma and urostomy appliances of ileal conduit (IC). Although this method has improved patients' quality of life, frequent incidence of metabolic acidosis (MA) have been reported. We compared occurrence of MA in INB group to IC group, and searched for risk factors affecting MA.

Methods: We conducted a retrospective study in 95 patients who underwent radical cystectomy and urinary diversion from January 2001 to December 2014 at Hallym University Medical Center. Patients who have any illness such as severe pulmonary disorder, take any medication that could lead to MA and sepsis were excluded. Acid-base balance and renal function were compared between INB and IC groups. MA was defined as a venous sample bicarbonate level of less than 21 mmol/L.

Results: MA was detected in 74.2% and 69.7% within 7 days (p=0.64), and in 31% and 14.8% at 1 month (p=0.1) after operation in INB and IC group. But cases on bicarbonate therapy were significantly more in INB group (p=0.02). Serum HCO₃ levels (p=0.05) and base excess (p=0.02) were significantly lower in INB group in spite of more cases on bicarbonate therapy. Acute kidney injury (AKI) at 1 month was higher in INB group (p=0.008). Serum creatinine concentrations were significantly correlated with bicarbonate levels. Multiple logistic analysis showed that 1 mg/dl increase of serum creatinine level result in a 5.38-fold higher risk of MA (95% confidence interval, 1.14-25.3; P = 0.03). Patients without AKI, MA was detected in 13.5% in INB group, 12% in IC group at 1 month (p = 1.0).

Conclusions: Despite there being no statistical difference, INB group may more easily develop MA compared with IC group especially in patients with elevated serum creatinine concentrations. In addition, a close association between the serum creatinine level and the degree of MA was observed in both groups.

Funding: Private Foundation Support

SA-PO897

Screening for Hyperlactatemia: Relationship Between the Anion Gap and Serum Lactate in Hypovolemic Shock Richard M. Treger,^{1,2} Tristan Grogan,² David Elashoff,² Craig Anderson,³ Scott Rudkin.³ *¹Nephrology, VHAGLA, LA, CA; ²Medicine and Statistics Core, UCLA, LA, CA; ³Emergency Medicine, UCI, Irvine, CA.*

Background: In lactic acidosis (LA), a discrepancy between the increase in serum anion gap (AG) and serum lactate concentration has been noted. Previous studies evaluated patients in the Intensive Care Unit with established LA. No study has examined the relationship between AG and serum lactate within the first hour of the development of LA, specifically the sensitivity and specificity of an elevated AG for predicting hyperlactatemia.

Methods: Data were obtained prospectively from adult trauma patients at a single level 1 trauma center. Venous samples were drawn prior to initiation of intravenous fluid resuscitation.

Results: 117 patients with elevated serum lactate levels (>2.1 mmol/L) were included. The sensitivity of an elevated AG (> 10) to reveal hyperlactatemia was only 43% whereas specificity was 84%. Sensitivity improved if the upper limit of normal AG was lowered and with increasing levels of serum lactate. (Table 1). The correlation between the AG and serum lactate level yielded an R² of 0.30 (p < 0.001) and the slope of this relationship was 0.29 ± 0.58 (95% confidence interval 0.23-0.35).

Table 1: Sensitivity and specificity from use of the AG as an indicator of hyperlactatemia for specific AG and lactate level thresholds

Sensitivity/Specificity		Threshold for increased lactate concentration			
		>2.1	>5	>8	>10
Threshold for Anion Gap	<6	0.92/0.25	0.96/0.15	1.00/0.14	1.00/0.14
	<8	0.74/0.57	0.84/0.39	0.88/0.37	1.00/0.37
	<10	0.43/0.84	0.60/0.70	0.88/0.68	1.00/0.68
	<12	0.24/0.98	0.48/0.88	0.63/0.85	0.67/0.85

Conclusions: Within the first hour of the development of LA due to hypovolemic shock, the AG was not a sensitive indicator of an elevated serum lactate level, but it was fairly specific. The sensitivity and specificity of the AG as an indicator of hyperlactatemia is consistent with prior studies examining later stages of LA. The AG increased to a greater extent than the serum lactate and approximately 70% of the change in AG could not be explained by increases in serum lactate. Our results suggest that other anions contribute to the AG in LA.

SA-PO898

The Δ Anion Gap/Δ Bicarbonate Ratio in Early Lactic Acidosis: Time for Another Delta? Richard M. Treger,^{1,2} Tristan Grogan,² David Elashoff,² Craig Anderson,³ Scott Rudkin.³ ¹Nephrology, VHAGLA, LA, CA; ²Medicine and Statistics Core, UCLA, LA, CA; ³Emergency Medicine, UCI, Irvine, CA.

Background: The ratio of Δ anion gap and Δ bicarbonate (ΔAG/ΔHCO₃) is used to detect co-existing acid-base disorders in patients with high AG metabolic acidosis. Classic teaching holds that in lactic acidosis (LA), the ΔAG/ΔHCO₃ is 1:1 within the first 60 minutes of onset (despite limited human data) and subsequently rises to 1.8:1. This study examined the ΔAG/ΔHCO₃ within the first hour of the development of LA.

Methods: Data were obtained prospectively from adult trauma patients at a level 1 trauma center. Venous samples were drawn prior to intravenous fluids.

Results: 108 patients were included. 63 patients had normal serum lactate levels (≤2.1 mM) with a mean AG of 7.1, the value used to calculate subsequent ΔAG values. ΔAG/ΔHCO₃ was calculated for 45 patients who had elevated serum lactate levels (>2.1 mM). The mean ΔAG/ΔHCO₃ for all patients with elevated serum lactate levels was 1.86 (SD 1.40). The correlation between ΔHCO₃ and ΔAG showed a 95% prediction interval of ±6.15 (Figure 1).

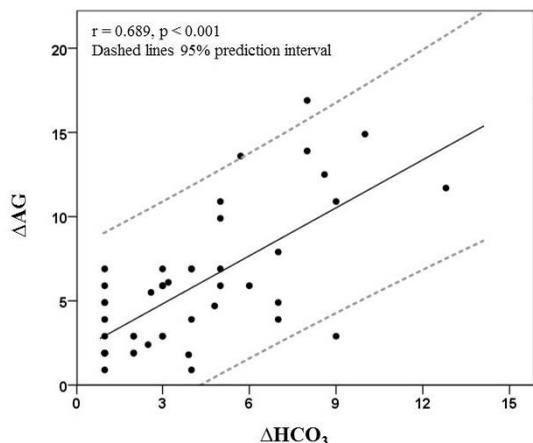


Figure 1: Correlation between ΔHCO₃ and ΔAG

Conclusions: The mean ΔAG/ΔHCO₃ was 1.86 within the first hour of the development of LA due to hypovolemic shock, confirming a small prior human study. This contradicts the traditional belief that in LA the ΔAG/ΔHCO₃ is 1:1 within the first 60 minutes. The classic 1:1 stoichiometry is based on animal models (in which lactic acid is infused into the extracellular [EC] space, facilitating EC buffering of protons by bicarbonate), while our results demonstrate a higher initial ΔAG/ΔHCO₃ ratio in early endogenous LA in humans (which originates intracellularly, resulting in intracellular buffering of protons while lactate is predominantly distributed in the EC fluid). The wide 95% prediction interval suggests that ΔAG/ΔHCO₃ should be used cautiously in the diagnosis of mixed acid-base disorders.

SA-PO899

Blood Lactate as a Predictor for Mortality in Sepsis Patients with Lactic Acidosis Treated Sodium Bicarbonate: A Retrospective Analysis Su Mi Lee,¹ Eu Gene Jeong,¹ Dongyeol Lee,² Hansae Kim,² Sung Hyun Son,³ Yun Jung Oh,⁴ Young Ki Son,¹ Seong Eun Kim,¹ Won Suk An.¹ ¹Dept of Internal Medicine, Dong-A Univ, Busan, Republic of Korea; ²Dept of Internal Medicine, Bong Seng Memorial Hospital, Busan, Republic of Korea; ³Dept of Internal Medicine, BHS Hanseo Hospital, Busan, Republic of Korea; ⁴Dept of Internal Medicine, Cheju Halla General Hospital, Cheju, Republic of Korea.

Background: Recent studies have reported that blood lactate level in the critically ill patients is associated with in-hospital mortality, but the use of lactate level to monitor and guide therapy remains under investigation. In this study, we evaluated the efficacy of blood lactate level as a predictor for mortality in sepsis patients with lactic acidosis treated with sodium bicarbonate.

Methods: We conducted a single center analysis from May 2011 through April 2014. We retrospectively analyzed 109 sepsis patients with lactic acidosis treated with sodium bicarbonate.

Results: Among the 230 patients with lactic acidosis treated with sodium bicarbonate, we finally included 109 patients (47.4%) with lactic acidosis caused by sepsis. The non-survivors had lower albumin levels (P=0.009), higher SOFA and APACHE II scores (P=0.002, P=0.047, respectively), and higher blood lactate level at 6 hours, 24 hours, and 48 hours after checking the initial lactate level (P=0.002, P<0.001, P=0.001, respectively). In particular, decrement of at least 10% in lactate clearance for the first 6 hours, 24 hours, and 48 hours of treatment were more dominant in non-survivors than survivors. Lactate clearance at 6 hours, 24 hours, and 48 hours was significantly associated with mortality after adjustment for confounding variables, including age, gender, CRP, albumin, SOFA and APACHE II scores, ventilator care, CRRT, and use of inotropic (HR: 2.201, 95% CI: 1.197-4.046, P=0.011; HR: 3.948, 95% CI: 1.269-12.281, P=0.018; HR: 4.970, 95% CI: 1.679-14.710, P=0.004, respectively).

Conclusions: Serial blood lactate levels monitoring is useful in terms of predicting mortality rather than single initial lactate or maximum lactate levels in sepsis patients with lactic acidosis treated with sodium bicarbonate.

SA-PO900

D-Lactate: It's All in the Gut Muhammad Deen, Roohi Khan. Dept of Nephrology, CHI St. Luke's Health, Houston, TX.

Background: D-Lactic acidosis is a rare form of lactic acidosis that can occur in patients with short bowel syndrome.

Methods: 88 yo M with PMH significant for HTN and small bowel obstruction s/p sub total small bowel resection presented to the ED with complains of nausea, vomiting, constipation, loss of appetite, altered mental status and decreased urinary output.

On admission:
Vitals: Blood pressure: 115/68 mmHg, Pulse: 80/min, Temperature: 98.5 F and SpO₂: 92%.

Examination: Distended abdomen with no peripheral edema.
Imaging: CT abdomen revealed dilated bowel loops but no bowel obstruction or free air in the abdomen/pelvis.

Labs: Na: 134mmol/L, K: 4.5mmol/L, Cl: 108mmol/L, CO₂: 16mmol/L, BUN: 45mg/dL, Creatine: 1.6mg/dL and Albumin 2.3g/dL. ABG: pH: 7.42, pCO₂: 31mmHg, HCO₃: 19mmHg. He was found to have anion gap metabolic acidosis with a non-anion gap metabolic acidosis. Venous lactate: 1.11 mmol/L (Normal 0.5- 2.2 mmol/L). Serum D-lactate was drawn revealing an elevation at 4.15mmol/L – thus confirming the diagnosis of D-lactic acidosis.

Treatment: Patient received IV fluids with bicarb. PO Flagyl was started and constipation was also treated. His neurological status along with his acidosis subsequently improved.

Diagnoses of anion gap metabolic acidosis in the setting of D-Lactic acidosis was made due to bacterial over growth because of his past history of small bowel resection.

Conclusions: The diagnosis of D-lactic acidosis should be promptly considered in patients with malabsorptive disorder such as short bowel syndrome or following a jejunioileal bypass especially when no other cause of anion gap metabolic acidosis is found. Diagnosis is confirmed by a special enzymatic test measuring serum D-Lactate. Treatment involves a low-carbohydrate diet, sodium bicarbonate infusion to correct acute acidemia and antibiotics to minimize D-lactate producing bacteria.

SA-PO901

Customized Base Solutions for Treatment of Acute Acidosis Thomas G. Mason,^{1,2} Jeffrey A. Kraut.³ ¹Dept of Chemistry and Biochemistry, Univ of California, Los Angeles, CA; ²Dept of Physics and Astronomy, Univ of California, Los Angeles, CA; ³Medical and Research Services VHAGLA Healthcare System, UCLA Membrane Biology Laboratory, and Div of Nephrology, VHAGLA Healthcare System and UCLA Geffen School of Medicine, Los Angeles, CA.

Background: Acute acidosis is associated with cell dysfunction and increased mortality. Intravenous administration of hypertonic sodium bicarbonate (NaHCO₃) does not improve cellular function or clinical outcome. This is attributed to undesirable generation of CO₂, which decreases intracellular pH, and also to undesirable osmotic stress. Thus, designing a base that can raise pH without generating CO₂ or producing osmotic stress would address an unmet need.

Methods: Theoretical modeling has been performed using Mathematica software to determine equilibrium ion concentrations in mixed strong-weak base solutions. If these solutions have a significant proportion of strong base yet lower concentration, they are predicted to raise blood pH without generating CO₂ or producing large osmotic stress. Strong bases examined include disodium carbonate (Na₂CO₃) and sodium hydroxide (NaOH); these were mixed with NaHCO₃. Acid-base parameters were measured in acidified canine blood mixed with the base solutions in a closed system using a blood gas analyzer. Treated blood was examined using an optical microscope.

Results: A near-isotonic base solution containing Na₂CO₃:NaHCO₃ at a ratio of 3:1 is predicted to raise blood pH without increasing CO₂ or causing osmotic stress. Addition of this base to acidified blood raised blood pH while reducing CO₂. By contrast, NaHCO₃ raised blood pH, but also generated CO₂. Examination of red blood cells exposed to the former 3:1 solution revealed no evidence of osmotic stress. Mixed base solutions of NaOH and NaHCO₃ are also promising as a lower sodium alternative.

Conclusions: Mixed strong-weak base solutions, rather than hypertonic NaHCO₃, can raise blood pH and serum bicarbonate levels, minimize osmotic stress, and limit CO₂ generation. A 3:1 mixture of Na₂CO₃: NaHCO₃ well below 1 M concentration appears to be effective in this regard.

SA-PO902

Chloride Alterations in Hospitalized Patients: Prevalence and Outcome Significance Qi Qian, Charat Thongprayoon, Wisit Cheungpasitporn. *Medicine/ Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Chloride (Cl) plays a fundamental role in the maintenance of serum osmotic pressure, acid-base balance, and cellular health. Cl channels are expressed in almost all cells in the body. Dysfunctions in the Cl channel result in a broad spectrum of diseases. Cl alterations in hospitalized patients have not been comprehensively studied in recent years.

Methods: We conducted a retrospective study of adult (>18 years old) hospital admissions at Mayo Clinic over a period of three years (2011 to 2013). Patients without admission Cl (€24hr of admission) were excluded. Outcome measures included all-cause mortality, length of hospital stay and discharge disposition.

Results: 76,719 unique patients from a total of 147,358 hospital admissions were enrolled. 55,523 (72.4%) had repeat Cl measurements within 48 hours. Admission serum Cl in the range of 105-108 mmol/L was found to be optimal based on hospital mortality. 60.6% (n=48, 999) had admission Cl<105 mmol/L, and 13% (n=11,999) >108 mmol/L. Cl <100 or >108 mmol/L independently predicted poor outcomes including hospital death, longer length of hospital stay, and being discharged to a care facility. 17.1% (n=13,089) of the patients had anion gap >12 mmol/L; their hospital mortality, when compared to those with anion gap €12 mmol/L, worsened progressively with rising Cl. Further examination of Cl evolution within 48 hours of admission showed Cl increase to be an independent predictor for hospital mortality. Further, the magnitude of Cl increase was inversely associated with days of patient survival.

Conclusions: Non-optimal serum Cl values are common in hospitalized patients. Cl alterations are independent predictors for poor clinical outcomes. Post-admission Cl increase not only predicted hospital mortality but also inversely correlated with length of patient survival. These results indicate that more attention should be paid to Cl value. Further prospective and randomized studies are needed to determine whether avoidance of post-admission Cl increase would improve patient survival.

SA-PO903

A Retrospective Review of Paediatric Patients with Bartter and Gitelman Syndrome Patrick Walsh, Marc Bienias, Detlef Bockenhauer. *ICH, UCL, London, United Kingdom.*

Background: Bartter and Gitelman syndrome are rare autosomal recessive disorders of renal salt handling. They are characterized by disturbed electrolyte and acid-base homeostasis with potentially severe complications. Currently little is known about the long-term disease course and best treatment is controversial. We performed a retrospective case review to investigate the long-term disease course of patients with a diagnosis of Bartter/Gitelman syndrome.

Methods: Demographic and Laboratory data was recorded at presentation, and ages 1,2,3,4,5,10 and 15.

Results: 42 patients with a genetic diagnosis of Bartter/Gitelman were reviewed with a median follow up of 7.85 years (Range 0 -18 Years).

Geno-type	Number of patients	Age at Presentation	Gestational Age	Nephrocalcinosis (% of patients)	GFR <90ml/min/ 1.73m2 at last follow-up (Schwartz)	Albuminuria (>2.5 Females 3.5 Males mg/mmol)	Average Height at last follow-up (Z-score)
1	6	Day 7	30.3	100	6	2	-1.2
2	10	0.8 Years	32.0	70	9	1	-1.82
3	14	2.7 Years	37.4	7	4	11	-1.28
4	1	Day 1	32.0	0	1	1	N/A
Gitelman	11	5 Years	39.4	9	1	0	-0.93

Bartter 1&2 presented earliest with prematurity and deranged electrolytes. All of the Bartter 1 patients and 70% of Bartter 2 had evidence of nephrocalcinosis on their first

ultrasound. Hypomagnesaemia (<0.7mmol/L) was seen in 11/14 Bartter 3 and 8/11 Gitelman patients; Hypomagnesaemia developed over time and was seen earlier in Bartter 3 (3.8 years) than in Gitelman (7.9 years). Obvious complications of hypokalaemia were only seen in one patient with Bartter 3 (despite potassium levels <2.5mmol/L in 10 patients) in the form of hypokalaemic paralysis; he was admitted twice at age 2 and 3 (Potassium 1.7 & 1.5 respectively). Decreased GFR was present in all Bartter 1 and 90% of Bartter 2 at last follow-up. 3 patients with Bartter 3 developed nephrotic range proteinuria and one demonstrated biopsy evidence of FSGS.

Conclusions: The overall prognosis during childhood was good. Final heights were within the normal range and no child developed ESRD. Albuminuria was common in Bartter 3, indicating the need for long-term monitoring of renal function. Interestingly, hypomagnesaemia is often absent at presentation and develops over time in both Bartter 3 and Gitelman.

SA-PO904

Urine Calcium to Magnesium Ratio Aids to Diagnose Gitelman's Syndrome without Hypocalciuria and Receiving Intravenous Magnesium Administration Chih-Jen Cheng,^{1,2} Shih-Hua P. Lin,^{1,2} Ming-Tso Yan.^{2,3} ¹Tri-Service General Hospital; ²National Defense Medical Center; ³Cathay General Hospital.

Background: Although hypocalciuria is widely used to distinguish Gitelman's syndrome (GS) from Bartter syndrome (BS), several patients with GS actually have not hypocalciuria and may be clinically misdiagnosed as BS. Intravenous magnesium administration to correct hypomagnesemia, another distinct finding in GS can significantly enhance urine calcium excretion and unmask the preexisting hypocalciuria. Because renal Mg²⁺ wasting is characteristic in GS, we hypothesize that urine Ca²⁺/Mg²⁺ ratio may be superior in diagnosing GS.

Methods: One hundred forty three Taiwanese GS patients (M:F =87:56, age 25 ± 10) with definite SLC12A3 mutations was enrolled. Nine cBS patients with CLCNKB mutations and 15 healthy subjects were enrolled as disease and normal control, respectively. Intravenous MgSO₄ was administered (elemental Mg 0.35 mmol/kg) in 8 GS patients with hypocalciuria. Relevant blood laboratory and at least two urine collection for all electrolytes excretion were determined. Hypocalciuria was defined as urine Ca/Cr ratio less than 0.1 mmol/mmol.

Results: Fourteen (9.8%) of 143 GS patients did not have hypocalciuria (Ca²⁺/Cr ratio 0.28 ± 0.09 mmol/mmol) and exhibited no significant difference in blood parameters compared with GS patients without hypocalciuria. Although their urine Ca²⁺/Cr ratio was significantly lower than that in cBS (0.51 ± 0.18 mmol/mmol), there was still overlapping between them. Notably, urine Ca²⁺/Mg²⁺ ratio was significantly lower in GS than cBS without overlap (0.46 ± 0.12 vs 1.57 ± 0.53 mmol/mmol, p< 0.001). Acute MgSO₄ administration in GS patients markedly enhanced urine Ca²⁺ excretion (Ca²⁺/Cr ratio 0.05 ± 0.01 to 0.64 ± 0.01 mmol/mmol, p < 0.001). However, urine Ca²⁺/Mg²⁺ ratio (0.21 ± 0.01 mmol/mmol) remained much lower than healthy subjects (1.35 ± 0.63 mmol/mmol, p<0.001) and cBS.

Conclusions: Urine Ca²⁺/Mg²⁺ ratio may be a good index to help diagnose GS without hypocalciuria and even receiving intravenous Mg²⁺ administration.

SA-PO905

A Blunted Response to Thiazide Diuretics Is Not Specific for Patients with Gitelman Syndrome Anneke Bech, Jack F. Wetzels, Tom Nijenhuis. *Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: In Gitelman syndrome (GS), a defective sodium-chloride co-transporter (NCCT) in the distal tubule classically leads to hypokalemia and hypomagnesemia. A challenge with thiazide diuretics, testing the functional presence of NCCT, has been shown to differentiate GS from Bartter syndrome (BS) and normal controls. However, the performance of the thiazide test in renal magnesium wasting disorders other than GS and BS has not been studied.

Methods: Eleven patients who presented to our clinic between 2010-2014 with renal magnesium wasting and in whom a thiazide test was performed were included. An abnormal test result is defined as a maximal change of fractional chloride excretion (ΔFeCl) < 2.3% [Colussi 2007]. The thiazide test in eight volunteers in our clinic showed a mean maximal ΔFeCl 3.12 ± 0.48% with the lowest value being higher than 2.3%. Additional DNA mutation analyses were performed.

Results: Three patients had a mutation in SLC12A3 (GS), one patient had a compound mutation in CLCNKB and KCNJ1 (BS), 1 patient had a mutation in FXYD2 and five patients had a deletion of one HNF1β allele. The patients with GS showed a blunted response, the patient with BS showed a normal response, the patient with a FXYD2 mutation showed a blunted response and the patients with HNF1β mutations showed different responses to thiazide diuretics.

	Mutation	Maximal Δ FeCl (%)
GS	c.1315G>A, exon 10	0.12
GS	c.602-16G>A, intron 4	0.18
GS	815T>C and 1670 C>T, exon 6	0.86
BS	CLCNKB: c.88C >T, exon 2 KCNJ1: c.1070 T>C, exon 5	6.10
FXYD2	c.115G>A	0.66
HNF1β	deletion one allele	0.01
HNF1β	deletion one allele	1.41
HNF1β	deletion one allele	1.48
HNF1β	deletion one allele	2.40
HNF1β	deletion one allele	3.90
unknown diagnosis	unknown	2.43

Conclusions: A blunted response to thiazide diuretics is not specific for GS and can also be found in other renal magnesium wasting disorders, such as caused by mutations in FXYP2 or HNF1β. Still, the thiazide test could prove to be a valuable tool for research and phenotyping patients, and increase our understanding of the pathophysiological processes and the interrelationship between transcription factors, transporters and ion channels.

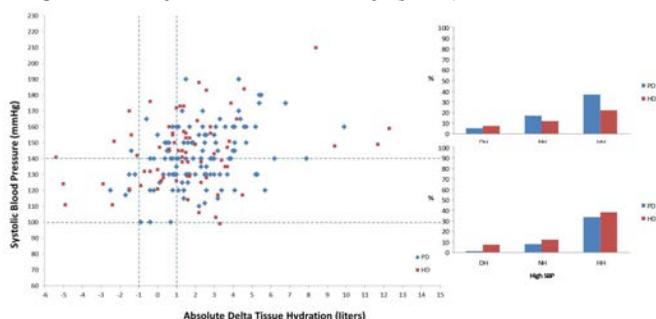
SA-PO906

Assessment of Hydration Status by Bioimpedance Spectroscopy in Peritoneal and Hemodialysis Patients from a Single Center Sara Samoni,^{1,2} Luis Ignacio Bonilla,¹ Carla Estremadoyro,¹ Alessandra Spinelli,¹ Salvador Roberto Lopez,¹ Faeg Husain-Syed,¹ Carlo Crepaldi,¹ Alessandra Brendolan,¹ Claudio Ronco.¹ ¹IRRV, Vicenza; ²Sant'Anna School of Advanced Studies, Pisa.

Background: Fluid overload(FO)is frequent in peritoneal dialysis(PD)and hemodialysis(HD)pts.Despite the identified correlation between systolic blood pressure(SBP)and FO,some conditions,i.e. vascular stiffness and heart failure,can cause a significant proportion of pts to fall out from this model.Our aim was to assess the relationship between hydration status(HYD)and SBP in PD and HD pts.

Methods: We enrolled all DP and HD pts of our center.HYD was evaluated by bioimpedance spectroscopy using Body-Composition-Monitor(BCM Fresenius Medical Care)and expressed by the absolute delta tissue hydration(ADTH).BCM and SBP were measured during routine ambulatory visits in DP pts.In HD pts,measurements were done before the intermediate HD treatment based on a 3-treatment per week program.We considered normohydrated(NH),hyperhydrated(HH)and dehydrated(DH)pts with ADTH -1/+1,>+1,<-1, respectively. We defined normal(NSBP),high(HSBP)and low SBP(LSBP) with values of 100-140,>140,<100mmHg,respectively.Considering both parameters,we subdivided the cohort into 9 groups.Continuous variables were expressed as means±SD for normally distributed data and compared with t-test.

Results: We enrolled 188 pts,120 DP,68 HD pts.Mean SBP was 141±18 and 144±22mmHg,respectively.Mean ADTH was 2.2±2 in PD and 1.6±3.1L in HD pts.Among NSBP,the percentage of HH pts was significantly higher in PD than HD pts(p=0.04)while among HSBP,the HD pts were more DH than PD pts(p=0.02).



Conclusions: We found that measurement of SBP is not sensitive to assess the HYD in PD and HD pts. We also found that PD pts with NSBP tend to be more HH than HD pts. We suggest that SBP should not be used alone as a marker for HYD in PD and HD pts, it should always be accompanied by other tools.

SA-PO907

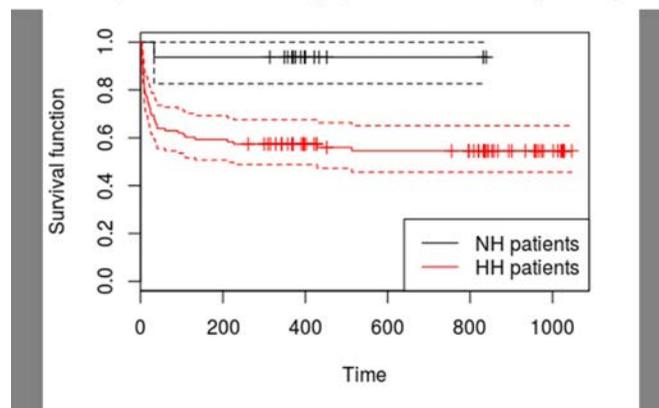
Impact of Hydration Status, Assessed by Bioelectrical Impedance Vector Analysis, on Mortality in Critically Ill Patients Sara Samoni,^{1,2} Valentina Vigo,³ Luis Ignacio Bonilla,¹ Gianluca Villa,¹ Silvia De Rosa,¹ Federico Nalesso,¹ Fiorenza Ferrari,¹ Alessandra Brendolan,¹ Carlo Donadio,³ Claudio Ronco.¹ ¹IRRV, Vicenza; ²Sant'Anna School of Advanced Studies, Pisa; ³Univ of Pisa, Pisa.

Background: Clinical trials have shown a positive correlation between fluid overload and adverse outcomes in pts admitted to intensive care unit(ICU).Currently,there is not a non-invasive method that can provide an accurate and timely assessment of whole body hydration status.Our aim was to evaluate the impact of hyperhydration,assessed by bioelectrical impedance vector analysis (BIVA),on ICU mortality in critically ill pts.

Methods: This is a prospective,dual-center study.We included 125 ICU pts with an ICU stay of 72 hrs or more.Anthropometric, medical history and laboratory data were collected. Assessment of hydration status was performed by BIVA,using a single frequency analyzer,at the baseline and daily for a period of 72-120 hrs.Pts were considered normohydrated(NH) or hyperhydrated(HH)if BIVA hydration level was 72.7%-74.3% or >74.3% of fat-free body mass,respectively.

Results: The logistic regression analysis performed found a significant correlation between ICU mortality and maximum hydration level reached in observation period,either in patients with or without acute kidney injury(p<0.001).

Kaplan-Meier estimate by hydration status during ICU stay



Conclusions: Our findings confirm and expand literature data about the correlation between hyperhydration and ICU mortality.Despite the importance of this problem,there are currently few methods to assess hydration status in critically ill pts.BIVA has been shown to be safe,non-invasive,easy to use and it may predict mortality,thus we suggest its routinely use in ICU pts.Randomized clinical trials are needed to define the precise role of BIVA in the goal-directed fluid management of critically ill pts in ICU.

SA-PO908

Sleep-Disordered Breathing Is Not Associated with Body Fluid Volume in Chronic Hemodialysis Patients Takahiro Masuda,^{1,2} Yumi Kijima,² Chuji Sekiguchi,² Yasuharu Miyazawa,² Eiji Kusano,³ Yasushi Asano,⁴ Daisuke Nagata.¹ ¹Div of Nephrology, Department of Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan; ²Nasu-Minami Hospital, Nasukarastuyama, Tochigi, Japan; ³Japan Community Health Care Organization Utsunomiya Hospital, Utsunomiya, Japan; ⁴Japanese Red Cross Koga Hospital, Koga, Ibaraki, Japan.

Background: Sleep-disordered breathing (SDB), characterized by nocturnal intermittent hypoxia, is frequent in patients with chronic hemodialysis (CHD). Fluid retention may promote SDB in these patients, but the detailed information is lacking.

Methods: Eighty-eight CHD patients in Nasu-Minami Hospital and Japanese Red Cross Koga Hospital were included in this study (male: 62.1%, age: 68.1 ± 11.5 years, body mass index: 21.7 ± 3.1, duration of CHD: 5.3 ± 5.9 years, diabetes mellitus: 50.0%). Overnight pulse oximetry and bioimpedance spectroscopy (InBody) for the assessment of body composition were performed after dialysis on a dialysis day. Patients were divided into three groups according to 3% oxygen desaturation index (3%ODI) assessed by pulse oximetry: normal (3%ODI<5), mild SDB (5£3%ODI£15) and severe SDB (15£3%ODI). We investigated the relationship between severity of SDB and body composition including body fluid volume.

Results: Sixty patients (68.2%) were classified into the SDB group (mild SDB 40 [45.5%] and severe SDB 20 [22.7%]). Fat mass (relative to body weight) in the SDB group was significantly higher than in the normal group (normal 24.3±8.5%, mild SDB 29.7±8.0%, severe SDB 30.2±9.2%, P=0.018). After adjusting for age, gender, diabetes mellitus, hemoglobin and serum albumin in a logistic regression analysis, SDB was independently associated with increased fat mass (odds ratio 1.22; 95% confidence interval 1.10-1.38; P< 0.01). Total body water, intracellular water and extracellular water were similar among the three groups.

Conclusions: SDB is associated with increased fat mass, but not body fluid volume in CHD patients. Further studies are needed to evaluate some factors that can explain the high frequency of SDB in CHD.

Funding: Private Foundation Support

SA-PO909

Association Between Brain Natriuretic Peptide and Fluid Volume Imbalance Between Intra- and Extracellular Water in Patients with Chronic Kidney Disease Yasushi Ohashi, Reibin Tai, Toshiyuki Aoki, Shizuka Kobayashi, Atsushi Aikawa, Ken Sakai. *Dept of Nephrology, School of Medicine, Faculty of Medicine, Toho Univ, Tokyo, Japan.*

Background: Malnourished and elderly patients with chronic kidney disease (CKD) may be susceptible to an extracellular volume overload due to a decreased intracellular volume capacity. We assume that excessive fluid volume is redistributed on the basis of the baseline fluid volume balance when they are exposed to fluid accumulation.

Methods: Using bioimpedance analysis, body fluid composition was measured in 129 patients with CKD from 2013 to 2015 and was separated into three components – (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW) content, and (c) extracellular water (ECW) content. Participants was also measured brain natriuretic peptide levels at the time of the body fluid composition measurement. The relationship between the ratio of ECW to ICW and brain natriuretic peptide was examined.

Results: Patients with higher log-transformed plasma level of brain natriuretic peptide was more likely to be older and have lower body mass index (BMI), glomerular filtration rate (GFR), and serum albumin levels and higher proteinuria. In body fluid composition analysis, the brain natriuretic peptide levels increased along with a decrease in all contents of free water mass consisting of muscle, fat, and mineral ($r = -0.49, P < 0.001$), ICW content ($r = -0.34, P < 0.001$), and ECW content ($r = -0.25, P < 0.01$). By the steeper decreased free water mass and ICW content than the decreased ECW content in those patients, the percentage of ECW in body weight increased, and the ratio of ECW to ICW had a positive correlation with the brain natriuretic peptide levels ($r = -0.58, P < 0.001$). In multivariate analysis, age, BMI, GFR, the ECW/ICW ratio remained independently associated with the brain natriuretic peptide levels.

Conclusions: Brain natriuretic peptide is elevated in leaner and elderly patients with fluid volume imbalance between intra- and extracellular water. Fluid volume imbalance between intra- and extracellular water may express a reserve capacity for fluid volume overload and impact on cardiac preload.

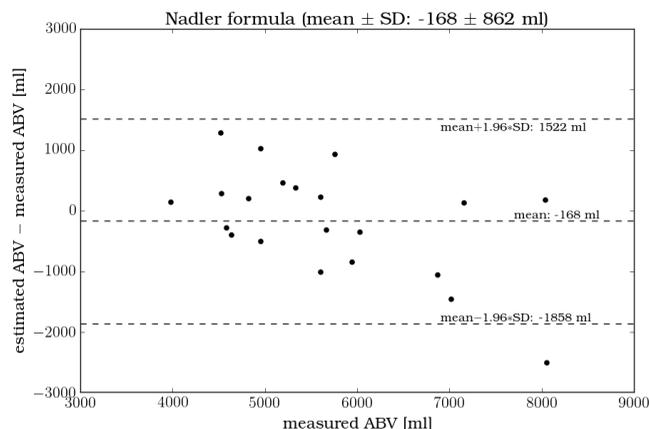
SA-PO910

Blood Volume Estimation in Hemodialysis Patients Doris H. Fuertinger,¹ Line Malha,² Peter Kotanko,¹ David S. Goldfarb,² Stephan Thijssen.¹ *¹Renal Research Inst, New York, NY; ²New York Harbor VAMC and NYU Langone Medical Center, New York, NY.*

Background: Anthropometric formulas used to estimate absolute blood volume (ABV) are generally derived from healthy subjects. Most hemodialysis (HD) patients have an expanded ABV prior to HD, rendering these formulas inappropriate for estimation of pre-HD ABV (pre-ABV). Here, we compare the performance of several ABV formulas, used in conjunction with Crit-Line data, for assessment of pre-ABV.

Methods: We assume that post-HD ABV is closer to normal ABV, which we calculated based on height, sex and post-HD weight using several published formulas. Pre-BV was then calculated from post-HD blood volume using pre- and post-HD Hct measured by Crit-Line®. The calculated pre-ABV was then compared to pre-ABV measured immediately before HD using ¹²⁵I-labeled albumin dilution.

Results: We compared 27 formulas for ABV estimation in 21 patients (♀: 3, mean ± SD: age 59 ± 14.7 years, height: 170.7 ± 10 cm, post-HD weight: 82.2 ± 16.7 kg). None of the equations showed good agreement with the measured data. The Nadler formula yielded the most accurate results (Fig 1). As exemplified in Fig 1, the equations yield a systematic trend in bias, with reasonable accuracy for ABV between 5-6 L but progressive underestimation and increasing heteroscedasticity towards higher ABV (caused by fluid overloaded patients).



Conclusions: Anthropometric equations such as the Nadler formula show reasonable accuracy (albeit unsatisfactory precision) for patients with close to normal end-HD ABV, but they fail in non-euvolemic patients. Their validity in HD patients depends on the patients' fluid status, which varies widely; hence their undifferentiated use in this population should be discouraged. More accurate and precise estimates of ABV would require a more sophisticated approach incorporating fluid status information, e.g. from bioimpedance.

Funding: Pharmaceutical Company Support - Daxor Corporation

SA-PO911

Impact of Hospital-Associated Hyponatremia on Outcomes in an Unselected Patient Population: A Retrospective Cohort Study Nicolaos E. Madias, Evangelos Tsiptotis, Bertrand L. Jaber. *Internal Medicine, St. Elizabeth's Medical Center, Boston, MA.*

Background: Although hyponatremia has been associated with an increased risk of adverse outcomes, the majority of available studies have examined selected populations questioning the generalizability of their results to unselected patients.

Methods: The discharge data of 20,072 unselected adult patients admitted to a tertiary care facility over a 7-year period were analyzed. Based on the crude relationship between [Na⁺] and mortality, hyponatremia was defined as [Na⁺] > 142 mEq/L. Patients with community-acquired hyponatremia (CAH) and those with hospital-acquired hyponatremia (HAH) were compared to patients with normonatremia at presentation ([Na⁺] of 138-142 mEq/L) in terms of in-hospital mortality, length of stay (LOS), and discharge disposition. Furthermore, patients with CAH in whom hyponatremia worsened during hospitalization (HAggH) were compared to those without aggravation. Multivariable logistic and negative binomial regression analyses were conducted.

Results: CAH occurred in 20% of hospitalized patients and was associated with an adjusted odds ratio (OR) of 1.67 (95% confidence interval [CI] 1.38, 2.01) for in-hospital mortality, and 1.44 (95% CI 1.32, 1.56) for discharge to a short-/long-term care facility, and an adjusted 10% (95% CI, 7%-13%) increase in LOS. HAH developed in 25.9% of hospitalized patients and was associated with an adjusted OR of 3.17 (95% CI 2.45, 4.09) for in-hospital mortality, and 1.45 (95% CI 1.32, 1.59) for discharge to a facility, and an adjusted 49% (95% CI 44%, 53%) increase in LOS. HAggH developed in 8.9% of patients with CAH. Compared to patients with CAH and no further increase in [Na⁺], HAggH was associated with greater risk of in-hospital mortality (adjusted OR 1.84; 95% CI 1.32, 2.56) and discharge to a facility (adjusted OR 1.90; 95% CI 1.49, 2.41), and an adjusted 13% (95% CI 4%-23%) increase in LOS.

Conclusions: All forms of hyponatremia encountered in unselected hospitalized patients are independently associated with increased in-hospital mortality and heightened resource consumption.

SA-PO912

Utility of Urine/Plasma Osmolality Ratio for Assessing Volume Status in Hyponatremia Sho Hasegawa, Maki Shibata, Takehiro Sugiyama, Fumihiko Hinoshita. *National Center for Global Health and Medicine, Tokyo, Japan.*

Background: Assessing volume status is critical for managing hyponatremia. Physical examination (P/E) and laboratory data are often used for the assessment, but the utility of each parameter has not been validated in hyponatremic patients. A body composition monitor (BCM) uses bioimpedance spectroscopy and can quantify extracellular water (ECW) and volume excess or deficiency. Here, we examined which parameter is superior in assessing volume status of hyponatremic patients, using BCM data as the reference standard.

Methods: We enrolled hospitalized patients (n=41) with hyponatremia (<130 mEq/L) at our institution and conducted P/E, laboratory tests and BCM measurement. Patients with high plasma osmolality (>275 mOsm/kg) were excluded (n=5). We used %ECW (ratio of volume excess or deficiency to ECW) derived from BCM data as the reference standard of volume status. First, patients were divided into overhydration (%ECW>0%, n=29) and dehydration (%ECW<0%, n=7) groups. Clinical signs obtained from P/E and parameters of volume status such as serum albumin (Alb), serum uric acid (UA), urine chloride, urine/plasma osmolality ratio (U/P Osm), UUN/BUN, BUN/creatinine, U/P creatinine, FENa, FEUN and FEUA were compared between the groups by Fisher's exact test or Mann-Whitney U-test. Next, we performed univariate and multiple linear regression analyses to identify associations between each parameter and %ECW.

Results: U/P Osm was significantly higher in dehydration than in overhydration (median: 2.0 vs 1.3, p=0.01), but other parameters and clinical signs showed no significant differences. Univariate regression analysis showed that Alb (β=-7.1±3.2, p=0.04), U/P Osm (β=-11.4±3.1, p=0.001), UUN/BUN (β=-0.3±0.1, p=0.01) and U/P creatinine (β=-0.10±0.03, p=0.01) were associated with %ECW. Since UUN/BUN and U/P creatinine strongly correlated with U/P Osm, we conducted multiple regression analysis using only Alb and U/P Osm. Results showed that compared with Alb (β=-7.7±2.7, p=0.007), U/P Osm (β=-12.0±2.9, p=0.0002) was more strongly associated with %ECW.

Conclusions: U/P Osm is superior to other commonly used parameters and clinical signs for assessing volume status in hyponatremic patients.

SA-PO913

Sodium Concentrations of Body Fluid Losses: A Systematic Review

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Background: Unexplained wide ranges and discrepancies of sodium concentrations [Na⁺] have been noted for different body fluids. This has led to use of “cumulative fluid balance” regardless of composition, which cannot account for specific water and sodium requirements. Appropriate water and volume management may be facilitated by an accurate and detailed knowledge of water and sodium composition of body fluid losses and gains.

Methods: We performed a systematic review of [Na⁺] of body fluids lost in adult humans. Particular attention was paid to gastric fluid with high and low acid states, diarrhea due to different mechanisms, and peritoneal, pleural and wound fluids. Inclusion criteria were met for 106 full-text articles.

Results: [Na⁺] are fluid-specific and consistent. Mean [Na⁺] were statistically lower for acid (mean±SD:44±12mEq/L) than for alkaline (55±13mEq/L) gastric fluid; the difference is not clinically relevant. [Na⁺] are higher for bile (184±24mEq/L) or pancreatic fluid (156±3mEq/L) than all other body fluids, and similar for intact small bowel (119±14mEq/L) and ileostomy outputs (116±25mEq/L). Specific mechanisms for diarrhea are associated with different [Na⁺]. [Na⁺] were significantly greater for cholera (128±18mEq/L) and lower for osmotic-induced (28±16mEq/L) than all other causes. Among osmotic diarrheas, sorbitol-induced [Na⁺] was higher (63±17mEq/L) than for carbohydrate malabsorption (43±20mEq/L), lactulose (26±19mEq/L), Idolax (16±13mEq/L) and polyethylene glycol (13±7mEq/L). Among secretory diarrheas [Na⁺] for idiopathic causes (53±22mEq/L) was lower than for neuroendocrine and villous tumors (75±13mEq/L) or non-osmotic laxatives (88±33mEq/L). Pleural, peritoneal, and edema fluid had [Na⁺] (137±13mEq/L) similar to plasma. [Na⁺] for sweat was 44±17mEq/L.

Conclusions: This is the first in-depth review of verifiable sodium concentrations of body fluids most commonly lost in hospitalized patients. We propose that these losses be replaced with appropriate water and sodium content of enteral and parenteral fluids to correct and avoid dysnatremias and perturbations of volume status.

SA-PO914

Hyponatremia in CKD: The Prevalence and Risk Factors

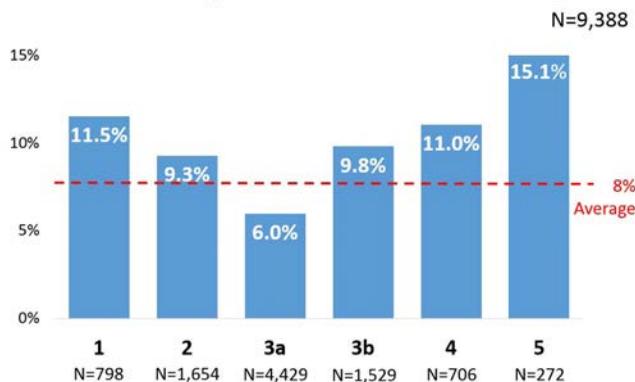
Masahiko Nagahama,¹ Daiki Kobayashi,² Fumika Taki,¹ Takuya Fujimaru,¹ Masataka Hasegawa,¹ Yuki Heath,¹ Yasuhiro Komatsu.¹ ¹Nephrology, St. Luke's International Hospital, Tokyo, Japan; ²Center for Clinical Epidemiology, St. Luke's International Hospital, Tokyo, Japan.

Background: Kidney is a vital organ regulating water and sodium homeostasis, and it is plausible that patients with CKD are more prone to develop hyponatremia due to diminished urinary dilution ability, reduced solute intake, and/or medication which affects free water clearance. However, the prevalence and risk factors of hyponatremia among CKD patients have not been elucidated. The aim of the present study is to clarify the prevalence and risk factors contributing to hyponatremia in CKD patients.

Methods: Among 32,438 patients who visited our outpatient clinic between 2011 and 2014, 9,388 patients met the criteria of CKD, which is defined as either eGFR ≤60 ml/min/1.73m² or the presence of proteinuria. Dialysis and transplant patients were excluded. Risk factors for hyponatremia were sought using multivariate logistic regression.

Results: Prevalence of hyponatremia (serum Na⁺135mEq/L) was 8% in all CKD patients. Among moderate and severe CKD (stage 3, 4 and 5, N=6397), the prevalence of hyponatremia is increased as CKD progresses.

Prevalence of hyponatremia in each CKD stage



On univariate analysis, patients developing hyponatremia in moderate and severe CKD were older (P<0.01), female sex (P<0.01), diabetic (P<0.01) and more likely to have decreased eGFR (P<0.01). Multivariate logistic regression analysis identified CKD stage (OR:1.7-2.4, P<0.01), diabetes (OR:1.4, P<0.01) and renin-angiotensin-aldosterone system (RAS) inhibitors (OR:0.68, P<0.01) as independent risk factors for hyponatremia in moderate and severe CKD.

Conclusions: The present study shows that the prevalence of hyponatremia was 8% in CKD patients, and development of hyponatremia is correlated with progression of CKD in moderate and severe CKD. Worsening CKD and Diabetes are risk factors, while RAS inhibitors are protective for hyponatremia in CKD.

SA-PO915

Mild Hyponatremia on Admission Is Associated with Sepsis and Increased Mortality in Patients Presenting with a Hip Fracture

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Background: Hyponatremia is associated with an increased risk of falls and hip fractures in the elderly (JAMA 281: 2299-2304, 1999). Moreover, sepsis is a frequent cause of death in patients with hyponatremia (AJKD 65:435-442, 2015). We assessed if hyponatremia on admission was associated with sepsis and increased mortality in patients presenting with a hip fracture.

Methods: A cohort study in adult patients admitted with a traumatic hip fracture and at least one serum Na performed at admission. Hyponatremic (H), Na < 135 mEq/L, and normonatremic (N) patients were evaluated for complications occurring within 30 days of surgery, length of hospital stay, readmission rate, in-hospital mortality and mortality during 1 year follow-up. An unadjusted and adjusted odds ratio (OR) and hazard ratio (HR) were calculated for in-hospital mortality and 1 year mortality. Adjustments were made for age, gender, propensity score for hyponatremia, CVA, CHF, ischemic heart disease, arrhythmias, thromboembolic disease, sepsis and dementia.

Results: 1571 patients were included of whom 366 (23.2%) were hyponatremic (Na 132 ± 4 mmol/L vs 138 ± 3; p < 0.001). Length of stay was 8 days in H vs. 7 days in N (p=0.053). There was an increased incidence of sepsis in hyponatremic patient, 9.8% in H vs. 6% in N (p<0.01) OR 1.7 (CI95%: 1.13-2.6). In-hospital mortality was significantly higher in H vs N patients (19.9 vs 14.7%; p= 0.016), with an un-adjusted OR of 1.45 (95% CI 1.07-1.96) and an adjusted OR of 1.15 (95% CI 0.84-1.6). Readmissions were 15.8% for H vs. 12.9% for N (p=0.14). One-year mortality was greater in H vs N patients (15.4 vs. 6.8%; p < 0.001), with an un-adjusted HR of 1.8 (95% CI 1.4-2.35) and an adjusted HR of 1.45 (95% CI 1.1-1.9).

Conclusions: Mild hyponatremia at admission is associated with sepsis and increased in-hospital and late mortality in patients presenting with a hip fracture.

SA-PO916

Characteristics of Tolvaptan Trial in Korean Patients with SIADH

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Background: This clinical study, a multicenter trial in 8 tertiary hospitals in Korea, was carried out to evaluate changes in serum sodium (Na) during 11 days on tolvaptan (TLV) daily and at the 7th day after stopping TLV in SIADH patients (pts) (<135 mEq/L).

Methods: A total of 39 pts (M:F, 23:16; age, 71±11.3 yrs) without neurologic symptoms were studied from Jun 1, 2013 to Dec 31, 2014. All pts received 15 mg/d of TLV as the initial dose and then further increased to 60 mg/d as needed in the hospital.

Results: Serum Na (mEq/L) increased prominently from baseline during first 24 hrs (127±4.3 vs 134±3.8, p<0.01), but gradually to day 4 (134±3.8 vs 136±3.6, p<0.01), and then maintained a plateau until discontinuation of TLV at day 11 (137±4.5). The changes in serum sodium (DsNa) from the baseline were 2.8±3.3 in 4 hrs, 5.9±4.1 in 8 hrs, and 6.8±4.2 in 24 hrs, respectively. The correlation between DsNa/24 hrs and baseline Na was significant (r=-0.613, p<0.01). When hyponatremia was stratified into 3 groups, mild (I, 130-134, n=12), moderate (II, 125-129, n=18), and severe (III, 124, n=9) groups, DsNa in III (11.1±4.8) during first 24 hrs was significantly higher than II (6.4±2.5, p<0.05) and I (4.3±3.3, p<0.01). Also, those of DsNa/24 hrs ≥8 mEq/L (n=18) compared to <8 (n=21) had significantly lower baseline serum creatinine (0.56 vs 0.73 mg/dL), Wt (53 vs 60 kg), BMI (21 vs 23), and body surface area (1.54 vs 1.63) (all, p<0.05). Then, serum Na after discontinuation of TLV for 1 wk was similar to the baseline (127±4.3 vs 129±8.6, p=NS). All pts underwent successfully this trial more than 24 hrs, but 4 pts were withdrawn due to rapid correction (1) and nausea (3).

Conclusions: Tolvaptan is effective and well tolerated in Korean with SIADH. However, Korean patients, particularly those with smaller frame and severe hyponatremia (<125 mEq/L), could be vulnerable to rapid correction by usual initial dose of Tolvaptan 15 mg.

Funding: Pharmaceutical Company Support - Korea Otsuka Pharmaceutical Co., Ltd.

SA-PO917

Risk Factors for the Development of Thiazide-Induced Hyponatremia

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Background: Thiazide and thiazide-like diuretics are commonly utilized for management of hypertension. However, thiazide diuretics are one of the most common causes of drug-induced hyponatremia. Previous studies have pointed to potential risk

factors that may lead to the development of thiazide-induced hyponatremia, but there is still much uncertainty surrounding their role in predisposing patients to the development of hyponatremia. With an increasing prevalence of hypertension, thiazide utilization will likely continue to increase. Thus, the ability to discern potential risk factors for the development thiazide-induced hyponatremia may offer significant clinical value.

Methods: A retrospective study was conducted on 450 veterans of the age >18 years with hypertension treated with a thiazide/thiazide-like diuretic (chlorthalidone, hydrochlorothiazide, indapamide, metolazone) between March 2004 and November 2014 at the Fargo VA Health Care System.

Results: 404 patients met inclusion criteria. 15% (n=63) of patients developed hyponatremia during treatment period with thiazide therapy. Average time to development of hyponatremia was 2.6 years (+3.3) from index date. Mean Charlson comorbidity scores were higher for those who developed hyponatremia (4.59 vs. 2.90; p < 0.001). Incidence of hyponatremia was found to be higher in patients who were active tobacco users (24.8% vs. 11.3%; p<0.001). Although there was no significant difference in serum creatinine and eGFR between groups, a statistically significant difference in eGFR was found to exist when comparing pre-thiazide eGFR to post-hyponatremia eGFR in those who developed hyponatremia (71 vs. 66; p=0.030). Patients who developed hyponatremia also had a lower serum albumin (3.78 vs. 3.95; p=0.033), and a lower BMI (30.1 vs. 31.8; p=0.035). All other values obtained were similar between groups.

Conclusions: Higher comorbidity index and tobacco use are positive predictors for the development of hyponatremia in patients treated with thiazide/ thiazide-like diuretics.

SA-PO918

Persistent Hyponatremia at 72 Hours in Cancer Patients with Severe Hyponatremia Is Associated with Mortality Independent of Cancer Stage Vesh Srivastava,¹ Xian Wu,² Edgar A. Jaimes,³ Ilya Glezerman.³ ¹Div of Nephrology, NYP-Weill Cornell Medical Center, New York, NY; ²Div of Biostatistics, Weill Cornell Medical College, New York, NY; ³Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Hyponatremia is a common problem and a known independent risk factor for mortality in cancer patients. The impact of rate of correction of sodium on mortality is unknown. The study aim was to determine if the rate of correction in cancer patients with severe hyponatremia (Na < 120 mEq/L) is linked to 90 day mortality.

Methods: Patients with a Na < 120 mEq/L were identified from the Memorial Sloan Kettering Cancer Center database from June 1, 2009 until June 30, 2014. 195 patients were identified. 55 patients were excluded from analysis because less than 72 hours after admission they either died (4), had no follow up data (16), were discharged (21), or made comfort care (14). The final cohort consisted of 140 patients who stayed in the hospital for at least 72 hours and had serial measurements of serum Na.

Results: The mean initial serum Na was 116.7 ± 3.0 mEq/L, the median rate of correction was 6 mEq/L with interquartile range 3-9 mEq/L in the first 24 hours, and the overall 90 day mortality was 39.3%. No patients with Na correction >8 mEq/L in the first 24 hours (n=54) developed osmotic demyelination syndrome. In patients who died within 90 days, the mean serum Na at 72 hrs was 128.3 ± 4.4 mEq/L compared to 130.5 ± 4.9 mEq/L in survivors (p<0.01). When adjusting for cancer stage and rate of correction in a multivariate Cox model, serum Na < 130 mEq/L at 72 hrs was independently associated with 90 day mortality with adjusted HR 2.62 (1.47-4.64, p<0.001).

Conclusions: Cancer patients with severe hyponatremia are at heightened risk for 90-day mortality independent of cancer stage and rate of Na correction if their serum Na at 72 hrs is < 130 mEq/L. Based on this finding we recommend that cancer patients with severe hyponatremia should be corrected to >130 mEq/L at 72 hrs.

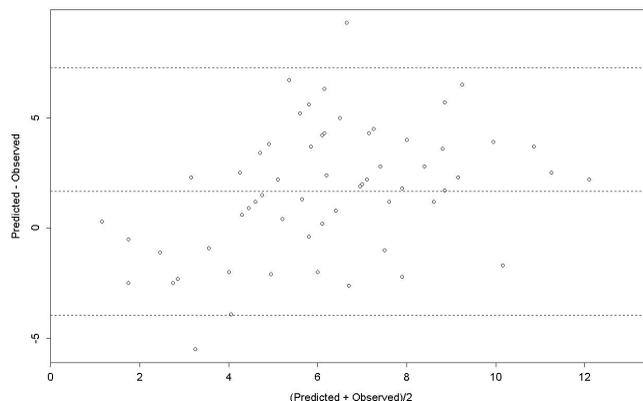
SA-PO919

Hyponatremia Correction Using CRRT: Does Kinetic Modeling Avoid Overcorrection? Saurabh Dasgupta,¹ Lenar T. Yessayan,² Balazs Szamosfalvi,² Sevag Demirjian.¹ ¹Nephrology, Cleveland Clinic, Cleveland, OH; ²Nephrology, Henry Ford Hospital, Detroit, MI.

Background: Hyponatremia is the most common electrolyte abnormality in inpatients. It must be corrected at a gradual rate of < 8 in 24 hrs to minimize the risk of central pontine myelinosis, which can be effectively achieved in patients with renal failure by CRRT. Sodium (Na) kinetic models can predict end dialysis water. A simplified single pool fixed volume kinetic model may be applicable when net Na generation (G) is ~0 mEq/h. Our goal was to measure the correlation of predicted rate of correction by the formula to that observed in ICU patients with hyponatremia treated with CRRT.

Methods: 66 critically ill subjects with serum Na <130 at time of CRRT initiation were retrospectively identified. Median age was 60, and 52% were male. The predominant CRRT modality was CVVHD (97%), using dialysate Na of 140 mmol/L in most patients (92%) with average cumulative dose of 61L, delivered over median duration of 23.2 hrs. Predicted Na correction in the first 24 hours was calculated using a single pool fixed volume kinetic model. The values were then compared to actual measured serum Na using simple correlation, and Bland-Altman plot.

Results: The correlation factor was calculated to be 0.49 with a p value <0.001. The Bland Altman plot (figure) showed a mean difference of 2 mmol/L between the observed and predicted delta Na values, with a trend for overestimation of Na correction as delta sodium levels increased.



Conclusions: In conclusion, observed serum Na correction rates are slower than that predicted by the simplified Na kinetic model, and err on the side of overestimation (avoid overcorrection). The feasibility to verify the model with empiric data is limited because of practical difficulties in estimating Na generation from fluid intake and output and the ability to ascertain TBW in critically ill patient.

SA-PO920

Hemoglobin Level (Hb) Biases the Measurement of Plasma Sodium (Na) by the Direct Ion-Selective Electrode (ISE) Method Andrea Roche-Recinos,¹ Robert H. Barth,² Philip Goldwasser.² ¹SUNY Downstate, Brooklyn, NY; ²VA NY Harbor Healthcare System, Brooklyn, NY; ³VA NY Harbor Healthcare System, Brooklyn, NY.

Background: Na is measured by indirect ISE (iNa) or direct ISE (dNa), on chemistry (chem) and gas panels, respectively. A spurious difference between these assays (DNa = iNa - dNa) can be confusing to the clinician. We recently quantified the negative effect of serum total protein (TP) on iNa (NDT 2015). Red cells have been suggested to interfere with dNa, but both positive and negative interference have been reported (Bijster 1983). In the present study, we examined the effect of gas panel Hb on DNa.

Methods: The data were 772 pairs of closely-timed chem and gas panels (<20 min. apart; median 4 min.), retrospectively collected from our critical care units, excluding hemolyzed/turbid samples, with 1 pair per patient. We used multivariate adjustment for 3 known effects on DNa—TP, bicarbonate (tCO₂), and the chem-gas panel glucose difference (ΔGlu)—and polynomial contrast to test for linear and non-linear trends.

Results: Mean (±SE) values were: Hb, 11.4±0.09 g/dL; DNa, 2.3±0.08 mEq/L. DNa rose across Hb categories (Table); trend analysis showed only a significant linear trend (p<.04). By simple regression, DNa rose 0.06 mEq/L per g/dL rise in Hb (p <.05); this estimate of the Hb effect is confounded, however, as Hb also correlated (p<.001) with TP, tCO₂, and ΔGlu. After adjusting for these confounders, the trend of adjusted DNa across the categories became clearer (Table), with, again, only the linear trend being significant (P<10⁻⁶). By multiple linear regression with the same covariates, DNa rose 0.15±0.03 mEq/L per g/dL rise in Hb (p<10⁻⁶).

Hb Category	Hb mean	N	ΔNa, unadjusted	ΔNa, adjusted
<6	5	17	1.4±0.4	1.2±0.5
6-7.9	7.2	43	1.8±0.3	1.5±0.3
8-9.9	9.1	166	2.3±0.2	1.9±0.2
10-11.9	11	240	2.4±0.1	2.4±0.1
12-13.9	12.9	185	2.4±0.2	2.6±0.2
14-15.9	14.8	82	2.5±0.3	2.8±0.2
≥16	17	39	2.6±0.3	3.1±0.3

Conclusions: Increasing Hb spuriously decreases dNa and increases DNa. A linear correction for this artifact can reduce the discordance between iNa and dNa, promoting their interchangeable use.

Funding: Veterans Administration Support

SA-PO921

HHV-6 Encephalitis Resulting in Cerebral Salt Wasting and Hyponatremia Jonathan A. Ducastel, Uday S. Nori. *Internal Medicine and Nephrology, Ohio State Univ, Columbus, OH.*

Background: Hyponatremia is a common electrolyte abnormality that can be associated with hypo-, hyper-, or euvolemic states. Low circulating volumes secondary to extra-renal losses, fluid overload states, and syndrome of inappropriate ADH are some of the more common causes of hyponatremia. One consideration that is uncommon and often overlooked is cerebral salt wasting (CSW). CSW is defined as “renal loss of sodium during intracranial disorders leading to hyponatremia and a decrease in the extracellular fluid volume.” It occurs in the setting of cerebral injury, most commonly associated with subarachnoid

hemorrhage, but also documented with other disorders of central nervous system. The mechanism of CSW is not completely understood, but is believed that a cerebral injury can lead to impairment of the sympathetic outflow causing primary natriuresis leading to hypovolemia and sodium depletion.

Methods: Here we describe a case of CSW in a patient with human herpes virus-6 (HHV-6) encephalitis. The patient was a 29 year old male with a history of AML who presented with increasing confusion. He was found to have hyponatremia with a sodium of 126 mmol/L, a urine osmolality of 615 mOsm/kg, and a urine sodium of 144 mmol/L. On exam, he had evidence of hypovolemia with dry mucus membranes and orthostatic hypotension. He was initially treated with normal saline IV fluids. He had increasing diuresis with fluid resuscitation, with 6 liters of urine output on hospital day 1. The patient was continued on IV saline with the addition of oral salt supplements and started on fludrocortisone for suspected CSW. His hyponatremia improved and by hospital day #5 was 133 mmol/L. CT and MRI imaging of the head and brain were unremarkable for acute changes or pathology. A serum HHV-6 PCR showed 13,960 copies. He was treated with IV foscarnet with normalization of the serum and CSF PCR within 10 days.

Conclusions: This case is important because the diagnosis of CSW is often confused with SIADH, as both share similar diagnostic criteria such as elevated urine sodium concentration and urine osmolality. The important clinical distinction is the patient, despite having a hypovolemic state would have polyuria and renal sodium wasting.

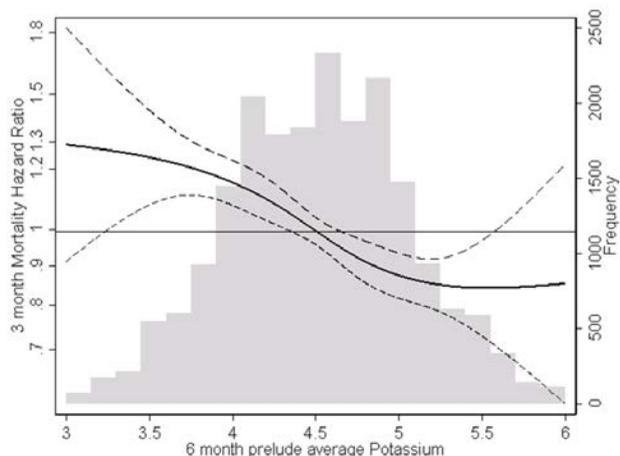
SA-PO922

Association of 6-Month Pre-ESRD Potassium with Immediate Post-ESRD Survival: A Transition to CKD Study Melissa Soohoo,¹ Connie Rhee,¹ Vanessa A. Ravel,¹ Elani Streja,¹ Jennie Jing,¹ Rajiv Saran,² Bruce M. Robinson,² Yi Li,² Danh V. Nguyen,¹ Csaba P. Kovacs,³ Kamyar Kalantar-Zadeh.¹ ¹UC Irvine; ²UM-KECC; ³UTHSC.

Background: Previous studies of the association between serum potassium level and mortality in dialysis patients have suggested that a range of 4.6-5.3 mEq/L portends greatest survival in this population. However, the optimal potassium range in the immediate pre-ESRD prelude period among pre-dialysis CKD patients transitioning to ESRD is not known. We hypothesized that a similar pre-ESRD serum potassium range is also associated with higher survival in this population.

Methods: We investigated a cohort of 20,404 US veterans who initiated dialysis between 10/2007-9/2011 and had at least 1 potassium measurement during the last 6 month period before ESRD transition (6 month-prelude). We examined the association of 6 month averaged potassium as a continuous predictor of all-cause mortality and early post dialysis mortality occurring in the first 3 months after transition using restricted cubic splines and Cox proportional hazard models adjusted for age, gender, race, ethnicity, geographic region and primary cause of ESRD.

Results: The analytic cohort had a mean±SD age of 68±11 years old, among whom 30% were African-Americans, 7% Hispanic and 50% had diabetes as the leading cause of ESRD. The potassium level in the prelude period was 4.5±0.6 mEq/L. Lower potassium levels (3.5-4.0 mEq/L) in the prelude period was associated with highest mortality in the first 3 months after transitioning to dialysis whereas potassium in 4.5-5.5 mEq/L range conferred the greatest early survival.



Conclusions: Lower serum potassium measurements during the final months prior to transition to ESRD are associated with higher early mortality. Whether pre-ESRD potassium should be kept between 4.5 and 5.5 mEq/L in the immediate pre-dialysis transition period warrants additional studies.

Funding: NIDDK Support

SA-PO923

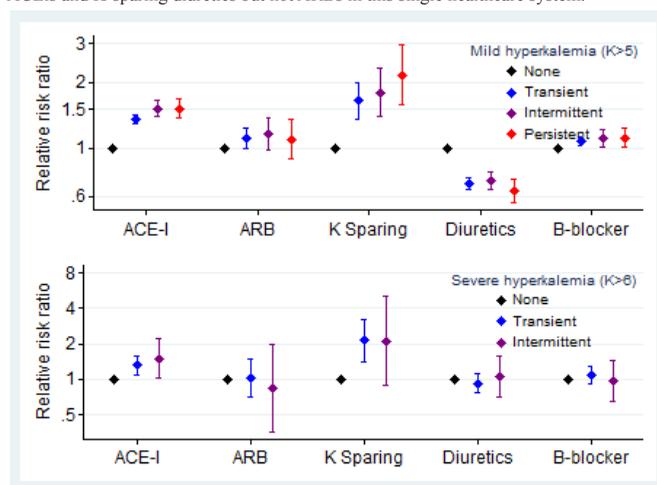
Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Healthcare System Alex R. Chang,¹ Yingying Sang,² H. Lester Kirchner,¹ Kunihiro Matsushita,² Shoshana Ballew,² Josef Coresh,² Morgan Grams.² ¹Geisinger Health System; ²Johns Hopkins Bloomberg School of Public Health.

Background: The association of outpatient medication use with patterns and prevalence of hyperkalemia has not been rigorously examined.

Methods: We evaluated the association between baseline antihypertension medications [angiotensin converting enzyme-inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, loop/thiazide diuretics, and K-sparing diuretics] with the frequency and pattern of mild (>5 mmol/L) and severe hyperkalemia (>6 mmol/L) over a 2 year window in 342,342 outpatients in the Geisinger Health System based on medication prescription orders. Patterns of hyperkalemia were classified as: never, transient (1-time), intermittent (>1-time but <50% of the time), and persistent (≥50% of the time). Analyses were adjusted for demographics, eGFR, systolic blood pressure, diabetes, and history of cardiovascular disease. Interactions between medication types with hyperkalemia risk were also tested.

Results: Potassium levels were checked ≥1 time/yr in 53% of the cohort; 4% had levels checked ≥5 times/yr. Overall, 7.4% had ≥1 episode of mild hyperkalemia; 0.4% had an episode of severe hyperkalemia. Among the different classes of antihypertensives, K-sparing diuretics had the strongest associations with both mild and severe hyperkalemia, followed by ACEis and then beta blockers, which were associated only with mild hyperkalemia (Figure). ARBs had similar effect size to beta blockers but were not statistically significant. Thiazide/loop diuretics were protective against mild hyperkalemia but not severe hyperkalemia. There were no consistent interactions between types of antihypertensive medication for risk of hyperkalemia.

Conclusions: Mild hyperkalemia is relatively common and associated with the use of ACEis and K-sparing diuretics but not ARBs in this single healthcare system.



Funding: Private Foundation Support

SA-PO924

Wide Range in Variation in Serum Potassium in Hyperkalemic Patients with CKD, Response to a Fixed 60 mEq Potassium Diet David A. Bushinsky,¹ Martha Mayo,² Dahlia Garza,² Yuri Stasiv,² Daniel J. Wilson,² Charles Dumond,² Lance Berman,² Murray Epstein.³ ¹Univ of Rochester; ²Relypsa, Inc; ³Univ of Miami.

Background: Serum K(s-K⁺) levels are affected by diurnal variation, fasting/feeding cycles, and medications. In this study we characterized the differences in inter-individual variation in s-K⁺ on a random diet prior to entry and the effect of a controlled K⁺ diet on s-K⁺ levels in hyperkalemic (HK) pts with CKD (stage 2-4) on stable doses of RAASi, during the run-in phase of a treatment trial.

Methods: A total of 27 pts with s-K⁺ ≥5.5 to ≤6.2 mEq/L were monitored in a clinical research unit. At baseline pts were fed a 60 mEq K⁺, 100 mEq Na⁺ diet. S-K⁺ was measured at baseline and at prespecified intervals for the next 72 h. We calculated individual difference (maximum-minimum) in s-K⁺ at each time point for the remaining observation period to determine variation in s-K⁺.

Results: Mean s-K⁺ at baseline was 5.86±0.22 mEq/L and rose to 5.94±0.17 mEq/L at 72 h following the start of the fixed K⁺ diet. Over 72 h, 6/27 pts had “low” (0.0–0.2 mEq/L), 9/27 “moderate” (0.3–0.4 mEq/L), and 12/27 “high” (0.5–1.1 mEq/L) variation in s-K⁺. Variation in s-K⁺ decreased at each time point over the 72-h period of observation on the controlled diet (Table).

Conclusions: A wide range of inter-individual variation in s-K⁺ occurred in HK pts with CKD on RAASi who were on an uncontrolled diet prior to entry. Variation decreased significantly after 24 h on a 60 mEq K diet. These findings have implications for management of pts with HK and CKD, and for interpreting clinical trials assessing directional change in s-K⁺ with an intervention.

Table. Variation in s-K⁺ (max-min) over 72 h during run-in on a 60 mEq K⁺ diet, n=27

Time	baseline	+10 h	+24 h	+36 h	+48 h	+62 h	+71 h
Mean±SD							
Δ in s-K⁺, mEq/L	0.44±0.24	0.42±0.24	0.39±0.24	0.34±0.24	0.29±0.21	0.15±0.12	0.12±0.09
P-value*	-	0.0830	0.0027	0.0001	0.0001	<0.0001	<0.0001

*Comparing values from baseline to values at +10, +24, +36, +48, +62 and +71 h via paired t-test with Bonferroni correction (α=0.05; P ≤ 0.0083 is significant).

Funding: Pharmaceutical Company Support - Relypsa, Inc.

SA-PO925

Best EKG Criteria for Hyperkalemia in Chronic Hemodialysis Patients
 Muzaffar Hussain, Jamr R. Cook, Gregory Lee Braden. Dept of Medicine, Baystate Medical Center/Tufts Univ School of Medicine, Springfield, MA.

Background: To date the effects of hyperkalemia(HK) on the EKG of chronic hemodialysis(CHD) patients(pts) are inconsistent. We studied the EKGs of 128 consecutive CHD pts with clotted grafts or fistulas. EKGs from 46 HK pts > 5.5 mEq/L were compared to 82 pts with normal potassium (NK) levels < 5.5 mEq/L. Pts with RBBB or LBBB or cardiac events within 3 months were already excluded. There were no differences between HK and NK pts for dialysis duration, causes for ESRD, cardiac disease or serum levels of Na, Ca, HCO₃, or phosphorus.

Methods: EKG analysis included: the height & width of the P waves, the T waves in V4 & the T waves in Lead 2, the time intervals of PR, QRS, QT, QTc, PR/QT, PR/QTc, & slopes of ascending & descending T waves in Lead 2 & V4. For the first time ever in HK CHD pts, the EKG measurements in 32 HK pts with complete data were compared to their NK EKGs obtained 3 to 6 months from the HK event.

Results: Univariate stats between the 46 HK & 82 NK pts showed 4 differences in mean values: V4 T wave height 4.0 vs 2.9 mm, Lead 2 T wave height 2.7 vs 2.0 mm, & the V4 T wave ascending (.03 vs .02) and descending slopes (.04 vs .03). Multivariate analysis for all clinical & EKG findings between HK & NK pts found only the increased height of the T wave in V4 was significant, p<.05. In contrast, the EKG analysis of the HK pts to their NK EKGs revealed more differences: higher T wave height in V4, 5.0 vs 3.7 mm, higher T wave height in Lead 2, 4.0 vs 2.7 mm, shorter width of T wave in V4, 2.4 vs 4.1 ms or Lead 2, 2.1 vs 4.1 ms, longer PR 188 vs 167 ms, & steeper slopes in the T waves in Lead 2 and V4. Regression analysis of the change in potassium from NK to HK to each EKG measurement showed that the only significant correlation was to the width, (r = -.433, p=.007) & height of the T wave in V4, r = .333, p=.03. In these HK CHD pts T wave tenting in V4 was now present in 56 %.

Conclusions: We conclude: 1) Comparison of a NK EKG to a HK EKG in CHD pts significantly helps to confirm HK EKG changes in CHD pts. 2) A shortened width and an increased height of the T wave in V4 are the most important HK EKG changes in CHD pts.

SA-PO926

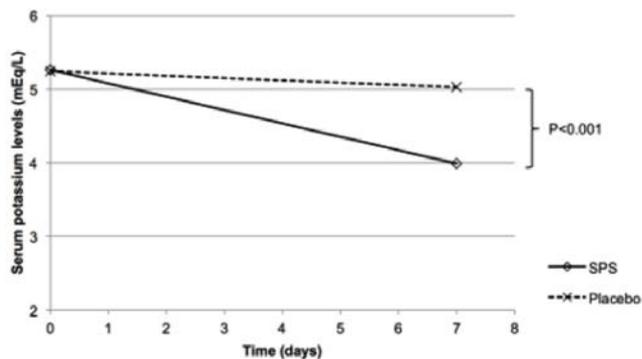
Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in Chronic Kidney Disease: A Randomized Clinical Trial
 Katherine Desforges, Laurence Lepage, Anne-Claude Dufour, Jessica Doiron, Katia Handfield, Robert Zoel Bell, Michel Vallee, Michel Savoie, Sylvie Perreault, Louis-Philippe Laurin, William Beaubien-Souigny, Vincent Pichette, Jean-Philippe Lafrance. Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada.

Background: Hyperkalemia affects up to 10% of patients with chronic kidney disease (CKD). Sodium polystyrene sulfonate (SPS) has long been prescribed for this condition even though evidence is lacking on its efficacy for the treatment of mild hyperkalemia over several days.

Methods: The aim of this double-blind, randomized trial was to evaluate the efficacy of SPS in the treatment of mild hyperkalemia (5.0 to 5.9 mmol/L) in pre-dialysis outpatients. We randomly assigned 33 patients on stable medication to receive either SPS or placebo 30g orally once a day for 7 days. Patients had to be on stable medication to be eligible for the study. The primary outcome was the comparison between study groups of the mean difference of serum potassium levels between the day following the last dose of treatment and baseline.

Results: The mean duration of treatment was 6.9 days. SPS was superior to placebo in the reduction of serum potassium levels (mean difference between groups of -1.04 mmol/L; 95%CI: -1.37 to -0.71). A higher proportion of patients in the SPS group tended to attain normokalemia (defined as a serum potassium level of at least 3.5 mmol/L and less than 5.0 mmol/L) at the end of their treatment compared to the placebo group (73% vs 38%, P=0.07). Patients in the group treated with SPS had an increase in hypomagnesemia, hypocalcemia, constipation and nausea compared to the control group.

Conclusions: SPS is superior to placebo in the treatment of mild hyperkalemia over seven days in CKD patients. Its use was generally well tolerated in our study population, but does require monitoring of gastrointestinal side effects and electrolytic disorders.



Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO927

Assessment of Systemic Absorption of Sodium Zirconium Cyclosilicate (ZS-9): Blood and Urine Zr Concentration in Dogs During a 9-Month Oral Toxicity Study
 Fiona Stavros, Henrik S. Rasmussen, Bhupinder Singh, Jose A. Menoyo. ZS Pharma, Inc., Coppell, TX.

Background: Hyperkalemia (HK; potassium [K⁺] ≥5.1 mEq/L) is a common and potentially life-threatening electrolyte disorder often occurring in patients with chronic kidney disease, heart failure and diabetes. Sodium zirconium (Zr) cyclosilicate (ZS-9), a potential HK therapy, is a selective K⁺ ion trap containing covalently bound Zr atoms within an insoluble 25µm particle. Zr has a long history as an inert substance used in biomedical implants and dialysis, and is present in normal diets and household items. Systemic absorption of Zr is expected to be minimal given the low solubility and particle size of ZS-9. Here we present Zr concentration data from urine and whole blood samples from ZS-9 treated dogs to assess systemic absorption of long-term, high-dose ZS-9.

Methods: Beagle dogs received Control (n=10/sex) or high-dose ZS-9 (2000 mg/kg/day, n=10/sex). Blood samples were collected by venipuncture at baseline, and Weeks 6, 13, 26, and 39. Urine samples were collected directly from the bladder at necropsy (Week 39) and recovery (Week 43). Zr levels in Control and ZS-9 treated dogs were determined using inductively coupled plasma mass spectrometry with a lower limit of quantification (LLOQ) of 10 ng/mL (ppb) for both whole blood and urine. The analytical method was designed to measure the presence of both free Zr and ZS-9 bound Zr.

Results: Zr was below the LLOQ in all dog urine samples (N=28) and in all but one Control group whole blood sample (N=226). The one dog in the Control group had a blood Zr level of 10.9 ng/mL at Week 26.

Treatment Group	ZS-9 Dose Level (mg/kg/day)	Blood Zr concentration >LLOQ, n (N=226)	Urine Zr concentration >LLOQ, n (N=28)
Control	0	1	0
High ZS-9	2000	0	0

Conclusions: There was no detectable Zr or increase in Zr in blood and urine samples following 39 weeks of 2000 mg/kg/day ZS-9 treatment; equivalent to a human dose of ~65 g/day. Zr was detected in one non ZS-9 treated animal. These results demonstrate an absence of systemic ZS-9 absorption after long-term, high-dose treatment in beagle dogs.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

SA-PO928

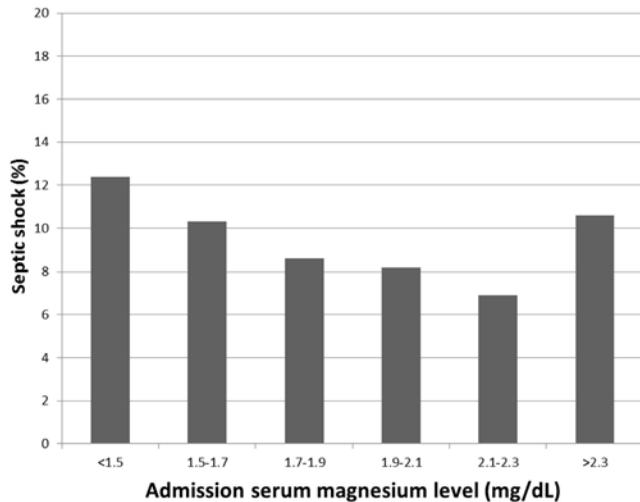
Admission Hypomagnesemia Linked to Septic Shock in Patients with Systemic Inflammatory Response Syndrome
 Wisit Cheungpasitporn,¹ Charat Thongprayoon,² Stephen B. Erickson.¹ ¹Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Internal Medicine, Bassett Medical Center, Cooperstown, NY.

Background: The association between admission serum magnesium (Mg) levels and risk of developing septic shock in patients with systemic inflammatory response syndrome (SIRS) is limited. The aim of this study was to assess the risk of developing septic shock in hospitalized patients with SIRS with various admission Mg levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients with SIRS at admission who had admission Mg available from January 2009 to December 2013 were analyzed in this study. Admission Mg was categorized based on its distribution into six groups (<1.5, 1.5 to 1.7, 1.7 to 1.9, 1.9 to 2.1, 2.1 to 2.3, and >2.3 mg/dL). The primary outcome was septic shock occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of septic shock of various admission Mg levels using Mg with lowest incidence of shock, 2.1 to 2.3 mg/dL as the reference group.

Results: Of 2,589 patients with SIRS enrolled, septic shock occurred in 236 patients (9.1%). The lowest incidence of septic shock was when serum Mg was within 2.1-2.3 mg/dL. A reverse-checkmark curve emerged demonstrating higher incidences of septic shock

associated with both hypoMg (<2.1) and hyperMg (>2.3). After adjusting for potential confounders, hypoMg (<1.5 mg/dL) was associated with an increased risk of developing septic shock with odds ratios of 1.86 (95% CI 1.07-3.27).



Conclusions: Patients with SIRS and hypoMg (<1.5mg/dL) at the time of admission had increased risk of developing septic shock during hospitalization.

SA-PO929

Risk Factors for Calcium-Alkali Syndrome in Post-Surgical Hypoparathyroidism Sayaka Kuroya, Masahiko Yazawa, Naoto Tominaga, Yugo Shibagaki. *Nephrology and Hypertension, St. Marianna Univ, Kawasaki, Kanagawa, Japan.*

Background: Post-surgical hypoparathyroidism is a common complication of total thyroidectomy. Patients complicated by permanent hypoparathyroidism often require either or both calcium or vitamin D supplement therapy to maintain serum calcium levels, and long-term therapy can lead to calcium-alkali syndrome (CAS). We examined the incidence rate, magnitude, and risk factors of CAS in patients being treated for post-surgical hypoparathyroidism.

Methods: We retrospectively observed 27 patients with neck tumors who had undergone total thyroidectomy with total parathyroidectomy without autotransplantation between January 2010 and October 2013 at St. Marianna University Hospital. All patients received calcium lactate and alfacalcidol. Medical records were reviewed for historical, clinical, laboratory and imaging data. Definitions were as follows: hypercalcemia, corrected serum calcium (cCa) ≥ 10.0 mg/dL; acute kidney disease (AKD), either or both $>50\%$ increase in serum creatinine (sCr) or $>35\%$ decrease in estimated glomerular filtration rate (eGFR); and metabolic alkalosis, difference in serum sodium (sNa) and serum chloride (sCl) >38 . Data were expressed as mean \pm standard deviation (SD). For statistical analysis, the paired t test, Student's t test, and chi-square test were used to compare two matched variables when appropriate. $P < 0.05$ was considered statistically significant.

Results: Average duration between surgery and reaching peak cCa level was 392.7 ± 403.8 days, with levels peaking at 11.1 ± 1.5 mg/dL. All patients tended to have significantly higher cCa and sCr levels and difference in sNa and sCl after surgery than at baseline ($p < 0.01$). Nineteen patients (70.3%) had hypercalcemia, 9 (33.3%) had AKD, and 7 (36.9%) had CAS. Calcium lactate dosage was significantly associated with hypercalcemia and AKD ($p < 0.01$). Higher doses of alfacalcidol tended to increase incidence of hypercalcemia and AKD, although not significantly so.

Conclusions: CAS in post-surgical hypoparathyroidism was common, and dosage of calcium supplement was correlated with CAS. cCa levels and kidney function should be closely monitored in patients with post-surgical hypoparathyroidism.

SA-PO930

Body Temperature Rise in the Cell-Free and Concentrated Ascites Reinfusion Therapy Is Correlated to Albumin Concentration Rather Than the Interleukin-6 Levels in the Ascites Noriaki Maruyama, Masanori Abe, Kazuyoshi Okada. *Div of Nephrology, Hypertension and Endocrinology, Dept of Internal Medicine, Nihon Univ School of Medicine, Tokyo, Japan.*

Background: There is a fever as a side effect of Cell-free and Concentrated Ascites Reinfusion Therapy (CART). Cytokines in ascites after concentration is thought to be involved in the generation of heat after intravenous injection. To examine the fever related factors, we examined the relationship between inflammatory cytokines levels, total protein (TP), albumin (ALB) in peritoneal fluid and the heating after intravenous injection.

Methods: In this study, we have measured interleukin-1 β (IL-1 β), interleukin-6 (IL-6), TP, ALB concentration in the ascites fluid before and after concentrated, and observed vital changes in the patient before and after intravenous injection. A total of 8 patients with refractory ascites were studied.

Results: IL-1 β was detected in ascites prior to concentration of the two cases, it could not be measured in the other specimen. IL-6 is present in high concentrations in all ascites

before concentration (mean 4218.75 pg/mL), it was further increased after concentration (mean 6508.75 pg/mL). Although body temperature rise was observed after the intravenous injection of concentrated ascites in six out of eight, IL-6 concentration in the ascites fluid ($r = 0.61063$; $P = 0.114$), the total dose of IL-6 ($r = 0.06755$; $P = 0.436$), dose rate ($r = 0.2876$; $P = 0.244$) was no obvious correlation between the body temperature rise. On the other hand, respectively in the TP concentration and the ALB concentration of ascites, it was found correlated with body temperature rise after intravenous injection. In particular, a strong correlation between the ALB concentration and the increase in body temperature was observed ($r = 0.8033$; $P < 0.01$).

Conclusions: The correlation of body temperature rise after intravenous injection and IL-6 is weak, while the correlation between the concentrated ALB and body temperature rise was very strong. From these results, we considered that any substance bound to the ALB or ALB itself are associated with elevated body temperature.

SA-PO931

Contrast-Related Hyponatremia: What We Could Be Missing Christine Joy C. Junia, Kalyani Perumal. *Internal Medicine, John H. Stroger Jr. Hospital, Chicago, IL.*

Background: Hyponatremia is a commonly encountered electrolyte abnormality. Long-established algorithms outline etiology and management guiding physicians to prevent neurologic sequelae. Close electrolyte monitoring is emphasized in acute hyponatremia due to higher morbidity and mortality. Contrast-related hyponatremia is an etiology of acute onset hyponatremia that is not routinely monitored and may easily be missed.

Methods: A 76 year-old woman with hypertension, diabetes and chronic kidney disease (CKD) III, eGFR of 44 was admitted for asthma exacerbation and received beta-agonist nebulizers and oral prednisone. Her home medications-Amlodipine and Insulin were restarted. She was tachypneic and wheezing, the rest of the physical exam was normal. Laboratory tests on admission: Na 135 meq/L, K 4.4 meq/L, BUN 11 mg/dL, Creatinine 1.2 mg/dL, and normal urinalysis. An elevated D-Dimer prompted evaluation with CT Chest with contrast Omnipaque 350 (840 mosm/kg) to rule out pulmonary embolism. Her symptoms improved, however her sodium dropped from 135 to 122 meq/L 48 hours after chest CT, creatinine 1.4 mg/dL. Work-up revealed plasma osmolality of 297 mosm/kg, osmolal gap of 30. On the 4th and 5th hospital day, sodium levels were stable at 125 meq/L and 124 meq/L respectively. Her sodium on Day 8 improved to 133 meq/L without any intervention.

Conclusions: The 2014 USRDS data reports a rise in prevalence of CKD III from 4.5 to 6.0 percent. Primary care doctors manage 80 to 90 percent of these patients. There is a simultaneous rise in diagnostic imaging. Over the past decade, CT Scan use in the emergency departments has increased over 200-300%. There are a few case reports of contrast-related hyponatremia, occurring mostly in patients with advanced CKD with eGFR < 30 . A consistent finding was the acute onset and an average drop in sodium of 12 meq/dL. Contrast hypertonicity generates a fluid shift and a dilutional effect on extracellular sodium. This is usually offset by osmotic diuresis that is impaired in chronic kidney disease. Our case highlights contrast-related acute hypertonic hyponatremia in the setting of mild kidney disease, a high-risk patient population that may benefit from post-diagnostic electrolyte monitoring.

SA-PO932

A Role for NHE3 in Renal Sodium and Acid-Base Handling in the Early Proximal Tubule and Further Downstream Segments Akira Onishi,¹ Yiling Fu,¹ Panai Song,¹ Meinrad Busslinger,² Manoocher Soleimani,³ Isabelle Rubera,⁴ Michel Tauc,⁴ Volker Vallon.¹ *¹Div of Nephrology, UC San Diego & VA San Diego Healthcare System, La Jolla, CA; ²Research Inst of Molecular Pathology, Vienna, Austria; ³Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; ⁴Univ de Nice Sophia Antipolis, Nice, France.*

Background: Systemic Na⁺/H⁺ exchanger 3 (NHE3) knockout in mice lowered blood pressure (BP) and induced metabolic acidosis, however, the role of intestine vs kidney and early proximal tubules (PT) vs downstream segments is unclear.

Methods: Male mice with floxed NHE3 expressing Cre recombinase under the control of i) the SGLT2 promoter to knockdown NHE3 in the early PT (SGLT2-Cre/NHE3^{fl/fl}, n=10) or ii) the Pax8 promoter for knockdown along the entire tubular system (Pax8-Cre/NHE3^{fl/fl}, n=9) were compared with corresponding Cre-negative controls (n=10 and 7). Blood and spot urine samples were collected, BP measured by automated tail cuff and arterial cannulation, and GFR by inulin clearance.

Results: Urine Na/creatinine (cr) ratios were higher in Pax8-Cre/NHE3^{fl/fl} vs controls (40 ± 5 vs 28 ± 2 , $P < 0.05$) but not significantly different in SGLT2-Cre/NHE3^{fl/fl} vs controls (31 ± 2 vs 27 ± 3). Urine pH and HCO₃⁻/cr ratio were strongly increased in Pax8-Cre/NHE3^{fl/fl} vs controls (7.83 ± 0.11 vs 6.44 ± 0.22 ; 15.5 ± 3.1 vs 0.55 ± 0.34 , each $P < 0.01$), and only modestly higher in SGLT2-Cre/NHE3^{fl/fl} vs controls (6.50 ± 0.15 vs 6.12 ± 0.13 , $P = 0.07$ and 0.45 ± 0.20 vs 0.14 ± 0.03 , $P = 0.16$). Urine pH and HCO₃⁻ were significantly higher in Pax8-Cre/NHE3^{fl/fl} vs. SGLT2-Cre/NHE3^{fl/fl} (each $P < 0.05$). Blood pH and HCO₃⁻ were not different between any groups. Based on the stronger phenotype, BP and GFR were determined in Pax8-Cre/NHE3^{fl/fl} and their controls and found to be similar. Urine protein/cr ratios were doubled in both knockdown mice vs their controls (Pax8-Cre: 32 ± 3 vs 17 ± 2 ; SGLT2-Cre: 22 ± 2 vs 10 ± 1 , each $P < 0.01$).

Conclusions: Tubule-specific NHE3 knockdown increased urine pH and excretion of sodium, HCO₃⁻ and protein without metabolic acidosis. Comparison of the Cre models is consistent with a role of NHE3 in urinary acidification and reabsorption of sodium and bicarbonate in the early PT as well as in further downstream segments.

Funding: NIDDK Support, Veterans Administration Support

SA-PO933

Effect of NBCe1 Deletion on Renal Ammonia Metabolism I. David Weiner,^{1,2} Mary E. Handlogten,¹ Gunars Osis,¹ Hyun-Wook Lee,¹ Jill W. Verlander.¹
¹Renal Div, Univ of Florida, Gainesville, FL; ²Nephrology Section, NF/SGVHS, Gainesville, FL.

Background: Metabolic acidosis typically increases renal ammonia excretion, but people with proximal renal tubular acidosis (pRTA), despite the associated metabolic acidosis, do not have increased ammonia excretion. Genetic forms of human pRTA typically involve the proximal tubule bicarbonate transporter, NBCe1. Based on these observations, we postulated that NBCe1 has a role in renal ammonia metabolism that is in addition to its role in bicarbonate reabsorption.

Methods: We used previously reported mice with NBCe1 deletion. Because $-/-$ mice have 100% mortality between d10-21, we studied mice at d8 \pm 1. Wild-type (WT), heterozygous (HET) and homozygous knock-out (KO) mice were generated by breeding HET male and female mice.

Results: Serum HCO₃ was 26.4 \pm 1.0 in WT, 19.8 \pm 1.9 in HET, and 10.3 \pm 0.6 mM in KO mice (P<0.05). Thus, NBCe1 deletion causes metabolic acidosis at d8. Although acidosis normally increases ammonia excretion, NBCe1 deletion decreased spontaneous ammonia excretion: 275 \pm 44, 212 \pm 11 and 94 \pm 69 mmol/g creatinine in WT, HET and KO mice, respectively (P<0.01). Serum Na and K were unchanged. Urine pH was 5.3 \pm 0.2, 4.8 \pm 0.1 and 4.2 \pm 0.1 in WT, HET and KO mice, respectively (P<0.01), indicating intact urine acidification and no ongoing HCO₃ loss. NBCe1 deletion did not alter urine osmolality significantly (WT, 596 \pm 74; HET, 693 \pm 51; and, KO, 726 \pm 34 mOsm/kg H₂O; P=NS), which, in combination with intact urine acidification, suggests intact collecting duct function. The regulation of multiple proteins involved in ammonia metabolism was atypical of acidosis. NBCe1 deletion decreased expression of PDG and PEPCK and increased expression of the ammonia recycling enzyme, glutamine synthetase. This pattern is the exact opposite of that expected with acidosis. Expression of the TAL ammonia transporter, NKCC2, and the collecting duct ammonia transporters, Rhbg and Rhcg, was unchanged.

Conclusions: We conclude: 1) NBCe1 deletion significantly alters proximal tubule ammonia metabolism, leading to decreased urinary ammonia excretion; and, 2) NBCe1, in addition to its role in HCO₃ transport, may have an important role in ammonia metabolism.

Funding: NIDDK Support, Veterans Administration Support

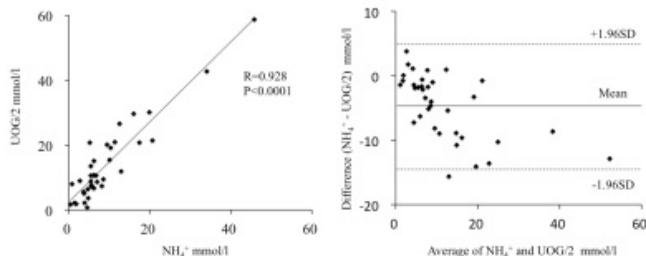
SA-PO934

Assessing Urine Ammonium Concentration by Urine Osmolal Gap in Chronic Kidney Disease Takuya Fujimaru, Yasuhiro Komatsu, Takuya Shuo.
Nephrology, St. Luke's International Hospital, Tokyo, Japan.

Background: Acidemia is one of the risk factor for end stage kidney disease and mortality for patients with chronic kidney disease (CKD). Although ammonium is the crucial component of renal acid excretion, measurement of urine ammonium concentration (NH₄⁺) is not routinely available in most hospital laboratories. To estimate NH₄⁺, urine osmolal gap (UOG = urine osmolality - [2(Na⁺ + K⁺) + urea + glucose]) is calculated and the formula (NH₄⁺ = UOG/2) has traditionally been used. However, studies evaluating it in CKD patients are scarce. The present study aims to assess the relationship between NH₄⁺ and UOG in CKD patients.

Methods: Spot urine samples were collected from 36 patients with CKD in our hospital (24 males, age 41-96 years, serum creatinine 0.9-12.4 mg/dl). We measured urine pH, Na⁺, K⁺, Cl⁻, urea, glucose and NH₄⁺. NH₄⁺ was measured by colorimetric assay (modified Fujii-Okuda method). The Bland-Altman plot was used to evaluate the agreement between NH₄⁺ and UOG/2.

Results: NH₄⁺ ranged from 0.3-45.8 mmol/l (median, 6.2 mmol/l). UOG/2 correlated positively and significantly with NH₄⁺ (r=0.928, p<0.0001).



The mean difference between UOG/2 and NH₄⁺ was 4.7 mmol/l, and the 95% limits of agreement were -5.0 mmol/l and 9.6 mmol/l.

Conclusions: UOG is an accurate method to estimate NH₄⁺ in CKD patients and can be used to assess urinary acidification ability in CKD patients.

SA-PO935

Vacuolar H⁺-ATPase Regulation by 14-3-3 Proteins Nuria M. Pastor-Soler,¹ Mohammad M. Al-bataineh,³ Hui Li,¹ Vivek Bhalla,² Kenneth R. Hallows.¹
¹Medicine, Div of Nephrology, Keck School of Medicine of USC, Los Angeles, CA; ²Medicine, Div of Nephrology, Stanford School of Medicine, Palo Alto, CA; ³Medicine, Renal-Electrolyte Div, U. of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: The vacuolar proton-ATPase (V-ATPase) is highly expressed at the apical membrane of type A intercalated cells (ICs) in the collecting duct. This pump mediates proton transport across a membrane often against a gradient. Defects in V-ATPase function can lead to renal tubular acidosis. In kidney cells we showed that the metabolic sensor AMP-activated protein kinase (AMPK) phosphorylates the V-ATPase A subunit at Ser-384. AMPK regulates some transport proteins by inhibiting their function and promoting their ubiquitination and degradation. These mechanisms are likely important for inhibition of the membrane transport during cellular metabolic stress. We noticed that Ser-384 exists within a 14-3-3 binding motif. Dimeric 14-3-3s bind to phosphorylated sites on target proteins and modulate protein function. We hypothesized that phosphorylation by AMPK and an additional kinase modulate A subunit binding to 14-3-3 proteins and A subunit ubiquitination.

Methods: We used transient transfections of V-ATPase A subunit mutants in Clone C ICs, followed by immunoprecipitation and immunoblotting.

Results: We have preliminary evidence that phosphorylation at Ser-384 and a new "Site III" in the V-ATPase A subunit are required for 14-3-3 binding. For example, 14-3-3 binding to the A subunit increased when we used a phosphomimetic mutant (Ser-to-Asp) at Site III compared to the WT sequence at that site, and this binding was not dependent of the presence of the AMPK activator AICAR. Furthermore, AICAR increased A subunit ubiquitination as compared to untreated cells.

Conclusions: We propose that V-ATPase A subunit binding to 14-3-3s promotes its ubiquitination and degradation. These pathways are downstream of phosphorylation of the A subunit at Ser-384 by AMPK and at Site III by another unidentified kinase. Our results link downregulation of the V-ATPase to metabolic depletion in kidney epithelial cells.

Funding: NIDDK Support

SA-PO936

Albuminuria Enhances Renal NHE3 Expression via the Activation of Mitochondrial Oxidative Stress/RAS Axis Aihua Zhang,^{1,2} Yibo Zhuang,¹ Guixia Ding,¹ Songming Huang,¹ Zhanjun Jia.^{1,2} *¹Nephrology Dept, Nanjing Children Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China; ²Nanjing Key Laboratory of Pediatrics.*

Background: Renal sodium-hydrogen exchanger 3 (NHE3) plays a known role in the reabsorption of bicarbonate and fluid. As a result, NHE3 is thought to be important in acid base balance and vascular volume homeostasis. The present study was to investigate the role albuminuria in regulating renal NHE3 expression as well as the underlying mechanisms.

Methods: An albumin overload mouse model was established by i.p injection of albumin. The mouse kidney tissues and kidney biopsy specimens from proteinuric patients were analyzed.

Results: Following 12-day albumin overload, we found that albuminuria increased NHE3 expression by 2-fold in mouse kidneys determined by Western blotting and qRT-PCR. Considering the known role of renin-angiotensin system (RAS) in modulating renal sodium transporters, we examined key components of RAS and found a striking elevation of angiotensinogen (AGT, +2.1 folds), angiotensin converting enzyme (ACE, +3.3 folds), and urinary angiotensin II (Ang II, +70%) output determined by Western blotting or ELISA. In proteinuric patients, we detected a 1.9-fold upregulation of NHE3 and 3-fold increase of ACE by immunohistochemistry in line with a 2-fold increment of urinary Ang II excretion. To further investigate the role of RAS in upregulating NHE3, we performed primary cultures of renal tubular cells and observed that albumin directly enhanced NHE3 accompanied by stimulated AGT/ACE/Ang II cascade, which was entirely abolished by ACE inhibitor captopril, indicating a key role of RAS in mediating albuminuria effect on NHE3 upregulation. More interestingly, albumin overload significantly induced mitochondrial oxidative stress evidenced by reduced mitochondrial superoxide dismutase (SOD2, -60%) and elevated ROS production. Notably, a SOD2 mimic (MnTBAP) completely normalized NHE3 upregulation and activated AGT/ACE/Ang II cascade in mice with albumin overload.

Conclusions: These results suggest that albuminuria is of vital importance in upregulating renal NHE3 expression in proteinuric patients via mitochondrial oxidative stress-initiated stimulation of AGT/ACE/Ang II cascade.

Funding: Government Support - Non-U.S.

SA-PO937

ATP6v1b1 Haploinsufficiency Lead to a Mild Incomplete Renal Tubular Acidosis (RTA) in Mice Soline Bourgeois, Carsten A. Wagner. *Inst of Physiology, Univ of Zurich, Zurich, Switzerland.*

Background: Mutations in ATP6V1B1 gene in man is considered as an autosomal recessive disease and lead to distal RTA by dysfunction of the B1 subunit of H-ATPase in type A intercalated cells. B1 subunit ablation in mouse causes also distal RTA with a decrease in ammonuria and alkaline urine pH.

Methods: Here we investigated on littermate mice whether ATP6v1b1^{+/}-mice also develop acid-base disturbances during an acute and chronic acid challenge performed by 0.2 M HCl added to powdered standard food.

Results: ATP6v1b1^{+/+} (WT) and ^{-/-} (HET) mice exhibited no difference in their blood and urine parameters under baseline conditions. During the acid challenge, while ATP6v1b1^{-/-} mice (KO) developed alkaline pH and low ammoniuria with hypercalciuria, HET mice showed no difference in their urine data over the whole acid load compared to WT mice. However, even though, HET mice did not exhibit low blood pH, as KO mice, they had a lower bicarbonatemia, higher chloremia and lower pCO₂ compared to WT mice at the end of the acid challenge. Both KO and HET mice drank more than WT mice over the acid load with a tendency to urinate more. After 4 days of acid load, subcellular localization of the a4 and B2 subunits of H-ATPase were not different within the 3 strains of mice and WT and HET mice exhibited the same localization of B1 subunit. However, western blot analysis of B1 and B2 expression in renal membrane fractions revealed a 2-fold decrease of B1 and B2 protein expression in HET mice compared to WT mice and no difference in the expression of B2 protein in KO mice compared to WT mice while B1 protein was totally absent from KO kidneys.

Conclusions: In conclusion, 1) HET mice developed a mild incomplete RTA during an acid challenge, undetectable regarding urine parameters. The RTA is partly compensated by the respiration and an increase in water consumption. 2) B2 subunit does not compensate for the decrease in B1 expression both in HET kidney tissues and seems to be inhibited by acid load.

Funding: Government Support - Non-U.S.

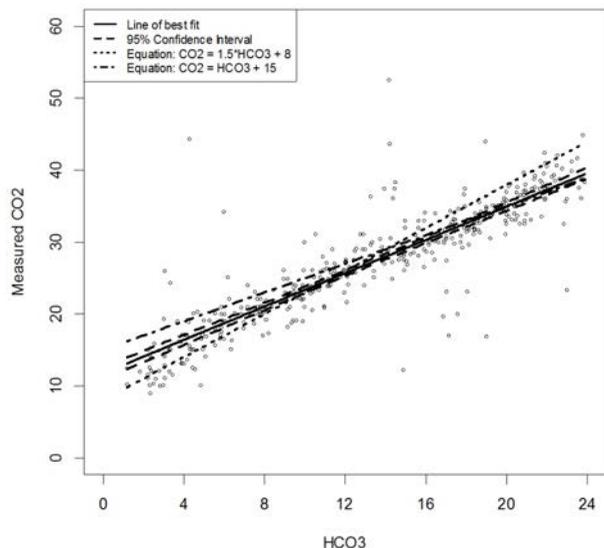
SA-PO938

Beside Rule (pCO₂=HCO₃+15) Is Reliable in Predicting Respiratory Response in Metabolic Acidosis with Bicarbonate Levels of More Than 7 meq/L Mohammad Kazem Fallahzadeh, Michael Emmett. *Dept of Internal Medicine, Baylor Univ Medical Center, Dallas, TX.*

Background: There is controversy about the reliability of the bedside rule (pCO₂=HCO₃+15) in prediction of respiratory response in metabolic acidosis. The aim of our study was to compare the accuracy of the bedside rule with Winter's equation in predicting respiratory response in metabolic acidosis.

Methods: We extracted the measured bicarbonate and pCO₂ levels of 382 patients with metabolic acidosis from the previously published articles evaluating the respiratory response to metabolic acidosis. We calculated the predicted levels of pCO₂ by bedside rule and Winter's equation for each patient. Then we compared the accuracy of these formulas in predicting the respiratory response to metabolic acidosis.

Results: As demonstrated in the figure 1, the values calculated by bedside equation (pCO₂=HCO₃+15) appear to be a reliable predictor of respiratory response in HCO₃ levels of more than 7 meq/L, as compared with the line of best fit and Winter's equation.



Conclusions: Our results show that bedside rule (pCO₂=HCO₃+15) is reliable in predicting respiratory response in metabolic acidosis with HCO₃ levels of more than 7 meq/L.

SA-PO939

TSS-Seq Analysis of Low pH-Induced Gene Transcripts in the Intercalated Cells of the Collecting Ducts Yuichiro Izumi,¹ Koji Eguchi,¹ Terumasa Nakagawa,¹ Yushi Nakayama,¹ Hideki Inoue,¹ Yutaka Kakizoe,¹ Takashige Kuwabara,¹ Hiroshi Nonoguchi,² Masashi Mukoyama.¹ *¹Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Japan; ²Dept of Internal Medicine and Education & Research Center, Kitasato Univ Medical Center, Japan.*

Background: Metabolic acidosis is caused by acute and chronic kidney disease due to the decrease of acid excretion in the intercalated cells of the collecting duct in the kidney. Although the effect of acidosis on renal function has been examined *in vivo*, direct effect of low pH on the intercalated cells has not been investigated.

Methods: We employed Transcription Start Site-Sequencing (TSS-Seq) to provide low pH-induced gene transcripts in a rat intercalated cell line (IN-IC cells). Two biological replicates were used for the analysis. Cells were grown in a FBS-free DMEM/F12 overnight and incubated in an isotonic solution for 24h in which pH was adjusted either to 7.4 or 7.0, then total RNA was extracted. cDNA library for CAGE (Cap Analysis Gene Expression) was created. Deep sequencing was performed by Illumina HiSeq2500 sequencer. TopHat 2 software was used to map TSS-Seq reads. RECLU was used to identify differentially expressed transcripts. Gene Ontology (GO) analysis was carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: 278 differentially expressed transcripts were identified. 261 transcripts were upregulated and 17 were downregulated. Among them, 225 upregulated and 13 downregulated transcripts were corresponded to known protein products. GO analysis of Biological Processes and Molecular Functions showed 9 clusters of the GO terms with high enrichment score (> 1.5) such as regulation of transcription, dephosphorylation, and enzyme-linked receptor protein signaling pathway. The upregulated transcripts included Jak2, Pten, and Gsk3a, that are involved in renal fibrosis and urine concentration mechanism.

Conclusions: The results suggest that metabolic acidosis could regulate the function of intercalated cells and further exacerbate the renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO940

Narrowing the Gap Between the Anion Gap and the Strong Ion Gap Kenrick Berend,¹ Andrew L. Lundquist.² *¹Nephrology, St. Elisabeth Hospital, Willemstad, Curacao, Netherlands Antilles; ²MGH Div of Nephrology, Massachusetts General Hospital, Boston, MA.*

Background: Despite its importance in understanding acid-base pathophysiology, many physicians do not understand the concept of the strong anion gap. The core of the Stewart acid-base approach is the "strong ion gap" (SIG). The concept of SIG is similar to the AG, but the main difference is that Stewart uses more strong ions and the contribution of albumin and phosphate are adjusted for the pH. Because SIG gives a more precise picture of the ion balance than the AG, one may postulate that it provides a more accurate analysis of acid-base disturbances. The exact differences, however, are not established. This paper will give insight into the difference between the anion gap and the strong anion gap and provide an adjusted formula for the anion gap to replace the need for the strong anion gap.

Methods: The change of the strong ion gap (SIG) and the albumin-corrected anion gap (AG_c) were calculated at a wide range of albumin, phosphate and pH levels.

Results: At a low albumin level of 1 to 3 g/dl and decreased pH from 6.9 to 7.3, the contribution difference of albumin in AG_c and SIG will be maximally -0.97 to 0.51 mEq/L. In metabolic alkalosis (pH up to 7.6) and hypoalbuminaemia (1 to 3 g/dl), the AG_c differs less than 2 mEq/L with SIG. There is a linear relationship of the serum phosphate and the ionic contribution of SIG: at a pH of 6.9, the phosphate_{SIG} is 1.66 times higher and at a pH of 7.6, 1.86 higher. In metabolic alkalosis and moderate hyperphosphatemia, the ionic contribution to the anion gap will increase, but less than 1 mEq/L.

Conclusions: SIG and AG_c are almost identical across a wide range of values, particularly when albumin and phosphate levels are low. The pH adjusted serum phosphate level in the SIG is about 1.76 higher, with a confidence interval of +0.5 mmol/L. The anion gap will be more precise and incorporate the major components of the SIG when using the equation: [Na⁺] - [Cl⁻] - [HCO₃²⁻] - 2.5 [albumin, in g/dL] - 1.76 [phosphate], with an arbitrarily set reference range of 1 +/- 5 meq/L.

SA-PO941

V-ATPase in Luminal Membrane of Renal Proximal Tubule Requires B2 Subunit and CLC-5 for Its Full Functional Activity Nobuhiko Sato,¹ Motonobu Nakamura,¹ Atsushi Suzuki,¹ Masashi Suzuki,¹ George Seki,² Shoko Horita.¹ *¹Nephrology, The Univ of Tokyo Hospital, Tokyo, Japan; ²Yaizu City Hospital, Shizuoka, Japan.*

Background: Using an isolated rat proximal tubule (PT) primary culture system, we have previously shown that the activity of basolateral Na/HCO₃ co-transporter (NBCe1) was preserved for 36 hours. Furthermore, gene silencing with siRNA enabled us to identify the signaling pathways involved in insulin-mediated NBCe1 stimulation (Nakamura M, Kidney Int, 2015). However, it remains unknown whether this technique is applicable to analysis of PT luminal transporters.

Methods: Freshly isolated mouse PT was attached to a glass coverslip with Cell-Tak glue and the lumen was exposed with a broken glass capillary. BCECF was used to measure intracellular pH (pHi). While the cariporide-insensitive luminal NHE activity was determined by the rates of pHi decrease in response to Na removal, the bafilomycin-sensitive V-ATPase activity was determined by the rates of pHi recovery in Na-free solution. These experiments were also performed after PTs were cultured overnight in the presence of siRNA against V-ATPase B2 subunit or CLC-5.

Results: The luminal NHE activity was at least partially preserved in isolated PT primary culture (0.89 +/- 0.08 vs 0.45 +/- 0.07 pH unit/min). The hypotonicity (210 mOsm)-stimulated V-ATPase activity was also largely preserved in PT primary culture (0.50 +/- 0.05 vs 0.32 +/- 0.04 pH unit/min). Overnight treatment with siRNA against B2 subunit or CLC-5 largely suppressed the V-ATPase activity by 81% and 70%, respectively, without affecting the luminal NHE activity. We also confirmed that transfection of wild-type CLC-5 into HEK293 cells not only decreased endosomal pH as estimated by ratiometric VAMP2-pHluorin but also induced the plasma membrane V-ATPase activity stimulated by hypotonicity (0.01 +/- 0.01 vs 0.59 +/- 0.07 pH unit/min).

Conclusions: These data revealed for the first time to our knowledge that the luminal V-ATPase in PT requires both B2 subunit and CLC-5 for its full functional activity. The requirement of CLC-5 may be a common feature of mammalian V-ATPase, either expressed in endosome or plasma membrane.

Funding: Government Support - Non-U.S.

SA-PO942

The Mechanistic Target of Rapamycin Regulates Solute Transport in Renal Tubules Nasir A. Shah,¹ Davide Pietro Cina,^{2,3} Tuncer Onay,^{2,3} Vera Eremina,⁴ Chengjin Li,⁴ Aline Martin,² Yashpal S. Kanwar,^{2,5} Susan E. Quaggin.^{2,3} ¹Mater Health Services North Queensland, James Cook Univ, Townsville, Queensland, Australia; ²Medicine, Div of Nephrology, Northwestern Univ, Chicago, IL; ³Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; ⁴Lunenfeld-Tanenbaum Researwch Inst, Mount Sinai Hospital, Toronto, ON, Canada; ⁵Pathology, Northwestern Univ, Chicago, IL, Canada.

Background: Inhibitors of the mechanistic target of rapamycin (MTOR inhibitors) belong to a family of drugs with potent immunosuppressive, anti-angiogenic and anti-proliferative properties. Despite their clinical potential, their use in humans has been hampered by a significant incidence of proteinuria and electrolyte disturbances. Although some studies suggest Mtor may play a role in regulating renal solute transporter expression and function, the exact mechanisms underlying these changes are largely unknown.

Methods: In this study we examine the contribution of MTOR inhibition in the renal tubules to the development of proteinuria and electrolyte disturbances by generating an inducible Pax8-driven, tubule-specific Mtor knockout mouse (Mtor Pax8-iKO).

Results: Loss of Mtor in the renal tubular epithelium resulted in increased 24-hour urine volume, diminished urine osmolality, and renal failure. Despite elevated 24-hour urine albumin, Ca²⁺, and Mg²⁺ Mtor Pax8-iKO mice were both hypercalcemic and hypermagnesemic. Histologically, Mtor Pax8-iKO mice exhibited generalized tubular atrophy with focal cystic dilations of the distal and cortical collecting tubules, and interstitial fibrosis. Immunohistochemistry showed decreased expression of aquaporin-2 (Aqp2), Calbindin D 28k (Calb1), and the sodium-potassium-chloride cotransporter (Nkcc2). Increased expression of the transient receptor potential cation channel subfamily V member 5 (Trpv5) was also noted.

Conclusions: Taken together, our results suggest that MTOR is a key player in maintaining electrolyte balance by modifying the expression, and function of solute transporters in the renal tubular epithelium.

SA-PO943

High Mobility Group Box 1 (HMGB1) Inhibits HCO₃⁻ Absorption in Medullary Thick Ascending Limb (MTAL) Through Receptor for Advanced Glycation End Products (RAGE)-Rho-Rock1-Mediated Inhibition of Basolateral Na⁺/H⁺ Exchange Bruns A. Watts, Thampi George, David W. Good. Univ TX Med Branch, Galveston, TX.

Background: HMGB1 is a damage-associated molecule that is released extracellularly in response to infection or injury and plays a role in mediating kidney dysfunction in sepsis and sterile inflammatory disorders. Recently we showed that basolateral HMGB1 inhibits HCO₃⁻ absorption in perfused rat MTALs through a RAGE-dependent pathway additive to TLR4-ERK-mediated inhibition by LPS. Here we examined signaling and transport mechanisms involved in inhibition by HMGB1.

Results: Inhibition of HCO₃⁻ absorption by HMGB1 was eliminated by the Rho-associated kinase (ROCK) inhibitor Y27632 and by a specific inhibitor of Rho, the direct activator of ROCK. HMGB1 increased ROCK1 activity in dissected inner stripe of outer medulla, a preparation that accurately reproduces changes in MTAL signaling proteins. Activation of ROCK1 by HMGB1 was eliminated by the RAGE antagonist FPS-ZM1 and by inhibition of Rho. Addition of a direct Rho activator reduced basal HCO₃⁻ absorption rate and prevented inhibition by HMGB1. The Rho and ROCK inhibitors had no effect on inhibition by bath LPS. The Rho-ROCK1 pathway regulates NHE1 and we have shown that inhibition of NHE1 decreases MTAL HCO₃⁻ absorption secondarily through cytoskeleton-dependent inhibition of apical NHE3. Inhibition of HCO₃⁻ absorption by HMGB1 was eliminated by bath amiloride, 0 Na⁺ bath, and the F-actin stabilizer jasplakinolide, three maneuvers that selectively prevent inhibition of HCO₃⁻ absorption mediated through NHE1. Bath amiloride and jasplakinolide did not affect inhibition by bath LPS.

Conclusions: We conclude: 1) HMGB1 inhibits HCO₃⁻ absorption in the MTAL through a RAGE-Rho-ROCK1 pathway coupled to inhibition of NHE1; 2) this pathway functions in parallel with the LPS-TLR4-ERK pathway to impair MTAL HCO₃⁻ absorption. Thus, during sepsis, endogenous damage-associated molecules and exogenous bacteria-associated molecules act directly and independently to inhibit MTAL HCO₃⁻ absorption through different receptor signaling and transport pathways. The RAGE-Rho-ROCK1 pathway is a potential target to attenuate sepsis-induced renal tubule dysfunction.

Funding: NIDDK Support

SA-PO944

Identification of IQGAP-1 as a Pendrin-Binding Protein in the Kidney Jie Xu,¹ Sharon L. Barone,² Kamyar A. Zahedi,^{1,2} Manoocher Soleimani.^{1,2} ¹Center on Genetics of Transport and Epithelial Biology, Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; ²Research Services, VA Medical Center, Cincinnati, OH.

Background: Networks of interacting proteins are crucial for all levels of cellular function. The Slc26 family of anion transporters [Slc26a3 (DRA), Slc26a5 (prestin), Slc26a6 (PAT-1), and Slc26a9] form multi-protein complexes with cytoskeleton, anchoring proteins, PDZ adaptor proteins, CFTR and/or protein kinases, which impart regulatory signals on these isoforms. No information is available on proteins that interact with pendrin (Slc26a4).

Methods: A yeast two hybrid system was employed to screen a mouse kidney cDNA library with a pendrin C-terminal fragment as bait. A total of 6 × 10³ interacting clones were identified, out of which 14 clones were confirmed to be positive when screened for β-gal expression. Plasmids from these clones were purified and their interaction with pendrin was confirmed.

Results: Our experiments identified IQGAP-1 as a pendrin C-terminus binding partner. IQGAP-1 is a scaffolding protein that binds and/or stabilizes ezrin, CDC42 and RAC1, and interacts with cytoskeletal and cell adhesion molecules. In the kidney, IQGAP-1 is strongly expressed in the DCT, CNT, CCD and podocytes. IQGAP-1 has also been shown to control tight junction formation through recruitment of claudin. Our results indicate that IQGAP-1 co-localizes with pendrin on the apical membrane of B-intercalated cells. IQGAP-1 is also detected on the basolateral membrane of A-intercalated cells in CCD. Functional studies in HEK293 cells demonstrated that the co-transfection of IQGAP-1 and pendrin increased pendrin-mediated Cl⁻/HCO₃⁻ exchange activity by more than 60%. Confocal microscopy showed more abundant plasma membrane expression of pendrin in the presence of IQGAP-1.

Conclusions: These studies demonstrate the interaction of IQGAP-1 and pendrin in B-intercalated cells, as well as the stimulatory role of IQGAP-1 on pendrin activity. We propose that pendrin interaction with IQGAP-1 is important in the regulation of CCD function and physiology, and that disruption of this interaction contributes to altered pendrin trafficking and/or activity in pathophysiologic states.

Funding: Veterans Administration Support

SA-PO945

Regulation of Rhcg by Aldosterone in Intercalated Cells of the Collecting Ducts Koji Eguchi, Yuichiro Izumi, Terumasa Nakagawa, Yushi Nakayama, Hideki Inoue, Yutaka Kakizoe, Takashige Kuwabara, Masashi Mukoyama. Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Acid-base balance is regulated by aldosterone which stimulates acid secretion in the intercalated cells of the collecting ducts of the kidney. Rhesus blood group C glycoprotein (Rhcg) is an ammonia transporter which cooperates with H⁺-ATPase to secrete H⁺ in the intercalated cells. *In vivo* experiments have shown that metabolic acidosis and hypokalemia, that change plasma aldosterone level, increases and decreases the expression of Rhcg, respectively. Direct effect of aldosterone on the regulation of Rhcg has not been examined.

Methods: We examined the effect of aldosterone on the regulation of Rhcg. Membrane fraction of the whole kidney was extracted from mice that were continuously administered aldosterone (40μg/body/day) or vehicle for a week. To further examine the effect of aldosterone on the regulation of Rhcg in the intercalated cells, mRNA, whole cell protein, and membrane fraction were extracted from IN-IC cells (a rat intercalated cell line) after the treatment with aldosterone (10⁻⁶ M) for 24 h. The Rhcg mRNA and protein expressions were measured by real-time PCR and Western blotting, respectively. The expression of serum and glucocorticoid-regulated kinase 1 (Sgk1) mRNA was also measured in IN-IC cells.

Results: Administration of aldosterone increased the expression of Rhcg protein in membrane fraction of the whole kidney. In IN-IC cells the expressions of Rhcg and Sgk1 mRNAs were 1.3- and 3.2-fold greater, respectively, in cells treated with aldosterone (10⁻⁶ M) than in cells with vehicle. The expression of Rhcg protein in whole cell extract was not changed by the treatment with aldosterone. However, the expression of Rhcg protein in membrane fraction was 3.2-fold greater in cells treated with aldosterone than in cells with vehicle.

Conclusions: The results suggest that aldosterone regulates membrane accumulation of Rhcg possibly through the activation of Sgk1.

Funding: Government Support - Non-U.S.

SA-PO946

Role of Adenylyl Cyclase 6 in Regulation of Urinary pH Søren Brandt Poulsen,^{1,2,3} Robert A. Fenton,³ Timo Rieg.^{1,2} ¹Dept of Medicine, UCSD, La Jolla, CA; ²VASDHS, San Diego, CA; ³Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark.

Background: Adenylyl cyclase isoform 6 (AC6) is expressed in all renal tubular segments and catalyzes the synthesis of cAMP. We have previously reported that AC6 knockout (AC6^{-/-}) mice have a urinary concentration defect, a mild Bartter syndrome and secondary hyperparathyroidism. A recent study (Am J Physiol Renal Physiol. 2012;303(6):F812-20) determined that cAMP can increase pendrin protein (Cl⁻/HCO₃⁻ exchanger) abundance. We therefore hypothesized that AC6-mediated cAMP formation was important for urinary pH regulation.

Methods: AC6 wild-type (WT) and AC6^{-/-} mice (n=6/genotype) were challenged with NaHCO₃ in their drinking water for a period of 8 days. As daily fluid intake is double in AC6^{-/-} mice, the NaHCO₃ was reduced by 50% in this genotype (0.14 mol/l vs. 0.28 mol/l in WT). Urine was collected daily; blood was collected under baseline conditions and at the end of the 8 day experimental period. Mice were euthanized, one kidney processed for Western blotting (pendrin, H⁺-ATPase B1 subunit and NBCe1), and the other kidney was perfused *in vivo* and processed for immunohistochemistry.

Results: Baseline urinary pH was significantly lower in AC6^{-/-} vs. WT mice (6.5±0.2 vs. 7.7±0.2, P<0.05) which was associated with higher blood pH (7.44±0.01 vs. 7.41±0.01, P<0.05). At the end of the experimental period urinary pH was comparable between genotypes (8.3±0.4 vs. 8.3±0.4, NS) and no significant change in blood pH was observed (7.45±0.01 vs. 7.43±0.01, P<0.05 vs. WT). NBCe1 protein abundance was not different, whereas pendrin and H⁺-ATPase B1 subunit were 1.8 and 1.5-fold higher in AC6^{-/-} vs. WT, respectively (P<0.05). The number of pendrin positive cells/mm² (WT: 32±2 vs. AC6^{-/-}: 28±2) in the renal cortex was not different between genotypes.

Conclusions: Our results imply a role for AC6 in expression of pendrin and H⁺-ATPase B1 subunit and subsequently regulation of urinary pH. The increase in urinary pH in AC6^{-/-} mice can only be achieved, or is the consequence of, higher pendrin abundance; however, this effect is independent of pendrin distribution changes. Further studies are needed to determine the signals causing baseline differences in urinary pH.

Funding: NIDDK Support, Private Foundation Support

SA-PO947

Prediction of the Development of Delayed Graft Function Using Acute Kidney Injury Criteria in Deceased Donor Kidney Transplantation Jeong Ho Kim,¹ Bum Soon Choi,¹ Cheol Whee Park,¹ Chul Woo Yang,¹ Yong-Soo Kim,¹ Young Soo Kim,² Byung Ha Chung.¹ ¹Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea; ²Internal Medicine, Uijeongbu St. Mary's Hospital, Uijeongbu, Korea.

Background: There is no clear consensus on the definition of acute kidney injury (AKI) in deceased donor. In this study, we determine the discriminative ability of the Kidney Disease: Improving Global Outcomes (KDIGO) compared to the Acute Kidney Injury Network (AKIN) criteria for the prediction of the development of delayed graft function (DGF) and allograft outcome in deceased donor kidney transplantation (DDKT).

Methods: We analyzed 285 kidney transplant recipients who took kidney from 228 deceased donors. We calculated the AKI stage of deceased donor according to the AKIN and KDIGO criteria and compared the predictability for the development of DGF and the change of allograft function.

Results: For 2 classification systems, DGF developed more frequently in the AKI group than non-AKI group (P<.05) and allograft function assessed by the Modification of Diet in Renal Disease (MDRD) equation showed a significantly deteriorating pattern at 2 weeks and 1, 3, 6, 12 months after kidney transplantation compared to that in the non-AKI group (P<.05, comparison at each time point). In the Receiver-Operating Characteristic(ROC) curve analysis, the KDIGO criteria showed better prognostic accuracy of the prediction of the development of DGF compared to the AKIN criteria (area under the curve = 0.72 versus 0.62; P<.05).

Conclusions: In DDKT, the KDIGO criteria may be more useful for predicting the development of DGF compared to the AKIN criteria.

SA-PO948

Impact of Cold Ischemia Time on Graft Failure and Death Douglas F. Arbetter,¹ Mariana C. Chiles,¹ Prativa Baral,¹ Geoffrey K. Dube,¹ Russell J. Crew,¹ Heather K. Morris,¹ Jai Radhakrishnan,¹ David J. Cohen,¹ Stephen O. Pastan,² Rachel E. Patzer,² Sumit Mohan.¹ ¹Dept of Medicine, Columbia Univ College of Physicians & Surgeons, New York, NY; ²Dept of Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: Patient and graft survival post kidney transplant (KT) are influenced by an interaction of multiple factors, including organ quality, preservation and cold ischemia time (CIT). Several small studies have suggested that even small increases in CIT adversely impact patient and graft outcomes. In this analysis we assess the impact of increasing CIT on patient and graft survival in the US.

Methods: We identified 75,660 first-time adult KT recipients, who received a deceased donor (DD) kidney from 2000-2011 in SRTR. Pearson's chi-square tests of independence and Kruskal-Wallis tests were performed to test for association between CIT and mortality, graft failure. Cox proportional hazard analyses, adjusting for donor factors (age, gender, serum creatinine, cause of death), recipient factors (age, dialysis duration, PRA status, HLA mismatch), machine perfusion, and specified effect measure modifiers, were performed to estimate the hazard of either event occurring given CIT.

Results: 60.7% of our cohort was male, and 31.4% were black. Mean age was 52.2±13.0 years and average CIT was 18.2±9.2 hours. By univariate analysis, CIT was associated with an increase in risk of both death-censored graft failure and mortality (both HRs=1.006; p<0.0001). Adjusting for covariates and effect measure modifiers, the relationship between CIT and recipient mortality risk and death-censored graft failure were both attenuated (HR=1.000; p=0.9692 and HR=0.997; p=0.7479, respectively) suggesting that each additional hour of CIT did not significantly increase the risk of graft failure or death.

Conclusions: Our results suggest that increases in CIT do not adversely impact patient and allograft outcomes following DDKT and should not be used to decline organ offers.

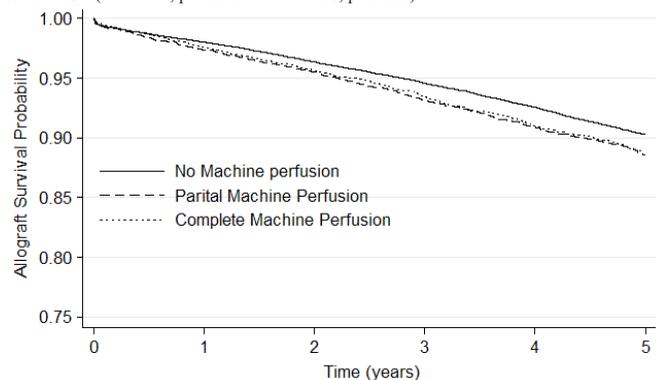
SA-PO949

Impact of Hypothermic Machine Perfusion on Outcomes following Kidney Transplantation Prativa Baral, Mariana C. Chiles, Douglas F. Arbetter, Russell J. Crew, Geoffrey K. Dube, Heather K. Morris, Hilda E. Fernandez, David J. Cohen, Sumit Mohan. Columbia Univ.

Background: Patient and allograft outcomes following deceased donor kidney transplantation (DDKT) are thought to be influenced by the intrinsic quality of the organ at procurement and any superimposed subsequent injury that occurs during cold preservation (CP). Hypothermic machine perfusion (HMP) is used in an attempt to decrease injury from CP especially for organs that have extended periods of cold ischemia. We analyzed the impact of complete, partial or no HMP use during CP on patient and graft survival following DDKT.

Methods: We identified 75,660 first-time adult renal transplant recipients, who received a DD kidney from 2000-2011 in SRTR. Pearson's chi-square tests of independence and Kruskal-Wallis tests were performed to test for association between HMP and mortality, graft failure, and delayed graft function (DGF). Cox analyses, adjusting for donor factors (age, gender, creatinine, cause of death), recipient factors (age, dialysis duration, PRA, HLA mismatch), CP time, and specified effect measure modifiers, were performed to estimate the hazard of either graft failure, or DGF occurring given HMP.

Results: On unadjusted analyses, compared to no HMP use, kidneys that received HMP for some or all of their CP time were less likely to experience DGF (OR=0.82, p<.0001 & OR=0.77, p<.0001) but more likely to experience allograft failure (HR=1.19, p<.0001 & HR=1.20, p<.0001, figure 1). On multivariable analyses, the use of HMP was associated with a lower incidence of DGF (OR=0.70, p<.0001 & OR=0.59, p<.0001) but continued to be associated with a higher risk of allograft failure even after adjusting for CIT and the lower DGF (HR=1.11, p= 0.023 & HR=1.26, p=0.002).



Conclusions: HMP improves short term outcomes by lowering rates of DGF but is associated with reduced long-term allograft survival.

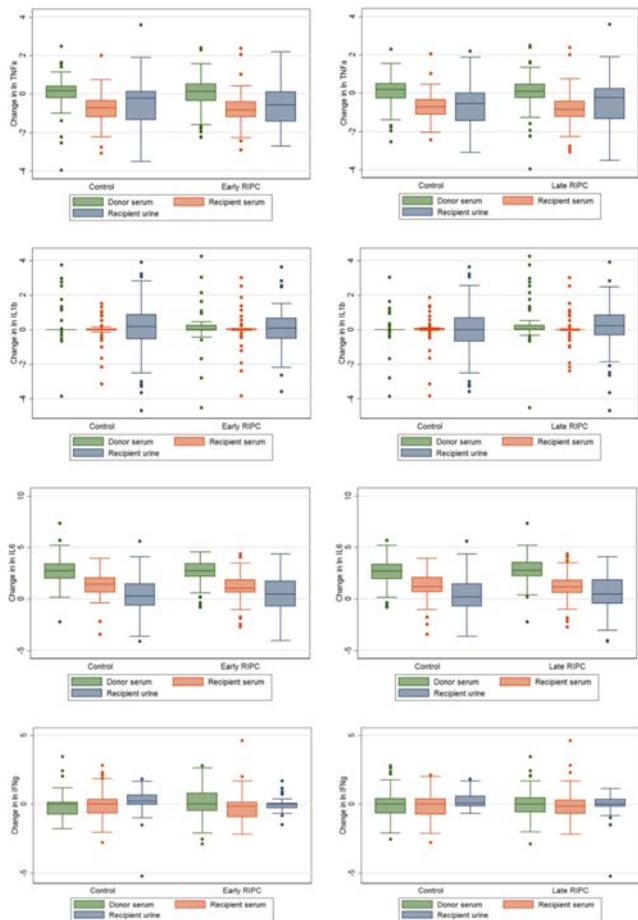
SA-PO950

The Impact of Remote Ischaemic Preconditioning (RIPC) on the Inflammatory Response following Live Donor Kidney Transplantation Kristin Vibeke Veighey,¹ Madhur P. Motwani,² Jennifer Nicholas,³ Raymond Macallister.² ¹Wessex Kidney Unit, Portsmouth Hospitals NHS Trust, United Kingdom; ²UCL Centre for Clinical Pharmacology & Therapeutics, Univ College London, United Kingdom; ³Clinical Trials Unit, London School of Hygiene and Tropical Medicine, United Kingdom.

Background: Ischaemia reperfusion (IR) injury at transplantation contributes to organ damage that limits allograft longevity. Animal studies have demonstrated a reduction in circulating proinflammatory cytokines following RIPC, which may contribute to tissue protective effects. REPAIR demonstrated a trend towards improved live donor kidney function following RIPC. We investigated the effects of RIPC on serum and urinary cytokines in this study.

Methods: 406 adult live donor/recipient pairs were recruited. Pairs were randomised using a factorial design to either: sham RIPC, early RIPC (immediately pre-surgery), late RIPC (24 hours pre-surgery) or dual RIPC. Donor and recipient received the same interventions (active or sham RIPC). Serum from donor and recipient and urine from recipients was analysed at baseline and on day 2 for pro-inflammatory cytokines IL-1β, IL-6, IFN-γ and TNFα, using multiplex ELISA. All analyses were conducted using linear regression adjusted for baseline (pre-treatment) values of the cytokine and indicator variables for early and late treatment group. Cytokine values were log transformed before analysis to account for skewed distribution.

Results: There was no difference in the expression of serum cytokines in donor serum or recipient serum and urine between baseline pre-surgery and day 2 post surgery.



From top: TNF α , IL-1 β , IL-6, IFN- γ ; graph on left = early RIPC, right = late RIPC.
Conclusions: In this large randomised trial, there was no evidence that RIPC attenuated the inflammatory response to transplant surgery in blood or urine.

SA-PO951

Remote Ischaemic Preconditioning (RIPC) Provides a Sustained Improvement in eGFR following Live Donor Kidney Transplantation: Four Year Follow-Up in the REPAIR Study Kristin Vibeke Veighney,¹ Jennifer Nicholas,² Steven Robertson,² Raymond Macallister.³ ¹Wessex Kidney Unit, Portsmouth Hospitals NHS Trust, United Kingdom; ²Clinical Trials Unit, London School of Hygiene and Tropical Medicine, United Kingdom; ³UCL Centre for Clinical Pharmacology & Therapeutics, Univ College London, United Kingdom.

Background: Ischaemia reperfusion (IR) injury sustained at transplantation contributes to organ damage that limits allograft longevity. The REEnal Protection Against Ischaemic Reperfusion in transplantation (REPAIR) study demonstrated a weak effect of early RIPC on the primary outcome iohexol glomerular filtration rate (GFR) at 1 year (adjusted mean difference 3.08 ml/min/1.73m²; 95% CI -0.89 to 7.04; p=0.13), but stronger evidence of an effect on eGFR at 1 year (difference 4.98; 95% CI 1.13 to 8.29; p=0.011), reflecting a potentially clinically important improvement of kidney function. There was no evidence that late RIPC alone had any benefit at 1 year. RIPC was safe and well tolerated. We used data from up to 4 years follow-up to examine the medium term effects of early and late RIPC on eGFR.

Methods: 406 adult live donor/recipient pairs were recruited and randomised using a factorial design to either: sham RIPC, early RIPC (immediately pre-surgery), late RIPC (24 hours pre-surgery) or dual RIPC (early and late RIPC). Donor and recipient received the same interventions (active or sham RIPC). The primary outcome was iohexol GFR at 12 months. eGFR up to 5 years post transplantation was an important secondary outcome.

Results: Provisional analysis of eGFR data up to 48 months suggested a sustained benefit of early RIPC and possible emergence of benefit of late RIPC. The mean (SD) 55.8 (23.0) in control vs 57.4 (20.4) in early RIPC at 2 years; 51.7 (18.6) vs 57.7 (21.3) at 3 years; and 51.8 (19.8) vs 60.5 (24.3) at 4 years. The mean (SD) in control vs late RIPC were 55.8 (20.4) vs 57.4 (22.9) at 2 years; 52.8 (19.8) vs 56.8 (20.5) at 3 years; and 52.4 (21.7) vs 59.7 (22.8) at 4 years.

Conclusions: The benefit of early RIPC on eGFR that was demonstrated at 1 year appears to be sustained during medium-term follow up, reflecting a potentially clinically important improvement of kidney function.

SA-PO952

Low Expression of the Messenger RNA TLRs 2-4,9 from Peripheral Blood Mononuclear Cells of the Kidney Recipients May Indicate Previous Delayed Graft Function Slawomir C. Zmonarski, Katarzyna Madziarska, Mirosław Banasik, Maria Magott, Marian Klingler. *Nephrology and Transplantation Med., Medical Univ, Wrocław, Poland.*

Background: The Toll-like receptors (TLR) 2-4,9 are engaged in the pathogenesis of acute renal injury. Earlier studies demonstrated that 24 hrs. after transplantation (KT), the expression of the messenger RNA (mRNA) TLR4 of peripheral blood mononuclear cells (PBMC) from patients (pts) with delayed graft function (DGF+) was lower than in recipients of kidneys without DGF (DGF-). The aim of study was to examine whether the reduced expression of TLR2-4,9 mRNA is a more permanent phenomenon associated with DGF.

Methods: Each of the 151 KT pts was more than 1 month after KT (from 1 to 128 months). Within this group: in 117 pts blood sample was taken for more than 3 months after KT, 45 pts experienced DGF, 13 DGF+ pts was HBeAb positive (DGF+HBe+). Control group (Con.) included 38 healthy volunteers. TLR2-4,9 mRNA expression (expr.) from PBMC was assessed by polymerase chain reaction (real-time PCR) and analyzed in terms of DGF and clinical course.

Results: KT DGF+ pts had generally lower TLR2-4,9 mRNA expr. than KT DGF- pts (TLR2: p=0,06; TLR3; p= 0,021; TLR4: p=0,07; TLR4 > 3 month after KT: p=0,032; TLR 9, p=0,027). TLR3 mRNA of DGF+HBe+ pts was: lower (p=0,046) than DGF+HBe-, lower (p=0,013) than DGF-ATN- and lower (p=0,008) than Con. TLR9 mRNA of DGF+HBe+ was lower (p=0,0002) than Con. In multiple regression analysis low expr. of TLR mRNA 2-4,9 was associated with the occurrence of DGF in the past.

Conclusions: Lower than typical expression of TLR 2-4,9 mRNA seems to be a permanent feature of peripheral blood mononuclear cells of the recipient of the transplanted kidney who experienced delayed graft function. Hepatitis B seems may be associated with additional decline of TLR3 and TLR9 mRNA expression. TLR3,4,9 mRNA expression could potentially be used as an indicator of the likelihood of delayed graft function.

Funding: Clinical Revenue Support

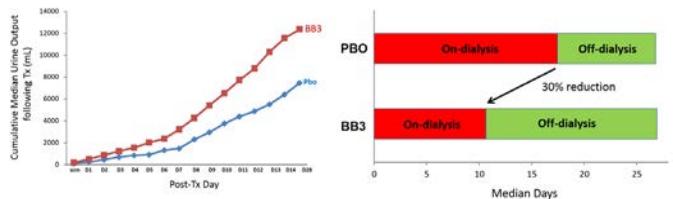
SA-PO953

BB3, a Hepatocyte Growth Factor-Like Small Molecule, Improves Outcome in Kidney Transplant Recipients with Delayed Graft Function Jonathan Bromberg,¹ Matthew R. Weir,² A. Osama Gaber,³ Matthew Cooper,⁴ Mark Laftavi,⁵ Barry Browne,⁶ Bo Zhang,⁷ Prakash Narayan,⁷ Michael A. Yamin,⁷ Itzhak D. Goldberg,⁷ Weizhong Cai.⁷ ¹Div of Transplant Surgery, Univ of Maryland School of Medicine, Baltimore, MD; ²Div of Nephrology, Univ of Maryland School of Medicine, Baltimore, MD; ³The Methodist Hospital, Houston, TX; ⁴MedStar Georgetown Univ Hospital, Washington, DC; ⁵Transplant Center at Erie County Medical Center, Buffalo, NY; ⁶BNMG, San Diego, CA; ⁷Angion Biomedica Corp, Uniondale, NY.

Background: Duration of delayed graft function (DGF) portends poor short- and long-term renal function and graft survival. We studied the safety and efficacy of BB3, a small molecule with HGF-like activities, dosed starting 24 hr post-transplant (Tx) in patients with reduced urine output (UO) in a double-blind Phase 2 study.

Methods: Patients producing <50 cc urine/hr over 6-8 h post-Tx were randomized (2:1) to BB3 (2 mg/kg IV QD X 3 d) or placebo (PBO). An interim analysis was performed on 12 BB3- and 7 PBO-treated patients.

Results: BB3 was safe and well-tolerated. BB3 reduced the median time to produce 1.2L UO/24 hr from > 28 d to 7.5 d, increased the % of patients reaching this UO within 28 d from 43% to 83%, increased cumulative UO (figure), decreased median duration of dialysis (figure), decreased % on-dialysis days during Days 7-28 (14.2% to 7.1%) and during Days 14-28 (10.9% to 3.6%), reduced median SCR, reduced BUN, and shortened median hospital stay (7 d to 5.5 d). BB3 reduced serum CRP and NGAL.



Conclusions: BB3 administered ~24 hours post-Tx significantly reduced severity of DGF in patients presenting with reduced UO. Confirmation of these results in a Phase 3 trial may translate to improved long-term outcome, decreased Tx costs, increased use of marginal organs, and a shorter waitlist.

Funding: NIDDK Support, Pharmaceutical Company Support - Angion Biomedica Corp.

SA-PO954

DSA Monitoring and Treatment in Kidney Transplant Recipients
 Monica Grafals,¹ Alexander Gilbert,¹ Olga A. Timofeeva,² *Medstar Georgetown Transplant Inst, Georgetown Univ, Washington, DC;* ²*Histocompatibility Laboratory, Georgetown Univ, Washington, DC.*

Background: The development of DSA monitoring is a new technique to detect antibodies in kidney transplant recipients. We previously showed that patients that developed de novo DSA (dnDSA) suffer a 35% graft loss. Because of this we have developed a protocol for treating patients that have developed dnDSA post kidney transplant.

Methods: Since the implementation of this treatment protocol on September 12, 2014, there have been 9 patients that have developed dnDSA after renal transplantation.

	LOW RISK	INTERMEDIATE RISK	HIGH RISK
DSA Criteria	DSA detectable only at titers less than 1:16 -AND- DSA which is c1q negative	DSA detectable at titers equal to or greater than 1:16 -OR- DSA which is c1q positive	DSA detectable at titers equal to or greater than 1:16 -OR- DSA which is c1q positive
Clinical Criteria	No biopsy findings of acute rejection (either ACR or AMR) -AND- Stable serum creatinine (within 25% of baseline)	No biopsy findings of acute rejection (either ACR or AMR) -AND- Stable serum creatinine (within 25% of baseline)	Biopsy findings consistent with ACR or AMR -OR- An acute rise in creatinine greater than 25% from baseline
Treatment Plan	NONE	IVig 1 gram/kg x2 doses given on day #1 and #2 Rituximab 375 mg/ meter ² x2 doses given on day#1 and day #8	Plasmapheresis x5 sessions (every other day) Bortezomib 1.3 mg/ meter ² on days #1, 4, 8, 11 IVig 1 gram/kg after the last plasmapheresis session.
Assessment of Treatment	N/A	Check DSA 1 month after start of treatment.	Check DSA on day #14, repeat renal biopsy 3-4 weeks after start of treatment.
Measures of Success	N/A	DSA becomes negative for c1q	DSA becomes negative for c1q -AND- Repeat biopsy shows resolution of earlier changes.

Results: Four of the patients that developed dnDSA were in the low risk category and in 3 of them the DSA has cleared. The 4th patient has a DSA against DP1 with an MFI of 1587 that has remained stable. All of these patients have a GFR >45 cc/min. Three patients were in the intermediate risk category. One of them has a creatinine of 3, BK viremia and he has a DSA against A1 with an MFI of 3150 which has been stable. Another patient in this group developed CMV viremia and his DSA became negative after treatment. The third patient just received treatment for DSA this past month and follow up DSA is not available at this time. Two patients were in the high risk category and both of them received treatment and their GFRs are >45 cc/min and their DSAs have become undetectable and weak respectively.

Conclusions: Since the development of dnDSA post kidney transplant is associated with worse graft outcomes, implementation of treatment protocols is necessary for kidney transplant patients. This preliminary data shows that treatment for dnDSA with this protocol seems to successfully treat the antibodies.

SA-PO955

On the Patterns of Early De Novo DSA Development in Kidney Transplant Recipients in the First 6 Months After Alemtuzumab Induction
 Chelsea Estrada, Yezina T Nigatu, Heesuck Suh, Frank Darras, Mersema Abate, Edward P. Nord. *Nephrology and Transplantation, Stony Brook Medicine, New York.*

Background: The presence of de novo DSA (dnDSA) is associated with antibody mediated rejection and suboptimal graft outcomes. The incidence of dnDSA post renal transplant varies according to immunosuppression protocols, screening, and detection methods, and ranges from 5-25%. A higher incidence of dnDSA after alemtuzumab (AL) has been observed. We sought to characterize the expression of early dnDSA development after AL induction in renal transplant recipients.

Methods: Consecutive kidney transplant recipients were screened for dnDSA from 7/1/2014 to 4/30/2015. DnDSA was detected by single antigen beads and luminex technology at months 1, 2, 3 and 6. Mean Fluorescent Intensity (mfi) > 500 was considered positive. Induction consisted of AL with rapid steroid withdrawal, and maintenance immunosuppression was with tacrolimus and mycophenolate mofetil.

Results: A total of 47 renal transplants, 13 from living donors and 34 from deceased, were performed from 7/1/14 to 4/30/15 and followed for 5.1 +/- 2.9 months (range 1-9). Of these, 17 developed dnDSA (36.2%) in the first 6 months; 7 class I, 7 class II and 3 both. Class I was detected at months 1 (6), 2 (2), 3(1) and 6 (1). Class II was detected at months 1 (3), 2 (3), 3(2) and 6 (2). Median class I mfi was 1,081 (range 535-2,787), and class II was 2,299 (range 502- 11,301). In 9/17 (52.9%) patients (5 class I and 4 class II) with peak mfi < 2,500, dnDSA resolved (5) or decreased (4) without intervention. Four patients with class II dnDSA found at month 6 (2) and month 2 (2) with peak mfi 2,600-11,000, were treated with plasmapheresis, IVIG, and rituximab, preemptively. Of these, 2 dnDSA resolved, 1 remained high but creatinine is stable and 1 had worsening renal function but no evidence of AMR on biopsy. Five patients with rising dnDSA, and stable creatinine are being followed.

Conclusions: In this cohort, dnDSA developed in 36.2% of recipients, with the majority developing in months 1 and 2 (76.5%). Despite the high rate of dnDSA detection, most resolved or decreased without change in immunosuppression or early deleterious effects to graft function.

SA-PO956

Low Level Class I or II Donor HLA-specific Antibodies Do Not Correlate with the Concurrent Presence of Antibody Mediated Injury on Biopsy
 Chelsea Estrada, Catherine Miranda, Heesuck Suh, Frank Darras, Edward P. Nord, Mersema Abate. *Nephrology and Transplantation, Stony Brook Medicine, New York.*

Background: Pre-transplant and de novo donor HLA-specific antibodies (DSA) have been identified as risk factors for adverse outcomes in renal transplantation, causing antibody-mediated graft injury and acute antibody mediated rejection (ABMR) and transplant glomerulopathy (TG). With improved detection techniques, DSA recognition is increasing but there is no consensus on the definition of DSA positivity. While low level pre-transplant DSA has been associated with the future occurrence of ABMR, low level DSA on the day of indication biopsy is of unclear significance.

Methods: All sera were tested for DSA using single antigen beads with Luminex technology on the day of indication renal transplant biopsy from 7/1/2015- 5/21/2015. DSA level <500 mfi were considered negative, between 500-1500 mfi low level and >1500 mfi high level. Acute ABMR and TG histology met Banff 2013 criteria. In this cohort, induction was with alemtuzumab and rapid steroid withdrawal, and maintenance immunosuppression was with tacrolimus and mycophenolate mofetil. Chi square analysis was used to assess the association between low and high levels of DSA and biopsy findings of antibody mediated injury.

Results: Fifty-three consecutive indication kidney transplant biopsies were performed from 7/1/2014- 5/21/2015. Of these 12 had evidence of ABMR (2 acute, 8 TG and 2 both). Six of the 8 patients with TG alone did not have DSA. At the time of biopsy, 12 class I (6 low and 6 high level) and 13 class II (3 low and 10 high level) were detected.

DSA	AMR/TG n=12 (%)	No AMR/TG n=41(5)	P value
Class I Low	1(8)	5(12)	0.97
Class I High	3(25)	3(7)	0.09
Class II Low	0(0)	3(7)	0.51
Class II High	5(42)	5(12)	0.02
None	7(58)	34(83)	0.05

Conclusions: 1. The presence of high level class II DSA was significantly associated with the concurrent biopsy finding of antibody mediated injury. 2. Of greater significance, the presence of class I DSA or low level class II DSA did not correlate with pathologic findings.

SA-PO957

Characteristics of Kidney Transplant Candidates with and without Antibody against Angiotensin II Type 1 Receptor (AT1R-Ab) Mary Carmelle Philogene,¹ S.M. Bagnasco,² Annette M. Jackson,¹ Mary S. Leffell,¹ Andrea A. Zachary,¹ *¹Medicine, Johns Hopkins Univ, Baltimore, MD; ²Pathology, Johns Hopkins Univ, Baltimore, MD.*

Background: In this study we sought to determine whether baseline characteristics of kidney transplant candidates when correlated with presence of AT1R-Ab are predictive of transplant outcomes.

Methods: 122 renal transplant recipients were tested for presence of AT1R-Ab using quantitative ELISA (CellTrend GmbH, Germany). Patient demographics were obtained from the hospital electronic record under an approved IRB.

Results: Patients were categorized according to AT1R-Ab levels: positive >17 Units/ml (30%); borderline 10-17 Units/mL (34%), negative <10 Units/mL (36%). There were fewer females (31% versus 61%, 55%) and African Americans (14% versus 24%, 16%) in the AT1R-Ab >17 Units/ml group compared to the other two groups. The presence of AT1R-Ab has been associated with development of inflammation and fibrosis; therefore, we examined AT1R-Ab among patients categorized by the following diseases: IgA nephropathy, glomerulosclerosis, lupus nephritis, FSGS, and membranoproliferative glomerulonephritis. We found no correlation between these diseases and AT1R-Ab levels (38%, 29% and 30%, respectively; p=0.7). We also found no association with diagnosis of hypertension and AT1R-Ab levels (16%, 17%, 18%). The most significant difference between the three groups was a higher percentage of positive patients among those who received more than one kidney transplant (78%, 22%, 45%; p=0.001). Post transplantation, sixty-one patients were biopsied to investigate graft dysfunction. There were more patients in the borderline and positive AT1R-Ab groups who were evaluated for graft dysfunction compared to the negative group (65%, 54% versus 34%) although this did not reach statistical significance. Importantly, the AT1R-Ab positive and borderline groups had fewer HLA antibody positive patients compared to the AT1R-Ab negative group (54%, 50%, 87%; p<0.001).

Conclusions: The only pre-transplant characteristic linked to presence of AT1R-Ab in patients who are being evaluated for kidney transplantation is the incidence of previous transplant.

Funding: Clinical Revenue Support

SA-PO958

Effect of B-Cell Activating Factor (BAFF) Inhibition (LY2127399; Tabalumab) on Highly Sensitized Patients with End Stage Renal Disease awaiting Transplantation Muhammad Ahmad Mujtaba,¹ Wendy Komocsar,³ Milagros D. Samaniego-Picota,⁴ Eric Nantz,³ Jayne Hague,³ Melissa D. Anderson,² Benita K. Book,² Nancy G. Higgins,² Tim E. Taber.² ¹Nephrology, Univ of Texas Medical Branch, Galveston, TX; ²Transplant Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; ³Bio-Medicines, Eli Lilly and Company, Indianapolis, IN; ⁴Nephrology, Univ of Michigan Health System, Ann Arbor, MI.

Background: B cell activation factor (BAFF) is critical in B-cell maturation. Inhibition of BAFF represents an appealing target for desensitization of highly sensitized end stage kidney disease patients.

Methods: We conducted a Phase 2a, single-arm, open-label exploratory study investigating the effect of tabalumab (BAFF inhibitor) in ESRD patients with cPRAs >50%. The treatment period had a total duration of 24 weeks. Eighteen patients received tabalumab, at a dose of 240-mg subcutaneous (SC) at Week 0 followed by 120-mg SC at 4-week intervals for 5 more months. Patients were then followed for an additional 52 weeks. Blood samples were analyzed for HLA antibodies, BAFF levels, serum immunoglobulins, T and B cell subsets at specified time intervals during the treatment and follow-up periods. Pre and post treatment tonsil and bone marrow biopsies were also performed.

Results: Significant reductions in cPRAs were observed at week 16 (p=0.043) and at week 36 (p=0.004), however the absolute reductions were small (<5%). Overall factor effect at week 76 compared to baseline was significant (p=0.04). Mean BAFF levels increased during treatment, reflecting binding to tabalumab and decreased in the follow-up period remaining slightly above baseline at week 76. Expected changes in B cell subsets and reductions in immunoglobulins were observed. Two tabalumab-related serious adverse events occurred (pneumonia and worsening of peripheral neuropathy) while the most common other adverse events were injection-site pain and hypotension. Three patients received a matched donor cadaveric transplant during the study follow up.

Conclusions: BAFF inhibition resulted in statistically significant, but not clinically meaningful reduction in the cPRA from baseline.

Funding: Pharmaceutical Company Support - Eli Lilly

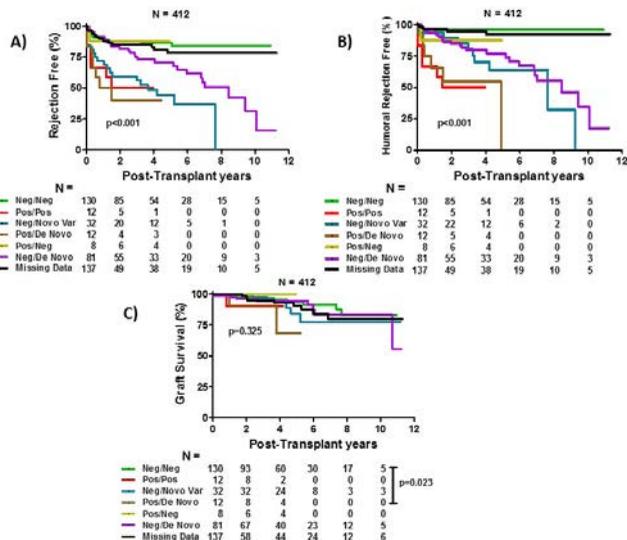
SA-PO959

Behavior and Impact of Donor-Specific Antibodies Before and After Kidney Transplant Araminta Guichard-Romero, Lluvia A. Marino-vazquez, Mayra Lopez, Natalia Castelan, Adrian De santiago, Norma O. Uribe-uribe, Josefina Alberú, Luis E. Morales-Buenrostro.

Background: Pre- and post-transplant DSA increases the risk for acute rejection, humoral rejection and graft loss. Every year a 5% of patients will develop DSA but other patients turn negative. It is unclear how the behavior of pre-transplant DSA under immunosuppression and their clinical impact is. This study evaluate the relationship between *de novo* DSA and the outcome of kidney transplantation, and whether the development of these antibodies is related to pre-transplant DSA status.

Methods: Prospective cohort study. From Jan/2004-Dec/2014 a total of 519 kidney transplant were performed. For analysis we include 412 with DSA determination plus negative Flow-Crossmatch (in DSA-positive cases). We classified the patients in 7 groups according to pre-/post-transplant DSA: 1) Neg/Neg (n=130) 2) Neg/De Novo (n=81) 3) Neg/De Novo-Variable (multiple changes in DSA, n=32) 4) Pos/Pos (same DSA, n=12) 5) Pos/De Novo (n=12) 6) Pos/Neg (n=8) 7) Without DSA post-transplant measure (n=137). The outcomes analyzed were graft and patient survival, acute rejection (AR), humoral rejection (AMR), and graft function by MDRD.

Results: From 412 patients, 58 patients (14.1%) had pre-transplant DSA. Patients with Pos/Pos or Pos/De Novo DSA had higher and earlier AR and AMR rate, followed by Neg/De Novo-Variable and Neg/De Novo, as you can see in the figure A) and B) respectively. For graft loss only those with Pos/De Novo was higher than Neg/Neg (Figure C). Interestingly, those who are Pos/Neg had similar outcomes than Neg/Neg.



Conclusions: Staying with the same DSA or developing De Novo-DSA after transplantation, regardless what the pretransplant condition was, were associated with development of AR, AMR, and graft loss.

SA-PO960

Course of Anti-HLA Antibodies After Induction Therapy with Rituximab in Renal Transplantation Luuk Hilbrands,¹ Wil Allebes,² Martijn W.f. Van den Hoogen,³ Irma Joosten,² Marije C. Baas.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Laboratory Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands; ³Nephrology, Erasmus Medical Center, Rotterdam, Netherlands.

Background: B-cell depletion protocols have shown to reduce donor-specific antibodies against HLA (DSA) and chronic antibody mediated rejection. We aimed to study the effects of rituximab as a single-agent induction therapy on the titers of pre-existent or de novo DSA and non-DSA after renal transplantation and relate this to rejection free and overall graft survival.

Methods: We collected sera in participants of a prospective double-blind randomized study on the efficacy and safety of the prophylactic use of one dose of rituximab, added to standard immunosuppressive treatment (prednisolone, tacrolimus and mycophenolate mofetil) in comparison with standard immunosuppressive treatment alone in renal transplantation (www.clinicaltrials.gov, NCT00565331).

Results: 280 patients were included (142 received placebo, 138 rituximab). Anti-HLA antibodies (Ab) were determined in serum taken pre-transplant and 12 and 24 months after transplantation. Serum was analysed pre-transplant and at 12 months from 126 placebo and 119 rituximab treated patients. Pre-existent anti-HLA Ab were present in 24/126 (19.0%) patients in the placebo group and in 20/119 (16.8%) patients in the rituximab group (P<0.05). In the placebo and rituximab treated patients HLA class I Ab disappeared in 55.6% and 50% and HLA class II Ab in 23.5% and 57%, respectively (P=0.06). At 12 months, 11 (8.7%) placebo treated patients and 4 (3.4%) rituximab treated patients (NS) developed de novo HLA Ab. 10/245 (4.1%) had de novo HLA class I Ab: 6 (4.8%) and 4 (3.4%) in the placebo and rituximab treated patients, respectively (NS). 12/245 (4.9%) had de novo HLA class II Ab: 9 (7.1%) in the placebo group and 3 (2.5%) in the rituximab group (P=0.09).

Conclusions: Induction therapy with rituximab compared to placebo does not significantly influence the course of anti-HLA Ab at 12 months, however it possibly decreases the levels of pre-existent class II anti-HLA Ab and inhibits the formation of *de novo* class II anti-HLA Ab.

Funding: Pharmaceutical Company Support - Roche, Astellas

SA-PO961

Benefit of Desensitization with Rituximab from the Viewpoint of Anti-A/B Antibody Titer and Pathological Findings in ABO-Incompatible Kidney Transplantation Kazuhide Saito, Shiro Takahara, Norio Yoshimura, Atsushi Aikawa, Shohei Fuchinoue, Takashi Yagisawa, Kazunari Tanabe, Yoshihiko Watarai, Motohide Shimazu, Kunio Morozumi, Kota Takahashi. *Japan ABO-incompatible Transplantation Committee, Japan.*

Background: We conducted a multicenter prospective clinical study in ABO-incompatible kidney transplantation (ABOi-KT) without splenectomy (UMIN00006635). To evaluate the benefit of desensitization with rituximab (R), we investigated the data of this study from the time course change of anti-A/B antibody (ab) titer and sequential pathological findings.

Methods: Desensitization protocol included low dose MMF and steroid started 28 days before and CNI started a few days before surgery. R 375 mg/m² was administered at day -14 and day -1. Minimum 2 sessions of plasma exchange were done for anti-A/B ab removal before transplant, and basiliximab was administered on day 0 and day 4. Anti-A/B

ab titer and eGFR were sequentially evaluated, 0 hr, 1 hr and protocol biopsies (4 weeks after transplant) were also sequentially performed as possible. Pathological specimens were centrally diagnosed by 3 pathologists.

Results: 18 pts received ABOi-KT. One-year pts and grafts survival were both 100%. The desensitization with R was well tolerated. Average anti-A/B ab (IgG) titer at baseline was 48.15x and decreased to 19.72x immediately before surgery, maintaining until the end of the study. In pts whose sequential pathological specimen available showed positive C4d deposition in 1/13 at 1 hr and 11/16(69%) at protocol biopsy. No pts developed AMR related to anti-A/B abs except for one who experienced AMR with anti-HLA ab (Banff07 type II). Her anti-A/B ab titers were slightly higher than the others (4x-32x). Pathological findings included arteriosclerosis in 8, nephrocalcinosis in 1, IF/TA (grade 1) in 1 and suspicious CNI acute nephrotoxicity in 1. Two pts showed C4d+ without other pathological signs.

Conclusions: In this series, anti-A/B ab titers were successfully decreased and no AMR occurred other than 1 caused by anti-HLA ab, whereas C4d deposition was detected in 69% of pts by protocol biopsy. Our desensitization protocol was confirmed both pathologically and clinically safe and effective for ABOi-KT.

Funding: Pharmaceutical Company Support - Zen-Yaku Kogyo Pharmaceutical Co.Ltd.

SA-PO962

Post-Transplant BAFF Levels Do Not Predict the Development of Anti-HLA Antibody in Kidney Transplant Recipients Ji Won Min,² Bum Soon Choi,^{1,2} Cheol Whee Park,^{1,2} Chul Woo Yang,^{1,2} Yong-Soo Kim,^{1,2} Byung Ha Chung,^{1,2} ¹Transplant Research Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; ²Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: It is well known that pre-transplant B cell activating factor (BAFF) levels are associated with the development of de novo anti-HLA antibodies and also antibody mediated rejection post-transplant. However, the clinical significance of BAFF values at allograft rejection has not been determined. In this study, we investigated the clinical significance of pre and post-transplant BAFF levels measured when indication biopsy was done.

Methods: In 130 kidney transplant (KT) recipients who required allograft biopsy due to an increase in serum creatinine, we checked for anti-HLA antibodies using Luminex single antigen assay, and measured BAFF levels using ELISA kits. In 78 of these patients we also measured pre-transplant BAFF and anti-HLA antibody levels. We investigated the relationship between pre-transplant, post-transplant and delta BAFF levels and the occurrence of anti-HLA antibodies.

Results: Pre-transplant BAFF levels showed significant association with pre-transplant sensitization, represented by positive PRA, high PRA, and presence of HLA-DSA. They also showed positive association with early rejection (rejection within 6 months from KT). Post-transplant BAFF levels showed significant association with pre-transplant sensitization, but did not show association with anti-HLA antibodies and positive donor-specific antibodies at the time of biopsy. We did not find any association between post-transplant BAFF levels and cumulative allograft survival, allograft biopsy results, Banff scores and microvascular inflammation scores.

Conclusions: In conclusion, pre-transplant BAFF levels are associated with pre-transplant sensitization and are useful in predicting allograft rejection. But post-transplant BAFF levels measured at the time of indicated biopsy are not associated with the appearance of de novo HLA-DSA, allograft rejection, biopsy findings and other allograft outcomes.

SA-PO963

Effectiveness of Bortezomib (BT) in the Treatment of Antibody Mediated Rejection (AMR) Among Pediatric Kidney Transplant Recipients (pKTx) Sarah J. Kizilbash,¹ Donna J. Claes,² Isa Ashoor,³ Ashton Chen,⁴ Sara E. Jandeska,⁵ Raed Bou Matar,⁶ Jason Misurac,⁷ Katherine Twombly,⁸ Priya Verghese,¹ ¹Pediatric Nephrology, Univ of Minnesota; ²Cincinnati Children's Hospital; ³Children's Hospital New Orleans; ⁴Wake Forest Univ; ⁵Rush Univ; ⁶Cleveland Clinic; ⁷Indiana Univ; ⁸Medical Univ of South Carolina.

Background: AMR has a poor prognosis despite a number of therapeutic options. BT is increasingly being utilized in adults but there are limited data on its safety and efficacy in pKTx with AMR.

Methods: Multicenter retrospective case series including all pKTx who received BT for biopsy proven AMR, from 2008-2015, at 8 centers within Midwest Pediatric Nephrology Consortium.

Results: Twenty-four pKTx from 8 centers were treated with BT for AMR. In addition to BT, 75% were treated with rituximab, 79.2% with plasmapheresis and 91.7% with IVIG. 62.5% were males, 45.8% were white, and 41.7% were African American. Two-thirds were deceased donor recipients, and mean age at transplant was 11.1 years (SD 5.19). Obstructive uropathy and dysplasia comprised 50% of the underlying diseases. At the time of transplant, 82.2% of patients had 0.0% panel reactive antibodies. Mean estimated GFR (eGFR) prior to AMR was 49.6 (SD 12.1). Prevalence of donor specific antibodies (DSA) and changes in eGFR are shown in table 1.

	Class 1 DSA	Class 2 DSA	Mean eGFR (ml/min/1.73m ²)
Initiation of BT	66.7%	91.7%	40.1
3 months after BT	40.0%	75.0%	37.8
6 months after BT	27.8%	76.5%	36.7

Side effects were documented in 54% of patients and most commonly included leukopenia, anemia, and hypertension. Less frequent side effects included hepatitis, headaches, vomiting, and rashes. Mean time to follow up after BT was 1.3 years (SD 0.96). At the end of follow up, patient survival was 100% and 17/24 patients (70.8%) had functioning grafts.

Conclusions: BT was used to treat AMR in pKTx without life-threatening side effects. The 6-month patient and graft survival were excellent. The efficacy and safety of bortezomib for pKTx AMR should be evaluated in randomized clinical trials.

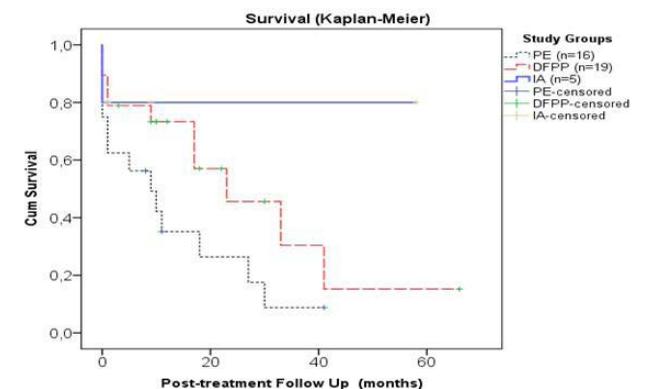
SA-PO964

Immunoabsorption Is Efficient in the Treatment of Late Antibody Mediated Rejection Yasar Caliskan,¹ Yasemin Ozluk,² Halil Yazici,¹ Aydin Turkmen,¹ Alaattin Yildiz,¹ Mehmet S. Sever.¹ ¹Div of Nephrology, Dept of Internal Medicine, Istanbul Faculty of Medicine, Istanbul, Turkey; ²Dept of Pathology, Istanbul Faculty of Medicine, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background: Plasmapheresis (PP) with IVIG, was proposed as a useful treatment for antibody mediated rejection (ABMR). As an alternative to plasma exchange (PE), double filtration plasmapheresis (DFPP) and immunoabsorption (IA) represent an attractive strategy for antibody depletion. We investigated whether PE or DFPP or IA is effective in the treatment of late ABMR.

Methods: 40 renal tx recipients diagnosed as biopsy confirmed ABMR at a mean time of 70±40 months after tx were included. Patients were randomly assigned to PE (n=16) or DFPP (n=19) or IA with protein A (n=5). The study groups were similar regarding age, gender, donor type, eGFR at randomization and post-tx follow-up time. Donor specific antibody (DSA) was positive in 62.5% of PE, 73.6% of DFPP and 100% of IA groups (p=0.25), and C4d was positive in 75%, 68% and 60% (p=0.79), respectively. All patients received 2 g/kg IVIG and Rituximab 375 mg/m².

Results: Tubulointerstitial scarring (ci+ct) (p=0.81), microcirculation inflammation (g+ptc) (p=0.38) and transplant glomerulopathy (cg) (p=0.21) scores were similar. However, the mean total inflammation (ti) score of IA group (2.60±0.55) was significantly higher than PE (1.69±0.70) and DFPP (1.79±0.71). The rates of graft loss were as follows; PE; 13/16 (81.3%), DFPP; 10/19 (52.6%) and IA; 1/5 (25%) (p=0.03). The graft survival was significantly higher for IA than PE (p=0.01). There was a tendency of better graft survival in DFPP compared to PE group (p=0.07). *Kaplan-Meier survival analysis revealed* better overall survival for IA than for PE and DFPP (p=0.03).



Conclusions: Even though limited by small patient numbers, this trial suggests efficiency of IA in the treatment of late ABMR.

SA-PO965

Pre-Transplant Phospholipase A2 Receptor Autoantibody Concentration Is Associated with Recurrence of Membranous Nephropathy Post-Kidney Transplantation Hasan Fattah,¹ Gaurav Gupta,¹ Dhiren Kumar,¹ Luis F. Quintana,² Anne L. King,¹ Rivka Ayalon,³ Laurence H. Beck.³ ¹Nephrology, Virginia Commonwealth Univ, Richmond, VA; ²Nephrology, Hospital Clinic de Barcelona, Barcelona, Spain; ³Nephrology, Boston Univ, Boston, MA.

Background: Idiopathic membranous nephropathy (iMN) has been associated with anti-phospholipase A2 receptor autoantibody (PLA2R-Ab) both in the native kidneys as well as in the setting of recurrence (rMN) post-kidney transplant (txp). Previous studies that have assessed pre-txp PLA2R-Ab for the prediction of rMN have yielded variable results. Many of these studies have been limited by the use of variable immunosuppressive protocols among patients, different ELISA assays as well as method of diagnoses (surveillance vs indication biopsies).

Methods: Sixteen consecutive txp patients with a history of rMN were tested for pre-txp PLA2R-Ab. ELISA titers (Euroimmun, NJ, USA) >14 RU/ml were considered positive, as per manufacturer instructions. All patients received similar post-transplant immunosuppression. A receiver operating characteristic (ROC) analysis was performed after combining data from Quintana et al. (n=21; Transplantation Feb 2015) to determine a PLA2R-Ab concentration which could predict rMN.

Results: Six (out of 16; 37%) patients had biopsy-proven rMN at a median of 3.2 years post-txp. Of these, 5/6 (83%) had a positive PLA2R-Ab pre-txp with a median of 82 RU/ml (range=31-1500). The only patient who had rMN with a negative PLA2R-Ab was later diagnosed with non-Hodgkin's lymphoma. 100% (n=10) patients with no evidence of rMN (median follow-up=5 years) had negative PLA2R-Ab though one patient did have a borderline titer of 13.8 RU/ml. Patients with rMN were treated with rituximab and had an improvement in proteinuria from a median of 6g/d to 0.6g/d. Among the patients with rMN and positive PLA2R-Ab, titers fell to a median of 4 RU/ml at most recent follow-up. In a combined ROC analysis (n=37) a pre-txp PLA2R-Ab >29 RU/ml predicted rMN with a sensitivity of 85% and a specificity of 92%.

Conclusions: Pre-transplant PLA2R-Ab could be a useful tool for the prediction of rMN. Patients with rMN in the absence of PLA2R-Ab should be screened for occult malignancy.

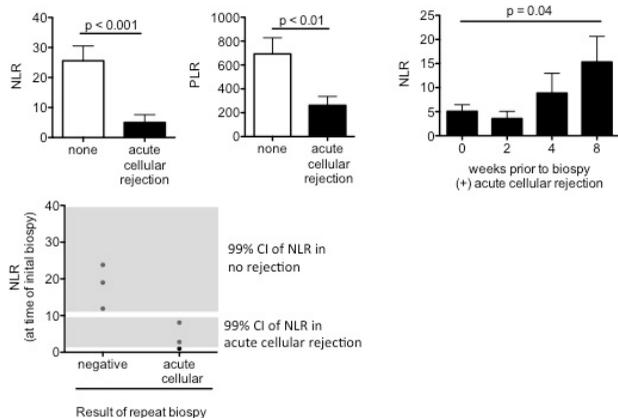
SA-PO966

Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio Predict Acute Allograft Rejection David S. Wheeler,¹ Scott Blumhof,¹ Manjula Balasubramanian,² Janani Rangaswami.³ ¹Internal Medicine, Albert Einstein Medical Center, Philadelphia, PA; ²Pathology, Albert Einstein Medical Center, Philadelphia, PA; ³Delaware Valley Nephrology and Hypertension Associates, Philadelphia, PA.

Background: Currently, allograft biopsy is gold standard for diagnosing rejection however there is intense interest in identifying non-invasive biomarkers. The goal of this study is to determine whether the neutrophil-to-lymphocyte ratio (NLR) or the platelet-to-lymphocyte ratio (PLR) correlate with acute allograft rejection.

Methods: This single center retrospective case-control study examined all kidney transplant biopsies conducted at Einstein Medical Center from Jan 2013 through Dec 2014. Biopsies were stratified for rejection (acute cellular, borderline, negative). The NLR and PLR was calculated from routine laboratory studies obtained at various time points preceding the biopsy.

Results: Of the 102 "for cause" biopsies, 37.3% showed clear evidence of acute rejection and 18.6% were borderline. NLR and PLR obtained within the week prior to the biopsy showed a significant reduction (4-fold and 3-fold respectively) in patients with acute cellular rejection. This reduction in NLR and PLR preceded the biopsy by 2-4 weeks suggesting a rejection prodrome. Interestingly, NLR at the time of borderline biopsy accurately predicted rejection status on subsequent biopsy conducted within 8 weeks.



Conclusions: NLR and PLR are highly sensitive biomarkers for acute rejection which become positive prior to other clinical manifestations. Furthermore, in cases of borderline biopsies NLR accurately predict the result of subsequent biopsies. The inclusion of NLR and PLR could revolutionize allograft rejection evaluation by reducing the need for biopsies and providing additional insight in cases where the biopsy is non-diagnostic.

SA-PO967

Transitional B Cell T1/T2 Ratio Is a Prognostic Marker for Human Renal Allograft Deterioration Aravind Cherukuri,¹ D. Rothstein,¹ Richard J. Baker.² ¹Univ of Pittsburgh; ²Univ of Leeds.

Background: Human transitional B cells (TrB) may play a significant role in auto and alloimmune disease. We previously showed that TrB express a high IL10:TNF α ratio and that this ratio fell with acute rejection. TrB are comprised of less mature T1 and more mature T2 cells.

Methods: We characterized the cytokine expression of T1 vs. T2 cells (identified by differences in CD24&CD38 expression) and investigated the utility of T1/T2 ratio as a biomarker for allograft deterioration (graft loss or 50% decline in eGFR).

Results: While both T1 and T2 cells expressed similar IL10, T1 cells expressed less TNF α and had a higher IL10:TNF α ratio. Thus T1 TrBs represent the B subset with the most anti-inflammatory profile. T1 cells were found to fall in rejection (resulting in lower T1/T2 ratio), contributing to the change in IL10:TNF α ratio. When analysed in a test set of 84 renal transplant patients, T1/T2 ratio was a strong predictor of allograft deterioration over a 5 year follow-up (ROC AUC 0.84, P<0.001). In a multivariate Cox model, T1/T2 ratio was independently associated with allograft deterioration (HR 4.8 95% CI 1.3-17.8, P=0.02). T1/T2 ratio was examined 2 years post-transplant in a prospective validation set of 97 stable patients derived from a steroid avoidance RCT comparing alemtuzumab (n=51) or basiliximab induction (n=46). T1/T2 ratio was a strong predictor of outcome over the next 5 years (ROC AUC 0.82, P<0.001) and was independently associated with allograft deterioration (HR 26.6, 95% CI 3.1-227.3, P=0.003). In both the test and validation sets, T1/T2 ratio was a much stronger predictor of graft deterioration than traditional markers like eGFR (test set, eGFR ROC AUC 0.76 vs. T1/T2 ratio 0.84, Z statistic 0.97; validation set, eGFR ROC AUC 0.64 vs. T1/T2 0.82, Z statistic 1.92), or the detection of DSA (test set, DSA ROC AUC 0.68 vs. T1/T2 ratio 0.84, Z statistic 2.9; validation set, DSA ROC AUC 0.66 vs. T1/T2 0.82, Z statistic 2.35).

Conclusions: We demonstrate a distinct subset of TrB (T1) characterized by an anti-inflammatory cytokine profile. A decrease in T1:T2 ratio (due to selective loss of T1 cells) is a strong prognostic biomarker for subsequent renal allograft deterioration.

Funding: Private Foundation Support

SA-PO968

The Pre-Transplant Ratio of T Regulatory Cells to Effector/Memory CD8+ T Cells Is Correlated with the Development of Acute Rejection Kentaro Sugisaki, Qizhi Tang, Sang-Mo Kang. *Surgery, Medical Center, Univ of California, San Francisco, San Francisco, CA.*

Background: Acute rejection (AR) or renal allografts are a major predictor for the development of chronic allograft nephropathy (CAN) and subsequent graft loss. Although clinical risk factors for the development of AR have been identified, few techniques exist to individually stratify patients for the risk of AR and provide a rational basis for the tailoring of immunosuppression regimens. Over the past two decades, regulatory T cells (Treg) have been identified and subsequently shown to be critical to the prevention of autoimmunity as well as the prevention on organ allograft rejection in numerous models. In parallel, the identification of various T lymphocyte subsets has been greatly refined, allowing a more precise quantitation and correlation with outcomes.

Methods: We hypothesized that Treg abundance pre-transplant could predict for the development of acute rejection in patients undergoing de novo renal transplantation. We prospectively enrolled 76 renal transplant patients undergoing first transplant from August 2013 to March 2014. We excluded patients undergoing second transplants, desensitization protocols, or involved in other clinical trials. Venous blood samples from all recipients at transplant date were isolated the peripheral blood mononuclear cells (PBMCs) and stored. We analyzed the samples in batches and normalized cell surface and intracellular staining using a standard control, using a NAVIOS flow cytometer (Beckman Coulter). All recipients were followed for a minimum of 1 year for the development of biopsy proven rejection.

Results: 12 recipients experienced AR. The pre-transplant ratio of Treg and Effector memory (EM) CD8 (Treg/EM CD8) T cells was significantly lower in patients who developed rejection, as compared to patients who did not experience rejection (45 recipients). Other T cell subsets were not associated with the development of acute rejection.

Conclusions: Our data suggests that the pre-transplant ratio of Treg/EM CD8 T cells may identify patients at increased risk of AR and should encourage larger scale studies to validate and quantify the magnitude of risk as well as to assess covariables.

SA-PO969

The Association of Th17 Cell Phenotype with Chronic Allograft Dysfunction in Kidney Transplant Recipients Byung Ha Chung, Hyunseon Kim, Chul Woo Yang. *Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea.*

Background: The purpose of this study is to determine the significance of the Th17 cell pathway in the progression of chronic allograft dysfunction.

Methods: We investigated the expression of T cell phenotype in long-term stable kidney transplant recipients (KTRs)(LTS, n=67), chronic allograft dysfunction group (CAD, n=52), and also in three control groups (early stable KTRs (ES, n=28), end stage renal disease (ESRD, n=45), and healthy control (HC, n=26)).

Results: The percentage of Th17 cells out of CD4⁺ T cells and the proportion of IL-17 producing cells out of effector memory T cells showed a significant increase in the CAD group compared to the LTS group and other control groups (P < 0.05). In addition, The percentage of CCR4⁺CCR6⁺CD4⁺ T cells and IL-17 producing cells out of CCR4⁺CCR6⁺CD4⁺ T cells was higher in the CAD group than in the LTS group (P<0.05). However, the percentage of Th1, Th2, and regulatory T cells did not differ significantly between the CAD and LTS groups (P > 0.05). Also, the serum level of IL-17, IL-33, and RAGE, and the expression of IL-1beta, RAGE, and HMGB1 mRNA showed an increase in the CAD group compared to the LTS group. Lastly, IL-17 induced acute and chronic injury in the human proximal renal tubular epithelial cell line in a dose-dependent manner.

Conclusions: In conclusion, we found the activation of the Th17 cell pathway in patients with chronic allograft dysfunction. The results of this study suggest that Th17 pathway may have a role in the progression of chronic allograft injury.

SA-PO970

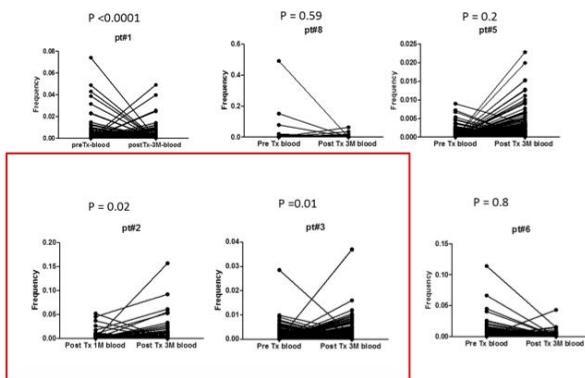
Quantitative Characterization of T Cell Repertoires in Kidney Transplant Patients Houda Alachkar,¹ Martin B. Mutonga,¹ Taigo Kato,¹ Sowjanya Kalluri,³ Vikas Vujjini,² Yusuke Nakamura,² Nada Alachkar,² ¹Univ of Chicago; ²Johns Hopkins Univ; ³Kendall Medical Center.

Background: Acute and chronic T cell mediated rejection remains a major cause of kidney graft failure. Despite the significant decrease in early acute rejection due to current potent immunosuppressions, long-term graft survival remains unsatisfactory. Thus, characterization of the T cell repertoire and the kinetic of the expanded clones in transplant (Tx) patients may shed a light on our understanding of the T cells' role in graft rejection.

Methods: We collected blood and urine samples from (46) patients before Tx, and at sequential time points post Tx and at time of T cell mediated rejection. We utilized next generation sequencing approach to characterize T cell receptor (TCR) repertoire. Sequencing using the illumina miSeq was performed on cDNA synthesized from RNA extracted from patients' samples. This approach enables to track each expanded TCR clone in the graft at 3 months post Tx, back to their first appearance in blood and urine samples obtained pre or 1 month post Tx. We also measured the RNA expression levels of CD8, CD4, FOXP3, Granzyme and Perforin in blood samples (N=43).

Results: Only patients with acute T cell mediated rejection (n=2) had TCR repertoires defined by the top 10 TCR clones appeared at any time point in blood, showed significant expansion in blood at 3 month post Tx compared with that at 1 month post Tx (P=0.01 and 0.02). CD8, FOXP3, Granzyme and perforin RNA levels were significantly higher in samples obtained from patients with rejection compared to that in patients with no rejection (P<0.02).

Fig.4: Pattern of changes of CDR3 Frequencies in Blood of Kidney Transplant Patients



Conclusions: Our study provides valuable comprehensive longitudinal analyses that define the kinetics of each TCR beta clone, and the changes in diversity of CDR3. This approach allows for identification of the expanded T cell clones that are possibly associated with graft rejection.

SA-PO971

Critical Appraisal of the New Banff Criteria for Chronic Antibody-Mediated Rejection in the Real Life Setting Isabelle Houde, Isabelle Côté, Mohsen Agharazii, Sacha A. De Serres. *Renal Div, Quebec Univ Health Center, Laval Univ, Quebec City, QC, Canada.*

Background: Significant changes in the criteria for chronic active antibody-mediated rejection (CAABMR) were made at the 2013 meeting, which is of major concern for clinical management. Here we compared the 2007 vs. 2013 criteria with regards to clinical outcomes.

Methods: Single-center, observational retrospective cohort study of all patients who received an indication biopsy between January 2006 and October 2014, during which EM evaluation, ptc scoring and C4d scoring by IH and IF was routinely performed. Patients were included if they met the criterion 1 for CAABMR: score cg1a>0, cg1b>0 or severe peritubular capillary basement membrane multilayering. GN, immune deposits, HCV+ status or suspicion of TTP-HUS were excluded. The endpoint was a composite of doubling of serum creatinine and death-censored graft loss.

Results: 123 patients were included. 18% met the full 2007 criteria, whereas an additional 18% fulfilled the full 2013 criteria. Only 25% of patients met the 2007 criterion #2-C4d, in contrast to 82% for the 2013 criterion #2-microvascular injury (MVI): 67% were C4d-positive and 55% were g+ptc positive, with substantial overlap. 45 patients experienced the endpoint at a median of 22mo post-biopsy. Overall, only a 2013 diagnosis of CAABMR was associated with the endpoint (adjusted HR=2.5 [1.2-5.2] for 2013 vs. HR=1.6 [0.7-3.8] for 2007 diagnosis). Adjusted Cox modelling revealed that the 2013 criterion #2-MVI was more strongly associated with the endpoint than the 2007 criterion #2-C4d (HR=4.0 [1.1-14.1] vs. HR=2.3 [1.03-5.3]). When the 2013 criterion #2 was dissected by component, the C4d-component was significant (HR=2.5 [1.1-5.4]), but not the g+ptc (HR=1.1 [0.5-2.3]).

Conclusions: Compared to the 2007 criteria, applying the 2013 criteria here doubled the proportion of patients with CAABMR. Importantly, it improved the association with clinical outcomes.

SA-PO972

Tissue Expression of Aquaporin 2 Is Correlated to Urine Output and Allograft Function in Sensitized Kidney Transplant Patients Luis Eduardo Becker,¹ Martin G. Zeier,¹ Christian Morath,¹ ¹Nephrology, Univ of Heidelberg, Germany; ²Pathology, Univ of Heidelberg, Germany.

Background: Salt and water disturbances often occur during acute kidney allograft dysfunction contributing to graft failure, but this condition has still been poorly investigated in the setting of alloreactivity. We evaluated the tissue expression of aquaporins (AQP1, AQP2) and of the epithelial sodium channel (ENAC) in kidney allograft biopsies from transplant patients with high immunological risk.

Methods: Eighty-six kidney transplant biopsies from thirty-three sensitized patients were divided into three groups according to the clinical context an possible pathological correlates as follows: time-zero (N=9), protocol (N=9) and indication (N=68) biopsies. The indication biopsies were further divided into three subgroups, according to the presence or absence of acute tubular necrosis or acute rejection. Normal kidney tissue samples (N=6) served as controls. Immunohistochemical expression of AQP1, AQP2 and ENAC was analyzed with assistance of an image software.

Results: We observed a significantly lower AQP1 expression in time-zero and indication biopsies with rejection compared to controls (7.7±2.0% and 9.1±0.6% vs. 14.3±2.9% of area positively stained; P=0.03 and P=0.04 respectively). AQP2 expression was significantly lower in patients with an indication biopsy when compared to controls and protocol biopsies (2.1±0.2% vs. 4.4±0.7 and 4.0±0.5% of area positively stained, P=0.05 and P=0.005, respectively). For ENAC, a lower expression in indication biopsies compared to controls was seen (P=0.04). Both AQP1 and AQP2 tissue expressions were significantly correlated to the urine output (r=0.45 and r=0.32; P=0.001 and P=0.02, respectively), and AQP2 was correlated to the MDRD-glomerular filtration rate at the time of biopsy (r=0.23; P=0.05).

Conclusions: Our findings can partially confirm previous experimental data showing downregulation of AQP1 expression after ischemia-reperfusion injury and during rejection. AQP2 downregulation seems to be rejection-independent occurring during deteriorating or poor kidney graft function.

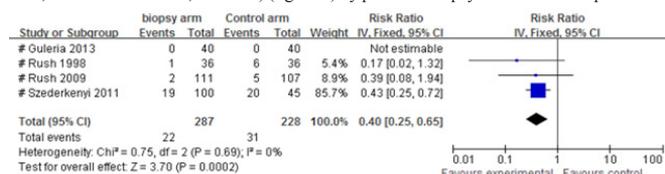
SA-PO973

The Utility of Protocol Biopsy in Renal Recipients: Meta Analysis and Systematic Review Guga Suri. *Kidney Disease, The First Affiliated Hospital of Zhejiang Univ, Hangzhou.*

Background: To evaluate the value of protocol biopsy in patients after renal transplantation.

Methods: Searches were applied to the following electronic database: Medline, Embase Database, Cochrane Library. Randomized controlled trails evaluating the value of protocol biopsy for renal allograft recipients were included. Data were extracted independently by two reviewer. The risk of bias of included studies was assessed by the Cochrane collaboration's tool for assessing risk of bias.

Results: 5 RCTs were included. Long term graft loss was significantly reduced (RR 0.40, 95%CI 0.25 to 0.65, P<0.001) (figure 1) by protocol biopsy after renal transplantation.



Protocol biopsy may reduce the long term serum creatinine (WMD 38.21, 95% CI 54.83 to 21.60, p<0.00001). For renal recipients whose basal immunosuppression is CNI (tacrolimus or cyclosporine), protocol biopsy can significantly improve the long term eGFR (SMD 0.78, 95% CI 0.51 to 1.05, P<0.00001). However, for those whose basal immunosuppression is tacrolimus, this effect is not notable. Protocol biopsy seems to have no significant beneficial effect of reducing clinical acute rejection episodes.

Conclusions: Treatment of subclinical rejection detected by protocol biopsy can significantly improve the graft survival and may improve the allograft function.

SA-PO974

Longitudinal Biopsy Findings Among Children, Adolescents, and Young Adult Renal Transplant Recipients from a Southeastern USA Cohort Jonathan Alexander Miles,¹ Panupong Hansrivijit,^{2,3} Katherine D. Westreich,³ Evan Zeitler,³ Randal K. Detwiler,³ Maria E. Ferris,³ ¹East Carolina Univ, Greenville, NC; ²Chulalongkorn Univ, Bangkok, Thailand; ³UNC at Chapel Hill, Chapel Hill, NC.

Background: Longitudinal procedure history in children, adolescent, and young adult renal transplant recipients needs to be characterized based on their primary cause of end-stage renal disease (ESRD). It is known that pediatric patients are a high risk group for transplant failure. Elucidating potential factors for transplant failure in this group is important for protecting valuable renal transplants.

Methods: Clinical, demographic and pathological records of patients who received a renal transplant at age ≤ 30 years of age and who underwent transplant biopsies between 2000 and 2014 at the UNC Hospitals were analyzed. This cohort was classified based on

the primary cause of ESRD as either glomerular or non-glomerular. Demographics, number of biopsies (total and adjusted for graft years), and transplant failure (rates and cause) were compared between the two groups.

Results: We enrolled 179 patients; 105 (58.7%) were male; 67 (38%) African American, 92 (51%) Caucasian, and 20 (11%) other race. Their mean age at transplant was 18.7 ± 8.2 years and 98 (55%) had a glomerular cause of ESRD. This cohort underwent a total of 505 graft biopsies. Comparing patients with glomerular vs. non-glomerular conditions, we found no significant differences in cellular or humoral rejections (p=0.430); mean number of biopsies (3.0 ± 1.9 glomerular; 2.7±1.9 non-glomerular; p=0.289); mean number of biopsies per year for failed transplants (p=0.702), current functioning grafts (p=0.090); time to a failed transplant (p=0.476); or age at time of transplant (p=0.136).

Conclusions: In this single institution cohort of children, adolescents and young adults, we found no statistical differences in renal biopsy findings regarding number of biopsies and transplant failure. This high risk age group shows no different longitudinal graft survival based on primary cause of ESRD. More analysis will follow.

Funding: Private Foundation Support

SA-PO975

Prospective Study of Risk Factors and Impact of Subclinical Rejection (SCR) and Acute Clinical Rejection (ACR) in Renal Transplant Recipients
 Rajil B. Mehta,¹ Puneet Sood,¹ Aravind Cherukuri,¹ Shan Shan Chen,¹ Chethan M. Puttarajappa,¹ Christine Wu,¹ Nirav A. Shah,¹ Parmjeet S. Randhawa,² Sundaram Hariharan.¹ ¹Starzl Transplantation Inst, Univ of Pittsburgh Medical Center, Pittsburgh, PA; ²Dept of Pathology, Univ of Pittsburgh Medical Center, Pittsburgh, PA.

Background: The long term outcomes of subclinical rejection (SCR) remain unclear. The current study evaluated the risk factors for SCR at 3 mths and followed up renal function upto 1 year in pts with SCR, ACR and no rejection.

Methods: We prospectively followed 340 pts who underwent an ABO compatible kidney transplant between Jan 2013 and Sep 2014. Eight pts were excluded. All patients received induction therapy with either thymoglobulin (95%) or Basiliximab for induction, CNI/MPA for maintenance therapy and rapid steroid withdrawal by day 7. Protocol biopsies were performed 3 months post transplant. Based on this, they were divided into 4 groups. Grp 1 - pts with SCR; Grp 2 - pts with normal biopsy; Grp 3 - pts with ACR; Grp 4 - pts with no biopsy. Banff classification was followed for biopsy grading. Steroids, thymoglobulin and PP/IVIg were used as indicated for the treatment of rejection.

Results:

	Grp 1 (SCR)	Grp 2 (Normal Bx)	Grp 3 (ACR)	Grp 4 (No Bx)	p value
	44/236 (18.6%)	159/332	33/332 (9.9%)	96/332	
Age (yrs)	50+/-16	52+/-15	48+/-15	55+/-12	0.07
Sex (M/F)	28/16	100/59	15/18	52/44	0.048
Race (W/O)	34/10	126/33	25/8	80/16	0.07
CIT (mins)	474+/-327	409+/-386	396+/-316	510+/-380	0.16
DGF (Y/N)	13/31	17/142	5/28	21/75	0.01
HLA mm	4.1+/-1.5	3.9+/-1.7	4.25+/-2	3.96+/-1.8	0.7
HLA DR mm	1.23+/-0.7	1.12+/-0.7	1.41+/-0.7	1.31+/-0.7	0.08
DSA (Y/N)	11/27	23/109	9/24	13/73	0.18
PRA I	6.7+/-17	6.5+/-19	7.9+/-19	14+/-37	0.13
PRA II	10.8+/-26	14.8+/-29	7.1+/-22	12.6+/-27	0.48
Cr 3m	1.52+/-0.4	1.42+/-0.5	1.69+/-0.48	1.33+/-0.46	0.0064
Cr 6m	1.52+/-0.5	1.46+/-0.5	1.54+/-0.37	1.26+/-0.42	0.012
Cr 1yr	1.6+/-0.46	1.5+/-0.77	1.66+/-0.48	1.38+/-0.63	0.20
Banff Gr (Bord/IA or >)	25/75	NA	27/73	NA	

Conclusions: 1. Incidence of SCR and ACR around 3 mths was 18.6% and 9.9% respectively 2. Significant risk variables for SCR/ACR were female recipients and DGF 3. No difference in renal function was noted between the groups at 1 year.

SA-PO976

Histological Scoring System Predicts Renal Outcome of Post Transplantation Acute Tubular Necrosis
 Tobias Pieters, Lucas Falke, Tri Q. Nguyen, Marianne C. Verhaar, Roel Goldschmeding, Maarten B. Rookmaaker. *Nephrology and Pathology, UMC Utrecht, Netherlands.*

Background: Acute Tubular Necrosis (ATN) is a common cause of Delayed Graft Function (DGF) after renal transplantation (RTX). Currently no histological model is available to predict renal outcome. Recovery of ATN is the result of the balance between damage and repair. In this study we evaluated the predictive value of immunohistochemical parameters of renal damage and regeneration and compared these to an accepted clinical prediction model for cadaveric renal transplantation.

Methods: We included 25 patients that underwent cadaveric RTX with DGF caused by ATN only, as shown in a renal biopsy 1 week after RTX. Biopsies were evaluated for histological tubular damage (atrophy, edema, casts, vacuolization), DNA damage (yH2AX staining) and apoptosis (cC3 staining). Regeneration was assessed by staining for stem cell marker CD133 and proliferation marker Ki67. Clinical parameters for renal outcome were collected as previously described in the Deceased Donor Score (DDS). The relation between these parameters and renal outcome, defined as eGFR at 6 months, was assessed using regression or one-way ANOVA. A corrected analysis for regenerative markers was performed to eliminate potential confounding by the amount of renal damage.

Results: The histological damage score significantly predicted renal outcome (R:-0.52 P:0.01), whereas the DDS only tended to correlate with renal outcome (F:3.12 R: P:0.05). Neither staining for DNA damage, nor for apoptosis could predict renal outcome (R:-0.24 P:0.91 and R:-0.16 P:0.44 respectively). In addition, the investigated parameters for regeneration (CD133 and Ki67) did not predict renal outcome (R:-0.25 P:0.23 and R:-0.10 P:0.63 respectively), also not after correction for renal damage.

Conclusions: We are the first to show that histological parameters can predict renal outcome of post transplantation ATN. Importantly, our histological damage score correlated better with renal outcome than the DDS. Despite the crucial role of regeneration in recovery after ATN, no relation was found between stem cell marker CD133, proliferation marker Ki67 and renal outcome.

Funding: Pharmaceutical Company Support - Dutch Kidney Foundation The Netherlands Institute for Regenerative Medicine

SA-PO977

Histopathological Changes and Graft Survival of Long-Term Kidney Allograft in Alport Syndrome: A Single-Center Experience in Japan
 Yasuyuki Nakada,¹ Izumi Yamamoto,¹ Akimitsu Kobayashi,¹ Yudo Tanno,¹ Hiroyasu Yamamoto,¹ Masayoshi Okumi,² Hideki Ishida,² Takashi Yokoo,¹ Kazunari Tanabe.² ¹Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ of Medicine, Tokyo, Japan; ²Dept of Urology, Tokyo Women's Medical Univ, Tokyo, Japan.

Background: Patients with Alport syndrome (AS) commonly develop progressive kidney dysfunction due to a hereditary type IV collagen deficiency, which results in an abnormality in the glomerular basement membrane (GBM). Recurrent glomerulonephritis does not occur in transplanted kidneys, and the allograft survival rate in these patients is similar to that in patients with other renal diseases. Several studies have shown that the type IV collagen of the GBM originates from the recipient's bone marrow-derived cells. Therefore, we postulated that recurrent glomerulonephritis could occur locally and should influence the long-term allograft survival. In this study, we investigated graft survival and histopathological changes in renal allograft recipients with AS, focusing particularly on whether the expression of GBM type IV collagen is altered.

Methods: We collected data on the clinical characteristics of 19 renal allograft recipients who had been diagnosed with AS. All data were obtained from a database at the Department of Urology, Tokyo Women's Medical University. Graft survival was evaluated using the Kaplan-Meier method and compared with a control group (n = 18). We assessed the double staining of α2 and α5 using frozen specimens obtained from long-term allograft survival samples.

Results: The graft survival rate was not statistically different between patients with AS and controls (log-rank p = 0.2240). Immunoreactivity to α5 antibody in four patients exhibiting long-term allograft survival showed strong linear positivity and no GBM abnormalities. In the case of chronic active antibody-mediated rejection, the immunoreactivity to anti-α2 antibodies increased in the mesangium and subendothelial space.

Conclusions: These results suggest that the GBM type IV collagen structure was histopathologically maintained for the long term after kidney transplantation, indicating better kidney graft survival in patients with AS.

SA-PO978

Histological Assessments from Kidney Transplant Biopsies: An Explorative Post Hoc Analysis of ZEUS 5 Year Data Ute Eisenberger,² Claudia Sommerer,¹ Ingeborg A. Hauser,¹ Frank Lehner,¹ Rudolf P. Wuthrich,² Petra Reinke,¹ Anja Susanne Mühlfeld,¹ Katharina M. Heller,¹ Rolf A. Stahl,¹ Heiner H. Wolters,¹ Klemens Budde,¹ Martina Porstner,³ Oliver Witzke,¹ Wolfgang Arns.¹ ¹ZEUS Study Group, Germany; ²ZEUS Study Group, Switzerland; ³Novartis Pharma, Germany.

Background: Analysis of pathologists' assessments and histological data allow for deeper insight on patient outcome when combined with investigators final clinical diagnoses. Here we present 5 year data from de novo kidney transplant (KTx) recipients after conversion to an everolimus(EVR) based regimen and withdrawal of CNI therapy vs. continued CNI regimen.

Methods: Post hoc analysis of histological and pathologists' assessments from ZEUS, a prospective, open-label, controlled, multi-center study. At mo 4.5 post Tx 300 KTx patients (pts) were randomized to either EVR + enteric coated-mycophenolate sodium (EC-MPS; n=154) or cyclosporine (CsA) + EC-MPS (n=146). After 12mo interventional study, observational follow-up (FU) on pts safety and efficacy was performed until mo60 post Tx. As per study protocol, graft core biopsies were indicated by suspected rejection episode. Biopsies were read and interpreted by local pathologists.

Results: Total number (nr) and mean nr of biopsies per patient performed are overall similar in both groups until mo60. Nr of pts with at least one rejection (as per final clinical diagnosis) was slightly higher in CNI group vs EVR group. Nr of pts with BPAR was higher in the EVR group especially due to mild, early acute rejections (mostly BANFF IA and IB). Nr of pts with histological evidence of chronic/sclerosing allograft nephropathy was similar in both groups (both 10%), C4d staining positivity was found slightly higher in the EVR group (11% EVR vs 7% CNI), however, pts with evidence of antibody mediated rejection was higher in the CNI group (2% EVR vs 4% CNI), same for CNI-induced toxicity lesions (16% EVR vs 23% CNI).

Conclusions: Data from histological assessments together with investigator reported final clinical pts outcome show that an EVR-based regimen with early elimination of CNI-therapy is as safe and efficacious as standard CNI-therapy offering the opportunity to reduce cumulative CNI-induced toxicities on the allograft.

Funding: Pharmaceutical Company Support - Novartis Pharma GmbH

SA-PO979

Endothelial Microvesicles as a Biomarker of Antibody-Mediated Endothelial Injury Erik Stites,¹ Moglie Le quintrec,² Brandon Renner,¹ Jennifer Laskowski,¹ Karissa Fetrow,¹ Joshua M. Thurman.¹ ¹Univ of Colorado Health Sciences Center, Aurora, CO; ²Transplantation Rénale, Hôpital Lapeyronie, Montpellier, France.

Background: Endothelial injury and inflammation are hallmark histopathologic features of antibody-mediated rejection (AMR) in renal transplantation. Antibodies against HLA on the endothelial cells activate the complement system via the classical pathway. The diagnosis of AMR is dependent upon pathologic examination of renal biopsy tissue. A clinical need exists for a noninvasive method for diagnosing AMR. Endothelial cells constitutively release sub-micron vesicles called microvesicles into the circulation, but the release of microvesicles is altered in response to a variety of stimuli. The aim of this study was to evaluate the effect of antibody binding and subsequent complement activation on the production of endothelial microvesicles *in vitro* and to explore endothelial microvesicles from human samples as a potential biomarker of AMR in renal transplant recipients.

Methods: We have developed an *in vitro* model of AMR using immortalized human endothelial cells (HMEC-1) and a monoclonal murine antibody against human HLA class I molecules (W6/32). We analyzed antibody binding and complement deposition with immunohistochemistry and flow cytometry. Microvesicle analysis was performed using flow cytometry.

Results: We have shown that W6/32 antibody binds HMEC-1 cells and activates the classical complement pathway upon exposure to normal human serum. This leads to deposition of complement split products on the cell surface (analogous to C4d deposition in biopsies from patients with AMR) and increased release of endothelial microvesicles. Furthermore, anti-HLA antibody (W6/32), C3, and C4 were deposited on the surface of the microvesicles.

Conclusions: Our results suggest that AMR will lead to an increase in production of microvesicles by the renal endothelium, and AMR-associated microvesicles will have surface-bound IgG and C4d. We have obtained human plasma samples from renal transplant recipients with AMR and healthy controls, and we are currently examining the potential of endothelial microvesicles as a biomarker of AMR.

Funding: NIDDK Support

SA-PO980

Dual Leukocyte/Endothelial Stain for Assessment of Endocapillary Inflammation in the Renal Allograft A. Rosenberg,¹ Jonathan Levi,² S.M. Bagnasco,¹ Naima Carter-Monroe.¹ ¹JHU; ²NIDDK.

Background: The pathologist's assessment of renal allograft rejection relies on the evaluation of the pattern of involvement by inflammatory cells. The Banff criteria for renal allograft rejection now includes semiquantitative evaluation of inflammation involving peritubular capillaries (ptc), glomeruli (g), arterial intima (v), tubulitis (t), interstitium (i) and

total renal parenchyma (ti) have been elaborated as indices of antibody (g and ptc) versus cell-mediated rejection (v, t, i and ti). Accurate assessment of these various compartments can be difficult and their reproducibility a particular challenge.

Methods: We evaluated a dual pan-leukocyte marker (LCA) and a vascular endothelial marker (CD34) immunohistochemical stain as an ancillary tool for evaluating intravascular (g and ptc) vs tubulointerstitial inflammation. Nineteen cases underwent blinded review of the dual stain.

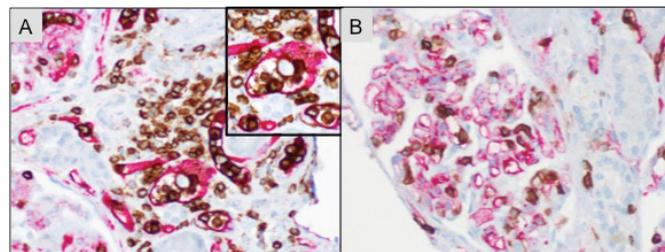


Figure: Dual leukocyte/endothelial stain highlighting in (A) peritubular capillaries (red) and leukocytes (brown); also highlighting in (B) glomerular capillaries (red) and leukocytes. Both dual CD34/LCA immunoperoxidase: Panel A (400x, 600x insert), Panel B (400x)

Results: Overall, good concordance was present between cases originally scored g3 and those meeting criteria on dual stain (9/10), but lesser agreement for cases originally scored g2 with only 1/9 (11%) meeting the same criteria on dual stain. Most cases (4/5) originally scored as ptc2 continued to meet criteria on dual stain, but approximately 35% (5/14) of cases originally scored as ptc3 met criteria for either ptc1 or ptc2 on dual stain.

Conclusions: Dual LCA/CD34 IHC aided the evaluation quantization of inflammatory infiltrate in renal allograft rejection, possibly allowing finer and more reproducible discrimination between ptc and i scores and identifying the extent of glomerulitis. Annotation of whole slide images will be performed to yield a quantitative metric for ptc on a continuous scale for comparison to the current quantized scale. Implementation in larger cohorts and in a consensus setting will be needed to determine improvement in the diagnostic and prognostic yield of the current Banff-based biopsy assessment.

Funding: NIDDK Support

SA-PO981

Intragraft Granzyme-B Is Associated with Chronic Renal Transplant Glomerulopathy Narayan Prasad,¹ Brijesh Yadav,¹ Vikas Agarwal,¹ Dharmendra Bhadauria,¹ Raj K. Sharma.¹ ¹Nephrology, SGPGIMS, Lucknow, UP, India; ²Immunology, I.

Background: Chronic transplant glomerulopathy (CTG) and Interstitial fibrosis and tubular atrophy (IFTA) are two major causes of chronic allograft loss. CTG is often associated with either C4d deposition or, circulating donor specific antibody. Pathogenesis of IFTA is unclear. We aimed the study to determine the role of CD3+CD8+Gzm-B+ Cytotoxic T cells in pathogenesis of CTG and IFTA and to determine its significance as peripheral blood signature of CTG.

Methods: Total 58 (CTG 20, IFTA 28 and stable functioning graft SGF 10) living donor renal transplant recipient were recruited. Patients were categorized into 3 group based on Banff's 2007. We analyzed peripheral blood cytotoxic T cell by flow cytometry, Granzyme-B mRNA transcript in renal biopsy tissue by Taqman real time PCR and soluble Granzyme B level by ELISA.

Results: Age of patients in CTG, IFTA, and SGF group was 41.8±12.7; 36.50±8.34, 46.28±8.65 years; post transplant period at biopsy 63.92±41.0, 51.71±3.06, 70.0±15.42 months; Creatinine at biopsy 2.38±0.84, 2.30±0.86, 1.41±0.33 mg/dl, and daily urine protein 2.67±0.73, 2.22±1.96, 0.22 ±0.060 g; respectively. Peripheral blood CD3+CD8+ T cell frequency was 17.20±6.61% in CTG; 17.39±5.78% IFTA; and 13.20±1.02% SGF respectively (p=0.436). Peripheral cytotoxic T cell frequency (CD3+CD8+Gzm-B+) was significantly low in CTG group (12.62±1.68%), as compared to IFTA (16.44±4.09%), (p=0.012) and SGF 26.35±2.95% (p=0.001). Intragraft mRNA of Granzyme-B in CTG was 3.05 fold high as compared to SGF. In IFTA intragraft Gzm B mRNA was 2.26 fold high compared to SGF (p<0.001). Soluble serum Granzyme B level was significantly high in CTG (423.7±135.20; p<0.001), as compared to IFTA (249.5±73.05; P<0.001), and SGF (91.88±30.89) pg/ml. This suggests that sequestration of cytotoxic T cells into graft resulted in low circulating cytotoxic cells and increased intragraft Gzm-B+ cells leading to Granzyme-B dependent injury and CTG.

Conclusions: Low peripheral blood cytotoxic T cell (CD3+CD8+Gzm-B+) frequency and high intragraft mRNA transcript of Granzyme-B in CTG suggest role of cytotoxic T cells in CTG. Lower circulating CD3+CD8+Gzm-B+ Cytotoxic T cells can be peripheral blood signature for CTG.

SA-PO982

Molecular Features of Kidney Transplant Biopsies with Interstitial Fibrosis/Tubular Atrophy in the Presence of Sterile Leukocyturia Maria Ajaimy, Enver Akalin. *Einstein-Montefiore Transplant Center, Albert/Einstein College of Medicine, Bronx, NY.*

Background: We hypothesized that sterile leukocyturia could reflect an increased intragraft immune activity and investigated gene expression profiles of transplant kidney biopsies of patients with sterile leukocyturia comparing to patients without leukocyturia.

Methods: We identified 15 normal transplant kidney biopsies without leukocyturia (Group 1) and 33 biopsies with non-specific interstitial fibrosis/tubular atrophy (IFTA) for gene expression profiling. Of the 33 biopsies with IFTA, 24 patients had no sterile leukocyturia (Group 2) and 9 patients had sterile leukocyturia (Group 3). Biopsies with a diagnosis of acute or chronic rejection, recurrent or de novo glomerular disease, or polyoma nephropathy were excluded. Sterile leukocyturia was defined by the presence of leukocytes in the urine (>10⁴/mL) without bacterial growth in urine culture. The analysis was done within 1 month before or after the biopsy. The gene expression profiles were studied by Affymetrix HuGene 1.0 ST expression arrays.

Results: There was no difference in terms of age, race, and sex, type of transplant, previous history of transplantation or acute rejection, donor characteristics, panel reactive antibody levels and immunosuppressive treatment between the Groups 2 and 3. Both groups also had similar acute and chronic Banff allograft injury scores. There was no statistically significant difference in gene expression profiles between the Groups 1 and 2. When Group 3 biopsies were compared to the Group 1 and 2 biopsies, significantly increased gene transcripts associated with cytotoxic and regulatory T cells, and macrophages (P-value for significance <0.05). There was a trend towards increased interferon-gamma and rejection associated transcripts but no statistically significant difference in expression of B-cell or natural killer cell associated transcripts.

Conclusions: The biopsies of the patients with sterile leukocyturia showed increased expression of gene transcripts associated with T cells indicating heightened intragraft immune activity. Those patients might require close monitoring of their allograft function.

SA-PO983

Elevated Glomerular Mechano-Growth Factor and Vascular Endothelial Growth Factor in Chronic Allograft Nephropathy Is Associated with Activation of Erk1/2 Yongxin Gao,¹ Raafat Farag Makary,² Carmela B. Monteiro,² Leighton R. James,¹ Charles W. Heilig,¹ ¹Medicine, Univ of Florida College of Medicine-Jacksonville, Jacksonville, FL; ²Pathology, Univ of Florida College of Medicine-Jacksonville, Jacksonville, FL.

Background: We previously identified increased GLUT1 glucose transporter, Mechano-Growth Factor (MGF) and Vascular Endothelial Growth Factor (VEGF) in human Chronic Allograft Nephropathy (CAN) kidneys which demonstrate glomerulosclerosis. Here we investigated a glomerular signaling pathway, Erk1/2, with potential to mediate effects of MGF and VEGF on extracellular matrix (ECM) genes. We employed IHC with specific antibodies to assess protein expression for MGF, VEGF and phospho-Erk1/2 (active Erk1/2) in human CAN kidneys vs. Normal Control kidneys.

Methods: This study involving examination of archived renal biopsy samples was approved by the Institutional IRB. N = 6 for each group of renal transplant - and native kidney biopsies. Immunolabelling of human CAN and Normal Control paraffin-mounted kidney sections was performed for assessment of selected proteins with specific antibodies, by use of immunoperoxidase staining. Scoring of glomerular immunolabelling for individual proteins was 0 - 4+ for semiquantitation. Data were normalized to open glomerular tuft area. P < .05 was considered significant in statistical analyses.

Results: Glomerular MGF protein was increased 3.9-fold in CAN kidneys vs Normal Control kidneys, P < .0001. Glomerular VEGF was elevated 3.0-fold in CAN vs Normal Control kidneys, P < .0001. Both of these growth factors have potential to signal via Erk1/2 to ECM expression. Glomerular Erk1/2 activation (i.e. phospho - Erk1/2) was examined and found to be increased 4.3-fold in CAN vs Control, P < .0001.

Conclusions: Human CAN, characterized by excessive glomerular MGF and VEGF expression, involved enhanced activation of Erk1/2 in the glomeruli. This provides a mechanism by which these glucose-responsive growth factors may induce glomerular ECM production and glomerulosclerosis. Therefore, MGF and VEGF activation of Erk1/2 may contribute to progressive glomerulosclerosis and renal failure in CAN.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO984

Microarray Analysis of Interstitial Fibrosis/Tubular Atrophy in Kidney Transplant Recipients Using Formalin-Fixed, Paraffin-Embedded Renal Biopsy Tissue Sanjeev Akkina,¹ Vishal K. Varma,² Michael J. Walsh,² Suman Setty,² ¹Medicine/Nephrology, Univ of Illinois at Chicago, Chicago, IL; ²Pathology, Univ of Illinois at Chicago, Chicago, IL.

Background: Interstitial fibrosis/tubular atrophy (IFTA) is a common and complex cause of kidney transplant failure that is difficult to predict. Early identification of progressive IFTA (pIFTA) may lead to alternative therapies that may attenuate irreversible injury. In this study, we used formalin-fixed, paraffin-embedded (FFPE) renal biopsy specimens with microarrays to conduct differential gene expression studies to identify predictors of IFTA in kidney transplant recipients.

Methods: We identified 22 individuals with multiple protocol biopsies within the first 3 years after transplant. Glomeruli and blood vessels were removed using laser capture microdissection and the remaining tissue was used for mRNA extraction. Affymetrix Primeview arrays were prepared using standard protocols. IFTA was determined by using image masking in Histolab to quantify the cortical interstitial fraction. pIFTA was defined as a 0.5% absolute increase in the interstitial fraction per month between serial biopsies. Data analysis was conducted using R 3.0.2 and Bioconductor 2.22. Significance was defined as an unadjusted p < 5 x 10⁻⁵.

Results: Of the 22 subjects in this study, 9 had pIFTA while the remaining 13 were considered stable IFTA (sIFTA). At baseline, the eGFR was 60.5 vs 58.5 mL/min/1.73m² (p=0.79) and log(Urine Albumin) was 3.44 vs. 3.17 (p=0.72) for the sIFTA and pIFTA groups, respectively. The baseline fibrosis was higher in the sIFTA group (18%) compared

to the pIFTA group (13%, p=0.04). Using linear modeling, 3 of the top 6 differentially expressed probes at baseline were mapped to metallothionein 1X and 2A. Paired analysis of serial biopsies did not reveal any significant differences between sIFTA and pIFTA.

Conclusions: Microarray analysis of FFPE specimens show that pIFTA is associated with the differential expression of multiple genes prior to phenotypic changes. Prospective investigation of these genes is needed to determine if these are predictive of pIFTA.

Funding: Private Foundation Support

SA-PO985

Pathological Analysis for Transplant Nephrectomy – 124 Consecutive Cases in a Single Center Study Over 10 Years Masaki Muramatsu,^{1,2} Abigail Lee,¹ Atsushi Aikawa,² Carmelo Puliatti,¹ Muhammad M. Yaqoob,¹ Michael Sheaff,¹ ¹Nephrology, Transplantation and Cellular Pathology, The Royal London Hospital, London, United Kingdom; ²Nephrology, Toho Univ Faculty of Medicine, Tokyo, Japan.

Background: Transplant nephrectomy (TNx) is performed for several indications. This study evaluates in depth histological analysis of TNx specimen.

Methods: We identified all cases at the Royal London Hospital between 2004 and 2014. The indication for TNx was divided into four groups: 47 cases with acute graft loss without significant blood flow (AGL); 44 cases of suspected ongoing rejection or graft intolerance syndrome (Rej/GIS); 24 cases with infection (INF); and 9 miscellaneous reasons (MIS). We examined the histological changes in detail and specifically looked at the artery, vein and ureter.

Results: AGL was less likely to have tubulointerstitial changes, but 74.5% had necrosis. In the AGL group, the majority of cases scored zero for t, i, ct and ci. Neutrophil rich arteritis at renal and small arteries was observed in 29.8% and 19.2%. Venous thrombosis was found in 61.7%. All cases in the Rej/GIS group showed ct3 and ci3 and 40.9% showed t3 and i3. Glomerulitis was observed in 52.3% and cg was detected in 75.1%. Arteritis of small and renal arteries was detected in 70.5% and 59.1%. C4d expression was present in 54.1%. Nearly 70% showed ureteric inflammation. Variable cellular infiltrate comprising of lymphocytes, plasma cells and eosinophil were seen in all cases. In the INF group, 66.7% (t1-3) and 79.2% (i1-3) were observed, and ct3 and ci3 were detected in 66.7%. Glomerulitis was rare although allograft nephropathy was detected in 62.5%. All cases had intimal thickening of small and renal arteries but arteritis was unusual. Lymphocyte and plasma cell were common at interstitium and ureter, but plasma cell, neutrophil and eosinophil rarely appeared at vascular lesions. In the MIS group, histological changes were minor. t3, i3, g1-3, arteritis and venulitis were not detected.

Conclusions: The histological changes were similar and specific within the TNx groups but different between the groups. A failed graft often showed substantial immunological response. In depth histological analysis may aid management of subsequent grafts.

SA-PO986

MiRNAs as Novel Biomarkers for Transplanted Patient's Evolution Esperanza Macarena Rodriguez serrano,¹ Cristina Galeano,² Edurne Ramos,¹ Elisa Conde,¹ Laura Martín-Gómez,¹ Sara Gimenez-Moyano,¹ Maria Laura Garcia-Bermejo,¹ Fernando Liano,² ¹Biomarkers and Therapeutic Targets Unit, IRYCIS; ²Nephrology, Ramon y Cajal Hospital.

Background: Transplanted patients evolution and outcome is dependent on many factors including allograft function, vascular homeostasis and immunogenicity. Up to this moments, apart from creatinine renal biopsy, there are no quantifiable and accurate biomarkers to predict the evolution of the allograft and the receptor, what would enable clinicians to improve the transplanted patient's management. Our group has validated a combination of serum miRNAs as accurate biomarkers for AKI from ischemic aetiology, including: miR-127, miR-101, miR-210, miR-126, miR-146a, miR-26b, miR-29a, miR-10a, miR-93 and miR-27a. Here we have determine the expression of these miRNA in serum from kidney donors and receptors and correlate this expression with clinical parameters of allograft evolution, including ATN development, delayed graft function, rejection and vascular complications.

Methods: For this purpose, serum sample from brain death donors and receptors along pos-transplantation period (6h, 1,2,3,4,5, 6 and 7days and 1,3,6 months) in 30 transplanted patients form our Hospital. After RNA extraction from serum, the combination of miRNAs has been determined by qRT-PCR and correlation with clinical data has been established using SPSS.

Results: The expression of these 10 miRNAs in serum samples from donors did not exhibited significant differences among them. This combination neither correlate with immediate delay graft function because NTA or immunological rejection. However, some of the miRNAs correlate with long term evolution of transplanted patients in terms of non-optimal graft function and they also discriminate patients with also exhibited renal vascular alterations.

Conclusions: In summary we have identified miRNAs that correlates with long term evolution of transplanted patients. These information could be useful for improve transplanted patient management in the context of personalized patient handling.

Funding: Other NIH Support - Fundación Mutua Madrileña de Investigación

SA-PO987

Plasma MicroRNA 17 Host Gene Protein level Cluster and Tumor Necrosis Factor-Alpha (TNF- α) in Patients with Renal Transplantation: Relation to Allograft Function and Survival Hayam A. El Aggan,¹ Sabah Abdel Hady Mahmoud,² Mohamed Mohamed Saker.¹ ¹Internal Medicine, Faculty of Medicine, Alexandria, Egypt; ²Medical Biochemistry, Alexandria, Egypt.

Background: Chronic allograft dysfunction (CAD) remains the leading cause of late graft loss after kidney transplantation. MicroRNAs (miR) are small (19-25 nucleotides) noncoding RNAs that regulate gene expression of diverse biological processes. The polycistronic miR-17~92 cluster is comprised of six miRs and its primary transcript may also encode for a polypeptide of 70 amino acids designated as the *miR-17 host gene* (*MIR17HG*) protein. So the aim of this work was to evaluate the plasma levels of *MIR17HG* protein, an index of miR-17~92 cluster activity, and the plasma level of tumor necrosis factor-alpha (TNF- α) in patients with renal transplantation in relation to renal allograft function and survival.

Methods: This study included 45 subjects; they were divided into three groups each 15, renal transplant patients with stable renal function (Group I), with CAD (Group II) and healthy subjects as controls (Group III). Quantitative determination of plasma levels of *MIR17HG* protein and TNF- α were performed using enzyme linked immunoassay (ELISA). Blood urea, serum creatinine and estimated glomerular filtration rate (eGFR), urinary albumin/urinary creatinine ratio and C-reactive protein (CRP) were done. Resistive index (RI) was calculated. Renal biopsy was done in patients with CAD.

Results: *MIR17HG* protein and TNF- α levels were significantly higher in renal transplant especially patients with CAD than the controls. In patients with renal transplantation *MIR17HG* protein and TNF- α level were positively correlated with each other and with serum creatinine, urinary albumin/creatinine ratio and CRP and was negatively correlated with e-GFR. The degree of fibrosis in renal biopsy was positively correlated with *MIR17HG* protein, TNF- α levels and RI ($P < 0.05$).

Conclusions: *MIR17HG* Protein and TNF-alpha plasma levels can be served as circulating biomarkers for early detection of renal allograft dysfunction and follow up of patients with renal transplantation. They can act as a pro-fibrotic factor and denoting ongoing inflammation in the pathogenesis of CAD.

SA-PO988

Polymorphisms of IL17 and CXCL9 Genes, but Not AIF1 Gene, Affect Early Kidney Allograft Function After Transplantation Leszek Domanski, Karolina Kloda, Ewa Kwiatkowska, Kazimierz Ciechanowski. *Clinical Dept of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical Univ in Szczecin, Szczecin, Poland.*

Background: Kidney transplantation outcome is determined by immunological and non-immunological factors, both the donor and the recipient dependent. There are reports suggesting that AIF1, IL17 and CXCL9 genes polymorphisms might influence the post-transplant immune response, and thus kidney function. Therefore the aim of this study was analysis of association between 8 AIF1, IL17 and CXCL9 genes polymorphisms and creatinine concentrations up to 1 year after transplantation.

Methods: The study enrolled 269 Caucasian renal transplant recipients (165 males, 104 females, mean age 47.63 \pm 12.96 years). Blood samples were collected for genetic analysis and creatinine concentrations evaluation 1, 3, 6, and 12 months after kidney transplantation. The analysis regarded rs2269475, rs2736182 and rs2259571 within AIF1 gene, rs2275913 within IL17A gene, rs2397084, rs11465553 and rs763780 within IL17F gene and rs3733236 within CXCL9 gene. Genotyping was performed using RT-PCR and PCR-RFLP methods.

Results: Creatinine concentrations 1, 3, 6 and 12 months after transplantation differed between the rs2275913 within IL17A gene promoter polymorphism genotypes and were higher among GG homozygotes (GG vs. GA+AA $p=0.03$, $p=0.08$, $p=0.06$ and $p=0.03$ respectively). In regard to rs2397084 IL17F gene polymorphism, creatinine concentrations differed between the genotypes 1, 2 and 6 months after transplantation and were higher among TT homozygotes (TT vs. CC $p=0.02$, $p=0.02$ and $p=0.09$ respectively). Creatinine concentrations 3, 6 and 12 months after transplantation differed between the rs3733236 CXCL9 gene polymorphism genotypes and were higher among GG homozygotes (GG vs. GA+AA $p=0.07$, $p=0.048$ and $p=0.02$ respectively). There were no significant differences between the studied AIF1 gene polymorphisms genotypes.

Conclusions: Polymorphisms of IL17 and CXCL9 genes, but not AIF1 gene, affect early kidney function after transplantation. These preliminary results indicate that there is a need of genome-wide association studies scoping on genes implicated in the immune response after transplantation.

SA-PO989

Urinary K Cadherin Predicts Renal Allograft Dysfunction Seema Jain,¹ Ekram Nabi,¹ Sharirose Abat,² Rajeshwar Ramkhalawon,² Sarah Yates,¹ Iain Macphree,² Mysore K. Phanish,¹ Mark E. Dockrell.¹ ¹South West Thames Inst for Renal Research, Epsom and St Helier NHS Trust, London, United Kingdom; ²St. George's Univ NHS Trust, United Kingdom.

Background: Renal transplantation is currently the optimal form of renal replacement therapy, however graft attrition remains a problem. Current non-invasive detection methods are insensitive and irreversible damage has often occurred at the time of detection. This study investigates the relationship between urinary Albumin (Alb), Retinal Binding Protein (RBP), N-Acetyl- β -D-glucosaminidase (NAG) activity and a novel marker, K cadherin (KCAD), and graft dysfunction 12 months after implantation.

Methods: 62 renal transplant recipients were recruited into a prospective longitudinal study. Urine was collected 3 months after transplantation. Decline in graft function was defined as a greater than 5ml/min/1.73m² fall in eGFR from 3 to 12 months after transplantation. Urine was analysed for NAG, RBP and Alb by enzymatic colorimetric assay, KCAD and RBP by in-house ELISA and Alb by immunoturbidimetry. Values were expressed after indexing for urinary creatinine concentration. Statistics were performed using GraphPad Prism 6 Linear regression analysis.

Results: 18% of patients had a decline in graft function. Of these, 64% tested positive for significant albuminuria (ACR>3mg/mmol), 73% for RBP, 100% for NAG and 45% for KCAD. Further analysis showed that NAG, RBP and Alb had high sensitivity but low specificity. KCAD had a sensitivity of 0.46 and a specificity of 0.75. All markers correlated positively with a decline in eGFR. However, KCAD had the strongest correlation ($R^2=0.2$), compared with Alb ($R^2=0.17$), NAG ($R^2=0.05$) and RBP ($R^2=0.01$).

Conclusions: This cohort study demonstrates that, when compared to conventional markers Alb, RBP and NAG, the novel marker KCAD has a higher specificity and correlation with patients who lose graft function after one year. The presence of the proximal tubule cadherin in the urine may be a prognostic indicator for patients who go on to develop chronic allograft dysfunction, and may occur due to the excretion of KCAD by proximal tubules in response to fibrogenic stimuli. Further analysis is required to evaluate this.

Funding: Private Foundation Support

SA-PO990

Detection of Endothelial Cell Specific Molecule-1 According to Allograft Status After Kidney Transplantation Se Yun Kim,¹ Kyung-Hwan Jeong,² Yu Ho Lee,² Tae Won Lee,² Chun-Gyoo Ihm,² Shin Yeong Lee,² Yang Gyun Kim,¹ Sang Ho Lee,¹ Da Won Jeong,¹ Ju-Yeong Moon.¹ ¹Kyung Hee Univ Hospital at Gangdong; ²Kyung Hee Univ Hospital.

Background: To investigate whether urine and plasma Endothelial Cell Specific Molecule-1 (ESM-1) level could differentiate rejection from non-rejection in kidney transplantation (KTP) recipients, we compared ESM-1 levels according to allograft status.

Methods: We measured plasma and urine ESM-1 in 77 patients with underwent KTP. The concentration of ESM-1 was analyzed by enzyme linked immunosorbent assay (ELISA). According to allograft status, Groups are divided stable, long-term good survival, immune tolerance, acute cellular rejection (ACR), acute antibody-mediated rejection (AMR) and chronic AMR.

Results: Plasma ESM-1 was not significantly different between all groups according to allograft status ($p=0.424$). Whereas, urine ESM-1 was significantly different between groups according to allograft status ($p<0.001$). Urine ESM-1 was higher in both ACR and acute AMR as well as chronic AMR than stable status. Patients with acute AMR showed significant higher level of urine ESM-1 compared with patients with ACR ($p<0.05$). Area under the curve (AUC) for differentiating acute AMR from ACR was 0.744 ($p=0.01$).

Conclusions: Urine ESM-1 may reflect endothelial injury of allograft and it could be used to differentiate the patient with acute AMR from ACR.

SA-PO991

Noninvasive Diagnostic and Predictive Value in Renal Transplant Recipients by Measurement of Urine BCA-1 Dajin Chen. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, P.R.China.*

Background: To investigate the relationship between early-stage renal acute rejection and the level of BCA-1 in urine, explore the diagnostic value and noninvasive monitoring in early stage after transplantation by measurement of urine BCA-1.

Methods: 145 patients were enrolled between January 2006 and October 2009., including 49 with biopsy-proved acute rejection, 58 patients with stable renal function and no abnormal histological findings, 9 patients with biopsy-proven acute tubular necrosis and 29 patients with biopsy-proven chronic allograft nephropathy. Additionally, urinary samples were also collected from 40 healthy controls. Urinary concentration of BCA-1 was determined by an enzyme-linked immunosorbent assay technique in 145 renal allograft recipients and 40 healthy controls.

Results: Patient with acute rejection excreted urinary BCA-1 at a significantly higher level (8.1 \pm 1.2, 95%CI: 3.9-12.4 pg/ μ mol creatinine) than levels of patients with No-AR and healthy controls ($P<0.001$). Patients with acute tubular necrosis excreted urinary BCA-1 at a significantly lower level (2.52 \pm 0.57, 95%CI: 1.21-3.84pg/ μ mol creatinine) than levels of patients with acute rejection. ROC curve was constructed to determine the discriminatory power of BCA-1 levels for diagnosis of acute rejection. The area under ROC curve was 0.881 (95%CI: 0.811-0.951), at a cut point of 0.23 pg/ μ mol creatinine, the sensitivity was 81.6% and the specificity was 87.9% ($P<0.001$). Patients with acute humoral rejection had significantly higher urinary BCA-1 concentration than patients with acute cellular rejection (24.2 \pm 6.68, 95%CI: 9.5-38.9pg/ μ mol creatinine vs 2.91 \pm 0.65, 95%CI: 1.6-4.22 pg/ μ mol creatinine, $P=0.0002$). ROC curve was constructed to determine the discriminatory power of BCA-1 levels for diagnosis of acute humoral rejection. The area under ROC curve was 0.867 (95%CI: 0.725-1.005), at a cut point of 8.3 pg/ μ mol creatinine, the sensitivity was 75% and the specificity was 91.9%.

Conclusions: The monitoring of BCA-1 in urine may be a new and noninvasive approach for detection acute rejection as well as useful to discriminate the type of rejection.

SA-PO992

B Cell Attracting Chemokine 1 in Urine Is a Biomarker of Acute Humoral Rejection

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Background: Presently, there are no noninvasive approaches which can be directly applied to clinical diagnosis of acute rejection (AR) or distinguish type of rejection in renal transplant recipients. The aim of this study was to construct diagnostic models of biomarkers in urine of patients with AR or acute humoral rejection (AHR) in renal transplant recipients.

Methods: Concentration of nine biomarkers in urine of 81 patients with AR and 167 patients with stable renal function (No-AR) was determined by ELISA technique. Firstly, by discriminant analysis, we screened a number of biomarkers to construct the diagnostic models for AR and AHR. Secondly, another 102 patients with No-AR and AR were analysed to test the accuracy of the diagnostic model.

Results: Four biomarkers were selected to set up the diagnostic model of AR or No-AR. Based on the model of AR, 84.3% patients were correctly diagnosed. Two biomarkers were selected to set up the complementary diagnostic model of AR. Based on the two model of AR, 100% patients with No-AR and 96.3% patients with AR were correctly diagnosed. Only B cell attracting chemokine 1 (BCA-1) was selected for the diagnostic model for AHR or acute cellular rejection (ACR). Rejection type of 81.5% patients with AR were correctly classified. Another 102 patients tested the accuracy of the diagnostic models. Diagnostic accuracy of AR or No-AR and AHR or ACR were 100% and 95.4% respectively.

Conclusions: Urinary BCA-1 was a valuable biomarker for determining AHR. These diagnostic models might directly identified AR and types of AR.

Funding: Government Support - Non-U.S.

SA-PO993

¹⁸F-DG-PET/CT Imaging in Suspected Acute Renal Allograft Rejection

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Background: The diagnosis procedure for kidney transplant recipients (KTR) with suspected acute rejection (AR) relies on needle biopsy. Still, noninvasive tests to predict nonrejection would be useful to save selected patients from undergoing essential biopsy. AR is associated with a recruitment of activated leukocytes into the transplant, which are characterized by a high metabolic activity and an increased uptake of glucose analog, ¹⁸Fluoro-deoxy-glucose (¹⁸FDG). Thus, ¹⁸FDG-Positron emission tomography coupled with computed tomography (PET/CT) may help noninvasively distinguish nonrejection from AR.

Methods: From January 2013 to February 2015, we prospectively performed 32 ¹⁸FDG-PET/CT in 31 adult KTR with suspected AR who underwent a biopsy. Biopsies were categorized as "normal", "borderline", "AR" or "others" according to Banff classification. PET/CT imaging was performed within 201 ± 18 minutes after i.v. administration of 3.2 ± 0.2 MBq/kg of ¹⁸FDG, before any modification of immunosuppression. The mean standard uptake values (SUV) of both upper and lower renal poles were measured, with no threshold activity.

Results: Biopsies were diagnosed as "normal", "borderline", "AR" or "others" in 8, 10, 8 and 6 (including 3 polyoma-BK nephropathies) cases. AR was antibody-mediated in 1 case, whereas Type I, II and III cellular AR were found in 5, 1 and 1 cases, respectively. Mean SUV reached 1.5 ± 0.2, 1.6 ± 0.3, 2.9 ± 0.8, 2.2 ± 1.2 in each category. Mean SUV of biopsy-proven AR was significantly higher than "normal" cases (p<0.01). No difference was found between "normal" vs. "borderline", or between "AR" vs. "others" histopathology. Still, a positive correlation between mean SUV and acute composite (g++t++v+pte) Banff score was found, with a coefficient of 0.70 (p<0.001). Sensitivity and specificity of ¹⁸FDG-PET/CT in detecting pathological biopsies were respectively 92.3 and 36.8, with a mean SUV threshold at 1.4.

Conclusions: ¹⁸FDG-PET/CT imaging may help discriminate nonrejection, thereby avoiding unnecessary transplant biopsy in KTR with suspected AR.

Funding: Government Support - Non-U.S.

SA-PO994

High Remnant-Like Particle-Cholesterol Is a Risk Factor of Worsening Graft Function in Japanese Kidney Transplant Recipients

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Background: Many factors cause dyslipidemia after kidney transplantation. Low density lipoprotein cholesterol (LDL-C) has been focused to reduce cardiovascular disease (CVD), but residual risk factors such as triglyceride (TG), remnants or small dense LDL-C are also important to reduce CVD. We investigated whether residual risk factors affected graft function in kidney transplant recipients.

Methods: This study is a retrospective cohort study at a single center. Three hundred and seventy seven kidney transplant recipients (male 223) in more than six months after transplantation were enrolled. TG, Remnant-like particle-cholesterol (RLP-C), non-high density lipoprotein cholesterol (HDL-C), LDL-C/apoB, eGFR (estimated glomerular filtration rate), Urine protein/day (UP), Body Mass Index (BMI) and other parameters at baseline were measured and we studied the association of residual risk factors with kidney function. DeGFR meant the difference between eGFR at baseline and eGFR 1 year after enrolment (eGFR 1y). Data are shown as n(%), mean (SD) or median (interquartile).

Results: Patients' characteristics of this study is shown.

Figure 1.

Patients' characteristics of this study (n=377)	
Age (years)	51.0 (13.2)
Gender (male) (n)	223 (59.1%)
Vintage after transplantation (months)	45.0 (24.0, 81.5)
Systolic BP (mmHg)	124.4 (12.1)
DMN (n)	39 (10.3%)
BMI (kg/m ²)	21.9 (3.79)
Hb (g/dl)	12.6 (1.4)
cCa (mg/dl)	9.6 (0.5)
IP (mg/dl)	3.3 (0.6)
iPTH (pg/ml)	105.7 (73.8)
T-cho (mg/dl)	187.5 (31.0)
HDL-C (mg/dl)	63.5 (18.2)
non HDL-C (mg/dl)	124.0 (24.6)
TG (mg/dl)	117.3 (57.2)
LDL-C (mg/dl)	100.5 (23.0)
RLP-C (mg/dl)	5.0 (2.4)
Apo B (ug/ml)	78.5 (15.2)
LDL-C/ApoB	1.3 (0.2)
eGFR at baseline (ml/min/1.73m ²)	41.6 (12.2)
eGFR 1y (ml/min/1.73m ²)	41.9 (12.5)
Urine protein (g/day)	0.1 (0.3)
Cyclosporine use (n)	263 (69.8%)
Tacrolimus use (n)	107 (28.4%)
statin use (n)	204 (54.1%)
ARB use (n)	199 (52.8%)
β blocker use (n)	49 (13.0%)

Mean age (years) was 51.0 (13.2), median vintage after kidney transplantation (months) was 45.0 (24.0, 81.5), and mean BMI (kg/m²) was 21.9 (3.79). DeGFR were associated with age (r=0.12, p=0.02), BMI (r=0.12, p=0.02), TG (r=0.12, p<0.001), UP (r=0.15, p=0.004), RLP-C (r=0.21, p<0.001). Multivariate analysis showed that High RLP-C was the associated with worsening graft function.

Conclusions: High RLP-C is a risk factor of worsening graft function in Japanese kidney transplant recipients.

SA-PO995

The Modification of Erythrocyte Membrane Fatty Acid Contents According to Kidney Transplantation: Prospective Study

Young Ki Son,¹ Sung Hyun Son,² Dongyeol Lee,³ Hansae Kim,³ Eu Gene Jeong,¹ Su Mi Lee,¹ Yun Jung Oh,⁴ Won Suk An,¹ Seong Eun Kim.¹ *¹Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; ²Dept of Internal Medicine, BHS Han Seo Hospital, Busan, Republic of Korea; ³Dept of Internal Medicine, Bong Seng Memorial Hospital, Busan, Republic of Korea; ⁴Dept of Internal Medicine, Cheju Halla General Hospital, Cheju, Republic of Korea.*

Background: Modifications of erythrocyte membrane fatty acid (FA) contents may effect on cellular function or transmembrane receptors. The high erythrocyte membrane oleic acid contents are related with acute coronary syndrome. It is known that kidney transplanted recipients have lower cardiovascular event than dialysis patients. Therefore, we prospectively evaluated whether erythrocyte membrane FA contents were modified after kidney transplantation (KTP).

Methods: We recruited 22 kidney transplanted recipients from September 2011 through May 2014. Blood samples were obtained just before KTP and at 6 months after KTP. The erythrocyte membrane fatty acid contents were measured by gas chromatography.

Results: The mean ages were 45.3±10.9 years. The erythrocyte membrane contents of omega-3 FA (10.1±3.9 vs. 5.5±3.63, p<0.001), omega-6 FA (26.6±6.2 vs. 20.7±7.7, p=0.008), arachidonic acid (11.6±4.1 vs. 7.7±4.7, p=0.001), eicosapentaenoic acid (1.4±0.7 vs. 0.7±0.5, p<0.001), docosahexaenoic acid (2.0±0.8 vs. 1.2±1.0, p=0.001), omega-3 index (7.9±3.2 vs. 4.1±2.7, p<0.001) were significantly higher but erythrocyte membrane contents of total saturated FAs (44.9±8.0 vs. 52.6±9.4, p=0.003), total monounsaturated FAs (17.2±1.6 vs. 19.9±2.2, p<0.001), total trans FAs (0.9±0.3 vs. 1.1±0.2, p=0.011), oleic acid (15.7±1.5 vs. 18.0±1.9, p<0.001), and omega-6/omega-3 ratio (3.1±1.4 vs. 4.6±1.7, p=0.14) were significantly lower at 6 months after KTP.

Conclusions: FA contents of erythrocyte membranes including increased omega-3 FAs, decreased oleic acid and omega-6/omega-3 were significantly modified after KTP. These changes of erythrocyte membrane FA contents may effect on lower cardiovascular event rate in kidney transplanted recipients compared to dialysis patients and further studies are necessary to confirm these effects.

SA-PO996

Diffusion Impairment Measured by Functional MRI Correlates with Allograft Fibrosis After Kidney Transplantation in Patients with Delayed Graft Function Jan H. Braesen,¹ Abedalrazag Ahmad Khalifa,¹ Faikah Gueler,² Frank Lehner,⁴ Wilfried Gwinner,² Dagmar Hartung,³ Hermann G. Haller,² Katja Hueper.³ ¹*Inst for Pathology, Hannover Medical School, Hannover, Germany;* ²*Clinic for Nephrology, Hannover Medical School, Hannover;* ³*Inst for Diagnostic and Interventional Radiology, Hannover Medical School, Hannover;* ⁴*Clinic for General, Abdominal and Transplant Surgery, Hannover Medical School, Hannover, Germany.*

Background: Functional MRI parameters derived from diffusion weighted (DWI) and diffusion tensor imaging (DTI) correlate with renal fibrosis and cell infiltration in experimental studies. Aim of this study was to investigate these non-invasive techniques in patients with delayed graft function (DGF) and to correlate diffusion parameters with renal function and renal histology of allograft biopsies.

Methods: 33 patients with initial graft function between day 4 and 11 after kidney transplantation and 31 patients with DGF were examined on a 1.5 Tesla MRI. DTI and DWI sequences were acquired and apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated. Kidney biopsies were available in 26 patients and analysed for acute rejection (Banff), amount of fibrosis, inflammatory infiltrates, and tubular injury as well as edema.

Results: ADC was significantly reduced in patients with DGF compared to patients with initial function. Similarly, FA, representing the degree of directed diffusion along anatomical structures such as tubules, collecting ducts and vessels, was impaired in DGF patients. ADC and FA positively correlated with renal function ($r=0.573$ and $r=0.53$, $p<0.001$) and negatively with the amount of renal fibrosis. Diffusion parameters in DGF patients did not discriminate between acute rejection and tubular injury. Histological evaluation of the allograft biopsies did not reveal any significant differences between DGF or initial function in the following parameters: leukocyte infiltration (CD4, CD8, CD15, CD20, CD68), CD31 pos. peritubular capillaries or edema (intertubular distance).

Conclusions: Functional MRI with diffusion techniques detects allograft dysfunction early after kidney transplantation correlating with allograft fibrosis. Biopsy is needed to verify rejection.

Funding: Government Support - Non-U.S.

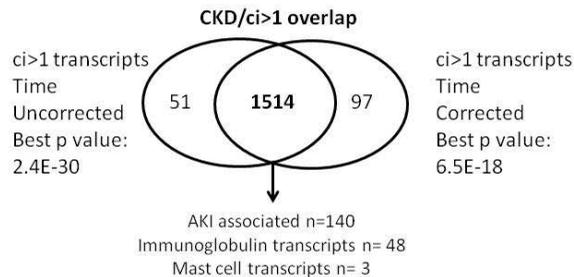
SA-PO997

Identification of Common Biological Mechanisms of Fibrosis in Transplanted and Native Kidneys with Chronic Diseases Konrad S. Famulski, Jeffery M. Venner, Jeff Reeve, Philip F. Halloran. *Univ of Alberta, Edmonton, AB, Canada.*

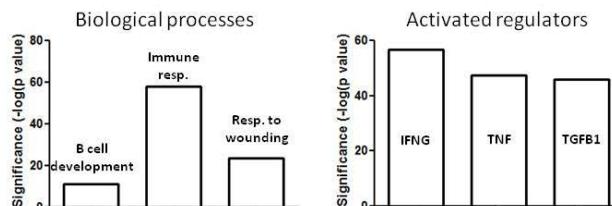
Background: In both primary kidney diseases and in transplants fibrosis is caused by chronic progressive diseases. Hence, we hypothesised that fibrosis has fundamental common biological pathways in native and transplanted kidneys.

Methods: We studied the molecular associations with fibrosis in 703 kidney transplant indication biopsies (bx) 3 days to 35 years post-transplant. The number of bx with fibrosis increased with time post-transplant and most bx with $ci>1$ (74%) were attributable to time-dependent diseases (ABMR, GN, TG).

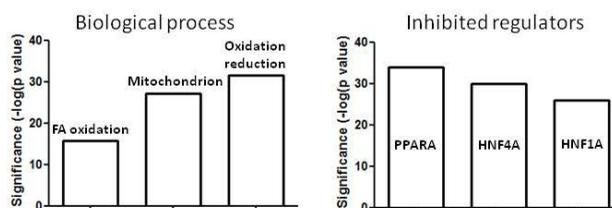
Results: By microarrays we compared bx with $ci>1$ to those with little or no fibrosis ($ci\leq 1$) and determined the association strength of transcripts (p-value) for $ci>1$. First we focused on transcripts previously associated with fibrosis: immunoglobulin, mast cells and AKI-associated transcripts. Strongest associations with $ci>1$ were for immunoglobulin and mast cell transcripts, but not for AKI transcripts. Because time of bx post-transplant is highly correlated with ci , we repeated the comparison of $ci>1$ vs. $ci\leq 1$ after correcting for time. This resulted in a massive reduction in association strength for the immunoglobulin and mast cell transcripts (from $10e-27$ to $10e-9$). However, AKI transcripts were now more strongly associated with fibrosis (from $10e-9$ to $10e-18$). Thus time correction emphasised the injury-repair response at expense of inflammation. We then analyzed the fibrosis associated transcripts in native kidneys (CKD). 73% of CKD transcripts overlapped with our transcripts.



CKD/ci>1 transcripts increased in fibrosis



CKD/ci>1 transcripts decreased in fibrosis



$ci>1$ /CKD overlap overrepresented pathways related to immunity, response to wounding and energy metabolism (Figure 1).

Conclusions: Fibrosis in transplants and native CKD is characterized by the same inflammatory compartment, response to injury and loss of metabolism. Some of these processes might be related to the duration of chronic disease.

SA-PO998

DNA Double Strand Breaks Induced Collagen Type VI Secretion of Glomerular Endothelial Cells in Renal Allografts Yuki Matsui, Norifumi Hayashi, Junko Imura, Keiji Fujimoto, Hiroki Adachi, Hideki Yamaya, Hitoshi Yokoyama. *Nephrology, Kanazawa Medical Univ, Uchinada, Japan.*

Background: The relationship between DNA injury and glomerular fibrosis in renal allografts remains unclear.

Methods: We examined renal allograft specimens from 35 patients in which DNA double-strand breaks and glomerular fibrosis were detected by phospho-histone H2A.X (γ -H2AX) expression and collagen (COL) types III, IV, and VI accumulation. We also examined the in vitro relationship between DNA damage and COL accumulation by mitomycin C (MMC)-induced DNA damage in human glomerular endothelial cells (HRGEC).

Results: The γ -H2AX and COL type VI, which mainly accumulated in the subendothelial and mesangial regions, were positively correlated with the duration of the post-renal transplant (RT) period ($r=0.691$, $p<0.01$; $r=0.760$, $p<0.01$, respectively). In multiple regression analysis, the duration of the post-RT period and cg in the Banff'07 classification were identified as significant predictors of COL type VI accumulation (β value= 0.699 , $p<0.001$; 5.558 , $p=0.035$, respectively) and γ -H2AX expression in the glomerular capillaries (β value 0.700 , $p<0.001$; 2.031 , $p=0.011$, respectively). In addition, the γ -H2AX-positive area was also identified as a predictor of glomerular accumulation of COL type VI (β value= 0.439 , $p=0.028$). In the immunohistochemistry examination, γ -H2AX was detected in most cells after 24 hours' MMC treatment, whereas no γ -H2AX expression had been detected before the MMC treatment. Although COL type VI was detected around the nuclei of the HRGEC before the MMC treatment, it was not present there after the MMC treatment. COL type VI was detected in the cytoplasm of the HRGEC, which was secreted into the supernatant after MMC stimulation with γ -H2AX expression. The number of γ -H2AX (-)/COL type VI (+) cells was inversely associated with the number of γ -H2AX (+)/COL type VI (-) cells ($r=-0.655$, $p<0.001$) during 24 hours' MMC treatment.

Conclusions: Our findings suggested that over the long term RT may induce DNA double-strand breaks and HRGEC-secreted COL type VI accumulation in the glomerular capillaries, which might progress to intractable glomerular fibrosis.

SA-PO999

Imatinib Improves Interstitial Fibrosis in Deceased Donor Kidney Transplant: A Case Report Ignatius Yun-Sang Tang,¹ Andres M. Acosta,² Vishal K. Varma,² Suman Setty.² ¹Medicine, Univ of Illinois at Chicago, Chicago, IL; ²Pathology, Univ of Illinois at Chicago, Chicago, IL.

Background: Imatinib (IM) is an oral inhibitor of tyrosine kinases. Early short term PDGF inhibition with IM had been shown to prevent interstitial fibrosis and tubular atrophy in pre-clinical kidney transplantation (KT). We assess the effect of long term IM therapy on renal allograft histology in a KT recipient who received IM for gastrointestinal stromal tumor (GIST).

Methods: Patient is a 47 year old female with ESRD due to hypertension, s/p living donor KT in 2007 which failed in 2010. She was then resumed on hemodialysis. A gastric mucosal mass was discovered incidentally in 5/2012. Fine needle aspiration showed c-KIT positive spindle cells consistent with GIST. Patient received deceased donor KT in 7/2012 with Thymoglobulin induction. Maintenance immunosuppression included tacrolimus and mycophenolic acid. Patient was started on IM 100mg daily on day 19 post-KT because of GIST. Post-KT course was complicated by biopsy proven acute tubular necrosis, requiring dialysis in the first month post-KT. Serum creatinine (CR) improved to 1.6mg/dl by 3 months post-KT when she underwent partial gastrectomy. Pathology showed low grade GIST (low mitotic count and low Ki67 labeling index). Surveillance KT biopsy was performed at 6 months, 1 and 2 years post-KT. We compared the 6-month and the 2-year post-KT biopsies for the presence of renal cortical interstitial fibrosis using the Histolab software (Microvision Instruments, France). The core sections stained with Masson trichrome were scanned at high-resolution, and divided into individual images at 200X for quantitative analysis. The software program was then run to quantify fibrosis of the selected areas.

Results: The cortical fibrosis percentage was 20.17% for the 6-month biopsy and 14.35% for the 2-year biopsy. The corresponding serum CR was 1.52mg/dl and 1.17mg/dl, respectively. Trough tacrolimus levels were maintained between 5 and 7ng/ml.

Conclusions: Long term low dose IM reduced cortical interstitial fibrosis in deceased donor KT. The role of long term IM in the prevention of interstitial fibrosis in renal allograft warrants further studies.

SA-PO1000

Factors Associated with Referral, Evaluation and Listing for Kidney Transplant: A Survey of Dialysis Patients Eric Chang, Ming Wang, Fareeha Khalil, Naman Trivedi, Nasrollah Ghahramani. Penn State Univ College of Medicine, Hershey, PA.

Background: Kidney transplant (KT) is the treatment of choice for most patients with end stage renal disease (ESRD). Disparities in referral, evaluation, listing and transplantation have been documented. We studied factors associated with the likelihood of referral, evaluation and listing for KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants who fulfilled inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent variables were demographic factors, location, and modes of education about KT. In multivariate analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of referral, evaluation and listing for KT.

Results: Of 673 participants, 401 had been referred, 361 had been evaluated and 201 were listed. Having received 3 or more modes of education about KT was associated with higher likelihood of referral (OR:5.03;CI:2.76-9.18), evaluation (OR:5.67;CI:3.23-9.96) and listing (OR:2.70;CI:1.43-4.18). Having attended a pre-ESRD class was associated with higher likelihood of referral (OR:2.20;CI:1.44-3.35) and evaluation (OR:2.47;CI:1.63-3.74). If the nephrologist had discussed the option of KT at least twice in previous year there was higher likelihood of referral (OR:2.19;CI:1.44-3.33), evaluation (OR:1.67;CI:1.10-2.53) and listing (OR:1.83;CI:1.19-2.80). A transplant center within 10 miles was associated with higher likelihood of referral (OR:1.64;CI:1.09-2.66) and listing (OR:2.17; CI:1.32-3.57). Age > 60 was associated with lower likelihood of referral (OR:0.51;CI:0.33-0.79), evaluation (OR:0.46;CI:0.30-0.72) and listing (OR:0.28;CI:0.17-0.45).

Conclusions: Many factors influence the decision about KT; a process that begins with referral. Though difficult to change, proximity to a transplant center unsurprisingly improves chances for KT evaluation. Emphasis on educating patients > 60 may improve referral and evaluation. In this study, the quantity and diversity of educational modalities are the most important contributors to the referral, evaluation and subsequent listing.

Funding: NIDDK Support

SA-PO1001

Patient Navigation Program in Kidney Transplant Evaluation: A Randomized Study Mohua Basu, Dawn L. Fletcher, Lisa Petgrave-nelson, Rachel E. Patzer. Emory Univ, Atlanta, GA.

Background: We developed a patient navigation program in a kidney transplantation (KTx) clinic to improve KTx evaluation completion for patients deemed "high-risk" of not being placed on the KTx waiting list, based on known disparities in completion of KTx evaluation. We examined whether the addition of patient navigation to standard care was associated with a decrease in the number of days from a patient's referral for KTx evaluation to KTx candidacy decision.

Methods: During evaluation scheduling at a single KTx center, patients answered questions from a risk assessment tool created using existing data; high-risk patients were randomized prior to KTx evaluation to either standard of care (control) or the additional assistance of a patient navigator (intervention). The patient navigator helped guide patients

through the KTx process, serving as a point of contact and providing support and education from the time of referral for KTx evaluation through candidacy decision (patient approved for placement on waiting list or deemed "not a candidate").

Results: From January 2013 to October 2014, 394 patients were enrolled in the study. Patient demographics were similar among intervention and control groups (80% Black, 80% Medicare, 50% < age 55). A total of 311 (79%) reached candidacy decision (79% of intervention and 79% of control patients) and were included in preliminary analyses. Intervention patients reached candidacy decision a median of 8 days faster than control patients (119 vs. 127 days). Shorter time to decision for intervention vs. control patients was observed in most examined subgroups, including black (8 days) and white patients (9 days), patients who completed high school (10 days), Medicare patients (15 days), patients with BMI>35 (30 days), married (11 days) and single patients (7 days), and patients < age 55 (19 days).

Conclusions: Preliminary results support the efficacy of a patient navigation program in reducing time from patient KTx referral to candidacy decision in a KTx setting. The use of a similar program in other KTx centers may help patients who require additional assistance during the KTx process complete KTx evaluation more quickly.

Funding: Private Foundation Support

SA-PO1002

Knowledge of Treatment Options in Patients Evaluated for Kidney Transplantation: iChoose Kidney Randomized Trial Mohua Basu,¹ Stephen O. Pastan,¹ Sumit Mohan,² John J. Friedewald,³ Daniela P. Ladner,³ Rachel E. Patzer.¹ ¹Emory Univ, Atlanta, GA; ²Columbia Univ, New York, NY; ³Northwestern Univ, Chicago, IL.

Background: Although kidney transplantation (KTx) provides a significant survival advantage over long-term dialysis, many end stage renal disease (ESRD) patients are not educated about KTx options. We developed a clinical decision tool (iChoose Kidney) to provide individualized risk estimates of patient survival on dialysis vs. KTx to evaluate whether use of the decision tool during KTx evaluation improved patient knowledge of the survival benefit of KTx vs. dialysis and of living vs. deceased donor KTx.

Methods: In December 2014, we began enrolling patients from three large KTx centers across the U.S. in a trial, where patients are randomized to usual KTx evaluation (control) or an appointment during which the nephrologist uses iChoose Kidney with the patient (intervention). Pre- and post-nephrology consultation, we surveyed patients on whether they believed their chance of survival was higher, lower, or the same with 1) dialysis vs. KTx and 2) living vs. deceased donor KTx. Improvement in knowledge was defined as a change from incorrect to correct post-nephrology consultation. Health literacy was measured using the Newest Vital Sign and categorized into low/moderate vs. high (0-3 vs. 4-6 correct out of 6, respectively).

Results: To date, 214 patients are enrolled (target enrollment n=450). Among 106 intervention patients, 29% improved their knowledge of the survival benefit of dialysis vs. KTx, vs. 19% of 108 control patients (p=0.07). Among patients with low or moderate literacy, 35% of intervention patients improved vs. 13% of control patients (p=0.01); this difference was not observed among high literacy patients (26% improved in each group). For knowledge of the survival benefit of living vs. deceased donor KTx, 19% of intervention patients improved, vs. 11% of control patients (p=0.17).

Conclusions: Preliminary results show that the use of the iChoose Kidney decision tool in comparing survival estimates for dialysis vs. KTx may improve patient knowledge of treatment outcomes during KTx evaluation, and the tool may be especially effective among a low-literacy population.

Funding: Private Foundation Support

SA-PO1003

Hemodialysis Social Networks Facilitate the Completion of Transplant Testing and Successful Kidney Transplantation Avrum Gillespie,^{1,3} Alexey Uversky,² Jonathan T. Hunt,¹ Heather Marie Traino,³ Sarah Bauerle Bass,³ Teri Browne,⁴ Zoran Obradovic.² ¹Nephrology, Hypertension, and Kidney Transplantation, Temple Univ School of Medicine, Philadelphia, PA; ²Center for Biomedical Informatics, Temple Univ, Philadelphia, PA; ³School of Public Health, Temple Univ, Philadelphia, PA; ⁴School of Social Work, Univ of South Carolina, Columbia, SC.

Background: Hemodialysis (HD) social networks may promote access to a kidney transplant (KT). We set out to observe the formation of HD social networks and their role in completing the steps of the transplantation process in a newly formed HD clinic.

Methods: Between 8/2012 - 2/2015, 46 patients admitted to a newly formed HD clinic were enrolled, 63% were new to HD. Patients spoke either English (78%) or Spanish (22%). All eligible patients were referred for transplant evaluation and testing. Progression of steps towards KT was tracked. Patients were surveyed on admission and then quarterly using a previously validated questionnaire. Social interactions and seating were recorded, this data was merged with survey data and analyzed in SPSS 21.

Results: Two thirds of patients were observed to participate in social networks. There were no demographic differences among the patients who participated in social networks "social" vs. those who didn't "non-social". More social patients wanted a KT, 100% vs 73.3% (p=0.008). Social patients reported talking to other patients about their health or KT 64.5% vs. 6.7% (p < 0.001). Social patients completed more steps, 2 steps (range 0-6) including 7 transplants vs 0.5 steps (range 0-3) and no transplants in the "non-social" group (p=0.037). In a multivariate regression analysis, only participating in a social network was positively associated with completing more steps (β 1.44 p = 0.028), and vintage was negatively associated (β -0.973, p = 0.029).

Conclusions: In this HD clinic, patients that formed and participated in social networks were more likely to complete the steps and receive a kidney transplant. These findings emphasize the importance of HD social networks and the transfer of health information among patients.

Funding: Private Foundation Support

SA-PO1004

Kidney Transplant Referral Among Incident Georgia Dialysis Patients with and without Systemic Lupus Erythematosus: The RaDIANT Community Study Laura Plantinga, Rachel E. Patzer, Sung S. Lim, Cristina Drenkard, Stephen O. Pastan. *Emory Univ, Atlanta, GA.*

Background: Although providers often wait to transplant patients with systemic lupus erythematosus (SLE), shorter overall times to transplant are generally associated with more favorable transplant outcomes in SLE patients. We examined whether referral for evaluation—the first step in the often years-long process of kidney transplantation—is delayed in dialysis patients with SLE, relative to other dialysis patients.

Methods: United States Renal Data System data on a cohort of 18,419 incident (1/1/05-9/30/12) adult (18-69 years) dialysis patients were linked to concurrent referral data from all three Georgia adult transplant centers. SLE was defined by the provider-assigned cause of ESRD. Logistic regression and Cox proportional hazards models were used to examine the associations of assigned cause and patient characteristics with preemptive referral (referral prior to the start of dialysis) and time from start of dialysis to referral [censored for death or last date of follow-up (9/30/12)], respectively.

Results: Of the 352 dialysis patients with SLE, 43 (12.2%) were preemptively referred—50% more often than other ESRD patients [1573/18,067 (8.7%); OR=1.5 (95% CI, 1.1-2.1)]. Adjustment for age rendered this association null [OR=1.1 (95% CI, 0.8-1.6)]. Among the 17,293 dialysis patients not preemptively referred, SLE patients were referred at twice the rate of other dialysis patients in crude analyses [HR=1.9 (95% CI, 1.6-2.2)] but not after adjustment for [HR=1.1 (95% CI, 0.9-1.2)]. Among SLE patients, black vs. white race was associated with lower likelihood of preemptive referral [OR=0.5 (95% CI, 0.2-1.2)] but higher rates of referral after dialysis start [HR=1.8 (95% CI, 1.1-2.9)]. Male vs. female sex was associated with higher rates of referral on dialysis [HR=1.6 (1.1-2.4)].

Conclusions: Referrals for kidney transplant evaluation do not appear to be delayed among dialysis patients with SLE, relative to other dialysis patients of similar age. Efforts to increase kidney transplant access in SLE patients should focus on potential race and sex disparities in referral as well as potential delays in other steps of the kidney transplant process.

Funding: Other NIH Support - NIMHD

SA-PO1005

Association of Kidney Transplantation Referral with Other Indicators of Quality Care Among Incident Georgia Dialysis Patients: The RaDIANT Community Study Laura Plantinga,¹ Stephen O. Pastan,¹ Jenna Krisher,² Eric M. Gibney,³ Laura L. Mulloy,⁴ Rachel E. Patzer.¹ *¹Emory Univ, Atlanta, GA; ²Southeastern Kidney Council, Inc., Raleigh, NC; ³Piedmont Transplant Inst, Atlanta, GA; ⁴Georgia Regents Univ, Augusta, GA.*

Background: Dialysis facility referral of patients for kidney transplant is a potential indicator of quality care. We examined whether referral within a year of dialysis start (1-year referral) was associated with other quality indicators among incident Georgia dialysis patients.

Methods: We examined a cohort of 14,120 incident (7/1/05-9/30/11; follow-up through 9/30/12) adult (18-69 years) dialysis patients using United States Renal Data System data linked to concurrent referral data from all three adult Georgia kidney transplant centers. Multilevel, multivariable logistic regression was used to examine the association of 1-year referral with dichotomous quality indicators [pre-ESRD nephrology care, dialysis modality, permanent vascular access in place at dialysis start (HD patients only), pre-ESRD erythropoietin use, and transplant information at dialysis start], with adjustment for demographic and clinical variables and accounting for variation across clinics.

Results: Overall, 1-year referral was 24.8% and was higher among patients with other indicators of quality care: 26.0% vs. 23.8%, with vs. without pre-ESRD care ($P=0.005$); 27.8% vs. 24.6%, PD vs. HD ($P=0.03$); 28.3% vs. 22.9%, with vs. without a permanent vascular access in place at HD start ($P<0.001$); and 27.2% vs. 16.5%, informed vs. not informed of transplant options at dialysis start ($P<0.001$). With adjustment, pre-ESRD care [OR=1.34 (95% CI, 1.22-1.47)], permanent vascular access in place [OR=1.54 (95% CI, 1.41-1.70)], and transplant information at dialysis start [OR=1.63 (95% CI, 1.45-1.85)] remained associated with higher 1-year referral.

Conclusions: These findings suggest that patients who receive quality care in multiple domains are more likely to be referred for kidney transplant evaluation within a year of starting dialysis, independent of demographic and clinical characteristics. Interventions to increase transplant access should be targeted to patients whose care fails to meet other quality indicators.

Funding: Other NIH Support - NIMHD

SA-PO1006

Feasibility and Sustainability of the RaDIANT Community Study Among Georgia Dialysis Facilities Jennifer C. Gander,¹ Leighann Sauls,² Teri Browne,³ Laura Plantinga,¹ Laura J. McPherson,¹ Eric M. Gibney,⁴ Laura L. Mulloy,⁵ Stephen O. Pastan,¹ Rachel E. Patzer.¹ *¹Emory Univ; ²Southeastern Kidney Council; ³Univ of South Carolina; ⁴Piedmont Hospital; ⁵Georgia Regents Univ.*

Background: The Southeastern Kidney Transplant Coalition developed the randomized, dialysis facility-level Reducing Disparities In Access to kidney Transplantation (RaDIANT) Community Study to address racial disparities and low rates of kidney transplantation (KTx) in Georgia. We aimed to evaluate the feasibility and sustainability of the RaDIANT intervention activities.

Methods: The 67 dialysis facilities that completed a 12-month intervention as part of the RaDIANT study consisted of 12 recommended activities intended to increase KTx referral, such as education and outreach activities targeting the patient, facility staff, and facility policy level. After the intervention, facility staff were asked to complete a 20-item questionnaire on the helpfulness (Likert scale) of each intervention activity and the likelihood (yes/no) of their facility continuing the activity.

Results: A total of 86 staff (51.2% social workers) at the 67 intervention facilities completed the survey. The median number of the 12 intervention activities completed by dialysis facilities was 9 (range 0,11). Most facilities reported discussing the benefits of KTx at a staff orientation (86.6%), attending monthly webinars (80.7%), and developing a referral improvement plan (76.3%) to be helpful or very helpful. The median number of prescribed intervention activities the facilities reported they would continue was 2, with the distribution of educational brochures (41.9%), a staff orientation focused on KTx (41.9%), and a patient and family education session (34.9%) among the most commonly cited.

Conclusions: Dialysis facility staff perceived that RaDIANT intervention activities were feasible to implement, with staff education potentially being the most helpful and sustainable component. Sustainability may be limited to intervention components that were the least expensive and time intensive to implement. Additional ongoing support from ESRD Networks may be necessary to sustain increased KTx referrals observed in the RaDIANT Community Study.

Funding: Other NIH Support - The RaDIANT Community Study is funded in part by NIMHD Award R24MD008077

SA-PO1007

Psychosocial Differences Between Living and Deceased Donor Renal Transplant Recipients Anna Bertram,¹ Selma Pabst,² Martina De zwaan,² Tanja Zimmermann,² Mario Schiffer.¹ *¹Clinic for Psychosomatics and Psychotherapy, Hannover Medical School, Hannover, Germany; ²Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany.*

Background: The specific impact of living donor (LD) as compared to deceased donor (DD) kidney transplants on psychosocial functioning has received surprisingly little attention. The present study aimed to assess whether LD and DD recipients differ in socio-demographic variables, time since transplantation, emotional variables, knowledge about immunosuppressant (IS) intake, and self-reported adherence to IS.

Methods: A questionnaire study was performed among 72 LD and 169 DD recipients who attended the kidney transplant outpatient clinic of Hannover Medical School for a follow-up visit at least 1 year after transplantation. Emotional responses were assessed using the Hospital Anxiety and Depression Scale (HADS) and the Transplant Effect Questionnaire (TxEQ). Patients' knowledge about IS intake was examined with a newly developed test consisting of 8 multiple choice questions, and IS adherence was measured by self-report (BAASIS), physicians' estimates, IS trough level variability, and allograft rejection.

Results: Overall, LD recipients were younger and had a shorter follow-up since transplantation. Our results indicate that LD and DD transplantation may lead to different emotional responses with more feelings of guilt towards the donor and perceived responsibility to do well and with a generally higher anxiety level in LD recipients. LD recipients apparently had more knowledge about IS medication. However, they did not report more adherence to IS. No differences between LD and DD recipients were found for gender, adherence level, depression, perceived social support, and allograft rejection.

Conclusions: Feelings of guilt and anxiety may be an important focus for interventions to improve emotional adjustment to transplantation, especially in LD recipients.

SA-PO1008

Physician-Reported Adherence with Immunosuppressants in Renal Transplant Patients: Prevalence, Agreement, and Correlates Anna Bertram,² Selma Pabst,¹ Martina De zwaan,¹ Mario Schiffer.² *¹Clinic for Psychosomatics and Psychotherapy, Hannover Medical School, Hannover, Germany; ²Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany.*

Background: Assessing adherence to immunosuppressants (IS) is difficult. We investigated (1) the prevalence of non-adherence with IS as estimated by physicians; (2) the agreement between the physicians' estimated and other adherence measures; (3) the difference between adherent and non-adherent patients according to the physicians' estimation with regard to socio-demographic variables, transplant-related variables, and psychological factors.

Methods: All kidney transplant patients attending the outpatient clinic for a follow-up visit from 11/2014 to 02/2015 were screened; 238 patients met inclusion criteria. Adherence with IS was assessed with several measures: 4-item Basel Assessment of Adherence to

Immunosuppressive Medication Scale (BAASIS) and the adherence subscale of the German version of the Transplant Effect Questionnaire (TxEQ) for self-reported adherence; the physicians were asked to estimate patients' adherence to IS on a scale ranging from 1=very good to 5=very poor. Other adherence measures included rejection treatment within the previous 12 months and IS trough level variability in the last 13 months. Psychological variables were assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) and the Questionnaire of Perceived Social Support (FSozU-7).

Results: The physicians rated 9.2% (n=22) of the patients as being non-adherent. There was no agreement between the physicians' estimate of adherence and the patients' self-assessment, IS trough level variability, and allograft rejection. Physicians' ratings were independently related to female sex, non-German native language, higher symptoms of depression and anxiety, and less perceived social support.

Conclusions: Physicians might rely on observable and interactional cues including sex, language, and psychopathology to make inferences about an individual patient's adherence. Also, overestimation of IS adherence may impede physicians's ability to provide high quality care for their renal transplant patients.

SA-PO1009

Evolution Through 20 Years of the Major Kidney Transplant Program from Living Donor in Mexico Edgar Solis,¹ Luis Alberto Evangelista-Carrillo,¹ Enrique Rojas-Campos,² Benjamin Gomez-Navarro.¹ ¹Dept de Nefrologia y Trasplantes, IMSS, Guadalajara, Jalisco, Mexico; ²Unidad de Investigación Médica en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico.

Background: According to the National Transplant Center, in 2013 a total of 2707 kidney transplants (KT) were performed in Mexico. Our program performed the highest single center number of transplants with 270 KT, mostly from living donors.

Methods: We use data collected in our registration program at Nephrology and Transplant Unit. All the KT in adult patients performed from January 1994-December 2014 in CMNO were included. We also analyzed the last 909 kidney recipients and their serum creatinine at the end of first year. Successful KT was defined as a Cr <1.5 mg/dl at 1 year following. Grafts lost were defined as Cr >4.0 mg/dl or replacement therapy initiation.

Results: During this period 3643 KT were performed, 3236 from living donors and 407 from cadaver donor. Of living donors, 2786 were from related donor and 450 were from genetically unrelated donors. The mean age of recipient was 28 years; 65% of our recipients were male. The evolution of the program is shown.

	1994-1999 N=525	2000-2004 N=733	2005-2009 N=1061	2010-2014 N=1323
Recipient Gender N(%)				
Male	330 (63)	477 (65)	674 (64)	920 (69)
Female	195 (37)	256 (35)	387 (36)	400 (31)
Recipient age	32±11	30±12	27±11	28±10
≤ 19 years	57 (11)	178 (24)	311 (29)	192 (14)
20-40 years	346 (67)	390 (53)	595 (56)	949 (72)
41-60 years	112 (21)	159 (22)	138 (13)	153 (12)
≥ 61 years	3 (1)	5 (1)	14 (2)	25 (2)
Donor Gender N (%)				
Male	260 (49)	391 (53)	504 (47)	673 (51)
Female	261 (51)	337 (47)	555 (53)	646 (49)
Donor age (Mean)	31.3±10	33±10	35±10	36±10
Modality N (%)				
Peritoneal Dialysis	423 (80)	452 (62)	563 (53)	536 (41)
Hemodialysis	39 (8)	104 (14)	190 (18)	310 (24)
PD y HD	54 (10)	137 (19)	261 (25)	393 (30)
Preemptive transplant	9 (2)	40 (5)	47 (4)	67 (5)
Months before kidney transplant	29 ± 44	21 ± 18	26 ± 26	38 ± 37
HLA matching				
0-2 antigens	285	455	256	274
>2 antigens	125	175	633	828
Identical	76	73	96	94
Induction therapy				
No induction	525	613	389	31
Basiliximab	0	110	319	781
Daclizumab	0	2	333	8
Thymoglobulin	0	3	20	504
OKT3	0	5	0	5
Immunosuppression				
TAC-MMF-PDN	0	218	793	1287
CSA-MMF-PDN	0	243	246	26
CSA-AZA-PDN	251	222	3	0

Success rate of KT following 1 year was 86.8%. Only female gender and younger donors were statistically significant associated with successful transplant. Graft lost during the first year was 3.6%. Death was 2.4% during the first year.

Multivariate analysis for succesful transplant			
	OR	IC 95%	p
Recipient gender	2.56	(1.26-5.13)	0.009
Donor age	1.04	(1.04-1.01)	0.002
Identical HLA	0.21	(0.12-0.21)	0.129
X² =24.50; p <0.001			

Conclusions: Each year we are still growing the number of KT. The age of our recipients is diminishing and age of donors is increasing. Months before KT are also increasing lately reflecting the great number of ESRD patients. Recipient age, HLA mismatching, induction therapy use and generic drugs can explain the 13.2% of patients with Cr above 1.5 mg/dl.

SA-PO1010

The Difficult Road for Native Americans in Kidney Transplantation: Decreased Access and Reduced Long-Term Survival Sarah Stith,¹ Kristina Piorowski,¹ Fidel Barrantes.² ¹Economics, Univ of New Mexico, Albuquerque, NM; ²Presbyterian Transplant Center; Renal Medicine Associates, Albuquerque, NM.

Background: Native Americans (NAs) have disproportionately high rates of end-stage renal disease, yet wait listed NAs have lower rates of kidney transplantation than other racial/ethnic groups and worse long-term post-transplant survival outcomes than whites. This study evaluates these disparities across multiple medical and socioeconomic dimensions.

Methods: Using data from the Organ Procurement and Transplantation Network (OPTN), we evaluated wait list removal reasons and post-transplant survival rates from 3/1/95 to 12/31/12. We use a logistic regression model, controlling for patient, donor, match characteristics, and center and year fixed effects, along with a Blinder-Oaxaca decomposition of the results.

Results: Among registered patients removed from the wait list, NAs were less likely to receive a transplant (odds ratio, 0.71 [95% CI, 0.64-0.80]), and more likely to die on the wait list (1.88 [0.89-3.94], compared to whites. NAs are less likely than whites to survive at least two years (odds ratio, 0.80 [95% CI, 0.70-0.92]) and at least three years (0.81 [0.71-0.94]), but these disparities become statistically insignificant with risk adjustment.

Conclusions: NAs experience higher rates of adverse wait list removal reasons than other racial/ethnic groups. Among NAs who do receive transplants, short term survival outcomes are similar to those of whites, but longer term survival outcomes are lower. The decomposition of our results indicates that the disparity in three-year post-transplant survival between NA and whites is driven primarily by the prevalence of lower quality donors among NAs and a greater negative impact from such donor characteristics on survival among NA. NAs also tend to receive transplants at centers associated with worse outcomes and would benefit disproportionately from receiving transplants at better centers.

Funding: Private Foundation Support

SA-PO1011

Estimated GFR for Living Kidney Donor Evaluation Naya Huang,¹ Meredith C. Foster,¹ Krista L. Lentine,² Amit X. Garg,³ Emilio D. Poggio,⁴ Bertram L. Kasiske,⁵ Lesley Inker,¹ Andrew S. Levey.¹ ¹Div of Nephrology, Tufts Medical Center, Boston, MA; ²Div of Nephrology, Saint Louis Univ, MO; ³Div of Nephrology, Western Univ, London, ON, Canada; ⁴Dept of Nephrology and Hypertension, Glickman Urological and Kidney Inst, Cleveland Clinic, OH; ⁵Dept of Medicine, Hennepin County Medical Center and Univ of Minnesota, Minneapolis, MN.

Background: All living kidney donor candidates undergo an evaluation of GFR. Guidelines recommend measured GFR(mGFR) rather than estimated GFR(eGFR), but measurement methods are difficult, time consuming and costly. We questioned whether eGFR using creatinine (eGFRcr) with or without sequential cystatin C (eGFRcr-cys) is sufficiently accurate to identify donor candidates with high probability that mGFR is above or below thresholds for clinical decision making.

Methods: We combined the pre-test probabilities for mGFR thresholds <60, <70, ≥80 and ≥90 mL/min/1.73 m² in varying age, sex and race groups estimated from the National Health and Nutrition Examination Survey (NHANES) with test performance of eGFR (categorical likelihood ratios [LRs] determined from the Chronic Kidney Disease Epidemiology Collaboration) to compute post-test probabilities of meeting a given mGFR threshold.

Results: Using NHANES pre-test probabilities, we found that that in some circumstances, eGFRcr and eGFRcr-cys provides high accuracy (post-test probability ≥95%) in candidate donors. Using data from the Scientific Registry of Transplant Recipients, we demonstrated that 54% and 82% of recent donors had pre-donation eGFRcr high enough to assure ≥95% probability that pre-donation mGFR was ≥90 and ≥80 mL/min/1.73 m² respectively, suggesting a large fraction of donor candidates might not require mGFR.

Conclusions: Implementation strategies could include eGFRcr as a first test and possibly eGFRcr-cys as confirmatory test. If post-test probabilities are of sufficient magnitude, eGFR could be used to accept or reject donors without measurement of GFR. We will provide a web-based application.

SA-PO1012

Change of Physical Activities in Male and Female Recipients in 12 Months After Living Kidney Donor Transplantation Makoto Tsujita. *Transplant Surgery, Nagoya Daini Red Cross Hospital, Japan.*

Background: Since renal dysfunction and immunosuppressive drugs cause muscle degeneration, physical activities decrease in CKD, dialysis patients and transplant recipients. In addition, elderly kidney transplant recipients are increasing in Japan, so improving physical activities and increasing muscle strength and volumes are important to prevent fracture and fall accident.

Methods: Consecutive 58 patients (male 33) older than 40 years were enrolled in this study from 2012. Immunosuppression basically contains steroid, cyclosporine or tacrolimus, and mycophenolatemofetil or everolimus. Hypertension, hyperlipidemia, and osteoporosis were treated as needed. Parameters of physical activities such as hand grip, SMI (skeletal muscle index) and Body fat mass using by DEXA(dual-energy x ray

absorptiometry), and Body mass index (BMI) were measured and compared at prior, 6, and 12 months after kidney transplantation. Recipients were encouraged to do daily exercise for 30 to 60 minutes everyday.

Results: Mean age (years) were 52.3±10.0 in male, and 53.6±10.4 in female. In male patients, any parameter did not change after transplantation in male patients. In female patients, SMI improved in 12 months (p<0.005), and Hand grip also tended to increase without statistically difference.

Figure 1
Results of this study for male and female (mean±SD)

Male (n = 33)	Baseline	6 months after transplantation	12 months after transplantation	P value
BMI (kg/m ²)	22.6±3.1	21.8±3.2	22.7±3.2	0.3
Body fat mass (%)	20.4±5.8	20.1±5.5	21.1±5.4	0.59
SMI (kg/m ²)	7.1±0.8	7.0±0.8	6.7±1.8	0.12
Hand grip (kgw)	31.6±9.5	32.0±9.1	32.1±8.2	0.56
Female (n = 25)				
BMI (kg/m ²)	21.1±3.6	20.2±3.7	21.5±4.2	0.31
Body fat mass (%)	25.4±6.1	27.0±6.8	28.3±7.0	0.03
SMI (kg/m ²)	5.4±1.8	5.5±1.5	5.9±0.9	0.005
Hand grip (kgw)	17.7±5.8	19.3±5.1	21.4±5.5	0.17

Physical activities seemed unchanged after transplantation in male patients than before.

Conclusions: In male recipients, physical activities do not seem to recover in 12 months after kidney transplantation. More interventions and more studies are needed to increase physical activities and know the effect of daily exercise clinically.

SA-PO1013

Search for New Data to Predict Kidney Transplant Outcomes in the Organ Procurement and Transplantation Network Database Mohamed A. Sheta,¹ Bertram L. Kasiske,² Charles E. Alexander,³ Joseph Kim.⁴ ¹Univ of Minnesota; ²Hennepin County Medical Center; ³Univ Health Network; ⁴The Living Legacy Foundation of Maryland.

Background: The Organ Procurement and Transplantation Network (OPTN) collects data used to monitor transplant program outcomes for quality assurance and regulatory oversight. It is imperative that the variables in the OPTN database used by the Scientific Registry of Transplant Recipients to determine expected outcomes after kidney transplant be reliable, complete, and up-to-date.

Methods: We conducted a systematic review to identify risk factors not included in current OPTN data that predict graft failure or mortality after kidney transplant. We searched for studies with publication date between Jan 1 2000-May 1 2015; at least 1000 subjects in one or more risk prediction models; multivariate analysis used to select variables predicting patient or graft survival; inclusion in the multivariate model of at least one risk factor collected before or at the time of transplant that is not already collected by OPTN; and English language. For duplicate publications we selected the most recent. For publications with overlapping but distinct cohorts, we selected the one with the largest cohort. We arbitrarily limited the search to studies including 1000 participants in at least one risk-prediction model. Although a small single-center study may convincingly show that a newly described risk factor predicts outcomes at that center, there are likely major barriers to measuring and collecting this risk factor uniformly at every program in the US.

Results: We identified 33 studies that met inclusion criteria; 6 (18%) were single-center, 4 (12%) were multicenter, and 23 (70%) were registry studies. Promising new variables included: myocardial infarction, coronary artery revascularization, atrial fibrillation, congestive heart failure, valvular heart disease, cerebral vascular accident, carotid artery revascularization, aortic aneurysm repair, ischemic leg amputation or revascularization, tobacco abuse, alcohol and illicit drug dependence, ZIP code, and socioeconomic status.

Conclusions: This review provides evidence for the new OPTN Ad Hoc Data Advisory Committee to update the OPTN database.

SA-PO1014

Prevalence of Mineral and Bone Disorders Among Living Kidney Transplant Recipients Essam Mohammed Khedr, Amr Mohab, Haitham Ezzat. *Nephrology Dept, Ain Shams Univ, Cairo, Egypt.*

Background: Mineral and bone disorders (MBD), frequent complications of chronic kidney disease (CKD), occur frequently in kidney transplant recipients. Still, little is known about its prevalence and clinical correlates in transplanted patients.

Methods: We conducted a cross-sectional analysis of 504 stable living kidney allograft recipients. Detailed medical history, demographic data and routine laboratory investigations, including s.creatinine, s.corrected Calcium, s.Phosphorus, serum iPTH and s.Alkaline Phosphatase (ALP) were collected. Estimated GFR was calculated using the abbreviated MDRD formula. Patients were stratified into three groups based on duration of kidney transplantation. Group I: 6 months to 1 year, group (II): from 1 to 5 years and group (III): more than 5 years. Correlations were done between bone minerals and all laboratory results. We also analyzed the possible relation between various immunosuppressant drugs and bone minerals, serum iPTH and serum ALP.

Results: The mean age was 32±8 years in group I, 45±3.7 years in group II, and 40±5 years in group III, with no significant difference between the three groups (p>0.05). There was no significant difference between the studied groups as regards results of laboratory parameters (p>0.05). 115 patients had iPTH levels > 170 ng/dl, while 365 patients (72.4%) had iPTH levels >70 ng/dl. Only 24 patients had hypercalcemia, and 34 patients had

hyperphosphatemia. We also found that 68 patients had hypophosphatemia. Serum iPTH and serum ALP levels were higher in group III (156±66 ng/dl, 135±54 IU respectively) when compared to group I (98±33.4 ng/dl, 120±33 IU) and group II (138±35 ng/dl, 122±60 IU) (p<0.001). In group I, iPTH levels were negatively correlated with eGFR (r value=-0.37, p<0.05). Both serum ALP and iPTH levels showed significant negative correlation with eGFR in groups II and III (p<0.05). In all groups, bone minerals, iPTH and serum Alkaline Phosphatase levels had no statistically significant relation with the immunosuppressant agent used (p>0.05).

Conclusions: Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function and transplantation duration.

SA-PO1015

Risk of Adverse Maternal and Fetal Outcomes During Pregnancy in Living Kidney Donors Jessica B. Kendrick,^{1,2} John R. Holmen,³ Gerard John Smits,¹ Michel Chonchol.¹ ¹Univ of Colorado Denver, Aurora, CO; ²Denver Health Medical Center, Denver, CO; ³Intermountain Health Care, Salt Lake City, UT.

Background: A frequently asked question by potential kidney donors is risk of nephrectomies on maternal and fetal outcomes in pregnancy. Studies regarding the risks of living kidney donation and pregnancy outcomes are conflicting. The purpose of this study was to determine the risk of adverse maternal and fetal outcomes in donors vs. non-donors.

Methods: Using data from an integrated health care delivery system in Utah from 2000 through 2014, a total of 72 women were living kidney donors that became pregnant after kidney donation. Using a pool of 74,105 women who were not donors, we selected 1223 to use for matches for the living kidney donors. These women were matched 1:3 by age and race. Adverse pregnancy outcomes were defined as preterm delivery, delivery via cesarean section, preeclampsia/eclampsia, length of stay in the hospital and low birth weight (<2,500 g). Logistic regression analysis was used to examine the association between living donation and adverse outcomes.

Results: Of the living kidney donors, the mean (SD) age and mean (SD) gestational age at delivery was 30±5 years and 38±2 weeks, respectively. The mean (SD) length of stay in the hospital was 2.7 ± 2.7 days. Six cases (8%) had a history of chronic hypertension. Living kidney donors did not have a higher risk of preterm delivery (OR 1.82, 95% CI 0.877-3.77), preeclampsia/eclampsia (OR 1.11, 95% CI 0.47-2.65), delivery via cesarean section (OR 1.51, 95% CI 0.85-2.66), length of stay > 3 days (OR 1.29, 95% CI 0.63-2.64) or low birth weight (OR 1.94, 95% CI 0.87-4.35) compared to non-donors.

Conclusions: Living kidney donation is not associated with a higher risk of adverse outcomes in pregnancy.

Funding: NIDDK Support

SA-PO1016

The Quality of Life of Parents of Pediatric Kidney Transplantation Yuko Hamasaki,¹ Miyako Tazaki,² Yusuke Takahashi,¹ Seiichiro Shishido,¹ Atsushi Aikawa.³ ¹Pediatric Nephrology, Toho Univ Faculty of Medicine, Tokyo, Japan; ²Psychology, Toho Univ Faculty of Medicine, Tokyo, Japan; ³Nephrology, Toho Univ Faculty of Medicine, Tokyo, Japan.

Background: The purpose of the study is to investigate how the Quality of life (QOL) of parents whose child had received kidney transplantation (KT) would change by delivering questionnaires four times; before, one month after, three months after and one year after KT.

Methods: The QOL of thirty-one parents (30 mothers and 1 father) with a mean age of 38.5 years old whose child received KT at Toho University Omori Medical Center from May 2012 to March 2015 was measured using WHO Quality of Life (WHOQOL), Visual Analogue Scale (VAS), and General Health Questionnaire (GHQ). The mean age of the recipients was 5.8 years old (18 boys, 13 girls). Congenital anomalies of the kidney and urinary tract were the most frequent primary diseases (54.8%). Among them, twenty-two children received dialysis before KT, and nine received preemptive KT.

Results: Based on the results, the average WHOQOL scores show the QOL of parents decreased one month after KT (3.15) with a statistical difference compared with before KT (p=0.042), but increased at three months (3.40) (p=0.0073), and maintained until one year (3.41). The average QOL of the parents of a child with frequent infection was statistically lower than those without any infection (p=0.448) at three months after KT and one year after KT (p=0.0406). The average QOL scores of nineteen donor parents had a statistically higher QOL before KT then reversed at one month after KT, but became higher again at three months after KT.

Conclusions: The QOL of the parents would decrease one month after KT when infection or other problems often occurred, but increased after three months when the condition of recipients stabilized and maintained until one year after KT, which became as high as before KT.

SA-PO1017

Disparities in Access to Renal Transplant in Puerto Rican Children
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Background: Disparities in access to renal transplant have been reported in racial minorities living in US. No data is available from children with ESRD living in Puerto Rico (PR), the largest Hispanic group in a single pediatric dialysis unit in US. We describe the pediatric population with ESRD in PR from 2003-2013, the renal transplant rates and possible barriers to receiving a graft.

Methods: Retrospective chart review of patients diagnosed with ESRD in PR from 2003-2013. Incidence, prevalence rates, means/standard deviations (SD), medians/interquartile range (IQR), frequencies and percentages were calculated and compared to national rates.

Results: From 2003-2013 99 patients, male: 52%, age:13.5yrs (8-16yrs), were diagnosed with ESRD. Congenital anomalies were the primary cause in 40%, and FSGS in 24%. Incidence of ESRD ranged from 3-14 subjects per million population/year, with prevalence per dialysis modality from 7-18 subjects per million population/year. 38% were transplanted in PR (Median age: 14yrs, IQR: 9-16), 23% from living donors. 14.1% received a transplant in the first year (National rate: 38%). 63% of transplanted children had Medicare coverage. None of 9 infants diagnosed with ESRD were transplanted during infancy. 46% of the children who were not transplanted stayed at our unit for a median time of 2 yrs (IQR: 1-3). The rest was transferred to a dialysis unit outside PR (15%) or to an adult facility without being transplanted (39%), 67% of these non-transplanted children were covered by Medicare. The mortality rate during the first year of diagnosis was 3% (National rate: 4%).

Conclusions: Children with ESRD in PR face striking disparities in access to renal transplant. Lack of pediatric transplant surgeons, geographical isolation and minimal living donation are potential barriers. Medicare coverage does not appear to be a factor, as it was similar between transplanted and non-transplanted. Interventions to reduce these inequities are needed.

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SA-PO1018

The Case against Declining Donors with Impaired Fasting Glucose
 Robert N. Foley, Naim S. Issa, Danielle M. Berglund, Arthur J. Matas, Hassan N. Ibrahim. Univ of Minnesota, Mpls, MN.

Background: The definition of diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have changed over time. IGF was defined in 1997 by fasting glucose 110-125 mg/dL and in 2003 the definition changed to fasting glucose 100-125 mg/dL. With the introduction of this new definition, many potential donors with fasting blood sugar between 100-110 mg/dL have been denied donation. This is highly relevant as many of these are potential donors to family members with type 2 diabetes mellitus.

Methods: We assessed the risk of death, new onset diabetes, hypertension, proteinuria and reduced GFR (<45 and <30 ml/min/1.73m²) in 3783 kidney donors according to fasting blood glucose(FBG) at the time of donation spanning the period between 1963-2013.

Results: 2900 donors had a FBG <100 mg/dL, 550 with 100-109, 205 with 110-125, and 128 donors with FBG > 126 mg/dL. Donors with IFG (100-109 mg/dL) after multivariable adjustment were not more likely to die, develop diabetes, proteinuria, hypertension, eGFR <45 ml/min/1.73m² or eGFR <30ml/min/1.73m² as compared to those with FBG <100 mg/dL (Table 1). In contrast, those with FBG between 110-125 mg/dL were more likely to become diabetic and hypertensive but not proteinuric or reduced GFR. Those with FBG ≥126 mg/dL were more likely to die, develop DM and HTN but not suffer any adverse renal consequences.

Outcome	Fasting Blood Glucose (mg/dL)		
	100-109	110-125	≥126
Death	1.08 (0.8-1.47)	1.41 (0.91-2.18)	1.57 (1.02-2.41)*
Diabetes	1.19 (0.83-1.69)	2.07 (1.36-3.14)*	2.89 (1.8-4.64)*
HTN	1.2 (0.99-1.47)	1.61 (1.23-2.11)*	1.76 (1.26-2.44)*
Proteinuria	0.68 (0.44-1.06)	0.76 (0.41-1.41)	1.62 (0.89-2.93)
eGFR <45 ml/min	0.78 (0.43-1.43)	1.26(0.54-2.94)	1.3 (0.52 - 3.27)
eGFR <30 ml/min	0.96 (0.73-1.25)	1.31(0.87-1.96)	1.06(0.66-1.7)

* p-value <0.05 compared to FBG <100 mg/dL.

Conclusions: Excluding potential donors with a fasting glucose (100-109 mg/dL) should be revisited as these donors do well in the long-term.

Funding: Other NIH Support - NIH (5P01 DK013083)

SA-PO1019

Psychosocial Distress and Adherence in Adolescents Post-Kidney Transplant
 Jessica L. Stahl,¹ Angela P. Presson,² Chong Zhang,² Raoul D. Nelson,¹ Matthew M. Grinsell.¹ ¹Pediatrics, Univ of Utah, Salt Lake City, UT; ²Study Design and Biostatistics Center, Univ of Utah, Salt Lake City, UT.

Background: Adolescents who are post-kidney transplant have comorbidities in medical and psychosocial arenas and high risk of non-adherence and graft loss. Limited data exists to describe the relationship between mental health and adherence in this population.

Methods: 22 parent-child dyads with children ages 12-17 were recruited at scheduled post-kidney transplant visits. They completed demographic and standardized Youth Outcomes questionnaires. Adherence was assessed using the standard deviation of the prior 1 year of tacrolimus levels and chart review for hospitalization for non-adherence. Descriptive statistics were used to assess the relationship of adherence to psychiatric diagnosis, psychosocial distress, gender, and time from transplant, as well as differences in parent-child reporting.

Results: Overall, 52% reported a psychiatric diagnosis, which is significant compared to 13% in the general adolescent population (p<0.001), with 38% evidencing elevated levels of psychosocial distress on self-report and 25% elevated per parent report. 68% of adolescents reported a different distress level than estimated by their parent. The psychiatric diagnosis rate was 64% in the non-adherent group and 36% in adherent adolescents. Only 40% of the adherent group reported elevated distress versus 57% of the non-adherent group. There was a gender bias toward male non-adherence in this group with 100% of the non-adherent population being male. The mean time from transplant of non-adherent groups was 6.1 years versus 3.9 years in the adherent group. These differences were not statistically significant except as above.

Conclusions: Our population's rate of psychiatric diagnosis was significantly elevated compared to community norms and also correlated with elevated psychosocial distress and non-adherence. Disagreement in parent and adolescent reporting was common regardless of adherence status. Our sample did demonstrate gender differences in non-adherent behavior as well. Interpretation of these results, as well as statistical significance is limited by the small sample size.

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SA-PO1020

Post Donation Diabetes and Risk of Death and ESRD Hassan N. Ibrahim, Robert N. Foley, Scott Reule, Danielle M. Berglund, Aleksandra Kukla, Naim S. Issa, Richard S. Spong, Arthur J. Matas. Univ of Minnesota, Mpls, MN.

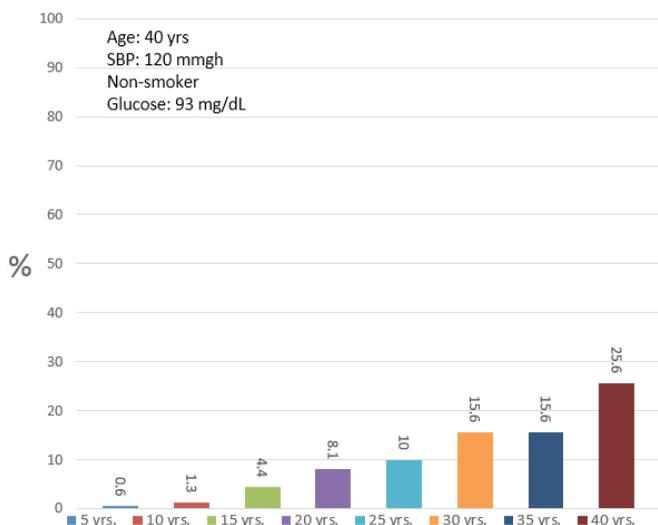
Background: We have previously shown that development of diabetes following live kidney donation does not result in accelerated GFR decline when compared to diabetics with two kidneys. Herein, we report on the development of a risk calculator for new onset DM in donors and address its contribution to mortality and also renal outcomes.

Methods: Donors are followed indefinitely through surveys including development and treatment of diabetes and renal outcomes. Risk factors for post donation diabetes were determined using stepwise proportional hazards regression.

Results: Development of DM was ascertained in 3874 donors with a mean follow-up of 16±12 years. In total, 279 (7%) developed DM. Pre-donation risk factors for development include older age, BMI, tobacco use, and fasting serum glucose at donation, p<0.01 for all (Table 1a). Diabetes following donation was associated with a nearly 5 fold increase in proteinuria and 2 fold increase for eGFR < 30 or ESRD (Table 1b). Coefficients from the regression model were then used to create an individualized risk calculator. This was developed in 1934 donors and validated in the remaining 1934 (C-statistic 0.77). The cumulative risk of developing DM at 5 yearly intervals is shown in figure 1.

Variable	Adjusted Hazard Ratio	p-value
1a) Pre-donation risk factors for DM		
Age	1.01 (1-1.03)	0.01
BMI	1.12 (1.1-1.15)	< 0.001
Tobacco use	1.37 (1.06-1.75)	0.01
Serum glucose	1.01 (1.01-1.02)	< 0.001
1b) Post donation DM, mortality and ESRD		
Death	0.71 (0.46-1.08)	0.11
Proteinuria	4.65 (3.28-6.59)	<0.0001
eGFR <30 or RRT	2.21 (1.32-3.69)	0.0026

Cumulative risk of DM for a typical White kidney donor.



Conclusions: Diabetes can be reasonably predicted in kidney donors using baseline data. Diabetes is a significant contributor to reduced GFR and proteinuria.

Funding: Other NIH Support - NIH (5P01 DK013083)

SA-PO1021

What Kind of Obesity Does Affect Kidney Function? Survey of Kidney Transplant Donors Mikiko Yoshikawa, Junko Nakano, Kentaro Nakai, Hideki Fujii, Shinichi Nishi. *Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan.*

Background: Currently obesity is a risk for chronic kidney disease. It is also suggested that sarcopenia is the independent risk factor of hypertension. It is unclear whether obesity and body composition affect to kidney function and other prognosis of donors in our country. The aim of this study was to investigate the influence of body composition, the findings of graft biopsy and 1-year after clinical outcome.

Methods: This is a retrospective single center study of 60 living kidney transplant donors from 2009 to 2014. Donors are stratified according to Body Mass Index (BMI) 25kg/m² is defined as an obesity in Japanese criteria) and skeletal muscle index (SMI) from the appearance of muscle on cross-sectional CT images (L3 SMI, Under 38.5cm²/m² for women and 52.4 cm²/m² for men are defined as a sarcopenia(1). We divided donors into four groups; (A) Obesity negative + Sarcopenia negative (ONSN)(B) Obesity positive + Sarcopenia negative (OPSN) (C) Obesity negative + Sarcopenia positive (ONSP) (D) Obesity positive + Sarcopenia positive (OPSP). We evaluated kidney function at donation, baseline kidney graft biopsy findings and clinical course 1 year-after donation.

Results: Seven patients were OPSN (11.7%), 22 patients ONSP (36.7%), and 4 patients OPSP (6.7%). Visceral fat area >100 m² (which is defined as central obesity in Japanese criteria) was significantly higher in OPSP group. S-Cre at donation was significantly lower in OPSN and ONSP groups. In multivariate analysis of graft biopsies, BMI 25kg/m² was a significant risk for small artery intimal thickenings and interstitial fibrosis/tubular atrophy. On the contrast, OPSP was an independent risk for global sclerosis. In multivariate analysis, central obesity was significantly correlated with 1-year after proteinuria. In addition, OPSP was a independent risk for 1-year after hypertension.

Conclusions: These results indicate obese donor already has a risk for arterial and interstitial damages at transplantation. In addition, central obesity and sarcopenia contribute to the late graft function and hypertension.[Reference] (1) Prado CM et al. *Lancet Oncol* 2008; 9: 629-635.

SA-PO1022

Living Donor Remaining Function Measured by CKD-EPI Correlates with Remaining Kidney Volume Asif A. Sharfuddin, Ali Khalil, Muhammad S. Yaqub, Tim E. Taber, Muhammad Ahmad Mujtaba. *Medicine/Neph, Indiana Univ.*

Background: The aim of our study was to evaluate whether preserved kidney volume correlates with donor renal function at 2-years post-donation using the CKD-EPI eGFR equation.

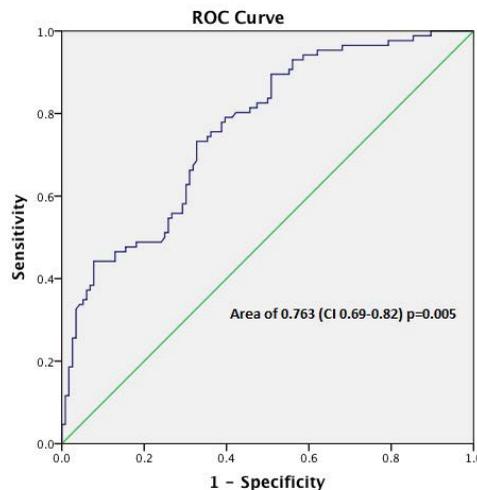
Methods: Demographics and renal function of living donors who underwent living nephrectomy between January 2008 and November 2012 were reviewed. All donors underwent computed tomography with an estimation of kidney volumes. Preserved Kidney Volume (PKV) was adjusted (aPKV) to Body Surface Area.

Results: A total of 208 donors with 2 year follow up data available. Pre-donation eGFR (β Coef. 0.344), age (β Coef. -0.318) and aPKV (β Coef. 0.11) were found to be independent predictors of 2yr eGFR (p<0.001). aPKV was divided into tertiles (low/medium/high) and a 2 year eGFR of <60ml/min was chosen as a cut off for dichotomous analysis as in Table 1.

	2yr eGFR<60	2yr eGFR> 60	Total
Vol Tertile 1 (low)	44(47.8%)	24(20.7%)	68(32.7%)
Vol Tertile 2 (medium)	31(33.7%)	35(30.2%)	66(31.7%)
Vol Tertile 3 (high)	17(18.5%)	57(49.1%)	74(35.6%)
Mean aPKV (ml)	165±29	194±30*	
Mean eGFR (ml/min)	52±6	76±15*	

* p value < 0.001

Mean 2yr eGFR was 57.9±12, 65±16 and 73±17 between the tertile groups (p<0.05). The odds ratio of having a 2yr post-donation eGFR <60 with a cutoff of median aPKV of 194ml was 5.8 (95%CI 2.9-11.6; p<0.0001), while that of 2yr post-donation eGFR <60 with a cutoff of < 25th percentile of aPKV of 159.9 was 5.6 (95%CI 2.7-11.22; p<0.0001). The odds ratio of having an eGFR <60 if the aPKV was above the 75th percentile was 0.13 (95%CI 0.05-0.3) p<0.0001. ROC and AUC for aPKV and eGFR (CKD-EPI) of <60 were 0.763 (CI 0.69-0.82) p=0.005 as in Figure 1.



Conclusions: Our study is the first to show using CKD-EPI equation that preservation of residual renal function in living donors needs to take into account remaining kidney volume, when selecting kidneys from healthy donors.

SA-PO1023

Assessing Adherence Barriers in Pediatric Kidney Transplant Recipients Charles D. Varnell,¹ Kristin Loisselle,² Ahna Lh Pai,² Avani Modi,² David K. Hooper.¹ *¹Div of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; ²Center for Treatment Adherence and Self-Management, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Nonadherence in pediatric kidney transplant recipients(KTRs) is associated with poor outcomes and poses a significant financial cost to society. Patient and family reported barriers to taking medications predict nonadherence, rejection, graft failure, and death. Despite their clinical importance and amenability to intervention, barriers to medication adherence are not routinely assessed in pediatric settings.

Methods: From Jan 2015 - May 2015, barriers to immunosuppressant adherence in KTRs were assessed using a standardized checklist of 14 common barriers. For KTRs<10 y.o. the caregiver completed the assessment. For KTRs>10 y.o. both the patient and caregiver, if present, completed the assessment. Assessments were completed during routine outpatient clinic appointments.

Results: 36 pediatric KTRs [M(SD)age=13.14(6.43)years;56.7%male] and 50 primary caregivers completed a barriers assessment. At least one barrier was reported by 47% of KTRs compared to 42% of caregivers. For KTRs the most frequent barriers were forgetting(22%), hating the taste(13.9%) and running out of medicine(8.3%). For caregivers, the most frequently endorsed barriers were forgetting(20%), side effects(6.0%) and patient refuses to take their medication(6.0%). There was excellent concordance(96.2%) in dyads where both KTR and caregiver reported barriers. Assessing for barriers to adherence was easy to perform in practice and required<60 seconds.

Conclusions: Nearly half of all patients report at least one barrier to taking their immunosuppression, and there is generally consistent agreement between patient and caregiver perception of barriers. Standardizing the approach to assessing barriers to immunosuppression adherence in the clinical setting can quickly produce information that might be missed by the provider. Future research should evaluate the effectiveness of interventions delivered as part of routine medical care to overcome identified barriers and prevent known complications associated with nonadherence.

SA-PO1024

A Longitudinal Follow-Up of Hispanic Living Kidney Donors
 Clarence E. Foster III,¹ Pinky J. Patel,² Hirohito Ichii,¹ Madeleine V. Pahl,² Elani Streja,² Jonathan R. Lakey,¹ Kamyar Kalantar-Zadeh.² ¹*Surgery/ Div of Transplantation, Univ of California, Irvine, Orange, CA;* ²*Medicine/ Nephrology, Univ of California, Irvine, Orange, CA.*

Background: This is a long-term follow-up of living kidney donors (LKD) in an ethnically diverse patient population. Hispanics are known to have an increased risk of developing chronic kidney disease, associated with hypertension and obesity. The hypothesis is Hispanic living kidney donors or uninsured living kidney donors would have poorer long-term outcomes secondary to lack of access to health care and secondary to the higher risk factors for developing chronic kidney disease.

Methods: The objectives : measure obesity, hypertension, diabetes, measure CrCl, post-donation and compare to the pre-donation CrCl. LKD were contacted & invited to participate & had a questionnaire about their general health & history and physical. Analysis included a CBC, serum chemistry, a 24-hour urine collection to measure creatinine, protein and albumin. A Patient Data Visit Sheet, RAND 35 Health Questionnaire. The IRB approved this study.

Results:

Demographics	(N=42)	Hispanics (23)	Non-Hispanics (19)	
Age @ Donation, Years (range)	36 +/- 12 (18 to 55)	32 +/-11 (18 to 52)	41 +/- 10 (22 to 55)	0.007
Female (%)	57	43	26	NS
U.S. Citizen (%)	55	35	79	<0.0001
Health Insurance (%)	57	26	95	0.0058
Years Post-Donation	3.8 (1.1 to 13.5)	3.6+/- 2.8 (1.2 to 11.8)	4.0 +/- 3.4 (1.1 to 13.5)	NS
Pre-Donation BMI, mean	25.6	27.9	24.7	0.0175
Pre-donation GFR, ml/min, mean	122	137	104.5	NS

Pre- and post-donation systolic and diastolic blood pressures were similar between Hispanics and non-Hispanic LKD. Non-Hispanic LKD had a greater decrease in systolic blood pressure post-donation -4.5 mmHg vs. 6 mmHg (p=0.0378). The decrease in CrCl post-donation was the same in Hispanic and Non-Hispanic LKD, 33 ml/min vs. 35 ml/min. None of the LKD in the study had significant proteinuria or micro albuminuria.

Conclusions: Post living donor kidney donation in our ethnically diverse patients are not at a higher risk for developing obesity, HTN, or CKD. Overall, our LKD feel they have a good overall quality of life including both physical and emotional realms.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals

SA-PO1025

Predictors of Low Estimated Glomerular Filtration Rate After Living Kidney Donation in a Southeast Asian Population from Singapore
 Ru Yu Tan,¹ John C. Allen,² Terence Kee Yi Shern,¹ Tazeen H. Jafar.² ¹*Dept of Renal Medicine, Singapore General Hospital, Singapore;* ²*Duke-NUS Graduate Medical School, Singapore.*

Background: We aim to investigate patterns of change in kidney function and factors associated with low estimated glomerular filtration rate (eGFR) following living kidney donation in Southeast Asian.

Methods: We retrospectively studied living kidney donors with nephrectomy performed at Singapore General Hospital between 1976 and 2012. Quantile regression analysis was performed on pre- to post-nephrectomy percent change in CKD-EPI eGFR levels. Donors were grouped according to elapsed time from donation as short-term (>6 months to <5 years after donation), medium-term (5 to <10 years after donation), and long term (≥10 years after donation), and compared on pre-nephrectomy demographic and clinical characteristics. Univariate and multivariate logistic regression were performed to evaluate predictors of low post-donation eGFR. A pre-nephrectomy eGFR cutpoint for prognosticating low post-donation eGFR was obtained using ROC analysis.

Results: 174 donors, predominantly female (63.8%) and of Chinese ethnicity (73%), of average age 40.6 years, were recruited. Median (range) follow-up was 7.8 (0.1–33.8) years during which 30 donors (17%) developed low eGFR, defined as <60 ml/min/1.73m². At 5 years post donation, 43.1% of donors recovered to at least 75% of pre-nephrectomy eGFR levels, and 9.8% exhibited 100% recovery to pre-nephrectomy eGFR levels at 19.2 years, on average. High pre-nephrectomy eGFR was protective for risk of low post-donation eGFR, with a 6% reduction in risk for each unit increase in pre-nephrectomy eGFR (OR, 0.94; 95% CI, 0.91–0.97; p=0.002). This relationship was stronger in the short-term than medium to long term (p=0.052). ROC analysis indicated pre-donation eGFR cutpoint of 100 ml/min/1.73m² for prognosticating low post-donation eGFR (sensitivity=0.80, specificity=0.61, PPV=0.30, and NPV=0.95); AUC (95% CI) was 0.75 (0.66–0.84).

Conclusions: In general, kidney function is well preserved following kidney donation in Southeast Asian donors. Pre-nephrectomy eGFR is a good predictor of post-donation eGFR, especially in the short-term.

SA-PO1026

Post-Kidney Transplant Follow-Up in Native American: An Opportunity for Improvement Fidel Barrantes,¹ Sarah Stith,² ¹*Presbyterian Transplant Center; Renal Medicine Associates, Albuquerque, NM;* ²*Economics, Univ of New Mexico, Albuquerque, NM.*

Background: Native Americans have been shown to face decreased access to waitlisting and transplantation. We explore the possibility that Native Americans might face decreased access to high quality post-transplant care, especially in the long-run, due to a decreased general access to healthcare, as is faced by many socioeconomically disadvantaged minority populations.

Methods: Using data from the OPTN, we evaluated the quantity and type of post-transplant care received by Native Americans. We compare Native American populations with other ethnic groups from October 1, 1987 to December 31, 2012 using multivariate regression analysis, controlling for time-invariant factors affecting all patients in a given year (year fixed effects) and time-varying factors associated with a specific transplant center (center fixed effects). (Standard errors are clustered at the center level to account for heteroskedasticity and spatial correlation among patients in a given center).

Results: Statistically significant regression results (p<0.05) indicate that Native Americans are less likely to receive transplant program-based aftercare than other racial/ethnic groups (Black, White, Hispanic and Asian/Pacific Islander), opting instead to see other types of specialists. They also are two percentage points more likely to be lost to follow-up (mean=0.15), one percentage point less likely to participate in an immunosuppression-related research study (mean=0.03), and receive 0.3 fewer follow-up visits (mean=2.2) than whites. They face the lowest number of follow-up visits, the lowest probability of participating in a research study, and the highest probability of being lost to follow-up. They are also 13% points less likely to work post-transplant (mean=0.35) than whites.

Conclusions: The results indicate that Native Americans have reduced access to high quality post-transplant care. Further research will explore how much of the disparity in post-transplant care is related to the high correlation between being Native American and poor and between being Native American and living in a rural area, especially on tribal lands.

Funding: Private Foundation Support

SA-PO1027

Medication Adherence Barrier Burden Predicts Subsequent Taking Adherence in Adolescent Kidney Transplant Recipients in the TAKE-IT Trial Bethany J. Foster,¹ Huaqing Zhao,² Ahna Lh Pai,² Nataliya Zelikovsky,² Crystal D. Holly,² Jodi M. Smith,² Vikas R. Dharnidharka,² Diane Hebert,² Douglas G. Matsuell,² Veronique Phan,² Susan L. Furth.² ¹*Pediatrics, McGill Univ, Montreal, QC, Canada;* ²*TAKE-IT Investigators.*

Background: Longitudinal studies of objectively-measured medication adherence among high-risk adolescent kidney transplant recipients are lacking.

Methods: We aimed to determine whether the burden of perceived barriers to medication adherence predicted taking adherence (proportion of prescribed doses taken) during the subsequent 3 mo., as monitored with a multidose electronic pillbox. We evaluated the 126 participants of TAKE-IT with electronic adherence data available for the 3-mo. run-in period during which no intervention was applied. Participants (11–24 y.; ≥ 3 mo. post-transplant) were followed in 8 transplant centers (Canada and USA). Adherence barriers were assessed at baseline using the Adolescent Medication Barriers Scale (AMBS). A higher score indicates greater barrier burden (possible range 17–85). We used linear regression to estimate the association between baseline AMBS scores (total score and ingestion, disease adaptation, and cognitive/organization subscores) and taking adherence. Models also included sex, age, race, and time since transplant.

Results: 60% were male and 67% were white. Median age at baseline was 15.8 (IQR 13.2–17.4) y. Median time since transplant was 3.1 (0.7–7.5) y. Mean±SD taking adherence for the interval was 87.0%±28.9. Higher barrier burden (median score 38 (IQR 30–44)) was significantly associated with poorer adherence: a 5 unit higher total AMBS score was associated with 1.5% (95% CI 0.04, 3.0) lower taking adherence. Males had 7.5% (0.8, 14.3) lower taking adherence than females. The only subscale score significantly associated with taking adherence was disease adaptation: a 5 unit higher sub-score was associated with 3.3% (0.4, 6.2) lower taking adherence.

Conclusions: While the absolute impact of barrier burden on adherence is small, higher burden of perceived barriers is a significant predictor of poorer adherence. Future analyses of the TAKE-IT data will determine the impact of an intervention targeting individual barriers on objectively-measured adherence.

Funding: NIDDK Support

SA-PO1028

Pre-Procurement Iodinated Contrast Exposure Is Associated with Early and Late Kidney Transplant Outcomes Fidel Barrantes,¹ Sarah Stith,² Abhijit S. Naik,³ Isaac E. Hall,⁴ Mark A. Perazella.⁴ ¹*Renal Medicine Associates, Albuquerque, NM;* ²*Economics, Univ of New Mexico, Albuquerque, NM;* ³*Internal Medicine, Univ of Michigan, Ann Arbor, MI;* ⁴*Internal Medicine, Yale Univ, New Haven, CT.*

Background: Iodinated contrast can cause acute kidney injury. We sought to evaluate the association of iodinated contrast exposure prior to organ procurement in deceased donors with subsequent kidney transplant outcomes.

Methods: Using OPTN data for kidney transplants between May 2000 and December 2012, we performed multivariate regression to model 2 different definitions of delayed graft

function as a function of donor exposure to coronary angiograms, controlling for time-invariant factors affecting all patients in a given year (year fixed effects) and time-varying factors associated with a specific transplant center (center fixed effects with standard errors clustered at the center level to account for heteroskedasticity and spatial correlation among patients in a given center).

Results: Of 93,811 donors listed in study period, 8.5 % (8012) were exposed to coronary angiograms. From this group, 14 628 kidneys were transplanted. Statistically significant regression results ($p < 0.01$) indicate that patients receiving organs from donors who received coronary angiograms are 2% points more likely to receive dialysis within the first week of transplant (mean=0.24) and are less likely to experience a >25% decline in serum creatinine in the first week of transplant (mean=0.56). These patients also face a 61 day shorter average graft survival time and a 1% point lower probability of 6-month post-transplant patient survival. At three years recipients from donors with contrast exposure have 2% decrease in survival rate ($P=0.005$).

Conclusions: This large database analysis provided statistical power to detect an association between donor exposure to iodinated contrast from coronary angiograms before organ procurement and subsequent adverse early as well as later kidney transplant outcomes. Further research into the effects of deceased-donor management strategies is warranted to expand the organ pool while decreasing adverse transplant outcomes.

Funding: Private Foundation Support

SA-PO1029

One Year Recovery After Kidney Donation: The Medical and Donor Point of View in a Prospective Cohort Study Briançon Serge,¹ Lucie Germain,¹ Michele Kessler,² Marie-Alice Macher,³ Marc Soudant,¹ Marie Thuong,² ¹*Epidemiologie CIC-EC, CHU de Nancy, Nancy, France;* ²*Nephrology, CHU de Nancy, Nancy, France;* ³*Transplantation, Agence de la Biomedecine, Paris, France.*

Background: Renal transplantation is the reference treatment for ESRD patients; the living donor kidney has been proven to provide better outcomes to recipients. Recovery of donors has been less studied and understood.

Methods: An exhaustive sample of 500 donors recruited in every French transplantation between October 2009 and January 2012 (T0) were followed at 3 (T1) and 12 months (T2) after surgery. Questionnaires investigating the donation course, quality of life (SF-36 and Euroqol) and recovery were sent home. Medical data were from CRISTAL register. 384 donors participated at 3(85%) and 12months(90%). The exceptional participation rate reflects the high commitment of donors.

Results: Before the donation, the physical health is incredibly high especially for older. On average a 75 year-old donor has the PCS SF36 level of 35 year-old men in the general population Three months after surgery, all outcomes exhibited decreased health indicators. Three quarters of the donors underwent laparoscopy, associated with less pulmonary complications, kidney failure, high blood pressure, persistent physical pain, better postoperative recovery. More than half the donors have at least one complication of which 8% was severe. The appearance of the scar is one of the dissatisfaction of the donor. One year after the donation, over 10 donors, 9 resumed work, 3 not all completely recovered, three still feel physical pain, 4 have not recovered their PCS pre-donation level, and 5 their MCS level. However their status remains better than that of the general population of the same age and sex. Donors are ready to do it again (98.2%) and recommend the donation (96%).

Conclusions: The experience alters neither the initial impetus nor the meaning attributed to the donation. The recommendations are to pursue the development of laparoscopy, to inform about and manage completely pain, to better prepare the donor to the surgical procedure, its risks and aftermath, including professional ones in younger, to perfectly plan the medical follow up with information to referee physicians.

Funding: Government Support - Non-U.S.

SA-PO1030

Discard of Deceased Donor Kidneys in the United States: The Weekend Effect Sumit Mohan,¹ Karl F.W. Foley,¹ Mariana C. Chiles,¹ Geoffrey K. Dube,¹ Russell J. Crew,¹ Stephen O. Pastan,² Rachel E. Patzer,² David J. Cohen.¹ ¹*Dept of Medicine, Columbia Univ College of Physicians & Surgeons, New York, NY;* ²*Dept of Medicine, Emory Univ School of Medicine, Atlanta, GA.*

Background: The discard rate of deceased donor kidneys (DDK) has slowly increased over time. The underlying reasons remain unclear. The impact of low resource availability over the weekends on the acceptance of DDK for transplantation is currently unknown. We attempt to measure the impact of weekends on organ utilization patterns.

Methods: The majority of DDK (80%) are transplanted over the weekend and are procured on either Friday or Saturday (Fri-Sat). Using data from the Scientific Registry of Transplant Recipients (SRTR), we identified and compared all DDK procured on Fri-Sat to those that were procured on other days of the week. Using logistic regression we estimated the adjusted odds of discard for DDK over the weekend.

Results: Among the available kidneys, the Fri-Sat period was associated with lower procurement (89.5 vs 90.2%, $p < 0.001$) and the procured kidneys were older (39.7 ± 17.7 v 39.1 ± 17.6 , $p < 0.001$) and of lower quality (KDRI 1.33 ± 0.49 v 1.31 ± 0.49 , $p < 0.001$). Not only were Fri-Sat DDK were more likely to be discarded (18.6 vs 16.4%, $p < 0.001$), these kidneys were of higher quality than those discarded during the rest of the week (KDRI 1.82 ± 0.57 vs 1.84 ± 0.56 , $p = 0.018$). Fri-Sat DDK were more likely to be shared without payback and be transplanted at a large transplant center. After adjusting for KDRI, Fri-Sat DDK were 20% more likely to be discarded than kidneys procured during other times during the week (OR=1.20, $p < 0.001$).

Conclusions: DDK procured on Fri-Sat are more likely to be discarded than at other times of the week while those that are transplanted are more likely to be shared with large transplant centers. Our results demonstrate the possibility that low resource availability over the weekends adversely impacts organ procurement, acceptance and transplantation.

SA-PO1031

Medication Adherence Barrier Burden Predicts Subsequent Adherence to Dosing Time Schedule in Adolescent Kidney Transplant Recipients in the TAKE-IT Trial Bethany J. Foster,¹ Huaqing Zhao,² Ahna Lh Pai,² Nataliya Zelikovsky,² Crystal D. Holly,² Jodi M. Smith,² Vikas R. Dhamidharka,² Diane Hebert,² Lorraine E. Bell,² Douglas G. Matsell,² Veronique Phan,² Susan L. Furth.² ¹*Pediatrics, McGill Univ;* ²*TAKE-IT Investigators.*

Background: Studies of adherence to timing of medication dosing in high-risk adolescent kidney transplant recipients are lacking.

Methods: We aimed to determine whether the burden of perceived barriers to medication adherence predicted timing adherence (proportion of doses taken ± 1 h. before to ± 2 h. after the prescribed dosing time) during the subsequent 3 mo., as monitored with a multidose electronic pillbox. We evaluated the 126 participants of TAKE-IT who had electronic adherence data available for the 3-mo. run-in period (no intervention). Participants (11-24 y.; ≥ 3 mo. post-transplant) were followed in 8 centers (Canada and USA). Adherence barriers were assessed at baseline using the Adolescent Medication Barriers Scale (AMBS). A higher score indicates greater barrier burden (possible range 17-85). We used linear regression to estimate the association between baseline AMBS scores (total score and ingestion, disease adaptation, and cognitive/organization subscores) and timing adherence. Models also included sex, age, race, and time since transplant.

Results: 60% were male and 67% were white. Median age at baseline was 15.8 (IQR 13.2-17.4) y. Median time since transplant was 3.1 (0.7-7.5) y. Mean \pm SD timing adherence for the interval was 82.6 ± 32.8 . Higher barrier burden (median score 38 (IQR 30-44)) was significantly associated with poorer timing adherence: a 5 unit higher total AMBS score was associated with 2.0% (95% CI 0.4, 3.6) lower timing adherence. A 5 unit higher score was associated with 4.3% (1.2, 7.5) lower timing adherence for the disease adaptation sub-scale, and with 5.9% (0.2, 11.6) lower timing adherence for the cognitive/organization sub-scale. Males had 10% (2.9, 17.6) lower timing adherence than females.

Conclusions: Higher burden of perceived barriers was a significant predictor of poorer timing adherence in this longitudinal study. Future analysis of the TAKE-IT data will determine the impact of an intervention targeting individual barriers on timing adherence.

Funding: NIDDK Support

SA-PO1032

Deceased Donor Procurement in the U.S.: Measurement of Surgical Damage Inflicted Upon the Procured Organ Tim E. Taber,¹ Nikole Neidlinger,² Muhammad Ahmad Mujtaba,³ Elling E. Eido,⁵ Anil S. Paramesh.⁴ ¹*Medicine, Indiana Univ School of Medicine / Indiana Donor Network, Indianapolis, IN;* ²*Surgery, Donor Network West, Berkeley, CA;* ³*Medicine, UTMB Galveston, Galveston, TX;* ⁴*Surgery, Tulane Univ School of Medicine, New Orleans, LA;* ⁵*Association of Organ Procurement Organizations, Vienna, VA.*

Background: Deceased organ donation provides healthy allografts for the majority of organ transplants done in this country. While there are many factors involved in determining suitability of allografts for transplantation, one of the most important is careful procurement of the organ.

Methods: In the winter of 2013, the medical directors of the Association of Organ Procurement Organizations (AOPO) agreed upon a standard for organ damage sustained during procurement. Organ damage was classified into three tiers, from 1 – 3 with the latter rendering the organ non-transplantable. For 12 consecutive months starting in January of 2014, 36 of 58 OPOs prospectively submitted quality data regarding organ damage seen on the procured organ. These 36 OPOs recovered 5,401 of the nation's 8,504 deceased donors for calendar year 2014.

Results: A total of 9501 kidneys were procured from this cohort. Organ damage determined at time of procurement was as follows: 156 class 1 (non-clinically relevant damage); 86 class 2 (damage requiring repair prior to transplantation); 43 class 3 (kidneys that were damaged to the extent that they could not be transplanted).

Conclusions: Damage done to the kidney at the time of procurement rendering the allograft non-transplantable occurred at a rate of approximately 0.45%. Smaller organ procurement organizations (measured by total number of donors) were more likely to have higher rates of damage. Class 1 and 2 damage was more frequent than class 3 but did not result in loss of the allograft for transplantation. While damage done to the kidney at the time of procurement was rare, it did exist. Further evaluation of this issue is warranted to maximize the opportunity for organ transplantation.

SA-PO1033

Short-Term Outcomes After Donor Nephrectomy in Individuals with Persistent Asymptomatic Non-Visible Haematuria Ben Talbot,¹ Simon K. Winn,² Lubna Rashid,² Seema Shrivastava,² Peter A. Andrews,³ Ed Kingdon.¹
¹Sussex Kidney Unit, Royal Sussex County Hospital, Brighton, United Kingdom; ²Renal Unit, St. George's Hospital, London, United Kingdom; ³Renal Unit, St. Helier Hospital, Epsom, United Kingdom.

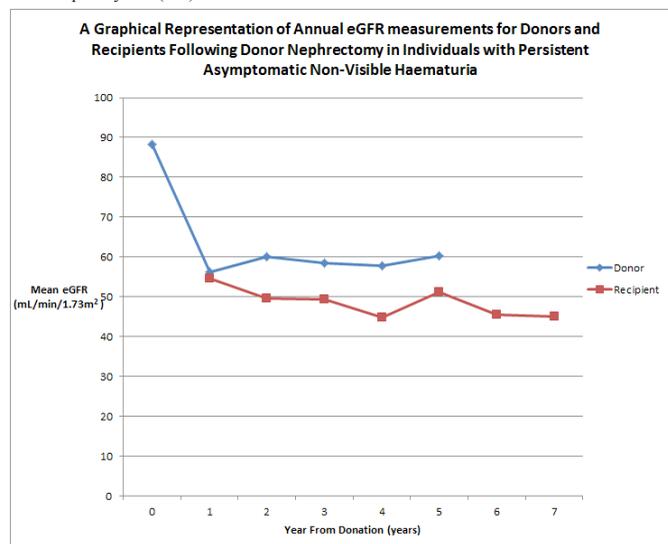
Background: National guidelines in the United Kingdom suggest investigation to exclude urological disease and identify glomerular pathology in potential donors with persistent asymptomatic non-visible haematuria (PANVH). There is currently no guidance on how to proceed where abnormal immunohistochemistry (IHC) is found without proliferative glomerular changes or electron dense deposits (EDD).

Methods: Demographic characteristics, renal function and biopsy details were obtained by retrospective case note review of kidney donors in the South West Thames transplant network who had undergone renal biopsy for PANVH between 2008-13. Light microscopy, IHC and electron microscopy (EM) findings were collected and clinical outcomes analysed for donors and recipients.

Results: Twenty four donors with PANVH proceeded to donation.

Biopsy findings in subjects proceeding to donor nephrectomy (n=24)		
Normal Mesangial Cellularity	24/24	
Focal interstitial fibrosis or tubular atrophy <10%	6/24	
Abnormal glomerular IHC:	15/24	Location:
IgM and C1q	11/24	Mesangial
Isolated IgM	3/24	Mesangial
Isolated C1q	1/24	Mesangial
Thin basement membrane (<250 nm)	7/21	(EM not available in 3 patients)

Mean eGFR before donation 88.2 mL/min/1.73m² (69-117) and one year after donation 56.2 mL/min/1.73m² (41-77). Five recipients are not followed up locally. The remaining recipients (n=19) had mean eGFR beyond one year 49.9 mL/min/1.73m² (24-82), mean follow up 2.9 years (1-7).



Conclusions: Renal biopsy in potential donors with PANVH will identify mesangial proliferation or EDD in a minority of cases. Early outcomes in our small cohort of PANVH donors are favourable. Longer term follow-up of PANVH donors and recipients is being undertaken.

SA-PO1034

Jeevandan: Deceased Donor Transplantation Programme from a Developing Country Swarnalatha Guditi. *Nephrology, NIMS, Hyderabad, Telangana, India.*

Background: In developing country like India the prevalence of end stage organ disease is increasing. Though transplantation has been in practice in India, its been grossly inadequate in terms of actual numbers, due to a shortage of resources and organs. The only solution for the shortage of organs is deceased donor transplantation.

Methods: In India the Human Organs Transplantation Act, was enacted in 1994 with the objective of promoting and regulating the transplantation of human organs like kidney, liver and heart - both live as well as cadaver there was no significant increase in cadaver transplantation over the past two decades for various reasons. India follows "opt in"

system and brain death declaration is not mandatory. Andhra Pradesh and Telangana are the two important states in India, situated on the country's southeastern coast. It is India's fourth largest state by area and fifth largest by population. Government of Andhra Pradesh, considering the shortage of organs and burden of end stage organ failure in the state, has come up with a Government Order⁶ called "Jeevandan" to streamline the procedure for facilitating and regulating the cadaver transplantations on an end-to-end basis.

Results: There were 129 deceased donations in 2 years. Male were 93 and female 36: female to male ratio being 1: 2.58 The mean age was 41 years (range 8 to 79). Most common Blood group was O in 51 (39.5%) donors followed by B in 39 (30.23%), A positive in 29 (22.48%) donors, and AB in 10 (07.75%) donors. Total 593 organs including minor organs were retrieved from 129 deceased donors; 233 kidneys, 126 livers, 7 hearts, 118 heart valves, 103 corneas, 5 lungs and 1 Pancreas. Total deceased donor renal transplantations done during this period were 24.67% . Out of 129 donors, 6.8 % kidneys and 3% livers were not utilized. Mean age of renal recipients was 44.07 years (range 13 to 72). There were 26.8% females and 73.2% males, female to male ratio being 1:2.73. Among deceased donor renal transplant recipients, O blood group was most common, seen in 36.79% followed by B in 32.38%, A in 22.64% and AB in 8.17% patients.

Conclusions: Deceased donor transplantation is the solution for organ shortage and increasing demand of organ requirement.

SA-PO1035

Deceased Directed Kidney Donations: A Three-Year Experience at a Single OPO Rebecca Hurst,¹ Michael D. Salvatore,¹ Nikole Neidlinger.^{1,2}
¹Donor Network West, San Ramon, CA; ²California Pacific Medical Center, San Francisco, CA.

Background: The UAGA allows for deceased directed organ donations. Our OPO has incorporated the practice of offering the option of directed donations during every donation discussion in response to routine donor family requests. However, facilitating directed donations for donor families remains a controversial topic. Opponents suggest that directing gifts is not only inequitable, but that it may encourage malfeasance in the form of organ solicitation via media or social networking campaigns or by groups who promote discrimination. The purpose of this research effort was to identify how many directed kidney requests were received and honored during a three-year period in order to assess the impact on our allocation scheme.

Methods: We analyzed retrospective data from our OPO for three years from 2012-2014. We evaluated the number of directed kidney donation requests in relation to the overall number of donors, as well as the transplant outcomes or reasons for decline when the request was not honored. Relationship of donors to potential recipients was also assessed.

Results: Over the three year period, 176 of our 1,056 authorized donors had a potential directed donation. Of these, 80% were directed to patients on the kidney waiting list. However, only 16% of the attempted directed kidney donations resulted in a transplant. The data illuminate that incompatibility/mismatch of potential directed kidney recipients is the most common reason that directed kidneys are not transplanted, despite the fact that directed donations are allocated ahead of highly sensitized patients, mandatory shares, multivisceral combinations, and the like.

Conclusions: Facilitating directed donations will continue as part of our routine practice. Each year approximately one in six of our donor families identified potential recipients, but transplants from these requests remained consistently less than 2% of our annual total. Future studies are planned to evaluate recipient outcomes, assess donor family satisfaction with a recipient known to them, as well as to examine our practice in detail in an effort to standardize the language and timing of the directed donation discussions.

SA-PO1036

Optimal Outcomes in Pediatric Renal Transplant Recipients Veronica A. Taylor,¹ Cassie L. Kirby,¹ Jens W. Goebel,^{1,2} David K. Hooper.^{1,2}
¹Cincinnati Children's Hospital Medical Center; ²Dept of Pediatrics, Univ of Cincinnati College of Medicine.

Background: Pediatric kidney transplant recipients (pKTRs) experience multiple sequelae of their condition, yet comprehensive assessment of these is lacking in the literature. Our objective was to develop a composite outcome measure for pKTRs that considers the most common comorbidities, and to evaluate a population of pKTRs at specific intervals post-transplant.

Methods: We retrospectively reviewed all KTRs at our center from 10/2008 through 2/2015. An optimal outcome composite measure was created consisting of 14 criteria in four domains: allograft function (CKD stage <3, urine protein/creatinine ratio < 0.5, absence of DSAs), histology (no or mild interstitial fibrosis and tubular atrophy, no transplant glomerulopathy, and no history of AMR or ACR), infection (BKV PCR <10,000, CMV PCR<E0, no history of PTLD or symptomatic EBV) and cardiovascular (CV) health (triglycerides<500, LDL <130, BP <90th %ile, fasting glucose < 126, and BMI < 85th %ile). Patients were evaluated on these pass/fail criteria at post-transplant yrs 1, 3, 5, and 10. Optimal outcome was defined as passing 3/13/14 criteria.

Results: A total of 177 patients and their 282 clinic visits were analyzed. Of 94 patients who completed their 1st year, only 32 patients (34%) achieved an optimal outcome. This was significantly higher than at yrs 3 (8/74, 11%), 5 (13/62, 21%), and 10 (9/52, 17%) (p < 0.01). The top two categories in which patients failed at 1 yr were cardiovascular health (which remained relatively stable: ~30% at each time point) and allograft function which decreased from 57/93 (61%) at yr 1 to 24/62 (39%) at yr 3 (p<0.01).

Conclusions: Only 1/3 of pKTRs achieved an optimal outcome at 1 year post-transplant, and this fell to 1/6 of patients by 10 years. Cardiovascular health and graft function were the

primary failure modes. Evaluation of all transplant-related outcomes at specific follow-up intervals will allow practitioners to assess the success of kidney transplantation and overall recipient health and focus clinical outcome improvement efforts.

SA-PO1037

Clinical Outcome of Elderly Living Kidney Donors: A Single-Center Study in Japan Jumpei Hasegawa, Kohei Unagami, Masayoshi Okumi, Kazuya Omoto, Hideki Ishida, Kazunari Tanabe. *Urology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Previous studies and current guidelines have suggested that elderly persons can be living kidney donors; however, reports on elderly donors >70 years old are limited. In order to clarify the donor safety and feasibility, we investigate the clinical outcomes of living kidney donors > 70 years old after nephrectomy.

Methods: We conducted a case-series study of living kidney donations involving 48 donors aged >70 years at the time of transplantation. The kidney donations occurred between 2001 and 2014 at Tokyo Women's Medical University in Tokyo, Japan. The primary outcomes were survival or end-stage renal disease (ESRD)-free rate and all crude event-free rates, including cardiovascular-, infection-, ESRD-, or death-free rate. The secondary outcome was serum creatinine level at the end of the follow-up period.

Results: The 48 cases were followed up for a median of 4 years. The survival rate among the donors was 100% until the fifth year, and only two donors died during follow-up. The ESRD-free rate was 100% during the follow-up period. The overall event-free rate was 100% at 1 year, 85.7% at 3 years, and 75.0% at 5 years. The mean serum creatinine level was 1.18 ± 0.24 mg/dL at the time of hospital discharge and did not increase (1.18 mg/dL) at the end of follow-up.

Conclusions: Living kidney donation from elderly donors >70 years old appears to be a safe and acceptable option for patients requiring renal-replacement therapy.

SA-PO1038

Immunosuppressive Medication Adherence following Kidney Transplantation in the Military Healthcare System Dustin J. Little,¹ Matthew Ward,² Robert Nee,¹ Christina M. Yuan,¹ Rahul M. Jindal.² ¹Walter Reed National Military Medical Center, Bethesda, MD; ²Uniformed Services Univ of the Health Sciences, Bethesda, MD.

Background: Limitations on the amount and duration of Medicare coverage of immunosuppressive medications (ISM) may contribute to ISM non-adherence and allograft failure. ISM adherence has not been reported in US patients who receive these medications at no cost. We therefore designed a prospective cohort to investigate the incidence of ISM non-adherence in Military Healthcare System (MHS) beneficiaries, who receive lifelong post-transplant ISM at no out-of-pocket cost.

Methods: Adult MHS kidney transplant recipients who provided informed consent completed the Immunosuppressive Therapy Adherence Scale (ITAS) and Beck Depression Inventory-II (BDI-II). Chart reviews were performed to obtain demographic and clinical data. Perfectly adherent subjects (P) (ITAS score of 12/12), were compared to not perfectly adherent subjects (NP; ITAS score ≤11/12) using Student's t-test and Fisher's exact test where appropriate. Exact logistic regression was performed to evaluate for factors associated with P versus NP adherence.

Results: Forty subjects completed survey instruments. 57.5% of subjects were male, 40% were black, 22.5% were aged <65 years, and 45% were >3 years from transplantation. One subject did not complete the ITAS. Mean overall ITAS score was 11.5±0.9, and 69% (27/39) of subjects reported P adherence. BDI-II scores were significantly lower in P vs. NP subjects (6.7±7.2 vs. 13.6±8.8; p=0.014). Exact LR adjusted for race, timing of transplant, sex, and age revealed an OR of 0.61 (0.32-0.98) for P adherence for every 5 point increase in BDI-II score. NP subjects were significantly more likely to have donor specific antibodies (DSA; 6 of 11 vs. 3 of 24; p=0.015).

Conclusions: MHS beneficiaries reported high levels of ISM adherence. Modest increases in BDI score associated with marked reduction in adherence, and subjects with NP adherence were significantly more likely to have DSA. Our results suggest that enhanced ISM coverage as well as prevention, identification, and treatment of depression should be prioritized for future study in order to improve outcomes following renal transplantation.

Funding: Other U.S. Government Support

SA-PO1039

Clinical Impact of Kidney Donor Follow-Up by Nephrologists Hee Jin Kwon, Jin Hae Kim, Jee Eun Park, Subin Hwang, Jung Eun Lee, Woosong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh, Hye Ryoung Jang. *Nephrology Div, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea.*

Background: Compensatory and adaptive mechanisms in the remnant kidney occur immediately after nephrectomy. The adaptability in early postoperative period may affect the renal function of the remaining kidney. Since the introduction of extended criteria living donor system, the numbers of marginal donors with risk of new morbidities are increasing. The aim of this study was to evaluate the clinical impact of kidney donor follow-up by nephrologists at a donor clinic (DC).

Methods: Our study included 427 living kidney donors from January 2010 to December 2014 in Samsung medical center. Nephrologist-run donor clinic was established in January 2013. The study period was divided into pre-DC and post-DC. Primary outcomes were

incidence of CKD and renal functional adaptability (%MDRD = post/pre eGFR X100) at 6 months after donation. Secondary outcomes were changes in compliance and incidence of co-morbidities; hyperuricemia and microalbuminuria.

Results: A total of 215 and 172 donors were included in pre-DC and post-DC, respectively. Before donation, age, sex, proportion of hyperuricemia and microalbuminuria were similar. Preoperative eGFR in pre-DC was significantly higher than post-DC (p<.001). After donation, poor renal adaptation (post-donation eGFR at 6 months < 60% of preoperative eGFR) was less frequent in the post-DC period compared to the pre-DC period (p=.026). CKD development tended to be higher in pre-DC period. Donors in the post-DC period had shorter mean outpatient clinic visit intervals (p<.001), more visits within 6 months after donation (p=.001), earlier detection of de-novo hyperuricemia (p<.001). The incidence and detection time of microalbuminuria were similar.

Conclusions: After establishment of kidney donor clinic operated by nephrologists, donors tended to show better renal adaptability and earlier diagnosis and treatment of hyperuricemia. In conclusion, donor clinic may be a good strategy for improving renal outcome and detecting potential risk factors of CKD in donors.

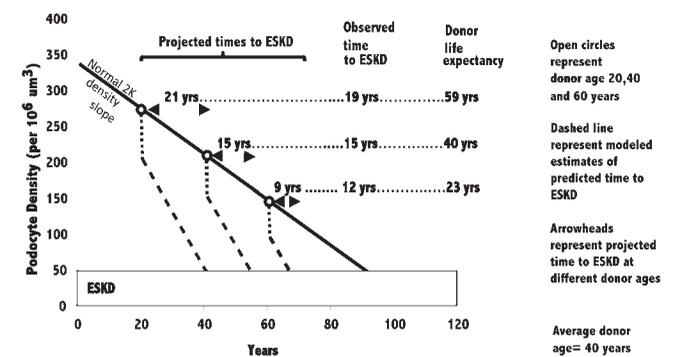
SA-PO1040

Predicting Kidney Allograft Half-Life Using a Podometric Approach Roger C. Wiggins, Abhijit S. Naik, Diane M. Cibrik, Jeffrey B. Hodgin, Farsad Afshinnia, Larysa T. Wickman, Milagros D. Samaniego-Picota. *Univ of Michigan.*

Background: Increasing donor age is a powerful predictor of worse renal allograft outcome. Podocyte depletion is part of the normal aging process (Hodgin, JASN, 2015). Recently we showed that kidney hypertrophy that occurs at time of transition from a 2 kidney to 1 kidney state (transplantation), leads to a 20% reduction in podocyte density and a 6-fold increased rate of podocyte detachment associated with transplant glomerulopathy and allograft failure (Yang, JASN, 2014). To test the hypothesis that podocyte depletion could impact allograft half-life we used a model combining age specific podocyte nuclear density decrease and rate of podocyte attrition after transplantation for comparison with actual allograft outcome data.

Methods: Podocyte density was estimated from immediate post perfusion biopsies from living and deceased donors or from non-diseased nephrectomy specimens. Projected allograft life was predicted based on modeling age-specific podocyte density and the observed attrition of podocytes. Observed data were drawn from the OPTN/UNOS STAR files as of Sept 2014, using all transplants performed between Oct 1987-June 2013. A "conditional" Kaplan Meier analysis using the "period" method was used to calculate observed half-lives at different donor ages.

Results: The podometric projected average half-life for a 40 year old donor is 15.1 years, similar to the observed average allograft half-life (15.1 years). The projected effect of increasing donor age on allograft half-life from podometric measurements is similar to the observed effect of donor age on allograft half-life at all calculated donor ages (p=NS).



Conclusions: Quantitative podometric modeling predicts both shorter-than-expected average renal allograft survival and the donor age effect, compatible with the concept that hypertrophic processes at transplantation significantly impact half-life.

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SA-PO1041

Abstract Withdrawn

SA-PO1042

Prediction of Patient Survival After Kidney Transplantation (Tx): Construction, Validation and Evaluation of Decision Models Using Data Mining Approaches Irina Scheffner,¹ Kaixun Hua,² Dan Simovici,² Tanja Abeling,¹ Hermann G. Haller,¹ Wilfried Gwinner.¹ ¹Hannover Medical School, Germany; ²Univ of Massachusetts.

Background: Understanding the risk factors that predispose to death is important to deliver the most appropriate therapy to Tx patients (pts). Aim of this study is to build reliable decision models and to identify the relevant risk factors for death using different data mining approaches.

Methods: We analyzed 761 pts transplanted between 2000 and 2007 (follow-up of up to 10 years). Data included biopsy results, clinical & laboratory factors. After conventional statistical feature selection of 28 variables we build Naïve Bayesian (NB), C5.0, RPART and Random Forest (RF) models.

Results: Compared to C5.0 and RPART, NB and RF resulted in models with a higher sensitivity to predict death and a high specificity. Using different partitions for training and test set, NB models had a sensitivity of 62-65% and a specificity of 89-91% to predict death. With RF, sensitivity was 64% and specificity 96%. Because of the imbalance of the outcome groups (13% deceased pts) modeling was repeated with balanced datasets obtained by oversampling. With the balanced data, sensitivity was 82% and specificity 79% with NB. With RF, sensitivity was 83% and specificity of 68%. These models were externally validated with two separate datasets showing sensitivities of 64 and 59% and specificities of 86% and 78% for the NB models and sensitivities of 84 and 61% and specificities of 60 and 65% for the RF models. Highly important variables were recipient age, pre-Tx diabetes mellitus, peripheral arterial and coronary heart disease, cold ischemia time, graft function within the first 6 weeks and annual GFR loss, and post-Tx systolic and diastolic blood pressure, urinary tract infections, and hyperparathyroidism. Modestly important variables included donor age, time on dialysis, HLA DR mismatches, delayed graft function.

Conclusions: The established models permit reliable prediction of death and survival and can be used to identify pts on risk. Moreover, with the identified (modifiable) risk factors pts can be assigned to different treatment strata to offer each patient the optimal therapy.

Funding: Government Support - Non-US.

SA-PO1043

The Decline of Dialysis in Northern Ireland Kathryn E. Larmour, Regoinal Nephrology Unit, Belfast City Hospital.

Background: The first session of haemodialysis in Northern Ireland (NI) was in 1959 for acute kidney injury. There has been an inexorably rise in the prevalent dialysis population in the province since then, with expansion of dialysis facilities to accommodate ever increasing numbers. However, in addition to inferior outcomes compared to transplantation, there are considerable capital and recurrent costs associated with chronic haemodialysis provision. This study considered the impact of an expansion in the living donor (LD) transplant programme on dialysis in NI and the financial implications.

Methods: The prevalence dialysis population from 1999-2014 (inclusive) data were retrieved retrospectively from collected data. The number of LD transplants in NI patients is prospectively recorded. The economic impact of the changes evident in our centre were then evaluated.

Results: In 1999 there were 479 patients in NI receiving maintenance dialysis treatment. This number increased annually until a zenith of 836 in 2009. There were no living donor transplant procedures in 1999, from 2000-2008 there were between 4 and 9 performed annually. There was an expansion of the LD programme thereafter, and for the past four years there have been between 53-60 LD transplants each year (>30 donor pmp). This increase has coincided in an initial plateau and then a decline in the prevalent dialysis population [figure 1]. The cost of maintaining a patient with end-stage renal failure on dialysis is £17,500 (\$27,000) per patient per year for a patient on peritoneal dialysis and £35,000 (\$54,000) per patient per year for a patient on hospital haemodialysis. The first year of care after a kidney transplant costs around £17,000 (\$26,000) and £5,000 (\$7,500) for every subsequent year. Live donor costs are approximately £9,000 (\$14,000). Transplantation results in a cost benefit in the second and subsequent years of £25,800 (\$39,500) per annum. The cost benefit of transplantation compared to dialysis over a period of ten years is £241,000 (\$370,000).

Conclusions: A proactive approach to living donor transplantation has benefits not only for individual patients but in reducing the prevalent dialysis population and the healthcare costs associated with renal replacement therapy.

SA-PO1044

Pre-Existing Donor-Related Diabetic Nephropathy Predicts Poor Allograft Survival Steven Salvatore,¹ Mohamad M. Alkadi,² Thangamani Muthukumar,² Surya V. Seshan.¹ ¹Pathology, Weill Cornell Med College; ²Nephrology, Weill Cornell Med College.

Background: Diabetic nephropathy (DN) is the most common cause of end stage renal disease in the US, and in the transplant setting may play a role in long-term graft dysfunction. In patients without diabetes, finding features of DN in the immediate pre-cause post-transplant biopsy may confer increase risk of allograft dysfunction.

Methods: From 2005-2014, 141 biopsies from 120 transplant patients with DN were studied. DN was classified as 1) donor related if present on biopsy <2 yrs from transplant or no diabetes in recipient, 2) recurrent if >2 yrs with history of pre-transplant DN, or 3) de novo in post-transplant diabetes (all >3 yrs). Clinicopathologic parameters were analyzed in 95 patients with adequate clinical history (25 excluded).

Results: Of 95 biopsies with features of DN, 43 were characterized as recurrent, 17 de novo, and 35 donor-related. Biopsies with donor-related DN were done 0.5 yrs (0 days-3.6 yrs) post-transplant and 6 had delayed graft function. Other non-DN related disease was seen, likely prompting biopsy: acute tubular injury (10/35), antibody mediated rejection (4), acute cellular rejection (1), CNI toxicity (3), AIN (4), TMA (1) and BKV (1). Pathologic class of DN were: Class 1-3, Class 2a-21, Class 2b-1, Class 3-10. Class 3 DN lesions are associated with higher proteinuria, Cr, and increased vascular sclerosis. 13/35 donors had known diabetes with mean hemoglobin A1c of 8.5% (range 4.7-14.6%). DN was not listed on any pre-implantation biopsy reports. Mean follow-up times were 3.8 yrs for donor-related, 7.8 for recurrent, and 10.3 for de novo. Despite shorter follow-up, transplants with donor-derived DN had significantly more failure than recurrent DN (49 v 14%, P=.0008) or de novo DN (49 v 18%, P=.024). Recurrent and de novo DN had similar rates of graft loss (P=.64).

Conclusions: Despite careful screening of transplant kidney donors, donor related DN may be missed on pre-surgical biopsy or not effectively reported and leads to renal dysfunction in the early post-transplant period. Donor related DN is a significant contributor to early allograft loss compared to recurrent or de novo DN and predicts poor long term graft survival.

SA-PO1045

Maternal and Fetal Outcomes in Living Kidney Donors in Korea Kyung Don Yoo, Hajeong Lee, Jae Yoon Park, Eunjin Bae, Jung Pyo Lee, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim. Seoul National Univ College of Medicine.

Background: Mild elevation of blood pressure was detected after unilateral nephrectomy in kidney donors. Consequently, female kidney donors at risk for complications such as gestational hypertension caused concern. However, the impact of kidney donation on maternal and fetal outcomes had not been well established in Asian kidney donors.

Methods: This study included young female kidney donors under 45years old (YO) at the time of kidney donation in Seoul National University Hospital between 1972 and 2014. In all, 417 female donor participants (≤45YO) were enrolled. A survey of pregnancy experiences was performed by medical chart abstraction and telephone poll. We additionally enrolled 3,608 pregnancies were enrolled as non-donor control. The questionnaires were approved by institutional review board in our institute.

Results: We tried to contact all of 417 female kidney donors. The thirty five donors had no experience of pregnancy, and finally we could have got 253 questionnaires of kidney donors. Donors were compared in the three groups according to pregnancy pre-, post- kidney donation group and non-donor control group. The proportion of pre-donation pregnancies were 82% (370cases, Mean age 38.8 years), and post-donation pregnancies were 14.0% (56cases, Mean age 27.2 years). In the majority of post-donation pregnancy cases were detected in recent years from 2007 to 2014 (72.3%). There were no differences of fetal outcomes such as incidence of prematurity, low-birth weight and fetal death between the groups. Gestational hypertension were no differences between the post-donation group and non-donor control group (5.4% vs. 5.8%). Donors with pregnancy after donation were more likely to have undergone Cesarean section (40.4%) than those with pregnancy before donation (21.9%).

Conclusions: This study revealed that maternal and fetal outcomes had little difference between the kidney donors and normal control. Further research using matched controls should be warranted.

SA-PO1046

Self-Monitoring Renal Function After Transplantation: A Clinical Trial on Safety and Usability Céline Lianne Van lint,¹ Sandra Van dijk,¹ Wenxin Wang,² Mark Neerinx,² Ton Rovekamp,³ Ton J. Rabelink,¹ Paul J. Van der boog,¹ Willem-Paul Brinkman.² ¹Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; ²Faculty of Computer Science, Delft Technical Univ, Delft, Netherlands; ³Dept of Technology in Healthcare, Prevention and Health, TNO, Leiden, Netherlands.

Background: Kidney transplantation requires intensive monitoring which is burdensome for both patient and healthcare. With the availability of an innovative creatinine device, patients are enabled to monitor renal function at home. To investigate safety and usability of self-monitoring during the first year after transplantation an RCT was conducted.

Methods: The intervention group used a Statsensor® Xpress™ to measure creatinine at home during the first year post-transplantation. Measurements were registered in a web-based system using a traffic light analogy to support interpretation of creatinine trends. Differences between groups regarding GFR were assessed at baseline (discharge) and at 1 year. Creatinine trends measured at home were compared to clinically relevant increases (>10%) measured in the hospital laboratory. A subsample of intervention patients was interviewed on self-monitoring experiences.

Results: In total 119 patients were included (intervention n=64; control n=55). GFR did not differ between groups at baseline, nor at 1 year (72.8 and 71.1 ml/min at 1 year for intervention and control group, respectively). For 34 out of 63 laboratory-based creatinine increases, sufficient home-based creatinine measurements were available for trend comparison. In 76% a similar trend was observed. Self-monitoring enhanced early detection of rejection in 3 out of 5 cases, none were missed. Satisfaction was high: 71% of the interviewed patients (n=26) would have liked to extend self-monitoring creatinine beyond 1 year.

Conclusions: Findings suggest that self-monitoring creatinine at home can be used for transplant follow up. With improvement of the detection rate of relevant creatinine increases (e.g. by increasing measurement frequency), self-monitoring creatinine allows number of outpatient visits to be reduced.

Funding: Clinical Revenue Support

SA-PO1047

Comparison of Heart Rate Variability in Kidney Transplantation and End-Stage Renal Disease Patients on Dialysis Lee Heeryong, *Internal Medicine, Bong Seng Memorial Hospital, Busan, Korea; Internal Medicine, Pusan National Univ Hospital, Busan, Korea.*

Background: Heart rate variability (HRV) is a method for evaluation of autonomic nervous system activity by expressing the balance of sympathetic and parasympathetic tones. Some studies of HRV in patients with end-stage renal disease (ESRD) have been performed. However, few have examined kidney transplantation (KT) patients. Therefore, we investigated autonomic nervous system activity by means of HRV in patients with KT due to ESRD.

Methods: We compared the pattern of cardiac sympathetic and parasympathetic activity by time- and frequency-domain analysis of HRV with 24-h Holter monitoring of 23 KT and 56 dialysis patients. Patients underwent KT between January, 2008 and June, 2011.

Results: The mean ages of KT and dialysis patients were 54.2 ± 12.3 and 53.7 ± 12.6 years, respectively. The KT group showed increased time- and frequency-domain HRV (including HRV index), very low frequency (VLF), means and standard deviations of all normal R-R intervals for all 5-min segments of the entire recording (SDNNi), low frequency (LF), LF in normalized units (LFnorm), and LF to high-frequency power ratio, compared with the dialysis group.

	HD/CAPD	KTP	p value
SDNN(msec)	173.8±700.0	98.0±31.8	0.017
rMSSD(msec)	447.2±54/5	35.7±53.9	0.424
SDNNi(msec)	34.5±34.1	35.3±35.7	0.048
pNN50(%)	10.4±20.1	7.1±17.6	0.589
HRV index	10.2±5.2	14.0±4.0	0.001

HRV index, integral of the density distribution divided by the maximum of the density distribution; pNN50, the percentage of adjacent R-R intervals that varied by more than 50 msec; rMSSD, root mean square of the difference between the coupling intervals of adjacent R-R intervals; SDNN, standard deviation of all normal sinus R-R intervals over 24h; SDNNi, means and standard deviation of all normal R-R intervals for all 5-min segments of the entire recording.

Conclusions: Autonomic tone in patients with KT is higher than that in patients with ESRD on dialysis.

Funding: Private Foundation Support

SA-PO1048

Physical Capacity and Function Are Associated with Body Composition, Cardiovascular Health and Quality of Life in Renal Transplant Recipients Danielle Richler-Potts, Jill Neale, Maurice Dungey, Patrick Highton, Emma L. Watson, Alice C. Smith. *Leicester Kidney Exercise Team, Dept of Infection, Immunity and Inflammation, Univ of Leicester, Leicester, United Kingdom.*

Background: A renal transplant can transform the life of patients with end stage renal failure but cardiovascular disease remains a major cause of morbidity and mortality. Post-transplant weight gain is common, and physical functioning often fails to improve in line with increased renal function. This study explored associations of physical function and capacity with body composition, cardiovascular status and quality of life (QoL) in renal transplant recipients (RTRs).

Methods: 35 stable RTRs participated (mean age 52 years (range 29-70), 66% male). Self-reported QoL and physical function were measured by EQ5D and Duke Activity Status Index (DASI) questionnaires. Physical capacity was measured by shuttle walk test (SWT), body composition by DXA, cardiac haemodynamic function by bioreactance (NICOM), and systemic inflammation by plasma IL-6 ELISA.

Results: SWT, DASI and EQ5D all showed significant correlations with percentage body fat (SWT: $r = -0.63$ $p < 0.001$; DASI: $r = -0.41$ $p = 0.02$, EQ5D $r = -0.47$, $p = 0.005$) and with IL-6 ($r = 0.34$ $p = 0.05$). On the other hand, fat-free mass showed positive correlation with cardiac output ($r = 0.79$) and stroke volume ($r = 0.81$, both $p < 0.001$), and inverse correlation with total peripheral resistance ($r = -0.67$ $p < 0.001$).

Conclusions: This study shows that in RTRs, poor physical function and capacity is significantly associated with lower QoL and also with higher percentage body fat and systemic inflammation, both of which are important cardiovascular risk factors. An increase in fat-free mass was significantly associated with superior cardiac function. Taken together, these results suggest that weight loss is desirable for those with excess body fat, and that gaining muscle mass is also important. Optimising body composition through appropriate exercise and nutrition may therefore improve physical function and capacity and enhance quality of life, and also reduce the risk of cardiac-related morbidity and mortality in this vulnerable population.

Funding: Private Foundation Support

SA-PO1049

Pregnancy in the Renal Transplant Recipient: Pregnancy Viability and Effects on Graft Function Andre Caires Alvino Lima, Cinthia Montenegro Teixeira, Igor Gouveia Pietrobom, Mayara Ivani de Paula, Geovana Basso, Laila Almeida Viana, Helio Tedesco Silva, J. Medina-Pestana. *Dept of Nephrology, Hospital do Rim - UNIFESP, Sao Paulo, Brazil.*

Background: Fertility in women is recovered few months after kidney transplantation. However, pregnancy viability and maternal complications remain unclear.

Methods: We studied data from patients from a kidney transplant center in Brazil from 2001 to 2012. In this retrospective study, we identified all pregnant kidney transplant recipient and collected clinical and laboratory data before pregnancy, every quarter and 12 months after delivery. Each pregnancy was considered a single event.

Results: We included 36 subjects and 53 events were found. The average age was 28 ± 5 years. Pregnancy occurred 4.4 ± 3 years after transplantation. Maintenance immunosuppression before pregnancy was prednisone, tacrolimus and azathioprine in 74% of the cases. The frequency of chronic hypertension was 38%, and 8% had preexisting proteinuria greater than 0.5g. 8 (15%) unintended termination of pregnancy (UTP) were observed in the first quarter and 4 (8%) occurred in the second quarter. Delivery was induced by medical conditions in 41% of cases. 9 (22%) premature births and 7 (17%) very premature births were observed. Two (5%) stillbirths and two (5%) neonatal deaths occurred. Maternal complications were proteinuria de novo (60%), urinary tract infection (23%), preeclampsia (9%) and high blood pressure (9%). During the follow-up period, two (6%) acute rejection and one (2%) graft loss occurred. Average baseline creatinine was compared with third quarter and 12 months follow-up creatinine and significant increase (1.17 vs. 1.46 vs. 1.59 mg/dL, $p < 0.001$) was found.

Conclusions: Although the sample is limited, the number of UTP was higher than the general population, with high rates of maternal complications. Besides, diagnosis of preeclampsia may be challenging because of the high frequency of hypertension and preexisting proteinuria. The sustained increase in creatinine suggests higher risk of long-term graft loss. Further research regarding the issue of pregnancy and kidney transplantation is required, in order to improve maternal safety and preserve graft function.

Funding: Private Foundation Support, Government Support - Non-USA.

SA-PO1050

Outcomes of Twin, Triplet and Quadruplet Pregnancies in Kidney Transplant Recipients Serban Constantinescu,^{1,2} Lisa Coscia,² Dawn Armenti,² Michael J. Moritz.^{2,3} *¹Medicine, Temple Univ School of Medicine, Philadelphia, PA; ²National Transplantation Pregnancy Registry (NTPR), Gift of Life Inst, Philadelphia, PA; ³Transplantation, Lehigh Valley Health Network, Allentown, PA.*

Background: The purpose of this study is to analyze multiple gestation pregnancy outcomes reported to the National Transplantation Pregnancy Registry (NTPR) in 50 kidney transplant recipients.

Methods: Data were collected via questionnaires, telephone interviews, and hospital records.

Results: Of 986 kidney recipients (1802 pregnancy outcomes) participating in the NTPR, there were 50 who reported 52 multiple gestations with 112 pregnancy outcomes (45 sets of twins, 6 sets of triplets, and 1 set of quadruplets). There were 94 live births, 11 miscarriages, 6 stillbirths, and 1 reduction (triplet to twin pregnancy). Pregnancy occurred after 1st kidney transplant in 47, after a 2nd in 4, and after 3rd in 1 recipient; 14 recipients had a prior post-transplant live birth and 2 recipients had 2 multiple birth pregnancies. Use of reproductive assistance was reported for 16 conceptions (medication 5, intrauterine insemination 5, *in vitro* fertilization 4, and unspecified 2). There were no reports of rejection during pregnancy or postpartum (PP). Mean serum creatinine (mg/dL) was pre-pregnancy 1.4 ± 0.6 , during pregnancy 1.4 ± 0.5 , and PP 1.4 ± 0.5 . There were 4 graft losses within 2 yrs PP. Mean gestational age was 32.1 ± 4.1 wks (range 23-37.4 wks) and mean birthweight was 1680 ± 652 g (range 454-3551 g). There were 11 neonatal deaths including all of the infants in the quadruplet pregnancy. There were 5 birth defects reported: soft cleft palate, hypospadias, unilateral kidney, undescended testicle, and Tetralogy of Fallot. Overall, the majority of the children were reported healthy and developing well at last follow-up.

Conclusions: Female kidney transplant recipients can successfully maintain a pregnancy with multiple gestations. Given the increase in multiple gestations with the use of assisted reproductive techniques and the greater risks to the resulting fetuses, heightened surveillance in the transplant recipient population is warranted.

Funding: Pharmaceutical Company Support - Astellas Pharma, US, Inc., Pfizer, Inc., and Bristol-Myers Squibb Co.

SA-PO1051

Kidney Transplantation for End-Stage Kidney Disease After Hematopoietic Stem Cell Transplantation Akihiro Tsuchimoto,¹ Kosuke Masutani,¹ Kei Kurihara,² Hidehisa Kitada,² Takehiro Nishiki,³ Morihito Ota,³ Masayoshi Okumi,⁴ Tomokazu Shimizu,⁴ Hideki Ishida,⁴ Kazunari Tanabe,⁴ Kazuhiko Tsuruya,¹ Takanari Kitazono.¹ ¹Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; ²Surgery and Oncology, Kyushu Univ, Fukuoka, Japan; ³Surgery, Tomishiro Central Hospital, Okinawa, Japan; ⁴Urology, Tokyo Women's Medical Univ, Tokyo, Japan.

Background: Hematopoietic stem cell transplantation (HSCT) is associated with various kidney diseases. The safety of kidney transplantation (KT) for end-stage kidney disease (ESKD) after HSCT has not been established. In this retrospective multicenter study, we investigated the immunological background, immunosuppressive regimens, and outcome in the KT patients after HSCT.

Methods: We report our experience with 5 KT patients following HSCT: 4 patients received bone marrow transplantation and 1 received umbilical cord blood transplantation. Median age at the time of HSCT was 29 years old (ranged 13-54 years old), and ESKD developed after 119 months (67-307 months). The median duration of pre-transplant dialysis therapy was 18 months (7-69 months). In one patient, bone marrow and kidney were from the same donor.

Results: Median observational period was 18 (5-60) months. All patients were treated antibody-induction with basiliximab followed by triple immunosuppression consists of tacrolimus, mycophenolate mofetil and methylprednisolone. In one patient with positive complement dependent cytotoxicity cross match, we added rituximab, splenectomy and plasmapheresis. In another one patient who received KT and BMT from the same donor, we temporary gave immunosuppressive drugs. After KT, only one patient experienced subclinical acute T-cell mediated rejection and bacterial pneumonia, and the other 4 patients had not experienced acute rejection or severe infectious complications.

Conclusions: Previous studies of KT patients after HSCT suggested low incidence of rejection and stable graft function, but high mortality caused by infections, whereas the patients in our file revealed rare infectious complications as well as mild allograft rejection. Current pre- and post-transplant management contributes favorable outcome of KT patients after HSCT.

SA-PO1052

The Risk Factors of Chronic Kidney Disease Occurrence in Patients Received Liver Transplantation Li Yuehong. *Nephrology, Tsinghua Changgung Hospital, Medical Center, Tsinghua Univ, Beijing, China.*

Background: Analysis the risk factors of chronic kidney disease (CKD) occurrence in patients with liver transplantation.

Methods: 190 patients received liver transplantation followed up during 2001 to 2013 were analyzed retrospectively. 40 patients developed CKD. The observation items included patients' gender, age, primary diseases, surgical approach, preoperative complications, laboratory examinations (hemoglobin, albumin, creatinine, glomerular filtration rate), intraoperative blood loss and blood transfusion volume, postoperative complications and average serum calcineurin concentration (from liver transplantation to the onset of CKD). Clinical data of CKD occurrence group were compared with the non-CKD group. Chi square test, t test, and logistic regression analysis were used.

Results: The incidence of CKD in patients with liver transplantation was 21.1%. Renal pathology included IgA nephropathy, hepatitis B virus associated nephropathy, membranous proliferative glomerulonephritis, focal segmental glomerular sclerosis and cryoglobulinemia associated renal injury. 85.7% patients had tubulointerstitial damage. Univariate analysis showed that preoperative renal function, hemoglobin, intraoperative blood loss and transfusion volume, postoperative acute kidney injury, average calcineurin concentration and hypertension were risk factors of CKD in patients with liver transplantation. Logistic regression analysis showed that preoperative glomerular filtration rate (OR=0.980, P=0.041), hemoglobin (OR=0.972, P=0.034), calcineurin concentration (OR=1.364, P=0.015) and postoperative hypertension (OR=4.833, P=0.048) were independent risk factors of CKD occurrence.

Items	B	OR	95%CI	P
eGFR	-0.020	0.980	0.962-0.999	0.041
Hemoglobin	-0.029	0.972	0.946-0.998	0.034
calcineurin concentration	0.311	1.364	1.063-1.751	0.015
postoperative hypertension	1.575	4.833	1.014-23.027	0.048

Risk factors of CKD occurrence in patients with liver transplantation by logistic regression analysis.

Conclusions: The incidence of CKD in patients with liver transplantation was higher. Independent risk factors included preoperative glomerular filtration rate, hemoglobin, postoperative average calcineurin concentration and hypertension.

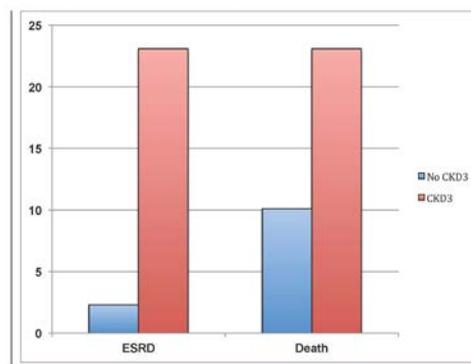
SA-PO1053

Pre-Transplant CKD, but Not AKI, Impacts Survival in Liver Transplant Recipients Yorg Al Azzi, Girish N. Nadkarni, Vinay Nair, Thomas Schiano, Madhav C. Menon. *Medicine, Icahn School of Medicine, New York, NY.*

Background: Chronic kidney disease (CKD) stage and duration of RRT pre-liver transplant (OLT) have been associated with increased risk of progression to ESRD in OLT recipients. Currently, allocation of dual organ transplantation (liver/kidney) is limited to CKD stage 4 and/or RRT > 4 weeks. The data regarding the associations of less severe pre-OLT AKI (RRT<4 weeks) and, of CKD stage 3, with ESRD post-OLT is unclear. We examined the renal outcomes of OLT recipients at our center.

Methods: We reviewed charts of OLT recipients at Mount Sinai for clinical, demographic, laboratory and outcome data from the medical record. We utilized multivariable logistic regression for analysis.

Results: We had data on 115 OLT recipients from 2008-14 (mean age 57.7 years, 66% male). 55/115(47%) patients developed AKI pre-transplant, most often from HRS (47%). Pre-existing CKD-3 was present in 26/115 patients. Pre-OLT AKI developed in 23/26 CKD-3 patients. RRT was required in 8/26 CKD-3 patients. Mean eGFR at 1- and 2-yr follow-up in the CKD-3 group compared to non-CKD group were 37.4 ± 16.6 vs. 33.3 ± 23.1 (p<0.01) and 59.8 ± 20.8 vs. 62.7 ± 22.3 (p<0.01) respectively. At a mean follow up of 1.4 years post OLT, proportion of patients developing ESRD was higher in CKD3 vs. non CKD group (23.1% vs. 2.3%; p<0.01) Although, AKI was a significant predictor of ESRD (adjusting for age, sex, race, diabetes), its effect was attenuated after adjusting for CKD. CKD3 was the strongest predictor of ESRD (aOR 8.34; 95% CI 1.25-55.7; p=0.02) (figure 1). Overall, patient survival at a mean of 2.4 years of follow-up was lower in CKD3 vs. non-CKD3 groups (76.9%vs. 91%; p=0.08).



Conclusions: Although limited by small sample size and low event rate, our analysis suggests that pre-OLT CKD3 may have an effect on development of ESRD post-OLT. These effects if generalizable in larger cohorts are important for organ allocation.

SA-PO1054

Can Acute-On-Chronic Liver Failure Classification Predict Post-Liver Transplant and Liver Kidney Transplant Outcomes? Giselle Guerra,¹ Panagiotis Tryphonopoulos,² Kalyan Bhamidimarri,² Ian Thomas,¹ Rodrigo Vienna.² ¹Div of Nephrology, Miami Transplant Inst, Miami, FL; ²Division of Transplantation, Miami Transplant Institute, Miami, FL.

Background: Recent evidence suggests that acute on chronic liver failure (ACLF) stratification is more accurate than other methods in predicting short term mortality rates pre-transplant. There is no evidence of ACLF stratification as predictor of post-transplant outcomes. We analyzed if ACLF could predict patient and allograft survival in liver transplant recipients (LTR) or simultaneous liver kidney transplant recipients (SLKTR) especially if hepatorenal syndrome (HRS) is present.

Methods: A retrospective analysis was performed on 86 adult patients, 77 LTR and 9 SLKTR transplanted in 2013. Patients were classified into different ACLF grades (0-3) based on their pre-transplant parameters: MELD labs (total bilirubin, serum creatinine, INR), hepatic encephalopathy, ventilator dependence and the presence of shock. Patient and allograft survival, and kidney function (serum creatinine < 1.5 mg/dL) were analyzed at 6 & 12 months post-transplant between LTR and SLKTR. A further analysis between recipients with HRS receiving either LT or SLKT was made. SLKTR received kidney transplants based on current International Club of Ascites (ICA) guidelines.

Results: Demographics of LTR and SLKTR cohorts: mean age of 58 and 59 years; males 63% and 56%; mean MELD of 21 and 33 respectively. Recipients with HRS pre-transplant had mean MELD of 38 vs. 30 in the LTR and SLKTR groups respectively. 27% of LTR had ACLF 0-1, 11% SLKTR had ACLF 0-1; 73% of LTR had ACLF 2-3; 89% of SLKTR had ACLF 2-3. LTR with HRS had 100% with ACLF 2-3; SLKTR with HRS had 83% with ACLF 2-3. One year post transplant outcomes: Patient Survival – 92% LTR, 66.7% SLKTR; Graft Survival – 89.6% LTR, 66.7% SLKTR; Kidney Function good – 81.8% LTR, 33.3% SLKTR. In patients with HRS both patient and graft survival are 83.3% SLKTR and 75% LTR, but kidney function trended to be better in LTR (50%) vs SLKTR (33.4%).

Conclusions: Patient/graft survival and kidney function appear to trend better overall in LTR vs. SLKTR. However, HRS patients fared the opposite favoring SLKTR vs LTR.

SA-PO1055

C3 Alone Is Not a Prognostic Indicator of Patient or Graft Survival in Post-Transplant Glomerulonephritis Amber Hertz-Tang, Arjang Djamali, Brad C. Astor, Sarah E. Panzer, Weixiong Zhong, Maha A. Mohamed, Didier A. Mandelbrot, Sandesh Parajuli. *Nephrology, Univ of Wisconsin Hospital and Clinics, Madison, WI.*

Background: The prognostic implications of glomerular C3 in the post-transplant setting are not well characterized.

Methods: We examined patient and graft outcomes in 71 kidney transplant recipients diagnosed with glomerulonephritis (GN). Biopsies were studied by immunofluorescence (IF) for glomerular C3 staining and divided into two categories, C3-positive or C3-negative. Primary outcomes were graft and patient survival at 3, 12, and 36 months and at last follow-up. Serum creatinine (Cr) at last follow-up was a secondary outcome.

Results: Thirty three (46%) patients were C3-positive and 38 (54%) were C3-negative. Mean follow up was 103 months for positive C3 and 117 months for negative C3 groups. There were no significant differences among groups by age, gender, type of donor, or prevalence of hypertension, diabetes, and hepatitis B or C. A total of 57% of C3-positive patients had a functioning graft at 36 months post-transplant, compared to 75.1% of C3-negative (p=0.16). A total of 88.2% of C3 positive patients were alive at 36 months post-transplant, compared to 85.7% of C3 negative (p=0.9). The mean serum Cr for C3 positive patients at 36 months was 1.59mg/dl compared to 1.71mg/dl for C3 negative (p=0.55). There were no significant differences in graft and patient survival between two groups.

Conclusions: There was no significant difference in patient or graft survival, or in serum Cr between patients with GN and C3-positive IF compared to patients with C3-negative IF. This suggests that the presence of C3 alone is not a prognostic indicator of patient or graft survival in post-transplant GN.

	Positive C3(%)	Negative C3(%)	P
Graft survival at 3 months	96.8	91.8	0.39
Graft survival at 12 months	74.2	80.7	0.58
Graft survival at 36 months	56.8	75.1	0.16
Graft survival at last follow up	27.3	44.7(17)	0.19
Mean serum Cr at last follow up	2.00(0.67)	2.06 ±1.30	0.88
Patient survival at 3 months	100	100	-
Patient survival at 12 months	92.6	97.2	0.41
Patient survival at 36 months	88.2	85.7	0.90
Patient survival at last follow up	75.7	65.7(25)	0.36

SA-PO1056

Pretransplant Hepatitis B Viral Infection Increased Risk of Death After Kidney Transplantation: A Multicenter Cohort Study in Korea Jin Ho Hwang,¹ Jeonghwan Lee,² Jang-Hee Cho,³ Jung Nam An,⁴ Chan-Duck Kim,³ Curie Ahn,⁵ Chun Soo Lim,⁴ Yon Su Kim,⁵ Young Hoon Kim,⁶ Jung Pyo Lee.³ ¹Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; ²Internal Medicine, Hallym Univ Hwang Sacred Heart Hospital, Seoul, Republic of Korea; ³Internal Medicine, Kyungpook National Univ Hospital, Daegu, Republic of Korea; ⁴Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea; ⁵Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea; ⁶Surgery, Ulsan Univ Seoul Asan Medical Center, Seoul, Republic of Korea.

Background: Outcomes in kidney transplant recipients (KTRs) with hepatitis B virus (HBV) have not been well evaluated. Here, we aimed to investigate the recent posttransplant clinical outcomes of KTRs with HBV comparing with those with hepatitis C virus (HCV) or seronegative patients.

Methods: Among 3885 kidney recipients from Apr. 1999 to Dec. 2011, 3490 patients were enrolled whose viral hepatitis serology data was available. Numbers of patients with HBV and hepatitis C virus (HCV) were 166 (4.8%) and 55 (1.6%). We analyzed the overall mortality and graft failure (GF) among patients who had taken KT.

Results: Patients with HBV showed poorer patient survival (P=0.030, adjusted HR=2.296, 95% CI 1.084-4.864) than KTRs without HBV. However HCV did not affect patient survival (P=0.763). Patients with chronic hepatitis C showed increased incidence of GF (P=0.015, adjusted HR=2.330, 95% CI 1.178-4.606). However, the GF of patients with chronic hepatitis B (CHB) was not different (P=0.066). Among causes of mortality of KTRs with HBV, hepatic failure was predominant (44.4%). The KTRs with HCV had increased incidence of acute rejection (log-rank P=0.005; crude HR=2.147, 95% CI 1.344-3.432, P=0.001). Among KTRs with HBV, mortality was significantly correlated with higher grade of inflammation in pretransplant liver biopsy (P=0.007) and lower rate of prophylactic antiviral treatment (P=0.019).

Conclusions: The KTRs with CHB could show poor survival due to post transplantation hepatic complications. Continuous close monitoring and antiviral management of KTRs with CHB patients will be needed, even if liver function is within normal range.

SA-PO1057

Does Hepatitis B Virus Impact the Outcomes in Kidney Transplant Recipients? Analysis by Phases of Infection Bhavna Chopra, Swati Arora, Richard J. Marcus, Sabiha M. Hussain, Khaled Nashar, Tina Y. Ko, Kalathil K. Sureshkumar. *Allegheny General Hospital, Pittsburgh, PA.*

Background: In kidney transplant recipients (KTRs) with hepatitis B virus (HBV) infection, immunosuppression may increase the risk for the progression of liver disease. HBV may contribute to allograft disease and anti-HBV therapy can have nephrotoxic potential. All these factors could adversely influence graft/patient outcomes. We aimed to analyze the impact of different phases of HBV infection on the outcomes in KTRs.

Methods: Using OPTN/UNOS database, we selected adult KTRs from 2001 - 2011 who received peri-operative antibody induction followed by calcineurin inhibitor/mycophenolate mofetil maintenance along with/without steroid. The cohort was divided into 4 groups based on the presence/absence of hepatitis B surface antigen (HBsAg) and core antibody (HBcAb) at the time of transplantation: HBsAg+/HBcAb- (acute infection); HBsAg+/HBcAb+ (developing immune response); HBsAg-/HBcAb+ (resolving infection) and HBsAg-/HBcAb- (HBV naive). Graft and patient survivals were compared among the groups as shown in the table by using multivariate Cox model. Donor, recipient and transplant related confounders including lamivudine therapy were adjusted in the model.

Results: Adjusted graft and patient survival comparisons are shown in the table.

	HBsAg+/HBcAb- (n=1098) vs. HBsAg+/HBcAb+ (n=467)		HBsAg+/ HBcAb+(n=467) vs. HBsAg-/HBcAb+ (n=6117)		HBsAg-/HBcAb+ (n=6117) vs. HBsAg-/HBcAb- (n=81968)	
Outcomes	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Death-censored graft survival	0.83 (0.71-0.98)	0.02	0.80 (0.71-0.91)	0.002	0.97 (0.9-1.0)	0.05
Patient survival	1.06 (0.93-1.25)	0.40	1.11(1.0-1.25)	0.10	0.97 (0.91-1.11)	0.10

Conclusions: Our findings favor delaying kidney transplantation in HBV infected patients until they start to develop an immune response to the virus (HBsAg+/HBcAb+ sero-status) and preferably till HBV infection begins to resolve (HBsAg-/HBcAb+ sero-status) in order to optimize graft outcomes. With the availability of newer anti-viral agents, transplant outcomes are likely to improve further in KTRs with HBV infection.

SA-PO1058

Incidence of Hepatitis B Viral Reactivation After Kidney Transplantation with Rituximab Administration Kosuke Masutani,¹ Kazuya Omoto,² Masayoshi Okumi,² Hidehisa Kitada,³ Tomokazu Shimizu,² Hideki Ishida,² Kazunari Tanabe,² Kazuhiko Tsuruya,¹ Takanari Kitazono.¹ ¹Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; ²Urology, Tokyo Women's Medical Univ, Tokyo, Japan; ³Surgery and Oncology, Kyushu Univ, Fukuoka, Japan.

Background: The efficacy of antiviral prophylaxis for rituximab (RIT)-associated hepatitis B virus (HBV) reactivation in patients with malignant lymphoma has been reported. However, the effect of single-dose RIT on HBV reactivation in kidney transplant patients with hepatitis B surface antigen-negative (HBsAg-) and hepatitis B core antigen antibody-positive (HBcAb+) results is unclear, and there is no evidence for the necessity of prophylaxis in those patients.

Methods: From 2001 through 2014, 1021 patients underwent kidney transplantation (KTx) at Kyushu University and Tokyo Women's Medical University, of whom 76 (7.4%) had HBsAg-/HBcAb+ results. Those patients showed hepatitis C virus (HCV)-RNA-negative, hepatitis B surface antibody-positive (HBsAb+), and HBV-DNA-negative. A RIT dose of 200mg/body was administered to 49 patients, and 45 patients did not receive prophylaxis. We monitored HBV-DNA and alanine transaminase levels every 1-3 months after KTx. HBV reactivation was defined as an elevation of serum HBV-DNA level ≥ 2.1 log copies/mL.

Results: HBV reactivation was found in 1 of 45 patients (2.2%) without prophylaxis. In the patient with HBV reactivation, serum HBV-DNA was detected at 6 weeks after KTx, and the minimum and maximum HBV-DNA levels were 2.1 and 2.6 log copies/mL, respectively. Although the patient was not treated with antiviral therapy, the HBV-DNA disappeared at 8 months after KTx. HBV reactivation was not found in the patients without RIT, and in the 4 patients who received both RIT and prophylaxis. Four (8.9%) of the 45 patients developed acute rejection, and 1 patient (2.2%) died of sepsis during the observation period.

Conclusions: The incidence of RIT-associated HBV reactivation in the HBsAg-/HBcAb+ patients without prophylaxis was less than 5%, suggesting that low-dose RIT might be associated with low incidence of HBV reactivation. However, sequential monitoring of HBV-DNA is necessary to prevent severe *de novo* hepatitis.

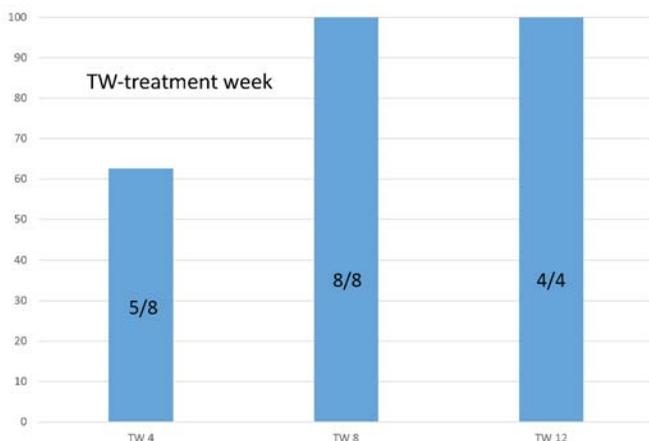
SA-PO1059

Direct Acting Antiviral Agents for HCV-Infected Patients Transplanted with a Kidney from a HCV Positive Donor David Roth, Michael J. Goldstein, Warren L. Kupin, Giselle Guerra, Linda J. Chen, Adela D. Mattiazzi, Gaetano Ciancio, Paul Martin, George William Burke, Kalyan Bhamidimarri. *Medicine, Univ of Miami Miller School of Medicine, Miami, FL.*

Background: The availability of direct acting antivirals (DAAs) has changed the treatment of hepatitis C virus (HCV) infection. The decision to treat a HCV (+) patient (pt) before or after transplant has important ramifications. The current study reports outcomes in HCV-infected pts who received a kidney from a HCV (+) donor followed by early post-transplant treatment with DAAs.

Methods: HCV RNA (+) pts on the waiting list were consented to receive a kidney from a HCV (+) donor. Induction immunosuppression (IS) included thymoglobulin and simulect followed by maintenance IS with tacrolimus and mycophenolate mofetil. At 3 months post-transplant sofosbuvir combined with either ledipasvir, simeprevir and/or ribavirin for 12 or 24 weeks was initiated.

Results: Ten pts have started DAA therapy (5 others pending); 6 blacks and 4 hispanics with a mean age of 49.4 yrs. No pts had HIV or HBV co-infected. All pts were treatment naïve, genotype 1 and non-cirrhotic. Median wait time was 30 days after consenting to accept a HCV (+) kidney. Viral clearance rates are shown in figure 1.



No viral relapses have occurred. Ribavirin was lowered or stopped in 2/3 pts for anemia. Two pts had ABMR after attaining viral clearance. Tacrolimus dose required upwards titration in 6 pts. from 17-400%.

Conclusions: This report describes the use of DAAs in HCV infected kidney recipients who received a kidney from a HCV (+) donor. Accepting a HCV (+) kidney significantly shortened wait time. Response to DAAs appears similar to that being reported for pts without kidney disease however IS dosing must be carefully monitored. This treatment strategy should be considered for non-cirrhotic HCV-infected pts awaiting deceased donor kidney transplantation.

SA-PO1060

Impact of Treatment of HCV Infection on Renal Transplant Outcome Sanjay K. Agarwal, Soumita Bagchi, Dipankar M. Bhowmik, Sandeep Mahajan, Akansha Agrawal. *Nephrology, All India Inst of Medical Sciences, New Delhi, Delhi, India.*

Background: Impact of HCV treatment on post renal transplant outcome has not been reported adequately. This retrospective study was done to evaluate impact of HCV treatment on the post renal transplant outcome.

Methods: Adult patients on dialysis with HCV infection treated with pegylated interferon and subjected to renal transplant (RT) formed the study group. Untreated patients subjected to RT during same period served as controls. Primary end points were patient's and graft survival and secondary end points were serious infections and NODAT. Factors which affect the outcome like age, gender, diabetes as basic disease, dialysis vintage, HBV co-infection, HCV genotype, viral load, liver biopsy grade and stage, induction and baseline immunosuppression were considered for analysis.

Results: At the time of study, 2010 RT were done in department of which 133 had HCV infection. 30 were treated with 68% SVR and 103 were untreated. In untreated group, there were more males (92% Vs 77%), less dialysis number (137 Vs 211), less HBV co-infection (0.9% Vs 10%), less use of Tacrolimus (13.6% Vs 30%). There was no difference in terms of age, diabetes, HCV genotype, viral load, liver biopsy grade and stage, use of induction, Mycophenolate mofetyl and duration of follow-up in two groups. With mean follow-up of 59 ± 22 months (range 12- 105), there was no statistically significant difference in term of acute rejection (23% vs. 15%), NODAT (10% vs. 16.7%) and overall serious infections (23% vs. 15%) between two groups. However, there were 11 deaths in untreated group (8 sepsis related, 3 liver failure and 1 coronary artery disease) while only one death related to sepsis in treated group. Patients survival (97% vs. 89%) and graft survival (97% vs. 84%) was significantly better (p<0.05) in treated group as compared to untreated group.

Conclusions: Treatment of HCV with pegylated interferon during dialysis results in significant improvement of patients and graft survival following transplantation as compared to untreated patients. There is also trend of decrease in serious infection in treated patients. Sepsis and liver failure are two most common cause of mortality in untreated patients.

SA-PO1061

Prospective Study of Urinary Tract Infection in Renal Allograft Recipients in India: Single Center Study Sanjay K. Agarwal, Muthu kumar B, Soumita Bagchi. *Nephrology, All India Inst of Medical Sciences, New Delhi, India.*

Background: Urinary tract infection (UTI) is common in renal transplant (RT) and in addition to morbidity, presumed to affects graft outcome also. Still it is least studied infection in RT. There is no data from India. We looked for incidence, risk factors and pattern of UTI in first 6 months after RT and its impact on graft function.

Methods: All RT between Dec 2013 and March 2015 were followed with urine exam and C/S at day 3, 7, 14, 21, 28 and then every two week till 3 months then monthly for another 3 months. Patients with asymptomatic bacteraemia (ASB) were randomized into treatment and no treatment group. Treatment was done for 7-10 days as per C/S. Study was approved by institute review board and informed consent was taken from each subject.

Results: During the study period 180 RT were done, (4 died, 2 nephrectomy, 1 graft failed, 4 lost to FU); 169 were analysed. Mean age of patients was 31.4 ± 10.4 (14-56) yrs and 81.6% were males. Diabetes was in 3.5%, renal stone in 3.5% and 3.5% had history of pre-RT recurrent UTI. All were on tacrolimus, MMF and steroid. 53% received induction. None got anti-reflux surgery. All were on cotrimoxazol for 6 months. 49 (29%) patients had at least one episode of UTI; 23 symptomatic and 26 ASB. Most common UTI was seen at 21 days followed by 14 days post surgery. 50-60% of these were symptomatic. Following RT, with time, frequency of UTI went on decreasing. Of the 84 UTI episodes, 47 (56%) were caused by E.coli followed by Klebisella (16.7%), Enterococci (12%) and Pseudomonas (8.3%). Of the patients who had UTI, there were more females (33% vs. 13%), more stone disease (8.2% vs. 1.7%) and more post-operative surgical complications (24.5% vs. 11.7%). Of the 26 ASB, 11 were treated and 15 untreated. Of the 15 untreated ASB, none developed symptomatic UTI or rejection. There was no difference in serum creatinine between treated and untreated ASB on last follow-up.

Conclusions: In conclusion, symptomatic UTI in RT in our setting is seen in 13.6% patients, mostly in first month with E.coli as causative organism in half of patient. Untreated asymptomatic UTI does not affect graft outcome and does not lead to symptomatic UTI.

SA-PO1062

High Dose Steroid Therapy in BK Viremia Adversely Affected Long Term Graft Function in Kidney Transplantation Hyosang Kim, Chung Hee Baek, Su-Kil Park. *Div of Nephrology, Dept of Internal Medicine, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea.*

Background: High dose steroid therapy has been tried for the management of confusing cases of BK nephropathy (±mixed cellular rejection). However, the eventual fate of renal allograft after steroid therapy in the long term is still unknown. Therefore we investigated the graft survival and the change of BK viral load after steroid therapy in patients with BK viremia.

Methods: The study population comprised 144 kidney transplant recipients with BK viremia (serum BK viral load >1x10⁴ copies/mL) consecutively detected at least two times, followed by steroid pulse treatment between July 2004 and March 2013. Patients were divided into two groups based on the amount of steroid: low dose (steroid 0-2g) or high dose (steroid >2g).

Results: A total of 123 patients belonged to low dose group and 21 patients were in high dose group. There were no differences in baseline characteristics, including age, gender, and the rates of biopsy-proven BK nephropathy and acute rejection. Serum BK viral loads at the time of steroid pulse therapy were 5.38±1.10 log copies/mL in low dose group and 6.00±0.98 in high dose group (p=0.054). They were changed into 5.25±1.05 and 6.14±1.45 in each group one month after steroid treatment (p=0.03) and 4.92±1.25 and 5.86±1.74 at two months (p=0.133), respectively. From three months to one year, serum BK viral loads were not different from each group. Kaplan Meier analyses demonstrated that the incidences of further 50% decline in renal function assessed by estimated GFR and graft failure were significantly higher in the high dose group (p=0.004 and p=0.04, respectively). In multivariate regression analysis, high dose steroid treatment (p=0.002, HR 9.61, 95% CI 2.25-40.99) and log serum BK viral load at two months after high dose steroid administration (p=0.027, HR 1.72, 95% CI 1.06-2.78) were important risk factors of further 50% decline in renal function.

Conclusions: In kidney transplant recipients with BK viremia, high dose steroid therapy induced BK viral activation and subsequently resulted in poor long term graft function and early graft failure.

SA-PO1063

Donor Seroreactivity Strongly Correlates with Recipient BKV-Viremia and Nephropathy Herman F. Wunderink,¹ Els Meijden van der,¹ Caroline van der Blij-de Brouwer,¹ Antoine Touze,² Marko Mallat,¹ Geert Haasnoot,¹ Erik Van zwet,¹ Eric Claas,¹ Johan W. De Fijter,¹ Aloys Kroes,¹ Frans Claas,¹ Joris I. Rotmans,¹ Mariet Feltkamp.¹ ¹Leiden Univ Medical Center, Netherlands; ²Univ François Rabelais, France.

Background: Incidence and severity of reactivating latent infections in kidney transplant (KTx) recipients are difficult to predict. In case of BK polyomavirus (BKV)-induced nephropathy, donor origin of infection is likely. Since BKV-seroreactivity reflects BKV-(re)activity, we hypothesized that donor BKV-seroreactivity correlates with infectivity and predicts BKV infection of recipients.

Methods: In a retrospective cohort of 407 living donor-recipient pairs transplanted between 2003 and 2013 at LUMC, pre-KTx sera from donors and recipients were tested for presence and intensity of BKV IgG-seroresponses. Measured seroresponses were compared with recipient BKV-loads (viremia) determined post-KTx and compared with other potential risk factors for BKV-infection.

Results: Within one year after KTx, BKV-viremia was observed in 27% of recipients. Baseline BKV-seroprevalence among donors (96%) and recipients (95%) was high and not correlated with viremia. However, a strong association was observed between the strength of donor BKV-seroreactivity and occurrence of both viremia and PVAN (p<0.001). Baseline recipient BKV-seroreactivity as such was not associated. The hazard ratio of viremia was almost 10-fold higher in recipients of high compared to low seroreactive donors. In multivariate analysis, donor seroreactivity was the strongest baseline factor associated with viremia and nephropathy post-KTx (p<0.001), outcompeting other described risk factors.

Conclusions: The strong association between donor BKV-seroresponse and recipient BKV-infection points directly to the donated kidney as the source of BKV-induced disease and possibly reflects the BKV allograft load. Our findings warrant further research into the usefulness of BKV-serological testing prior to transplantation.

Funding: Private Foundation Support

SA-PO1064

The Role of BK Viral Subtypes in BK Viral Infection After Renal Transplantation Anke Schwarz,¹ Silvia Linnenweber-Held,¹ Hermann G. Haller,¹ Corinna Schmitt.² ¹Nephrology, Hannover Medical School, Hannover, Germany; ²Virology, Hannover Medical School, Hannover, Germany.

Background: Risk factors for developing BK virus (BKV) infection after renal transplantation are unresolved, including the role of BKV subtypes.

Methods: We report on 146 patients with viral replication in urine tested by quantitative PCR (Cepheid-Affigene Kit) before transplantation (29 donors and 11 recipients, spontaneous replication in urine) and after transplantation (106 infected recipients, routine recipient BKV testing). Genotyping of BKV DNA subtypes was performed. Patients with post-transplant BKV nephropathy or high viremia of >10000 copies/mL (n=32, group 1) were compared to post-transplant recipients with viruria alone or with low viremia of <10000 copies/mL (n=43, group 2) and with donors and recipients before transplantation (n=40, group 3).

Results: BKV subtype Ib-1 was seen in 14/146 (10%), subtype Ib-2 in 92/146 (63%), subtype II in 9/146 (6%), subtype III in 1/146 (2%), and subtype IV in 30/146 (21%) of all patients. Thus, subtype Ib-2 was the first and subtype IV the second in frequency of subtypes in all patients. Comparing the 3 groups (group 1 vs group 2 vs group 3), there was no stat. sign. difference in the prevalence of subtype Ib-1 (8 vs 12 vs 10%), subtype Ib-2 (60 vs 70 vs 60%), subtype II (3 vs 7 vs 10%), subtype III (2 vs 0 vs 0%), and subtype IV (27 vs 12 vs 20%). However, after transplantation, subgroup IV had a trend to be less prevalent in patients with viruria/ low viremia (group 2) compared to patients with BKV nephropathy or high viremia of >10000 copies/mL (group 1) (5/43 vs 17/63, p=0.054).

Conclusions: BKV subtype Ib-2 is the most frequent subtype in all patients of the three groups. In the situation after renal transplantation, patients being infected with BKV subtype IV could be more likely to develop BKV nephropathy or high viremia than patients being infected with other subtypes. This has to be investigated in larger patient groups.

SA-PO1065

Inflammation and Reconstitution Injury in Resolving Polyomavirus Nephropathy: Good or Bad? Insights from a Protocol Biopsy Based Prospective Study Harsharan Kaur Singh, A. Gasim, Volker Nickenleit. *Div of Nephropathology, The Univ of North Carolina, Chapel Hill, NC.*

Background: Polyomavirus nephropathy (PVN) has been extensively studied at time of disease onset and in index biopsies. In contrast, little is known about acute and chronic changes occurring during PVN resolution under low dose maintenance immunosuppression. **Aim:** Enhance understanding of resolving PVN.

Methods: From 1/2009-9/2014 423 adult renal transplants with an 8.5% incidence of PVN (n=37) were prospectively followed at UNC. PVN patients were monitored with the urinary PV-Haufen test and protocol biopsies collected in 9/37 patients when the test turned from positive to negative as marker for PVN resolution. Histology in index PVN (n=9) versus corresponding protocol biopsies (n=9) was compared; clinical, treatment and long-term outcome data were obtained from electronic medical records.

Results: Serum creatinine and Banff scores at time of PVN index biopsy and follow-up protocol biopsy in Table 1.

	Serum Creatinine (median) mg/dl	BANFF Scores (mean)			
		Tubulitis - t	Interstitial inflammation-i	Scarring - ci	Tubular atrophy-ct
A] Index Biopsy at time of PVN diagnosis	1.78	1.4	1.3	0.7	0.9
B] Follow-up Protocol Biopsy at time of PVN resolution	2.7	2.4	2.0	1.2	1.3
C] 12 month follow-up post protocol biopsy	1.75				

Index biopsy: 5/9 cases with PVN grade 1 and 4/9 grade 2. *Treatment:* reduction tacrolimus and/or MMF. *Protocol biopsy* (median 6 weeks post index, range: 4-60); 5/9 cases resolved PVN, 4/9 residual minimal PVN; 1/9 recurrent MPGN, 3/9 acute ABMR or Banff type 2 definitive rejection. Anti-rejection therapy 6/9 cases with decrease in S-Cr in 4/6 and deterioration in 2/6; function stable in 3/9. *Further 12-month follow-up:* Serum creatinine 1.75 mg/dl (median), no graft losses.

Conclusions: Resolving PVN under 'low-dose' immunosuppression shows significant increases in Banff acute inflammation scores and S-Cr. "Bad" inflammation is in part secondary to acute rejection and responds to anti-rejection therapy. "Good" self limiting reconstitution inflammation can be postulated in 1/9 cases (10%) of resolving PVN. PVN results in only mild increases in chronic tissue injury.

SA-PO1066

Effectiveness of Simeprevir and Sofosbuvir in the Treatment of Hepatitis C Virus in Genotype 1 Post-Kidney Transplant Recipients Karolyn S. Horn,¹ Michelle T. Martin,¹ Ignatius Yun-Sang Tang,² ¹Pharmacy Practice, Univ of Illinois at Chicago; ²Medicine, Univ of Illinois at Chicago.

Background: The 2014 American Association for the Study of Liver Diseases (AASLD) guidelines recommended the use of simeprevir (SMV) + sofosbuvir (SOF) for the treatment of liver transplant recipients with genotype (GT) 1 hepatitis C virus (HCV). There is a paucity of data on the treatment of other solid organ recipients. We conducted a retrospective, single-center analysis of kidney transplant recipients (KTRs) who received HCV treatment.

Methods: All KTRs who received HCV treatment with 12 weeks of SMV + SOF between January and November 2014 were evaluated. The primary endpoint was the sustained virologic response at 12 weeks after the end of treatment (SVR12). Secondary outcomes included HCV PCR levels, serum creatinine, urine protein/creatinine ratio, trough calcineurin inhibitor (CNI) levels and dose changes, and AST to platelet ratio index (APRI) at week 4, end of treatment (EOT), and 12 weeks post-treatment.

Results: Twelve patients met inclusion criteria: mean age of 60±5.3, 11 males, 8 African American, 6 GT 1a and 6 GT 1b. There were 6 liver-kidney, 4 kidney, and 2 pancreas-kidney transplant recipients. All but 1 patient received tacrolimus as their CNI. Ten of 12 patients (83.3%) achieved SVR12. Mean tacrolimus levels increased significantly by 1.5 ng/mL between week 0 and 4 (p=0.041). Five (41.7%) required a mean tacrolimus dose decrease of 2 mg during treatment. Nine (75%) required a mean dose increase of 2 mg between EOT and SVR12. The APRI scores decreased from 0.64 to 0.17 between baseline and 12 weeks of treatment, but this is not statistically significant (p=0.216). Both serum creatinine and urine protein/creatinine ratio remained stable pre- and post-treatment (p=0.260 and p=0.973, respectively).

Conclusions: SVR12 was achieved in 83.3% of KTRs treated with SMV + SOF. Renal allograft function was stable during and after HCV therapy. Treatment with SMV + SOF increased CNI levels during treatment. CNI dose adjustment is needed to maintain therapeutic levels after SMV + SOF therapy.

SA-PO1067

25-Hydroxyvitamin D Insufficiency Is Associated with Higher Risk of BK Virus Re-Activation After Kidney Transplantation Nisreen Elfadawy, Stuart M. Flechner, Emilio D. Poggio, Brian R. Stephany, Richard A. Fatica, Jesse D. Schold, Sherif B. Mossad. *Cleveland Clinic.*

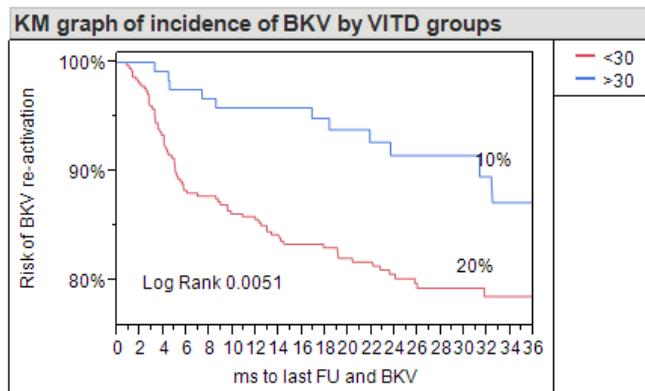
Background: The past decade has seen increased interest in vitD, because new data suggest that it plays a role in the immune system. The purpose of this study was to evaluate the association of 25-hydroxyvitD level (25[OH]D) after kidney transplant with the risk of BK virus reactivation.

Methods: We identified 498 kidney transplant recipients (2007-2011) who had serum levels of (25[OH]D), and PTH. We evaluated the relationship between the average levels of 25(OH)D and PTH and BKV reactivation in blood.

Results: VitD insufficiency (25[OH]D <30 ng/mL, defined by The Endocrine Society Clinical Practice 2011) was observed in 377 (75%) of 498 kidney recipients after transplant. The VitD insufficient and sufficient groups were comparable in terms of gender, age, BMI, race, and immunosuppressio. VitD insufficiency was more frequent in recipients of cadaveric allografts (P=0.009, Fisher test). By multivariable Cox regression analysis, vitD insufficiency was an independent risk factor for BKV reactivation after kidney transplantation (HR=2.4, 95% CI 1.3-4.7, P=0.002). Moreover, vitD insufficiency was associated with significantly earlier onset of BKV reactivation (9 compared to 16 months, P 0.01). ROC analysis using logistic regression showed that 25[OH]D <24ng/mL was predictive of BKV

reactivation (OR: 82.9, 95% CI: 17.2–744.6, $P < 0.001$, AUC 0.7). VitD insufficiency was not associated with higher risk of CMV reactivation (17 vs 19% resp, $p = 0.5$). The positive BKV group had significantly higher PTH compared to the negative group (196 vs 148 resp, $P = 0.01$). No significant associations of 25[OH]D with clinical outcomes were observed in time-dependent or fixed-covariate Cox models.

Conclusions: Vitamin D insufficiency is a risk factor for BKV reactivation after kidney transplantation. D3 supplementation may help reduce BKV reactivation.



SA-PO1068

Different Types of Cytomegalovirus DNAemia and Long-Term Outcomes After Renal Transplantation Tomas Reischig,¹ Martin Kacer,¹ Ondrej Hes,² Daniel Lysak,³ Mirko Bouda.¹ ¹Internal Medicine I, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic; ²Pathology, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic; ³Hematology, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic.

Background: Although occurring very often the role of cytomegalovirus (CMV) DNAemia in patients managed by preemptive therapy or by universal antiviral prophylaxis is not established. The aim of the study was to determine the impact of different types of CMV DNAemia during 4 years after transplantation.

Methods: A total of 180 consecutive renal transplant recipients at risk for CMV (donor and/or recipient CMV seropositive) were included and followed prospectively. Universal prophylaxis for 3 months was given to 132 (high-dose valganciclovir, $n = 87$; valganciclovir $n = 45$) patients, 48 patients were managed by preemptive therapy. Based on CMV DNAemia status during the first year after transplantation patients were stratified to 1) no DNAemia, 2) early-onset (< 3 months) DNAemia, late-onset (≥ 3 months) DNAemia, and 4) combined early+late-onset DNAemia groups, respectively.

Results: Early-onset, late-onset, and combined early+late-onset CMV DNAemia occurred in 18%, 25%, and 13% of the patients being asymptomatic in majority (91%) of cases. Graft survival at 4 years was inferior in patients with late-onset CMV DNAemia compared to patients without CMV DNAemia (73% vs. 94%, $P = 0.002$) while no significant differences were observed in patients with early-onset (85%, $P = 0.139$) or combined early+late-onset CMV DNAemia (96%, $P = 0.682$). Patient survival was comparable in all groups. Moderate to severe interstitial fibrosis and tubular atrophy assessed by protocol biopsy at 36 months was not increased in early-onset (15%, $P = 0.05$), late-onset (21%, $P = 0.180$), and combined (29%, $P = 0.609$) CMV DNAemia compared to no CMV DNAemia group (36%). Likewise, renal function was not different at 36 months.

Conclusions: Late-onset CMV DNAemia is a risk factor for graft loss after renal transplantation.

Funding: Government Support - Non-U.S.

SA-PO1069

Assessment of Cytomegalovirus-Specific Cell-Mediated Immunity for the Prediction of Cytomegalovirus Spontaneous Clearance in High-Risk Kidney Transplant Recipients with Cytomegalovirus Viremia Marine Lochouart,¹ Sylvia Benzaken,² Laetitia Albano,¹ Elisabeth Cassuto,¹ Ahmed Jeribi,¹ Anne Caramella,³ Valerie Giordanengo,³ Ghislaine Bernard,² Vincent L.M. Esnault,¹ Barbara Seitz-Polski.^{1,2} ¹Nephrology and Kidney Transplantation Dept, Univ Hospital, Nice, France, Metropolitan; ²Laboratory of Immunology, Univ Hospital, Nice, France, Metropolitan; ³Laboratory of Virology, Univ Hospital, Nice, France, Metropolitan.

Background: Cytomegalovirus (CMV) is the most common virus pathogen in kidney transplant recipients (KTR) and CMV disease impacts patient and graft survival. CMV-specific CD8 T cell-mediated immunity (CMI) kinetics may help to assess the risk of CMV disease and to adapt preventive treatment strategies.

Methods: High risk KTR with CMV seropositive donor/seronegative recipient (D+/R-), were longitudinally monitored after CMV prophylaxis discontinuation and during the first year post-transplant for CMV viremia (WHO standardization) and CMI (QuantiFERON®-

CMV). We analyzed the ability of the CMI-test to predict subsequent spontaneous viral clearance in case of asymptomatic viremia after prophylaxis discontinuation or CMV disease recurrence after curative treatment.

Results: We enrolled 12 consecutive (D+/R-) KTR. Eleven patients developed viremia during follow-up. Spontaneous viral clearance occurred in 7 of 11 (63.6%) patients and 4 of 11 (36.4%) developed CMV disease. At viremia onset, 6 of 11 (54.5%) patients had a positive CMI-test. In those patients, the incidence of subsequent spontaneous viral clearance was 6 of 6 (100%) compared with only 1 of 5 (20%) among patients displaying a nonreactive CMI ($p = 0.02$). This latter patient revealed a positive CMI-test one month later. In the 4 patients who developed CMV disease, persistence of a nonreactive CMI after treatment in one patient was associated with disease recurrence, while patients whose CMI-test became positive under treatment showed no recurrence.

Conclusions: We show for the first time that D+/R- KTR with asymptomatic viremia attested by WHO standardized CMV viral load monitoring after prophylaxis discontinuation may benefit from QuantiFERON®-CMV to predict spontaneous viral clearance or CMV disease.

Funding: Pharmaceutical Company Support - Cellestis GmbH, a QIAGEN company, Darmstadt, Germany provided equipment entity (QuantiFERON®-CMV blood collection tubes)

SA-PO1070

Prevalence of Double Stranded DNA (dsDNA) Viral Infections Among Kidney Transplant Recipients Essy Mozaffari,¹ Jay Lin,² Melissa Lingohr-Smith.² ¹Chimerix Inc., Mendham, NJ; ²Novosys Health, Green Brook, NJ.

Background: Management of immunosuppression following solid organ transplant is a delicate balance between preventing graft rejection and minimizing the risk of infection. Antimicrobial prophylaxis can decrease the risk of infection, while increased immunosuppression can increase these same risks. Our objective was to estimate the occurrence of opportunistic infections, specifically dsDNA viral infections, in kidney transplant recipients.

Methods: Patients who received a kidney transplant between January 2009 and September 2013 were identified from the Premier Hospital database using ICD-9-CM codes. The first transplant procedure was defined as the index event. The frequencies of opportunistic infections, documented by diagnostic codes, were evaluated during the first 12 months after kidney transplant.

Results: Of patients who received kidney transplant ($n = 5,402$; mean age: 50.8 years) 61% were male. Most patients received transplant in urban (98%), large (≥ 600 beds: 61%), teaching hospitals (84%). During the 12 month post kidney transplant, 33% (1,800 patients) had a diagnostic code for ¹ opportunistic infection, and among these 25% ($n = 448$) had at least one dsDNA viral infection. Among the 448 dsDNA viral infections, 81% ($n = 365$) were cytomegalovirus (CMV), 8% ($n = 36$) BK virus, and 16% ($n = 70$) other dsDNA viral infections (HSV, VZV, HHV, HPV, EBV).

Conclusions: Opportunistic infections frequently result from the immunosuppression required following kidney transplantation. In our study, one-third of the kidney transplant recipients had a discharge diagnosis for at least one opportunistic infection. One of four opportunistic infections were classified as dsDNA viral infections, with the majority caused by human herpesviruses including CMV despite the common use of anti-CMV agents. Our study also highlights the rate of BKV-related complications, which represent an unmet need given the absence of therapeutic options for this dsDNA virus and the known association with BK-associated nephropathy.

Funding: Pharmaceutical Company Support - Chimerix Inc.

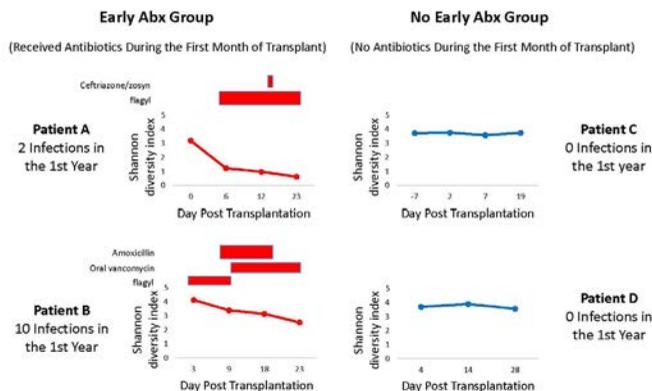
SA-PO1071

Antibiotics, Gut Microbial Diversity, and Infectious Complications in Kidney Transplant Recipients Anjali Masand,¹ John R. Lee,¹ Thangamani Muthukumar,¹ Darshana Dadhania,¹ Lilan Ling,² Eric Pamer,² Manikkam Suthanthiran.¹ ¹Medicine, Weill Cornell Medical College, NY, NY; ²Medicine, Memorial Sloan Kettering Cancer Center, NY, NY.

Background: Emerging data suggests that antibiotic usage can decrease gut microbial diversity and predispose patients to future bacterial complications.

Methods: We profiled serial fecal specimens by 16S rRNA deep sequencing in 26 kidney transplant recipients. Microbial diversity was assessed using the Shannon diversity index in subjects exposed to antibiotics in the 1st post-transplant month and in subjects not exposed. Based on a higher number of infections in antibiotic-exposed subjects, we conducted a retrospective study of 301 consecutive kidney transplant recipients and evaluated antibiotic usage in the 1st month of transplantation and development of bacterial complications in post-transplant months 2-12.

Results: Subjects exposed to antibiotics during the 1st month of transplant had decreased gut microbial diversity and an increased number of infections in the 1st year of transplant.



In 301 transplant recipients, the most common infections (N=255) were UTIs (61%) and pneumonia (9%). 74 kidney transplant recipients received antibiotics during the first month of transplantation (Early Abx Group) and 227 did not (No Early Abx Group). The Early Abx Group had a significantly higher number of infections during post-transplant months 2-12 than the No Early Abx Group (1.2±0.2 vs. 0.3±0.1, P<0.001, Wilcoxon rank-sum test). Within the Early Abx Group, subjects who received anaerobic coverage had a significantly higher number of infections during post-transplant months 2-12 than subjects who did not (1.8±0.5 vs. 0.9±0.2, P=0.050).

Conclusions: Early antibiotic usage was associated with increased future bacterial infections in kidney transplant recipients. A decrease in gut microbial diversity is a biologically plausible pathogenic mechanism.

Funding: Other NIH Support - KL2 Scholars Award from the Weill Cornell Clinical and Translational Science Center (KL2 TR-000458)

SA-PO1072

Successful Treatment of Hepatitis C in Renal Transplant Recipients with Directly Acting Antiviral Agents Michelle L. Lubetzky, Enver Akalin, Paul Gaglio, Graciela De Boccado. *Transplantation, Montefiore Medical Center, Bronx, NY.*

Background: Hepatitis C infection (HCV) in kidney transplant (KTx) recipients has been shown to be an independent risk factor for decreased patient and allograft survival. Historically treatment of HCV has been interferon-alpha based, which is associated with acute rejection in KTx patients. With the development of new, oral, interferon-free directly acting antiviral (DAA) medications, treatment of HCV in renal transplant recipients is possible, but limited data exists on its safety and efficacy.

Methods: We performed a retrospective review of all KTx patients at our center with HCV started on DAA for treatment of HCV. Any patient with at least 30 days of follow up was included in the analysis (n=10). Clinical data including graft function, survival, and response to therapy was collected.

Results: Patient demographics are in Table 1. At a median of 92 days of follow up (range 33, 438), all patients have undetectable viral load. Median time from KTx to treatment was 781 days (range 173,10404). At most recent follow up, mean creatinine is 1.48±0.51 mg/dl and mean proteinuria is 0.47±1.07 g/day with no adverse side effects reported. No patients have lost their grafts or developed acute rejection, but 2 patients had detectable CMV. For the 8 patients on tacrolimus (Tac), there was a drop in 12-hr trough level during therapy (mean 6.3±2.1 ng/mL pre-treatment, and mean of 4.9±2.1ng/mL after 6 weeks of treatment); during treatment 3 patients had a level < 4 ng/mL. All patients with level <4 ng/mL had dose increase and repeat level was in normal range.

Characteristics	N=10
Age (median, range)	61.6 (42, 74)
Sex	7 Male
Race	5 Hispanic 3 Black/African American
Type of Transplant	8 DDRT 2 Dual Organ (combined liver-kidney)
Cause of ESRD	4DM 1 HCV
Induction Immunosuppression	5 Anti-Thymocyte Globulin
Maintenance Immunosuppression	7 Prednisone, Tacrolimus, Mycophenolate
HCV Genotype	8 type 1 2 type 2
Prior Therapy	8 treatment naive
Mean Viral Load at start of therapy	3460819±3823258
Mean Creatinine at start of therapy	1.3±0.4
Proteinuria at start of therapy	0.9±0.6
Treatment regimen	5 ledipasvir/sofosbuvir 4 sofosbuvir/ribavirin 1 ledipasvir/sofosbuvir/ribavirin

Conclusions: Our data demonstrates that DAAs can be used safely and effectively in patients after KTx. Tac levels should be monitored closely during therapy. Longer follow up of KTx recipients treated for HCV is needed determine the effects treatment has on graft and patient survival.

SA-PO1073

A Systematic Review and Meta-Analysis of Cytomegalovirus Infection in Renal Transplant Recipients Receiving Alemtuzumab versus Anti-Thymocyte Globulin for Induction Therapy Payvand Milani, Nasrollah Ghahramani. *Medicine, Pennsylvania State Univ College of Medicine, Hershey, PA.*

Background: Use of antibody induction for kidney transplant has improved patient outcomes over the past decade. One common induction agent is rabbit anti-thymocyte globulin (ATG), a polyclonal anti-human T-cell antibody. Alemtuzumab, a humanized monoclonal anti-CD52 antibody with stronger lympho-depleting properties, has been used as an induction agent in steroid-sparing or steroid-minimizing protocols. Like all immunosuppressive agents, these agents are associated with opportunistic infections, including cytomegalovirus (CMV). Our aim was to compare the relative risk of CMV infection between the two induction regimens.

Methods: We used five comprehensive search themes (CMV, ATG, alemtuzumab, transplant, and induction) to search electronic databases from 1980 to 2014 using PubMed and The Cochrane Library while also manually reviewing recent abstracts from the American Society of Nephrology and the American Transplant Congress meetings. Studies reporting the number of cases of CMV infection in patients receiving one of the two agents were included. The outcome was the pooled relative risk (RR) of CMV infection in the alemtuzumab group compared to that in the ATG group.

Results: A total of 73 studies were identified and reviewed, 64 of which were excluded upon initial screening. Analysis of the 9 studies (8 complete articles and 1 abstract; 1,735 patients) showed a RR of 0.58 (95% CI: 0.31-1.07) for incidence of CMV infection in patients receiving alemtuzumab versus ATG. Other reported adverse effects in both induction groups (infections, post-transplant lymphoproliferative disorder (PTLD) and/or malignancy, decrease in estimated glomerular filtration rate, and post-transplant diabetes mellitus) were similar in both groups.

Conclusions: This study suggests that for induction therapy in kidney transplant, the incidence of CMV infection associated with alemtuzumab is not significantly different than that associated with ATG.

SA-PO1074

Occurrence and Determinants of Antibiotic Resistance in Bacteriuria After Kidney Transplantation Habib Mawad, Alexandre Tavares-Brum, Claude Lemieux, Alain Ducloux, Azemi Barama, Heloise Cardinal. *Nephrology, Centre Hospitalier de l'Univ de Montréal.*

Background: Asymptomatic bacteriuria is often treated after kidney transplantation, which can result in the development of antibiotic resistance. Our aim was to assess the antibiotic resistance profile of gram-negative bacteriuria in our kidney transplant population, and to determine the factors associated with antibiotic resistance.

Methods: We performed a single center, retrospective cohort study in patients who received a kidney allograft at our center between January 1st, 2008 and June 1st, 2013. Through chart review, information on all bacteriuric episodes involving gram negative bacilli was collected during follow-up, which ended on June 1st, 2014. Bacteriuria was defined as growth exceeding 10⁴ CFU/ml. Multivariable logistic regression using a generalized estimating equation (GEE) procedure was performed to identify the factors associated with resistance to antibiotics.

Results: Amongst the 318 patients studied, 629 bacteriuric episodes involving gram negative bacilli occurred in 143 patients. Resistance to TMP-SMX occurred in 336 episodes (53%), resistance to ciprofloxacin in 142 episodes (23%) and extended beta-lactamase production occurred in 30 episodes (5%). An increased risk of resistance to ciprofloxacin and/or extended spectrum beta lactamase production was statistically associated with the number of previously treated bacteriuric episodes (compared to no prior treatment, 2-4 previous treatments (odds ratio (OR):2.29, 95%confidence interval (CI):1.16-4.52), and ≥5 previous treatments (OR:3.05, 95%CI:1.28-7.26)), diabetes (OR:2.57, 95%CI:1.01-6.55), caucasian race (OR:0.38, 95%CI:0.16-0.91) and a longer time elapsed between bacteriuria and transplantation (OR:0.32, 95%CI 0.15-0.66, for episodes supervening >1 year post transplant versus ≤ 1 year).

Conclusions: Elevated resistance rates to TMP-SMX and ciprofloxacin were observed in our kidney transplant population, which can reduce the usefulness of prophylaxis with TMP-SMX and argue against treating asymptomatic bacteriuria, given the association we observed between the number of previous treatment of bacteriuric episodes and resistance to ciprofloxacin/ESBL production.

Funding: Government Support - Non-U.S.

SA-PO1075

Carbapenem-Sparing Antibiotic Regimens for the Treatment of Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae Infections: A Comparative Study Tiffany Ebony Bias,¹ Gregory Malat, PharmD,¹ Akshay Sharma,² Dong Heun Lee,³ Alden Michael Doyle.² ¹Pharmacy, Hahnemann Univ Hospital, Philadelphia, PA; ²Surgery, Drexel Univ, College of Medicine, Philadelphia, PA; ³Infectious Diseases and HIV Medicine, Drexel Univ, College of Medicine, Philadelphia, PA.

Background: Extended spectrum beta lactamase producing Enterobacteriaceae (ESBL-PE) has been recognized as a significant cause of mortality in solid organ transplant recipients. Carbapenems are considered the drug of choice for the treatment of ESBL-PE infections. However, antibiotic selective pressure associated with carbapenem use may

contribute to resistance, further stressing hospital epidemiology. Our study sought to compare the effectiveness of carbapenem sparing regimens to carbapenem containing regimens on clinical outcomes in transplant patients with ESBL-PE infections.

Methods: A retrospective, observational cohort study was conducted to evaluate adult patients who underwent a successful kidney transplant (defined as graft survival >30 days) prior to August 2014 with a ESBL-PE infection post-transplant. Patients were stratified into 2 cohorts according to antibiotic regimens: carbapenem-containing and carbapenem-sparing. The outcomes of clinical cure, 30-day mortality, and recurrence were assessed.

Results: Fifty-two kidney transplant patients were included in our analysis: 29 in the carbapenem-sparing group and 23 in the carbapenem-containing group. Majority of infections were caused by *Escherichia coli* (46%) and *Klebsiella pneumoniae* (44%). The most common infection type was urinary tract infections (46%) followed by bloodstream infections (23%) and nosocomial pneumonias (15%). There was no statistically significant difference in clinical cure rates (91% vs. 76%, p=0.268) and 30-day mortality (24% vs. 9%, p=0.268) in the carbapenem sparing and carbapenem containing groups respectively.

Conclusions: ESBL-PE infections pose a serious threat to transplant recipients. Carbapenem sparing regimens may be adequate for the treatment of ESBL-PE infections, while offering advantages against minimizing selective pressure.

SA-PO1076

Clinical Recurrence of Primary Glomerular Disease in Kidney Transplantation Saul Enrique Pampa, Ana M. Fernandez Rodriguez, Sara Jimenez Alvaro, Fernando Caravaca-Fontan, Estefania Yerovi, Maria Delgado Yagüe, Maite Rivera, Cristina Galeano, Sandra Elias, Fernando Liano. *Nephrology, Hospital Ramón y Cajal. UAH, Madrid.*

Background: Recurrence of primary glomerular disease (PGN) in renal transplantation (RT) is a major cause of failure and renal allograft lost which determines the prognosis of the patient. We analyzed the prevalence, clinical course and survival of graft in this group of patients.

Methods: We conducted a retrospective analysis of 1513 renal transplants between January 1980 and December 2013, included in our database, medical records and biopsy register, collecting all patients who presented recurrence of PGN. We excluded from the study patients with secondary GN and those without biopsy study. Renal biopsy was indicated according the following criteria: impairment of renal function, proteinuria>1g/day and/or microhematuria. The analysis statistic was SPSS version 18.

Results: 414 of 1513 RT (27%) had chronic GN as underlying disease. 317 patients (260 man;57 woman) were primary GN (21%). The most frequent primary GN was IgA nephropathy (IgAGN) n=122(38,4 %); Membranoproliferative GN (MPGN), n:90(28 %); Focal segmental GN(FSGS), n: 58(15,1 %); membranous GN(MGN), n: 33(10,4 %) and rapidly progressive GN (RPGN), n:14(4,4%). Forty(12.6%) patients with primary GN recurred. IgA GN (5%), FSGS (20%), MPGN (17%), MNGN(12%) and GRNP (12%). Three MPGN patients recurred in the second RT. The mean time of recurrence was: 48.18, 33.2, 18 and 33.2 months respectively Patients with graft loss due to GN recurrence were: IgAGN (n=10;75%), MPGN (n=14;93%), FSGS(n=10,75%), MNGN(n=3,70%). No significant difference was observed between GN types(p=0,15) and graft survival. In the Kaplan Meier analysis and COX test, recurrence primary GN had low survival at 10 years (p: 0.002). No significant differences was observed at 20 years(p: 0.15).

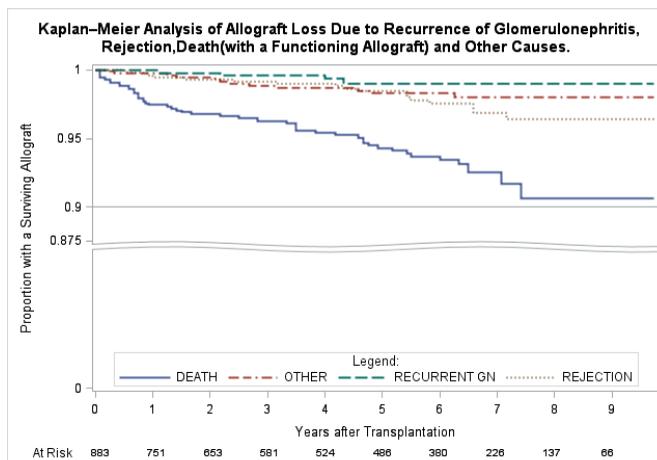
Conclusions: Clinical Recurrence of primary GN is an important cause of graft loss. GN with most recurrence was GSF and graft lost was MPGN. We didn't observe differences in graft survival between tipe of primary glomerular disease. Graft survival was higher in the group without recurrence at 10 years and no differences at 20 years.

SA-PO1077

Glomerular Diseases following Prednisolone Free Transplant with Low Dose Rituximab and ATG Induction and Protocol Biopsies Vivek Pathak. *Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil-Nadu, India.*

Background: The purpose of this study is to document the incidence of post transplant glomerulonephritis in a steroid free protocol and other recurrent renal diseases leading to graft loss.

Methods: 883 patients, who underwent renal transplantation at our institute in nine years and eight months since July 2005 till March 2015 were studied. Thymoglobulin was used for induction at a dose of 1.5mg/kgm 3 doses. Rituximab 200 mg was given before transplant to those patients who were considered to be at high risk for rejection. Maintenance immunosuppression was Tacrolimus and Mycophenolate mofetil. Prednisolone was rapidly discontinued by fifth post operative day. All patients underwent protocol biopsies at 3 months, 1 year and 5 years and indicated biopsies whenever required. The total number of biopsies was 2928. Discussion Our results show only 1% graft loss due to cumulative recurrent Glomerulonephritis at nearly 10 years. Our figures could be low due to Thymoglobulin induction therapy. We could prevent graft loss due to recurrent FSGS by achieving complete or partial remission by using Rituximab in 15/19(79%) patients.



Results: The number in glomerulonephritis group was 412 of which 158 were biopsy proven and others suspected on clinical grounds. The histologically confirmed recurrent IgA was seen in 23 patients and 3 lost the graft. Prednisolone was added to this group. Recurrent FSGS was observed in 21 patients of which 3 lost the graft. We saw 1 case each of recurrent DDS, DHA crystallopathy, de novo anti GBM disease and post infectious glomerulonephritis.

Conclusions: Our aggressive biopsy policy detected recurrence at a stage of urinary abnormalities. We use Rituximab to treat FSGS to reduce the graft loss. Unique induction policy probably had a protective effect and thus recurrent glomerulonephritis is lower than published literature.

SA-PO1078

Post-Transplant Focal Segmental Glomerulosclerosis Recurrence Among Patients with Native Kidney Collapsing Variant: A Single-Center Retrospective Cohort Study Panupong Hansrivijit,^{1,2} Katherine D. Westreich,¹ Jonathan Alexander Miles,¹ Evan Zeitler,¹ Maria E. Ferris,¹ Randal K. Detwiler.¹ ¹Univ of North Carolina, Chapel Hill, NC; ²Chulalongkorn Univ, Bangkok, Thailand.

Background: Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of end-stage kidney disease (ESKD), and is known to recur in renal transplant grafts. The collapsing variant of FSGS (CvFSGS) is clinically distinct from other variants: it has a stronger association with African-American race, more severe proteinuria, and rapid progression to ESKD. The impact of native FSGS subtype on post-transplant FSGS recurrence rate and subtype is not known.

Methods: Clinical and pathological records were reviewed for renal transplant recipients at UNC between 2000 and 2014 with FSGS as the cause of ESKD. Native FSGS subtype was dichotomized into CvFSGS and FSGS-Other. Baseline demographics (sex, age, and race), and rates and subtypes of post-transplant FSGS recurrence were compared between the two groups.

Results: Of 879 patients reviewed, FSGS was the cause of ESKD in 101. Among this subgroup, mean age at time of transplant was 45±17 years; 62% male; 50% non-Hispanic black, 45% non-Hispanic white, and 5% Hispanic. Ten patients (10%) had CvFSGS as the native lesion. Over a mean follow-up time of 2.4 years, the overall rate of recurrent FSGS was 34%. Compared to those with native FSGS-Other, patients with native CvFSGS had a higher rate of post-transplant FSGS of any type (50% vs 31%, RR 1.6), and were also more likely to have collapsing variant as the recurrent lesion (60% vs 11%, RR 5.5).

Native lesion (n)	Recurrence n (%)	Recurrent lesion n (%)	
		CvFSGS	FSGS-Other
CvFSGS (10)	5 (50%)	3 (60%)	2 (40%)
FSGS-Other (91)	28 (31%)	3 (11%)	25 (89%)
Total (101)	33 (34%)	6 (18%)	27 (82%)

Conclusions: In a population of predominantly black and Hispanic patients in the Southeastern US, native CvFSGS predicts a 60% higher post-transplant FSGS recurrence rate, and the recurrent lesion is likely to be CvFSGS. However, 11% of patients with native FSGS-Other developed de novo CvFSGS post-transplant. Further study of this cohort will determine the predictive power of native and recurrent CvFSGS with regard to clinical outcomes.

SA-PO1079

Pre-Transplant Rituximab in Recurrent Focal Segmental Glomerulosclerosis John Manllo,¹ Dany Matar,¹ Sami Alasfar,¹ Jochen Reiser,² Nada Alachkar.¹ ¹Johns Hopkins Univ; ²Rush Univ.

Background: Focal segmental glomerulosclerosis (FSGS) recurs in 30-40% of patients after kidney transplant (Tx). Rituximab was suggested to have cross-reactivity with podocyte sphingomyelin-phosphodiesterase-acid-like-3b (SMPDL-3b), which was found

to be reduced in post perfusion biopsies of kidney Tx recipients who later on developed recurrent (r)FSGS. However, the use of rituximab to prevent rFSGS remains controversial. In this study, we assessed the efficacy of pre-Tx rituximab in preventing or delaying the recurrence of FSGS.

Methods: We enrolled 56 adult patients, 50 with biopsy proven FSGS and 6 with a pre-Tx course highly suggestive of FSGS. Patients underwent kidney transplant between 2008-2014. We compared FSGS recurrence and allograft survival between recipients who received rituximab and those who did not.

Results: Mean time of follow-up was 28.6 months. 24 patients received rituximab (table 1). 35 patients developed rFSGS, 17 (48%) of them received rituximab. Of the 21 who did not develop recurrence, 7 patients (33%) received rituximab. This difference was not statistically different (p=0.26). The time from Tx to rFSGS in the patients who received rituximab was 9.4 ±3.4 vs 8.7 ±3.7 months in patients who did not receive rituximab (p=0.7). The mean and standard deviation (SD) of eGFR at the most recent follow-up in the patients with rFSGS who received rituximab was 42 ±28 versus 39 ±21 mL/min/1.73m² in those who did not receive it, respectively (p=0.74). There was no difference in allograft survival in the two groups.

Conclusions: Our data showed that pre-transplant rituximab did not decrease the incidence or delayed the development of recurrent FSGS, and did not improve allograft survival.

	Pre-Tx rituximab (n=24)	No-rituximab (n=32)	P-value
Mean Age at Diagnosis (SD), yrs	28.5 (±18)	33.2 (±15)	0.33
Mean Time from Dx to RRT (SD), yrs	4.8 (±5.6)	10.1 (±11.5)	0.03
Mean of cumulative dialysis duration (SD), yrs	4.8 (±3.8)	2.9 (±3.7)	0.07
Mean Age at current tx (SD), yrs	43 (±13)	44.8 (±13)	0.62
Male, n (%)	12 (50%)	16 (50%)	1
Prior tx, n (%)	13 (54%)	6 (18%)	0.006
ABO Incompatible Tx, n (%)	5 (20%)	3 (9%)	0.22
Allograft failure, n (%)	3(12%)	3(9%)	0.91

SA-PO1080

Role of Plasmapheresis in Post-Transplant Focal Segmental Glomerulosclerosis Sami Alasfar,¹ Dany Matar,² John Manllo,¹ Jochen Reiser,³ Nada Alachkar.¹ ¹ Johns Hopkins Univ, Baltimore, MD; ²McKinsey & Company, Washington, DC; ³Rush Univ, Chicago, IL.

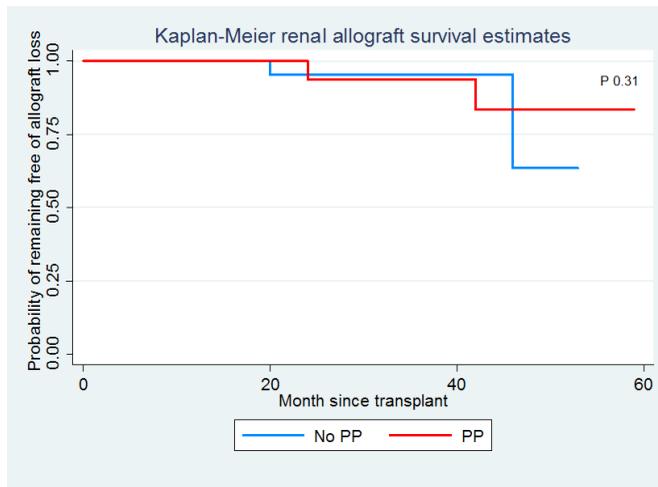
Background: Focal segmental glomerulosclerosis (FSGS) commonly recurs after kidney transplant(Tx). This is attributed to the presence of a circulating permeability factor that may be removed or diminished by plasmapheresis (PP). In this study, we assessed the efficacy of PP in prevention and treatment of post-Tx (r)FSGS.

Methods: We prospectively enrolled 56 Tx-patients with biopsy proven FSGS(50) or de novo FSGS with a pre-Tx course suggestive of FSGS(6); patients were transplanted between 2008-2014. We compared between the preventive and non-preventive PP groups.

Results: Mean time of follow-up was 28 months. Differences between the 2 groups are as following:

	Preventive PP(n26)	No PP(n30)	P
Male(n)	15	13	0.2
White(n)	17	14	0.23
Time from FSGS diagnosis to renal replacement initiation,y(SD)	6.1(8.6)	10.1(9.1)	0.04
Prior Tx(n)	11	8	0.21
Living donor(n)	21	12	0.008
Induction with rATG(n)	25	26	0.23
rFSGS (n)	19	16	0.12
Time to rFSGS, month(SD)	7.7(3.7)	10.5(3.5)	0.6
Mean of most recent UPC, g/g(SD)	2.7(0.5)	0.2(0.1)	0.001

rFSGS developed in 35 patients (62%); of whom preventive PP was performed in 19. Out of the 21 cases that did not develop rFSGS, 7 received PP (P=0.1). Patients who received preventive PP had a shorter time from FSGS diagnosis to ESRD compared to those who did not [(6.1±8.6 yr vs 10.1±9.1 yr (p 0.047)]. 33 out of the 35 patients (95%) with rFSGS received therapeutic PP, and 24 also received anti-CD20 therapy. Only 5(15%) did not respond; 2 lost their grafts. Of the 28 who responded, 14 (50%) subsequently relapsed. 71% of the relapses responded to a second course of PP; only 4 lost their grafts. Kaplan-Meier allograft survival in both groups is shown in figure 1.



Conclusions: Preventive PP does not reduce the incidence or delay the development of rFSGS. However, PP remains an effective therapy for post-transplant FSGS.

SA-PO1081

Post-Transplant Thrombotic Microangiopathy: A Single Center Experience Cinthia Montenegro Teixeira,¹ Igor Gouveia Pietrobon,¹ Andre Caires Alvino Lima,¹ Gianna Mastroianni-kirsztajn,^{1,2} Laila Almeida Viana,¹ J. Medina-Pestana,^{1,2} Helio Tedesco Silva.^{1,2} ¹Hospital do Rim- Fundação Oswaldo Ramos, Sao Paulo, Brazil; ²Univ Federal de Sao Paulo, Sao Paulo, Brazil.

Background: Thrombotic microangiopathy (TMA) occurs in 1-15% of kidney transplant allografts and predicts poor outcomes.

Methods: We reviewed 35 cases of TMA in the kidney allograft diagnosed at our institution between 2011-2015.

Results: The mean age was 39±14 years with 18 (51%) women. Three (9%) patients were recipients of simultaneous pancreas-kidney transplant. Among the recipients of kidney transplant alone, 21 (66%) received deceased donor grafts. The cause of end stage renal disease was unknown (37%), chronic glomerulonephritis (31%), obstructive uropathy (11%), diabetes (9%), hemolytic uremic syndrome (3%) or others (9%). Induction with thymoglobulin or basiliximab was performed in 24 (63%) patients. Maintenance immunosuppression was prednisone (PRED), tacrolimus (TAC), and azathioprine in 15 (43%), PRED, TAC and mycophenolate sodium in 12 (37%) and PRED, TAC and everolimus in 3 (9%) patients. Patients were diagnosed with TMA at a median of 71 days (range: 5-1645) from transplant, wherein 37% patients developed TMA within 1 month of transplantation and 31% after 1 year. Mean serum creatinine was 4.5±3.3 mg/dL and 13 (47%) patients needed renal replacement therapy after TMA diagnosis. TMA was renal-limited in 23 (66%) patients. Concomitant acute rejection was present in 12 (34%) cases and cellular rejection was the most common (92%) type of rejection related to TMA. Cytomegalovirus infection occurred in 5 (14%) and other infections were present in 19 (54%) patients. Following diagnosis of TMA, calcineurin inhibitor (CNI) withdrawal was the first step in the management of 22 (63%) patients and 8 (23%) also received fresh frozen plasma (FFP) and/or plasmapheresis. The mean follow-up was 375 days (range: 2-4840); 22 (62%) patients had improvement or stabilization of renal function and 11 patients (31%) had allograft failure.

Conclusions: High clinical suspicion is essential for early diagnosis of TMA after kidney transplant. Withdrawal of CNI and treatment of concomitant rejections and infections contribute to renal function maintenance.

Funding: Private Foundation Support

SA-PO1082

Outcome After Eculizumab Therapy to Prevent Recurrence of Atypical Hemolytic Uremic Syndrome: Experience in Eleven Renal Transplant Recipients Charlene Levi,^{1,2} Veronique Fremeaux-bacchi,^{3,2} Anne Scemla,¹ Julien Zuber,^{1,2} Christophe M. Legendre,^{1,2} Rebecca Sberro-Soussan.¹ ¹Dept of Renal Transplantation, Assistance Publique-Hôpitaux de Paris, Hôpital Necker, Paris, France; ²Medicine Faculty, Paris Descartes Univ, Paris, France; ³Dept of Immunology, Assistance Publique-Hôpitaux de Paris, Hôpital Georges Pompidou, Paris, France.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. aHUS is associated with histological lesions of thrombotic microangiopathy (TMA) that mainly leads to graft loss. The successful use of Eculizumab (Ecu) to prevent or to treat post-transplantation aHUS recurrence has been scarcely reported. In this study, we describe 11 patients who received a renal transplantation for aHUS and who were treated by Ecu after renal transplantation.

Methods: Eleven renal transplants recipients, with aHUS on their native kidney, received Ecu at our center between 2010 and 2015. Nine patients received prophylactic

Ecu at day 0. Two were treated at time of recurrence (day 6 and 25). We reviewed clinical, genetic testing and histological data, and posttransplant course. Mean follow-up was 21.6±19 months.

Results: Five patients had at least one previous transplantation that failed secondary to recurrent aHUS. A genetic mutation was identified in ten patients (H factor (4); I factor (2), CFH-CFH1 hybrid gene (1); C3 (1), CFHR1 deletion and anti-H-factor antibody (2)). There was no graft loss and mean serum creatinine was 135±60mmol/l at last follow-up. No patient experienced biological TMA recurrence under treatment. We found transient histological lesions in the 2 patients with later Ecu introduction. Three antibody mediated rejections (AMR) occurred during treatment including one associated with TMA lesions.

Conclusions: These data confirm that Ecu is highly effective to prevent post-transplantation aHUS recurrence, without graft loss and with a good renal function. However, Ecu doesn't prevent AMR. The best treatment duration remains to be defined.

SA-PO1083

Recurrence of Scleroderma Renal Crisis After Renal Transplant Is Associated with Decreased Rates of Graft Survival and Earlier Graft Failure Andrew A. Collins, Donald A. Molony. *Internal Medicine, UT Health Houston, Houston, TX.*

Background: The recurrence of Scleroderma Renal Crisis (SRC) after renal transplant has been previously described though its effects on outcomes and allograft survival are uncertain. Prior estimates suggest a recurrence rate of 20-50% (Pham et al, American Journal of Transplantation 2005, 5:2565-2569). Such rates of recurrence if leading to graft failure will have important implications. This study was conducted to better define the probability of recurrence and understand its impact on allograft and patient survival.

Methods: We identified all cases of renal transplantation for patients with SRC and all cases of disease recurrence in the UNOS database from 1987 to 2014. We analyzed the impact of recurrence on graft survival and compared this to outcomes of patients with other renal diseases: SLE, FSGS, and HUS.

Results: 492 patients were identified as having SRC as their primary diagnosis. Of those, 5.28% (26) had documented disease recurrence, which was similar to those with SLE (2.59%), FSGS (7.38%), and HUS (8.71%). Graft failure for any reason excluding death occurred in 80.8% (21) of patients with recurrence, compared to 24.5% (114) of those without recurrence (p=0.00). Recurrent disease accounted for 11.9% (16) of graft failures in SRC, compared to 6.10% in patients with SLE as the cause of ESRD, 16.4% with FSGS, and 20.9% with HUS. The 5 year graft survival rates were similar: 68.7%, 63.2%, 67.8%, and 57.1% for SRC, SLE, FSGS, and HUS, respectively. SRC recurrence was associated with earlier graft loss; graft failure occurred an average of 628 days sooner in the recurrence group compared to non-recurrence, 1072 days versus 1700 (p=0.021). Age, gender, and ethnicity were not associated with an increased risk of recurrence.

Conclusions: Identification of disease recurrence after renal transplantation holds prognostic significance. Both the rate and timing of kidney transplant failure is made more severe by recurrence. Post-transplant recurrence rates for SRC appear to be similar to those observed with SLE, FSGS, and HUS. Monitoring for recurrence of disease in these patients should be part of routine measures to reduce risk of allograft failure.

SA-PO1084

Clinical Characteristics of Recurrent IgA Nephropathy within the First Year After Renal Transplantation: Single Center Study Yasuhiro Otsuka, Daijo Inaguma, Yoshihiko Watarai, Asami Takeda. *Kidney Center, Nagoya Daini Red Cross Hospital, Nagoya, Japan.*

Background: There are a few studies showing that the long-term allograft survival of patients with IgA nephropathy (IgAN) is lower than that of non-IgAN, indicating that the cause of lower graft survival is recurrence of IgAN. There have been no large, prospective studies defining the risk factors contributing to the development of recurrent IgAN, and preventive therapy for recurrent IgAN is unknown.

Methods: Retrospective data was collected from 2008 to 2013 on 61 consecutive biopsy-proven IgAN patients who underwent renal transplantation (RTx) in a single center, excluding one case of medication nonadherence. Protocol biopsies were obtained one hour, three weeks, six months and one year after RTx. Recurrent IgAN (rIgAN) is defined as positive for IgA in mesangial area and previously negative for IgA in immunofluorescence study.

Results: Of 61 patients, 7 had rIgAN within the first year after renal transplantation. There were no significant differences between rIgAN group and NOT rIgAN group in recipient age (mean±SD) (39.1±18.6, 41.8±12.3)years, sex (6M;1F, 31M;23F), donor age (55.0±8.5, 56.3±9.8)years, diabetes mellitus (2, 8)cases, PEKT (3, 23)cases, living-related donor kidney (5, 33)cases, immunosuppressants, tonsillectomy before transplantation (4, 11) cases, ABO incompatible (0, 18)cases, HLA matching, HLA alleles in recipient including HLA-B35, DR4, B8, DR3, serum IgA concentration (263.0±66.4, 254.4±105.0)mg/dL, and urinary protein (0.57±1.29, 0.07±0.13)g/day. Duration of dialysis before transplantation (months) was significantly shorter in rIgAN group (11.1±20.3 vs 34.9±54.9, p=0.0383, Fisher's exact test). Urine occult blood was also significantly higher in rIgAN group (p=0.000841, Mann-Whitney U test).

Conclusions: Albeit PEKT was not risk factor for recurrence of IgAN in this study, short-duration dialysis before transplantation could be novel risk factor for recurrence of IgAN. Further analysis is needed to determine risk factors for rIgAN and to establish preventive therapy for rIgAN for better graft survival.

SA-PO1085

An Investigation of 13 Cases of Membranous Nephropathy of the Donor Origin Accidentally Detected by 0-h Renal Biopsy During Kidney Transplantation Kohei Unagami,¹ Masayoshi Okumi,² Anri Sawada,¹ Daisuke Toki,² Taichi Kanazawa,² Yasuyuki Sato,¹ Jumpei Hasegawa,³ Kazuya Omoto,² Hidetoshi Ishigooka,² Kazuma Tsujimura,² Tomokazu Shimizu,² Masashi Inui,² Hideki Ishida,² Kazunari Tanabe,² Kosaku Nitta.² ¹*Nephrology, Tokyo Women's Medical Univ;* ²*Urology, Tokyo Women's Medical Univ;* ³*Nephrology, Ohkubo Hospital.*

Background: Membranous Nephropathy (MN) is a type of glomerulonephritis characterized by thickening of the glomerular basement membrane with immunoglobulin deposition. Proteinuria is a primary symptom, and the condition may sometimes present as nephrotic syndrome. MN is usually diagnosed by a renal biopsy. Therefore, without symptoms, such as proteinuria, hematuria or renal dysfunction, MN is rarely suspected. Here we describe 13 cases of MN of donor origin that were accidentally detected by 0-h renal biopsy, which is routinely performed at the time of kidney transplantation in our hospital.

Methods: During the period between January 1995 and April 2015, 13 cases of MN of donor origin were accidentally detected by 0-h renal biopsy during kidney transplantation. We evaluated the histopathological characteristics of these cases and the clinical course of donors and recipients.

Results: MN virus was disappeared in 7 recipients by transplanted renal biopsy at 1035.1 ± 776.2 days after transplantation. Three donors have past histories such as hepatitis B past infection, prostatic cancer, or the internal past taking of thiamazole, all of which are well known causes of secondary MN. In the pre-transplantation evaluation, two donors had hematuria, however, all donors were negative for proteinuria and had normal kidney function (serum Cr 0.92 ± 0.25mg/dl, eGFR 70.1 ± 20.2ml/min/1.73m²). After follow-up of 972.3 ± 916.5 days after operation, significant proteinuria, hematuria and decreased kidney function (serum Cre 1.17 ± 0.44mg/dl, eGFR 50.0 ± 20.0 ml/min/1.73m²) were not observed. In terms of malignancies, one donor had undergone a prostatectomy for prostatic cancer before transplantation.

Conclusions: Among cases of MN of the donated kidney accidentally detected in the 0-h renal biopsy, several donors did not have symptoms such as proteinuria and hematuria.

SA-PO1086

The Occurrence of Post-Transplant Malignancies Among Kidney Transplant Recipients Is Not Associated with the Level of Tacrolimus Exposure Over Time Shelly Lichtenberg, Ruth Rahamimov, Avry Chagnac, Benaya Rozen-zvi. *Nephrology, Rabin Medical Center, Petah Tikva, Israel.*

Background: Immunosuppressive therapy plays a major role in the development of post-transplant cancer. In this case-control study of kidney transplant recipients, we investigated whether the occurrence of post-transplant cancer is associated with the level of tacrolimus exposure over time.

Methods: We screened the Rabin Medical Center registry data base for adults who received kidney transplants during the years 2001 to 2014, and developed post-transplant nonskin cancer. Those patients were matched with controls by sex, age, type of induction therapy, time of transplantation and length of follow-up. All patients included in the study received a maintenance immunosuppression with tacrolimus, micophenolate mofetil and corticosteroids. Exposure to tacrolimus was estimated using all blood level values of tacrolimus measured until time of cancer diagnosis. The time-averaged value of tacrolimus blood levels was calculated as the area under the curve divided by time at 1, 6 and 12 months after transplantation, and at the time of cancer diagnosis.

Results: 32 patients who met the inclusion criteria developed nonskin cancer. They were matched with 64 controls. The time-averaged tacrolimus blood level at time of cancer diagnosis was 7.97±1.37 ng/mL in the cancer group and 7.9±1.32 ng/mL in the control group (p=0.8). The time-averaged tacrolimus blood levels at 1, 6 and 12 months were 9.86±1.94 ng/mL in the cancer and 9.98±1.9 ng/mL in the control groups (p=0.97), 9.85±2.3 ng/mL in the cancer and 9.97±1.14 ng/mL in the control groups (p=0.75) and 8.95±2.03 ng/mL in the cancer and 8.96±1.04 ng/mL in the control groups (p=0.97), respectively. By multiple logistic regression, only smoking status was associated with cancer. The time-averaged tacrolimus blood level at time of cancer diagnosis was not significantly associated with cancer after adjustment for this variable (Hazard ratio=1.08 per ng/mL, 95% confidence interval - 0.78 to 1.5, p=0.65).

Conclusions: The development of de novo nonskin cancer after kidney transplantation was not associated with the level of tacrolimus exposure over time.

SA-PO1087

Renal Cell Carcinoma Post Renal Transplant: The Case for Post-Transplant Ultrasound Surveillance William M. Bennett, Alison M. Garre, Thomas D. Batiuk, Kevin M. Mcevoy, Erica Simonich. *Legacy Transplant Services, Legacy Good Samaritan Medical Center, Portland, OR.*

Background: Following successful renal transplantation, there is an increased relative risk of renal cell carcinoma in retained native kidneys. Stimulated by a case of widespread metastatic cancer nine months after transplant with a normal pre-transplant ultrasound, we began routine 6-18 month post-transplant surveillance on all recipients except those with known autosomal dominant polycystic kidney disease.

Methods: 128 consecutive patients were entered into the study. At 6-12 months post-transplant.

Results: 16 suspicious masses were detected (12.5%). Of these only 9 had evidence of acquired cystic disease (ACD) (four or more cysts) pre-transplant. The remainder had normal pre-transplant scans showing only small contracted kidneys or less than the required number of cysts to make a diagnosis of acquired cystic disease. We are following 14 of these patients with scans every 6-12 months to detect growth in newly discovered, less than 1 cm solid lesions. We have found 2 patients in which frank renal cell cancers were discovered. We have now adopted an annual screening process for all post-transplant patients at their one-year post-transplant visit.

Conclusions: Routine screening of native kidneys post-transplant appears critical to detect renal cell carcinoma at a stage early enough to achieve a cure by nephrectomy.

SA-PO1088

Non-Melanoma Skin Cancer Mortality in Kidney Transplant Recipients

Michael Thomas Burke,¹ Annie-Claire Nadeau-Fredette,¹ Carmel M. Hawley,¹ Elaine M. Pascoe,⁴ Stephen P. McDonald,² Sunil V. Badve,¹ David W. Johnson,¹ Adele Green,³ Robert Peter Carroll,² Nicole Isabel.¹ ¹Dept of Renal Medicine, The Univ of Queensland, Princess Alexandra Hospital, Brisbane; ²Central Northern Adelaide Renal and Transplantation Services, Adelaide; ³Cancer and Population Studies Group, Queensland Inst of Medical Research, Brisbane; ⁴School of Medicine, The Univ of Queensland, Brisbane.

Background: Non-melanoma skin cancer (NMSC) frequently occurs in kidney transplant recipients (KTRs). However, the frequency of, and risk factors for NMSC mortality in KTRs are poorly characterised.

Methods: Aims: To determine the proportion and predictors of fatal NMSC in KTRs. This cohort study included all KTRs transplanted in Australia and New Zealand between 1980 and 2013, using Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry data. A multivariable competing-risk survival analysis was used to calculate risk factors for fatal NMSC in KTRs.

Results: During the study, 21875 transplant episodes occurred in 19344 patients. Of the 6780 patients who subsequently died, 231 (3.4%) died from NMSC. Of these, 172 (74%) were male, 226 (98%) were Caucasian, 219 (95%) were first graft recipients and 213 (92%) died with a functioning graft. Amongst first graft KTRs who died from NMSC, the mean age at transplantation was 48.8 +/- 13.7 years and the mean age at death was 61.8 +/- 11.1 years. Male sex (HR 2.0, 95% CI, 1.48-2.74); Caucasian ethnicity (HR 5.31, 95% CI, 2.15-13.11) and pre-transplant skin cancer (HR 3.79, 95% CI, 2.38-6.04) were associated with NMSC mortality. Age at transplantation and multiple kidney transplants had time-dependent associations for NMSC mortality with the 5-year post-transplant HR 1.08 per year (95% CI, 1.06-1.1) and 2.90 (95% CI, 1.39-6.05); and the 15-year post transplant HR 1.03 per year (95% CI, 1.02-1.04) and 1.29 (95% CI, 0.66-2.55) respectively.

Conclusions: NMSC is an important contributor to mortality in KTRs. Risk factors for mortality from NMSC include male sex, Caucasian ethnicity, pre-transplant skin cancer, multiple kidney transplants and older age at transplantation.

SA-PO1089

NFAT-Regulated Gene Expression in Patients Developing Non-Melanoma Skin Cancer

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Background: After transplantation the risk of non-melanoma skin cancer (NMSC) is significantly increased. Immunosuppression with calcineurin-inhibitors (CNIs) is associated with the development of NMSC. Association to the individual immunosuppressive loads of CNIs assessed by residual NFAT-regulated gene expression was investigated in renal allograft recipients.

Methods: Renal allograft recipients from the Department of Nephrology, University Hospital Heidelberg, Germany, were included. All patients had a regular annual skin examination. Residual expression of NFAT-regulated genes (IL-2, IFN γ , GM-CSF) in PMA/ionomycin-stimulated peripheral blood was measured by quantitative real-time PCR at predose and 2h after Cyclosporin A (CsA) intake.

Results: 258 renal allograft recipients were enrolled (160 male, age 51±14y). Of these patients 75 allograft recipients developed NMSCs after renal transplantation (29.1%). The following NMSCs were histologically confirmed: 36 basal cell carcinoma, 34 squamous cell carcinoma, 33 actinic keratosis, 27 Bowen disease, 8 kerato-acanthoma. As risk factors to develop NMSC were identified: age 60 years, skin type (Fitzpatrick 1 and 2), and load of immunosuppression. NFAT-regulated gene expression was significantly lower in patients who developed NMSCs compared to patients without NMSCs (8.3±6.5 vs. 12.7±12.8%, p<0.001). Squamous cell carcinoma and actinic keratosis were significantly associated with a high inhibition of IL-2 and IFN γ . Patients with basal cell carcinoma and Bowen disease showed a general low expression of NFAT-regulated gene expression. However, in patients with kerato-acanthoma no significant inhibition of NFAT-regulated gene expression could be detected.

Conclusions: The immunosuppressive load contributed to the risk of NMSCs. NFAT-regulated gene expression was significantly inhibited in patients developing NMSCs. Monitoring of NFAT-regulated gene expression in CNI treated transplant recipients provides an individual profile of response to CNIs and is a useful tool for an individual immunosuppression with respect to safety and toxicity.

SA-PO1090

T Cell Immunosenescence Is a Stable and Strongly Performing Predictor of Recurrent Squamous Cell Carcinoma in High-Risk Renal Transplant Recipients

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Background: Cutaneous squamous cell carcinoma (SCC) is a major cause of morbidity in renal transplant recipients (RTR). 50% of RTR develop recurrent SCC, but current methods to stratify this risk are limited. Screening thus represents a major healthcare burden. We hypothesised RTR demonstrating increased immunosenescence, associated with ageing and increased infection risk, would be at high risk of recurrent SCC.

Methods: RTR at high clinical risk of SCC were recruited. Predictive value of previously published risk equations, clinical phenotype and immunosenescence (assessed by CD57 expression on CD8+ T cells, using FACS) for SCC development were compared using Cox regression. CMV serology was assessed at enrolment.

Results: 117 RTR participated. Half had a history of previous SCC. Median follow-up was 594 days. CD57 expression on CD8+ T cells correlated with other established markers of immunosenescence. RTR who developed SCC during follow-up and had >50% CD57-expressing CD8+ T cells (CD57hi) were 2.6 (95% CI: 1.0-6.7, p=0.04) times more likely to develop a further SCC (median time between SCC: 449 days in CD57hi cohort, not reached in CD57lo). Previously defined clinical risk scores provided no predictive value for SCC in this cohort when adjusted for age at enrolment. CD8+ T cells from CD57hi RTR displayed normal cytotoxic and cytokine-secreting function. CD57hi phenotype was not associated with greater CD4+ Treg number in peripheral blood. CMV IgG titres correlated with CD57 percentage but CMV seropositivity was not, in itself, a predictor of SCC development. CD57 expression was stable over a one year period and with SCC development.

Conclusions: Immunosenescence, partly driven by CMV and identified by the CD57hi phenotype, is a stronger predictor of SCC in high-risk RTR than previously identified clinical scores. Quantifying CD57 expression on CD8+ T cells may enable stratification of RTR at increased risk of recurrent SCC, who may benefit from increased screening and early reduction of immunosuppression.

Funding: Private Foundation Support

PUB001

Role of Toll-Like Receptors in Aristolochic Acid Nephrotoxicity

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Background: Studies demonstrated that aristolochic acid (AA) is toxic to renal tubular epithelium and carcinogenic to urethral epithelium. Although the exact extent of AA nephropathy (AAN) is unknown, case series have been reported in throughout the world and it has been implicated in the etiology of Balkan endemic nephritis (BEN) suggesting that this is a global health problem. The precise mechanisms of AA nephrotoxicity are not known. We investigated the role of Toll-like receptors (TLRs) in the pathophysiology of AAN using human renal proximal tubule epithelial cells (RPTECs).

Methods: Confluent RPTECs were exposed to AA (30 μ M – 480 μ M) for 24 – 48 hr and cytotoxicity was measured using lactate dehydrogenase (LDH) assay. RNA and protein were isolated from AA-exposed and unexposed RPTECs. Real time RT-PCR was performed for various gene primers to evaluate the role of innate immunity in AAN development.

Results: At 240 μ M after 48 hr exposure, AA induced significant toxicity in RPTECs as measured by LDH release in the culture medium and significant cell injury was observed morphologically. AA significantly increased mRNA expression of acute kidney injury (AKI) biomarker neutrophil gelatinase-associated lipocalin (NGAL), but at the same time significantly decreased the expression of another AKI biomarker kidney injury molecule 1 (KIM-1). AA also significantly upregulated the expression of prominent AKI-related TLRs (TLR2, TLR4 and TLR6) and their adaptor molecules (MyD88 and TICAM-1) followed by the activation of pro-inflammatory cytokines (IL-6 and TNF- α) and the tumor suppressor protein and a biomarker for apoptosis, p53, in the down-stream signaling pathways of TLRs. AA also significantly upregulated expression of multi drug resistant family gene MDR1 in RPTECs.

Conclusions: AA is toxic to RPTECs and restricts cell growth. NGAL but not KIM-1 could be a diagnostic biomarker for AAN. AKI prominent TLR2 and TLR4 could be potential candidates for therapeutic target in developing new strategies for AAN and BEN treatment.

PUB002

A Case of Severe Symptomatic Iatrogenic Hypermagnesemia

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Background: Hypermagnesemia is an uncommon but a potentially life threatening condition. Symptoms may develop in patients with acute kidney injury (AKI) or chronic kidney disease with the administration of pharmacologic dose of magnesium (Mg), and with use of oral laxatives or magnesium containing enemas.

Methods: A 30-year-old African American man with baseline Cr of 1, admitted for management of multiple fractures, subdural hemorrhage and traumatic brain injury sustained in a motor vehicle accident, suddenly became hypotensive and developed AKI. UOP declined from 2-3L/day on admission to 700 ml over the next 24 hours. He became areflexic and developed ARDS, with increasing FiO2 requirements. Repeat laboratory data showed Cr 3.9, hemoglobin 6.9 and Mg 9.5 mg/dl. Review of his chart revealed he had received a total of 8.75g of magnesium citrate through enemas on the previous day. Aggressive resuscitation was started, including IV calcium, but he continued to require multiple pressors. Hypermagnesemia was presumed to be the cause of his ongoing hemodynamic instability. Intermittent hemodialysis was initiated for 2 hours to rapidly remove magnesium and he was then switched to CVVHD for continuous magnesium removal. Within 12 hours of RRT, pressor requirements decreased, UOP improved to 50-60 ml/hr and Mg levels ranged between 2-3 mg/dl. CVVHD was discontinued after 72 hrs and the patient had complete renal recovery to his baseline Cr of 1.

Results: Severe symptomatic hypermagnesemia can develop even with small doses of Mg containing laxatives. It prevents presynaptic acetylcholine release resulting in blockade of neuromuscular transmission. Clinical features of Mg toxicity range from delayed deep tendon reflexes, flaccid paralysis, respiratory failure, to hypotension, bradycardia, complete heart block and cardiac arrest. Management includes rapid supportive measures, fluids, IV calcium, loop diuretics. Urgent hemodialysis can rapidly reverse shock and respiratory failure preventing significant morbidity and mortality.

Conclusions: In summary, we report a case of severe hypermagnesemia, in the setting of AKI, presenting with shock and respiratory failure, requiring RRT.

PUB003

Ischemic and Non-Ischemic Acute Kidney Injury Cause Gut Damage

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Background: Chronic uremia induced gut injury has been well documented in a number of studies. However, remote effects of acute kidney injury (AKI) on the intestine are far less investigated. Here we studied whether the gut also suffers damage during induction of renal ischemia-reperfusion in rats and compared this to bilateral nephrectomy.

Methods: To test our hypothesis, six groups of SD rats (n=6 in each group) were studied: 1) sham operation for 6h; 2) ischemic AKI for 6h (60 min of renal pedicle clamping and then reperfusion for 6h); 3) bilateral nephrectomy for 6h; 4) sham operation for 24h; 5) ischemic AKI for 24h (60 min of renal pedicle clamping and then reperfusion for 24h); 6)

bilateral nephrectomy for 24h. Ileum and blood were collected. The damage of gut mucosa was assessed by histological staining. Malondialdehyde (MDA) and apoptosis of the ileum were measured to determine the underlying mechanism of the AKI-induced gut injury.

Results: We found histological evidence of ileum injury following both ischemia and bilateral nephrectomy. MDA, an index of lipid peroxidation, increased in both the renal ischemia and nephrectomy groups, suggesting activation of oxidative stress. Ileum apoptosis, which was quantified by histone-associated DNA fragmentation enzyme-linked immunosorbent assay, were increased after 6 and 24 h of renal ischemia or nephrectomy.

Figure 1. The comparison of damage parameters between different groups

	Sham 6h	RIR 6h	Bilat.neph 6h	Sham 24h	RIR 24h	Bilat.neph 24h
BU(N(mg/dl))	23±7.2	70±14.2*	72±16.2*	22±6.2	70±14.2*	170±44.2*
Scr(mg/dl)	0.5±0.1	1.5±0.3*	1.6±0.4*	0.65±0.1	3.6±0.93*	5.0±0.1*
Ileum MDA(nmol/g pto)	0.3±0.11	1.1±0.12*	1.3±0.13*	0.35±0.12	1.15±0.1*	1.2±1.15*
histone-associated DNA fragmentation(absorbance units/15ug pto)	0.35±0.06	0.6±0.15*	0.65±0.12*	0.35±0.07	0.71±0.06*	0.73±0.08*

*p<0.05 compared with sham 6h; *p<0.05 compared with sham 24h

Conclusions: Our study shows that acute kidney ischemia or renal failure activates oxidative stress and promotes apoptosis, and tissue damage in gut. Whether the AKI induced-gut injury by itself is sufficient to provoke systemic inflammatory response need further investigation.

Funding: Government Support - Non-U.S.

PUB004

Serum from Rats with Acute Kidney Injury Contains Reactive Oxygen Species Generating Activity That Causes Oxidative Stress In Vitro

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Background: The uremic state that is induced by Acute Kidney Injury (AKI) adversely affects multiple organ systems by mechanisms that are still poorly characterized, including through reactive oxygen species (ROS).

Methods: Serum was obtained from rats 24 hrs post ischemia/reperfusion-AKI (50 min bilateral pedicle clamp, AKI serum), and control sera was obtained from rats 24 hrs following SHAM surgery (SHAM serum), or from rats 24 hrs post bilateral nephrectomy (NPHX serum). Serum samples were evaluated for ROS activity with the sensitive Amplex Red H₂O₂ assay. For in vitro assays, NRK cells (normal rat kidney cells, proximal tubular) or rat mesenchymal stem cells (MSC) were cultured in rat serum for 48 hours, and then assayed for gene expression, GSH levels, and oxidative stress markers.

Results: Compared to SHAM or NPHX serum, serum from rats with AKI had increased amplex red activity compared to SHAM and NPHX serum controls. Adding catalase to rat serum reduced—but did not eliminate—the ROS activity of AKI serum in a dose-dependent manner. The ROS generating properties of AKI serum were completely destroyed with strong (90°C for 1 hr) but not mild (45°C for 30 min) heat inactivation. Culturing normal rat kidney cells (NRK, proximal tubular) or rat mesenchymal stem cells (MSC) in 10% AKI serum (compared to SHAM or NPHX serum) resulted in increased oxidative stress, including increased anti-oxidant gene expression (HO-1, catalase), increased GSH levels, and increased cellular ROS activity (CMH₂DCFDA and mitoxox).

Conclusions: At comparable levels of azotemia (AKI vs. NPHX), AKI serum contains ROS generating activity that is heat labile, but that is not blocked by catalase incubation. These results suggest that the injured kidney releases heat-sensitive factors into the blood stream (likely proteins) that generate ROS and may adversely affect renal tissue and distant organs. The Amplex Red H₂O₂ assay provides a useful tool for the determination and mechanistic dissection of the ROS activity found in AKI serum.

Funding: Veterans Administration Support

PUB005

Properdin Deficiency Enhances Renal Ischemia Reperfusion Injury in Mice

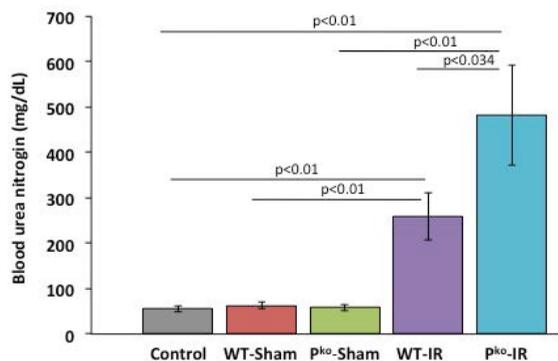
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Background: Properdin is the only positive regulator of the alternative pathway of complement activation via stabilizing C3bBb convertase. Properdin has been detected on proximal tubular epithelial cells associating with proteinuric renal damage. Previous studies showed that mice with combined deficiencies of properdin (P^{ko}), DAF and CD59, the negative regulators of complement activation, had less renal ischemia reperfusion injury (IRI) in 24 hours.

Methods: P^{ko} mice (n=9) and their wildtype (WT) littermates (n=7) were used to assess the role of properdin in renal IRI. Ischaemia was induced by bilateral clamping of the renal pedicle for 30 minutes followed by 72-hour reperfusion using normal (n=2) and sham operated mice (n=4 or 5) as controls.

Results: Renal IRI was successfully induced in the WT and P^{ko} mice with more prominent injury in P^{ko} mice as evidenced in renal function. Serum creatinine was significantly increased after IRI compared with the sham groups, which was further increased

in P^{ko} in relation to WT mice (1.78 ± 0.29 vs. 1.19 ± 0.18 , $P=0.046$) post IRI. Similarly, blood urea nitrogen in IRI mice was higher than the sham animals, with significant increase in P^{ko} in comparison with WT mice.



This difference was supported by histological examination, in which P^{ko} mice showed a worse score of tubulointerstitial damage than WT (2.67 ± 0.26 vs. 1.94 ± 0.22 , $P=0.025$) post IRI.

Conclusions: This study shows, for the first time, that properdin deficiency alone enhances IRI shown by worsened renal function and histology. The underlying mechanisms for these unexpected phenotype are under present investigation.

Funding: Government Support - Non-U.S.

PUB006

Neurogenic Function of Neurons with Renal Afferents Is Altered by Lipopolysaccharides -LPS Kristina Rodionova,¹ Martin Ziemer,¹ Tilmann Ditting,¹ Stefan Karl,¹ Sonja Heinlein,¹ Peter Linz,¹ Peter Reeh,³ Kerstin U. Amann,² Roland Veelken.¹ ¹Dept of Medicine 4 - Nephrology and Hypertension, Universitätsklinikum Erlangen-Nuernberg, Erlangen, Bavaria, Germany; ²Dept of Nephropathology, Universitätsklinikum Erlangen-Nuernberg, Erlangen, Bavaria, Germany; ³Dept of Physiology and Pathophysiology, FAU Erlangen-Nuernberg, Erlangen, Bavaria, Germany.

Background: Renal afferent nerves (RNs) exert complex neurogenic sympathomodulatory and paracrine effects. Recently, we could demonstrate that lipopolysaccharide (LPS) sensitized TRPV1 receptors and increased the release of CGRP from afferent axons in kidney. Hence, we wanted to test the hypothesis that LPS alters firing patterns and acid induced inward currents in cultured neuron sample.

Methods: Dorsal root ganglion neurons (Th11-L2) of rats were incubated with LPS (E. coli O127/B8, 20mg/l) 12h before patch clamp recordings. Inward currents were assessed during stimulation of TRPV1 and ASICs with protons (pH6,9 and 5,0). Current clamp mode was performed at physiological conditions and after 12h of LPS-incubation. Neurons were characterized as tonic, i.e. sustained AP firing or phasic, i.e. <5 APs in response to current injections.

Results: Firing patterns and currents induced by acidic superfusion were studied in 246 neurons. Renal neurons (RNs) exhibited in 59% tonic firing pattern under control conditions. The number of neurons with tonic response was significantly reduced by exposure to LPS (59% vs. 42%, $p<0,05$). Under control conditions 70,8% of RNs exhibited both sustained and transient inward current, whereas 29,2% showed sustained current. LPS exposure significantly increased sustained, i.e. TRPV1 induced current ($-793,18 \pm 66$ pA vs. -1224 ± 200 pA, $p<0,05$) and transient, i.e. ASICs induced inward current even under subthreshold proton stimulation (pH6,9) and could not be enhanced further by pH5,0.

Conclusions: LPS altered the properties of neurons with renal axons in a complex way: while the ease of AP production was significantly decreased, the responsiveness to acidic milieu was increased. In how far these alterations subserve different effects (e.g. decreased sympathetic control, altered peptide release) in experimental sepsis needs further research.

Funding: Other NIH Support - Germany, Bavaria, Erlangen

PUB007

Protective Effect of Nitric Oxide in Aristolochic Acid-Induced Toxic Acute Kidney Injury Inès Jadot,¹ Anne-Emilie Declèves,² Vanessa Colombaro,¹ Blanche Martin,¹ Isabelle Habsch,¹ Eric De Prez,² Joelle L. Nortier,² Nathalie Caron.¹ ¹Molecular Physiology Research Unit - URPHYM, Faculty of Medicine, Univ of Namur, Namur, Belgium; ²Laboratory of Experimental Nephrology, Faculty of Medicine, Univ Libre de Bruxelles, Bruxelles, Belgium.

Background: Aristolochic Acid (AA) nephropathy is a pertinent example of tubulointerstitial (TI) nephritis characterized by an early phase of acute kidney injury (AKI) leading to progressive fibrosis and chronic kidney disease (CKD). Nitric oxide (NO) has been shown to play a critical role in the AKI-to-CKD transition. Here, the AAN model was used to determine the role of NO in this process, focusing on the acute phase.

Methods: C57BL/6J male mice were randomly subjected to daily i.p. injection of control solution or AAI (3,5mg/kg) for 4 days and L-Arginine (L-Arg; substrate for NO synthesis) was supplemented in drinking water (5%) until mice were euthanized, 5 days after the beginning of AAI injections.

Results: At day 5, AA-treated mice displayed polyuria, increased plasma creatinine level and proteinuria. In addition, histological analyses revealed severe proximal tubular cell necrosis, renal inflammation and increased oxidative stress in AA-treated mice. These changes were associated with a significant reduction of NO bioavailability, as attested by urinary NOx and cGMP levels. L-Arg supplementation in AA-treated mice significantly improved kidney function, as reported by a significant reduction in urine volume, plasma creatinine level and proteinuria. Moreover, L-Arg treatment resulted in a significant reduction of tubular cell necrosis, renal inflammation and oxidative stress. These were concomitant to normalized NO levels.

Conclusions: Our findings demonstrated that sustaining NO bioavailability due to L-Arg supplementation improve the renal outcome of AA-induced AKI phase. Further investigations are ongoing to determine whether increasing NO bioavailability can also prevent chronic injuries in the AAN model.

PUB008

The Study of Curcumin-Loaded Nanoparticles against Renal Ischemia-Reperfusion Injury Function and Mechanism Yong Xu, Lili Zhong. Dept of Nephrology, Huaian Second Hospital, Huaian, Jiang Su, China.

Background: To study the effects of curcumin-loaded nanoparticles against ischemia-reperfusion renal injury, and to investigate its mechanism.

Methods: Synthetically controlled releasing curcumin-loaded nanoparticles by amphiphilic mPEG-PCL block copolymers and cultivated renal tubular epithelial cell (cell line HK-2) in vitro. HK-2 cells were divided into four groups: Control group; Ischemia reperfusion injury group (IRI group); Curcumin group (Cur group); Curcumin nanoparticle group (CurNP group). In each group, HK-2 cells viability was assessed by dimethyl-thiazol-diphenyltetrazoliumbromide (MTT) tests. Apoptotic Cells were measured by Flow Cytometry. H2DCF-DA was used to detect intracellular generation of ROS. BCA were used to detect SOD activation and the Concentration of MDA. Protein levels of procaspase-3 were analyzed by Western Blot.

Results: Successfully constructed curcumin-loaded nanoparticles by amphiphilic mPEG-PCL block copolymers. We found the differences between four groups. In IRI group, cells viability reduced gradually, cells apoptosis was obvious, SOD activity declined, the level of ROS and MDA activation increased significantly, the expression of Caspase-3 was increased. In Cur group and CurNP group, cells viability was improved. A great reduction in the level of apoptosis was observed. SOD activity was improved. The level of ROS and MDA activation were inhibited, the expression of Caspase-3 was decreased. Compared with Cur group, it also showed a marked improvement in CurNP group. Difference Had Statistics Meaning ($P<0.05$).

Conclusions: 1. Efficiently produce controlled releasing Curcumin-loaded nanoparticles by amphiphilic mPEG-PCL block copolymers. Drug loading content (DLS) and encapsulation efficiency (EE) were more than other reports. Data indicated that incorporated Cur could be slow released from the core-shell structure of polymeric nanoparticles. 2. CurNP can ameliorate ischemia-reperfusion renal injury in vitro. 3. The protective effects of Cur-NP against ischemia-reperfusion renal injury were involved in the suppression of oxidative stress reaction.

PUB009

Disruption of Polyamine Catabolism Reduces the Severity of Cisplatin Nephrotoxicity Kamyar A. Zahedi,^{1,2} Sharon L. Barone,^{1,2} Marybeth Brooks,¹ Jie Xu,¹ Manoocher Soleimani.^{1,2} ¹Dept of Internal Medicine, Univ of Cincinnati, Cincinnati, OH; ²Research Services, Veterans Affairs Medical Center, Cincinnati, OH.

Background: Platinum-based drugs (e.g. cisplatin) are used for treatment of many types of solid organ tumors. Cisplatin crosslinks the DNA, interferes with mitosis, activates the DNA repair response and leads to apoptosis when repair proves impossible. The latter is the primary anti-tumor mechanism of cisplatin. Platinum-based drugs also cause oxidative cell injury, which may mediate their general toxic effects. Acute kidney injury (AKI), due to oxidative damage, is a major side effect of cisplatin that necessitates dose reduction or withdrawal from treatment thereby reducing the effectiveness of cancer therapy. We hypothesized that treatments that reduce the oxidative tissue damage caused by cisplatin lessen the severity of AKI without interfering with its anti-proliferative DNA damaging effects and obviate the need for dose reduction or drug withdrawal.

Methods: Cisplatin-AKI was compared in wild type and SSAT-KO mice using functional and molecular parameters. Mechanism of polyamine catabolism mediated-cell injury were assessed in cultured cells.

Results: The expression of polyamine catabolic enzymes, spermidine spermine-N1-acetyl transferase (SSAT) and spermine oxidase (SMO) increase in the kidneys of cisplatin-treated mice. SSAT-KO mice are protected against tissue damage and renal dysfunction caused by cisplatin. Using cultured cells capable of inducible expression of SSAT, the effect of SSAT on the induction of endoplasmic reticulum stress and unfolded protein response (ERS/UPR). Our results indicate that up-regulation of polyamine catabolism in general, and enhanced production of SSAT in particular, activated the ERS/UPR.

Conclusions: These studies suggest that polyamine catabolism is involved in the mediation of cisplatin-AKI. These and our previous results indicate that the activation of polyamine catabolism causes cell injury through both genotoxic response and ERS/UPR pathways. Our studies suggest that short-circuiting or neutralization of toxic products of polyamine catabolism can be novel therapies that reduce the severity of cisplatin nephrotoxicity.

Funding: Veterans Administration Support, Private Foundation Support

PUB010

Renoprotective Effect of NADPH Oxidase 4 Inhibition in Contrast Induced Nephropathy Se-Hee Yoon,¹ Won Min Hwang,¹ Sung-Ro Yun,¹ Sukyung Lee,² Hee-Yeon Jung,² Ji-Young Choi,² Sun-Hee Park,² Chan-Duck Kim,² Yong-Lim Kim.² ¹Internal Medicine, Konyang Univ, Deajeon, Korea; ²Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Korea.

Background: The objective of this study was to investigate the renoprotective effect of NADPH oxidase 4 (Nox4) inhibition in contrast induced nephropathy.

Methods: HK-2 cells were incubated with iohexol (nonionic low-osmolar radiocontrast agent) at a concentration of 75 mg/l/ml, 150mg/l/ml for 2 h. Cells were pre-exposed to GKT137831, a selective Nox1&4 inhibitor (Genkyotex, Switzerland), for 30 min before exposure to iohexol. Cell viability was measured at 0, 3 and 22 h after removal of iohexol by ATPlite assay. Apoptosis was investigated by caspase 3/7 activity assay. Reactive oxygen species (ROS) production was assessed by DHE assay, NADPH oxidase activity by the luciferin-enhanced chemiluminescence method, and Nox4 expression by western blot and real time PCR.

Results: Nox4 protein expression significantly increased at 30 min after iohexol exposure. GKT137831 pre-exposure showed significantly less cytotoxicity at 3h after removal of iohexol. Caspase 3/7 activity was significantly lower in GKT137831 pre-exposed cells than only iohexol exposed cells at 22 h after removal of iohexol. ROS generation was higher with only iohexol exposed cells compared to GKT137831 pre-exposed cells.

Conclusions: A selective Nox4 inhibition induced fewer cytotoxic effects on cultured HK-2 cells than iohexol along with a lower induction of Nox4-dependent ROS generation. This enzyme may represent a potential therapeutic target to prevent iodinated radiocontrast media related oxidative stress.

PUB011

Autophagy Increased in the Early Stage of Rat Acute Kidney Injury Model Junyi Lin,¹ Xing Mao,² Yiwen Shen,¹ Huijuan Wu,² Aimin Xue.¹ ¹Department of Forensic Medicine, Shanghai Medical College, Fudan University, Shanghai, China; ²Department of Pathology, Shanghai Medical College, Fudan University, Shanghai, China.

Background: Acute kidney injury (AKI) is a major kidney disease without effective therapies, and thus associated with a high mortality. The pathogenesis of AKI is very complex and still unclear. Recently, researches have shown the induction of autophagy in proximal tubular cells and kidneys during AKI. In the present study, we investigated the role of autophagy in the pathogenesis of rat renal ischemia-reperfusion (I/R) model which causes AKI.

Methods: All male Sprague-Dawley rats were subjected to clamping of bilateral renal artery only for 25 min except sham group, and then they were randomly divided into four groups depended on different reperfusion time point, including 3h, 6h, 12h and 24h. The Sham group underwent surgical procedures without ischemia was as the control.

Results: The level of blood urea nitrogen (BUN) and serum creatinine were increased from 3h after I/R. By H&E staining, protein casts were found at 3h after I/R, which kept increasing at 6h and 12h after I/R. At 24h after I/R, we found some necrotic proximal tubules. Immunoblotting showed the protein level of Beclin-1 and Vps34 and the ratio of LC3 II/I was increased from 3h after I/R, which was confirmed by electron microscopy showing the formation of autophagic vacuoles in proximal tubule cells. Moreover, immunohistochemical staining clearly showed an increasing positive staining of Vps34 and LC3 at 3h after I/R compared to the control.

Conclusions: Taken together, our results demonstrate the occurrence of autophagy in the very early stage of rats AKI model.

Funding: Government Support - Non-U.S.

PUB012

The Previous Cardio Exercise (Exe) Normalizes Renal Function of Wistar Rats Subjected to Acute Kidney Injury by Ischemia, and Reperfusion Wesley Vicente Lima, Waldemar S. Almeida, Nestor Schor. *Nephrology, Federal Univ of Sao Paulo, São Paulo, Brazil.*

Background: The acute kidney injury (AKI) is characterized by acute reduction of renal function and has a high mortality rate in hospitalized patients and in severe cases may progress to chronic kidney disease (CKD). The AKI by ischemia and reperfusion (I/R) causes tubular damage mainly in the proximal convoluted tubule, reducing mitochondrial activity in renal cell and increasing the reactive oxygen species (ROS). It is known that aerobic Exe lower blood pressure (BP), slows the heart rate (HR), improves muscle aerobic capacity, increases both the number and size of muscle mitochondria, however little is known about the effects of the previous Exe in AKI. We suspect that aerobic Exe may be a non-pharmacological resource in the prevention of AKI. Thus, we investigated the effect of previous aerobic Exe on renal injury resulting from I/R. To evaluate the effects of the previous aerobic Exe on renal function in Wistar rats subjected to I/R.

Methods: We used male Wistar rats with 10 week of life and they were separated into two groups Sham clamp (SC) and trained control clamp (TC), moreover the TC were subjected to a prior physical training protocol for four weeks. After completed 14 weeks each group were underwent acute kidney injury surgery by I/R, the rats recovering for 24 hours after that they were placed in metabolic cages for 24 hours. We evaluate renal function (serum creatinina and proteinuria). Then they will be realized: renal morphological study by light microscopy and mitochondrial (number and size) by electron microscopy. Finally, we will evaluate apoptosis through caspases 3 activity.

Results: The SC group increased weight compared to the TC group (399±5vs365±5g, P<0.05). Proteinuria was significantly different in SC vs. TC group (25.62±4.93vs14.54±1.65 mg/24h, P<0.05). Now the creatinina serum showed significant difference in SC vs TC group (0.30±0.8vs0.67±0.6 mg/dL; P<0.05). We evidenced that SC group had a damage renal function after 48 hours recovery.

Conclusions: The results of this study are preliminary in nature, but suggest that the previous aerobic Exe can be renoprotective in the model I/R.

PUB013

Angiogenin Mediates a Non-Cell Autonomous Response to Endoplasmic Reticulum Stress in the Kidney Nicolas Pallet,¹ Dany Anglicheau,³ Eric Thervet,² Iadh Mami.¹ ¹INSERM U1147, Paris, France; ²Nephrology, Georges Pompidou European Hospital, Paris, France; ³Nephrology, Necker Hospital, Paris, France.

Background: Endoplasmic Reticulum (ER) stress is involved in the pathophysiology of kidney diseases, but the molecular basis of its biological outputs remain to be established. Angiogenin (ANG), a secreted ribonuclease, is a previously unappreciated component of the mammalian stress response that acts both in cell-autonomous and non-cell autonomous fashions to promote tissue adaptation to injury. Whether ANG signaling is a genuine component of the ER stress response is currently unknown.

Methods: In the present study, we explored the molecular mechanisms by which ANG is secreted under ER stress, and determined how it contributes to the modulation of the inflammatory microenvironment.

Results: Our results indicate that i) ANG secretion is specifically induced during ER stress and ii) this mechanism is under the selective control of IRE1a signaling. We demonstrate that ANG canonical secretion is induced upon ER stress, similar to the proinflammatory cytokine IL-6, and as such might play an instrumental role in macrophage activation. These data are relevant to human disease since we identified ANG as a urinary marker of immune-mediated acute kidney injury.

Conclusions: Collectively, our data identify ANG as a key mediator of ER stress-dependent inflammatory response in kidney diseases, and is a potential non-invasive biomarker of acute kidney injury.

PUB014

Sustained Infiltration of Th17 Cells Is Associated with Pulmonary Fibrosis in Rats with Salt Induced CKD Secondary to Renal Ischemia Purvi Mehrotra, Jason Andrieu Collett, David P. Basile. *Dept of Cellular and Integrative Physiology, Indiana Univ of Medicine, Indianapolis, IN.*

Background: Acute kidney injury (AKI) is associated with high mortality rates and is a leading cause of prolonged hospitalizations. The high risk of death is due in part to distant organ damage (e.g., lungs, heart, brain). It is well established that experimental AKI induced by renal ischemia and reperfusion (I/R) induces an increase in pulmonary infiltration of various immune cells like T cells as early as 24 hours post surgery, which may alter endothelial barrier function in the lung. However, the long-term effect of kidney injury induced pulmonary inflammation on lung function and structure and function is not known. We hypothesize that T cells infiltrate into the lung post kidney injury with potential effects on pulmonary structure.

Methods: SD rats were subjected to a model of AKI-to-CKD in which rats are allowed to recover from unilateral I/R (40 min ischemia) for 5 weeks on standard salt diet (0.4% NaCl) and then subjected to contralateral UNX and 4% NaCl diet for 4 additional weeks.

Results: Consistent with prior reports, infiltration of CD4+ T cells were detected as early as 24 hours post surgery in the BAL fluid, and these were shown to be predominantly of Th17 phenotype (63%±10.1, p³ 0.05). Interestingly, Th17 cells persisted in the lungs even after 5 weeks of post surgery after resolution of kidney injury (2.3X10⁴±0.1, p⁰.05), when compared to sham (0.53X10⁴±0.0.3). Exposure of rats to high salt diet to hasten CKD further increased the number of Th17 cells in the lungs (4.1X10⁴±0.23, p⁰.05). There was a corresponding increase in pulmonary fibrosis in post-AKI rats on high salt relative to sham-controls.

Conclusions: Taken together, these data suggest that AKI leading to CKD is associated with pulmonary fibrosis, an activity that may be due in part to the infiltration of Th17 cells into the lung and influenced by dietary salt.

Funding: NIDDK Support

PUB015

Endothelial-to-Mesenchymal Transition and Endothelial Cilia in EPC-Mediated Postischemic Kidney Protection Daniel Patschan, Susann Patschan, Gerhard A. Mueller. *Clinic of Nephrology and Rheumatology, Dept of Internal Medicine, Göttingen, Niedersachsen, Germany.*

Background: AKI increases the risk for CKD. Ischemia induces peritubular capillary rarefaction and interstitial fibrosis with the latter partly resulting from mesenchymal transition of endothelial cells (EndoMT). Endothelial cilia are mechanosensory organelles responsible for transmitting forces of the blood flow into the cell. Early Endothelial Progenitor Cells (eEPCs) have reproducibly been shown to protect mice from AKI in the short-term. Aim of the study was to analyze mid-term consequences of eEPC treatment of murine AKI. Our special interest focused on dynamics of endothelial cilia and EndoMT.

Methods: Male, 8-12 weeks old C57/Bl6N mice were subjected to unilateral renal ischemia (40) post-uninephrectomy. Syngeneic murine eEPCs (0.5×10⁶) were injected once at the time of reperfusion. Animals were investigated 1, 4, and 6 weeks later (renal function,

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

fibrosis, EndoMT, endothelial alpha-Tubulin). Cultured mature endothelial cells (ECs) were exposed to a variable flow with versus without treatment with eEPC supernatant. Later (24 h) cells were investigated for the presence of cilia, alpha-Tubulin, and EndoMT, respectively.

Results: Systemically injected eEPCs significantly improved postischemic kidney function at week 1 (35 and 45 minutes) and 4 (45 minutes). Interstitial fibrosis was significantly diminished by cell treatment at all time points as well, EndoMT was less pronounced at week 4 (35 minutes) and 6 (45 minutes). eEPC supernatant reduced α SMA expression and alpha-tubulin abundances in flow-treated cultured mature endothelial cells while percentages of cilium+ cells increased. The loss of peritubular capillaries was prevented by eEPCs. Intrarenal endothelial alpha-tubulin decreased postischemia and was further reduced after eEPCs. The latter effect exclusively occurred in the 35 minutes groups.

Conclusions: We conclude that eEPCs are capable of reorganizing the endothelial cytoskeleton in an indirect manner, ultimately resulting in stabilization of the endothelial cilium. The investigation indicates an anti-mesenchymal role of endothelial cilia in the process of postischemic tissue fibrosis / EndoMT.

PUB016

Mediators of Kidney Recovery following Ischemia-Reperfusion Injury Casper Lassen, Marie Louise Vindvad Kristensen, Henrik Birn, Bente Jespersen, Rikke Norregaard. *Dept of Clinical Medicine, Aarhus Univ.*

Background: Ischemia-reperfusion injury (IRI) is a major cause of acute kidney injury. Remote ischemic conditioning (rIC) performed as brief episodes of intermittent ischemia and reperfusion in a distant tissue may protect the kidney against IRI. We investigated the renal effects of rIC applied either prior to or during ischemic kidney injury.

Methods: One week after uninephrectomy Wistar rats were randomly divided into 4 groups; sham (n=7), IR (n=10), IR+rIPC (n=10), and IR+rIPerC (n=10). rIC consisted of 4 episodes of 5 min clamping of the infrarenal aorta and 5 min of release either before (rIPC) or during (rIPerC) 37 min of left renal artery clamping (IRI). Urine and blood were sampled prior to ischemia or sham operation as well as 3 and 7 days after reperfusion. At day 7 the kidney was harvested for purification of mRNA and protein.

Results: Three days after IRI the decline in creatinine clearance (CrCl) from baseline values was similar comparing the IR group (Δ :-1.59 ml/min/kg [-2.55;-0.64]) to both the IR+rIPC group (Δ :-1.19 ml/min/kg [-2.22;-0.15], $p>0.99$) and the IR+rIPerC group (Δ :-1.48 ml/min/kg [-2.17;-0.79], $p>0.99$). At day 7 all groups exposed to IRI recovered to baseline CrCl. This was associated with a significant up-regulation of mediators of kidney recovery including phosphorylated Akt, ERK1/2 and HSP27 in all 3 groups. rIC was not associated with any significant differences in the expression of tubular damage markers, inflammatory or fibrosis markers, as well as anti-oxidant enzymes following IRI (see table).

Conclusions: In our study rIC did not protect the kidney against IRI. However, from day 3 to day 7 after IRI all groups recovered full renal function. This was associated with an up-regulation of pAkt, pERK1/2 and pHSP27 at day 7.

	IR	IR+rIPC	IR+rIPerC
pAkt	9±1.8	12±1.6	8±1.1
pERK1/2	5±1.2	5±0.8	3±0.4
pHSP27	15±3.9	16±2.8	12±3.3
SOD2	0.6±0.0	0.7±0.0	0.6±0.0
KIM-1	972±216	1228±192	956±185
ICAM-1	5±0.5	5±0.4	6±0.4
α -SMA	2±0.5	2±0.2	2±0.3

Mean±SEM. Normalized to the sham group. All values shown are statistically different from the sham group

Funding: Private Foundation Support

PUB017

Effect of Double Genes Transfected Adipose-Derived Stem Cells on Cisplatin-induced Renal Tubular Epithelial Cells Injury Nanmei Liu. *Jinmi Hospital of Shanghai.*

Background: To observe the effects of adipose-derived stem cells (ADSCs) transfected with CXCR4 and EPO gene on renal tubular epithelial cells (HKC) injury.

Methods: To construct lentivirus expression system consisting of CXCR4 and EPO genes and transfected the system to adipose-derived stem cells (ADSCs), which co-culture with the cisplatin-induced HKC for 48 and 72 hrs. CCK8 detected cell proliferation of HKC. Electron microscope observed the ultrastructure of HKC cells and ADSCs migration was assayed. Western blot detected the expression of apoptosis proteins in HKC. ELISA detected the expression of inflammatory cytokines in culture medium.

Results: No significant changes were observed in the morphology of ADSCs after gene transfection, and the multiple differentiation ability were not affected. After co-culture the inhibitory effect of cisplatin on HKC cell proliferation was alleviated. Compared with the control group, the migration index of ADSCs was increased after co-culturing with cisplatin-induced HKC, and the gene transfection group were increased significantly as the extension of the culture time, indicating that the target gene transfection can promote the ADSCs migration to the damaged parts. Incubation with cisplatin, HKC cells EPO-R protein expression decreased. After co-culturing with ADSCs, the EPO-R expression increased. After incubated with cisplatin, the expression of Caspase-3, Bax expression in HKC cells

increased significantly, which mediates the apoptosis. After co-cultured with ADSCs, the protein expression decreased, and the transfection groups decreased more obviously. After incubated with cisplatin, bcl-2 expression of HKC cells decreased obviously and the expression increased when ADSCs were cultured, and co-transfection group was more obviously. After incubated with cisplatin, IL-6 and RANTES were significantly increased in the cisplatin group. The inflammatory factor content decreased when ADSCs were cultured, and decreased more obviously in gene transfection group.

Conclusions: EPO has the protective effects on the damaged cells and CXCR4 could promote the migration of stem cells to damage sites. Double genes transfected to ADSCs may enhance the protective effect on HKC cells injury.

Funding: Government Support - Non-U.S.

PUB018

The Role of Endosialin in Renal Ischemia-Reperfusion Injury Chia-Hao Liu,¹ Fang Ling Liao,¹ Shun-Yang Cheng,¹ Shuei-Liong Lin.^{1,2} *¹Physiology, National Taiwan Univ College of Medicine, Taipei, Taiwan; ²Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.*

Background: Many studies reported that Endosialin deficiency can attenuate the inflammation, fibrosis or growth, invasion and metastasis of tumors. It is highly expressed during embryonic development, but largely absent in adult tissue except kidney and uterus. We are intrigued by the role of endosialin in the acute kidney injury.

Methods: We performed unilateral nephrectomy and then ischemia-reperfusion injury to induce acute kidney injury in the endosialin-deficiency (lacZ knock-in) and littermate wild type mice. Plasma levels of blood urea nitrogen and creatinine were analyzed at day 2, 5 and 10 after injury. We analyzed the cells expressing endosialin, tubulointerstitial injury, and specific cells by X-Gal staining, Periodic acid-Schiff staining and immunohistochemistry respectively.

Results: Positive X-Gal staining was shown in the glomeruli, small arteries and interstitial cells of the kidney. The capillary density determined by CD31 staining did not show significant difference between endosialin-deficiency and wild type mice. Nephrectomy and ischemia-reperfusion injury led to marked elevation of plasma blood urea nitrogen and creatinine in wild type mice, however the elevation of plasma blood urea nitrogen and creatinine was less in endosialin-deficiency mice at day 2 after injury. Interestingly the protective property of endosialin deficiency was lost since day 5 after injury.

Conclusions: Endosialin-deficiency can attenuate acute kidney injury induced by ischemia-reperfusion injury, but the protective property is lost during the repair/regenerative phase after acute injury. The protective property of endosialin deficiency is not related to capillary density which has been shown increased in previous study. Further study needs to delineate the mechanism underlying the protective property of endosialin deficiency and why the protective property is lost during repair/regenerative phase.

Funding: Government Support - Non-U.S.

PUB019

The Mechanism of β 2-Adrenergic Receptor /Protein Kinase A Signal Transduction Pathway in Restoration of Acute Kidney Injury by Endothelial Progenitor Cells Ying Zhou, Chen Yu. *Dept of Nephrology, Tongji Hospital, Tongji Univ, Shanghai, China.*

Background: Endothelial progenitor cells (EPCs) could improve renal microenvironment, stimulate endothelial repair and angiogenesis, and promote AKI restoration. However, the molecular mechanism has not been elucidated. In this study we investigated the role of β 2-adrenergic receptor (β 2-AR) and its downstream factors (protein kinase A, protein kinase B, protein kinase C) in restoration of acute kidney injury by EPCs.

Methods: The model of ischemia-reperfusion acute kidney injury (I-R AKI) was used in vivo, while sham operation was performed in control group. Renal tissue was got after 7 days. Renal histology was measured by HE staining. The expression of β 2-AR was examined using Q-PCR and immunofluorescence staining. The specific antigens on surface of EPCs (CD34, CD133 and VEGFR-2) were examined by Q-PCR; while VEGFR-2 was examined using immunofluorescence staining too. The downstream factors (PKA, PKB, PKC) were measured by Q-PCR and Western blotting.

Results: Renal histology suggested acute tubular necrosis, and β 2-AR was positive by immunofluorescence staining in I-R AKI group; while neither appeared in control group. The mRNA levels of CD34, VEGFR-2, β 2-AR and PKA were significantly up-regulated in I-R AKI group than in control group ($p<0.05$). The protein level of PKA was significantly higher expressed in I-R AKI group than in control group ($p=0.04$); while the protein levels of PKB and PKC were not. According to Pearson's correlation analysis, there were significant positive-correlations between VEGFR-2 and CD34 ($p=0.005$), VEGFR-2 and β 2-AR ($p<0.05$), CD34 and β 2-AR ($p<0.05$), β 2-AR and PKA ($p<0.05$).

Conclusions: When I-R AKI occurred, the mRNA levels of specific antigens on surface of EPCs (CD34 and VEGFR-2) were significantly up-regulated, which suggested that I-R AKI might induce EPCs homing to kidney. At the same time, the mRNA levels of β 2-AR and PKA were significantly up-regulated, and most of them were positive-correlated, which suggested that β 2-AR/PKA pathway may play a role in the restoration of AKI by EPCs.

Funding: Government Support - Non-U.S.

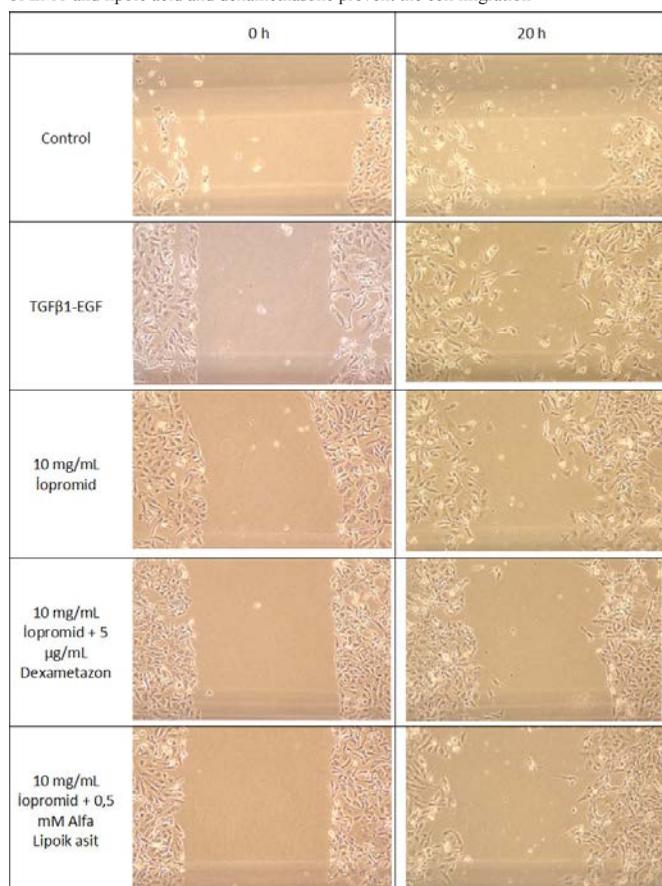
PUB020

Alpha Lipoic Acid and Dexamethasone Counteract Contrast Media-Induced Proximal Tubule Cell Dysfunction Hayriye Sayarlioglu,¹ Ali Okuyucu,² Abdulkemir Bedir,² Osman Salis,² Eser Yenen.² ¹Dept of Nephrology, Ondokuz Mayıs Univ Medical Faculty, Samsun, Turkey; ²Dept of Medical Biochemistry, Ondokuz Mayıs Univ Medical Faculty, Samsun, Turkey.

Background: Contrast medium induced nephropathy (CIN) is one of the most common cause of hospital-acquired acute renal failure. But its pathogenesis is unclear. In this study, we observed the effect of iopromide, low osmolar contrast medium, on tubular cells in HK-2 cell line.

Methods: We observed the effect of iopromide, low osmolar contrast medium, on tubular cells in HK-2 cell line. First, we examined the effects of different doses of iopromide (10, 20, 40 and 80 mg/mL iodine) on proliferation of HK-2 cells by the real time cell analyser (RTCA). According to the results of RTCA we examined whether the non-toxic doses of iopromide (10 and 20 mg/mL iodine) is causing of the EMT by scratch assay for 20 h. We also observed whether alpha lipoic acid (0,5 mM) and dexamethasone (5 µg/mL) is preventing to EMT in this assay.

Results: We observed whether alpha lipoic acid (0,5 mM) and dexamethasone (5 µg/mL) is preventing to EMT in this assay. Although cytotoxic effect was observed for iopromide with concentration of 80 mg/ml iodine, the iopromide with lower doses did not show any effects for HK-2 cells. In scratch assay, we observed that the non-toxic doses of iopromide (10 and 20 mg/mL iodine) is causing of the cell migration which an indicator of EMT and lipoic acid and dexamethasone prevent the cell migration



Conclusions: In conclusions, the EMT caused by contrast medium is prevented or reduced by dexamethasone and lipoic acid in HK-2 cells. This result suggest that dexamethasone and lipoic acid may be a potential treatment to prevent the development of CIN in individuals with high-risk.

PUB021

Contribution of Proliferating Endothelial Cells for Endothelial Repair After Site Specific Endothelial Injury of the Mouse Kidney Jan Sradnick, Anika Luedemann, Vladimir T. Todorov, Christian Hugo, Bernd Hohenstein. Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany.

Background: Our previous studies have shown that renal endothelial cell regeneration occurs exclusively via local mechanism. To further dissect the relevance of local mechanisms for endothelial repair, we now investigated the contribution of local endothelial cell proliferation in the kidney in our model of site selective endothelial injury (ECI).

Methods: Selective ECI was induced in 9 out of 15 mice by renal arterial perfusion with ConcanavalinA (ConA)/anti-ConA, while 6 mice served as sham operated controls. Edu (15µg/g), a marker of proliferation, was injected starting 24hours after ECI every 12hours intraperitoneally. Kidneys were harvested on day 7 and Edu+ cells were analyzed using flow cytometry and histology. Endothelial cells were stained using CD31, CD105, CD34 and CD146 and hematopoietic cells were detected as CD45+. Inflammatory cells (macrophages, dendritic cells and neutrophils) were analyzed via GR1, CD11c, CD11b and F4/80 positivity. By histology, proliferating EC were detected as anti-ERG/EdU double positive cells.

Results: Significantly more Edu+ cells could be detected after ECI on day 7 (sh: 1.2%±0.7; ECI: 7.6%±4.8). Most of those Edu+ cells were positive for CD45 (65%±8) and 5% (sh) up to 7% (ECI) were positive for EC surface markers. In diseased kidneys more endothelial cells were found (sh: 5.5%±0.7; ECI: 7.3±0.5; p<0.01). A larger amount of Edu+ EC was found in injured kidney (sh: 1.5%±0.8 Ø160 cells; d7: 5%±1.5 Ø630 cells p<0.01). Histological analysis supported these findings. Glomeruli of ECI kidneys had more ERG/EdU+ cells (Ø sh: 0.23±0.16; d7: 1.22±0.6; p<0.01). Inflammatory cells in injured kidneys were slightly increased. Many macrophages (21%±13), neutrophils (38%±17) and dendritic cells (19%±13) were Edu+.

Conclusions: Enhanced endothelial proliferation was detected following ECI. Therefore EC proliferation reflects an relevant repair mechanism following site selective ECI. The further investigation of EC repair will have to dissect the contribution of the proliferative response by adult local EC from other contributors such as local progenitor cells.

PUB022

Injury of Proximal Tubular Cells in Neonate Rats with Hypoxic-Ischemia Brain Damage Dong Li,¹ Mei Han.² ¹Pediatric Dept, The Second Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning Province, China; ²Pediatric Internal Medicine Dept, Dalian Children's Hospital, Dalian, Liaoning Province, China.

Background: Proximal tubular cells play a critical role in renal injury. To investigate the consequence of mitochondria in renal proximal tubular cells after hypoxic-ischemia brain damage (HIBD) in rats and the apoptosis in it.

Methods: Neonatal (7 days old) Sprague Dawley rats were randomly divided into 2 groups: sham group and operation group (n=5 per group). The Rice method was used for establishment of HIBD model, proximal tubular cells Mitochondria pathology and histology were examined under electron microscope at 1 day, 7days, 14days and 21days after the hypoxic-ischemic treatment, and apoptosis was analyzed by TUNEL.

Results: After the HIBD, the mitochondria of proximal tubular cells were showed damage under EM, some membrane and ridges were broken, the mitochondria bodies were swelling, and partial crista fragmentation were observed from the 1day till 21days after. And the 21days was the most worst for mitochondria under EM. For the TUNEL, after HIBD, it showed significant increased for 1day, 7days, 14days and 21days groups comparing with sham group. (p<0.05).

Conclusions: After the hypoxic and ischemic brain injury of neonate rats, the mitochondria were damaged in proximal tubular cells, even in 21days after HIBD. And the apoptosis maybe one of the causes of this damage.

Funding: Government Support - Non-U.S.

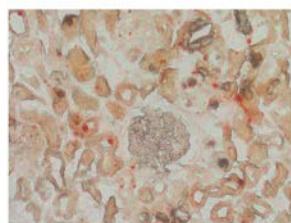
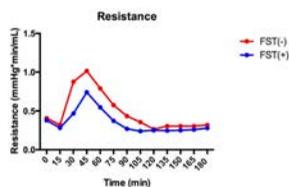
PUB023

Ex-Vivo Normothermic Perfusion (EVNP) to Repair Monoethylene Glycol Toxicity in Human Kidneys Ivonne Palma,¹ Sasha Karan Narayan,¹ Ivania Palma,¹ Rajendra Ramsamooj,² Junichiro Sageshima,¹ Jakub Woloszyn,¹ Nam Tran,² Chandrashankar Santhanakrishnan,¹ Richard V. Perez.¹ ¹Surgery, Univ of California-Davis, Sacramento, CA; ²Pathology and Laboratory Medicine, Univ of California-Davis, Sacramento, CA.

Background: Monoethylene glycol (MeG), a component of radiator fluids, results in crystal-induced acute kidney injury, hypocalcemia and often death, if ingested. Utilization of kidneys from deceased donors with MeG poisoning may not be suitable for transplant. EVNP may be utilized to potentially assess/repair high-risk kidneys in this setting.

Methods: A pair of transplantable human kidneys from a brain dead 38 year old female suicide victim from MeG poisoning were discarded due extensive intratubular crystal deposition. The kidneys were placed on 3 hours of EVNP with leukocyte depleted packed red blood cells at 37°C. Oxygenation via a hollow fiber membrane oxygenator supplemented with parenteral nutrition/insulin. One kidney was given Furosemide (10 mg) at the beginning to induce diuresis and assess acute kidney injury. Hemodynamic pump parameters and urine output were monitored. Blood and urine samples were collected at the start and every 30 minutes and analyzed for pH, oxygen, electrolytes, creatinine, and lactate. Wedge biopsies were collected pre & post perfusion & stained with alizarin red to measure calcium oxylate tubular deposition.

Results: Blood flow and resistance improved over time in both kidneys. EVNP reduced calcium deposits compared to baseline wedge biopsies. Kidney treated with furosemide showed slightly better hemodynamic profile and fewer crystals after EVNP.



Furosemide Positive Pre-Perfusion
10% Alizarin Red Stain



Furosemide Positive Post-Perfusion
10% Alizarin Red Stain

Conclusions: EVNP may have the potential to repair MeG acutely injured kidneys rendering them suitable for transplantation. Ex vivo administration of furosemide may be a useful tool to assess injured deceased donor kidneys being considered for transplantation.

PUB024

Abstract Withdrawn

PUB025

Transfusion of Red Blood Cell as Predictor of Acute Kidney Injury in Patients Undergoing Cardiac Surgery Eduesley Santana-Santos, Luiz Aparecido Bortolotto, Ludhmila Abrahão Hajjar. *ICU-Cardiac Surgery Postoperative Care, Heart Inst (InCor) Inst do Coração do Hospital das Clínicas da Faculdade de Medicina da Univ de São Paulo, São Paulo, Brazil.*

Background: The red blood cell transfusion in the perioperative period of cardiac surgery have been associated with acute kidney injury. Our purpose was to analyze the influence of transfusion of red blood cell in the incidence of acute kidney injury after cardiac surgery.

Methods: We performed a prospective cohort study carried out in a tertiary hospital specialized in Cardiology. Adult patients who had undergone elective myocardial revascularization surgery, valvular and aortic surgery and who had agreed to participate in the study were included. The primary endpoint was acute kidney injury defined by KDIGO criterion. Secondary outcomes was serious clinical complications defined according to the guidelines of the Society of Thoracic Surgeons.

Results: According to KDIGO criterion, the incidence of AKI was 46.5%. The mean age was 60±12 years old in the AKI group and 58±13 in the no AKI group (p=0.145), and mostly male (56%). The surgical risk assessed by EuroSCORE was greater in the AKI Group 5 (1-25) when compared to the no AKI group 4 (2-10), (p=0.047). There were no differences between the groups for the secondary outcomes. The use of red blood cells in the perioperative period (OR=3.166, p=0.001) and the presence of prior chronic kidney disease (CKD) (OR=2.027, p=0.036) was associated with AKI postoperatively.

Variable	OR	CI (95%)	p (value)
Age, years	1.486	0,990 – 1,043	0,223
Cardiac Heart Failure	2,549	0,116 – 1,247	0,110
Male gender	0,661	0,395 – 1,469	0,416
Chronic Kidney Disease	2,027	1,406 – 3,052	0,036
Red Blood Cell Transfusion	3,166	1,572 – 6,380	0,001
Use of Cardiopulmonary Bypass	0,841	0,308 – 2,296	0,736

During the period of hospitalization the mortality rate was 6.9%. When we compare the mortality rate between the groups it was 4.3% in the no AKI Group and 10% in the AKI Group (p=0.229).

Conclusions: In our study the use of perioperative red blood cells influenced the primary outcome. Patients who had used red blood cells had 3 times more risk of AKI.

Funding: Government Support - Non-U.S.

PUB026

A Picture Is Worth a Thousand Words: Simultaneous ATN, AIN, and Post Infectious GN Ankur Shah,¹ Rachel Criner,¹ Jean Lee.² ¹Internal Medicine, Temple Univ Hospital, Philadelphia, PA; ²Nephrology, Temple Univ Hospital, Philadelphia, PA.

Background: The differential diagnosis of hospital acquired acute kidney injury in its most general terms often is described as pre-renal, intrinsic ,or post-obstructive. Further differentiating the intrinsic causes of AKI, we are given the differential of Acute Tubular Necrosis, Acute Interstitial Nephritis, and Glomerulonephritis. We present a case of a patient who presented with sepsis and developed acute kidney injury whose biopsy revealed a plethora of pathology.

Methods: We present a case of a 54 y/o male with a pmhx of only HTN and DJD who presented with leg pain and weakness for 2 weeks and hematuria found to be bacteremic with MSSA with L spine epidural abscess and bilateral psoas muscle abscesses. He developed acute kidney injury thought clinically and based on microscopy to be secondary to hypotensive acute tubular necrosis and was started on hemodialysis on HD6. He was being treated with cefazolin and over weeks had minimal return of renal function, the differential diagnosis was revisited and concern for AIN from the penicillin agent was raised, the patient was switched to Daptomycin, but remained RRT dependent. After 25 days on hemodialysis, a biopsy was obtained which revealed diffuse interstitial inflammation with eosinophils, focal mild-moderate tubular injury with vacuolization, as well as by electron microscopy, subepithelial deposits but not subendothelial deposits, most of which are largely absorbed, including in “notch” areas. These findings are consistent with an acute post-infectious glomerulonephritis, resolving stage; drug induced acute interstitial inflammation, as well as mild-moderate focal tubular injury.

Conclusions: This case demonstrates a variety of the potential causes of AKI. The patients course was long and provided multiple opportunities for re-evaluation and a return to the differential diagnosis process. This is an excellent case for the teaching of the fundamentals of medicine, as the differential diagnosis is truly the instrument of the master clinician. This patients aberrance from the expected course prompted reevaluation and his pathology was staggering.

PUB027

Monitoring and Follow-Up of Acute Kidney Injury Post-Discharge: Retrospective Case Review Series Kosmas Papailiadis,¹ Judith H. Veis.² ¹Medicine, Washington Hospital Center, Washington, DC; ²Nephrology, Washington Hospital Center, Washington, DC.

Background: AKI during hospitalization increases risk of progression to CKD and death upon discharge. Recent KDIGO guidelines suggest patients should be evaluated 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. We determined factors associated with whether patients with AKI had kidney function assessed 3 months post-discharge.

Methods: Restrospective chart review of hospitalizations in 2013 complicated by AKI, who had follow-up in Ambulatory Medical Clinic to assess discharge communication; serum Cr, urine protein:Cr at 3 and 4-9 months; 1 year outcomes including progression to CKD, death and referral to nephrology.

Results: 77 inpatients with AKI (48(66%) stage 1, 9(12%) stage 2, 20(26%) stage 3; and 6(8%) requiring RRT) had a post-discharge visit. Of these, 51(66%) had serum Cr and 16(21%) had urine protein:Cr checked by 3 months. For 4-9 months, 13(17%) had serum Cr and 5(6%) had urine protein:Cr checked; 3(4%) were deceased by 1 year. 26(34%) had normal kidney function pre-AKI and of this group, 10(38%) had CKD by 1 year. Of these 26, only 5(19%) were referred to nephrology. For documentation, 54(77%) had AKI as a problem in the inpatient hospital summary, 42(54%) had AKI documented in the brief outpatient hospital summary and 29(41%) had AKI addressed in the follow-up visit. There was no significant association between AKI severity, need for RRT, or documentation with checking kidney function by 3 months nor between AKI inpatient documentation and addressing AKI at follow-up (p<0.05). There were significant associations between addressing AKI at follow-up and checking kidney function; p=0.043 and between AKI stage and addressing AKI at follow-up; p=0.022 and between AKI outpatient summary and addressing AKI at follow-up; p=0.004.

Conclusions: Outpatient follow-up of inpatient AKI is inconsistent despite evidence of poorer outcomes and recent guidelines which suggest the need for closer monitoring. Improving transitions of care through more effective documentation and streamlined EMRs, as well as increasing primary care physician awareness could reduce the risk of progression to CKD and death.

PUB028

Late Recovery of Renal Function in Atypical Hemolytic Uremic Syndrome (aHUS) After Eculizumab Therapy Jeffrey D. Clement, Delin Wang, Maoyin Pang, Tanmay Sahai, Keith R. Bartolomei. *Roger Williams Hospital.*

Methods: A 33-year-old woman with hypertension and left renal agenesis presented with fever and acute kidney injury with serum creatinine of 2.1 mg/dL. Initially, hemoglobin was 11.3 mg/dL and platelets 193,000/ul. Over the next three days platelets dropped to 55,000/ul and LDH rose to 770 U/L; renal function worsened. Thrombotic microangiopathy was suspected. Stool culture was negative. Urine protein was 6.8 g per 24 hours. Serologic assessment, including C3, C4, ANA, ANCA, HIV, cryoglobulins, dsDNA, lupus anticoagulant, anticardiolipin antibodies, and β-2-glycoprotein I antibodies, was unremarkable. The patient was treated with cryo-poor plasma exchange and steroids. Hemodialysis was started for uremia. ADAMTS13 was 67% of normal. Renal biopsy

showed acute thrombotic microangiopathy, acute tubular injury, and moderate interstitial fibrosis. The presentation suggested the diagnosis of aHUS. Eculizumab, an anti-C5 antibody, was initiated at 900 mg weekly for four weeks followed by 1200 mg every two weeks. Eculizumab therapy resulted in resolution of hemolysis. Dialysis was continued thrice weekly. Eculizumab was continued every two weeks, and LDH and platelet counts remained normal. Twelve months after initial presentation urine output improved and interdialytic weight gains were negligible. Pre-dialysis serum creatinine was 3.9 mg/dL, and a urine collection showed creatinine clearance of 30 ml/minute. She has remained off dialysis for twenty weeks, and latest serum creatinine is 3.4 mg/dL. Screening for complement genetic defects has been negative.

Conclusions: Experience with eculizumab is ongoing. Most patients with aHUS have a rapid hematologic response. If they need dialysis, then recovery of renal function is usually prompt; late recovery is rare. We hypothesize that sustained control of complement activation has eliminated the microangiopathy and allowed for vascular remodeling and tubular regeneration, even months later. Patients are at risk for relapse if they stop treatment. This case points out that the presumed genetic defect may require lifelong treatment, and that late recovery of renal function is possible with complement inhibition and supportive care.

PUB029

The Effectiveness of Theophylline in Preventing Cisplatin Related Nephrotoxicity in Patients with Cancer Ismail Kocycigit,¹ Derya Karademir,¹ Fatma Dogruel,¹ Cevat Yazici,² Aydin Unal,¹ Murat H. Sipahioglu,¹ Oktay Oymak,¹ Bulent Tokgoz.¹ ¹Nephrology, Erciyes Univ Medical School, Kayseri, Turkey; ²Biochemistry, Erciyes Univ Medical School, Kayseri, Turkey.

Background: Cisplatin is a potent antineoplastic agent used in treatment of many solid tumors. The major limiting side effect of cisplatin is nephrotoxicity. Theophylline is a competitive antagonist of adenosine which has antiinflammatory activity. In this study, early detection of acute kidney injury with biomarkers such as neutrophil gelatinase associated lipocalin (NGAL) and cystatin C and investigation of the potential nephron-protective effects of theophylline were aimed.

Methods: Sixty patients who are planned administration of cisplatin for the first time were included in the study. Patients were divided into two groups as group I (n=30) (standard treatment arm) and group II (n=30) (theophylline arm). Glomerular filtration rate (GFR), NGAL, cystatin C were measured at 5th day in all of the patients. Also, these parameters were repeated measured after the administration of cisplatin, at 2nd hour, 5th and 20th days.

Results: In both groups after the administration of cisplatin, glomerular filtration rate (GFR) showed a significant decrease within time (p=0.006). In creatinine, in spite of the decline in GFR, no significant difference was observed between groups and within time. After 2 hours of cisplatin administration, in spite of the decline in GFR, a significant decline was detected in serum cystatin C (p<0.001). Urine NGAL was significantly high after 2 hours of cisplatin administration (p<0.001). No significant difference was observed between groups. However, when the time*group effects were considered together, higher NGAL was detected in the group not receiving theophylline (p=0.025). After 5 days of cisplatin administration, urine protein levels were significantly higher in both groups (p<0.001).

Conclusions: Results showed that urine NGAL level is a superior biomarker compared to creatinine and cystatin C in the detection of early acute kidney injury. Theophylline was found not to bring a complete protection for the kidneys, but less nephrotoxicity was developed when compared to the group not receiving theophylline.

PUB030

IgA Nephropathy Presenting as RPGN After G-CSF Administration: An Interesting Case Talal A. Khan,¹ Ahmad Hassan,² Agha Syed Shabbir Ali,² Hafiz Armaghan Saeed,² Abdul Mateen Nagaria,¹ Azka Arif.¹ ¹Freeman Health System; ²Rawalpindi Medical College.

Background: IgA nephropathy is the most common form of primary glomerulonephritis & a major cause of ESRD in the world, its pathogenesis involves lymphocyte infiltration within renal interstitium as well as glomerulus. Selectins are adhesion molecules that play very important role in leukocytes to endothelial cell attraction. G-CSF is commonly used to induce neutrophil production. It induces E-selectin expression on endothelial cells & E selectin ligand on leukocytes. We present an interesting case of IgA nephropathy presenting as RPGN after G-CSF administration.

Methods: 66-year-old male with past medical history significant for T-cell leukemia on Cyclophosphamide(CYC) who presented with epistaxis was found to have acute agranulocytosis, he was admitted for further evaluation and management ,his CYC was held & on the day of discharge he was given 1 dose of G-CSF. He presented in 2 days with acute renal failure, gross hematuria & rash in his lower extremities, his creatinine went up from 1.3 to 5.1mg/dl. He was evaluated by nephrology service, and emergent renal biopsy was performed which showed rapidly progressive glomerulonephritis (RPGN) with IgA deposition in mesangium. Glomeruli showed diffuse mesangial hypercellularity and matrix increase with focal nodule formation. 3/17 Glomeruli had epithelial crescents & focal necrosis with fibrin deposits. The sections were stained for IgG, IgM, IgA, C3, C4, C1q, albumin, fibrinogen, & kappa and lambda light chains. There were mesangial granular deposits with IgA (3+), C3 (1+), lambda (1+); kappa was negative. The remaining stains showed no significant deposits. Patient underwent induction with CYC and pulse steroids, his creatinine improved to 1.4mg/dl.

Conclusions: The pathogenesis of IgA nephropathy involves E selectin interactions, which are induced by G-CSF administration. In our case development of RPGN with IgA nephropathy might be linked to G-CSF administration especially with the timeline of presentation. IgA nephropathy has not been linked to G-CSF administration before in adults, we suggest underlying complex genetic predisposition.

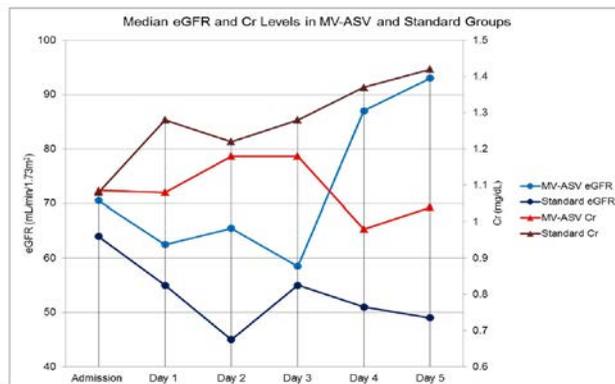
PUB031

Minute Ventilation-Targeted Adaptive Servo Ventilation Protects Renal Function in Acute Decompensated Heart Failure Patients Matt Kawahara,² Trenton Gluck,² Elizabeth Lee,² Boris Arbit,¹ Kathleen Sarmiento,³ Atul Malhotra,³ Alan S. Maisel.¹ ¹Div of Cardiovascular Medicine, Univ of California, San Diego, La Jolla, CA; ²Cardiac Research, VA San Diego Healthcare System, La Jolla, CA; ³Div of Pulmonary and Critical Care Medicine, Univ of California, San Diego, La Jolla, CA.

Background: Acute kidney injury (AKI) in patients admitted for acute decompensated heart failure (ADHF) carries a poor prognosis. Minute ventilation-targeted adaptive servo ventilation (MV-ASV) therapy relieves apneas and renal hypoxia. Serum creatinine (Cr) and estimated glomerular filtration rate (eGFR) are markers that signal kidney injury and improvement of kidney function. MV-ASV may mitigate kidney injury and improve renal function in patients admitted with ADHF compared to standard therapy.

Methods: This is a study where twenty-one patients with ADHF were randomized to receive either MV-ASV therapy (S9 VPAP Adapt, ResMed Corp.) with standard care, or standard care alone. MV-ASV therapy was administered for a minimum of six hours per day for up to 5 days, or until discharge. Cr was measured daily and used to calculate eGFR.

Results: The median baseline Cr levels in the MV-ASV and standard groups were 1.09mg/dL and 1.08mg/dL, respectively. After therapy, Cr levels were unchanged in the MV-ASV group and increased by 0.34 mg/dL (31.5%) in the standard care group. The median baseline eGFR levels in the MV-ASV and standard groups were 70.5mg/dL and 64mg/dL, respectively. Upon completion of therapy, the eGFR levels in the treatment group increased by 22.5mg/dL (32%) and decreased in the control group by 15mg/dL (23%).



Conclusions: MV-ASV therapy in patients with ADHF stabilizes Cr levels during a period of aggressive diuresis. MV-ASV may be a valuable for renal protection and could improve kidney function in patients with ADHF.

Funding: Pharmaceutical Company Support - Resmed

PUB032

Evaluation of Acute Kidney Injury in Patients Continued on Renin-Angiotensin System Blockers During Hospitalization Numan Alabdian,¹ Elvira Gosmanova,^{1,2} Carrie Oliphant,^{1,2} Joyce E. Broyles,^{1,2} Pan Hu,² Quynh Tran,² Joanna Hudson.^{1,2} ¹Methodist Univ Hospital, Memphis, TN; ²Univ of Tennessee Health Science Center, Memphis, TN.

Background: Acute kidney injury (AKI) occurs in over 20% of hospitalized patients and is associated with adverse outcomes. Whether continuation of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) during hospitalization increases the risk of AKI has not been fully assessed. We evaluated the development of AKI and its associated risk factors in patients continued on ACEIs/ARBs in the inpatient setting.

Methods: This was a retrospective cohort study that included adult patients who were continued on ACEIs/ARBs within 24 hours of hospitalization. Patients who developed AKI within 48 hours of admission or received cancer treatment were excluded. AKI was defined using KDIGO criteria. Risk factors for AKI were compared between the AKI and non-AKI groups.

Results: Among the 184 patients included, 92 patients developed AKI (age 66±13 yrs (mean±SD), 52% male, 54% Black). Patients with AKI had a higher baseline serum creatinine (1.2±0.4 vs. 1±0.4 mg/dL, p<0.001), a lower eGFR (54±10 vs. 56±7mL/min/1.73m², p=0.03), and were more likely to have a diagnosis of CKD (40% vs.14%, p<0.001), an ICU stay (44% vs. 17%, p<0.001), a surgical procedure (34% vs. 14%, p<0.001), hypotension (24% vs. 2%, p<0.001), and concomitant loop diuretic therapy (52% vs. 36%, p=0.03). The AKI group had a longer length of stay (14±11 vs. 8±3 days, p<0.001) and a higher rate of all cause hospital mortality (8% vs. 1%, p=0.03). Factors associated with a significant increase in risk of AKI in the multivariable analysis were CKD (OR=4.3, 95% CI 1.6-9.3, p<0.001), hypotension (OR=14.2, 95% CI 3.1-65.0, p<0.001), and surgical procedures (OR=3.5, 95% CI 1.6-7.9, p<0.001).

Conclusions: Continuation of ACEIs/ARBs during hospitalization may increase the risk of AKI in select patients. Temporary discontinuation of ACEIs/ARBs may be warranted during hospitalization in patients with CKD, hypotension, or planned surgical procedures.

PUB033

Serum Neutrophil Gelatinase-Associated Lipocalin: A Novel Biomarker for Prediction of AKI Development in Critically Ill Patients

Magdy M. Elsharkawy, Abdel Rahman Khedr, Amr Mohab, Haitham Ezzat. *Nephrology, Ain Shams Univ, Cairo, Egypt.*

Background: Acute kidney injury (AKI) is a frequent complication in critically ill patients and is associated with high morbidity and mortality; therefore, its prophylaxis, diagnosis and intervention positively impact patient evolution. Neutrophil gelatinase-associated lipocalin (NGAL) is thought to be a novel biomarker of AKI of several etiologies and is increased in both serum and urine before the increase of serum creatinine.

Methods: A prospective cohort study was conducted on 100 critically ill patients in ICU. Patients were stratified into 2 groups based on AKI development. Group I which included 50 patients who did not develop AKI, and group II which included 50 patients who developed AKI. AKI was defined based on acute kidney injury network (AKIN) classification. The Sequential Organ Failure Assessment (SOFA) scores were also calculated for all patients. Detailed medical history, demographic data and routine laboratory investigations were done. Serum NGAL was measured upon admission to ICU and upon AKI development.

Results: 60 males and 40 females were included in the study with mean age 37.52 years. As regards risks of AKI development, 9% of patients had sepsis, 15% were dehydrated, 11% had contrast exposure, 12% had rhabdomyolysis, 29% had shock and 24% had history of NSAID intake recently. On admission, there were no significant differences between the patients as regards s.creatinine, hemoglobin level and other laboratory parameters ($p > 0.05$). Serum levels of NGAL were significantly higher in group II, before AKI development, with mean value 958.5 ng/ml, when compared with group I, mean value 272.17 ng/ml ($p < 0.01$). Serum NGAL levels were significantly higher in group II after AKI development when compared with the levels before AKI development in the same group (1660.35 ng/ml) ($p < 0.01$). There was no significant correlation between NGAL levels and AKIN classification stages.

Conclusions: In the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes. Reassessment of AKI classification and stages should be considered.

PUB034

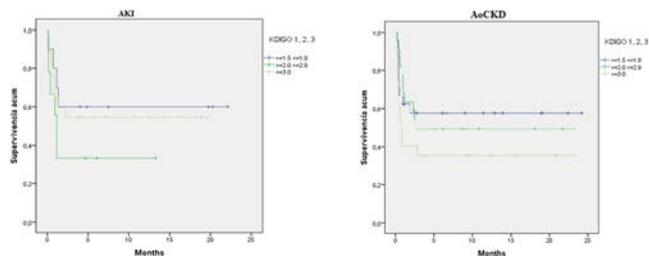
Does Previous CKD Affect Renal Recovery After Acute Kidney Injury?

Maria Isabel Acosta-Ochoa, Josefina Martin, Alicia Mendiluce. *Nephrology, Hospital Clinico Univ, Valladolid, Spain.*

Background: AKI definition includes a sharp increase of serum creatinine (SCr), essentially reversible. There is a lack of consensus of a standard definition of Renal Recovery (RR). The exact course of the repair process is subject of thorough investigation. Few studies have engaged in comparing rates of RR in patients with previous impaired vs. normal renal function.

Methods: Retrospective cohorts study, 12-months period. We defined RR as discharge SCr with maximum increment $\leq 25\%$ over basal value, and non recovery as $\geq 26\%$, HD persistence, and death. We studied 2 groups: AKI and Acute on Chronic Kidney Disease (AoCKD). We tested epidemiological features, Charlson Index (ChI), and KDIGO stage. We plotted a Kaplan-Meier survival curve 24 months post-discharge.

Kaplan-Meier Curves for 2 Years Survival



Results: 270 patients, AKI=125, AoCKD=145, clinical features and KDIGO stages: see table 1.

Features	AKI (N=125)	AoCKD (N=145)	P Value
Male (%)	77 (62)	98(68)	0,30
Age (SD)	66.9 ± 15	75.4 ± 11.9	<0.001
HT (%)	96 (77)	131 (90)	<0.001
DM (%)	44 (35)	70 (48)	0.003
ChI (SD)	3.8 ± 2.5	4.4 ± 2.3	<0.001
KDIGO			
Stage1 (%)	43 (34)	47 (32)	0,19
Stage2 (%)	17 (14)	16 (11)	0,52
Stage3 (%)	65 (52)	82 (57)	0,45
Results			
RR (%)	44 (35)	51 (35)	0,99
HD Dependence (%)	1 (1)	7 (5)	0.05
Mortality (%)	21 (17)	38 (26)	0,06

65% were males, AoCKD were older 66,9y, worst ChI 4.4. In AKI group 35% met RR criteria, 1% were HD dependent and 17% died. AoCKD group 35% recovered, 26% died, 5% were HD dependent at discharge $P=0.05$. Kaplan-Meier curves show a worst survival in the KDIGO Stage 2 for AKI and Stage 3 in the AoCKD group.

Conclusions: In spite of older age and worst ChI AoCKD cohort recovered similarly with the AKI group, except for HD dependence at discharge. The finding that KDIGO Stage 2 means worst medium term survival for the AKI group needs further study.

PUB035

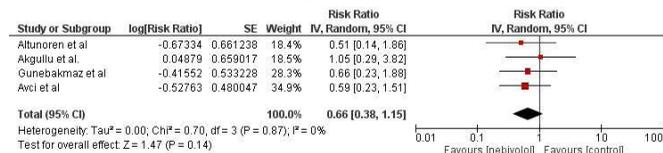
The Effect of Nebivolol on Contrast-Induced Acute Kidney Injury: A Meta-Analysis

Natanong Thamcharoen,¹ Charat Thongprayoon,¹ Wisit Cheungpasitporn.² ¹Dept of Medicine, Bassett Medical Center and Columbia Univ College of Physicians and Surgeons, Cooperstown, NY; ²Div of Nephrology and Hypertension, Dept of Internal Medicine, Mayo Clinic, Rochester, MN.

Background: Nebivolol provides protective effect on contrast-induced acute kidney injury (CIAKI) in animal models. However, the reports on the efficacy of nebivolol for the prevention of CIAKI in human remain unclear. The objective of this meta-analysis was to assess the effect of nebivolol for the prevention of CIAKI.

Methods: Comprehensive literature searches were performed using MEDLINE, EMBASE, and Cochrane Database from inception through February 2015. Studies that reported relative risks, odd ratios or hazard ratios comparing the risk of CIAKI in patients who received nebivolol versus those who did not were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Four studies (2 RCT and 2 cohort studies) with 543 patients were included in our analysis to assess the risk of CIAKI and the use of nebivolol. Of 543 patients with contrast exposures, 30 patients (5.32%) had CIAKI. Patients in the nebivolol group had an overall lower incidence of CIAKI (14.35%) compared to the control group (17.43%). The pooled RR of CIAKI in patients receiving nebivolol was 0.66 (95% CI, 0.38-1.15, $I^2 = 0$).



When meta-analysis was limited only to RCTs, the pooled RR of CIAKI in patients receiving nebivolol was 0.79 (95% CI, 0.35-1.79, $I^2 = 0\%$).

Conclusions: Despite no statistical significance, there was a trend toward reduced CIAKI risk in patients receiving nebivolol. This finding suggests the need of further studies on the use of nebivolol in addition to standard IV crystalloid hydration in the prevention of CIAKI.

PUB036

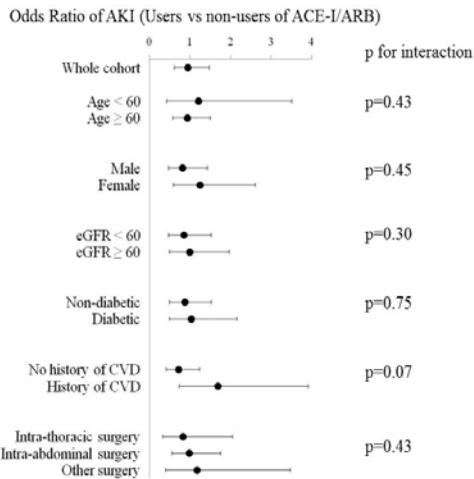
Patients with Cardiovascular Diseases Are Susceptible to Acute Kidney Injury After Non-Cardiac Surgery Under Preoperative Use of Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

Miho Tagawa,¹ Takayuki Hamano,² Masaru Matsui,¹ Katsuhiko Morimoto,¹ Ken-ichi Samejima,¹ Yasuhiro Akai,¹ Yoshihiko Saito.¹ ¹Nara Medical Univ, Nara, Japan; ²Osaka Univ, Osaka, Japan.

Background: It is unknown in which subgroups of patients the preoperative use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) is a predictor for acute kidney injury (AKI) after non-cardiac surgery.

Methods: This is a retrospective cohort study on patients who underwent non-cardiac surgery from 2007 to 2009. After exclusion of urological surgery, missing creatinine values, and preoperative dialysis, the data for 2,725 patients were available. The exposure of interest was preoperative use of ACE-I/ARB. Primary outcome was postoperative AKI (AKIN criteria). The odds ratio (OR) of postoperative AKI among ACE-I/ARB users compared to non-users was analyzed using multivariable logistic regression models, adjusted for the logit of propensity score for ACE-I/ARB use. $P < 0.1$ was considered statistically significant for interaction.

Results: Mean (SD) age was 61 (16) and estimated glomerular filtration rate was 81 (24) ml/min/1.73m². There were 40/460 (8.7%) cases of postoperative AKI in ACE-I/ARB users and 97/2,265 (4.3%) in non-users. The adjusted OR of AKI were shown.



History of cardiovascular diseases(CVD) (either coronary artery disease, stroke, peripheral arterial disease, atrial fibrillation, or left ventricular ejection fraction<40%) was a significant effect modifier for the association of ACE-I/ARB and AKI (p for interaction 0.07). The OR(95% CI) of AKI among ACE-I/ARB users was 1.70(0.73-3.93) and 0.72(0.42-1.24) in patients with CVD and without CVD, respectively.

Conclusions: ACE-I/ARB use was associated with higher OR of AKI in patients with prior CVD compared to patients without, suggesting that patients with CVD are more prone to AKI with the use of ACE-I/ARB.

PUB037

Whole Ischemia-Reperfusion Injury: The Effect of Whole-Body Cooling on Renal Function Silvia De Rosa,¹ Zaccaria Ricci,³ Salvador Roberto Lopez,¹ Jose Luis Salas,¹ Stefano Marcante,¹ Sara Samoni,¹ Massimo de Cal,¹ Silvia Maria Pulitano,² Massimo Antonelli,² Raffaele Bonato,¹ Claudio Ronco.¹ ¹IRRV; ²Intensive Care Unit, UCSC, Rome; ³Paediatric Cardiac Intensive Care Unit, OBG, Rome.

Background: Hypothermia is able to reduce the risk of renal failure after renal ischemia-reperfusion injury in animals. In humans, Cardiac Arrest(CA), a whole-body ischemia-reperfusion syndrome, causes warm renal ischemia-reperfusion injury, similar to animal models of ischemic acute kidney injury(AKI). Induced hypothermia(IH) is a treatment potentially efficacious for post-ischemic injury. It is unclear what effect could have on renal function. The aim of the study was to investigate the development of AKI during the IH.

Methods: Between Jan2013-Mar2015, we performed a prospective observational study of 36 comatose pts resuscitated from CA and treated with IH performed with 2 different surface cooling devices: 1) Arctic Sun Temperature Management System (Medivance, Louisville CO); 2) Blanket. Temperature rate and trend, and the development of AKI during induction (0-6hrs), maintenance (24hrs), rewarming (48hrs) and normothermia (72hrs) was assessed with RIFLE and KDIGO criteria.

Results: Pts were enrolled and followed for the development of AKI during intensive care unit stay. In the induction and maintenance phases, the rate and the target temperature was similar; conversely, the rewarming phase was shorter with a target temperature higher in Blanket than in Arctic Sun group (458 min vs 615 min; 37.2°C vs 36.3°C). The trend and the rate of temperature, but also the development of AKI is showed in figure 1.



Conclusions: IH could be associated with development of AKI in the rewarming phase (rate 0.25 to 0.5 °C). The optimal rewarming rate is unknown. Randomized controlled trials are needed to determine the real effect of temperature on kidney, the optimal rewarming strategy and applications of this treatment for kidney in other settings.

Funding: NIDDK Support

PUB038

Decongestion-Associated Worsening Renal Function Does Not Increase Mortality of Patients with Acute Heart Failure Girish Singhanja, Kawther Farouk Alquadan, Amir Kazory. *Nephrology, Univ of Florida, Gainesville, FL.*

Background: A significant subset of patients admitted for acute decompensated heart failure (ADHF) develop worsening renal function (WRF). While there is consistent data regarding the negative impact of baseline renal dysfunction on the outcomes of these patients, the evidence on the prognostic implication of WRF during admission for decongestion is less well-understood. The aim of this study is to provide a reappraisal of the effect of decongestion on the prognostic value of WRF in patients admitted for ADHF.

Methods: Articles cited in PubMed database from 1995 to 2015 using key words "congestion", "heart failure", "worsening renal function", and "hemoconcentration" were searched. Those studies evaluating the relationship between decongestion, renal function, and ADHF in patients treated with diuretic-based conventional therapies were selected. Ultrafiltration trials were excluded. Relevant data including change in renal function, diuretic dose, change in weight, and mortality were extracted and compared.

Results: A total of 12,843 patients from 13 trials (9 retrospective and 4 prospective) with data pertaining to decongestion in ADHF patients were included in this study. The mean age of the patients was 67.1 years with follow up periods ranging from 60 days to 5.3 years. Eleven studies reported development of WRF following decongestion. The incidence of WRF was reported to be 10 to 50.1% with weight reduction ranging from 2 to 5.4 kg. Twelve studies did not observe any negative impact for WRF on the mortality of patients with ADHF unless associated with markers of persistent congestion such as lack of hemoconcentration.

Conclusions: Decongestion is associated with markers of fluid removal and WRF in the setting of ADHF. Currently available data suggest that decongestion-associated WRF does not result in increased mortality whereas persistent congestion is likely to be the driving factor for adverse outcomes in these patients. Randomized controlled trials are needed to confirm these findings as they could portend significant therapeutic implications in cardiorenal syndrome.

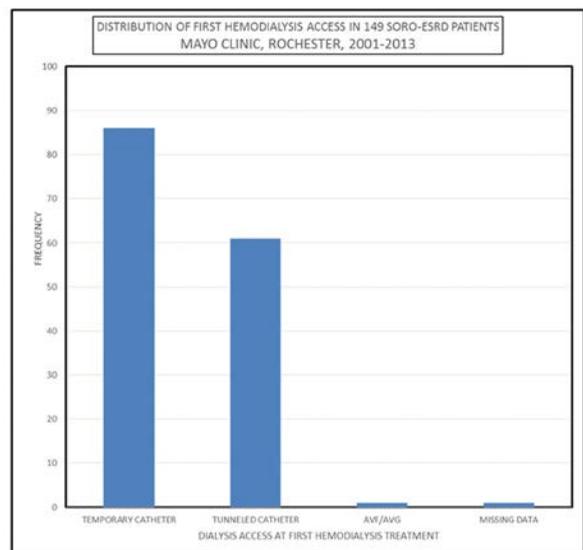
PUB039

A 13-Year Mayo Clinic Retrospective Study of the Syndrome of Rapid Onset End Stage Renal Disease (SORO-ESRD) in an Incident Hemodialysis Cohort Macaulay A. Onuigbo,^{1,2} Nneoma Agbasi,¹ LaTonya J. Hickson.³ ¹Medicine, Mayo Clinic College of Medicine, Rochester, MN; ²Nephrology, Mayo Clinic Health System, Eau Claire, WI; ³Psychiatry Nursing, North East London NHS Foundation Trust, London, United Kingdom.

Background: We first described the syndrome of rapid onset end stage renal disease (SORO-ESRD) in 2010 - acute yet irreversible ESRD after AKI. However, its overall impact on ESRD outcomes in the general US ESRD population remains speculative.

Methods: A retrospective examination of SORO-ESRD among the incident Mayo Clinic ESRD population, 2001-2013 was completed in November 2014.

Results: 149 of 1461 (10%) incident ESRD patients had SORO-ESRD - M:F = 76:73, mean age 62 years (19-95), 139 (93%) native kidneys, 10 (7%) kidney transplant recipients (KTRs). Ninety-nine percent of SORO-ESRD patients' initial vascular access was a dialysis catheter. Kidney biopsy - the commonest pathologic diagnoses were acute tubular necrosis (ATN) in 3 (25%) KTRs and in 7 (21%) native kidneys. Cardiac arrest was the leading cause of death in SORO-ESRD.



Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: Among 1461 incident ESRD patients seen at Mayo Clinic Dialysis Services, Rochester, 2001-2013, 149 (10%) had SORO-ESRD. There was no gender nor age disparity between SORO-ESRD patients and the general ESRD cohort. Ninety-nine percent (99%) SORO-ESRD patients' initial vascular access was a dialysis catheter. ATN was the leading pathologic diagnoses for AKI among KTRs and in native kidneys. Cardiac arrest was the leading cause of death in SORO-ESRD, similar to the general ESRD population. We conclude that SORO-ESRD contributes significantly to incident ESRD here in the USA both among KTRs and in native kidneys. Furthermore, it negatively impacts on the success of AVF-First Programs. Efforts to mitigate AKI in CKD patients must be given more attention and priority by practicing nephrologists in particular, and by physicians in general.

PUB040

Saline-Induced, Diuretics-Responsive Acute Renal Failure (ARF): Evidence that Anasarca Is Nephrotoxic and Diuresis Is Therapeutic Grant Meltzer,¹ Kai Lau,^{1,2} *¹Nephrology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; ²Medicine, VA Medical Center, Oklahoma City, OK.*

Background: Recent studies showed the association of fluid overload in ARDS & surgical patients and increased ventilator dependency, ICU & hospital stays, short-term mortalities, & incidence of ARF. But a cause-and-effect relationship was unproven in cross-sectional observations. In grossly edematous in-patients with unexplained ARF, we tested the hypothesis that anasarca caused the renal failure & diuresis induced recovery.

Methods: Entry criteria were fully evaluable patients, ³3 kg weight or ³3 L fluid gain, $\geq 50\%$ acute loss of estimated creatinine clearance (CrCl) or $\geq 2 \times$ rise in serum creatinine (Scre) without identifiable causes. All data were reviewed, recorded, tabulated & statistically analyzed, notably vital signs, weight, intake, output & lab. 36 qualified patients were diuresed by IV furosemide at rates keeping normotension off anti-hypertensives. Serial volume markers & renal responses were noted. Palliative care & hepatorenal syndrome were excluded.

Results: Fluid overload was due to heart failure (40%), liver failure (22%), CKD (16%), proteinuria (9%) & iatrogenic factors (10%). During 42 ARF episodes, mean weight was up 12.5 kg in 13.7d. Scre rose (4.41 vs. 1.27mg%) & CrCl fell (25 vs. 76 ml/min). Decrements in CrCl correlated with edema weight gain (p<0.02). Over 11.9 d, 15.2 kg of fluid were diuresed. Renal function greatly improved in 33 patients & unchanged in 3 despite >4 kg diuresis. As an entire group, Scre fell to 1.45 mg% & CrCl rose to 67 ml/min. Increments of CrCl also correlated with diuresis volume (p<0.04). At a diuretic rate of 1.5 kg/d, no adverse events occurred.

Conclusions: 1. Our data support the hypothesis for the entity of Saline-Induced, Diuretics-Responsive Acute Renal Failure. 2. Likely mediated by reduced cardiac output, venous congestion, renal interstitial edema &/or abdominal hypertension, it is analogous to congestive kidney failure. 3. Preventable & treatable, it could cause or aggravate ARF from other etiologies. 4. Diuresis in cohorts at rates & monitored as ours should be safe & efficacious.

Funding: NIDDK Support, Veterans Administration Support, Private Foundation Support

PUB041

Is RIFLE Classification a Good Shot for Staging Acute on Chronic Kidney Disease? Maria Isabel Acosta-Ochoa, Josefina Martin, Alicia Mendiluce. *Nephrology, Hospital Clinico Univ, Valladolid, Spain.*

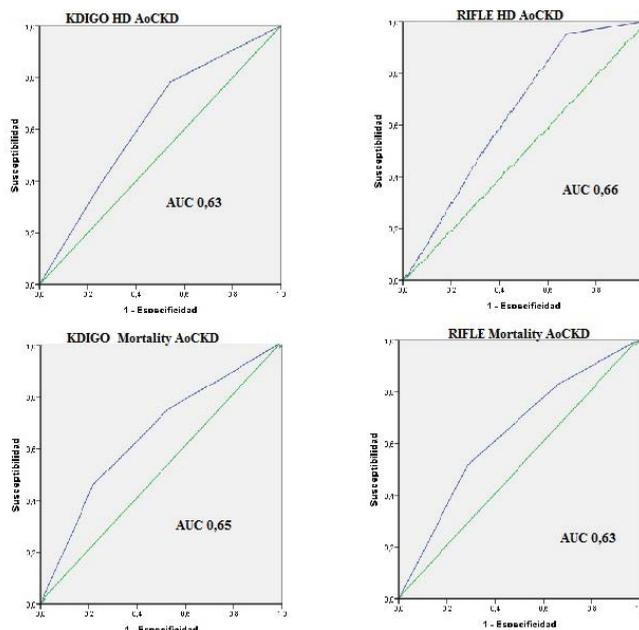
Background: 8-16% of worlds population may have CKD, which is a risk factor and promoter of AKI. We tested the performance of RIFLE and KDIGO classifications in staging severity and predicting outcomes in Acute on CKD (AoCKD) individuals. KDIGO with a 0,3mg/dL SCr increase includes patients in stage 1 category, and includes automatically in stage 3 patients with peak SCr ≥ 4.0 mg/dL.

Methods: Retrospective cohorts study. Patients were divided in 2 groups: AKI and AoCKD. We collected clinical data, and classified AKI severity contrasting distribution strata between groups by RIFLE and KDIGO criteria. And tested the ability of both classifications for predicting need for HD and in hospital mortality with a AUC ROC analysis.

Results: 270 patients were included, AKI=125, AoCKD=145. Clinical features and RIFLE and KDIGO stages are listed in table 1.

FEATURES	AKI (N=125)	AoCKD (N=145)	P Value
Male (%)	77 (62)	98(68)	0,30
Age (SD)	66.9 ± 15	75.4 ± 11.9	<0.001
HT (%)	96 (77)	131 (90)	<0.001
DM (%)	44 (35)	70 (48)	0.003
ChI (SD)	3.8 ± 2.5	4.4 ± 2.3	<0.001
RIFLE			
No AKI (%)	21 (17)	23 (16)	0,83
Risk (%)	22 (17)	35 (24)	0,18
Injury (%)	17 (14)	44 (30)	0,001
Failure (%)	65 (52)	43 (30)	<0.001
KDIGO			
Stage1 (%)	43 (34)	47 (32)	0,19
Stage2 (%)	17 (14)	16 (11)	0,52
Stage3 (%)	65 (52)	82 (57)	0,45

65% males, AoCKD individuals were older 66,9y, and had worst Charlson Index (ChI) 4,4. In figure 1 are shown AUC ROC curves for adverse outcomes.



Conclusions: With the KDIGO staging criteria we obtain more homogeneous distribution strata. With the ROC analysis neither classification performs better in predicting adverse outcomes. We found no practical advantage when using neither classification. In the noAKI (by RIFLE) stratum no adverse event was present, so by including a 0,3mg/dL SCr increase augments sensibility, but may be not specificity.

PUB042

Incidence of Acute Kidney Injury, Risk Factors for Acute Kidney Injury and Absence of Renal Recovery in Patients on Aminoglycosides Francois Paquette,¹ Amelie Bernier-Jean,¹ Veronique Brunette,¹ Vincent Pichette,² Helene Ammann,¹ Stephan Troyanov,¹ Josee Bouchard.¹ *¹Hopital du Sacre-Coeur de Montreal, Canada; ²Hopital Maisonneuve-Rosemont, Canada.*

Background: The KDIGO guidelines recommended to avoid aminoglycosides (AG) in patients at risk or with acute kidney injury (AKI). We determined the frequency of administration, incidence of AKI, and risk factors for AKI and absence of renal recovery in patients receiving AG over the last decade.

Methods: We performed a retrospective cohort study on AG administration in two university-affiliated centers, and then performed a nested case-control study, pairing AG-AKI cases to 2 controls for age and gender. AKI was defined by a 50% increase in creatinine after ≥ 5 days of AG up until 7 days after cessation of AG, and renal recovery, by a decrease in creatinine to within 50% of baseline creatinine over 3 weeks after cessation of AG.

Results: Between 2001 and 2015, the frequency of AG administration and drug dosing progressively declined. Out of 562 patients, sixty-five developed AKI attributed to AG (12%). In the case-control study (n=195), age was 71 (IQR 58-81) and 46% were male. The duration of AG administration was 10.0 (IQR 7.0-15.0) days, excluding days after AKI diagnosis in AKI patients. Maximal AKI stage was 1 for 55.3%, 2 for 29.2% and 3 for 15.4% of patients. Independent risk factors associated with AKI were concomitant vancomycin administration, high trough levels, heart failure, and site of infection (endocarditis and febrile neutropenia vs. other). Only fifty-one percent (50.8%; 33/65) of patients recovered their kidney function. These patients had an AKI duration of 7.0 (IQR 4.0-11.5) days. Heart failure was associated with a lower likelihood of renal recovery, while cancer patients more likely recovered their kidney function.

Conclusions: Over the last decade, the frequency of AG administration and dosing have progressively decreased but the incidence of AKI remained unchanged. In our cohort, vancomycin administration, high trough levels, heart failure, and site of infection were independent risk factors associated with AKI. Almost half of patients did not recover their kidney function, which was more often seen in patients with heart failure.

PUB043

Prairie Continuous Renal Replacement Therapy (CRRT) Study – Outcomes of CRRT in a Single Canadian Tertiary Centre Bhanu Prasad,¹ Michelle Urbanski,² Erwin Karreman.³ ¹Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada; ²College of Medicine, Univ of Saskatchewan, Regina, SK, Canada; ³Research and Performance Support, Regina Qu Appelle Health Region, Regina, SK, Canada.

Background: Patients with stage III Acute Kidney Injury (AKI) requiring Renal Replacement Therapy (RRT) have the highest short-term and long-term mortality of any group with AKI. Our study aimed to prospectively follow patients with stage III AKI on Continuous Renal Replacement Therapy (CRRT) during their hospitalization in our tertiary care centre from April 2013 to September 2014.

Methods: We prospectively gathered the following: date and time of hospital admission, transfer to ICU, and starting CRRT, creatinine at admission and at CRRT initiation, weight on admission and at CRRT initiation. Duration of oliguria and anuria, exposures (sepsis, critical illness, circulatory shock, trauma, cardiac surgery, major non cardiac surgery, nephrotoxic medications, and radio contrast agents) and susceptibilities (dehydration, >65 years of age, female, pre existing CKD), APACHE score II, Inotrope support, FiO₂, ECMO. Survival on CRRT, in ICU and hospital survival and renal recovery was documented.

Results: Of the 2634 patients: (2201/2634)83.6% had no AKI, and (269/2634)10.2% had stage III AKI of whom 106/269 (40%) were started on CRRT. 8/106 died in ICU whilst on CRRT, 58 died after CRRT was discontinued in ICU and 4 died on the ward. Mean (± SD) were: Creatinine (mmol/L) 337.2 (±260.1), Norepinephrine dose 22.5 (±19.6), APACHE II scores 34.8 (±9.0). The prescribed CRRT dose was 35 ml/minute and the mean delivered dose was 34.6±2.6(SD). Survivors were younger (years)(54.5± 15.6 vs. 62.0±15.4), had lower Norepinephrine dose (mcg/minute) (16.95±13.58 vs. 26.09±21.18), and had a shorter stay in ICU prior to starting CRRT (6:06 hours vs. 12:26 hours). Stage III AKI needing CRRT was associated with 62% mortality in hospital. 17/106 died within 24 hours of initiating therapy. 5/106 patients recovered within 24 hours.

Conclusions: AKI is associated with 62% in centre mortality. 16% died within 24 hours of initiating CRRT. This raises a clinical concern of the benefit vs futility of initiating CRRT in specific settings.

PUB044

Urinary Liver Fatty Acid Binding Protein Predicts Acute Kidney Injury Associated with Abdominal Aortic Repair Daisuke Ichikawa,¹ Atsuko Ikemori,¹ Takeshi Sugaya,¹ Kenjiro Kimura,² Yugo Shibagaki.¹ ¹Nephrology and Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; ²Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Acute kidney injury (AKI) is common problem after cardiovascular surgery. AKI is usually diagnosed on the basis serum creatinine (Scr) and urinary output. However, Scr is of low sensitivity in patients with poor renal function. Because urinary liver-type fatty acid binding protein (L-FABP) reflects renal tubular injury, we evaluated whether perioperative changes in urinary L-FABP can predict AKI.

Methods: Subjects were 68 patients who underwent EVAR and 32 patients who underwent open repair. We obtained urine samples before surgery, after anesthesia induction, upon stent placement, at the end of surgery, 4 hours after surgery, and on postoperative day (POD) 1, 2, and 3 for measurement of urinary L-FABP and urinary albumin in the EVAR patients. We obtained urine samples before surgery, after anesthesia induction, before aortic cross clamping (AXC), 1 and 2 hours after AXC, at the end of surgery, and on PODs 1, 2, and 3 for measurement of urinary L-FABP and urinary albumin in the open repair patients. We obtained serum samples before surgery, immediately after surgery, and on POD 1, 2, and 3 for measurement of Scr.

Results: AKI developed in 5 (7.4%) EVAR patients and in 9 (28.1%) open repair patients. With EVAR, urinary L-FABP was increased 4 hour after the procedure (P = 0.002), and it decreased but remained elevated for 3 POD (P = 0.003). With AKI, Scr increased (P = 0.004) and eGFR decreased (P = 0.003) by POD2. Scr and eGFR did not change in patients in whom AKI did not develop. With open repair, urinary L-FABP increased significantly to its maximum by 2 h after AXC (P = 0.008) and then decreased gradually over the 3 PODs (P = 0.038). The increase in urinary L-FABP was greater with open repair than with EVAR. ROC analysis showed urinary L-FABP to be more sensitive than Scr, eGFR, and urinary albumin for early detection of AKI.

Conclusions: Urinary L-FABP appears to be a sensitive biomarker of AKI in patients undergoing abdominal aortic surgery, especially those treated by EVAR.

PUB045

Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Biomarker for Acute Kidney Injury in Patients with Chronic Kidney Disease Ha yeon Kim, Eun Hui Bae, Soo Wan Kim, Seong Kwon Ma. *Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.*

Background: The aim of this study was to evaluate plasma NGAL levels as a predictor of early AKI in patients with with/without chronic kidney disease (CKD) and to assess whether plasma NGAL level could represent a useful marker of recovery in patients undergoing continuous renal replacement therapy (CRRT).

Methods: This single center retrospective observational study included 343 patients with AKI or CKD. The patients were classified into 3 groups: AKI (N=69), AKI on CKD (N=162), CKD (N=112). The cut-off values of NGAL was 200 ng/ml and those of cystatin-C

was 1.0 mg/L. **Study II:** The retrospective observational study included 404 patients treated with CRRT. The patients were divide into 2 groups: renal recovery (N=120) vs. renal non-recovery (N=284) and survivor (N=193) vs. non-survivor (N=211).

Results: The prevalence of abnormal NGAL values was 69.0 % in AKI group, 94.5 % in AKI on CKD group and 91.8 % in CKD group. The value of NGAL was positively correlated with eGFR (r = 0.41, p < 0.001), and cystatin-C (r=0.45, p = 0.021). The mean values of follow-up NGAL were 475.9 ± 435.9 ng/ml in AKI group, 773.2 ± 370.6 ng/ml in AKI on CKD group, 709.4 ± 401.6 ng/ml in CKD group (p < 0.001). In AKI group, the difference of NGAL (baseline NGAL – follow-up NGAL) was the highest (110.8 ± 325.0 ng/ml in AKI group, 35.7 ± 205.2 ng/ml in AKI on CKD group, 14.1 ± 201.3 ng/ml in CKD group, p < 0.001). In comparisons between renal recovery group and non-recovery group and survivors and non-survivors in CRRT patients, both baseline NGAL and follow-up NGAL were not different, but the difference of NGAL (baseline NGAL – follow-up NGAL) was increased significantly in a renal recovery and survivors group (90.6 ± 82.9 ng/ml in renal recovery group vs. 33.8 ± 53.7 ng/ml in renal non-recovery group, 129.8 ± 182.4 ng/ml in survivor group vs. -98.5 ± 162.6 in non-survivor group, p < 0.001, respectively).

Conclusions: The value of serum NGAL per se has a limitation on diagnosis of AKI in patients with underlying CKD. In patients treated with CRRT, hourly urine output and follow up of serum NGAL value may predict renal recovery and survival.

PUB046

C3 Glomerulopathy: A Pediatric Case Luis A. Ortiz,¹ Daniel Kleven,² Harika Gorti.³ ¹Ped. Nephrology, Georgia Regents Univ, Augusta, GA; ²Pathology, Georgia Regents Univ, Augusta, GA; ³MCG, Georgia Regents Univ, Augusta, GA.

Background: C3 glomerulopathy (C3G) is characterized by C3 deposit in the glomeruli with minimal Ig deposition. C3G is described as an unregulated activation of the alternative complement pathway due to a genetic mutations in Factor H or I, or acquired factors such as C3 nephritic factor, an IgG autoantibody stabilizing C3 convertase. The pattern of the injury varies from mesangio-proliferative, membranoproliferative, to endocapillary proliferative glomerulopathy. EM finding demonstrate hump shaped sub epithelial deposits, characteristic of acute post-infectious glomerulonephritis (PIGN). We present a pediatric case that met the initial criteria for PIGN, but was diagnosed as C3G according the pathology.

Methods: 15 y/o AA/M with Thin Basement D., HTN, asthma presented with one Hx of sore throat, gross hematuria, facial swelling, no distal edema. Initial oliguria and high Cr. PE revealed periorbital edema, no pharyngeal erythema, lung clear, abdomen with no ascites. On admission, Hb 11.6 g, Cr:3.26mg, Albumin:2.5 gr, UA20-50 RBC, UOP: 0.37 ml/kg/hr. Despite treatment with methylprednisolone, albumin and furosemide, his Cr. increased to 6.48, ASO 654 UI, aDNAseB normal., CRP 12.6. Group A strep was negative for growth. Kidney biopsy: glomeruli w/segmental sclerosis, endocapillary infiltration of neutrophils, IF: extensive C3 staining with scant IgG and small fibrin deposition (focal necrosis). EM: large subepithelial deposits. Worsening kidney function required hemodialysis. After 6 months, he continues on Hemodialysis.

Conclusions: Kidney biopsy with C3 dominant on IF, large subepithelial deposits on EM, hypocomplementemia and clinical of gross hematuria preceded by URI suggested acute PIGN, but this overlaps with the histological presentation of C3G of C3 dominant staining with scant IG deposition, subepithelial deposits and low serum C3. No resolution of AKI after 8 weeks of presentation was unusual for PIGN, steering diagnosis towards C3G. Clinicians should note the high overlap between the clinical and histology of PIGN and C3G. It is imperative to conduct further studies to accurately diagnose and treat patient with C3G.

PUB047

Predictors of End Stage Renal Disease in Scleroderma Renal Crisis – A Single Center Experience Sunedha Dhar, Cybele Ghossein. *Div of Nephrology, Northwestern Univ - Feinberg School of Medicine, Chicago, IL.*

Background: Scleroderma renal crisis (SRC) is one of the most acute and life-threatening complications of systemic sclerosis (SSc). It is typically characterized by accelerated hypertension and acute kidney injury (AKI). Angiotensin converting enzyme inhibitors (ACEI) are currently the treatment of choice for this disease. Despite use of ACEI, 50% of patients with SRC develop end stage renal disease (ESRD) which is associated with poor long term outcomes. Our aim was to define the clinical characteristics and outcomes of SRC patients admitted to our institution.

Methods: This was a retrospective chart review of all patients admitted with SRC to Northwestern Memorial Hospital (NMH) between the years of 1/1994 to 4/2015. ESRD was defined as the need for chronic dialysis during admission for SRC.

Results: There were 23 patients with a diagnosis of SRC made either clinically or by renal biopsy during this time period. Mean time to SRC was 1.3 years after diagnosis of SSc. 47% of patients developed ESRD during the same admission. Development of ESRD was not associated with age, gender, race, anti-RNA polymerase III test positivity, intensive care unit (ICU) admission, prior ACEI or angiotensin receptor blocker (ARB) use, or creatinine on admission. ESRD was significantly associated with time to control blood pressure.

	Not requiring HD N = 12 (%)	Requiring HD N = 11 (%)	P value
Mean Age (yr)	57	57.36	0.95
Gender Female Male	11 (91) 1 (8)	8 (72) 3 (27)	0.32
Race White Afro-American Other	8 (66) 3 (25) 1(8)	7 (63) 2 (18) 2 (18)	0.87
anti-RNA polymerase III	3 (25)	5 (45)	0.39
ICU initial admission	6 (50)	2 (18)	0.19
ACEI/ARB on admission	3 (25)	7 (63)	0.09
Mean days to start ACEI	0.9	1	0.88
Mean days to control BP	3.1 (N = 11)	5.83 (N = 6)	0.03
Normotensive on admission	2 (16)	4 (36)	0.37
Mortality	2 (16)	2 (18)	1.00
Mean Creatinine on admission (mg/dl)	2.04	2.95	0.07

Conclusions: SRC is a serious kidney and life threatening complication of SSc. Delay in blood pressure control increases risk of ESRD in SRC patients.

PUB048

Acute Kidney Injury Risk Assessment at the Hospital Front Door: What Is the Best Measure of Risk? Aled O. Phillips,¹ Dafydd Phillips,¹ Mohamed Hassan,⁵ John Geen,² Vikas Lodhi,⁶ Hemanth Bolusani,⁴ Gareth Roberts.³
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Background: We examined the prevalence of AKI-risk factors in the emergency medical unit, generated a modified risk assessment tool and tested its ability to predict AKI.

Methods: 1196 patients admitted to medical admissions units were assessed for patient associated AKI-risk factors. Subsequently, 898 patients were assessed for a limited number of fixed risk factors with the addition of hypotension and sepsis. This was correlated to AKI episodes.

Results: In the first cohort the prevalence of AKI risk factors was 2.1±2.0 per patient, with a positive relationship between age and the number of risk factors and a higher number of risk factors in patients ≥65yrs. In the second cohort 12.3% presented with or developed AKI. Patients with AKI were older and had a higher number of AKI risk factors. In the AKI cohort 72% of the patients had ≥2 AKI risk factors compared to 43% of the cohort with no AKI. When age ≥65 yrs was added as an independent risk factor 84% of those with AKI had ≥2 AKI risk factors compared with 55% of those with no AKI. ROC analysis suggest that use of common patient associated known AKI risk factors performs no better than age alone as a predictor of AKI.

Conclusions: Detailed assessment of well established patient associated AKI-risk factors may not facilitate clinicians to apportion risk. This suggests that additional work is required to develop a more sensitive validated AKI predictive tool which would be useful in this clinical setting.

PUB049

Acute Kidney Injury, Requiring Renal Replacement Therapy – Incidence, Causes and Outcomes: One Center Experience Elena Zakharova.
Nephrology, City Clinical Hospital n.a. s.P. Botkin, Moscow, Russian Federation.

Background: Acute Kidney Injury (AKI) is complex condition, associated with high mortality and morbidity. We aimed to evaluate AKI incidence, causes, risk factors and outcomes in patients, managed in nephrology unit of general hospital and urgently requiring Renal Replacement Therapy (RRT).

Methods: Using electronic database for 2010-2014 (4531 admissions, 2257 patients), we searched 604 cases which met KDIGO AKI definition, and selected patients, required RRT.

Results: Study group included 115 patients (19% of all AKI cases), 51 (44%) male, 64 (56%) female, median age 61 [22; 89] years. In 102 (89%) cases AKI was community acquired. Median serum creatinine prior to start of RRT was 981 [242; 2665] μmol/l, 37 (32%) patients had known CKD. Causes and susceptibilities for AKI are shown in table.

Cause/exposure	n of patients	%
Decreased kidney perfusion	33	29
Vasculitis	8	7
Thrombotic microangiopathy	2	2
Interstitial nephritis	8	7
Sepsis	10	9
Critical illness	7	6
Circulatory shock	3	3
Nephrotoxic drugs	6	5
Radiocontrast agents	1	1
Poisoning	2	2
Hantavirus infection	2	2
Hemolysis	2	2
Rhabdomyolysis	9	8
Cast-nephropathy	8	7
Urinary tract obstruction	14	12
Underlying conditions		
Chronic kidney disease	37	32
Dehydration/volume depletion	33	29
Diabetes	9	8
Chronic heart, lung or liver disease	22	19
Multiple myeloma/lymphoma	13	11
Systemic amyloidosis	7	6
Cancer	10	9
Age over 75	18	16

76 (66%) patients partially or completely recovered kidney function, 27 (23%) were still dialysis-dependent after 3 month of follow-up, and 12 (10%) patients died

Conclusions: In our cohort incidence of AKI was 27%, proportion of patients requiring RRT constituted 19% of AKI cases. Vast majority had community acquired AKI, 1/3 developed AKI on the top of pre-existing CKD, 16% were elder than 75 years. Main trigger for RRT-requiring AKI in 29% of cases was initially considered as decreased kidney perfusion, with volume-unresponsiveness due to severe underlying conditions, such as CKD, chronic heart and liver diseases, multiple myeloma, cancer, diabetes and amyloidosis. Other most frequent causes of AKI were sepsis, rhabdomyolysis, vasculitis, and interstitial nephritis. Mortality rate was 10%, ESRD developed in 23% of cases.

PUB050

Renal Manifestations in Paroxysmal Nocturnal Haemoglobinuria Ram R,¹ Dakshinamurthy Kv,² Krishna Parasd A.³ ¹Nephrology, Sri Venkateswara Inst of Medical Sciences, Tirupati, AP, India; ²Nephrology, Mahatma Sri Ramchandra Centenary Memorial Hospital, Hyderabad, Telengana, India; ³General Medicine, NIMS, Hyderabad, India.

Background: Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired chronic disorder characterized by a triad of clinical features- haemolytic anaemia, pancytopenia, and thrombosis. Not many reports of renal involvement in PNH are available in literature.

Methods: We present a case series of PNH with renal involvement. We present the data of PNH patients attended to departments of General Medicine and Nephrology at a government run tertiary care institute in South India. The diagnosis of PNH in these patients during initial phase, between 1998 and 2004 was based on sucrose lysis and Ham’s test. After 2004, the diagnosis was based on flow cytometry to detect CD59 (MIRL), a glycoprotein, and CD55 (DAF) in regulation of complement action. The patient data was collected from 1998 to 2014.

Results: There were 13 patients of paroxysmal nocturnal haemoglobinuria in this period. The mean age was 37 years and the range was 16 to 68 years. There were 7 females. Acute renal failure was noted in 5 patients. Dialysis was performed in three of them. The mean serum creatinine and urea at the initiation of dialysis was 5.4 ± 0.6 mg/dL and 64.1 ± 6.1 mg/dL respectively. The median number of haemodialysis sessions done was four. Renal biopsy was done in four patients. The indication for the biopsy was acute renal failure of more than four weeks. The median number of glomeruli was 9. The tubules showed prominent brown granular pigment within the epithelial cells. It was confirmed as hemosiderin with the Perls’ Prussian blue reaction. A few deposits of hemosiderin were also seen within the tubular lumina. The pathological diagnosis in these four patients was acute tubular necrosis secondary to hemosiderin deposition. In three patients the urinalysis and serum chemistry was suggestive of Fanconi syndrome.

Conclusions: In our patients, three renal manifestations of PNH were identified. They were acute renal failure, renal vessel thrombosis and Fanconi syndrome. Chronic renal failure was not identified.

PUB051

Filling the Gaps in Acute Kidney Injury Epidemiology: A Multicenter Prospective Study in Amazon Fernando de Assis Ferreira Melo,^{1,2} Waledya Araujo lopes de Melo,² Tarcisio Andrade Souza,² Natali Mendes,² Luis Yu,³ Emmanuel A. Burdmann,³ Dirce M T Zanetta.¹ ¹Epidemiology, Univ of Sao Paulo, São Paulo, Brazil; ²Medicine, Federal Univ of Acre, Rio Branco, Acre, Brazil; ³Medicine, Univ of Sao Paulo, São Paulo, Brazil.

Background: In some areas of developing countries, infectious tropical diseases or animal venoms may be important causes of Acute Kidney Injury (AKI). Epidemiological studies of AKI incidence in these areas are scanty and prospective population-based studies are even scarcer.

Methods: Prospective data on all adult patients admitted in all intensive care units (ICU) of the Western Amazon region (600 square kilometers and 800,000 inhabitants) were collected for 6 months in 2014. Patients with chronic kidney disease stage 5, kidney transplant or ICU stay < 48 hours were excluded. AKI was diagnosed by KDIGO and mortality was assessed 30 days after ICU discharge. Data are presented as mean±SD or percent.

Results: 367 patients aged 57.8 ± 19.2 years and with 39% white were evaluated. Main reasons for ICU admission were postoperative (34%), hemodynamic instability (22%) and respiratory failure (13%), with only 1% with tropical diseases. AKI incidence was 38%, but was lower in postoperative patients (28% vs 43% in non-postoperative, p = 0.005). Mortality was higher in AKI patients (53% vs 30% in non-AKI, p < 0.001). Postoperative patients who developed AKI had similar mortality to those non-operative (46% vs 56%, p = 0.302).

Conclusions: AKI has a high incidence in ICU patients of the Western Amazon area. The causes of ICU admission did not differ from those seen in developed countries. The few number of patients with the typical tropical diseases of Amazon may be due to poor access to health care. The peculiar social geographical region characteristics, with rivers that are not navigable most of the year, long rain period that difficult access to larger cities and the lack of health services in diverse areas, may be associated to the present findings.

Funding: Government Support - Non-U.S.

PUB052

Uncovering Complement Mediated Thrombotic Microangiopathy: Use of a Real Time Genetic Assay in the Diagnosis of Atypical Hemolytic Uremic Syndrome Jan C. Hofmann. Dept of Medicine, California Pacific Medical Center, San Francisco, CA.

Background: Improved diagnostic tests and greater understanding of pathophysiology of thrombotic microangiopathy (TMA) have led to more rapid differentiation of various types of TMAs. While ability to rapidly diagnose TTP (ADAMTS13 activity < 5-10%) has improved, atypical HUS (aHUS) remains diagnosis of exclusion due to poor sensitivity, high cost, and long turnaround time (TAT) of aHUS genetic assays. We describe a patient (pt) with hypothyroidism and renal insufficiency diagnosed with aHUS, using appropriate clinical algorithms for TMA, including “real-time” aHUS genetic assay (TAT 2-5 days).

Methods: 59 y.o. female with 1-2 week (wk) history of fatigue, anemia, thrombocytopenia, renal insufficiency, and recent diagnosis of hypothyroidism with changes in CBC and creatinine (Cr) over 3 wks: hemoglobin (hgb) 13.9 to 7.1 g/dl, platelet count (plt ct) 241 to 68 X 10⁹/L, and Cr 0.71 to 1.41 mg/dl (baseline Cr 0.56, BMI 19.5). Pt's CNS status normal; no other signs/symptoms of systemic thrombosis noted. Additional labs: haptoglobin < 9 mg/dl, LDH 1942 U/L (312-618 U/L), direct coombs negative, PT/INR/PTT/fibrinogen normal, 5-6 schistocytes/high power field, ADAMTS13 activity 79% (40-130%) ruling out TTP.

Results: Pt received 11 plasma exchange (PE) treatments (txs) (hospital day [HD] 3-21). By day 4 of PE (HD 7), plt ct 197 X 10⁹/L; despite 11 PE txs, LDH remained elevated (886-2123) and Cr rose to 2.72 (3.8-4.9X higher than baseline). aHUS genetic panel (sent HD 10, results on HD 17) revealed: positive variant in CFI gene (predicted to be significant, but not previously described) and heterozygous mutations for 3 CFH polymorphisms. Pt clinically diagnosed with aHUS, received meningococcal vaccine (HD 20), and ciprofloxacin (2 wk course). Induction eculizumab started and PE stopped (HD 21). After 2nd months of eculizumab, pt's Cr normalized.

Conclusions: With development of improved genetic testing (ie, increased sensitivity and speed), aHUS genetic assays may represent “real-time” diagnostic tools enabling more rapid assessment of selected TMA cases leading to more targeted treatment.

PUB053

Oral Hydration: The Way Forward in the Prevention of Contrast-Induced Nephropathy Hsu pheon Chong, Matthew L p Howse. Nephrology, Royal Liverpool Univ Hospital, United Kingdom.

Background: Contrast induced nephropathy is defined as increased serum creatinine of 0.5 mg/dL (44.2 mol/L), or a 25% increase of creatinine from baseline levels checked 48 hours after exposure to iodinated contrast medium. Studies have suggested the use of intravenous fluids such as sodium chloride 24 hours prior to contrast exposure. However, this step would require the patient to be admitted prior to contrast medium exposure and incur extra cost for this hospital. This audit explores the use of oral hydration in the prevention of contrast induced nephropathy.

Methods: Using the ICE computer system, all patients who were diagnosed with Type 2 Diabetes Mellitus and taking metformin were identified from the time period of January 2008 until January 2014. They were then advised to stop their metformin prior to contrast exposure. Recommended regime for contrast prophylaxis was given which was 2 litres of oral fluids before and after the procedure. Patients were also given advice to get their renal

function checked, 48 – 72 hours after contrast exposure. Their renal function pre and post contrast exposure was documented and any patients with a reduction of their eGFR more than 20% were then referred to the nephrology department for follow up.

Results: A total of 277 patients were included in this audit. The mean eGFR was 47 ml/min/1.73m². 79% of patients had their renal function checked within 48 – 72 hours, 15% of patients had their renal function checked after that time period and 6% of patients did not have their renal function rechecked at all. Only 0.7% of patients had deterioration of their renal function that met the criteria above. However it was important to note that, these patients had also other multiple co-morbidities and the exposure to contrast was not the sole cause to the deterioration of their renal function.

Conclusions: Oral hydration should be considered as part of the protocol for the prevention of contrast-induced nephropathy. This regime has reduced the need for patients to be admitted into hospital admission for intravenous fluids, thus reducing waiting times for imaging and as well as reducing hospital cost.

PUB054

Gemcitabine-Mediated Thrombotic Microangiopathy – A Rare Cause of Hemolytic Uremic Syndrome Natalie M. Ertz-Archambault,¹ Ibrahim Qaqish,² Leslie F. Thomas.² ¹Internal Medicine, Mayo Clinic Arizona; ²Nephrology and Hypertension, Mayo Clinic Arizona.

Background: Thrombotic microangiopathy (TMA) is a pathological diagnosis of endothelial cell injury and microvascular thrombosis. TMA has been categorized in the present era as one of three distinct disease processes: 1) classical hemolytic uremic syndrome, 2) atypical hemolytic uremic syndrome (aHUS), and 3) thrombotic thrombocytopenic purpura. Our focus, aHUS, reflects an underlying aberrancy in regulation of the alternative complement cascade. Several genetic defects have been identified leading to an affinity to develop uncontrolled activation of this cascade which may commence after exposure to a trigger. Gemcitabine is one rare trigger described in the literature.

Methods: A 66 year-old female with locally advanced, unresectable pancreatic cancer who had completed 12 cycles of gemcitabine-abraxane therapy with no major oncologic progression of disease was hospitalized with acute kidney injury. Two months prior to admission, she developed hypertension, nausea, and profound cytopenias requiring platelet and red cell transfusion. She endured a progressive decline in renal function with a nadir eGFR 19 mg/mL/1.73 m². One month prior to admission, her urinalysis reflected active sediment. Admission labs demonstrated microangiopathic anemia with thrombocytopenia. ADAMTS13 activity was normal (88%), consistent with aHUS. Renal biopsy confirmed subacute changes consistent with TMA. Despite discontinuation of the gemcitabine-abraxane therapy, she continued to demonstrate progressive anemia and thrombocytopenia in addition to persistent proteinuria, hematuria, and impaired eGFR. The patient was subsequently initiated on eculizumab therapy.

Conclusions: Gemcitabine-mediated aHUS is rare and associated with a 75% mortality rate at four months. Previous attempts at therapy have included apheresis. However, current guidelines discourage apheresis in this patient population. To date, six cases of gemcitabine-mediated aHUS have reported the successful use of eculizumab, a terminal complement inhibitor.

PUB055

Intravenous Contrast Material Administration Increases Mortality in Patients with Acute Kidney Injury Requiring Renal Replacement Therapy Katsuhito Ihara, Atsuki Ohashi, Yoshito Iida, Makiko Kobayashi, Hitomi Tanaka, Seiji Inoshita. Internal Medicine, Tokyo Metropolitan Bokutoh Hospital, Japan.

Background: Contrast material exposure is well known to induce acute kidney injury (AKI); however, it is yet unclear whether contrast material administration is related to the prognosis of AKI. We hypothesized that intravenous contrast material administration might be a poor prognostic factor for short-term mortality in AKI requiring renal replacement therapy (RRT).

Methods: We enrolled AKI patients in our hospital, who have been prescribed RRT for the first time, from January 2012 to December 2013 and collected the baseline information and data. Patients already initiated on continuous hemodialysis or peritoneal dialysis, patients almost reaching end-stage kidney disease with vascular access, and patients admitted to our hospital with cardiopulmonary arrest were excluded. The primary outcome was 28 days mortality from initiation of RRT. We divided the patients into two groups, either with or without exposure to contrast material after admission to our hospital. The effect of contrast material exposure was evaluated by univariate and multivariate Cox proportional hazard ratio.

Results: One hundred and seventy patients were eligible. Seventy one percent was male, and mean age was 65.3 ± 14.9 years old. Mean serum creatinine was 5.5 ± 5.0 mg/dL, and mean urine output for six hours was 2.64 ± 2.93 mL/kg. Contrast material was administered in 50.6% of the patients. Each the exposure group and non-exposure group included 86 and 84 patients, respectively, and the 28 day mortalities of each group were 55.8% and 36.9%, respectively. The hazard ratio in the exposure group was 2.666 [95% Confidence Interval (C.I.) 1.573-4.517] (p = 0.000) by univariate analysis. After adjustment by hypertension, sepsis, ischemia, and diuretics usage, which were the significantly different cofounders between the two groups, the hazard ratio was 1.987 [95% C.I. 1.093-3.610] (p = 0.024).

Conclusions: Our results demonstrated that intravenous contrast material administration is an independent risk factor for mortality in patients with AKI requiring RRT.

PUB056

Dabigatran Induced Acute Kidney Injury and Management with Hemodialysis Darren W. Grabe,^{1,2} Syed S. Haqqie,² ¹Dept of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, NY; ²Dept of Medicine, Div of Nephrology and Hypertension, Albany Medical College, Albany, NY.

Background: A 55-year-old man with a history of A Fib, cirrhosis, portal HTN, esophageal varices arrives in the ED, transferred from an outside hospital following initial presentation with multiple episodes of hematemesis and melena. Medication regimen recently changed with a switch from warfarin to dabigatran 8 months prior to admission in order to avoid frequent INR checks.

Methods: On admission, initial blood work was obtained and revealed: Hg 6.3 g/dL, INR 6.9, SCr 15.6 mg/dL and BUN 189 mg/dL. Patient was admitted to the intensive care unit for management of acute blood loss and AKI. On physical exam shows a pulse of 95 bpm and BP of 111/75 mmHg and mild hepatosplenomegaly, the physical exam was unremarkable. Dabigatran was discontinued and patient was transfused with packed red blood cells and fresh frozen plasma and administered vitamin K. Hemodialysis was initiated and continued throughout the hospital course. Kidney biopsy was performed and was consistent with ATN, chronic tubulointerstitial nephritis, and IgA Nephropathy (HAAS class I).

Results: Serum dabigatran concentration (conc) drawn on admission was 860 ng/mL. Following the initial emergent hemodialysis (HD) procedure, subsequent dabigatran conc. were determined during the second HD procedure. Predialysis and postdialysis dabigatran conc. were 130 ng/mL and 30 ng/mL, respectively. Pharmacokinetic parameters were calculated and shown in the table.

Dabigatran pharmacokinetics while on hemodialysis		
K _d (h ⁻¹)	t 1/2 (hrs)	Cl _D (mL/min)
0.489	1.4	571

k=elimination rate constant; t_{1/2}= half-life; D =dialytic

Over the hospital course, patient required regular HD, Hg stabilized following transfusion and vitamin K. Patient was stable on discharge with a serum creatinine of 5.9 mg/dL and remained on dialysis.

Conclusions: Dabigatran induced AKI is rare. The mechanism of the insult in this case was unclear but acute blood loss leading to prolonged ischemic insult was largely contributive. Hemodialysis was successful in removing the offending agent with resolution of bleeding but patient remains dialysis dependent.

PUB057

Relation Between BNP And NGAL, with Bioelectrical Cardiothoracic Impedance Hemodynamics Parameters in Patients with Cardiorenal or Renocardiac Syndrome Francisco Javier Lavilla, Maria Jose Molina Higuera, Nuria Garcia-Fernandez, Paloma L. Martin Moreno, Diana Lopez Espinosa, Pelayo Moiron Fdez-Felechosa, Pedro Errasti. *Nephrology, Clinica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: Evaluate the application of cardiothoracic bioelectrical impedance (CTBIA) in the classification of patients with cardiorenal or renocardiac syndrome.

Methods: We use a cohort with 18 patients (mean age 72 years SD 2.6, males 77 %) with cardiorenal or renocardiac syndrome. We evaluate hemodynamic parameters (cardiac output -CO-, cardiac output index -COI-, left ventricular work index -LVWI- and systemic vascular resistance index -SVRI-) with BNP (pg/ml, limits 0-100) and NGAL (ng/ml, limits 0-149).

Results: Mean levels of BNP were 545.71 (SD 128.8) and mean levels of NGAL were 500.11 (SD 96.25). Only vascular resistance index was associated with NGAL (r=-0.461, p=0.054). Not found associations with BNP. However we classify patients in four groups: Group 1 (BNP high, NGAL normal) (n=7), Group 2 (BNP high, NGAL high) (n=1), Group 3 (BNP normal, NGAL high) (n=7) and Group 4 (BNP normal, NGAL normal) (n=3).

The associations indicate that in Group 1 are patients with cardiac dysfunction (cardiorenal) and higher BNP (BNP>NGAL), with lower cardiac output and higher vascular resistance, and in group 3 are patients with renal dysfunction (renocardiac) and higher NGAL (NGAL>BNP, with higher cardiac output and lower vascular resistance.

Table 1.

Group	mean/Sd	BNP pg/ml	NGAL ng/ml	CO l/min	COI l/min/m2	LVWI Kg m/m2	SVRI dyn s cm-5 m2
1		1068 185.9	252 36.3	4.3 0.47	2.56 0.23	2.5 0.25	2338 245.3
2		1420	1300	4.8	2.9	2.6	1842
3		189.4 52.4	706 141	6.2 0.5	3.05 0.20	3.26 0.36	2082 206.83
4		158 49.7	177 65.3	3.03 0.20	1.53 0.08	1.73 0.12	4282 394.5
	p	0.001	0.005	0.01	0.008	0.085	0.001

CO: CARDIAC OUTPUT. COI: CARDIAC OUTPUT INDEX. LVWI: LEFT VENTRICULAR WORK INDEX. SVRI: SYSTEMIC VASCULAR RESISTANCE INDEX.

Conclusions: The use of CTBIA is useful to evaluate and classify patients with cardiorenal or renocardiac syndrome. There are association between vascular resistance and renal tubular necrosis.

PUB058

Recovery of Renal Function After Removal of Functional Causes of Advanced Renal Failure Maria-Eleni Roumelioti,¹ Faraz Khan Luni,² Sandeep Vetteth,² Darlene Melinda Vigil,^{1,3} Kavitha Ganta,^{1,3} Deepak K. Malhotra,² Antonios Tzamaloukas,^{1,3} ¹Univ of New Mexico; ²Univ of Toledo; ³Raymond G. Murphy VA Medical Center.

Background: It is important to predict whether renal function recovers completely, early in the course of functional azotemia. We hypothesized that the level of renal function can be predicted from the early change in serum creatinine concentration ([Cr]) during treatment of functional azotemia.

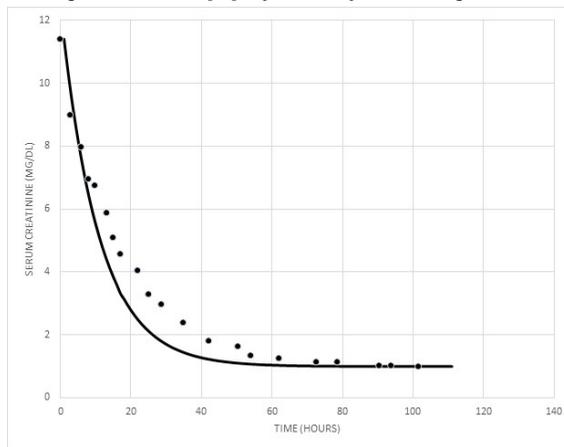
Methods: Taking into account the changes in the body pool of Cr at diagnosis and Cr production during treatment, we calculated the Cr clearance (C_{Cr}) between the [Cr] levels in the blood sample obtained at presentation ([Cr]₀) and in the first blood sample after the initiation of non-dialytic treatment ([Cr]₁) in 6 pts, 5 men with urinary retention and a woman with prerenal azotemia. The calculated C_{Cr} value was used to predict [Cr] levels corresponding to times of subsequent [Cr] measurements. We compared the predicted [Cr] levels to the corresponding measured ones.

Results: The table shows [Cr]₀ and [Cr]₁ levels, calculated C_{Cr} values, predicted and measured [Cr] levels at steady state after correction of the azotemia (Cr)_{ss}. Predicted and measured [Cr]_{ss} values were close.

Patient	1	2	3	4	5	6
[Cr] ₀ , mg/dL	42.70	17.67	11.35	35.23	8.10	6.86
[Cr] ₁ , mg/dL	34.70	5.58	8.97	8.11	7.77	5.16
[Cr] ₀ to [Cr] ₁ hours	3.6	14.7	2.9	12.3	3.2	5.4
C _{Cr} , mL/min	45	56	59	88	34	39
Predicted [Cr] _{ss} , mg/dL	1.97	1.24	0.99	0.99	2.41	1.48
Measured [Cr] _{ss} , mg/dL	1.60	1.52*	1.18	0.87	2.17	1.41

*Patient 2 died while [Cr] was decreasing

A modeling of the decline in [Cr] of patient 3 is presented in figure



(solid line: exponential decline of the [Cr] predicted by the C_{Cr}, full circles: measured [Cr] levels)

Conclusions: Computation of early C_{Cr} after removal of the cause of functional azotemia may provide estimates of post-treatment [Cr] levels reasonably close to the measured levels. More observations are needed.

Funding: Veterans Administration Support

PUB059

Relation of Cardiothoracic Bioelectrical Impedance Hemodynamics and Volemics Parameters with Acute Kidney Injury Prognosis Francisco Javier Lavilla, Nuria Garcia-Fernandez, Diana Lopez Espinosa, Paloma L. Martin Moreno, Maria Jose Molina Higuera, Pelayo Moiron Fdez-Felechosa, Pedro Errasti. *Nephrology, Clinica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: Evaluate the relation of hemodynamics and volemics parameters with cardiothoracic bioimpedance (CTBIA) and Acute Kidney Injury (AKI) prognosis.

Methods: We use a cohort of 21 patients (mean age 69 years SD 2.8, 76.2% males) with AKI. We evaluate hemodynamic parameters (cardiac output -CO-, cardiac output index -COI-, left ventricular work index -LVWI- and systemic vascular resistance index -SVRI-) and thoracic volemics parameters (Thoracic fluid volumen -TFV-, Thoracic fluid volumen index -TFVI- and systolic volumen -SV-) with clinical index prognosis (severity individual index -ISI), analytical parameters (c-reactive protein -CRP-, prealbumin -PRALB, albumin -ALB-) and chronic health index (Karnofsky -K-).

Results: Patients with lower vascular resistance and higher cardiac work have worse prognosis, associated with inflammatory state and thoracic hypovolemia, oliguria and higher renal replacement therapy requirements. But patients with higher thoracic volumen have higher risk of respiratory failure.

Table 1.

	CO l/min	COI l/min/m2	TFV l/kOhm	TFVI l/kOhm/m2	SVRI dyn s cm-5 m2	SV ml
ISI r p	0.556 0.009	0.585 0.005	ns	ns	-0.483 0.026	0.383 0.087
CRP r p	ns	ns	-0.392 0.097	-0.480 0.038	ns	ns
Hypo. p. YES/NO	0.019 4.3/6.5	0.009 2.3/3.3	ns	ns	0.016 2992/1920	0.056 61/87
Vent.Asis.R. p. YES/NO	ns	ns	0.037 33.5/50	0.064 18.3/25.8	ns	ns
RRT. p. YES/NO	0.022 4.4/6.7	0.064 2.4/3.2	0.016 33./51.7	0.073 18.3/25.6	0.181 2845/2177	0.066 62/89

CO: CARDIAC OUTPUT. COI: CARDIAC OUTPUT INDEX. TFV: THORACIC FLUID VOLUME. TFVI: THORACIC FLUID VOLUME INDEX. SVRI: SYSTEMIC VASCULAR RESISTANCE INDEX. VOLUME SYSTOLIC: VS. ISI: INDIVIDUAL SEVERITY INDEX. CRP: C-REACTIVE PROTEIN. HYPO: HYPOTENSION. VENT. ASIS. R: VENTILATORY ASSISTANCE REQUIREMENT. RRT: RENAL REPLACEMENT REQUIREMENT.

Conclusions: CTBIA can be used to evaluate prognosis and therapy of higher risk AKI, as a patients with vasoplegic state (with inflammatory origen and higher multiorgan failure risk) or thoracic hypervolemia (with higher respiratory failure and intubation risk).

PUB060

Abruptio Placenta as a Complement Amplifying Condition for Atypical Hemolytic Uremic Syndrome Syed S. Haqqie, Amro Elshoury, Daniel Sedhom, Arif Asif. *Albany Medical College, Albany, NY.*

Background: Endothelial injury resulting in microvascular thrombosis is the underlying pathology leading to target organ injury in aHUS. The syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to multiple organs including the kidney. Complement amplifying conditions often lead to the activation of complement cascade involved in the pathogenesis of atypical HUS. In this report, we present 33-year-old Hispanic women with abruptio placenta at 33 weeks of gestation and fetal death who underwent cesarean section. Post procedure, patient developed microangiopathic hemolytic anemia (6.7 mg/dl), thrombocytopenia (39,000/ μ L) and renal failure necessitating initiation of hemodialysis. Fibrinogen (267 mg/dl), PT, PTT were normal while LDH was markedly elevated at 2670 IU/L haptoglobin was severely reduced at 5.8 mg/dl. Market schistocytosis was observed on peripheral smear. ADAMTS 13 was ordered and plasma exchange was initiated. Five sessions failed to show any improvement and ADAMTS 13 activity returned at 56%. Plasma therapy was discontinued and Eculizumab (monoclonal antibody directed against complement C5) was initiated for the diagnosis of aHUS. At a follow-up of two weeks patient is off dialysis with a serum creatinine of 3.4 mg/dl, hemoglobin of 8.8 mg/dl and platelet count of 147,000/ μ L. We believe that abruptio placenta acted as a complement amplifying condition in this case. However, pregnancy, fetal loss and caesarean section can all serve as complement amplifying conditions for aHUS.

Methods: Clinical Case Report

Results: Successful outcome with Eculizumab therapy.

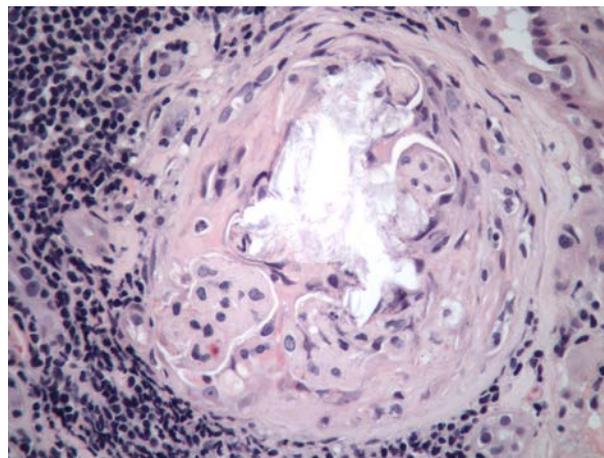
Conclusions: aHUS responding to Eculizumab therapy.

PUB061

Foscarnet Crystal-Induced Nephropathy in a Patient with Diminished Native Renal Capacity Sadiq Ahmed,² Patrick J. Hensley,¹ Virgilius Cornea.¹ ¹Pathology, Univ of Kentucky; ²Nephrology, Univ of Kentucky.

Background: Drug-induced crystalline nephropathies are characterized by glomerular, tubular or interstitial injuries with rising creatinine, hematuria and low grade proteinuria. Foscarnet is a pyrophosphate analog that inhibits DNA polymerase in ganciclovir-resistant CMV. Tubular-interstitial damage due to Foscarnet is common but reports of crystalline-induced nephrotoxicity are rare. We report this unique case of Foscarnet crystal-induced nephropathy in a patient with lymphoma and solitary functioning kidney.

Methods: A 56 year old female with history of solitary functioning left kidney with remote history of right kidney atrophy due to obstructive uropathy was diagnosed with stage IV mantel cell lymphoma. Renal function was normal prior to chemotherapy and stem cell transplant. This was complicated by CMV infection requiring IV Foscarnet for 8 weeks. She developed AKI with nephrotic range proteinuria and hematuria. The patient was initiated on hemodialysis. Renal biopsy showed deposition of calcium crystals in the mesangium and interstitium characterized by short sticks with angular edges and birefringence on polarized light microscopy.



Conclusions: Foscarnet crystal-induced nephropathy has been reported in a limited number of immunosuppressed states resulting in CMV infection, including AIDS and solid organ transplantation. Foscarnet is solely eliminated by glomerular filtration and renal injury is typically characterized by reversible tubular necrosis. Foscarnet chelates metallic ions and frequently complexes with ionized calcium to form a highly insoluble salt that cannot be filtered by the kidney. This patient's pre-treatment renal function was adequate despite history of a solitary functioning kidney. Altered renal hemodynamics in the solitary kidney may have enhanced precipitation of Foscarnet-calcium salts despite adequate hydration.

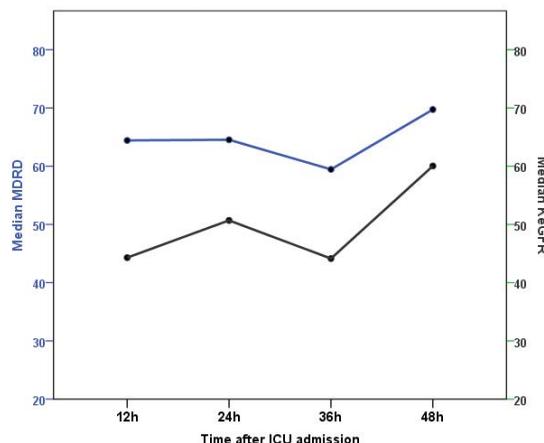
PUB062

Comparison of Estimated Glomerular Filtration Rate (eGFR) and Kinetic eGFR (KeGFR) in Critically Ill Intensive Care Unit (ICU) Patients Rakesh Malhotra,¹ Etienne Macedo,² Josee Bouchard,³ Ravindra L. Mehta.² ¹VUMC; ²UCSD; ³Univ de Montréal.

Background: Estimation of kidney function in critically ill patients is important for appropriate drug dosing and therapeutic strategies. However, current GFR equations are not applicable when plasma serum creatinine (sCr) is rapidly changing. Chen et al (JASN 2013) has recently proposed KeGFR formula to calculate GFR from fluctuating sCr values. The aim of this study was to compare KeGFR values with eGFR using the Modification of Diet in Renal Disease (MDRD).

Methods: We analyzed data from a cohort of 735 ICU patients screened in a prospective observational study on the incidence of AKI from Jun06 to Dec08 at an academic center. Demographic data, co-morbidities, clinical course, and laboratory parameters were recorded from ICU admission. We estimated KeGFR and eGFR for each patient during the first 48 hr of ICU stay. We defined KeGFR = (SSPer \times CrCL / Mean Per) \times (1 - 24 \times Δ Per / Δ Time (h) \times Max Δ Per/Day) and MDRD eGFR = 175 \times (S_{cr})^{-1.154} \times (Age)^{0.203} \times (0.742 if female) \times (1.212 if African American). We compared estimated GFR assessed by kinetic formula and MDRD GFR equation.

Results: Thirty-two patients with only one time sCr measurements were excluded from the analysis. In remaining 703 patients for analysis, the median age was 55 (IQR 23) years; 62% (n=436) were men and 53% (n=373) were white. In total, 4329 eGFR and KeGFR measurements were performed. Estimated GFR predicted by kinetic formula declined earlier and remained diminished as compared to eGFR till steady state was achieved.



Conclusions: Our study highlights the overestimation of renal function by MDRD equation in critically ill patients with acute kidney injury (AKI). KeGFR may be more accurate in tracking renal function changes in AKI. Further studies are needed to confirm these findings.

PUB063

Contrast Induced Nephropathy Among Hospitalized South Africans – Impact of Serum Albumin

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Background: Despite ranking 3rd as cause of hospital acquired acute kidney injury in hospitalized patients, contrast induced nephropathy (CIN) causes significant morbidity, mortality and high hospital costs. In sub-Saharan Africa, information on rates of CIN is lacking. This study investigated the rates of CIN and influence of serum albumin on CIN.

Methods: This is an on-going prospective case controlled study conducted at Charlotte Maxeke Johannesburg Academic Hospital, in South Africa. In-patients undergoing contrast media administration in the Divisions of Radiology and Cardiology were consecutively recruited to the study. Ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. CIN was defined as serum Creatinine >25%µmol/l or >44µmol/l from baseline over a 48-72 hours post exposure to contrast media. Creatinine clearance was calculated using the CKD-EPI. The following were exclusion criteria; age below 18years, evidence of AKI (clinical or laboratory), ESRD and prior contrast media administration.

Results: Among 285 recruited hospitalized patients, a rate of CIN was 16.9%. Serum albumin below 35g/dl positively predicted development of CIN (RR 2.3, 95% CI 1.14-4.64, p=0.020). The mean album was 28.4±4.6 SD and 41±2.39 SD in the CIN and non CIN groups respectively. An eGFR <60ml/min was associated with a 6 fold risk of developing CIN (P<0.00001).

Conclusions: Rates of CIN is significantly higher in developing countries and the presence of hypoalbuminemia, a traditional bio-maker is significantly associated with development of CIN.

PUB064

A Curious Case of Evans Syndrome

Sagar R. Patel, Imara Dissanayake. Internal Medicine, Albert Einstein Medical Center, Philadelphia, PA.

Background: Evans syndrome is a rare autoimmune condition in which antibodies attack their own RBC and platelets resulting in an hemolytic anemia (AIHA) and ITP in the absence of a known etiology. Both of these can occur simultaneously or sequentially. Although many cases are idiopathic in origin, ES has been associated with other conditions in half of the cases, including infections and lymphoproliferative disorders.

Methods: A 45 year old African American male seen in ED with a Hgb of 6.4 and asymptomatic. The patient has a history of autoimmune hemolytic anemia (AIHA), immune thrombocytopenic anemia (ITP), anti-phospholipid syndrome (APS) with a previous DVT/PE and non-compliant with warfarin. labs On admission Hgb 6.4, Plts 114,T Bil 1.3, D Bil 0.4, LDH 346, Haptoglobin <8. He had AKI (Cr 0.9), with new onset nephrotic range proteinuria. Renal US showed medical renal disease. ANA 1:160, double stranded DNA was negative. Anti MPO, P-ANCA, C- ANCA, antiproteinase 3, atypical P-ANCA and glomerular basement membrane antibody were negative. CH 50,C3 and C4 were all low. No cryoglobulins were detected in the blood assay. Urine Electrophoresis was negative for monoclonal light chains. Renal biopsy was performed and showed findings consistent with lupus nephritis stage 4/5. The patient was treated with PRBCs and given pulse dose steroids for 3 days after which his hemoglobin remained stable.

Results: ES is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at onset. Since it is thought to be secondary to immune dysfunction, a high clinical suspicion should be maintained for underlying autoimmune disease. However this patient was unique, he did not meet the standard criteria for SLE but demonstrated lupus nephritis on biopsy. This has a significant implication in management, and should be treated for his underlying SLE which could help in reducing recurrence of Evans syndrome. He responded well to first line therapy with corticosteroids and did not require further acute therapy such as IVIG. He was started on hydroxychloroquine for SLE and referred to renal clinic for cellcept.

Conclusions: This case reflects that we should have a high suspicion for SLE and lymphoproliferative diseases even in asymptomatic patients with Evans Syndrome.

PUB065

Anticoagulation-Free Continuous Renal Replacement Therapy: A Single Center Observation

Akshatha Rao, Ziauddin Ahmed. Div of Nephrology, Drexel Univ.

Background: Renal failure in the ICU setting is associated with 40-60% mortality. Continuous renal replacement therapy (CRRT) is used for volume and electrolyte management in critical care units. To avoid clotting of hemofilters, patients are routinely started on anticoagulation. In literature, anticoagulation has been associated with complications of increased risk of bleeding and metabolic or electrolyte disturbances based on type of anticoagulation used. We aimed to investigate the length of cartridge use and the association of anticoagulation.

Methods: We conducted a retrospective review of 20 ICU patients who were started on CRRT over a course of two months for acute renal failure. We looked at the number of cartridges used per day. Prescription for CRRT was dialysate flow rate of 25-35 ml/kg/hr and blood flow rate of 250 ml/hr. No anticoagulation was ordered initially due to bleeding risks in this cohort. All patients were ordered 100 ml of normal saline flushes every 4 hours.

Results: For 70% of the patients, the hemofilter cartridge lasted >24 hours. 30% of the patients required more than 1 filter per day, of which only 1 patient was started on a heparin drip for anticoagulation due to multiple filter changes. We used predilution replacement fluid to reduce the blood viscosity and hemoconcentration for the patients

requiring > 2 filter changes per day. Decreased requirement of filter change was noted after these changes were made. Among the patients with increased filter clotting, 33% had femoral non-tunneled dialysis catheters and 50 % had internal jugular tunneled dialysis catheters. Longer duration of dialysis was associated with increased cartridge use per person correlation 0.818 (p=0.000). No documentation was made in the nursing notes to distinguish between vascular access problems versus filter clotting.

Conclusions: Recurrent filter clotting leads to interruption of RRT. Frequent filter changes is not cost effective. However anticoagulation in critical care settings poses multiple potential problems. There was an association between permcatheters and increased cartridge use.

PUB066

Rosuvastatin Has a Protective Effect against Hypertonicity-Induced Cell Damage

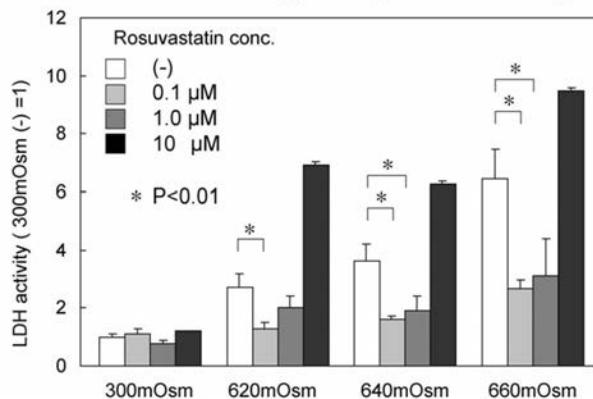
Miku Sato, Masaru Horio. Functional Diagnostic Science, Osaka Univ Graduate School of Medicine, Suita, Japan.

Background: Contrast-induced nephropathy (CIN) is one of the causes of acute kidney injury. Some studies raised a concern that statins have protective effect against CIN. Hypertonic stress in renal tubular cell is a possible factor inducing cell damage in CIN. Reactive oxygen species (ROS) can induce apoptosis. We studied the effect of rosuvastatin on hypertonicity induced cell damage in MDCK cells.

Methods: Hypertonic medium was made by addition of NaCl. Rosuvastatin was added 24 hours before the hypertonic exposure. Cell damage was assessed by LDH activity in culture medium. Apoptosis was evaluated by caspase-3 activity. Content of cellular glutathione (GSH), an important antioxidant, was measured.

Results: Hypertonicity more than 600 mOsm showed significant cytotoxic effect in MDCK cells. LDH activity in culture medium of 620, 640 and 660mOsm cells increased in osmolality dependent manner (Figure). Low concentration (0.1 and 1.0 µM) of rosuvastatin had a protective effect against the hypertonicity-induced cell damage. On the other hand, 10 µM rosuvastatin that had no significant cytotoxic effect in 300mOsm condition, stimulated hypertonicity induced cell damage.

Effect of rosuvastatin on hypertonicity-induced cell damage



Caspase-3 activity in 660mOsm cells was 13 fold higher compared with 300mOsm cells. Rosuvastatin (1µM) inhibited the increase of caspase-3 activity about 50%. Cellular GSH contents in 300mOsm, 660mOsm and 660mOsm with rosuvastatin after 8h were not significantly different (35.7±11, 33.0±8.1 and 34.2±19.2 nmoles/mg protein, respectively). Mevalonolactone (100µM)inhibited the protective effect of rosuvastatin, suggesting the inhibition of HMG-CoA reductase by rosuvastatin plays an important role of the protective effect against hypertonicity induced cell damage.

Conclusions: Low concentration of rosuvastatin has a protective effect on hypertonicity-induced cell damage in MDCK cells.

Funding: Government Support - Non-U.S.

PUB067

Transcription Factor SRF Promotes Renal Fibrosis in IgA Nephropathy

Lijie He, Shiren Sun. Dept of Nephrology, Xijing Hospital, Xi'an, Shaanxi, China.

Background: The role of transcription factors SRF, which regulate CARg element contained genes, in IgA nephropathy is unknown.

Methods: Here we performed expression of SRF in human IgA nephropathy tissues from ItoV stage and the cultured proximal tubular cells (HK-2) under hypoxia or induced by TGF-β compared with control conditions.

Results: we performed SRF expression from formalin-fixed, paraffin-embedded tissues from renal biopsies diagnosis as IgA nephropathy. We noted the greatest change in SRF expression, which was significantly higher in IgAV stage compared with early presenters, like IgA I or IIstage. Furthermore, in individual biopsies, high expression of SRF correlated with tubulointerstitial fibrosis and low estimated GFR. Next, in vitro, we identified overexpression of SRF was observed in hypoxia-induced HK-2 cells. Treatment of HK-2 with TGF-β-increased SRF expression. Lower expression of SRF suppressed expression of the CARg element snail1, thereby opposing TGF-β-mediated downregulation of E-cadherin.

Conclusions: In summary, high expression of SRF associates with increased fibrosis and decreased estimated GFR in IgA nephropathy in vivo, perhaps by enhancing TGF- β -mediated downregulation of snail and E-cadherin in HK-2.

PUB068

Increased Erythrocyte Reactive Oxygen Species Production Induced by Indoxyl Sulfate Precedes Red Blood Cell Death Gabriela Ferreira Dias,¹ Viktoriya Kuntsevich,² Lia S. Nakao,³ Fellype C. Barreto,¹ Stephan Thijssen,⁴ Peter Kotanko,^{2,4} Roberto Pecoito-Filho,¹ Andrea Novais Moreno-Amaral,¹ ¹Pontifícia Univ Católica do Paraná, Brazil; ²Icahn School of Medicine at Mount Sinai, New York; ³Univ Federal do Paraná, Brazil; ⁴Renal Research Inst, New York.

Background: The uremic toxin indoxyl sulfate (IS) triggers eryptosis, an event characterized by phosphatidylserine (PS) exposure on red blood cell (RBC). The aim of the present study was to evaluate whether increase in RBC reactive oxygen species (ROS) induced by IS precedes eryptosis.

Methods: RBC from healthy controls (HC) were incubated for 4, 12 or 24h with IS (free concentration 4.5 mg/L) in the presence or absence of free radicals scavenger N-acetylcysteine (NAC 0.5mM). Flow cytometry was employed to assess eryptosis (annexin-V+ binding) and ROS (DCFH-DA).

Results: Incubation of HC-RBC with IS over 4h did not trigger significant eryptosis compared to control cells incubated without IS (4.5 \pm 1.2% vs 3.4 \pm 0.2%). However, 12h and 24h incubation with IS increased levels of eryptosis in a time-dependent manner (10.4 \pm 3.4% and 16.6 \pm 6.1, respectively). This IS-induced PS exposure on HC-RBC was inhibited in the presence of NAC (6.0 \pm 1.3% and 6.5 \pm 1.4%, respectively). On the other hand, ROS production by HC-RBC was increased even after only 4h of incubation with IS in a time-dependent manner (14 \pm 4.2%, 22.1 \pm 5.3 and 34.8 \pm 15.8% for 4h, 12h and 24h respectively) when compared to control cells (4.6 \pm 2.3%, 4.2 \pm 0.5% and 5.2 \pm 8%, respectively). ROS production was inhibited in the presence of NAC (6.6 \pm 3.4%, 6.3 \pm 2% and 13.4 \pm 10.5%) demonstrating the ability of an antioxidant to reverse the oxidative stress induced by IS.

Conclusions: Taken together our results suggest that IS in a high free concentration, which is in accordance with reported free toxin concentration in patients, induces ROS production in HC-RBC that precedes PS exposure. Thus, imbalance of RBC redox status induced by IS appears to be an important mechanism of elevated eryptosis observed in CKD that consequently may contribute to renal anemia.

PUB069

Impact of Constitutive C-MIP Expression on Mouse T-Cell Proteome Mario Ollero,¹ Pauline Vachin,¹ Cerina Chhuon,² Kéllia Sendeyo,¹ Melanie Mangier,¹ Ida Chiara Guerrero,² André Pawlak,¹ Djillali Sahali.¹ ¹INSERM, U955 (Eq. 21), Créteil, France; ²Plateau Protéomes Necker, Paris, France.

Background: The protein c-mip is overexpressed in lymphocytes and podocytes of MCNS patients. In order to dissect its role in INS pathogenesis, we generated a transgenic mouse expressing c-mip in peripheral mature T-cells. We aimed to evaluate the impact of c-mip expression on T-cell proteome in basal and stimulating conditions.

Methods: T-cells from transgenic (Tg) and control (Wt) mice (n=3) were purified by negative immunoselection, and subjected to anti-CD3 and anti-CD28 stimulation, to mimic activation by antigen presenting cells. At 0 and 60 min post-activation, total proteins were extracted, trypsin digested, and peptides analyzed by nano-RSLCC Q Exactive Plus MS. Protein quantification was performed by a label-free approach using MaxQuant and Perseus softwares on three parallel technical replicates per sample.

Results: The expression levels of 2660 proteins were compared in the four conditions. As a result, 46 proteins were found differentially expressed between Tg and Wt as a function of T-cell activation (two-way ANOVA interaction, p<0.05). Among these, GO annotation showed a significant enrichment in proteins bearing ATPase activity. Hierarchical clustering by K-means algorithm displayed, most remarkably, a cluster of 14 proteins upregulated upon T-cell activation in Wt mice but depleted in Tg mice in the same conditions - including KEGG annotations for tight junction, Wnt signaling, TLR signaling, RIG-I-like receptor signaling, Notch signaling, spliceosome, riboflavin metabolism, and DNA replication-, and a cluster of 11 proteins depleted in Wt and augmented or unchanged in Tg after activation - involved in aminoacid and nicotinamide metabolism, proteasome, and regulation of actin cytoskeleton-. Studies are underway to explore the mechanisms involved.

Conclusions: c-mip overexpression exerts profound alterations in the protein expression pattern following T-cell activation in mice, involving diverse signaling, metabolic pathways and cellular functions. These results, along with other preliminary data obtained from the same mouse model, point at a defect in T-cell activation associated with c-mip expression.

Funding: Government Support - Non-U.S.

PUB070

An Investigation into the Prognosis of Nephrotic Syndrome and Regulatory T Cells in Elderly People Tetsuhiko Yasuno. *Internal Medicine, Fukuoka Univ, Fukuoka, Japan.*

Background: Peripheral blood flow cytometry analysis of nephrotic syndrome (NS) in children has been performed, and among T cells, regulatory T cells (Tregs) are involved in NS. In adults, there are reports about Tregs and ANCA-associated glomerulonephritis, and the nephritic inhibitory effect of Tregs has become clear. As there has been no investigation focusing only on NS in elderly people, we conducted the analysis in this study.

Methods: In this investigation, we examined 7 patients aged 65 years or older who had NS. Regarding the primary disease, 3 of these patients had membranous nephropathy, 1 had minimal change, 1 had immunotactoidglomerulopathy (ITG), 1 had diabetic nephropathy, and 1 had Lupus nephritis. Flow cytometry using peripheral blood was conducted, and among T cells, the percentage of Th1, Th2, Treg, and Th17 was examined.

Results: The average value of Th1 cells was 31.8%, Th2 was 4.2%, Treg was 9.3%, and Th17 was 2.6%. The patient with ITG had a higher percentage of Treg (19.9%), but this patient achieved complete remission after 2 years owing to the administration of a steroid and mizoribine. For the other patients, there were no distinctive features for the 2-year prognosis.

Conclusions: The Treg value was higher for the patient with ITG. However, as only 1 such patient was examined, it is unclear whether this was because of a disease or was a unique phenomenon for this patient. It is possible that peculiar T cell actions could be involved in elderly people, so various ailments of NS should be further investigated by using flow cytometry.

PUB071

Antibodies against Linear Epitopes on $\alpha 3(\text{IV})\text{NC1}$ in Patients with Antineutrophil Cytoplasmic Antibodies Associated Vasculitis Xiaoyu Jia,¹ Juntao Yu,² Zhao Cui,¹ Minghui Zhao.^{1,3} ¹Renal Division, Peking Univ First Hospital, Beijing, China; ²Academy for Advanced Interdisciplinary Studies, Peking Univ, Beijing, China; ³Peking-Tsinghua Center for Life Sciences, China.

Background: In a substantial number of patients with crescentic glomerulonephritis, both anti-glomerular basement membrane (GBM) antibodies and antineutrophil cytoplasmic antibodies (ANCA) are detected simultaneously. ANCA is presumed to be the initial event leading to the production of anti-GBM antibodies. In the present study, we investigated the antibodies against linear epitopes on $\alpha 3$ chain of type IV collagen ($\alpha 3(\text{IV})\text{NC1}$) in patients with ANCA associated vasculitis who had no classical anti-GBM antibodies, aiming to reveal the mechanisms of the coexistence of the two kinds of autoantibodies.

Methods: Twenty-four overlapping linear peptides were synthesized across the whole sequence of $\alpha 3(\text{IV})\text{NC1}$ and antibodies were detected by ELISA.

Results: We found 25/31 (80.6%) ANCA associated vasculitis patients possessing antibodies against linear peptides on $\alpha 3(\text{IV})\text{NC1}$. These antibodies were detected from 50% of patients with normal renal function (Scr<133mmol/L), 70% of patients with moderate renal dysfunction (133mmol/L<Scr<600mmol/L), and 94% of patients with renal failure (Scr>600mmol/L). Patients with more aggravated renal damage had higher frequency of peptide recognition (P=0.032). The highest recognition frequencies were found for peptides P4 (51.6%), P14 (54.8%) and P24 (54.8%), which contained the sequences that constitute the epitopes E_A (P3) and E_B (P14 and P24) on $\alpha 3(\text{IV})\text{NC1}$. The level of anti-P4 antibodies was positively correlated with the percentage of crescents in glomeruli ($r=0.764$, P=0.027). Patients with anti-P24 antibodies had a significantly higher prevalence of renal dysfunction on diagnosis (88.2% vs. 42.9%, P=0.018).

Conclusions: In conclusion, antibodies against linear peptides on $\alpha 3(\text{IV})\text{NC1}$ could be detected in patients with ANCA associated vasculitis who had no classical anti-GBM antibodies and were associated with clinical features.

PUB072

Urine suPAR and CD80 Levels in Patients with Focal Segmental Glomerulosclerosis and Minimal Change Nephrotic Syndrome Chang-Yien Chan, Yaochun Zhang, Wee Song Yeo, Isaac Liu, Hui Kim Yap. *Pediatrics, National Univ of Singapore, Singapore.*

Background: Recent studies suggested soluble urokinase-type plasminogen activator receptor (suPAR) as the plausible circulating factor in the pathogenesis of focal segmental glomerulosclerosis (FSGS) while patients with minimal change nephrotic syndrome (MCNS) were reported to have increased CD80 levels in the urine. This study aimed to determine the value of urine suPAR and CD80 levels in distinguishing between FSGS and MCNS in patients with nephrotic relapse.

Methods: Plasma and urine suPAR and CD80 levels were analyzed in 51 primary nephrotic patients in relapse with urine protein:creatinine ratio of >0.2g/mmol (26 MCNS, 25 FSGS) and 24 healthy controls, using Quantikine Human uPAR Immunoassay (R&D Systems) and Human sCD80 Elisa kit (eBioscience). Urine were concentrated using centrifugal filter units with molecular weight cut-offs at 3kDa (Amicon) before quantification of sCD80. Urine levels of suPAR and CD80 were normalised with urine creatinine. Results were expressed as mean \pm SEM. Statistical analysis was done using Mann-Whitney test.

Results: Plasma suPAR levels in patients with FSGS (3216.8 \pm 295.2pg/ml) were significantly higher than controls (2330.8 \pm 207.2pg/ml) and MCNS patients in relapse (2178.9 \pm 196.7pg/ml) (p<0.02). Urine levels of suPAR were significantly higher in both MCNS (351.8 \pm 52.3pg/ μ mol, p=0.02) and FSGS (381.6 \pm 52.9pg/ μ mol, p=0.012) compared to control (210.4 \pm 20.2pg/ μ mol). There was modest correlation between suPAR levels in plasma and urine (Spearman's $\rho=0.509$, p<0.001). We were unable to detect CD80 levels in plasma samples even after removal of high-abundance proteins in the plasma samples with the combinatorial peptide ligand library beads (ProteoMiner). Urine CD80 levels were 2.5-fold higher in MCNS (0.31 \pm 0.13ng/ μ mol) compared to controls (0.13 \pm 0.03ng/ μ mol, p=0.19) and 1.6-fold compared to FSGS (0.19 \pm 0.49ng/ μ mol, p=0.44).

Conclusions: Our study suggested that neither urine suPAR levels nor the CD80 levels are useful to distinguish patients with FSGS or MCNS.

PUB073

Effects of 1,25-Dihydroxy Vitamin D₃ on Treg cells, Interleukin -17, RORgt in Rats with IgA Nephropathy Hui Guo. *Div of Nephrology, 2nd Affiliated Hospital of Shanxi Medical Univ, Taiyuan, Shanxi, China; Div of Rheumatology, 2nd Affiliated Hospital of Shanxi Medical Univ, Taiyuan, Shanxi, China.*

Background: To investigate the relationship between Treg cells, RORgt, IL-17 and rats with IgA nephropathy; to explore the intervention effect of 1,25(OH)₂D₃ on Treg cells, RORgt, IL-17 expression in rats with IgA nephropathy.

Methods: We choosed Wister 52 rats, with witch 8 rats were choosed in control group (group E) in random, while other 44 rats were established the IgA nephropathy model by mucosal immune with bovine serum albumin and were divided into model group, 1,25(OH)₂D₃ treated group, prednisone treatment group and prednisone + 1,25(OH)₂D₃ treatment group. The change of 24 hours of urinary protein, red blood cells in urine, creatinine and blood calcium of rats were detected. Foxp3, RORgt and IL-17 levels were detected by using RT-PCR, Immunohistochemistry and Westernblot.

Results: The level of RORgt, IL-17 in model groups were higher than prednisone treatment group, prednisone+1,25(OH)₂D₃ treatment group, 1,25(OH)₂D₃ treatment group and control group (p<0.05). After treatment the expression of RORgt, IL-17 of each group were declined significantly (p<0.05). The prednisone+1,25(OH)₂D₃ treatment group declined significantly compare to prednisone treatment group and 1,25(OH)₂D₃ treatment group (p<0.05). **The expression of Foxp3 decreased significantly in IgAN group. After treatment with 1,25(OH)₂D₃ the level of Foxp3 increased significantly.**

Conclusions: Treg cells, IL-17 and RORgt may participate in the occurrence/development of IgAN; 1,25(OH)₂D₃ may play a role in immune regulation by regulating the expression of Treg cells, IL-17 and RORgt directly or indirectly.

Funding: Government Support - Non-U.S.

PUB074

MGRS, Complement and C3 Glomerulopathy Yuzhou Zhang,¹ Fernando C. Fervenza,² Christopher D. Blosser,³ Peter M. Fitzpatrick,⁴ Dingwu Shao,¹ Niamh Kieran,³ Carla M. Nester,¹ Sanjeev Sethi,² Nicolae Leca,³ Richard J. Smith.¹ ¹Carver College of Medicine, Univ of Iowa, Iowa City, IA; ²Mayo Clinic, Rochester, MN; ³Univ of Washington Medical Center, Seattle, WA; ⁴Mayo Clinic, Jacksonville, FL.

Background: Monoclonal gammopathy of renal significance (MGRS) implies a causal relationship between clonal B cell proliferation and renal disease. By definition, these patients do not meet criteria for overt multiple myeloma/B-cell proliferation, however their hematologic disorder is not of undetermined significance. Rather, it is associated with high morbidity secondary to renal compromise induced by circulating monoclonal immunoglobulins (MIg). Recently, a subset of MGRS with dominant glomerular C3 deposition or MGRS-C3 glomerulopathy (C3G) has been reported.

Methods: Factor H (FH) autoantibodies, free light chains against FH and factor B (FB) autoantibodies were detected by ELISA. C3 nephritic factors were detected using ELISA and hemolytic-based assays.

Results: Six patients developed MGRS-C3G triggered by four different mechanisms of action. The first mechanism of action, identified in three patients, was an IgG form of MIg to FH. These FH autoantibodies compromised function of FH, the only fluid-phase negative regulator of the alternative pathway (AP) of complement. The second mechanism, identified in one patient, was a free light chain (FLC) form of MGRS against FH. The FLCs acted as mini autoantibodies against the N-terminus of FH and impaired cofactor activity. The third mechanism, also identified in one patient, was an IgG form of MIg to FB as FB autoantibodies, resulting in increased activity of C3 convertase (C3bBb). The final mechanism, identified in one patient, was an IgG form of MIg, as a C3 nephritic factor that bound to and stabilized C3bBb.

Conclusions: These findings highlight the variability in autoantibodies associated with MGRS-C3G, thus mandating a comprehensive and detailed analysis of the alternative pathway in these patients. Acknowledgment: We gratefully acknowledge both the clinicians across North America who allow us to study their patients, and the patients, whose participation enhances our understanding of rare complex renal diseases.

PUB075

Elucidation of Tubulo-Interstitial Injury in Chronic Kidney Ischemia by Use of Novel Renal Artery Coiling Model Kentaro Fujii, Kazutoshi Miyashita, Hiroyuki Inoue, Aika Hagiwara, Masanori Tamaki, Masaaki Sato, Hiroshi Itoh. *Internal Medicine, School of Medicine, Keio Univ, Tokyo, Japan.*

Background: Recent studies emphasize an essential role for tubulointerstitial hypoperfusion in the progression of chronic kidney disease (CKD) as a common pathway to end stage renal disease (ESRD). However, the mechanism of renal injury needs further to be elucidated.

Methods: Most previous animal models which aimed to simulate renal ischemia have been ischemic-reperfusion injury model, which shows major characteristics of acute kidney injury. To elucidate the progression of kidney dysfunction with chronic ischemia, we developed novel renal ischemia model by setting a coil around a left renal artery of right hemi-nephrectomized mice and reducing the kidney bloodstream for 80%. The coil was made of the titanium and the inside diameter is from 0.17 to 0.28 mm.

Results: After transient decline in renal function until post-operative day 14, slowly progressive renal dysfunction and elevation of N-acetyl-β-D-glucosaminidase (NAD) in urine were observed in the chronic renal ischemia model from post-operative day 14 to 84. A histological observation of the ischemic kidney on post-operative day 7 revealed no

remarkable changes from control kidneys and there are no findings of tissue injury and infiltration of inflammatory cells. However, the progression of tubulointerstitial fibrosis and the increase in the markers for apoptosis and oxidative stress were significant from post-operative day 28 to 84. Real-time quantitative PCR analysis in ischemic kidney revealed the progressive changes of the hypoxia-responsive gene expressions such as pyruvate dehydrogenase kinases.

Conclusions: These data suggests that the novel chronic renal ischemia model by coiling renal artery is an appropriate animal model for CKD, which shows a slowly progressive tubulointerstitial injury.

Funding: Government Support - Non-U.S.

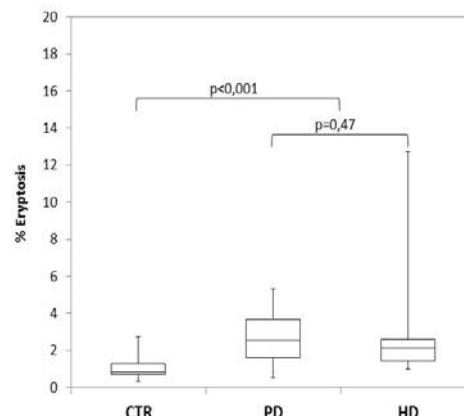
PUB076

Dialysis Induces Morphological Changes and Eryptosis in Erythrocytes Grazia Maria Virzi, Sabrina Milan Manani, Anna Clementi, Alessandra Brocca, Massimo de Cal, Claudio Ronco. *IRRIV and Dept Nephrology Vicenza.*

Background: Suicidal death of erythrocytes (eryptosis) is characterized by cell shrinkage, membrane blebbing, activation of proteases, and phosphatidylserine (PS) externalization. Exposed PS is recognized by macrophages that engulf and degrade affected cells. Eryptosis is a physiological mechanism under complex regulation. During their daily life, erythrocytes (RBCs) are exposed to several stressors, such as oxidative stress, osmotic shock, energy depletion. Eryptosis is observed in a wide range of clinical conditions, such as CKD, malignancy, diabetes and sepsis. The aim of this study was analysed cell volume and PS abundance at the RBC surface in peritoneal dialysis (PD) and hemodialysis (HD).

Methods: 40 PD patients, 30 HD patients and 17 healthy subjects (CTR) were included in the study. All measurements were made in isolated RBCs. RBC volume and morphology was estimated from forward scatter, PS exposure at the cell surface was estimated from FITC-AnnexinV binding using flow cytometric analyses.

Results: We observed that the RBCs of PD and HD patients are indeed rather dramatically deranged in their morphology. Furthermore, the PS externalization on the RBC surface was significantly higher in these groups than in CTR (PD patients: 2.6%; IQR 1.6-3.7, HD patients: 2.2%; IQR 1.2-4.1 versus CTR: 0.8%; IQR 0.7-1.3; p=0.000001). We did not find significant differences in PS exposure between the PD and HD patients (p=0.47).



Conclusions: In conclusion, the percentage of eryptosis has indeed been shown to be significantly higher in patients on dialysis than CTR. Our data suggest that dialysis may induce morphological changes in erythrocytes and may lead to a significant increase in eryptosis, but no differences in its level were observed between PD and HD. Additional efforts will be required to define major eryptosis-inducing components in uremic, PD and patients.

Funding: Private Foundation Support

PUB077

Toll Like Receptor 2, 4 and 9 Expression Is Enhanced in Kidneys of Patients with Anti Neutrophil Cytoplasmic Antibody Associated Vasculitis (AAV) Kim M. O'Sullivan,¹ Anthony Longano,³ A. Richard Kitching,^{1,2} Stephen R. Holdsworth.^{1,2} ¹Dept of Medicine, Monash Univ, Clayton, Victoria, Australia; ²Dept of Nephrology, Monash Health, Clayton, Victoria, Australia; ³Pathology Dept, Monash Health, Clayton, Victoria, Australia.

Background: Toll like receptors (TLRs) may be the possible link between infection and autoimmunity. This study investigates the distribution of TLR2, 4 and 9 in human kidney biopsies from patients with AAV (40), lupus (8) and controls (with non proliferative glomerular lesions, minimal change and thin membrane disease, 10).

Methods: Biopsies were examined by confocal microscopy with immunofluorescent staining in serial sections for the cellular distribution of TLR2, 4 and 9. Mean fluorescent intensity (MFI) was measured by imaging software (Image J) and was correlated with histopathological parameters.

Results: TLR2, 4 and 9 in the AAV group, (for both MPO and PR3 patients) had significantly stronger staining than controls in glomeruli (1.5 vs 13.3AU; 0.25 vs 32.0AU; 0.7 vs 36.2AU, all P<0.05, respectively) and the interstitium (7.4 vs 63.0AU; 0.41 vs 53.8AU; 1.6 vs 59.6 AU, all P<0.05, respectively). The lupus patients also had higher

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

expression of TLR2 (4.8AU), 4 (12.6AU) and 9 (7.3AU, $P < 0.05$) compared with controls, but their staining was significantly less than that of the AAV group for all TLRs ($P < 0.05$). Cellular infiltrates contained intense staining for TLR2, 4 and 9 on macrophages and neutrophils in both glomeruli and interstitium. TLR2 and TLR4 staining was prominent on both endothelial cells and podocytes, although TLR9 was particularly evident on podocytes. In AAV glomerular TLR4 expression correlated with the % of normal glomeruli ($r = 0.48$, $P < 0.05$) suggesting TLR4 prominence occurs in early glomerular lesions. Glomerular TLR2 and 9 were present concurrently in more severely affected glomeruli ($r = 0.71$, $P = 0.0001$). TLR2, 4 and 9 were prominent in all crescentic glomeruli of AAV and lupus patients.

Conclusions: This study demonstrates that TLR expression is most prominent in AAV. Significant expression of TLRs was evident on leukocytes and intrinsic glomerular cells. TLR4 is prominent in early glomerular lesions, while TLR2 and 9 correlate with severe glomerular lesions.

Funding: Government Support - Non-U.S.

PUB078

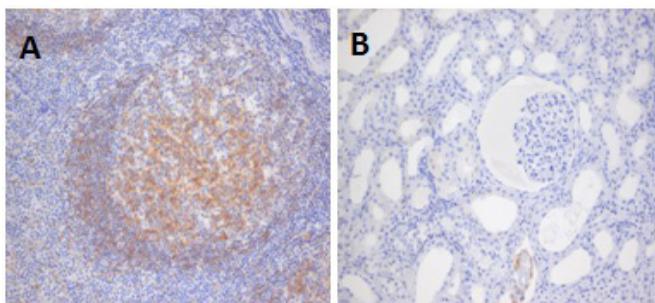
Podocyte CD40 Expression in Patients with Post-Transplant FSGS Recurrence Rutger J. Maas,¹ Brigith Willemssen,² Henry Dijkman,² Jeroen Deegens,¹ Jack F. Wetzels.¹ ¹Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ²Pathology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: antibodies against CD40 were recently reported to predict post-transplant recurrent FSGS (rFSGS) with 78% accuracy (Delville et al. Sci Transl Med 2014). Using immunohistochemistry, the authors reported strong focal podocyte CD40 expression in glomerular lesions of two patients with rFSGS. We sought to validate this novel finding of podocyte CD40 expression as a potential marker of rFSGS.

Methods: we used formalin-fixed, paraffin embedded kidney tissue from five patients with rFSGS. Two samples were obtained from nephrectomy specimens, and three were needle biopsy specimens. All patients had nephrotic range proteinuria at the time of tissue sampling. A human tonsil was used as a positive control. For immunohistochemistry, four mm slides were cut and deparaffinised. After endogenous peroxidase block, antigen retrieval was performed by boiling in a microwave with EDTA buffer (pH 9.0). Slides were incubated with primary antibody mouse anti CD40 (clone 11E9, Abcam ab50849) diluted in PBS with 1% BSA overnight at 4°C. Detection was done with Brightvision biotin-free goat anti rat/rabbit/mouse poly HRP (Immunologic) and DAB as substrate.

Results: specificity and adequacy of the staining was confirmed by strong CD40 expression in tonsillar germinal centers (Figure, panel A). In kidney samples from patients with rFSGS, CD40 staining was found in areas of interstitial cellular infiltration, and some tubular epithelial cells (Figure, panel B). However, no glomerular CD40 was detected in any of the rFSGS samples.

Conclusions: we could not confirm glomerular CD40 staining in rFSGS with immunohistochemistry. The role of CD40 antibodies in rFSGS pathogenesis needs further study and validation.



Funding: Private Foundation Support

PUB079

Increased Cellular Microchimerism in Women with Systemic Lupus Erythematosus Suzanne Wilhelmus,¹ Malu Zandbergen,¹ Emilie Rijnink,¹ Juan D. Diaz de Pool,² Mathilde M.M. Almekinders,¹ Hans J. Baelde,¹ Jan A. Bruijn,¹ Ingeborg M. Bajema.¹ ¹Pathology, Leiden Univ Medical Center, Leiden, Netherlands; ²Gynaecology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Microchimerism (Mc) has been suggested to play a role in the development of systemic lupus erythematosus (SLE). We previously showed that Mc occurs twice as often in kidney biopsies of patients with lupus nephritis as in controls. Recently, it was demonstrated that the amount of Mc in lupus nephritis is associated with renal function (Arthritis Research & Therapy, 2015). Because in previous studies the Y chromosome was used to detect Mc, these studies were limited to detecting male Mc and the origin of the chimeric cells remained largely unknown. The aim of the present study was to determine the frequency, amount and origin of chimeric cells in SLE patients and controls, by using insertion-deletion polymorphisms and null alleles for the detection of Mc.

Methods: We included 11 SLE patients and 22 controls, as well as their children and mothers. A quantitative PCR for insertion-deletion polymorphisms and null alleles was used to detect Mc in peripheral blood mononuclear cells and granulocytes. The relationship between the presence of Mc and disease onset, disease activity and accumulated damage since disease onset was investigated.

Results: Mc was detected more often in SLE patients than in controls (54.4% vs 13.6%, $p = 0.03$), and was fetal in origin in almost all cases. The median total number of fetal chimeric cells was significantly higher in patients than in controls ($5/10^6$ versus $2.5/10^6$, $p = 0.048$). In 50% of SLE patients with Mc, Mc originated from multiple relatives whereas in controls Mc was derived from only one relative. We found no relationship between Mc and clinical or laboratory parameters.

Conclusions: SLE patients had Mc in peripheral blood more often than controls, and at higher levels. We showed that Mc was mostly fetal in origin and, in SLE patients, could be derived from multiple relatives. Our findings substantiate the role for Mc in autoimmune diseases such as SLE.

Funding: Private Foundation Support

PUB080

An Oxalate-Induced Mouse Model of CKD That Displays Common CKD Complications Hans J. Anders,¹ Shrikant R. Mulya,¹ Jonathan Nicodemus Eberhard,¹ Victoria Pfann,² Julian A. Marschner,¹ Simone Romoli,¹ Jayasi Desai,¹ Santhosh Kumar Vr,¹ Peter S. Aronson,³ Felix Knauf.² ¹Univ of Munich; ²Univ of Erlangen-Nürnberg; ³Yale Univ School of Medicine.

Background: Chronic kidney disease (CKD) research is limited by the lack of a convenient inducible C57BL/6 mouse model mimicking relevant human CKD complications. We have reported a high soluble oxalate diet (50 μ moles/g sodium oxalate mixed with virtually calcium free diet) that induces a progressive decline in glomerular filtration rate (GFR) reflected by increasing creatinine as well as blood urea nitrogen levels in C57BL/6 mice.

Methods: All in vivo experiments were approved by the local government authorities. Computed tomography, ultrasound and MRI were used for imaging. IHC, RT-PCR were used for data analysis. GFR was measured using single i.v. bolus injection of FITC sinistrin in conscious mice.

Results: We now demonstrate that mice fed this high soluble oxalate diet develop typical CKD complications such as sustained hypertension, normochromic anemia, metabolic acidosis, hyperphosphatemia, hyperparathyroidism, and hyperkalemia. Renal histology is characterized by calcium-oxalate crystal plugs in the tubular lumen, tubular atrophy, interstitial fibrosis, and atubular glomeruli. This pathophysiology of CKD resembles that of primary hyperoxaluria type I, also in terms of renal ultrasound, computed tomography, and magnetic resonance imaging. The duration of feeding a high soluble oxalate diet determines the amount of nephron loss, interstitial fibrosis, and impaired GFR equivalent to different stages of CKD. This can be used to produce various levels of stable impaired baseline GFR, a useful way to study, for example, AKI on precedent CKD.

Conclusions: We conclude that feeding a high soluble oxalate diet is a convenient way to induce progressive and stable CKD with clinically established complications in C57BL/6 mice. This model should serve to be useful for many areas of CKD research and avoid surgery to induce nephron loss or renal fibrosis.

PUB081

Cyclosporine A Reduces Renal Injury Through Protecting Glomerular Charge Barrier in Passive Heymann Nephritis Zilong Li, Juan Wang, Lining Wang. *Dept of Nephrology, First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning, China.*

Background: Cyclosporine A (CsA) has been reported to reduce proteinuria in several kinds of kidney diseases. Glomerular charge barrier plays an important role in preventing urinary protein loss. The aim of this study was to elucidate the effects of CsA on glomerular charge barrier in passive Heymann nephritis (PHN).

Methods: Wistar rat PHN model was established by injecting antiserum against renal tubular epithelial antigens (anti-Fx1A) following pre-immunization. The experiment included Group 1: PHN control, Group 2: PHN plus CsA treatment before anti-Fx1A injection, Group 3: PHN plus CsA treatment for the first 7 days after injection, and Group 4: PHN plus CsA treatment from the 8th day after injection. Serum creatinine (sCr) and urinary protein (uPro) were measured at the 7th and/or the 14th day. Kidney tissues were obtained at the 14th day and labeled with a cation tracer polyethyleneimine (PEI) to study the distribution of negative charges on glomerular basement membrane (GBM). Kidney pathological changes were investigated.

Results: PHN model was established showing proteinuria and kidney injury of thickened GBM, a mass deposition of immune complex (IC), and decreased density and disturbed distribution of negative charges along the GBM. sCr was not increased in all of groups. With CsA treatment, uPro was significantly declined in Group 2 and 3 at 7th day, and in Group 2 and 4 at 14th day. In Group 2, it showed little pathological changes in kidney with less IC deposition and negative charges distributed evenly. In Group 3 and 4, the deposition of IC was reduced, and the negative charges distribution was repaired showing stronger density compared to Group 1, while less regularly arranged compared to Group 2.

Conclusions: Using a rat model of PHN, CsA was able to protect glomerular charge barrier, which might benefit from the regulation of Ca^{2+} influx and reduction of IC deposition, thus minimizing proteinuria and renal injury.

PUB082

Absence of Caspase-1 Attenuates Adriamycin-Induced Nephropathy
 Jinghui Luo,¹ Yingbao Yang,¹ J. Michelle Kahlenberg,² Tamra J. Reed,² Stephanie Wylie,¹ Christopher Lund O'Connor,³ Jeffrey B. Hodgin.¹ ¹*Pathology, Univ of Michigan, Ann Arbor, MI;* ²*Rheumatology, Univ of Michigan, Ann Arbor, MI;* ³*Univ of Michigan, Ann Arbor, MI.*

Background: Recent studies have demonstrated a pathogenic role of caspase-1 in mediating proteinuria-associated renal injury. As a chronic proteinuric renal disease model, adriamycin (ADR)-induced nephropathy (AIN) has been characterized by podocyte injury followed by glomerulosclerosis (GS), tubulointerstitial inflammation and fibrosis, but the mechanisms underlying it remain poorly understood. Based on the evidence that oxidative stress stimulates inflammasome activation which subsequently contributes to renal injury, we hypothesize that abolishing caspase-1 expression in the kidney may be protective.

Methods: Male caspase-1 knockout (KO) and wildtype (WT) mice on the BALB/c background were injected with ADR (10.5 mg/kg) or saline at 8-10 weeks of age. Twenty four-hour-urine was collected and the mice were sacrificed 14 days post the injection. Creatinine (Cr), triglycerides, and total cholesterol (TCH) were determined in serum, and histological analyses, western blot, and RT-qPCR were performed in kidney tissue.

Results: ADR triggered overexpression of caspase-1 and IL-1 β in kidney tissue of WT mice, but not in that of KO mice. ADR induced albuminuria and GS, which was accompanied with decreased kidney weight/body weight ratio (Kw/Bw), and increased Cr and TCH levels in both KO and WT mice. Compared with WT animals, KO mice showed significantly lower ACR, reduced GS scores, increased Kw/Bw, and attenuated Cr levels (P<0.05 each). Meanwhile, elevated expression of TNF- α and INF- γ , augmented 12-LO, and decreased PPAR- α , SDHA, and SOD2 levels were observed in ADR-treated kidneys, and all these changes were shown to be significantly ameliorated in KO mice. In addition, positive correlation between Cr and TCH was recognized in both KO and WT ADR-treated mice.

Conclusions: Cytokine-mediated inflammatory cascade, hyperlipidemic injury, and impaired mitochondrial function are all responsible for ADR-induced kidney injury. Caspase-1 might be a potential therapeutic target in proteinuric renal disease.

Funding: NIDDK Support, Other NIH Support - ASN-Nephcure Foundation

PUB083

Glomerular HO-1 Expression Control by Hemin: Role of Hemopexin
 Maria Detsika,¹ Vasileios Atsaves,¹ Emanuela Tolosano,³ Pu Duann,² Elias A. Lianos.^{1,2} ¹*Medicine, Univ of Athens, Greece;* ²*Medicine, Rutgers Biomedical and Health Sciences, NJ;* ³*Molecular Biotechnology Center, Univ of Torino, Italy.*

Background: Hemopexin (HPX) maintains low free heme levels in serum thus mitigating heme-associated cell injury. HO-1 induction also minimizes injury by degrading heme to CO and bile pigments. In hemolytic disorders, heme scavenging by HPX is overwhelmed and glomeruli may be exposed to high free heme, exceeding 200 μ M. However, while HO-1 prominently increases in tubules, it is barely detectable in glomeruli. We hypothesized that this is due to presence of a HO-1 expression "threshold" above which HO-1 induction in glomeruli is not sustainable.

Methods: *hmx1*^{-/-} rats were generated by Zinc Finger Nuclease (ZFN)-mediated HO-1 gene disruption and rats with GEC targeted HO-1 overexpression (GEC^{HO-1}) by Sleeping Beauty Transposon mediated transgenesis using a nephrin promoter. Glomeruli from wild type (WT) or *hmx1*^{-/-} or GEC^{HO-1} rats were incubated for 18 h with 10% HPX replete (HPX⁺) or HPX-deficient (HPX⁻) serum obtained from HPX knock-out mice. Exogenous heme was added at concentrations encountered in hemolytic disorders (100-400 μ M). HO-1 protein levels were assessed by western blot.

Results: HO-1 protein was reduced by 70% in *hmx1*^{-/-} and increased by 2-fold in GEC^{HO-1} glomeruli. HO-1 protein levels were no different between 10% HPX⁺ serum vs serum-free media. In incubations with varying dilutions of HPX⁻ serum (1.25, 2.5, 5, 10%) HO-1 levels in WT glomeruli progressively increased and were 2.5-fold higher with 10% HPX⁻ serum compared to 10% HPX⁺ serum. Co-incubation with 10% HPX⁺ serum and heme (200, 400 μ M) markedly reduced HO-1. This reduction was attenuated in incubations with higher dilutions (2.5%) of HPX⁻ serum or with 10% HPX⁻ serum. The effect of heme on HO-1 levels in glomeruli incubated with HPX⁻ serum was recapitulated in GEC^{HO-1} glomeruli. In contrast, heme further increased HO-1 in *hmx1*^{-/-} glomeruli.

Conclusions: Heme-mediated HO-1 induction in glomeruli is limited by HO-1 expression levels attained. This may serve to limit level of HO activity thereby preventing excessive heme-derived Fe²⁺ in hemolytic disorders.

Funding: Government Support - Non-U.S.

PUB084

GEC-Targeted HO-1 Over Expression: Protective Effects in Secondary but Not Primary GEC Injury
 Vasileios Atsaves,¹ Maria Detsika,¹ Elias A. Lianos.^{1,2} ¹*Medicine, Univ of Athens, Athens, Greece;* ²*Medicine, Rutgers Biomedical and Health Sciences, N. Brunswick, NJ.*

Background: In contrast to tubular epithelial cells, induction of the cytoprotective enzyme, Heme Oxygenase (HO-1), in response to injury in glomerular epithelial cells (GEC) is limited or absent and this may increase their vulnerability to injury. We, therefore, explored whether targeted HO-1 over expression in GEC can protect against primary injury induced by puromycin aminonucleoside (PAN) or secondary injury resulting from anti-GBM Ab induced glomerulonephritis (GN).

Methods: HO-1 over expression in GEC of Sprague-Dawley (SD) rats was achieved by targeting a FLAG-human(h)HO-1 sequence under the control of a murine nephrin promoter using transposon-mediated gene-trap insertional mutagenesis based on a *Sleeping*

Beauty(SB) transposon system (SB rats). GEC-targeted over expression was validated by FLAG immunolocalization and by western blot. PAN-mediated GEC injury was induced in SD rats by a single intraperitoneal injection. GN was induced by a single intravenous injection of a rabbit anti-rat GBM Ab. At defined points following PAN or anti-GBM Ab injection, albuminuria (Ualb/Ucreat) was assessed and glomeruli were isolated to determine changes in HO-1 and nephrin expression (GEC integrity marker).

Results: In glomeruli from SB rats HO-1 levels (protein) increased compared to Wild type (Wt). Administration of either PAN or anti-GBM to Wt rats increased glomerular HO-1. In SB rats receiving PAN, HO-1 markedly decreased compared to Wt. In contrast, HO-1 was preserved following anti-GBM Ab. Nephrin expression was markedly decreased in glomeruli from SB rats treated with PAN. In contrast, nephrin was preserved in glomeruli from SB rats treated with anti-GBM Ab. Ualb/Ucreat was significantly higher in WT compared to SB rats treated with anti-GBM Ab. In contrast, there was no difference in Ualb/Ucreat between Wt and SB rats receiving PAN.

Conclusions: Augmentation of HO-1 expression in primary GEC injury is impaired. This could be yet another mechanism contributing to GEC vulnerability in primary podocytopathies.

Funding: Government Support - Non-U.S.

PUB085

Comparative Evaluation of Cellular Injury Models Based on Conditionally Immortalized and Primary Podocytes
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Background: Podocyte injury is a hallmark of proteinuric chronic kidney disease. The response of podocytes to injury includes cytoskeletal reorganization, oxidative stress, de-differentiation & detachment. The purpose of this study was to compare commonly used conditionally immortalized podocytes with primary podocytes, by measuring podocyte markers and responses to injury.

Methods: Primary human podocytes were isolated and cultured from a healthy human donor kidney and compared to 1) a subclone (C5) of conditionally immortalized human podocytes (selected based on podocyte specific gene expression) and 2) conditionally immortalized mouse podocytes. Cellular phenotypes and gene expression were measured using high content screening (HCS), qPCR and western blots. For assessment of diabetic serum as a stressor, serum was pooled from db/db and control mice. Differential cytotoxicity of db/db sera was measured by quantifying cytoskeletal integrity, cell morphology, heme oxygenase-1 expression and cell adhesion.

Results: C5 podocytes were benchmarked to primary human podocytes using 1) expression of WT-1, podocin, synaptopodin and a-smooth muscle actin and 2) cytoskeletal and cell cycle phenotypes. C5 cells were also evaluated by comparing gene expression profiles in response to TGF- β treatment. C5 podocytes were judged to be similar to primary human podocytes based on these analyses. Current cellular models of podocyte protection often use the stressors puromycin aminonucleoside and TGF- β . We demonstrate cytoprotection by multiple reference compounds with these insults. We have also increased the disease relevance of stressors by showing that serum isolated from proteinuric db/db mice differentially elicits podocyte injury across multiple parameters.

Conclusions: Our results validate the use of conditionally immortalized C5 podocytes by benchmarking against primary human podocytes. We have also enhanced the pathologic relevance of models of podocyte injury by incorporating key disease-relevant stressors and readouts.

Funding: Pharmaceutical Company Support - AbbVie

PUB086

Hypoxia Stimulates the Expression of Tissue Factor in Human Podocytes in Culture
 Ikuyo Narita,¹ Michiko Shimada,¹ Reiichi Murakami,¹ Masayuki Nakamura,¹ Norio Nakamura,¹ Moïen Saleem,² Peter W. Mathieson,³ Hideaki Yamabe,¹ Ken Okumura.¹ ¹*Nephrology, Hirotsuki Univ, Hirotsuki, Japan;* ²*Renal Academic Unit, Univ of Bristol, Bristol, United Kingdom;* ³*Univ of Hong Kong, Hong Kong, China.*

Background: Hypoxia contributes to tubulointerstitial injury, however, the effect on podocytes and its underlying mechanisms are less well understood. Tissue factor (TF) is the initiator of extrinsic coagulation pathways and is also related to various biologic effects such as proliferation, inflammation, and cell motilities. In this study, we tested the expressions of TF and tissue factor pathway inhibitor (TFPI) in the hypoxic conditions. We further tested the roles of known transcription factors of TF such as, nuclear factor- κ B (NF- κ B) and early growth response gene-1 (Egr-1), as well as hypoxia-inducible factor-1 α (HIF-1 α) which regulates numerous changes in hypoxia.

Methods: Conditionally immortalized human podocytes were grown at 33°C and differentiated at 37°C. The cells were treated in normoxic or hypoxic conditions. mRNA expressions of TF and TFPI were analyzed by quantitative RT-PCR, and protein levels of TF in the cell lysate and TFPI in the supernatant were tested by ELISA. The expression of TF and HIF-1 α were demonstrated by immunofluorescent staining. We used siRNA for the temporal knockdown of HIF-1 α and Egr-1, and pyrrolidine dithiocarbamate (PDTCT) for the inhibition of NF- κ B.

Results: Hypoxia increased mRNA expression of TF (6h: 2.3 \pm 0.05 fold, p<0.001, 24h: 5.6 \pm 2.4 fold, p<0.05) and suppressed TFPI (6h: 0.54 \pm 0.04 fold, p<0.05, 24h: 0.24 \pm 0.06 fold, p<0.001) compared with normoxia. The protein levels of TF in the cell lysate were increased and TFPI in the supernatant were decreased. The TF staining was enhanced in

the cytoplasm of podocyte. As expected, HIF-1 α was strongly stained in the nuclei of podocytes exposed to hypoxia for 6h. The expression of TF was not affected by HIF-1 α siRNA, and neither Egr-1 siRNA. Whereas, PDTC reduced the induction of TF by hypoxia.

Conclusions: Hypoxia upregulated the expression of TF in human podocyte NF- κ B dependently, and HIF-1 α and Egr-1 independently. These changes may be related to the podocyte disorders and lead to proteinuria in the hypoxic condition.

PUB087

Integrity of the Mature APOL1 Protein Is Indispensable for Its Toxicity Xiqian Lan,¹ Hongxiu Wen,¹ Ashwani Malhotra,¹ Karl Leon Skorecki,² Pravin C. Singhal.¹ ¹Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; ²Medicine, Rambam Health Care Campus, Haifa, Israel.

Background: Several clinical reports have demonstrated that the development of higher rates of non-diabetic glomerulosclerosis (GS) amongst African Americans can be attributed to two coding sequence variants (G1 and G2) in the APOL1 gene. Recent studies indicate that the gene products of these APOL1 risk variants have augmented toxicity in kidney cells. The APOL1 protein is composed of several functional domains, including signal peptide (SP), pore forming domain (PFD), membrane address domain (MAD), and SRA-interacting domain. However, it is not clear, which domain contributes to APOL1 induced cellular toxicity. In case, specific domain is contributing to APOL1-induced cellular toxicity, it will suggest us to design therapeutic strategy to target the specific domain.

Methods: To investigate the relative contribution of each domain to cell injury, we constructed serial of expression vectors to delete each domain, we transfected these vectors into the human embryonic kidney cell line 293T, and then compared the cytotoxicity. In addition, we conducted studies in which APOL1 wild type (G0) was co-transfected in combination with G1 or G2 to see whether G0 could counteract the toxicity of the risk variants.

Results: The results showed that deleting the SP did not abolish the toxicity of APOL1, though deletion of 26 amino acid residues at the N-terminal partially decreased the toxicity. Deleting PFD or MAD or SRA-interacting domain abolished toxicity, while, overexpressing each domain alone could not cause toxicity to the host cells. Deletion of the G2 sites while retaining G1 sites in the risk state resulted in persistent toxicity. Either deletion or exchanging the BH3 domain in the PFD led to complete loss of the toxicity in this experimental platform. Adding G0 to either G1 or G2 did not attenuate the toxicity of the either moiety.

Conclusions: These findings indicate that the integrity of the mature APOL1 protein is critical for its toxicity.

Funding: NIDDK Support

PUB088

Human Podocyte Depletion: The Effects of Aging and Hypertension Victor G. Puelles,¹ Luise A. Cullen-McEwen,¹ Jinhua Li,¹ Peter G. Kerr,² Wendy E. Hoy,³ John F. Bertram.¹ ¹Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Victoria, Australia; ²Dept of Nephrology, Monash Medical Centre, Melbourne, Victoria, Australia; ³Centre for Chronic Disease, The Univ of Queensland, Brisbane, Queensland, Australia.

Background: Podocyte depletion plays a major role in the development and progression of glomerulosclerosis. Many kidney diseases are more common in older age, and usually coexist with the presence of hypertension. We hypothesize that podocyte depletion develops with aging and is exacerbated by the presence of hypertension.

Methods: Kidneys from 21 adult Caucasian American males without overt renal disease were collected at autopsy in Mississippi, USA. Subjects were categorized based only on age as young adults, middle-aged adults and older adults. Subjects were also categorized based on age and hypertension as young normotensives, older normotensives, and older hypertensives. Demographic data were collected from available medical records. Design-based stereology was used to estimate individual glomerular volume (IGV), podocyte number and podocyte density. Data are presented as mean \pm SD.

Results: Glomeruli from young adults (22.0 \pm 2.7 years; n=6) were small (1.72 \pm 0.50 x10⁶mm³), and contained 457 \pm 97 podocytes and 278 \pm 66 podocytes per 10⁶mm³ of glomerular tissue. Glomeruli from older adults (60.0 \pm 8.6 years; n=7) were larger (2.94 \pm 1.41 x10⁶mm³; P<0.001), contained fewer podocytes (390 \pm 105; P<0.05) and had lower podocyte density (156 \pm 65 podocytes per 10⁶mm³; P<0.0001). Among normotensives, older age was associated with a 15% increase in IGV (P=0.28), a 12% decrease in podocyte number (P=0.06) and a 17% decrease in podocyte density (P<0.01). Glomeruli from hypertensives and normotensives contained similar numbers of podocytes, but hypertensives had larger glomeruli (P<0.0001) and a markedly lower podocyte density (P<0.001).

Conclusions: These findings demonstrate that both aging and hypertension are independent and additive contributors to podocyte depletion in this cohort of white American men without overt kidney disease.

PUB089

Alport Nephropathy Progression Involves Altered Glomerular Mechanical Properties and Activation of the Unfolded Protein Response Addie Embry,¹ Liping Liu,¹ Leslie A. Bruggeman,² Paul A. Janmey,³ R. Tyler Miller.¹ ¹Medicine, UTSW, Dallas, TX; ²Medicine, CWRU, Cleveland, OH.

Background: Tissue and cell mechanics are important factors in the development and maintenance of tissues but are not well defined in renal disease. We determined the biophysical properties of glomeruli over the course of disease in the Col4a3^{-/-} (Alport) mouse.

Methods: Glomerular EMod was measured with microindentation, gene transcript levels with qRT-PCR and immunofluorescence, and kidney structure with histology.

Results: Col4a3^{-/-} kidneys have normal histology, no proteinuria, and a normal glomerular E_{Mod} (2,200Pa) through 2 mo of age. At approximately 4 mo, early interstitial and glomerular fibrosis and proteinuria appear, and the glomerular E_{Mod} decreases (~1400Pa). Glomerular softening is characteristic of injured glomeruli, is associated with injured podocytes, and could lead to capillary injury even with normal hemodynamics. By 6 mo, the glomeruli regain their original E_{Mod} (~ 2,200 Pa) but with increased proteinuria and more severe glomerular and interstitial fibrosis. By 7-8 mo, the glomerular E_{Mod} increases (~ 2,600 Pa) with further increases in proteinuria and glomerular and interstitial fibrosis. At 2 mo, glomerular transcripts for matrix and fibrotic factors (CTGF, α -SMA, filamin, lysyl oxidase) are increased and remain so, demonstrating early responses of cells to alter their mechanical environment. Transcripts associated with UPR activation (BiP, CHOP, grp94) are elevated, suggesting that loss of the Col4a3 chain leads to activation of the UPR. Tunicamycin-treated glomeruli demonstrated a markedly reduced E_{Mod} (~1100Pa), suggesting that UPR activation causes glomerular injury.

Conclusions: Biophysical abnormalities occur early in the course of this Alport model, suggest that the reduced E_{Mod} of glomeruli (increased deformability) may lead to mechanical injury of capillaries even with normal hemodynamic force, that cells of glomeruli respond by producing proteins that will reduce deformability, and that glomerular or podocyte injury may be attributable to activation of the UPR.

Funding: NIDDK Support, Veterans Administration Support, Private Foundation Support

PUB090

A New Assay to Study Podocyte (De)Differentiation Frances Kindt, Karlhans Endlich, Nicole Endlich. *Anatomy and Cell Biology, Univ Medicine Greifswald, Greifswald, Germany.*

Background: Podocytes play an essential role in the formation and maintenance of the glomerular filtration barrier. Glomerular disease is associated with podocyte damage, frequently resulting in podocyte dedifferentiation. The loss of podocyte differentiation is poorly understood. Moreover, there are no drugs available that could halt or even reverse podocyte dedifferentiation. Since podocytes of isolated glomeruli have long been known to spontaneously lose their highly differentiated state over time, we established an assay to follow dedifferentiation of living podocyte in isolated glomeruli over time.

Methods: Using magnetic separation with dynabeads, glomeruli were isolated from transgenic mice that express cyan fluorescence protein (CFP) under control of a nephrin promoter fragment (Cui et al., <em style="font-family: 'Times New Roman'; font-size: 16px;">J. Am. Soc. Nephrol.[itali]c 16: 3247-55, 2005).

Results: Isolated glomeruli were mostly free of Bowman's capsule, exhibited minimal cell damage as assessed by propidium iodide, showed intact immunostaining for nephrin, and possessed intact interdigitating foot processes as judged by scanning electron microscopy. Isolated glomeruli were cultured for up to 9 d in RPMI containing 10% FBS. To quantify CFP fluorescence as a measure of differentiation, we recorded z-stacks of several glomeruli by confocal laser scanning microscopy on each day. Mean total fluorescence intensity per glomerulus (MFG) was calculated from z-stacks after background correction. MFG remained stable for 5 d. Thereafter, MFG gradually decreased to 10% of the initial value on day 9. Dedifferentiation of podocytes could be accelerated by treatment of isolated glomeruli with doxorubicin, strongly decreasing MFG within the first three days.

Conclusions: In summary, we established a new assay to study podocyte (de) differentiation. This assay may help to understand the molecular mechanisms of the loss of podocyte differentiation, and may allow to screen for compounds that stabilize podocyte differentiation.

Funding: Government Support - Non-U.S.

PUB091

Methods to Selectively Remove Murine Endothelial Glycocalyx *In Vivo* Using Glycosaminoglycan Digesting Enzymes without Causing Non-Target Effects Karen L. Onions, Anjiola Onifade, Chris R. Neal, Monica Gamez, Gavin Iain Welsh, Andy Salmon, Simon C. Satchell, Rebecca R. Foster. *Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.*

Background: The endothelial glycocalyx (e-GLX) is an important component of the glomerular filtration barrier (GFB), damage to which increases vascular permeability and microalbuminuria. Jeansson and Haraldsson previously used glycosaminoglycan (GAG) digesting enzymes to study the role of the e-GLX in glomerular permeability. However, e-GLX removal was not directly quantified. The aim of this research was to confirm removal of systemic e-GLX and identify any non-targeted effects in the glomerular or coronary microcirculation.

Methods: Mice were injected I.V with chondroitinase (Ch) and hyaluronidase (Hy) at a high (Ch: 87 mU/g, Hy: 15U/g) or low (Ch: 0.087 mU/g, Hy: 15 mU/g) dose. Mice

were whole body (cardiac) perfusion fixed with glutaraldehyde containing Alcian blue to stain the e-GLX. Transmission electron microscopy (TEM) was used to image the ultrastructure of the heart and glomerular microcirculation, which was quantified using defined parameters in ImageJ.

Results: In the heart, the low dose significantly reduced glycocalyx coverage to 62% compared to sham (84%) and high (87%) dose groups ($p=0.0227$ one way ANOVA). The high dose caused an increase in vesicle number within the endothelial basement membrane (3.3/ μm) compared to controls (1.2/ μm) ($p = 0.0328$ t-test). Within the parameters of this analysis there were no structural changes to other components of the GFB or coronary circulation at either enzyme concentration.

Conclusions: These results indicate that a low dose of GAG digesting enzymes targets systemic e-GLX loss and does not cause any non-target effects. This technique will be utilised to study the role of the e-GLX in glomerular permeability. Increasing understanding in this area will identify how e-GLX contributes to glomerular albumin permeability in different pathological scenarios and may highlight new therapeutic targets. This work was funded by the British Heart Foundation (FS/13/9/29957).

PUB092

Dietary Salt Restriction Induces New, Single Mesenchymal Stem Cell-Derived Progenies in the Glomerulus and Proximal Tubule Donna Ralph, Kengo Kidokoro, Anne Riquier-Brisson, Janos Peti-Peterdi. *Physiology & Biophysics, Univ of Southern California, Los Angeles, CA.*

Background: Salt restriction is known to slow down the progression of chronic kidney disease (CKD) and improve albuminuria via blood pressure-independent structural changes in the glomerulus, however the underlying mechanisms have been elusive. We aimed to track the migration and fate of individually identified resident mesenchymal stem/progenitor cells in the renal cortex in intact mouse kidneys.

Methods: In vivo serial multiphoton microscopy (MPM) of the same glomeruli over several days, and genetic cell fate tracking using histology in tamoxifen-induced NG2CreERT2-Confetti mice expressing either CFP/GFP/YFP/RFP were performed during salt deficient diet+ACE inhibition for 10 days.

Results: At baseline, a few cells belonging to the NG2 lineage (NG2+) were observed in a scattered pattern throughout the renal interstitium. Serial MPM showed that in response to salt deprivation, monochromatic (either blue/green/yellow or red) multi-cellular tracing units appeared at the glomerular vascular pole, mesangium, Bowman's capsule, and in the proximal tubule within 10 days. Subsequent histology of NG2-Confetti mouse kidneys found that the highest density of NG2+ cells was in the outer medulla, and confirmed the presence of 3-10 cells-containing monochromatic (clonal) tracing units along the cortical vasculature, afferent arteriole, and within the glomerulus (including mesangial and parietal epithelial cells, and a very few podocytes) and the proximal tubule. Spherical or stellate-shaped NG2+ cells were observed in the Bowman's space and in the proximal tubule lumen suggesting cell migration.

Conclusions: In summary, our data are consistent with highly dynamic cellular remodeling of the renal interstitium, vasculature, glomerulus, and the proximal tubule by single progenitor cells. These results also suggest the presence of a complex nephron repair program which is augmented in response to salt deprivation.

Funding: NIDDK Support

PUB093

Beraprost Ameliorates Renal Function and Reduce Uremic Toxin in GBM Nephropathy in Rat and in Humans (Small Number Study) Yasuno Mukaiyama, Yuki Oba, Koichi Kikuchi, Hisato Shima, Eikan Mishima, Yasutoshi Akiyama, Takehiro Suzuki, Daisuke Saigusa, Sadayoshi Ito, Takaaki Abe. *Tohoku Univ Graduate School of Medicine.*

Background: In CKD patients, the accumulation of uremic toxins exacerbates renal damage. Beraprost sodium (BPS) is prostacyclin analogue and is mainly used to treat atherosclerotic obliterans. Recently, Several reports show that BPS reduced progression of renal damages in CKD. To identify the reno-protective effect of BPS, we measured uremic solutes by capillary electrophoresis with mass spectrometry (CE-MS) in anti-GBM Glomerular Nephropathy(GN) rat model as well as 4 CKD patients before and 5 month after BPS administration.

Methods: A comprehensive and quantitative analysis of charged metabolites by CE-MS was performed. We obtained serum from (1) Normal rats, GBM GN rats and BPS-administered GBM GN rats and (2) 4 CKD patients treated with BPS. We performed CE-MS and a comprehensive and quantitative analysis of charged metabolites. All the experiments were performed under Animal and Ethical Committee approval.

Results: Among 500 organic anions and cations, 16 anionic solutes and 42 cationic solutes were further examined. Among the anionic solute that increased in GN rats, the concentration of 2 anionic solutes(Gluconate and Citrate) are ameliorated by BPS treatment. Among the cationic solute that increased in GN rats, the concentration of 10 cationic solutes (N,N-Dimethylglycine, Creatinine, Uridine, Citrulline, Creatine, Hydroxyproline, Alanine, Arginine, Glycine, Cystathionine) also increased in GN and all of them are reduced by BPS treatment. Conversely, the concentration of 8 metabolites were decreased in GN rats, and by BPS treatment, the reduced concentration of tryptophan recovered to the normal level. Well-known uremic toxins such as ADMA, SDMA and 1-methyladenosine are also reduced by BPS in GN rats. In addition, in humans, the serum concentration of creatinine and Indoxyl sulfate are reduced by BPS after 6 month administration.

Conclusions: BPS reduced uremic toxins in CKD rats and ameliorates renal dysfunction and the serum level of indoxyl sulfate in CKD patients. These results suggest that BPS has a potential to prevent the progression of CKD.

Funding: Pharmaceutical Company Support - Reserch grant from Toray

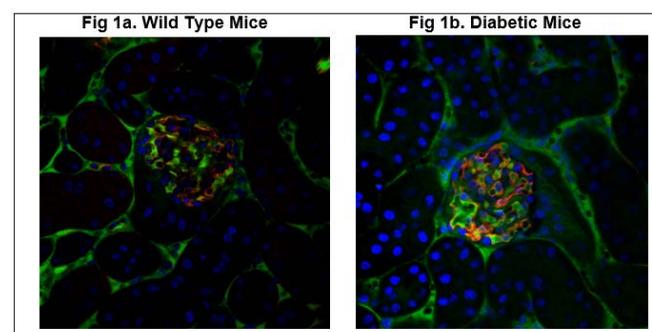
PUB094

A Novel Method to Measure Glomerular Permeability Jin Wei, Shaohui Wang, Lei Wang, Gensheng Zhang, Jie Zhang, Byeong Cha, Kay-Pong D. Yip, Ruisheng Liu. *Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL.*

Background: Glomerular capillaries are relatively impermeable to proteins, but in certain kidney diseases, such as diabetic nephropathy, the glomerular permeability (GP) is increased and some of the lower molecular weight (LMW) proteins, especially albumin, are filtered through the glomerular barrier into the Bowman's space. Increased GP is a hallmark for many kidney diseases. Proteinuria is often implicated for impaired GP. However, since LMW proteins can be reabsorbed by proximal tubules, proteinuria is detected only when the GP is significantly increased. Recently, real-time quantification of GP can be visualized by two-photon microscopy, but it can only be applied to superficial nephrons, where laser can penetrate, in Munich-Wistar rats. We developed a novel method to monitor GP in C57/BL6 mice by using florescent lysine-fixable dextran conjugates without these limitations.

Methods: 100 μl Tomato Lectin 594 (endothelial cell marker) plus 50 μl 40 KD lysine-fixable dextran 488 (fluid phase marker) were injected intravenously. The kidneys were removed 1 min later and put into liquid nitrogen immediately for 10 minutes followed by fixation with 10% Formalin on ice overnight. Then 100 μm thick sections were prepared using a vibratome and the florescent images were collected with two-photon microscopy. The ratio of florescent intensity in bowman's space over that in glomerular capillary lumen was used as an index of GP.

Results: In WT mice, the GP is extremely low with a ratio of $0.16\pm 0.08\%$, N=6 (figure1). In contrast, in diabetic mice induced by alloxan for 8 weeks, the GP is significantly increased with a ratio of $5.9\pm 1.3\%$, N=6 .



Conclusions: In summary, we developed a novel and sensitive method to monitor changes in GP using two-photon microscopy, which can be used for rodents and bigger animals.

PUB095

Vasopressin Regulates the Uptake of Extracellular Vesicles by Kidney Collecting Duct Cells Wilna Oosthuyzen,¹ Jessica R. Ivy,¹ Jonathan Street,² Andrea Caporali,¹ David J. Webb,¹ Chris Gregory,³ Matthew A. Bailey,¹ James W. Dear,¹ ¹Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom; ²National Inst of Diabetes and Digestive and Kidney Diseases, National Insts of Health; ³MRC/Univ of Edinburgh Centre for Inflammation Research, Univ of Edinburgh, United Kingdom.

Background: Urine contains extracellular vesicles (ECVs) originating from the circulation and all cells lining the urinary tract. ECVs are a route of inter-cellular communication along the nephron able to transfer protein and RNA. It is not known whether this is a regulated process analogous to other cell-to-cell signalling systems.

Methods: Kidney cortical collecting duct cells (CCDs) were stimulated with desmopressin, a vasopressin analogue, and uptake of fluorescently-loaded or microRNA-loaded ECVs was measured. In mice, fluorescently-loaded ECVs were intravenously injected before and after administration of the V2 antagonist, tolvaptan, and urinary ECV excretion was measured. By combining antibodies to nephron segment-specific proteins with nanoparticle tracking analysis we measured human urinary ECV excretion in central diabetes insipidus (DI) and after radiocontrast exposure (n=37).

Results: Desmopressin stimulated ECV uptake into CCDs via V2 receptor stimulation. Intra-cellular uptake of ECVs was confirmed by microRNA specific mRNA down-regulation. Mechanistically, ECV uptake in response to desmopressin required cyclic AMP production, was mediated by clathrin-dependent endocytosis and was selective for ECVs from kidney tubular cells. In mice, basally, 2.5% of injected ECVs were recovered in urine; tolvaptan treatment resulted in a 5-fold increase. In DI, desmopressin reduced the excretion of ECVs derived from upstream glomerular and proximal tubule cells. In patients exposed to radiocontrast, urinary ECVs from the glomerulus were positively correlated with the tubular injury markers KIM-1 and NGAL.

Conclusions: Tubular ECV uptake is a specific, hormonally regulated process that is reduced with injury. Physiologically, ECVs are a mechanism of inter-cellular communication; therapeutically, ECVs represent a novel vehicle by which RNA therapy could be targeted for the treatment of kidney disease.

PUB096

Systemic Hypothermia and Pro-Inflammatory Cytokines Massimo de Cal,¹ Grazia Maria Virzi,¹ Alessandra Brocca,¹ Salvador Roberto Lopez,¹ Jose Luis Salas,¹ Stefano Marcante,² Silvia De Rosa,¹ Claudio Ronco.¹ ¹Nephrology, S.Bortolo Hospital, Vicenza, Italy; ²ICU, S.Bortolo Hospital, Vicenza, Italy.

Background: Cytokines produced by renal tubular epithelial cells are critical factors in inflammatory processes of renal ischemia-reperfusion injury. Increased levels of cytokines have been reported after resuscitation from cardiac arrest. Pro-inflammatory cytokines, such as IL-1 β , IL-6 and IL-18, produced in the kidney during ischemia-reperfusion injury, are able to contribute to the renal damage. The purpose of this investigation was to define the proinflammatory cytokines response after resuscitation and during extended observation following therapeutic hypothermia phases.

Methods: We performed a prospective observational study in 36 post-cardiac arrest patients treated with Induced Hypothermia (IH) with two different cooling device: 1) Artic Sun; 2) Blanket. On Admission time and at 12, 24, and 72 hours after the start of treatment, blood and urine samples were collected. Plasma cytokines were measured by ELISA.

Results: During IH, we observed a decrease of IL-6, IL-1 β and IL-18u levels in both groups, and an increase of inflammatory during rewarming phase. The results are showed in table.

Variable		Artic Sun (26 pts)	Blanket (10 pts)	p value
IL-1 β	Adm	18 (12-20)	27 (9-43)	0.227
	12hrs	17 (13-18)	17 (9-18)	0.841
	24hrs	19 (13-21)	28 (10-51)	0.179
	72hrs	20 (12-24)	35 (13-53)	0.089
IL-6	Adm	102 (40-121)	79 (29-104)	0.136
	12hrs	100 (28-148)	72 (12-138)	0.194
	24hrs	57 (33-77)	63 (20-112)	0.406
	72hrs	59 (34-61)	67 (30-84)	0.713
IL-18u	Adm	412 (363-978)	847 (189-1071)	0.749
	12hrs	327 (326-365)	265 (201-327)	0.028
	24hrs	348 (290-371)	140 (42-295)	0.0005
	72hrs	505 (332-538)	264 (44-337)	0.048

Conclusions: Optimal rewarming rate is unknown. Adverse effects from suboptimal rewarming could diminish a protective effect from hypothermia. These biomarkers may serve as indicator of an individual patient's place in the injury-repair continuum. Further investigations are needed.

PUB097

Impact of Different I.V. Iron Preparations on Monocyte Function and Differentiation Adam M. Zawada,¹ Lisa H. Fell,¹ Sarah Seiler,¹ Martina Sester,² Danilo Fliser,¹ Gunnar H. Heine.¹ ¹Internal Medicine IV, Saarland Univ Medical Center, Homburg, Saarland, Germany; ²Dept of Transplant and Infection Immunology, Saarland Univ Medical Center, Homburg, Saarland, Germany.

Background: Treatment of iron deficiency with intravenous (i.v.) iron is a first-line strategy to improve anemia and quality of life in patients with chronic kidney disease (CKD). However, in vitro experiments demonstrated that certain i.v. iron preparations may have immunological side-effects. In the present study we now investigated substance-specific impacts of different i.v. iron preparations on monocytic function and differentiation.

Methods: We in vitro stimulated monocytes with different concentrations (0.133 mg/ml, 0.266 mg/ml, 0.533 mg/ml) of iron sucrose (IS), sodium ferric gluconate (SFG), ferric carboxymaltose (FCM), and iron isomaltoside 1000 (IIM) and assessed monocytic adhesion and transmigration capacity. Monocyte differentiation into M1 and M2 macrophages and dendritic cells (DCs) was flow-cytometrically analyzed, and functional characteristics of monocyte derived cells were tested. Finally, we performed ultra-deep miRNA sequencing to characterize dysregulated signaling pathways in iron stimulated monocyte derived cells.

Results: IS and SFG increased monocytic adhesion, while transmigration was not affected by any preparation. The expression of M1 (CD40) and M2 (CD16, CD206) markers as well as the phagocytosis capacity were significantly reduced in IS and SFG stimulated macrophages. IS and SFG down-regulated CD1c and CD86 in DCs and up-regulated CD141 and HLA-DR. FCM affected macrophage and DC phenotype and function to a lesser degree, and IIM had no measurable immunological effects. In miRNA expression analysis we found IS to strongly dysregulate miRNAs which are linked to TLR and MAPK signaling pathways (e.g. miR-146b-5p, miR-155-5p).

Conclusions: Our findings demonstrate that less stable i.v. iron preparations like IS and SFG substance-specifically affect monocyte function and differentiation into macrophages and DCs in vitro. Future clinical trials should delineate in how far these observations will lead to clinically relevant changes in immune responses and thus affect the infection risk in CKD patients.

Funding: Pharmaceutical Company Support - Pharmacosmos

PUB098

The Involvement of p38 MAPK in Neutrophil Bactericidal Dysfunction of Hemodialysis Patients Yasutaka Kamikawa, Shinji Kitajima, Akinori Hara, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Yasunori Iwata, Takashi Wada. *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.*

Background: Mortality from infection has been reported to be higher in hemodialysis (HD) patients than that in healthy subjects. However, the precise mechanism causing it remains to be investigated. Neutrophils play crucial roles in host defenses against bacterial infection. Therefore, we investigated the impact of neutrophil inflammatory signal on bactericidal function in HD patients.

Methods: Four HD patients and six healthy subjects were recruited for this study. None of HD patients had diabetes, cardiovascular disease and cancer. Neutrophils were isolated from peripheral blood by density gradient centrifugation. The purity was tested by flow cytometry after lactoferrin staining. Microarray analysis was performed to assess global gene expression in leukocytes. Neutrophil bactericidal function was evaluated by the growth rate of *Staphylococcus aureus* (*S.aureus*) after co-culture of it with neutrophils obtained from HD patients or healthy subjects. Reactive oxygen species (ROS) production and myeloperoxidase (MPO) activity were analyzed by fluorescence intensity.

Results: Microarray analysis showed the impairment of p38 mitogen activated protein kinase (MAPK) signal in neutrophils from HD patients. The growth rate of *S.aureus* was higher in HD patients than that in healthy subjects (490.1 \pm 147.1%, 144.5 \pm 49.4%, respectively; p<0.01) suggesting that neutrophil anti-bacterial killing function was dysregulated in HD patients. The levels of ROS from neutrophils after co-culture with *S.aureus* were lower in HD patients than those in healthy subjects (14.6 \pm 8.3, 32.4 \pm 15.4, respectively; p<0.01). On the other hand, there was no difference of MPO activity between both groups. To confirm the importance of p38 MAPK, we examined the effect of the selective pharmacological p38 MAPK inhibitor SB202190 on neutrophil bactericidal function. The treatment with SB202190 suppressed anti-bacterial killing function as well as ROS production in neutrophils.

Conclusions: Impaired of p38MAPK signaling pathway might contribute to the suppression of neutrophil bactericidal function in HD patients through the dysregulation of ROS production.

PUB099

Detached c-Abl from Nephrin Contributes to Cytoskeleton Remodeling in Podocytes Yiqiong Ma, Qian Yang, Zhentong Zhong, Zhilong Ren, Wei Liang, Cheng Chen, Huiming Wang, Guohua Ding. *Div of Nephrology, Renmin Hospital of Wuhan Univ, China.*

Background: Previous studies showed that nephrin is required for cytoskeleton remodeling in podocytes. However, its specific mechanism remains incompletely understood. c-Abl is a non-receptor tyrosine kinase involved in cytoskeleton regulation, which is a candidate of signaling proteins interacting with SH2/SH3 domains of nephrin. The present study evaluated whether c-Abl contributes to nephrin-dependent cytoskeleton remodeling of podocytes.

Methods: Colocalized expression of nephrin and c-Abl was evaluated in glomeruli of patients with nephrotic syndrome (NS) by double immunolabeling assays. In vitro, AngII was used to promote cytoskeleton remodeling of podocyte. Differentiated murine podocytes were exposed to Ang II (10⁻⁷M) for 24h. Cytoskeleton configuration was evaluated by FITC-phalloidin staining. Western blotting was performed to evaluate the expression and phosphorylation of nephrin and c-Abl. Colocalization of nephrin and c-Abl was determined by confocal microscopy and co-immunoprecipitation analysis. Co-immunoprecipitation was conducted in COS7 cells co-transfected with CD16-CD7-nephrin and SH2/SH3-defective c-Abl vectors to identify the domain of c-Abl binding with nephrin.

Results: The glomerular staining of nephrin and c-Abl indicated that the colocalization in patients with NS was decreased compared with that in control patients. In cultured podocytes, AngII treatment induced dephosphorylation of nephrin and diminished the interaction between nephrin and c-Abl. In addition, F-actin disruption was aggravated by treatment of both AngII and overexpression of c-Abl. Furthermore, the disorganized cytoskeleton stimulated by cytochalasin D in COS7 cells was restored by cotransfection with phosphorylated CD16-CD7-nephrin and c-Abl full-length constructs. Co-immunoprecipitation showed that phosphorylated CD16-CD7-nephrin interacted with wild type c-Abl, not with SH2/SH3-defective c-Abl.

Conclusions: These results indicate that phosphorylated nephrin is able to recruit c-Abl in a SH2/SH3-dependent manner and detached c-Abl from nephrin contributed to cytoskeleton remodeling in podocyte.

Funding: Government Support - Non-U.S.

PUB100

Nrf2 and NF- κ B mRNA Expression in Chronic Kidney Disease: A Focus on Non-Dialysis Patients Denise Mafra,¹ Viviane Oliveira Leal,² Juliana Saldanha,¹ Milena Barcza Stockler-Pinto,³ Ludmila Fmf Cardozo,³ Felipe Rizzetto Santos,⁴ Alex Sandro Duarte Albuquerque,⁴ Maurilo Leite.⁴ ¹Graduate Program in Medical Sciences, Federal Univ Fluminense, Rio de Janeiro, Brazil; ²Pedro Ernesto Univ Hospital, State Univ of Rio de Janeiro (UERJ), Rio de Janeiro, Brazil; ³Graduate Program in Cardiovascular Sciences, Federal Univ Fluminense, Rio de Janeiro, Brazil; ⁴Div of Nephrology, Federal Univ of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.

Background: Nuclear factor erythroid 2-related factor 2 (Nrf2), a regulator of genes encoding antioxidant and detoxifying enzymes appear to be downregulated in chronic kidney disease patients undergoing hemodialysis (HD). However, data regarding the expression of Nrf2 in non-dialysis patients are scanty. Thus, the aim of this study was to evaluate Nrf2 and nuclear factor kappa-B (NF- κ B) mRNA expression in non-dialysis patients, comparing with data from HD patients.

Methods: 20 non-dialysis patients, 20 HD patients and 11 healthy subjects were enrolled. The peripheral blood mononuclear cells were isolated and processed for the evaluation of NF- κ B and Nrf2 expression by quantitative real-time polymerase chain reaction.

Results: Nrf2 mRNA was significantly higher in non-dialysis when compared to HD patients but similar to healthy individuals. Inversely, NF- κ B mRNA was lower in non-dialysis when compared to HD patients and also similar to healthy individuals i.e.

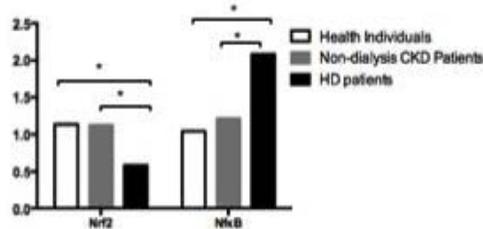


Figure 1. Nrf2 and NF- κ B mRNA expression health individuals, non-dialysis and HD patients.

Nrf2 mRNA was positively correlated with NF- κ B mRNA in non-dialysis patients and healthy individuals. By contrast, Nrf2 mRNA was inversely correlated with NF- κ B mRNA in HD patients.

Conclusions: Non-dialysis patients may conserve regular homeostatic balance between Nrf2 and NF- κ B expressions, being comparable to healthy individuals. As renal disease progresses to more advanced stages, an impaired Nrf2/NF- κ B balance can be observed, as in HD patients.

Funding: Government Support - Non-U.S.

PUB101

ERK 1/2 and ERK 5 Signaling Pathways via Renin Angiotensin System Activation Play Differential Regulatory Roles During the Progression of Glomerulonephritis Takashi Nagai,¹ Maki Urushihara,¹ Shuji Kondo,¹ Toshiaki Tamaki,² Shoji Kagami.¹ ¹Dept of Pediatrics, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan; ²Dept of Pharmacology, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.

Background: Although extracellular signal regulated kinase (ERK)1/2 and ERK5 are key kinases of signaling pathway involved in various cellular functions in kidney injury, the mechanism between those kinase and renin-angiotensin system (RAS) activation in glomerulonephritis (GN) have not been fully elucidated. This study was performed to clarify the potential role of ERK1/2 and ERK5 via RAS activation in the pathogenesis of GN.

Methods: We examined the expression of ERK1/2 and ERK5 in rat progressive model of GN induced by anti-glomerular basement membrane antibodies in Wistar Kyoto rats. In addition, the signal transduction pathway in angiotensin II (Ang II)-induced glomerular pathologic alterations were investigated in primary cultured mesangial cells (MCs).

Results: GN rat developed typical cellular crescent in glomeruli on day 7 and severe fibrocellular crescent and glomerulosclerosis were found on day 28. Immuno-staining of kidneys revealed that strong expression of phospho-ERK1/2 was observed on day 7 and phospho-ERK5 expression was markedly increased on day 28 of GN. Ang II type 1 receptor blocker (ARB) suppressed those augmentations. Macrophage infiltration and PCNA positive cells were seen on day 7 and collagen type 1 expression was enhanced on day 28, and ARB treatment reduced these expressions. Next, cultured MCs stimulated by Ang II showed significantly increases in MCP-1 and collagen type 1 expression, and cell proliferation. While optimized PD98059 that inhibited ERK1/2 phosphorylation abolished the elevation of MCP-1 expression (P<0.01) and cell proliferation (P<0.01), optimized BIX02189 that inhibited ERK5 phosphorylation abolished the elevation of collagen type 1 expression (P<0.01). ARB treatment attenuated these augmentations.

Conclusions: These data suggest that ERK1/2 regulates acute inflammatory reactions and ERK5 induces the development of chronic glomerular fibrosis during RAS activation in GN.

PUB102

Chinese Herbal Medicine for IgA Nephropathy, ShenPing Decoction, Blocks Platelet-Derived Growth Factor Signaling Pathway Activated by IgA1-Containing Immune Complexes in Human Mesangial Cells Xianwen Zhang,^{1,2} Zhi qiang Huang,² Stacy D. Hall,² Lin Wang,¹ Yueyi Deng,¹ Bruce A. Julian,² Yiping Chen,¹ Jan Novak.² ¹Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; ²Univ of Alabama at Birmingham, Birmingham, AL.

Background: IgA nephropathy (IgAN) is characterized by mesangial immunodeposits containing galactose-deficient IgA1 (Gd-IgA1) usually associated with mesangial proliferation and matrix expansion. There is no disease-specific therapy of IgAN, although a herbal medicinal prescription, ShenPing decoction (SP), has been used in China for decades to effectively treat IgAN. Mesangial cell proliferation in IgAN is likely induced by Gd-IgA1-containing immune complexes (CIC) and this process may involve activation of platelet-derived growth factor (PDGF) signaling pathway. We have shown previously that SP blocks the activation of PDGF pathway induced by PDGF. In this study, we investigated the effect of CIC on PDGF signaling pathway in human mesangial cells (hMC) and assessed the effects of SP on this pathway.

Methods: CIC were isolated from sera of IgAN patients using size-exclusion chromatography. Primary hMCs were incubated with PDGF or CIC for 15 min or 24 h with or without SP. Cellular proliferation was measured with Syto60. PDGF signaling was evaluated by SDS-PAGE and Western blotting.

Results: 24-h incubation with CIC increased MC proliferation and SP inhibited this effect. Stimulation of hMC with CIC increased phosphorylation of PDGFR and ERK1/2 after 15 min and 24 h. PDGFR degradation was not observed in CIC-treated group, which is different from PDGF. SP inhibited CIC- and PDGF-induced phosphorylation and degradation of PDGFR.

Conclusions: CIC induced cellular proliferation of hMC and activation of PDGF pathway without degradation of PDGFR, a normal negative feedback observed for PDGF. CIC possibly caused persistent activation of PDGF pathway. SP inhibited these effects. These findings indicate that SP likely contains component(s) targeting the PDGF/PDGFR system that may play a role in the mesangial injury of IgAN.

Funding: NIDDK Support, Private Foundation Support

PUB103

Effects of Fluorfenidone on the Expression of Thioredoxin-Inter-Acting Protein and Thioredoxin of Human Peritoneal Mesothelial Cell in High Glucose and Lipopolysaccharide Yichen Chen, Jianfei Ma. *Nephrology, The First Affiliated Hospital of China Medical Univ, Shenyang, China.*

Background: Peritoneal dialysis is one of an important alternative therapies for end-stage kidney disease. But the occurrence of peritoneal dialysis correlation peritonitis has brought great resistance for the development of peritoneal dialysis. Significance of oxidative stress in peritoneal dialysis related peritonitis has been paid more and more attention. In cells that did not receive stimulation, Txnip combined with thioredoxin, when the elevated ROS concentration inside the cell, the formation of the compounds are separated. After dissociation Trx play its functions to remove ROS, whereas Txnip participation NLRP3 activation. Objective: To observe the effects of Fluorfenidone on the Expression of Txnip, Trx of HPMCs in High Glucose and Lipopolysaccharide.

Methods: The expression of Txnip and Trx mRNA was measured by real time-PCR. The level of Trx, Txnip, IL-6, TGF- β 1 in the supernatants of HPMCs (HMR5V5) were measured by ELISA. Experimental groups: Control group; High glucose and LPS for different concentrations and different times group; Fluorfenidone intervene group.

Results: Compared with the normal control, high glucose and LPS can significantly increase the expression of Txnip, Trx, IL-6 and TGF- β 1 in a concentration and time dependent manner, all have statistically significant (P<0.05). Compared with 2.5% glucose and 10mg/L LPS group, Fluorfenidone can reduce the expression of Txnip, IL-6 and TGF- β 1, increase the expression of Trx, all have statistically significant (P<0.05).

Conclusions: High glucose and LPS up-regulate the expression of Txnip, Trx, in the protein and gene levels, and increase the expression of IL-6 and TGF- β 1. Fluorfenidone could reduce the increase of Txnip, IL-6 and TGF- β 1, and increase the express of Trx in HPMCs that have been pre-treated with high glucose and LPS. Fluorfenidone have the effect of anti-oxidant and anti-fibrosis.

PUB104

Effects of Resveratrol on NRF2 Expression in Raw 264.7 Macrophages Cells and Non-Dialyzed CKD Patients Denise Mafra,¹ Juliana Saldanha,¹ Milena Barcza Stockler-Pinto,² Viviane Oliveira Leal,³ Denis Fouque,⁴ Christophe O. Soulage.⁵ ¹Pos-Graduate Program in Medical Sciences, Fluminense Federal Univ (UFF), Niterói, Rio de Janeiro, Brazil; ²Pos-Graduate Program in Cardiovascular Sciences, Fluminense Federal Univ (UFF), Niterói, Rio de Janeiro, Brazil; ³Div of Nutrition, Pedro Ernesto Univ Hospital, State Univ of Rio de Janeiro (UERJ), Rio de Janeiro, Brazil; ⁴Dept of Nephrology, Centre Hospitalier Lyon Sud, Univ de Lyon, Pierre Bénite, France; ⁵INSA de Lyon, CarMeN, INSERM U1060, Univ de Lyon, Villeurbanne, France.

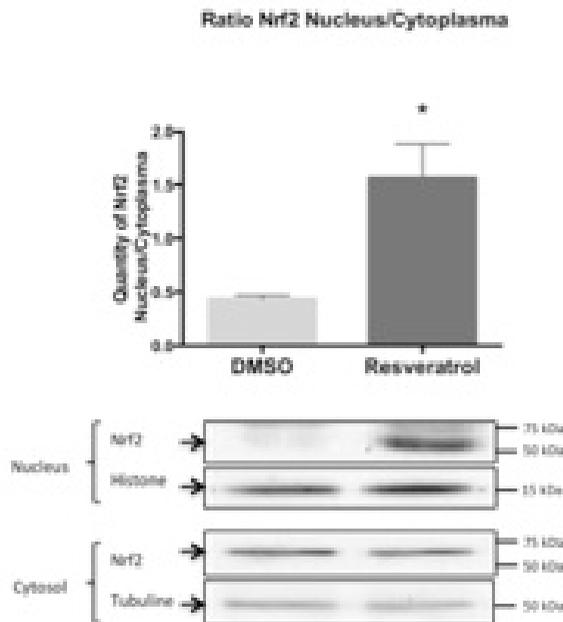
Background: Oxidative stress and inflammation are common in CKD. Bioactive compounds as resveratrol may modulate the Nrf2 expression, a transcription factor that could up-regulate cellular antioxidant systems. The aim of this study was observe Nrf2 expression in macrophages cells and in non-dialyzed CKD patients treated with resveratrol.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: Mouse RAW 264.7 macrophages cells were treated with 50µM of resveratrol in DMSO 1% (v/v). Nucleus and cytoplasm were separated. Western Blot (WB) was performed to quantify Nrf2. qRT-PCR was performed to evaluate Nrf2 expression. 7 non-dialyzed CKD patients (5 women; 64.0±6.5 years; GFR 37.9±10.4mL/min) received 500mg of resveratrol/day for 4 weeks. qRT-PCR to evaluate Nrf2 expression was performed in PBMC before and after supplementation.

Results: Cells treated with resveratrol showed a significant activation of Nrf2 with an increase in the ratio nucleus/cytoplasm compared to control cells i.e.



$p=0.02$). The same was observed in qRT-PCR ($p=0.02$). In patients, we observed a trend to increase Nrf2 expression with resveratrol supplementation ($p=0.06$).

Conclusions: We concluded that both cells and patients treated with resveratrol increased Nrf2 expression. So, we suppose that supplementation with resveratrol can lead to an increase in oxidative stress and inflammatory status among CKD patients.

PUB105

Mitochondrial Implications of Glycolate Metabolism in Primary Hyperoxaluria Sonia Fargue, Tanecia Mitchell, John Knight, Ross P. Holmes. *Urology, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: The primary hyperoxalurias (PH) are rare but severe inherited diseases characterized by an increased endogenous production of oxalate and calcium oxalate kidney stones in patients. Deficiency in alanine glyoxylate aminotransferase (AGT, deficient in PH1) or glyoxylate reductase (GR, deficient in PH2) have repercussions on the metabolism of the oxalate precursors glyoxylate and glycolate. Excessive amounts of glycolate are characteristic of PH1, through glyoxylate to glycolate cycling in the presence of glycolate oxidase (GO) and GR. Perturbations in glycolate metabolism may affect mitochondrial function in PH patients. The objective of this study is to assess how over-expression of these enzymes regulates glycolate and glyoxylate generation and mitochondrial function.

Methods: An established transformed CHO cells model was used in which cells express GO ± AGT or GR. Cells were incubated with glycolate or glyoxylate and the extracellular concentrations of oxalate and glyoxylate, and the induction of oxidative stress were analyzed. Cellular bioenergetics were assessed with a Seahorse XF-96 extracellular flux analyzer.

Results: The metabolism of glycolate by GO generated glyoxylate, oxalate and H₂O₂. Intracellular ROS were produced and cell viability was reduced. Mitochondrial respiration and the cellular bioenergetic reserve capacity were decreased following glycolate oxidation. The expression of AGT or GR reduced the untoward effects of glycolate metabolism to glyoxylate and oxalate.

Conclusions: The disruption of normal glycolate metabolism by GO, AGT and GR in a cell model causes the production of stress related metabolites and mitochondrial dysfunction. Limiting mitochondrial dysfunction might be a therapeutic approach in treating PH patients.

Funding: Private Foundation Support

PUB106

Effect of Fasudil on Response Oxidative Stress in High Glucose and Lipopolysaccharide Induced Human Peritoneal Mesothelial Cells Ye Hu, Jianfei Ma. *Nephrology, The First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning Province, China.*

Background: Peritoneal fibrosis is a common cause of chronic peritoneal dialysis patients withdrew from peritoneal dialysis. Research shows that, there are oxidative stress exists in peritoneal dialysis patients. Rho/Rho kinase signaling pathway is involved in

the regulation of multiple biological process, including inflammation, oxidative stress and fibrosis. The transcription factor NFE2 related factor is a central regulator of cellular antioxidant responses. Rho kinase inhibitor fasudil is a Rock inhibitor which currently used in clinic and experiment, it can regulate cell proliferation, migration, adhesion and movement at the cellular level, it also can regulate a variety of factors in inflammation, thrombogenesis, oxidation and fibrosis at the molecular level.

Methods: By using the method of Real Time-PCR to detect the expression of RhoA, Rock1, Nrf2 and HO-1 mRNA; Western Blot to detect the expression of RhoA, Rock1, Nrf2 and HO-1 protein; chemistry fluorescence test to detect the expression of ROS protein; chemical colorimetry to detect the expression of GSH-PX protein; ELISA detect the expression of TGF-β1 protein in the human peritoneal mesothelial cell. Experimental groups: Control group; High glucose and LPS for different concentrations group; Fasudil intervene group.

Results: Compared with the normal control, high glucose and LPS can significantly increase the expression of RhoA, Rock-1, ROS and TGF-β1, reduce the expression of Nrf2, HO-1 and GSH-PX in a concentration dependent manner, all have statistically significant ($P<0.05$). Compared with 2.5% glucose and 10mg/L LPS group, fasudil can reduce the expression of RhoA, Rock-1, ROS and TGF-β1, increase the expression of Nrf2, HO-1 and GSH-PX, all have statistically significant ($P<0.05$).

Conclusions: High glucose and LPS up-regulate the expression of RhoA and Rock1 but reduce Nrf2 in the protein and gene levels, and increase the expression of ROS and TGF-β1 but reduce the expression of HO-1 and GSH-PX. Fasudil could reverse the increase of RhoA and Rock1 and the reduce of Nrf2 in HPMCs that have been pre-treated with high glucose and LPS, play the role of anti-oxidant and anti-fibrosis.

PUB107

Glucose Induces Mitochondrial Reactive Oxygen Species Through Carbonyl Stress and Respiratory Chain in Rat Peritoneal Mesothelial Cells Satoshi Shimada,¹ Takefumi Mori,¹ Yusuke Ohsaki,² Ikuko Oba,¹ Shinichi Sato,¹ Kenji Koizumi,¹ Sadayoshi Ito.¹ *¹Nephrology, Endocrinology and Vascular Medicine, Graduate School for Medicine, Tohoku Univ, Sendai, Miyagi, Japan; ²Div of Integrative Renal Replacement Therapy, Graduate School of Medicine, Tohoku Univ.*

Background: Glucose and its degradation products (GDPs) play a major role in the peritoneal injury and affect peritoneal dialysis vintage. Peritoneal mesothelial cell dysfunction has been demonstrated to involve in peritoneal injury by glucose and GDPs. GDPs induced carbonyl stress has been demonstrated to induce mitochondrial dysfunction in several cell types. The present study was designed to determine the role of GDPs and respiratory chain in glucose induced mitochondrial ROS in peritoneal mesothelial cells.

Methods: Primary rat peritoneal mesothelial cells (RPMC) were isolated from Wistar rats. Real-time mitochondrial superoxide was monitored using a specific fluorescent indicator Mito SOX red under fluorescence microscope equipped with temperature controlled chamber. RPMC was stimulated with 90 mmol/L of glucose and compared to those of vehicle. In separate experiments, RPMC was pre-incubated with a mitochondrial specific superoxide dismutase mimetic mitoTEMPO, respiratory chain inhibitor rotenone or carbonyl stress inhibitor pyridoxamine to determine the mechanism of glucose induced mitochondrial ROS production.

Results: 90 mmol/L glucose significantly increased mitochondrial superoxide production within 200 seconds in primary cultured RPMC ($0.21±0.07$ AU, $n=8$, $P<0.05$ vs vehicle). These responses were abolished when RPMC was pre-incubated with mitoTEMPO ($-0.04±0.15$ AU, $n=5$, $P=0.34$ vs vehicle), rotenone ($0.00±0.06$ AU, $n=6$, $P=0.42$ vs vehicle) and pyridoxamine ($-0.34±0.34$ AU, $n=5$, $P=0.26$ vs vehicle), indicating that mitochondrial superoxide production through respiratory chain and GDP.

Conclusions: The results in the present study indicate that glucose and GDP present in the PD effluent is responsible for oxidative stress in the peritoneal mesothelial cells by stimulation of mitochondrial ROS production, which could play a role in peritoneal function and injury during PD.

PUB108

Renal Cell Carcinoma Models: Effect of Chemopreventative Agents on the Carcinogenic Potential of Potassium Bromate in Human Renal Epithelial Cells Ismael Obaidi, Tara McMorrow. *School of Biomolecular and Biomedical Science, Conway Inst, Univ College Dublin, Ireland.*

Background: Renal Cell Carcinoma (RCC) is a leading cause of renal cancer worldwide. The cause of RCC remains unknown, with many chemicals implicated in its development. We have developed an in vitro model of RCC using the carcinogen, potassium bromate, to investigate potential prevention and possible treatment options of RCC. Chemoprevention is the use of different chemicals, natural or synthetic, to halt, block or reverse the process of carcinogenesis. It is one of the novel approaches that is being used to control cancer and it is a good alternative to the conventional therapies that are associated with a long list of side effects and limitations. These agents have antioxidant, anti-inflammatory, antiangiogenic effects and induce phase II enzymes, apoptosis, cell cycle arrest, and differentiation. They antagonize hormones and growth factor-induced tumor proliferation. The aim of this study was to examine the functional and mechanistic effects of chemopreventative agents on chemically induced RCC using human (RPTEC/TERT1) renal cells and cancerous (ACHN) renal cell lines.

Methods: Morphological changes, viability and cytotoxicity assays were used to assess the toxicity of both the chemopreventatives and the carcinogen when RPTEC/TERT1 cells were exposed to them individually and in combinations. Oxidative stress was also

assessed by measuring the intracellular concentration of H₂O₂. Oxidative stress-induced DNA damage was estimated quantitatively by measuring 8-OHdG concentrations. Western blot analysis was used to detect the changes in particular oxidative stress-induced proteins.

Results: The carcinogenic effects induced by potassium bromate were reduced by the co-administration with all of the chemopreventative agents used. Oxidative stress markers, H₂O₂ and DNA adduct formation, were reduced.

Conclusions: The results suggest that these chemopreventative agents show significant potential against KBrO₃-induced carcinogenicity. Further analysis is being carried out to understand the functional mechanisms of this chemoprevention on the cells, in particular on the genetic and epigenetic mechanisms involved.

Funding: Government Support - Non-U.S.

PUB109

The Podocyte as a Target for the Actions of Levamisole in Nephrotic Syndrome Lulu Jiang,¹ Charles Colin Thomas Hindmarch,¹ Mark Rogers,¹ Peter W. Mathieson,² Gavin Iain Welsh.¹ ¹School of Clinical Sciences, Univ of Bristol; ²Univ of Hong Kong.

Background: Levamisole is an antihelminthic agent that has also been shown to be effective as a second line treatment for steroid-dependent or frequently-relapsing nephrotic syndrome (SD/FRNS) in children. Levamisole is able to decrease steroid dosages and reduce the relapse frequency and severity. We have recently reported the effectiveness of levamisole in a small cohort of adult patients and provided evidence which suggests that levamisole's mode of action in SSNS is attributable to its direct effects on podocytes.

Methods: To further clarify its therapeutic effectiveness and identify the therapeutic targets of this drug, we have employed RNA-sequencing technology to profile transcriptome changes of human podocytes in response to levamisole.

Results: We have identified a number of genes which are differentially expressed in podocytes in response to levamisole. These include genes linked to the cellular interferon response pathways and a number which overlap with those regulated by dexamethasone in podocytes. These have been validated in vitro and are now being studied in animal models of nephrotic syndrome.

Conclusions: Together, our molecular evidence strongly supports the promising use of levamisole in treating nephrotic syndrome.

PUB110

The PRIMAVERA Study: A Prospective, Randomized, Multicenter Trial Assessing the Effect of Continuous Erythropoiesis Receptor Activator (C.E.R.A.) on Renal Function in Non-Anemic Patients with Chronic Kidney Disease (CKD) Danilo Fliser,¹ Frank Dellanna,² Michael Koch,³ Jochen Seufert,⁴ Oliver Witzke,⁵ Alfons Wiggenhauser,⁶ Ingeborg A. Hauser,⁷ ¹Saarland Univ Medical Center, Homburg/Saar, Germany; ²DaVita Renal Center, Düsseldorf, Germany; ³Center of Nephrology, Meitmann, Germany; ⁴Univ Hospital of Freiburg, Freiburg, Germany; ⁵Univ Hospital Essen, Essen, Germany; ⁶Roche Pharma AG, Grenzach-Wyhlen, Germany; ⁷Frankfurt Univ Medical Center, Frankfurt, Germany.

Background: Erythropoiesis stimulating agents (ESAs) are the mainstay of renal anemia management. ESAs may provide a beneficial non-hematopoietic effect on deterioration of kidney function in CKD, but such an effect has not been examined in a prospective controlled trial. PRIMAVERA is the first randomized study to assess whether low-dose ESA therapy can slow CKD progression in patients with near-normal hemoglobin levels (11–14g/dL) (NCT01194154).

Methods: PRIMAVERA was a single-blind, 2-year, multicenter trial which enrolled patients with type 2 diabetes or recipients of a kidney transplant, all with CKD stage 3, urinary albumin to creatinine ratio <3000mg/g or total urine protein <3000mg/24h. Patients were randomized in a 1:1 ratio to placebo or once-monthly low-dose C.E.R.A. (30–75µg per dose). The primary efficacy endpoint was annual change in estimated GFR using the abbreviated MDRD formula. Secondary efficacy endpoints were the changes from baseline in urinary albumin to creatinine ratio, serum cystatin C and serum creatinine. Safety endpoints included adverse events and discontinuation due to pre-specified adverse events.

Results: 241 patients were randomized: (139 type 2 diabetes, 102 kidney transplant recipients). The 2-year study was completed by 159 patients (66%).

Conclusions: The PRIMAVERA study provides the first prospective examination of a potential effect for low-dose ESA therapy in ameliorating kidney function decline in CKD patients. Analysis of the study data is planned shortly.

Funding: Pharmaceutical Company Support - Roche Pharma AG

PUB111

A New Approach to Phosphate and FGF23 Lowering: Design of the COMBINE Trial Joachim H. Ix,¹ Tamara Isakova,² Stuart M. Sprague,⁹ Kalani L. Raphael,³ Jennifer J. Gassman,⁵ Linda F. Fried,⁴ Dominic S. Raj,⁶ Alfred K. Cheung,³ Andrew N. Hoofnagle,¹⁰ John W. Kusek,⁷ Michael F. Flessner,⁷ Geoffrey A. Block,⁸ Myles S. Wolf,² The pilot clinical trials in Ckd study group.⁷ ¹UCSD; ²Northwestern; ³U of Utah; ⁴U of Pittsburgh; ⁵Cleveland Clinic; ⁶George Washington U; ⁷NIDDK; ⁸Denver Nephrology; ⁹Northshore; ¹⁰U Washington.

Background: Elevated serum phosphate and FGF23 are associated with CVD, CKD progression, and mortality in CKD. Phosphate binders inconsistently reduce phosphate and FGF23 levels. Nicotinamide (vitamin B3) decreases active phosphate transport by down regulating NaPi2b in the gut. Whether nicotinamide alone or in combination with binders can safely and tolerably lower phosphate and FGF23 levels in CKD is unknown.

Methods: We designed a 4 arm parallel group randomized double blind trial comparing lanthanum carbonate (1000mg tid), nicotinamide (750mg bid), neither, or both. Supported by the NIDDK CKD Pilot Clinical Trials U01, 200 participants with eGFR 20-45 ml/min/1.72m² recruited from 7 centers across the US will be randomized 1:1:1:1 and treated for 12 months. Main exclusions include phosphate < 2.8mg/dL, liver disease, anemia, and thrombocytopenia. The dual primary efficacy endpoints are change in phosphate and FGF23. Secondary endpoints are change in LV mass and renal fibrosis by MRI. Enrollment began in March 2015.

Results: To date, 45 persons were screened, 33 were eligible, 26 entered run-in, and 18 were randomized. Baseline characteristics of randomized participants are shown in the table. Updated data will be available at presentation.

Randomized Patients (n)	18
Age±SD	65±14
Male, n(%)	12 (67%)
Black, n(%)	5 (28%)
Diabetes, n(%)	7(44%)
eGFR±SD	30±9
Urine ACR mg/g, median (IQR)	505 (48, 905)
Serum Phosphate±SD	3.9±0.6
Serum Calcium±SD	9.5±0.4
Intact PTH, median (IQR)	104 (71, 133)

Conclusions: Simultaneous blockade of NaPi2b and intestinal phosphate binding using nicotinamide and binders provides a new strategy for phosphate and FGF23 lowering in CKD, but efficacy, safety, and tolerability are uncertain. The COMBINE trial will inform us about combined therapy compared to either therapy alone, and to dual placebo in CKD 3b-4.

Funding: NIDDK Support

PUB112

Sofosbuvir plus Ribavirin Combination Therapy for Hepatitis C Virus Infection in Hemodialyzed Patients: New Simpler, Shorter and Safer but Costly Option Achour Laradi,¹ Christian Pilette,² Francois Babinet,¹ Stephanie Lanoiselee,¹ Guillaume Seret,¹ Jean baptiste Pain,³ Laurent Martin,⁴ Gilles Peytavin.³ ¹Néphrologie-Dialyse, ECHO-CMCM -Pôle Santé Sud, Le Mans, France; ²Gastro-enterologie, Centre Hospitalier du Mans, Le Mans, France; ³Laboratoire de Pharmacologie-Toxicologie, Hôpital Bichat-Claude Bernard, Paris, France; ⁴Biologie, Labomaine Pôle Santé Sud, Le Mans, France.

Background: Hepatitis C virus (HCV) infection is a serious issue in hemodialyzed patients (HD pts) and treatment is complex and rapidly evolving with the advent of newer direct-acting antivirals.

Methods: We evaluated SOF given with RBV in an 86 years old male HD pt, 90 kg, on HD since 7 years for a diabetes-related ESRD and infected by a nosocomial transmission of HCV genotype 2 overseas. SOF was given at a dose of 400 mg three times a week after dialysis session and RBV given 200 mg daily during 12 weeks. Plasma HCV RNA values were measured with the COBAS Taqman HCV Test, Roche diagnostics. Safety, efficacy and pharmacokinetics issues were studied as well as standard laboratory tests. Sustained virologic response (SVR) is evaluated six months after treatment.

Results: HCV infection was associated with cirrhosis with Fibroscan staging score of 10.3 KPa. HCV viral load at diagnosis was 7.52 log. The viral decline was < 1.18 log only 3 weeks after treatment and negative after 1 month therapy. SVR with a value of HCV NRA < 1.18 log occurred six months after. Side effects are mainly anemia and thrombocytopenia. No life threatening adverse event was noticed. Mean Plasma SOF values before and after HD session was < 1 ng/mL in accordance to the dose given. Mean Plasma value of metabolite 007 before HD session was 2394 ng/mL and failed to 938 ng/mL after HD.

Conclusions: Treatment for 12 weeks with all-oral combination of Sofosbuvir and Ribavirin of our old age HD pt with HCV genotype 2 hepatitis resulted in a high degree of antiviral efficacy with an excellent tolerability and safety profile with a dose recommendation of 400 mg 3 times a week. But the very high cost (41000 euros) make access extremely limited. A reduction of the costs is mandatory to make these new therapies accessible to the majority of the patients in the world who are left untreated.

PUB113

The Rationale for and Design of TREVI TR02: A Multicenter Randomized, Double-Blind, Placebo-Controlled Trial of Nalbuphine ER for the Treatment of Uremic Pruritus in Hemodialysis Patients Vandana S. Mathur,¹ Michael J. Germain,² Roberta Duncan,³ Thomas Sciascia,³ ¹Mathur Consulting, Woodside, CA; ²Western New England Renal & Transplant Associates, PC, Hamden, MA; ³Trevi Therapeutics, New Haven, CT.

Background: Uremic pruritus (UP) is common in hemodialysis patients, but there are no FDA-approved treatments or “regulatory roadmap” for the development of new drugs. Nevertheless, the significant quality of life (QOL) burden of chronic itching underscores need for treatments. The striking bilateral, non-dermatomal distribution of itching and perception of non-pruriticogenic skin stimuli as itch suggest that UP is centrally mediated, like neuropathic pain. Reduction in endogenous κ/μ opioid ligand ratio is hypothesized to be a mechanism. Our goal was to evaluate nalbuphine ER tablet (NAL), a κ-agonist and μ-antagonist as a treatment for UP.

Methods: The study was powered for an α = 0.05, β = 0.9 for a group difference of 1.5 (SD = 3.5) in worst itching numerical rating scale (NRS, 0-10): N = 120/arm (NAL 120 mg BID, NAL 60 mg BID, and placebo BID). Patients with NRS ≥ 4.5 (moderate to severe pruritus) were enrolled at ~45 US and 6 EU sites.

Results:

Key Scientific or Logistical Consideration	Study Design Solution
1. Itch is subjectively perceived. Itching intensity and QOL were relevant endpoints.	Used patient-reported outcomes previously validated in UP patients including NRS and Skindex-10 (1° and 2° endpoints)
2. Opioid drugs require titration to minimize opioid side effects	To perform a blinded opioid titration with a self-administered oral drug, we used blister cards that were labeled for each study day
3. Long enough duration to demonstrate durability and lack of tolerance but short enough to avoid excessive dropouts due to background comorbidities.	Used an 8-week blinded treatment duration
4. Post-treatment safety	Added a 2-week washout period after the blinded treatment period
5. Day-to-day variability in NRS was expected	The mean of 2 weeks of measurements at baseline and on treatment (Wks 7 and 8) were used for the calculation of the 1° endpoint.

Conclusions: The trial design overcame the challenges. Unblinded results will be presented.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

PUB114

The Rationale and Design of Trevi TR02 Extension: A Multi-Center Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl Extended Release Tablets in Uremic Pruritus Patients on Hemodialysis Thomas Sciascia,¹ Howard Hait,² Amale Hawi,³ Roberta Duncan,¹ Vandana S. Mathur,⁴ ¹Trevi Therapeutics, Inc., New Haven, CT; ²Edenridge Associates LLC, Wilmington, DE; ³Hawi Consulting, Ridgefield, CT; ⁴Mathur Consulting, Woodside, CA.

Background: Nalbuphine HCl is a mu antagonist/kappa agonist being investigated for the treatment of pruritus in hemodialysis patients (UP). The safety and long-term benefits of Nalbuphine ER in the treatment of uremic pruritus is being investigated in this ongoing open-label extension study.

Methods: TR02ext is a 26-week multicenter open-label extension study of a double-blind placebo controlled study in which UP patients with a baseline NRS ≥4.5 were treated with Nalbuphine ER or placebo for 8 weeks followed by a 2-week washout period. At the end of study, patients that opt to roll over into the extension study, and have an NRS > 2 enrolled in a 26-week Treatment Period (TP), while patients with an NRS ≤2 entered a 13-week Observation Period (OP). If a patient’s itch worsened (NRS > 2) within the OP, they entered the TP for the remainder of the study.

All patients on treatment were titrated between 30 mg QD-120 mg BID over a 3-4 week period based on reported tolerability and efficacy and then maintained their dose until end of study. Patients whose itch intensity failed to improve during the TP were discontinued from treatment.

Key Scientific Considerations	Study Design Solution
1. Characterize the time course of worsened itch intensity following 8 weeks on blinded study drug or placebo followed by a 2-week wash-out period	Separate subjects into TP and OP
2. Dose distribution of flexible dosing to optimize efficacy and safety	Individualized titration to understand preferred doses
3. Individualized titration to maximize drug efficacy with tolerable side effects	Up to 26 weeks of treatment with discontinuation of subjects who do not respond to treatment

Conclusions: Approximately 70% of the eligible patients who completed the blinded controlled study, enrolled in the extension study. Final study data will be presented once the study is complete.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

PUB115

Assessing Treatment Safety and Efficacy of a New Patient-Centered Hemodialysis System Luis Alvarez,¹ Geoffrey A. Block,² May L. Yau,³ Glenn Matthew Chertow,⁴ ¹Palo Alto Medical Foundation, Palo Alto, CA; ²Denver Nephrology, Denver, CO; ³Outset Medical, San Jose, CA; ⁴Stanford School of Medicine, Stanford, CA.

Background: Many studies designed and conducted for the evaluation of new technologies utilized in hemodialysis have been small, observational studies. These studies may have underestimated the rate of clinical symptoms yielding biased safety results.

Methods: We designed a prospective, multicenter, open-label, non-randomized, cross-over study where patients serve as their own control. The study was designed with novel approaches to ensuring accuracy of clinical symptom reporting both in the home and clinic setting. Up to 50 patients will be enrolled in the study for 19 weeks and will use the Tablo™ Hemodialysis System for treatments 4 times/week.

Phase	Description
Run-in	clinic staff administered in-center hemodialysis treatment for <u>1 week</u> .
In-Center treatment	clinic staff administered hemodialysis treatment for <u>8 weeks</u> in-center.
In-Home transition	device training, perform self-care dialysis for approximately <u>2 weeks (1 week in-center and 1 week in-home)</u> , and assessment for stability in the home environment.
In-Home treatment	self-care dialysis treatment for <u>8 weeks</u> at home.

During each study phase, patients will record inter- and intra-dialytic symptoms for each treatment via questionnaire. Research staff will review all responses weekly to determine if an adverse event (AE) has occurred. In addition, research staff will conduct weekly visits to the dialysis clinic and to home to educate patients on AEs and to collect questionnaires. Patients will also be assessed to determine if a standardized weekly Kt/V of 2.1 has been achieved.

Results: Study enrollment is expected to begin in 2015 with results expected in 2016.

Conclusions: By utilizing patients to collect AE data both in-center and at home, we should more accurately capture AE rates due to the uniformity of the reporting mechanism. In terms of the clinical efficacy endpoint of the study, modelled clearance data suggests the majority of patients will achieve the weekly standard Kt/V target. Actual clearance data will be forthcoming at the completion of the trial.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

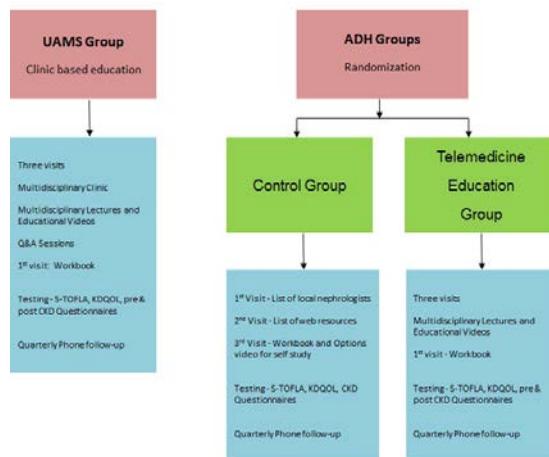
PUB116

Interim Analysis of Comprehensive CKD Education Modality Choice Outcomes Andrea K. Eason,¹ Dumitru Rotaru,¹ Fahd Syed,¹ Manisha Singh,¹ Ashutosh M. Shukla,² Sudhir V. Shah.¹ ¹Univ of Arkansas for Medical Sciences; ²University of Florida.

Background: Preliminary data from a study comparing telemedicine vs conventional CKD education is presented here. The primary aim is to see if patients are able to make a modality choice by the end of the third visit.

Methods: Patients are enrolled in three groups as shown in the pilot study design.

Study Design



Each group attends 3 sessions and are given handouts or an 82 page workbook designed specifically for the study. They are asked about their modality choice pre-education and at the end of each session.

Results: To date 80 subjects have been enrolled and 32 have completed all sessions. After 3 sessions, 38% chose peritoneal dialysis (PD), 28% chose home hemodialysis (HHD), 28% chose in center hemodialysis (ICHD), 3% chose no dialysis (ND), 3% could not make a choice (NC) and 84% chose transplant. On enrollment, 47% made a modality choice with 40% choosing home modalities. At the end of 3 session, 97% were able to make a modality choice with 66% choosing home modalities. Of the 6 subjects who have completed 3 visits and started renal replacement therapy (RRT), 5 started PD and 1 had a pre-emptive transplant. Additionally, 4 subjects did not complete all visits: 3 started ICHD (2 with AVFs) and 1 died. Enrollment in the telemedicine arm has been slower than expected. Strategies to involve community leaders and local providers were developed and are being implemented. Communities interested in the program have been added as telemedicine sites.

Conclusions: This preliminary data shows that at the end of 3 education sessions there is a significant increase in subjects being able to make a RRT choice (97% vs. 47%) and most chose home dialysis (66% vs. 40%). Community engagement is key to a successful outreach of this state-wide CKD education program. Further strategies are being developed to improve local involvement.

Funding: Pharmaceutical Company Support - Baxter Renal Discoveries Extramural Grant Program

PUB117

Determination of Oxidative Stress and Inflammation Index in Patients with Different Dialysis Modalities and Analysis of Related Factors Linshan Jiao, Jianfei Ma. *Nephrology, The First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning, China.*

Background: This study through the determination of serum AOPPs, GSH-PX, PTX-3, IL-6 level in ESRD patients with different treatment groups, to explore the changes and influence factors of oxidative stress and inflammation in dialysis patients.

Methods: 70 cases of ESRD patients divided into three groups: 26 cases of PD patients, 26 cases of MHD patients, 18 cases of CKD5 patients. Select 14 normal persons as control group. Age, gender and other data of the four groups were matched. Get Serum of each group of subjects, using ELISA for determination of serum AOPPs, GSH-PX, PTX-3, IL-6 content in each group.

Results: 1. The concentration of AOPPs: PD Group (25.04±12.18) ng/ml, MHD group (18.46±10.47) ng/ml, CKD5 group (17.96±9.81) ng/ml, healthy group (15.73±6.68) ng/ml. PD group was statistically significant different with other groups ($p < 0.05$). 2. The concentration of GSH-PX: PD group (188.54±112.04) U/ml, MHD group (157.12± 82.47) U/ml, CKD5 group (133.59±65.59) U/ml, healthy group (176.03±98.25) U/ml. There was no significant difference between the groups. 3. The concentration of PTX-3: PD Group (9.85±5.13) ng/ml, MHD group (7.54±4.07) ng/ml, CKD5 group (6.69±3.12) ng/ml, healthy control group (6.08±2.49) ng/ml. The PD group was statistically significant different with other groups ($p < 0.05$). 4. The concentration of IL-6: PD group (123.69±84.46) ng/L, MHD group (81.17±72.48) ng/L, CKD5 group (64.92±36.92) ng/L, healthy control group (59.08±19.27) ng/L. The PD group was statistically significant different with other groups ($p < 0.05$). 5. Through Correlation analysis in PD group ($P < 0.05$): AOPPs was positively correlated with PTX-3 ($R = 0.956$, $P = 0.000$), AOPPs was positively correlated with IL-6 ($R = 0.934$, $P = 0.000$), PTX-3 and IL-6 levels were positively correlated ($R = 0.939$, $P = 0.000$).

Conclusions: Determination of serum AOPPs, GSH-PX, PTX-3, IL-6 content in Experience group is significantly increased compared with the control group. The PD patients compared with patients in other treatment groups has more severe oxidative stress and microinflammation state. Oxidative stress is closely related to the state of inflammation in PD patients.

PUB118

Impact of Type of Referral and Dialysis Start on Clinical Outcomes and Final Renal Replacement Therapy in a Multicenter Integrated Care Setting Belen Marron,¹ Janusz Ostrowski,² Marietta Torok,³ Delia Timofte,⁴ Jose C. Divino-Filho,¹ ¹Diaverum Home Therapies, Medical Office, Diaverum, Munich, Germany; ²Wloclawek Diaverum Clinic, Diaverum, Wloclawek, Poland; ³Szeged Diaverum Clinic, Diaverum, Szeged, Hungary; ⁴Sema Diaverum Clinic, Diaverum, Bucharest, Romania.

Background: Early referral, choice of RRT modality and planned start increase patient survival, however international reports show disparities between desirable patterns and practice. Objectives: To analyze the effects of Integrated Care and education on dialysis start (planned vs. non-planned) and RRT modality choice.

Methods: Retrospective analysis of 547 incident patients starting dialysis in 23 HD/PD clinics from PL, HU and RO during 2012. Scheduled initiation of dialysis with a permanent vascular or peritoneal access was considered as planned start.

Results: Population: 30% DM, mean age 64 years, 84% with previous medical care of renal disease, 49% late referral, 58% unplanned start, 92% on HD as modality. 37% of those with unplanned start had previous Nephrology follow-up. Patients (n=332) with GFR <30 ml/min were followed up mainly by "general nephrologists" (68%) and 29% in structured predialysis units. Modality information (80% of all patients) and general renal education (87%) were more frequent ($p < 0.001$) in planned start. Half of patients were involved in therapy choice whereas informed and dialysis start consents were signed by 57% and 77%. The median time from information to dialysis start was 2 months. Unplanned start

($p \leq 0.05$) correlated with nephropathy of uncertain origin, worse clinical status, shorter time from information to RRT start and less PD. Patient non-compliance (36%) and unexpected GFR loss (19%) contributed to unplanned start. "Optimal care" defined as combination of Nephrology follow-up (> 3 months), modality information and planned start occurred in 22% of the patients.

Conclusions: Despite the high rate of late referral, information and education were widely provided. Unplanned start was frequent and may underlie the low frequency of PD choice. Measures such as implementation of structured predialysis units may facilitate better and timely referral and improve well-being and planning of RRT start as well as increased PD use.

PUB119

ATHENA: A Natural History Study to Observe Disease Progression, Standard of Care, and Investigate Biomarkers in Alport Syndrome Patients Jacqui Blem,¹ Paul C. Grint,¹ Victoria Pratola,¹ James F. Simon.² ¹Regulus Therapeutics Inc., San Diego, CA; ²Cleveland Clinic, Cleveland, OH.

Background: Alport syndrome (AS) is a rare genetic disorder caused by mutations in genes coding for type IV collagen (COL4) $\alpha 3$, $\alpha 4$ and $\alpha 5$ proteins leading to hematuria, renal failure, hearing loss and eye involvement in affected patients. Patients with COL4A5 mutations develop end stage renal disease (ESRD). While there are currently no approved therapies for AS, ACE-inhibitors have been shown to delay the onset of ESRD. A better understanding of the decline of kidney function in AS is necessary to design clinical trials to enable the development of new therapeutics.

Methods: Regulus' Natural History of Disease Study, ATHENA, is an international multi-center observational study designed to characterize the progression of renal dysfunction in up to 120 subjects that have been clinically or genetically diagnosed with AS with a measured GFR (mGFR) between 30-75cc/min/1.75m². Genetic mutation analysis is performed at enrollment. mGFR (iohexol), 24 hour urine protein excretion and serum creatinine levels are measured every 3-6 months. Serum and urine biomarkers of renal stress (microRNAs, ADMA, TGF β , CTGF and NGAL) will also be collected.

Results: 48 subjects with clinically or genetically diagnosed Alport syndrome have been enrolled to date. The population has an age range of 20 to 67 years of age and 29% are male. Average baseline mGFR was 54.8 cc/min/1.75m². Ethnicity is reported at 91% Caucasian, 2% Hispanic or Latino, 2% African American and 5% Asian.

Conclusions: Data gathered from the ATHENA study will investigate links between genetic mutations, biomarkers of renal stress and disease progression in AS patients. The correlative data collected from the ATHENA study will provide clinically important basis for the design of the Phase 2 clinical proof of concept study to determine efficacy of RG-012 (an anti-miR targeting microRNA-21) on the decline in renal function and time to end-stage renal disease in Alport syndrome patients.

Funding: Pharmaceutical Company Support - Regulus Therapeutics Inc., Clinical Revenue Support

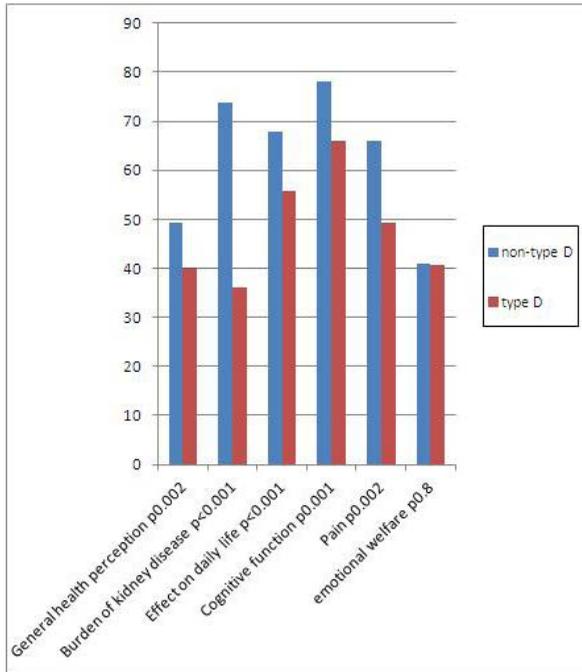
PUB120

Health-Related Quality of Life in Dialysis Patients: Effect of Type D Personality Christopher Susanto,¹ Constantijn Konings,² Jeroen Kooman.³ ¹Nephrology, Elkerliek Hospital, Helmond, Netherlands; ²Nephrology, Catharina Hospital, Eindhoven, Netherlands; ³Nephrology, Maastricht Univ Medical Centre, Maastricht, Netherlands.

Background: Measurement of HRQoL is a useful tool to describe the burden of illness and the impact of treatment. These information's could be essential to develop a personal care. Type D (distressed) personality is defined as a tendency to experience both negative affectivity (NA) and social inhibition (SI). The prevalence of this personality and his effect on HRQoL in dialysis patients are assessed.

Methods: Participants were from outpatient clinic. DS 14 was used. A score of ³10 on both NA and SI subscales indicates that the person has a type D personality. HRQoL was measured using the Dutch version of the Kidney Disease Quality of Life. Six components of the KDQOL were the primary end points (general health perceptions, burden of kidney disease, effect on daily life, cognitive function, pain, emotional welfare).

Results: 147 patients with mean age of 71.2 (± 11.7). Mean time on dialysis 37 months. The prevalence of type D personality was 30%. HRQoL in patients with type D personality was lower compared with non type D. It was statistically significant in all components except for emotional welfare.



NA was significantly related to all components except for emotional welfare. SI was found to be significantly correlated especially with effect on daily life

	NA		SI	
	r	p-value	r	p-value
Age	-0.20	0.02	-0.13	0.11
Duration of RRT	-0.09	0.3	-0.07	0.43
General health perception	-0.28	0.001	-0.20	0.02
Burden of kidney disease	-0.47	<0.001	-0.27	0.001
Effect on daily life	-0.36	<0.001	-0.30	<0.001
Cognitive	-0.40	<0.001	-0.26	0.002
Pain	-0.29	<0.001	-0.16	0.006
Emotional welfare	0.15	0.07	-0.03	0.7

Conclusions: Type D personality may be an important determinant of individual differences in HRQoL and should be an important consideration in a personal care of dialysis patients.

PUB121

Sleep Disorder and mRNA Expression Profile of Sleep-Related Gene in Peripheral Blood Cells in Patients with CKD Shinji Kitajima, Yasunori Iwata, Yasuyuki Shinozaki, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Takashi Wada. *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.*

Background: Although uremic substances would be candidates involved in sleep disorder, detailed mechanisms remain unclear so far. we performed polysomnographic analysis in CKD patients and used PBCs to examine the expression of genes related to sleep and wakefulness states.

Methods: Polysomnographic analysis was performed in 9 CKD patients and 6 healthy controls. Genes related to sleep and wakefulness were evaluated by RNA microarray in 19 subjects, including CKD patients and control subjects.

Results: Polysomnographic analysis revealed that the duration of the rapid eye movement (REM)/non-REM phases during total sleep time was different between CKD patients and healthy controls. In mRNA microarray evaluation, hierarchical clustering analysis showed the different pattern of sleep related gene expression in the patients with HD. The mRNA expression levels of GABA receptor, noradrenaline receptor, dopamine receptor and histamine receptor showed an inverse correlation with renal function. Moreover, orexin and its receptor mRNA expression also showed an inverse correlation with renal function.

Conclusions: These data raise the possibility that sleep related gene expression on PBC in CKD/HD patients may be associated with sleep disorder.

PUB122

Potential Link Between Iron, Inflammation and FGF23 in Patients with Early Stages of Chronic Kidney Disease Ewelina Lukaszzyk,¹ Mateusz Lukaszzyk,² Jolanta Malyszko.¹ ¹2nd Dept of Nephrology and Hypertension with Dialysis Unit, Medical Univ of Bialystok, Bialystok, Poland; ²Dept of Allergology and Internal Medicine, Medical Univ of Bialystok, Bialystok, Poland.

Background: Fibroblast growth factor 23 (FGF23) is a hormone commonly increased in patients with chronic kidney disease and alike inflammation and iron deficiency is a known risk factor of cardiovascular outcomes and death in patients with chronic kidney disease (CKD). The aim of the study was to evaluate the potential link between FGF23 concentration, novel iron status and inflammatory parameters among patients with early stages of CKD.

Methods: 96 patients with early stage of CKD and 54 with normal renal function were enrolled in the study. Standard laboratory methods were used to measure serum hemoglobin, fibrinogen, creatinine, iron, total iron binding capacity (TIBC) and ferritin. Intact FGF23, hepcidin-25, sTfR (soluble transferrin receptor), GDF-15 (growth differentiation factor-15), IL-6 (interleukin 6) and hsCRP (high sensitivity C-reactive protein) were measured using commercially available kits. Data was analyzed in different group of patients according to iron status (absolute and functional iron deficiency and normal iron levels).

Results: There was no difference of FGF23 concentration regarding to iron status. Significant correlations in patients with CKD are presented in Table.

	iFGF23
eGFR	-0.49
hepcidin-25	-0.21
IL-6	0.22
GDF-15	0.31

There were no statistically significant associations between FGF23 and TSAT, ferritin and hsCRP. We revealed significantly higher concentrations of FGF23 in patients with type 2 diabetes (mean logFGF23: 4±0.5 vs 3.8±0.5, P=0.03) and with heart failure (mean logFGF23: 4±0.6 vs 3.8±0.5, P=0.04) in comparison to those without these diagnoses.

Conclusions: Kidney function, inflammation and iron status were the parameters affecting FGF23 in the early stages of CKD. Our data are paving the way for further studies on the role of FGF23 in cardiorenal anemia-iron deficiency syndrome, in particular in the early stages of CKD.

PUB123

Echocardiography and Cardiovascular Risk: What's the Relationship in the Renal Transplant Recipient? Miguel Goncalves,¹ Micaela Neto,² Pedro Vieira,¹ Luis Resende,¹ Nuno Rosa,¹ Susana Gomes,² Jose Duraes,¹ Jose Alves Teixeira,¹ Gil Silva.¹ ¹Nephrology, Hospital Dr. Nélito Mendonça, Funchal, Portugal; ²Cardiology, Hospital Dr. Nélito Mendonça, Funchal, Portugal.

Background: Cardiovascular (CV) disease is the major cause of death among renal transplant recipients (RTR). Unlike end stage renal disease, it is unknown whether echocardiographic abnormalities are useful to identify RTR with high cardiovascular risk of death.

Methods: Retrospective review of 107 RTR with a functioning and stable graft for longer than 12 months and an echocardiography performed in the last year. Risk of MACE and death using a CV risk calculator specific for RTR and all echocardiographic parameters were reviewed and analyzed.

Results: Among 107 patients (57,9% males, 50,4±13,9 years old), 7-years risk for MACE was >10% in 30,9% of patients and 7-years risk for death >10% in 56,1%. Left ventricular hypertrophy (LVH) was found in 55,1%, diastolic dysfunction in 39,3%, dilated left atrium (LA) in 53,3%, high pulmonary artery systolic pressure (PASP) in 29,0%, valvular calcifications in 22,4% and moderate to severe mitral regurgitation in 3,7%. Mean Ejection Fraction was 68.36±6.87%. Univariate analysis showed with statistical significance an increased risk of MACE in patients with LVH, diastolic dysfunction, dilated LA, high PASP, valvular calcifications and mitral regurgitation. Univariate analysis also showed statistical relationship on increased risk of death in patients with LVH, diastolic dysfunction, dilated LA, high PASP, valvular calcifications and mitral regurgitation. Multivariate analysis identified an independent association between the risk of MACE >10% and valvular calcifications [OR 3.499 (1.115-10.982, P=0.032)] and high PASP [OR 7.954 (2.412-26.238, p=0.001)]. Risk for death >10% in multivariate analysis had an independent association with diastolic dysfunction [OR 3.909 (1.261-12.115, p=0.018)] and with high PASP [OR 4.319 (1.201-15.535, p=0.025)].

Conclusions: Echocardiographic abnormalities identify RTR at increased risk of MACE and death. Valvular calcifications and high PASP are significant predictors of MACE whereas diastolic dysfunction and high PASP are significant predictors of death.

PUB124

Hemodynamic Determinants of Glomerular Filtration Rate in Pulmonary Hypertension: A Prospective Cohort Analysis Laurent Bitker,¹ Cecile Payet,³ Florence Sens,^{1,4} Turquier Segolene,² Antoine Duclos,^{3,4} Vincent Cottin,^{2,4} Laurent Juillard,^{1,4} ¹Nephrology, Hospices Civils de Lyon, Lyon, France; ²Pneumology, Hospices Civils de Lyon, Lyon, France; ³Medical Research and Statistics Dept, Hospices Civils de Lyon, Lyon, France; ⁴Univ of Lyon, Lyon, France.

Background: Up to date, renal dysfunction incidence and determinants remain unevaluated in pulmonary hypertension (PHT). We aim to assess hemodynamic and demographic factors associated with a decrease in glomerular filtration rate (GFR) in the context of PHT.

Methods: The regional competence center for PHT of Lyon (France) prospectively compiles demographic, hemodynamic and biological variables among newly diagnosed patients. We retrospectively analyzed data for patients with pulmonary arterial hypertension (PAH, group 1 of PHT classification) after exclusion of the following causes of PHT: thromboembolic, lung diseases and/or hypoxia and left heart disease. Hemodynamic variables from the right heart catheterization and estimated GFR (eGFR, CKD-EPI formula) were assessed at PAH diagnosis time.

Results: 209 patients (mean age 59.1±17.1, 63.2% women) were included from October 1998 to July 2012. 40.2% presented with systemic arterial hypertension (HT) and 12.9% with diabetes. Mean eGFR was 83.9±27.1 ml/min/1.73m² (eGFR inferior to 60 ml/min/1.73m² in 18.5% of cases). Mean values of mPAP, right atrial pressure (RAP) and cardiac index (CI) were 43.5±12.6 mmHg, 7.8±5.3 mmHg and 2.6±0.9 L/min/1.73m². In multivariate analysis, age, male gender, HT, anorectic-related PAH and a CI inferior to 2.5 L/min/1.73m² were associated with a significant decrease in eGFR of 1.0 ml/min/1.73m²/year, (95% confidence interval, 0.8 to 1.2), 11.8 ml/min/1.73m² (5.8 to 17.8), 6.6 ml/min/1.73m² (0.1 to 13.2), 13.4 ml/min/1.73m² (2.3 to 24.5) and 10.1 ml/min/1.73m² (4.4 to 15.9). RAP were not statistically related to eGFR levels.

Conclusions: Renal dysfunction is frequent from diagnosis among PAH patients. A low CI is associated with a significant decrease in eGFR, whereas RAP seem unrelated. Equally, male gender, HT and anorectic-related PAH are correlated with a significant decrease in eGFR. These results should incite renal prevention in PAH patients presenting these risk factors.

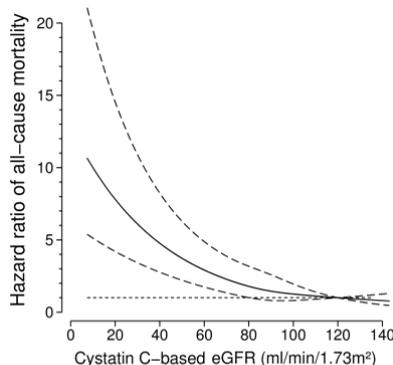
PUB125

Kidney Function and Cause-Specific Mortality in Drug-Treated Older Cardiac Patients: A 10-Year Follow-Up Study Ellen K. Hoogeveen,¹ Johanna M. Geleijnse,² Daan Kromhout,² Theo Stijnen,³ Erik Giltay.⁴ ¹Nephrology, LUMC, Leiden, Netherlands; ²Human Nutrition, WU, Wageningen, Netherlands; ³Medical Statistics and Bioinformatics, LUMC, Leiden, Netherlands; ⁴Psychiatry, LUMC, Leiden, Netherlands.

Background: Chronic kidney disease (CKD) is highly prevalent among older (>60y) cardiac patients. The relation between CKD and cause-specific mortality among older cardiac patients who are treated with state-of-the-art pharmacotherapy is unclear.

Methods: From 2002-2006, 60-80 years old Dutch post-myocardial infarction patients were enrolled in the Alpha Omega Trial and followed until death or January 2012. We estimated Glomerular Filtration Rate (eGFR) with serum cystatin C (cysC) and creatinine using the CKD-EPI equations. Kidney function was available in 4,561 (94.3%) participants and analyzed in relation to major causes of death using Cox models and four-knot restricted cubic splines.

Results: At baseline mean age was 69y, 79% were men, 21% had diabetes, 90% used antihypertensive drugs, 85% used statins. Patients were divided into four categories of eGFR_{cysC}: ≥90 (33%, reference), 60-89 (47%), 30-59 (18%), and <30 (2%) ml/min/1.73m². Median follow-up was 6.4y. During follow-up, 873 (19%) patients died, of which 370 (42%) from cardiovascular causes, 309 (35%) from cancer, and 194 (22%) from other causes. The hazard ratios (95%-CI) for any death according to eGFR_{cysC} category, after adjustment for major risk factors, were: 1 (reference), 1.4 (1.1-1.7), 2.9 (2.3-3.6) and 4.4 (3.0-6.4). For cardiovascular mortality the corresponding figures were 1.6, 3.6 and 6.0, for cancer 1.2, 2.1 and 1.6, and for other causes 1.4, 3.1 and 6.7. Similar, but weaker, results were obtained with creatinine-based eGFR.



Multivariable adjusted hazard ratios. An eGFR of 120 ml/min/1.73m² was taken as the reference point (hazard ratio 1). Risk of all-cause mortality increased significantly below an eGFR of 80 ml/min/1.73m².

Conclusions: We found a strong inverse graded relation between kidney function and mortality in drug-treated older cardiac patients, in particular due to cardiovascular and non-cardiovascular-non-cancer causes.

Funding: Other NIH Support - Dutch Kidney Foundation (PV41) US National Institute of Health (NIH) Netherlands Heart Foundation

PUB126

The Association Between Serum Uric Acid and Incidence of Non-Fatal Stroke in a Community-Based Population: A Longitudinal Survey of a Nationwide Cohort in Japan Keita Kamei,¹ Kazunobu Ichikawa,¹ Tsuneo Kanta,¹ Shouichi Fujimoto,² Kunitoshi Iseki,² Toshiki Moriyama,² Kunihiro Yamagata,² Kazuhiko Tsuruya,² Kenjiro Kimura,² Ichie Narita,² Masahide Kondo,² Koichi Asahi,² Tsuyoshi Watanabe.² ¹Dept of Cardiology, Pulmonology, and Nephrology, Yamagata Univ School of Medicine, Yamagata, Japan; ²Steering Committee of Research on Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based on the Individual Risk Assessment by Specific Health Checkup, Japan.

Background: Hyperuricemia is a risk for adverse renal outcomes in chronic kidney disease. This study investigated the effect of uric acid on incidence of non-fatal stroke in a community-based population.

Methods: We used a nationwide database of 160,164 subjects (aged 29-74, male 39%), participated in an annual health check, "The Specific Health Check and Guidance in Japan" between 2008-2010, and examined the relationship between the gender-specific quintiles of serum uric acid level at baseline and the 2-year incidence of non-fatal stroke.

Results: During the follow-up period 2,081 non-fatal stroke occurred (1.3%). The incidence of non-fatal stroke showed a significant J-shaped association with the increase in serum uric acid levels (P for trend <0.001, lowest [1.2%] in the 3rd quintile of uric acid [Q3: males 5.7-6.2 mg/dL, females 4.4-4.8 mg/dL] and highest [1.6%] in the 5th quintile [Q5: males ≥7.1 mg/dL, females ≥5.5 mg/dL]). After adjusting for possible confounders, the odds ratio for incident stroke was significantly higher in Q5, compared with Q3 (OR 1.21, 95%CI 1.05-1.39, P = 0.007). The odds ratio of hyperuricemia (serum uric acid ≥7 mg/dL) for incident stroke was significantly increased in total subjects (OR 1.22, 95%CI 1.07-1.39), especially in females (OR 1.46, 95%CI 1.04-1.99) and non-hypertensive subjects (OR 1.34, 95%CI 1.04-1.70). In contrast, the association between serum uric acid levels and incident stroke was not significant in subjects with diabetes, proteinuria and renal insufficiency.

Conclusions: This study showed that serum uric acid level is significantly associated with incident non-fatal stroke and that hyperuricemia might be an independent risk for non-fatal stroke in the general population.

Funding: Government Support - Non-U.S.

PUB127

The Association Between Serum Calcium and Mortality in a Community-Based Population: The Takahata Study Sayumi Watanabe, Keita Kamei, Kazunobu Ichikawa, Tsuneo Kanta, Isao Kubota. Dept of Cardiology, Pulmonology, and Nephrology, Yamagata Univ School of Medicine, Yamagata, Japan.

Background: The low intake of calcium is a risk for cardiovascular events. This study investigated the association between serum calcium and mortality in a community-based population.

Methods: This study included 1,314 participants (aged 40-87, males 45%) at local health checkup in Takahata, Japan. We divided them into 3 groups according to the tertiles of serum calcium at baseline and compared the mortality during 8-year follow-up period. Serum calcium was corrected for serum albumin.

Results: At baseline serum calcium level was 9.8 ± 0.4 mg/dL (mean ± SD). In the multivariate linear regression analysis serum calcium was positively associated with serum sodium, potassium, phosphorus, albumin, uric acid and total cholesterol, and was negatively associated with serum chloride and HDL-cholesterol, and urinary beta2-microglobulin. During the follow-up period 62 deaths, including 14 cardiovascular deaths occurred. In Kaplan-Meier analysis all-cause mortality was significantly increased along with the decrease in serum calcium (Log-rank P = 0.03). In Cox proportional hazard analysis adjusted for confounders including age, gender, smoking and drinking habits, comorbidities and other serum electrolytes, the association of serum calcium was of borderline significance with all-cause mortality (HR 2.09, 95%CI [0.94-4.75], P = 0.07, low tertile [≤ 9.6 mg/dL] vs. high tertile [≥ 10.0 mg/dL]) and was significant with cardiovascular mortality (HR 6.33, 95%CI [1.13-43.7], P = 0.04, low tertile vs. high tertile). In addition, there was a significant interaction between serum calcium and sodium on all-cause mortality (P = 0.03) and the association of serum calcium with the mortality was significant in the subjects with low serum sodium (≤ 150 mEq/L), but not high sodium.

Conclusions: This study showed that serum calcium was significantly associated with various environmental factors and low serum calcium was an independent predictor for the mortality in the general Japanese population.

Funding: Government Support - Non-U.S.

PUB128

Endothelial Dysfunction According to Classification of Serum Phosphorus Level within Normal Range in Chronic Kidney Disease

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Background: Hyperphosphatemia is a important problem because of its affect on endothelial dysfunction as well as homeostasis of bone. Chronic kidney disease (CKD) patients tend to have higher serum phosphorus values than those in healthy population due to their positive balance of phosphorus in kidney. There are a few studies which reported that serum phosphorus level was correlated with endothelial function. Recently it has been reported the patients with higher serum phosphorus level related to the worse endothelial function in healthy population. Thus, the following study was carried out in an effort to redefine the relationship between serum phosphorus level and endothelial dysfunction to those on chronic kidney disease.

Methods: This is a cross-sectional study and the enrolled 85 CKD patients with exception of CKD stage 5 or receiving renal replacement therapy. They were subjected to the measurement with laser doppler flowmetry with iontophoresis, reactive hyperemia peripheral arterial tonometry (RH-PAT) and ankle brachial index, which represented endothelial function assessment. The average serum phosphorus level in patients was measured for the last three months including examination month. The Pearson's correlation coefficient analysis and multiple regression analysis were performed to define the association of serum phosphorus and endothelial function.

Results: When participants were divided into four groups according to estimated GFR, serum phosphorus level had significant higher values in CKD stage 4. From univariate analysis, phosphorus level was associated with RH-PAT values ($r=0.296$, $p=0.008$). Multivariate analysis showed serum parathyroid hormone was independent predictor for endothelial dysfunction assessed with RH-PAT.

Conclusions: This study showed that serum phosphorus level may associate with endothelial function even in CKD. Furthermore, it is required a prospective study of larger population to identify the relationship between phosphorus and endothelial function and to establish optimal reference range of phosphorus level for protection from endothelial dysfunction.

PUB129

Coronary Artery Calcification in Predialysis Diabetic and Nondiabetic CKD Patients

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Background: Risk factors for coronary artery calcification may include low vertebral bone mineral density (BMD), and may differ in diabetic and nondiabetic CKD patients.

Methods: We examined Agatston coronary artery calcium score (CACS), BMD of T8 vertebra using MDCT, age, sex, presence of diabetes, hypertension, smoking history, statin administration, BMI, eGFR, urinary protein, blood urea, glucose, serum iron, calcium, phosphate, uric acid, alkaline phosphatase, albumin, LDL-cholesterol, and triglyceride in 128 predialysis CKD patients, 82 nondiabetics, and 46 diabetics. Factors related to CACS were assessed by multivariate regression and logistic regression analyses using all of the above independent variables.

Results: Coronary artery calcification was present in 106 (82.8%) patients. Significant associations between CACS \geq 400H and age, diabetes, and statin administration were observed, and odds ratios were 1.1, 3.4, and 3.7, respectively, in all subjects ($P<0.05$). Log CACS showed a significant association with age, diabetes, statin administration, serum phosphate, and iron in all subjects ($P<0.05$). Mean age and eGFR were 70 ± 14 vs. 70 ± 9 years (ns) and 37 ± 20 vs. 30 ± 19 ml/min/1.73m² ($P<0.05$), in nondiabetics and diabetics, respectively. Serum phosphate levels were not significantly different in the both groups. CACS (H) was 239 ± 411 in nondiabetics and 942 ± 1258 in diabetics ($P<0.001$). Significant associations were observed between Log CACS and age ($P<0.0001$, $\beta:0.42$), statin administration ($P<0.01$, $\beta:0.31$), and serum phosphate ($P<0.05$, $\beta:0.20$) in nondiabetics, and between Log CACS and blood urea ($P<0.01$, $\beta:0.55$), serum iron ($P<0.01$, $\beta:-0.41$), age ($P<0.01$, $\beta:0.41$), BMI ($P<0.05$, $\beta:0.29$) and smoking history ($P<0.05$, $\beta:0.29$) in diabetics. BMD showed no association with CACS.

Conclusions: Hyperphosphatemia is a risk factor for coronary artery calcification in nondiabetic but not diabetic CKD patients, and an association between CACS and BMD of T8 vertebra was not observed.

Funding: Private Foundation Support

PUB130

Association of APOL1 Risk Variants with Cardiovascular Events Among HIV-Infected Individuals

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Background: HIV+ individuals have higher risk of cardiovascular disease versus HIV- individuals. Recently, the APOL1 risk variants that are associated with CKD among African Americans were also associated with adverse cardiovascular events (CVE). Given the potential interaction between HIV and APOL1 variants, we examined the association between the APOL1 risk variants and CVE in HIV+ adults.

Methods: We conducted a cohort study among HIV+ African Americans who underwent clinically indicated kidney biopsies from 1996-2011 and were successfully

genotyped for the APOL1 G1 and G2 alleles. Multivariable logistic regression was used to compare the high-risk (2 copies) vs. the low-risk (0/1 copy) genotype and the odds of CVE (diagnosis of acute myocardial infarction, percutaneous cardiac intervention, CABG or stroke).

Results: Of 203 individuals, 64% were male with mean age of 46 years, eGFR of 38.4 ml/min/1.73m², and urine protein-to-creatinine ratio (UPCR) of 4.1g/g. Mean CD4 count was 259 cells/mm³; only 29% had HIV RNA levels <400 cps/mL. During follow-up, 12% had CVE and 40% died from all causes. Individuals with the high-risk vs. low-risk genotype had similar odds of CVE, adjusting for age, CVD risk factors, statin and aspirin use, eGFR and proteinuria (OR 1.13, 95% CI: 0.34 - 3.81). Similarly, APOL1 risk genotype was not associated with the composite outcome of CVE and death from all causes, adjusting for age, CVD risk factors, statin and aspirin use, and viral suppression status (OR 1.17; 95% CI: 0.58-2.34).

Conclusions: There is no clear relationship between the APOL1 risk variants and CVE or death from all causes in adults with advanced CKD and HIV.

Funding: Other NIH Support - 5P01DK056492-13 and R01 DA026770

PUB131

Proteinuria: Is It a Therapeutic Target or Only a Cardiovascular Risk Marker?

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Background: Studies published over the last decade had illustrated that despite the successful reduction in proteinuria there were either no benefit or a negative impact on renal and cardiovascular outcomes.

Methods: Review recent published trials, which have shown an evidence of decreased proteinuria and have renal and cardiovascular outcome.

Results: The following studies were identified: The IDNT; The final outcome revealed that although Irbesartan succeeded in lowering doubling of S. Creatinine as well as proteinuria, it failed to show a significant difference in CV mortality, non-fatal MI, heart failure, or stroke. The DIAB-HYCAR; the result confirmed a successful reduction in albuminuria by 14%. However, no significant difference was found on CV outcome, including death, non-fatal MI, stroke or heart failure. The ONTARGET, in a sub analysis; looking at renal outcome, including doubling S. Cr., dialysis and death, it revealed that although the ACE Inh. and the ARB combination had successfully reduced proteinuria, but it resulted in worse renal outcome. The TRANSCEND; by looking specifically at the renal outcome, including dialysis and doubling serum Cr., it was found that GFR had decreased. The AASK trial; the results did not show a positive solid endpoint associated with lowering proteinuria, no statistical difference was encountered. The ROADMAP; the result revealed that decreasing microalbuminuria as well as blood pressure in the Olmesartan subgroup was not reflected in decreased cardiovascular death. The Altitude trial; decreased proteinuria did not show a significant evidence in the primary renal or cardiovascular composite endpoints. Moreover, the study was terminated prematurely because of severe decline in eGFR, hyperkalemia and hypotension. The VA-NEPHRON-D; The final outcome was not statistically different. The study was stopped prematurely because of more acute renal injury and hyperkalemia in the combination arm.

Conclusions: Decreased proteinuria was associated with negative cardiac and renal outcomes. This could be due to the effect of RAAS combination, but we have to admit that these repeated observations carries an evidence, at least to question our standard belief, and that proteinuria might not be more than a cardiac risk factor indicator.

PUB132

Prevalence of Hematuria and Associations with All-Cause and Cardiovascular Mortality in China

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Background: Hematuria is one of the indicators of kidney damage. We aimed to estimate the prevalence of hematuria in China and evaluate its association with mortality and cardiovascular adverse outcome.

Methods: A nationally representative sample of 47,204 Chinese adults was obtained during the survey conducted between January 2009, and December 2012. Each participant's survival status was identified through Dec 31, 2013. Causes of death in ICD code 100-199 were classified as cardiovascular disease. Hematuria was defined as ≥ 3 red cells per high-power field in microscopic examination. Subjects with pyuria and women undergoing menstruation were excluded from the analysis. The associations between hematuria and all-cause and cardiovascular mortality were studied by using the Cox regression model.

Results: The mean age of the population at baseline was 49.6 ± 15.2 years, and 42.7% of the participants were male. Altogether, 2126(4.5%) of the population was detected with hematuria. The all-cause and cardiovascular mortality for participants with hematuria were 3.8 and 2.6 per 1000 person-years, while those for participants without hematuria were 3.4 and 1.3 per 1000 person-years. Hematuria was found to be significantly associated with increased risk of cardiovascular mortality with the multivariable adjusted hazard ratio of 1.7 (95% confidence interval: 1.1-2.7), compared with those without hematuria. However, no significant associations were found between hematuria and all-cause mortality.

Table 1. Mortality risk estimation and hazard ratios for mortality according to hematuria status

Hematuria	% Events	Events per 1000 person-years	Fully adjusted hazard ratio (95% confidence interval)
All-cause mortality			
No	1.8%(805/45078)	3.4	Reference
Yes	2.0%(43/2126)	3.8	0.9(0.6,1.3)
Cardiovascular mortality			
No	0.6%(285/45078)	1.3	Reference
Yes	0.9%(20/2126)	2.6	1.7(1.1,2.7)

Conclusions: Mortality, especially due to cardiovascular diseases, was greater among the Chinese patients with hematuria. These results suggest the possible effect of hematuria on cardiovascular mortality.

Funding: Government Support - Non-U.S.

PUB133

Glomerular Filtration Rate Is a Predictor of Subclinical Left Ventricular Diastolic Dysfunction in Patients with Rheumatoid Arthritis Suad Ma Hannawi, Kashif Naem, Issa AL Salmi. *Medicine, MOH, United Arab Emirates; Medicine, MOH, United Arab Emirates; Medicine, The Royal Hospital, Oman.*

Background: Rheumatoid arthritis(RA)is a systemic disease effecting primarily joints with subclinical kidney involvement. Subclinical cardiovascular disease(CVD)is a leading cause of morbidity& mortality in RA& chronic kidney disease(CKD) at early stages. Left ventricular diastolic dysfunction(LVDD) is a principal pathophysiologic mechanism& essential diagnostic indexes of HF with preserved ejection fraction(HFPEF).

Methods: Renal parameters correlated with echocardiographic findings in patients with RA& eGFR,as estimated(MDRD equation). Doppler echocardiography was performed by pulse wave Doppler with sample volume at tip of mitral valve in apical 4-chambers view. Peak early(E)&late(A)diastolic velocities were measured as indicator of LVED pressure. Assessment of peak early(E')& late(A)diastolic mitral annular velocity was performed by pulsed wave tissue Doppler imaging(TDI)of lateral wall in apical 4-chamber view &to diagnose LVDD(E/E'>8).

Results: Interim analysis:29(3M,26F) with RA diagnosed(ACR1988), aged46±12year&GFR 130±36 ml/min. Univariate regression showed a negative linear relationship of GFR&age(p<0.001,CI-2.77,-1.03),age@RA onset(p=0.001,CI-2.32,-0.65),age@RA diagnosis(p=0.002,CI-02.55, -0.66),SBP(p=0.032,CI-1.51,-0.07),ESR(p=0.005,CI-1.09,-0.21),ferritin level(p=0.008,CI-0.45,-0.08),EE'(p=0.005, CI-20.76,-4.26). Multiple regression maintained a negative relationship between GFR& each of age (p=0.004,CI-2.59,-0.57)&EE(p0.04,-15.25, -0.011)&R2 was 0.54.

Conclusions: RA patient have subclinical CKD and cardiac dysfunction &eGFR independently & negatively correlated to LVDD with moderate correlation(0.54). E/E' increased with decreasing GFR& higher than in patients GFR≥90. LVDD influenced by increase LV preload due CKD progression& it's a pre-clinical predictor of future HF& mortality. However, milder form of LVDD may stabilize or improve& subset of patients may, over time, be at risk for functional deterioration. Inflammation as a major pathological key in RA may be underlying cause for increased subclinical kidney& VD.

PUB134

The Association Between Creatinine versus Cystatin-C-Based eGFR and Cardiovascular Risk Factors in Children with Chronic Kidney Disease Sheena Sharma,¹ Ji Young Kim,² Susan L. Furth.¹ ¹*Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA;* ²*Biostatistics Core, Clinical and Translational Research Center, Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular events (e.g. stroke, myocardial infarction) in adults. Children with mild-moderate CKD have a high prevalence of cardiovascular risk factors (CRF). Higher levels of cystatin-C demonstrate a stronger predictive value for cardiovascular events compared with creatinine-based eGFR in adults. However, whether similar associations exist in children and young adults has yet to be determined. We hypothesize that cystatin-C-based eGFR will demonstrate a stronger association with CRF compared with creatinine-based eGFR in children and young adults.

Methods: We used cross-sectional data of 93 subjects aged 8-25 years with CKD and 70 healthy controls. eGFR was calculated using age appropriate creatinine and cystatin-C based formulas. The CRF included were anemia (hemoglobin < 2 standard deviations below the mean), hypertriglyceridemia (>130mg/dL) and proteinuria (urine protein/ creatinine >0.2mg/dL or urine albumin/creatinine >30mcg/g). Multivariate analysis assessed the association between creatinine and cystatin based eGFR and each risk factor after adjusting for age, gender and race.

Results:

CRF	eGFR creatinine estimate [95% CI]	eGFR cystatin-C estimate [95% CI]
Hemoglobin (g/dL)	0.22 [0.15, 0.3]	0.23 [0.16, 0.31]
Triglycerides (mg/dL)	-5.08 [-7.83, -2.34]	-6.23 [-8.89, -3.58]
Urine protein/creatinine (mg/dL)	-0.18 [-0.26, -0.09]	-0.20 [-0.28, -0.11]
Urine albumin/creatinine (mcg/g)	-53.03 [-69.93, -36.13]	-56.45 [-72.84, -40.06]

Conclusions: These results suggest that creatinine and cystatin-based eGFR have similar associations with CRF.

Funding: Other U.S. Government Support

PUB135

The Influence of Selected Demographics and Clinical Factors on Left Ventricular Function Presented by Echocardiographic Study in Patients Treated with Peritoneal Dialysis Maria Wanic-Kossowska, Krzysztof Pawlaczyk, Krzysztof Schwermer, Krzysztof Hoppe. *Dept of Nephrology, Transplantology and Internal Medicine, Poznan Univ of Medical Sciences, Poznan, Poland.*

Background: The purpose of the study was to perform a cross-sectional analysis between the selected demographics including age, sex, BMI as well as peritoneal dialysis treatment vintage, volume of residual diuresis, presence of arterial hypertension, anemia, inflammatory states, malnutrition, mass of the left ventricle, problems with the contractile function of the left ventricle as well as decreased relaxation of the left ventricle in the group of patients treated with peritoneal dialysis with regard to survival prognosis.

Methods: The study was conducted on 105 patients (49 men, 56 women) treated with peritoneal dialysis with the average time of 36.1±23.7 months. The control group consisted of 30 healthy volunteers (20 women, 10 men, mean age 55.0±23.8 years). Based on general known vascular and cardiac risk factors the patients were divided into subgroups: elderly patients (>65 years of age), male, patients treated on peritoneal dialysis over 3 years, daily diuresis <500 ml, Kt/V<2.1, arterial hypertension, anemia, inflammatory states, malnutrition.

Results: Analyzing the frequency of vascular and cardiac risk factors resulting in inadequate echocardiogram results showed the inflammatory states were the most common reason for increased left ventricular mass, diastolic dysfunction of the left ventricle as well as decreased ejection fraction. In the model of logistical regression taking into account age, sex, dialysis vintage, concentration of CRP, ejection fraction of the left ventricle, left ventricle mass, and factoring E/A from the echocardiogram study only advanced age of the patient treated on peritoneal dialysis decreased survival rate.

Conclusions: Chronic low-grade inflammation and advanced age seem to be two most common negative prognostic factors decreasing life expectancy. Further research is necessary to verify the intricate relationships between demographic factors and prognosis in the group of patients undergoing peritoneal dialysis.

PUB136

ANKle Brachial Index and Exertional Leg Pain Among Hemodialysis Patients without a Clinical Diagnosis of Peripheral Arterial Disease Pranav S. Garimella,¹ Lucia Kwak,² Kunihiro Matsushita,² Esther D. Kim,³ Michelle M. Estrella,² Stephen M. Sozio,³ Lucy A. Meoni,² Rulan S. Parekh,⁴ Bernard G. Jaar.² ¹*Tufts Medical Center;* ²*Johns Hopkins Univ;* ³*Univ of Toronto.*

Background: Exertional leg pain is considered pathognomonic for diagnosing peripheral artery disease (PAD). However, patients on dialysis may have multiple comorbidities causing or masking leg pain, potentially precluding its use to diagnose PAD. Furthermore, the utility of the ankle-brachial index (ABI) to diagnose PAD in this population is questionable due to the presence of arterial calcification. In this context, there are no data on the association of leg symptoms with ABI in dialysis patients despite them having an extremely high burden of PAD.

Methods: We evaluated the cross-sectional association of exertional leg symptoms with the spectrum of ABI in 247 incident hemodialysis patients without clinical diagnosis of PAD enrolled in the Predictors of Arrhythmia and Cardiovascular Events (PACE) study. The presence of exertional leg pain was based on questionnaire and ABI was categorized as low (<0.90), borderline (0.90-<1.00), normal (1.00-1.39) and high (≥1.4). We used logistic regression analysis to report odds of exertional leg pain.

Results: Mean age was 54 years, 76% were black and 51% had diabetes. The prevalence of exertional leg pain was lowest in the normal ABI category and increased towards both ends of the spectrum. Compared to normal ABI, low ABI was associated with 2.8 fold higher odds of exertional leg pain, although it did not reach significance. After adjusting for age, gender and race this association was attenuated to 2.5 fold odds. Borderline and high ABI were also similarly associated with exertional leg pain.

ABI	Proportion without exertional leg pain, (%)	Unadjusted OR (95% CI)	P value
<0.9	6/12 (50%)	2.80 (0.85 - 9.18)	0.09
0.9 ≤ to < 1.0	7/21 (33%)	1.40 (0.53 - 3.72)	0.50
1.0 ≤ to < 1.4	39/148 (26%)	ref	--
≥ 1.4	22/66 (33%)	1.40 (0.74 - 2.62)	0.30

Conclusions: Low ABI tended to be associated with higher risk of exertional leg pain. A low ABI value may be useful to identify ischemic etiology of leg pain even among dialysis patients with high prevalence of leg symptoms due to various conditions.

Funding: NIDDK Support

PUB137

Chronic Kidney Disease Is Highly Prevalent at Emergency Department and Associated with Cardiovascular Comorbidity Jolanta Malyszko,¹ Anita Swietochowska,² ¹*Nephrology, Medical Univ, Bialystok, Podlaskie, Poland;* ²*Emergency, Regional Hospital, Lomza, Poland.*

Background: Different stages of CKD affects more than 10% of the population, while in high-risk patients, the incidence of 30-50% is reported. The aim of this work was to evaluate the prevalence of CKD in patients admitted to the non-surgical emergency department in one year, the impact of CKD risk factors, rate of hospitalization and mortality.

Methods: From 10500 patients admitted to ED, the group of patients with serum creatinine measured, i.e. 3835 (40%) patients over 18 years was selected, including 2095 (55%) subjects over 70 years. Gender, age, medical history of hypertension, heart failure, ischemic heart disease, acute coronary symptoms (ACS), diabetes, inflammation, current medications, physical examination, laboratory results: creatinine, C-reactive protein (CRP), leukocyte count, hemoglobin, the alcohol level in serum, urinalysis were analyzed.

Results: 2179 patients were hospitalized (57%) mainly for cardiovascular reasons, remaining were discharged home. 561 (15%) were admitted to the ED more than once. Abnormal serum creatinine was found in 27%, while 19% have CKD stage 3 and 5% stage 4. Active urine sediment was present in 20% of studied patients. Patients and physicians were unaware of this finding. A small percentage of patients were under nephrology care. Accumulation of risk factors such as gender, age, hypertension, diabetes, results in an increased prevalence of CKD. Prevalence of hypertension in the population of patients with CKD is high (59% vs 29% in non-CKD, $p < 0.001$), similarly to prevalence of CAD (24%), DM (15%) and CHF (16%). In CKD, 30% of patients have anemia. In-hospital mortality was 6%. Analysis of mortality of patients admitted to the emergency department and then hospitalized showed that the majority of patients were over 70, with CKD (64%), CHF (75%), DM (35%), ACS (25%) and anemia (56%). Deaths were mainly from cardiovascular causes.

Conclusions: Prevalence of CKD is high in patients admitted to ED, and associated with mainly cardiovascular disease. Education is of utmost importance to diagnose and treat CKD in a timely manner and decreased cardiovascular morbidity and mortality in this population.

Funding: Government Support - Non-U.S.

PUB138

Predictors of In-Hospital Mortality of CKD4-6 Patients with Takotsubo Cardiomyopathy Fernando Rodrigo Aguilar, Mark Abi Nader, Wen Shen, Serban A. Dragoi, Alex Montero, Ping Li. *Internal Medicine, Div of Nephrology, Medstar Georgetown Univ Hospital, Washington, DC.*

Background: The pathophysiology of Takotsubo cardiomyopathy (TTC) remains poorly understood and little is known about the factors predicting mortality in these patients among those with chronic kidney disease. We aimed to study the epidemiology of TTC and predictors of mortality in these patients.

Methods: All patients with CKD 4 to CKD 6 (ICD9 585.4-585.6) diagnosed with TTC (ICD9 429.83), in the Nationwide Inpatient Sample database between 2007 and 2012, were compared to CKD4-CKD6 patients without TTC. Capturing only cases undergoing left heart catheterization (ICD9 procedure code 32.22) and excluding those receiving stent (ICD9 procedure code 00.66; 36.01 - 07;00.45-00.48) as a main treatment. Both groups were matched, using propensity matching score for chronic conditions including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, obesity, alcohol use, smoking, heart failure and ventricular arrhythmias. Non-cardiovascular conditions were also used to match individual cases. Multivariable logistic regression analysis was performed.

Results: 143 cases of TTC were diagnosed from 2007-2012 in patients having CKD4-6. Were 138 cases were matched (n to 1) and posteriorly analyzed. Among to control group, CKD 4-6 patients with TTC was more commonly diagnosed in Women (86.23% vs 13.77 $p = 1.0$). Alcohol, older, smoking and anxiety, were significantly more prevalent in TTC group. In-hospital mortality rate was not different among both groups even after multivariable regression analysis. Contrary to epidemiologic studies in the general population, Age, Race Stress, anxiety, smoker, Obesity and HTN did not predict mortality with TTC.

Conclusions: In CKD4-6 patients, TTC does not carry a higher mortality outcome compared to the general CKD4-6 patients. Older CKD4-6 females, with anxiety disorder and smokers are at higher risk to develop TTC.

PUB139

The Importance of Evaluating Coronary Artery Disease by Multi-Director Row Computed Tomography in Advanced CKD Masataka Hasegawa,¹ Daiki Kobayashi,² Masahiko Nagahama,¹ Takuya Fujimaru,¹ Yuki Heath,¹ Fumika Taki,¹ Miyuki Futatsuyama,¹ Yasuhiro Komatsu.¹ ¹*Nephrology, St. Luke's International Hospital, Tokyo, Japan;* ²*General Internal Medicine, St. Luke's International Hospital, Tokyo, Japan.*

Background: There is a growing body of evidence that CKD contributes to the severity of coronary artery disease (CAD). Although Multi-director row computed tomography (MDCT) provides valuable information about CAD, its use for patients with CKD is difficult due to the risk of contrast induced nephropathy (CIN). To our knowledge, there have been no studies to explore the association of CAD and advanced CKD. The objectives of this study are to assess the severity of CAD in advanced CKD patients by MDCT and clarify the association between CAD and renal function.

Methods: We retrospectively collected the data from 168 advanced CKD patients, stage 3b to 5, who underwent MDCT angiography at St Luke's international hospital between 2011 and 2014. We assessed CAD by coronary artery calcification score (CASC), coronary plaque characteristics and number of vessel disease. Risk factors for CAD were sought using univariate and multivariate logistic regression.

Results: Among the 168 patients (56 females, age 60.0±17.0), 108 patients were CKD stage 3b, 42 patients were stage 4, and 18 patients were stage 5. No patient developed CIN by MDCT. On univariate analysis, patients with CASC³100 were older ($P = 0.003$), male sex ($P = 0.011$), diabetic ($P = 0.045$), and more likely to be a smoker ($P = 0.014$). Multivariate logistic regression analysis identified age (hazard ratio = 1.08, $P < 0.01$), male sex (hazard ratio = 2.97, $P = 0.013$), and CKD stage (hazard ratio = 2.58, $P = 0.041$) as independent risk factors for CASC³100.

Conclusions: Coronary artery calcification is worsened significantly with decreasing renal function in advanced CKD. Given the high morbidity and mortality of cardiovascular disease in CKD, our study underscores the importance of evaluating CAD in advanced CKD.

PUB140

Cardiovascular Biomarkers and Coronary Calcification in CKD Patients Joquin Manrique,¹ Diana Izquierdo,¹ Patricia Restituto,² Nuria Garcia-Fernandez,³ Maria Fernanda Slon,¹ Diana Lopez Espinosa,³ Maria Jose Molina Higuera,³ Nerea Varo.² ¹*Servicio de Nefrologia, Complejo Hospital de Navarra, Pamplona, Spain;* ²*Servicio de Bioquímica, Clínica Univ de Navarra, Pamplona, Spain;* ³*Servicio de Nefrologia, Clínica Univ de Navarra, Pamplona, Spain.*

Background: Cardiovascular calcification and mortality are highly prevalent in patients with CKD. Biomarkers can help to an early diagnose, like Osteoprotegerin (OPG) a glycoprotein from TNF family that has been associated with cardiovascular (CV) disease. FGF-23, a phosphaturic protein has been linked to vascular calcification, ventricular hypertrophy and mortality. Coronary artery calcification (CAC) measured with Agatston score (AS) by CT is associated to CV disease in CKD patients. We hypothesized that OPG and FGF-23 are abnormally elevated in CKD and are associated CAC measured with AS.

Methods: An observational study including 138 CKD 3-5 patients, and 20 control subjects were included. Serum FGF-23 and OPG levels were measured by ELISA and CAC was determined by multi-detector computed tomography (AS). Biochemical regular labs (sCr, Ca, P and PTHi) were measured.

Results: Compared with control subjects, CKD patients exhibited significantly augmented serum FGF-23 (16.2 vs 304.8pg/mL; $p < 0.001$) and OPG levels (157.0 vs 1711.7pmol/L; $r^2 = 0.58$; $p < 0.001$), and increased proportionally to CKD stage. FGF-23 and OPG were correlated to PTHi and P ($p < 0.001$) and OPG correlated with renal function (sCr) in non-dialysis patients ($p < 0.05$). CKD 5 patients showed significantly higher coronary calcification (AS: 1344.3) compared with CKD 3 (144.3; $p < 0.05$) or CKD 4 (527.7; $p < 0.05$). FGF-23 and OPG were associated with AS ($r^2 = 0.20$; $p < 0.05$ and $r^2 = 0.37$; $p < 0.001$, respectively). Among CKD patients, high CAC (AS >800) compared to low CAC patients (AS levels <150) showed higher FGF-23 (374.9 vs 156.1; $p < 0.05$) and OPG levels (2121.2 vs 1305.2; $p < 0.001$).

Conclusions: CKD is related to high coronary artery calcification levels. FGF-23 and OPG are higher in CKD patients and are significantly associated to coronary artery calcification. Further investigations are needed to determine if they could promptly assess increased cardiovascular risk in CKD patients.

PUB141

Rate of Kidney Function Decline and Risk of Hospitalizations Yan Xie,¹ Benjamin Charles Bowe,¹ Sumitra Balasubramanian,¹ Ziyad Al-Alaly,^{1,2} ¹*Research and Development, VA Saint Louis Health Care System, Saint Louis, MO;* ²*Medicine, VA Saint Louis Health Care System, Saint Louis, MO.*

Background: Risk of hospitalizations is increased in patients with chronic kidney disease (CKD). We sought to examine the association between rate of kidney function decline and risk of hospitalization in a cohort of patients with early CKD.

Methods: We built a cohort of 241,274 United States veterans with an estimated glomerular filtration rate (eGFR) between 60 and 45 ml/min on October 1, 1999 and who had at least 1 additional eGFR measurement between October 2003 and September 2004. Patients were followed longitudinally from October 2004 until September 2013. We built

survival models to examine the association between rate of kidney function decline and risk of hospitalization, and readmission. We built linear regression models to estimate the length of hospital stay.

Results: Over a median follow up of 9 years (IQR 5.42 – 9.00), compared to patients who experienced mild eGFR decline, patients with moderate and severe eGFR decline exhibited an increased risk of hospitalizations HR=1.10 (CI:1.07-1.12), and HR=1.29 (CI:1.26-1.32); respectively. The number of hospitalizations modified the association between rate of decline and risk of hospitalizations in that the risk was increasingly more pronounced with increased number of hospitalizations (p value for interaction <0.0001). Compared to patients with mild decline in kidney function, patients with moderate and severe kidney function decline had increased risk of future readmission, HR=1.16 (CI:1.10-1.21), and HR=1.47 (CI:1.39-1.55); respectively. Among patients with severe kidney function decline, the risk of readmission was increasingly stronger with increased number of readmissions (p value for interaction <0.0001). Compared to patients with mild decline in kidney function, patients with moderate and severe decline experienced an additional length of stay of 0.91 (CI: 0.58-1.25) and 2.82 (CI: 2.43-3.20) day/year; respectively.

Conclusions: Our findings suggest that rate of kidney function decline is associated with future risk of increased health care utilization.

Funding: Veterans Administration Support

PUB142

Racial Influences on the Association of Albumin and Hemoglobin in Chronic Kidney Disease Divya Shankaranarayanan, Avaneesh Jakkaju, Goutham Gudavalli, Ziad Maurice Ashkar. *Dept of Internal Medicine, Louisiana State Univ, Lafayette, LA.*

Background: In CKD, anemia is associated with reduced kidney function, female gender, diabetes, older age, African-American race(AA), iron deficiency, low albumin, renin-angiotensin blockade, and chronic inflammation. There is a paucity of studies evaluating relationship of albumin and hemoglobin(Hb) in CKD among racial groups.

Methods: Retrospective cross section design of 196 patients with CKD stages 2-5, in a community clinic over a 7 months period. Averages of hemoglobin, albumin, body mass index (bmi), and glomerular filtration rate(GFR) were obtained for each individual patient. Patients on dialysis and on erythropoiesis-stimulating agents were excluded. Multi-linear regression analysis (MLR) was then done between serum albumin and hemoglobin adjusting for age, sex, diabetic status, GFR, bmi, and Ace inhibitors/angiotensin receptors blockers intake (ACEi) among African-Americans(AA) and Caucasians(W).

Results: 51% were AA. 49% were diabetics. Mean Hb was 11.7 in AA compared to 12.3 in Caucasians. Mean serum albumin was also lower (3.5 AA versus 3.8 in W). Bmi and GFR were higher in AA (36.4 and 42.8 in AA vs 32.3 and 39.9 in W respectively). Using MLR, there was a statistically significant positive association between GFR(coefficient=0.02,p<0.001), albumin (coefficient=0.77,p=0.002),and hemoglobin. AA race was negatively related to hemoglobin(coefficient= -0.68,p=0.02). When MLR was done separately among racial groups, there was a persistent positive relationship between albumin and hemoglobin among AA (coef=0.95, p=0.001). In Caucasians however there was no association between albumin and hemoglobin (p=0.181).

Conclusions: In CKD2-5, using multilinear regression analysis, there was a positive association between serum albumin and hemoglobin. This relationship occurs only in AA and disappears among Caucasians. It is of interest that in our sample AA had higher baseline bmi and GFR and lower serum albumin and hemoglobin. More needs to be done to understand the interplay between bmi, albumin and markers of inflammation and nutrition among African Americans with chronic kidney disease and their relationships to hemoglobin levels.

PUB143

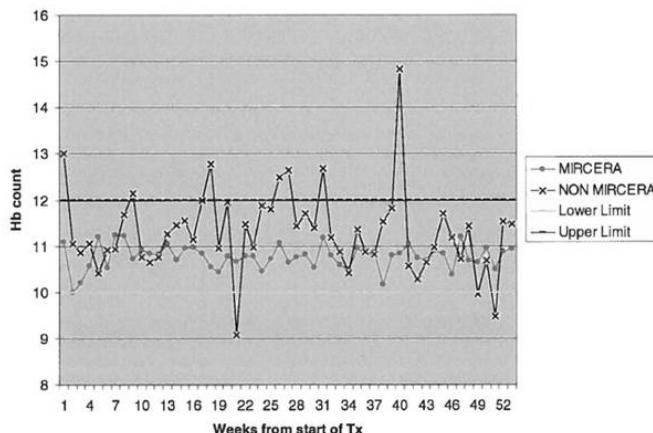
Mircera Use in Chronic Kidney Disease Patients with Symptomatic Renal Anemia: The Real Life Setting Sai Krishna Duraisingham, Suzanne H. Forbes, Muhammad M. Yaqoob. *Renal and Transplantation Medicine, Barts Health NHS Trust on behalf of the Mircera Audit Consortium, London, United Kingdom.*

Background: Randomized controlled trials have confirmed non inferiority of Mircera in the management of renal anemia when compared to other erythropoietin stimulating agents (ESAs). Many of these trials had strict exclusion criteria which perhaps confounded any benefit that may be seen in an unselected cohort of patients. This multicenter audit assessed the outcomes of Mircera use in the real life setting.

Methods: A prospective audit was conducted by 6 UK Renal Centers between 2009 and 2011. Demographic data, as well as hematological and biochemical parameters were longitudinally collected from 1000 adult patients requiring ESAs, over a 1 year period. A cohort of 500 patients were switched from previous ESAs to Mircera and 500 patients remained on their existing ESA therapy. Patients with hemoglobinopathies or malignancies were excluded. Achievement of target hemoglobin (Hb) as per the National Institute of Clinical Excellence (NICE) guidelines was ascertained as the primary objective. Hb variability was reviewed as a secondary objective.

Results: Demographic data confirmed both cohorts were comparable. Only 11% of Mircera treated patients had their Hb maintained within range (10-12g/dl) over the entire 1 year versus 4% in the non-Mircera group (p<0.05). (If an Hb recording was out of range the patient was classified as ‘not maintained’). Parameters such as B12, folate and iron were similar in both cohorts. Hb was less variable in the Mircera group

Comparison of Average values of Hb count for MIRCERA and non MIRCERA



Conclusions: The results of this audit confirm that Mircera use in the correction of anemia associated with CKD is equally efficacious as other ESA therapies in this real life setting. Over a year period, Hb variability was noted to be reduced in the Mircera treated cohort suggesting a role for its use in patients with fluctuating Hb levels.

Funding: Pharmaceutical Company Support - Extramural grant: Roche Products Limited UK

PUB144

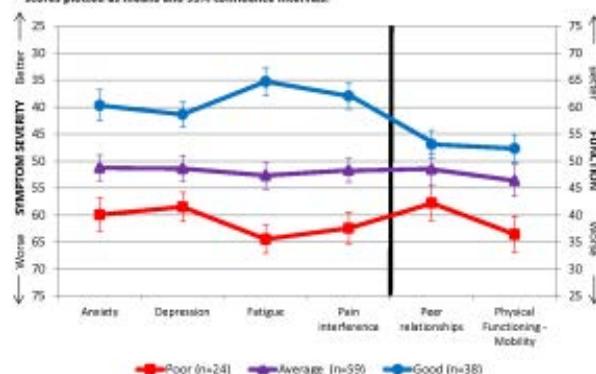
Latent Profiles of Patient Reported Outcomes in Nephrotic Syndrome Patients Jonathan P. Troost,¹ Debbie S. Gipson,¹ Bryce B. Reeve,² Patrick H. Nachman,² Rasheed A. Gbadegesin,³ Jichuan Wang,⁴ Frank Modersitzki,⁵ Susan F. Massengill,⁶ John D. Mahan,⁷ Howard Trachtman,⁵ David T. Selewski.¹ ¹Univ of MI; ²Univ of NC; ³Duke Univ Medical Center; ⁴George Washington Univ; ⁵New York Univ; ⁶Levine Children’s Hospital; ⁷The Ohio State Univ.

Background: Nephrotic syndrome (NS) can significantly impair the quality of life in children and adults. The purpose of this study was to demonstrate the feasibility and utility in using a latent profile analysis (LPA), a type of cluster analysis, to identify subgroups of patients based on their patient reported outcomes using the Patient Reported Outcomes Measurement Information System® (PROMIS®) measures as well as identifying significant predictors of those subgroups.

Methods: Prospective data were collected on 121 children with NS from the PROMIS-II study. Data from 55 children and 254 adults with biopsy confirmed NS from the NEPTUNE cohort were used as validation. LPA was used to identify patterns and subgroups of patients based on PROMIS domain scores. Classification was assessed using entropy statistics. Generalized multinomial logit models were used to identify predictors of profile membership as well as transitions between profiles over time.

Results: We identified three patient reported outcome profiles (figure1) in the PROMIS-II cohort with strong indicators of membership classification (entropy>0.86).

Figure: PROMIS latent profiles for 121 children with nephrotic syndrome from the PROMIS-II cohort. Domain scores plotted as means and 95% confidence intervals.



Initial subgroups derived from the PROMIS-II cohort were also present in NEPTUNE. Reaching complete proteinuria remission, reduction in symptom number, increase in serum albumin, and shorter disease duration were significant predictors of better quality of life over time.

Conclusions: LPA may be an effective tool in stratifying NS patients by quality of life. Profile membership changed in response to changes in disease status over time.

Funding: NIDDK Support

PUB145

Sex Hormone Status in Women with Chronic Kidney Disease: A Survey of Nephrologists Sharanya Ramesh,¹ Ellen Wells Seely,² Matthew T. James,^{1,3} Jayna M. Holroyd-Leduc,³ Stephen B. Wilton,^{3,4} Sofia B. Ahmed.^{1,3,4} ¹Medicine, Cumming School of Medicine; ²Brigham and Women's Hospital; ³Community of Health Sciences, Univ of Calgary; ⁴Libin Cardiovascular Inst of Alberta.

Background: Chronic kidney disease (CKD) in women is often accompanied by menstrual and fertility disorders due to kidney-mediated endocrine disturbances. Whether this issue is recognized by nephrologists and discussed by them with their patients is unknown.

Methods: We electronically surveyed 111 nephrologists in Canada, identified via Canadian Society of Nephrology membership (39% response rate), regarding their impressions of sex hormone status, menstrual cycle, fertility and the role of postmenopausal hormone therapy (HT) in women with CKD. Responses were stratified by kidney transplant nephrologist status.

Results: Fourteen percent of respondents were transplant nephrologists. There were no differences in age or sex between transplant and non-transplant nephrologists. Ninety-three percent of respondents agreed that kidney function has an important impact on regulation of sex hormones. However, only 35% reported discussing fertility, and even fewer (14%) reported discussing menstrual irregularities with their patients. Only 40% of respondents advised their patients to address these concerns with their family physician or an endocrinologist or gynecologist. Most of the nephrologists responded that they do not know if there is a role for hormone replacement therapy in patients with CKD (48%), 23% of nephrologists disagreed with the statement. Nephrologists did not know whether the potential benefits of postmenopausal hormone therapy outweighed the risks in CKD (51%) or if the formulation (44%), route of administration (46%), and time of HRT initiation (50%) play a role in the actions of postmenopausal hormone therapy.

Conclusions: While nephrologists recognize the impact of CKD on sex hormone status in women, few address fertility and menstrual disorders with their patients. Our survey highlight existing uncertainties of nephrologists about how to manage disturbances of sex hormones in people with CKD.

Funding: Private Foundation Support

PUB146

Clinical and Pathological Analysis of Elderly Hospitalized Patients with Chronic Kidney Disease Fu-You Liu, Yinghong Liu. *Inst of Nephrology, the Second Xiangya Hospital, Central South Univ, Changsha, Hunan, China.*

Background: To investigate the primary disease and to examine the pathological patterns of renal in elderly patients with CKD.

Methods: Medical histories, laboratory test results and renal biopsy datum were collected and retrospectively analyzed from 967 elderly patients with CKD.

Results: (1) The average age of 967 cases of elderly patients was 68.27 ± 6.41 years old. The leading cause of CKD was primary glomerular diseases (37.33%), followed by diabetes nephropathy (23.27%) and hypertensive nephropathy (19.75%). (2) The left kidney was larger than the right, and kidney of male patients was larger than the female (P < 0.05). There was a positive correlation between eGFR and the left kidney width, depth, and the right kidney width, depth. (3) In 75 patients who underwent renal biopsy, the most common renal histopathology in primary glomerular disease was membranous nephropathy (MN) (48.08%). In patients with MN, 88.00% presented as nephrotic syndrome. (4) The prevalence of hypertension was 80.66%. eGFR was negatively correlated with systolic blood pressure levels. (5) The anemia rate of elderly patients with CKD was 77.97%. eGFR and hemoglobin levels were positively correlated (6) There was a positive correlation between eGFR and HDL-C, LDL-C, total cholesterol and triglyceride respectively. (7) Calcium-phosphorus metabolism were mainly hypocalcemia (27.92%) and hyperphosphatemia (54.91%). eGFR was negatively related to the level of blood phosphorus and intact parathyroid hormone (iPTH), and positively related to blood calcium levels.

Conclusions: (1) This study shows that primary glomerular disease is still the leading causes of elderly patients aged 60 and above with CKD, followed by diabetes nephropathy and hypertensive nephropathy. (2) In elderly patients receiving renal biopsy, the most common renal histopathology pattern was MN in primary glomerular disease. (3) It indicated that high systolic blood pressure, renal atrophy, anemia, low HDL-C, hyperphosphatemia and secondary hyperparathyroidism may be associated with deterioration of renal function level.

Funding: Government Support - Non-U.S.

PUB147

Measurement of Breath Ammonia for Detection of Patients with Chronic Kidney Disease Sebastian Bevc,¹ Evelina Mohorko,² Mitja Kolar,² Polonca Brglez,³ Andrej Holobar,³ Daniela Kniepeiss,⁴ Matej Podbregar,⁵ Nina Hojs,¹ Masa Knehtl,¹ Robert Ekart,¹ Radovan Hojs.¹ ¹Univ Clinical Centre Maribor, Slovenia; ²Faculty of Chemistry and Chemical Engineering Maribor, Slovenia; ³ECHO d.o.o. Slovenske Konjice, Slovenia; ⁴Medical Univ Graz, Austria; ⁵Univ Clinical Centre Ljubljana, Slovenia.

Background: In a healthy individual, ammonia is converted to urea in the liver through urea and citric acid cycles. Urea is then transported through the bloodstream to be excreted into the urine by the kidneys. In patients with chronic kidney disease (CKD) an equilibrium concentration of ammonia and urea becomes imbalanced, concentrations

exceeding physiological values and breath ammonia can be used for detecting increased nitrogen-bearing wastes in the body. In our pilot study, the electrochemical sensor was used to measure and analyze breath ammonia in healthy volunteers and CKD patients.

Methods: Six CKD patients and eight healthy volunteers were enrolled. The mean age of CKD patients was 47.2 years, mean age of healthy volunteers 61.3 years. One controlled breath sample was given from each participant. Immediately after the sample was collected gas analyzer (BA-NH3, Echo, d.o.o.) was used for measuring breath ammonia in our participants. BA-NH3 detects breath ammonia in parts per million (ppm) and measures the electric current in milliamperes (mA). BA-NH3 was validated with reference gas concentrations prepared with a precise accredited gas mixing device (M4-1-S-220, Echo, d.o.o.) using calibrated mass flow controllers controlled with computer software.

Results: Mean serum creatinine in CKD patients was 455.17 ± 294.12 μmol/L and 62.13 ± 7.5 μmol/L in healthy volunteers. BA-NH3 detected more ppm of ammonia in breath of CKD patients (mean ppm 3.32 ± 2.19; range 1.26-6.33) comparing to healthy volunteers (mean ppm 0.49 ± 0.08; range 0.38-0.64 ppm) (p = 0.003) and measured higher electric current from breath samples of CKD patients (mean mA 4.33 ± 0.25; range 4.10-4.67 mA) comparing to healthy volunteers (mean mA 4.01 ± 0.01; range 4.00-4.03 mA) (p = 0.003).

Conclusions: Results of our pilot study show that breath monitoring of ammonia can be an useful simple, fast and noninvasive tool for detection of kidney impairment.

PUB148

Use of Urine Biomarker-derived Clusters to Predict CKD Risk and All-Cause Mortality in HIV+ Women Rebecca Scherzer,¹ Heather Thiessen Philbrook,² Chirag R. Parikh,³ Michael R. Bennett,⁴ Mardge H. Cohen,⁵ Anjali Sharma,⁶ Mary A. Young,⁷ Phyllis Tien,¹ Vasantha Jotwani,¹ Michael Shlipak.¹ ¹UCSF; ²London Health Sciences Centre; ³Yale; ⁴Cincinnati Children's Hospital; ⁵Rush; ⁶Albert Einstein; ⁷Georgetown.

Background: Individual urine biomarkers are associated with CKD incidence and all-cause mortality in the setting of HIV infection, but their combined utility for prediction remains unknown.

Methods: We measured 8 urine biomarkers in 902 HIV+ women: NAG, KIM-1, alpha 1 microglobulin (a1m), IL-18, NGAL, ACR, L-FABP, and AAG. A novel cluster method classified each participant into 3 groups using the three most distinguishing markers (NAG, KIM-1, and a1m). We evaluated associations of each cluster with incident CKD and all-cause mortality, adjusting for traditional and HIV-related risk factors.

Results: Over 8 years of follow-up, 177 CKD events and 128 deaths occurred. As shown in the Table, incidence of CKD and mortality increased incrementally across the 3 clusters. After multivariable adjustment, cluster 3 remained associated with a nearly 3-fold risk of both outcomes compared with cluster 1. Addition of the clusters to the multivariable model improved discrimination for CKD (c-statistic = 0.72 to 0.76, p = 0.0029), but only modestly for mortality (c = 0.79 to 0.80, p = 0.099). Clusters derived with all 8 markers were no better for discrimination than the 3-biomarker clusters.

Conclusions: Among HIV+ women, clusters developed from 3 urine biomarkers moderately improved discrimination for CKD risk, but not for all-cause mortality.

Association of biomarker-derived cluster* with incident CKD and all-cause mortality in HIV+ women			
	Cluster 1 n=289	Cluster 2 n=435	Cluster 3 n=94
Incident CKD			
Event rate	13%	21%	50%
Unadjusted Risk Ratio (95%CI)	Ref	1.7 (1.2, 2.4)	3.9 (2.7, 5.6)
Adjusted Risk Ratio (95%CI)	Ref	1.6 (1.1, 2.3)	2.9 (2.0, 4.3)
All-cause mortality	Cluster 1 n=301	Cluster 2 n=470	Cluster 3 n=131
Event rate	7%	13%	34%
Unadjusted Hazard Ratio (95%CI)	Ref	1.9 (1.1, 3.0)	5.4 (3.2, 9.0)
Adjusted Hazard Ratio (95%CI)	Ref	1.5 (0.9, 2.5)	2.8 (1.6, 4.8)

* Clusters were derived using NAG, a1m, and KIM-1. Adjusted models control for traditional kidney risk factors and HIV-related risk factors.

Funding: Other NIH Support - The WIHS Kidney Aging Study is funded by grant 1 R01 AG034853-01A2 (PI, Shlipak), which was administered by the Northern California Institute for Research and Education, and with resources of the Veterans Affairs Medical Center, San Francisco, California. Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). WIHS (Principal Investigators): UAB-MS WIHS (Michael Saag, Mirjam-Colette Kempf, and Deborah Konkle-Parker), U01-AI-103401; Atlanta WIHS (Ighoverhera Ofotokun and Gina Wingood), U01-AI-103408; Bronx WIHS (Kathryn Anastos), U01-AI-035004; Brooklyn WIHS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (Mardge Cohen), U01-AI-034993; Metropolitan Washington WIHS (Mary Young), U01-AI-034994; Miami WIHS (Margaret Fischl and Lisa Metsch), U01-AI-103397; UNC WIHS (Adaora Adimora), U01-AI-103390; Connie Wofsy Women's HIV Study, Northern California (Ruth Greenblatt, Bradley Aouizerat, and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WIHS (Alexandra Levine and Marek Nowicki), U01-HD-032632 (WIHS I – WIHS IV). The

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PUB149

Minimizing Erythropoietin Stimulating Agents Requirement by Comprehensive Clinical Care Rachita Singh Dhull, Rossana Baracco, Melissa J. Gregory, Tej K. Mattoo. *Pediatric Nephrology, Children's Hospital of Michigan, Detroit, MI.*

Background: Anemia is a common problem in children with chronic kidney disease (CKD). The objective of the study was to evaluate prevalence of anemia, use of iron supplement and erythropoietin stimulating agents (ESA) in children with CKD stage 2-4, and compare the same with previous pediatric studies.

Methods: This is a retrospective chart review of children with CKD stage 2-4 (defined per KDOQI), aged between 1-18 years followed at Children's Hospital of Michigan (CHM) in 2013. Data on transferrin saturation, hemoglobin level, use of iron supplements and ESA was collected.

Results: Total number of patients were 62. The mean age was 10.12 ± 5.52 years and 27.4% were female. The main causes of CKD were renal dysplasia (20%), obstructive uropathy (18%), reflux nephropathy (14.5%), cystic dysplasia (13%), glomerular pathology (11.2%) and others (23.3%). In our cohort, 27% patients had anemia compared to 44% in CkiD study and 43.5% in study by Wong et al. Also, only 6.5% of CKD patients were on ESA, compared to 18% in Ckid study and 19.5% in study by Wong et al. Results are elaborated in the table below.

CKD STAGE	CKiD STUDY (2008)	Wong et al (2006)	CHM DATA			
	Pateints(%) with anemia ^a / ^b	Patients(%) with anemia ^a / ^b	Patients (%)with anemia/ ^a / ^b	Transferrin saturation >=20%	On iron supplement	on ESA
2	21/39	28.57/106	7.7/13	7(53.8%)	9(69.2%)	0
3	39/217	65.8/38	27/37	24(64.8%)	21(56.7%)	0
4	73/82	93.3/15d	50/12	8(66.6%)	9(75%)	4(33.3%)
TOTAL	45/338	43.5/159	27.4/62	39(63%)	39(63%)	4(6.45%)

^aAnemia as defined by hemoglobin (Hb) level < 5th percentile for age and sex according to NHANES III data.

^bn= number of children with CKD in that group.

^cAnemia as defined by Hb <12 g/dl or on medical management for anemia.

^dincludes children with stage 4 and 5 CKD.

Conclusions: Our CKD patients had a lower prevalence of anemia and lower use of ESA compared to other pediatric studies. We maintain adequate iron stores by using iron supplements even in children with normal hemoglobins. The administration of supplemental iron prior to the development of anemia in children with CKD decreases the need for ESA.

PUB150

Validation of Urinary Biomarkers for the Diagnosis of Urothelial Carcinoma in Patients with Chronic Kidney Disease Chiu-Ching Huang,¹ Che-yi Chou,¹ Chao-Jung Chen,² ¹*Kidney Inst, China Medical Univ and Hospitals, Taichung, Taiwan;* ²*Proteomics Core Laboratory, Dept of Medical Research, China Medical Univ, Taichung, Taiwan.*

Background: Many urine biomarkers for diagnosis of urothelial carcinoma(UC) have been published. CKD patients are prone to have UC. Most of the studies are tested in healthy controls and UC patients. Whether these biomarkers are specific to diagnose UC in CKD patients have not been studied before. **AIMS:** To investigate if current urinary biomarkers are specific to diagnose UC in CKD patients.

Methods: This is a multicenter prospective case-control study, carried out at 7 tertiary medical centers in Taiwan (Taiwan UC Consortium). Subjects were healthy adults (healthy controls), patients with CKD but without UC (disease controls) and patients with ongoing UC. Urine was collected from each patient and frozen immediately after collection. We measured 9 urinary UC biomarkers : BLCA-1, HAI-1, HtrA1, NMP22, CYFRA21-1, TSCSTD2, BLCA-4, BTA and Midkine. Mann-Whitney Rank Sum Test was used for statistical analyses.

Results: A total of 47 UC cases, 288 CKD patients and 20 healthy controls were recruited. We selected 47 CKD control patients who were age, sex and CKD-staging best matched with 47 UC patients. Among the 9 biomarkers tested, six biomarkers, e.g. NMP22, CYFRA21-1, TSCSTD2, BLCA-4, BTA and Midkine showed significant increase of urinary concentrations in UC patients when compared to healthy controls. Nevertheless,

only Midkine and CYFRA 21-1 had significantly increased concentrations in UC patients when compared to CKD controls. The other 4 UC biomarkers did not show significant higher concentrations in UC patients than CKD controls.

Urine biomarker	P value		
	Healthy controls vs. CKD controls	CKD controls vs. ongoing UC	Healthy controls vs. ongoing UC
BTA	0.023	0.420	0.175
Blca-4	0.002	0.379	<0.001
NMP22	<0.001	0.486	0.007
TACSTD2	0.005	0.265	0.001
Midkine	0.027	0.050	<0.001
CYFRA21-1	0.676	0.003	0.007

Conclusions: Among 9 urine biomarkers tested, only two showed statistically significant higher urinary concentrations in UC patients than matched CKD patients. Our findings would raise caution of interpreting urinary biomarkers for UC diagnosis in CKD patients.

Funding: Government Support - Non-U.S.

PUB151

Predictors for 30-Day Hospital Readmission in a Nephrology Ward Carla S. Moreira,¹ Ligia Bessa,² Vanda Guardado,² Jorge Malheiro,¹ Josefina S. Lascasas,¹ António Cabrita.¹ ¹*Nephrology, Centro Hospitalar do Porto, Porto, Portugal;* ²*Nephrology, Hospital Militar de Luanda, Luanda, Angola.*

Background: Rehospitalization, particularly 30-day hospital readmission is a growing concern in health care services. In this study we searched for predictors of 30-day readmissions (including emergency department visits) and 12-months hospitalization rate in patients admitted to a nephrology ward.

Methods: A group of 144 patients admitted to our nephrology ward from 2012 to 2013 were randomly selected. Their medical records regarding demographic and clinical-laboratorial data were collected. The statistical analysis was performed using univariate and multivariate logistic regression, and poisson regression.

Results: Median age was 66yo (IQ 56-81), with 63% of male patients. The majority of the patients had an emergent admission (63%) and regular hospital follow-up (55%). The median length of hospital stay was 7 days. The readmission rate was 23% and the median length until readmission was 13 days. The prevalence of chronic kidney disease was 89%, with 30% of these patients undergoing chronic intermittent hemodialysis and 11% peritoneal dialysis. The median Charlson Comorbidity Index (CCI) was 7 points (IQ 4-11). In the univariate analysis we found a statistical significant association between diabetes mellitus (OR =2.45, p=0.04), lower (<3.5g/dL vs ≥ 3.5g/dL) albumin level (OR=8.73, p=0.006), higher (<8 vs ≥ 8) CCI score (OR=2.94, p=0.02) and 30-day hospital readmission. In the binary logistic regression only albumin level kept its significant association (OR=7.9, p=0.01), with diabetes mellitus maintaining a tendency for significance (OR=2.97, p=0.09). The rate of rehospitalizations at the first year adjusted for gender was 2.6 vs 6.4 rehospitalizations/100 patients-month in the lower and higher CCI score groups, respectively (p=0.01). The rate of emergency department episodes adjusted for gender was 29 versus 75 episodes/100 patient-month in the lower and higher CCI score groups, respectively (p<0.001).

Conclusions: The Charlson Comorbidity Index and albumin level may be valuable predictors of hospital readmission risk in patients from a nephrology ward.

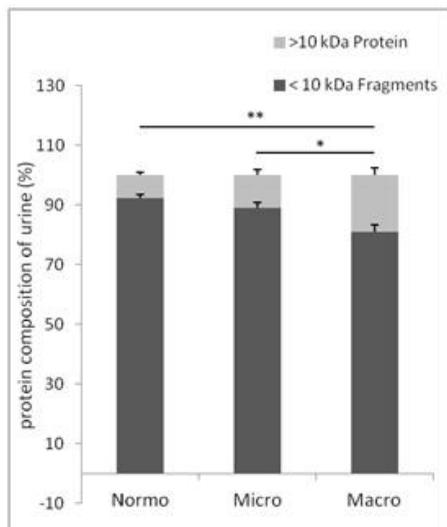
PUB152

Urine Protein Fragment Excretion in Diabetic Patients with Chronic Kidney Disease Michele V. Clarke,¹ Elif Ekinci,^{1,2} Nicholas J. Radcliffe,^{1,2} Richard J. MacIsaac,³ George Jerums,¹ Wayne Comper.⁴ ¹*Austin Health, Melbourne;* ²*Univ of Melbourne, Melbourne;* ³*St. Vincent's Hospital, Melbourne;* ⁴*Sal Aqua Diagnostics, New York.*

Background: Albuminuria is an established marker for the development of diabetic nephropathy. Normal renal handling of albumin involves endocytosis by proximal tubule cells through a lysosomal pathway. This returns small albumin fragments, undetectable by standard clinical assays, to the tubular lumen. Albuminuria has been shown in patients with type 1 diabetes to be associated with an impaired degradation pathway, and urinary peptides have been shown to be reduced in patients with macroproteinuria. However, urine peptide excretion studies have not controlled for changes in estimated glomerular filtration rate (eGFR) in patients with diabetes.

Methods: Patients with diabetes and eGFR <60ml/min were stratified into normo- (<20mg/min, n=9), micro- (20-200mg/min, n=12) or macroalbuminuric (>200mg/min, n=9) groups. 24 hr urines were passed through a 10kDa protein filter, and the <10kDa and >10kDa fractions were assayed separately using the BCA protein assay to detect peptide bonds.

Results: Macroalbuminuric patients had a reduced proportion of peptide fragment excretion (<10kDa) compared to micro- and normoalbuminuric patients (81.1% vs 89.0%, p<0.05 & 96.8%, p<0.001 respectively); however there was no difference between micro- and normoalbuminuric groups (Figure 1). Mean fragment concentrations were lower in micro- and macro- groups compared to normoalbuminuric patients, (3389µg/ml and 3480µg/ml vs 4396µg/ml) but did not reach statistical significance.



Conclusions: In patients with diabetes and reduced renal function, we have demonstrated a reduction in peptide fragment proportional excretion in macroalbuminuric patients. These findings are consistent with the hypothesis that albuminuria is linked to defects in the renal tubule resorption and fragmentation pathways.

PUB153

Chronic Kidney Disease of Uncertain Etiology: A Systematic Review
Joseph Lunyera, Dinushika Mohottige, Megan Von Isenburg, Uptal D. Patel, Marc A. Jeuland, John W. Stanifer. *Duke Univ.*

Background: Epidemics of chronic kidney disease of uncertain etiology (CKDu) are emerging around the world. Highlighting common risk factors for CKDu across various regions and populations may be important for health policy and public health responses.

Methods: We conducted a systematic review of the PubMed, Embase, Scopus and Web of Science databases to identify published studies on CKDu. Two independent authors reviewed all abstracts for inclusion, assessed each study for quality, and extracted the data. We used a vote-counting method to evaluate the exposures across all studies.

Results: We identified 2535 articles of which 25 met inclusion criteria. Eighteen (72%) were conducted in CKDu-endemic countries: Sri Lanka (40%), Nicaragua (20%) and El Salvador (12%). The other studies were from India, Japan, Australia, Mexico, Sweden, Tunisia and the United States. Risk factors most frequently measured were agricultural occupation (48%), age (48%), gender (44%), and agrochemical use (40%). Heavy metals, heat stress and dietary exposures were reported in studies across all geographical regions. In South Asia, family history, agrochemical use, and heavy metal exposures were reported most frequently while altitude and temperature were reported only in studies from Central America. Across all regions, CKDu was most frequently associated with a family history of CKDu, farming occupation, male gender, middle-age, snake bites and heavy metal exposures. Among high risk populations, CKDu prevalence was reported to be 7.3%-14.9% in South Asia and 13%-25.9% in Central America.

Conclusions: Studies examining etiologies of CKDu have reported many potential exposures that are heterogeneous and vary by region. It remains unknown whether the regional variation in CKDu risk factors reflects inconsistencies in measurement across studies or complexity in the interactions between global exposures and local factors such as environment, genetics, and lifestyle. Thus, to identify the causative factors of CKDu, one important approach could be to design consistent and comparative multi-site studies in high-risk populations that would provide insights into the importance of region-specific versus global risk factors.

PUB154

Understanding the Socio-Demographic Status of Patients Receiving Care at Sonar Bangla Foundation Dialysis Centers in Bangladesh: A Cross-Sectional Pilot Study
Tamanna M. Noyon,¹ Mahmood Hussain,^{1,2} Imtiaz M. Islam,^{1,3} Akm Monoarul Islam,^{1,4} Abu hena M. Kamal.¹ ¹Sonar Bangla Foundation, Santa Clara, CA; ²Marketing, San Francisco State Univ, San Francisco, CA; ³Nephrology, Good Samaritan Specialists, Kearney, NE; ⁴Nephrology, Rajshahi Medical College & Hospital, Rajshahi, Bangladesh.

Background: This study constitutes an exploratory investigation to understand the socio-demographic status of patients receiving care at the nine dialysis centers operated by Sonar Bangla Foundation (SBF) in Bangladesh. SBF is a leading non-profit organization, exclusively dedicated to the care of patients suffering from End-Stage Kidney Disease (ESKD). Although ESKD is very common, there is little to no data addressing prevalence of ESKD in Bangladesh. Without understanding its prevalence and the socio-demographic status of patients, little can be done to increase effectiveness and quantity of dialysis centers throughout Bangladesh. This study was launched in April 2015 and will continue throughout the dialysis centers' operations.

Methods: A one-time survey is being conducted to obtain clinical and demographical information on all existing and new patients at SBF centers.

Results: Currently, the study reveals a large gender disparity amongst dialysis recipients, 1 out of 4 patients is female (n=101). The average age of male patients is 44.7 years (SD ±12.7), while the average age of female patients is 45.3 years (SD ±14.2). Furthermore, patients from at least 20 different districts receive dialysis at the centers. The study also finds a significant positive correlation between education level and the frequency of dialysis received.

Conclusions: Data collected throughout this study will be incorporated into an expanding database, first of its kind in Bangladesh. ESKD is a devastating disease that forces patients to become dependent on a machine. By understanding the education level, financial status, distance traveled and other factors in relation to the frequency of dialysis received, services provided by SBF centers could be greatly improved. The study aims to change the quality of kidney care in Bangladesh.

PUB155

Clinical and Pathological Features of Idiopathic Membranous Nephropathy in Young Adults
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Background: Membranous nephropathy (MN) is a common pathological types in elderly nephrotic syndrome (NS) patients. Few researches focus on the young idiopathic MN population.

Methods: 583 patients hospitalized between Jan 2009 and Dec 2014 in our department, with biopsy-proved MN eliminating secondary causes, are enrolled. All patients were divided into 3 groups: 150 patients (25.1%) in young adults group (≤44 yrs), 202 (34.7%) in middle-aged group (45-59 yrs) and 231 (39.6%) in elderly group (≥60 yrs). We collected and compared their clinical and pathological data as well as therapy regimes.

Results: 310 male and 273 female enrolled. The young adults group had a lower rate of NS (P=0.022), higher serum albumin (P<0.01), estimated-GFR (P<0.01) and hemoglobin level (P<0.01), and lower fast blood glucose level (P<0.01).

	young adults group (n=150)	middle-aged group (n=202)	elderly group (n=231)	P value
proteinuria(g/24h)	4.7±3.8	4.6±3.9	5.1±3.4	0.271
serum albumin(g/L)	23.8±7.8	23.9±6.9	21.2±6.0	<0.01
nephrotic syndrome	73	105	143	0.022
fast blood glucose (mmol/L)	4.5±0.9	4.8±0.9	4.9±1.1	<0.01
serum creatinine(μmol/L)	64.2±175	71.0±24.8	85.2±40.5	<0.01
eGFR(ml/min/1.73m ²)	124.4±31.2	102.2±29.3	83.8±25.3	<0.01
hemoglobin(g/L)	135.4±18.1	132.8±18.1	123.2±17.4	<0.01

Table 1. Clinical features in three groups

There's no significant difference in the disease staging or immunofluorescences staining. However, the young adult patients had fewer mesangial, interstitial, tubular and arteriole lesions, and fewer inflammatory cells infiltration as well (P<0.01). For the therapy, the number of ACEI/ARB regime applied in the three groups was 72/95/75, while corticoid associated with immunosuppressive agents regime was 66/92/140 (P<0.01).

Conclusions: About a quarter of all IMN patients are young adults. They had fewer cardiovascular risk factors, higher serum albumin level and better renal function. Their pathological lesions were milder. ACEI/ARB regime is more widely applied in young adults patients.

PUB156

Effect of Glycemic Control on Estimated Glomerular Filtration Rate by Cystatin C
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Background: Cystatin C has been proposed as an alternative marker for estimating glomerular filtration rate (GFR). But, some factors other than GFR affect the accuracy of estimated GFR (eGFR). Some studies raised a concern that poor glycemic control may cause inaccuracy of estimation of GFR. We studied the effect of glycemic control on eGFR based on serum cystatin C (eGFRcys).

Methods: GFR was measured by inulin clearance (Cin). Estimated GFRs were calculated by CKD-EPI equation (CKD-EPI) and Japanese GFR equation (J-Eq) based on standardized cystatin C. Glycemic control was evaluated by serum glycated albumin (GA). Three hundred and forty five Subjects with normal GA (12.4-16.3%) and 126 subjects with high GA (>16.3%) were included. Effects of age, gender, BMI, GA and serum albumin on eGFRcys / Cin ratio was analyzed by multiple regression analysis.

Results: Cin, eGFRcys(J-Eq) and eGFRcys (CKD-EPI) in normal GA were 57.9±34.0, 56.1±31.7 and 57.9±33.9 ml/min/1.73m², respectively. Cin, eGFR(J-Eq) and eGFR (CKD-EPI) in high GA were 36.2±28.9, 36.71±27.5 and 36.7±28.5 ml/min/1.73m², respectively. There was no significant difference among Cin, eGFRcys (J-Eq) and eGFRcys (CKD-EPI) in both subjects. Slopes (95%CI) of the regression lines with zero intercepts in subjects

with high GA were 0.989 (0.944-1.033) in J-Eq and 0.965 (0.922-1.009) in CKD-EPI. The slopes were not significantly different from 1.0, suggesting that eGFRcys performed well in subjects with high GA. Multiple regression analysis showed that age, gender, BMI, GA and serum albumin were not significant factors affecting both eGFRcys(CKD-EPI) /Cin and eGFRcys(J-Eq) /Cin.

Conclusions: Estimated GFR based on cystatin C performed well in subjects with high GA.

Funding: Government Support - Non-U.S.

PUB157

Renal Hyperfiltration and Outcome in HIV-Infected Subjects Gianni Cappelli,¹ Elisabetta Ascione,¹ Giovanni Guaraldi,² Andrea Malagoli,² Elisabetta Rubbiani,¹ Antonio Bellasi.³ ¹Univ Hospital of Modena, Nephrology Dialysis and Renal Transplantation Unit, Modena, Italy; ²Univ Hospital of Modena, Metabolic Clinic, Infectious and Tropical Diseases Unit, Modena, Italy; ³Azienda Ospedaliera S. Anna, Como; Dept of Health Sciences, Univ of Milan, Nephrology and Dialysis Unit, Como, Italy.

Background: Although highly active antiretroviral therapy (HAART) improves life expectancy of HIV-infected subjects, it is also associated with numerous comorbidities. Evidence suggests that renal hyperfiltration (RHF) is associated with various lifestyles, clinical conditions and portends poor prognosis in the general population. We sought at determining prevalence of RHF and its associations with traditional and HIV-related risk factors as well as all-cause mortality in a large cohort of HIV-infected subjects.

Methods: Retrospective study of 3875 HIV-infected patients attending at the "Modena Metabolic HIV Clinic". The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was used to estimate glomerular filtration rate (eGFR). Linear regression was used to model eGFR against age and sex. RHF was defined as eGFR with residuals above the 95th percentile. Anova, Chi-square, logist regression and survival analyses were used to identify factors and the risks associated with RHF.

Results: Overall, we investigated middle-age (44.5±7.5 years) men and women (male 65.1%) with preserved renal function (eGFR 94.5±17.1 ml/min/1.73 m²). RHF was inversely associated with age (Odds Ratio 0.93), hemoglobin (OR 0.8), WBCs (OR 0.9) and positively associated with HIV-infection (OR 1.07). Of interest, no association with HAART was noted. Over mean follow-up of 7 years, 75 persons died. RHF was associated with all-cause mortality independently of potential confounders (Hazard ratio: 4.17, 95%CI: 1.81 - 9.6; p<0.001).

Conclusions: RHF is influenced by HIV infection duration independently of established factors and is related with the risk of all-cause of death. Future efforts are needed to clarify what are the mechanisms that link RHF with poor prognosis and if RHF modulation improves survival in HIV-infected subjects.

PUB158

Bioelectrical Impedance Analysis as a Screening Tool for Chronic Kidney Disease Anita Saxena, Amit Gupta. Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.

Background: Chronic Kidney Disease (CKD) has a latent period during which the disease is present but asymptomatic. With increasing incidence of hypertension and diabetes, incidence and prevalence of CKD is on increase. Bioelectric impedance analysis (BIA) a noninvasive method for estimation of body composition in clinical setting but it has not been used for CKD screening. Purpose: To evaluate applicability of BIA as a screening tool for presence of kidney disease in general population with creatinine clearance and glomerular filtration rate (GFR).

Methods: A pilot-cross-sectional CKD screening study on randomly selected 52 subjects from general population. Maltron BIOSCAN analyzer 915/916 was validated with Hume et al's equation for estimation of total body water. BIA derived GFR was validated with ^{99m}Tc-DTPA nuclear scan derived GFR, a study done on voluntary healthy kidney donors.

Results: There was no significant difference between total body water estimated with BIA and Hume et al's equation and BIA derived GFR and DTPA nuclear scan GFR. Mean serum creatinine for males was 0.94 ± 0.14mg% and 0.91 ± 0.84mg% for females. BIA derived creatinine clearance was 97.39 ± 28.98 in males and 107.60 ± 34.03 in females, GFR was 74.1 ± 25.98 ml/min/1.73 m² in males and 65.17 ± 21.14 ml/min/1.73 m² in females. Based on GFR subjects were classified into CKD. Out of 52 subjects 8 were in CKD stage 1 (15.5%), 23 (44.2%) were in CKD stage 2, 18 (34.6%) were in CKD stage 3, 1 (1.9%/1.9%) each in CKD stage 4 and CKD stage 5 respectively. Incidentally, 13.5% were diabetic, and 65.8% were hypertensive. Mean blood pressure was 133.99 ± 40.89/82.76 ± 27.79 mmHG in males and 132.10 ± 16.20/ 83.46 ± 7.85 mmHG in females. Based on American Heart Association classification for hypertension, 19 (36%) patients had normal blood pressure, 8 (15.5%) were in prehypertensive stage, 16 (30.7%) patients were in hypertension stage 1, 6 (11.5%) were in hypertension stage 2 and 2 had crisis hypertension.

Conclusions: Population-based CKD screening programs can identify people with renal injury for early intervention. BIA can be used for screening CKD in general population. It can also be a routine test as ^{99m}Tc-DTPA scan for estimation of GFR.

PUB159

Design and Implementation of a Chronic Kidney Disease Prevalence Study in Rivas, Nicaragua Kailey Minnings,¹ Martha Mosco,² Madeline M. Fiore,³ Eric S. Kerns,⁴ Juan Jose Amador,⁵ Rulan S. Parekh,⁶ Louis D. Fiore.⁵ ¹Faculty of Medicine, Univ of Toronto, Toronto, ON, Canada; ²Lowering Poverty and Disease, Boston, MA; ³Tulane Univ, New Orleans, LA; ⁴Warren Alpert Medical School, Brown Univ, Providence, RI; ⁵School of Public Health, Boston Univ, Boston, MA; ⁶Hospital for Sick Children, Toronto, ON, Canada.

Background: High rates of chronic kidney disease of unknown etiology (CKDu) have been noted in certain populations along the Pacific coast of Central America. CKDu is unlike traditional CKD in that the usual underlying risk factors are not present. CKDu in Nicaragua has been noted to affect mainly sugarcane workers although there is a paucity of data for the general population.

Methods: A population based cross sectional study using a random sampling of 32 communities was carried out in the department of Rivas in Nicaragua. Visits were conducted in Spanish in 2012 for screening and in 2014 for repeat evaluations. Participants were consented and completed a baseline questionnaire. Serum creatinine was initially screened using a finger stick creatinine measurement device. Repeat measurements to confirm CKD were performed centrally at the Centro Nacional de Diagnostico y Referencia in Managua using the Cobas Integra Jaffe Generation 2 assay, which has been standardized to the IDMS method.

Results: The study sample consisted of 1240 individuals representing 75% of adults living in the 533 homes visited. The refusal rate was 9.3%. The median age was 36.4 years, 57% were female, 6.6% reported DM, and 27% reported HTN. The study cohort is slightly enriched for women, while young people are slightly underrepresented when compared to census data. Repeat measurement was done in 320 with elevated creatinine to confirm CKD over 2 years. The re-contact rate was 85%.

Conclusions: This cross sectional study population is representative of the general population of the department of Rivas in Nicaragua. Establishment of this study population will allow investigators to determine the prevalence of CKD in a random selection of the general population in both urban and rural areas of Nicaragua not previously studied.

Funding: Private Foundation Support

PUB160

Validation of the Lund Model Combining Simultaneous Cystatin C and Creatinine-Based eGFR Emil Den bakker, Arend Bokenkamp. Pediatric Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

Background: Estimated GFR (eGFR) based on serum creatinine (crea) and/or cystatin C (cys) is used to monitor GFR. Based on known limitations of either marker (muscle wasting for crea, corticosteroids for cys) Grubb et al have proposed the "Lund model" to identify such patients by calculating the difference between crea and cys-based eGFR (Scand J Clin Lab Invest 70 (2010): 65-70). If the difference is below a certain cut-off, the mean of eGFRcrea and eGFRcys is used. Otherwise a choice is made for one or the other as a more accurate estimate based on patient history. The aim of this study was to test the "Lund model" using eGFR equations from the CKiD study (Kidney Int 82 (2012): 445-53).

Methods: Retrospective analysis of 449 single injection inulin clearance (mGFR) studies, in which serum crea, cys and urea had been measured simultaneously. Calculation of eGFR using crea (CKiD1), cys (CKiD2) or crea+cys+urea (CKiD3) as well as the average of CKiD1 and CKiD2 (avCKiD1-2). For the Lund approach, the relative difference (ΔCKiD1-2) between CKiD1 and CKiD2 was calculated as percentage of avCKiD1-2 and categorized as >40%, 30-40%, 20-30%. If ΔCKiD1-2 was > 40%, a choice was made for CKiD1 (corticosteroid) or CKiD2 (neuromuscular disease, wasting, malignancy). The performance of the different approaches was studied using bias (mGFR minus eGFR in ml/min/1.73m²) and accuracy (% of measurements within ±30% of mGFR).

Results: CKiD1, CKiD2 and CKiD3 had a bias of 4.6, 14.2 and 2.8 and an accuracy of 81.7, 80.6 and 90.4, respectively. avCKiD1-2 had a bias of 9.4 and an accuracy of 88.9. ΔCKiD1-2 was >40% in 11.4%, 30-40% in 18.9% and 20-30% in 33.9% of the studies. The Lund model was applied in 51 studies with ΔCKiD1-2 >40%. In 42/51 studies, a choice could be made based on history (CKiD1 n=16, CKiD2 n=26). This resulted in a bias of 10.5 and an accuracy of 86.4.

Conclusions: The various CKiD equations performed comparably to the original publication. The arithmetic mean between creatinine-based and cystatin C-based eGFR yielded similar results to the complex CKiD3 equation while the Lund model did not improve the diagnostic performance. This may be due to the higher bias of CKiD2.

PUB161

Evaluation of Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI), Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) Equations to Assess Glomerular Filtration Rate (GFR) in Kidney Cancer Patients Veronica T. Costa e Silva,¹ Celso Marialva,² George Augusto Monteiro Lins de Albuquerque,³ Renato Antunes Caires,¹ Giuliano Betoni Guglielmetti,³ Maurício Dener Cordeiro,³ Rafael Ferreira Coelho,³ Elerson Costalonga,¹ Eduardo J. D. de Sa Carneiro Filho,¹ Emmanuel A. Burdmann,¹ William C. Nahas.³ ¹*Cancer Inst of Sao Paulo, Univ of São Paulo School of Medicine, Sao Paulo, Brazil;* ²*Urology, Garcia de Orta Hospital, Lisboa, Portugal;* ³*Urology, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Equations used to estimate GFR were not validated in kidney cancer patients. The aim of this study was to assess the performance of CKD-EPI, abbreviated (a) MDRD and CG equation in these patients.

Methods: Prospective evaluation of 124 outpatients with kidney cancer admitted to treatment at São Paulo State Cancer Institute between September 2012 and February 2015. Estimated (e) GFR was calculated using CG, aMDRD and CKD-EPI equations and compared to ⁵¹Cr-EDTA radioisotopic (r) clearance. The bias was given as the mean difference between the eGFR and rGFR values and the precision as the SD of the differences. Accuracy was described as the number of eGFR studies within 10 and 30% of the rGFR values.

Results: Patients were 59.0 ± 10.3 years old, 50.2% were women. rGFR (ml/min/1.73 m²) was 78.7 ± 24.6 and eGFRs (ml/min/1.73 m²) using the CKD-EPI, aMDRD and CG (ml/min) equations were respectively 80.7 ± 22.1, 83.4 ± 25.3 and 87.8 ± 26.5. Equations bias is detailed on table 1.

Mean bias of differences

	CKD-EPI	aMDRD	CG
Mean Bias (mL/min)	2.0	4.7	9.1
SD	21.5	21.5	24.1
p	0.306	0.017	<0.001

The accuracy of eGFR equations within 10% of rGFR were 31.4%, 27.4% and 19.4% with CKD-EPI, aMDRD and CG, respectively. Within 30% of rGFR, the accuracy of eGFR equations were 75.8%, 78.2% and 68.5% with CKD-EPI, aMDRD and CG, respectively.

Conclusions: CKD-EPI equation showed smaller bias and satisfactory accuracy when compared with the GFR assessed by ⁵¹Cr-EDTA in this group of kidney cancer patients.

PUB162

Correlation Between Equation for Estimating Glomerular Filtration Rate : CKD -EPI, Cockcroft-Gault -CG- and MDRD in Colombia Carlos H. Mejia. *Nephrology, Cuenta de Alto Costo, Bogota, Cundimarca, Colombia.*

Background: The determination of the GFR has been recommended the calculation from different equation , mainly Cockcroft- Gault (CG) or the Modification of Diet and Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD -EPI); we have found differences of over and underestimation of renal function by these equation.

Methods: Between July 1 2013 and June 30 2014 3,055,568 patients diagnosed with hypertension, diabetes mellitus and chronic kidney disease of all members of the general social security system in health in Colombia were reported. The inclusion criteria for this analysis was older than 18 years. Quantitative variables were described by their mean and standard deviation and qualitative variables using frequency distribution. They were compared equation pairs of CG -MDRD4, CG-CKD-EPI and CKD-EPI-MDRD by calculating and plotting, prediction limits for differences between pairs and the values of the correlation coefficients Lin-matching.

Results: 1,348,214 patients were included, 832. 129 women (61.7%). The mean age was 64.3 years (standard deviation (SD) 13.2), 50% of patients are 60 - 74 yo. 94% had diagnosis of HTA and 26% had diagnosis of DM. The mean creatinine was 0.95 mg/dl for population. The correlation coefficient between interclass (ICC)CG and MDRD is 0.704 IC95%(0.703, 0.705) and limits of agreement of Bland and Altman from -31.65 to 43.83; ICC being CG and CKD-EPI is 0.728 CI 95% (0729-0730) and limits of agreement of Bland and Altman from -37.26 to 40.62 and the correlation coefficient being intraclass CKD-EPI and MDRD is 0.855 IC 95%(0.855, 0.856) and limits of agreement of Bland and Altman between -25.61 and 21.89.

Conclusions: General population studies have reported a good correlation comparison between MDRD and CKD -EPI, our results show a good correlation between them, rather than between CKD -EPI and CG .A higher GFR greater are the limits of agreement, both the overall analysis and analysis stages, similar findings have been observed in other reports. Despite some limitations MDRD4 and CKD -EPI remain the most comparable and used to estimate kidney function.

PUB163

Family Caregivers in Chronic Kidney Disease: A Missed Opportunity to Improve Overall Care Jason Christopher George,¹ Andrea Lynn Berger,² Christina Yule,³ Jamie Alton Green.^{2,4} ¹*Dept of Medicine, Geisinger Medical Center, Danville, PA;* ²*Center for Health Research, Geisinger Medical Center, Danville, PA;* ³*Center for Clinical Innovation, Geisinger Medical Center, Danville, PA;* ⁴*Dept of Nephrology, Geisinger Medical Center, Danville, PA.*

Background: Many patients with chronic illness rely on the assistance of loved ones to adequately manage their disease. While there is increased recognition of the role of family caregivers in end-stage renal disease, little attention has been given to this role among patients with chronic kidney disease (CKD) not on dialysis. The aim of this study was to assess CKD patients' degree of dependency on non-professional caregivers for their self-management needs.

Methods: We conducted a survey-based study of 208 patients with non-dialysis dependent CKD stages 3-5 to identify 1) whether they receive help from an informal caregiver to perform health-related activities and 2) the nature of this relationship. We excluded patients residing in a nursing facility as well as those with an assigned formal caregiver, since their self-management needs are different.

Results: Mean age of participants was 72, 57% were male, 98% were white, and 53% had a high school or lower level of education. Overall, 65% (133/205) of patients reported receiving help from another individual with at least one health-related task. Help with activities included medical decision making (51%), medication management (32%), scheduling medical appointments (30%), attending office visits (43%), understanding medical providers (23%), and activities of daily living (13%). The majority stated that the main person who helped them was their spouse (70%) or adult child (16%) vs. other family members (6%). Nearly half (46%) reported that another individual had access to their electronic health information through the online health portal to assist with their care.

Conclusions: A significant number of independently functioning CKD patients rely on the help of family members to navigate their care. Efforts are needed to acknowledge and support these informal caregivers in the medical management of complex patients with kidney disease in order to provide optimal care.

PUB164

Impacts of Chronic Kidney Disease on Other Non-Communicable Chronic Diseases – The Burden in the Health System of China Luxia Zhang, Jinwei Wang, Ming Hui Zhao. *Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.*

Background: The spread of non-communicable diseases (NCDs) presents a global crisis, and accumulating evidence based on individual disease reveals that major NCDs including heart disease and stroke have a worse prognosis in the presence of chronic kidney disease (CKD). However, there is neither large-scale study quantitatively evaluating the burden of CKD on various NCDs, nor study comparing the burden of CKD with other NCDs, especially among low- and middle-income countries like China.

Methods: A national in-patient database involving 19.5 million patient-records was used. Diagnoses of CKD and other major NCDs, including hypertension, coronary heart disease, stroke, chronic obstructive pulmonary diseases, and cancer, were extracted from International Classification of Diseases-10 codes of the discharge diagnoses. The effect of CKD on costs, length-of-stay, and in-hospital mortality were analyzed for each NCD. Then the effect of CKD on those outcomes was compared with other major NCDs.

Results: For each NCD, the presence of CKD was associated with increased length-of-stay and in-hospital mortality. And the costs were also increased by 0.1-20.3%, except for coronary heart disease and diabetes. Among those NCDs, CKD was associated with the highest length-of-stay, and with in-hospital mortality only lower than that of cancer.

Conclusions: Using database with large sample size and broad geographic coverage in China, we found that the presence of CKD was associated with substantial increased healthcare resources utilization and increased risk of in-hospital mortality.

Funding: Government Support - Non-U.S.

PUB165

Patient Empowerment in a Multi-Disciplinary Chronic Kidney Disease (CKD) Clinic Therese T. Adamowski, Jonathan H. Segal, Julie A. Wright Nunes. *Internal Medicine, Univ of Michigan, Ann Arbor, MI.*

Background: Existing research shows economic and health gains associated with multi-disciplinary CKD care, but there is little data examining associations with patient-centric measures. We collected patient-centric measures on perceptions related to care in a multi-disciplinary CKD clinic.

Methods: Our multi-disciplinary CKD clinic includes a pharmacist, physician assistant, social worker, dietician and RN educator-with oversight by a medical doctor. Patients see each provider during visits. Most patients have an eGFR ≤ 40 ml/min/1.73m². As part of assessing quality patients were asked to: 1. Report their level of comfort asking questions (“please circle the number that indicates how comfortable you feel asking your doctor questions about kidney disease: 1=not at all comfortable to 6=very comfortable”), and 2. Rate perceived confidence and empowerment in kidney care (ten questions with responses, 1 =not confident to 5 =confident, averaged as a summary measure of confidence / empowerment).

Results: Data were available on 51 patients. The mean (SD) age was 62 (15) years. 53% were male, 65% Caucasian, and 33% African American. Patients reported being comfortable asking their doctor questions, mean (SD) 5.5 (0.97). The mean (SD) of the confidence / empowerment measure was 4.3 (0.74). In univariate analysis, higher ratings

of comfort asking questions was associated with higher confidence / empowerment, β 0.23 CI (0.04, 0.45); $p=0.02$. Multivariate analysis adjusted for age, sex, race and comfort asking questions revealed comfort asking questions was independently associated with higher confidence / empowerment, β 0.31 (0.09, 0.53); $p=0.007$. Our 10-item confidence / empowerment measure showed excellent internal reliability (Cronbach alpha =0.89).

Conclusions: Patients in a multi-disciplinary CKD clinic reported being comfortable asking their doctor questions and rated confidence and empowerment as high. Comfort asking the doctor questions was positively associated with patient confidence and empowerment in care. More work is needed to compare patient-centric quality measures across care models and assess changes over time.

PUB166

Factors Affect Use of Healthcare Services Among Different Ethnicities Enchi K. Chang,¹ Li-Li Hsiao,² ¹Harvard College, Cambridge, MA; ²Renal, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: Use of healthcare services by medically underserved minority populations varies by ethnicity and cultural factors. Healthcare providers may address ethnicity-specific barriers to healthcare service usage to decrease disparities in healthcare use. Through free community health screenings provided by the Kidney Disease Screening and Awareness Program (KDSAP), we seek to elucidate ethnicity-specific differences and sociocultural barriers to healthcare service use.

Methods: A questionnaire available in English, Chinese, and Spanish was administered to KDSAP participants in Massachusetts, New Jersey, and Toronto from 2012 to 2014. Participants were asked to provide their ethnicity, health insurance, primary care physician, and difficulties and alternatives to receiving care.

Results: 330 Asian, 190 African-American, 82 Hispanic, and 50 Caucasian participants were surveyed. Participants lacking health insurance comprised 29.1% of Asian and 45.1% of Hispanic participants, compared with 17.3% of African-American and 8% of Caucasian participants. 25% of Asian and Hispanic participants reported language barriers with their healthcare professional, compared with 6% of African-American and Caucasian respondents. 50% of Asian and Hispanic participants were prevented from seeking care due to lack of insurance, and as an alternative, 51% of Asian participants would ignore the problem. African American participants without insurance primarily reported seeking emergency care (51%), and Hispanic participants reported seeking free clinics (40.5%) or emergency care (37.8%).

Conclusions: Culture and ethnicity-specific barriers to receiving care affect use of healthcare resources for medically underserved populations. Asian and Hispanic populations experience greater difficulty accessing healthcare services and are less likely to have health insurance compared to African-American and Caucasian populations, suggestive of linguistic and sociocultural barriers to healthcare for immigrant populations. Healthcare services targeting medically underserved populations must address ethnicity-specific sociocultural differences to reduce healthcare disparities between ethnic populations.

Funding: Private Foundation Support

PUB167

Trends in Access to Care in Adults with Kidney Disease, United States 2002-2011 Mukoso N. Ozieh,¹ Kinfe Gebreegziabher Bishu,² Rebekah J. Walker,² Leonard Egede,² ¹Nephrology, MUSC; ²Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: Access to healthcare is essential in other to attain health equity in the US. Studies on access to healthcare in kidney disease (KD) are scant and there are no studies on national trends in access to healthcare in people with KD. This study aims to evaluate trends in access to healthcare, prescription medication and factors associated with access to healthcare in people with KD.

Methods: Data on 4,399 adults with KD aged ≥ 18 from the Medical Expenditure Panel Survey were analyzed. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157-acute/unspecified renal failure; 158-chronic renal failure; 160-calculus and; 161-other diseases of kidney and ureters. Access to healthcare was defined as having a usual provider, ability to get necessary medical care and no delay in getting medical care. Access to prescription medications was defined as ability to get necessary prescription and no delay in getting prescription. We used unadjusted and adjusted logistic regression to examine factors associated with access to care overtime. Covariates included demographics and comorbidities.

Results: Of the 4,399 adults with KD, 81% and 97% reported having access to medical care and prescription medications respectively. Access to medical care was stable while access to prescription improved over time in people with KD. Factors associated with increased access to medical care were age ≥ 45 , gender, high income and comorbidity-hypertension while marital status, being uninsured, residential region and comorbidity-joint pain were associated with decreased access to medical care. Factors associated with increased access to prescription were Hispanic race, age ≥ 65 and college degree while being uninsured, residential region and comorbidities - diabetes and joint pain were associated with decreased access to prescription medication.

Conclusions: Access to medical care has remained stable and access to prescription medication in people with KD has improved over time. Further studies on access to healthcare in people with KD compared to the overall US population are needed.

PUB168

Patient-Centered Care in United States Adults with Kidney Disease Mukoso N. Ozieh,¹ Kinfe Gebreegziabher Bishu,² Rebekah J. Walker,² Leonard Egede,² ¹Nephrology, MUSC; ²Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: Patient-centered care is a quality of personal, professional, and organizational relationships. There no studies on factors associated with patient-centered care in patients with kidney disease (KD). This study examines trends in and factors associated with patient-centered care (PCC) in people with KD.

Methods: Data on 3,868 adults with KD aged ≥ 18 from the Medical Expenditure Panel Survey (MEPS) Household Component were analyzed. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute and unspecified renal failure; 158 - chronic renal failure; 160 - calculus or urinary tract and; 161 - other diseases of kidney and ureters. Patient-centered care was ascertained if the usual care provider asked about prescription medications and treatments other doctors may give them; showed respect for medical, traditional and alternative treatments that the person is happy with; asked the person to help make decisions between a choice of treatments; presented and explained all options to the person; and spoke the persons language or provided translator services if person is uncomfortable speaking in English. We used unadjusted and adjusted poisson regression to examine the association of patient-centered care overtime. Covariates included demographics and comorbidities.

Results: Of the 3,868 adults with KD, 3%, 7%, 22%, 63% and 4% reported a positive response to 1, 2, 3, 4, and 5 out of 5 questions on patient-centered care respectively. Patient-centered care was significantly reported in 2010/2011. Hispanic race was significantly associated with increased while residence in the west was associated with decreased patient-centered care. Compared to 2002/2003, year 2004/2005 and 2010/2011 were significantly associated with increased patient-centered care in the poisson regression analysis.

Conclusions: Patient-centered care in people with kidney disease has improved in recent years. Prospective studies examining the impact of patient-centered care on kidney disease outcomes especially end stage renal disease is imperative.

PUB169

Hypertension and Correlating Factors in a Minority-Rich Population Andrew A. Lin,¹ Jennie Kuo,² Li-Li Hsiao,² ¹Harvard College, Cambridge, MA; ²Renal, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: Analysis of demographic variations in hypertension (HTN) in minority-specific populations presents a major opportunity for understanding the factors that influence chronic kidney disease (CKD). This study analyzes the influence of various factors in BP control in a minority-rich population.

Methods: Data from 417 participants from minority populations in the Boston area (38.4% Asian, 37.6% Black, 8.2% Hispanic, 10.8% White, and 5.0% other races) was sampled via Kidney Disease Screening and Awareness Program screenings from 2012-2014. Participants were assessed via questionnaire for awareness of their BP, healthcare/insurance, and an assessment of their own health as well as their race, gender, age, & education. Participants then had their systolic (SBP) & diastolic (DBP) blood pressure measured, which was in turn classified according to American Heart Association guidelines & analyzed via T-tests & one-way ANOVA.

Results: Of the 417 participants, 28.8% had normal BP, 47.2% were pre-HTN (130-140/80-90), 18.5% had stage I HTN (140-160/90-100), & 5.5% had stage II HTN (>160/100). Participants aware of their HTN had higher SBP ($p<0.0001$) & DBP ($p=0.007$) than those who self-reported no HTN. Men had significantly higher SBP & DBP than women ($p=0.002$, $p=0.0003$, respectively), & individuals with little/no education had higher SBP than those with college ($p=0.005$) or post-graduate degrees ($p<0.0001$). Younger age groups (below 30 years: mean BP 125/76) had significantly lower BP than older age groups (60-69+ years: mean BP 136/81); $p<0.0001$ & $p=0.037$ for SBP & DBP. Notably, no significant differences in SBP among ethnicities emerged.

Conclusions: Our results revealed that awareness of HTN status, gender, education level & age influence BP variations in minority-rich communities. Services tailored to these factors may help reduce HTN prevalence among minorities.

Funding: Private Foundation Support

PUB170

Veterans Affairs (VA) eKidneyClinic: A Freely-Available Online Tool to Help Close the Chronic Kidney Disease (CKD) Patient Education Gap Devasmita Choudhury,¹ R. Brooks Robey,² Rosemary M. Pries,³ Dorian R. Schatell,⁴ Susan T. Crowley,⁵ ¹Medicine, Salem Veterans Affairs Medical Center, Salem, VA; ²Medicine, White River Junction Veterans Affairs Medical Center, White River Junction, VT; ³Veterans Health Education & Information Program, Veterans Health Administration, Durham, NC; ⁴MEI INC., Madison, WI; ⁵Medicine, Veterans Affairs Connecticut Health Care System, West Haven, CT.

Background: Patient education remains an important tool in the management of CKD and end stage renal disease (ESRD)- diseases with significant patient and economic burden. Patient knowledge and understanding of CKD are dismal, particularly amongst highly-affected populations (e.g. African Americans). For Veterans with CKD, limited health literacy, and varied, fragmented presentation of patient education materials (PEMs) compound the gap in understanding CKD.

Methods: To address these deficiencies, VA developed a comprehensive web tutorial, VA eKidneyClinic (<http://ckd.vacloud.us>). This freely-available, Veteran-centered, virtual

PEM details at 5th grade reading level (using Flesch-Kincaid formula), basic disease process, nutritional, laboratory, social, pharmacy, and treatment aspects of all stages of CKD in written and graphical format, supplemented by video narrative vignettes. Pre- and post-tutorial questions engage, test, and reinforce understanding through action planning. Links to additional Internet resources allow for further knowledge acquisition.

Results: Despite the absence of a national marketing campaign, annual web traffic on VA health portals featuring eKidneyClinic has tripled from 5,374 (~15/d; 01 Apr 2013 to 31 Mar 2014) to 16,730 views (~46/d; 01 Apr 2014 to 31 Mar 2015) over the past 2 y.

Conclusions: VA eKidneyClinic provides a novel, patient-centered, readily accessible Internet resource to remedy knowledge gaps in Veteran CKD education. Use of VA online resources has progressively increased over the past 2 y. Better metrics of use and targeted research correlating use with clinical outcomes are needed to fully validate the utility of this education tool and its impact on organizational health literacy.

Funding: Veterans Administration Support

PUB171

Should All Patients with Diabetic Nephropathy Be Treated in a Joint Renal Diabetic Clinic? Jonathan P. Wong, Tara Lee, Tracy Maryan, Jocelyn Berdeprado, Suresh Mathavakkannan. *Lister Renal Unit, United Kingdom.*

Background: The natural history of diabetic nephropathy is variable. Some patients have rapidly declining kidney function and would benefit from close monitoring in a joint renal-diabetic clinic, however joint renal-diabetic clinics are not widely available in the UK health system. We studied outpatient attendance patterns, rate of eGFR decline and other clinical parameters in patients with diabetic nephropathy to determine potential need for development of a joint renal-diabetic clinic at our unit.

Methods: A cross-sectional survey of all patients with CKD and diabetes mellitus (DM) at our unit was performed. Demographic, diabetic clinic attendance and clinical parameters including HbA1c, BP, urine protein:creatinine ratio (uPCR) and eGFR for the previous 5 years were collected. Patients who had a rate of decline in eGFR²ml/min/1.73m² were defined as having progressive CKD.

Results: 630 CKD patients with DM attending CKD clinic at our trust were identified. 195/630 (31%) of patients had diabetic nephropathy. 54.6% (100/195) had progressive CKD, but only 37% (37/100) of these patients attended a diabetic clinic. Conversely, 45.4% did not have progressive CKD, potentially representing a group of patients who could be safely monitored by general physicians. Patients with progressive diabetic nephropathy were more proteinuric than those with stable CKD (161 vs 46mg/mmol, p=0.004) but did not significantly differ in terms of age, weight, glycemic control or BP. 9.2% (58/630) were lost to follow-up from nephrology services, 31% (18/58) of this subset of patients continued to attend the diabetic clinics and 69% (40/58) were lost to follow-up from both diabetic and renal services.

Conclusions: Not all patients with diabetic nephropathy develop progressive CKD. Identifying patients (e.g. low-level proteinuria) who could be safely monitored by general physicians may relieve pressure on CKD clinic and reduce hospital visits for patients. However, many patients with progressive CKD were not being monitored in a diabetic clinic, potentially missing out on specialist interventions. Development of a joint diabetic-renal clinic could streamline care and improve management for these patients.

Funding: Clinical Revenue Support

PUB172

Leveraging Predictive Modeling to Improve the Participant Identification Process for Transition to Dialysis Support Programs Meghan Martin Cockrell, Yanting Dong, Huyi Hines, Gilbert Haugh, Vipin Gopal, Roy Beveridge, Todd Prewitt. *Humana, Louisville, KY.*

Background: Evidence demonstrates that renal care management is beneficial to patients suffering from late-stage chronic kidney disease (CKD) and end-stage renal disease (ESRD), especially around the time of transition to dialysis. Integrated care management solutions provide assessment, education, and care coordination. Engagement in these programs improves health outcomes, including compliance with dialysis schedules and vascular access, and also reduces costs.

Methods: Traditionally, patients are identified for renal care management programs via a qualified estimated glomerular filtration rate (eGFR) lab value of <20mL/min/1.73 m². However, since eGFR is not always available, there may be a gap in identifying people who could benefit from this type of support. A predictive model (PM) was developed to identify candidates for a transition to dialysis program. The PM identifies individuals with CKD over the prior 12 months and determines their likelihood of starting dialysis within the subsequent 12 months. It is based on claims, demographics, and lab and consumer data. To assess the effectiveness of the PM, a random portion of individuals scored in the top 2% most likely to transition to dialysis were referred directly to the program for

Results: Thirteen percent of people referred by the PM ultimately transitioned to dialysis and all were invited into a renal care management program. Seventeen percent of the people identified by the PM and observed to see if they would be referred by the current standard process ultimately transitioned to dialysis, but 27% (n=68) were never identified for the renal care management program. Hence, the model is effective in identifying those that will not get identified via the standard referral process.

Conclusions: Application of advanced predictive modeling permitted identification of participants who may not have otherwise had the opportunity to benefit from renal care management.

PUB173

Does the Kidney “Age” with Time? Umbar Ghaffar, Page Casey Moore. *Nephrology, UAMS, Little Rock, AR.*

Background: Studies show that eGFR declines with advancing age but it is unclear if this is related to co-morbidities or aging per se. The objective was to study predictors of eGFR decline in elderly individuals with and without pre-existing CKD.

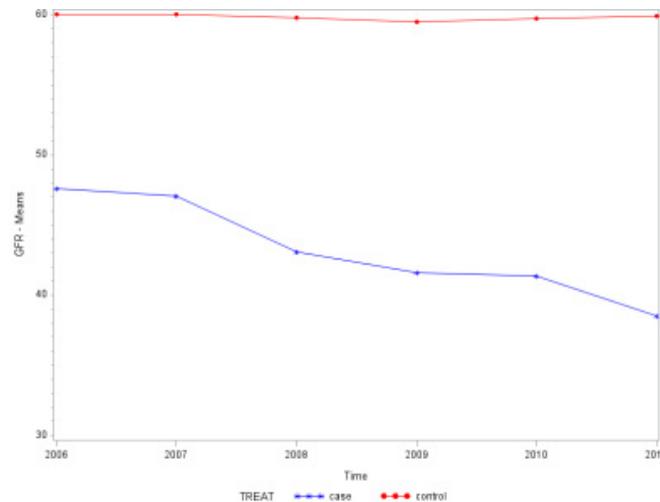
Methods: Chart review for patients >65 years of age with and without CKD at baseline was done over 5 years. Data regarding risk factors like proteinuria, medications, contrast use was obtained. Repeated measures models were used to test difference in GFR between CKD cases versus controls. Semi-partial correlations were used to determine factors with largest contribution to GFR decline.

Results: CKD cases were more likely to have DM, HTN and receiving drugs like diuretics and antibiotics. Age, proteinuria and IV contrast exposure were identified as the most significant predictors of eGFR decline. In the CKD group, rate of GFR decline was 1.7% to 10 % per year. In the group without preexisting CKD, GFR did not decline over 5 years.

	CKD cases		Controls ^a	
Year	eGFR means	% change in eGFR	eGFR means ^a	% change in eGFR
2006	53.166	-	72.481	-
2007	51.104	2006-2007 3.88%	72.543	2006-2007 -0.08%
2008	50.224	2007-2008 1.72%	67.368	2007-2008 7.13%
2009	47.449	2008-2009 5.43%	61.982	2008-2009 8.00%
2010	47.651	2009-2010 -0.32%	67.539	2009-2010 -8.97%
2011	42.846	2010-2011 10.08%	71.864	2010-2011 -6.4%
Net change in eGFR		2006-2011 19.41%		2006-2011 0.85%

Table 1. Adjusted rate of decline in GFR across time

^aLS means based on repeated measures model with the following independent variables: treatment, time, treatment*time, age, Sex, HTN, DM, AKI, AKI type, NSAIDs, contrast and proteinuria.
^bGFR values 60 or greater were reported as ≥60 in lab reports.



Conclusions: Results suggest that GFR decline may not be attributed to aging only. Each episode of AKI related to contrast or nephrotoxic drugs increases risk for CKD progression/GFR decline in elderly. Preexisting CKD is a strong predictor of GFR decline after adjustment for other co-morbidities.

PUB174

Oxidative Stress: Dual Pathway Induction in CKD Pathogenesis Grazia Maria Virzi, Alessandra Brocca, Massimo de Cal, Claudio Ronco. *Nephrology Dept-IRRI, San Bortolo Hospital, Vicenza, Italy.*

Background: Oxidative stress is defined as the imbalance between excess formation and insufficient removal of highly reactive molecules (Reactive Oxygen Species-ROS and Reactive Nitrogen Species-RNS) that attack DNA, protein and lipids, either denaturing or altering their structure. The variations and the correlation of inflammation and oxidative stress in CKD have not been thoroughly understood. In this study, we examined the putative role of ROS and RNS in the pathogenesis of CKD and the interaction with inflammation.

Methods: 25 patients with CKD(5 for each stage) and 18 healthy subjects (CTR) were included in the study. Determinations for IL6, Myeloperoxidase (MPO), Nitric Oxide (NO) and Endogenous Peroxidase Activity (EPA) were performed by ELISA. A p-value of <0.05 was considered statistically significant.

Results: CKD patients displayed significant augmentation in circulating ROS and RNS, as well as expression of inflammatory cytokines, as IL6 (all, p<0.01).

	CKD	CTR
EPA U/L	1963.6 (1081.0-2728.6)	5,9 (2.6-9.9)
MPO pg/mL	5987.0 (3989.6-11469.8)	10.2 (6.0-19.3)
NO μ M	710.1 (575.6-781.6)	13.4 (12.8-14.7)
IL6 pg/ml	59.8 (45.6-104.3)	5.9 (3.4-7.6)

There is a positive correlation between IL6 and all oxidative stress markers and an inversely correlation with eGFR (all, p<0.05). We divided CKD patients in CKD1-2 (n=10) and CKD3-5 (n=15): a significant higher level of oxidative stress was observed in CKD3-5 (p=0.008).

Conclusions: CKD is characterized by ROS and RNS disequilibrium and inflammation that promote additional damage to the kidney and to distal tissues with development and progression of concomitant diseases. This pilot study demonstrates the significantly heightened presence of dual oxidative stress pathway induction in CKD patients that increase with the progression of CKD: each stage of CKD could be characterized by differing levels of ROS/RNS disequilibrium. Our findings indicate that oxidative stress is a potential therapeutic target, as it promotes inflammation by ROS/RNS-linked pathogenesis. Future research should focus on interventions that aim to reduce oxidative stress and inflammation in patients with various stages of CKD and slow the progression of CKD during its early stages.

PUB175

Comparative Biomarker Analysis Reveals Serum and Urine sTNFR1 Correlate with eGFR and Albuminuria in Man Diana L. Donnelly-Roberts, Marian T. Namovic, Mark T. Houser, Murali Gopalakrishnan, Timothy A. Esbenshade. *Renal Discovery, Abbvie, North Chicago, IL.*

Background: It has been demonstrated that soluble tumor necrosis factor receptors (sTNFR1 & sTNFR2) are elevated in serum of patient cohorts with various renal disease etiologies with a strong association to early renal decline with or without proteinuria. The current study was designed to gain further insight into the relationship of renal function to sTNFR1 and other biomarkers (BMs) from a recently completed clinical study in high-risk subjects undergoing non-cardiac surgery. A subset of baseline serum and urine samples from patients with and without CKD (mean age of 70, 64% male, mean eGFR of 58 ml/min/1.73 m², and mean total urinary protein concentration 70 g/l) were evaluated to assess sTNFR1 and other select BMs reflective of progression of DN, CV risk, inflammation, fibrosis or renal injury.

Methods: Samples were selected based on medical history (DM, DN, other CKD, or no renal disease) and stratified for analysis based on eGFR values. All samples examined were from baseline/pre-dose collections prior to drug administration or surgery and analyzed in a blinded manner.

Results: In serum, several BMs correlated with eGFR with sTNFR1 (P<0.0001) and uromodulin (P=0.0004) being significant but moderate for FGF-23 (P<0.01), and ADMA (P<0.01). In urine, results revealed that several BMs correlated with eGFR with a strong significance for sTNFR1 (P<0.001) as well as for complement C9 (P=0.011) and iC3b (P=0.013). Significant correlations were also observed for qualified biomarkers such as NGAL (P<0.01), albumin (P<0.01), and cystatin C (P=0.05). sTNFR1 in urine also strongly correlated with albuminuria (P=0.0002) and UACR (P<0.0001).

Conclusions: Our studies demonstrate that sTNFR1 correlates with renal functional decline across a wide eGFR range (22 to 116 ml/min/1.73 m²) regardless of renal disease, which was assessed in both serum and urine. Limitations of this preliminary study are small sample size and use of static eGFR values. Additional correlation analyses in longitudinal cohorts can shed further light into the relationships of sTNFR1 and other BMs to CKD.

Funding: Pharmaceutical Company Support - Abbvie

PUB176

The Association of Plasma Uric Acid with Renal Vascular Lesions and Interstitial Fibrosis in Biopsy-Confirmed Kidney Disease Anand Srivastava,¹ Venkata Sabbiseti,¹ Isaac Ely Stillman,³ Helmut G. Rennke,² Sushrut S. Waikar.¹ *¹Renal Div, Brigham & Women's Hospital, Boston, MA; ²Dept of Pathology, Brigham & Women's Hospital, Boston, MA; ³Dept of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Elevations in plasma uric acid (PUA) have been hypothesized to play a pathogenic role in the development of chronic kidney disease (CKD) through multiple mechanisms, including mitochondrial dysfunction, oxidative stress, endothelial dysfunction, vascular smooth muscle proliferation, and intra-renal inflammation.

Methods: We measured PUA in plasma samples obtained from 272 patients on the day of native kidney biopsy at three tertiary care hospitals in Boston, MA. We compared PUA against measures of kidney function and pathology, including estimated glomerular filtration rate (eGFR) and adjudicated semi-quantitated measures of kidney pathology

using Spearman correlation coefficients. Arterial and arteriolar sclerosis/hyalinosis were classified as none (1), mild (2), moderate (3), or severe (4). Fibrosis was classified as 0% (1), 1-10% (2), 11-25% (3), 26-50% (4), and > 50% (5) of cortical volume.

Results: The primary indications for kidney biopsy were proteinuria in 61%, hematuria in 33%, abnormal eGFR in 35%, and nephrotic syndrome in 14% (sum exceeds 100% due to multiple indications). Mean age was 51.2 ± 16.0 yrs, 53% were women, 18% were black, and median eGFR was 50 (IQR, 30-83) ml/min/1.73m². Median PUA was 6.3 [IQR 5.1-7.5] mg/dl, and was inversely correlated with eGFR (r=-0.43) and positively correlated with arterial sclerosis (r=0.21), arteriolar hyalinosis (r=0.23), and interstitial fibrosis (r=0.28) (P for all < 0.001). The associations between PUA and kidney pathology were attenuated and no longer statistically significant after adjustment for eGFR. Findings were generally consistent in subgroup analyses of those with diabetes, glomerulonephritis, vascular disease, and tubulointerstitial disease.

Conclusions: We found no independent associations between PUA and semi-quantitated measures of kidney pathology. The cross-sectional associations of PUA with renal vascular lesions and interstitial fibrosis appear to be confounded by eGFR.

Funding: NIDDK Support

PUB177

Association of Plasma Sphingomyelins and Ceramides with Chronic Kidney Disease and Glomerular Filtration Rate Maria Lourdes Gonzalez Suarez,¹ Vesna D. Garovic,¹ Norman James Haughey,^{2,3} Veera Venkata Ratnam Bandaru,² Susan Resnick,⁴ Luigi Ferrucci,⁴ Michelle M. Mielke.⁵ *¹Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Dept of Neurology, Johns Hopkins Univ School of Medicine, Baltimore, MD; ³Dept of Psychiatry, Johns Hopkins Univ School of Medicine, Baltimore, MD; ⁴Intramural Research Program, NIA/NIH, Baltimore, MD; ⁵Dept of Health Sciences Research, Mayo Clinic, Rochester, MN.*

Background: Sphingolipids are a class of bioactive lipids linked to insulin resistance and diabetes. Ceramides have been implicated in acute renal failure and diabetic nephropathy. We cross-sectionally examined the associations of plasma ceramides and sphingomyelins (SM) with glomerular filtration rate (GFR) and Chronic Kidney Disease (CKD).

Methods: Baltimore Longitudinal Study of Aging participants (N=486) with plasma ceramides, SM and GFR were included (median age 63, 58% men); 23 had CKD defined as GFR<60 ml/min. Ceramides and SM were quantitatively measured using a HPLC-coupled electrospray ionization tandem mass spectrometer. Logistic regression was used to determine the association between the log transformed sphingolipids and odds of CKD, adjusting for age, sex, and race. Among participants without CKD, linear regression was used to examine the association between the sphingolipids and GFR adjusting for age, sex, race, BMI, and hypertension.

Results: Higher levels of all SM were associated with increased odds of CKD: each log unit increase in SM C18:1 was associated with six-fold increased odds of CKD (OR=6.92, p=0.002). Among individuals without CKD, higher SM were also associated with lower GFR. This association was most pronounced among the 290 individuals without diabetes or pre-diabetes: each log unit increase in SM C18:1 was associated with lower GFR (b=-8.40, p=0.002).

Conclusions: These results suggest that elevated plasma SM are associated with CKD. Likewise, among those without CKD, elevated SM are associated with lower GFR. The cross-sectional study design limits specific conclusions on the mechanisms and temporality of these associations but suggests that further research is warranted.

Funding: Other NIH Support - U01 AG37526 (National Institutes of Health/National Institute on Aging)

PUB178

Clinical and Pathologic Predictors of Progression to End Stage Renal Disease following Renal Biopsy Andrew S. Allegretti,¹ Ivy A. Rosales,² A. Bernard Collins,² Nina E. Tolckoff-Rubin,² Robert B. Colvin,² Ishir Bhan,¹ Julia Beth Wenger, Joshua Wibecan, Rex Neal Smith. *¹Div of Nephrology, MGH, Boston, MA; ²Dept of Pathology, MGH, Boston, MA.*

Background: The value of renal biopsy in prognosis of chronic kidney disease remains unclear. Irreversible, chronic changes such as interstitial fibrosis and glomerulosclerosis are thought to provide prognostic information. We sought to define the relative prognostic value of biopsy pathology and clinical factors for predicting progression to end stage renal disease (ESRD).

Methods: Retrospective, single center review of renal biopsies performed between 2004-2014 in four kidney diseases. Cox regression was used to evaluate nine pathologic findings on light microscopy and 21 clinical variables as potential predictors of progression to ESRD.

Results: 231 cases were reviewed (34% IgA nephropathy, 29% focal segmental glomerulosclerosis, 19% tubulointerstitial disease, 18% diabetic nephropathy). 83/231 (36%) subjects progressed to ESRD within 5 years follow-up. Median estimated glomerular filtration rate (eGFR) at time of biopsy was 32 [IQR: 18, 54] mL/min. Median percent interstitial fibrosis was 20% [IQR: 10%, 40%]. In multivariable Cox regression adjusting for pathologic diagnosis and eGFR at the time of biopsy, independent predictors of progression to ESRD within 5 years of biopsy were: interstitial fibrosis > 20% (HR 1.94 [95% CI 1.09, 3.44]; p = 0.02), presence of endocapillary inflammation (HR 2.35 [1.22, 4.53]; p = 0.01), presence of arteriosclerosis (HR 2.03 [1.01, 4.05]; p = 0.05), history of liver disease (HR 1.55 [0.95, 2.53]; p = 0.08) and congestive heart failure (HR 1.85 [0.99, 3.49]; p = 0.06).

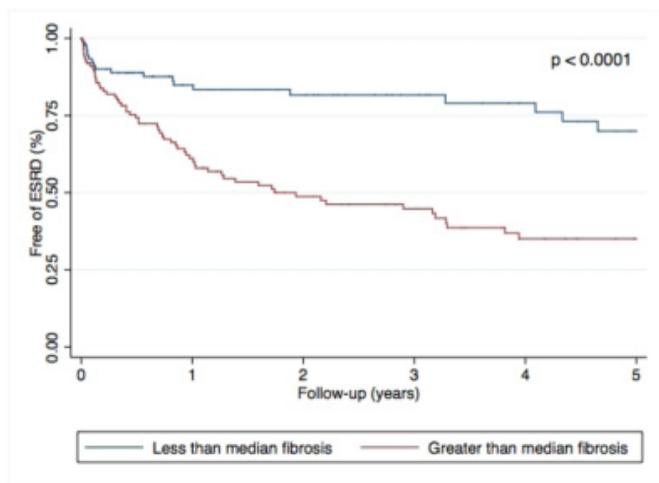


Figure: Kaplan Meier curve depicting time to end stage renal disease (ESRD) by above or below median percent interstitial fibrosis.

Conclusions: Pathologic findings of interstitial fibrosis greater than 20%, endocapillary inflammation, and arteriosclerosis as well as a clinical history of congestive heart failure and liver disease were the strongest predictors of progression to ESRD.

Funding: NIDDK Support

PUB179

The Influence of Mutagenic Lactobacilli on Concentration of IS in Blood and the Renal Expression of Renal Fibrosis Related Factors Yafen Jiang,¹ Yunhuan Bai,² Fang Wang,³ Yunsheng Jiang,¹ Fuyou Liu,¹ ¹Nephrology Inst, Central South Univ, Changsha, Hunan, China; ²Div of Nephrology, Xuzhou Central Hospital; ³Ningbo Medical Treatment Center Lihuili Hospital.

Background: to observe the concentration changes of Indoxyl Sulfate (IS) in blood and the renal expression of renal fibrosis related factors (transforming growth factor- β (TGF- β 1) and Fibronectin (FN) after administration of mutagenic lactobacilli by oral.

Methods: 60 male SD rats aged 6 weeks were divided into 3 groups randomly: normal control group (Sham group, n = 20) who received SHAM operation of just incision of skin without kidney removed. The other two groups of rats were all renal failure models selected from survivals of the other 40 rats who received real operation with 5/6 of the kidney removed. Then 35 rats finally got were randomly divided into 2 groups: pathological control group (Model group) (n = 17), administered of 2ml Sterile Saline Solution once a day by gavage. Experimental group (LB group) (n = 18) administered of 2ml mutagenic lactobacilli (1.5×10^8 cfu/ml) once a day by gavage. 8 weeks later, blood specimens were taken to test the concentration of IS by High performance liquid chromatography-fluorescence detection (HPLC-FLU) and urea and creatinine by automatic biochemical analyzer, while the rats were killed to get kidney tissues for pathological examination.

Results: the concentration of IS in the experimental group were 3.18 ± 1.39 ug/ml, while 3.67 ± 2.13 ug/ml in the Model group. Two groups were significantly different ($P < 0.05$). And also Blood urea and creatinine levels were statistically different between two groups ($P < 0.05$). Both the level of renal tubular damage and renal interstitial fibrosis were less in the experimental group when comparing with the Model group ($P < 0.05$); TGF- β 1 and FN expression in renal tissues were also decreased.

Conclusions: Mutagenic lactobacilli can not only reduce serum concentration of IS, urea and creatinine in renal failure rats, but also lowering the expression of TGF- β 1 and FN in renal tissue.

PUB180

Lower Dietary Intake of Magnesium Is Associated with Faster Decline in Kidney Function: The Healthy Aging in Neighborhoods of Diversity across the Life Span Study Adrienne Tin,¹ Casey Rebholz,¹ Yang Liu,¹ Alan B. Zonderman,² Marie Kuczmarski,³ Deidra C. Crews,¹ ¹Johns Hopkins Univ; ²National Inst on Aging; ³Univ of Delaware.

Background: Lower dietary magnesium intake has been associated with higher prevalence of chronic kidney disease (CKD). We hypothesized lower dietary magnesium intake would be associated with more rapid decline in kidney function.

Methods: Participants with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² at baseline (2004-2008) of the population-based, Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study were followed for a median of 4.7 years. Baseline dietary magnesium intake was calculated from two 24-hour dietary recalls. eGFR was calculated from serum creatinine using the CKD-EPI equation. We defined rapid decline as eGFR decline $\geq 3\%$ per year. The association between dietary magnesium intake and eGFR decline was evaluated using Cox regression.

Results: Among 1,326 participants, those with lower dietary magnesium intake (tertile 1 vs. 3) were significantly younger (mean age of 46 vs. 49 years), more likely to be African-American (67% vs. 48%) and male (45% vs. 31%); had lower mean body mass

index (BMI, 29 vs. 30 kg/m²), higher mean baseline eGFR (99 vs. 94 mL/min/1.73 m²) and lower prevalent diabetes (10% vs. 18%); $p < 0.05$ for all. In the overall study population, eGFR was stable without any decline (mean change: 0.1 mL/min/1.73 m²), while 189 participants experienced an eGFR decline $\geq 3\%$ per year. Lower dietary magnesium intake was associated with higher risk of eGFR decline $\geq 3\%$ per year (tertile 1 vs. 3, hazard ratio 1.9, 95% confidence interval: 1.1, 3.3) adjusted for socio-demographics, baseline eGFR, prevalent diabetes and hypertension status, BMI, serum magnesium, total energy intake, and dietary intake of calcium, potassium, and phosphorus.

Conclusions: Among persons with preserved eGFR, we detected a significant association between lower dietary Mg intake and increased risk of rapid kidney function decline independent of traditional CKD risk factors. These results highlight the importance of magnesium intake in the overall diet for the preservation of kidney function.

Funding: NIDDK Support, Other NIH Support - NIA

PUB181

Renin-Angiotensin System: A Possible Mechanism for AKI-CKD Continuum Shun-Yang Cheng, Shuei-Liong Lin, Ching-Chin Yang, Yu-Hsiang Chou, Fang Ling Liao, Ming-Hsuan Tsai. Graduate Inst of Physiology, National Taiwan Univ.

Background: Based on many clinical observations and studies, acute kidney injury (AKI) was now regarded as an important risky factor causing chronic kidney disease (CKD). Not only does CKD lead to end-stage renal disease (ESRD), but also increases the risk of cardiovascular disease or even death. Clinical studies often disclose that the higher the AKI severity of a patient is, the more likely her/his kidneys progress into CKD. To this day, the mechanism underlying the progression of kidneys into CKD after AKI remains elusive. Since the higher severity of the AKI leads to more reduction of nephron numbers, we propose that activation of renin-angiotensin system (RAS) may be involved in the progression to CKD after recovery from AKI.

Methods: Severe AKI was induced in male adult CD-1 mice by right uni-nephrectomy (Nx) followed by ischemia-reperfusion injury of left kidney 2 weeks later. Drinking water with or without type 1 angiotensin II receptor blocker losartan or direct vasodilator hydralazine was administered to mice from 4 weeks after surgery. Mice with Nx only were served as the control. Blood pressure, urinary albumin-creatinine ratio (ACR) and plasma levels of creatinine were evaluated.

Results: Compared to Nx group, AKI mice showed acute rise of plasma creatinine levels on day 2 after Nx+IRI surgery, which decreased to baseline on day 7. Moreover, elevated systolic blood pressure and increased urinary ACR were noted since 4 weeks after Nx+IRI. During the 4-month experimental period, progressive increase of urinary ACR and plasma levels of creatinine were noted. On the contrary, systolic blood pressure, urinary ACR and plasma creatinine level were normalized in mice administered with losartan since 4 weeks after Nx+IRI surgery. However the increase of urinary ACR and plasma creatinine level were not prevented in mice administered with hydralazine despite similar normalization in blood pressure.

Conclusions: These data suggest that RAS activation may underlie the mechanism for development of CKD in mice after recovery from AKI. Future studies are needed to explore the effect of RAS blockade in prevention of CKD and its progression in patients recovered from AKI.

Funding: Government Support - Non-U.S.

PUB182

The Renal Effects of Nephilysin Inhibition in Heart Failure and Hypertension Girish Singhanian, Abhilash Koratala, Amir Kazory. Nephrology, Univ of Florida, Gainesville, FL.

Background: Nephilysin inhibitors (NEPi) represent an emerging therapeutic option for treatment of hypertension (HTN) and heart failure (HF) through enhancement of natriuresis. While these agents have shown promising results with regards to lowering blood pressure (BP) and HF events, their impact on the kidney remains largely unknown. The aim of this study is to evaluate the currently available evidence on the effect of NEPi use on kidney-related parameters in patients with HTN or HF.

Methods: A search of articles cited in PubMed database from 1995 to 2015 using key words "nephilysin", "heart failure" and "hypertension" found 237 articles. Animal studies were excluded. Those studies containing kidney-related parameters such as serum creatinine, glomerular filtration rate (GFR), or BP were selected. Relevant data including changes in renal function, blood pressure and mortality were extracted and compared.

Results: A total of 42,487 patients from 12 randomized controlled trials with data pertaining to NEPi use were included (8 in HTN and 4 in HF). Seven studies used NEPi combined with ACE-i, 4 with ARB, and 1 with endothelin converting enzyme inhibitors. The follow up periods ranged between 7 days and 27 months. All studies in HTN (including 27,401 patients) reported significantly better BP lowering effect for NEPi compared to control group, while 94% of the patients in the HF studies presented with improvement in HF events or mortality. Although change in renal function was not the primary endpoint, all HF studies (including 15,086 patients) showed less frequent renal impairment (expressed as an adverse event, incidence of worsening renal function, change in GFR, or serum creatinine) compared to the control group. In contrast, only 3 HTN studies (including 466 patients) explored the impact on renal function and reported no significant benefit.

Conclusions: Current evidence suggests that in patients with HF, NEPi can lower HF-related events and mortality while portending favorable impact on renal function. In patients with HTN, although NEPi have been shown to reduce BP, there is no conclusive evidence of their role in improvement of renal function in this setting.

PUB183

The Differences of Renal Protective Effect by Hyperuricemia Treatment Using Febuxostat in Various CKD Subgroups *Akinori Yamaguchi, Makoto Harada, Yosuke Yamada, Koji Hashimoto, Makoto Higuchi, Yuji Kamijo. Dept of Nephrology, Shinshu Univ, Matsumoto, Nagano, Japan.*

Background: We often experience the CKD cases exhibiting the attenuation of eGFR decline by hyperuricemia treatment using febuxostat. However, renal protective effect by the hyperuricemia treatment has not yet been established. We hypothesize that the therapeutic response of febuxostat treatment might differ among various subgroups of CKD patients.

Methods: To investigate the difference of the therapeutic response in CKD patients, 272 outpatients with hyperuricemia who were treated by febuxostat from May 2011 to March 2015 were enrolled. Patients undergoing hemodialysis and/or peritoneal dialysis treatment, and patients lacking essential clinical data were excluded. Finally, 178 patients were analyzed. Correlation coefficient between the average of serum uric acid level and the eGFR variation during 6 months after the treatment were statistically investigated in various clinical subgroups.

Results: In all patients, significant correlation between the average of serum uric acid levels and the eGFR variation was detected (spearman's correlation coefficient: $r=-0.163$, $p=0.019$). This significant correlation was also detected in each patient groups as follows: male patients ($n=121$, $r=-0.211$, $p=0.020$), non-elderly (below 70 years old) patients ($n=107$, $r=-0.261$, $p=0.007$), patients whose systolic blood pressure were below 130 mmHg ($n=72$, $r=-0.238$, $p=0.044$), patients without dyslipidemia ($n=133$, $r=-0.316$, $p=0.005$) and non-diabetic-nephropathy patients ($n=133$, $r=0.184$, $p=0.034$). However, the significant correlation was not detected in each opposite subgroups.

Conclusions: The current study suggest that therapeutic response of febuxostat treatment might be well in each CKD subgroups, including male, non-elderly, non-hypertension, non-dyslipidemia and non-diabetic-nephropathy. It is possible that various risk factors of atherosclerosis conceal the beneficial renal protective effects of hyperuricemia treatment using febuxostat.

PUB184

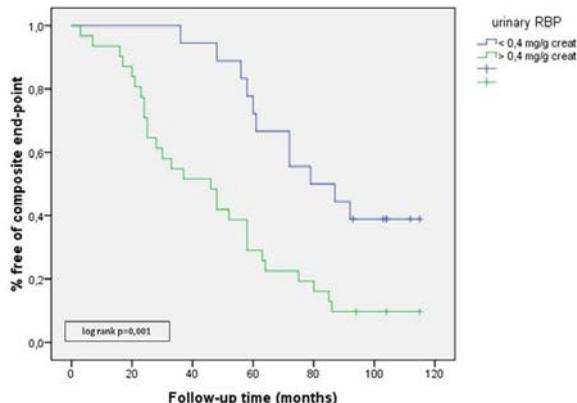
Urinary RBP as an Independent Predictor of "Hard Composite Outcome" in Albuminuric Diabetic Nephropathy *Gesiane Fernandes Tavares, Roberto Zatz, Silvia M. Titan. Renal Div, Dep. Clinical Medicine, Faculty of Medicine, Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: The current search for new biomarkers in CKD is intense, with particular emphasis on hard end-points, such as ESRD, creatinine duplication and cardiovascular and overall mortality. In this analysis, we sought to evaluate which baseline clinical and laboratorial variables were related to ESRD/mortality in 56 patients with albuminuric diabetic nephropathy after mean follow-up time of 5 years.

Methods: Baseline clinical and laboratorial data of 56 participants of a clinical trial were evaluated as predictors of major outcomes (primary outcome, PO: ESRD, creatinine duplication or mortality). Mann-Whitney and chi-square tests were used for univariate analyses. Several univariate and multivariate COX regression models were built on the risk of PO. Kaplan-Meier curve and LOG rank test were also performed.

Results: PO occurred in 39 participants after a mean follow-up time of 5 years (70%). In univariate analyses, sex, creatinine clearance, 24h proteinuria, uRBP, urinary VEGF and serum TGF-beta were related to the event group. In univariate COX regression models, sex, proteinuria, creatinine clearance, VLDL-cholesterol, ferritin, PTH, RBP and uMCP-1, uVEGF and uTGF-beta were significantly associated to the risk of the PO. However, after adjustments for creatinine clearance and proteinuria, only uRBP and uMCP-1, uTGF-beta and uVEGF remained significantly associated to PO. In a stepwise model, only creatinine clearance (HR 0,98, 95%CI 0,97 - 1,00, $P=0,06$) and uRBP (HR 1,13, 95%CI 1,07 - 1,20, $P<0,0001$) were left as independent predictors of PO in this population. KM curve for uRBP is shown in figure 1.

Kaplan-Meier Curve



Conclusions: Urinary RBP is an independent predictor of PO in albuminuric diabetic nephropathy. Its role as a risk biomarker should be further explored in larger studies of CKD patients.

Funding: Government Support - Non-U.S.

PUB185

Association Between Urinary RBP and Renal and Cardiovascular Risk Factors in a Population with CKD: The ProgreDir Study *Maria Alice Muniz Domingos,¹ Alessandra C. Goulart,² Paulo Lotufo,² Isabela M. Bensenor,² Silvia M. Titan.¹ ¹Renal Div, Dep. Clinical Medicine, Faculty of Medicine, Univ of Sao Paulo, Sao Paulo, Brazil; ²Clinical Research Center, Univ Hospital, Sao Paulo Univ, Sao Paulo, Brazil.*

Background: Urinary RBP (uRBP) has been related to the risk of ESRD in glomerulonephritis and renal transplant. However, its role in CKD is not well established.

Methods: Baseline clinical and laboratorial data on 454 participants of the ProgreDir Study was analysed. uRBP was measured by an immunoenzymatic assay with monoclonal antibody. Descriptive data is presented according to tertiles of uRBP, and correlation coefficients were calculated. Several univariate and multivariate linear regression models were built. Lastly, binary regression models were built on the risk of presenting more advanced CKD (class IV+V versus class II+III).

Results: In the descriptive data, the tertiles of uRBP were significantly related to sex, diabetes, renal function, SBP, glycated hemoglobin, HDL, proteinuria, WHR, phosphorus, acidosis, albumin, pulse-wave velocity (PWV), left atrium diameter (LAD), systolic and diastolic left ventricular diameters and ejection fraction. These results were confirmed by correlation. In the univariate regression models, diabetes, SBP, WHR, renal function, proteinuria, phosphorus, albumin, lipids, glycated hemoglobin, PWV and echographic variables remained related to uRBP. However, after adjustments, only renal function, proteinuria, SBP, bicarbonate and LAD remained associated to uRBP.

Table1: Stepwise multivariate linear regression models on log of urinary RBP.

Model	B	Std. Error	95,0% IC	p
24H proteinuria	,303	,033	,238 ,369	<0,001
24H proteinuria	,235	,033	,170 ,299	<0,001
eGFR-MDRD	-,021	,003	-,027 -,015	<0,001
24H proteinuria	,209	,033	,145 ,274	<0,001
eGFR-MDRD	-,021	,003	-,027 -,015	<0,001
SBP	,006	,002	,003 ,010	<0,001
24H proteinuria	,219	,032	,155 ,282	<0,001
eGFR-MDRD	-,021	,003	-,027 -,015	<0,001
SBP	,006	,002	,003 ,009	<0,001
LAD	-,026	,007	-,039 -,012	<0,001
24H proteinuria	,210	,032	,146 ,273	<0,001
eGFR-MDRD	-,019	,003	-,025 -,014	<0,001
SBP	,007	,002	,003 ,010	<0,001
LAD	-,023	,007	-,037 -,009	,001
Bicarbonate	-,027	,013	-,053 -,001	,041

*eGFR-MDRD: estimated glomerular filtration rate using MDRD; SBP: systolic blood pressure; LAD: left atrium diameter.

Lastly, uRBP was associated to an increased risk of class IV+V CKD (OR 1,16, 95%CI 1,08 - 1,25, $p<0,0001$), even after adjustments for age, sex, diabetes, proteinuria and SBP.

Conclusions: uRBP is independently related to cardiovascular risk factors in the CKD population. Its role as a biomarker of hard clinical end-points should be further explored.

Funding: Government Support - Non-U.S.

PUB186

Treatment of Subclinical Hypothyroidism and the Progression of Chronic Kidney Disease *Padmavathi Mali,¹ Sudheer Muduganti.² ¹Internal Medicine, Marshfield Clinic, Marshfield, WI; ²Nephrology, Univ of Wisconsin Hospitals and Clinics, Madison, WI.*

Background: Evidence suggests that treatment of subclinical hypothyroidism may slow the progression of chronic kidney disease (CKD) and delay or prevent development of end stage renal disease (ESRD). The goal of this study was to provide additional evidence regarding the same.

Methods: Patients with subclinical hypothyroidism and CKD stages 3 or 4 were identified by retrospective chart review over a period of 6 years. Subjects were grouped based on L-thyroxine treatment. Subjects treated with L-thyroxine before first elevated thyroid stimulating hormone (TSH) were excluded. Index date was defined as the date of first L-thyroxine for treated patients. Index dates for untreated patients were assigned by random sampling of dates for treated patients. TSH and serum creatinine values were captured from the electronic medical record. Change in eGFR (glomerular filtration rate) over time in treated and untreated patients was assessed using a linear random coefficients model in the subset with two or more eGFR results spanning a period of at least 6 months, both before and after the index date.

Results: A total of 258 patients meeting inclusion criteria were identified; 181 were treated with L-thyroxine and 77 were not. Treatment initiation began after the first elevated TSH in the study period for 110/181 subjects. Upon analysis, before the index date, eGFR showed a significantly decreasing trend ($p<0.001$) that was not significantly different

between treated and untreated patients ($p = 0.593$). After the index date, the rate of eGFR change showed a significant positive change ($p < 0.001$) toward a gradual increase, but again this was not significantly different between groups ($p = 0.522$).

Conclusions: The similar results in the two groups, regardless of L-thyroxine treatment status, provides no evidence that treatment of subclinical hypothyroidism influences progression of CKD in individuals with stage 3 or 4 disease. Although previous studies have suggested that treatment of subclinical hypothyroidism in this population may delay or prevent the progression of ESRD, our results do not support the hypothesized treatment benefits.

PUB187

Effect of Hyperuricemia on the Blood Pressure-Dependent Proteinuria in Non-Nephrotic Chronic Kidney Disease Kentaro Kohagura,^{1,2} Ryo Zamami,² Tsuyoshi Miyagi,² Masako Kochi,² Yusuke Ohya,² ¹Dialysis Unit, Univ Hospital of the Ryukyus, Nishihara-cho, Okinawa, Japan; ²Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Nishihara-cho, Okinawa, Japan.

Background: Patients with chronic kidney disease (CKD) are suggested to be highly susceptible for hypertensive renal damage due to disrupted autoregulation system in afferent arteriole. We reported that hyperuricemia was associated with renal arteriolar hyalinosis in the CKD patients. However, effect of hyperuricemia on a relationship between blood pressure (BP) and proteinuria is unknown in CKD patients.

Methods: A total of 208 consecutive patients who underwent renal biopsy at our department between 2003 and 2007 were considered for the study. We excluded patients receiving renin angiotensin inhibitor and nephrotic CKD patients defined as serum albumin equal or more than 3 g/gCr, leaving us with 117 patients (57 men and 60 women) for analysis. Arteriolar hyalinosis were assessed by semi quantitative grading for arterioles. We compared the relationship between systolic BP and logarithm-transformed urine protein (g/gCr) in the patients with or without hyperuricemia.

Results: The mean \pm standard deviation values for age, BP, estimated glomerular filtration rate (eGFR), and urine protein were as follows: 40 ± 18 years, $126 \pm 20/75 \pm 12$ mmHg, and 84 ± 37 ml/min/1.73 m², and 0.9 ± 0.8 g/gCr, respectively. In the patients with hyperuricemia ($n=63$), systolic BP was significantly correlated with log-transformed urine protein ($r=0.43$, $p=0.004$). In contrast, there was no significant correlation between them in the patients without hyperuricemia ($n=53$, $r=0.07$, $p=0.60$). In the multiple regression model ($R^2=0.25$, $p=0.01$), systolic BP was significantly correlated with logarithm-transformed urine protein ($\beta=0.33$, $p=0.02$) independent of age, sex and classical risk factors in the patients with hyperuricemia. However, its statistical significance was disappeared after additional adjustment with arteriolar hyalinosis.

Conclusions: These results suggested that hyperuricemia might potentiate the susceptibility for hypertensive glomerular damage via disrupted autoregulation in non-nephrotic CKD patients.

PUB188

HCV Independently Affects Kidney Function Among HIV Co-Infected Individuals Maya Balamane,¹ Richard A. Teran,¹ Joseph G. Timpone,¹ Jason G. Umans,^{2,3} Princy N. Kumar,¹ Seble Kassaye,¹ ¹Georgetown Univ Medical Center, Washington, DC; ²Georgetown Howard Univs Center for Clinical & Translational Science, Washington, DC; ³MedStar Health Research Inst, Hyattsville, MD.

Background: Predictors of chronic kidney disease (CKD) include increasing age, hypertension and diabetes. Hepatitis C (HCV) infection has also been associated with increased risk for CKD. We sought to determine the relative contribution of HCV vs other co-morbidities on kidney dysfunction among individuals with HIV.

Methods: We analyzed data from HIV-positive patients enrolled in the DC HIV Clinical Cohort study at Georgetown University Hospital (2011-2014). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. Analyses were conducted stratified by HCV status. Chi square, Cochran-Mantel-Haenszel and Breslow Day Test statistics were performed to determine factors associated with normal kidney function (eGFR > 90 ml/min/1.73²), compared with participants with decreased kidney function, stage 2 and 3 (≤ 89 eGFR) using SAS v9.4.

Results: Among 771 participants, median age was 48, 73.4% male, 50.3% black, median CD4+ T cell count 546.5 cells/ μ L, and HIV-RNA < 20 copies/mL. 93 (12.1%) had HCV co-infection. There was significantly higher prevalence of stage 2-3 kidney dysfunction with HIV/HCV co-infection than HIV mono-infection (35% vs. 19%, $p=0.0016$; OR, (95% CI) 2.2 (1.3-3.6)). Prevalence of hypertension, diabetes, hyperlipidemia and chronic Hepatitis B was similar between HIV and HIV/HCV co-infected groups. Presence of these co-morbidities was not a confounder in the increased risk for CKD with HIV/HCV, (Mantel-Haenszel chi-square OR, (95% CI) of 2.2 (1.3-3.6) for hypertension, 2.18 (1.3-3.6) diabetes and 2.2 (1.3-3.6) hyperlipidemia (Breslow Day test p values $< .05$ for each co-morbidity).

Conclusions: We identified a strong association between HIV/HCV co-infection and reduced kidney function independent of co-morbidities usually associated with kidney dysfunction in this group with well controlled HIV. Further investigation is needed to study the mechanisms by which HCV affects kidney function.

Funding: Other NIH Support - Division of AIDS- NIAID

PUB189

Vitamin D Deficiency Is a Cause and a Result of Renal Dysfunction in Rheumatoid Arthritis Suad Ma Hannawi, Issa AL Salmi. *Medicine, Ministry of Health, Dubai, United Arab Emirates.*

Background: Asymptomatic kidney dysfunction is common in RA. Low vitamin D (VD) increases susceptibility to development of RA & disease activity. Sequential hydroxylations occurs in liver & kidney to form active 1,25-VD & patients with kidney failure are often resistant to VD & suffer from 2nd hyperparathyroidism & renal osteodystrophy. In addition to its role in maintaining Ca&PO₄ homeostasis, VD is important for maintaining maximum muscle strength & prevention of chronic diseases. Our objective is to evaluate eGFR & VD status in RA.

Methods: RA diagnosed by ACR 1988 criteria. 25-VD level obtained & GFR calculated by MDRD at Rheumatology clinic visit. Univariate linear regression analysis carried out to determine the relation between 25-VD and eGFR, other renal parameters & RA inflammatory markers.

Results: Interim analysis of 52 RA(47F,5M) with mean age 46 ± 13 year ($F46 \pm 12$, $M45 \pm 21$). 25-VD level is 40 ± 29 nmol/l (NR50-80) & GFR is 134 ± 49 ml/min/m². Univariate linear regression showed a negative relationship between 25-VD level & GFR ($p=0.041$, CI -0.23, -0.01), micro-albuminuria ($p=0.046$, CI -0.63, -0.01), CRP ($p=0.01$, CI -1.16, -0.16), neutrophil count ($p=0.03$, CI -1.67, -0.11). A positive linear relationship between GFR & weight ($p=0.03$, CI 0.06, 1.04), BSA ($p=0.02$, CI 11, 119) & BMI ($p=0.009$, CI 0.65-4.05), Ca ($p=0.003$, CI 7.24, 133.12 mmol/l).

Conclusions: Negative relationship between eGFR & 25-VD, indicating a higher 25-VD as failure to convert to active form as GFR decreases. Extra-renal formation of active VD requires high level of 25-VD > 78 nmol/L (30 ng/mL) & is necessary for maximal extra-renal production of 1,25VD. 1,25-VD is one of the most potent regulators of cellular growth & very effective modulator of the immune system. VD receptors are present in most cells & tissues in the body including activated T and B lymphocytes. Surveillance for VD deficiency, should be part of follow-up as it may be linked to underlying kidney dysfunction in RA. On the other hand, reduced VD might worsen RA & hence, increase the possibility of renal deterioration. VD supplementation may be needed early in management for prevention of kidney dysfunction & to reduce RA severity.

PUB190

Associations Between the Progression of Chronic Kidney Disease and Patient Demographics Danqing Xu,¹ Mark Stuart,³ Barbara Cannon,³ Chad Sowers,³ John W. Larkin,² Sophia Rosen,² Carly R. Van Zandt,⁴ Len A. Usvyat,² Yuedong Wang,¹ Terry Ketchersid,² Dugan Maddux,² Franklin W. Maddux,² ¹Univ of California, Santa Barbara; ²Fresenius Medical Care North America; ³Acumen Physician Solutions; ⁴Fresenius Renal Research.

Background: It is not well known if demographic factors are related to the progression of chronic kidney disease (CKD). We aimed to investigate whether age, sex, race, marital status and geography are associated with significant changes in kidney function determined by linear slopes of mean annual glomerular filtration rate (GFR).

Methods: We analyzed data from 90,240 CKD patients (Pts), who had significant declines in GFR, in the Fresenius Medical Care CKD Data Registry. Annual average decline in GFR was estimated on a per pt basis using linear regression with time as the predictor and GFR as the outcome variable. Univariate linear models were fitted for age groups (15-30, 31-45, 46-60, 61-75, and 76-90 years old), sex (female or male), race (African American, Caucasian, or other), marital status (married, unmarried) and geography (10 divisions of zip codes); a multiple linear regression model was utilized to investigate associations in mean annual GFR slope and demographics.

Results: This analysis identifies significant associations between mean annual GFR slope and Pt demographics. CKD Pts age 15-30 years old were found to decline faster in GFR versus older Pts in all other age groups ($p < 0.001$). Males were observed to decline slower in GFR versus females ($p < 0.001$). Pts with a race of "other" were seen to decline slower in GFR versus Pts of African American or Caucasian race ($p < 0.001$). The geographical location of Pts by zip code was observed to be associated with differences in GFR slope ($p < 0.001$). The marital status of Pts was not found to be related to differences in slopes of GFR ($p = 0.218$).

Conclusions: This study identifies that during the progression of CKD, younger Pts tend to have faster declines in GFR, as compared to older Pts; males have slower declines in GFR, as compared to females; Pts with a race of "other" have slower declines in GFR, as compared to Pts of African American or Caucasian race; and declines in GFR are related to Pt geography.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB191

Correlation of Increased Th17 to Treg Cell Ratio with Endoplasmic Reticulum Stress in Chronic Kidney Disease Ou Yan. *Kidney Dept, Second Affiliated Hospital of Xi'an Jitong Univ, Xi'an, Shaanxi Province.*

Background: The study aimed to investigate the relationship between the regulatory immune network and endoplasmic reticulum stress (ERS) in patients with different stages of chronic kidney disease (CKD).

Methods: A total of 91 patients diagnosed with CKD were divided into different groups according to the stage of disease. Routine blood and biochemical tests were performed in patients and in healthy controls ($n = 20$). The frequencies of T helper type 17 (Th17) and regulatory T (Treg) cells in the overall T cell population was measured by flow cytometric analysis. Levels of Th17 cell (IL-17) and Treg cell (IL-10) cytokines and the ERS markers

CHOP and GRP78 were measured by ELISA in serum samples collected from controls and patients in the different CKD groups. Correlations between each parameter and serum creatinine, an indicator of renal function, were analyzed by Spearman's rank correlation and regression test.

Results: CKD stage showed a positive correlation with serum creatinine level, and increased and decreased percentages of Th17 and Treg cells, respectively, reflected in an increased Th17/Treg cell ratio. Consistent with this, CKD stage was positively correlated with serum concentrations of IL-17 and negatively correlated with serum IL-10 levels. Moreover, serum levels of CHOP and GRP78 increased with advancing CKD stage. These correlations were most pronounced in patients in the CKD5 group, who also had the poorest response to hemodialysis and peritoneal dialysis treatment, compared with CKD5 patients in the non-dialysis group. Correlation analysis showed that serum levels of CHOP and GRP78 were independently and positively correlated with the ratio of Th17/Treg cells.

Conclusions: We have found that an increased Th17/Treg cell ratio and increased serum levels of ERS markers correlate with the progression of CKD. Our results indicate that the interplay between regulation of the immune network and management of ERS is closely associated with the pathogenesis of CKD. Although hemodialysis and peritoneal dialysis treatment manage chronic kidney conditions and prevent further deterioration of renal function, they have limited effects on improving the immune disorder and relieving ERS.

Funding: Government Support - Non-U.S.

PUB192

Metabolic Phenotyping in Thin Basement Membrane Nephropathy Claire Boulange,¹ Manuja Kaluarachchi,¹ Elaine Holmes,^{1,2} John C. Lindon,^{1,2} Joram Matthias Posma,² Konstantinos Voskarides,³ Isavella Savva,³ Alkis Mikis Pierides,³ Constantinos Deltas.³ ¹Metabotrix Ltd, London, United Kingdom; ²CSM, Dep of Surgery & Cancer, Imperial College London, London, United Kingdom; ³MMRC, Dep of Biological Sciences, Univ of Cyprus, Nicosia, Cyprus.

Background: Thin basement membrane nephropathy (TBMN) is the commonest cause of familial microscopic hematuria in children and adults, usually associated with benign clinical conditions i.e. minimal proteinuria and normal renal function. In a Greek-Cypriot cohort of TBMN patients, 35% of patients were shown to develop ESRD by age 70-years while ~50% of patients over 50-years developed CKD of variable degree. 40% of TBMN patients inherit heterozygous mutations in the COL4A3/A4 genes. What predisposes these TBMN patients to an adverse outcome and chronic kidney function decline during aging is presently unclear. Using Metabolic phenotyping techniques (NMR and mass spectrometry) our study should provide new biological insights in the development of extreme conditions in adult TBMN patients.

Methods: Spot urine samples from 81 patients with the same founder mutation, COL4A3-G1334E. Patients were classed; Severe (S) (n=55): proteinuria > 500 mg/day and CKD, irrespective of age. Mild (M) (n=26): normal kidney function with no proteinuria, regardless of age. It is expected that some will proceed to CKD on follow-up. Samples were analysed by 600 MHz ¹H NMR spectroscopy (detecting predominantly small molecules >1 μM) and UPLC-MS (detecting water-soluble molecules > 0.05 nM). Multivariate analysis (MVA) was used to elucidate class differences.

Results: MVA of M vs S samples revealed significant metabolic differences between the groups. From the UPLC-MS 15 MS features discriminate M and S. Among the discriminating metabolites discovered using NMR; citrate, glycine and creatinine were negatively correlated with S. Metabolite identification is ongoing, as well as application of additional metabolic profiling technologies.

Conclusions: Urine metabolic profiling may prove useful to classify renal disorders such as the M and S cases of TBMN by their specific renal metabolite signatures and lead to the discovery of novel molecular disease biomarker profile patterns.

Funding: Other NIH Support - The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 305608 (EURenOmics)

PUB193

Uric Acid and Its Association with Glomerular Filtration Decline Rate in an Incident Pre-Dialysis Population Pedro Veiira, Miguel Goncalves, Gil Silva. *Nefrologia, Hospital Central do Funchal, Funchal, RAM, Portugal.*

Background: Hyperuricemia is highly prevalent and there is cumulative evidence based on experimental models of its likely detrimental role in multiple pathologies, namely hypertension, vascular and renal diseases. Given hyperuricemia's high occurrence on chronic kidney disease patients, we have tried to assess the association between uric acid basal levels (UABL) in an incident pre-dialysis population with renal function decline rate.

Methods: We have randomly selected incident patients with chronic kidney disease stages IV-V, referred to low clearance nephrology assessment from 2010 to 2014. We kept follow up until dialysis initiation, death or lost of follow-up.

Results: Sixty-six patients were selected with mean UABL of 8,15 (±10,21) mg/dl and a mean glomerular filtration decline rate of -4,00 (±10,81) ml/min/1,73m²/year. Of notice that by each unit increase in UABL an added variation of -1,41 ml/min/1,73m²/year on glomerular filtration decline rate was perceived (CI 95%, p=.039). Adopting a linear mixed model analysis on UABL' impact on glomerular filtration decline rate, despite adjustment for multiple demographic confounders and comorbidities, statistical significance (p=.006) was conserved.

Conclusions: High UABL were associated, with statistical significance, to enhanced deterioration of kidney function.

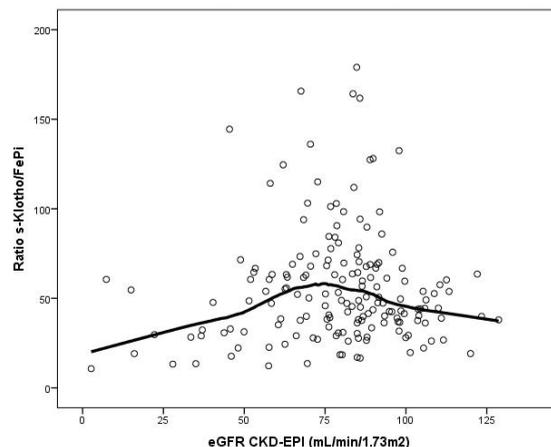
PUB194

Soluble α-Klotho in HIV-Infected Patients and Kidney Dysfunction Clara Dias,¹ Sara Maia,¹ Fernando G. Pereira,² Pedro Pereira Campos,² Ana Luisa Papoila,³ Alberto Ortiz,^{4,5,6,7} Sofia Pereira,¹ Karina Soto.^{2,3} ¹Centro de Estudos de Doenças Crónicas, NOVA Medical School/Faculdade de Ciências Médicas; ²Nephrology, Hospital Fernando Fonseca; ³Centro de Estatística e Aplicações, Univ de Lisboa (CEAUL), Portugal; ⁴Nephrology, IIS-Fundacion Jimenez Diaz, Madrid, Spain; ⁵REDinREN, Madrid, Spain; ⁶REDinREN, Madrid, Spain; ⁷Univ Autonoma de Madrid, Madrid, Spain; ⁸IRISIN, Madrid, Spain.

Background: Kidney disease is common among HIV-infected patients. Klotho is a new endocrine protein that exerts modulation of kidney solute transport and nephroprotection in AKI and CKD. We aim to explore whether levels of serum soluble α-Klotho are related with CKD progression in HIV-population.

Methods: As a part of an on-going prospective study of HIV-infected patients, a cross-sectional analysis was performed. Glomerular filtration rate (eGFR) was estimated by CKD-EPI equation being Early Kidney Disease (EKD) when <90 mL/min/1.73m². Fractional excretion of phosphate (FePi) was also assessed and serum soluble α-Klotho was quantified by ELISA.

Results: A total of 169 HIV+ patients were included, 66% men, 75% non-Black, 55yo (48-62). Median values Klotho: 957 pg/mL (717-1213) and FePi: 21% (14-25). Klotho/FePi ratio was negatively correlated with eGFR when ≥75 mL/min/1.73m² (Spearman r=-0.213, p=0.024); while the correlation was positive if eGFR<75 (Spearman r=0.410, p=0.002)



No direct relation between Klotho and eGFR was found, while FePi was only related with eGFR<75 (Spearman r=-0.396, p=0.002).

Conclusions: In HIV-infected patients, the association between Klotho and CKD progression has only significance when normalized by FePi levels. This association differed in opposite directions between patients with EKD and with normal kidney function, or in very early CKD stages. Of note, Klotho/FePi ratio seems to be better biomarker of EKD than Klotho itself.

Funding: Other NIH Support - Financial support: EXPL/DTP-FTO/1792/2013; PD/BD/105892/2014 (CGD)

PUB195

Association of hsCRP and Kidney Damage Indicators in 5667 Adults Receiving Physical Examination Hao Zhang, Juan Mao, Bin Yi, Guo Xu, Wei Li. *The Third Xiangya Hospital of Central South Univ.*

Background: Chronic kidney disease and cardiovascular disease share many risk factors. Injury to the vascular endothelium, measured by elevated levels of serum high-sensitivity C-reactive protein (hsCRP), may play a role in kidney disease. We therefore examined the association of hsCRP with kidney damage indicators (uACR, eGFR) among 5667 participants receiving physical examination in the Third Xiangya Hospital.

Methods: We conducted a cross-sectional analysis of 5667 adults who received healthy physical examination in 2014. Spearman correlation analysis, multiple linear regression and multivariable logistic regression analysis were used to analyze the correlation between hsCRP with uACR, eGFR. ROC curves was drawing to explore the statistically significant intercept point of hsCRP in predicting the occurrence of albuminuria and declining in eGFR. Multivariable logistic regression analysis was used to calculate the ORs for albuminuria, declining in eGFR according to the quartile of hsCRP levels and other risk factors.

Results: Spearman correlation analysis showed that uACR was positively correlated with serum hsCRP (r=0.233, p<0.01). While eGFR showed negative correlation with hsCRP (r=-0.135, p<0.01). Multiple linear regression analysis showed that hsCRP was independently correlated with uACR (B=0.205, β=0.156, P<0.01). While hsCRP didn't enter the multivariate linear regression model of eGFR. Multivariable logistic regression analysis showed that male, central obesity, hypertension, diabetes and high hsCRP levels were independent risk factors for albuminuria. Based on the ROC curve, the 0.85mg/L of hsCRP was the best numerical value to predict the risk of albuminuria. Multivariable logistic regression analysis showed that the risk of albuminuria significantly increased in male, central obesity, hypertension, or diabetes combined with high hsCRP levels.

Conclusions: HsCRP was correlated with kidney damage indicators, and hsCRP was an independent risk factor of albuminuria. The 0.85mg/L of hsCRP was the best numerical value to predict the risk of albuminuria. Male, central obesity, hypertension, diabetes accompanying high serum hsCRP levels are more likely to have albuminuria.

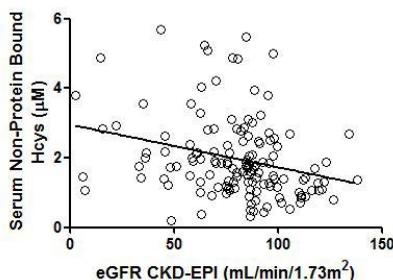
PUB196

Serum Non-Protein Bound Homocysteine Levels Are Related with Chronic Kidney Disease Progression in HIV-Infected Patients Clara Dias,¹ Nelson Casimiro,¹ Nuno Coelho,¹ Ana R. Lemos,¹ Pedro Pereira Campos,³ Ana Luisa Papoila,² Sara Maia,¹ Karina Soto,^{1,3} Sofia Pereira.¹ ¹Centro de Estudos de Doenças Crónicas, NOVA Medical School/Faculdade de Ciências Médicas (NMS/FCM), Univ Nova de Lisboa; ²Centro de Estatística e Aplicações da Univ de Lisboa (CEAUL), NOVA Medical School/Faculdade de Ciências Médicas, Univ Nova de Lisboa; ³Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal.

Background: Homocysteine (Hcys) is present in serum in two major forms: disulfide protein-bound (PB) (70-80%, mostly albumin) and non-protein bound (NPB) (20-30% combined thiol dimers + 1% thiol free). Only the NPB-fraction of Hcys is able to enter into the cell and accumulates. In both kidney failure and HIV-infected patients, hyperhomocysteinemia is a common feature. The present study was aimed to explore the relation of Hcys NPB-fraction and chronic kidney disease (CKD) progression in HIV-infected patients.

Methods: As a part of an on-going prospective study of HIV+ population, a cross-sectional analysis was performed in a cohort of HIV-infected patients under combined antiretroviral therapy. Serum NPB-fraction of Hcys was quantified by HPLC with fluorescence detection. Glomerular filtration rate (eGFR) was estimated by CKD-EPI equation. The fractional excretion of phosphate (FePi) was also assessed.

Results: A total of 141 HIV-infected patients were included, 65% men, 73% non-Black, and 55 years old (IQR44-63). Median values of eGFR and FePi were 85 ml/min/1.73m² (66-95) and 19% (13-25) respectively. Univariable analysis was performed for eGFR, FePi and age. Only eGFR remained in the multivariable model (r=-0.332, p<0.0001).



Conclusions: Serum NPB-Hcys fraction was independently related with kidney dysfunction. The present data suggest that monitoring this sub-fraction of Hcys could be a tool for early kidney dysfunction detection in HIV-infected patients.

Funding: Other NIH Support - Financial support: EXPL/DTP-FTO/1792/2013; PD/BD/105892/2014 (CGD)

PUB197

Diabetic Foot Ulcers and Acute Kidney Injury Are Associated with a Decline in Renal Function Huda Mahmoud,¹ Maarten W. Taal,^{1,3} Frances Game,^{1,3} Laura M. Proctor,¹ Heather Sherriff,¹ Christina Udani Peter,¹ Hana Baig,¹ Faaiza Asma,¹ Emma J. Lincoln,¹ Nicholas M. Selby.^{1,3} ¹Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; ²Diabetes, Royal Derby Hospital, United Kingdom; ³Div of Medical Sciences and Graduate Entry Medicine, Univ of Nottingham, United Kingdom.

Background: There is an increased incidence of foot ulcers in patients with diabetes in the period immediately prior to the initiation of chronic dialysis; this may be explained if chronic foot ulcers accelerate a decline in renal function. We sought to examine this further by describing changes in renal function associated with hospitalisation for diabetic foot ulcer management.

Methods: All patients admitted to our centre during 2013 with ICD10 coding for diabetes and a primary diagnosis of foot ulcer (L97x) were identified. Data were manually extracted for those with a relevant clinical episode and sufficient biochemical results from routine clinical care. Patients undergoing amputation were excluded. Absolute creatinine and eGFR (CKD-EPI) values were collected from 6 months (+/- 1 month) pre and post hospital admission.

Results: 95 patients were included. 67 men, median age 68 years (range 31-96). Renal function was worse after an admission with an active diabetic ulcer; 6 months prior to hospital admission the mean eGFR was 72 +/- 25 SD ml/min/1.73m² compared to 67 +/- 27 SD ml/min/1.73m² 6 months after admission, p=0.01. 27% of the admissions were associated with acute kidney injury (AKI stage 1, 2, 3: 19, 6, 1 patients respectively). Patients who sustained AKI during the admission had larger changes in eGFR than those patients without; median decline of -2ml/min/1.73m²/year(IQR 6,-11) versus -5 ml/min/1.73m²/year(IQR 2,-28), p=0.008.

Conclusions: These data add strength to the hypothesis that an active diabetic foot ulcer may contribute to a decline in renal function, particularly when associated with an episode of AKI. This decline may also be under-estimated due to loss of muscle mass and subsequent over-estimation of eGFR in the post hospitalisation period. These results support additional prospective epidemiological and mechanistic studies to further explore the relationship between diabetic foot ulcers, AKI and CKD progression.

PUB198

Gender – An Additional Cardiovascular and Chronic Kidney Disease Risk Factor in an Apparently Healthy Population Attilio Di Benedetto,¹ Annalisa Ciotola,¹ Fabrizio Cerino,¹ Annamaria Colao,² Daniele Marcelli,³ Bernard J. Canaud.³ ¹NephroCare Italy, Naples, Italy; ²Medicina Clinica e Chirurgia, Univ Federico II, Naples, Italy; ³Fresenius Medical Care, Bad Homburg, Germany.

Background: Cardiovascular disease (CVD) is on the rise, presenting significant societal and economic burden. Early detection of CVD and chronic kidney disease (CKD) risk factors may prevent related complications. We report results of a CVD and CKD risk factor screening program in an apparently healthy population.

Methods: Participants and spectators of the “Prevention Races” held in 2013/2014 in Naples/Salerno (Italy) were screened for CVD and CKD risk factors by different specialists, including nephrologists. Parameters assessed were: systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, waist circumference, BMI, and body composition. Lean (LTI) and Fat (FTI) tissue indexes and overhydration were evaluated by Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany) using multi-frequency bioimpedance spectroscopy at 50 different frequencies.

Results: 701 subjects (38.5% m; 61.5% f) were evaluated. Mean age was 54.54 + 15.6 (m) and 50.06 + 15.2 (f). 3.7% m and 6.8% f had dyslipidemia; 5.9% m and 3.0% f were diabetic; 18.6% m and 11.4% f were hypertensive; 2.2% m and 0.7% f had heart disease; 0% m and 3.5% f had hypothyroidism; 1.5% m and 1.2% f had CKD. Gender differences in SBP, DBP, overhydration, FTI, LTI and BMI are shown (Table).

GENDER	SBP (mmHg)	DBP (mmHg)	Overhydration (% of ideal BW)			FTI (%)			LTI (%)			BMI (kg/m ²)			
			<-1.0L	>-1.0 <-0.5L	>1.0L	low	normal	high	low	normal	high	<25	25-30	>30	
Male	135.39 ± 18.4	79.97 ± 10.9	8.7%	43.6%	47.7%	1.5%	80.3%	18.2%	28.0%	47.4%	4.5%	0.7%	25.7%	49.1%	24.5%
Female	121.85 ± 18.0	79.28 ± 10.0	15.3%	50.7%	34.0%	3.5%	79.7%	16.7%	21.5%	72.9%	5.7%	4.4%	41.7%	31.2%	22.6%

Waist circumference was higher than normal (i.e. ≥88 cm for f and ≥102 cm for m) in 38.4% (m) and 51.6% (f).

Conclusions: In a large sample of apparently healthy persons, males had more CVD and CKD risk factors than females, such as SBP, overhydration, and FTI. In association with other CVD risk factors, these increase morbidity and mortality. Evaluation of body composition is important in the general population for identification of CVD and CKD risk.

PUB199

Potential Effect of Treatment of Metabolic Acidosis on Reducing the Risk of End Stage Renal Disease in Chronic Kidney Disease Solomon Dalezman, Candace D. Grant, Vladimir Liberman, Alejandro Pepen Romero, Shayan Shirazian, Nobuyuki (Bill) Miyawaki, Joseph Mattana. *Medicine, Winthrop- Univ Hospital, Mineola, NY.*

Background: There is increasing evidence that low serum bicarbonate levels impact adversely on the progression of chronic kidney disease (CKD) to end stage renal disease (ESRD). It is plausible that treatment could result in a significant reduction in ESRD incidence though the potential impact in a CKD population and number needed to treat (NNT) are incompletely understood. We carried out the present study to estimate the potential impact of treatment of metabolic acidosis on the incidence of ESRD in a population of CKD patients.

Methods: We evaluated a cross section of 623 Stage 3 and 4 CKD patients at our institution. Their risk of developing ESRD at 2 and 5 years was estimated using the method of Tangri et al (*JAMA* 2011;305:1553-1559) which incorporates age, gender, eGFR, urine albumin to creatinine ratio, calcium, phosphorus, albumin, and bicarbonate. ESRD risk was then recalculated after assuming correction of all serum bicarbonate levels to 28 mEq/L.

Results: The population had a mean serum bicarbonate level of 24.3 mEq/L, with 79.5% having levels below 28 mEq/L. When ESRD risk was calculated following correction of low serum bicarbonate levels to 28 mEq/L, 16 fewer patients were predicted to develop ESRD at 2 years and 27 fewer at 5 years (relative risk reductions of 0.31 and 0.23 respectively). This effect was greatest for patients with CKD stage 4, accounting for 13 fewer ESRD patients predicted at 2 years and 20 fewer at 5 years. For the population as a whole, the NNT to prevent one case of progression from CKD to ESRD was 40 and 23 at 2 and 5 years respectively, while for those with CKD stage 4 the NNT was only 16 and 11.

Conclusions: Our findings suggest that in a population of CKD patients correction of metabolic acidosis could potentially result in a substantial reduction in the number who reach ESRD given the large numbers of patients with low serum bicarbonate levels. Prospective studies are needed to determine whether sodium bicarbonate therapy in populations of CKD patients could prevent many cases of ESRD.

PUB200

The Impact of Vascular Disease on Risk of Development of End Stage Renal Disease in Patients with Chronic Kidney Disease Vladimir Liberman, Sairah Sharif, Candace D. Grant, Alejandro Pepen Romero, Shanza Mujeeb, Nobuyuki (Bill) Miyawaki, Shayan Shirazian, Joseph Mattana. *Medicine, Winthrop-Univ Hospital, Mineola, NY.*

Background: Patients with chronic kidney disease (CKD) are not only at higher risk for development of end stage renal disease (ESRD) but also suffer disproportionately from vascular disease (VD), with associated high cardiovascular mortality. VD can plausibly impact progression of CKD and increase the risk of ESRD. However, VD also shortens survival, and may therefore reduce the risk of ESRD by increasing the competing risk of death. In the present study we evaluated the relationship between VD and the risk of development of ESRD in patients with CKD.

Methods: We carried out a retrospective cross sectional study of 623 CKD patients and recorded demographic, clinical and laboratory variables. We divided them in two groups based on presence or absence of VD and stratified them into different age groups. We estimated the risk of ESRD progression using the method of Tangri et al (*JAMA* 2011;305:1553-1559) and compared the risk levels between each group.

Results: Out of 623 patients with CKD 285 had VD (coronary artery disease and/or peripheral vascular disease) documented in the record. Patients with VD were significantly older than patients with no VD (76 vs 70 years), had lower serum albumin (4.0 vs 4.1 g/dL) and lower eGFR (33.8 vs 36.4ml/min/1.73 m²). We found that older patients with VD had significantly higher risk of developing ESRD. For the 70 to 79 year age group the 2 year risk was 2.45 vs 1.50 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03) in patients with and without VD. For patients ≥80 years the 2 year risk of developing ESRD was 2.18 vs 1.35 (p=0.029) and 5 year risk of developing ESRD was 6.80 vs 4.31 (p=0.03).

Conclusions: Our findings suggest that older patients with VD may be at increased risk for the development of ESRD despite the higher competing risk of death. This may be partly due to shared pathophysiological mechanisms between atherosclerosis and CKD progression. If validated in an ongoing prospective study this finding would suggest that VD should be considered a risk factor predisposing to an increased risk of developing ESRD.

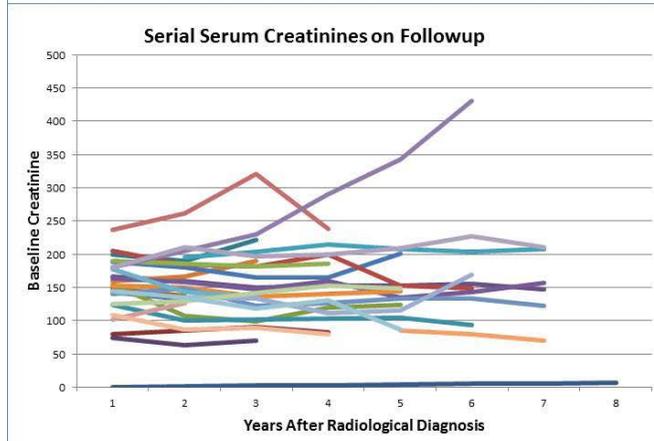
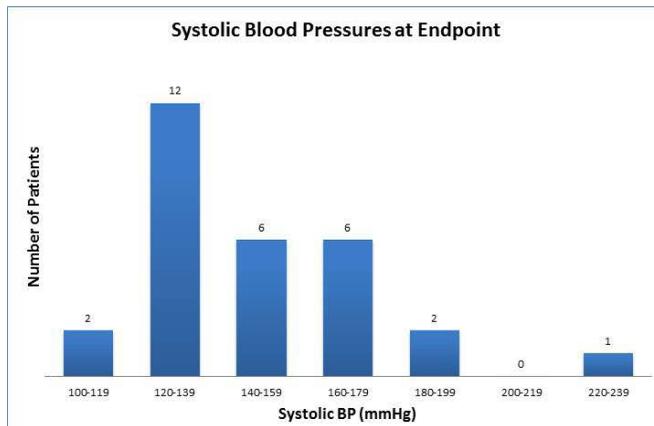
PUB201

Management of Renal Artery Stenosis Post-ASTRAL and CORAL: Outcome of Patients with Radiologically Confirmed Atherosclerotic Renal Artery Stenosis Treated Conservatively Moheen Mohammed Ahmed,¹ Nicholas John Railton,² Abdelgalil Abdelrahman Ali,¹ Anthony Chan.¹ *¹Renal Medicine, Mid Essex NHS Trust, Chelmsford, United Kingdom; ²Radiology, Mid Essex NHS Trust, Chelmsford, United Kingdom.*

Background: Following the publications of ASTRAL and CORAL trials, the use of percutaneous renal artery angioplasty and stenting (PRAS) in the treatment of atherosclerotic renal artery stenosis (ARAS) has fallen dramatically. We report the outcomes of patients with radiologically confirmed diagnosis of ARAS who did not undergo PRAS and were managed medically.

Methods: Retrospective review of all patients undergoing CT/MRI angiography for suspected ARAS from 2008-2014 in Broomfield Hospital, Essex. Patients with more than >50% stenosis in a renal artery who were medically managed and did not undergo PRAS were included in analysis. They were followed for blood pressure control, renal events and mortality.

Results: 29 patients were identified, all Caucasians with a median age of 78 (49-85 years) of which 59% were males. None underwent PRAS. They were followed up from diagnosis till December 2014 or date of death with a mean period of 51 months. Systolic BP at end of study was <140 mmHg in 48%, 140-200 in 48% and >200 in 4% of patients. 69% were on 3 or more antihypertensives with 34% on renin-angiotensin system blockade. 20 patients were CKD 3 and 8 with CKD 4 at baseline, with 3 patients progressing from stage 3 to 4 and 1 to stage 5 CKD, requiring dialysis.



13 out of 29 patients were dead at the end of study.

Conclusions: From this study of patients with ARAS not indicated for PRAS, only a small number progressed to higher grades of CKD. Blood pressure control appeared adequate in a significant proportion of patients. This is in keeping with the findings from ASTRAL/CORAL trials and may be of significant benefit in terms of cost and reducing patient morbidity.

PUB202

Clinical, Laboratorial and Immunological Characteristics of Membranous Nephropathy in Kidney Transplantation Patients Artur Quintiliano Silva, Juliana Busato Mansur, Marisa Petrucelli Dohar, Gianna Mastroianni-kirsztajn. *Dept of Nephrology, UNIFESP, Sao Paulo, Brazil.*

Background: Membranous nephropathy (MN) is one of the more common causes of nephrotic syndrome in the adult population and may occur in the transplanted kidney. The goal of this study was to describe clinical and laboratorial characteristics of membranous nephropathy in kidney transplantation patients. A total of 41 patients was studied. The first proteinuria was with 48 months and time at diagnosis was 57.9 months. Eleven patients had a secondary cause of MN. Independently of the immunosuppressive regimen occurred MN.

Methods: The characteristics evaluated were graft survival, time to onset of symptoms, patient profiles, treatment evolution, time from onset of symptoms to graft loss, immunosuppression used before and after the diagnosis of membranous nephropathy post transplant (MNPT), blockers of the renin-angiotensin-aldosterone system, proteinuria levels and time of biopsy x beginning of the onset of symptoms with disease progression.

Results: The mean age of the receptor was 49.4 years and 58.5% were males. The most common comorbidities were HBP (96.7%), dyslipidemia(22%), neoplasia (12.2%), diabetes (9,1%), SLE (7.3%) and hepatitis (7.3%). Induction therapy to prevent acute rejection during the early post transplant period was used in 9 (21.9%) patients (8 antithymocyte and 1 basiliximab) followed up by initial immunosuppression with PRED+CNI+AZA (56.1%) and PRED+CNI+MPA (34.1%). The end immunosuppression was Pred+CNI+AZA (29.2%), Pred+CNI+MPA (41.1%). Secondary MN causes had a more benign course (graft function) than the primary causes. Death censored graft survival in 10 years was 58.6%.

Conclusions: About 50% of grafts which develop de novo MGN eventually fail. This rather poor outcome may not represent the natural history of de novo MGN per se but rather the consequences of associated chronic rejection. Evidence is presented that many of the cases of so-called de novo MGN may be a complication of transplant glomerulopathy rather than being caused by mechanisms totally independent from rejection. The beneficial effects of immunosuppression agents have not been validated.

PUB203

Factors Influencing Initiation and Choice of Immunosuppressive Therapy in Primary FSGS Louis-Philippe Laurin,¹ Bethany J. Foster,⁴ A. Gasim,² Caroline J. Poulton,³ J. Charles Jennette,² Ronald J. Falk,³ Patrick H. Nachman.³
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Background: The treatment of patients with primary focal segmental glomerulosclerosis (FSGS) may include immunosuppressive therapy in patients not responding to conservative treatment or considered at high risk of progression to renal failure. We sought to determine the patient and disease characteristics associated with choice of therapy early in disease course.

Methods: Inception cohort of biopsy-proven patients with primary FSGS diagnosed between 1980 and 2012. Factors influencing choice of therapy were identified using multiple logistic regression; we report odds ratios (OR) with 95% confidence interval (CI).

Results: 458 patients were studied (183 on no immunosuppressives; 173 treated with glucocorticoids [GC] alone; 90 with calcineurin inhibitors [CNIs] ± GC; 12 with other immunomodulatory agents).

	No immunosuppression N=183	Immunosuppression N=275
Median age (yr)	48 (32-63)	36 (18-55)
Female sex (%)	48.1	49.1
Black race (%)	45.1	45.9
Median eGFR (mL/min/1.73m ²)	43.8 (27.2-69.9)	62.8 (41.7-85.7)
Median proteinuria (g/d)	3.8 (2.4-6.6)	6.0 (3.5-12.0)

Tip lesion variant (OR 3.00; 95% CI 1.23-7.32), eGFR ³30 mL/min/1.73m² (OR 1.89; 95% CI 1.01-3.45) and hypoalbuminemia (OR 2.22 per g/dL lower; 95% CI 1.59-3.13) were associated with a higher likelihood of any immunosuppressive treatment. Only tip lesion was associated with choice of GC alone vs. CNIs (OR 0.17; 95% CI 0.05-0.53).

Conclusions: Presence of tip lesion, preserved renal function at baseline and more severe hypoalbuminemia are associated with immunosuppressive therapy in primary FSGS, but only tip variant appears to influence choice of GC alone over CNIs.

PUB204

A Performance-Enhancing Drug and Its Depressing Effects Wajdi Bader
Internal Medicine, John Stroger Hospital of Cook County, Chicago, IL.

Background: Anabolic steroid use is a habit with a global 3.3% lifetime prevalence rate and is well known for its adverse effects on the renal, endocrine, hepatic, and hematologic systems. We bring a case of focal segmental glomerular sclerosis (FSGS) in a known user of anabolic steroids.

Methods: A previously healthy 28 year old male had presented to our hospital after being told he had kidney damage during a recent routine check up. On presentation, he complained of generalized weakness of one month's duration; the social history was significant for use of Mutant Plexx, a bodybuilding supplement that contained an anabolic steroid, methylstebolone. On admission, his vitals were pertinent for a blood pressure of 189/109 and a heart rate of 82. His physical exam noted a muscular male with normal cardiovascular, respiratory, and abdominal exams. On labs the patient had a BUN of 59, a creatinine of 5.6, and a hemoglobin of 13.1. A urinalysis showed 1 WBC, 2 RBCs, and 1+ protein. Nephrology team was consulted for further workup. Urine microscopy was performed and showed no dysmorphic RBCs. Spot urine protein/creatinine ratio was 2.2 grams. HIV was negative; HBsAg, HBsAb, and hepatitis C antibody were negative. Three days into his admission, the patient had an ultrasound guided kidney biopsy. On biopsy, half of the glomeruli had segmental scars, some with collapsing features. The interstitium had areas of fibrosis and the arteries showed mild sclerosis and arterioles with hyalinosis. The patient was diagnosed with collapsing FSGS secondary to anabolic steroid use; he was educated on control of hypertension and was advised to stop using anabolic steroids.

Conclusions: FSGS, the third most common cause of nephrotic syndrome after minimal change and membranous nephropathy, is usually attributed to HIV or obesity. The pathophysiologic cause of FSGS secondary to anabolic steroids is thought to be due to intraglomerular hypertension. In addition, high protein diets are known to cause an elevation in glomerular pressure. Collapsing FSGS is most common variant in anabolic steroid users, and is associated with the poorest prognosis. The treatment is discontinuation of steroid use and control of hypertension, preferably with an ACEi or ARB.

PUB205

Uric Acid Is Independent Risk Factor for Progression of Renal Dysfunction in IgA Nephropathy Female Patients Yasuyuki Nagasawa,¹ Ryohei Yamamoto,² Maki Shinzawa,² Sayuri Kawada,¹ Katsuyuki Nagatoya,³ Aritoshi Kida,¹ Tatsuya Shoji,⁴ Yukiko Hasuike,¹ Terumasa Hayashi,⁴ Takahiro Kuragano,¹ Atsushi Yamauchi,³ Yoshitaka Isaka,² Takeshi Nakanishi.¹
¹Dept of Internal Medicine, Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; ²Dept of Nephrology and Geriatric Medicine, Osaka Univ, Suita, Osaka, Japan; ³Dept of Internal Medicine, Osaka Rousai Hospital, Sakai, Osaka, Japan; ⁴Dept of Nephrology, Osaka General Hospital, Osaka, Japan.

Background: IgA nephropathy is one of common primary glomerulonephritis. Hyperuricemia could be caused by reduced renal function. Therefore, it was difficult to distinguish hyperuricemia from the factors which promote renal dysfunction. Recently, several reports indicated that hyperuricemia might be independent risk factor for renal worsening, but there was little information about the effect of hyperuricemia itself upon progression of kidney diseases, especially in IgA nephropathy patients. Aim is to reveal effect of uric acid upon renal prognosis in IgA nephropathy patients.

Methods: This study is retrospective cohort study. Subjects were 923 IgA nephropathy patients who had not been treated uric acid lowering drugs, from 1001 IgA nephropathy patients who were diagnosed by renal biopsy, and over 15 years old in Osaka University Hospital, Osaka general medical center, Osaka Rosaki Hospital. Outcome was 1.5 times of serum creatinine. Exposure is uric acid at renal biopsy. Explanatory variables included sex, age, BMI, blood pressure, baseline eGFR, proteinuria, smoking status.

Results: Mean age was 34[23-46] years, proteinuria was 0.40[0.18-0.89] g/day. Uric acid was 6.5+-1.3mg/dl in male patients, and 4.8+-1.3mg/dl in female patients. Multivariate Poisson regression analysis revealed that uric acid was significant risk for progression of renal disease [Hazard Ratio 1.30[1.01-1.65] UA per 1mg/dl] in female patients along with proteinuria(g/day) [HR 1.27[1.08-1.47],p<0.001], Creatinine (mg/dl) [HR 2.73[1.84-3.74]]. In male patients, uric acid was not independent risk factor.

Conclusions: Hyperuricemia is independent risk for progression of kidney disease in female IgA nephropathy patients.

PUB206

Long-term H.P. Acthar® Gel Treatment of Relapsing Idiopathic Membranous Glomerulopathy: A Case Study Firas Marayati. *Southwest Kidney Inst, Gilbert, AZ.*

Background: Long-term treatment with H.P. Acthar® Gel (repository corticotropin injection, Questcor Pharmaceuticals, Inc., Hayward, CA), an FDA-approved treatment for remission of proteinuria associated with nephrotic syndrome, was examined in a patient with biopsy-confirmed idiopathic membranous glomerulopathy (iMN).

Methods: A retrospective clinical record review examined Acthar Gel treatment over 2 years and 8 months in a patient with iMN who received prescription-based treatment in a clinical practice. Outcomes included proteinuria level (mg/g), serum creatinine (SCr), serum albumin and treatment-related side effects. Complete remission was defined as proteinuria <500 mg/g. Partial remission was defined as ≥50% reduction in proteinuria from baseline and proteinuria 500-3500 mg/g.

Results: The 54-year-old Vietnamese patient with iMN was treated over 7 years. At diagnosis, the patient's proteinuria was 8000 mg/g, SCr 0.7 mg/dL, and serum albumin 2.1 g/dL. Initial treatment included prednisone, cyclosporine, mycophenolate mofetil, tacrolimus, and rituximab over 4.5 years. The patient showed partial or complete remissions followed by relapse. At Acthar Gel initiation, proteinuria was 3400 mg/g, SCr 0.6 mg/dL, and serum albumin 4.2 g/dL. The patient did not tolerate 80 U twice weekly but did tolerate 40 U twice weekly. At 4 months, she showed complete remission (proteinuria <150 mg/g). Dose reduction to 20 U twice weekly resulted in relapse 7 months later (proteinuria 2300 mg/g). Dose increase to 40 U twice weekly led to complete remission 4 months after that. Loss of insurance and cessation of Acthar Gel for 4 months led to relapse (proteinuria 7700 mg/g). Acthar Gel was re-started at 32 U twice weekly followed by 24 U twice weekly. Partial remission occurred 4 months later (proteinuria 2100 mg/g) with greater improvement at 10 months (proteinuria 800 mg/g). The patient has maintained partial remission (proteinuria 970 mg/g) 4 months post-therapy. Side effects over the course of Acthar Gel therapy included fatigue, myalgia, hyperglycemia, and weight gain.

Conclusions: Long-term treatment with H.P. Acthar Gel may help meet an important treatment need in patients with treatment-resistant and frequently-relapsing iMN.

Funding: Pharmaceutical Company Support - Funding for editorial support provided by Mallinckrodt Pharmaceuticals.

PUB207

Outcome of Steroid Dependent (SDNS) and Frequent Relapsing Nephrotic Syndrome (FRNS) in Children Isabel Roberti, Shefali Vyas. *Children's Kidney Center, Saint Barnabas Medical Center, Livingston, NJ.*

Background: Management of SDNS and FRNS in children can be frustrating. With the goal of minimizing steroid toxicity while achieving a sustained remission multiple regimens have been used with variable results. We reviewed our cases of SDNS/FRNS who had kidney biopsy (Bx) after failing MMF, for the past 12 yrs.

Methods: Charts of children with Bx due to SDNS or FRNS (after failure of MMF) were reviewed. Congenital and secondary causes of NS were excluded. Demographics, medications, side effects and response to therapy were studied. IV cytoxan (CYP) was considered in non-FSGS cases with suspected non-adherence (800 mg/m2/dose monthly

x 3). Others received tacrolimus (TAC) (0.1mg/kg BID; trough up to 6 ng/ml). Rituximab (705mg/m² x 2 doses IV) was given if child became TAC dependent or resistant. Response to therapy was classified as: complete remission (CR), partial remission (PR), infrequent relapse (IR)(<2 /yr), failure (F).

Results: 32 children had kidney biopsy (Bx) for primary SDND/FRNS. 14 females; 14 H, 10 AA, 6 C, 2 other race. **Age at presentation:** 2-14 yrs (median= 3 yrs). **Bx:** 15 MCNS (4 diagnosed later with FSGS), 9 IgMN, 5 FSGS, 3 C1QN, 1 idiopathic immune mediated GN. All children had normal GFR at the time of the bx. **24 children received TAC:** 21 CR (13 became TAC dependent with IR), 2 PR, 1 F; **15 received CYP:** 6 CR, 9 F (4 had initial diagnosis MCNS but later bx had FSGS); **7 received rituximab:** all had CR (5 IR). The rates of CR were significantly higher for TAC (87.5%) and rituxan (100%) as CYP had a failure rate 60% (p<0.01), including 4 cases with MCNS. However, those who had CR from CYP didn't have further relapses. Rate of IR among those who initially had CR was similar between rituximab and TAC. **Follow-up time:** 2-12 yrs (median= 4 yrs), including 6 discharged due to stable CR and 3 ESRD (all with FSGS). **Side effects:** 4 AKI with TAC (reversible), 2 respiratory distress/allergy in rituximab group (IV D/C). Late TAC resistance was seen in 3 patients.

Conclusions: Children with SDND/FRNS despite failure to respond to MMF had an excellent outcome. Some required sequential use of tacrolimus and rituximab after failure of CYP with a rate of CR/IR >88% with minimal side effects.

PUB208

Granulomatosis with Polyangiitis (GPA) versus Sarcoidosis *Sruthi Jinna,¹ Sami S. Zarouk,² ¹Internal Medicine, Beaumont Health, Royal Oak, MI; ²Nephrology, Beaumont Health, Royal Oak, MI.*

Background: An African American male was diagnosed at age 18 with GPA by kidney biopsy with negative serology. He was treated with intravenous cyclophosphamide and steroids. Four months post treatment a repeat kidney biopsy showed focal segmental glomerulosclerosis (FSGS). At age 25, he presented with fever, fatigue and cough for few weeks, chronic postnasal drip with bloody secretions, nausea, vomiting, and 40-pound weight loss in the last two months.

Methods: His BUN was 18 mg/dl, and creatinine 1.33 mg/dl. Urinalysis showed 3+ blood, 2+ protein, over 100 RBCs, 10 WBCs. Serology for Hepatitis B and C, HIV, EBV and CMV were negative. Antinuclear antibody, anti-neutrophil cytoplasmic antibody, anti dsDNA antibody, smith antibody, RNP antibody, myeloperoxidase antibody, proteinase 3 autoantibody, anti SSA antibody, anti SSB antibody, and complement levels were negative. An angiotensin converting enzyme (ACE) level was 81 U/L (8-52). A chest Computed Tomography scan showed mediastinal, hilar lymphadenopathy, and multiple pulmonary nodules.

Results: Suspicion for relapsing GPA prompted renal biopsy. It showed 3 out of 13 glomeruli with pauci-immune crescentic glomerulonephritis. There were extensive non-caseating granulomas in the interstitium with interstitial fibrosis and associated tubular atrophy. No microorganisms were noted on AFB and PAS stained sections. Nasal septum biopsy showed non-necrotizing granulomatous inflammation. Mediastinal lymph node biopsy showed necrotizing granulomatous lymphadenitis. These 3 biopsy sites were consistent with sarcoidosis.

Conclusions: This case highlights the difficulty in differentiating between ANCA negative GPA versus sarcoidosis as both can cause granulomatous lesions. Glomerular involvement in sarcoidosis can show membranous glomerulonephritis, FSGS and rarely a crescentic glomerulonephritis. In our opinion, high ACE level combined with extensive presence of non-caseating granulomas in the nasal septum, mediastinal nodes and renal interstitium are more characteristic of sarcoidosis. He responded well to steroids and his urine sediment became inactive, which is in favor of sarcoidosis and not GPA.

PUB209

Epidemiology of Glomerulonephritis in Southern Arizona *Benjamin Kwesi Sarsah, Irfan K. Moinuddin, Bijin Thajudeen, Amy Nicole Sussman, Pradeep V. Kadambi. Nephrology, Univ of Arizona, Tucson, AZ.*

Background: Knowledge about the incidence and prevalence of GN and its regional trends are mandatory for health care planners to adopt measures for preventing patients with glomerular disease from progression to dialysis. The aim of the study was to look at the patterns of biopsy proven non-diabetic glomerulopathy in Southern Arizona.

Methods: Renal biopsy specimens from adult patients above the age of 18 years with glomerular renal disease were included. Renal transplant biopsies showing glomerulonephritis and biopsies showing co-existing diabetic nephropathies were excluded. Histological diagnoses were grouped into one of the following 8 categories: minimal change disease, FSGS, membranous nephropathy,membrane-proliferative glomerulonephritis, pauci-immune glomerulonephritis, IgA nephropathy, lupus nephritis and others. Demographic parameters were systematically collected from the medical records archive.

Results: The most common histopathological diagnosis was FSGS followed by membranous nephropathy and IgA nephropathy. There was male preponderance in all histological variants except IgA nephropathy, lupus nephritis and pauci-immune glomerulonephritis. The race distribution was uneven, and all histological variants except minimal change disease and lupus nephritis were more commonly seen in whites. In separate analysis of the histological pattern in Hispanics, lupus nephritis was found to be the most common pathology followed by FSGS. In American Indian population the most common pathology was IgA nephropathy followed by FSGS. Bar diagram represents frequency of each glomerular disease

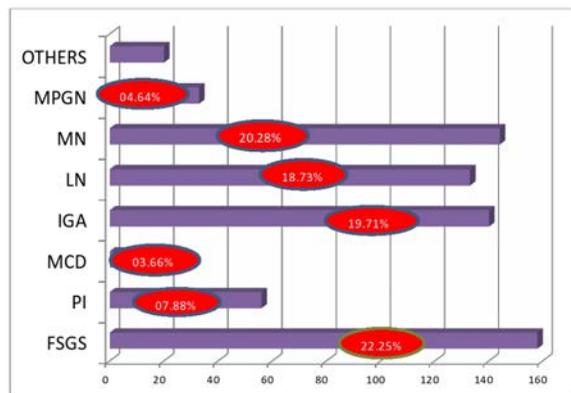


Figure 1: Bar diagram showing frequency of glomerular diseases

MPGN: membranoproliferative glomerulonephritis; **MN:** membranous nephropathy; **LN:** lupus nephritis; **IGA:** IgA nephropathy; **MCD:** minimal change disease; **PI:** pauci-immune glomerulonephritis; **FSGS:** focal segmental glomerulosclerosis.

Conclusions: This survey highlights the histopathological patterns of glomerular disease in southern Arizona. The data suggest regional and ethnic variations in glomerular disease that may suggest genetic or environmental influence in the pathogenesis of glomerular diseases.

PUB210

Use of Rituximab to Induce Remission in Frequently Relapsing Pediatric Nephrotic Patients *Jason Peter Thomas,¹ Teri L. Crumb,² Alejandro Quiroga,² ¹Pediatrics, Helen DeVos Children's Hospital, Grand Rapids, MI; ²Pediatric Nephrology, Helen DeVos Children's Hospital, Grand Rapids, MI.*

Background: Rituximab has been shown to be effective in patients with frequent relapsing nephrotic syndrome (NS) with a reported 82% response rate. We evaluated the clinical response of pediatric nephrotic patients for induction of remission following one dose of rituximab.

Methods: This is an IRB approved, prospective clinical research trial. Informed consent was obtained from each family. Four pediatric patients with NS were enrolled prior to their clinically indicated rituximab infusion. Urine Protein/Creatinine ratio and albumin blood levels were collected.

Results: Urine Protein/Creatinine ratios obtained post infusion of rituximab decreased between 37-93% from pre infusion levels. 50% of patients identified had resolved edema noted on physical exam post infusion.

Conclusions: Rituximab may be an effective agent for inducing remission for pediatric patients with frequently relapsing nephrotic syndrome. 50% of patients had clinical response on physical exam post infusion and 100% of our patients had a decrease in the amount of protein excreted in their urine. The use of rituximab for the induction of remission is a novel and innovative treatment option for children with frequently relapsing nephrotic syndrome, warranting further investigation.

Funding: Private Foundation Support

PUB211

Lupus Nephritis: An Exploration of Management Style *Abhishek Nandan, Huzaifah J. Syed, Christen Vagts, Jason M. Kidd. Internal Medicine, Virginia Commonwealth Univ Medical Center, Richmond, VA.*

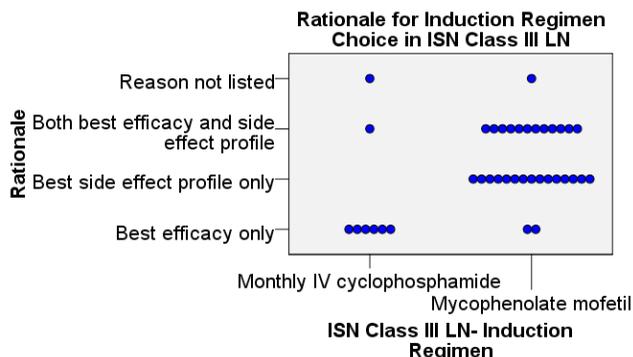
Background: We aim to evaluate the differences and rationale behind the diagnostic and therapeutic approaches to proliferative lupus nephritis (LN) among nephrologists and rheumatologists.

Methods: A de-identified, multiple-choice survey was distributed to nephrologists and rheumatologists. The survey consisted of a demographic questionnaire and two case vignettes exploring the decision of when to biopsy, management of ISN Class III LN, and management of refractory ISN Class IV LN.

Results: There were 38 respondents to our survey: 12 rheumatologists and 26 nephrologists. Work setting: 81% academic, 19% non-academic. Management of abnormal UA findings in an asymptomatic lupus patient: 33% of rheumatologists versus 76% of nephrologists chose to biopsy. Induction regimen of ISN Class III LN: 79% of all providers chose MMF and 21% chose IV cyclophosphamide.

Choice of Induction Regimen in ISN Class III LN per Specialty

	Mycophenolate Mofetil	IV Cyclophosphamide	Total
Nephrology	18	8	26
Rheumatology	12	0	12
Total	30	8	38



Maintenance regimen of ISN Class III LN: all surveyed rheumatologists chose MMF as a sole maintenance agent compared to 32% of nephrologists who elected the addition of low-dose corticosteroids to MMF. Choice of an adjunctive agent in refractory ISN Class IV LN: 68% of providers chose rituximab, 14% chose tacrolimus, 5% chose CTLA-4 IgG, and 14% elected not to add any agents listed.

Conclusions: The results of this survey suggest a significant difference among rheumatologists and nephrologists on the decision to perform initial kidney biopsy and management of ISN Class III LN. The results suggest that perception of side effect profiles play an important role in the choice of therapeutics. This study emphasizes the need for a multi-disciplinary approach toward renal disease in lupus patients. We continue to recruit subjects to complete this survey.

PUB212

Maintenance of Proteinuria Treatment Response to H.P. Acthar Gel® in Patients with Nephrotic Syndrome: A Follow-Up Case Series Anupa Khastgir,¹ Geoffrey S. Teehan,² ¹Nephrology Practice, Oklahoma City, OK; ²Lankenau Medical Center, Wynnewood, PA.

Background: The duration of proteinuria response to H.P. Acthar® Gel (repository corticotropin injection, Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO) treatment is not yet known. The current case series examined maintenance of proteinuria response in 7 patients who were included in a previously presented case series of Acthar Gel treatment of treatment-resistant NS in clinical practice.

Methods: Five patients with partial remission (500-3500 mg/d proteinuria and ≥50% reduction from baseline), 1 patient with clinical response (≥30% reduction without meeting remission criteria), and 1 patient with clinical response and ongoing treatment following initial prescription-based Acthar Gel treatment for NS, and who had follow-up clinical care, were included. Medical charts were reviewed for proteinuria levels. Follow-up ranged from 2 to 19 months.

Results: Biopsy-confirmed NS etiological diagnoses included focal segmental glomerulosclerosis (FSGS, n=3), membranous lupus nephritis (MLN, class V, n=2), membranoproliferative glomerulonephritis (MPGN, n=1), and diabetic nephropathy (DN, n=1). 5/5 patients (2 FSGS, 2 MLN, 1 MPGN) with initial partial remission maintained partial remission during the follow-up period from a minimum of 2 months up to 19 months post-Acthar Gel treatment. The patient with MPGN and 1 with FSGS showed increased proteinuria with relapse at 12 months and 19 months post-treatment, respectively. The patient with DN received ongoing Acthar Gel treatment and maintained a proteinuria clinical response during the 11-month follow-up period. The patient reported fatigue but did not require cessation of Acthar Gel treatment. The patient with FSGS who showed an initial clinical response had further improved proteinuria at 2 months post-Acthar Gel treatment and showed partial remission at 12 months post-therapy without intervening immunosuppressive medications.

Conclusions: These follow-up proteinuria outcomes in 7 patients treated with H.P. Acthar® Gel for varied etiology NS suggest the proteinuria treatment response can be maintained long-term in some patients during treatment and beyond treatment cessation.

Funding: Pharmaceutical Company Support - Funding for editorial support provided by Mallinckrodt Pharmaceuticals.

PUB213

Pauciimmune Glomerulonephritis with Immune Deposits: A Clinicopathologic Outcome Study Benjamin Kwesi Sarsah, Irfan K. Moinuddin, Bijin Thajudeen, Amy Nicole Sussman, Pradeep V. Kadambi. Nephrology, Univ of Arizona, Tucson, AZ.

Background: The clinical impact of the immune complexes in pauciimmune GN remains unclear. The objective of this study is to compare the clinical outcome of patients with pauci-immune GN and positive ANCA in the presence and absence of immune deposits on immunofluorescence.

Methods: Cases of pauci-immune GN were identified retrospectively from the archives of native renal biopsies. For inclusion in the study the cases have to meet the following criteria 1) should have full spectrum of histopathological analysis 2) complete follow up information in the chart 3) ANCA positivity 4) negative serologies 5) EM showing absent or scant immune deposits 6) absence of comorbidities 7) absence of co-existing histopathological diagnosis 8) less than 25% glomerulosclerosis. Patients' medical records were reviewed for age, race, gender, parameters of renal function, treatment, and outcome.

Results: Two groups- group which had immune deposits (group 1) and group with no immune deposits(group 2).All patients in group 2 had complete or partial improvement in renal function. None of them were dialysis dependent at any stage of their treatment. On the contrary in group 1, four patients required hemodialysis. (36% vs 0%, p value =0.0001). The group with immune deposits presented with higher mean creatinine (5.10±3.27 mg/dl vs 3.67±1.03 mg/dl, p value 0.195). Relevant demographic,lab and histologic variables are represented in table 1.

Variable	Positive immune deposits N=11 (group 1)	Negative immune deposits N=8 (group 2)	P value
Age (mean±SD) (years)	54.82±21.27	57.75±19.54	0.76
Gender (M/F)	4/7	2/6	0.12
Race (W/H)	6/5	7/1	0.0001
Initial creatinine mg/dl	5.11±3.27	3.67±1.03	0.19
ANCA(P/C)	9/2	7/1	0.33
Crescents (>50/<50)	4/7	3/5	0.88
TIF(mild/mod-severe)	6/5	2/6	0.0001
Type of crescents (C/CF,F)	7/4	1/7	0.0001

Conclusions: Pauciimmune GN with immune deposits has poorer prognosis compared to those without immune deposits. Pauciimmune GN with immune deposits likely represent patients with severe immune complex deposition and partial clearance of immune complex. These are patients who might benefit from plasmapheresis in addition to standard treatment.

PUB214

Eosinophilic Pneumonia with Renal Involvement Gabrielle Goldet,¹ Rachel Hung,¹ Michael Sheaff,² ¹Basildon and Thurrock Univ Hospital; ²Pathology, Barts and the London School of Medicine.

Background: Eosinophilic pulmonary renal syndromes are well established and can be either vasculitic or infectious in aetiology. We describe a novel case of a patient whose presentation could not be fitted into either category.

Methods: A fifty year old male presented with increasing weight loss, night sweats and shortness of breath of 3 months duration. Additionally he noted some swelling of his lower limbs and frothy urine. He was extensively investigated with urinalysis, blood tests, imaging and histopathology till a novel diagnosis was made.

Results: The patient was found to have nephrotic range proteinuria with stable renal function, He had multifocal consolidation on computed tomography of the lungs and eosinophilic infiltrates on lung histology. A kidney biopsy revealed dense subcapsular inflammatory cell infiltrate including eosinophils with possible subendothelial deposits on light microscopy. A vasculitic screen excluded vasculitis as the underlying pathology and no signs of vasculitis were seen on either the lung or kidney biopsies. Additionally fibrin was excluded with negative serology. The patient was treated with steroids and his pulmonary and systemic symptoms resolved. Unfortunately, he has been found to relapse when an attempt at a steroid wean was made and is thus maintained on a low dose of prednisone.

Conclusions: We describe a novel pulmonary-renal syndrome and provide an approach to its investigation and management. This case opens the way for further research into eosinophilic pulmonary-renal syndromes.

Funding: Government Support - Non-U.S.

PUB215

Role of Remission of in Idiopathic Membranous Nephropathy on Long Term Renal Function Outcome Abdulkareem Alsuwaida,¹ Hala M. Kfoury,² Sufia Husain,² Tariq Aljohani,² Saad S. Alobaili,¹ Mohammed A. Al-Ghonaim,¹ Jamal S. Al Wakeel.¹ ¹College of Medicine, King Saud Univ, Riyadh, Saudi Arabia; ²College of Medicine, King Saud Univ, Riyadh, Saudi Arabia.

Background: Heavy proteinuria is considered a poor prognostic marker among patients with idiopathic Membranous Nephropathy (iMN). However, the impact of the remission status on the renal out come in patients with iMN is not well studied. The purpose of this study was to evaluate the long-term prognosis after achieving a complete or partial remission among patients with iMN presenting with heavy proteinuria.

Methods: In this study, 25 patients with iMN with heavy proteinuria defined as ≥ 6 gm per day were evaluated for the effect of a partial remission (50% reduction in baseline proteinuria to ≤ 3 g/d and ≤ 25% increase in baseline creatinine) and complete remission (proteinuria ≤ 0.5 g/d and serum creatinine ≤123 μmol/l) on renal outcomes compared with patients who did not attain a remission. Worse renal outcomewas defined as doubling of the baseline serum creatinine value or development of end-stage renal disease at the last follow up.

Results: The cohort consisted of 20 men and 5 women. The median proteinuria at presentation was 9.4 gm per day (IQR: 6.7-12.1 gm per day) and the median of follow up duration was 7.0 years. The median base line creatinine was 91 μmol/l (IQR: 74-98 μmol/l). A complete remission was attained in 7 (28%) patients, a partial remission in 12 (48%) patients, and no remission in 6 (24%) patients. The worse renal outcome was not observed in all patients who achieved complete remission, but it was seen in 16.7% of the partial remission group and in 66.7% of the no remission group (P value 0.14).

Conclusions: Achieving a complete or partial remission compared to no remission in patients with iMN is associated with a significantly better renal outcome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PUB216

Comparison of Short- and Long-Term IgA Nephropathy Clinical Remission Rates Between Tonsillectomy plus Consecutive and Intermittent Steroid Pulse Therapies Kazuhiro Yoshikawa, Izaya Nakaya, Karen Kato, Yuta Tezuka, Satoshi Kumakura, Jun Soma. *Div of Nephrology, Iwate Prefectural Central Hospital, Morioka, Iwate, Japan.*

Background: Tonsillectomy (Tx) plus steroid pulse therapy (TSP) is widely performed across Japan for clinical remission (CR) of IgA nephropathy (IgAN) but treatment protocol lacks consensus. We used both TSP (methylprednisolone at 0.5 g/day iv for 3 days*) thrice/3 consecutive weeks (TSP-C) and intermittent pulse (*) thrice/6 months (TSP-I). Oral prednisolone (oPSL) between pulse therapies began at 0.5 mg/kg on alternate days. After the third pulse, oPSL was tapered over 1 and 0.5 years in TSP-C and TSP-I groups, respectively. Tx was performed before or during steroid therapies. We compared the effects of two regimens for CR.

Methods: This is a retrospective cohort study of 169 patients newly diagnosed with IgAN during January 2007 to December 2013 in our institute. We enrolled 90 patients we could follow to oPSL cessation and compared short- and long-term CR rates in both groups. CR was defined as urine protein < 0.3 g/gCr and urinary red blood cells < 5/high-power field.

Results: Before treatments, there were no significant clinical [TSP-C (n = 57) vs. TSP-I (n = 33): age, 31.0 ± 11.2 vs. 34.0 ± 11.9 years; male:female, 17:40 vs. 12:21; eGFR, 82.2 ± 29.9 vs. 77.4 ± 28.7 mL/min; blood pressure, 121 ± 17/72 ± 12 vs. 120 ± 17/76 ± 13 mmHg; urinary protein, 0.41 (0.18, 1.19) vs. 0.79 (0.20, 1.08) g/gCr; and positive occult blood, 91.2 vs. 90.9%] and histological grade stratification differences between the groups. At oPSL cessation, short-term CR rates were equivalent between the groups [TSP-C vs. TSP-I: 68.4 vs. 61.0%]. Long-term CR rates at 1, 2, and 3 years after oPSL cessation were equivalent between the groups [TSP-C vs. TSP-I: 1 year, 64.1 (n = 39) vs. 59.1% (n = 22); 2 years, 64.0 (n = 25) vs. 80.0% (n = 10); 3 years, 73.7 (n = 19) vs. 66.7% (n = 6)]. CR continuation rates by Kaplan–Meier method also revealed no significant differences between the groups.

Conclusions: Tx plus either consecutive or intermittent steroid pulse therapies may be equally beneficial for short- and long-term IgAN CR. IgAN patients can flexibly choose therapies.

PUB217

Clinical Characteristics of Multiple Myeloma Patients Diagnosed by Nephrologist Byoung Geun Han, Jae seok Kim, Hyeon-Cheol Park, Shinhan Song, Jae Won Yang, Seung-Ok Choi. *Internal Medicine, Yonsei Wonju College of Medicine, Wonju, Korea.*

Background: Early diagnosis of multiple myeloma (MM) that is in early phase or has atypical presentation may be difficult. Even though MM is a hematologic malignancy, clinicians in different departments can make a diagnosis with a suspicious eye. In our department, we routinely performed protein electrophoresis in the patients with renal failure for the early diagnosis of MM.

Methods: We reviewed the medical records of 151 patients and examined the data of 117 patients diagnosed with MM in our hospital between January, 2003 and December, 2014. The patients were divided into three groups: group I presented to nephrologist prior to diagnosis (n=31), group II presented to hemato-oncologist directly (n=53), and group III presented to the other departments of our institute. The age, sex, initial symptoms, hematologic and biochemical parameters, and survival data were retrospectively analyzed.

Results: The main findings were anemia (n=30), renal failure (n=25), back pain (n=17), paraproteinemia (n=10), rib pain (n=7), mass (n=7), proteinuria (n=7), fracture (n=5), infection (n=4), bleeding (n=3), etc. Osteolytic bone lesion, survival rate, % of plasma cell in bone marrow study, Hb, platelet, CRP, serum albumin and calcium were not significantly different between three groups. 24 hours urine study (amount of proteinuria, protein-albumin ratio, protein-creatinine ratio) did not show any differences. Beta-2 microglobulin and serum uric acid were significantly higher in group I than those in the other groups (p<0.05). Immunoglobulin G, total protein, globulin, and amount of serum M protein were significantly lower in group I than those in the other groups (p<0.05). Distribution of BJ protein positive patients in group I was higher (p<0.05). ISS score was also higher in group I (p<0.05).

Conclusions: Multiple myeloma patients diagnosed by nephrologist did not show typical features of disease. Low levels of total protein and globulin in the patients with renal failure could be a cause of delayed diagnosis of MM. We recommend the protein electrophoresis should be routinely performed in the patients with renal failure.

PUB218

Screening for Renal Involvement in Newly Diagnosed ANCA-Associated Vasculitis Patients in Clinical Practice – Differences Between Hospital Departments Eline Houben,¹ Willem A. Bax,¹ Bastiaan Van Dam,¹ Walentina A. Slieker,² Gideon Verhave,¹ Fenneke C.P. Frerichs,¹ Erik Lars Penne,¹ ¹*Dept of Nephrology, MCA-Gemini Group, Alkmaar, Netherlands;* ²*Laboratory of Clinical Chemistry, Hematology and Immunology, MCA-Gemini Group, Alkmaar, Netherlands.*

Background: Kidney involvement occurs in a majority of ANCA-associated vasculitis (AAV) patients and requires early and aggressive immunosuppressive therapy. The aim of the present study was to evaluate screening procedures for renal involvement in newly diagnosed AAV patients and to identify differences between hospital departments.

Methods: All AAV patients with a positive ANCA (PR3 and/or MPO) between 2005 and 2015 in a secondary care hospital in the Netherlands were included. Patient demographic

data and the department making the diagnosis were recorded, as well as whether or not a complete screening for renal involvement had been made. The latter was defined as assessment of serum creatinine, analysis for erythrocyturia and proteinuria within two weeks before or after the diagnosis AAV.

Results: We included 110 newly diagnosed AAV patients (age 62± 14 years (mean±SD); 63% male). 81 patients (68%) had renal involvement (defined as: rise in creatinine >30%, ³10 RBC/hpf and/or proteinuria ≥500mg/24h). Complete screening was performed in 90 patients (82%), depending on department: Nephrology 100% (21 of 21), Internal Medicine 88% (29 of 33), Pulmonology 68% (15 of 22), Ear Nose Throat 62% (8 of 13), other departments 81% (17 of 21). Of the 20 patients with incomplete screening, assessment of proteinuria was missing in 100% (20 of 20), erythrocyturia in 55% (11 of 20) and serum creatinine in 5% (1 of 20). Serum creatinine was higher in patients with complete renal screening (72 versus 109 μmol/l, p=0.01). Screening was completed within 2 months (n=12), 4 years (n=3), or never (n=5). One patient was found to have erythrocyturia 6 weeks after the diagnosis, but had not been treated accordingly.

Conclusions: In a substantial amount of newly diagnosed AAV patients, screening for renal involvement was incomplete, especially in patients with a normal creatinine level outside the renal department. Incomplete screening may have led to suboptimal treatment in some patients.

PUB219

A Case Series on the Treatment of Nephrotic Syndrome with Natural Adrenocorticotropic Hormone Gel in an Office Setting Marco A. Bonilla, Xavier F. Parada, Mario A. Henriquez. *Nephrology, Bronx Nephrology-Hypertension, Bronx, NY.*

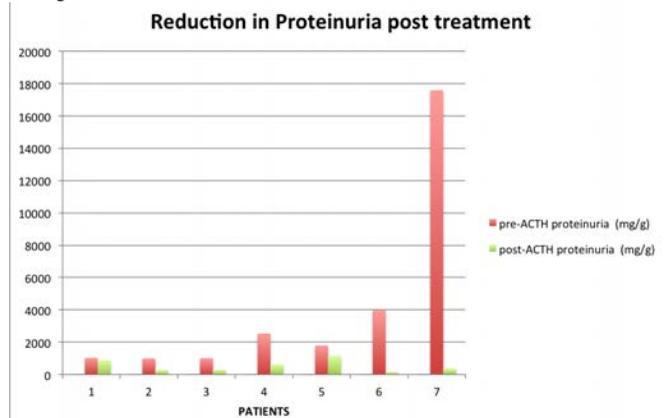
Background: ACTH is a promising treatment for the nephrotic syndrome, associated with significant improvement in proteinuria and relatively few adverse effects. We present our experience using natural ACTH gel for nephrotic syndrome in patients with diverse diagnosis.

Methods: Retrospective case series of 7 Adults patients with nephrotic syndrome, treated with ACTH gel. Data was gathered by chart review, from the clinic EMR and paper based records. ACTH was given in the form of ACTHAR gel 80 USP units/ml SC twice a week for 6 months. Complete remission defined as stable or improved renal function with final proteinuria of <500 mg/day; partial remission as stable or improved renal function with ≥50% reduction in proteinuria and final proteinuria 500 to 3500 mg/day. Failure to meet this criteria was classified as treatment failure.

Results: Table 1. Outcomes

Patient	Age	Gender	Race	Diagnosis	Previous immunosuppression	eGFR (ml/min/1.73 m ²)	Proteinuria pre-ACTH (mg/g)	Proteinuria post-ACTH (mg/g)	Outcome
1	52	M	Hispanic	IgA nephropathy	None	20	1031.2	871	Failure
2	52	M	Hispanic	MGN	Prednisone, MMF	104	1001	290	Failure
3	62	F	Black	MGN	Prednisone	20	1010.4	295.4	Complete
4	73	M	Hispanic	IgA nephropathy	None	48	2540	623	Partial
5	47	M	Hispanic	FSGS	Prednisone, MMF	48	1796	1157	Failure
6	39	F	Hispanic	IgA nephropathy	None	94	4000	161	Complete
7	42	F	Hispanic	MGN	MMF	36	17578	386	Complete

Figure 1.



Conclusions: ACTH gel is an effective therapy in patients with nephrotic syndrome, as significant reductions in proteinuria were seen in the majority of patients, it was not only patients with membranous nephropathy who responded to treatment with ACTH but also patients who were nephrotic due to other diagnosis such as IgA nephropathy; this data highlights a need of further studies on natural ACTH gel in the treatment of nephrotic syndrome.

PUB220

Efficacy of Rituximab in Severe Lupus Nephritis in Children: A Case Series Julien Hogan, Véronique Baudouin, Georges Deschenes. *Pediatric Nephrology, Robert Debré Hospital, Paris, France.*

Background: The association of cyclophosphamide or Mycophenolate Mofetil (MMF) with prednisolone is the treatment of reference of lupus nephritis(LN), both in adults and children but is associated with major side effects. Rituximab (RTX) failed to demonstrate an improvement of patient outcome when associate with MMF and prednisolone. However, recent data suggest that it might allow to spare prednisolone. We report our experience of the use of RTX in first LN flair in children.

Methods: We included patients treated by RTX for a first flair of LN class III to V between 2006 and 2014. Treatment associated methylprednisolone (500mg/m2) followed by RTX (1000mg/1.73m2) at day one and 15 and MMF 1200mg/m2/day. Tapered down and withdrawal of prednisolone was left to each physician appreciation. Complete remission (CR) was defined as a proteinuria over creatinuria ratio (Pu/creat) <50mg/mmol and normal serum creatinine and partial remission (PR) as a Pu/creat<300mg/mmol and no raise of creatininemia over 15% of baseline.

Results: Seven patients were included with a median follow-up of 14.0months [6.0-69.1]. They presented with proteinuria (median 0.24g/mmol [0.05-0.71]), hematuria and 4 out of 7 had impaired renal function (mean GFR 78.4ml/min/1.73m2 [62.6-133.6]). Three had a LN stage IV, three a class IV+V and one a class III+V. Median CD20 depletion time was 10.0 [6-25] months. Prednisolone was rapidly tapered down, the median dose were 0.2, 0.11, 0.05 mg/kg at 3, 6 and 12 month respectively. At 3 months, two patients achieved CR and three PR. Patients without remission had a nephrotic range proteinuria and no renal failure and had LN stage III+V and IV+V. At 6 and 12 months all patients achieved remission. No patient experienced renal relapse, two had an infectious complication and one presented a mild pancreatitis.

Conclusions: A treatment combining RTX, MMF with a rapid decrease of prednisolone seems efficient in severe lupus nephritis. Such protocol may be of major interest in children, since steroids are known to have major side effects in this population. More studies are needed to assess the safety and the efficacy of this treatment and to evaluate the amount of steroids that can be spared through this strategy.

PUB221

Clinical Prognosis of Anti-Neutrophil Cytoplasmic Antibody (ANCA) Negative Pauci-Immune Necrotizing Crescentic Glomerulonephritis: A Retrospective Cohort Study in Korea Sung Woo Lee, Seon Ha Baek, Shin-Young Ahn, Sejoong Kim, Ki Young Na, Dong-Wan Chae, Ho Jun Chin. *Seoul Nation Univ Bundang Hospital.*

Background: Very few studies have reported on the prognosis of anti-neutrophil cytoplasmic antibody (ANCA) negative pauci-immune necrotizing crescentic glomerulonephritis (piNCGN).

Methods: Between July 2003 and December 2013, 48 patients were diagnosed with piNCGN. The ANCA status was tested using indirect immunofluorescence and enzyme-linked immunosorbent assay. The primary and secondary outcomes were 1-year renal and patient survival, respectively.

Results: Among the 48 patients, 6 (12.5%) had ANCA negative piNCGN, while 42 (87.5%) had ANCA positive piNCGN. All ANCA negative piNCGN patients were male and showed high proportion of protein ³3 positive with dipstick test. No significant differences in renal pathology, clinical manifestation, or treatment were noted between the groups. The trend of 1-year end stage renal disease was higher for ANCA negative than ANCA positive piNCGN (66.7% vs. 23.8%; p=0.052). In Kaplan-Meier estimation, ANCA negative

piNCGN showed poorer 1-year renal survival than ANCA positive piNCGN [median (95% CI) 9 (0.0-51.0) vs. mean (95% CI) 287.5 (244.8-330.2) days; log-rank p = 0.010]. In Cox-proportional hazard analysis, ANCA negativity was found to be an independent factor for 1-year renal survival with a hazard ratio (95% CI) of 10.93 (1.03-115.94) compared to ANCA positivity (p=0.047). In contrast, the 1-year all-cause mortality and patient survival did not differ depending on ANCA status.

Conclusions: Although the proportion of ANCA negative piNCGN was not high in our study population, poor 1-year renal survival was noted among these patients. We believe that particular caution should be exercised while treating ANCA negative piNCGN.

PUB222

Clinical Implication of Serum Free Light Chain in Patients with IgA Nephropathy Woo Jin Jung,¹ Sang Heon Song,¹ Su Min Park,¹ Jong Man Park,¹ Il Young Kim,¹ Dong Won Lee,¹ Soo Bong Lee,¹ Harin Rhee,¹ Eun Young Seong,¹ Ihm Soo Kwak,¹ Min Jung Kim,¹ Joo Hui Kim.¹ ¹Dept of Internal Medicine, Pusan National Univ School of Medicine, Busan, Republic of Korea; ²Dept of Internal Medicine, Pusan National Univ School of Medicine, Busan, Yangsan, Republic of Korea.

Background: Free light chains (FLCs) are produced in excess during immunoglobulin synthesis by plasma cells and other cells of the B-cell lineage. Recent studies demonstrated that elevated polyclonal FLCs are associated with increased mortality in chronic kidneys disease. But little is known about the clinical implication of FLCs in patients with IgA nephropathy which is caused by the overproduction of an aberrant form of IgA1 and the activation of B-cells responding to mucosal infection. Therefore, we investigated the relationship between the serum levels of combined FLCs (cFLCs) and prognostic markers in IgA nephropathy.

Methods: This retrospective study analyzed consecutive 42 patients with biopsy-proven IgA nephropathy without renal function impairment (estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73m²) at the Pusan National University Hospital from January 2010 to December 2013. cFLCs was defined as a sum of kappa and lambda FLCs and clinical and laboratory data were collected by medical records reviewing.

Results: The mean (±SD) age were 41.4 (±14.9) years and the median (inter-quartile range) of cFLC and urinary protein-to-creatinine ratio (uPCR) were 40.5 (32.6 – 47.8) mg/L and 666.3 (364.8 – 1306), respectively. In correlation analyses, log-transformed cFLCs was positively related to age, serum cystatin C, IgG and log-transformed uPCR, and negatively associated with serum albumin and hemoglobin levels. In multivariate regression models, increased cFLCs was significantly associated with higher log-transformed uPCR(β(SE)=0.0124(0.006), p=0.045) after adjusting confounding factors. However, no significant association of cFLCs with pathologic classification was observed.

Conclusions: The cFLC level was independently correlated with the magnitude of proteinuria in patients with IgA nephropathy. Further longitudinal studies are needed to clarify the role of cFLC as a prognostic maker in IgA nephropathy.

PUB223

Long Term Renal Outcomes in Lupus Nephritis in a Multi-Racial Asian Population: A Retrospective Study Hui Zhuang Tan, Cynthia Ciwei Lim, Jason Choo Chon Jun, Chan Choong Meng. *Dept of Renal Medicine, Singapore General Hospital, Singapore, Singapore.*

Background: Lupus nephritis causes significant morbidity with racial predilection affecting prognosis and treatment responses. We aimed to evaluate risk factors for progressive CKD in lupus nephritis (LN) in a multi-racial Southeast Asian population.

Methods: We retrospectively reviewed 113 consecutive patients with newly diagnosed biopsy-proven LN diagnosed between 10 May 2001 to 30 May 2009. Demographics, indices of renal function and disease activity, histopathological data and pharmacotherapy were evaluated. Primary endpoint was progressive chronic kidney disease (CKD) defined by doubling of serum creatinine or end stage renal failure.

Results: Median age was 41.6 (IQR 29.2, 51.6) years, predominantly Chinese (76.1%) and female (81.4%). Twelve patients (10.6%) had Class I or II LN, 13 (11.5%) Class III LN, 62 (54.9%) Class IV LN and 25 (22.1%) isolated Class V LN. Eight patients (7.1%) had mixed proliferative and membranous LN. Most patients received either angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (100 patients, 88.5%). Induction immunosuppressants included glucocorticosteroids in 109 patients (96.5%), cyclophosphamide 26 (23.0%), mycophenolate mofetil or mycophenolate sodium 51 (45.1%), cyclosporine 9 (8.0%), and azathioprine 14 (12.4%). Median follow up was 79.0 (61.5, 104.0) months. One hundred and eight patients (95.6%) achieved remission, with complete remission in 89 patients. Among patients who achieved remission, 61 patients had disease relapse. Thirteen patients had progressive CKD at last clinic visit, with ESRD occurring in 5 patients at median 12.0 (1.0, 59.5) months from biopsy. Patients with progressive CKD tended to be non-Chinese (53.8% vs. 20.0%, p=0.01), with higher serum complements [median C3 0.66 (IQR 0.48, 0.87) vs. 0.38 (0.29, 0.60), p=0.04 and C4 0.17 (0.12, 0.22) vs. 0.06 (0.05, 0.12), p=0.004], fewer remissions (69.2% vs. 99.0%, p=0.001) and more relapses (100% vs. 52.5%, p=0.005).

Conclusions: In this multi-racial Asian cohort, race, higher serum complement levels, failure to achieve remission and relapses were associated with poor renal outcomes in lupus nephritis.

PUB224

The Clinical Predictors for Outcome of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis Patients with Renal Involvement

Pu Lei, Guisen Li, Li Wang. *Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Primary anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are chronic multisystem autoimmune diseases and result in dysfunctions of multisystem. Renal involvement is the most common manifestation and is closely associated with the outcome of patients with vasculitis. We investigated the clinical determinants of the early mortality of patients with vasculitis-related renal injury followed up 2 years in a single west Chinese center to study the factors associated with patient outcome.

Methods: A total of 123 consecutive patients with AAV-related renal injury diagnosed in our center were recruited. Clinical and laboratory data were collected retrospectively. All the patients were followed up for 2 years after diagnosis. The predictive values of variables associated with mortality were analyzed.

Results: During 2 years follow up duration, 54 (43.9%) died, of whom 41 died within the first 12 months after diagnosis. Compared with surviving patients, the deceased patients had higher BVAS scores and higher incidence of pulmonary hemorrhage. They also had higher serum creatinine and ESR, lower hemoglobin and complement C3, more patients accepting renal replacement therapy than surviving patients during hospitalization. Higher BVAS scores and serum creatinine >400 μmol/L were the predictors of death in patient with AAV-related renal injury independently.

Conclusions: the incidence of early mortality in patients with AAV-related renal injury was higher. Prudent monitoring and therapy should be given to patients with active vasculitis and serious renal dysfunction to reduce adverse events.

PUB225

Significance of Resistive Index in Renal Arterial Ultrasonography as a Clinical Parameter for Tubulo-Interstitial Nephropathy

Minoru Hatano,¹ Kaori Takayanagi,^{1,2} Taisuke Shimizu,¹ Hiroaki Hara,¹ Nobuyuki Onizawa,¹ Koki Ogawa,¹ Yuka Tanaka,¹ Kunihiko Yasuda,¹ Tomonari Ogawa,¹ Akihiko Matsuda,¹ Hajime Hasegawa.¹ *¹Nephrology and Hypertension, Saitama Medical center, Saitama Medical Univ, Kawagoe, Saitama, Japan; ²Ishikawa Kinenkai Kawagoe Ekimae Clinic, Kawagoe, Saitama, Japan.*

Background: Renal arterial ultrasonography (RA-US) has been principally applied to evaluate the stenosis of the renal artery and the indication of catheter intervention by the measurement of peak systolic velocity (PSV). Resistive index (RI) is calculated as (PSV-EDV)/PSV, where EDV indicates end-diastolic velocity, and is reported to be related to the renal function. In this study, we aimed to investigate the possible clinical benefit of RI for the assessment of tubulo-interstitial nephropathy (TIN).

Methods: We studied 51 patients (51.6±2.3 years old) who underwent RA-US and sufficient laboratory tests for the analysis in the past 10 years in our hospital. PSV and RI were measured at both main renal arteries (RA-measurement) and intra-renal arteries roughly corresponding to the inter-lobular arteries (IRA-measurement). NAG index (urine excretion ratio of N-acetylglucosaminidase (NAG) to creatinine) was used as a conventional clinical parameter for the assessment of TIN.

Results: Stratified analysis by median value of RI (0.69) showed significant difference in eGFR in the RA-measurement (43.4±4.7 vs 60.3±4.2), but not in the IRA-measurement. In contrast, the analysis showed significant difference in NAG index in the IRA-measurement (median: 11.6 vs 5.4), but not in RA-measurement. When the patients showing NAG index ≥ 15, indicating advanced renal insufficiency, would be excluded from the analysis, NAG index significantly correlated with RI of IRA-measurement (R=0.50, p<0.05), but not RA-measurement. In addition, ROC analysis revealed that the cut-off value of RI to NAG index was 0.65.

Conclusions: In addition to the previous report showing the relevance of RI to the histological severity, the present study demonstrated the correlation of RI with the conventional parameter of TIN, NAG index. Particularly, for the assessment of TIN, RI value measured at intra-renal artery would be more beneficial.

PUB226

Recovery of Renal Function with Eculizumab in a Girl with Dense Deposit Disease and Normal Soluble C5b-9 Levels

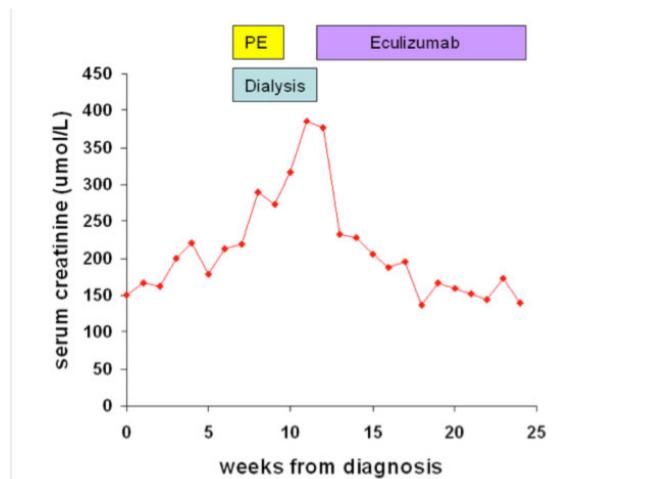
Martin Kömhoff,¹ Arjan Diepstra,² Marc Maj Seelen,³ Coen A. Stegeman,³ Valentina Gracchi.¹ *¹Pediatrics, UMCG, Groningen, Netherlands; ²Pathology, UMCG, Netherlands; ³Nephrology, UMCG, Netherlands.*

Background: Dense Deposit Disease (DDD) is a rare glomerulopathy characterized by electron-dense deposits in the glomerular basement membrane (GBM) and glomerular complement deposition. 50% of patients progress to ESRD and have recurrences after kidney transplantation. Dysregulation of the alternative complement pathway plays a key role in the pathogenesis. Increased soluble C5b-9 in blood is considered to predict response to eculizumab, an anti-C5 monoclonal antibody.

Methods: We report the case of a previously healthy 15-year-old girl who presented with acute kidney injury, hypertension, nephrotic syndrome (10.8 gr protein /24 hours) and microscopic hematuria.

Results: Biochemical (C3 & 4, sC5b-9, factors H & I, C3 nephritic factor and anti-FH) and genetic workup of the complement system (CFI, CFB, C3 and MCP) showed normal results, except for a slightly increased C3d and a risk allele in the CFH gene. Renal biopsy showed cellular crescents and electron-dense deposits in the GBM. Glomerular

C3 and C5b-9 immunofluorescence staining was positive. Despite escalating therapy, including methylprednisolone pulses followed by oral prednisolone, cyclophosphamide and plasma exchange (PE), the renal function further deteriorated and hemodialysis was started. Eculizumab was administered. This led to a rapid improvement of renal function (discontinuation of dialysis and increase of endogenous creatinine clearance from 11 to 53 ml/min/1.73m²). Three months later the girl is in a good clinical condition but proteinuria is still in the nephrotic range (3.6 gr/24 hours). Treatment with eculizumab is ongoing. Up to now no side effects have been observed.



Conclusions: Response to eculizumab in DDD cannot be predicted merely on the basis of levels of sC5b-9 in blood.

PUB227

Ten-Year Experience of IgA Nephropathy in the South East of Ireland

Heather Martha Gunning, Sean F. Leavey, Vivian Elizabeth Abernethy, Catherine M. Brown. *Nephrology, Univ Hospital Waterford, Waterford, Ireland.*

Background: Worldwide IgA nephropathy (IgAN) is the most common non-infectious glomerulonephritis¹. Its presentation varies widely from asymptomatic urinalysis abnormalities to nephrotic syndrome and renal failure. There are few randomised controlled trials to guide its best management and many patients continue to be treated on 'best opinion'¹.

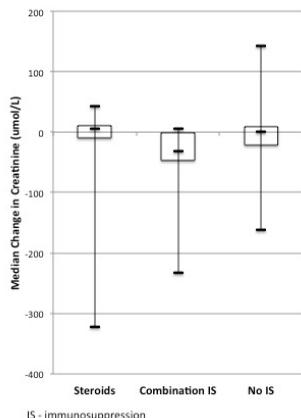
Methods: All renal biopsies undertaken in our institution between January 2005 and December 2014 were retrospectively reviewed and those diagnostic of IgAN were identified. Data collected included patient characteristics, presentation, treatment and disease course, serum creatinine and urinary protein creatinine (uPCR) ratio at six months and one year.

Results: 426 native renal biopsies were reviewed. IgAN was diagnosed in 65 (15%); 51 (78% male and 14 (22% female). At time of biopsy median age was 39 years (IQR 19), median creatinine was 139 μmol/L (IQR 146) and median uPCR was 234 mg/mmol (IQR 334). Presenting features are detailed in table 1.

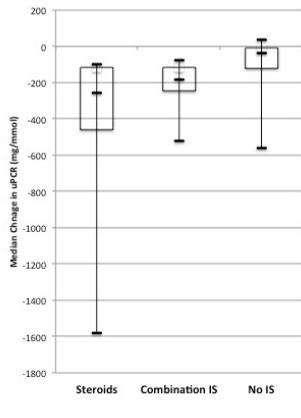
	Patient number (n = 65)	Percentage (%)
Vasculitic rash	7	11
Frank haematuria	17	26
Nephrotic range proteinuria	25	38
Hypertension	44	68
Creatinine ≥ 200 μmol/L	19	29
Creatinine ≥ 300 μmol/L	11	17

56 (86%) received renin-angiotensin blockade. 31 (48%) received immunosuppressive therapy; 19 (29%) steroids, 9 (14%) combination immunosuppression and 3 (5%) mycophenolate. Follow-up data at one year was available in 58 (89%), 6 were receiving renal replacement therapy. Median changes in creatinine and uPCR at one year are detailed in figure 1.

Comparative Change in Creatinine Across Treatment Groups at One Year



Comparative Change in uPCR Across Treatment Groups at One Year



Conclusions: Manifestations of IgAN vary widely. The mainstay of therapy consists of supportive measures, which the majority of our cohort received. Immunosuppressive regimens are reserved for a select group, and in our cohort both mycophenolate and steroid based regimens yielded a reduction in proteinuria.

PUB228

Effect of Rituximab on Immunoglobulin Levels and Infection Risk in ANCA Associated Vasculitis Shivani Shah,¹ M-Hafizur Rahman,² Duvuru Geetha,¹ ¹Div of Nephrology, Dept of Medicine, Johns Hopkins Hospital, Baltimore, MD; ²Bloomberg School of Public Health, Johns Hopkins Univ, Baltimore, MD.

Background: Rituximab (RTX), a B cell depleting anti-CD20 monoclonal antibody, is approved for treatment of ANCA associated vasculitis (AAV). Low immunoglobulin (Ig) levels are a consequence of RTX treatment. The association between the degree of Ig deficiency and infection risk is unclear in AAV patients.

Methods: AAV patients treated with RTX in a single center with available serum Ig measurements were included. The rates and types of infection after RTX administration were correlated with Ig level using correlation matrix and logistic regression analysis.

Results: Our cohort of 27 patients had a median age of 68 years, eight males, 15 GPA patients, and 17 with a new diagnosis of AAV. Twenty five received four doses of RTX 375 mg/m² weekly and two received RTX 1000 mg biweekly for two doses. Nine received concomitant cyclophosphamide. Twenty three patients had low serum IgG levels (<751 mg/dL) greater than one month following RTX treatment. Ten out of these 23 developed infections over the median follow up time of 338 days. Pneumonia was the most common infection. The odds of having an infection with IgG level ≤500 mg/dL is 3 times higher than with IgG level between 501-750 mg/dL, though p= 0.26. There is a significant association between infection and IgM level £20 mg/dL (p = 0.047).

	Odds Ratio	SE	Z	p-Value	95% CI
IgM (normal ≥ 46 mg/dL, reference ≥ 46 mg/dL)					
21-45 mg/dL	1.16	1.33	0.13	0.89	0.12-10.99
≤20 mg/dL	8.17	8.64	1.99	0.047	1.103-64.94
IgG (normal ≥ 751 mg/dL, reference 501-750 mg/dL)					
≤500 mg/dL	3	2.93	1.13	0.26	0.44-20.31

Conclusions: Severely low Ig levels due to RTX therapy may increase the risk of infection in AAV patients, and these patients may benefit from IVIG therapy. Further investigation is warranted given our study is limited by small sample size, concomitant cyclophosphamide use, and variable timing of Ig measurement.

PUB229

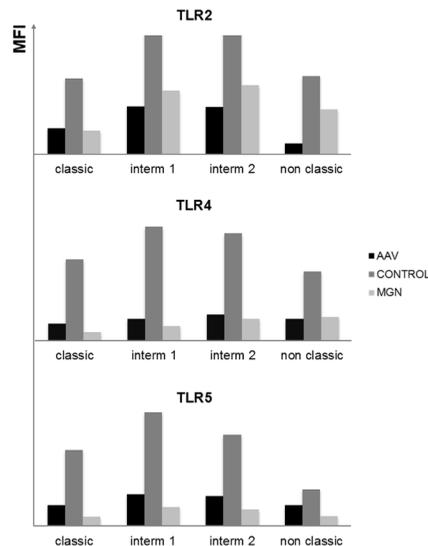
Monocyte Subpopulations of Patients with Different Forms of Glomerulonephritis Exhibit Distinct Changes of Toll Like Receptor Expression Leon Brian Schubert,¹ Florian Gunnar Scurt,¹ Noemi Rose emma Doll,¹ Marius Früh,¹ Tobias Hölscher,² Andreas Jeron,² Dunja Bruder,² Peter R. Mertens,¹ Christos D. Chatzikyriakou. ¹ Nephrology, Hypertension, Diabetes and Endocrinology, Otto-von-Guericke Univ Magdeburg; ²Inst of Microbiology, Otto von Guericke Univ Magdeburg.

Background: We are still in need for more reliable markers to monitor disease activity in primary glomerulonephritis.

Methods: In patients with active primary glomerulonephritis monocyte subpopulations were first differentiated by flow cytometry with the use of the surface markers CD 14, CD

16 CCR2 and CxCR3. The expression of different proteins reflecting antigen presentation or activation status as well as scavenger receptor and toll like receptor functions was then quantified. Blood samples of healthy individuals were used as controls. Preliminary results regarding toll like receptors 2, 4 and 5 in a patient with treatment naïve MPO positive vasculitis, a patient with treatment naïve membranous glomerulonephritis and a control are presented here.

Results: The expression of the toll like receptors 2, 4 and 5 was lower in patients with primary glomerulonephritis compared to the controls.



This was the case in all monocyte subpopulations: classical (CD14++CD16-CCR2highCXCR1-), intermediate type 1 (CD14++CD16+CCR2highCXCR1-) non-classical (CD14+CD16++CCR2lowCXCR1high) and intermediate type 2 (CD14+CD16+CCR2lowCXCR1high).

Conclusions: Toll like receptors seem to be down regulated in monocytes of patients with primary untreated glomerulonephritis during the active phase. The pathophysiological significance of these findings is unclear and remains to be elucidated.

PUB230

Lipoprotein Glomerulopathy Hostensia M. Beng, Basema I. Dibas, Hsiao Ling Lai, Guillermo Hidalgo. Pediatrics, ECU, Greenville, NC.

Background: Lipoprotein glomerulopathy has been associated with mutations in the Apolipoprotein E (APOE) gene. The average age of reported cases is 32 years and the youngest patient described to date is 4yrs old. Here we present the first case of a 3 years old AA male with right hemihypertrophy, malignant hypertension, severe proteinuria & lipoprotein glomerulopathy, with a heterozygous mutation on APO E2 gene.

Methods: 3 year old African American male presented to pediatrician complaining of hemihypertrophy, short stature, polydipsia & hypertension. physical examination remarkable for right leg soft tissue hemi hypertrophy. Echocardiogram revealed left ventricular hypertrophy likely secondary to chronic hypertension. Hypertension and proteinuria persisted despite adequate treatment. Renal US showed persistent echogenic kidneys. Kidney biopsy showed Lipid vacuolization of podocytes, endothelial cells, tubular epithelial cells, and glomerular capillary lumens. Labs & imaging studies AFP and abdominal US have been normal with exception of proteinuria and increased lipid profile. Patient currently on a trial treatment with fibric acid and dietary modification.

Results: eGFR is stable at 60 ml/min/1.73 m², proteinuria has improved from a ratio of 2.1 to 0.8 mg/mg and lipid profile has significantly improved.

Conclusions: APOE is an important LDL in transporting cholesterol to the liver for processing. Four main alleles of the APOE gene located on chromosome 19 have been described and different alleles have been associated with various medical conditions. Mutations of near the LDL bind domain of the APOE gene coexist and may be associated with certain kidney diseases. Renal biopsy shows lipid deposits and thrombi which results in glomerular damage and glomerular sclerosis. No effective preventative or curative treatments have been identified for apolipoprotein glomerulopathy. In our patient a trial of fibrates to lower cholesterol, Gemfibrozil and effective management of hypertension has resulted in some improvement but it is uncertain if these medication can effectively lower lipid and prevent long term progression of kidney disease. More research to find more effective treatment and management strategies of this disease in children.

PUB231

Proliferative Lupus Nephritis (LN) – 60 Month Evolution of an Argentinian Cohort Gabriel Pedro Alvarez,¹ Marcelo Alejandro De Rosa,² Luis Alberto Touceda.¹ ¹Hospital San Martin. La Plata, Buenos Aires; ²Univ of Buenos Aires, Argentina.

Background: Remission of proteinuria predicts good evolution in many glomerular diseases; we describe the behavior of the proteinuria, renal function and flare up in a group of patients with proliferative LN in a 60 month period.

Methods: Data from 55 patients were obtained. Proteinuria and Creatinine were shown at 0 (time of the biopsy), 6 and 60 months; renal biopsies were classified using ISN-RPS 2003. All patients received an induction with at least 6 gr. of cyclophosphamide plus prednisone and a maintenance treatment with sodium mycophenolate 1440 mg/d and low doses of prednisone for at least 3 years. Flares was considered in case of 50% proteinuria increase or an active urinary sediment.

Results: Results are in table

	N	%	range 18-64	
Age (mean)	31,2			
Sex f/m	52/3			
Bx class II	1	2		
Bx class III	7	12		
Bx class IV	40	72		
Bx class V	1	2		
Bx class V+ III/IV	7	12		
	T0	6m	60m.	p
Proteinuria gr/d (median)	3,04 (0,2-28)	1,2 (0,1-16,6)	0,2 (0,1-3,8)	< 0,05
Creatinine mg/dl (median)	0,94 (0,5-4,23)	0,9 (0,6-4,22)	0,91 (0,55-7,22)	NS
Flares up			17/ 32%	
Treatment months			36 (30-60)	

Conclusions: We observed a sustained decline in proteinuria and a preservation of renal function in most of patients; Treatment was well tolerated and flares up were in a high number of patients.

PUB232

A Case Study Comparing Cyclophosphamide plus Methylprednisolone versus Cyclophosphamide Alone in Idiopathic Membranous Nephropathy
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Background: In the treatment of high risk idiopathic membranous nephropathy the modified Ponticelli protocol with the use of alternative month Cyclophosphamide and steroid is the most used treatment protocol. The scientific bases for the use of intermittent alternating month Cyclophosphamide and Methylprednisolone versus Cyclophosphamide alone in the treatment protocol is not well established and in many studies showed that steroid alone has limited role in the treatment of idiopathic membranous nephropathy. Weather this intermittent use of Cyclophosphamide and Methylprednisolone lead to a fluctuating response to therapy and prolong the recovery or not need to be investigated.

Methods: This is a case study of a 26 years old male with idiopathic membranous nephropathy and a positive AntiPLA2R antibody who needed to be started on Modified Ponticelli protocol with alternative month Cyclophosphamide and Methylprednisolone for a persistent massive Proteinuria of 16 gram per day and who failed cyclosporine in the past. Initially the patient was given the six month the modified Ponticelli protocol but he failed to reach a complete or a partial remission with persistent Proteinuria of more than 6 gram per day and high Anti-PLA2R antibody titer and later he was given an extra three months of Cyclophosphamide alone.

Results: There was a fluctuating in antibody titer during the course of therapy with increase Anti-PLA2R antibody titer at the end of the Methylprednisolone month and reduce level after the month of Cyclophosphamide use. After the start of the extra three months of continues Cyclophosphamide the anti-PLA2R antibody titer was reducing in each month and at the end of the extra three months it disappeared completely with a remission of the Proteinuria.

Conclusions: This case shows that the use of Cyclophosphamide is more effective in the treatment of idiopathic membranous nephropathy than Methylprednisolone and it might provide a better control of the disease activity. Future study to evaluate this with the use of novel biomarker like Anti-PLA2 R antibody is recommended.

PUB233

Plasma Cytokines and Chemokines Profile in Patients with Systemic Lupus Erythematosus: Its Potential Use as Biomarkers of Kidney Damage
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Background: Systemic lupus erythematosus is an autoimmune disease in which the innate and adaptive response plays a significant roll, mainly mediated by cytokines. Lupus nephritis-LN-is the most severe complication associated with SLE. **Objective:** To identify differential expression of cytokines profiles and circulating chemokines in plasma of SLE patients with different degrees of Caribbean region.

Methods: This was a case- control study. Plasma samples from 10 patients with NL class-II 10 patients with NL class-III, and 30 patients with NL class-IV were analyzed. As a control plasma from 30 SLE patients without nephritis were used. Plasma samples were analyzed using the Luminex technology of 38 analytes (EGF, Eotaxin, FGF-2, Flt-3 ligand, Fractalkine, G- CSF, GM-CSF, GRO, IFN- α 2, IFN - γ , IL-10, IL-12 (p40), IL 12(p70), IL-13, IL-15, IL-17, IL-1R α , IL-1 α , IL-1 β , IL-2, IL 3, IL4, IL-5, IL-6, IL-7, IL-8, IL-9, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1 α , MIP-1 β , TGF- α , TNF- α , TNF- β , VEGF, sCD40L, RIL-2Ra) using MILLIPEX[®]-MAP-Human Cytokine/Chemokine-Magnetic-Bead-Panel-Premixed 39 Plex.

Results: Significant differences(p<0.05) was between concentrations of cytokines EGF, G-CSF, GM-CSF, GRO, IFN, IL4, IL8, IP10, MCP, MDC, MIP.1a, sIL2Ra,TNFB when SLE-patients with LN vs SLE-patients without LN were compared.

Conclusions: These preliminary data suggest that there are differences in the LN plasma patients level of some chemokines and proinflammatory cytokines. Results support the hypothesis that circulating levels in plasma samples of these molecules may be considered.

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PUB234

Clinical Outcomes of IgA Nephropathy with Necrotizing and Crescentic Lesions in Inner City Hospital
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Background: IgA nephropathy is the most common cause of glomerular disease worldwide. Segmental necrosis and crescents are seen only in small subset of patients and literature regarding their clinical outcomes is sparse.

Methods: Retrospective analysis of cases with primary IgA nephropathy from Stroger Renal biopsy database from January 2005 to May 2015 was performed. Demographic and clinical information was obtained from medical charts. Study was approved by IRB.

Results: Of 66 cases of IgA nephropathy, 10 (15%) had lesions with segmental necrosis and/or crescents. These patients responded well to cyclophosphamide based therapy with improvement in creatinine and proteinuria after a mean follow up of 4.6 years. However, patients without vasculitic lesions had a progressive decline in renal function despite immunosuppressive therapy. This group had longer follow up period (mean 7.1 yrs) and 21% required dialysis.

	With necrotizing/ crescentic lesions (n=10)	Without necrotizing/ crescentic lesions (n=56)	P value
Age (in years)	44.6	46.2	
Gender (M:F %)	30:70	54:46	
Ethnicity Hispanic or Latino Non Hispanic/Latino	5 5	27 29	
S. creatinine (mg/dl) at biopsy	1.4	1.7	0.26
Estimated proteinuria at biopsy (g/g of Cr)	3.5	2.7	0.21
Prednisone(%)	90	34	
Immunosuppressants(%) Cyclophosphamide based Others	80 70 30	23 1 99	
ACEI/ARB (%)	80	81	
Length of follow up (in years)	4.6	7.1	0.001
Last S. creatinine (mg/dl)	1.0	1.8	0.65
Last estimated proteinuria (g/g of Cr)	1.2	2.3	0.47
Biopsy			
Mesangial hypercellularity (%)	80	73	
Endocapillary proliferation (%)	50	5	
Segmental sclerosis (%)	70	66	
Tubular atrophy T0<25% T1>25% T2 >50%	50 30 0	34 37 28	

Conclusions: Patients with vasculitic lesions (necrosis and crescents) carry a favorable prognosis when treated with Cyclophosphamide based therapy. When applying MEST criteria among patients with and without vasculitic lesions, only tubular atrophy was predictive of future decline in renal function (p=0.007). In this cohort, 21% reached ESRD within a mean follow up of 7 yrs which highlights the aggressive nature of this disease in ethnic minorities.

PUB235

Acute Tubulo-Interstitial Nephritis (ATIN): Predicting Long Term Outcomes Victoria C. Robins,¹ Aravind Cherukuri,² Padmini Prasad,¹ Richard J. Baker.¹ ¹SJUH; ²Pittsburgh.

Background: ATIN is a relatively common potentially reversible cause of acute kidney injury. It has become clear over the last 2 decades that the disease is not always reversible, particularly in the elderly. We present a large contemporary single centre retrospective series concentrating on factors that predict poor outcomes.

Methods: 62 cases retrospectively diagnosed histologically via pathology records as primarily ATIN were included. An experienced histopathologist, blinded to outcomes, graded biopsies according to the presence, absence and degree of 8 different parameters: Interstitial inflammation, tubular atrophy, eosinophilia, plasma cell infiltration, chronic vascular lesions, hyalinosis, granulomas + oedema. Patients were classified as a poor outcome if eGFR(4 variable MDRD) after 12 months was less than 30ml/min/1.73m² or they died.

Results: 62 patients with biopsy proven ATIN were identified. 15 had a poor outcome. Baseline demographics are presented in Table 1.

	Good (eGFR>30)	Poor (eGFR<30)	p value
n	47	15	
age	56.2+/-16.8	56.6+/-19	Not significant(-)
Sex M/F	19/28	6/9	-
Creatinine:diagnosis	366+/-245	545+/-334	0.02
Creatinine:6 months	130+/-40	220+/-90	<0.0001
PCR:diagnosis	103+/-72	126+/-90	-
Treatment: prednisolone	87%	80%	-
Serum eosinophil count	0.4+/-1.0	0.4+/-0.5	-
Biopsy degree of:interstitial Inflammation	2.1+/-0.8	2.1+/-0.7	-
tubular atrophy	1.2+/-0.4	1.3+/-0.6	-
eosinophilia	0.9+/-0.8	1.3+/- 1.0	-
plasma cell infiltration	2.0+/-0.9	2.0+/-0.8	0.03
chronic vascular lesions	1.3+/-0.5	1.6+/-0.5	-
hyalinosis	0.6+/-0.7	0.6+/-0.7	-
granulomas	0.3+/-0.6	0.9+/-1.1	0.03
oedema	0.3+/-0.5	0.5+/-0.8	-

Aetiology was difficult to definitely ascertain but consisted of drug induced, infectious, sarcoid or sjogrens. Parameters significantly associated with poor outcomes include higher creatinine at presentation & 6 months, presence of granulomas and chronic vascular lesions on biopsy at diagnosis. The effect of steroid treatment was difficult to assess since most patients were treated at the outset.

Conclusions: ATIN usually carries a good prognosis but some patients experience poor outcomes. Poor renal function at diagnosis and the presence of granulomas and chronic vascular lesions are predictive of poorer outcomes.

PUB236

Cotreatment of Olmesartan and Caterpillar Fungus Attenuate Albuminuria in Patients with Glomerulonephritis Hua Zhou, Ye Zhang, Ya Li, Hairong Tang, Congcong Jiao, Lining Wang. *Nephrology Dept, 1st Hospital of China Medical Univ, Shenyang, China.*

Background: Angiotensin II receptor blockers (ARBs) were demonstrated to reduce proteinuria since a decade ago. However, proteinuria still remains as the top of clinical symptoms in glomerulonephritis (GN). We aim to investigate the effect of cotreatment with olmesartan (Olm), an ARB and caterpillar fungus capsule (CF) on proteinuria in patients with GN.

Methods: 491 patients with GN were retrospectively studied. GN was diagnosed by moderate albuminuria and/or dysmorphic hematuria. Patients were divided into seven groups by treatment: 1) CF alone, 2) Olm alone, 3) other ARBs defined as non Olm ARBs, 4) all ARBs include Olm and other ARBs, 5) CF + Olm, 6) CF + other ARBs, and 7) CR + all ARBs. High blood pressure is not necessary indication for ARBs treatment. Urinary albumin concentration (uAlb, mg/L) were examined before and 1, 2, and 3 months of the treatment.

Results: uAlb was significantly attenuated in the groups with Olm alone, all ARBs, CF + Olm, and CF + all ARBs at 1 and 2 months after the treatment compared to pretreatment (Olm alone 343±82 vs 483±77, p=0.009, n=92; all ARBs 351±68 vs 494±68, p=0.004, n=125; CF+Olm 509±81 vs 853±105, P=0.0002, n=118; CF+all ARBs 544±81 vs 836±92, P=0.0006, n=138 at 1 month. Olm alone 264±54 vs 466±107, p=0.006, n=35; all ARBs 295±50 vs 606±117, p=0.0003, n=58; CF+Olm 395±92 vs 814±157, P=0.001, n=60; CF+all ARBs 438±80 vs 902±135, P<0.0001, n=77 at 2 months). At 3 months after the treatment, the significant reduction of uAlb was only seen in cotreatment with CF and Olm/all ARBs (CF+Olm 357±141 vs 559±112, P=0.026, n=28; CF+all ARBs 368±102 vs 631±119, P<0.019, n=41). The decrease of uAlb was not found in groups of CF alone,

other ARBs, and CR+other ARBs (numbers of patients received other ARBs are 33, 13, 8 and received CF+other ARBs are 21, 9, 7 at 1, 2, and 3 months, quite smaller than Olm). The cotreatment with CF showed an increased statistical p value.

Conclusions: Cotreatment of Olmesartan and caterpillar fungus significantly attenuated albuminuria in patients with GN. caterpillar fungus might be a promising agent to treat glomerular proteinuria via synergizing the effect of ARBs in glomerulonephritis.

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PUB237

Tubulointerstitial Involvement in Lupus Nephritis Angela Pakozdi,¹ Dev Pyne,¹ Michael Sheaff,² Ravindra Rajakariar.³ ¹Rheumatology, Barts Health NHS Trust, London, United Kingdom; ²Histopathology, Barts Health NHS Trust, London, United Kingdom; ³Nephrology, Barts Health NHS Trust, United Kingdom.

Background: Tubulointerstitial disease is frequent in lupus nephritis (LN), and interstitial infiltration, tubular atrophy and interstitial fibrosis are all independent risk factors for LN renal outcome. We aimed to analyze tubulointerstitial changes on a series of repeat renal biopsies (RB) and identify correlations with clinical variables.

Methods: Histopathological changes of 39 LN patients were analysed using the revised Austin's semi-quantitative grading system of 0 to 3 (0, normal; 1, mild <25%, 2, moderate 26-50%; 3, severe >50% of the interstitium affected). Spearman's rank-order correlation was run to determine relationship between clinical variables and histological findings.

Results: We found a progression in both tubular atrophy (p=0.001) and interstitial scarring (p<0.001), but not in inflammatory cell infiltration by the time of RB. The mean total tubulointerstitial score (± SD) has progressed from 2.69 ± 2.03 to 3.78 ± 2.03 (p=0.001). There was a positive correlation between serum creatinine and the severity of tubular atrophy at time of both reference biopsy (r=0.33, p=0.048) and RB (r=0.56, p<0.001). Serum creatinine at time of RB showed a strong correlation with interstitial scarring (r=0.60, p<0.001). A trend was identified between the severity of interstitial inflammation on reference biopsy and the amount of tubular atrophy and interstitial scarring on RB (r=0.349, p=0.19; r=0.385, p=0.009). Chronicity indices (CI) also progressed by the time of RBs. Patients with proliferative histopathology on initial biopsy had higher CI at both the reference biopsy (p=0.047) and RBs (p=0.019). Treatment decisions did not seem to be influenced by the progression of CI (p=0.982).

Conclusions: Tubulointerstitial lesions show progression in time illustrated by our study using RBs, and serum creatinine level showed good correlation with the severity. Interstitial inflammation on reference biopsies correlated with the severity of tubular atrophy and interstitial scarring on repeat biopsies, suggesting a possible predictive role for damage.

PUB238

Seasonal Variations of Renal ANCA Associated Vasculitis Juliana Bordignon Draibe, Joan Torras, Xavier Fulladosa. *Nefrology, Hospital Univ de Bellvitge, Barcelona, Spain.*

Background: Filling the gaps in the genetic research of etiological factors related with ANCA associated vasculitis (AAV) is a major challenge in the current investigation. Descriptive and analytical epidemiological studies may improve our understanding of environmental influences on the disease. Seasonal variations in AAV have been previously described, mainly related to Wegener's disease, showing an increased number of cases during the winter months. It has been hypothesized that infection could be the underlying factor for these observations. Our goal is to study seasonal variations of AAV diagnosed in the city of Barcelona.

Methods: Our study included 209 AAV patients diagnosed between 2001 and 2013 in 5 different University Hospitals of Barcelona. We analyzed their medical records, including the date of diagnosis and the approximate date of the first symptoms in 194 patients. We have also analyzed data related to ANCA subtypes in each patient.

Results: Of the 209 patients, 160 (76.5%) were MPO-positive, 28 (13.3%) were PR3 positive and 21 (10%) were ANCA negative. Regarding the onset of symptoms, we have found a greater number of cases in the months of January, February and March, compared with the rest of the year. This data correlates positively with the higher incidence of flu symptoms in Barcelona between 2009 and 2013.

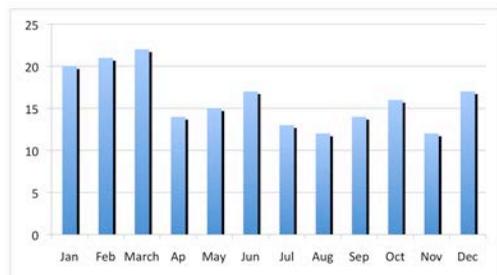


Figure 1

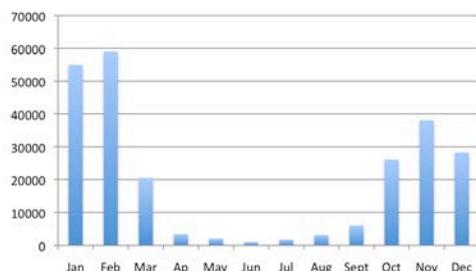


Figure 2

Considering the date of diagnosis we found a greater number of cases in two periods of the year; the months of May, June and July, and the months of October, November and December.

Conclusions: In our population, predominantly ANCA MPO-positive related vasculitis, we found a higher incidence of the disease in the winter months, being diagnosed more frequently in May, June and July or October, November and December. One potential environmental factor, influenza disease, may explain this finding.

PUB239

Mycophenolate Mofetil for the Treatment of Idiopathic Nephrotic Syndrome: A Meta-Analysis of Randomized Controlled Trials Bin Zhu, Yongjun Wang. *Nephrology, Hangzhou Hospital of Traditional Chinese Medicine (Guangxing Hospital) Affiliated to Zhejiang Chinese Medical Univ, Hangzhou, Zhejiang, China.*

Background: This meta-analysis was performed to investigate the efficacy and safety of mycophenolate mofetil (MMF) in treating idiopathic nephrotic syndrome.

Methods: We searched MEDLINE, EMBASE, the Cochrane Library database, the Database for Chinese Technical Periodicals, Wanfang, Chinese National Knowledge Infrastructure and the Chinese Database of Biology and Medicine for randomized controlled trials compared MMF with the other immunosuppressive agents for the treatment of idiopathic nephrotic syndrome. Weighted mean difference (WMD) and summary estimates of relative risk (RR) reductions with 95% CIs were calculated.

Results: We identified 36 trials that included 2007 patients, mainly on membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and refractory nephrotic syndrome without clearly pathological diagnosis (RNS). Overall, MMF therapy significantly reduced proteinuria (WMD: -462.31 mg/d, CI: -219.69 to -704.92 $P < 0.001$), increased the likelihood of complete remission (RR: 1.25, CI: 1.11 to 1.41, $P < 0.001$), complete or partial remission (RR: 1.15, CI: 1.09 to 1.22, $P < 0.001$) compared with the other immunosuppressors. The subgroup analyses shown that MMF was superior to cyclophosphamide in lowering proteinuria, serum creatinine, relapse, and increasing the remission rate. In the MN patients, MMF therapy was better than cyclophosphamide in reducing proteinuria, increasing remission rate, whereas it was poorer than chlorambucil in lowering proteinuria. MMF therapy also significantly decreased proteinuria in FSGS compared with cyclophosphamide. MMF was safer than most of the other agents, particularly than cyclophosphamide.

Conclusions: MMF seems superior to the other immunosuppressive regimens for the treatment of idiopathic nephrotic syndrome with mild adverse effects, particularly in MN, FSGS and RNS. High-quality large-sample trials are still required to reliably define the balance of efficacy and safety.

PUB240

A Retrospective Analysis of Acute Kidney Injury in Adult-Onset Minimal Change Disease Yosuke Nakagawa, Takuya Isegawa, Masahiro Koizumi, Masafumi Fukagawa. *Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.*

Background: Minimal change disease (MCD) is a major cause of primary nephrotic syndrome in adults, accounting for 10 to 25 percent of cases. In terms of treatment, steroid therapy is very effective, however in some cases an acute onset of moderate to severe

decline in kidney function is seen, occasionally requiring transient dialysis. To the best of our knowledge, the risk factor for acute kidney injury (AKI) and clinical course of cases with AKI had not been fully elucidated.

Methods: This study is a single center, retrospective observational study. The clinical records of adult (older than 18 years old) who had biopsy-proven MCD and were followed at Tokai University Hospital from 2000 to 2015 were retrospectively reviewed. The diagnosis of AKI was based on KDIGO criteria, namely, serum creatinine changes ≥ 1.5 times baseline within 7 days and a 0.3 mg/dl increase in serum creatinine within 48 hours.

Results: 57 patients were enrolled, and AKI occurred in 24 patients at presentation or subsequently, among whom five patients underwent hemodialysis. Patients with AKI showed lower level of serum albumin and higher rates of use of diuretics, renin-aldosterone system (RAS) inhibitors, and NSAIDs. Logistic-regression analysis showed that use of these drugs before presentation at our institution could predict the development of AKI (odds ratio, 2.8; 95% CI, 2.2 to 3.2). Furthermore, use of these drugs could determine the time to remission (Hazard ratio, 2.4, 95% CI, 1.8 to 3.0), as well as the initial serum creatinine. All cases were initially treated with steroid, and there was no difference in the time to remission between oral and parenteral administration of steroid.

Conclusions: There is a high incidence of AKI in adult-onset MCD. The use of several drugs such as diuretics could influence the onset of AKI and clinical course of MCD.

PUB241

Expression of HLA-G Molecule in Crescentic Glomerulonephritis and Its Clinical Significance Guisen Li, Li Wang. *Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: In recent years, human leukocyte antigen-G (HLA-G) was found to be an important immune-regulatory molecule. Our purpose of this study is to assay the concentrations of serum soluble HLA-G (sHLA-G) in patients with CGN and to analyze its clinical significance.

Methods: 48 patients with CGN from 2009 to 2014 were involved in this study. The clinical data were collected, include demographic characteristics, laboratory parameters, pathological examinations, prognostic information and immunosuppressive therapy. Analyze if oliguria or anuria, serum creatinine levels, the crescent formation ratio and therapy would affect the prognosis of patients. 22 patients with CGN, 15 patients with MCD, and 30 healthy adults in control group were enrolled with serum levels of sHLA-G measured by ELISA. The relationship between the clinical or pathological features and sHLA-G was studied and the value of the HLA-G in crescentic glomerulonephritis was analyzed.

Results: 3-years kidney survival rate was only 38% with one case of death. Cox regression analysis showed higher serum creatinine was associated with the patients with a poor prognosis (HR=4.04, 95% CI: 1.548-10.544, $P = 0.004$). Serum level of sHLA-G in CGN was significantly higher than in healthy control (2198.81 \pm 1924.17 pg/ml vs. 1311.86 \pm 448.84 pg/ml, $P = 0.0408$), while higher than in MCD, (2198.81 \pm 1924.17 pg/ml vs. 1181.33 \pm 320.10 pg/ml, $P = 0.023$). Kaplan Meier survival analysis showed elevated levels of HLA-G was associated with poorer patients.

Conclusions: High serum creatinine level (>5mg/dl) at admission is an independent risk factor for the development to be ESRD. sHLA-G was significantly elevated in the serum of patients with CGN, and the level of sHLA-G had relationship with the prognosis of the patients with CGN. sHLA-G may be used as a new biomarker in CGN with clinical value in the early diagnosis and prognosis.

PUB242

A Treatment of Nutcracker Syndrome Leads to a Resolution of Unexplained Proteinuria Badamkhand Baatarkhuu, Raymond Raut, Winston Y. Shih, Panupong Lisawat. *Nephrology and Hypertension, WCHN Danbury Hospital, Danbury, CT.*

Background: The nutcracker syndrome is rare and can be a cause of unexplained proteinuria. We report a case of nutcracker syndrome related proteinuria and resolution of the proteinuria is observed after the entrapment was surgically corrected.

Methods: This is a 22-year-old male with a history of unexplained proteinuria since he was 17 years old. He has moved to a new location and presented to our clinic with proteinuria. The patient's initial work up at an outside hospital revealed 1.4g proteinuria per 24 hours. A left kidney biopsy showed mesangial hypercellularity and preserved foot processes. The patient at that time was treated with prednisone, cyclosporine and lisinopril. His proteinuria decreased to 196 mg per 24 hours. Due to intolerance, lisinopril was stopped and urine protein subsequently rose. At the time of evaluation, the patient's 24 hour urine protein was 700 mg and the autoimmune and infectious work up was negative. Upon reviewing the medical record from 2 years ago, he had inferior vena cavalogram as a part of varicocele treatment. It showed compression of the left renal vein between the aorta and superior mesenteric artery. Nutcracker syndrome was suspected. Subsequently, he was referred to vascular surgery, and underwent an open reconstructive surgery. Postoperatively the patient remained off lisinopril and repeated 24 hour urine protein was down to 102 mg.

Conclusions: Nutcracker syndrome can cause significant proteinuria. Although it is rare, an early recognition could lead to a definitive treatment, help avoid unnecessary medications and invasive procedure such as a kidney biopsy.

PUB243

Parvovirus B19 Immune Complex Glomerulonephritis Beth Lynne Braunhut, Erika R. Bracamonte. *Pathology, Univ of Arizona College of Medicine, Tucson, AZ.*

Background: A 14 year old girl underwent a cadaveric renal transplant due to end-stage renal disease from obstructive uropathy and developed parvovirus B19 viremia and graft dysfunction. Renal biopsy showed de novo immune complex glomerulonephritis with parvovirus B19 DNA detected in renal tissue by PCR. We herein review of B19-associated glomerular disease.

Methods: A search of the English-language medical literature was conducted. PubMed, Medline, and Google scholar were used. Adult and pediatric cases were included. Sources included case reports and series, including prior reviews. Articles were evaluated for demographic data, clinical findings, laboratory data, and renal biopsy results.

Results: 67 cases were identified. 51 involved native kidneys and 16 transplants. 66 of 67 cases had serologic evidence of B19 infection (98.5%). B19 DNA testing by PCR of various samples was positive in 82.9% of cases. Biopsy results were reported in 52 cases. Of native cases, 92.5% reported a proliferative glomerulonephritis. Allografts most commonly showed TMA (66.7%). IF showed C3 in 84.4%, IgM in 68.8%, IgG in 62.5% and IgA in 40.6%. IF was negative in all transplant cases, save for our patient who showed IgG, IgM, C1q and C4d. EM results were reported in 24 cases with subendothelial deposits being most common (91.7%).

Conclusions: The findings in B19-associated glomerular disease are different in the native kidney versus transplant setting. In a native kidney, proliferative immune complex glomerulonephritis is most common. In the transplant setting, most cases showed TMA. The pathogenesis of this discrepancy remains unclear. To our knowledge, this is the first report of B19 immune complex glomerulonephritis in a renal transplant patient. Our patient showed findings more commonly seen in native-kidney B19 disease. We believe this discrepancy may be explained by insufficient immunosuppression in our patient, as evidenced by concurrent AMR. B19 infection in a transplant patient has practical implications. B19 glomerular disease represents a largely reversible form of renal injury. But, adverse outcomes have been reported. Management may require a balancing act with the risk of rejection on one hand and B19 disease on the other.

PUB244

A Case of ANA-Negative Systemic Lupus Erythematosus Ankur Shah,¹ Rachel Criner,¹ Jean Lee.² *¹Internal Medicine, Temple Univ Hospital, Philadelphia, PA; ²Nephrology, Temple Univ Hospital, Philadelphia, PA.*

Background: Systemic Lupus Erythematosus is a chronic autoimmune disorder hallmarked by several autoantibodies targeting intracellular antigens. The most sensitive of these antibodies is the anti-nuclear antibody. Various studies show that this antibody is present in 95-98% of individuals with the disorder. As methodology improves, the incidence of ANA-negative Lupus has been decreasing.

Methods: We report a case of a 53 year old female whose known past medical history included only hypertension who presented to the outpatient clinic with arthralgias, pancytopenia, alopecia, proteinuria and skin rash whose labwork to this point included an elevated ESR of 115, negative ANA, neg HIV, Hep B, and Hep C serology. She was then lost to followup until presenting to the hospital with anisarcia and acute kidney injury. Her further workup confirmed a negative ANA but also revealed positive Anti-SSa, and anti-DsDNA as well as low titer Anti-Phospholipid. Her C3 and C4 were decreased at 43 and 66 respectively. She had a renal biopsy performed revealing focal proliferative and membranous lupus nephritis, Class III/V. The patient was started on mycophenolate, plaquenil, and prednisone.

Conclusions: Once a byproduct of a technically variable laboratory test, the entity of ANA negative Lupus has been decreasing in its frequency. The adoption of the human epithelial substrate has brought standardization to this assay and also increased its sensitivity. Nonetheless, the entity still exists, and has been described before. The majority of ANA-Negative Lupus cases will present with antibodies to cytoplasmic components – SSA or SSB, as did our case. ANA negative cases of SLE have been shown to have a decreased incidence of renal manifestations, with our case being an interesting exception. Our case serves as a reminder that the entity of systemic lupus erythematosus remains a clinical one, and that while the ACR criteria do include immunologic studies, the absence of the hallmark antibody does not rule out the disorder.

PUB245

Patients with Combined Membranous Nephropathy and Focal Segmental Glomerulosclerosis Have Comparable Clinical and Autoantibody Profiles with Primary Membranous Nephropathy Qiu-hua Gu, Zhao Cui, Jing Huang, Gang Liu, Minghui Zhao. *Renal Div, Peking Univ First Hospital, Inst of Nephrology, Peking Univ, Beijing, China.*

Background: Patients with combined membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS) have been reported with different clinical significance. Investigation on the possible mechanisms of the combined glomerular lesions is necessary but scarce.

Methods: 20 patients with both MN and FSGS lesions were enrolled, 29 patients with primary MN and 27 patients with primary FSGS were used as disease controls. Clinical data were collected on renal biopsy and during follow-up. Circulating anti-phospholipase A2 receptor (PLA2R) antibody, glomerular PLA2R expression and IgG4 deposition, and soluble urokinase receptor (suPAR) levels were detected.

Results: We found that patients with combined lesions presented with elder age, less proteinuria, higher serum albumin, better renal function on biopsy, more complete remission

after treatments and better renal outcome during follow-up. These were comparable to the patients with primary MN, but different from the patients with primary FSGS. Patients with combined lesions showed higher stages of MN, no cellular variant on FSGS classification and more common (100%) tubulointerstitial injury than both primary MN and primary FSGS patients. In the patients with combined lesions, 80% had circulating anti-PLA2R antibody and 68.4% had IgG4 predominant deposition in glomeruli, which were comparable to primary MN. No circulating antibody or IgG4 deposition was detected in primary FSGS patients. The patients with combined lesions had significantly lower urinary suPAR concentration, compared to the primary FSGS patients (315.6±302.0 vs. 691.3±1223.5pg/umol, P=0.014), but similar to the primary MN patients (275.7±253.4pg/mmol).

Conclusions: We conclude that patients with combined MN and FSGS may share the same underlying pathogenesis with primary MN. The FSGS lesion might be secondary to primary MN.

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PUB246

Glomerulosclerosis Is Prevalent but Not Associated with Kidney Function in Healthy Japanese Elderly Koji Sato, Tsukasa Naganuma, Daisuke Ichikawa, Sayuri Shirai, Yugo Shibagaki. *Div of Nephrology and Hypertension, St. Marianna Univ, Kawasaki, Kanagawa, Japan.*

Background: Previous western studies have shown that global glomerulosclerosis (GS) is common in healthy elderly but is not associated with kidney function. We here conducted a study to determine whether healthy Japanese elderly, whose glomerular filtration rate (GFR) are much lower than that of western counterparts, have also same relationship among kidney function and prevalence of GS.

Methods: We analyzed 81 kidney biopsy specimens from Japanese living donors obtained at donor nephrectomy between 2009 and 2014. Using the 2007 Banff classification system, GS, tubular atrophy (TA), interstitial fibrosis (IF), and arteriosclerosis (AS) on kidney samples were evaluated. Donor characteristics such as age, serum creatinine (sCr), Cr-based estimated GFR (eGFR), proteinuria, and the prevalence of hypertension, were also evaluated. Data were expressed as mean ± standard deviation or median and interquartile range (IQR). We performed univariate and multivariate analyses to identify the relationship between the parameters.

Results: Average age was 59.5 ± 9.1 years, male accounted for 38 (46.9%), with sCr 0.68 ± 0.15 mg/dl (eGFR 80.0 ± 12.9 ml/min/1.73m²), proteinuria 125.5 ± 61.0 mg/gCr, and hypertensive 28 (34.6%). Each kidney sample had the average of 16 glomeruli (IQR, 12 to 23) and 1 GS (IQR, 0 to 2), so the proportion of GS among total glomeruli was 6.25% (IQR, 0 to 14.3). The prevalence of any GS was 65.4%, any TA, 51.9%, IF greater than 5%, 48.1%, and any AS, 91.4%. Statistical analyses revealed that donor age was the only independent factor related to GS, and also to TA, IF, and AS. Among kidney biopsies of our 53 normotensive donors, 5 (9.4%) had more GS than the 95th percentile of the number of GS in western studies.

Conclusions: Although Japanese healthy adults had lower GFR and a higher number of GS than western counterparts, GS was still not associated with kidney function. Pathological significance of GS in otherwise healthy Japanese is not supported as in western counterparts.

PUB247

241 Case of Monoclonal Gammopathy with Renal Biopsy Analysis Yuqing Chen, Beini Lv, Yan Wang, Yu Xiaojuan, Ming Hui Zhao. *Renal Division, Dept of Medicine, Peking Univ Frist Hospital, Beijing, China.*

Background: Patients with monoclonal gammopathy can accompany various renal lesions related or unrelated to the monoclonal gammopathy. We aim to describe the renal lesions with monoclonal gammopathy in china.

Methods: Data of renal biopsy and clinical presentation of patients with monoclonal gammopathy on serum and/or urine immunofixation electrophoresis in our center from 1999 to 2014 were collected.

Results: 241 patients met the inclusion criteria and were classified as renal disease related to multiple myeloma (MM) (n=18, 7.5%), monoclonal gammopathy of renal significance (MGRS) (n=85, 34.9%) and monoclonal gammopathy of undetermined significance (MGUS) (n=138, 57.4%). Among patients with MGRS, Amyloidosis (n=69, 28.6%) is the most common diagnosis, followed by Light Chain Deposition Disease (LCDD) (n=7, 2.9%), Cryoglobulinemic glomerulonephritis (n=6, 2.5%), and 56 cases (40.6%) received clone-responsible treatment. Among patients with MGUS, a variety of renal lesions were found, including membranous nephropathy (n=48, 20.2%), IgA nephropathy (IgAN) (n=17, 7.05%), interstitial nephritis (n=13, 5.4%), membranous proliferative glomerulonephritis (MPGN) (n=9, 3.3%) and so on.

Conclusions: We analyzed the data of monoclonal gammopathy with renal biopsy in china for the first time. A growing number of renal diseases were found to be associated with monoclonal gammopathy. MGUS is the most common diagnosis of patients with monoclonal gammopathy, while membranous nephropathy and IgAN are most common among MGUS. Further work are in need to determine whether some MGUS are truly underdetermined or with renal significance and whether or not early treatment is in need for these patients.

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Underline represents presenting author.

PUB248

Urine Microscopy in a Case of Acute Kidney Injury: A Report of an Interesting Case *Azka Arif*,¹ Ahmad Hassan,² Muhammad Awais Arif,² Hafiz Armaghan Saeed,² Agha Syed Shabbir Ali,² Abdul Mateen Nagaria,¹ Talal A. Khan.¹ ¹Freeman Health System; ²Rawalpindi Medical College.

Background: RBCs casts are usually present in the urine of patients presenting with AKI secondary to RPPGN. They are sometimes seen in patients with AIN. A single RBC cast seen in urine is enough to consider glomerulonephritis as underlying pathology. We report a case of biopsy proven Myoglobinuric AKI with urine RBC casts.

Methods: 68-year-old male presented with AMS and was found to have AKI with BUN of 106 mg/dL. & creatinine of 28.6 mg/dL. He had severe hyperkalemia. His urine analysis showed 20-30 RBCs and 3+ Blood. His urine microscopy was done which revealed RBC casts, pigmented casts and renal tubular epithelial cells as reviewed by nephrologist on call, based on such acute presentation and positive RBC cast, glomerulonephritis was considered as possible etiology in addition to acute tubular necrosis and rhabdomyolysis. He underwent emergent hemodialysis for severe hyperkalemia and uremia, he was started on pulse steroids and underwent CT guided kidney biopsy. It showed extensive myoglobinuric ATN, with no evidence of any glomerulonephritis. His ANCA serology, complements levels, Anti GBM antibodies & ANA were negative. He required hemodialysis for few days and then recovered with residual CKD.

Conclusions: RBC casts are important component of rapid and early diagnosis of RPGN. RBCs in a cast are almost always pathological and marker of acute glomerular injury. Our case represents an unusual finding of RBC casts in myoglobinuric ATN. We purpose extensive renal glomerular injury secondary to severe rhabdomyolysis as possible etiological factor. Renal tubular epithelial cells are marker for acute tubular necrosis and pigmented casts are usually found in rhabdomyolysis which were seen in urine microscopy in our case. Urine microscopy though less commonly used provides a vital & faster way of diagnosing etiology of AKI and it should be considered in our evaluation of acute kidney injury.

PUB249

Acute Renal Failure in Thrombotic Microangiopathy and C3 Glomerulopathy? *Tiziana Stellato*,¹ Paolo Fabbrini,¹ Sonia Sirtori,² Andrea Stella.^{1,2} ¹Dept of Nephrology, San Gerardo Hospital, Monza, Italy; ²Univ of Milano Bicocca, Milan, Italy.

Background: Thrombotic microangiopathy is a rare disease characterized by arteriolar and capillary thrombosis with endothelial damage. Clinical manifestations include renal involvement such as acute renal failure associated with haematuria and proteinuria.

Methods: We report a case of a 75 years old man without past medical history that referred to us with oliguric acute renal failure dialysis-dependent. Laboratory work up revealed creatinine of 7.5 mg/dl, prolonged activated *partial thromboplastin time* (aPTT) in order to 2.2 Ratio, normal *Prothrombin time* (PT), reduced C3 (65 mg/dl) with normal C4, VES augmented, positive low titer anti-cardiolipine and anti-beta2 glycoprotein1 antibodies, positive LAC screening. Urinalysis showed microhaematuria and proteinuria 2.5 g/24 h, ANA, ANCA, antiDNA are negative. A renal biopsy was performed and showed mesangial proliferative glomerulonephritis associated to thrombotic microangiopathy with sub-endothelial and mesangial C3 deposits. Considering the clinical history, the laboristic tests and the biopsy result, suggestive of antiphospholipid syndrome (APS), we start treatment with plasma-exchange (total 4 sessions) with plasma substitution and corticosteroids (500 mg IV methylprednisolone for 3 days, followed by 0.5 mg/Kg/die oral prednisone). So we obtained rapidly recovery of diuresis that resulted in a progressive recovery of renal function till serum creatinine 1.4 mg/dl. The post-biopic course was complicated by macrohaematuria and a formation of a pseudoaneurysm immediately treated with selective embolization. Because of this complication we waited start oral anticoagulant till 7 days after missing macrohaematuria.

Conclusions: Acute renal failure is a reversible kidney damage that can revert with a specific diagnosis and treatment. Kidney biopsy was always gold standard and a combination treatment with multiple sessions of plasma exchange and oral and corticosteroids, even in presence of contrasting data in literature, may be useful in case of thrombotic microangiopathy.

PUB250

Differences Between Clinical Parameters at Diagnosis and After Treatment in Membranous Nephropathy *Sanjana Gupta*,¹ Horia Stanescu,¹ Kieran Mccafferty,² Alan D. Salama,¹ Stephen H. Powis,¹ John Connolly,¹ Neil Ashman,² Muhammad M. Yaqoob,² Robert Kleta,¹ Stephen B. Walsh.¹ ¹UCL Centre for Nephrology; ²Royal London Hospital.

Background: Membranous Nephropathy is the leading cause of nephrotic syndrome in adults. Idiopathic (IMN) and secondary (SMN) forms exist. Clinical parameters such as serum creatinine (sCr), serum albumin (sAlb) and urine protein creatinine ratio (PCR) are important to make a diagnosis, and are used as surrogate markers for evidence of remission from disease.

Methods: We performed a retrospective analysis of all patients with biopsy proven IMN at the Royal London and Royal Free Hospitals that were under follow between 1995 - 2015. Clinical data was collected using renal databases.

Results: We identified 240 patients with biopsy proven MN. 171 patients still had native renal function. 69 reached end stage renal failure (ESRF). 188 had IMN, 52 had SMN. There was no significant difference in age between IMN and SMN (56.8 ± 1.5 vs. 52.6 ± 1.9 years respectively). At the time of diagnosis, there was no difference between IMN and SMN in PCR (924 ± 73 vs 863 ± 154, ns) or sCr (116 ± 12 vs 101 ± 10 μmol/L, ns). At presentation

the sAlb was significantly lower in IMN (24.9 ± 0.8 vs 28 ± 1.2 mmol/L, p=0.02). In IMN, treatment significantly improved the PCR (924 ± 73 to 337 ± 57, p<0.0001) and sAlb (24.9 ± 0.8 to 39.7 ± 0.6 mmol/L, p<0.0001), but sCr significantly worsened (116 ± 12 to 123 ± 7.2 μmol/L, p=0.017). In SMN, treatment again significantly improved the PCR (863 ± 154 to 221 ± 36, p=0.001) and sAlb (28 ± 1.2 to 39 ± 0.8 mmol/L, p<0.0001), but sCr significantly worsened over the treatment period (101 ± 10 to 126 ± 12 μmol/L, p=0.0045). Of the MN patients who reached ESRF, the sCr was significantly worse on presentation (235 ± 42 vs 111 ± 8 μmol/L, p<0.0001). These patients had significantly higher sAlb (30.8 ± 1.4 vs 26 ± 0.6 mmol/L, p=0.001) and accordingly PCR tended to be lower at presentation, but this difference failed to reach significance (628 ± 79 vs 901 ± 78, p=0.06).

Conclusions: In our cohort of patients with membranous nephropathy, sAlb is lower in IMN compared to SMN. Treatment improves proteinuria and albumin but does not prevent a decline in serum creatinine.

PUB251

An Unusual Case of Seronegative Lupus Nephritis with ANCA-Positive Serology *Amibahen Gandhi*, Varun Malhotra, Shani C. Kotadia, Medha Joshi. *Conemaugh Memorial Medical Center, Johnstown, PA.*

Background: Seronegative lupus nephritis is a condition with renal histology typical for lupus nephritis without clinical and serologic evidence of systemic lupus nephritis (SLE).

Methods: Here, we report an unusual presentation of seronegative SLE diagnosed with kidney biopsy who does not meet any other diagnostic criteria for SLE established by American Rheumatism Association. Our patient was 60-year-old woman with past medical history of only hypothyroidism, presented with new onset of kidney injury and hypertension. Laboratory data showed BUN and creatinine of 74mg/dl and 10.3mg/dl respectively, hypocomplementemia and nephrotic range proteinuria and hematuria. Serology tests including serum ANA, anti ds DNA, anti-smith and smooth muscle antibodies, anticardiolipin IgG and IgM titers, C1Q binding assay were negative. HIV, hepatitis B and C viruses serologies were negative too. C-ANCA (0.7 U) and P-ANCA (1.5U) were positive. Renal biopsy showed proliferative crescentic and membranous glomerulonephritis with a full house immuno-fluorescence pattern with extra-glomerular tubular basement deposits suggestive of Lupus like glomerulonephritis. Patient required hemodialysis for her renal failure and was treated with oral cyclophosphamide and corticosteroids. Seven months into treatment, patient still requires twice a week hemodialysis with only minimal recovery of renal function and has not yet experienced any clinical symptoms of SLE.

Conclusions: In conclusion, we present an unusual case of ANCA positive, ANA negative full house nephropathy. ANA negative lupus nephritis is very rare presentation with incidence rate of 1-5%. At this point we are not sure if in the future patient will develop further clinical or serological evidence of SLE and then be diagnosed as "SLE with positive immunological response to ANCA". ANCA vasculitis is pauci-immune and hence it would be extremely unlikely and rare if it turns out that she has ANCA vasculitis with full house on renal immuno-fluorescence. The treatment and prognosis of renal-limited lupus-like glomerulonephritis remains unclear, although limited data suggest a poor prognosis.

PUB252

Pathological and Clinical Analysis of the Kidney Puncture Biopsy in 1,551 Cases *Mei Li*,¹ Qiong-li Yin,¹ Zhenda Zheng,² Cai-Lian Cheng,³ Xun Liu,³ Cheng-gang Shi.³ ¹VIP Healthcare Center, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou; ²Cardiovascular Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou; ³Nephrology Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.

Background: To summarize all the renal biopsy cases in the Past ten years in the Third Affiliated Hospital of Sun Yat-sen University; analyze the pathological type distribution, and their relationship with clinical manifestations.

Methods: Pathological and clinical data in 1,551 cases with renal biopsy with complete clinical data were analyzed retrospectively from January 2005 to December 2014.

Results: Among 1,551 cases, age 6-83 (34.81±14.28 years), including primary glomerular disease (63.8%), secondary glomerular diseases (33.5%). The first three pathological types of primary glomerulonephritis are IgA nephropathy (38.6%), glomerular minor lesion (25.9%) and membranous nephropathy (MN) (19.3%). The first three pathological types of secondary glomerulonephritis are lupus nephritis (LN) (65.2%), diabetic nephropathy (DN) (8.5%) and hepatitis B virus associated glomerulonephritis (HBV-GN) (7.3%). Acute and chronic rejection are the most common pathological type of renal transplantation in 26 cases. Chronic nephritis syndrome and nephrotic syndrome are the most common clinical manifestations. For male versus female, the ratio is 1.32:1 in the primary glomerulonephritis, while 0.73:1 in the secondary glomerulonephritis.

Conclusions: Primary glomerulonephritis is still the most common form of renal disease, and almost in male. IgA nephropathy is the most common pathological type of primary glomerulonephritis followed by glomerular minor lesion. While for the secondary glomerulonephritis, female is more than male, and LN is the most common pathological type followed by DN. And Chronic nephritis syndrome is the most common clinical manifestations of renal biopsy.

PUB253

Iodine-123 MIBG Imaging of Renal Cell Carcinoma with Pathological Correlation Ken Hiratsuka,¹ Isao Kurihara,¹ Sayuri Suzuki,¹ Shintaro Yamaguchi,¹ Toshiaki Monkawa,¹ Koichi Suzuki,² Hiroshi Itoh.¹ ¹Dept of Internal Medicine, Keio Univ School of Medicine, Japan; ²Dept of Mycobacteriology, Leprosy Research Center, National Inst of Infectious Diseases, Japan.

Background: The incidence of renal cell carcinoma has continuously increased during the last fifty years. Despite the increase in number, the five year survival rate has been reduced by the advances in renal imaging. Chromophobe renal cell carcinoma (ChRCC) is an uncommon variant of RCC, accounting for approximately 5% of renal cancer. Although its prognosis is usually favorable, preoperative diagnosis is difficult because there is no marker for this variant. Here, we reported a novel method to distinguish ChRCC from other RCC (especially, clear cell carcinoma).

Methods: We experienced a case of ChRCC with adrenal pheochromocytoma in a 69-year-old Japanese female. We noticed that iodine-123 MIBG scintigraphy showed uptake in ChRCC in addition to pheochromocytoma; uptake was not observed in other cases of clear cell carcinoma. As a candidate transporter that mediate iodine-123 uptake in ChRCC, we determined the expression of pendrin, a Cl/HCO₃⁻ exchanger expressed in the kidney cortex. The pendrin messenger RNA (mRNA) expressions, and protein expressions were analyzed in 4 cases of ChRCC and 3 cases of clear cell carcinoma.

Results: The protein expression of pendrin, the candidate transporter, which related to iodine-123 uptake, was highly detected in ChRCC compared with clear cell carcinoma. Moreover, the mRNA expression was also exclusively increased in ChRCC.

Conclusions: We identified specific transporter, pendrin, which is highly expressed in ChRCC. Our results indicates that iodine-123 MIBG scintigraphy may be a useful tool for the diagnosis of ChRCC and represents a substantial advance in the diagnosis of ChRCC.

PUB254

Clinical Significance of Glomerular IgG Deposits in IgA Nephropathy Anthony Alvarado,¹ Nicole K. Andeen,² Sergey V. Brodsky,³ Alice Hinton,⁴ Tibor Nadasdy,³ Charles E. Alpers,² Christopher D. Blosser,⁵ Behzad Najafian,² Brad H. Rovin.¹ ¹Faculty of Medicine, Nephrology Div, The Ohio State Univ, Columbus, OH; ²Pathology Dept, Univ of Washington, Seattle, WA; ³Pathology Dept, The Ohio State Univ, Columbus, OH; ⁴Div of Biostatistics, College of Public Health, The Ohio State Univ, Columbus, OH; ⁵Faculty of Medicine, Nephrology Div, Univ of Washington, Seattle, WA.

Background: IgAN is characterized by IgA dominant or IgA-IgG co-dominant mesangial immune deposits. It is not clear whether the presence of IgG in IgAN affects disease prognosis. We evaluated the significance of IgG co-deposits in IgAN.

Methods: Consecutive IgAN biopsies (n=80) from Ohio State University and University of Washington (2001-2013) were retrospectively classified into IgA only and IgA+IgG (IgG > trace). The presence or absence of IgG was correlated to the combined primary outcome of renal replacement therapy, death, OR doubling of serum creatinine (SCr). The change in estimated GFR (eGFR) was also assessed. Covariates were age, sex, race, SCr and proteinuria at biopsy, length of follow-up, treatment, Oxford score, and presence of crescents.

Results: This cohort was 64% male, 69% Caucasian and 14% Asian. IgA+IgG deposits were seen in 25 of the patients. There was no difference between IgA and IgA+IgG with respect to any of the covariates or between initial and follow-up proteinuria. There was a tendency for more endocapillary hypercellularity to be seen in IgA+IgG biopsies (p=0.08). The primary outcome was reached in 24 patients, 16 with IgA and 8 with IgA+IgG (p=0.82). Using multivariate modeling the change in eGFR over time was not different between IgA and IgA+IgG.

Conclusions: In this cohort of IgAN patients the presence of IgG co-deposits in the mesangium did not affect clinical outcomes.

PUB255

Idiopathic Cryoglobulinemic Crescentic Glomerulonephritis – A Rare and Atypical Case Pedram Joseph Kohan,¹ Akshatha Rao,² Sandeep Aggarwal.² ¹Internal Medicine, Drexel College of Medicine/Hahnemann Univ Hospital, Philadelphia, PA; ²Nephrology, Drexel College of Medicine/Hahnemann Univ Hospital, Philadelphia, PA.

Background: Cryoglobulinemic Glomerulonephritis is a rare entity, manifesting in middle-aged females. We report an atypical case of cryoglobulinemic crescentic glomerulonephritis in an 18-year-old African American Male without an identifiable viral, autoimmune or lymphoproliferative etiology.

Methods: Our case is an 18 y/o AAM with no significant PMH who presented for an incidental hematuria and proteinuria. Patient did not complain of edema, recent illness, joint pains, rash, night sweats or weight loss. No history of IVDA. BP was 114/72, without significant physical exam findings. **Urine microscopy:** cellular casts and dysmorphic RBCs. Serum creatinine was 1.27 mg/dL.

Renal Biopsy

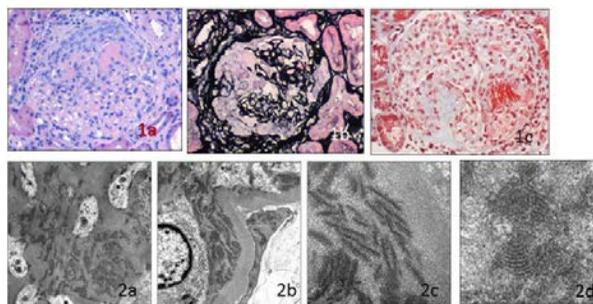


Figure 1. (1a). H&E Crescentic GN (1b) Jones Silver: MPGN with Crescents. Trichrome staining (1c) reveals eosinophilic intra-glomerular deposits with collagen deposition and obliteration of Bowman's space. Substantial mesangial (2a; 30000x) and subendothelial (2b; 30000x) electron dense deposits of randomly arranged, slightly curved microtubular/fibrillary structures of approximately 20-25nm in diameter (2c; 120000x), and fingerprinting (2c: 30000x)

LM: crescents and endocapillary proliferation. EM showed subendothelial, subepithelial and paramesangium 20.5-25nm microtubular fibrils. **IF:** only C1q 2-3+ granular GBM and mesangial deposits. **Labs:** UPCR: 2.1 grams/day, ESR and CRP levels were markedly elevated. Viral hepatitis/HIV PCR, ANA, anti-DsDNA, anti-RNP, anti-smith, SSA/SSB, anti SM and Rh factor/CCP, C3, C4, ASO, cryocrit, SPEP/UPEP/free light chains/Immunofixation, peripheral flow cytometry were negative. Patient was treated with IV methylprednisolone pulse and rituximab with improvement of renal function and proteinuria.

Conclusions: The uniqueness of this case is underscored by a variety of factors; clinical presentation, laboratory, serologies, and pathology. Laboratory and serological studies in cryoglobulinemia generally follow a characteristic pattern, detection of circulating cryoglobulins, low levels of complement, viral, autoimmune or lymphoproliferative etiology- yet a limited number of cases have presented with normal serological results, similar to the case presented here.

PUB256

Development of a Clinicopathologic Kidney Biopsy Database Using Billing and Diagnosis Codes: A Descriptive Study Nosayaba Enofe,¹ Anju A. Oommen,¹ Jason Cobb,¹ Jose E. Navarrete,¹ Demilade Adedinsowo,² Oluwatobiloba A. Osikoya,³ Helene B. Fevrier,⁴ Frederic F. Rahbari-Oskoui,¹ Alton Brad Farris,⁵ Laura Plantinga,¹ Titilayo O. Ilori.¹ ¹Dept of Nephrology, Emory Univ School of Medicine, Atlanta, GA; ²Morehouse School of Medicine, Atlanta, GA; ³Lee Univ, Cleveland, TN; ⁴Dept of Epidemiology, Rollins School of Public Health, Emory Univ, Atlanta, GA; ⁵Dept of Pathology and Laboratory Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: A growing kidney disease population coupled with expanded use of electronic medical records (eMR) presents a unique opportunity for regional translational clinical research. We developed a comprehensive registry of all native renal biopsies at a major hospital in Southeastern US and described the pattern of glomerular diseases.

Methods: We identified all native percutaneous renal biopsies (n=2,245) performed on adults (>18) between 2000 and 2011 using CPT and ICD-9 billing codes (50200 and 55.23). Transplant biopsies (V42.0) and cytopathology were excluded. Renal pathology reports were reviewed by at least two independent clinical nephrologists. Clinical, laboratory and demographic data were extracted and validated by independent chart review. A clinicopathologic diagnosis was subsequently entered. Descriptive and bivariate statistics were used to analyze patient characteristics at biopsy.

Results: Patients in the registry had a mean age of 44.2 years; approximately half were male and majority were African American (40.7%). Overall, lupus nephritis (n=278, 12.4%) was the most prevalent renal clinicopathologic diagnosis. Among primary glomerular diseases, FSGS (136, 9.2%) was the most prevalent, followed by IgA nephropathy (123, 8.3%), membranous glomerulonephritis (GN) (69, 4.6%), membranoproliferative GN (24, 1.6%) and minimal change disease (27, 1.8%). Diabetic nephropathy was the second most common secondary GN (97, 6.5%) followed by ANCA-associated vasculitis (31, 2.1%). Other diagnoses were all less than 2%.

Conclusions: We successfully established a kidney biopsy registry at our center, which will be instrumental to studying outcomes in this rare group of diseases, the most prevalent of which were lupus nephritis and FSGS.

PUB257

Is There Clinical Significance of IgM and Complement Staining in Idiopathic Focal Segmental Glomerulosclerosis *Yasanth M. Muthuppalaniappan,¹ Kieran Mccafferty,¹ Michael Sheaff,² Muhammad M. Yaqoob.¹* ¹*Nephrology, Barts & The London NHS Trust, London, United Kingdom;* ²*Pathology, Barts & The London NHS Trust, London, United Kingdom.*

Background: Experimental evidence suggest that focal segmental glomerulosclerosis with complement deposits is associated with poor outcome. Whether this is transferable or relevant in human disease is unclear.

Methods: We performed a proof-of-concept observational study on all patients with a diagnosis of idiopathic focal segmental glomerulosclerosis (iFSGS) on native renal biopsies from January 2004 to December 2014. A total of 40 renal biopsies were identified. Clinical outcome data were obtained to seek an association with complement deposits (CD) and outcomes. Immunosuppression administered was according to the local trust policy which included prednisolone and cyclophosphamide or calcineurin inhibitor.

Results: See Table 1

	No CD (n= 21)	CD (n= 19)	P
Age	43 (35-50)	39 (30.5-54.5)	0.6
Sex Male	11 (52)	7 (27)	0.35
Race Black/Asian/White	6 / 9 / 6	8 / 5 / 6	0.39
Type of lesion : Tip/Collapsing/NOS	2 / 2 / 17	3 / 0 / 16	0.34
IgM	0 (0)	18 (95)	<0.0001
Immunosuppression	12 (57)	12 (63)	0.75
Baseline urine protein creatinine ratio (UPCR)	540 (330-1000)	1000 (560-1200)	0.07
Baseline albumin	29 (24-38)	26 (21-36)	0.47
Baseline eGFR	49 (25-71)	60 (48-81)	0.26
Change in UPCR	- 370 [-700 - (-140)]	- 430 [-790- (-260)]	0.7
Change in serum albumin	8.5 (2.3-13)	4 (0-17)	0.55
Change in eGFR	4.5 (-5.5 - 21)	4 (-15-11)	0.44

CD was present in approximately 50% of the biopsies, but there was no significant association between CD and baseline clinical or demographic characteristics, furthermore, there are no association between CD and markers of disease progression (change in proteinuria, serum albumin or GFR between baseline and 1 year follow up). IgM staining was strongly co-associated with CD.

Conclusions: Our results indicate that, unlike animal models of iFSGS; IgM and complement deposition does not alter outcomes. However, these findings will need to be confirmed in a larger study.

PUB258

A Case of Intra-Ocular Lucentis (Ranibizumab) Induced Minimal Change Disease *Ashwin Reddy Ganta. Dept of Nephrology, Archbold Memorial Hospital, Thomasville, GA.*

Background: Intravitreal Monoclonal antibodies like Lucentis (Ranizibumab) , Eylea and Avastin are being increasingly used for the treatment of Wet Age related Macular Degeneration (wAMD) and Diabetic Macular Edema (DME) of the eye. Though the systemic toxicity of these VEGF inhibitors is well known, not much is known about the renal toxicity profile of these agents when administered intravitreally.

Methods: A 78 y/o WM presented with worsening shortness of breath and anasarca. His PMH was significant for Afib, h/o Lung Cancer s/p RLL resection 8 years ago and he was receiving Lucentis intravitreal shots for his AMD and had just had his 5th monthly dose a few days ago. His urine showed 3 + protein with some RBCs and we were consulted for worsening renal function with a Scr of 2.4 mg/dl , up from a baseline of 1.0 mg/dl. Given his h/o cancer with almost 3 gms of proteinuria, MCD (Minimal Change Disease) was high in the differential. Serology for HIV, SPEP, Hep C, SIEP, ANA and ANCA was negative . His Scr continued to worsen and reached a peak of 4.6 and he had to undergo Dialysis for volume overload . Renal Biopsy performed showed 9 glomeruli with no evidence of IC mediated injury and MCD pattern confirmed on EM. He was started on high dose steroids and discharged with a diagnosis of MCD 2/2 Lucentis. He was taken off HD after he started showing signs of renal recovery in a few weeks and he was gradually tapered of Steroids over the next 4 months. His proteinuria has completely subsided and his Scr is back to his baseline .

Conclusions: Systemic use VEGF inhibitors and their renal toxicity is well documented. Now , they are currently being to treat wAMD and DME. However, there is some evidence that intravitreal use may result in systemic absorption, with the potential for AKI. We report the first case to our knowledge of a patient who developed severe AKI needing HD with MCD pattern of injury after 5 intravitreal injections of ranibizumab that was successfully treated with cessation of Lucentis and Steroids. Because of the increasing use of these agents, ophthalmologists and nephrologists should be aware of the associated risks.

PUB259

Eculizumab in a Patient with Lupus Nephritis and Thrombotic Microangiopathy: Outcome After One Year *Maria Izabel Neves de Holanda Barbosa,¹ Lilian M. Pereira,² Alicia Imada,¹ Luiz Fernando Christiani.¹* ¹*Nephrology and Kidney Transplant, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil;* ²*Pediatrics Nephrology, Univ Estadual de Campinas, Campinas, São Paulo, Brazil.*

Background: Lupus Nephritis is a severe disease and when is associated with Thrombotic microangiopathy the prognosis is worst.

Methods: This is a case report of a female patient, 18 years old, with no past history of disease, started fever, abdominal pain and dysuria treated initially as UTI. She evolved with skin rash and a few days later, oligoanuria, nausea and vomiting. She was admitted and started hemodialysis on the same day. Initial exams showed thrombocytopenia, anemia, High LDH, schistocytes on blood smear, direct Coombs test negative, urinalysis with hematuria and proteinuria. ANA and anti DNAs were positive, ADAMST13 96%, C3 and C4low. SLE was diagnosed and she received standard therapy with methylprednisolone and cyclophosphamide. She needed RBC transfusions at least twice a week. After 55 days of treatment, she still presented over hemolysis and anuria in hemodialysis.

Results: We decided to start eculizumab and after one week, platelet count increased allowing for a renal biopsy that showed lupus nephritis class IV with thrombotic microangiopathy. After the third dose of eculizumab, there was improvement of anemia and she started to present diuresis. She was discharged from hospital one week later with creatinine of 2.3 mg/dL and off dialysis. After one year, she is on maintenance eculizumab every two weeks with low dose prednisone and mycophenolate mofetil 1per day. Creatinine is 1.7 mg/dL, hemoglobin 11 g/dL, normal platelet count and LDH.

Conclusions: This is a successful case of eculizumab in a patient with Lupus nephritis and thrombotic microangiopathy refractory to classical treatment. A putative explanation is that autoantibodies may have primed the endothelium, unmasking a complement defect that was successfully controlled by terminal complement blockade. A genetic analysis may reveal a mutation in regulator factors of the alternative complement pathway or auto-antibodies against Factor H or I. Eculizumab may be an option for the treatment of refractory lupus nephritis with thrombotic microangiopathy.

PUB260

Diagnostic Items for Renal and Hepatic Cyst Infection – A Delphi Survey *Marten A. Lantinga,¹ Alexander J.M. Darding,¹ Rudolphe De Sevaux,¹ Ron T. Gansevoort,² Marie C. Hogan,³ Ahsan Alam,⁴ William M. Bennett,⁵ Chantal P. Bleeker-Rovers,¹ Mickaël Bobot,⁶ Arlene B. Chapman,⁷ Emilie Cornec-Le Gall,⁸ Gregory T. Everson,⁹ Tom J.G. Gevers,¹ Jose L. Gorritz,¹⁰ Ziad Hassoun,¹¹ Esther Meijer,² Michal Mrug,¹² Frederik Nevens,¹³ Luiz F. Onuchic,¹⁴ Hayne C. Park,¹⁵ York P. Pei,¹⁶ Giorgina B. Piccoli,¹⁷ Yves A. Pirson,¹¹ Gopala K. Rangan,¹⁸ Darius Soonawala,¹⁹ Roser Torra,²⁰ Folkert W. Visser,² Terry J. Watnick,²¹ Francois Jouret,²² Nada Kanaan,¹¹ Wim J.G. Oyen,¹ Tatsuya Suwabe,²³ Vicente E. Torres,³ Joost P.H. Drenth.¹* ¹*Radboudumc;* ²*UMCG;* ³*Mayo Clinic;* ⁴*McGill;* ⁵*Legacy Health;* ⁶*AMU;* ⁷*Emory Med;* ⁸*CHRU;* ⁹*CU Med;* ¹⁰*Dr Preset Hosp;* ¹¹*UCL Saint-Luc;* ¹²*UAB;* ¹³*UZ Leuven;* ¹⁴*Univ São Paulo;* ¹⁵*SNUH;* ¹⁶*U of T;* ¹⁷*San Luigi Gonzaga Hosp.;* ¹⁸*WMI;* ¹⁹*LUMC;* ²⁰*IIB Sant Pau;* ²¹*Hopkins Med;* ²²*ULg CHU;* ²³*Toranomon Hosp.*

Background: Diagnosis of renal and hepatic cyst infection is made on the presence of a positive cyst aspirate culture. If that is absent, diagnosis is made on a mix of clinical, biochemical, and imaging findings. The weight of these diagnostic items is uncertain, hence our aim to establish a set of items for cyst infection diagnosis.

Methods: We used a Delphi survey among acknowledged experts to achieve consensus on diagnostic items. We retrieved items from literature and physician/patient interviews. Items were rated on a nine-point scale in a three-round online survey. We categorized items by median rating (£3.4=inappropriate; 3.5-6.4=uncertain; ≥6.5=appropriate).

Results: Of 58 invited experts, 35 (60%) responded to round one (round two: 91% n=32; round three: 86% n=30). The final panel included 23 nephrologists, five hepatologists, a nuclear medicine specialist, and an infectiologist from 11 countries (male 67%, age 47±11 yrs, median clinical experience 21 yrs). We identified 59 items and rated each for renal and hepatic cyst infection. Majority was derived from literature (n=46). Ultimately, 26 renal and 22 hepatic items were rated as appropriate. Remaining items were rated inappropriate (renal n=18; hepatic n=12) or uncertain (renal n=15; hepatic n=25).

Conclusions: We identified diagnostic items for renal and hepatic cyst infection and on this basis we developed a diagnostic algorithm.

Funding: Clinical Revenue Support

PUB261

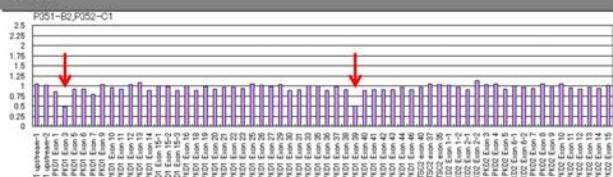
The Use of Multiplex Ligation-Dependent Probe Amplification Technology for Genetic Analysis of the Entire PKD1 Gene and PKD2 Gene *Tetsuhiko Yasuno. Fukuoka Univ, Fukuoka, Japan.*

Background: In common cases of autosomal dominant polycystic kidney disease (ADPKD), diagnosis is relatively simple using a combination of diagnostic imaging of the kidney and analysis of ADPKD in the patient's family history. Therefore, in most patients with ADPKD, genetic testing for ADPKD is not necessary for diagnosis. However, in ADPKD cases where a definitive diagnosis is not obtained by imaging or living relative related donor is identified for kidney transplantation, genetic testing may be necessary.

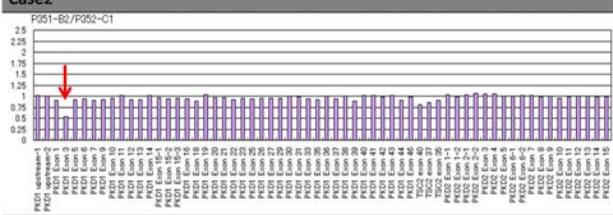
Methods: Multiplex ligation-dependent probe amplification (MLPA) kits have been developed for genetic analysis by MRC-Holland using proprietary MLPA technology. We obtained informed consent from nine patients (mean age, 45 years) and collected 8 mL of blood from each patient for analysis of genetic mutations in PKD1 and PKD2 genes using the MLPA method.

Results: In case 1 (a 39-year-old man), we found deletions in exons 3 and 39 of the PKD1 gene. The kidney was extracted due to enlargement and cyst infection. Dialysis was initiated when the patient was 39 years of age. The kidney capacity was 5013 mL. In case 2 (a 32-year-old woman), we found a deletion in exon 3 of the PKD1 gene. Renal function was maintained, and the serum creatinine level was 0.7 mg/dL. She has hope of the delivery. Tolvaptan does not have the safety about the dosage to a pregnant woman. Tolvaptan was administered after delivery.

Case1



Case2



No mutations were identified in the other subjects.

Conclusions: Genetic screening of the PKD1 and PKD2 genes using the MLPA method may decrease cost and labor. Indeed, the MLPA method was especially useful in cases exhibiting juvenile onset and rapid kidney enlargement.

PUB262

Short-Term Effects of Tolvaptan to a Body Water Balance in Patients with ADPKD Minoru Makita, Saori Nishio, Junya Yamamoto, Tasuku Nakagaki, Tatsuya Atsumi. *Internal Medicine 2, Hokkaido Univ, Sapporo City, Hokkaido, Japan.*

Background: In the clinical trials of Tolvaptan, reversible serum creatinine elevation and adverse events related to increased aquaresis were reported in some patients with autosomal dominant polycystic kidney disease (ADPKD). To clarify the mechanism of those adverse events, we preliminarily evaluated a volume status before and after administration of tolvaptan in ADPKD patients by analysing body composition with multiple-frequency bioelectrical impedance analyser (InBody720[®]) and associating with renal function.

Methods: Nineteen ADPKD patients who started administration of tolvaptan were examined. Body weight and renal function were measured before (baseline) and 2 days (day2) after initial tolvaptan administration. Height-corrected total kidney volume (htTKV) were measured at baseline. Total body water (TBW), intracellular water (ICW) and extracellular water (ECW) [whole body, limbs and trunk, respectively], were measured using InBody720[®] at baseline and day2.

Results: The administration of tolvaptan significantly reduced body weight, eGFR, TBW, ICW and ECW in whole body and TBW in limbs. However, TBW in trunk were sustained (Table).

	baseline	day2	p-value
Body weight(kg)	64.0±12.5	62.1±11.8	<0.001
eGFR(ml/min/1.73m ²)	53.9±27.2	51.4±24.8	0.013
TBW whole(kg)	38.2±8.1	36.0±7.4	<0.001
ECW whole(kg)	14.8±2.9	13.9±2.7	<0.001
ICW whole(kg)	23.3±5.2	22.2±4.8	<0.001
TBW trunk(kg)	16.8±3.7	16.5±3.5	0.75
ICW trunk(kg)	10.3±2.4	10.2±2.2	0.58
TBW limbs(kg)	16.9±4.3	15.7±4.1	<0.001

HtTKV at baseline correlated with rate of ICW in trunk and TBW in whole at baseline (r=0.39, p=0.049). There were no significant correlation between eGFR decrease and rate of change in body weight (r=0.02, p=0.46). Rate of TBW in limbs and TBW in whole at baseline correlated with rate of change in eGFR (r=0.45, p=0.028). These results suggest that cyst fluid might be measured as ICW by InBody720[®]. TBW in limbs can predict eGFR decline.

Conclusions: Measuring body water balance by InBody720[®] could be useful as predictors of htTKV and eGFR decline in short term after administration of tolvaptan in ADPKD patients.

PUB263

Abstract Withdrawn

PUB264

A Rare Presentation of Acute Kidney Injury: Have a Look at the Skin Alper Alp,¹ Sarenur Esener,² Didar Gursoy,³ ¹Nephrology, Van Education and Research Hospital, Van, Turkey; ²Dermatology, Van Education and Research Hospital, Van, Turkey; ³Pathology, Van Education and Research Hospital, Van, Turkey.

Background: Tuberous sclerosis(TS) is a multisystem,rare,genetic disorder of autosomal dominant inheritance which can involve different organs.Most commonly involved organ system is skin.We describe a case presented with periungual fibromas,multiple renal cysts and Shagreen patch without other features of TS.

Methods: A 33 yo woman presented with fatigue and renal failure.On physical examination,she had multiple non traumatic periungual fibromas in both hands and feet. Also Shagreen patch was seen in the right lumbosacral region.



On admission biochemical tests;urea 132 mg/dl,creatinine 4,7 mg/dl,potassium 4,7 mmol/L,pH 7,32,HCO3 18,4,Urinary output was satisfactory,no uremic symptoms were present.Renal ultrasonography revealed bilateral renal cysts with normal size and parenchymal thickness.Histopathology of the Shagreen patch revealed dense collagen bundles in the dermis.Due to the skin lesions and renal cysts the patient was diagnosed as TS.Other manifestations of TS were not present.Renal biopsy was suggested but she did not accept the procedure.

Conclusions: As stated in diagnostic criterias,physical examination has a strong impact on diagnosis of TS.Hypomelanotic macules(>3),Shagreen patch,forehead plaque,non traumatic periungual fibromas,adenoma sebaceum,facial angiofibromas should remind the physicians TS.Kidneys are involved in almost 50-80% of the adult patients.Most frequent renal lesions in TS are angiomyolipomas.Bilateral and multiple characteristics of angiomyolipomas are pathognomonic.They may progress to end stage renal disease. However in some rare cases frank renal lesions may be absent.With a detailed inspection it is possible to recognize these specific dermatological signs,making the Tuberous sclerosis diagnosis and taking these patients under nephrological follow up.

PUB265

Use of Antidepressant Medications During the HALT-PKD Randomized Trials Vicente E. Torres,¹ Kaleab Z. Abebe,² Theodore I. Steinman,³ Charity G. Moore,² Ronald D. Perrone,⁴ Arlene B. Chapman,⁵ Robert W. Schrier,⁶ Alan S.L. Yu,⁷ William E. Braun,⁸ Kyongtae Ty Bae,² Peter C. Harris,¹ Charity G. Moore,² Michael F. Flessner,⁹ The HALT PKD Investigators,¹⁰ ¹Mayo; ²U. Pittsburgh; ³BIDMC; ⁴Tufts U.; ⁵U. Chicago; ⁶U. Colorado; ⁷KS U. Med. Ctr.; ⁸Cleveland Clinic; ⁹NIH; ¹⁰Multi-Ctr.

Background: Depression occurs in CKD more commonly than in the general population and is associated with poor outcomes. The use of antidepressants (ADs) has been associated with inappropriate release of vasopressin and hyponatremia. Since vasopressin is thought to aggravate the progression of ADPKD, AD use could be deleterious.

Methods: Examine the use of ADs in the participants of the HALT-PKD randomized clinical trials (RCTs) and whether their administration is associated with faster disease progression. Post-hoc analysis of two HALT-PKD RCTs (A and B) studying the effect of rigorous vs standard BP control (A) and of ACE inhibitor alone vs ACE inhibitor/ARB combination (A and B) on rates of change of TKV (A) and eGFR (A and B) in ADPKD patients with eGFR >60 (A) or 25-60 (B) ml/min/1.73 m².

Results: Female used ADs more frequently than male participants (39.7% of 526 vs 20.4% of the 518, P<0.0001). Study A used ADs as frequently as study B participants (31.7% and 28.4%, respectively). Participants with PKD2 mutations used ADs (42.4%) more frequently than those with PKD1 mutations (27.9%, P=0.0009) despite having milder disease. Ages of those using or not using ADs were similar. To assess the effect of ADs on disease progression we divided the participants into three groups, no exposure to ADs, exposure for less £30% and exposure for >30% of the time:

Study	AD Use	S. Sodium* (mEq/L)	Ucr/Pcr*	U. Sodium* (mEq/24 hrs)	LnTKV change (% per yr)	eGFR change (ml/min/1.73m ² /yr)
A	None (N=381)	138.7	65.1	178.3	6.32	-2.85
A	>30% (N=128)	138.4	65.9	175.1	5.81	-3.32
P-value		0.031	0.89	0.37	0.22	0.07
B	None (N=348)	139.3	30.5	168.2	-	-3.81
B	>30% (N=112)	138.8	31.9	151.6	-	-3.82
P-value		0.06	0.46	0.005	-	0.98

*Average of measurements for each participant during the trial

Conclusions: AD use, defined as >30% use, does not affect the progression of ADPKD. Whether a particular AD class has an effect is under evaluation.
Funding: NIDDK Support

PUB266

Dysregulation of miR-378a-3p and ADAMTS1 Gene in *cpk* Mice: A Model of ARPKD Masashi Sato,¹ Koichi Nakanishi,¹ Taketsugu Hama,¹ Hironobu Mukaiyama,¹ Hiroko Togawa,¹ Yuko Shima,¹ Masayasu Miyajima,² Kandai Nozu,³ Shizuko Nagao,⁴ Hisahide Takahashi,⁴ Kazumoto Iijima,³ Norishige Yoshikawa.⁵ ¹*Pediatrics, Wakayama Medical Univ, Wakayama, Japan;* ²*Laboratory Animal Center, Laboratory Animal Center, Wakayama, Japan;* ³*Pediatrics, Kobe Univ, Kobe, Japan;* ⁴*Education and Research Center of Animal Model for Human Disease, Fujita Health Univ, Aichi, Japan;* ⁵*National Center for Child Health and Development, Tokyo, Japan.*

Background: The pathophysiology of cystic epithelia in PKD is characterized by altered proliferative activity, a secretory rather than absorptive function, and an abnormal matrix microenvironment. miRNAs are clarified to be involved in PKD. However, the detail has not been fully investigated. We reported that *cpk* cystic epithelia partially share cell pathophysiology with colorectal carcinoma (JASN 25:414A, 2014). Recently, dysregulation of miR-378a-3p/ADAMTS1 axis was reported in colorectal carcinoma (Kara, et al. Gene, in press). ADAMTS1 is one of the ADAMTS (A Disintegrin And Metalloproteinase with Thrombospondin motifs) metalloproteinase family. Elevated ADAMTS1 promotes pro-tumorigenic changes such as increased tumor cell proliferation and altered extra cell matrix environment.

Methods: To identify miRNAs that are differentially expressed between *cpk* and control kidneys, we performed miRNA microarrays, and assessed the target molecule gene and its product expression using real-time PCR and western blotting.

Results: miRNA microarray analysis revealed that 22 (up 4, down 18) miRNAs were differentially expressed (more than 4-fold) in *cpk* (day 21, n=7) kidneys. Of 22 miRNAs, miR-378a-3p was significantly downregulated in *cpk* (5.1-fold). Real-time PCR confirmed that miR-378a-3p was significantly downregulated in *cpk* (day 14, n=14, 5.0-fold, p=0.002; day 21, n=12, 9.1-fold, p<0.0001) and that one of the target molecules of miR-378a-3p, ADAMTS1 mRNA was significantly upregulated in *cpk* (day 14, n=20, 1.4-fold, p=0.01; day 21, n=12, 3.5-fold, p=0.0002). Western blotting showed that ADAMTS1 was increased in *cpk* (day 21, n=6, 1.8-fold, p=0.03) kidneys.

Conclusions: Results suggest that miR-378a-3p/ADAMTS1 axis is involved in *cpk*. In conclusion, this axis may be a therapeutic target in PKD.

Funding: Government Support - Non-U.S.

PUB267

Identifying and Integrating Consumer Perspectives in Clinical Practice Guidelines on Autosomal Dominant Polycystic Kidney Disease David J. Tunnicliffe,¹ Allison Tong,¹ Pamela Andrea Lopez-Vargas,¹ Jonathan C. Craig,¹ Gopala K. Rangan.^{2,3} ¹*The Univ of Sydney, Australia;* ²*Westmead Millennium Inst, Australia;* ³*Westmead Hospital, Australia.*

Background: Integration of consumer perspectives into clinical practice guidelines is widely advocated as it ensures that recommendations are relevant to all stakeholders. We aimed to identify consumer perspectives on topics and outcomes to include in clinical practice guidelines on autosomal polycystic kidney disease (ADPKD).

Methods: A workshop involving three concurrent focus groups with consumers was convened. Guideline topics, interventions and outcomes were identified, and integrated into guideline development. Thematic analysis was used to analyze the reasons for their choices.

Results: Eighteen consumers (patients with ADPKD [n=15], caregivers [n=3]) participated and 22 priority topics (including interventions) were identified, with most focused on non-pharmacological management (diet, fluid intake, physical activity, complementary medicine), pain management, and psychosocial care (mental health, counseling, cognitive and behavioral training, education, support groups). They also identified 27 outcomes including quality of life, progression of kidney disease, kidney function, cyst growth, and nephrotoxicity. Almost all topics/outcomes had already been identified by health professionals in the guideline working group with the exception of

five topics/outcomes (surgical management of cysts, patient education about end-stage kidney disease, psychosocial impact of diagnosis, need for dialysis, knowledge). Many more topics (33) and outcomes (44) were identified as priorities by health professionals than consumers. Six themes reflected reasons for consumer choices: clarifying ambiguities, resolving debilitating pain, concern for family, preparedness for the future, taking control, and significance of impact.

Conclusions: Although there was considerable concordance between the priority topics and outcomes of health professionals and consumers for guidelines of ADPKD, there was also important discordance with consumers focused on fewer issues but particularly on lifestyle, psychosocial support, pain management, and quality of life and renal outcomes.

Funding: Government Support - Non-U.S.

PUB268

Urine AQP2 Is One of the Candidates for a Surrogate Marker in the Treatment of ADPKD Patients by Tolvaptan Kenichi Akiyama, Toshio Mochizuki, Miki Nishida, Masayo Sato, Hiroshi Kataoka, Hidekazu Sugiura, Ken Tsuchiya, Kosaku Nitta. *Medicine IV, Tokyo Women's Medical Univ, Shinjyuku, Tokyo, Japan.*

Background: Tolvaptan, arginine vasopressin (AVP) V2 receptor antagonist is accepted for autosomal dominant polycystic kidney disease (ADPKD) patients in Japan since 2014. TEMPO study showed tolvaptan from 60 to 120 mg per day slowed renal cyst expansion and renal function decline. Tolvaptan dose is decided by preliminary study (TEMPO²) which showed the maximum dose that meet both urinary osmolality (Uosm) under 300 mOsm/kg and patient's tolerance. So that adequate dose for individual patient has not been suggested. Moreover, tolvaptan cause polyuria, thirsty, polydipsia due to aquaresis. Thus, it is necessary to find surrogate markers to determine the maximum effects and minimum side effects for long-term administration.

Methods: Seventeen ADPKD patients initiated tolvaptan of 60 mg were investigated. Physical data, plasma osmolality (Posm), Uosm, AVP, urine cyclic AMP (UcAMP), and urine AQP2 (UAQP2) were assessed. UcAMP was measured by radioimmunoassay (Yamasa corp.) and UAQP2 was measured by a sandwich enzyme-linked immunosorbent assay method (Otsuka Pharmaceutical Co. Ltd.).

Results: After initiation of tolvaptan, average urine volume was 8621 ml/day and delta body weight was -1.42 kg/day on day1. One month after, AVP increased from 3±3 to 7.3±11.2 pg/mL (p= 0.001), Uosm decreased from 367±349 to 243±436 mOsm/kg (p<0.001). Posm and UcAMP were not statistically associated. UAQP2 decreased from 0.029±0.068 to 0.012±0.028 pmol/mgCr (p<0.001). In our preliminary data (n=5), the serum copeptin, a precursor of vasopressin, was shown to be no consistent level.

Conclusions: It has been reported that 3% of total production of AQP2 excreted into the urine, it reflected directly the intracellular action of AVP. Thus, UAQP2 is likely to be one of surrogate markers of tolvaptan effect, moreover it could provide additional information of determination of individual dosage and monitoring for long-term usage.

Funding: Private Foundation Support

PUB269

Abnormalities in the Radius of Patients with Autosomal Dominant Polycystic Kidney Disease Measured by High-Resolution Peripheral Quantitative Computed-Tomography Imaging Danielle Diarra,¹ Janina M. Patsch,² Claudia Schueller-Weidekamm,² Michael Weber,² Arastoo Nia,³ Gere Sunder-Plassmann.¹ ¹*Dept of Medicine III, Medical Univ of Vienna, Austria;* ²*Dept of Radiology, Medical Univ of Vienna, Austria;* ³*Dept of Medicine II, St. Vincent Hospital, Medical Univ of Vienna, Austria.*

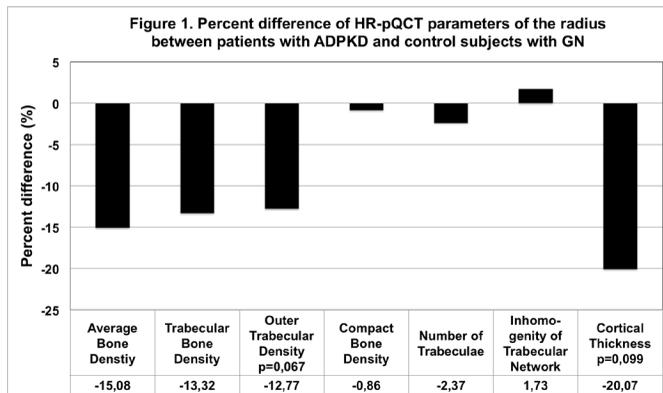
Background: ADPKD is a multi-organ disorder and the most common of all cystic kidney diseases. Mutation of the *PKD1* or -2 gene causes epi- and endothelial ciliopathies, which lead to the dysfunction of various organs. Animal studies show that primary cilia are present in osteoblasts of mice and point mutation of the osteoblastic *PKD1* gene induces osteopenia.

Methods: In this pilot-study, we examined the bone structure in 6 ADPKD patients in comparison to 6 matched patients with glomerular disease (GD), both in CKD stages I-II, by HR-pQCT of the radius and the tibia. The aim of the study was to identify microarchitectural target parameters for a subsequent larger study in patients with ADPKD.

Results: Demographic data see Table 1.

Parameter	GD Patients (controls)	ADPKD Patients
Patient number	6	6
Gender (male)	3	3
Age (years)	27±6,4	26±7,6
Serum creatinine (mg/dl)	0,81±0,17	0,83±0,19
eGFR (ml/min per 1.73 m ²)	109±18	108±23

We found reduced cortical and trabecular microstructural parameters by HR-pQCT, mainly affecting the radius. The outer trabecular density, the cortical thickness and the total density of the radius showed the biggest differences between the two groups, see Figure 1.



The total density of the radius was the best parameter to distinguish between the bone structure of ADPKD- in comparison to GD patients (AUC=0,861).

Conclusions: We provide evidence of microstructural bone deterioration of the radius in patients with ADPKD. We thus hypothesize that ADPKD is associated with microstructure bone changes in men.

PUB270

An Accurate Formula for a Quick Estimate of Total Liver Volume in Polycystic Liver Disease Patients Hedwig M.A. D’Agnolo,¹ Wietske Kievit,² Melissa Chrispijn,¹ Joost P.H. Drenth.¹ ¹*Gastroenterology and Hepatology, Radboud Univ Medical Center, Nijmegen, Netherlands;* ²*Radboud Inst for Health Sciences, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: Polycystic liver disease (PLD) appears in two disorders; autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD). The primary aim of treatment of PLD is reduction of total liver volume (TLV) as patients often suffer from hepatomegaly. The gold standard to assess TLV is CT volumetry which involves manual delineating of the liver outline. Unfortunately this is a time-consuming method (45-60 minutes per CT scan) and requires a certain level of expertise. An easily accessible and fast method to estimate TLV in routine clinical practice is needed. Therefore we aimed to develop an accurate formula for quick estimation of TLV.

Methods: We collected a cohort of PLD patients in whom CT scans were available. Manual delineation of TLV served as gold standard. PLD patients were distributed in 2 cohorts, a development cohort (N=80) and a replication cohort (N=50). We measured anterior-posterior (AP), transverse (T) and cranial-caudal (CC) distance (in meters) of the liver on CT. TLVs were logarithmically transformed as data were not normally distributed. R² was measured as it indicates the goodness of fit of the prediction model. The prediction model was tested in a replication cohort.

Results: Median liver volumes in the development and replication cohort were 4749mL [1084-14816] and 4684mL [1287-16746] respectively. All three diameters significantly correlated with TLV (p < 0.0001). Linear regression analysis resulted in the following formula: Logarithm of TLV = 5.240 + T*5.608 + CC*2.522 + AP*6.041. Our model predicted TLV accurately in the development cohort (R²= 0.898). The correlation in the development cohort was 0.948 and validation in the replication cohort resulted in a correlation of 0.937.

Conclusions: Our model accurately and quickly (< 2 minutes) predicts TLV in PLD patients based on three liver dimensions.

PUB271

Clinical Significance of Urine NAG and L-FABP Excretion for the Assessment of ADPKD-Progression Yoshimi Okada,¹ Mai Aoyagi,¹ Kaori Takayanagi,^{1,2} Takatsugu Iwashita,¹ Tota Kiba,¹ Tatsuro Sano,¹ Kento Hirose,¹ Yuichiro Kawai,¹ Ryo Yamamoto,¹ Yuya Shioda,¹ Yosuke Tayama,¹ Hajime Hasegawa.¹ ¹*Nephrology and Hypertension, Saitama Medical Center, Saitama Medical Univ, Kawagoe, Saitama, Japan;* ²*Ishikawa Kinenkai Kawagoe Ekimae Clinic, Kawagoe, Saitama, Japan.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) shows various renal prognosis. Because the progression of renal damage in ADPKD is principally caused by tubulo-interstitial nephropathy (TIN), the present study focused to study the relationship between TIN-related clinical parameters and progression of ADPKD.

Methods: In this study, 59 ADPKD cases with consents were retrospectively analyzed. Average age, duration of the observation, median values of kidney volume (KV) and kidney growth rate (KGR), average estimated GFR (eGFR) were 50.5 years old, 3.4 years, 1423 mL and 1.74% growth/year, respectively. KV was calculated by using the ellipsoid formula.

Results: In all cases, KV and eGFR showed exponential correlation (R=0.47). We focused kidney volume (KV), kidney growth rate (KGR), eGFR, and urine excretion ratio of N-acetylglucosaminidase (NAG) to Cr (NAG index) for the clinical assessment of TIN. We stratified patients by the average or median value of the parameters mentioned above, and analyzed their differences in each stratified group. KV, eGFR and KGR showed significant difference only in the eGFR-, KV- and eGFR-stratified group. However, NAG index showed significant difference in both KV-stratified (median: 7.42 vs 6.09 U/mgCr) and eGFR-stratified (8.00±5.98 vs 3.93 U/mgCr) groups. Additionally, urine liver type fatty

acid binding protein (L-FABP), as a biomarker of the tubular ischemia, showed significant difference in all stratified groups (KV: 7.29±9.98 vs 1.76±1.68, eGFR: 4.15±7.76 vs 2.45±2.34, KGR: 4.46±7.68 vs 2.09±2.30, NAG index: 4.33±7.20 vs 1.88±2.10).

Conclusions: Progression of ADPKD has been primarily assessed by the kidney volume. However, the present study may show that the assessment of TIN might be more helpful to evaluate the severity and prognosis of ADPKD. It might be suggested that TIN-related markers such as NAG index or L-FABP index should be actively utilize in the clinical management of patients with ADPKD.

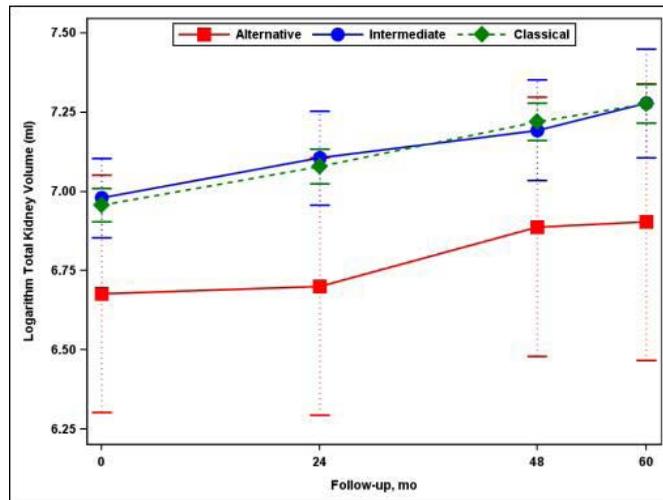
PUB272

Classic and Alternative Criteria for the Diagnosis of Autosomal Dominant Polycystic Kidney Disease: Genetics and Disease Progression in HALT-PKD William E. Braun,¹ Kaleab Z. Abebe,² Arlene B. Chapman,³ Peter C. Harris,⁴ Godela M. Brosnahan,⁵ Peter G. Czarnecki,⁶ Kyongtae Ty Bae,² Charity G. Moore,² Robert W. Schrier.⁵ ¹*Cleveland Clinic;* ²*Univ of Pittsburgh;* ³*Univ of Chicago;* ⁴*Mayo Clinic;* ⁵*Univ of Colorado;* ⁶*Brigham & Women’s Hospital.*

Background: The HALT-PKD trials based the diagnosis of ADPKD on classic criteria (CC) as well as on alternative criteria (AC) with no ADPKD family history(-FH). Patients with AC and genetically no mutation detected (NMD) were analyzed as a distinct subset (AC-NMD).

Methods: Of 959 HALT-PKD patients with genetic testing 835 (87.1%) had CC, and 124 (12.9%) had AC. Three groups: **Alternative** (AC-NMD), **Classical** (CC-PKD1/PKD2 mutation), and **Intermediate** (combined CC-NMD + AC-PKD1/PKD2 mutation) were compared for annual change in total kidney volume (TKV, htTKV) in early ADPKD (n=17, 410, 81, respectively), and eGFR in early/late ADPKD (n=17/8, 414/375, 81/64, respectively).

Results: TKV baselines were not significantly different (P=0.66). The TKV annual increase was 4.21% in **Alternative** (AC-NMD) compared to 6.39% in **Classical** (CC-PKD1/PKD2), and 6.68% in **Intermediate** (CC-NMD + AC-PKD1/PKD2) (lnTKV P=0.0346; lnhtTKV P=0.0355) and was not affected by BP level.



NMD patients were 20.2% of AC but just 5.5% of CC patients which was true in both early (P<.0001) and late ADPKD (P=0.0066). Annual eGFR change in early and late ADPKD was not significantly different in the 3 groups, and Low vs Standard BP, or lisinopril+telmisartan vs lisinopril+placebo, did not alter that.

Conclusions: AC-NMD (Alternative) patients with early ADPKD have a significantly lower annual increase in TKV/htTKV. The -FH factor in AC appears to be the clinical portal to a genetically complex population enriched 3.7-fold for NMD. Patients with AC-NMD might have mosaicism, atypical mutations, or even polycystic kidney disease(s) other than ADPKD.

Funding: NIDDK Support

PUB273

Lifestyle Counseling in Polycystic Kidney Disease Patients Wen-Ching Tran, Jonathan Chan, Chi-yuan Hsu, Meyeon Park. *UCSF.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common cause of end-stage kidney disease worldwide, affecting all ethnicities. Although there is no cure for this condition, dietary modification and water intake may attenuate progression of disease, yet lifestyle counseling is not consistently implemented by providers. Furthermore, cardiovascular risk is high in this group, and exercise may benefit cardiovascular health. Patients with ADPKD often express a desire to be able to “do anything” to modify their disease. We designed this study to determine the prevalence of lifestyle counseling in nephrology clinic visits with individuals with ADPKD.

Methods: We performed a systematic chart review. Using our electronic medical record system, we identified patients with ADPKD whose most recent visit at UCSF with a nephrologist occurred during the previous six months. We reviewed the notes associated with these visits to assess for nephrologists’ discussion of dietary advice, water drinking parameters, and exercise recommendations based on documentation in clinic notes.

Results: We identified 56 unique patient visits in the previous six months. Mean age was 44.6 (+/- 14.9) years. 29 (52%) were women. 28 patients had documentation of dietary discussions; 26 received water intake recommendations; and 8 received exercise advice. Only 5 patients received counseling on all 3 parameters.

Number of patients receiving counseling on X of 3 parameters (Diet, Water intake, Exercise)				
0 of 3	1 of 3	2 of 3	3 of 3	Total
21	13	17	5	56

Conclusions: Prevalence of lifestyle counseling was moderate as ascertained by chart review of our electronic medical record. Discussion of exercise recommendations was low. Nephrologists could consider focusing more attention on offering lifestyle counseling to individuals with ADPKD.

Funding: Clinical Revenue Support

PUB274

Lipid Alterations in Murine Models of Polycystic Kidney Disease Christine Podrini,^{1,2} Isaline Rowe,² Marco Chiaravalli,² Alessandra Boletta,² ¹Univ Vita-Salute San Raffaele, Milan, Italy; ²Dibit San Raffaele Scientific Inst, Milan, Italy.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disorder characterized by massive bilateral renal cyst formation. ADPKD results from mutation in the *PKD1* or *PKD2* genes, encoding Polycystin-1 (PC-1) and 2 (PC-2) proteins respectively. Previous studies have suggested that the mTORC1 cascade might play an important role in PKD. Further, mTORC1 regulates the activity of SREBP which regulate the expression of genes required for the synthesis of fatty acids and cholesterol. However, the regulation of fat synthesis in ADPKD remains poorly understood. In this study, we seek to understand the relationship between fatty acid regulation and defective PKD1 function.

Methods: We analyzed newborn kidneys of *Ksp-Cre;Pkd1^{fllox/+}* mice and detected an increased expression of SREPB1 and its target genes including fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD) when compared to control, non-cystic kidneys (*Ksp-Cre;Pkd1^{fllox/+}* or *Pkd1^{fllox/+}*).

Results: As expected the increased expression of SREPB1 also correlated with increased transcript levels of SREPB2 concomitant with an increased transcript levels for sterol biosynthesis mevalonate kinase (MVK) and acetyl-CoA synthetase (ACSL). Next, we performed a lipidomic profiling of *Ksp-Cre;Pkd1^{fllox/+}* kidneys compared to controls *Ksp-Cre;Pkd1^{fllox/+}* collected at P4 using shotgun lipidomics technology. The profiles confirmed the alteration of some lipid classes, particularly sphingolipids and sterol esters (cholesterol). Of interest both have been implicated in regulating membranes trafficking and they may cross-talk to mTORC1 in response to altered nutrient/fatty acid signals. Notably, some of the lipid alterations that we observed appear to be gender-specific.

Conclusions: We are currently characterizing this aspect further and trying to determine which lipid alterations might be dependent and/or independent of mTORC1 upregulation.

PUB275

Reactive Hyperaemic Index in Early Disease Stages of Autosomal Dominant Polycystic Kidney Disease Adebowale Olayinka Adekoya,¹ Andrew J. Streets,¹ Albert C. Ong,¹ ¹Academic Nephrology Unit, The Medical School, Univ of Sheffield, Sheffield, South Yorkshire, United Kingdom; ²MRC Centre for Developmental and Biomedical Genetics, Univ of Sheffield, Sheffield, South Yorkshire, United Kingdom.

Background: ADPKD is the commonest inheritable cause of ESKD. Cardiovascular complications are the commonest cause of death in ADPKD. Endothelial dysfunction (ED) has been reported to precede CV events. In our pilot study of sixty ADPKD patients in the late stages of disease (CKD 3 and above), ADMA and 8 isoprostane were found to be increased suggesting ED. The aim of this study is to investigate ED in the ADPKD patients in early stages of the disease (CKD 1 and 2) and to identify factors associated with its severity.

Methods: This is a single centre cross sectional study of ADPKD patients in the early stages of disease. Individuals with HBP, DM, eGFR < 60ml/min/1.73m² and smokers were excluded. 23 patients and 26 age, sex and eGFR matched controls were recruited. 24hr urine was collected for creatinine clearance and protein. Reactive hyperaemic index (RHI) was measured using endoPAT 2000.

Results: The mean±SD age of the patients was 40.80±14.18 years. M:F was 1:2.3. Patients' mean±SD eGFR was 81.87± 18.02ml/min/1.73², creatinine clearance was 125.75± 55.69 while SBP was 129.35 ± 7.47 mmHg. There was no significant difference in RHI between patients and control. Furthermore, there was no significant difference in cholesterol, C reactive protein, uric acid, calcium phosphate product and homocysteine between patients and controls (p>0.05). Conversely, there was a significant difference in the level of proteinuria between the patients and controls. Proteinuria and homocysteinemia correlate with RHI on univariate and multivariate analysis.

Conclusions: Pulse arterial tonometry as measured by RHI was not significantly reduced in ADPKD patients in the early stages of disease. However, increased proteinuria and hyperhomocysteinemia were detectable in ADPKD patients with preserved kidney function suggesting more subtle changes in endothelial function which may not be detected by RHI.

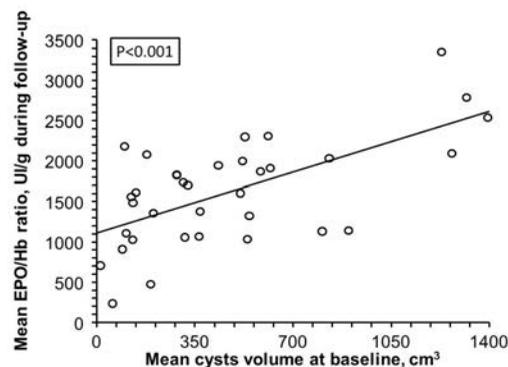
PUB276

Baseline Renal Cysts Diameter Predicts the Erythropoietin Requirement in Autosomal Dominant Polycystic Kidney Disease Paolo Lentini,¹ Luca Zanoli,² Massimo de Cal,¹ Stefania Rastelli,² Andrea Contestabile,¹ Antonio Granata,³ Roberto Dell'Aquila,¹ ¹Nephrology, St. Bassiano Hospital, Bassano Del Grappa, Italy; ²Internal Medicine, Univ of Catania, Catania, Italy; ³Nephrology, St. Giovanni Di Dio Hospital, Agrigento, Italy.

Background: Subjects with autosomal dominant polycystic kidney disease (ADPKD) require classically low recombinant human erythropoietin (EPO) to reach haemoglobin target levels. We hypothesize that EPO requirement in subjects with ADPKD is more dependent to the enlargement of the cysts than the reduction of glomerular filtration rate. Aim: To evaluate the role of renal cyst and kidney size on EPO requirement in severe chronic kidney disease (stage 4-5).

Methods: A total of 35 pts with ADPKD and anaemia treated with EPO were enrolled (14 pts with CKD Stage 4 and 21 pts Stage 5), the mean volume (V) and diameter (D) of the four largest cysts and the mean antero-posterior renal diameter (AP) were prospectively followed-up for 18 months with computer tomography.

Results: The overall mean age was 65±14 years, male sex 57%. At baseline, AP was 19.7±2.2cm, D 4.6±1. cm, V 749±641 cm³. During the 18 months follow-up, rHu-EPO dose was 8543±6626 UI/week, and EPO/haemoglobin ratio (E/H) was 1983±1039. In a multivariate linear regression model, adjusted for age and sex, at baseline both AP and V were significantly associated with E/H; after 18 months, only V remains significantly associated with E/H. Baseline V (100cm³ increase: β=115UI/g week, 95%CI 65-164, P<0.001) was also associated with mean E/H during follow-up and explain 42% of E/H variability.



Conclusions: The Cysts volume is useful to predict prospectively the EPO requirement in ADPKD in stage 4-5 CKD.

PUB277

A Novel Method to Determine Glomerular Volume Distribution from Few Serial Sections on a Single Slide Mohan C. Abraham,¹ Rishi Singh,² Krishnamurthy P. Gudehithlu,² Jose A.L. Arruda,^{1,2,3} Ashok K. Singh,^{1,2,3} ¹Div of Nephrology, John H Stroger Hospital, Chicago, IL; ²Hektoen Research Inst, Chicago, IL; ³Section of Nephrology, Univ of Illinois at Chicago, Chicago, IL.

Background: Estimating glomerular volumes is important in understanding pathogenesis of glomerular diseases. Some methods are convenient but give a single mean volume for the entire kidney and do not provide volume profiles. Methods for volume profiling are too laborious for routine use. We describe here a new method to obtain glomerular volume profiles from few serial sections. The method uses the formula, $R^3 = r_1^3 + [(r_2^3 - r_1^3 - h^3)/2h]^3$, where R is the radius of a sphere and r_1 and r_2 are the radii of two parallel circular planes cut across the sphere h distance apart.

Methods: To validate our method we compared glomerular volumes between normal (n=5) and STZ diabetic rats (n=4) by measuring 100 random glomeruli from each group. Three (or four) serial sections each 5μm apart were obtained on the same slide. Sections were stained with H&E and glomerular diameter was measured at four points to arrive at a mean diameter and radius r_1 . The same glomerulus was identified on the third ($h = 10 \mu\text{m}$) (or fourth; $h = 15 \mu\text{m}$) serial section to similarly determine r_2 . R was calculated by the formula to obtain the glomerular volume ($4/3 \pi R^3$).

Results: The mean glomerular volume ($10^6 \mu\text{m}^3$) of normal rats was 1.04 ± 0.06 , a value very close to that determined by MRI recently (Heilmann et al 2012). The mean glomerular volume of diabetic rats was 1.48 ± 0.06 , which was 45% higher ($P<0.05$) than normal, confirming glomerular hypertrophy. While the volume distribution in normal rats was Gaussian, the distribution of glomerular volumes in diabetic rats was skewed towards higher volumes (42% glomeruli $>1.4 \times 10^6 \mu\text{m}^3$ compared to 12% in normals), suggesting that not all glomeruli but only a population of glomeruli hypertrophied in diabetic rats.

Conclusions: Precise glomerular volumes can be conveniently determined by our method using a few serial sections of the kidney, making it possible to obtain glomerular volume distribution from experimental as well as human kidney biopsies.

Funding: Private Foundation Support

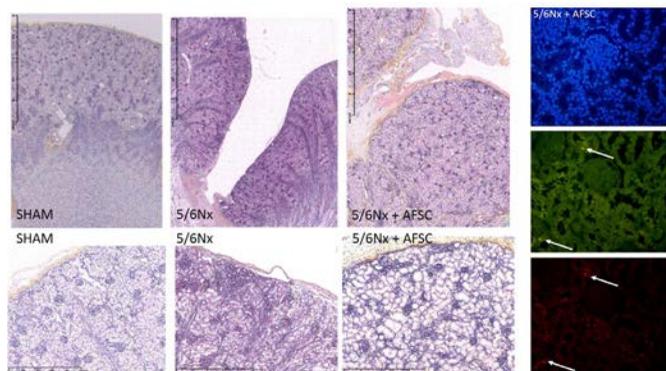
PUB278

Amniotic Fluid Stem Cells Transplantation in Fetal Kidney to Regenerate Nephrons Loss Kathleen Laborde,¹ Sebastien Sammut,² Mehrak Hekmati,² Agnieszka Anna Ksiazek,³ Benedikt Weber,³ Luc Behr.² ¹Necker Hôpital-Paris5 Univ, Paris, France; ²IMMR, Paris, France; ³Swiss Center for Regenerative Medicine, Univ Hospital, Zurich, Switzerland.

Background: Amniotic fluid stem cells (AFSC) harbour the potential to differentiate toward renal lineages and contribute to the development of primordial kidney structures. To investigate whether AFSC can improve prenatal renal compensatory growth, cells were transplanted in a model of subtotal nephrectomy (5/6NX) in the fetal sheep.

Methods: Ovine AFSC labelled with GFP were selected using c-kit. In absence of LIF, AFS formed embryonic bodies which cultured in an optimized medium generated a renal epithelial progenitor population (oAFSCd), expressing PAX-2. 5/6NX was performed at 70 days of gestation in 10 fetal lambs; 5 were injected with oAFSCd in the kidney poles. Sham-operated did not received oAFSCd (SHAM, n=8). At 134 days of gestation, fetuses were euthanized, kidneys removed and processed.

Results: Body weight did not differ significantly among the groups and no morphologic abnormalities were observed, in spite of a severe reduction in amniotic fluid in 5/6NX+oAFSCd. Compensatory renal growth of the remaining kidney was observed in all 5/6NX, but in spite of oAFSCd injection, catch-up kidney growth was similar in both 5/6NX groups: SHAM: 3.2±0.6; 5/6NX: 4.6±2.4; 5/6NX+oAFSCd: 5.5±1.4 KW/BW. Glomeruli number/section was similar in all groups: SHAM: 2711±237; 5/6NX: 2155±694; 5/6NX+oAFSCd: 1962±199. In 5/6NX+oAFSCd, GFP cells were present in renal proximal tubules, and proximal tubule hypertrophy was observed.



No striking changes were observed in PAX2, WT1 or PCNA expression.

Conclusions: Transplantation of oAFSCd predifferentiated toward renal epithelial progenitor cells during nephrogenesis increases proximal tubule mass but has no effect on the number of glomeruli in the 5/6NX and do not restore fully kidney damage.

Funding: Private Foundation Support

PUB279

Low Birth Weight Impairs Renal Development and Function Christina M. Barnett, Michael S. Shen, Kunzhan Aleem Syed, Joseph A. Zullo, David L. Payne, Oluwadara Nnoli, Wasan Abdulmahdi, Amy R. Patel, Tala F. Azar, May M. Rabadi, Brian B. Ratliff. *New York Medical College.*

Background: Low birth weight (LBW) results in a significant risk to the newborn, with many of these babies developing acute kidney failure and dying soon after birth due to underdeveloped vascular and renal systems. Surviving LBW neonates are also susceptible to a variety of health problems later in life during adulthood including hypertension, diabetes and chronic kidney disease with an associated 70% increased risk of end-stage kidney failure.

Methods: Using a maternal malnourished mouse model, we examined the causes of vascular and renal underdevelopment and impaired function in the LBW neonate. Parameters measured in the LBW offspring included nephron development, stem cell levels, apoptosis, gene expression, circulating cyto-/chemokines, renal blood flow and renal function.

Results: Within 24 hours after birth, LBW male offspring had 40% reduced weight, while only 49% of LBW neonates survived the first week after birth. Within the first week after birth, LBW neonates had an up to 40% reduction in renal blood flow and elevation of serum creatinine up to 3.0 mg/dL. Nephrogenesis was impaired in the LBW neonates with a 75% reduction in renal vesicle formation and a significant downregulation of Wnt9B (which induces differentiation of progenitor cells into tubular epithelia) at day E17.5, which ultimately resulted in a 30% reduction in glomeruli at the conclusion of nephrogenesis. During nephrogenesis, six2-positive nephron progenitor cells were reduced by up to 70% in the LBW embryonic kidney, which was accompanied by 6-fold increase in apoptosis. At birth, the LBW neonate had significantly elevated circulating levels of proinflammatory IL-1beta. Using explanted embryonic kidneys, we observed IL-1beta dramatically reduces six2+ cell populations and their ability to aggregate and form renal vesicles during kidney development.

Conclusions: LBW impairs vascular and renal function due to underdeveloped renal and vascular systems that result from enhanced IL-1beta, increased apoptosis, altered Wnt9b expression, and reduced six2 nephron progenitor cells in the embryonic and neonate kidney.

Funding: Private Foundation Support

PUB280

Increasing Podocyte Number in Neonatal Kidney Reduced Renal Injury in Adulthood Jianyong Zhong,^{1,2} Ji Ma,² Taiji Matsusaka,³ Agnes B. Fogo,¹ Valentina Kon,² Haichun Yang.¹ ¹Pathology, Microbiology and Immunology, Vanderbilt Univ, Nashville, TN; ²Pediatric Nephrology, Vanderbilt Univ, Nashville, TN; ³Dept of Molecular Life Science, Inst of Medical Science, Tokai Univ School of Medicine, Isehara-shi, Kanagawa, Japan.

Background: Preterm birth increases the risk of hypertension and renal disease, which have been linked to decreased nephron number. We previously found that puromycin injection in mice at birth impairs glomerular maturation, and has renal pathology phenotype which is similar to that observed in human preterm births. In the present study, we tested the hypothesis that increasing podocyte number during glomerular maturation can rescue glomerular loss and thus reduce renal injury in adulthood.

Methods: We mated podocin-rTA with TRE-SV40T mice to generate double-transgenic mice (RS), in which podocyte proliferation can be activated by doxycycline (Dox). rTA mice (R) served as controls. After a single puromycin injection, doxycycline was given at P1 until P8. At 12 weeks of age, mice underwent uninephrectomy (UNx) and were started on a high salt diet. At 14 weeks of age, angiotensin II (Ang II) was given by minipump for the next 8 weeks. All mice were sacrificed at week 22.

Results: At week 3, there were more WT1 positive glomerular cells in RS than R mice (RS 10.34±0.41 vs. R 8.15±0.58 X10³/μm², p<0.05), while glomeruli in superficial cortex were less mature (RS 2.13±0.05 vs. R 2.32±0.06, maturity scale 1-3, P<0.05). At week 6, glomerular number increased in RS (RS 9039.2±644.2 vs. R: 6932.1±244.7/kidney, P<0.05). Glomerular volume and albuminuria did not differ between groups at week 3 and 6. At week 22, after UNx, high salt and Ang II, blood pressure, albuminuria and glomerular number were similar in RS and R. However, RS mice had lower KW/BW ratio (RS 0.976±0.143 vs. R 1.263±0.041, p<0.05) and less mesangial expansion (0-4 scale) (RS 0.72±0.10 vs. R 1.14±0.14, p<0.05).

Conclusions: We conclude that increasing podocyte number in developing kidney rescues puromycin-induced impairment of glomerular growth, which in turn reduces renal injury following a second hit in adulthood.

PUB281

Exploring Ciliopathies – Cep164 Tissue Expression in a Murine Model Simon Ramsbottom, Shalabh Srivastava, Colin Miles, John Andrew Sayer. *Inst of Genetic Medicine, Newcastle upon Tyne, United Kingdom.*

Background: Nephronophthisis (NPHP) is the major cause of paediatric renal failure, yet the disease remains poorly understood, partly due to the lack of appropriate animal models. Joubert Syndrome (JBTS) is an inherited ciliopathy giving rise to NPHP and neurodevelopmental abnormalities and mutations in *CEP164* are one of the known genetic causes. Clinical phenotypes of patients with *CEP164* mutations include NPHP with retinal degeneration and cerebellar vermis aplasia. In cultured cells *CEP164* localises to centrosomes as well TIP-60 positive nuclear foci, and *CEP164* has an established role in DNA damage response signalling. However, there has been no previous documentation of *CEP164* spatial expression during development.

Methods: We have recently acquired heterozygous *Cep164* mice from the International Mouse Phenotyping Consortium (MRC/Harwell) (B6N-Tac;B6N-Cep164^{tm1a(EUCOMM)Wsl/H}). We used these animals for tissue expression studies, including X-gal staining from heterozygote adults and whole embryos. Homozygote *Cep164* animals had 100% perinatal lethality.

Results: In heterozygote *Cep164* animals, specific X-gal staining representative of *Cep164* expression was observed in all tissues examined. This included the brain (olfactory bulbs and cerebellum); the eyes (within the retina layers); the testis and renal tissues. In E13.5 embryos, staining was observed globally at a low level. Stronger staining can be seen in discrete regions including the developing eyes and limbs, areas undergoing high levels of proliferation and apoptosis, further indicating a role for *Cep164* in these processes.

Conclusions: These data support a role for *Cep164* in multiple organs throughout development and explain the wide phenotypic spectrum of JBTS mutations in man.

Funding: Government Support - Non-U.S.

PUB282

Specific Deletion of Early B Cell Factor 1 from Podocytes Does Not Recapitulate the Developmental Defects Observed in the Globally Deficient Animals but Does Provide Protection from Injury Jackie A. Fretz, Tracy Nelson, Li Li. *Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT.*

Background: Globally deficient mice lacking the transcription factor Ebf1 (Ebf1 KO) are extremely sick owing to the multiple functions of Ebf1 across the body. We recently described a novel function of Ebf1 as an essential component of the latest stages of metanephric development. Mice globally deficient in Ebf1 have impaired formation of peripheral glomeruli and a thinned cortex. Within the kidney Ebf1 is present within multiple cell types including distinct tubular epithelium, interstitial pericytes, glomerular mesangium, and podocytes. This investigation aimed to identify if the actions of Ebf1 in the podocyte were driving the developmental defects present in the global knockout.

Methods: In this study we made a specific deletion of Ebf1 within the podocytes using the podocin-driven cre mouse. These were mated with mice where the 3rd exon of Ebf1 (encoding part of the DNA-binding domain) is flanked by flox sites. This is the same genetic region that is excised in the global deletion model. BSA overload injury was also performed on 3 month old animals (100mg/kg, IP daily for 4 weeks).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Results: Restricted deletion of Ebf1 from podocytes did not result in any observable developmental changes as assessed at the functional and histological level. Renal mass, glomerular number, and glomerular development were unchanged regardless of genotype. The mice were followed for up to 6 months. During this time renal function did not decline in the mice with podocyte-specific deletion of Ebf1, and in fact baseline proteinuria was reduced in Podocin-cre+, Ebf1-fl/fl animals compared to littermate controls. To examine if Ebf1-deficient podocytes harbored differential response to injury 3 month old animals were subjected to BSA-overload and exhibited reduced proteinuria.

Conclusions: Taken together these results suggest that Ebf1 regulates metanephric development through other cell types than the podocyte. While Ebf1 does not control glomerular development through its actions in the podocyte, it appears to participate in proper damage response by podocytes as its removal appears to be protective.

Funding: NIDDK Support

PUB283

Remote Ischemic Pre Conditioning and Pharmacological Treatment in Prevention of Renal Damage in Experimental Diabetes Marcelo Rodrigues Bacci, David Feder, Fernando Luiz Affonso Fonseca, Matheus Polly, Jaqueline Victoria Ciancaglini, Giuliana Petri, Guilherme Zaremba. *ABC Medical School, Brazil.*

Background: The main features of diabetic nephropathy are glomerular hypertrophy, thickening of the basal membrane, tubular atrophy, interstitial fibrosis and nodular and focal glomerulosclerosis. Remote ischemic preconditioning (RIPC) is a procedure that generates a brief period of ischemia followed by reperfusion. Its role in preventing glomerular and tubular changes is still under debate. The aim of the study was to evaluate the nephroprotective effect of RIPC in a diabetic rat model.

Methods: Five groups of 10 Wistar male rats were formed: control without diabetes; untreated diabetes; diabetes treated with pharmacological treatment (PT); diabetes with RIPC and diabetes with RIPC and PT. For the induction of diabetes, alloxane was infused intraperitoneally at a dose of 160 mg/kg. PT consisted of daily use of metformin (250 mg/kg), sitagliptin (8 mg/kg) and valsartan (30 mg/kg). RIPC was performed with an external tourniquet placed on the back leg for three 5-minute rounds alternated with the same rounds of reperfusion, resulting in a total duration of 30 minutes. This was performed every week on all mice in RIPC groups. All mice were kept in a biological cage with controlled temperature and humidity and routine feeding. Blood and urine samples were collected weekly to evaluate serum glucose, creatinine and urine glucose levels and albumin/creatinine urine ratio (ACR). At the end of the observation period, animals were sacrificed and their kidneys were biopsied for microscopic analysis.

Results: Animals subjected exclusively to PT showed a significant reduction in serum and urine glucose levels but these reductions were not greater in the group that underwent RIPC in addition to PT. There were no significant differences in creatinine level between any of the groups but ACR was significantly reduced in all treated animals compared to controls. Tubular atrophy was observed in all diabetic rats and was greatest in the untreated group.

Conclusions: PT was more effective at reducing ACR and tubular atrophy than RIPC. RIPC alone or in combination with PT did not cause the expected effect of preventing histological and urinary abnormalities.

Funding: Government Support - Non-U.S.

PUB284

Cross Talk Between TLR4 Signaling and Angiotensin II Induces Pathophysiological Changes in Human Tubular Epithelial Cells Under High Glucose Conditions Jinlei Ly, Guohua Ding, ¹Nephrology, The First Affiliated Hospital of NanChang Univ, NanChang, Jiangxi, China; ²Nephrology, Renmin Hospital of WuHan Univ, WuHan, China.

Background: To investigate the cross talk between TLR4 and angiotensin II by observe the expression of TLR4 in tubular epithelial cells under high glucose conditions, and observe the changes of fibrogenic and inflammatory factors in human renal tubular epithelial cells, revealing the innate immune pathogenesis in diabetic nephropathy.

Methods: Cells were divided into five groups after cultivated with normal glucose medium: 1. normal-glucose group 2. mannitol group 3. AngII group 4. high-glucose group (25mmol/L) 5. high-glucose+Irbesartan group, extract total RNA and total protein after 24 hours. Real time PCR was used to analyze the expressions of TLR4, MyD88, HSP47 mRNA, western blot was used to observe the expressions of TLR4, MyD88, NF-κB, CoIV, HSP47 protein, analyse the effect of high-glucose and AngII to TLR4 / MyD88 / NF-κB signaling pathway.

Results: Compared with normal group, TLR4, MyD88, HSP47 mRNA and TLR4, MyD88, NF-κB, CoIV, HSP47 protein were highly expressed under high glucose condition and after AngII stimulate ($p < 0.01$). The expression of IL-6 and MCP-1 also increased ($p < 0.01$). Compared with HG group, the expression of TLR4, MyD88, HSP47 mRNA and TLR4, MyD88, NF-κB, CoIV, HSP47 in the high-glucose+Irbesartan group were significantly reduced ($p < 0.01$). The difference of above indicators between the negative transfected group and high-glucose group and AngII group were statistically significant ($p > 0.05$). The expression of IL-6 and MCP-1 in the group that cells were transfected with TLR4-siRNA also reduce ($p < 0.01$).

Conclusions: Cross talk between angiotensin II and TLR4 can up-regulate the expression of inflammatory factors and fibrogenic factors in HK-2 cells. Irbesartan can block the activation of TLR4 signaling pathway induced by high glucose and angiotensin II. TLR4 signaling pathway is the major pathway induce the release of inflammatory and fibrogenic factors in tubular epithelial cells under high glucose conditions.

Funding: Government Support - Non-U.S.

PUB285

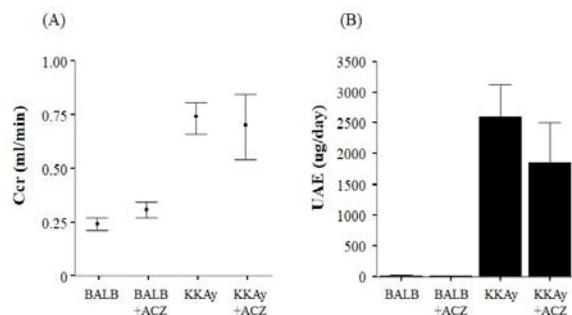
Possible Renoprotective Effects of Acetazolamide Administration in Obese Diabetic Mice with Nephropathy Yushi Nakayama, Koji Eguchi, Terumasa Nakagawa, Tomoaki Onoue, Yuichiro Izumi, Hideki Inoue, Yutaka Kakizoe, Takashige Kuwabara, Masashi Mukoyama. *Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.*

Background: Administration of carbonic anhydrase inhibitors (CAI) is thought to decrease glomerular filtration rate (GFR) by activation of the tubuloglomerular feedback (TGF) system. Acetazolamide (ACZ), a major CAI, has been shown to decrease urinary albumin excretion in the patients of type 1 diabetes with nephropathy. Previously, we showed that ACZ treatment in mice could ameliorate the onset of diabetic nephropathy due to the reduction of intraglomerular pressure by activating the TGF system.

Methods: In the current study, we treated obese diabetic mice (KK-Ay/TaJcl) with ACZ for 14 weeks, and evaluated the long-term effects on urinary albumin excretion and glomerular hyperfiltration.

Results: The blood glucose levels were significantly higher in KK-Ay/TaJcl mice compared to the control mice (BALB/cAJcl) at 14 weeks. The blood glucose levels were significantly reduced in KK-Ay/TaJcl mice treated with ACZ (547 ± 37 vs 250 ± 75 mg/dL). Interestingly, urinary glucose excretion levels in the ACZ group were not significantly different compared to the non-treated group. Creatinine clearance was higher in KK-Ay mice, which was not changed by ACZ (0.73 ± 0.07 vs 0.69 ± 0.15 ml/min) (Figure A). Urinary albumin excretion was reduced with ACZ treatment by 29% (Figure B). The plasma renin activity was not reduced by ACZ in this model.

Conclusions: These results suggest that the long-term oral treatment with ACZ may exert renoprotective effects in obese diabetic models with nephropathy, not due to activation of the TGF system but to better glycemic control.



Funding: Government Support - Non-U.S.

PUB286

Inhibition of miR-34a Reduces Podocyte Apoptosis by Targeting Bcl-2 and Autophagy Yang Liu, Ruixi Li, Wai Han Yiu, Hao-Jia Wu, Dickson W.L. Wong, Joseph C K Leung, Loretta Y.Y. Chan, Kar Neng Lai, Moin Saleem, Peter W. Mathieson, Sydney C.W. Tang. ¹Dept of Medicine, The Univ of Hong Kong, Queen Mary Hospital, Hong Kong, China; ²Academic and Children's Renal Unit, Univ of Bristol, Bristol, United Kingdom.

Background: Podocyte apoptosis is a key event in the pathogenesis of diabetic nephropathy. miR-34a has been reported to be involved in cell proliferation and apoptosis, but its potential roles in podocytes under the diabetic condition remains unknown.

Methods: Type 2 diabetic nephropathy was established by uninephrectomy (Unx) in nine-week-old *db/db* mice. In cultured immortalized human podocytes, miR-34a was over-expressed or knocked down by transfection with miR-34a precursor (pre-34a) or inhibitor (anti-34a), respectively. Podocytes were exposed to glycated human serum albumin (AGEs) and then examined for the expression of apoptosis and autophagy markers. The expression of miR-34a in mouse renal cortex and cultured podocytes were determined by quantitative PCR (Q-PCR) using specific Taqman miRNA assay.

Results: Compared with control group, Unx *db/db* mice ($n=7$) showed significantly higher expression level of miR-34a in renal cortex. In cultured human podocytes, exposure to AGEs also markedly increased miR-34a expression. The anti-apoptosis genes Bcl-2 and survivin, podocyte cytoskeleton molecule synaptopodin, tight junction protein ZO-1, as well as autophagy marker LC3-II, were all reduced after AGE treatment. Moreover, inhibition of miR-34a by transfection with anti-34a in podocytes prevented AGE-induced apoptosis by rescue of Bcl-2 and LC3-II expression.

Conclusions: Our data demonstrated that miR-34a is involved in podocyte injury under diabetic conditions. Inhibition of miR-34a in podocytes attenuates apoptosis induced by AGEs via enhancing expression of Bcl-2 and regulating autophagy. These results indicate that targeting miR-34a might be a potential therapeutic strategy for diabetic nephropathy. This study is supported by the National Basic Research Program of China 973 program no. 2012CB517600 (no. 2012CB517606), Small Project Funding (project code 201309176123) from The University of Hong Kong, and Hong Kong Society of Nephrology Research Grant 2014.

Funding: Government Support - Non-U.S.

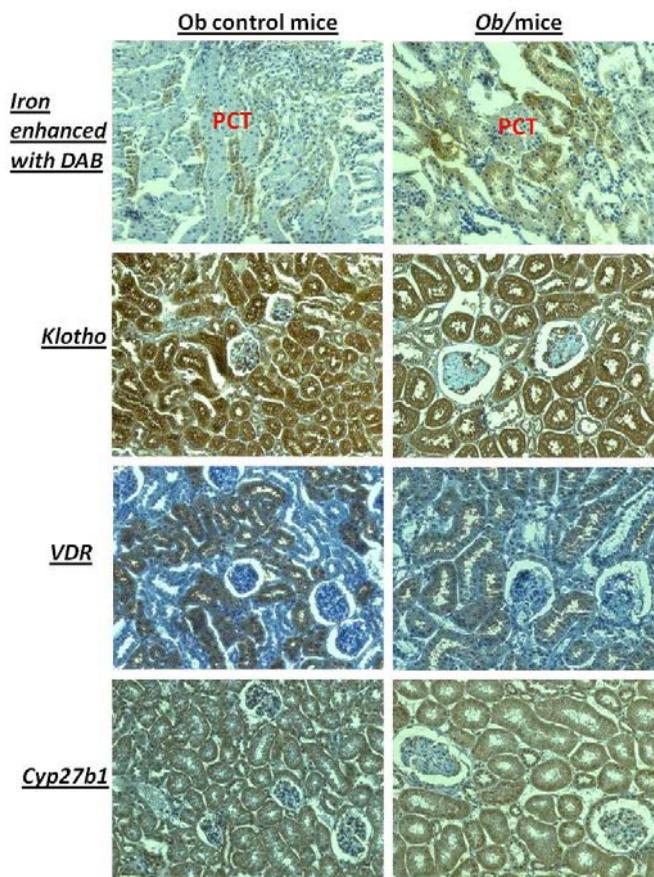
PUB287

Increased Iron Deposition Is Associated with Decreased α -Klotho and Vitamin D Receptor Expression in the Renal Proximal Tubules in Ob/Ob Mice Farid M. Nakhoul,¹ Deb Dilip,¹ Inbal Dahan,² Lei Li,¹ Yan Chun Li.¹
¹Dept of Medicine, Biological Sciences Div, Univ of Chicago, IL; ²Diabetic Nephropathy Lab, Baruch Padeh Poriya M Ctr, Lower Galilee, Israel.

Background: Diabetic nephropathy is the most common renal complication of diabetes. Diabetes increases oxidative stress and promotes iron deposition in proximal convoluted tubules (PCT) of the kidney, leading to renal damage. Mutations in the *LEP* (*ob*) gene product lead to severe obesity and type 2 diabetes, and ob/ob mice in BTBR background develop severe diabetic nephropathy. Klotho and vitamin D receptor (VDR) have been shown to involve in renal protection against diabetic injury. The goal of this study is to assess the relationship between iron deposition and klotho and VDR expression in the kidney of ob/ob mice.

Methods: One- and three-month old ob/ob BTBR mice and ob/+ control mice were studied in parallel. After sacrifice, the kidneys were harvested. The expression of α -klotho, VDR and Cyp27b1 was examined by immunohistochemistry, Western blotting and qRT-PCR, and iron deposition was assessed by staining with Perl's enhanced with Dab.

Results: Compared with ob/+ mice, ob/ob BTBR mice showed increased iron deposition in the PCT and decreased expression of α -klotho, VDR and Cyp27b1 in the renal PCT and kidney lysates.



Conclusions: In ob/ob BTBR mice, increased iron deposition in the renal PCT is associated with a decrease in klotho expression, vitamin D hormone synthesis and VDR signaling in the PCT. These changes together contribute to the progression of diabetic renal injury in these mutant mice, and future treatments.

PUB288

Erythropoietin Protects Endothelial Cells from High Glucose Induced Injury Haruka Yasuda,¹ Yasunori Iwata,^{2,3} Kengo Furuichi,^{3,4} Takashi Wada.^{1,3}
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Background: Diabetic nephropathy (DN) is a major cause of end stage kidney disease and a strong risk factor for cardiovascular diseases. High glucose induces endothelial injury in vasculature, resulting in tissue injury in diabetic condition. Chronic inflammation has been reported to play an important role for the progression of high glucose induced cell injury. Growing data showed that erythropoietin (EPO) protect the tissues from some kind of injury, such as hypoxia and mechanical stress. However, the contribution of EPO to

high glucose induced the aberrant immune balance remains to be explored. Therefore, we hypothesized that EPO modulates endothelial cells from high glucose (HG) induced injury via the regulation of inflammatory and anti-inflammatory balance.

Methods: To explore this possibility, we performed genome-wide transcriptome profiling in human umbilical vein endothelial cells (HUVEC), which were stimulated by high glucose (HG) with/without EPO treatment and detected the expression of inflammation associated genes.

Results: Hierarchical clustering and principal component analysis showed the different pattern of mRNA expression in HG stimulated HUVEC with/without EPO. While inflammatory cytokines/chemokines mRNA expression were increased by the HG stimulation in HUVEC, Th2 related cytokine receptors and intracellular signaling molecules showed the reduced mRNA expression levels. EPO treatment reduced inflammatory cytokines/chemokines mRNA expression and increased Th2 related cytokine mRNA expression levels. Real-time PCR analysis confirmed the increased expression of inflammatory related genes, those were decreased in HG stimulated HUVEC with EPO treatment. Moreover, EPO stimulation increased mRNA expression of EPO receptor and b-common receptor. EPO signaling affect neither cell proliferation nor cell death.

Conclusions: Taken together, EPO signaling might protect high glucose induced cell injury by the regulation of immune balance.

PUB289

The Possible Mechanisms of Ameliorating Diabetic Mice Renal Insulin Resistance by NF- κ B Inhibitor Parthenolide Xuemei Li, Baobao Wang.
Nephrology, Peking Union Medical College Hospital, China.

Background: Diabetic nephropathy (DN) was the severe complication of Diabetes Mellitus (DM). The treatment of DN was limited. Insulin resistance (IR) was associated with diabetic complications. The concrete forms of insulin resistance in diabetic renal tissue lacked research. AS160 could regulate the transportation of many transporters including glucose transporters. In kidney, AS160 was found can regulate sodium and water channel protein, while its role on glucose transporters has not been reported. Glucose transporter 4 (GLUT4) was an important effector of insulin signaling, which related to insulin resistance closely. Sodium glucose transporter 2 (SGLT2) and sodium glucose transporter 1 (SGLT1) were important to promote renal tubular glucose re-absorption and were the new target of anti-diabetic drug. Our previous results showed NF- κ B inhibitor Parthenolide (PTN) could improve db/db mice systemic insulin resistance and renal tissues injury. The aim of the study was to study the expression of AS160 and GLUT4 in diabetic kidney tissue and correlation between AS160 with GLUT4 and SGLT2/SGLT1. To explore whether PTN could improve renal IR and the possible mechanisms.

Methods: Set up db/m mice as control group, the db/db mice as diabetic nephropathy model group and db/db mice with PTN intervention as treatment group. The mice were sacrificed at week 8, 12, 16 and 20 and using blood, urine and kidney specimens for the study.

Results: 1) The db/db mice showed increased body weight, blood cholesterol, blood glucose and insulin, as well as glomerular hypertrophy and the increased mesangial matrix. PTN could improve the systemic insulin resistance and renal pathological changes of db/db mice. 2) AS160 and p-AS160, GLUT4 were all mainly expressed in renal tubules. 3) The expression of p-AS160 and GLUT4 reduced gradually in db/db mice kidney with the increase of weeks. 4) p-AS160 showed co-expression with part of GLUT4, but no significant co-expression with SGLT2/SGLT1.

Conclusions: The diabetic kidney tissue may have insulin resistance resulted from abnormal glucose transport by AS160 and GLUT4. The NF- κ B inhibitor improved kidney insulin resistance may by increasing the expression of p-AS160 and GLUT4.

PUB290

Hypertension Results in Moderate Diabetic Nephropathy in a Mouse Model of Metabolic Syndrome Reinout Stoop,¹ Arianne van Koppen,^{1,2} Roel Goldschmeding,² ¹MHR, TNO, Leiden, Netherlands; ²Pathology, UMCU, Utrecht, Netherlands.

Background: Diabetic nephropathy (DN) is a major complication in metabolic syndrome/diabetes patients. We have developed a metabolic syndrome mouse model characterized by non-alcoholic steatohepatitis and atherosclerosis upon high fat diet feeding. These animals show mild renal changes, but don't progress to moderate DN. Therefore, we investigate whether inducing hypertension on top of metabolic syndrome leads to progression of DN.

Methods: Male LDLr^{-/-} mice (8 wk old) received high fat (45%) + high salt (6%) diet for 6 wk. To induce hypertension, combinations of several pro-hypertensive components were used (uninephrectomy (UNX), angiotensin II (ANGII), DOCA and a vasoconstrictor) for an additional 10 wk. At regular intervals, systolic blood pressure (SBP), 24h diuresis and albumin/creatinine ratio (UACR) were assessed. 17 wk after start diet, mice were terminated and renal injury was scored. We used age-matched chow fed animals as controls.

Results: Cholesterol and diuresis were significantly elevated in all groups vs chow from wk 5 onwards. ANGII induced a 20 mmHg increase in SBP at wk 13 vs. chow. At wk 8, UACR was significantly increased by ANGII in combination with HFD+HS (264±303µg/mg) and UNX+HFD+HS (438±781µg/mg) vs chow (62±24µg/mg). At wk 13, ANGII further elevated UACR in HFD+HS (593±737µg/mg) but decreased it in UNX+HFD+HS (287±263µg/mg). Combining ANGII, DOCA and L-NNA strongly induced albuminuria (717±585µg/mg) at wk 5 but also caused fatal thoracic bleedings. This group was terminated at wk 11. Renal injury score showed glomerular hypertrophy, mesangium expansion, nodular glomerulosclerosis, mild hyalinosis and micro-aneurysms.

Conclusions: We show that exposure of LDLr^{-/-} mice to HFD+HS and ANGII induces hypertension and mild progressive DN, in addition to NASH and atherosclerosis in a single

model providing broad coverage of metabolic syndrome complications. Administration of additional hypertensive compounds (DOCA and L-NNA) further aggravated the model but also led to early fatal thoracic bleedings thus precluding further studies.

Funding: Government Support - Non-U.S.

PUB291

Autophagy Activation in Proximal Tubular Epithelial Cells in Diabetic Nephropathy Acts as a Renoprotective Role Ying Xu,¹ Lei Liu,² Wei Xin,² Xu Zhao,² Liyong Chen,² Qiang Wan.³ ¹Renal Div, Shandong Provincial Hospital Affiliated to Shandong Univ, Jinan, Shandong, China; ²Shandong Provincial Hospital Affiliated to Shandong Univ, Jinan, Shandong, China; ³Shandong Provincial Qianfoshan Hospital Affiliated to Shandong Univ, Jinan, Shandong, China.

Background: Previous studies revealed that lipotoxicity participated in epithelial-to-mesenchymal transition (EMT) of proximal tubular epithelial cells (PTECs) under diabetic conditions. Based on evidences that autophagy and lipid metabolism are closely related, the aim of the present study was to investigate autophagy under diabetic conditions and its role in lipotoxicity and EMT.

Methods: HK-2 cells were cultured in normal (5.5 mmol/L glucose) and high glucose medium (30 mmol/L glucose). At 6h, 24h, 48h, and 96h, autophagy activity was evaluated by western blot of LC3I/II, Beclin1 and p62. Next, the inhibition of autophagy was achieved by chloroquine diphosphate (CQ), 3-methyladenine (3-MA), or *Atg5* knockdown using siRNA transfection. Rapamycin, which is a mammalian target of rapamycin (mTOR) receptor specific inhibitor and a known autophagy activator, was used to induce autophagy in HK-2 cells. Lipid accumulation was detected by Oil-Red O staining; EMT was estimated by western blot of vimentin and E-cadherin.

Results: In high glucose cultured HK-2 cells, Beclin1 and LC3-II were elevated, while p62 was decreased. These results indicate that autophagy activity was elevated under diabetic conditions. Autophagy deficiency induced by autophagy inhibitors, CQ and 3-MA, or by *Atg5* siRNA transfection exacerbated lipid accumulation and EMT. Treatment of rapamycin attenuated high glucose induced lipid accumulation and EMT. The *Atg5* silence counteracted the protective effect of rapamycin.

Conclusions: In conclusion, these results demonstrate that autophagy activity in PTECs is elevated under diabetic conditions and the elevated autophagy activity acts as a renoprotective response.

Funding: Government Support - Non-U.S.

PUB292

Insulin Sensitivity Before and Six Months After Kidney Transplantation Morten Buus Jørgensen,¹ Mads Hornum,¹ Gerrit van Hall,² Claus Bistrup,³ Jesper Hansen,⁴ Bo Feldt-Rasmussen.¹ ¹Dept of Nephrology, Rigshospitalet, Denmark; ²Clinical Metabolomics Core Facility, Rigshospitalet, Denmark; ³Dept of Nephrology, Odense Univ Hospital, Denmark; ⁴Dept of Nephrology, Herlev Univ Hospital, Denmark.

Background: Severe uraemia is a known cause of insulin resistance. We aimed to investigate the effect of kidney transplantation (Tx) on peripheral and central insulin sensitivity.

Methods: Nine non-diabetic patients awaiting living related kidney Tx were examined prior to Tx (Pre-Tx) with an oral glucose tolerance test (OGTT) and a 3h hyperinsulinaemic euglycaemic clamp. The clamp was repeated six months after Tx (Post-Tx). Nine age, gender and BMI matched individuals with normal kidney function were examined once with an OGTT and clamp serving as controls (Ctrl). Endogenous glucose production (EGP, N = 6), glucose rate of disappearance (Gd, N = 6) and lipolysis (glycerol rate of appearance, N = 5) were measured in a subgroup of patients with corresponding controls using stable isotope tracer technique. Results are in mean mmol/kg/min [95% confidence interval] during the clamp.

Results: Two patients had pre-Tx prediabetes whereas all other had both normal fasting plasma glucose and normal glucose tolerance. The amount of glucose utilized during clamp was non-significantly lower in patients before Tx (Pre-Tx: 15.1 [11.2–19.0], Ctrl: 20.2 [13.4–27.0], P = 0.17) but significantly reduced after Tx (Post-Tx: 9.8 [6.7–12.9], P = 0.01). The suppression of EGP were comparable before Tx (Pre-Tx: 7.0 [5.4–8.5], Ctrl: 7.0 [1.3–12.7], P = 0.99) but was significantly impaired after Tx (Post-Tx: 9.4 [7.8–11.1], P = 0.04). Gd were comparable both prior to and after Tx (Pre-Tx: 18.1 [13.6–22.5], Ctrl: 22.3 [15.1–29.5], Post-Tx: 17.1 [13.4–20.8], P > 0.22). The suppression of glycerol rate of appearance were comparable before Tx (Pre-Tx: 1.1 [0.9–1.4], Ctrl: 1.1 [0.6–2.1], P = 0.96) but significantly impaired after Tx (Post-Tx: 2.0 [1.0–3.8], P = 0.04).

Conclusions: The reduced insulin sensitivity after kidney Tx is characterized by a central insulin resistance with impaired suppression of endogenous glucose production, impaired suppression of lipolysis and comparable peripheral insulin sensitivity.

Funding: Private Foundation Support

PUB293

Renal Functional and Morphological Changes Related to Obesity and Hyperglycemia in Göttingen Minipigs Rikke Lindgaard Thomsen,¹ Berit Østergaard Christoffersen,² Trine P. Ludvigsen,² Rikke Kaae Kirk,² Jonas Kildegaard,² Lisa Tidman Fuchs,¹ Pall Leifsson,¹ Henrik D. Pedersen,² Lisbeth Højer Olsen.¹ ¹Dept of Veterinary Disease Biology, Univ of Copenhagen, Frederiksberg, Denmark; ²Novo Nordisk A/S, Maaloev, Denmark.

Background: Obesity and diabetes, two major health problems worldwide, both lead to renal functional and morphological changes; with diabetic nephropathy being the leading cause of end-stage renal failure. A large animal model displaying human-like features of obesity-related and diabetic nephropathy would be very valuable to study pathogenesis and effects of new drug candidates on these syndromes. The aim of the present study was to evaluate renal function and morphology in diet-fed obese, atherosclerotic Göttingen minipigs with or without mild diabetes.

Methods: Male castrated Göttingen minipigs, aged 8 weeks at study start, were fed normal chow (n=6) or high-fat, high-cholesterol diet (n=16) for 43 weeks. Mild diabetes was induced in 11 pigs after 18 (n=6) and 25 (n=5) weeks of diet-feeding, using streptozotocin (125 mg/kg IV) preceded by nicotinamide (67 mg/kg IV). The study included two cohorts. Parameters of interest were: Body fat percentage (BF) estimated by dual-energy X-ray absorptiometry, inulin clearance (IC), kidney resistive index (RI), plasma fructosamine reflecting plasma glucose (FRA), plasma urea, plasma creatinine (PCr), plasma total cholesterol (TC), urinary protein excretion (protein (UPCr) and albumin (UACr) adjusted for creatinine). Glomerulus area and number of nuclei/glomerulus area were estimated post mortem. Influence of BF, TC and FRA on in vivo kidney function and post mortem kidney changes was evaluated using ANOVA with cohort as fixed covariate.

Results: BF was positively associated with urea (P<0.01), IC (P<0.05), Glomerulus area (P<0.001) and UPCR (P=0.05), and negatively with PCr (P<0.001). FRA was positively associated with UACr (P<0.05) and number of nuclei/glomerulus area (P<0.05). RI was not associated with BF, TC or FRA.

Conclusions: In conclusion, functional and histological renal changes were found in diet-fed obese, atherosclerotic Göttingen minipigs with and without mild diabetes. The changes were associated with obesity and hyperglycemia.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

PUB294

Activation of Toll-Like Receptors Through Fetuin-A Leads to an Inflammatory Response in Podocytes and Exacerbates Palmitic Acid-Induced Cell Death Jana Orellana,¹ Kapil Dev Kampe,¹ Andreas Werner Jehle,¹ ¹Dept of Biomedicine, Univ Hospital Basel, Basel, Switzerland; ²Dept of Biomedicine, Univ Hospital Basel, Basel, Switzerland; ³Dept of Biomedicine, Univ Hospital Basel, Basel, Switzerland.

Background: Inflammation participates in the pathogenesis of type 2 diabetes and contributes to diabetic nephropathy (DN). There is growing evidence that chronic elevated free fatty acids (FFAs) contribute to this chronic inflammatory milieu. Studies in pancreatic β -cells suggest that the inflammatory response mediated by FFAs depends on toll-like receptor (TLR) 4 and Il-1 receptor (Il-1R). The signaling pathways of TLRs and Il-1R involve activation of the transcription factor nuclear factor- κ B (NF- κ B) which induces a wide range of cytokines/chemokines including monocyte-chemoattractant protein-1 (MCP-1), and Il-1 β . Here, we addressed whether fetuin-A together with FFAs leads to an inflammatory response in podocytes and whether this exacerbates palmitic acid-induced podocyte death.

Methods: Conditionally immortalized murine podocytes were used. Murine and bovine fetuin-A were used alone or in combination with palmitic acid complex to BSA. MCP-1 was measured by ELISA. Podocyte death was determined by flow cytometry (annexin V and propidium iodide staining).

Results: Palmitic acid alone did not, but fetuin-A induced MCP-1 in podocytes and this was further increased by palmitic acid. The MCP-1 release was prevented by C1095 (TLR4 blocker). Fetuin-A or LPS exacerbated palmitic acid induced podocyte death, and CLI095 as well as the Il1 receptor antagonist anakinra or an anti Il1 β antibody attenuated cell death.

Conclusions: Fetuin-A alone and in combination with palmitic acid leads to an inflammatory response in podocytes and promotes palmitic acid induced podocyte death. As inhibition of TLR4 as well as Il1 β prevents these effects, both pathways are promising targets to attenuate the progression of DN.

Funding: Other NIH Support - Swiss National Science Foundation Grants 31003A-144112/1, Pharmaceutical Company Support - Gottfried und Julia Bangerter-Rhyner-Stiftung, unrestricted grant

Bär-Spycher-Stiftung, unrestricted grant

PUB295

IL-1 β Mediates the High Glucose Induced Endothelial-to-Mesenchymal Transition in Human Aortic Endothelial Cells Dongdong Zhu, Ri-ning Tang, Kun Ling Ma, Bi-Cheng Liu. *Zhong Da Hospital, Southeast Univ Medical School, Nanjing, Jiangsu.*

Background: Studies have shown that endothelial-to-mesenchymal transition (EndMT) induced by high glucose (HG) contributed to cardiac fibrosis. Additionally, proinflammatory cytokine interleukin-1 β (IL-1 β) has been implicated as one of the dominant players in the development of fibrosis and diabetic heart. In vitro studies, retinal endothelial cells (ECs), human intestinal ECs and human dermal ECs have been reported to undergo EndMT by

IL-1 β stimulation. Interestingly, most IL-1 β immunoreactivity is localized to endothelial cells and interstitial macrophages in an animal model of cardiac hypertrophy. However, the potential role of IL-1 β in high glucose induced EndMT remain unknown. Here, we hypothesize that IL-1 β might mediate the process.

Methods: Primary human aortic endothelial cells (HAECs) were divided into three groups: a normal glucose (NG) group, HG group, and anti-interleukin1 β antibody treated (HG+Anti-IL-1 β) group. The concentration of IL-1 β in the supernatant was detected by Elisa. Pathological changes were investigated using fluorescence microscopy and electron microscopy. Immunofluorescence staining was performed to detect the co-expression of CD31 and FSP1. The expressions of FSP1 and α -SMA were detected by RT-PCR and Western blot.

Results: The treatment of HAECs in the HG group resulted in significant increases in the expressions of FSP1, α -SMA and IL-1 β in dose- and time-dependent manners. The incubation of HAECs exposure to HG resulted in a fibroblast-like phenotype, wherein increased microfilamentation and a roughened endoplasmic reticulum structure were observed in the cytoplasm. The expressions of FSP1 and α -SMA were significantly increased in the HG group, and these changes were inhibited by anti-interleukin1 antibody or IL-1 β siRNA treatment ($P < 0.05$). Double staining of the HAECs indicated a colocalization of CD31 and FSP1, while treatment with anti-interleukin1 antibody or IL-1 β siRNA attenuated the expression of EndMT ($P < 0.05$).

Conclusions: These findings suggest that IL-1 β mediates the HG induced EndMT, which was inhibited by anti-interleukin1 antibody or IL-1 β siRNA treatment.

PUB296

Serum Bilirubin and Asparagine Aminotransferase Concentrations Predict Loss of Renal Function in Type 2 Diabetes Kevin M. Wheelock,¹ Gudeta D. Fufaa,¹ William Knowler,¹ Madhumita Sinha,¹ Frank C. Brosius,² Robert G. Nelson.¹ ¹NIDDK, Phoenix, AZ; ²Univ of Michigan, Ann Arbor, MI.

Background: Higher serum bilirubin concentration is reported to slow the progression of nephropathy in type 2 diabetes. We examined associations of serum bilirubin and asparagine aminotransferase (AST) concentrations with renal function loss (RFL) in a post-hoc analysis of a clinical trial of renoprotection with losartan in Pima Indians with type 2 diabetes (ClinicalTrials.gov number, NCT00340678).

Methods: Serum bilirubin and AST were measured at baseline in 168 subjects who underwent annual measurement of GFR by the urinary clearance of iothalamate. RFL was defined by $\geq 40\%$ decline in GFR from baseline. Cox regression was used to compute hazard ratios (HRs) for the association of a 1 standard deviation (SD) increment in bilirubin and AST concentrations with RFL adjusted for age, sex, treatment group, HbA1c, GFR, and urinary albumin/creatinine ratio (ACR). The sum of standardized AST and bilirubin was standardized to create a liver index variable with mean=0, SD=1.

Results: Participants (73% female, mean age 42 \pm 11 years, bilirubin 0.6 \pm 0.2 mg/dL, HbA1c 9.3 \pm 2.2%, GFR 163 \pm 43 ml/min, and median AST 19 U/L (IQR=13.0-31.5 U/L), ACR 31 mg/g (IQR=12-77 mg/g)) were followed for a median of 7.0 years (IQR=4.5-9.9 years); 73 subjects (43%) developed RFL. After multivariable adjustment, serum bilirubin (HR=1.33) and serum AST (HR=1.39) predicted RFL. The combination of these liver function tests provided the strongest prediction (HR=1.52).

Variable	Renal Function Loss (95% CI), P-value	
	Univariate	Multivariate
Log AST (per SD)	1.34 (1.04-1.74), P=0.025	1.39 (1.07-1.80), P=0.015
Bilirubin (per SD)	1.30 (1.05-1.62), P=0.016	1.33 (1.05-1.67), P=0.017
Liver index (per SD)	1.43 (1.13-1.81), P=0.003	1.52 (1.18-1.95), P=0.001

Conclusions: Higher serum bilirubin and AST concentrations predict loss of renal function in Pima Indians with type 2 diabetes.

Funding: NIDDK Support

PUB297

Baseline Data from the Multinational Prospective Cohort Study in Patients with Type 2 Diabetes for Validation of Biomarkers (PROVALID) Gert J. Mayer,¹ Susanne Eder,¹ Laszlo Rosivall,² Peter Voros,³ Hiddo Jan Lambers Heerspink,³ Dick de Zeeuw,³ Beata Czerwińska,⁴ Andrzej Wiecek,⁴ Dianne Z. Hillyard,⁵ Patrick B. Mark,⁵ Georg Heinze,⁶ Peter Rossing.⁷ ¹Internal Medicine IV, Medical Univ Innsbruck, Innsbruck, Austria; ²Inst of Pathophysiology, Semmelweis Univ, Budapest, Hungary; ³Egyesített Szent István és Szent Laszlo Korház, Budapest, Hungary; ⁴Dept Clinical Pharmacy and Pharmacology, Univ Medical Center Groningen, Groningen, Netherlands; ⁵Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ Silesia, Katowice, Poland; ⁶Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom; ⁷Section for Clinical Biometrics, Medical Univ Vienna, Vienna, Austria; ⁸STENO Diabetes Center, Gentofte, Denmark.

Background: We recruited 4065 subjects at the primary healthcare level in Austria, Hungary, Netherlands, Poland and Scotland, who will be treated according to local practise and followed for 4 years to compare the incidence and progression of renal and cardiovascular disease between the countries. Additionally extensive biobanking is performed.

Methods: We will determine the cumulative incidence of progression of albuminuria, doubling of creatinine, end stage renal disease as well as fatal and not fatal cardiovascular events. Exclusion criteria are active malignancy and age <18 years.

Results: The mean age of the population was 62 years, mean duration of diabetes as 9.9 years. 9% of the patients had eGFR values <45 and 22% <60 ml/min/1.73m². Baseline data

	"lowest" country	"highest" country
SBP (mmHg)	134 \pm 15	140 \pm 19
DBP (mmHg)	78 \pm 9	84 \pm 12
HbA1c (%)	6.7 \pm 1.1	7.3 \pm 1.4
eGFR<45 (%)	4	12
albuminuria (mg/day)	8 (5,26)	15 (6,40)
microalbuminuria (%)	10	26
LDL cholesterol (mg%)	91 \pm 34	118 \pm 39

We observed marked variability in treatment pattern between the countries (use of metformin 49-74, RAS blocking agents 59-77, β -blockers 28-59, statins 21-81%).

Conclusions: We conclude that health care practices in patients with type 2 diabetes at the primary level of care vary widely between European countries. Whether these differences affect outcome remains to be established.

Funding: Pharmaceutical Company Support - abbvie; North Chicago, Illinois, USA, Government Support - Non-U.S.

PUB298

FGF-23 and Magnesium Are Independent Risk Factors for an Increased Albumin-to-Creatinine Ratio in Type 2 Diabetics with Chronic Kidney Disease Filipa Brito Mendes,¹ Ana Paula Silva,^{1,2} André Frago, ¹Nélio Santos,¹ Teresa M. Jeronimo,¹ Ana Pocinho Pimentel,¹ Pedro L. Neves.^{1,2} ¹Centro Hospitalar do Algarve- Hospital de Faro, Portugal; ²Univ do Algarve, Portugal.

Background: Microalbuminuria is the earliest sign of glomerular involvement in diabetes mellitus. The multiple physiopathological mechanisms involved are complex and not completely understood. Recently, it appeared that fibroblast growth factor- 23 (FGF-23) and magnesium play a role in the emergence and maintenance of albuminuria in type 2 diabetics. The aim of this study is to investigate the role of FGF-23 and magnesium in relation to the urine albumin-to-creatinine ratio in type 2 diabetics with chronic kidney disease (CKD) stages 2-4.

Methods: In a cross-sectional study we included all eligible type 2 diabetic patients with CKD stages 2-4, followed in our outpatient Diabetic Kidney clinic. We included 150 patients, f=53 m=97, with a mean age of 66.6 \pm 9.7 years (40-85) and a mean follow-up of 76 months. We used descriptive statistics, the Student's test, ANOVA and the chi-square test. We divided our population according to the urine albumin-to-creatinine ratio (G1=30-300 mg/g and G2 \geq 300 mg/g) and compared these groups regarding the several biological and laboratorial parameters analyzed. We employed a multiple regression model to identify risk factors of increased urine albumin-to-creatinine ratio. In this model we used the urine albumin-to-creatinine ratio as the dependent variable and as independent ones age, duration of diabetes, systolic blood pressure, HgA1c, eGFR, HOMA-IR, manonaldehyde, hs-CRP and 1,25(OH)₂D3 levels.

Results: The patients in G2 displayed a lower eGFR (p=0.0001) and magnesium (p=0.004) levels, as well as higher levels of FGF-23 (p=0.043) compared to patients in G1. In the multivariate linear regression model we found that FGF-23 (β =0.562, P=0.0001) and the magnesium (β = -8.916, p=0.0001) are independent risk factors for increasing the urine albumin-to-creatinine ratio.

Conclusions: The present study shows that a dysregulation of mineral metabolism, reflected by altered levels of magnesium and FGF-23, correlates with an increased urine albumin-to-creatinine ratio in type 2 diabetic patients with CKD stages 2-4.

PUB299

FGF-23 and Klotho Influence the Pulse Pressure in Diabetic Patients with Nephropathy Ana Paula Silva,^{1,2} Filipa Brito Mendes,¹ André Frago, ¹Teresa M. Jeronimo,¹ Ana Pocinho Pimentel,¹ Nélio Santos,¹ Pedro L. Neves.^{1,2} ¹Nephrology, Centro Hospitalar do Algarve, Faro, Portugal; ²Dept of Biomedical Sciences and Medicine, Univ of Algarve, Faro, Portugal.

Background: The last decade have shown that FGF23 and Klotho may have relevant independent actions on the renal and CV systems. They interfere with vascular functions and may play a role in vascular calcification, atherosclerosis and arteriolosclerosis. Their interactive activities may also have direct and indirect effects on interdependent renal and CV pathophysiology. The aim of this study is to investigate the relationship between FGF-23 and Klotho with pulse pressure in type 2 diabetic with chronic kidney disease (CKD) stages 2-3.

Methods: In a cross-sectional study we included 107 type 2 diabetic patients (67 males, 62,6%), a mean age of 66.6 \pm 9.7 years and CKD stage 2-3. We used descriptive statistics, the Student's t and the chi-square tests. We also divided our population according to the pulse pressure (G I <50 mmHg and G2 \geq 50 mmHg), and compared these groups regarding the several biological and laboratorial parameters analyzed. We employed a multiple regression model to identify risk factors of increased pulse pressure (PP). In this model we used as dependent variable the pulse pressure, and as independent ones age, metabolism mineral, urine albumin-to-creatinine ratio, insulin resistance, oxidative stress and eGFR.

Results: We found that G2 patients showed higher age (p=0.017), phosphorus (p=0.0001), iPTH (p=0.0001), urine albumin-to-creatinine ratio (p=0.001), Homa-IR (p=0.001), FGF-23 (p=0.0001) and OxLDL (p=0.0001) and lower levels of eGFR (p=0.0001), Klotho (p=0.0001) and 1.25(OH)2D3 (p=0.0001). In the multivariate linear regression model we found that FGF-23 ($\beta=0.377$, P=0.047) and the Klotho ($\beta= - 0.567$, p=0.023) are independent risk factors for increasing the pulse pressure.

Conclusions: In conclusion, in a population of type 2 diabetic with chronic kidney disease stages 2-3, the Klotho and FGF-23 levels are independently associated with PP. Further studies with more patients are warranted to confirm whether an increase in Klotho and a decrease in FGF-23 would reduce the PP and consequently the cardiovascular risk of our patients.

Funding: NIDDK Support

PUB300

Prediction of Renal Outcome in Type 2 Diabetic Nephropathy by Estimating GFR from a Combination of Serum Creatinine and Cystatin C Yu Pan, Song Jiang, Dandan Qiu, Yu An, Yongchun Ge, Honglang Xie, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Serum cystatin C is an alternative to serum creatinine for estimating glomerular filtration rate (GFR), however, the utility of estimated GFR from combination of serum creatinine and cystatin C as marker to predict long-term renal outcome is uncertain, particularly in the Type 2 diabetic nephropathy (DN).

Methods: A total of 501 patients (The National Clinical Research Center of Kidney Diseases, 2003-2011) were recruited in prospective cohort study. Follow-up was 5-year. Renal outcome was defined by eGFRcre-cys<15 ml/min per 1.73m² or renal replacement therapy.

Results: The distributions of standardized serum cystatin C with eGFRcre and eGFRcre-cys are shown in. Kaplan-Meier curves showed significantly increased renal end points with higher quartile of cystatin C (p <0.001) and lower eGFRcre-cys (p <0.001). The highest AUROCs was eGFRcre-cys in predicting the renal endpoint compared with eGFRcre or eGFRcys. The best cut-off value for predicting the renal endpoint was 29.28% decline in the 24-month, which value showed 79.6% sensitivity and 82.6% specificity. Cox regression models with restricted cubic splines shows a change of -30% in eGFRcre-cys was associated with adjusted HRs for ESRD of 27.92 (95%CI, 3.95-197.48) over 2-year.

Conclusions: eGFRcre-cys was a precision, and accuracy marker in the predicting of the renal outcome and 30% decline of eGFRcre-cys over 2 years was strongly associated with the risk of ESRD, suggesting it could be used as an alternative end point in T2DN.

Funding: Government Support - Non-U.S.

PUB301

Prevalence and Prognostic Role of Uncontrolled Risk Factors in Diabetic CKD (DM-CKD) Treated in Nephrology Clinics Roberto Minutolo,¹ Michele Provenzano,¹ Paolo Chiodini,² Giuseppe Conte,¹ Luca De Nicola.¹ *¹Nephrology, Second Univ, Naples, Italy; ²Med Stat, Second Univ, Naples, Italy.*

Background: Knowledge of prognosis of DM-CKD mainly derives from RCTs and cohorts followed in the diabetology setting. Epidemiologic features are less defined in patients with overt disease managed in renal clinics.

Methods: We studied 763 DM-CKD patients derived from 3 prospective cohorts that in 2000-2010 enrolled 2,488 CKD patients stage III-V under stable care for ≥6 months in 40 Italian renal clinics. Endpoints were ESRD (chronic dialysis-transplant) and first major cardiovascular (CV) events (fatal and non fatal) assessed through 12/2014. Uncontrolled risk factors were defined as high blood pressure (BP>140/90 or >130/80 if proteinuria >0.150 g/24h), HbA1c >7.5%, hemoglobin <10.5 g/dL, serum phosphorus (P) >4.5 mg/dL, LDL-C ≥100 or 70 mg/dL according to ESC 2012 guidelines, proteinuria (Uprot)>0.5 g/24h.

Results: HbA1c was 6.9%, (IQR 6.2-7.8), Uprot 0.5 g/24h (IQR 0.1-1.4), P 3.9±0.8 mg/dL, Hb 12.3±1.7 g/dL and BP 142±19/78±11 mmHg. During follow-up (43 months, IQR 21-56), 171 ESRD and 170 CV events occurred (incidence rate 6.4 and 6.9/100 pts/y). Multivariable Cox analyses for ESRD and CV risks (HR, 95% CI) stratified by cohort are in the Table.

	Descriptive	ESRD	CV
Age, years	70±10	0.98 (0.96-0.99)	1.03 (1.02-1.05)
Males, %	57.9	1.93 (1.36-2.72)	1.36 (0.97-1.91)
Smokers, %	9.7	1.07 (0.62-1.87)	1.06 (0.60-1.88)
CV disease, %	46.7	1.56 (1.13-2.15)	1.77 (1.29-2.43)
BMI, Kg/m ²	29.3±5.3	1.00 (0.97-1.03)	1.00 (0.97-1.03)
GFR-EPI, ml/min/1.73m ²	31.2±14.1	0.90 (0.88-0.92)	0.97 (0.96-0.99)
High BP, %	53.1	1.30 (0.91-1.88)	1.60 (1.13-2.26)
HbA1c>7.5, %	33.0	0.78 (0.55-1.10)	1.45 (1.06-1.99)
Hemoglobin<10.5, %	13.8	1.58 (1.09-2.28)	1.43 (0.94-2.18)
LDL-C≥100-70, %	83.6	1.01 (0.66-1.56)	1.03 (0.65-1.62)
Uprot>0.5, %	49.8	1.95 (1.26-3.00)	1.07 (0.74-1.54)
P>4.5, %	18.1	1.49 (1.05-2.12)	0.92 (0.60-1.41)
Anti-RAS, %	78.6	0.98 (0.67-1.44)	1.04 (0.71-1.54)

Similar results were obtained when testing continuous variables.

Conclusions: Epidemiologic peculiarities emerge in DM-CKD patients treated in renal clinics. This information can be helpful to optimize risk stratification and adequately design RCTs.

PUB302

Serum NGAL and Cystatin C Accuracy in Early Detection of Kidney Dysfunction in Type 2 Diabetes Marcelo Rodrigues Bacci, Fernando Luiz affonso Fonseca, Livia Yadoya Vasconcelos, Mariana Rigolo, Ross Rozier-Alves, Beatriz Alves. *General Practice, ABC Medical School, Brazil.*

Background: Diabetic nephropathy is associated with specific histological changes. An early detection of depletion of glomerular and tubular function can be done with biomarkers of diabetic disease. The aim of this study is to evaluate the accuracy of early kidney dysfunction biomarkers in diabetes.

Methods: Patients with diabetes were split according to their levels of glycated hemoglobin (GHb): greater than 7% or below this value. Urine samples were taken to measure cystatin C (uCYS), uNGAL, beta-trace protein (uBTP) and albuminuria (ACR). In blood, sCYS, sNGAL, creatinine. Patients with end stage renal disease or in dialysis were not included. ROC curve was used to evaluate the accuracy of the markers relative to renal dysfunction according to their simplified MDRD estimated glomerular filtration rate (eGFR). Spearman's correlation and regression models were built to evaluate the markers.

Results: Ninety patients with diabetes were recruited. The mean eGFR was 79.1 ml/min/1.73m² and 76.7 in GHb > 7% group. sCYS was positively correlated with creatinine (p<0.001), eGFR (p<0.001) and uBTP (p=0.01). The ROC curve showed value of 0.635 for sCYS, 0.621 to sNGAL and 0.660 for ACR. Urine had lower values for CYS (0.569), 0.526 for NGAL and 0.567 for uBTP. The crude logistics regression model observed a positive association between sCYS (p=0.01) and sNGAL (p<0.001). The linear regression model showed positive association with sCYS and creatinine and eGFR (p<0.001) but not with GHb (p=0.892). ACR showed the same parameters (p=0.005 for creatinine and 0.018 for eGFR).

Conclusions: In this study, a comparative panel of tubular and glomerular dysfunction markers was built in diabetics with eGFR > 60. There was a worse performance of the markers in urine except for ACR that had the best value in ROC analysis. The sCYS and sNGAL presented the best association with worse GFR and glyemic control. In another study of our group uBTP had better performance to distinguish early kidney dysfunction between diabetics and non diabetics. Finally, with worse eGFR, sNGAL, sCYS and ACR performed better in diabetics. A worse glyemic control was positively associated with sCYS and sNGAL.

PUB303

Comparison of Renal Outcome Between “Chronic Kidney Disease due to Diabetes” and “Chronic Kidney Disease with Diabetes” in Gonryo Study Toshiki Iwai,² Mariko Miyazaki,¹ Gen Yamada,¹ Tae Yamamoto,¹ Hiroshi Sato,² Masaaki Nakayama,³ Sadayoshi Ito.¹ *¹Nephrology, Hypertension, and Endocrinology, Tohoku Univ Department of Pharmacology, Sendai, Miyagi, Japan; ²Clinical Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Tohoku Univ, Sendai, Japan; ³Kidney and Hypertension, Fukushima Medical Univ, Fukushima, Japan.*

Background: Diabetic nephropathy (DN) is defined as chronic kidney disease (CKD) due to diabetes mellitus (DM) in a narrow sense. The difference is not unclear between DN and CKD patients of other cause but complicated DM (CKD with DM) in clinical outcome. This study mentioned the clinical difference and renal outcome of DN, CKD with DM, and CKD without DM.

Methods: This is a part of Gonryo CKD study. It is the multicenter prospective observational survey for 5 years. From May 2006, 4,015 patients were registered. We include 2,484 of them into this analysis who could classify to DN (n=249), CKD with DM (n=448), and CKD without DM (n=1,787). The classification was performed at registration by clinical finding and history of other diabetic complication such as retinopathy if case without kidney biopsy.

Results: The characteristics of age, gender, systolic blood pressure (SBP), and dyslipidemia in “DN” (66.6 y.o., male 67.9%, sBP 136.6mmHg, dyslipidemia 50.1%) and “CKD with DM” (58.7 y.o. male 58.7%, sBP 132.3mmHg, dyslipidemia 54.4%) were similar compared with “CKD without DM” (50.5 y.o. male 50.5%, 129.8 mmHg, 40.1%). For renal outcome analysis of each CKD stage was performed. The hazard ratio of “DN” was significantly higher than “CKD without DN” for end stage kidney disease (ESKD) in G3b 7.10 (2.46-20.49 95% CI), G4 2.31 (1.35-3.94), G5 1.67 (1.16-2.42). On the other hand, that of “CKD with DM” didn't elevate in G3b 0.89 (0.19-4.24 95% CI), G4 1.21 (0.66-2.23), G5 1.36 (0.74-2.51) compared with “CKD without DM”. Kaplan-Meier analysis revealed G3b and G4 in “DN” showed significantly poor outcome. The evaluation of annual decline of eGFR revealed stage G3b in DN was the largest. (-3.7 ml/min/1.73m²/year).

Conclusions: Renal risk between “CKD with DM” and “DN” was completely different. G3b was most important critical point in renal prognosis of DN.

Funding: Clinical Revenue Support

PUB304

Prevalence of Proteinuria, Albuminuria and Associated Factors in Obese Patients Undergoing Bariatric Surgery Max R. Pommier, Gaurang P. Mavani, Maria V. DeVita, Michael F. Michelis, Jordan L. Rosenstock. *Dept of Medicine Div of Nephrology, Lenox Hill Hospital Northshore/LLJ, NYC, NY.*

Background: Obesity is associated with proteinuria. But the exact prevalence of proteinuria or albuminuria with and without additional risk factors in obese patients is unclear.

Methods: Consecutive patients undergoing bariatric surgery were included in study. Participating patients had a urine sample for protein creatinine ratio and albumin creatinine ratio prior to their surgery. We defined a positive protein to creatinine ratio as greater than or equal 300 mg and a positive albumin to creatinine ratio as greater than or equal to 30 mg. Associated factors such diabetes mellitus (DM), hypertension (HTN), body mass index (BMI), and ACEi/ARB use were collected.

Results: One hundred forty-three patients were included. The mean age was 43 years +/- 11. Twenty five percent of the patients had DM, 50% had HTN, and the mean BMI was 44 +/- 9. The prevalence of proteinuria and albuminuria was 8.5% (95% CI 4.5- 14.4%) and 21% (95% CI 14- 30%) respectively. Sixty six percent of the patients with proteinuria had DM as did 43% of the patients with albuminuria. Eighty three percent of patients with proteinuria had either DM or HTN. Seventy eight percent of patients with albuminuria had either DM or HTN. Of patients with neither DM nor HTN (n=58), only 3.4% and 8.6% had proteinuria and albuminuria respectively. In contrast to patients who did not have proteinuria, the mean BMI was higher in those with proteinuria (44 vs. 40). However, the BMI did not differ between those with and without albuminuria. The BMI for diabetics did not differ from non-diabetics. The use of ACEi/ARB was 33% and 30% in patients with proteinuria and albuminuria and 25% and 20% in those without.

Conclusions: The majority of patients with proteinuria and albuminuria had diabetes and/or hypertension and there was a much lower prevalence of proteinuria/albuminuria in patients without these risk factors. Patients who had proteinuria had a higher BMI than patients who did not have proteinuria, though for albuminuria the BMI did not differ.

PUB305

Plasma Uric Acid and Cardio-Renal Function in Adolescents with Type 1 Diabetes Yuliya Lytvyn,¹ Farid H. Mahmud,² Livia Deda,² David B. Dunger,³ John Eric Deanfield,⁴ Yesmino Elia,² Ronnie Lok-Hang Har,¹ Timothy J. Bradley,⁵ Rahim Moinuddin,⁶ Heather N. Reich,¹ James W. Scholey,¹ Luc Mertens,⁵ Etienne Bertrand Sochett,² David Cherney.¹ ¹Nephrology, Univ Health Network, Univ of Toronto; ²Endocrinology, The Hospital for Sick Children, Univ of Toronto; ³Pediatrics, Univ of Cambridge, Cambridge, United Kingdom; ⁴Univ College Hospital, London, United Kingdom; ⁵Cardiology, The Hospital for Sick Children, Univ of Toronto; ⁶Family and Community Medicine, Univ of Toronto.

Background: Plasma uric acid (PUA) correlates with higher blood pressure (BP), lower GFR and lower renal blood flow in adults with type 1 diabetes (T1D). Our overall aim was to determine if similar relationships exist in adolescents with T1D, analyzed on the basis of low-, middle- or high- albumin to creatinine ratio (ACR) tertile within the normal range, compared to healthy controls (HC). We hypothesized that PUA within the normal range would be associated with lower GFR and higher values for BP and arterial stiffness in T1D adolescents but not HC.

Methods: PUA, BP, GFR_{cystatin c} and carotid-femoral pulse wave velocity (Car-Fem PWV) were measured in 65 HC, 64 low-, 74 middle- and 50 high-tertile T1D participants from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT).

Results: PUA was lower in T1D vs. HC (242±55 vs. 306±74mmol/L, p<0.0001). There were no differences in PUA between the 3 ACR tertiles. Higher PUA correlated with lower GFR in T1D after correcting for age, gender, HbA1c, BMI z-score, BP z-score, T1D duration and plasma HDL (p<0.0001). This association was not seen in HC. In the T1D group, PUA did not correlate with BP z-score before or after correcting for HbA1c, T1D duration and plasma HDL. Higher PUA correlated with higher Car-Fem PWV (r=0.18, p=0.018) in T1D, but not in HC. This association in T1D was abolished after correcting for age, gender, HbA1c, BMI z-score, T1D duration and HDL.

Conclusions: PUA correlates with lower GFR in T1D adolescents and may also be associated with increased arterial stiffness, despite lower PUA in T1D vs. HC. The presence of T1D may potentiate the hemodynamic impact of PUA, thereby modifying future cardio-renal risk.

PUB306

Risk Factors for Renal and Cardiovascular Events in Type 2 Diabetic Patients with Biopsy-Proven Nephropathy in Japan Akinori Hara,¹ Kengo Furuichi,¹ Miho Shimizu,¹ Yukio Yuzawa,² Hiroshi Kitamura,³ Hiroshi Sato,⁴ Takashi Wada.¹ ¹Div of Nephrology, Kanazawa Univ Hospital, Japan; ²Dept of Nephrology, Fujita Health Univ Hospital, Japan; ³Dept of Pathology, Clinical Research Center, National Hospital Organization Chiba East National Hospital, Japan; ⁴Clinical Pharmacology and Therapeutics, Tohoku Univ Graduate School of Pharmaceutical Sciences.

Background: Standardized pathological classification is an essential tool in the evaluation of disease progression and/or efficacy of clinical management. In this nationwide, multicenter, retrospective study, we examined pathological findings as risk factors for renal and cardiovascular events in Japanese patients with type 2 diabetes.

Methods: Renal biopsy and clinical data were retrospectively collected from 356 patients with type 2 diabetes in 13 centers in Japan. The mean observation period was 76.3 months and the observation period was 2264 person-year in total. Nine glomerular lesions, two interstitial lesions, and two vascular lesions were classified and evaluated as pathological predictors.

Results: One hundred sixty nine composite renal events (dialysis and doubling of serum creatinine or half of estimated glomerular filtration rate (eGFR)), 94 kidney deaths (dialysis), 34 cardiovascular events, and 30 deaths occurred. Specific pathological risk factors were detected for composite renal end points, renal death, and cardiovascular events in normo- to microalbuminuria and preserved eGFR group (G1-3a, A1-2). Among them, the presence of double contour of the glomerular basement membrane/subendothelial space widening (SubendW) and advanced interstitial cell infiltration (ICell) were particular risk factors for composite renal events, and glomerulomegaly (GMeg) was a risk factor for cardiovascular events.

Conclusions: This study revealed that specific pathological parameters (presence of SubendW, ICell, and GMeg) were predictors for renal and cardiovascular events in patients with preserved eGFR and normo- to microalbuminuria.

Funding: Government Support - Non-U.S.

PUB307

The Effect of Carbohydrate – Blood Glucose Feedback Method with Basic Carbohydrate Counting for Glycemic Control in Diabetic Dialysis Patients Toru Hyodo. *Dialysis Center, Eijin Clinic and Kurata Hospital, Hiratsuka, Kanagawa, Japan.*

Background: Basic carbohydrate counting (BCC), a method used in the dietary management of diabetes, is based on the concept that the postprandial rise in blood glucose levels is primarily affected by ingested carbohydrates. In this method, patients are instructed to eat a consistent amount of carbohydrates across their three daily meals to minimize fluctuations in postprandial blood glucose levels. We applied the carbohydrate glucose feedback method (CBGFM) with BCC for the diabetic dialysis patient whose HbA1c levels did not keep each favorable level only by BCC. CBGFM is to measure the predialysis blood glucose and show the results to patients in every dialysis session. Patients can estimate their carbohydrate intake balance and doses. The effect of CBGFM with BCC is reported in this study.

Methods: Eight diabetic patients undergoing maintenance hemodialysis (6 men and 2 women; mean age, 64.4 ± 11.9 years; mean dialysis period, 4.0 ± 5.0 years; 2 insulin users, 6 nonusers) were instructed in CBGFM with BCC and followed for 3 months to assess changes in their predialysis blood glucose (BG), hemoglobin A1c (HbA1c), Hemoglobin (Hb), triglycerides (TG), Potassium (K), Phosphorus (P), albumin (Alb), total cholesterol (T-Chol), high-density lipoprotein-cholesterol (HDL-cho), low-density lipoprotein-cholesterol (LDL-cho), protein catabolic rate (PCR), dry weight (DW), body mass index (BMI), and the Geriatric Nutritional Risk Index (GNRI).

Results: HbA1c levels were significantly decreased from the pre-instruction values (P=0.0054). The GA and BG showed the tendency toward decrease, but no marked changes were observed for the other parameters. Pre BG: 173.1 ± 50.9 mg/dL Pre HbA1c: 7.0 ± 0.4 % Pre GA: 19.2 ± 4.5, 3M BG: 131.5 ± 29.5 (P=0.066), 3M: HbA1c: 6.1 ± 0.6 (P=0.0054), 3M GA: 17.7 ± 2.3 (P=0.111).

Conclusions: The results demonstrated that the CBGFM with BCC is a useful method of dietary management for glycemic control that can be applied independently of, but concurrently with, the control of potassium and phosphorus intake in dietary therapy for dialysis patients.

PUB308

The Clinical Effects of Renoprotection with DPP-4 Inhibitors Koichi Kanozawa, Saeko Sato, Yoshimi Okada, Hiroaki Hara, Minoru Hatano, Nobuyuki Onizawa, Takatsugu Iwashita, Tomonari Ogawa, Hajime Hasegawa. *Nephrology and Hypertension, Saitama Medical Center, Saitama Medical Univ, Kawagoe, Saitama, Japan.*

Background: Recently, not only animal models of diabetic nephropathy, but also non-diabetic nephropathy models, DPP-4 inhibitors (DPP-4i) was reported to have the renoprotective effects that improve albuminuria or tissue damage, through inhibition of oxidative stress, inflammation, and fibrosis. The aim of study is to clarify the mechanisms of renoprotective effect by DPP-4i in human diabetic nephropathy (DMN), clinically.

Methods: We gave DPP-4i (either of vildagliptin 50-100mg, alogliptin 25mg, teneligliptin 20-40mg) for Japanese Type 2 diabetes patients with nephropathy. We were compared surrogate marker of oxidative stress/adrenal injury, before and after three months.

Results: The administration of the DPP-4i, HbA1c was improved from 6.9 ± 0.4 to 6.3 ± 0.3% (p<0.01), either 1,5-anhydro-D-glucitol (1,5AG) was increased from 11.0 ± 6.4 to 15.3 ± 6.9% (p<0.01). Although eGFR_{creat} was no change (p=0.05), but eGFR_{cys} was significantly increased from 92.1 ± 23.8 to 96.7 ± 21.7 ml/min/1.73m² (p=0.03). MDA-LDL is an oxidative stress marker, was decreased from 128 ± 39 to 110 ± 34 μU/L (p<0.01), urinary 8OHdG was reduced from 10.8 ± 5.3 to 8.1 ± 4.5 ng/mgCr (p<0.01). Although log urinary albumin to creatinine ratio (UACR) was reduced from 1.52 ± 0.63 to 1.36 ± 0.64 (p<0.01), and urinary liver-type fatty acid binding protein (L-FABP) was improved from 8.1 ± 8.3 to 4.5 ± 4.6 mg/gCr (p=0.02), but NAG and urinary b2-microglobulin (MG) were no change (p=0.65, 0.47). In inflammation, or fibrosis, log urinary MCP-1 was decreased from 2.41 ± 0.53 to 2.12 ± 0.32 (p<0.01), and urinary collagen IV was from 5.2 ± 3.3 to 3.9 ± 2.4 mg/gCr (p<0.01). In the context of blood glucose change, strong association was observed between the change rate of 1,5AG and urinary 8OHdG (p<0.01), also was also associated with the change rate of UACR (p=0.03). On the other hand, HbA1c and these were not associated (p=0.31, 0.14).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Conclusions: In DMN, DPP-4i have oxidative stress relief and renoprotective effect, by the improvement of short-term blood sugar fluctuations, also by oxidative stress reduction which independently of the improving glycemic control.

PUB309

Fibrinogen: A Potential Predictive Factor for the Progress of Diabetic Kidney Disease Wenbo Zhao, Hui-qun Li, Zhenda Zheng. *The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong.*

Background: To evaluate the potential of fibrinogen as a predictor of the progress of proteinuria in diabetic kidney disease.

Methods: For a Cross-Sectional Study, collecting 1121 type 2 diabet patients without or with microalbuminuria or massive proteinuria were treated during January 2008 to January 2013. Proteinuria was negative in 755 cases, 285 cases i with microalbuminuria, and 171 cases with massive proteinuria; We analyzed the correlation factors of the negative protein urine group and the microalbuminuria group; the correlation factors of the microalbuminuria group and the massive proteinuria group. Fibrinogen levels were compared between three groups.

Results: Retinopathy, hypertension grading, SBP, Fibrinogen levels, serum albumin, serum cystatin were the related progress factors of Microalbuminuria; Diabetes course, retinopathy, waist to hip ratio, Fibrinogen levels, serum albumin levels, serum cystatin C, serum creatinine were the related progress factors of the massive proteinuria; Except fibrinogen, other factors had been known relating to the progress of diabetic kidney disease. There were differences in the levels of three groups of fibrinogen (P< 0.05), which were 3.43 + 0.91 g/L, 4.15 + 1.31 g/L, 5.16 + 1.44 g/L.

Conclusions: Fibrinogen was a potential predictive factor for the development of diabetic kidney disease. The conclusion needs to be confirmed by further study.

PUB310

Interaction of HDLc, Iron, and Diabetes on Kidney Function Baqiyah Conway,¹ Tina Costacou,² John M. Arthur.³ ¹Epidemiology, West Virginia Univ; ²Epidemiology, Univ of Pittsburgh; ³Univ of Arkansas for Medical Sciences.

Background: The effect of HDL cholesterol (HDLc) on kidney function has recently received attention, partly due to the finding of increased hemoglobin (hb) inside of the HDL protein in persons with high risk haptoglobin (hp) genotypes. Such hb w/in the HDL protein may lead to iron induced lipid peroxidation products. These lipid peroxidation products may lead to iron-induced kidney damage. We have recently shown an interaction between HDLc and iron w/ kidney function (eGFR) in persons with diabetes such that after controlling for hb, higher serum iron levels were associated w/ reduced eGFR but only in those w/ HDLc levels above the median for the population. Because of the diabetes-specific association of increased hb inside the HDL protein in those w/ high risk hp genotypes, we hypothesize that this interaction between HDLc and iron w/ kidney function varies by diabetes status. To test this hypothesis, we examined the inter-relationship between HDLc, iron, and diabetes status w/ eGFR in approximately 55,000 individuals in West Virginia and Ohio.

Methods: Data on adults aged ≥20 years were obtained from the C8 Health Project. eGFR was estimated using the CKD-EPI formula. Linear regression analysis was used to test the relationship between HDLc, serum iron, and diabetes status, and their interactions, with eGFR.

Results: Mean age was 57.8 in those w/ diabetes and 45.1 in those w/out diabetes. In multivariable analyses controlling for age and sex, iron was positive related w/ eGFR in those w/ (p=0.03) and inversely in those w/out diabetes (<0.0001), while HDLc was positively associated w/ eGFR only in those w/out diabetes (p=0.97 in diabetes; p<0.001 in those w/o diabetes). As previously reported, an interaction existed between HDLc and iron in diabetes (p=0.04). Here we report that this relationship was even stronger in those w/out diabetes (interaction p=0.0008). A significant 3-way interaction existed between HDLc, serum iron, and diabetes status w/ eGFR (p=0.008). Controlling for hb, the interaction between iron and HDLc disappeared in those w/ diabetes but remained robust in those w/out diabetes.

Conclusions: The divergent relationship between iron and HDL on the eGFR by diabetes status needs further investigation.

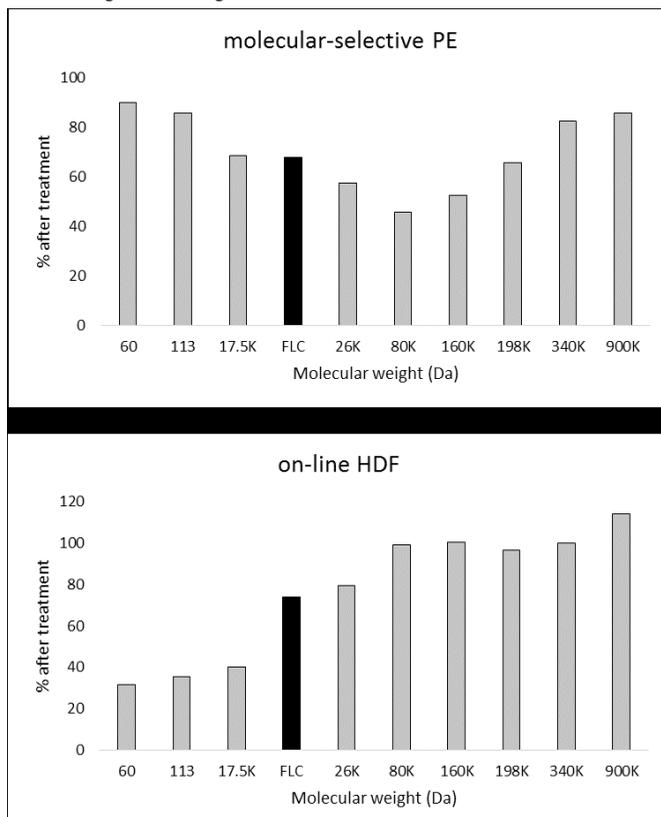
PUB311

Molecular-Selective Plasma Exchange in Acute Kidney Injury due to Multiple Myeloma Manabu Kanda, Satoru Sanada, Shinichi Mizuno, Shu Yamakage, Mitsuhiro Sato, Yoshio Taguma, Toshinobu Sato. *Nephrology, Japan Community Health Care Organization Sendai Hospital, Sendai, Miyagi, Japan.*

Background: Benefit of plasma exchange in overall survival of patients with multiple myeloma (MM) remains to be determined, however, it is evident that lowering free light chain (FLC) reverses renal function in acute kidney injury (AKI) due to MM. High cut-off hemodialysis is recommended to remove FLC as an initial treatment for MM related AKI, which is different from traditional plasma exchange (PE) in preventing loss of large size molecules. As another option, we show the effect of molecular-selective plasma exchange to remove FLC, which enables target size removal without losing other size molecules.

Methods: A 49 year male with Bence-Jones type M protein was admitted with AKI; serum creatinine rose from 3.8 to 7.9mg/dL in 1 month. Past history included bone fracture and anemia. Serum FLC lambda was elevated to 29800 mg/dL. MM was confirmed by plasma cells in the bone marrow. The patient was treated with sequential molecular-selective plasma exchange (Evacure) and on-line HDF every other day combined with Bortezomib.

Results: PE was performed 6 times and removed 43.1% of FLC each on average without losing small and large size molecules.



On-line HDF removed 11.6% on average. Few, if any, rebounds were found in the FLC concentration between the treatments. Serum FLC level decreased to 411mg/dL after a series of treatments (day 14) and serum creatinine reversed to 2.7mg/dL at day 21.

Conclusions: A molecular-selective plasma separator is designed to limit the loss of high molecular weight substances. Using this machine, FLC can be removed effectively while preserving large size molecules. Moreover, the use of plasma substitute fluid can be reduced compared to that of conventional PE. We conclude that molecular-selective plasma exchange could be an effective treatment option for MM associated AKI.

PUB312

Preliminary Evaluation of a New CRRT Machine: Kibou™ Mauro Neri, Francesco Garzotto, Anna Lorenzin, Silvia Guggia, Alessandra Brendolan, Federico Nalesso, Monica Zanella, Claudio Ronco. *IRRV and San Bortolo Hospital, Vicenza, Italy.*

Background: Kibou™ (Asahi Kasei Medical Co., Tokyo, Japan) is a new multifunctional automatic machine for Continuous Renal Replacement Therapy (CRRT) system (figure 1).



CRRT TREATMENT	REPLACEMENT		DIALYSATE		ADULT		PEDIATRIC		
	PRE	POST	PRE & POST	COUNTER-CURRENT	COUNTER-CURRENT	HEPARIN	CALCIUM-CITRATE	HEPARIN	CALCIUM-CITRATE
SOIF	•	•	•	•	•	•	•	•	•
OVHF	•	•	•	•	•	•	•	•	•
CVVHD	•	•	•	•	•	•	•	•	•
CVVHDF	•	•	•	•	•	•	•	•	•
TRF	•	•	•	•	•	•	•	•	•

Kibou can perform different CRRT therapies with the possibility to use only a single platform; in particular, modalities for both adults and pediatrics, counter-current and co-current configuration, the use of heparin or citrate-calcium anticoagulation therapies and plasma exchange can be delivered (figure 1).

Methods: Based on the traditional experience of International Renal Research Institute of Vicenza (IRRV), *in vitro* and *a test* evaluations of Kibou and related disposables have

been conducted. 12 treatments were performed. Machine's usability and accuracy has been evaluated by the staff through scores table. The measurement of fluid balance accuracy was even performed.

Results: Based on score given by the staff (engineers, nurses and physicians), the machine hardware results compact and well organized, with 3 well separated compartments (dialysate/replacement, blood and effluent) that facilitate the preparation phase. Auto-priming function allows short priming time. The interface is user friendly in all the modalities (SCUF, CVVH, CVVHD, CVVHDF, TPE both for adults and pediatrics). The measured fluid balance error was always lower than 0.3%. On the contrary CVVHDF pre-infusion and pre+post infusion are not performable. For pediatric treatment the continuity of the flow of blood pump need to be maintained and improved.

Conclusions: Kibou is a promising CRRT machine that can perform multiple continuous therapies with just one platform. In particular, we evaluated a highly accurate gravimetric fluid balance control system and a user friendly interface. Kibou is one of the first machines of the new frontier of CRRT devices: the fourth generation of CRRT machines.

PUB313

The Effect of MySleeve on Fluid Restriction Adherence in Hemodialysis Patients Idowu B.I Ayoola,¹ Marijke J.E. Dekker,² Marc Schonck,² Jeroen Kooman,³ Erik Korsten,^{1,2} Wei Chen,¹ Constantijn Konings,² Loe M. Feijs.¹
¹Industrial Design, Technology Univ Eindhoven, Eindhoven, Netherlands; ²Medicine, Div of Nephrology, Catharina Hospital Eindhoven, Eindhoven, Netherlands; ³Medicine, Div of Nephrology, Maastricht Univ Medical Center, Maastricht, Netherlands.

Background: In hemodialysis patients, non-adherence to fluid restriction is associated with high interdialytic weight gain (IDWG) and adverse outcomes. Monitoring drinking behaviour and direct feedback to the patient can lead to better adherence. We developed the MySleeve, a device that can be wrapped around a drinking glass to monitor fluid intake throughout the day. The MySleeve will also provide a subtle vibration on the glass when the amount drunk exceeds target. The information about drinking behaviour can be found in the accompanying application on a mobile phone. In this study, we investigate the effect of direct feedback and information to the patient on fluid restriction adherence, measured by the IDWG.

Methods: We will include 40 prevalent, anuric hemodialysis patients from the Catharina Hospital Eindhoven, The Netherlands in a randomised controlled trial. Patients in the intervention group are provided a MySleeve device, a mobile phone and an activity tracker. BCM measurements are performed weekly and IDWG will be calculated before every dialysis session. The patients in the control group will continue with regular hemodialysis.

Results: We expect that by providing patients insight in fluid intake, there will be an increase in fluid restriction adherence and an increase in activity levels and better quality of sleep. Due to less IDWG, patients will experience less discomfort of fluid overload.

Conclusions: Introducing a MySleeve device to provide direct insight into drinking behavior will help the patients to adhere to their fluid restriction, leading to less IDWG and better quality of life measured by daily activity and better sleep.

Funding: Private Foundation Support

PUB314

A Time and Motion Study of Erythropoiesis Stimulating Agent Administration in United States Dialysis Centers Mark Stephens,¹ Larry C. Emerson,² Leslie A. Spry,² John P. Caloyeras,³ Ernest R. Anderson,⁴ John Reitan,⁴ Akhtar Ashfaq,³ ¹Prima Health Analytics; ²Dialysis Center of Lincoln; ³Amgen, Inc.; ⁴RJM Group.

Background: Previous research suggests that ESA administration in dialysis is a time-consuming task and switching to less frequently dosed ESAs may offer opportunities for more efficient and effective patient care. This study estimated the time required for activities involved in the ESA process at US dialysis centers using epoetin alfa (EPO) or darbepoetin alfa (DPO), and examined potential time savings of switching from EPO to DPO.

Methods: Time and motion study conducted from 10/2014 to 1/2015 to assess activities involved and staff time required to prepare, administer and document ESA doses. A sample of 11 dialysis centers using either 3 times-per-week (TIW) EPO or once-weekly (QW) DPO were selected in pairs (one EPO, one DPO), where possible, from the same organization or nephrology practice to help control for anemia management protocols and staffing patterns. ESA-related tasks were timed by trained nurse observers. Time savings expected from switching from TIW EPO to QW DPO were estimated. Staff were interviewed about alternate patient-focused activities that could be accomplished if time were saved in the ESA process.

Results: 200 administrations were observed (81 DPO, 119 EPO). A mean of 2.3 (95% CI: 2.1-2.5) minutes per dose were required for ESA-related activities. RNs performed 95% of tasks; LPNs 5%. ESA process time did not vary significantly between EPO and DPO (>p=0.83). Staff time savings would accrue due to fewer ESA administrations using QW DPO: 10-20 minutes per nurse/day. For an average facility, the total monthly nurse time that could be re-purposed was 24 hours. Patient education, fulfillment of care plans and more frequent review of labs were identified as opportunities for improved care processes that could be implemented after conversion.

Conclusions: Switching from TIW EPO to QW DPO for anemia management in dialysis patients can result in time savings and opportunities to redirect nurse time towards activities aimed at improving patient care while still offering the ability to respond to changing clinical circumstances to effectively manage anemia.

Funding: Pharmaceutical Company Support - Amgen, Inc.

PUB315

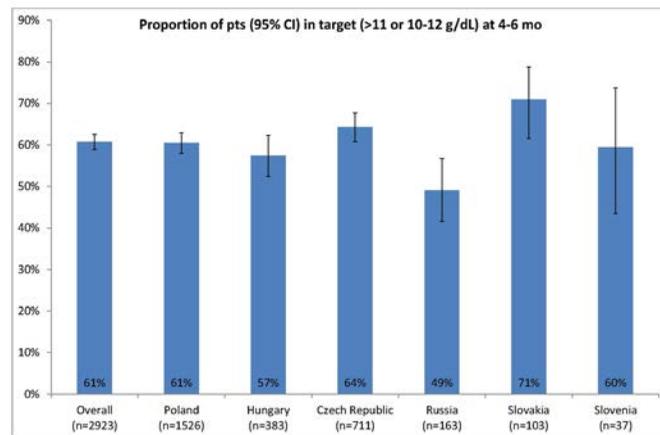
Observational Study on the Use of Darbepoetin Alfa in Hemodialysis Patients in Central Eastern Europe –ANREG Final Analysis Tomasz Jerzy Irzyniec,¹ Alena Parikova,² Alexander Selyutin,³ Botond Csiky,⁴ Jaroslav Rosenberger,⁵ Igor Rus,⁶ Kinga Jedynasty.⁷ ¹Dept of Nephrology/ENDO, MSW Hospital, Katowice, Poland; ²Dept of Nephrology, Inst for Clinical and Experimental Medicine, Prague, Czech Republic; ³B. Braun Avium, Orenburg, Russian Federation; ⁴FMC Dialysis Center, Pécs, Hungary; ⁵Nephrology and Dialysis Center Fresenius, Kosice, Slovakia (Slovak Republic); ⁶Dept of Hemodialysis/ Nephrology, General Hospital Jesenice, Jesenice, Slovenia; ⁷CEE Headoffice, Amgen GmbH, Vienna, Austria.

Background: This study observed anemia treatment patterns in HD patients (pts) treated with darbepoetin alfa (DA) in clinical practice in CEE.

Methods: Multicenter observational study in HD pts treated with DA. From 2007 to 2014, 14 cohorts were observed for 6 months (mo) each. Primary outcome: % pts maintaining an average Hb at >11 (cohorts 1/2 enrolled prior to label change in 02/2008) or 10-12 g/dL (cohorts 3-12) during mo 4-6. Secondary: conversion versus *de novo* pts, Hb trends, ESA and iron use, adverse drug reactions (ADR).

Results: Of 2923 enrolled pts (n=1101 *de novo*; n=1822 converted from other ESAs), 2647 (91%) completed 6 mo of DA, 276 (9%) discontinued (155 [5%] due to death). At baseline (BL) 83% received iron.

	all	<i>de novo</i>	conversion
Median Hb at BL, g/dL	10.2	9.5	10.5
Median Hb at 6 mo, g/dL	11.2	11.3	11.2
% with Hb >11 or 10-12 g/dL at 4-6 mo	61	61	61
% with Hb 11-12 g/dL at 4-6 mo	36	36	36



The median DA dose was 10.6 mcg/wk at mo 1 and mo 6. Approx 75% received DA i.v. and once weekly (84% at mo 1, 75% at mo 6). 12 ADR were reported (8 serious, 3 fatal: intracranial hemorrhage; myocardial infarction, death).

Conclusions: Hb increased substantially in *de novo* and conversion pts after DA initiation; >60% reached target by mo 4-6 with some variation between countries.

Funding: Pharmaceutical Company Support - Amgen

PUB316

Dysutilization of Iron for Erythropoiesis Is a Significant Predictor for Adverse Events and Survival in Maintenance Hemodialysis Patients Takahiro Kuragano, Takeshi Nakanishi. Dept of Internal Medicine Div of Kidney and Dialysis, Hyogo College of Medicine, Nisnomiya, Hyogo, Japan.

Background: Patient with high serum ferritin and low transferrin saturation (TSAT) levels could be considered as dysutilization of iron for erythropoiesis. Long-term safety iron administration to these patients has not been well studied.

Methods: Study design was the observational multicenter study for period of 3 years. In 805 patients with maintenance hemodialysis (MHD), we evaluated Hb, ferritin, TSAT levels in every 3 months, and high sensitive C reactive protein (hsCRP) and b2microglobulin (MG) levels every 6 months. We defined dysutilization of iron for erythropoiesis as the patients with lower TSAT (<20%) and higher ferritin (≥100 ng/mL) levels. The association between dysutilization of iron for erythropoiesis and adverse event was investigated with the time dependent cox hazard model.

Results: Compared with low TSAT (≤ 20%) level, patient with normal TSAT (20-30%) was significantly lower risk for cerebrovascular and cardiovascular disease (CCVD) (HR:0.25, P=0.04), and patients with higher TSAT (≥30%) were significantly lower risk for death (HR:0.12, P=0.01). In multivariate logistic regression analysis, male, younger patients, without diabetes, low hsCRP, and low b2MG were selected as significant predictors of high TSAT, but iron administration or ferritin were not. Compared with low ferritin (<100 ng/mL) and high TSAT (≥20%), patients with high ferritin (≥100ng/mL) and low TSAT (<20%)

(HR: 4.5, $p < 0.001$), and with high ferritin and high TSAT (HR: 2.9, $p < 0.001$, respectively) had a significantly higher risk of CCVD. Moreover, patients with high ferritin and low TSAT had a significantly higher risk of death (HR: 5.8, $p < 0.001$) compared with those with low ferritin and high TSAT.

Conclusions: Although patients with low TSAT had a significantly higher risk of CCVD or death, higher TSAT was not associated with iron administration or iron storages. Patients with high ferritin and low TSAT who were suspected as dysutilization of iron for erythropoiesis had a higher risk of CCVD and death. From these results, the administration of iron should be cautious to the patients with dysutilization of iron for erythropoiesis.

PUB317

Inflammatory and Metabolic Syndrome Biomarkers Analysis of Vascular Outcomes in End-Stage Renal Disease Vinod K. Bansal,¹ Patrick Sweigert,² Debra Hoppensteadt,² Jennifer Saluk,² Daneyal Syed,² Jawed Fareed.² ¹Nephrology, Loyola Univ Medical Center, Maywood, IL; ²Pathology, Loyola Univ Medical Center, Maywood, IL.

Background: The relevance of some biomarkers of inflammation and metabolic syndrome to vascular outcomes in end stage renal disease (ESRD) is not clear. To study these relationships, biochip array technology method was used to profile the complex plasma biomarkers in the setting of various comorbid outcomes such as Stroke or Transient Ischemic Attack (TIA), Acute Coronary Syndrome (ACS), Congestive Heart Failure (CHF), and Coronary Artery Disease (CAD).

Methods: Plasma samples were collected from 83 ESRD patients (mean age 65) prior to hemodialysis and were profiled using biochips for metabolic and inflammatory biomarker levels. Inflammatory cytokine and Metabolic Syndrome arrays were used to profile C peptide, ferritin, insulin, leptin, resistin, TNFa, PAI-1, IL1a, IL1b, IL2, IL4, IL6, IL8, IL10, VEGF, EGF, IFNG, and MCP1. Retrospective review was performed to group patients based on history of Stroke or TIA, ACS, CHF, and CAD.

Results: Of the 83 ESRD patients, 25 (30.1%) were found to have history of Stroke/TIA, 14 (16.9%) were found to have history of ACS, 30 (36.1%) were found to have history of CHF, and 39 (47.0%) were found to have history of CAD. Stroke/TIA patients were found to have decreased plasma IFNG levels ($p = 0.042$) and elevated plasma resistin, IL1a, and leptin levels ($p = 0.008, 0.021, 0.026$; respectively) when compared to patients without Stroke/TIA. ACS patients had elevated plasma IL6 levels ($p = 0.040$) when compared to those without ACS. CHF patients had decreased plasma leptin levels ($p = 0.031$) and elevated plasma IL1b levels ($p = 0.042$) when compared to patients without CHF. CAD patients had elevated plasma IL1a levels ($p = 0.049$) when compared to ESRD patients without CAD.

Conclusions: Profiling of multiple inflammatory and metabolic syndrome biomarkers may aid in the risk stratification of ESRD patients for cerebrovascular and cardiovascular disorders. These studies demonstrate that biomarker profiling of vascular comorbidities in ESRD may provide useful diagnostic and prognostic information in the management of ESRD patients.

PUB318

Individualized Anemia Management in Pediatric Nephrology Patients Adam E. Gaweda,¹ Jason Misurac,² Michael E. Brier,¹ Jeffrey D. Leiser.² ¹Medicine, Univ of Louisville, Louisville, KY; ²Nephrology, Riley Hospital for Children at Indiana Univ, Indianapolis, IN.

Background: Anemia management in pediatric patients on dialysis poses a great challenge to the nephrologist. In this study, we tested the hypothesis that individualized approach anemia management, previously demonstrated successfully in adult patients, improves hemoglobin maintenance within target range in pediatric dialysis patients.

Methods: We performed prospective evaluation of Clinical Decision Support System "Smart Anemia Manager" (SAM) in pediatric dialysis patients at Riley Hospital for Children at Indiana University. SAM was implemented as a stand-alone software on a desktop computer used by the nurse anemia manager and connected to a database containing Hemoglobin (Hgb) and ESA dose data. The anemia manager was allowed to override dose recommendations from the system and each override was documented. The followup period was 10 months, including 4 month washout period. We compared the hemoglobin distribution within 9-12 g/dL range during 6 months immediately before SAM implementation and 6 months after the washout period. Only patients who received ESA and had at least 4 Hgb values within each period were included in the analysis.

Results: 13 patients satisfied the inclusion/exclusion criteria. The percentage of monthly Hgb within target range varied between 82% and 92% in 6 months prior to deployment of SAM and between 69% and 100% during 6 months after SAM deployment. Quarterly Hgb distribution varied between 86% to 87% prior to SAM deployment and 87% to 95% after. There was a significant decrease in low Hgb numbers after SAM deployment, but no change in high Hgb levels, compared to the period before SAM deployment.

	Quarter	Month	< 9 g/dL	9 - 12 g/dL	> 12 g/dL	N
Pre-SAM	Q1	Nov-13	18%	82%	0%	11
	86%	Dec-13	9%	91%	0%	11
		Jan-14	15%	85%	0%	13
	Q2	Feb-14	0%	92%	8%	13
	87%	Mar-14	8%	85%	8%	13
	Apr-14	15%	85%	0%	13	
SAM	Q3	Sep-14	8%	92%	0%	13
	95%	Oct-14	0%	100%	0%	13
		Nov-14	8%	92%	0%	13
	Q4	Dec-14	0%	100%	0%	13
	87%	Jan-15	8%	92%	0%	13
		Feb-15	23%	69%	8%	13

Conclusions: Individualized anemia management in pediatric patients improves distribution of Hgb within the target range, compared to a standard population-based protocol approach.

Funding: NIDDK Support

PUB319

Extracorporeal Ultrafiltration Therapy for Acute Decompensated Heart Failure Negiin Pourafshar, Ashkan Karimi, Amir Kazory. *Medicine, Univ of Florida, Gainesville, FL.*

Background: There has been a renewed interest in the use of ultrafiltration (UF) for management of patients with acute decompensated heart failure (ADHF). While a number of studies reported on the efficacy of this therapy and lack of any significant adverse impact, the more recent trials have challenged its safety. The aim of this study is to provide a reappraisal of the current evidence on the use of UF in ADHF.

Methods: Articles cited in PubMed database from 2000 to 2015 using key words "ultrafiltration" and "heart failure" were searched. Those randomized and non-randomized trials using recent portable devices dedicated for UF were selected. Case reports, and case series were excluded. Relevant data such as renal function, cardiac status, and weight change were extracted and compared.

Results: A total 940 patients from 15 trials (7 randomized and 8 non-randomized) that used dedicated UF devices were included. Eleven studies reported either no change or non-significant decrease in serum creatinine, while 4 found worsening renal function after UF therapy; these studies had included patients with more severe renal dysfunction at baseline. Concerning weight, a reduction of 2 to 9 Kg was reported that was similar to conventional therapies in 9 studies but was significantly lower with UF in 6 trials. Length of stay was evaluated in 5 studies, 2 of which showed a significant reduction. Three studies showed fewer re-hospitalizations in the UF group at 30 days, 90 days, and 1 year follow ups. None of the studies evaluated long-term outcomes of patients undergoing UF therapy.

Conclusions: Based on the currently available data, UF is efficient for management of volume overload in ADHF. However, these studies do not support any beneficial impact for this therapy on renal function, and suggest that it might be associated with suboptimal renal outcomes if used for patients with more severe renal dysfunction at baseline. Currently there is no data on the effect of UF on long-term outcomes of patients with ADHF. Whether this would translate into a lack of effect for UF on these outcomes needs to be elucidated by future studies.

PUB320

Ultra-Sensitive Troponin I Predictive Value in Remote Ischemic Pre Conditioning in Hemodialysis: A Randomized Double Blinded Clinical Trial Marcelo Rodrigues Bacci, Livia Yadoya Vasconcelos, Felipe R. Bruniera, Felipe Moreira Ferreira, Neif Murad, Antonio Carlos palandri Chagas, Fernando Luiz affonso Fonseca. *ABC Medical School, Brazil.*

Background: Remote ischemic cardiac preconditioning (RIPC) is a procedure that generates a brief period of ischemia followed by reperfusion. Areas submitted to RIPC in the experimental ischemia models have less occurrence of necrosis. RIPC role in protecting myocardial ischemia during hemodialysis is not established yet. The aim of the study was to evaluate RIPC as myocardial protection evaluated by ultra sensitive I troponin in hemodialysis outpatients.

Methods: It is a double blind randomised trial with two groups: intervention; submitted to RIPC with external compression in the right arm with sphygmomanometer with 200mm/Hg of pressure with three-5 minute rounds alternating with deflation totalling 30 minutes and control group; without RIPC. Intervention group received RIPC in three consecutive hemodialysis sessions. Blood samples were taken before and after each session. Randomization was made by a software stratified by sex and age. BUN for calculation of single pool Kt/v and ultra sensitive I troponin were measured to evaluate dialysis adequacy and myocardial injury.

Results: A total of 47 patients were randomized. About 60.8% were men and 54% diabetic. The mean single pool Kt/v was 1.51 in the intervention group and 1.49 in control.

There was a trend to higher mortality in the control group(26%,p=0.09).The ultra sensitive troponin I measured no significant change from the time of collection: before or after dialysis, however it showed a high negative predictive value in all models tested.

Conclusions: The RIPC applied in 3 consecutive sessions did not demonstrate superiority to control therefore another study tested RIPC in 12 consecutive sessions with a positive result in myocardial protection with RIPC. In our study more than half of the patients were diabetic. Diabetic patients have a trend to show a lower response to RIPC because of the greater presence of collateral coronary circulation. In summary, in this model there was no interference of RIPC in ultra sensitive troponin I values but troponin had a high negative predictive value for myocardial infarction in all tested models.

Funding: Government Support - Non-U.S.

PUB321

Racial Differences in the Evolution of Subclinical Cardiovascular Disease from CKD to ESRD: The CRIC Study Nisha Bansal,¹ Jason Roy,² Hsiang-Yu Chen,² Alan S. Go,³ Martin Keane,⁴ Rajat Deo,² Elyse Foster,⁵ Sankar D. Navaneethan,⁶ Jiang He,⁷ Mahboob Rahman,⁸ Mirela A. Dobre,⁸ John W. Kusek,⁹ Michael J. Fischer,¹⁰ Emile Mohler,² Chi-yuan Hsu.⁵ ¹UW; ²UPenn; ³KPNC; ⁴Temple; ⁵UCSF; ⁶Case Western; ⁷Tulane; ⁸UH; ⁹NIDDK; ¹⁰UIC.

Background: Studies have reported that black incident dialysis patients have better survival compared with white dialysis patients, even after accounting for adverse profile of comorbidities among blacks. We hypothesized that differences in subclinical cardiovascular disease (CVD) may explain this paradox.

Methods: We studied incident dialysis patients in the CRIC study who had a research echocardiogram performed before and after the initiation of dialysis. Left ventricular mass index (LVMI) and ejection fraction (LVEF) were measured at CKD (mean eGFR 24 ml/min/1.73 m²) and at dialysis initiation (median time after initiation 7.9 months).

Results: Of 316 participants, 74% were black and 26% were white. After initiation of dialysis, there were 88 deaths. In multivariable models, black (vs. white) race was independently associated with a 38% (95% CI: 1%, 61%) lower risk of mortality. From CKD to incident dialysis, mean LVEF worsened in whites (51±10% to 47±11%; p-value for change <0.0001) and blacks (52±9% to 48±10%; p <0.0001). LVMI trended worse in whites (54±16 g/m^{2.7} to 57±15 g/m^{2.7}; p=0.1) and significantly improved in blacks (61±16 g/m^{2.7} to 58±13 g/m^{2.7}; p=0.004). Adjusting for LVMI, change in LVMI, LVEF and change in LVEF did not change the association between black race and lower risk of death.

Association of race for risk of mortality after initiation of dialysis

	Model 1*	Model 1 + LVMI at incident ESRD	Model 1 + change in LVMI from CKD to ESRD	Model 1 + LVEF at incident ESRD	Model 1 + change in LVEF from CKD to ESRD
White	ref	ref	ref	ref	ref
Black	0.62 (0.39, 0.99)	0.55 (0.32, 0.94)	0.57 (0.32, 1.0)	0.57 (0.35, 0.94)	0.60 (0.36, 0.99)

*adjusted for gender, age, tobacco use, systolic blood pressure, body mass index, diabetes, and history of cardiovascular disease

Conclusions: In CRIC, black dialysis patients had better survival than whites. This association was not explained by differences in subclinical CVD at incident dialysis or by differences in the evolution of CVD from CKD to ESRD. Further studies are needed to understand mechanisms underlying the differential survival by race among dialysis patients.

Funding: NIDDK Support

PUB322

Study Design and Baseline Characteristics in the “Outcome Study of Lanthanum Carbonate (LC) Compared with Calcium Carbonate (CC) in Hemodialysis (HD) Patients (LANDMARK) Study” Hiroaki Ogata,¹ Masafumi Fukagawa,² Hideki N. Hirakata,³ Tatsuo Kagimura,⁴ Tadao Akizawa.¹ ¹Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan; ²Div of Nephrology, Endocrinology, and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; ³Div of Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; ⁴Translational Research Informatics Center, Kobe, Japan.

Background: The LANDMARK study is planned to elucidate whether a non-calcium (Ca)-based phosphate (P) binder, LC treatment reduces cardiovascular (CV) mortality and morbidity compared with a Ca-based P binder, CC treatment in HD patients.

Methods: This is a multicenter, randomized, open-label, parallel comparative study between LC and CC (NCT01578200/UMIN000006815). Adult HD patients who had at least one of following criteria: age>65 yrs, postmenopausal women, or type 2 diabetes mellitus with intact parathyroid hormone (iPTH) ≥240pg/mL and life expectancy ≥3 years, were eligible. In LC group, patients initially received LC of 750mg/day or previous used dose and were titrated up to a maximum of 2250mg/day to achieve serum P levels of 3.5-6.0mg/dL. In CC group, patients received CC of 3g/day or previously used dose, and were titrated to achieve same P range as LC group. If serum P level was not achieved within the target with maximum tolerated dose, non-Ca-based P binders (other than LC) could be also added in CC group. The primary endpoint is the CV events (CV death, non-fatal myocardial infarction and stroke, unstable angina, hospitalization for heart failure and ventricular arrhythmia) free survival time.

Results: 2309 patients were allocated to LC (N=1154) or CC group (N=1155). At baseline, mean age was 68.7 yrs, 40.6% were female and 51.7% were diabetes. 13.4% had a history of ischemic heart disease, and 13.3% had cerebrovascular disease. 8.0% had undergone coronary intervention procedure. Mean serum Ca, P and iPTH concentrations were 8.9mg/dL, 5.4mg/dL, and 122.4pg/mL, respectively. Baseline characteristics were well balanced between the two groups.

Conclusions: The LANDMARK study will determine whether a non-Ca-based P binder, LC, reduce CV mortality and morbidity in HD patients.

Funding: Pharmaceutical Company Support - Bayer Yakuhin, Ltd

PUB323

The Relationship Between Prescription of Ultrafiltration in Hemodialysis and Intradialytic Hypotension: A Retrospective Study of Chinese Hemodialysis Patients Fei Deng, Daqing Hong, Guisen Li, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: Our study aims to explore the relationship between prescribed ultrafiltration and intradialytic hypotension (IDH) and, to demonstrate risk factors of intradialytic hypotension in order to reduce the incidence of relevant complications and improve patient prognosis.

Methods: 312 patients maintenance hemodialysis patients in our dialysis center were enrolled with 33224 HD/HDF treatment sessions recorded. Hypotension was defined as a decrease of systolic blood pressure >20mmHg or mean arterial pressure decline ≥10 mmHg whether presence of hypotensive symptoms or not. ROC curve was applied to study the cut-off point of UF/Wt (ultrafiltration/weight) ratio for the presence of hypotension. Pearson analysis and logistic regression was used to study the risk factor associated with hypotension.

Results: The prevalence of intradialytic hypotension was 38.7%. Decrease of SBP and MAP positively correlated with UF/Wt and age, and negatively correlated with blood flow. The cut-off point of UF/Wt was 4% for all patients, diabetes and non-diabetic patients with AUCs of 0.575, 0.570, and 0.622 respectively. The AUC for diabetic patients was higher than that of non-diabetic patients (P<0.001). Multivariate logistic regression showed that age (OR=1.005, 95%CI: 1.004-1.007), diabetes (OR=1.209, 95%CI: 1.122-1.303), and UF/Wt>4%(OR=1.605, 95%CI:1.532-1.682) was associated with hypotension.

Conclusions: Asymptomatic intradialytic hypotension is prevalent. Increased intradialytic SBP/MAP variability is associated with greater UF and UF/Wt, but is not associated with greater blood flow. To Chinese hemodialysis patients, UF/Wt>4% is sensitive and specific in predicting intradialytic hypotension, especially in patients with diabetes mellitus. UF/Wt>4%, diabetes mellitus and age are independent risk factors for asymptomatic intradialytic hypotension.

PUB324

Whole Blood Viscosity at Low Shear Rate Is Associated with Cardiovascular Mortality in Patients with Hemodialysis Jong-Hwan Jung,¹ Dong Hwan Lee,² Young I. Cho,³ Kyung Pyo Kang,¹ Sik Lee,¹ Sung Kwang Park,¹ Won Kim.¹ ¹Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Republic of Korea; ²Dept of Mechanical Design Engineering, Engineering College, Chonbuk National Univ, Jeonju, Republic of Korea; ³Dept of Mechanical Eng. and Mechanics, Drexel Univ, Philadelphia, PA.

Background: The change of whole blood viscosity (WBV) may increase risk of major atherosclerotic events, including congestive heart failure, myocardial infarction, and stroke. However, there is few report about the relationship between WBV and mortality rate due to atherosclerotic vascular disease. The objective of the present study was to investigate correlation between values of WBV at shear rates of 1, and 5 S⁻¹ before and after hemodialysis in patients with end-stage renal disease (ESRD) and mortality; especially cardiovascular or cerebrovascular mortality.

Methods: Forty three patients with ESRD receiving maintenance hemodialysis had initially participated in this study. In a prospective observational study, we examined the effect of WBV in pre- or post-dialysis on cardiovascular or cerebrovascular mortality in dialysis patients for approximately 5.8 years.

Results: Twenty seven patients among total 43 patients died and 2 patients had received transplantation of kidney within period of this study. Cardiovascular deaths occurred in 8 patients among 27 patients, and cerebrovascular deaths occurred in 5 patients among the 27 patients. The hazard ratios for overall survival in the patient with hemodialysis according to increase of predialytic diastolic WBV at low shear rate of 1 S⁻¹ in an univariate Cox proportional analysis were 1.585 (95% CI, P=0.382) in the group of moderate blood viscosity and 2.351 (95% CI, P=0.128) in the group of high blood viscosity. However, pre-DBV1 was not still statistically significant after adjustment for covariates. In addition, the HRs for overall survival according to increase of pre-DBV5 were 1.527 and 1.930 in each moderate and high blood viscosity group. In Kaplan-Meier’s survival analysis, when pre-DBV1 increased, cumulative mortality relatively showed rising tendency, but, unfortunately there was no statistical significance.

Conclusions: These results suggest that the diastolic low-shear WBV may impact on cardiovascular or cerebrovascular mortality in hemodialysis patients. New prospective and large-scaled studies to more exactly evaluate the correlation between WBV and mortality will be needed in the future.

PUB325

Survival of Patients Over 75 Years Old in a Chronic Hemodialysis Program

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Background: The intensity of medical care for people over 75 years of age has increased over the past decade. In this surrounding context is increasing the number of individuals with this profile that has clinical indication starting renal replacement therapy. Published data have shown a varied patient survival after initiation of hemodialysis (HD) according to the presence of comorbidities. The aim of this study was to evaluate the survival of elderly patients with chronic kidney disease on regular HD.

Methods: From analysis of medical records was assessed the rate of survival of incident patients in a chronic HD program from 2000 to 2010. Demographic and clinical data were also collected. It was made a comparison, based on these data, among the elderly (over 75 years old) and non-elderly groups who died.

Results: During the study period, 158 patients started HD program, 69% male and 46% were older than 75 years. The overall mortality rates at 6 and 12 months were, respectively, 7.5% and 17%. Considering only the elderly, mortality rates at 6 and 12 months were respectively 14 and 27%. The median survival of these patients was 33 months. Considering only patients younger than 75 years mortality rates at 6 and 12 months were, respectively, 2% and 8%. Comparing elderly patients with non-elderly, we observed that the first group had a higher proportion of diabetic and hypertensive patients and with a history of cardiovascular disease and cancer. Considering only the patients who died, there were no important significant differences in the presence and score of comorbidities, when the elderly was compared with the non-elderly.

Conclusions: Patients over 75 years in HD had a mortality rate two times higher than younger patients and the presence of comorbidities may be a contributing factor to the age to explain this data.

PUB326

The Difference of Cognitive Function and Brain Magnetic Resonance Findings Between Chronic Hemodialysis and Peritoneal Dialysis Patients

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Background: Cognition decline and cerebrovascular lesions has been gradually realized by clinicians nowadays. But it is still not clear whether there are some difference in cognitive function and cerebrovascular disease between chronic hemodialysis (HD) and peritoneal dialysis (PD) patients.

Methods: This is a cross-sectional study in a single center. 124 HD patients and 74 PD patients were recruited. Cognitive function was evaluated with Chinese-MMSE and Chinese-MoCA. MR images and MR Angiography were assessed. Demographic information, Clinical features, laboratory data were collected. Results were analyzed with SPSS.

Results: (1) Age, gender and educational level were comparative between HD and PD patient. Average age was 56.2±13.2 yrs and 56.6±16.1 yrs, respectively in HD and PD groups. (2) Average dialysis voltage was longer in HD than PD group, 70.0±60.6 months v.s. 40.7±35.7 months. Average blood pressure was 136.7/79.6±19.5/11.3 v.s. 138.4/76.7±21.4/11.8 mmHg, Hgb was 110.9±13.7 v.s. 114.0±13.6 g/L, SCr 961.1±251.2 v.s. 857.0±276.6 umol/L, Alb 39.6±3.9 v.s. 35.4±3.8 g/L, respectively in HD and PD groups. SCr and Alb level was higher in HD group (P<0.05). (4) In cognitive function evaluation, HD compared with PD groups, MMSE score was 28.0±2.5 v.s. 29.6±3.1 (p=0.84), MoCA score was 22.7±4.4 v.s. 21.1±5.7 (p=0.108), respectively. (5) For the brain MR results, in severity of brain artery stenosis, number of cortical infarcts, lacunar infarcts, microbleeds, chronic hematoma and Fazeka score of brain white matter lesions, only artery stenosis is more severe in PD groups (P<0.05). For the two kinds of bleeding lesions, there was a more severe tendency in HD group, but there was a more severe tendency of two kinds of ischemic lesions in PD group. (5) MoCA Score was relative to SCr and Alb, negative relative with age, artery stenosis, lacunar infarcts and WMLs.

Conclusions: Compared with HD patients, there was a tendency of more severe cognitive function decline in PD patients. Also we found a tendency of more brain bleeds lesions in HD patients, on the contrary, a tendency of more ischemic lesion in PD patients. But we need a larger sample size to prove those.

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PUB327

Paucity of Evidence for Use of Postmenopausal Hormone Therapy for Cardiovascular Prevention in Women with Chronic Kidney Disease: A Systematic Review

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Background: Women with chronic kidney disease (CKD) have low sex hormone levels due to kidney-mediated endocrine disturbances, and are at increased risk of cardiovascular adverse events. Whether postmenopausal hormone therapy (PHT) alters cardiovascular risk in this population is unknown. We aimed to summarize current knowledge about the association between use of PHT and (1) cardiovascular outcomes, and (2) established cardiovascular risk factors, in women with CKD.

Methods: Setting and population: Adult women with CKD (eGFR≤90 mL/min/1.73m²) **Selection Criteria for Studies:** Randomized control trials and observational

studies, studying PHT with either placebo or untreated control groups. **Outcome measures:** All-cause and cardiovascular mortality, non-fatal cardiovascular event (myocardial infarction, stroke), and surrogate measures of cardiovascular risk (blood pressure, serum lipids).

We searched electronic bibliographic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials) (inception to 2014 September), relevant conference proceedings, tables of contents of journals and review articles.

Results: Of 2928 references retrieved, 4 RCTs (N=142 patients) were identified. No studies reported on cardiovascular outcomes or mortality. Three studies examined the effect of PHT on lipid profile (mean age 60 years, all patients end-stage kidney disease on dialysis). Compared with placebo, PHT led to increased high density lipoprotein cholesterol (weighted mean difference (WMD) 0.82 mmol/L 95% CI: 0.47, 1.17), but no difference in low density lipoprotein (WMD -0.39 mmol/L 95% CI: -0.85, 0.07) or total cholesterol levels (WMD 0.11 mmol/L 95% CI: -0.23, 0.45). One study examined the effect of PHT on blood pressure, with PHT causing no change in blood pressure.

Conclusions: Studies examining the effect of PHT on cardiovascular outcomes in women with CKD are lacking. Further prospective study of the role of PHT in improving cardiovascular outcomes in this high-risk group is required.

Funding: Private Foundation Support

PUB328

Prevalence of Abnormal Ankle – Brachial Index in Haemodialysis Patients in Mexico and Its Association with Other Cardiovascular Risk Factors

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Background: Abnormal Ankle-Brachial index (ABI), defined as ≤ 0.9 or ≥ 1.3, is considered an independent predictor of mortality in hemodialysis patients, in other countries abnormal ABI is found between 35% and 80 % of hemodialysis patients. In Mexico the prevalence of abnormal ABI has not been reported. The aim of the study was to determine the frequency of abnormal ABI and its association with other cardiovascular risk factors.

Methods: Prevalent hemodialysis patients over 16 years old were included; data were obtained from medical records and interviews. ABI was measured by oscillometry (Model HEM-705CPINT) and classified as a normal result between 0.91 - 1.3 (NABI), ≤ 0.9 (LABI) or ≥ 1.3 (HABI). NABI was considered as the control group and the data were analyzed using descriptive and inferential statistics, using T Student and Chi2.

Results: Of the 119 patients analyzed abnormal ABI was present in 36 (30%); 10 (8.4%) with LABI and 26 (21.9%) with HABI. The mean age was 44.9 years, 68% were male, duration of dialysis of 7.1 years. In univariate analysis LABI was significantly associated with older age (p=0.03), smoking history (p<0.001), diabetes mellitus (DM) (p=0.04), lower creatinine (p<0.001) and albumin (p<0.001) and higher calcium (p<0.001); HABI was significantly associated with lower age (p=0.01), smoking history (p=0.05), lower systolic blood pressure (SBP) (p=0.02), high levels of sodium (p=0.04) and calcium (p=0.001). No association was found between abnormal ABI and history of hypertension, dyslipidemia, heart disease, stroke; there were no differences with the dose of calcium carbonate or calcitriol, the value of Kt / V, the type of vascular access and serum phosphorus.

Conclusions: Abnormal ABI was less prevalent than in other populations, among these HABI is the most common. LABI was associated with older age, DM, smoking history, high calcium and low creatinine and albumin (probably associated with poor nutritional status). HABI patients were younger, with smoking history, lower SBP, high serum sodium and calcium levels.

PUB329

A Lower Serum Uric Acid Is Associated Not Only with All-Cause Mortality but Also Cardiovascular Mortality Among Patients Receiving Hemodialysis in Japan

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Background: High level of serum uric acid is prevalent in chronic kidney disease (CKD), however it has a controversy whether high or low serum uric acid level appears to be a risk factor of cardiovascular event and mortality in the patients of receiving renal replacement therapy.

Methods: We collected the baseline data of 222,434 patients receiving HD thrice weekly (males: 63.0%, 66 ± 12 years, median HD vintage of 60 months, females: 68 ± 13 years, median HD vintage of 72 months) extracted from a nationwide dialysis registry at the end of 2011 in Japan. Then we evaluated the patient survival and development of complication using the registry at the end of 2012.

Results: During one-year follow-up, 18775 (8.4%) died of all causes including 8094 (3.6%) cardiovascular death. All-cause mortality, and cardiovascular mortality were lower in line with the increase of baseline uric acid. In a multivariable logistic regression analysis, patients of the highest quartile of uric acid had lower all-cause, and cardiovascular mortality compared with those of the lowest quartile (males: OR, 0.745; 95% CI, 0.6753 to 0.8207, females: OR, 0.8333; 95% CI, 0.7206 to 0.9636, and males: OR, 0.7202; 95% CI, 0.6266 to 0.8278, females: OR, 0.8575; 95% CI, 0.7029 to 1.0462, respectively).

Conclusions: In this large observational cohort study, lower levels of serum uric acid were independently associated not only with all-cause mortality but also cardiovascular mortality among Japanese HD patients. Close monitoring of serum uric acid is thought to be necessary for the management of HD patients.

PUB330

Post Stroke Disability Deterioration and Mortality of Hospital Onset Stroke in Patients with and without End-Stage Renal Disease Tomoko Usui,¹ Norio Hanafusa,¹ Hideo Yasunaga,² Masaomi Nangaku.¹ ¹Dept of Hemodialysis and Apheresis, The Univ of Tokyo Hospital, Japan; ²Dept of Clinical Epidemiology and Health Economics, School of Public Health, the Univ of Tokyo, Japan.

Background: Increasing evidence suggests that end-stage renal disease is associated with higher risk and severity of cerebrovascular disease. However, the risk factors for post stroke disability and mortality is not clear. We examined the association between risk factors including dialysis treatment and disability deterioration and mortality during the hospital stay of hospital onset stroke.

Methods: The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data of about 50% of all acute-care inpatients in Japan. Using this database, we extracted data of inpatients age ≥ 20 years old, hospital-onset stroke between July 2010 and March 2013. Disability level was divided into modified Rankin Scale (mRS) 0-1, 2-3, 4-5, and 6 (death). Deterioration of disability was defined as an increase in disability level. The odds ratio (OR) for in-hospital deterioration of disability and mortality was calculated using a logistic regression model.

Results: Out of 26,834 patients, 593 (2.2%) had dialysis therapy. The median length of stay was 39 and 33 days for patients with and without dialysis, respectively. During the hospital stay, there were 7,655 (28.5%) disability deterioration and 3,851 (14.4%) death. The patients with dialysis had higher disability deterioration (47.0%) and mortality rate (31.3%) compared to those without. After adjustment with age, gender, BMI, mRS, Activities of Daily Living, smoking habits, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular complications, antiplatelet, anticoagulant, and thrombolytic medications, multivariate-adjusted ORs of dialysis for disability deterioration was 2.88 (95%CI 2.40-3.45), and in-hospital mortality was 3.57 (95%CI 2.94-4.33).

Conclusions: Dialysis treatment was an independent risk factor for in-hospital disability deterioration and mortality of hospital onset stroke.

PUB331

Role of Bioimpedance as Tool for Fluid Management in Hemodialysis Patients Maria Cecilia Recalde,¹ Manuela Bello,¹ Cecilia Arruabarrena,¹ Alvaro Herou,¹ Fabian Cano,² Laura Solá.^{1,2} ¹Hemodialysis Unit, CASMU, Uruguay; ²Preventive Medicine, Univ of the Republic, Uruguay.

Background: Fluid management in hemodialysis patients is difficult, hypertension and fluid overload is frequent as well as hypotensive episodes leading to cerebral and cardiac injury and increased mortality risk. The objective of the study is to evaluate if bioimpedance could be a tool to optimize fluid management in hemodialysis patients.

Methods: Patients were included after giving informed consent when fulfilled inclusion and exclusion criteria. Were recorded age, gender, diabetes status, dialysis vintage, body mass index (BMI) estimated dry weight, and mean in previous month: systolic blood pressure (SBP), diastolic blood pressure (DBP), interdialytic weight gain, ultrafiltration volume (UF VOL), hypotensive episodes and use of antihypertensive drugs. A multi-frequency bioimpedance device (BCM Fresenius Medical Care) was used to evaluate fluid overload. Patients were categorized according post dialysis fluid overload and analyzed regarding SBP, DBP, hypotensive episodes and drugs. Data were analyzed in free software (epi info 7). Quantitative data were expressed as mean \pm standard deviation and compared by t test, and categorical variables were compared by chi square. Were considered significant differences when $p < 0.05$.

Results: Fifty patients were included, 32 (64%) men, age 66.1 ± 13.1 years, 14 (28%) diabetics, and BMI 30.9 ± 9.5 . Mean SBP 128 ± 13 , DBP 72 ± 8.0 , interdialytic weight gain 2.1 ± 0.1 kg, and UF VOL 2.0 ± 0.9 lts. Of them 26 patients (52%) had hypotensive episodes, and 29 (58%) were on antihypertensive drugs. Only 5 patients had mean SPB³140, of which 4 were overhydrated postdialysis. None had DPB ≥ 90 . The 22 (44%) patients with weight below the estimated by BMC presented more frequent hypotensive episodes during dialysis ($p < 0.05$), and had significant higher mean BMI (33.9 vs 27.5), UF VOL (2.3 vs 1.7 l) and weight gain (2.4 vs 1.7). No association was found between interdialytic weight gain and SPB ≥ 140 .

Conclusions: Obtaining tight SBP and DBP was accompanied with reduced total body water and frequent hypotensive episodes. Adjusting dry weight according BMC estimation could improve dialysis tolerance.

PUB332

Effect of Renin Angiotensin Aldosterone System Blockade on Clinical Outcomes in Patients with End-Stage Renal Disease: A Prospective Cohort Study in Korea Kyung Don Yoo,¹ Jung Pyo Lee,¹ Jung Nam An,¹ Yun Kyu Oh,¹ Shin-Wook Kang,² Chul Woo Yang,³ Yong-Lim Kim,⁴ Chun Soo Lim,¹ Yon Su Kim.¹ ¹Seoul National Univ College of Medicine; ²Yonsei Univ College of Medicine; ³The Catholic Univ of Korea College of Medicine; ⁴Kyungpook National Univ School of Medicine.

Background: Adequate blood pressure control plays a key role in the management of patients with end-stage renal disease (ESRD). Although renin angiotensin aldosterone system (RAAS) blockade is known as the best treatment option for chronic kidney disease with hypertension, there is debate in the ESRD patients maintaining dialysis.

Methods: A total of 5,223 patients in the Clinical Research Center for ESRD (CRC for ESRD) prospective observation cohort from Aug 2008 to Dec 2014 were enrolled to this study. We compare overall survival and major cardiovascular event (MACE)-free survival between RAAS group and control group for using 1:1 propensity score matching (PSM) analysis. We defined the RAAS group as using ACE inhibitor or angiotensin receptor blocker more than 3month.

Results: Before matching, the RAAS group was younger; however, had more comorbidities such as diabetes and cardiovascular disease. The RAAS group had higher systolic blood pressure and was prescribed more number of other antihypertensive drugs than control group. After matching, there were no differences in age, sex, dialysis modalities, comorbidities and number of other antihypertensive medications. Before PSM, patient survival was significantly better in the RAAS group using the Gehan-Wilcoxon test ($P=0.001$), however, this difference disappeared after matching ($P=0.450$). Cardiovascular event-free survival was not different between RAAS group and control group before and after PSM analysis.

Conclusions: RAAS blockade did not affect all-cause mortality and MACE-free survival in the Korean ESRD patients. Further researches such as randomized control study will be needed.

PUB333

Lipidemic Profile and Sleep Apnea Syndrome in Hemodialysis Patients Olga Nikitidou,¹ Vassilios Liakopoulos,¹ Aikaterini A. Papagianni,² Euphemia Daskalopoulou,³ Nicholas V. Dombros.¹ ¹Div of Nephrology and Hypertension, 1st Dept of Internal Medicine, AHEPA Hospital, Aristotle Univ of Thessaloniki, Thessaloniki, Greece; ²Dept of Nephrology, Hippokraton Hospital, Aristotle Univ of Thessaloniki, Thessaloniki, Greece; ³Sleep Laboratory, "Aghios Pavlos" General Hospital, Thessaloniki, Greece.

Background: Dyslipidemia, characterized by low high density lipoprotein-HDL, high triglyceride-TG levels and normal levels of low density lipoprotein-LDL, is one of the traditional cardiovascular risk factors in hemodialysis-HD patients. On the other hand, sleep apnea syndrome-SAS, which is very common in this population, is one of the newest non-traditional cardiovascular risk factors. We investigated the impact of SAS and nocturnal hypoxia on the lipidemic profile of HD patients.

Methods: 37 HD patients (23 males) participated in the study. The night between two consecutive midweek HD sessions, they underwent an overnight polysomnography study. The following morning fasting blood samples were obtained and serum levels of total cholesterol-TC, TG, LDL, HDL, apolipoprotein A-apo A, apolipoprotein B-apo B and lipoprotein α -Lp (α) were measured.

Results: We investigated the correlation of the patients' lipidemic profile with their characteristics [age, Body mass index-BMI, duration of HD] and their sleep parameters [Apnea/Hypopnea Index-AHI, Respiratory Disturbance Index-RDI, Desaturation Index-DI, mean and minimum SpO₂, percentage of sleep time with SpO₂<90%and total sleep time] and found that: 1) TC correlated negatively with minimum SpO₂ ($r=-0.454$, $p=0.005$), 2) TG correlated positively with BMI ($r=0.490$, $p=0.002$) and RDI ($r=0.438$, $p=0.007$), 3) HDL correlated negatively with duration of HD ($r=-0.350$, $p=0.037$) and BMI ($r=-0.391$, $p=0.02$), 4) apo A correlated negatively with duration of HD ($r=-0.344$, $p=0.046$), 5) Lp (α) correlated negatively with minimum SpO₂ ($r=-0.364$, $p=0.034$) and 6) LDL and apo B showed no correlation.

Conclusions: The results of the present study indicate that in HD patients with SAS the severity of the syndrome and the nocturnal hypoxia correlates with many parameters of their lipidemic profile which might contribute in the augmented cardiovascular risk in this population.

Funding: Government Support - Non-U.S.

PUB334

Hemodynamic Changes in Maintenance Hemodialysis Patients with Intradialytic Hypotension Meijuan Meng, Hong Ye, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Intradialytic hypotension (IDH) is a common complication in patients undergoing maintenance hemodialysis (MHD) which leads to high mortality. This study is to explore the hemodynamic changes in MHD patients with IDH.

Methods: Thirty-seven patients were included in our study. IDH were defined as a decrease of systolic blood pressure (SBP) >20 mmHg or the lowest SBP below 90 mmHg during dialysis. Twenty-three patients were diagnosed with IDH. Among them, 13 were

asymptomatic while the other had the hypotensive symptoms, such as abdominal discomfort, sighing, nausea, vomiting, muscle cramps and restlessness. All of them underwent a noninvasive hemodynamic evaluations before, during and after dialysis.

Results: Compared to the patients without IDH, the dialysis age was longer and the prevalence of diabetes was higher in the patients with IDH. There were no difference in age, amount of ultrafiltration, pre-dialysis cardiac index (CI), systemic vascular resistance index (SVRI) and thoracic fluid capacity (TFC) between these two groups. During dialysis, CI decreased while SVRI increased gradually especially in patients with IDH. At the end of dialysis, ΔCI was markedly higher in patients with IDH. However, there was no significant difference in the change of CI, SVRI and TFC ten minutes before and after hemodialysis between these two groups. Meanwhile, the hemodynamic changes were analyzed in IHD patients with or without symptoms. It was found that there were no difference of change values and absolute values of CI and SVRI in these subgroups.

Conclusions: It was found that CI decreased while SVRI increased during hemodialysis. In the mid and later period, the CI decreased much more in patients with IDH. It was suggested that CI might be an indicator of IDH.

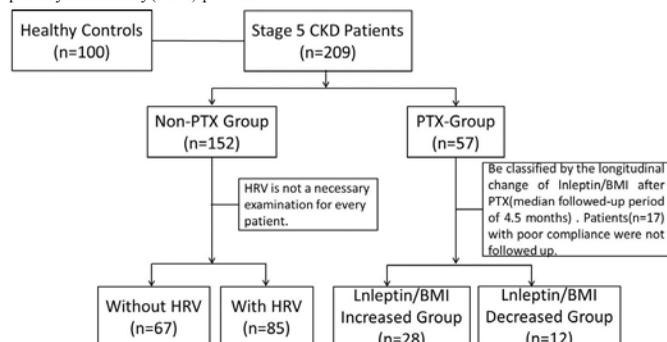
Funding: Government Support - Non-U.S.

PUB335

Dual Relationships of Serum Leptin on Heart Rate Variability in Patients with Stage 5 Chronic Kidney Disease Ningning Wang, Yao Jiang, Jingjing Zhang, Changying Xing. *Nephrology, First Affiliated Hospital of Nanjing Medical Univ, Nanjing, China.*

Background: Leptin regulates nutrition, bone metabolism and cardiovascular function. Lower heart rate variability(HRV) in chronic kidney disease(CKD) predicts higher risk of cardiovascular disease(CVD).Relationships between leptin and HRV in CKD is obscure.

Methods: This included cross-sectional observation and longitudinal followed-up on parathyroidectomy(PTX) patients.



Serum leptin/BMI is transformed using natural logarithm(Inleptin/BMI).

Results: Inleptin/BMI showed no difference between stage 5 CKD and controls. However, quartile 2 of Inleptin/BMI level in CKD patients prone to have higher HRV indices

Quartile	1(n=34)	2(n=33)	3(n=36)	4(n=39)	P
Mean 24-h HR (beats/min)	87.4±12.7	79.4±11.6	81.9±10.5	81.1±9.2	0.020
Time domain measures					
Mean NN(ms)	702.1±103.2	772.3±118.3	740.9±100.9	754.6±86.2	0.039
SDNN(ms)	72.0±33.9	78.2±33.8	73.4±24.3	73.1±22.3	0.827
SDANN(ms)	64.5±32.9	72.3±31.6	64.5±23.1	62.9±19.1	0.483
rMSSD(ms)	17.5±9.8	21.4±9.7	16.4±7.1	20.0±10.5	0.111
pNN50(%)	2.8±6.1	3.8±4.2	1.8±2.9	4.2±6.4	0.212
Frequency domain measures					
ln VLF	5.3±1.1	5.6±0.9	5.5±0.8	5.5±1.0	0.609
ln LF	3.7±1.5	3.9±1.3	3.8±1.4	3.7±1.4	0.945
ln HF	2.7±1.5	2.7±2.0	2.6±1.9	2.5±2.1	0.944
ln LF/HF	0.9±0.9	1.1±1.1	1.2±0.9	1.2±1.2	0.720

Inleptin/BMI in PTX group is correlated with serum Ca, P and PTH. Compared with Inleptin/BMI decreased group, Inleptin/BMI increased group has higher serum PTH before PTX and their HRV indices were significantly elevated after PTX.

Conclusions: Serum leptin has dual relationships with HRV and keeping its proper level contributes to reduce CVD in stage 5 CKD. PTX can reverse above disorders in severe SHPT patients.

Funding: Government Support - Non-U.S.

PUB336

Association of Geriatric Nutritional Risk Index and Responsiveness to Erythropoiesis-Stimulating Agent in Mortality of Chronic Hemodialysis Patients Kosaku Nitta, Ken Tsuchiya. *Dept of Medicine, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan.*

Background: Responsiveness to erythropoiesis-stimulating agent (ESA) may be associated with mortality in hemodialysis (HD) patients. The aim of the present study was to assess the effects of geriatric nutritional risk index (GNRI) and responsiveness to ESA in outcome in HD patients.

Methods: The ESA resistance index (ERI) was determined as the weekly weight-adjusted dose of ESA divided by hemoglobin concentration. Patients were divided into four groups by quartiles of ERI. Odds ratios were estimated using a Cox proportional model for the association between GNRI and ERI and mortality, adjusting for potential confounders. Patients were divided into four groups by quartiles of ERI.

Results: Of the 298 subjects enrolled, 51 died with 31 cardiovascular deaths during the follow-up period of 34.6 ± 6.1 months. The ERI was inversely correlated with the GNRI (r = 0.287, p <0.0001). Age, gender, serum total cholesterol, phosphorus levels, transferrin saturation and GNRI were independent predictors of ERI. Older age, female gender, serum total cholesterol, transferrin saturation and GNRI were independent predictors for ESA hyporesponsiveness. Receiver operating curve analyses indicated the cut off values of GNRI and ERI for mortality were 94.9, 13.5, respectively. When subjects were stratified by ERI and GNRI value into four groups, those who had low GNRI and high ERI were associated with the highest risk of mortality among the four groups (log-rank p <0.001).

Conclusions: high ERI and low GNRI were associated with an increased risk of all-cause mortality.

PUB337

A Multidisciplinary Approach Is Required to Reduce Hospitalizations for Cardiovascular Disease in Maintenance Hemodialysis Patients David L. Epstein,^{1,2} Thomas Parker,^{1,2} Daniel Levine,^{1,2} Jeffrey I. Silberzweig,^{1,2} *Medicine, The Rogosin Inst, New York, NY; ²Medicine, Weill Cornell Medical College, New York, NY.*

Background: Patients receiving maintenance hemodialysis have hospital admissions rates significantly greater than patients with other chronic diseases¹. Approximately 40% of the hospital admissions are related to cardiovascular disease including both acute events and pulmonary edema¹. We sought to assess the contribution of fluid weight gains to hospital admissions.

Methods: We compared inter-dialytic weight gains as a percentage of target weight and changes in blood pressure for the approximately 1200 patients receiving maintenance hemodialysis in our seven dialysis clinics in New York City between January and April 2015. We compared these data to total and cardiovascular hospital admissions using t-tests.

Results: Greater relative weight gains were significantly associated with pre-treatment systolic blood pressure (2.7 mmHg increase in BP per 1% increase in weight; p < 0.0001) and hospitalizations for cardiovascular complications (p=0.03). In contrast, neither greater relative weight gain nor pre-treatment systolic blood pressure was significantly associated with all-cause hospitalization (p>0.5). The clinic with both the greatest relative weight gains and the highest rate of hospitalization for cardiovascular disease was without a full-time dietitian for the months of the study.

Conclusions: In our population of maintenance hemodialysis patients, we report a statistically significant association between relative weight gains, hypertension and hospitalization for cardiovascular disease. We suggest that this relationship may be related to the absence of a full-time dietitian leading to a lack of a true multidisciplinary team approach to fluid management in these patients. **References:** 1. U.S. Renal Data System: USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.

PUB338

Acute Effects of Cinacalcet on Arterial Stiffness and Ventricular Function in Hemodialysis Patients Mohsen Agharazii, Karine Marquis, Catherine Fortier, Sacha A. De Serres, Fabrice Mac-Way. *CHU de Quebec Research Center, Hotel-Dieu de Quebec Hospital, Quebec, QC, Canada.*

Background: Ionized calcium concentrations are crucial for vascular smooth muscle tone and myocardial contractility. The aim of the present study was to investigate whether a reduction in serum calcium concentration by the calcimimetic cinacalcet can reduce aortic stiffness and improve diastolic dysfunction.

Methods: This is a randomized, double blinded, cross-over study comparing the effects of 30 mg/d of cinacalcet for 7 days to 7 days of placebo. Aortic stiffness was measured by determination of carotid-femoral pulse wave velocity (cf-PWV), central aortic pressure wave form was performed by radial tonometry using generalized transfer function, and cardiac function was evaluated by an echocardiogramme. Linear mixed model with fixed effects including period, treatment and sequence, while a random effect for the patients nested in sequence was used.

Results: 21 patients were enrolled. After administration of cinacalcet the total serum calcium decreased (2.28 ± 0.18 versus 2.15 ± 0.14 mmol/L, p<0.001), with a significant reduction of PTH levels as expected (558 ± 293 to 306 ± 333 ng/l, p<0.001). There were no significant differences in central pulse wave profile. Taking into account changes in the mean blood pressure, sequence, carryover and treatment effect, there was a numerically lower cf-PWV under cinacalcet that was not statistically significant (0.35, 95% CI -0.13 – 0.83

m/s, p=0.139). In 14 subjects, who underwent echocardiogramme, there were no significant changes in cardiac output, stroke volume and ejection fraction. However, left ventricular end-systolic volume (52 ± 22 versus 57 ± 25 ml (p=0.20) and end-diastolic volumes (92 ± 35 versus 97 ± 17, p=0.08). were numerically higher under cinacalcet, but not statistically significant. There were no significant changes in the parameters of diastolic dysfunction.

Conclusions: In this short term study, there were no detectable effects of cinacalcet on aortic stiffness and diastolic dysfunction despite the expected reduction in serum calcium concentration. The numerically higher left ventricular volumes with cinacalcet, may need to be investigated. Clinical trials: NCT01250405.

Funding: Pharmaceutical Company Support - Amgen

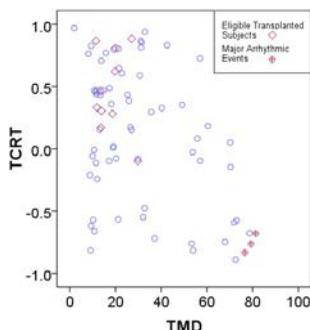
PUB339

Kidney Transplantation and Cardiac Repolarization Descriptors
 Dimitrios J. Poulidakos,¹ Debasish Banerjee,² Marek Malik,³ ¹Renal, Salford Royal, United Kingdom; ²St. George's Univ of London, United Kingdom; ³Imperial College, London, United Kingdom.

Background: Selected descriptors of cardiac repolarization derived from the computerized analysis of electrocardiogram (ECG) can predict cardiac risk in hemodialysis (HD) patients. Kidney transplantation improves cardiovascular survival. The aim of the study was to investigate the impact of kidney transplantation on these descriptors.

Methods: The study was conducted in two phases. In phase 1, Holter ECGs were obtained during HD sessions and repeated 5 times at 2-weeks intervals in stable HD patients. The repolarisation descriptors QRS-to-T angle (TCRT) and T wave morphology dispersion (TMD) were calculated in overlapping 10 second ECG segments and averaged over the first hour of recordings. In phase 2, continuous 1-hour ECG recordings were obtained in patients who received a kidney transplant minimum three months after transplantation and if they were stable with EGFR>30 ml/min/1.73m2. Average values of post transplant repolarisation descriptors were compared with average values over the first hour of HD using Wilcoxon test and t-test was used for baseline comparisons.

Results: In 80 HD patients in phase 1 both descriptors showed intrasubject stability and exhibited extreme values in subjects that suffered major arrhythmic events. During a period of 35.9 ± 3 months 10 eligible transplanted subjects were recorded and although TMD and TCRT improved 7 months following kidney transplantation (see table) the difference did not reach statistical significance (p>0.05). However these subjects had better baseline TCRT and TMD values compared to the study population (TCRT 0.463 vs 0.078 p < 0.05 and TMD 17.9 vs 32.4 p<0.05).



Characteristics of eligible transplanted subjects (n=10)	
Age	47 (range 27-73)
Females	50% (n=5)
Diabetes	20% (n=2)
Months from last HD recording to transplantation	7.5 (range 2-25)
Months from transplantation to post transplantation recording	7 (range 3-8)
QRS-T angle (TCRT) before transplantation	0.349±0.423
QRS-T angle (TCRT) post transplantation	0.438±0.331
TMD pre-transplantation	17.4±7.1
TMD post transplantation	15.2±5.7

Conclusions: In transplant recipients with healthier baseline repolarization profiles the improvement did not reach statistical significance in the early post transplant period. Larger studies with longer follow up are needed.

PUB340

Prognostic Significance of Cardiopulmonary Exercise Test and 6-Minute Walk Test in Chronic Dialysis Patients
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Background: Dialysis patients (pts) are burdened by significant morbidity and mortality from cardiovascular causes. Identifying patients with an increased risk of ominous prognosis is of essential clinical relevance. The aim of the study was to evaluate prognostic value of cardiopulmonary exercise test (spiroergometry) and 6-minute walk test (6MWT) in chronic dialysis pts.

Methods: In prospective study 90 pts receiving high-flux dialysis (12h/week) were examined by means 6MWT and spiroergometry (VO2max, VE, VCO2, METS). After 3 years of follow-up data were evaluated in term to assess prognostic value of physical performance tests. Patients were divided into 2 groups: survivors and non-survivors (died within 3 years).

Results: Mortality at 3 years was 22.2% (20 pts) – non-survivors. They showed significantly lower values in cardiopulmonary exercise test and achieved shorter distance in 6 MWT compared to survivors – table. In multivariable analyses controlling for age,

and sex lowed distance in 6 MWT was significantly correlated with all lower measures of spiroergometry (r 0.5-0.6). VO2max and 6 MWT were independently (from age) associated with death within 3 years.

	Non-survivors; n=20 (median)	Survivors; n=70 (median)	P (U Mann Whitney)
Age [y]	67	62	0,008332
Body weight [kg]	74	76	0,729153
6 MWT distance [m]	224,5	448,0	0,000143
Exercise test time [min]	6,0750	9,450	0,000000
VT [l/min]	1,17	1,65	0,000137
VE [l/min]	27,35	46,20	0,000062
VO2 [ml/min]	799,0	1290,0	0,000005
VCO2 [ml/min]	755,0	1252,0	0,000006
VO2/kg [ml/min/kg]	11,680	16,830	0,000008
HR bpm (max)	102	124	0,006712
Load Watt [W]	35	65	0,000213
METS	3,30	4,80	0,000009
Sys BP before exercise [mmHg]	146,50	152,00	0,211892
Dia BP before exercise [mmHg]	78,	89,	0,013769
HR bpm before exercise	76,0000	76,000	1,000000
HR bpm after exercise	83,5000	85,000	0,325878
Sys BP after exercise [mmHg]	159,5000	162,000	0,297672
Dia BP after exercise [mmHg]	84,0000	96,000	0,004283

Conclusions: Both cardiopulmonary exercise test and 6-minute walk test were able to differentiate survivors and non-survivors within 3 years. National Science Centre grant 2011/03/B/NZ7/01764.

Funding: Government Support - Non-U.S.

PUB341

Adaptive Servo-Ventilator Therapy Improves the Cardiac Dysfunction in Hemodialysis (HD) Patients with Sleep-Disordered Breathing
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Background: Cardiac dysfunction is a very serious problem in HD patients. Sleep Disordered Breathing (SDB) is considered to cause cardiac dysfunction. Dialysis patients have a disordered respiratory center and a high prevalence of central apnea. Adaptive Servo-Ventilator (ASV) is automated modality used to treat heart failure patients with SDB, especially central apnea. The aim of this study is to explore the relationship between sleep apnea and cardiac dysfunction, and to evaluate the effects of ASV therapy in HD patients.

Methods: Sleep study was performed using a portable sleep test device (Sleepster LS-300, Fukuda Denzhi Co., Ltd, Japan). We measured the variables of cardiac function by echocardiogram. The relation between apnea index and the echocardiogram indicates was evaluated. We also collected baseline information on demographics, laboratory values, plasma BNP level, medications, and clinical conditions. ASV therapy was used in the patients diagnosed with severe SDB and/or central apnea. The cardiac function variables were evaluated in comparison to the previous year.

Results: The 27 dialysis patients (sixteen diabetics, eleven non-diabetics) are included in this study. Out of them, echocardiogram, SDB indications showed a connection. The obstructive apnea hypopnea index was related to the left ventricular posterior wall thickness (LVPWT) (r=0.49, p=0.02). Seven patients received ASV therapy. There has been improvement of overall of their cardiac function with significant increase of ejection fraction (p=0.02) 1 year after ASV introduction.

Conclusions: In this study, we demonstrated the efficacy of ASV therapy in hemodialysis patients with SDB. Near future, ASV is possible to be one of attractive devices for HD patients, with aging, several complications, to improve their poor prognosis.

PUB342

Endovascular Renal Denervation: Effects on Dyslipidaemia and Vascular Inflammation in Dialysis Patients
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Background: Endovascular renal denervation (RDN) reduces afferent and efferent sympathetic nerve activity. Its effects on vascular inflammation and cholesterol levels in dialysis patients are unknown. We hypothesized RDN would reduce sympathetic activity, resulting in improvement in biomarkers of vascular inflammation and dyslipidaemia.

Methods: Nine dialysis patients with uncontrolled office BP (>140/90mmHg despite two or more agents at maximal tolerated dosages) were recruited into this feasibility study. Office and ambulatory BP monitoring (ABPM) were performed at baseline, one and three months post RDN, along with supine muscle sympathetic nerve activity (MSNA) and venepuncture. Bilateral RDN was undertaken with an EnligHTN™ catheter.

Results: Similar to previous, office systolic BP reduced and the effect on ABPM was attenuated. MSNA did not change, a novel finding. Despite lack of change in MSNA, total cholesterol:HDL ratio increased along with a falling trend in CRP and rising trend in albumin, all novel findings.

	Baseline	1 Month	3 Months	P value
Office Systolic BP (mmHg)	179±28	156±24	152±25	<0.05
Office Diastolic BP (mmHg)	90±17	76±13	82±12	0.137
Mean Systolic ABPM (mmHg)	173±19	173±23	166±24	0.544
Mean Diastolic ABPM (mmHg)	92±11	89±13	88±11	0.906
MSNA Burst Frequency (n=6) (bursts/min)	59±12	59±15	59±13	0.872
Albumin (g/L)	38±5.0	39±6.3	41±4.6	0.068
Total Protein (g/L)	66±6.1	68±8.2	69±5.9	0.282
CRP (mg/L)	27±28	20±20	15±18	0.056
Chol (mmol/L)	4.1±0.9	4.1±1.0	4.4±1.2	0.228
HDL Chol (mmol/L)	1.2±0.3	1.2±0.2	1.1±0.2	0.388
Chol:HDL Ratio	3.6±1.1	3.5±0.9	4.1±1.1	<0.05
LDL Chol (mmol/L)	2.2±0.7	2.4±0.9	2.5±1.0	0.071
Triglycerides (mmol/L)	1.4±0.8	1.2±0.6	1.6±0.7	0.160

Conclusions: RDN in dialysis patients improves office systolic BP, impacts uraemic dyslipidaemia and possibly reduces vascular inflammation. Further controlled studies are warranted.

PUB343

Comparative Study of Non Survivors and Survivors Among Twice Weekly Hemodialysis Patients in India Topoti Mukherjee, Naksha Jagannath Anchan, Geetha S, Gayathri Devi R.G., Avinash Ignatius, Tanmay Pandya, Vidyashankar Panchangam, Sylvia Paz B. Ramirez, Suresh Sankarasubbaiyan. *Nephrology, Davita Care India Private Limited, Chennai, Tamilnadu, India.*

Background: Hemodialysis practice varies based on health system, payer practice, patient choice and socioeconomic environment. We analyzed the practice pattern and characteristics of non survivors and survivors among twice weekly hemodialysis patients across 9 centers in India.

Methods: Retrospective study of patients on HD between July 1, 2013 to Dec 31, 2014. Inclusion criteria: > 30 days of HD & 1.8 - 2.3 HD sessions/week. Demographic characteristics, comorbidities, hospitalizations, cumulative follow up, hemoglobin, Albumin, Calcium and Phosphorus were compared among non survivors and survivors. We compared mean and proportion using Student T test and chi-square test respectively.

Results: N=255; 63.9% males. Non survivors 61, survivors 194. Data presented as non survivors vs survivors: Hospitalizations: 42.6% vs 25.8% (<0.01), DM: 63.2% vs 34.5%, (<.01)CAD: 17.5% VS 6.4% (<.05),CVA: 1.8% vs 2.3%; HCV: 1.8% vs 10.9% (p< 0.05), HBV: 7% vs 1.1% (< 0.05), HIV: 5.3% vs 3.4%

	Non survivors (n=61)	Survivors (n=194)	
Age	59.5 (12.5)	51.6 (14.3)	<.01
Cumulative follow up (pt yrs)	41.3pt yrs	186.8 pt yrs	
Median follow up (days)	209	385	
Total sessions	83.6(59)	118(74.6)	<.01
Avg HD /week	1.9(0.2)	1.9(0.2)	ns
S. Hb (G%)	8.9 (1.7)	9.5 (1.6)	<.05
URR (%)	68.8 (5.5)	67.9 (7.9)	ns
Std Kt/V	1.6 (0.30)	1.7 (0.4)	ns
S. Alb (g%)	3.5 (0.9)	4.0 (1.4)	<.01
S. Ca (mg%)	8.4 (0.8)	8.4 (0.9)	ns
S. Ph (mg%)	5.6 (1.3)	5.7 (1.6)	ns
S. K (mEq/L)	5.2 (0.8)	5.3 (0.7)	ns
Pre HD MAP standing	100.9(9.9)	103.4(13.5)	ns
Post HD MAP standing	99.7(8.7)	103.6(28.3)	ns
IDWG	3.8(1.4)	3.9(1.5)	ns
UF rate	0.6(0.2)	0.6(0.2)	ns
Mean hospitalization/patient	0.6(0.9)	0.3(0.7)	ns
No of hospitalizations	37	69	

Non survivors were significantly older, had lower number of total sessions, lower albumin and Hb.

Conclusions: Non survivors were characterized by older age, higher prevalence of diabetes, CAD, lower Hb & Albumin. But dialysis adequacy and UF were comparable. Short duration of follow up may limit the ability to study other factors influencing outcomes.

PUB344

New Anticoagulant Free Strategy for Non Valvular Atrial Fibrillation in Hemodialysis Patients Teresa Arcidiacono, Patrizio Mazzone, Marco Simonini, Donatella Spotti, Maria Teresa Sciarone Alibrandi, Rita Quartagno, Marco Melandri, Stefano Tentori, Giorgio Slaviero. *San Raffaele Scientific Inst, Italy.*

Background: Vascular calcification in patients with CKD-5 is associated with increased cardiovascular morbidity and mortality. An excessive calcification of coronary arteries and of aortic valve has been reported during Warfarin treatment. In addition use of oral anticoagulation (OAC) seems to be an important risk factor for calciphylaxis. Atrial fibrillation (AF) is the most frequent reason for OAC use in CKD patients.

Methods: An alternative to OAC could be the percutaneous Left Atrial Appendage (LAA) closure. With this technique an implantable component is permanently fixed in the LAA to prevent thrombus embolization. Different studies demonstrated that this procedure is not inferior to systemic anticoagulation with OAC in prevention of thromboembolic risk. We reported our clinical experience with the use of this technique in haemodialysis patients with non valvular AF.

Results: In the last few months seven (7) haemodialysis patients were treated with percutaneous LAA closure. Bleeding and stroke risks were evaluated by HAS-BLED score and CHA2DS2-VASc score: HAS-BLED score was 4.5±0.58 (equal to 9%±0.11 yearly risk of major bleeding) and CHA2DA2-VASc was 4±0.81 (equal to 4.47%±1.5 yearly risk of stroke). This procedure was well tolerated by each patient. OAC treatment was interrupted after the procedure and doubled antiplatelet therapy was introduced for a month. At this moment median of 9 months of follow-up was archived [IQ 3-12]; no adverse events has been assessed.

Conclusions: To the best of our knowledge this is the first consecutive series of LAA closures in haemodialysis patients. This procedure represents a real clinical alternative to the use of coumarin derived drugs. Our experience leads the way to the possible routine use of this procedure in CKD-5D patients. As well as this procedure could be used in those patients with contraindications to OAC, even more this treatment should be used in haemodialysis population, in which the use of OAC should be avoided for both increased risk of life-threatening bleeding events and well known negative cardiovascular effects.

PUB345

Management of Subclinical Thyroid Dysfunction Can Reduce Cardiovascular Events in Patients with End-Stage Renal Disease on Hemodialysis Hong Joo Lee. *Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea.*

Background: Normal thyroid function influences basal metabolic rate and general body metabolism and thyroid dysfunction is often associated with dyslipidemia and increased cardiovascular risk in general population. It is known that about 25% of patients with end-stage renal disease(ESRD) on hemodialysis had subclinical thyroid dysfunction. We investigated that subclinical hypothyroid dysfunction associate with dyslipidemia and cardiovascular event in hemodialysis patients. Hence, we conducted our study to elucidate whether subclinical thyroid dysfunction treated or not in ESRD patients.

Methods: All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. Thyroxine-3 (T3), free thyroxine-4 (FT4), Thyroid Stimulating Hormone (TSH) and lipid profiles in the serum were estimated and death from all causes and CV events served as outcome variables over a median follow-up period of 12 months. Participants were divided into groups based on the thyroid function. Statistical analysis was carried out by using SPSS.

Results: Among the 92 cases, 28.2% of the patients were having thyroid disorder. In which 2.1% were of hypothyroid, 13.7% were of subclinical hypothyroid, and 0.8% were of hyperthyroid, 11.6% were of subclinical hyperthyroid. We observed negative correlation between TC & FT3. Total cholesterol was raised in hypothyroidism in comparison to euthyroid ESRD patients. However, thyrooid function didn't have significant association with lipid profiles. Cardiovascular disease significantly often occurred in subclinical thyroidism patients than other group.

Conclusions: Our results show that the blood thyroid hormone level isn't affected by dyslipidemia but affected by occurrence of CVD. Therefore, the management of subclinical hypothyroidism in hemodialysis patients should be considered.

PUB346

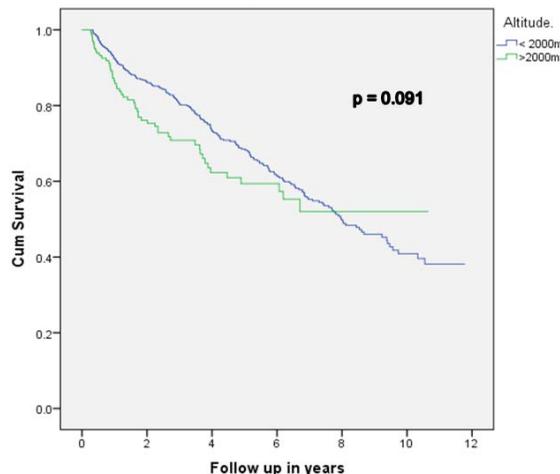
Effect of Altitude on All-Cause Mortality in End-Stage Kidney Disease Patients Ongoing Hemodialysis in Peru Katia Bravo-Jaimes,¹ Viky Y. Suncion,² Jose Ernesto Rojas,³ Christian R. Mejia,⁴ Sandra C. Schult.⁵ ¹Medicine, Univ of Rochester Medical Center, Rochester, NY; ²Medicine, Jackson Memorial Hospital, Miami, FL; ³Inst de Investigaciones de Altura, Univ Peruana Cayetano Heredia, Lima, Peru; ⁴Asociación Médica de Investigación y Servicios en Salud, Lima, Peru; ⁵Pediatrics, Inst Nacional de Salud del Niño, Lima, Peru.

Background: Worldwide, end-stage kidney disease (ESKD) prevalence has tremendously risen. Previous studies suggested that receiving hemodialysis (HD) at high altitude confers mortality benefits; however this effect has not been proved above 2000 m or in developing countries.

Methods: This historical cohort study analyzed medical records from six HD centers of the Peruvian Social Security System. Adult ESKD patients who started HD between 2000 and 2010 were included. Patients were classified into two strata (<2000 and >2000 m). The outcome variable was death from any cause. Cox proportional hazards models were built for the time from first dialysis to death from any cause, stratifying by year and censoring patients at 5 years after first dialysis; loss to follow-up; transference to another HD center out of the city; renal transplantation or migration to peritoneal dialysis during follow-up.

Results: 723 patients were enrolled, including 248 women (38.2%). The mean age was 52.8 ±16.9 years. 166 patients lived >2000 m (22%). In first years after follow-up, survival rates were lower in the group >2000 m, however after 8 years of follow-up this trend reversed. Age and gender were not significantly associated to mortality at altitude levels >2000 m. Patients with diabetes had higher mortality rates at >2000 m (p=0.003), independently of age.

Conclusions: In Peru, patients receiving HD at high altitude do not experience mortality benefits. In fact, diabetics have higher mortality rates at >2000 m.



Funding: Private Foundation Support

PUB347

End-Stage Renal Disease in North Region of Oman/Epidemiology, Incidence, and Aetiology Ruqiyah Khamis Al-Za'abi,^{1,2} Elizabeth P. Tolmie,¹ Ann marie Rice,¹ Nabil Mohsin,² Ahmed Said Al-Busaidi.¹ ¹Nursing and Health Care, Univ of Glasgow, Glasgow, United Kingdom; ²Nursing Education, Ministry of Health, Muscat, Sohar, Oman.

Background: The epidemiology of renal failure in Oman is scarce. There is a paucity of information on the size and burden of renal failure in Oman. Therefore, our research was conducted to measure the prevalence, incidence and death rate (epidemiology) among patients who have renal failure and undergo renal dialysis in four dialysis centers in the North of Oman; and to provide a description of the major characteristics of the studied patients.

Methods: A cross-sectional study was conducted. A proportional sample (n = 341) patients from four Renal Dialysis Centres (RDC) were interviewed face to face or via telephone using a structured questionnaire. Data collection took place between October and November, 2014. The incidence, prevalence and death rate are under collection until the end of December, 2015.

Results: Over the period January 1st, 2014 to December 31st, 2014, a total of 96 new patients started dialysis in the four observed RDCs. The overall incidence rate was 13 patients per 100,000. The period prevalence for the patients undergoing renal dialysis was 52 patients per 100,000. The mortality rate for the same period of time was four patients per 100,000. Demographic data are summarized in table1.

	N	%
Subjects	380	100
Included	341	89.7
Excluded	39	10.3
Gender		
Male	187	54.8
Female	154	45.2
Ethnicity		
Omani Asian	237	69.5
Omani White	55	16.1
Omani Black	49	14.4
Age Groups		
0-17	6	1.8
18-45	102	29.9
46-64	164	48.1
65-75	52	15.1
>75	17	5
Marital Status		
Married	214	62.8
Single	54	15.8
Widowed	51	15
Divorced	22	6.4
Education		
Illiterate	164	48.1
Read and Write	51	15
Primary Education	47	13.7
Secondary Education	58	17
College Degree	18	5.3
Post-College	3	0.9
Employment Status		
Unemployed	292	85.6
Employed	49	14.4

Conclusions: Renal failure is a burden on patients, and the health and social systems of Oman. The expenditure on these 380 patients in 2014 was 6.5 million dollars. However, to determine the size of the burden, we need a comprehensive study covering the whole country of Oman and we need to receive data from neighbouring countries to compare with.

Funding: Government Support - Non-U.S.

PUB348

Low Potassium Bath Protocol Experience in Hemodialysis Patients in Qatar Abdullah Hamad, Fadwa S. Al-Ali, Eiman Mohamed Hamid, Shaza Yousif Elsanooi, Mohamed Yahya Mohamed, Hany Ezzat Ismail. *Nephrology, Fahad Bin Jassim, Hamad General Hospital, Doha, Qatar.*

Background: Hyperkalemia is a major problem in hemodialysis (HD) patients affecting their morbidity and mortality. HD patients receiving low potassium (K) bath for hyperkalemia have double the risk of sudden cardiac death. We noticed high rate of use of low K dialysate due to high prevalence of hyperkalemia in our dialysis unit. We are studying this phenomenon.

Methods: Our study was done in the biggest out-patient HD facility in Qatar (306 patients). We identified patients who required low K bath (based on an existing rigorous protocol, any K over 5.5 will be started on low K bath 1 mmol/L with checking K level every HD treatment till corrected) in 6 months period from 10/1/2014 to 3/31/2015. We collected background data in these patients and their potassium levels during that period.

Results: 62 out of 306 hemodialysis patients required low K bath continuously (5 patients) or intermittently (57 patients). Mean age was 59.9 +/- 15 years. There were 36 females on low K bath out of total 137 females versus 26 males out of 169 (p Value 0.014) . 39 out of 62 were Qatari (62% versus 65% in patients not on low K bath). Table 1 summarize number of patients on low K bath and number of low k bath HD treatments on monthly base versus average temperature in Doha, Qatar.

	October	November	December	January	February	March
number of patients on low K bath	35	34	28	17	9	27
number of HD treatments done with low K bath	349	362	178	79	65	160
average temperature in Doha, Qatar (degree centigrade)	35	29	25	22	25	27

Conclusions: In a study of using low K bath in a major HD clinic in Qatar we found a statistically significant higher number of female patients who required low K bath than males. This might be attributed to dietary habits based on our dietitians experience and vascular access issues but further study is needed to explain these findings. There was a significant decrease in need for low k bath in January and February compared to other months both in the number of patients and HD treatments . We attributed that to combination of cooler weather and seasonal change in dietary habits. Further study again is needed to evaluate that prospectively.

PUB349

Co-Morbidity Rather Than Clinical Practice Patterns Determines Mortality in an Aged Dialysis Population An Vanacker,¹ Bert Bammens,² Bart De Moor,³ Bart D. Maes.¹ ¹Nephrology, AZ Delta, Roeselare, Belgium; ²Nephrology, Univ Hospitals, Leuven, Belgium; ³Nephrology, Jessa Hospital, Hasselt, Belgium.

Background: Hemodiafiltration (HDF), by adding convective to diffusive transport, is more effective in removing larger uremic retention solutes than hemodialysis (HD). As these solutes are thought to have a role in the accelerated cardiovascular disease of dialysis patients, HDF might result in lower mortality compared to HD.

Methods: All patients treated with thrice weekly HD (high-flux) or online HDF at 3 Belgian dialysis centers for ≥ six and < 42 months were included in July 2008. Hospitalized patients or patients with access-related problems were excluded. The effect of HDF versus HD on all-cause mortality at 6 years was evaluated. Multi-variate analysis taking into account all relevant baseline variables was performed to determine independent predictors of outcome.

Results: 242 patients were included (142 male, mean age 70.9 ± 11.8 years): 84 treated with HD, 158 with HDF. After 6 years, the incidence of all-cause mortality was significantly higher in HD than in HDF: 54 of 84 patients in HD-group (64,3%), 70 of 158 patients in HDF-group (55,7%) (P = 0,04). Based on univariate associations with survival (*) and/or significant association with center or HD/HDF variable, following parameters were introduced in multivariate analysis: HD/HDF*, vintage, age*, weight, CCI*, use of calcium(Ca)-based and non-Ca-based phosphate (P) binders, dialysis hours/week, Qb, Qd, dialysate Ca concentration*, vascular access*, mean P*, Ca-P product*, hemoglobin, albumin*, interdialytic weight gain and center. The final multivariate model is shown in the table below.

Variable	HR	95% CI	p-value
Age	1,03	1,01 – 1,06	0,003
Charlson Comorbidity Index CCI	1,30	1,16 – 1,45	< 0,0001
Weight	0,98	0,97 – 0,99	0,02
Calcium concentration of dialysate	3,60	1,06 – 12,24	0,04
Vascular access	1,43	1,19 – 1,72	0,0002
Interdialytic weight gain	1,31	1,07 – 1,61	0,009
Albumin	0,38	0,39 – 0,97	0,04

Conclusions: In an aged Western dialysis population, treatment with HDF did not improve all-cause mortality compared to high-flux HD. Mortality seems to be determined by comorbidity rather than by clinical practice patterns.

PUB350

Depression Is Associated with Frailty and Malnutrition but Not Comorbidity Load in Chinese Peritoneal Dialysis Patients Cheuk-Chun Szeto,¹ Shin Man Choy.² ¹Dept of Medicine & Therapeutics, The Chinese Univ of Hong Kong, Shatin, Hong Kong; ²Dept of Medicine & Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong.

Background: Depression is common amongst patients with chronic kidney disease and is associated with excessive mortality in dialysis patients. This study determines the prevalence and risk factors of depression in Chinese peritoneal dialysis (PD) patients.

Methods: We studied 178 prevalence PD patients (103 males). Depression was screened by the 15-item self-reported Geriatric Depression Scale (GDS). We also determined patients' comorbidity load, dialysis adequacy, residual renal function, nutritional status, and degree of frailty.

Results: The mean age was 60.7 ± 11.7 years; vintage of dialysis 42.5 ± 44.1 months. Average GDS score was 4.9 ± 4.4. GDS score is closely associated with the frailty score (r = 0.692, p < 0.0001), malnutrition inflammation score (r = 0.406, p < 0.0001), and subjective global assessment score (r = -0.386, p < 0.0001). GDS score also has a modest but significant correlation with Charlson's comorbidity index (r = 0.164, p = 0.028) and serum albumin level (r = -0.192, p = 0.019), but not with patient age, vintage of PD, dialysis adequacy, or residual renal function. When defined as a GDS score ≥ 8, 50 patients (28.1%) had depression.

Conclusions: Depression is common amongst Chinese PD patients. Frailty and malnutrition are the major risk factors of depression in our cohort, while comorbidity load and dialysis adequacy have little effect.

Funding: Clinical Revenue Support

PUB351

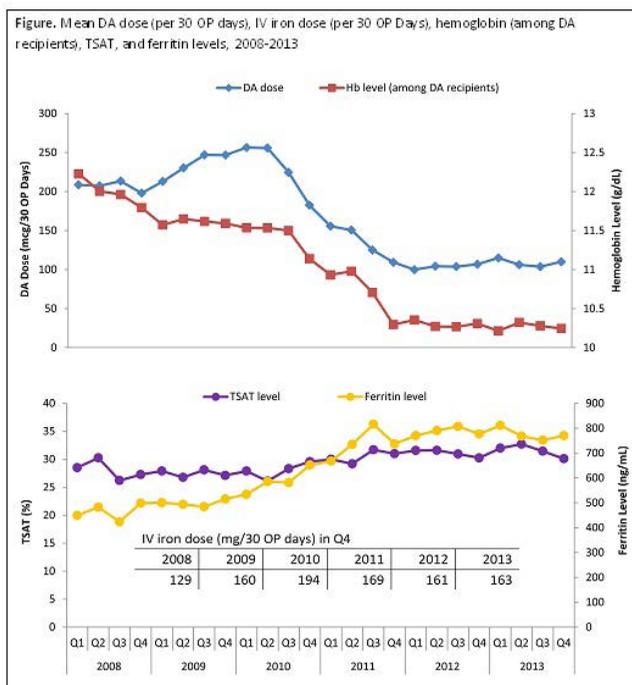
Trends in Anemia Management with Darbepoetin Alfa in Patients on Maintenance Hemodialysis Robert H. Yencheck,¹ Anne C. Beaubrun,² Jeffrey Petersen,² David G. Dalpiaz,¹ Alfred K. Cheung.¹ ¹Univ of Utah, Salt Lake City, UT; ²Amgen, Inc., Thousand Oaks, CA.

Background: In the US, darbepoetin alfa (DA) is primarily used to treat anemia in patients receiving treatment in hospital-based dialysis centers. Epoetin alfa (EA) doses and hemoglobin (Hb) levels declined in response to recent regulatory and reimbursement events but little is known about trends in anemia management with DA in the US maintenance hemodialysis (HD) population receiving treatment in free-standing dialysis centers (FSDCs). We describe herein anemia management in FSDCs within the University of Utah (UU) Dialysis Program who switched from the use of EA to DA program-wide in 2005.

Methods: We included ~650 adults (age ≥ 18 yrs) with 1+ months on HD between 2008-2013 in 18 FSDCs within the UU Dialysis Program. We summarized quarterly intravenous DA and iron use and dose, Hb, and serum transferrin saturation (TSAT) and ferritin levels.

Results: 70-78% of patients received DA over the study period. Mean Hb levels among patients who received DA fell from 12.2 g/dL in 2008 before leveling around 10.3 g/dL from Q4 2011 to 2013 (Figure). The mean monthly DA dose was 209 mcg in Q1 2008, reached a peak of 256 mcg in Q1 2010, and decreased to ~105 mcg in 2013. Quarterly iron use rose from 52% in 2008 to 67% of patients in 2013. Iron dose also rose from 129 mg in Q4 2008 to 194 mg in Q4 2010, but declined to 163 mg in Q4 2013. Mean serum TSAT levels remained relatively constant at ~30% between 2008-2013 but serum ferritin levels increased from 449 ng/mL in Q1 2008 to 770 ng/mL in Q4 2013.

Conclusions: Trends in anemia management parameters among patients on HD treated with DA within FSDCs in the UU Dialysis program were consistent with national reports of patients treated with EA.



Funding: Pharmaceutical Company Support - Amgen, Inc.

PUB352

Shorter Dialysis Session Time Was Associated with Higher Risk of Hospitalization and Death in Maintenance Hemodialysis Patients Takahiro Kuragano, Takeshi Nakanishi. *Dept of International Medicine, Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.*

Background: Recently, dialysis efficiency was dramatically improved by using super flux dialysis membrane. However, in the condition of the common use of high flux dialysis, it has not been well studied the relationship between treatment time and adverse events or survivals of maintenance hemodialysis (MHD) patients.

Methods: Subject: 805 patients undergoing MHD. Study design: Prospective, observational multi-center study of 3 years. We measured serum levels of urea nitrogen (UN), creatinine (Cr), b2microglobulin (MG), total protein, albumin, prealbumin, high sensitive C reactive protein (hCRP) every 3month. We also evaluated body mass index (BMI), and Kt/V. The associations between dialysis intensity and adverse events or death were investigated with the cox proportional hazards model for time-dependent variables.

Results: Although there was no significant correlation between pre-dialysis levels of b2MG or UN and adverse event or survival, high pre-dialysis Cr level was associated with lower risk of hospitalization (HR:0.89, P=0.003) and death (HR:0.71, P=0.002). Moreover, high Kt/V was also associated with lower risk for cerebrovascular and cardiovascular

disease (CCVD) (HR:0.37, P=0.039) and hospitalization (HR:0.55, P=0.026). There was no significant difference in serum levels of prealbumin, albumin, Cr, Kt/V and hCRP levels among 3 groups of treatment time (<4hours(h), 4-5h, >5h). On the other hand, BMI in the patients treated with >5h was significantly (p=0.012) higher than those of patients treated with <4h. In time dependent cox hazard model, the risk of hospitalization (HR:0.43, P=0.001) and death (HR:0.49, P=0.013) of patients treated with 4-5h were significantly lower than that of patients treated with <4h. Moreover, the risk of death in patients treated with >5h was significantly (HR:0.45, P=0.024) lower than that of treated with <4h.

Conclusions: Higher Kt/V was associated with lower risk of CCVD and hospitalization of MHD patients, but not pre-dialysis level of b2MG levels. Shorter dialysis session time was associated with higher risk of hospitalization or death than that of longer treatment time.

PUB353

A Randomized, Factorial Pilot Study to Evaluate the Feasibility of an Intradialytic Exercise Intervention (DIALY-SIZE!) Stephanie E. Thompson,¹ Scott Klarenbach,¹ Anita Molzahn,¹ Mark Haykowsky,¹ Anita Lloyd,¹ Marcello Tonelli,² ¹Univ of Alberta, Edmonton, AL, Canada; ²Univ of Calgary, Calgary, AB, Canada.

Background: Intradialytic exercise (IDE) is associated with improved dialysis adequacy and amelioration of dialysis-related symptoms. However, the uptake of IDE is limited by knowledge gaps on efficacy—what type of exercise to prescribe to optimize outcomes, and on feasibility. The results of this pilot will inform the design of a full-scale efficacy study evaluating two types of IDE (aerobic and resistance) and will also provide research users with practical information on IDE.

Methods: In this single center, randomized, factorial (2 x 2) study, chronic adult hemodialysis patients were randomized to one of four IDE groups: cycling, resistance, cycling and resistance, or stretching (an attention control). Exercise was semi-supervised by a kinesiologist. Outcomes focused on a priori feasibility criteria: recruitment, fidelity to the protocol, and participant and unit staff response to IDE. As a secondary outcome, we evaluated the main effect of cycling and weights each compared with control on quality of life and physical performance at baseline and 12-weeks. To better understand feasibility, we conducted interviews with users.

Results: We exceeded targeted accrual of 28 people over 12 weeks. Of 100 patients screened, 31 were enrolled (36 did not meet inclusion criteria, 33 declined participation); 16% dropped out after randomization. Fidelity to the intervention was high: of 1,039 training sessions offered, 87% were delivered. Participant response to the intervention was favorable: 92% of participants continued exercising after the trial. There were no crossovers and no reported contamination. Dialysis staff were not consistently available to assist with implementation, so study staff were necessary to deliver IDE. Secondary outcomes were not statistically significant.

Conclusions: This pilot study demonstrated feasibility of recruitment, high patient acceptability, and low risk of contamination. However, IDE will not be feasible in the long term unless dialysis staff assist with implementation. This will need to be addressed before executing a definitive trial.

PUB354

A Prospective Study of Routine Heparin-Free Hemodialysis (HFD) with Streamline® Bloodlines (SL) in a Large Tertiary Acute Care Inpatient Practice Sami Safadi,¹ Mary Ann Ryan,² Amanda L. Severson,² Fares Alahdab,³ John J. Dillon,¹ Robert C. Albright,¹ Amy W. Williams,¹ Marie C. Hogan.¹ ¹Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Nursing, Mayo Clinic; ³KSP Unit, Mayo Clinic.

Background: Extracorporeal circuit (EC) anticoagulation (AC) with heparin was a key advancement in hemodialysis (HD). However, AC in patients at risk of bleeding remains a frequently encountered problem. SL bloodlines eliminate blood-air contact, and reduce turbulence in HD circuit. Small studies suggest that SL reduces heparin use and improves HD efficiency. We prospectively evaluated EC clotting rates, impact on dialysis efficiency, and associated risk factors in our inpatient practice.

Methods: In this complete study, we followed acute care inpatients requiring HD without routine EC heparin. Patients could be on ACs for other non-HD indications. All sessions were performed using SL and Fresenius 2008K. HD sessions were observed for clotting events (CE) defined as interruption of HD session, loss of HD circuit, or inability to return blood.

Results: 1200 HD runs were performed. Demographics & HD session characteristics are summarized in table 1. Overall CE rate was 5.2%. Determinants for CE were temporary HD catheters (OR=2.8, p<0.01), transfusions (OR=2.3, p=0.05), systemic AC (OR=0.2, p<0.01), & antiplatelets (OR=0.4, p<0.01). CE were associated with a lower delivered KT/V (diff-0.39, p<0.01). Most CE during transfusions (71%) occurred when blood products were given by the HD circuit.

Conclusions: We successfully adopted HFD with SL as our standard inpatient protocol. This protocol is feasible and safe in acute care inpatient HD. CE risk is low, and is associated with temporary HD catheters and transfusions. Use of antiplatelets and systemic AC is protective.

	Floor	ICU
Patients	n=173	n=201
Median age	66 yrs	63 yrs
Males	64%	61%
Caucasians	84%	88%
ESRD	75%	52%
HD sessions	n=600	n=600
Median time (min)	210	213
HD Access		
-Tunneled Cath	51%	57%
-AV Fistula	34%	15%
-Temp. Cath	11%	24%
-AV Graft	2%	2%
Median BFR (ml/min)	350	350
Median UF (liters)	2	2
Median KTV	1.4	1.5
Antiplatelets within 7 days	46%	61%
-Aspirin	43%	58%
AC within 7 days	25%	45%
-Heparin	16%	37%
-Warfarin	22%	39%
Transfusions	4.5%	4.5%
CE	5%	5.5%

Funding: Pharmaceutical Company Support - Medisystems, a NxStage Company

PUB355

Patterns of Oral Disease in Adults with Chronic Kidney Disease Treated with Long-Term Haemodialysis: A Multinational Ecological Study Giovanni F.M. Strippoli,^{1,2,3,4} ¹On behalf of the ORAL-D Study Investigators*; ²Diaverum Medical Scientific Office; ³Univ of Bari; ⁴Univ of Sydney.

Background: Oral disease is a potentially treatable risk factor for premature death and impaired quality of life. However, the oral disease burden and candidate preventative strategies are uncertain in the dialysis setting.

Methods: ORALD was a prospective study in 4726 adults treated with hemodialysis in Europe and Argentina recruited from a convenience sample of 80 dialysis clinics within a treatment network. Oral disease was assessed using standardized WHO methods. Participants self-reported oral health practices and symptoms. Socio-demographic and clinical factors associated with oral diseases were assessed within nation states.

Results: Of 4726 eligible adults from 80 dialysis units, 4205 (88.9%) participated. Overall, 20.6% were edentulous (95% CI, 19.4-21.8). Participants had on average 22 (21.7-22.2) decayed, missing or filled teeth while moderate to severe periodontitis affected 40.6% (38.9-42.3). Oral disease patterns varied markedly across countries. Participants in Spain, Poland, Italy and Hungary had the highest mean adjusted odds of edentulousness (2.31, 1.90, 1.90, and 1.54) whilst those in Poland, Hungary, Spain and Argentina had highest odds of ³14 decayed, missing, and filled teeth (23.2, 12.5, 8.14, 5.23). National levels of tobacco consumption (R²=0.79), diabetes (R²=0.49), and child poverty (R²=0.66), were associated with edentulousness within countries.

Conclusions: Oral disease in adults on hemodialysis is very common, frequently severe, and highly variable among countries, with much of the variability unexplained by participant characteristics or oral practices. Given the substantial variation among countries and high burden of disease, strategies to improve oral health in hemodialysis patients will require national strategies. *List of ORAL-D Investigators: S Palmer, M Ruospo, G Wong, JC Craig, M Petrucci, M De Benedittis, P Ford, DW Johnson, M Tonelli, P Natale, V Saglimbene, F Pellegrini, E Celia, R Gelfman, MR Leal, M Torok, A Bednarek-Skublewska, J Dulawa, P Stroumza, L Frantzen, D del Castillo, AG Bernat, J Hegbrant, C Wollheim, L Gargano, CP Bots and GFM Strippoli.

PUB356

Low Serum Albumin Is a Risk Factor for In-Hospital Mortality Among Hemodialysis Patients Hospitalized with Infectious Diseases: A Multicenter Retrospective Cohort Study in Japan Shun Minatoguchi,^{1,2} Hideaki Shimizu,^{1,2} Takaya Ozeki,² Daisuke Uchida,² Hiroo Kawarazaki,² Hiroki Nishiwaki,² Takahiro Imaizumi,² Yoshiro Fujita,^{1,2} Yugo Shibagaki,² ¹Nephrology, Chubu Rosai Hospital, Nagoya, Aichi, Japan; ²TOMEI Nephrology Group for Clinical Research, Japan.

Background: Serum albumin is the known marker of nourishment and inflammation. Several studies in the past have shown the relationship between low serum albumin and long-term mortality among dialysis patients. However, There is insufficient data on the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

relationship between serum albumin levels and short-term mortality among chronic dialysis patients who are hospitalized with infectious diseases. This multicenter retrospective cohort study in Japan evaluated if serum albumin levels at the occurrence of infection is a risk factor for in-hospital mortality among hemodialysis patients.

Methods: From June 2011 to July 2013, a total of 418 hemodialysis patients who took blood cultures were reviewed retrospectively in five tertiary dialysis units participating the "TOMEI Nephrology Group for Clinical Research" study. After exclusion of 232 patients diagnosed with non-infectious diseases, 186 patients diagnosed with infections were analyzed. Patients were divided into two groups according to the serum albumin level at hospitalization; low serum albumin (Serum albumin < 3.5g/dL) or not. Outcome measure was in-hospital mortality. For statistical analysis, cox proportional hazard model was used.

Results: Among 186 patients with infectious diseases, there were 117 patients (62.9%) in low albumin group, and 69 patients (37.1%) in normal albumin group. During hospitalization (median 19 days, interquartile range 10-37), 29 patients (15.5%) died; 25 of 117 (21.4%) in low albumin group, and 4 of 69 (5.8%) in normal albumin group. The cox proportional hazard model verified that low serum albumin and bacteremia were associated with in-hospital mortality. The hazard ratio of in-hospital mortality among low albumin group was 4.293 (95% CI: 1.36-13.55).

Conclusions: Although low serum albumin is a known risk factor for long-term mortality, this study showed that low serum albumin strongly predicts short-term mortality among hemodialysis patients hospitalized with infectious diseases.

PUB357

Usefulness of High-Frequency Wave-Length Ultrasonography as a Diagnostic Tool for Carpal Tunnel Syndrome in Hemodialysis Patients Tadashi Yamazaki,² Tokie Hayasaka,² Tetsuo Saito,² Shuichi Tsuruoka.¹
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Background: Carpal tunnel syndrome (CTS) is a common complication in dialysis-induced amyloidosis. In orthopedics, high-frequency wave-length ultrasonography (US) with improved resolution is recently used for diagnosing disorders of the upper extremities. We aimed to determine the value of US for diagnosing CTS in hemodialysis (HD) patients, through a cross-sectional analysis.

Methods: All maintenance HD patients (N = 150) at our hospital were recruited after providing written informed consent. Patients with apparent paralysis or pain in the upper extremities due to causes other than CTS were excluded. Longitudinal scan of the median nerve around the carpal tunnel area was performed with US (Toshiba Viamo TM, 12-MHz probe) during HD, and the compression rate (CR) of the nerve was calculated as (1 - shortest diameter/longest diameter of the nerve around the carpal tunnel area). The CTS symptoms were evaluated with the visual-analogue scale (VAS) of pain around the index finger area and the quick form of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) questionnaire. Pinch strength was also measured. Serum C-reactive protein (CRP) and b2-Mg concentrations, and medical histories related to CTS or dialysis-induced amyloidosis were extracted from the patients' record.

Results: Total 250 wrists from 125 patients (Mean age = 65.6±10.6 years) were studied. The mean CR was 11.8±0.7% and the cut-off values of CR from ROC curve for history of carpal tunnel release was 25.7% (sensitivity 0.80, specificity 0.91). Multivariate analysis revealed that CR was significantly positively correlated with dialysis career, VAS and Quick-DASH scale, positive Tinnel's sign, and serum CRP and b2-Mg concentrations, whereas it showed a significantly negative correlation with pinch strength. Especially, patients with >4 years of HD and serum b2-Mg concentrations >20 mg/L showed significantly high CRs.

Conclusions: Measurement of CR with US is an easy and reproducible method for diagnosing dialysis-related CTS. The CR significantly correlated with symptoms and factors associated with dialysis-induced CTS.

Funding: Government Support - Non-U.S.

PUB358

Technique Failure in Korean Incident Dialysis Patients: A National Population-Based Study Shina Lee,¹ Hyunwook Kim,² Seung-Jung Kim,¹ Duk-Hee Kang,¹ Kyu Bok Choi,¹ Dong-Ryeol Ryu.¹ ¹Dept of Internal Medicine, School of Medicine, Ewha Womans Univ Mokdong Hospital, Seoul, Republic of Korea; ²Dept of Internal Medicine, Wonkwang Univ College of Medicine Sanbon Hospital, Gunpo, Republic of Korea.

Background: Technique failure is an important issue for dialysis patients. In this study, we aimed to analyze a detailed technique failure rate and to determine the predictors for technique failure in Korea.

Methods: We identified all patients who had started dialysis between January 1, 2005 and December 31, 2008 in Korea, using the Korean Health Insurance Review and Assessment Service database. A total of 32,357 eligible patients [24,743 hemodialysis (HD) patients and 7,614 peritoneal dialysis (PD) patients] were included, and the median follow-up was 26.4 months.

Results: The crude incidence rates of technique failure among HD patients and PD patients were 3.4 and 54.1 per 1000 patient-years, respectively. When comparing technique survival rate between HD and PD in both Kaplan-Meier analysis and competing risks analysis, it was significantly higher in patients on HD than in those on PD. However, the gap of technique failure incidence between HD and PD was exaggerated in Kaplan-Meier analysis compared to competing risks analysis. In multivariate analyses, diabetes mellitus and Medical aid as a crude reflection of low socioeconomic status were independent risk

factors in both Cox proportional hazard model and Fine and Gray subdistribution model. In addition, cancer was independently associated with a lower risk of technique failure in Fine and Gray model.

Conclusions: Technique failure in PD is higher than that in HD, and it is major concern in patients initiating dialysis in Korea. The results of our study offer a basis for risk stratification and customized care for technique failure.

PUB359

Frequency of Not Achieving Target Weight in Hemodialysis Patients and the Reasons Behind It Line Malha,^{1,2} Frank Modersitzki,¹ Lada Beara Lasic.^{1,2}
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Background: Volume overload and volume depletion have both been associated with morbidity and mortality in patients with end stage kidney disease (ESKD) on hemodialysis (HD). A recent study demonstrated an increased mortality risk when post HD weight is more than 2kg above or below the prescribed estimated dry weight (EDW) for >30% of HD sessions. Our aim was to determine the frequency of sessions with weight difference (WD) >±2kg, determine the prevalence of patients WD >±2kg for >30% of sessions and identify the possible reasons in our outpatient chronic HD population.

Methods: 32 outpatients on chronic HD at the New York Harbor VA Healthcare System in Manhattan were monitored for 2 months. Data for 631 sessions was obtained. Charts and HD nursing notes were reviewed every 2-4 weeks for: weight, prescribed EDW, ultrafiltration (UF) rate, intradialytic complications (hypotension with systolic BP < 90, dizziness, cramping, administration of intravenous fluids). Sessions with a missing documented EDW or post HD weight were excluded. 502 sessions were used in the analysis.

Results: The mean WD for all sessions was 0.67±1.64 kg with a majority (83.7%) of HD sessions ending with post HD weight within 2kg of EDW which is consistent with the literature, 6 out of 31 (19.3%) patients had WD >±2kg for >30% of the evaluated sessions. The inability to achieve post HD weight within 2 kg of EDW was most commonly (51.2%) associated with an elevated UF rate (defined as >875ml/hour). Possible reasons for not achieving EDW also included cramps (4.9%) and hypotension (2.4%).

Conclusions: Failing to achieve EDW within 2kg range is most commonly associated with high UF rates, indicating high weight gains between treatments. Proposed strategies to continue aiming at achieving EDW while compensating for the constraints of elevated UF include: decreasing intradialytic weight gain, increasing treatment frequency or treatment time. Further studies identifying the best strategies to achieve this goal are needed.

PUB360

Comparative Effectiveness of Dialyzers: A Longitudinal Propensity Score-Matched Study Scott Sibbel,¹ Abigail Hunt,¹ Suzanne Laplante,² Werner Beck,² Mary Gellens,² John Alan Laich,¹ Steven M. Brunelli.¹ ¹DaVita Clinical Research, Minneapolis, MN; ²Baxter Healthcare Corporation, Deerfield, IL.

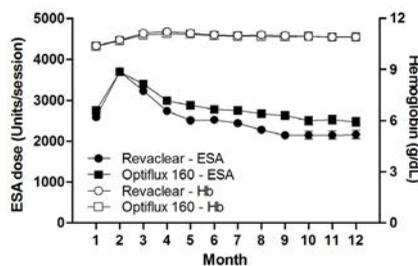
Background: Differences in dialyzer design may affect systemic inflammation and extracorporeal blood sequestration and thereby impact anemia management and control. We evaluated the comparative effectiveness of commonly used dialyzers with respect to longitudinal hemoglobin (Hb) levels, and ESA and IV iron utilization.

Methods: Patients included in the analysis received hemodialysis between 01 Jan 2009 and 31 Dec 2013 and were new users of Revaclear, Optiflux 160, or Optiflux 180 dialyzers. Patients were followed for 1 year or until end of study or censoring for dialyzer switch, modality change, or loss to follow up. For each comparison, eligible patients were propensity score-matched 1:1 on a range of demographic, comorbidity history, and baseline laboratory parameters. Outcomes were assessed using generalized linear mixed models including fixed effects for dialyzer type, time, and their interaction term.

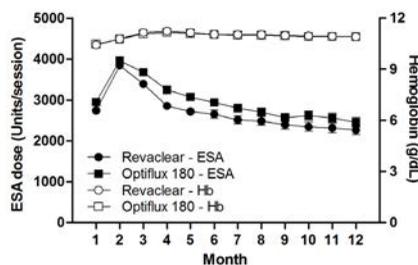
Results: Matched patient pairs (21,551 for Revaclear-Optiflux 160 comparison; 21,008 for Revaclear-Optiflux 180 comparison) were assessed. ESA doses evolved differently over time among Revaclear patients versus both Optiflux 160 and Optiflux 180 patients (p interaction < 0.001 for both). Differences in ESA dose were significant from month 3 for Revaclear versus Optiflux 160 (range, 173-483 U/treatment) and at all time points for Revaclear versus Optiflux 180 (range, 120-392 U/treatment). Hb levels were equivalent between Revaclear and Optiflux patients at all times. IV iron dosing was lower for Revaclear patients than Optiflux 160 and 180 patients (p < 0.001 for each) but differences were small (1-5 mg/month).

Conclusions: Use of Revaclear versus Optiflux dialyzers was associated with lower ESA doses, modestly lower IV iron doses, and equivalent Hb concentrations.

Revaclear vs Optiflux 160



Revaclear vs Optiflux 180



Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

PUB361

Lack of Leukocytic Response to Infections in End Stage Renal Disease
 Deepa Amberker,¹ Ritesh J. Rampure,¹ Mary C. Naglak,¹ Harold D. Stein.²
¹Internal Medicine, Abington Jefferson Health, Abington, PA; ²Hypertension Nephrology Associates, Abington Jefferson Health, PA.

Background: Patients with end stage renal disease (ESRD) on dialysis are at increased risk of infection resulting from a relatively immunosuppressed state. Dysfunctional immunity may be the result of uremia, dialyzer membrane interactions, poor nutritional status and impaired leukocyte responsiveness. Abnormal leukocytic response in such situations may result in missed diagnosis in the clinical setting as well as increased morbidity and mortality. The nature and magnitude of the leukocytic response to infection in this population has not been well characterized. This study is an attempt to assess the degree of leukocytosis in ESRD patients and compare it with the general population in the presence of an infection.

Methods: This was a retrospective study wherein all patients with ESRD on hemodialysis admitted to our hospital between December 2011 and December 2014 with any kind of infection were taken as the ESRD group and compared to others without ESRD or significant chronic kidney disease. Analysis of total WBC as well as percentage of Bandemia were compared and analyzed for statistical significance. Patients were excluded if on steroids, less than 18 years of age, presence of cancer, HIV, pregnancy, CKD stages 3-5 or if sent from dialysis unit.

Results: After reviewing the medical records of approximately 600 patients admitted for infection, 201 patients were studied based on selection criteria, of which 100 had ESRD and 101 did not. Pneumonia followed by sepsis were the most common infections in both groups. The variables studied were as shown in following table:

	ESRD group	Comparison group	P-Value
Average WBC count per microliter	10, 800	15, 700	< 0.0005
No. of patients with leukocytosis (>11000 WBC/mcl)	32 %	87 %	< 0.005
No. of patients with Bandemia (>700 bands/mcl)	26 %	41 %	0.03
Mean neutrophil percent	78.6 %	81.9 %	0.018

Conclusions: The results of this study demonstrate impaired leukocytic response in ESRD patients on dialysis with infection. Leukocytic response in this population is not a reliable infectious biomarker and if used clinically may lead to diagnostic error and potentially adverse outcomes.

PUB362

Fluid Overload Predicts Mortality Risk in Maintenance Hemodialysis Patients
 Carlo Donadio, Valentina Vigo. *Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.*

Background: Maintenance hemodialysis (MHD) patients have a high mortality rate, mainly due to cardiovascular disease and malnutrition. The aim of this study was to evaluate the efficacy of the analysis of body composition by bioimpedance (BIA) to predict the mortality risk in hemodialysis patients.

Methods: Observational longitudinal study lasting six years on 78 prevalent MHD patients (68% male, mean age 65 ± 14 years; dialysis vintage 7 ± 7 years). Every two years, starting from the baseline, we collected clinical, laboratory and BIA data, including vectorial analysis (BIVA) and hydration scale, that is the hydration as percentage of lean body mass. We compared the BIA data of patients dead during the study period (n = 45; 65%) with those of survivors (n = 24; 35%). The significance of the differences between the mean values of the two groups at the baseline was evaluated.

Results: Nine patients moved to another hemodialysis facility. The patients dead at different times during the six years had significantly higher values of BMI (28 ± 6 vs 24.8 ± 3.1 kg /m², p <0.01) and fat mass index (11.2 ± 4.1 vs 8.4 ± 2.8 kg /m², p <0.003) compared to the survivors, while there were no significant differences for body cell mass (BCM) index (7.1 ± 1.7 vs 7.9 ± 1.8 kg /m²) and serum albumin (4.1 ± 0.4 vs 4.1 ± 0.1 mg/dl). Furthermore, deceased patients had lower values of reactance (53.5 ± 11.7 vs 67.3 ± 13.7 Ohm, p <0.000003), phase angle (5.1 ± 0.9 vs 5.9 ± 0.8 degrees, p <0.00003) and the percentage of extracellular water was higher (50.6 ± 5.2 vs 46.1 ± 3.6 %, p <0.00003). Finally the BIVA analysis confirmed that the hydration was significantly higher in the deceased (73.3 ± 1.8 vs 71.2 ± 3.3 %, p <0.00006). In summary survivors had normal values of BMI and fat mass, a smaller reduction in BCM and less fluid overload than deceased patients.

Conclusions: The survival of HD patients is influenced by the nutritional status. In particular, fluid overload and decrease in muscle mass play a decisive role on survival. Fluid overload, low values of electrical resistance and phase angle predict mortality risk in MHD patients.

Funding: Government Support - Non-U.S.

PUB363

A Single Center 2-Year Experience with Haemodialysis Care in Nigeria
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Background: In Nigeria, sustaining maintenance haemodialysis while awaiting renal transplantation is largely being hampered by high cost of care. Furthermore, the scarcity of dialysis units, lack of government funding or subsidy on haemodialysis have made survival very difficult for patients with End Stage Renal Disease in Nigeria. Thus the aim of this study was to share our experience with the challenges of providing maintenance haemodialysis in a developing country.

Methods: We retrospectively reviewed records of all the patients with ESRD who had haemodialysis at our dialysis facility over a period of 24 months. Data on their demographic characteristics, etiology of Chronic Kidney Disease, types of vascular access for dialysis, frequency of haemodialysis, history of blood transfusion and patient outcomes were collected.

Results: This study included 64 patients on maintenance haemodialysis. The mean age was 43.9±18.1 years, and there were 39 males (60.9%) and 25 females (39.1%). The underlying presumed etiology of Chronic Kidney Disease were hypertension (73.4%), diabetes mellitus (3.1 %) chronic glomerulonephritis (1.6%) and (21.0%) was unknown. Their mean haemoglobin level at the time of commencing dialysis was 7.2±2.2g/dl , with 37.5 % receiving 3-4 pints of blood transfusion. The mean systolic and diastolic blood pressure were 169.1±37.6mmHg and 103.3±15.5mmHg respectively. A significant inverse correlation between haemoglobin level and serum creatinine was observed (r = -0.413, p<0.001). A predominant proportion of the patients 60(93.8%) were dialyzed via femoral cannulation, while 3 (4.7%) and 1(1.6%) received dialysis through tunneled internal jugular catheter and A-V fistula respectively. Majority of the patients 43 (67.2%) had less than thrice weekly dialysis. At the time of review, more than half of the study population 37 (57.8%) had died, while 23 (35.9%) are alive and 3(4.7%) have had kidney transplant.

Conclusions: The high mortality in this study, is likely due to a combination of inadequate dialysis with other predictors of cardiovascular events such as anaemia and uncontrolled hypertension as demonstrated in our results.

PUB364

Characteristics and Patient Survival in Nursing Home Residents on Maintenance Dialysis
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¹Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; ²NIDDK, National Insts of Health, Bethesda, MD.

Background: There is limited data on the growing nursing home (NH) population with end-stage renal disease (ESRD) in the United States. We evaluated the characteristics and predictors of mortality of NH patients on dialysis.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 782,161 patients initiated on maintenance dialysis from January 1, 2007 through December 31, 2013, followed until 31 May 2014. Covariates include age, gender, race, dialysis modality, body mass index, serum albumin, indicators

of poor functional capacity and other co-morbid conditions from the Medical Evidence Form 2728. We conducted both Kaplan-Meier and adjusted Cox regression analyses with death as the outcome variable.

Results: 56,194 (7.18%) were identified as nursing home residents upon initiation of dialysis. Among NH patients, 50.53% were female, 69.92% were white, and 99.49% were on hemodialysis and the mean age was 71.1 ± 12.1 years. The overall incidence rates of death of NH vs. non-NH patients were 51.8/100 and 17.6/100 patient-years, respectively (p<0.001). The unadjusted 1-year mortality was 50% in NH patients (vs. 20% in non-NH patients, p<0.001). Adjusted Cox analysis showed that NH patients were at significantly higher risk of death compared to non-NH patients (adjusted hazard ratio [AHR] 1.37; 95% confidence interval 1.35-1.38). Within this NH cohort, age (AHR 1.02; 95% CI 1.02-1.02), inability to transfer (AHR 1.25; 95% CI 1.22-1.29), inability to ambulate (AHR 1.08; 95% CI 1.05-1.11), cancer (AHR 1.15; 95% CI 1.12-1.19) and other co-morbid conditions were significantly associated with death.

Conclusions: NH patients on dialysis have a high mortality rate, even when compared to the broader ESRD population. Further studies on modifiable risk factors of mortality in this particularly high-risk ESRD population are warranted. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense, or the United States government].

PUB365

Bicarbonate as Nutrition Marker in Hemodialysis Patient
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Background: Protein-energy malnutrition (PEM) is prevalent in the hemodialysis (HD) population and is associated with a high morbidity-mortality burden. Metabolic acidosis and PEM are closely related. Protein intake, which constitutes an acid load, is an important factor of pH regulation in end-stage renal disease patients. Therefore, could a higher bicarbonate serum level be the result of insufficient protein intake and be a useful marker of malnutrition?

Methods: We conducted a retrospective study in our HD service using a computer database with measurements obtained simultaneously for all 342 patients. Correlation between pre-HD session bicarbonate, albumine, prealbumine and normalized protein catabolic rate (nPCR) was assessed by the use of Pearson's and Spearman's correlation test. Subgroup analysis was realised for patients with negative C-Reactive Protein (CRP < 5) and patients classified as clinically stable.

Results: We found a significant, negative and moderate, correlation between bicarbonate and nPCR, (spearman's p : -0.27, p<.0001). Subgroup analysis showed similar results, (spearman's p : -0.28, p<.0001) for 198 clinically stable patient and (spearman's p : -0.24, p<.003) for 144 patients with a negative CRP. There was no association between albumin (spearman's p : -0.06, p=0.1511) or prealbumin (spearman's p : -0.08, p=0.1511) and bicarbonate in any group.

Conclusions: A higher serum level of bicarbonate is associated with a lower nPCR, reflecting of poor protein intake, but not with a malnutrition state define by albumin or prealbumin criteria. These patients are at risk to develop a clinically apparent malnutrition state after a prolonged period.

PUB366

Scope and Consistency of Outcomes Reported in Randomized Trials of Hemodialysis
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Background: Inconsistent outcome selection and reporting in clinical trials may limit their capacity to inform evidence-based decision making and the ability to combine findings in systematic reviews. **Aim:** We aimed to assess the scope and consistency of outcome selection and reporting in trials included in systematic reviews of interventions for patients on hemodialysis (HD).

Methods: The Cochrane Database of Systematic Reviews was searched from 1999 to January 2015 for published systematic reviews of interventions for patients on chronic HD. The description and frequency of outcomes reported within the source randomized controlled trials were assessed.

Results: The 18 systematic reviews included 282 trials that reported over 518 outcomes. There was considerable heterogeneity among the outcomes reported. Across all trials, 320 outcomes occurred only once, and 198 outcomes were identified twice. The five most common outcome domains were mortality (50 trials, 18%), blood pressure (46 trials, 16%), calcium (44 trials, 16%), parathyroid hormone (41 trials, 15%) and quality of life (39 trials [14 %]). There was considerable variation in how the domains were measured, the time at which they were measured, and the units and threshold changes that defined an outcome. For example, blood pressure was reported as pre-dialysis, post-dialysis, maximum, difference in pre and post dialysis, ambulatory, resting, rise, and time to restore.

Conclusions: A wide array of outcomes are reported in trials of interventions in HD, with large heterogeneity in timing of measurements, units of measure, and threshold changes that define an outcome. This highlights the need for a well-defined set of standardized core outcomes to improve the comparability of trial findings in meta-analysis and to provide greater confidence around treatment decisions for patients undergoing HD.

Funding: Government Support - Non-U.S.

PUB367

Blood Pressure and Cognitive Decline in Hemodialysis Patients
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Background: Cognitive impairment is common in hemodialysis (HD) patients; however, the relationship between measures of blood pressure (BP) and longitudinal decline in cognitive function is unknown in this population.

Methods: 314 participants in the Cognition and Dialysis Study underwent an annual comprehensive battery of cognitive tests. Using principal components analysis (PCA), we reduced individual test results to two domain scores representing memory and executive function. Adjusted joint mixed models accounting for death, transplant, and drop-out were used to explore the association of blood pressure [systolic (SBP), diastolic (DBP) and pulse pressure (PP)] with change in cognitive function over time.

Results: Mean (SD) age was 63 (16) years, 47% were women, 22% were African American, and 44% had cardiovascular disease (CVD). Mean (SD) SBP, DBP, and PP were 141 (21), 73 (12) and 68 (15) mmHg, respectively. Median follow up time was 1.8 years (IQR 1.0-3.4). Mean slopes of PCA memory and executive were 0.03 (95% CI -0.01, 0.07) and -0.11 (95% CI -0.15, -0.06) per year, respectively. Lower DBP and higher PP were associated with decline in measures of both memory and executive function. There was no association between SBP and cognitive decline.

Changes in Slopes of Test Scores per Year (with 95% CI)*

	Test	Slope: per 1SD ↑ SBP	Slope: per 1 SD ↑ DBP	Slope: per 1 SD ↑ PP
	PCA Memory	0.00 (-0.04, 0.04)	0.03 (-0.01, 0.06)	-0.03 (-0.07, 0.01)
	PCA Executive	0.00 (-0.03, 0.04)	0.05 (0.01, 0.08)	-0.05 (-0.09, -0.01)
Contribute to PCA Memory	Recall total	-0.04 (-0.33, 0.25)	0.23 (-0.02, 0.49)	-0.34 (-0.64, -0.04)
	Delayed Recall	0.07 (-0.04, 0.18)	0.15 (0.06, 0.25)	-0.09 (-0.20, 0.03)
	Short Delay Recall	-0.02 (-0.12, 0.09)	0.03 (-0.06, 0.13)	-0.06 (-0.18, 0.05)
Contribute to PCA Executive	Digit Symbol	0.25 (-0.27, 0.76)	0.85 (0.43, 1.27)	-0.77 (-1.33, -0.21)
	Trails A	1.75 (-1.48, 4.98)	-2.34 (-5.27, 0.59)	5.28 (1.99, 8.57)
	Trails B	0.37 (-2.96, 3.71)	-3.41 (-6.19, -0.63)	4.91 (1.38, 8.45)
	Blocks	0.34 (0.00, 0.68)	0.53 (0.23, 0.82)	-0.14 (-0.51, 0.23)

*Adjusted for baseline BP measure, age, sex, race, education, vascular access and CVD. Negative coefficients are associated with worse scores except on Trails Tests. Bold results are significant.

Conclusions: Lower DBP and higher PP are associated with faster rate of cognitive decline, in particular that related to executive function. Because impairment in executive function is a manifestation of vascular disease and lower DBP and higher PP are associated with CVD in HD patients, our results suggest that cognitive decline may be mediated by vascular disease in this population.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.

PUB368

High Ferritin Levels Achieved with Ferric Citrate as a Phosphate Binder Do Not Associate with Adverse Events
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Background: Ferric citrate (FC) as a phosphate binder increases Fe stores and reduces IV iron/ESA use while maintaining hemoglobin. This analysis compares effects of higher achieved ferritin levels in subjects on FC to those in subjects on sevelamer carbonate and/or calcium acetate (active control, AC).

Methods: Data were obtained from the 52-wk active control period of the FC pivotal trial. Subjects with a baseline ferritin ≥ 1000 ng/mL or TSAT $\geq 50\%$ were excluded from the trial. We randomized 292 subjects to FC and 149 to AC. Any subjects who developed ferritin level ≥ 1500 ng/mL at any time over 52wks were identified. CV, ID, and dialysis access related adverse events (AE) occurring at any time over the 52-week period were tabulated.

Results: 57 subjects (19.8%) in the FC group and 14 subjects (9.5%) in the AC group had at least a single ferritin ≥ 1500 ng/mL (p=0.012) during the 52 wks. CV events including MI, CHF, and arrhythmias, occurred in 12.3% of the FC group compared to 21.4% AC. ID AEs occurred in 42.1% FC and 50% AC. Dialysis access related AE occurred in 15.7% FC and 42.9% AC. IV iron administration was statistically lower (p=0.003) in the FC group (2.95 \pm 3.57mg/wk) than the AC group (6.20 \pm 3.64mg/week), consistent with the full FC cohort that saw a significant reduction in IV iron use. Cumulative ESA dosing was 1016 \pm 906 Units/wk FC and 1781 \pm 1756 Units/wk AC (p=0.256).

Conclusions: This study in the subset who developed ferritin ≥ 1500 ng/mL shows that fewer subjects experienced a CV, ID, or dialysis access related AE in those receiving FC vs AC. IV iron use was statistically lower and ESA dosing was numerically lower. As previously reported the majority of ferritin ≥ 1500 ng/mL resolved and 90.1% were adjudicated to be related to IV iron and/or inflammatory AEs. This analysis, although limited by small sample size, supports the contention that FC is clinically useful and safe vs traditional binders.

Funding: Other U.S. Government Support, Pharmaceutical Company Support - Keryx Biopharmaceuticals, Inc.

PUB369

Association Between Employment Status and KDQOL Scores in Dialysis Patients Duane V. Dunn,¹ Deborah S. Evans,¹ Elizabeth I. Jones,¹ Caroline Hann,¹ Rich Mutell,² Allen R. Nissenson,¹ Deborah A. Benner.¹ ¹DaVita HealthCare Partners Inc, Denver, CO; ²Apex Health Innovations, Simi Valley, CA.

Background: Studies have shown that unemployment negatively impacts dialysis patients' quality of life (QOL).¹⁻³ QOL can be quantified and low scores on the Kidney Disease Quality of Life (KDQOL) survey are associated with poor outcomes.⁴ Our study examines employment/unemployment status and KDQOL scores.

Methods: We collected employment status data on 122,166 adult patients at a large dialysis organization from Nov 2014-Apr 2015. Patients were grouped as either employed (received pay or in training), unemployed (including retirees and those on long- or short-term disability or Workers Compensation) or other (involved in work/activity but not paid). Data were matched with patients' most recent KDQOL scores.

Results: The employed group (n=16,216) had the highest KDQOL scores in all categories, followed by the other (n=7936) and unemployed groups (n=98,014) [Table]. A clinically meaningful difference (6.8) in Physical Component Score was found between the employed (42.0) and unemployed (35.2) groups. This difference was greater (~10 points) between full-time employed and Workers Compensation patients, who scored lowest in all categories.

Table: Employment Status Among Adult Dialysis Patients at a Large Dialysis Organization and KDQOL Scores

Employment Status	n (%)	KDQOL Scores (Mean)					Age, yr (Mean)	Vintage, yr (Mean)
		PCS Score	MCS Score	Effects Score	Burden Score	Symptoms Score		
Employed Group	16,216 (13.3)	42.0	50.3	71.1	51.9	77.5	48.2	4.2
Regular Full-Time	8444 (6.9)	43.8	50.7	70.3	54.4	78.0	49.1	3.3
Training	50 (0.04)	42.9	51.0	77.1	51.2	80.7	42.5	4.8
Regular Part-Time	5622 (4.6)	41.8	50.0	69.3	52.7	76.7	48.8	4.5
Per Diem <24 Hours	2100 (1.7)	39.7	49.6	67.6	49.3	74.7	52.4	4.3
Other Group	7936 (6.5)	38.7	48.5	67.4	49.0	72.6	49.3	4.3
Student	1282 (1.0)	41.3	49.3	66.6	49.2	75.2	32.8	4.3
Caregiver	294 (0.2)	39.2	47.0	65.9	47.2	69.1	49.4	4.2
Volunteer	372 (0.3)	37.9	50.1	69.4	53.0	73.8	54.8	4.7
Homemaker	5988 (4.9)	36.2	47.7	67.7	46.8	72.1	60.4	4.0
Unemployed Group	98,014 (80.2)	35.2	47.7	63.8	44.3	71.1	55.8	3.3
Unemployed	33,929 (27.8)	36.6	47.6	65.7	45.8	71.3	50.9	4.3
Long-Term Disability	19,166 (15.7)	35.4	47.2	65.0	44.5	71.6	53.0	4.2
Short-Term Disability	937 (0.8)	36.7	47.5	62.3	43.1	71.5	48.9	1.6
Retired	43,874 (35.9)	35.3	49.7	70.9	50.0	75.0	71.7	3.4
Workers Comp	108 (0.1)	32.1	46.7	55.2	37.9	66.1	54.6	2.9
Total	122,166 (100.0)	36.8	48.7	68.0	48.2	73.5	58.7	3.9

Abbreviations: Comp, compensation; KDQOL, Kidney Disease Quality of Life; MCS, Mental Component Score; PCS, Physical Component Score; yr, years

Conclusions: Preliminary analysis found employment is positively associated with KDQOL scores among dialysis patients. More studies are needed to better understand whether patients with higher QOL are more likely to work or whether working contributes to improve QOL. References) Lopes AA et al. *Qual Life Res.* 2007;16(4):545-557. 2) Curtin RB et al. *Am J Kidney Dis.* 1996;27(4):533-540. 3) Kutner NG et al. *Clin J Am Soc Nephrol.* 2010;5(11):2040-2045. 4) Mapes DL et al. *Kidney Int.* 2003;64(1):339-349.

PUB370

Reduction of Pruritus in Hemodialysis Patients by Adjustment of Serum B-Type Natriuretic Peptide Yoshio Shimizu,¹ Nao Nohara,² Eri Nomura,² Kaori Yamada,² Mayumi Matsumoto,² Toshiaki Kano,² Yasuhiko Tomino.² ¹Juntendo Univ Shizuoka Hospital, Izunokuni, Japan; ²Juntendo Univ, Tokyo, Japan.

Background: Pruritus reduces the quality of life (QOL) and worsens the prognosis in hemodialysis patients. It was reported that the neuropeptide natriuretic polypeptide B (Nppb; alias BNP) is a neurotransmitter of pruritus. We reported that serum BNP was a factor that contributed to the exacerbation of pruritus in hemodialysis patients. We determined whether pruritus could be reduced by controlling serum BNP.

Methods: Forty-eight patients participated in this study. (Test 1) Serum BNP was measured with common laboratory tests and visual analogue scale (VAS) in a single hemodialysis session. The factors influencing the changes of VAS during the dialysis session were analyzed. (Test 2) The fluid volume was strictly managed to decrease serum

BNP level by reporting the weight gain during each dialysis session. Patients who gained more than 5% of the target dry weight were warned with a document and the session was extended until they reached the target dry weight. VAS, DLQI (Dermatology Life Quality Index) and an inventory survey using the KDQOL (the kidney disease quality of life short form, Ver.1.3) were examined once a month.

Results: (Test 1) VAS decreased significantly after dialysis. Similarly, a significant decrease was found in BNP. Using univariate analysis, a significant correlation was found in the change in serum BNP, urea nitrogen, iron and ferritin. In multivariate analysis the BNP change and serum iron were extracted as factors that influenced a decrease of the VAS. (Test 2) BNP reduced the overall mean. Monthly VAS did not decrease for the first two months, but after three months, a significant decrease was observed (p=0.031). DLQI did not correlate with the BNP at the beginning of the study, but one month later, a significant correlation was found between DLQI and BNP. No improvements in either a renal disease-specific standard or the comprehensive standard in KDQOL were observed as a result of the intervention.

Conclusions: It was suggested that the adjustment of serum BNP by strictly managing the weight reduced pruritus in hemodialysis patients but it was difficult to improve long-term QOL.

Funding: Pharmaceutical Company Support - Novartis, Kowa, Tanabe-Mitsubishi, Kyowa-Kirin, Private Foundation Support

PUB371

The Mechanisms Study on Neointimal Hyperplasia of Autogenous Arteriovenous Fistula in Maintenance Hemodialysis Patients Nanmei Liu, Jimin Hospital of Shanghai.

Background: To evaluate the influence and the possible mechanism about neointimal hyperplasia of autogenous internal arteriovenous fistula in hypertensive nephropathy and diabetic nephropathy patients which was going maintenance hemodialysis and provide possible theory about how to prevent from intimal hyperplasia, extend the life of AVF in clinic.

Methods: Collecting cephalic vein when the hemodialysis patients had the surgery of AVF angioplasty and reconstruction. Vascular tissues were divided into chronic glomerulonephritis group, hypertensive nephropathy group and diabetic nephropathy group. Immunohistochemistry was used to detect the expression of vascular smooth muscle actin (a-SMA). Selecting the control group and fistula vascular tissue which the useful life was 12-18 months, basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-1), matrix metalloproteinase2 (MMP2) and matrix metalloproteinase9 (MMP9) were to detect expression change by immunohistochemical staining.

Results: Compared with chronic glomerulonephritis group, intima thickness of hypertensive nephropathy and diabetic nephropathy were significantly increased and the increase was more significant in diabetic nephropathy. Hyperplasia intima was eccentric thickening and the hyperplasia intima showed obvious inflammatory cells infiltration and vacuolar degeneration. Immunohistochemical staining showed that compared with the group of chronic glomerulonephritis, hypertensive nephropathy and diabetic nephropathy groups' a-SMA, bFGF, IGF-1 and MMP9 expression levels were significantly increased, expression of VEGF was significantly reduced, MMP2 was no significant change (P>0.05). Univariate regression analysis revealed that the expression levels of a-SMA was positively correlated with bFGF, IGF-1 and MMP9, negatively correlated with the VEGF. AVF intimal hyperplasia mainly dominated by the vascular smooth muscle cells (VSMC) proliferation.

Conclusions: Hypertension and diabetes can accelerate the process of intimal hyperplasia, shorten the life of fistula and diabetes promote intimal hyperplasia more significant. This study provides a theory and therapeutic targets for the prevention and treatment on intimal hyperplasia of AVF in dialysis patients.

Funding: Government Support - Non-U.S.

PUB372

Association of Nutritional Status with Depression and Sleep Disorders in Elderly Hemodialysis Patients Avsin Ibis,¹ Emre Tural,² ¹Nephrology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey; ²Nephrology, Baskent Univ Hospital, Ankara, Turkey.

Background: The relationship between depression, sleep quality, and malnutrition in an elderly population in maintenance hemodialysis is very complex and not yet fully understood. We aimed to determine the association between nutritional status and psychological factors such as depression and sleep disturbance in elderly dialysis patients.

Methods: Seventy three dialysis patients (41 female, 32 male; aged, 72.5 \pm 6.0 years) older than 65 years of age, were enrolled in the study. Nutritional status was determined by Subjective Global assesment (SGA). Beck Depression Inventory (BDI) questionnaire was used to measure presence and degree of depression. Quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI). Demographic and biochemical parameters and Charlson Comorbidity Index and frequency of infection in previous year period of all patients were recorded.

Results: In our elderly patients 15 (%20.5) had sleep disorder and 24 (%32.9) had mild to moderate depression and 11 (%15.1) had moderate to severe depression. According to SGA 48 (%65.8) patients were well-nourished and 25 (%34.2) patients had mild-moderate and severe malnutrition. When the well-nourished and malnourished patients were compared, well-nourished group had higher albumin levels (4.28 \pm 0.25 g/dL vs 3.50 \pm 0.36 g/dL), lower CRP levels (7.51 \pm 4.23 vs 16.02 \pm 19.45), better quality of sleep (3.50 \pm 0.82 vs 5.56 \pm 1.73) and better depression scores (8.68 \pm 2.75 vs 16.28 \pm 4.56) than malnourished group. By multivariate analysis when factors affecting nutritional status were taken into account BDI (p=0.001; OR=1.79; CI, 1.26-2.56) and PSQI (p=0.022; OR=4.33; CI, 1.23-15.2) was associated with SGA.

Conclusions: Depression and sleep disorders are important factors influencing the nutritional status and could be an independent risk factors for malnutrition in elderly patients receiving maintenance dialysis. Psychological assessment should be mandatory in the follow up of these patients to identify depression and sleep disturbance because many of them are reversible.

PUB373

Predialysis Hyponatremia and Mortality in Elderly Patients with Incident Maintenance Renal Replacement Seon Ha Baek, Sung Woo Lee, Shin-Young Ahn, Sejoong Kim, Ki Young Na, Dong-Wan Chae, Ho Jun Chin. *Internal Medicine, Seoul National Univ Bundang Hospital, Republic of Korea.*

Background: Predialysis hyponatremia recently have been reported to be associated with mortality in incident hemodialysis patients. However, little is known about whether predialysis hyponatremia is associated with unfavorable outcomes in elderly patients.

Methods: We retrospectively assessed mortality in 397 (mean age 73.0 year, male/female 226/171) patients aged ≥ 65 years with non-diabetic end-stage renal disease (ESRD) who initiated renal replacement therapy (RRT) at a tertiary university hospital between 2000 and 2010. 1 year all-cause mortality (ACM) was analyzed in relation to predialysis serum sodium (sNa). We divided subjects into 3 groups according to sNa: Group1, < sNa 125; Group 2, sNa 125-134, Group 3, sNa ≥ 135 mEq/L. Patients with sNa levels >145mEq/L were excluded.

Results: The median value of sNa was 137 mEq/L (interquartile range 133-140 mEq/L). Chronic comorbidities including congestive heart failure ($r = -0.215$, $P < 0.001$) and liver cirrhosis ($r = -0.174$, $P < 0.001$), late referral ($r = 0.230$, $P < 0.001$), use of thiazide ($r = -0.160$, $P = 0.001$), lower estimated glomerular filtration rate ($r = 0.152$, $P = 0.005$) and albumin ($r = 1.296$, $P = 0.002$), higher white blood cell count ($r = -0.136$, $P = 0.006$) were associated with lower sNa levels in elderly patients after fully adjustment. One hundred and five (26.4%) patients had died at the 1-year follow up. Higher sNa level was associated with lower adjusted ACM in a continuous model (HR 0.433, 95% CI 0.261-0.718, $P = 0.001$). Group 1 had a higher mortality than normonatremia group in a categorical model (reference group 3, HR 5.048, $P = 0.018$) and mortality difference was not observed between group 2-3 (reference group3, HR 1.511, $P = 0.161$).

Conclusions: Predialysis hyponatremia was associated with increased 1-year mortality in elderly ESRD patients who initiated RRT. However, the higher mortality was only observed in elderly patients with severe hyponatremia (sNa < 125mEq/L). These finding suggested that compared to adults <65 years, other comorbidities or factors rather than sNa may affect mortality in elderly.

PUB374

Observation of the Correlation Between the Uremic Toxins with Clinical Feature in Uremia Patients Mei Li,¹ Qiong-Li Yin,¹ Zhenda Zheng,² Cai-Lian Cheng,³ Xun Liu,³ Cheng-Gang Shi.³ *¹VIP Healthcare Center, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China; ²Cardiovascular Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China; ³Nephrology Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.*

Background: To investigate the correlation between the uremic toxins with age, dialysis duration, and the different blood purification techniques on removal uremic toxins with hemodialysis (HD) and hemodiafiltration (HDF).

Methods: 72 cases of maintenance hemodialysis patients were observed, age 28~80years(59.75 \pm 13.86), dialysis duration 4~192months (34.46 \pm 39.15), HD group (n = 50), HDF group (n = 22)(once 1~2 weeks).Before each conventional HD and HDF therapy, blood was sampled for small molecule water-soluble toxins BUN with automatic biochemical analyze, Middle molecular and macromolecular toxins (MMS) with Ultraviolet spectrophotometry, pentosidine(PENT) with enzyme-linked immunosorbent assay method(from ADL Company, USA), Protein-bound toxins, indoxyl sulfate(IS) with high performance liquid chromatography method.

Results: For HDF versus HD, there was no significant differences between BUN,MMS, pentosidine and IS. There was low positive correlation between MMS, PENT, IS and the age of the patients (r being 0.322, 0.263 respectively, $P < 0.05$). MMS, PENT and IS were positively related with dialysis months (r being 0.406, 0.427, 0.742 respectively, $P < 0.05$).

Conclusions: HD and HDF therapy maybe not good enough in clearing middle molecular toxins and protein-bound toxins, which results in their accumulation in patient's body with the increase of dialysis course. It is recommended that better dialysis methods be adopted for patients who have received hemodialysis for a long time.

PUB375

Parathyroid Hormone Response in Chronic Hemodialysis Patients Converted from Intravenous Doxercalciferol to Oral Calcitriol Three Times a Week Anna Jeanette Jovanovich,^{1,3} Annegret Howe,² Morgan E. Marcuccilli,³ Michel Chonchol.³ *¹Denver VA Medical Center; ²Fresenius Medical Care; ³Univ of Colorado Denver.*

Background: The purpose of this study was to characterize serum calcium, phosphorus and intact parathyroid hormone (iPTH) level response during the initial 24 weeks following conversion from intravenous doxercalciferol to oral calcitriol three times a week in a real-world setting.

Methods: Data was collected by a retrospective chart audit of end stage renal disease patients on hemodialysis in an outpatient chronic dialysis unit. We identified 33 chronic

hemodialysis patients that had a record of treatment with intravenous doxercalciferol (6 months) and conversion to oral calcitriol three times a week (6 months) between June 2014 and May 2015 following a conversion algorithm. The change in serum calcium, phosphorus, and iPTH between treatment periods (intravenous doxercalciferol vs. oral calcitriol) was analyzed.

Results: Patient characteristics were as follows: mean age, 63 \pm 16 years; 39% women; and 55% black. The mean (SD) for serum calcium and phosphorus and median (IQR) serum iPTH during the 6 months of intravenous doxercalciferol were 8.8 \pm 0.7 mg/dL, 4.5 \pm 1.3 mg/dL and 643 (384 to 908) pg/mL, respectively. The corresponding values after 6 months of oral calcitriol were 8.8 \pm 0.6 mg/dL, 4.5 \pm 1.2 mg/dL and 545 (368-812) pg/mL. None of the comparisons achieved statistical significance ($p > 0.43$ for all). 48% of participants were on cinacalcet during each of the treatment periods. The median (IQR) change in iPTH increased slightly among those patients receiving oral calcitriol and sevelamer (34 (-132 to 147)) pg/mL while iPTH decreased among patients receiving oral calcitriol and other non-sevelamer binders (-102 (-294 to 155) pg/mL; $p = 0.177$).

Conclusions: This small retrospective study suggests that conversion from intravenous doxercalciferol to oral calcitriol using a conversion algorithm maintains iPTH within KDIGO recommended targets and does not appear to cause hypercalcemia or hyperphosphatemia. The clinical significance of higher iPTH values among those treated with oral calcitriol and sevelamer needs further study.

Funding: NIDDK Support, Veterans Administration Support

PUB376

Pregnancy and Dialysis in Chronic Kidney Disease – A Case Study Morgan E. Lindsay, Syed S. Haqqie, Arif Asif. *Albany Medical College.*

Background: For women with underlying renal disease, pregnancy remains high risk. Case series have provided guidance on the interdisciplinary management of these patients. Herein, we report one institution's management of five patients requiring dialysis in pregnancy. The present case series includes patients with chronic kidney disease secondary to lupus nephritis (n=2), cystinosis (n=1), malignant hypertension (n=1), and diabetic nephropathy (n=1). All five patients, one of whom was on dialysis prior to pregnancy and the rest were CKD 5 were placed on six-times weekly dialysis upon the presentation with pregnancy. Three of the patients, two with Lupus and one with Malignant HTN delivered infants with whom they were able to discharge home after NICU stays, two patients one with cystinosis and one with DM delivered infants who subsequently died in the NICU secondary to prematurity. All 5 patients post-delivery continued on maintenance hemodialysis. Although improving, maternal and fetal outcomes in those with chronic kidney disease remain variable. Our experience adds to the growing literature on dialysis for chronic kidney disease in pregnancy.

Methods: Restrospective study of patients at one institution.

Results: Out of five pregnancies three had successful outcome with intensive dialysis.

Conclusions: Pregnancy is rare in dialysis patients and outcomes are generally poor. There are improved results with intensive dialysis and multidisciplinary approach to the management.

PUB377

When Shall the Advanced Chronic Kidney Disease Patients Start Dialysis? Lee Ying Yeoh, Sri Fairuz baizuri Saiffull, Bek Choon How, Yan Lun Allen Liu, Milind Nikam. *Medicine, Khoo Teck Puat Hospital, Singapore.*

Background: Recent guidelines suggest dialysis should be initiated when estimated glomerular filtration rate (eGFR) drops below 10-12ml/min. The aim of the present study was to analyse outcomes of those initiating dialysis at very low eGFRs.

Methods: A single center, prospective study of new ESRD patients who were initiated on dialysis between 2012 –2014 and dialysis was performed for >90 days. The patients were categorized into 2 groups according to eGFR ≤ 5 and > 5 ml/min upon initiation. The patients with incomplete data, and those who underwent transplantation were excluded.

Results: A total of 251 patients were included with mean age of 59.0 \pm 11.9 years, mean eGFR of 5.4 \pm 2.9ml/min; 57% were males and 51.4% were Chinese. Majority started on hemodialysis (81.7%) and 69.7% were unplanned. The survival rate till May, 31 2015 was 88.4%; 61% were initiated when eGFR ≤ 5 (mean 3.6 \pm 1.1 ml/min) and 39% with eGFR > 5 (mean 8.3 \pm 2.6 ml/min). Dialysis vintage was shorter in the group with eGFR ≤ 5 (18.5 \pm 9.5 vs. 21.7 \pm 11.1 months). The patients with eGFR ≤ 5 had lower Charlson Comorbidity Index (4.0 \pm 1.3 vs. 4.7 \pm 1.2), and hemodialysis was preferred (90.9% vs. 67%). The disease burden was significantly lower in the group with eGFR ≤ 5 , including diabetes mellitus (72.1 vs. 88.7%), ischemic heart disease (23.4% vs. 37.1%) and peripheral arterial disease (4.5 vs. 12.4%). However, there were trends showing that these patients were younger, had higher serum albumin and shorter hospitalization for index admission. Underlying diabetes, ischemic heart disease, modality selection and dialysis vintage remained significant after adjusted. Mean survival for both groups were comparable (36.3 months, 95% CI: 34.4-38.2 vs. 34.5 months, 95% CI: 32.0-37.0). Among the patients who survived, 97.7% remained on their initial modality.

Conclusions: Our study suggests that the ESRD patients without significant morbidities may be able to delay dialysis initiation without significant short term adverse outcomes. Further studies are required.

PUB378

The Incidence and Type of Cancer in Patients with End-Stage Renal Disease: A Prospective Cohort Study for End-Stage Renal Disease in Korea Kyung Don Yoo,¹ Hajeong Lee,¹ Jung Pyo Lee,¹ Dong Ki Kim,¹ Shin-Wook Kang,² Chul Woo Yang,³ Yong-Lim Kim,⁴ Chun Soo Lim,¹ Kwon Wook Joo,¹ Yon Su Kim.¹ ¹Seoul National Univ; ²Yonsei Univ; ³The Catholic Univ; ⁴Kyungpook National Univ.

Background: In patients with end-stage renal disease, urinary tract kidney cancer is known to be higher than in the general population. However, the incidence and type of cancer is affected by variable factor such as age, gender, ethnic differences. Moreover, the causality of dialysis and cancer incidence in certain type of cancer is still needed to be clarified.

Methods: A total of 5,225 patients in the clinical research center for ESRD cohort were enrolled from Aug 2008 to Dec 2014. The primary outcome is to compare the cancer incidence rate of ESRD patients with the general population. We obtained cancer incidence data from National Cancer Information Center Registry in healthy counterpart.

Results: A total of 2,200 incident and 3,035 prevalent dialysis patients was included the analysis. The mean follow up duration was 25.6 ± 16.2 months, and 116 (2.2%) patients were diagnosis with cancer during the observation periods. ESRD with cancer group was significantly older, longer dialysis duration and more comorbidity than control group. The incident rate of cancer in prevalent dialysis patients was higher than those in incident dialysis patients (2.5% vs. 1.3%, p=0.002). The proportion of primary organ was highest in digestive organ (33.6%) including stomach, colon. The mean time to discovery of cancer from dialysis initiation was 58.6 months in digestive cancer, 52.0 months in urinary tract cancer. The standardized incidence ratio (SIR) of overall cancer was 0.94 [95% CI: 0.72–1.19]. Urinary tract cancer showed the highest SIR [SIR: 4.7, 95% CI: 4.42–8.19] and had the second highest frequency (16.1%). Interestingly, the highest frequency (33.3%) of digestive organ cancer showed no difference in the incidence of cancer compare to the general population [SIR : 0.607, 95% CI: 0.36–0.94].

Conclusions: Further research was needed to compare the organ-specific cancer incidence of ESRD patients with the general population. The screening test could be necessary for digestive and urinary tract cancer.

PUB379

The Role of Social Support in Hemodialysis Patients Gun Woo Kang. *Internal Medicine, Catholic Univ of Daegu School of Medicine, Daegu, Korea.*

Background: A number of patients with End-Stage Renal Disease (ESRD) have significant impairment in social support. Especially, the limited function of patients with hemodialysis (HD) prevents them from social activities and even makes them social withdrawal. There are few studies of the factors affecting the social support in HD patients. The aim of the current study was to identify the clinical and psychosocial factors including quality of life related to impaired social support in HD patients.

Methods: The 101 participants on HD from the Daegu Catholic University Medical Center were assessed from September in 2013 to September in 2014. Patients on HD for acute kidney injury were excluded from this study. Multidimensional Scale of Perceived Social support(MSPSS) was used for evaluating patients' social support. Psychosocial factors including quality of life, anxiety, depression and sleep disorder were evaluated. Laboratory and clinical information including hemoglobin, vitamin D (25(OH)D, 1,25(OH)₂D₃), albumin, Kt/V, normalized protein catabolic rate, ferritin, bone mass index, duration of HD were assessed. Stepwise multivariate logistic regression with backward selection was performed.

Results: The mean of MSPSS (social support) score was 36.8±9.3. In subgroups of social support, the MSPSS-family, MSPSS-friend, and MSPSS-medical team scores were 14.79±4.28, 10.44±4.76, and 10.74±4.39, respectively. The variables showed significant association with social support were quality of life (r=0.332, p=0.001), depression (r=-0.290, p=0.003), anxiety (r=-0.372, p<0.001), and serum creatinine (r=-0.270, p=0.007). Multiple regression showed that quality of life (95% CI; 0.615–19.799, p=0.037) and serum creatinine (95% CI; -1.543–0.319, p=0.003) were independent predictors of impaired social support.

Conclusions: This study explored the determinants of high susceptibility to the impaired social support in HD patients. We found that the impaired social support is associated with the quality of life and serum creatinine. Further study will be needed because of the possibility of different results depending on culture and ethnicity. As well as, we should consider the psychosocial interventions to improve the impaired social support.

PUB380

Use of Portable Fundoscopic Photography to Screen for Diabetic Retinopathy in the Hemodialysis Unit Beckie Michael,¹ Yasmin G. Brahmhatt,² Nika Bagheri,³ Laura T. Pizzi,⁴ Benjamin Leiby,⁴ Anne P. Murchison.³ ¹Marlton Nephrology and Hypertension; ²Thomas Jefferson Univ; ³Wills Eye Hospital.

Background: Over 40% of dialysis patients have diabetes, yet only 25% get annual eye exams. Due to the frequency and duration of visits to dialysis centers, patients on dialysis likely have increased barriers to receiving eye exams and other recommended preventive care. This study evaluated the need for ophthalmic care, barriers to care, and prevalence of diabetic retinopathy (DR) in this population.

Methods: Prospective cohort study at two dialysis centers (1 urban, 1 suburban). A patient survey (measuring eye care utilization, barriers to eye care, and self-reported visual functioning) and eye screening (visual acuity test and non-mydratric fundus photos) was completed for diabetics who consented to the study. Other variables were obtained from medical records and included demographics, duration of diabetes, co-morbidities, and

insurance type. Descriptive analyses examined barriers to eye care and presence of DR. Qualitative data on satisfaction with eye screening were also obtained from both staff and patients.

Results: 58 patients (79.5% of diabetics at the two sites) were screened. Of the readable fundus photos, 50% had DR and only 10% had no ocular abnormalities. The majority (64%) knew diabetes can cause severe eye problems. Only 11% of patients reported that getting an annual eye exam is a priority. The most commonly reported barriers to eye care were cost (89%) and transportation difficulty (82%). Qualitative data indicated that staff and patients were overall very satisfied with the program.

Conclusions: There is a significant unmet need for ophthalmic care among diabetics receiving dialysis. Since cost and transportation were reported as main barriers to eye exams, providing the screening at dialysis centers could improve adherence to eye care thereby improving ophthalmic and other health outcomes.

Funding: Private Foundation Support

PUB381

Recent Dialysis Beginning Is a Mortality Predictor for In-Patients Treatment Nadia Guimaraes- Souza, Ana C M S Ramos, Thais Nemoto Matsui, Adriano Luiz Ammirati, Maria C.C. Andreoli, Fabiana Dias Carneiro, Marisa Petrucelli Dohr, Bento C. Santos. *Dialysis Center, Hospital Israelita Albert Einstein, Brazil.*

Background: Acute kidney failure occurs in 5% of hospital admitted patients. Dialysis need during patients stay in hospital is associated with higher mortality risk. The main objective was to evaluate patients profile in our dialysis center and the impact in the outcomes.

Methods: Prospective observational study. A check list was applied for every patient originating from intensive care or in clinics who need hemodialysis section in our dialysis center from 2010 to 2014. Patients were older than 18 y. o. and signed a consentment term. For analysis purpose patients were assigned as undergoing previously dialysis (PD) or patients that initiated dialysis in this hospital stay (ND). The possible outcomes were: kidney recovering function (KRF), kidney transplantation (KT), mortality (M) and maintained dialysis (MD). 437 patients were included. 231 (53%) were patients PD, 47% of ND.

Results: From all patients in our follow-up 27% were from kidney transplant program (KTP) and 33% were from liver transplantation program (LTP). 15 % started dialysis with arterial-venous fistula, 14% tunneled cuffed catheter and 51% with non-tunneled cuffed catheter. PD groups had more hypertension and were more likely came from KTP (p<0.01). ND group had significantly more C hepatitis (p<0.01) and came from LTP. In the outcomes we observed ND patients had higher mortality (25% vs 13%; p<0.01) and also significantly higher KRF (63% vs 10%; p<0.01). MD outcome was more prevalent in PD group (47% vs 11%; p<0.01) as expected. When risk factors for our outcomes were analyzed patients coming from KTP, LTP and positives for C hepatitis had significantly higher KRF. Mortality were similar among the groups. Hypertensive patients had worse outcomes. Recovery time in days was shorter in ND group (56±140 vs 148±283;p<0.01).

Conclusions: It's well known that patients treated with chronic dialysis have an increased risk of death. Surprisingly we observed a higher mortality rate on the ND group. Hypertension is a risk factor for worse outcomes. Check list is an important tool for analyzing and follow patients undergoing dialysis.

PUB382

Awareness and Beliefs Towards Organ Donation in Chronic Kidney Disease Patients in Western India Manish Ramesh Balwani. *Nephrology, IKDRC, Ahmedabad, Gujarat, India.*

Background: In India, there seems to be paucity of information and awareness regarding organ donation in general population. The study was conducted to see the awareness and beliefs towards organ donation programme in chronic kidney disease patients in western india.

Methods: The author conducted a cross sectional study among 85 CKD patients to evaluate the knowledge about and attitude towards organ donation at a large tertiary academic hospital in western india. The author used a questionnaire that included items on knowledge, attitude and demographics.

Results: Age of respondents participated in study ranged from 15 to 75years. Around 2/3rd participants were males. About eighty-two percent belonged to hindu religion. All were aware of term organ donation and cadaver donation. About 47% of people heard about organ donation through hospital or from doctor. The audiovisual media such as television (21%) followed by newspaper/magazines (14%) were the major source of information about organ donation. Strikingly, radio was not the source of information to any of the respondents who participated in this study, despite radio being one of the most common medium of mass communication in india. Fourteen percent of people heard about organ donation through a friend or colleague. Almost 1/3 rd of patients were unaware about any legislation regarding organ donation. All respondents felt that the organs should go to the needy irrespective of their religion. About 70% feel that medical colleges/government institutions should make decisions about organ donation in case of unclaimed dead bodies. About 64.70% believe that there is a danger that donated organs could be misused, abused or misappropriated.

Conclusions: The study shows about 64% of our participants believe that there is a danger that donated organs could be misused, abused or misappropriated. There seems to be paucity of information and awareness regarding organ donation among CKD patients. Mass media, religious and political leaders may be involved to maximize awareness about organ donation.

PUB383

Enhancing Patient Engagement in Future Clinical Trials – The Effects of Age and Ethnicity Territa Santhakumaran, Kieran Mcafferty. *Renal, Royal London Hospital, London, United Kingdom.*

Background: Increasing patient engagement from ethnic minority populations is crucial to the widespread applicability of research findings, but this represents a challenge in nephrology clinical research. Ethnicity, socio-cultural and language barriers along with a lack of understanding and awareness of clinical trials are potential factors that affect patient involvement in clinical trials.

Methods: We developed a patient survey in English, Urdu and Bengali to represent our ethnically diverse population in East London to explore the attitudes and understanding of clinical research using a 1-7 scoring system to rate various statements about research. The surveys were offered to all patients attending the haemodialysis and renal outpatients department over a 2 week period.

Results: 151 forms were completed, 143 in English, 7 in Bengali and 1 in Urdu. 41% of forms were from patients who attended transplant clinic and 31% from patients who attended for haemodialysis. Overall there was a strong message that patients wanted more trials in nephrology and felt that taking part in trials would help them take a more active role in their health. They also felt there was a lack of information on how to access research opportunities. Of those who completed the survey there was no significant ethnicity differences in their attitudes and understanding of clinical research, however transplant patients who identified themselves as White British were significantly more likely to take part in the survey (p<0.02). Patients who identified themselves as Black British were significantly less likely to take part in the survey (p<0.02). In the dialysis cohort, patients who identified themselves as White British were significantly more likely to take part in the survey (p<0.02). Whereas patients who identified themselves as Bangladeshi were significantly less likely to take part in the survey (p<0.04). Age did not appear to have an effect on patients' perception and understanding of clinical trials.

Conclusions: From our work it is clear that there is a patient led demand for greater engagement in translational research. However, challenges remain in engaging ethnic minority cohorts in clinical research.

Funding: Other NIH Support - National Institute for Health Research

PUB384

Deferred Educational App Personalization Increases Registration Completion Daniel Schwartz,¹ Chan Kruse,² ¹Faculty of Medicine, Univ of British Columbia, Vancouver, BC, Canada; ²QxMD, Vancouver, BC, Canada.

Background: 'Read by QxMD' (<http://qxmd.com/read>) is an app that curates the nephrology literature and personalizes reading recommendations based on a clinician's or researcher's interests. In order to provide highly accurate recommendations, the app must collect content preferences such as preferred journals and topics. In addition, it must collect email address and personal identifiers in order to complete registration and offer CME. When the registration process is too onerous, mobile app users may not complete registration. If the registration process fails to collect necessary user data, this may negatively impact the educational value of the app. We hypothesized that allowing users to delay providing personal information until after they set their preferences would increase registration completion.

Methods: We randomly assigned all users registering on the Android version of Read to two different registration processes. In version 1, "upfront personalization", users are asked to provide personal identifiers prior to setting their preferences, while in version 2, "deferred personalization", users set preferences first and after this has been completed are asked for personal identifiers. The Leanplum SDK was used to implement and automate the randomization of alternate registration pathways. The primary outcome was completion of registration.

Results: Between April 6, 2015 and June 1, 2015, a total of 5660 users who registered using the Android version of 'Read' were randomized with 2824 users randomized to upfront personalization and 2836 to deferred personalization. Upfront personalization yielded a 47.4% (95% CI 46.0 to 48.8) registration completion rate versus 50.7% (95% CI 49.0 to 52.4) with deferred personalization (p < .05).

Conclusions: A strategy of deferred collection of personal identifiers yielded slightly higher completion rates. To maximize user registration when onboarding users to educational medical apps, consider deferring the collection of personal information until user preferences have been provided. Further research is required to maximize app registration when data requested is extensive as in 'Read'.

PUB385

Onconeurology Abstracts Trends in ASN Kidney Week 2012-2014 Jyotsana Thakkar, Rimda Wanchoo, Kenar D. Jhaveri. *Nephrology, Hofstra NSLIJ School of Medicine.*

Background: Onconeurology is an emerging new specialty of nephrology. The ASN created a forum dedicated to the field of Onconeurology in 2011 to improve collaborative care for cancer patients with kidney disease. One of the aims was to allow for collaborative research strategies in the field of onconeurology. However, the number of onconeurology related abstracts accepted to be presented at ASN Kidney Week (ASN-KW) 2012-2014 is not known.

Methods: We reviewed the abstracts presented in the ASN-KW over past 3 years from 2012-2014 which were related to Onconeurology. Search terms used to identify abstracts included cancer, myeloma, chemotherapy, tumor lysis, paraneoplastic syndrome and

hypercalcemia. They were then categorized into: basic science, chemotherapy, myeloma, epidemiology, electrolyte disorders, AKI, tumor lysis, GN, paraneoplastic syndromes and obstructive uropathy. Abstracts were also categorized based on study design.

Results:

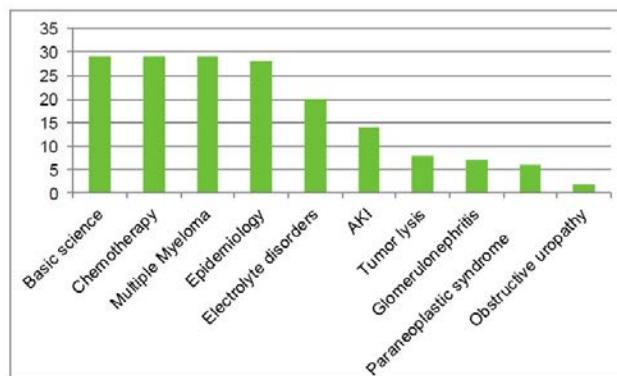


Figure above breaks down the total number(n) of abstracts(Y axis) in the last 3 years presented at ASN-KW by category. There has been an increase in the number of onconeurology abstracts over last 3 years. A total of 175 abstracts were reviewed. In 2012, there were 50 onconeurology related abstracts, increased to 54 in 2013 and 71 in 2014. Abstracts related to basic science(16%), chemotherapy toxicities(16%), myeloma(16%) and epidemiology (16%) dominated most of the accepted abstracts. Of the clinical abstracts, > 50% were case reports, 41% were retrospective studies, 4.5% database studies and <1% RCT.

Conclusions: Over the last 3 years, we have seen a growing trend in the number of abstracts submitted in the ASN-KW related to the field of onconeurology. We suggest creating a separate section dedicated to onconeurology in the ASN meetings to allow for collaborative research and greater understanding of cancer related nephrology, leading to improved patient outcomes.

PUB386

Patients-Initiated Educational Research in a Digital Age Chayakrit Krittanawong,¹ Zhen Wang,² Sakkarin Chirapongsathorn,^{3,4} Hua Ann Jenny Lu,⁵ ¹Div of Cardiovascular Disease, Mayo Clinic, Rochester, MN; ²Dept of Healthcare Policy and Research, Mayo Clinic, Rochester, MN; ³Div of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; ⁴Div of Gastroenterology, Dept of Medicine, Phramongkutklo Hospital and College of Medicine, Royal Thai Army, Bangkok, Thailand; ⁵Div of Nephrology, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Background: The emergence of web-based technology in the digital age has become popular in the healthcare industry, particularly in the educational research field. A web-based technology can bridge the educational gap between researchers and patients.

Methods: We aimed to develop a user-friendly interface between a virtual community that can be used by patients and researchers and a preliminary knowledge-building activity. Wikiheart is a web research environment that creates a real-time community between researchers and patients without geographical restrictions.

Results: Once patients have registered for free, the system allows these users to write their own articles or to edit other articles, which often leads to thought provoking medical research questions. Wikiheart also demonstrates a novel approach to population science that is based on huge databases with multiple cloud servers that reach the web research community. Nowadays Wikiheart has more than one million visitors, and serves as an educational web technology that provides its users with both a variety of learning methods, and several areas of research focus.

Conclusions: Wikiheart is an innovative web-based program for conducting educational research in the digital community. It is an excellent tool for researchers and patients to generate new hypotheses via the scientific method in an online environment.



PUB387

Detailed Subject Lines Increase Engagement with Educational Emails
Daniel Schwartz,¹ Chan Kruse,² Stephane Boyer.² ¹Faculty of Medicine, Univ of British Columbia, Vancouver, BC, Canada; ²QxMD, Vancouver, BC, Canada.

Background: 'Read by QxMD' (<http://qxmd.com/read>) is an educational service and mobile app that curates the nephrology/medical literature and personalizes reading recommendations based on a clinician's or researcher's interests. Each week, registrants receive an email alert that highlights the most popular medical articles in the reader's clinical or research area of specialty. The content of email subject lines have been shown to have a significant impact on whether email is read or deleted prior to being read. We hypothesized that providing more details in the subject line would result in greater engagement with the email content.

Methods: We randomly assigned all emails sent containing the "Most Read" articles of the week to either a generic/consistent email subject line or a subject line that included the title of the most commonly read article of the week (detailed/variable). SendGrid, an email delivery service provider, was utilized for email delivery and to automate the subject line randomization. The primary outcome was email open rate. Secondary outcome was email click through rate.

Results: Between January 7, 2014 and May 1, 2015, a total of 1,287,442 emails were sent. 643,475 were generic/consistent and 643,967 were specific/variable. A specific/variable email subject line yielded a 70.76% (95% CI 70.68 to 70.84) open rate versus 48.85% (95% CI 48.76 to 48.94) with an email subject line that was generic ($p < .01$). A detailed/variable subject line did not increase click through rate as compared to a generic/consistent subject line, 9.87% (95% CI 9.82 to 9.92) vs 9.85% (95% CI 9.8 to 9.9) $p > 0.05$.

Conclusions: Including details about the content of an educational email in the subject line resulted in a greater email open rate but did not increase the click through rate. Further research is required to increase engagement with the content of educational emails provided by the 'Read' educational service.

PUB388

Teaching Ethics and EBM in the Medical School: Case Discussion as a Teaching Tool on End-of-Life Issues – Dialysis or Palliative Treatment in a 92 Year Old Patient? Giordina B. Piccoli,¹ Laura Sacchetti,² Laura Verze,² Franco Cavallo.² ¹SS Nephrology, Clinical and Biological Sciences, Univ of Torino, Italy; ²Course of EBM and Ethics, Univ of Torino, Italy.

Background: History of Nephrology follows and influences the development of Bioethics and offers insights for teaching: the first Ethics Committee (the "God's Committee"), brain death, the sale of organs, the limitation of resources, up to the global needs (as in the 0-by-25 project). Case discussion within the Medical school may be a useful tool to acquire bioethical skills and analytical tools.

Methods: Discussion of a clinical case: patient in his nineties, high comorbidity, good cognitive status (writer), GFR 10 mL / min. The case raises questions about the choice diet-dialysis-palliation. 50 medical students of the curricular course of ethics and EBM are tutored for an academic year through the collection of information from databases (Pubmed), web, talk with experts, tutors and teachers. The analysis is performed according to the 4 main ethical principles (beneficium, non maleficium, justice, autonomy) to a narrative approach.

Results: The students produces a text, here summarized: from a clinical standpoint, beneficium and non-maleficium suggest to postpone dialysis (intent-to-defer) with the start of low-protein diet (equal to or greater survival, minimal damage, favorable context). Distributive justice favors less expensive therapies (diet, palliation), in the context of individual justice, the start of dialysis, if necessary, has a role in life support. The patient, by consulting more doctors, has expressed his desire for autonomy. Considering the chronic disease, the intellectual level, a doctor-patient relationship of "shared decision making" is advisable. Sharing the choice improves results, reduces dropout rate of dialysis, if undertaken. Since the four principles of bioethics take on different priorities depending on the socio-cultural context, the approach to the patient will be modulated in a narrative than his views or religious beliefs.

Conclusions: Nephrology offers suggestions for bioethical discussion. Conversely, bioethics offers analytical tools for the analysis of complex decisions such as dialysis in the "very old".

PUB389

SLIT2 Is Upregulated in Proximal Tubules and Urine following Folic Acid Induced Kidney Injury Jonathan Street, Ana C. Souza, Xuzhen Hu, Yuning George Huang, Peter S.T. Yuen, Robert A. Star. NIDDK, Bethesda, MD.

Background: SLIT2, signaling via ROBO receptors, was originally described for its role in neuronal guidance, and has since been linked with leukocyte chemotaxis and angiogenesis. As both processes might be involved in kidney injury and repair, we tested whether SLIT2 signaling is involved in folic acid induced kidney injury.

Methods: Eight-week old male CD-1 mice were injected i.p. with 250 mg/kg folic acid. Groups were euthanized 0-7, or 14 days later. Expression levels were determined by RT-qPCR and western blot of whole kidney lysates. Localization was determined by immuno-histochemistry. In a second experiment mice received folic acid and then 70 mg/kg i.p. recombinant human SLIT2 or vehicle on days 2, 4, and 6. On day 14 GFR was measured in conscious mice by transcutaneous fluorescence monitoring of FITC-Sinistrin elimination.

Results: Following folic acid injection, whole kidney SLIT2 mRNA and protein levels decreased two-fold by day 3, whereas SLIT2 protein increased in proximal tubule cells by immunohistochemistry on day 3. Expression of SLIT2 protein was observed in the proximal tubule derived HK-2 cell line, and urinary SLIT2 protein was increased by

2-fold 2 to 7 days after folic acid injection, supporting tubules as a site of SLIT2 synthesis. In a separate experiment mice were given folic acid, then recombinant human SLIT2 i.p. on days 2, 4, and 6. Kidney function measured directly as GFR or indirectly via BUN 14 days after injection was not significantly improved by SLIT2 treatment.

Conclusions: Folic acid induced injury increased expression of SLIT2 in proximal tubule cells followed by detection of SLIT2 in the urine, which points to SLIT2 as a candidate urine biomarker for tubular injury. Amelioration of injury with systemic SLIT2 treatment was not observed, suggesting better utility as a marker than a mediator.

Funding: NIDDK Support

PUB390

Urinary Trefoil Factor 3 Is Significantly Associated with Renal Tissue Fibrosis in Patients with Tubulointerstitial Nephritis Keiko Tanaka, Hitoshi Sugiyama, Toshio Yamanari, Ayu Akiyama, Akifumi Onishi, Masashi Kitagawa, Hiroshi Morinaga, Yoko Kikumoto, Tatsuyuki Inoue, Jun Wada. Dept of Medicine and Clinical Science, Okayama Univ Graduate School, Okayama, Japan.

Background: Trefoil factor 3 (TFF3) is a small peptide involved in mucosal protection. TFF3 is widely expressed in multiple tissues including kidney. Previous studies have suggested that serum and urinary TFF3 significantly increases in patients with chronic kidney disease and that urinary TFF3 level decreases in rats with acute kidney injury. However, it is unclear whether serum or urinary TFF3 is associated with human renal tissue injury. The aim of this study is to elucidate the relationship between serum and urinary TFF3 levels and the degree of renal tubulointerstitial injury.

Methods: The total study population included 52 patients (tubulointerstitial nephritis: 31, minor glomerular abnormalities and thin basement membrane disease as controls; 21) who underwent renal biopsy. The serum and urinary TFF3 concentrations were determined by a specific ELISA. The degrees of tubulointerstitial cell infiltration and fibrosis were semiquantitatively graded in biopsy specimens and defined by the inflammation score and the fibrosis score, respectively. An immunohistochemical analysis was performed to reveal the localization of the TFF3 protein.

Results: The median serum and urinary TFF3 levels of the disease group were significantly higher than those of the controls ($p=0.002$ and $p=0.008$, respectively). A statistically significant positive correlation was observed between the urinary TFF3 levels and the renal fibrosis score in the disease group. However, there was no correlation between the serum or urinary TFF3 level and the renal inflammation score in disease group. TFF3-positive cells were observed in the renal tubular epithelium.

Conclusions: The data indicate that serum and urinary TFF3 levels are significantly increased and, in particular, that urinary TFF3 could reflect renal tissue fibrosis in patients with tubulointerstitial nephritis. Further studies are required to elucidate the precise distribution of renal TFF3 protein and mRNA, and the mechanism underlying the contribution of TFF3 to renal fibrosis.

PUB391

Induction of Epithelial-to-Mesenchymal Transition and Fibrosis Signals via AKT and Peroxisome Proliferator-Activated Receptor Pathway in Renal Tubular Cells Induced by a Plasticizer Di(2-ethylhexyl) Phthalate Shing-Hwa Liu,¹ Li-Chen Huang,¹ Bo-Lin Chen,¹ Chih-Kang Chiang.^{1,2} ¹Inst of Toxicology, College of Medicine, National Taiwan Univ, Taipei, Taiwan; ²DIDT, NTUH, Taipei, Taiwan.

Background: Di(2-ethylhexyl)phthalate (DEHP) is a plasticizer and a probable endocrine disruptor. More than two million tons of DEHP were used each year worldwide. Recent studies have suggested that DEHP has potential adverse effects on the liver, kidney, and reproductive system. It could also cause carcinogenicity and developmental toxicity. DEHP exposure might exacerbate kidney progression. Tubular epithelial-to-mesenchymal transition (EMT) is recognized to play pivotal role in the process of renal fibrosis. However, the mechanisms of nephrotoxicity induced by DEHP remain unclear. Here, we investigated whether DEHP could induce renal fibrosis via EMT process.

Methods: A rat renal proximal tubular cell model (NRK-52E cells) was used to evaluate EMT and fibrosis signaling. Cell morphology was observed by microscope. Cell viability evaluated by MTT assay. The molecule signals of EMT and fibrosis were analyzed by flow cytometry, confocal laser scanning microscopy, immunocytochemistry, and Western blotting.

Results: Treatment with DEHP (5-25 μ M) for 72h caused the change in renal tubular cell morphology shifting to spindle-like shape. DEHP did not induce cell apoptosis, but significantly induced G2/M cell cycle arrest. Moreover, the expressions of vimentin, α -SMA, and CTGF, which are the markers of the mesenchymal phenotype, were significantly increased. The expressions of E-cadherin, a maker of epithelial cells, was significantly decreased by DEHP. DEHP could also inhibit the expression of peroxisome proliferator-activated receptor (PPAR) α and γ . The phosphorylation of Akt and Smad 2/3 was also significantly increased by DEHP. Notably, treatment with MK2206 (an Akt inhibitor) significantly inhibited DEHP-induced phosphorylation of Akt and EMT. Further investigation revealed that MK2206 suppressed the expression of Akt downstream proteins (NF- κ B and GSK3).

Conclusions: These findings suggest that DEHP is capable of inducing the EMT process through AKT and PPAR signaling pathway, which may lead to renal fibrosis.

Funding: Government Support - Non-U.S.

PUB392

Src Kinase Is a Potential Therapeutic Target in Renal Fibrosis Yanli Yan,^{1,2} Murugavel Ponnusamy,² Evelyn Tolbert,² George P. Bayliss,² Shougang Zhuang.²
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Background: Increased activity of Src, a non-receptor tyrosine kinase, has been associated with the pathogenesis of renal tumors and some glomerular diseases, but its role in renal interstitial fibrosis remains elusive.

Methods: In this study, we investigated the effect of Src inhibition on renal interstitial fibroblast activation in vitro and renal fibrogenesis in a murine model of unilateral ureteral obstruction and the mechanisms involved.

Results: Exposure of cultured renal interstitial fibroblasts (NRK-49F) to PP1, a selective inhibitor of Src, resulted in decreased expression of α -smooth muscle actin (α -SMA), and fibronectin and collagen I, in response to serum- or transforming growth factor- β 1 (TGF- β 1). Silencing Src with siRNA also inhibited expression of those proteins. Furthermore, inhibition of Src activity blocked renal fibroblast proliferation as indicated by a dose-dependent down-regulation of cyclin D, cyclin E and PCNA (proliferating cell nuclear antigen), three proteins involved in cell cycle progression and up-regulation of p21 and p27, two major cell cycle inhibitors. In a murine model of renal interstitial fibrosis induced by unilateral ureteral obstruction (UUO), the active form of Src (phospho-Src Tyr416) was upregulated in the fibrotic kidney, and its inactivation with PP1 reduced renal fibroblast activation and attenuated extracellular matrix protein deposition. Src inhibition also suppressed expression of TGF- β R1, activation of Smad3 and STAT3, and phosphorylation of epidermal growth factor receptor. Finally, PP1 treatment reduced renal epithelial cells arrested at G2M phase of cell cycle, a phenotype that produces profibrotic growth factors/cytokines, after UUO injury.

Conclusions: Our results demonstrate the importance of Src in mediating renal interstitial fibroblast activation and renal fibrogenesis and suggest Src as a potential therapeutic target for treatment of chronic renal fibrosis.

Funding: NIDDK Support

PUB393

MiRNAs as Novel Biomarkers and Therapeutic Target in Chronic Kidney Disease Laura Martín-Gómez,¹ Elia Aguado fraile,¹ Eduarne Ramos,¹ Elisa Conde,¹ Esperanza Macarena Rodríguez serrano,¹ Sara Gimenez-Moyano,¹ Lira Jimenez alvaro,² Fernando Liano,² Maria Laura Garcia-Bermejo.¹ ¹Biomarkers and Therapeutic Targets Unit, IRYCIS, Madrid, Spain; ²Nephrology, Ramon y Cajal Hospital, Madrid, Spain.

Background: Statistical meta-analysis demonstrates that episodes of Acute Kidney Injury (AKI) eventually promote development of chronic renal damage (CKD). So far, there aren't quantifiable and accurate biomarkers to predict the evolution of AKI to CKD, what would enable clinicians to monitor these patients. Our group has validated a combination of serum miRNAs as AKI biomarkers, including: miR-127, miR-101, miR-210, miR-126, miR-146a, miR-26b, miR-29a, miR-10a, miR-93 and miR-27a. Here we have identified some of this miRNAs as novel biomarkers for CKD and potential new therapeutic targets for renal fibrosis.

Methods: For this purpose, in vitro experimental model of proximal tubular epithelial cells under TGF β treatment as pro-fibrotic stimulus and human samples from patients with established CKD (stage 1-5) have been used.

Results: We characterize in vitro model by estimation of: loss of E-cadherin expression, increase of α -SMA expression, expression of collagen I and fibronectin and activation of metalloproteinase (MMP-2 and MMP-9), by qRT-PCR and zymogram. Furthermore, we have modulated miR-127 in TGF β treated cells, pre-miRs and anti-miRs transfection, finding that miR-127 overexpression maintains epithelial phenotype and miR-127 blockage induces epithelia-mesenchymal transition (EMT), estimated as mentioned above. In addition, we have determined the expression of miRNAs combination in the serum of CKD patients by qRT-PCR and statistical correlations with clinical data indicate: 1) miR-127 is downregulated along CKD development; 2) miR-126 and miR-26b are significant in diabetic nephropathy; 3) miR-146 discriminates patients exhibiting dyslipidemia.

Conclusions: In summary we have identified miRNAs involved in renal fibrosis development as well as miRNAs correlated with CKD features, suggesting that miRNAs could have a potential clinical use for CKD patient's management and they can be point out as novel therapeutic target in this clinical context.

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PUB394

Clofarabine Induced Acute Kidney Injury Sameer Gupta, Ramapriya Sinnakirouchenan, Kamlesh Reddy Kurre. *Nephrology, Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Clofarabine induced acute kidney injury (AKI) has been documented but the mechanism leading to AKI has not been well understood. Here we describe a case of clofarabine treated relapsing ALL leading to anuric AKI and death.

Case Description: A 30 year old male with relapsing ALL was admitted to the hospital for AKI. His creatinine was 1.2mg/dl 2 weeks prior to admission. He received his first cycle of clofarabine at 40mg/m² for 5 days one month ago. On the fifth day of cycle 2 he was admitted for AKI with creatinine of 2.5 mg/dl. Nephrology was consulted next day for oliguria and creatinine elevation up to 3.3 mg/dl. Urine microscopy revealed acute tubular necrosis (ATN). His hospital stay was complicated by anuria and septic shock

necessitating continuous renal replacement therapy. Proteinuria could not be assessed due to anuric AKI. After a prolonged and complicated hospital course patient expressed his wishes for comfort care.

Discussion: Clofarabine is approved for the treatment of relapsed or refractory ALL in children but is also used out of label in adults. It acts by inhibiting DNA synthesis, the enzyme ribonucleotide reductase and repair and activation of mitochondrial repair processes. It is postulated based on animal studies and its mechanism of action that collapsing glomerulopathy or tubular injury alone or in combination may be the etiology. In our case, there is a temporal relationship between clofarabine use and AKI.

The risk factors for clofarabine-associated AKI include older age, higher AUC (area under the curve) and, lower baseline GFR. While the current recommendation is a 50% dose reduction for renal impairment, this only applies to patients with a baseline creatinine clearance of 30–60 mL/min. There are currently no guidelines for those patients with ostensibly "normal" creatinine clearance values.

We suggest that dosing based on baseline GFR even among patients with apparently normal serum creatinine deserves consideration in the future use of clofarabine. Careful monitoring for renal toxicity and minimizing other renal insults in older patients and those with lower baseline GFRs should help prevent this adverse effect.

PUB395

Orthostatic Hypotension as the Presenting Feature of Primary Systemic Amyloid Light-Chain (AL) Amyloidosis Scherly Leon,¹ Farouk Talakshi,¹ Rajiv A. Perinbasekar,¹ Gary R. Briefel,² Moro O. Salifu.¹ ¹Medicine, Renal Div, Downstate Medical Center, Brooklyn, NY; ²Medicine, Renal Div, Kings County Hospital Center, Brooklyn, NY.

Introduction: Orthostatic hypotension is a common disorder among the elderly, often associated with hypovolemia, adrenal insufficiency, and autonomic neuropathies. Primary systemic amyloid light-chain (AL) amyloidosis is a rare acquired plasma cell disorder. Morbidity results from extracellular depositions of amyloid fibrils in vital organs. Deposition of amyloid protein in the nervous system leads to autonomic neuropathy, resulting in orthostatic hypotension, early satiety, erectile dysfunction and intestinal motility dysfunction. We report a case of primary systemic amyloidosis, presenting initially as orthostatic hypotension.

Case Description: A 61-year-old man was admitted for orthostatic hypotension with syncopal episodes and proteinuria. He was well until six months prior to admission, when he began experiencing severe recurrent orthostatic lightheadedness, anorexia, and dysgeusia. He reported weight loss and paresthesias. He had been admitted to an outside hospital and underwent extensive evaluation including a chest CT which revealed lung and liver granulomas. Fludrocortisone was started for hypotension. He noted no improvement and stopped fludrocortisone two weeks prior to presentation to our hospital.

Extensive evaluation of his orthostasis, including an adrenocorticotropic hormone stimulation study was normal. Cardiac and endocrine evaluation revealed no abnormalities. Laboratory exam showed serum creatinine of 0.74 mg/dL, Hgb of 10 g/dL, MCV of 90fL, total protein 6.4 g/dl and albumin 2.5 g/dl. A 24-hour urine protein excretion was 5g. Free kappa (436 mg/L) and lambda light chains (6.5 mg/L) with a ratio of 67. A monoclonal spike was noted on serum protein electrophoresis. Additional rheumatologic workup was negative. Bone marrow biopsy was consistent with multiple myeloma and congo red stain was positive for amyloidosis.

Discussion: The finding of heavy proteinuria in conjunction with orthostatic hypotension should lead one to consider the diagnosis of primary systemic (AL) amyloidosis in the differential diagnosis.

PUB396

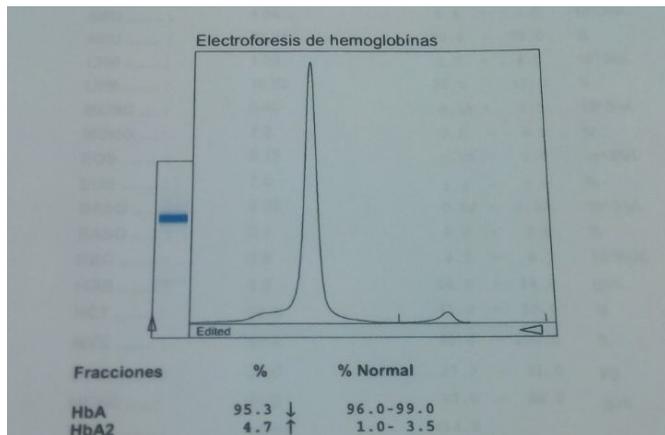
Refractory Anemia Secondary to B Thalassemia in a Patient with CKD: Case Report Lilia Maria Rizo Topete, Giovanna Y. Arteaga Muller, Jesus Cruz Valdez, Elisa Maria Guerrero Gonzalez, Concepcion Sanchez Martinez. *Nephrology, Univ Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, Mexico.*

Introduction: We present a case of a Male patient, 28 years old, Mexican, diagnosed with CKD of unknown etiology.

Case Description: He denies chronic diseases. Mother with SLE, Sd. Evans and DM. The renal sonogram showed small kidneys. Viral panel negative as immunological tests. The patient comes as ERC G5 with uremic syndrome. RRT starts with PD, 3 months after an episode of peritonitis for candida and HD was initiated. He presented hemoglobin of 7.5 g/dl, microcytichypochromic anemia, treated with erythropoietin 12 000 IU a week, oral Iron and folic acid. Months later the patient came up with anemic syndrome and hemoglobin of 6.6 mg/dl, 2 units of blood were transfused. He presented 3 similar episodes, so 6 more units were transfused. Erythropoietin exchanged for darbepoetin and. Direct Coombs test was negative. He did not respond to treatment, iron test was performed and IV iron therapy was initiated. Hematology reported aspiration and biopsy Bone marrow normal, with megakaryocytes, M:E ratio 2:1m without blasts. Biopsy reported hypocellular. Abdominal US reported normal. Hemoglobin electrophoresis was performed which reported increased A2 hemoglobin

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.



Discussion: The B Thalassemia is a hereditary disorder of hemoglobin synthesis in the B-globin gene that present clinically with microcytic hypochromic anemia, erythropoiesis ineffective, normal reticulocyte counts or slightly elevated and high levels of A2 hemoglobin. In the kidneys can cause tubular injury and GFR decline. Developing glomerulosclerosis and fibrosis. We can not rule out that CKD is secondary to B-thalassemia, a genetic study would be necessary. It is an uncommon diagnosis in Latin America, but should be considered in patients with CKD and microcytic hypochromic anemia refractory to convecional treatment.

PUB397

Empirical Antifungals in Peritoneal Dialysis Patients with Bowel Obstruction: Time to Reconsider? Ravinder Pal S. Bhatti, Elwaleed Elnagar, Dumitru Rotaru. *Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Intestinal obstruction, even without perforation or ischemia, predisposes patients on peritoneal dialysis (PD) to peritonitis by gut commensals including fungi. Fungal peritonitis (FP), with (Secondary) or without (Primary) prior antibiotic use, is associated with increased mortality and technique failure. This raises the question of empirical antifungal use in PD patients with bowel obstruction. We present our experience with such a patient.

Case Description: A 74 year old male who had been on Continuous Cycling Peritoneal Dialysis for the past four years with his prescription being 5 exchanges of 2 liters of 1.5% and 2.5% dianeal with a last fill of 2 liters of icodextrin, presented with worsening abdominal pain. His dialysate was clear and had just 3 leucocytes. His CT abdomen showed small bowel obstruction (SBO) with conservative management pursued. Over the next few days, the SBO resolved and dialysate cell counts remained unremarkable. On day 5, he became hypotensive. Examination was notable for increased abdominal tenderness and a cloudy dialysate. Repeat dialysate studies were sent and intraperitoneal vancomycin and cefepime were started. Imaging suggested SBO. He responded appropriately to the antibiotics over the next three days with no growth on any cultures thus far. However, the dialysate grew yeast the next day. Fluconazole was started, later being switched to micafungin with the yeast identified as *Candida cruzi*. His Tenckhoff catheter was removed and hemodialysis (HD) was initiated. He completed 4 weeks of micafungin and opted to continue on HD.

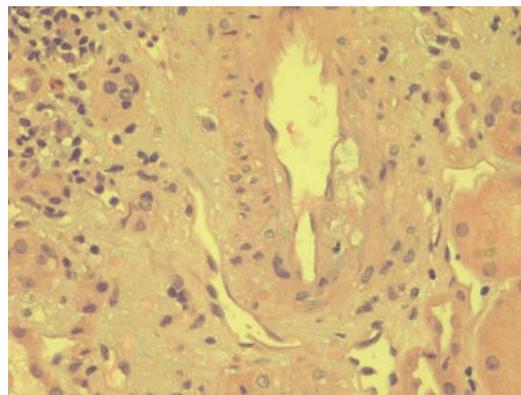
Discussion: Evidence on antifungal prophylaxis while treating PD related bacterial peritonitis has been mixed, with the decision being individualized on a per-center basis. Additionally, no clear role has been defined for prophylactic antimicrobials in PD patients with bowel obstruction. With a high risk for both primary and secondary FP, these patient present a conundrum. Our case highlights this while also suggesting a role for prophylactic antifungals even when antibiotic exposure is brief. We conclude that it may prudent to provide empirical antifungal coverage in PD patients with SBO.

PUB398

Leukocytosis and Peripheral Blood Eosinophilia Are Early Signs of Acute Cellular Rejection of a Transplanted Kidney Elwaleed Elnagar, Ravinder Pal S. Bhatti, Aziz Bakhous. *Nephrology, UAMS, Little Rock, AR.*

Introduction: Leukocytosis and peripheral blood eosinophilia were well described in acute rejection of transplanted livers and pancreas rejection. This laboratory abnormality was not well evaluated in kidney allograft rejection. In this case report, we explore leukocytosis and peripheral blood eosinophilia as possible laboratory abnormalities preceding ACR.

Case Description: We are presenting a 65 years old woman with a history of ESRD due to ADPKD, who had a DDKT in 2012. Her medications included Prednisone, Tacrolimus, and Mycophenolate Mofetil. She maintained a stable allograft function, with a creatinine of 1-1.2. She was found to have leukocytosis and peripheral blood eosinophilia. Evaluation for infections and malignancy was negative. 6 weeks later she was noted to have AKI. She complained of mild lower extremities swelling. Physical examination was unremarkable. Labs evaluation revealed a creatinine of 2 mg/dl, WBCs count of 15.9 k/uL, and eosinophilia. Renal biopsy however, showed ACR (figure 1). There were abundant infiltrates with neutrophils and eosinophils. She was treated for ACR with return of creatinine to baseline.



Discussion: Several reports have evaluated the predictive value of peripheral blood eosinophilia as a simple noninvasive diagnostic marker for ACR of transplanted livers and of acute pancreatic rejection. However, peripheral blood eosinophilia was not evaluated as a possible test predicting renal ACR. In a case report, Baradhin et al, described the etiology of AKI following treatment with armodafinil for narcolepsy. They indicated that both (AIN and ACR) has similar biopsy characteristics. However, our patient had no clinical features to suggest AIN, including no new medications. We conclude that leukocytosis and peripheral blood eosinophilia could represent signs of impending acute cellular rejection of transplanted kidneys.

PUB399

A Case of IgA Nephropathy in an HIV-Positive Patient Hermes Garcia-Sanchez, Vandana Niyyar, Thomas E. Rogers. *Nephrology, Emory Univ, Atlanta, GA.*

Introduction: IgA nephropathy has been described in patients infected with HIV. Though IgA levels are commonly elevated in HIV, these patients may also develop IgA antibodies against specific HIV antigens. Renal lesions may result from HIV antigen-specific immune complexes that are derived from the circulation and from in-situ complex formation.

Case Description: We present a case of a patient with HIV/AIDS, on highly active antiretroviral therapy (HAART), who was evaluated for microscopic hematuria and worsening renal function. The patient's only complaint was early morning peri-orbital edema. On examination, BP was 103/72 mm Hg with a BMI 23 kg/m². Labs showed normal electrolytes, serum creatinine 1.7 mg/dL (baseline 0.7mg/dL), urine protein/creatinine ratio of 2.5 grams/dl. Other serologies were negative. HIV VL was undetectable, and CD4 count was 183. Renal US showed bilateral enlarged, echogenic kidneys.

Renal biopsy revealed sclerosing glomerulopathy with IgA immune type deposits on immunofluorescence. The patient was initiated on an ACE inhibitor and a low salt and protein diet, with resolution of his proteinuria to 0.7 Grams/dL. His renal function stabilized, with a creatinine of 1.6 mg/dL.

Discussion: In conclusion, IgA glomerular disease arising in HIV positive patients has clinical and pathologic aspects similar to idiopathic IgA nephropathy. IgA nephropathy should be suspected in patients with HIV presenting with unexplained hematuria, and renal biopsy should be performed as soon as possible for early diagnosis and therapy. Current management recommendations are similar to those with idiopathic IgA, including ACE inhibitors or ARB for control of proteinuria (>1 g / day) or hypertension.

PUB400

Calcium Channel Blocker Toxicity: Management Strategies and Considerations Sreesh G. Iyengar, Mark I.C. Hong, Seyed-Ali Sadjadi. *Nephrology, Loma Linda Univ, Loma Linda, CA.*

Introduction: Calcium channel blocker overdose is rare but carries a high mortality due to cardiovascular complications. Generally the management is supportive with use of vasopressors, IV fluids, cardiac pacing, and insulin therapy. There are reports of CVVHDF, hemodialysis or hemofiltration alone and charcoal hemoperfusion for the treatment of CCB overdose. Effective management strategies are needed to improve outcomes.

Case Description: Here we describe a patient who presented to the ER after a suicide attempt with ingestion of Norvasc. On arrival to the ER he was awake but later he was intubated. The patient developed acute kidney injury and became anuric. Patient was started on CVVHD that lasted 48 hours. Unfortunately after two days the patient continued to decompensate and expired.

Discussion: Amlodipine is a CCB of the dihydropyridine group acting primarily on vessel walls whereas the non-dihydropyridines act more on cardiac muscle and pacer cells. In our case it was clear Norvasc selectively took its effect on the vasculature with profound hypotension with preserved systolic function and no arrhythmia. The case was complicated with ARDS related to diffuse pulmonary edema, a well known complication with CCB overdose. In our case renal failure was likely related to severe hypoperfusion leading to ischemia. There was development combined respiratory and metabolic acidosis. The metabolic acidosis was attributed to renal failure but it is possible that CCB induced inhibition of insulin secretion leading to ketoacidosis may also have contributed. In terms of management of CCB overdose, if recent ingestion then GI decontamination is reasonable with activated charcoal or whole bowel irrigation. The use of high dose insulin therapy has been tried and its role may include increasing ionized calcium levels, improvement of hyperglycemic acidosis, and improved myocardial function. Most case reports, though

few, have shown little benefit from hemofiltration or hemodialysis theoretically due to high protein binding, high tissue distribution and rapid metabolism of the drug. One case report did show some promise when multiple therapies were used including IV lipid emulsion, CVVHDF and charcoal hemoperfusion.

PUB401

A Rare Case of IgG1-Heavy Chain Deposition Disease Using Oral Prednisone and Therapeutic Plasmapheresis Sacha Baldeosingh, Madhu Kandarpa. *Internal Medicine, Kettering Medical Center.*

Introduction: Heavy chain deposition disease (HCDD) is rare, especially without light chain deposition and when causing non-amyloid tissue deposits.

Case Description: A 75-year-old male with chronic kidney disease (CKD) stage 3 (baseline creatinine 2.3mg/dL) and right single lung transplant for idiopathic pulmonary fibrosis in 2008 presented with extremity edema and decreased urine output. He has no history of diabetes or uncontrolled hypertension. Admission labs showed BUN 77 mg/dL, creatinine 4.37 mg/dL, and subtherapeutic tacrolimus levels at 3.9 ng/mL. Urine protein/creatinine ratio was 6.6. A 24-hr urine protein collection revealed 5822 mg/24hr. Serum protein electrophoresis showed hypoalbuminemia, but no monoclonal proteins were identified. Urine protein electrophoresis was negative for Bence Jones proteins or monoclonal proteins. Urine protein concentration was 713 mg/dL, consisting of 57.8% albumin and 42.2% globulins. C3 and C4 complement levels were low at 46.5 mg/dL and 8.92 mg/dL respectively. Antinuclear antibodies (ANA), anti-streptolysin O (ASO), anti-neutrophil cytoplasmic antibodies (C-ANCA and P-ANCA), and cryoglobulins were negative. Renal ultrasound showed multiple renal cysts without hydronephrosis. Renal biopsy revealed nodular sclerosing glomerulopathy and IgG1-heavy chain deposition disease. Bone marrow biopsy was negative for multiple myeloma. The patient was placed on oral prednisone and therapeutic plasmapheresis in an effort to prevent further renal damage and delay hemodialysis. The patient underwent eight plasmapheresis treatments, however still required hemodialysis for fluid overload.

Discussion: HCDD is a monoclonal plasma cell proliferative disorder characterized by tissue deposits of heavy chain fragments which can lead to renal disease. In HCDD, deposits do not have a fibrillar structure and do not stain positive with Congo red such as with heavy-chain amyloidosis. The rarity of the disease and limited data on evidence-based guidelines for treatment make HCDD challenging to treat. We describe a rare case of IgG1-HCDD with no plasma cell dyscrasia. To our knowledge, no cases have been described using oral prednisone and therapeutic plasmapheresis to treat HCDD renal dysfunction.

PUB402

Cocaine-Induced Vasculitis David Agyapong. *Nephrology, Univ of New Mexico, Albuquerque, NM.*

Introduction: An increasing number of cases of Cocaine -induced vasculitis are being found among cocaine users in the United States which is due to the use of Levamisole laced cocaine. It is estimated that about 70% of the cocaine used here in the US is contaminated with Levamisole.

Case Description: We describe a 65 year old male, with a 20 year history of cocaine abuse, who presented with a 1 month history of a progressively worsening, non-healing and painful rash on his trunk and extremities. He denied fever, weight loss and myalgias but admitted to itchiness. Examination revealed multiple tender, erythematous and violaceous plaques with central necrosis on the trunk and extremities. These plaques were found to be in different stages of healing with their size ranging from 1cm-7 cms. Lab investigations revealed an elevated creatinine of 2.9 mg/dL, an elevated ESR, a low C3, presence of Myeloperoxidase (MPO) antibody and perinuclear Anti Neutrophil Cytoplasmic Antibody (p- ANCA), and an absence of Antinuclear Antibody (ANA) and Anti Proteinase 3 (PR-3) antibody. Urine drug screen was positive for cocaine and urine microscopy showed dysmorphic RBCs. Skin biopsy showed thrombotic vasculopathy with overlying re-epithelialization. Kidney biopsy revealed focal endocapillary proliferative glomerulonephritis with crescents involving 10% of glomeruli and interstitial fibrosis and tubular atrophy involving approximately 70% of the specimen.

•Treatment is mainly abstinence and supportive. •The clinical course of patients is difficult to assess due to the fact that few patients are able to abstain from cocaine use. •Our patient was able to abstain from cocaine use for about 30 days ,and that almost resulted in clinical resolution after 30 days of being cocaine-free (Fig 3.) •Although ,in the setting of worsening skin lesions and ongoing cocaine use ,some patients have been treated with anticoagulation or thrombotic vasculopathy , immunosuppression and corticosteroids with varying degrees of success , robust evidence lacking.

Discussion: •With more than 2 million Americans using cocaine , occurrences of levamisole -induced vasculitis will increase Levamisole exposure should be included in the differential of patients with purpuric vasculitis , neutropenia and cocaine.

Funding: Clinical Revenue Support

PUB403

Morbidity Associated with Uremic Ascites Among Emergent Dialysis Patients Shobana Sivan, Rajeev Raghavan. *Nephrology, Baylor College of Medicine.*

Introduction: Patients with end-stage renal disease(ESRD) on emergent dialysis often develop complications of inadequate dialysis such as pleural effusion, ascites and pericardial effusion. Uremic ascites is characterized by exudative ascites with SAAG usually <1.1 and

is diagnosed after excluding liver, cardiac, infectious and malignant causes. The incidence of uremic ascites in standard dialysis population was described as 0.7-20%. We believe that emergent dialysis patients with uremic ascites have higher morbidity and mortality.

Case Description: Total of 463 emergent dialysis patients, who were initiated on dialysis between July 2010 and April 2015 were analyzed. Among 36 patients with Ascites of any cause, 12 patients were included in the study group of uremic ascites. A cohort of 36 patients without ascites was randomly selected for comparison. Two groups were compared based on demographics and morbidity indicators.

The mean age was 50 years with predominance of Hispanic male in both groups. The serum albumin in the uremic ascites group and the cohort group was 2.6±0.4 and 3.29±0.2 respectively. The mean emergency center(EC) visits and hospital admissions in uremic ascites and cohort group were 79.6, 9 and 63.4, 5.2 respectively. Volume overload and abdomen pain were the major reasons for admissions in the study group. They underwent paracentesis and frequent dialysis during the hospital course.

	Cohort Group(36)	Study Group(12)
Age	50.7±3.9	50.1±
Sex	31M/5F	9M/3F
Ethnicity	91.6%(33)Hispanic	80%(10)Hispanic
Serum Albumin (g/dl)	3.3±0.2	2.6±0.4
EC Visits/Year	63.4	79.6
Hospital Admissions/Year	5.2	9

Discussion: The Emergency room visits and hospital admissions are more in emergent dialysis patients with the complication of uremic ascites. The serum albumin, a marker for increased cardio-vascular events and death is lower in these patients. We conclude that uremic ascites increase the morbidity and mortality in emergent dialysis population with ESRD. The modalities such as Continuous ambulatory peritoneal dialysis, scheduled outpatient dialysis and kidney transplant may prove beneficial.

PUB404

A Case of Multiple Vertebral Compression Fractures due to Glucocorticoid-Induced Osteoporosis in a Pediatric Patient with Nephrotic Syndrome Akihiko Shirasu,¹ Akira Ashida,¹ Yuko Fujii,¹ Hideki Matsumura,¹ Hyogo Nkakura,¹ Motoshi Hattori,² Hiroshi Tamai.¹ ¹Dept of Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; ²Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.

Introduction: Glucocorticoid therapy has a number of adverse effects, among which osteoporosis and bone fracture are major complications. However, there are few reports of this condition in pediatric patients. Here we describe a pediatric case of multiple vertebral compression fractures due to glucocorticoid-induced osteoporosis during treatment for steroid-dependent nephrotic syndrome in a child.

Case Description: A 12-year-old boy was referred to our hospital for treatment of nephrotic syndrome with massive proteinuria and generalized edema. He was treated with the standard corticosteroid regimen stipulated by the International Study of Kidney Disease in Children (ISKDC). Although he achieved complete remission, he suffered two relapses of nephrotic syndrome during administration of prednisolone on alternative days. In the second relapse, the disease became resistant to the steroid therapy, and therefore he received two courses of steroid pulse therapy followed by steroid tapering concomitant with cyclosporine administration. Two months after the diagnosis of steroid-resistant nephrotic syndrome, the patient complained of back pain. Magnetic resonance imaging demonstrated compression fractures from the sixth thoracic vertebra to the first lumbar vertebra. Therefore, the steroid dosage was rapidly reduced and then withdrawn because he was able to maintain remission under cyclosporine therapy.

Discussion: It is necessary to evaluate the state of bone particularly the bone mineral density of the lumbar spine, at an early stage of treatment for nephrotic syndrome in children, even though the incidence of glucocorticoid-related vertebral fracture is low in this patient population.

PUB405

First Use of Lixelle Beta 2-Microglobulin Apheresis Column (Lixelle Column) for Dialysis Related Amyloidosis in the United States Yesh Srivatana,¹ Anjali Masand,¹ Jeffrey I. Silberzweig,² ¹Dept of Nephrology and Hypertension, NYP- Weill Cornell Medical Center, New York, NY; ²Dept of Nephrology, The Rogosin Inst, New York, NY.

Introduction: Dialysis related amyloidosis (DRA) is a debilitating complication of long-term hemodialysis characterized by excess accumulation of Beta 2-microglobulin, which deposits as amyloid fibrils in the bones, joints, and organs of affected patients. The Lixelle Beta 2-microglobulin apheresis column (Lixelle column) is a recently FDA approved medical device that contains specialized beads that selectively remove Beta 2-microglobulin from the blood. This device has been used successfully in Japan to relieve symptoms and prevent progression of DRA. We describe the anticipated first use of this device in the United States.

Case Description: The patient is a 65 year-old man diagnosed with end-stage renal disease of unknown etiology in 1968. A deceased donor renal transplant in 1969 failed within 6 months, and a second transplant in 1970 functioned for 3 years. He has been

treated by maintenance hemodialysis since 1973. In 1995, biopsies documented beta 2-microglobulin amyloid deposits in his tongue, consistent with a diagnosis of DRA. Over time, it has progressed to involve his shoulders bilaterally, his hips, knees, wrists and most recently his colon. He has undergone bilateral total hip replacements and carpal tunnel release procedures. Given his extensive disease burden as a result of DRA despite adequate dialysis, we intend to enroll him in a post-approval study using the Lixelle column. Measures of disease burden will include pre- and post-treatment Beta 2-microglobulin levels, presence of bone cysts, and quality of life (QOL) scores.

Discussion: The Lixelle Beta 2-microglobulin apheresis column appears to increase the Beta 2-microglobulin reduction rate in a single dialysis session, and therefore may be an effective treatment option to improve symptoms and quality of life for patients with dialysis related amyloidosis.

PUB406

An Unusual Case of Anticoagulant-Like Nephropathy in a Non-Anticoagulated Patient Elyas Safar, Apurv Khanna. *Internal Medicine, Div of Nephrology, SUNY Upstate Medical Univ, Syracuse, NY.*

Introduction: Anticoagulant-related nephropathy is a well-known cause for Acute Kidney Injury (AKI), which was first described in Coumadin anti-coagulated patients, usually with excessive anticoagulation (INR >4). It was also reported to be associated with other Anticoagulants such as direct thrombin inhibitor Dabigatran. We report a case of Anticoagulant-related Like Nephropathy in a Non-anticoagulated patient.

Case Description: A 71-year-old male was admitted to the VA medical center for shortness of breath and hemoptysis. Past medical history was significant for Non Small cell Lung Cancer, cryptogenic liver cirrhosis and COPD. CT chest, showed no pulmonary emboli. He was treated with Vancomycin and Zosyn for Pneumonia. The patient reported gross hematuria initially, which resolved spontaneously. His admission creatinine was 1.1 mg/dl, (baseline 0.6 mg/dl), and went up to 2.4 mg/dl. The patient had another episode of gross hematuria and his creatinine went up to 3.5 mg/dl. The patient remained non-oliguric throughout the course of his AKI. Kidney biopsy showed Tubular epithelial cells injury with red cell casts, but no inflammatory changes and no Immune complexes by Immunofluorescence. The histopathologic pattern shown by the kidney biopsy was consistent with Anticoagulant-related nephropathy. However, the patient was not anticoagulated with Coumadin, Heparin, or any other anticoagulants. His Prothrombin time (PT) was 13.1 seconds (normal 9-12 seconds) and INR 1.2. His PTT was 20.1 seconds (normal 25-34 seconds). He had a low platelets count between 55-100K/mm³, due to liver cirrhosis.

The findings in this case, suggest a role for Thrombocytopenia in liver cirrhosis, in causing anticoagulant like intra-glomerular hemorrhage, which may result in an AKI.

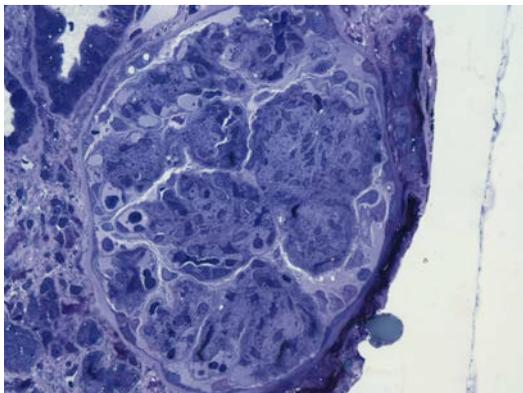
Discussion: Thrombocytopenia and likely Platelets dysfunction in Liver cirrhosis can cause intra-glomerular Hemorrhage and results in Anticoagulant-like Nephropathy, even in the absence of excessive coagulopathy as evidenced by a normal PTT & near normal INR. To our knowledge, there has not been a reported case of Anticoagulant-like Nephropathy in Non-Anticoagulated patients.

PUB407

Smoking Related Idiopathic Nodular Glomerulosclerosis with Crescents Tahir Zaman,¹ Frederic Clayton,² Josephine Abraham.¹ *¹Nephrology, Univ of Utah, Salt Lake City, UT; ²Pathology, Univ of Utah, Salt Lake City, UT.*

Introduction: Idiopathic nodular glomerulosclerosis (ING) is a rare but important cause of nephrotic syndrome. There have been case series reported in the literature regarding the association of ING and smoking.

Case Description: A 37-year-old female with a history of rheumatoid arthritis (RA) presented to the hospital with cough and hemoptysis. Her RA treatment consisted of leflunomide, prednisone and folic acid. Her social history is pertinent for a history of smoking (20 pack-years). Urine analysis was with dysmorphic hematuria and proteinuria (spot protein/creatinine ratio 3.2gms). Serologic workup was unremarkable. Renal biopsy revealed nodular glomerulosclerosis with sparse crescents. Due to sparse crescents, hemoptysis, and AKI the patient was started on high dose steroids which exacerbated patient's nephrotic syndrome. Ultimately steroids were discontinued which lead to an improvement in proteinuria. Smoking cessation was encouraged.



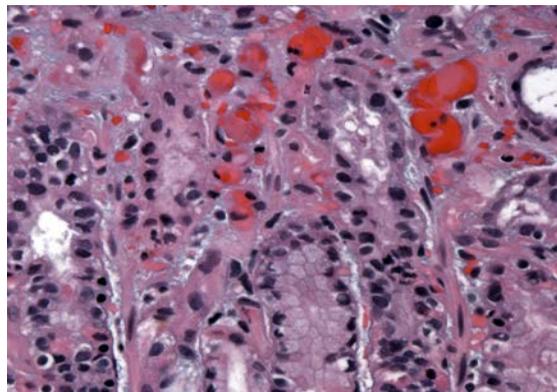
Discussion: ING with crescents has not been described in the literature. In a case series reported by Markowitz et al, patients with ING had renal failure with a mean sCr of 2.4 mg/dL and proteinuria. The main clinical predictors of progression included lack of angiotensin II blockade and continued smoking.¹ In retrospect, it is likely the severity of her intra-glomerular pressures which lead to proteinuria was exacerbated with steroid treatment and resolved with discontinuation.

PUB408

Thrombotic Microangiopathy Secondary to Hepatocellular Carcinoma Tahir Zaman,¹ Frederic Clayton,² Josephine Abraham.¹ *¹Nephrology, Univ of Utah, Salt Lake City, UT; ²Pathology, Univ of Utah, Salt Lake City, UT.*

Introduction: Thrombotic microangiopathy (TMA) is a microvascular occlusive disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia and end organ damage. We report a case of malignancy associated TMA.

Case Description: 65-year-old female presented with diarrhea and was noted to be in acute renal failure with microangiopathic hemolytic anemia and thrombocytopenia. Therapeutic plasma exchange was discontinued after ADAMST 13 activity was normal. Patient underwent colonoscopy and EGD with evidence of microthrombi in bowel wall concerning for TMA.



Serologies were remarkable for negative APS, SLE, ANCA-vasculitis but Ca-125 was 753. Stool Shiga toxin was negative. Patient was treated for atypical hemolytic uremic syndrome (aHUS) with weekly eculizumab. Diagnostic laparoscopy on HD 24 with peritoneal washings were negative for malignancy. The patient died on hospital day 25 from septic shock secondary to bowel perforation. Autopsy revealed 2.5 x 2.0 x 2.0 cm lesion within the liver consistent with hepatocellular carcinoma (HCC).

Discussion: TMA occurring in older patients who fail to respond to TPE should increase suspicion of malignancy-associated TMA.¹ HCC is a rare but known cause of malignancy-associated TMA as noted in the literature. HCC-associated TMA is quite severe leading to rapid progression to a fatal outcome.² 1. George, J. N. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. *Oncology* 25, 908-14 (2011). 2. Seo, D. W. et al. Hepatocellular carcinoma associated hemolytic uremic syndrome unrelated to chemotherapy. *J. Korean Med. Sci.* 9, 254-8 (1994).

PUB409

Charcot Foot Syndrome in a Nondiabetic Hemodialysis Patient Werner Kleophas,^{1,2} Sebahat Sat,¹ Barbara Klein,¹ Andreas Westhoff,^{1,2} Frank Dellanna,^{1,2} Gerd R. Hetzel.^{1,2} *¹MVZ Davita Karlstrasse, Duesseldorf, Germany; ²Heinrich-Heine Univ, Duesseldorf, Germany.*

Introduction: The prognosis is very poor for diabetic hemodialysis (HD) patients with foot lesions. Foot lesions are associated with risk of systemic inflammation and cardiovascular (CV) morbidity. Severe cases of diabetic foot with neuropathic arthropathy, microvascular changes from mediasclerosis, and alteration of foot architecture are known as Charcot Foot Syndrome (CFS). Since diabetic and nondiabetic HD patients may experience changes in calcium and phosphate metabolism and secondary hyperparathyroidism, the question arises whether CFS can occur in HD patients in the absence of diabetes.

Case Description: Presented is a decade-long case study of a male HD patient (DOB 1961) who was treated since Dec 1999 for biopsy-proven nephrotic syndrome due to glomerulosclerosis. The patient began thrice weekly HD in Sept 2005 without prior treatment for diabetes mellitus (A1C 4.9%). In Apr 2012 he presented with a painless inflammatory acute foot syndrome, then presented in Apr 2013 with a planar ulceration. After conservative wound management, prophylactic shoes were prescribed. In clinical examination he showed signs of chronic CFS and arthropathic changes in ossa metatarsalia 2 and 3 with osteolysis and luxation of tarsometatarsal joints. Lab results indicate secondary hyperparathyroidism: parathyroid hormone 465 pg/mL, phosphate 6 mg/dL, and calcium 2.2 mg/dL.



Discussion: We believe this is the first description of chronic CFS in a nondiabetic HD patient. Acute CFS diagnosis is important because its symptoms (red warm skin, foot edema) are similar to those of phlegmon and osteomyelitis, and thus may be considered a differential diagnosis. Further investigations are necessary to determine whether this is an authentic entity of a foot syndrome, and if it's associated with CV morbidity.

Funding: Pharmaceutical Company Support - Davita

PUB410

Crescentic Glomerulonephritis (GN) in a Lupus Patient with Normal Serum Creatinine – A Treatment Challenge Venkata Buddharaju, Rishikesh Morey, Rudrick V. Ledesma, Savneek S. Chugh, Praveen N. Chander. *Nephrology, Westchester Medical Center, Elmsford, NY.*

Introduction: Crescentic GN is usually manifested by features of active glomerular disease in the urine and by progressive rapid loss of significant renal function. SLE can present as predominantly crescentic GN often as Class III or IV lupus nephritis (LN) usually resulting in rapid deterioration of renal function requiring RRT.

Case Description: 18 y/o female recently diagnosed with SLE, on Plaquenil presented to ER with nausea, vomiting and epigastric pain after consuming “tiny tea” and was found to have serum creatinine (Scr) 4.5 mg/DL, which further increased to 4.74 with 3+ protein (2.5g/day), 3+ blood and RBC casts on urinalysis. Other relevant lab data: ANA 1:600, negative dsDNA, positive RNP, anti-SM Ab and normal complements. She was initiated on IV fluids and Scr normalized within 2 days. Renal biopsy showed Pauci immune Crescentic GN, class IV-S (A/C) with minimal IF staining. The clinical course was complicated by seizures; the diagnostic considerations included lupus cerebritis vs. PRESS. She was put on valproate to be started on immunosuppression as outpatient. She was admitted a week later with acute liver failure due to valproate and Tylenol at which time she was pulsed with IV Solu-Medrol and discharged on oral steroids with a plan to start MMF after normalization of LFTs.

Discussion: Crescentic and focally necrotizing GN can be infrequently present in the spectrum of diffuse proliferative LN. Such cases are generally ANCA negative. Normalization of Scr after hydration in this case suggest pre renal as the likely etiology which poses a treatment dilemma for biopsy proven crescentic GN. While there is not much literature available regarding the treatment of lupus with crescentic GN and normal Scr, a retrospective case series reported that even <50% crescents portend a significant renal risk despite clinically evident preserved renal function. We believe that intense immunosuppression should be used in patients with crescentic GN and preserved renal function, despite the absence of any controlled studies. Our patient was started on MMF and prednisone with improvement in proteinuria from 2.6 gm to 150 mg with normal Scr.

PUB411

Anti-Thymocyte Globulin Induced Non Cardiogenic Pulmonary Edema Jaya Kala, Amit Lahoti. *Nephrology, Univ of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction: Anti-Thymocyte globulin (ATG) is used in treatment of hematologic malignancies and solid organ transplantation. Immediate local and systemic reactions are known. There has been only one reported case of non cardiogenic pulmonary edema (NCPE) caused by ATG.

Case Description: Our patient was a 59-year-old man with Marginal Zone Lymphoma which had progressed to diffuse large B cell lymphoma. Despite Hyper CVAD and Rituximab his disease continued to progress. He received Matched Unrelated Bone marrow transplantation after conditioning with ATG and rituximab. The next day he was admitted to the ICU with respiratory distress and bilateral lung infiltrates initially thought to be pulmonary edema. He was started on Lasix drip but did not improve. His CVP was 5, and his echocardiogram showed normal ejection fraction. Based on these findings he was diagnosed to have NCPE. Bronchoscopy revealed pulmonary hemorrhage. His condition worsened and he was intubated and started on Continuous Renal replacement therapy. He was given additional doses of steroids but without improvement. He died due to respiratory failure after two days of ICU stay.

Discussion: Non cardiogenic pulmonary edema is a clinical syndrome characterized by presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph without evidence of left atrial hypertension, fluid overload or congestive heart failure. Drug related NCPE is usually diagnosed after other causes of pulmonary infiltrates such as gastric

aspiration, sepsis and pneumonia are excluded. The presence of normal echocardiogram and pulmonary hemorrhage within a day of administration of ATG, pulmonary infiltrates which did not resolve after intense attempts of volume removal indicated that the patient had NCPE. ATG is known to cause acute respiratory distress syndrome, alveolar hemorrhage and rapidly progressive interstitial fibrosis likely secondary to Cytokine release syndrome. Providers need to be aware of such complications as even though rare these cause increased morbidity and mortality. It is beneficial to give ATG infusions slowly and accompanied by high dose systemic steroids.

PUB412

Hypomagnesemia After Treatment with Pertuzumab Lilian Saro-Nunez,¹ Tiffany A. Traina,² Karen A. Cadoo,³ Teresa Gilewski,² Ilya Glezerman.⁴
¹Nephrology, NYP-Weill Cornell Medical Center, New York, NY; ²Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY; ³Gynecologic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; ⁴Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

Introduction: Hypomagnesemia is a known side effect of epidermal growth factor receptor (EGFR) inhibitors such as cetuximab and panitumumab. Pertuzumab blocks HER (human epidermal growth factor receptor) 2 dimerization with HER3 and EGFR, and is used in HER2+ breast cancer. We present two cases of hypomagnesemia with pertuzumab use.

Case Description: Case 1 58 year-old woman with history of breast cancer treated with trastuzumab (T), docetaxel, pertuzumab (2 doses of 840mg and one dose of 420mg) and carboplatin (AUC6). Patient developed hypomagnesemia with serum magnesium (Mg^{2+}) 0.7 (1.7-2.6)mg/dl and symptomatic hypocalcemia of 5.9 (8.5-10.5)mg/dl. Since initiation of chemotherapy she experienced diarrhea controlled with loperamide. Fractional excretion of magnesium (FeMg) was 2%. Parathyroid hormone (PTH) was 309.2 (12-88)pg/ml. Pertuzumab and carboplatin were stopped. Mild hypomagnesemia persisted 6 months later.

Case 2 56 year-old woman with history of breast cancer on treatment with T, paclitaxel and pertuzumab (one dose of 840mg and 2 doses of 420mg) was admitted with Mg^{2+} of 0.3 (1.4-2.2) mEq/L and corrected calcium of 6.1mg/dl. She complained of chronic diarrhea which improved with loperamide and was receiving proton pump inhibitor (PPI). FeMg was 3%. PTH was 16.1 (12-88)pg/ml. PPI was stopped but patient received another dose of pertuzumab (840mg). She remained hypomagnesemic and required IV supplementation until her death from progression of disease 22 months later.

Discussion: Although there were other confounding factors that could have caused hypomagnesemia including diarrhea, PPI and carboplatin, hypocalcemia (a manifestation of hypomagnesemia) did not develop until patients were started on pertuzumab. Carboplatin has been associated with hypomagnesemia but not with the degree of hypomagnesemia seen in these two patients. We postulate that pertuzumab may interfere with reabsorption of Mg^{2+} similar to EGFR inhibitors.

PUB413

Acute Renal Infarction: Case Series Yelda Deligoz bildaci,¹ Rumez Kazancioglu.² ¹Nephrology, Bezmialem Vakif Univ, Istanbul, Turkey; ²Nephrology, Bezmialem Vakif Univ, Istanbul, Turkey.

Introduction: Acute renal infarction (ARI) occurs from interruption of kidney's blood supply either partially or totally. Causes of renal infarction include; thromboembolism (usually from injured or replaced heart valves, congenital heart defects etc.) vasculitic disorders, trauma to the kidneys or hypercoagulable state. We present five cases of ARI with different etiologies.

Case Description: Description of Cases : Two female, three male, mean age 52 (range 26-72) patients presented to the emergency department between 2013 and 2015 in a university based hospital setting. Presenting complaint was severe flank pain lasting between 2 to 5 days for all of them. At initial examination all patients had costo-vertebral angle tenderness at the effected side. Contrast enhanced abdominal tomography was useful for showing renal artery occlusion and also renal infarction. Trans thoracic echocardiography were all normal and were not adequate in identifying patients having had heart defects, trans esophageal echocardiography was obviously superior in finding cases with possible paradoxical embolism. All patients were treated with enoxaprin therapy. During follow-up there was neither further complication nor kidney damage.

	Age	Gender	History of Hypertension	trans thoracic echocardiography	trans esophageal echocardiography	Initial creatine levels before treatment	Follow up creatine levels
CASE 1	26	FE-MALE	NEGATIVE	NORMAL	PATENT DUCTUS ARTERIOSUS	0,8	0,7
CASE 2	72	MALE	POSITIVE	NORMAL	-	4,2	3,8
CASE 3	69	MALE	POSITIVE	NORMAL	-	0,8	0,8
CASE 4	38	MALE	NEGATIVE	NORMAL	-	0,8	0,9
CASE 5	56	FE-MALE	POSITIVE	NORMAL	PATENT DUCTUS ARTERIOSUS	0,8	0,8

Discussion: ARI usually is a hidden disease, which can easily be missed without any specific suspicion for patients presenting with flank pain. It should be kept in mind that there is no specific biochemical test for ARI and diagnosis process must involve evaluation of cardiac pathologies preferably with trans esophageal echocardiography.

PUB414

Disseminated Cryptococcal Infection in a 24-Year-Old Man with Primary Focal Segmental Glomerulosclerosis Judith J. Wilber,^{1,2,3} Caitlin Dugdale,^{1,2,3} George P. Bayliss,^{1,2,3} ¹Rhode Island Hospital, Providence, RI; ²Miriam Hospital, Providence, RI; ³Alpert Medical School, Providence, RI.

Introduction: Focal segmental glomerulosclerosis (FSGS) is commonly treated with high doses of corticosteroids and calcineurin inhibitors to induce remission of proteinuria, however immunosuppression carries with it the risk of infection. We present here the case of a 24-year-old African American man following seven months of intermittent treatment for biopsy-proven FSGS with high-dose prednisone and cyclosporine.

Case Description: Our patient initially responded to prednisone 80 mg daily with proteinuria reduced to 37 mg/g from 3.5 g/g, but then suffered frequent hospitalizations for infection necessitating interruption of immunosuppression, now with decreased responsiveness to prednisone. Cyclosporine was added but interrupted after he developed skin findings concerning for necrotizing fasciitis. A surgical wound became infected, and he developed Clostridium difficile diarrhea. He was placed on ethacrynic acid and atovaquone because of a sulfa allergy. His albumin remained < 1.5 mg/dL. Renal function worsened, now with ascites requiring paracenteses and subsequently developed E coli peritonitis. He was admitted to our medical ICU with hypoxia seven months after initial presentation. Chest xray at this time demonstrated pulmonary edema versus multilobar pneumonia. White blood cell count was 18.5, and increased to 30.0 after beginning prednisone taper. Broad-spectrum antibiotics and hemodialysis were initiated with no improvement. Head CT after seizure demonstrated diffuse hemorrhaging. Fungal cultures were sent, and patient was started on empiric voriconazole. Cultures returned after he expired positive for Cryptococcus. Autopsy showed disseminated Cryptococcus with cause of death attributed to cryptococcal pneumonia.

Discussion: This case demonstrates the infectious risk of high dose immunosuppression in treating resistant focal segmental glomerulosclerosis and the need to balance efficacy of treatment against these risks.

PUB415

A Rare Case of Kidney Amyloidosis Caused by Heroin Abuse Ravina Patel, Nilson D. Feliz, Roberto L. Collazo-Maldonado. *Nephrology, Dallas Methodist Medical Center, Dallas, TX.*

Introduction: Secondary(AA)Amyloidosis nephropathy is a rare manifestation of IVDA. Is a condition characterized by deposition of insoluble fibrils in various organs; most commonly the liver and kidneys. Occurs as a result of chronic inflammatory states such as RA, IBD, chronic osteomyelitis, or familial Mediterranean fever. Kidney involvement in amyloidosis is a significant source of morbidity as it can progress to CKD.

Case Description: A 40 y/o AA man with no past medical history just 20 years of IV heroin abuse presented to the ED with the CC: Worsening lower extremity edema and a weight gained of 20 lbs. in the past few months. Patient denied any other medical problems or complaints. On PE, afebrile, normotensive, with clear lungs, normal heart at auscultation and benign abdominal findings, but with 3+ lower extremity edema. Multiple skin popping in upper and lower extremities with scarring, and no evidence of active infection. Creatinine 0.8 mg/dL on arrival. The UA showed >600mg/dL of protein and no hematuria. A 24 hour urine collection showed 35 gm of proteinuria and serum albumin 2.1g/dL. Cholesterol 232mg/dL, LDL 192 mg/dL and Trig. 189mg/dL. LFT's were normal and the rest of serologic workup including HIV, Hep B and C were negative. A biopsy showed a nodular increase in mesangial matrix material that was congophilic and stained positive with both amyloid A and P, consistent with AA amyloidosis. The EM, showed the presence of nonbranching fibrils that measure 7 and 12 nm in size. The mainstay treatment for secondary renal amyloidosis consists of tackling the underlying cause. In this case of heroin induced amyloidosis, the patient was counseled extensively about heroin cessation. Per the literature, not many other treatment options exist. We started him on colchicine as there are studies indicating its

efficacy on disrupting the amyloid fibrils and decreasing progression of disease. He was also started on anti-coagulation and diuretics, but we were unable to start him on ACEI's/ARB's due to low blood pressure.

Discussion: AA kidney amyloidosis is a rare manifestation of IVDA, especially after a prolonged exposure. We should always considered this diagnosis in chronic heroin users presenting with proteinuria.

PUB416

Addressing Fertility and Management of a Patient with PCOS and C1q Nephropathy Monica Sircar,¹ Ivy A. Rosales,² Rex Neal Smith,² A. Bernard Collins,¹ Robert B. Colvin,² Ravi I. Thadhani,¹ Andrew L. Lundquist.¹ ¹Nephrology, MGH, Boston, MA; ²Pathology, MGH, Boston, MA.

Introduction: C1q nephropathy is a rare disease that can present in a variety of ways. We present the case of a 26 year-old female with PCOS and borderline diabetes who developed non-nephrotic-range proteinuria with preserved renal function who wished to become pregnant.

Case Description: Her serologic workup was unrevealing. She did not have any classical symptoms of SLE and her ANA was only mildly positive at 1:40. Biopsy of the kidney revealed predominant immunofluorescent staining for IgG and C1q with mesangial deposits of C1q. There was no clear evidence of focal segmental glomerulosclerosis to portend a worse prognosis. Her decision to pursue pregnancy prompted further inquiry into the effects of pregnancy on her renal disease.

Review of existing literature, limited as it may be, suggested that C1q autoimmunogenicity may be associated with normal placental growth and development in the context of hormonal changes.

Discussion: Therefore, interpretation of typical parameters, including urinary protein excretion alone, may not be sufficient in determining disease status. This case demonstrates the importance of renal biopsy in defining the underlying pathology in young women with evidence of glomerular disease who wish to become pregnant as it can help guide prognosis.

Funding: Other NIH Support - NIH T32 award

PUB417

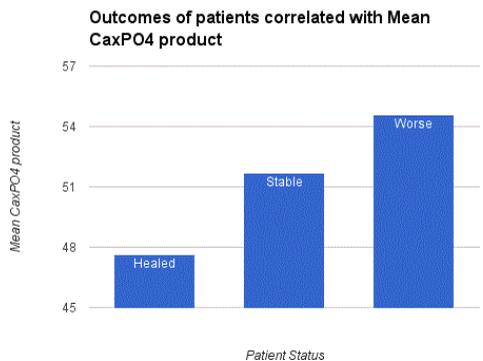
Outcomes of Calcific Uremic Arteriopathy (CUA) Management: An Inner City Tertiary Center Experience Marwan M. Abu Minshar, Nanette S. Chua, Sahrish Ilyas, Najibah Rehman, Nashat Burhan Imran, Zeenat Yousuf Bhat, Yahya M. Osman Malik. *Nephrology, Wayne State Univ S.O.M, Detroit, MI.*

Introduction: CUA is a rare, necrotizing skin condition caused by medial calcification of sub/cutaneous arterioles leading to tissue ischemia and eventual necrosis. It predominantly occurs in patients with chronic kidney disease, associated with high morbidity, mortality and variable outcomes-- posing a difficulty in management.

Case Description: We conducted a retrospective chart review from 2010-15. 17 patients were diagnosed and treated for CUA in a tertiary university center. Diagnostic methods and multi-disciplinary treatment included parathyroidectomy, medical management of bone mineral disease, standard wound care, and sodium thiosulfate. We classified outcomes as No Improvement, Stable, and Improvement of Lesions related to the mean Calcium-Phosphate product (CaXPhos). Table 1 shows patient characteristics.

Characteristics	Subjects N=17	Range (min-max)		
Gender			Comorbidities	
Female	13(76.4%)	—	CAD	7 (41.17%)
Male	4 (23.5%)	—	CVA	3 (17.64%)
Ethnicity		—	PAD	8(47.05%)
African American	16 (94.1%)	—	DM	13(76.4%)
White	1 (5.9%)	—	HTN	17 (100%)
Mean Age	56.68	28-81	DVT/PE	7 (41.2%)
Mean PTH	1244.68	35-9262	ESRD	16(94.1%)
Mean Calcium	8.95	7.6-10.3	HD	15(93.8%)
Mean PO4	5.75	3.5-8.7	PD	1(6.2%)
CaXPO4 product	51.3	29.1-78.2	Renal Transplant	1(5.9%)
Mean Ferritin	829.7	98-1640	Biopsy Proven Dx	10(58.8%)
Mean Transferrin Sat%	29%	7-51.6	Outcome	
Cinaclet use	10(58.8%)	—	Healing	5(29.4%)
Parathyroidectomy	1 (5.8%)	—	Stable	4(23.5%)
Wound Care Consult	14(82.4%)	—	Worsening	8(47.1%)
Sodium thiosulfate	17(100%)	—		

Figure 1 shows mean CaXPhos product was higher in patients with no response vs. those that remained stable or improved.



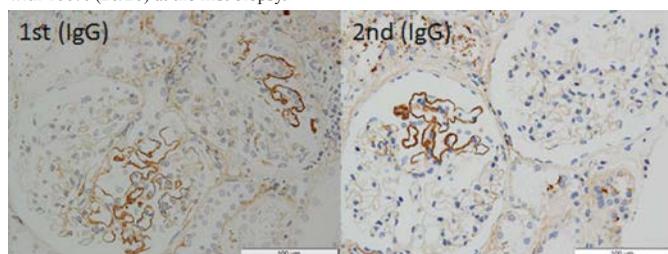
Discussion: CUA management still remains multi-faceted, with unpredictable responses, and no definitive cure.

PUB418

A Case of Adult-Onset Segmental Membranous Glomerulonephritis
 Mao Watanabe, Toshiyuki Imasawa, Takehiko Kawaguchi, Takafumi Yamakawa, Maiko Nagata, Moritoshi Kadomura, Hiroshi Kitamura. *Internal Medicine, National Hospital Organization Chiba East Hospital, Chiba, Japan.*

Introduction: Generally, adult-onset membranous glomerulonephritis (MN) has diffuse and global glomerular changes. We experienced a rare case of segmental MN (SMN).

Case Description: A 66 years old Japanese male was firstly noted proteinuria in an annual health check-up. Serum creatinine was 0.76 mg/dl, urine protein excretion was 2.1 g/gCr, and 10-19 red blood cells/high-power field were observed in the urine sediment. A percutaneous renal biopsy revealed segmental spike formation on the glomerular basement membrane (GBM) and segmental subepithelial deposits in all glomeruli. Granular deposits of IgG, IgM, IgA, C3, C1q were segmentally positive with granular patterns at the same regions. In electron microscopy, electron dense deposits were also found segmentally. The glomerular tufts with deposits included inflammatory cells (mainly macrophages). Any autoimmune disease, malignancies, and infections were detected by further examinations. Because urine protein decreased less than 1g/gCr during the hospitalization, only temocapril hydrochloride has been prescribed from 67 years old. He has never taken immunosuppressive drugs. In 68 years old, because urine protein increased to 3g/gCr, the second renal biopsy was performed. Similarly to the first biopsy, segmental spike formation on GBM and segmental staining of immunoglobulins and complements were observed. The percentage of glomeruli with subepithelial deposits decreased to 60% (6/10) compared with 100% (20/20) at the first biopsy.



Discussion: Adult-onset SMN was rarely reported in spite of 30% of MN cases in childhood. Here, we firstly reported the sequential pathological changes of adult-onset SMN without any immunosuppressive therapy. We will also discuss about the pathogenesis about SMN.

PUB419

Hyporeninemic Hypaldosteronism with Hypokalemia: A Rare Association
 Julia Brown, Shankho Shuvro Ganguli, David J. Leehey, Kavitha Vellanki. *Dept of Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Introduction: Hyporeninemic hypoaldosteronism is characterized by diminished renin and aldosterone secretion, with hyperkalemia and mild hyperchloremic metabolic acidosis being the hallmark clinical manifestations. It is often seen in diabetic patients with mild to moderate renal insufficiency or in patients taking calcineurin inhibitors. Here, we describe a rare case of hyporeninemic hypoaldosteronism in the setting of severe hypokalemia.

Case Description: A 19 year old male with a liver transplant due to cryptogenic fulminant liver failure presented to our institute with nausea, emesis, and fevers. He was 3 months post-transplant and taking tacrolimus, mycophenolate, and prednisone for immunosuppression. During the hospital stay, he developed hyponatremia, hypokalemia, and severe orthostatic hypotension (table 1). While hyponatremia improved with hydration and hypokalemia with aggressive potassium supplementation, orthostatic hypotension persisted despite volume repletion and high dose corticosteroids. Further work up revealed a normal morning cortisol level of 13.8 ug/dl but very low renin and aldosterone levels (table 1). He was started on fludrocortisone 0.1 mg daily, which was subsequently increased to 0.1 mg twice daily. His serum potassium levels improved and remained stable without

potassium supplementation. The etiology of his hyporeninemic hypoaldosteronism was thought to be calcineurin inhibitor use, with hypokalemia caused by persistent nausea, emesis, and poor oral intake.

Discussion: In conclusion, hypokalemia should not exclude work up for hyporeninemic hypoaldosteronism in the appropriate clinical setting.

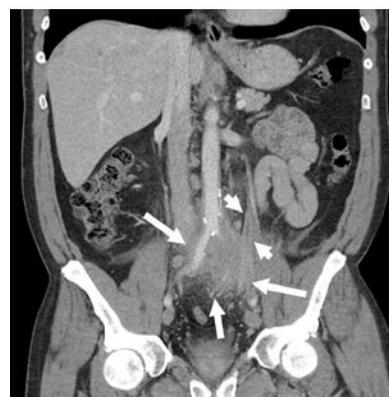
Time	Admission	Day 9	Day 17	Day 23
Serum Sodium (mm/L)	133	127	137	135
Serum Potassium (mm/L)	4.0	3.9	3.6	4.1
Serum Bicarbonate (mm/L)	19	20	23	22
Serum Chloride (mm/L)	105	99	107	106
Serum Glucose (mg/dL)	106	91	93	99
Serum Urea Nitrogen (mg/dL)	14	6	10	4
Serum Creatinine (mg/dL)	1.04	0.74	0.58	0.53
Blood Pressure Supine (mmHg)	101/66	99/52	102/68	128/74
Blood Pressure Sitting (mmHg)	-	79/42	72/46	121/69
Blood Pressure Standing (mmHg)	-	69/30	83/46	100/54
Plasma Renin Activity (ng/mL/h)	-	0.09	0.10	0.13
Plasma Aldosterone (ng/dL)	-	<1	<1	<1

PUB420

A Case of Hydronephrosis due to Bilateral Retroperitoneal Fibrosis
 Zachary Freestone, Akram M. Shaaban, Josephine Abraham. *Nephrology, Univ of Utah, Salt Lake City, UT.*

Introduction: Retroperitoneal fibrosis is characterized by inflammatory and fibrous retroperitoneal tissue. It is believed to be due to an exaggerated inflammatory reaction to aortic atherosclerosis resulting from an immunologic trigger. Retroperitoneal fibrosis can be classified as primary or secondary. Secondary causes include medications, malignancy, infection, radiotherapy, and trauma. Patients diagnosed with retroperitoneal fibrosis should undergo thorough evaluation for infectious causes and malignancy.

Case Description: A 55 year old male presented to the clinic with a chief complaint of left side flank and groin pain. He had additional symptoms of night sweats, left leg edema, and weight loss. He was referred to our clinic after initially presenting to the emergency department and receiving a CT scan of the abdomen identifying left side hydronephrosis and a retroperitoneal mass. His past medical history included melanoma 4 years prior and cutaneous follicular lymphoma of the right mandible one year prior. Repeat ultrasound prior to initiation of therapy showed new right sided hydronephrosis. The patient was started on monotherapy with prednisone 1 mg/kg/day. Imaging after initiation of therapy showed improvement in fibrosis with resolution of ureteral obstruction. The patient's serum creatinine improved from 1.93 to 1.2 after initiation of therapy. No secondary causes of retroperitoneal fibrosis was identified.



Discussion: Retroperitoneal fibrosis can present as obstruction of the ureters. It is often idiopathic, but secondary causes should be ruled out. Secondary causes include malignancy, infection, and medications. Recommended therapy includes decompression of obstruction if renal function is compromised. If the cause of the disease is idiopathic, then immunosuppressive therapy is recommended. If the disease is due to secondary causes, the underlying cause should be immediately addressed.

PUB421

BK Virus-Associated Uropathy: A Culprit Mimicking Mechanical Post-Renal Obstruction in Early Post-Kidney Transplantation
 Ekamol Tantisattamo, Aneesha A. Shetty, Bing Ho, Mohammed Javeed Ansari. *Nephrology and Hypertension, Northwestern Univ.*

Introduction: BK virus has a predilection towards infecting the uroepithelial cells and is a known but rare cause of ureteral obstruction of kidney allografts.

Case Description: A 26-year-old woman with ESRD underwent renal transplantation. Maintenance immunosuppression included tacrolimus(FK) and mycophenolic acid(MPA). FK and MPA levels were 8-16ng/mL and 2-5mg/L, respectively. Three months posttransplant,

she developed new onset BK viremia. One month later, she had a new onset BK viremia and worsening BK viremia up to 3 million and 67.5 billion copies/mL, respectively (Figure 1). Concurrently, she had AKI with a serum creatinine (SCR) of 4mg/dL from a baseline of 1.4mg/dL. Ultrasound showed moderate hydronephrosis (Figure 2). Allograft biopsy revealed acute tubular injury with negative SV40. A percutaneous nephrostomy (PCN) tube was placed and antegrade nephrostogram showed high-grade ureteral stricture (Figure 3). A ureteral stent was placed. FK and MPA target levels were decreased to 5-7ng/mL and 2-4mg/L, respectively. One week later, a repeat nephrostogram showed no obstruction and PCN tube was removed. SCR trended down to 1.2mg/dL. Ureteral stent was removed 6 weeks later. BK viremia became undetectable 6 months posttransplant with low-level BK viremia. The high-level BK viremia but negative SV40 in the kidney biopsy in the context of ureteric obstruction suggested that there was extensive BK replication within the urothelium leading to ureteral stricture and mechanical obstruction. The obstruction improved with resolution of BK viremia following reduction in immunosuppression.

Discussion: Medical management of BK virus with lowering immunosuppression can be an effective treatment to reverse ureteral obstruction due to BK virus infection, while surgical intervention is used to temporarily relieve obstruction.

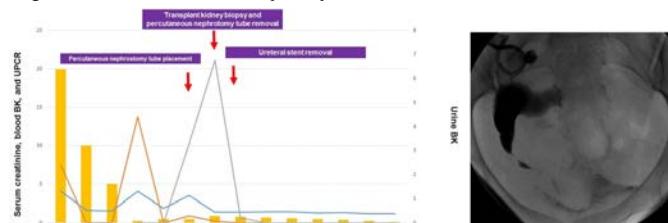


Figure 1: Clinical course after living-related renal transplantation

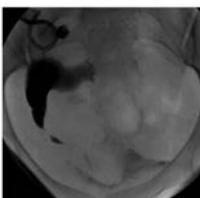


Figure 3: Antegrade nephrostogram demonstrated high-grade mid and distal ureteral stricture.

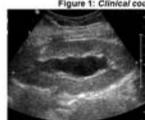


Figure 2: Transplant renal ultrasound (longitudinal) showed markedly dilated collecting system.

PUB422

Impact of Cannulation Technique on Access-Related Complications in Hemodialysis Patients *Shriharsha Kallahalli Jayaramu, Abhilash Koratala, Amir Kazory. UFL; UFL; Div of Nephrology, Univ of Florida.*

Introduction: There is growing interest in home hemodialysis therapy leading to increased involvement of patients in their own care. Buttonhole cannulation technique (BHCT) is considered a practical option for self-cannulating patients due to perceived lower incidence of access-related complications such as pain. The aim of this study is to provide a reappraisal of the current evidence on the complications of BHCT and conventional rope-ladder cannulation technique (RLCT) in hemodialysis patients.

Case Description: Articles cited in PubMed database from 2000 to 2015 using key words “hemodialysis”, “cannulation”, and “buttonhole” were searched. Original articles evaluating hemodialysis access cannulation techniques were reviewed; randomized controlled trials (RCT) were selected. Relevant data including primary outcomes and access-related complications (i.e. pain, infection, bleeding, and aneurysm) were extracted and compared.

A total of 70 articles were found, of which 6 RCT were reviewed and 5 were included in this study (1 duplication). There were a total of 472 patients (BHCT 227 and RLCT 245) with follow up periods ranging from 2 to 12 months. Two studies reported more pain with RLCT while it was similar in 2 studies and one found more pain with BHCT. Importantly, there was a significant tendency for infection with BHCT compared to RLCT in all 4 studies that could evaluate this complication and included 73% of the patients; the overall rate of infection being too low in one trial to be conclusive. Bleeding complications were similar in 4 studies while 1 found higher risk with BHCT. Only 2 studies reported higher tendency for increase in the size of the access in the RLCT group while 3 did not evaluate this complication.

Discussion: BHCT is associated with only a modest favorable impact on access-related pain in hemodialysis patients while it portends a significant increased risk of infection. There is inconclusive data regarding the impact of cannulation technique on bleeding complications and aneurysmal changes. Based on the findings of the currently available RCT, routine use of BHCT cannot be recommended for hemodialysis patients.

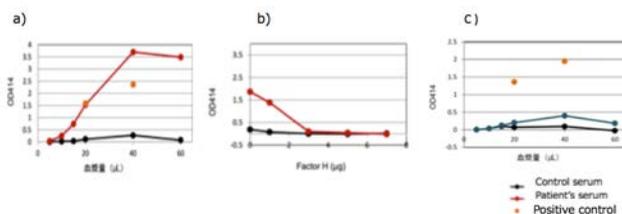
PUB423

A Case of Lupus Nephritis Accompanied with Long-Term Thrombotic Microangiopathy *Kazuhito Fukuoka,¹ Shinya Kaname,¹ Yoko Yoshida,² Hideki Kato,² Masaomi Nangaku,² Yoshihiro Arimura.¹ ¹1st Dept of Internal Medicine, Div of Nephrology and Collagen Disease, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan; ²Dept of Nephrology and Endocrinology, The Univ of Tokyo School of Medicine, Bunkyo-ku, Tokyo, Japan.*

Introduction: Although TMA is sometimes complicated in collagen disease, the features and its cause are still unclear.

A 39-year-old woman with a history of lupus nephritis (class V) for 19 years was admitted to our hospital due to complicated microangiopathic hemolytic anemia (MHA). Coombs test and anti-phospholipid antibodies were both negative. Considering that SLE played some roles, we reinforced immunosuppressive treatment and plasma exchange,

which was only partially effective. MHA fluctuated, and seven years later renal function began to decline gradually, with an exacerbation of MHA. TMA was suspected, but ADAMTS13 activity showed within normal ranges without anti-ADAMTS13 antibody, thus TTP was neglected. Serum C3 levels proved low, thus we considered the possible involvement of complement activation, and performed hemolysis test for sheep RBCs using the patient’s plasma



(a). The results showed that hemolysis was observed with recovery by adding complement factor H, suggesting that complement system was activated (b). Based on these results, she was diagnosed as atypical HUS. Despite intensive treatment, she finally progressed to maintenance HD, but the findings of TMA were gradually improved. Two months later, we examined the hemolysis test again, showing the negative results. Sequence analysis of the aHUS-related genes revealed two SNPs, none of which have been reported before.

Discussion: Our case report shows that a SLE patient can complicate TMA caused by complement-mediated HUS, which may be reversed during the treatment course, suggesting the possible involvement of genetic predisposition and some triggering factors/conditions.

PUB424

Glomerulonephritis Crescentic Pauci-Immune ANCA Related IgA – A Case Report *Maria C. Piraciaba, Precil Diego Miranda de Menezes Neves, Cristiane B. Dias, Luis Yu, Leonardo Abreu Testagrossa, Denise M. Malheiros, Viktoria Woronik, Irene L. Noronha, Lecticia Jorge. Univ de São Paulo.*

Introduction: The pauci-immune crescentic glomerulonephritis (PICG) are mostly related to antineutrophil cytoplasmic antibodies (ANCA). IgG is detected in 80-90% of cases. PICG reports related to ANCA IgA are rare due to low suspicion and research of IgA ANCA. We report a case of PICG ANCA related IgA.

Case Description: Patient female with 83 years, asthenia and abdominal pain for 4 months and 10 days ago emergence of purpuric lesions in upper and lower limbs and trunk. Biopsy of purpuric lesion showed leukocytoclastic vasculitis with granular IgA deposits in the vessels of the papillary dermis. After diagnosis of Henoch-Schonlein, prescribed treatment with prednisone 1 mg / kg for two weeks, with drug weaning. The skin lesions disappeared, but the patient evolves with important asthenia. Renal biopsy, 15 glomeruli, 7 completely sclerotic, 3 with increasing cell and 3 with increasing focal fibroblast. Positive immunofluorescence for Fibrinogen + 2 / + 3 in the growing, being the framework compatible with glomerulonephritis crescentic pauci-immune, mixed form. By previous cutaneous involvement with IgA deposits, requested assessment of ANCA IgA by immunofluorescence. As the result was positive, the patient was treated with methylprednisolone and mycophenolate sódico, with recovery of renal function.

Discussion: The ANCA IgA evaluation should be considered in cases where there PICG increased serum IgA levels.

PUB425

Acute Interstitial Nephritis Associated with Probiotic Use *Sandar Win, Gaurang P. Mavani, Joshua A. Schwimmer. Div of Nephrology, Lenox Hill Hospital of the North Shore-LIJ Health System, New York, NY.*

Introduction: Acute interstitial nephritis (AIN) is associated with a variety of etiologies, including infections, autoimmune conditions, and medications. Probiotics are over-the-counter microorganisms used for their potential health benefits, and studies show probiotics may have immunostimulatory and immunomodulatory effects. We report the first potential case of AIN associated with the use of probiotics.

Case Description: A healthy 44-year-old man was found to have a stable baseline Cr of 1.16 mg/dL with a measured CrCl in the normal range. 42 d later, to treat infrequent loose bowel movements (2x/wk), he consumed a probiotic regimen of 10 billion cells of Lactobacillus GG bid for 14 d. There was no diarrhea, fevers, rash, blood in the stool, or exposure to NSAIDs, antibiotics, herbs, or other medications. 11 d after probiotics use, during a routine physical, he was found to have an increase in his Cr to 1.66 mg/dL (an increase of .5 mg/dL in 52 d). There was no proteinuria or hematuria, and an ANA was negative. A renal sonogram revealed echogenic, normal-sized kidneys. His Cr remained 1.4-1.6 mg/dL and did not return to baseline. 135 d after exposure to probiotics, a renal biopsy was performed. The biopsy revealed patchy tubular atrophy and interstitial fibrosis affecting 10% of the cortical area with a few mononuclear inflammatory cells and focal mild lymphocytic tubulitis, consistent with resolving AIN.

Discussion: In this case, the temporal association between the use of probiotics with kidney injury and the absence of other causes of AIN implicates the probiotic Lactobacillus GG as the etiologic agent. The mechanisms by which probiotics could potentially cause AIN include manipulation of intestinal microbial communities, immunomodulation, alteration of

responsiveness of intestinal epithelial and immune cells, and altering the immunogenicity of degraded enteric antigens. Given the frequent over-the-counter use of probiotics, multiple potential coexisting etiologies for AIN, the often indolent nature of this disease, the rarity of this association, and the need for a renal biopsy to establish the diagnosis, the association between probiotics and AIN may be under-recognized.

PUB426

Decision-Making for the Critically Ill Un-Befriended Patient Aprajita Mattoo, Jennifer S. Scherer. *Nephrology, NYU School of Medicine, New York, NY.*

Introduction: The “un-befriended” patient is one that lacks decision-making capacity & a surrogate decision-maker (SDM). Nephrologists encounter un-befriended patients often, yet limited literature exists to guide decision-making for these vulnerable patients. This case describes an organized approach to caring for a critically ill un-befriended patient.

Case Description: Mr. S was a 74 year old wheelchair bound nursing home (NH) resident who underwent an urgent right hemicolectomy for a perforated colon. His post-operative course was complicated by septic shock & multi-organ failure including AKI due to ATN. During this time his serum Cr increased from 0.8 to 3.6 mg/dl, with a urine output of <50cc/day. Mr. S was obtunded & had diffuse anasarca. He lacked advance directives & any SDM. The primary service believed that dialysis (HD) should be withheld given his overall poor prognosis. The consulting renal service utilized the four-topic approach to ethical decision-making to guide their recommendations. An estranged sister was asked to partake in an inter-disciplinary team (IDT) family meeting with renal, palliative care, bioethics, & the primary service to explore Mr. S’s values. It was established that Mr. S cherished his life in the NH & would have appreciated time there even if on HD. Given this information, the IDT decided that a time-limited trial of HD would be reasonable. Before HD was needed however, Mr. S decompensated due to fungemia. The IDT agreed that death was imminent, even with HD. Under provisions of the NY State Family Health Care Decisions Act (FHCDA), it was determined to be ethically appropriate to withhold HD & transition Mr. S to comfort care.

Discussion: Utilizing the four-topic approach to decision-making, established legal policies, & an IDT, nephrologists can manage un-befriended patients within an organized, legally sound, & ethically sensitive framework.

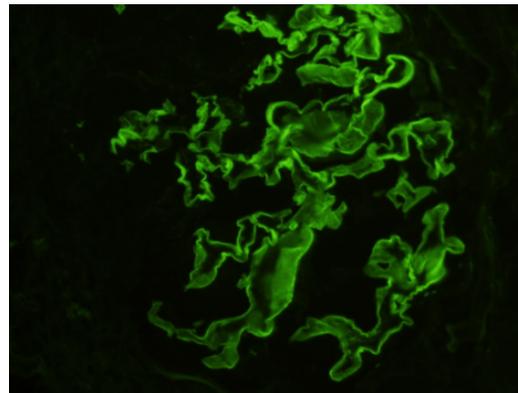
MEDICAL INDICATORS <i>Beneficence and Non-maleficence</i>	PATIENT'S PREFERENCES <i>Respect for Patient Autonomy</i>
Medical Problems: Acute renal failure due to septic shock with resolved surgical and infectious complications.	Does The Patient Have Capacity?: The patient is without capacity.
Prognosis: Uncertain, but likely weeks to months. Patient's AD is acute and potentially reversible. He would likely tolerate HD. However, given his frail state and co-morbid medical conditions (HTN, wheelchair bound, recent emergent surgery) his long term prognosis is likely limited.	If incapacitated, Who is the Appropriate Surrogate?: The patient's next of kin is an estranged sister who is unwilling to act as a SDM.
Goal of Treatment: Life extension (continued dialysis so that he may return to his NH). Conflict of quantity versus quality given the high likelihood of complications.	Has the Patient Expressed Prior Preference?: The patient is without advanced directives.
QUALITY OF LIFE <i>Beneficence, Non-maleficence, and Respect for Patient Autonomy</i>	CONTEXTUAL FEATURES <i>Justice and Fairness</i>
What Are The Prospects FWD Treatment For The Patient Returning To A Normal Life?: Patient has a potentially reversible kidney injury and may be able to return to NH stable on dialysis for the remainder of his lifespan.	Are There Religious Or Cultural Preferences?: Patient is not religious. No cultural preferences were highlighted by his sister.
Is The Patient's Present Condition Such That His Continued Life May Be Judged As Undesirable?: Patient has limited mobility at baseline. Patient had expressed that he loved his NH at his current QOL. This implied he would be happy there, even on HD.	How Does The Law Effect Treatment Decisions?: The NY FHCDA provides the following guidance: -if the patient has no surrogate, then the hospital must identify, to the best extent possible, the patient's wishes and preferences for health care decisions. -in an un-befriended patient, a decision to withhold or withdraw life sustaining treatment can be made if the patient is imminently dying even if treatment is provided, and the provision of the treatment would violate accepted medical standards. https://www.nyba.org/FHCDA/
Is There A Potential For Provider Bias About His Quality Of Life?: The ICU team was very worried about the possibility of chronic critical illness, complications, and a life marred by several hospitalizations.	

PUB427

Persistent Kidney and Alveolar Damage in Patients with Goodpasture's Disease and Negative Anti-GBM Antibodies Giovanna Y. Arteaga Muller,¹ Lilia Maria Rizo Topete,¹ Elisa Maria Guerrero Gonzalez,¹ Concepcion Sanchez Martinez,¹ Jesus Cruz Valdez,¹ Gabriela Alarcón-Galván.² ¹*Nephrology, Univ Hospital José E. González UANL, Monterrey, Mexico;* ²*Anatomic Pathology, Univ Hospital José E. González UANL, Monterrey, Mexico.*

Introduction: Goodpasture's disease is characterized by the presence of basement membrane antibodies which act against type 4 collagen in the glomerular basement membrane (GBM) and alveoli, it represents 20% of all crescentic glomerulonephritis.

Case Description: 21 year old woman, with anemic syndrome presenting Hb 4.33g/dl, Cr 0.8mg/dl, receiving a red cell transfusion. Is readmitted 15 days later Hb 2.7g/dl and Cr 1.9 mg/dl, whereby three globular packages were transfused and she was referred to our hospital. On admission, the patient was hypertension, lower limb edema and gross hematuria, Hb 11g/dl, Cr 1.7mg/dl, negative ANA's and ANCA'S and positive anti-GBM antibodies. Renal biopsy showed crescentic glomerulonephritis and linear staining deposits of IgG in GBM (4+).



Direct immunofluorescence technique (400X). Linear glomerular basement membrane staining for IgG.

Immunosuppressive therapy begins with methylprednisolone and CYCLOPS protocol. Later hemoptysis which improves with plasmapheresis, negative control anti-GBM antibodies. After presented sudden hypoxemia, bronchoscopy with abundant hemosiderin-laden macrophages, whereby plasmapheresis is performed again together with methylprednisolone, cyclophosphamide and rituximab. Currently the patient is in chronic hemodialysis, with negative anti-GBM antibodies.

Discussion: In patients with positive anti-GBM antibodies renal involvement may occur alone or associated with pulmonary hemorrhage, our patient despite having negative anti-GBM antibodies presented pulmonary hemorrhage. The literature recommends confirm the sustained absence of anti-GBM antibodies and signs of recurrence every 6 months.

PUB428

Gitelman Syndrome: Use of Dual Potassium-Sparing Agents in Refractory Hypokalemia Maria Bernadette Yballe, Sandeep Aggarwal. *Div of Nephrology, Drexel Univ, Philadelphia, PA.*

Introduction: Hypokalemia is one of the most frequently encountered electrolyte disturbances. Chronic hypokalemia with hypomagnesemia should prompt further investigation to include rare genetic disorders such as Gitelman syndrome. Despite the appropriate diagnosis, treatment can be challenging.

Case Description: We present a case of a 49 year-old non-hypertensive Caucasian female who presented to our outpatient clinic for an evaluation of her polyuria, chronic hypokalemia and hypomagnesemia. Her polyuria started in the first trimester of her first pregnancy in her 20s. She has one sibling with similar complaints, sparing her parents and her daughter. She complained of paresthesia and lower extremity weakness. She reports no diuretic use, OTC weight loss regimen, and no diarrhea. She has been on potassium and magnesium supplements with spironolactone without a definitive diagnosis. Despite these interventions, electrolytes remained abnormal with a potassium of 2.8, magnesium of <1.0, and a serum creatinine of 0.5 mg/dL with a renin activity of 1.78 ng/dL and aldosterone level of 36 ng/dL (ARR 20.2). A 24-hour urine study revealed a low urine calcium of <5.0 mg/day consistent with Gitelman syndrome. Genetic testing revealed two distinct heterozygous missense autosomal recessive mutations of the SLC12A3 gene from Athena Diagnostics: c. 1315G>A; p.Gly439Ser and c. 2221G; p.Gly741Arg. She was continued on spironolactone along with potassium and magnesium supplements. Despite supplementation, she often required hospital visits which prompted magnesium and potassium infusions. Addition of amiloride improved her electrolyte levels, decreasing the need for hospitalizations and supplementations.

Discussion: Gitelman syndrome occurs in only ~1% of the Caucasian population which presents as chronic, sometimes severe and symptomatic hypokalemia, hypomagnesemia, hypocalciuria, and normotensive aldosteronism. The existence of 2 unique recessive alleles inherited by two siblings makes this case even more of a rarity. Our case also demonstrates the effective addition of a second potassium-sparing agent such as amiloride in ameliorating the need for more supplementation.

PUB429

Cerebral Ethylene Glycol Toxicity Despite Prompt Renal Replacement Therapy Maria Bernadette Yballe, Sandeep Aggarwal. *Div of Nephrology, Drexel Univ, Philadelphia, PA.*

Introduction: Acute cerebral edema is a rare consequence of ethylene glycol toxicity. Despite prompt initiation of therapy with fomepizole and renal replacement therapy, rare case reports of central hypodensities on CT imaging with neurologic abnormalities have been reported.

Case Description: We present a case of a 38 year-old female with PMH of HTN and anxiety who was brought in for agitation. One hour later, the patient became obtunded with significant respiratory distress requiring intubation. Home medications included bupropion. It was unclear if she ingested any toxins but the patient did have a history of marijuana use. On physical examination, the patient was hypertensive 210/114 mm Hg with reactive pupils. She was found to have high anion gap metabolic acidosis with a pH of 6.808, a serum bicarbonate of 4, an osmolal gap of 68, and a lactic acid of 5.6. Levels of ethanol, acetaminophen, phenobarbital, salicylate, and valproic acid levels were undetectable while urine drug screen was only positive for THC. Head CT did not reveal any acute

pathology. Urine microscopy revealed multiple ovoid colorless crystals in rosette formation consistent with monohydrate calcium oxalate crystals. Fomepizole was immediately started and intermittent dialysis initiated promptly within 10 hours of ingestion. However, due to hemodynamic instability, RRT had to be converted to a continuous veno-venous hemodialysis. After 2 days, patient then experienced an acute hypertensive episode with a BP of 27/120 mm Hg from a radial arterial line with pinpoint pupils and a repeat head CT revealing cerebral hypodensities in the basal ganglia, thalami, and brainstem along with transtentorial and tonsillar herniation. On day 5, patient met criteria for brain death and was assessed for organ donation.

Discussion: Despite prompt initiation of dialysis, rare case reports of acute cerebral edema from ethylene glycol toxicity have been reported. It is unknown whether these abnormalities are due to direct cellular toxicity or deposition of crystals in the cerebral vasculature causing ischemia and subsequent edema and inflammation. Our case demonstrates a rare neurologic sequela of ethylene glycol toxicity despite appropriate and prompt treatment.

PUB430

Encapsulating Peritoneal Sclerosis – Case Reports
André Luiz De Andrade Araújo, Maria Alina G.M. Cavalcante, Amadeu Marinho, Teg Marcos Veiga, Luis H.B.C. Sette, Lucila Maria Valente. *Nephrology, Univ Federal de Pernambuco, Recife, Pernambuco, Brazil.*

Introduction: Encapsulating Peritoneal Sclerosis (EPS) is a rare but serious and potentially lethal complication in peritoneal dialysis (PD), first described in 1980. Intestinal obstruction, serious malnutrition and sepsis are the causes of death. This uncommon condition is the result of chronic abdominal inflammation of multifactorial origin. High risk patients include PD for more than 8 years and with frequent peritonitis (two-hits theory). The exact incidence is unknown.

Case Description: We described outcomes of 6 cases followed in a referral service of PD between 2010 and 2015.

Case	Gender/ Age (years)	CKD etiology	Time on PD (years)	EPS related infectious agent	Previous Peritonitis (number)	Clinical Features	Radio-logic Finds	Peritoneal Biopsy	Outcome
1	F / 47	SAH	8	<i>Candida sp / Staphylococcus aureus</i>	6	Acute abdominal obstruction + Bloody effluent	Loculated ascites + Peritoneal thickening and calcifications	Chronic peritonitis + Peritoneal thickening + Fibrin depositions	HD since 2010
2	F / 47	SAH	4	<i>Pseudomonas aeruginosa</i>	3	Partial bowel obstruction + Bloody effluent	Loculated ascites + bowel thickening	--	HD at 08 months
3	F / 18	PIGN	10	<i>Staphylococcus coagulase negative</i>	5	Partial bowel obstruction + pain	Moderate ascites + Peritoneal/Bowel calcification.	--	HD since 2013
4	M / 68	T2DM	2,5	<i>Escherichia coli / Klebsiella oxycata.</i>	2	Partial bowel obstruction + pain	High volume loculated ascites + bowel tethering	--	HD since 2012
5	F / 39	SLE	8	<i>Enterococcus sp</i>	1	Bowel obstruction + Severe malnutrition + Chronic abdominal pain + Bloody effluent	Peritoneal calcification + bowel distention + high volume ascites	--	Death for sepsis after 8 months
6	M / 53	T2DM	2,5	<i>Streptococcus viridans</i>	2	Abdominal distention + pain	High volume unique peritoneal collection + intestinal cocoon	--	HD since 2014

SAH: Sístemic Arterial Hypertension; SLE: Sístemic Lupus Eritematosus; T2DM: Type 2 Diabetes Mellitus; PIGN: Post Infectious Glomerulonephritis;CKD: Chronic Kidney Disease.

Discussion: EPS is a severe event related a long term on peritoneal dialysis or severe cases of peritonitis.

PUB431

AM Tolvaptan to Avert Hyponatremic Seizures in a Patient with Primary Polydipsia and New Mildly Impaired Free Water Excretion Amít N. Shah, Adam G. Winkler, Claude Bassil, Bassem H. Rouphael, Jacques A. Durr. *Div of Nephrology, Univ of South Florida, Tampa, FL.*

Introduction: A former pilot with a history of primary polydipsia PP (past urines >6 l/day) complained of confusion. Plasma (P_{Na}) and urine sodium were 123 and 37 mEq/l, and plasma (P_{osm}) and urine osmolalities, 251 and 207 mOsmol/kg H₂O. With cessation of Prozac and advised fluid restriction (FR) P_{Na} corrected. Interim P_{osm} was 286 mOsmol/kg and urine SG 1.005. Following multiple surgeries (decompressive laparotomy, subtotal colectomy, ileostomy, feeding gastrostomy, for compartment syndrome/pancreatitis), she had a first hyponatremic seizure (HS). No cause for impaired free water excretion (iFWE) was found. Her PP made FR difficult, as she was thirsty at P_{Na} <125 mEq/l, and caused repeat HSs.

Case Description: After her 4th seizure, we replaced FR and salt tablets with AM tolvaptan. This normalized P_{Na}, abolished her recurrent HSs, and was tailored to her new dreaded PP-SIADH combination.

Indeed, since thirst is constant in DI but only diurnal in PP, the AM tolvaptan-induced daytime DI allowed her to quench her thirst without fear of HSs, since iFWE recurred only by hs, when the drug effect wore off, and her PP abided. She was reluctant giving up this diurnal/nocturnal PP-DI/SIADH, for fear of seizures.

Discussion: Given the high capacity for FWE, a syndrome of inappropriate antidiuresis (SIAD) or impaired diuresis-aquaresis (SIDA), due or not to ADH (SIAD/H or SIDA/H) must coexist in PP, for HS to occur; conversely some PP or other source of free H₂O must exist in the 'SIAD/H – SIDA/H' spectrum of iFWE to cause HS, since FR alone increases the low P_{Na}, and prevents HS during depot ADH in man, or chronic dDVP infusion in rats. This is the first report of successful compassionate off label use of AM tolvaptan, instead of FR, to prevent HS in a patient where PP is the culprit. However FR instead of vaptans is the first line treatment of low P_{Na} in SIADH, yet here ADH is the culprit. The fact that PP and SIAD/H (or iFWE state) must coexist to cause HS, and that ADH, as assessed by sensitive assays is rarely totally suppressed, resolves this paradox.

PUB432

Atypical Presentation of Calcium Oxalate Nephropathy Young-Soo Song,¹ Joel M. Henderson,² David J. Salant,¹ Sandeep Ghai.¹ *¹Renal Medicine, Boston Univ Medical Center, Boston, MA, ²Pathology and Laboratory Medicine, Boston Univ Medical Center, Boston, MA.*

Introduction: Ethylene glycol ingestion can cause multi-organ dysfunction including acute kidney injury (AKI) and death. The diagnosis can be made based on history, a high anion gap metabolic acidosis with an elevated osmolar gap, oxalate crystalluria and an elevated ethylene glycol level. The diagnosis may be challenging with the concurrent use of other substances such as cocaine as it causes vasomotor AKI or ANCA vasculitis. To elucidate the diagnosis, a renal biopsy may be required. Herein, we present a patient with biopsy proven calcium oxalate nephropathy who presented with unexplained AKI likely related to unintentional low dose regular ethylene glycol use. She did not have any symptoms or classic biochemical features of ethylene glycol intoxication.

Case Description: A 57-year-old homeless woman with a history of rheumatoid arthritis, COPD presented with a productive cough and dysgeusia and was found to have a Cr of 8.9 mg/dl, elevated from a recent baseline of 0.9 mg/dL. Her anion gap was 17, with no other electrolyte abnormalities. Toxicology was negative for ethanol or salicylates. Her BP was 157/77 mm Hg and physical exam was unremarkable. Her last use of cocaine was 3 days prior to admission. She was initially given normal saline and maintained an adequate urine output, but her Cr continued to rise to 13.0 mg/dL. Urine sediment showed a few isomorphic RBCs only. A renal ultrasound revealed normal sized kidneys. Serological tests for autoimmune, post-infectious and dysproteimic causes of AKI were normal or negative. Renal biopsy revealed acute tubular injury with calcium oxalate deposition. An in depth history did not reveal a high oxalate diet nor a medical history predisposing her to hyperoxaluria, however she admitted to the regular ingestion of "juiced" street alcohol. She did not require dialysis. Her follow-up Cr was 1.8 mg/dl two months later.

Discussion: In conclusion, a thorough history is required when encountering unknown AKI in patients with a history of drug abuse or homelessness, while keeping a high index of suspicion for drug intoxications including ethylene glycol.

PUB433

Thrombotic Microangiopathy (Hemolytic-Uremic Syndrome) Induced Acute Kidney Injury Associated with Brucella Infection Thomas E. Craig, Jonathan G. Owen. *Dept of Medicine, Section of Nephrology and Hypertnesion, LSUHSC, New Orleans, LA.*

Introduction: Thrombotic microangiopathies (HUS, TTP and DIC) have been associated with a host of infectious agents. Its association with Brucellosis is uncommon. We present a case of a patient who developed TMA associated with a case of Brucellosis.

Case Description: 52 year-old woman with minimal past medial history presented to the hospital with abdominal pain, fevers/chills and generalized body aches. History was significant for intermittent bloody diarrhea approximately 2 weeks prior to ED presentation. Physical examination revealed epigastric and right upper quadrant tenderness to palpation and patient was started on broad-spectrum, empiric IV antibiotic therapy with

Vancomycin, Piperacillin/Tazobactam, and Ciprofloxacin. Shortly thereafter, her clinical status deteriorated resulting in acute respiratory failure requiring intubation and mechanical ventilation. CBC was notable for a white blood cell count of 27,000, hemoglobin of 7.3 g/dL and a platelet count 80,000. Other labs were notable for total bilirubin 2.3 mg/dL, LDH 509 U/L, haptoglobin less than 10, lactic acid 5.7 mmol/L and elevated transaminases. Peripheral Smear was notable to be positive for numerous schistocytes. Patients was anuric and Nephrology consulted to begin CRRT in setting of sepsis requiring three vasopressors. Patient had a rapid improvement in symptoms after initiation of sepsis protocol and was weaned off all vasopressors by 72 hours. Initial workup including abdominal imaging and blood cultures were negative for a source of infection. Patient had remarkable spontaneous clinical recovery and was later found to be positive for Brucellosis by immunoglobulin assay.

Discussion: Brucella infection has uncommonly been associated with the development of Hemolytic Uremic Syndrome. In addition, clinical course is widely variable, ranging from spontaneous recovery, as occurred with this patient, to disease requiring long-term renal replacement therapy.

PUB434

Patient with Clinical Diagnosis of Scleroderma Presenting with Sjögren's Associated Renal Disease Aala Jaber, Jasvinder S. Bhatia. *Nephrology, Boston Medical Center, Boston, MA.*

Introduction: Overlap rheumatologic syndromes can occur in a substantial number of patients with renal disease. The clinical manifestations often favor one diagnosis over another, which can make diagnosing and treating the renal disease very challenging.

Case Description: 69-year-old female with no known history of previous rheumatologic disease presented with cough, fever and AKI and was diagnosed with multifocal pneumonia. Initial laboratory tests revealed a creatinine level of 2.2mg/dl, and persistent non anion-gap metabolic acidosis. On further history, she complained of long standing heartburn and Raynaud's symptoms in her fingers. Her physical exam disclosed telangiectasia on palms and skin thickening of the face and PIP joint. These features were consistent with systemic scleroderma, which prompted a rheumatologic work-up. Serologies were significant for a positive ANA and SSA antibody as well as hypocomplementemia. Urine sediment revealed many WBCs with no casts and some non-dysmorphic RBCs. A decision was made to proceed with kidney biopsy to identify the cause of her renal disease since the sediment was not supportive of Scleroderma associated renal disease. Kidney pathology showed acute interstitial nephritis with mild chronic changes which, when combined with the serologic tests, was highly suggestive of Sjögren's syndrome-associated renal disease. She was commenced on corticosteroid therapy and two months post-initiation, her renal function has stabilized.

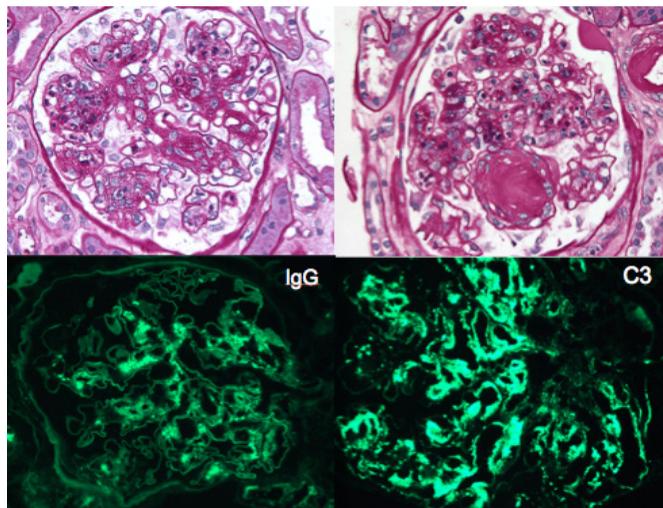
Discussion: This case demonstrated the importance of kidney biopsy in elucidating a diagnosis in a challenging case of overlap syndrome. The rapid diagnosis of interstitial nephritis was particularly important in this patient since most cases of renal associated Sjögren's go unrecognized until significant renal dysfunction has occurred. It has been proposed to consider kidney biopsy findings of tubulointerstitial disease as additional supportive criteria in the classification of Primary Sjögren's syndrome, which is a sentiment we also support.

PUB435

More Than Just Diabetic Glomerulosclerosis – “A Challenge to the Epidemiological Paradigm” Juan Antonio Meda, Jeffrey D. Wallach. *Nephrology, Harlem Hospital Center, New York, NY.*

Introduction: Acute post infectious glomerulonephritis (APIGN) most frequently affects children and is relatively uncommon in adults. The incidence has declined sharply in industrialized countries over the last 50 years. Adults with an immune compromised background, especially due to alcoholism and/or diabetes are at higher risk for developing the disease.

Case Description: A 61 year old Hispanic male with medical history of uncontrolled diabetes, Hypertension and chronic alcohol abuse presented to the emergency department due to shortness of breath and swelling of his legs since one week. Patient was afebrile, blood pressure 200/102 mm Hg. On exam he had clear signs of fluid overload. Pitting edema was seen over the lower extremities bilaterally, up to the shins. He also had an oval ulcer on his right leg anteriorly measuring 2 cm discharging pus. The remainder of the physical exam was grossly normal. Relevant laboratory results potassium of 6.4 meq/L, BUN 51 mg/dl, Creatinine 1.7 mg/dl (Baseline unknown) and Albumin 2.8 gr/dl. Urinalysis: protein 300 mg/dl, blood MOD, WBC 61/hpf, RBC 87/hpf, Hyaline casts 7/hpf. Urine eosinophils present. Urine 24 Hr Protein: 6.7 gr. Wound cultures positive for Beta Hemolytic Streptococcus Group A. Complement C3: 19 Ch50: <10, C4:34 Antistreptolysin O:400 [<200 IU/ml] Anti DNase B Titre: 967. Kidney biopsy results: acute post-infectious glomerulonephritis superimposed on background changes of moderate nodular diabetic glomerulosclerosis.



Discussion: Most children with APIGN recover completely, but there is general agreement that the prognosis is more guarded in adults. Full recovery of renal function can be expected in just over half of patients, and prognosis is dismal in those with underlying diabetic glomerulosclerosis.

PUB436

Two Cases of Kidney Injury Induced by Anti-VEGF Therapy for Carcinoma Yudai Isozaki, Yosuke Nakagawa, Takuya Isegawa, Masahiro Koizumi, Masafumi Fukagawa. *Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.*

Introduction: Anti-vascular endothelial growth factor (VEGF) agents have been widely used in the treatment of various types of advanced-stage malignant tumor, including lung carcinoma and renal cell carcinoma. Although these agents are generally well tolerated, there are increasing reports of renal adverse events, especially proteinuria.

Case Description: **Case 1:** A 69 year-old male started chemotherapy including bevacizumab (monoclonal antibody of VEGF) with a diagnosis of advanced lung adenocarcinoma of left upper lobe. The completion of four-course chemotherapy resulted in reduction of tumor volume, and then converted to bevacizumab monotherapy. At one year after the start of therapy, proteinuria with renal insufficiency developed. He was referred to our service for further evaluation and management. Renal biopsy demonstrated microthrombi in the loop wall with duplication of GBM, which was consistent with thrombotic microangiopathy (TMA). Thereafter, with cessation of anti-VEGF agent, proteinuria was gradually ameliorated to less than 1.0 g/day and renal function returned to normal range. **Case 2:** A 56 year-old male with renal cell carcinoma, who had undergone nephrectomy with three years before, subsequently proved to have metastatic lesion in lumbar vertebra. He started treatment with sunitinib, a tyrosine kinase inhibitor which blocks the intracellular domain of the VEGF receptor. This patient had baseline renal insufficiency due to nephrectomy and diabetes. After the introduction of therapy, he exhibited progression of kidney disease with nephrotic-range proteinuria in a short time. In addition to the cessation of sunitinib, hemodialysis was initiated because of fluid overload. After several times of dialysis, urine output was gradually increased and renal function returned to the baseline level.

Discussion: The renal adverse effects of anti-VEGF agents are supposed to arise from inhibition of podocyte-endothelial VEGF signaling pathway. VEGF signaling pathway plays an essential part in glomerular development and endothelial maintenance. We need to pay attention to renal adverse effects with anti-VEGF therapy.

PUB437

Concurrent Development of Eculizumab (ECU) (Anti-C5 Antibody)-Responsive Atypical Hemolytic Uremic Syndrome (aHUS) and Siltuximab (SLT) (Anti-IL-6 Antibody)-Sensitive Multicentric Castlemans Disease (MCD): Evidence for the Pathogenic Role of Inflammatory Cytokines Joe Ghata,¹ Abdulmawla Albirini,¹ Kai Lau.^{1,2} *¹Nephrology, Univ of Oklahoma, Oklahoma City, OK; ²Medicine, VA Medical Center, Oklahoma City, OK.*

Introduction: The literature has a few cases on the association of MCD with thrombotic microangiopathy (TMA), but the pathogenesis & therapy are unknown.

Case Description: We describe a 29-year-old previously healthy man initially presented with non-specific symptoms of what later proved to be MCD. Diagnosis was delayed due to explosive full-blown systemic & biopsy-proven renal TMA, producing dialysis-dependent ARF, severe thrombocytopenia & transfusion-dependent hemolytic anemia till eculizumab (ECU). The appearance of diffuse lymphadenopathy 8 weeks after acute renal failure (ARF) led to node-biopsy proven MCD diagnosis & therapy with SLT. We postulate MCD was the trigger for TMA & full resolution needs both ECU & SLT directed at the etiology.

10 d before ARF, patient had abdominal pain, treated as cholecystitis by cholecystectomy. Mild splenomegaly & trace ascites were overlooked. Day 7 after ARF, bilateral pleural & pericardial effusion & moderate ascites emerged but overlooked as serum creatinine rose

from 0.9 to 11.3 mg% by day 33. At this point, Hgb fell to 6 g%, platelet to 45 k/mm³, LDH peaked at 760, C3 down to 50 & C4 to <0.8. aHUS was diagnosed by normal (nl) ADAMTS13 level, absent Ab & negative Shigatoxin. After 4 doses of ECU, by day 50 all features of TMA improved. Negative were ANA, ANCA, cryo, antiphospholipid Ab, hepatitis profile, SPEP, HHV 6, 8, & HIV. On day 54, diffuse large lymphadenopathy appeared on CT of chest & abdomen with 18.8 cm spleen & generalized anasarca & polyserositis. HS-CRP was up 25 x nl. [IL-6] & [VEGF] were 2-12 fold nl. Lymphadenopathy regressed 50% after 4 & >75% after 8 doses of SLT. Edema fully resolved after 2 doses.

Discussion: We conclude that intense cytokine activation due to MCD played a pathogenic role in his aHUS, as evidenced by the precedence of splenomegaly & anasarca to his TMA & by the dependency of anti-IL-6 Ab for full resolution of his MCD.

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PUB438

Severe Hypercalcemia Presenting During Recovery Phase of Ischemic Acute Kidney Injury Buthayna A. Dinary,¹ Fazel Dinary,² Lavinia A. Negrea.¹
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Introduction: AKI is frequently complicated by multiple electrolyte abnormalities, including hyperkalemia, hyperphosphatemia, and hypo/hypercalcemia. Hypercalcemia is often seen in the recovery phase of rhabdomyolysis associated AKI, can be severe and life-threatening. Several etiologies for delayed hypercalcemia have been proposed, including mobilization of calcium deposits out of the recovering muscles, secondary hyperparathyroidism, increase in calcitriol, and resolution of hyperphosphatemia.

Case Description: A 31 yo Caucasian male with recently diagnosed Type I DM. Admitted for DKA complicated by cardiac arrhythmia, cardiac arrest, respiratory failure, septic shock, and oliguric AKI requiring a prolonged period of renal replacement therapy. Ultimately renal function recovered and patient was taken off dialysis. There was no evidence of rhabdomyolysis clinically or biochemically at any time during his hospitalization. He was hypocalcemic during the oliguric phase of AKI but during the diuretic phase he developed severe symptomatic hypercalcemia. Improved with volume replacement and administration of calcitonin. Hypercalcemia reached a peak of 14.1 mg/dL, corrected for serum albumin and urine output was as high as 3.5 liters daily. Hypercalcemia lasted for 3 weeks and then calcium returned back to normal levels. Plasma levels of 25-OH and 1-25(OH)₂ vitamin D were not elevated, intact parathyroid hormone level was appropriately suppressed, and 24-hour urine calcium was 520 mg. Immobilization hypercalcemia as well as mobilization of calcium from calcium deposited in various tissues seems to account for hypercalcemia and hypercalciuria in this case.

Discussion: Hypercalcemia is uncommon during the recovery phase of non-rhabdomyolysis associated ATN. Unattended, it can cause severe morbidity. Fluid administration, calcitonin, and bisphosphonates are some of the methods used for its treatment.

PUB439

A Case of Hyponatremia from Adrenal Insufficiency Mimicking Siadh Pradeep Reddy Thodima, Rasib Raja, Siddhesh R. Lotlikar, Imara Dissanayake, Eric J. Bloom. *Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA.*

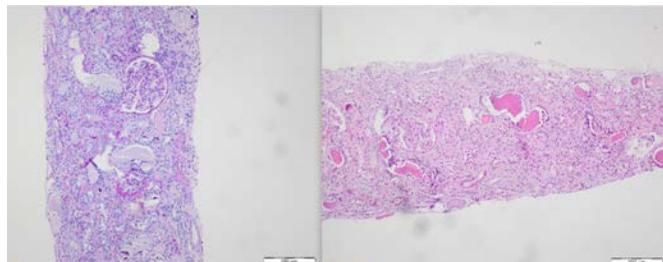
Introduction: A 40 yr old male with a diagnosis of nasopharyngeal carcinoma was admitted for dysphagia and decreased oral intake. He had severe hyponatremia with serum Na 126 meq/l, other labs including K -4.2, Cl- 94, HC03-26. He was euvolemic and normotensive. A urine panel showed Na - 122 meq/l and Uosm of 932 osm/l. He was deemed to have euvolemic hyponatremia from SIADH and started on fluid restriction. There was no improvement in hyponatremia and Una increased to 235 meq/l. He was diagnosed with adrenal insufficiency with a co-syntropin test. Imaging studies did not demonstrate pituitary invasion by nasopharyngeal carcinoma. He was started on high doses of hydrocortisone with rapid improvement of hyponatremia and Una dropped to 35meq/l. Hyponatremia with high Una (280 meq/l) recurred during hydrocortisone taper. He required prolonged high doses of hydrocortisone to maintain normal serum sodium level. Although there have been many case reports of hyponatremia with adrenal insufficiency, to the best of our knowledge there has been no reports of hyponatremia with very high Urine sodium (> 200 meq/l). This case highlights that euvolemic hyponatremia can occur with adrenal insufficiency with clinical and biochemical manifestations mimicking SIADH. Adrenal insufficiency should be considered in all cases of hyponatremia especially with very high urine sodium.

PUB440

Acute Tubulointerstitial Nephritis Preceding the Diagnosis of Multiple Myeloma Alper Alp,¹ Hakan Akdam,² Aysegul Ormeci,³ Ibrahim Meteoglu,³ Harun Akar,⁴ Yavuz Yenicierioglu.² ¹Nephrology, Van Region Education and Research Hospital, Van, Turkey; ²Nephrology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; ³Pathology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; ⁴Internal Medicine, Nephrology, Tepecik Education and Research Hospital, Izmir, Turkey.

Introduction: Multiple myeloma (MM) is characterized by a neoplastic proliferation of monoclonal plasma cells-usually-originating in the bone marrow. Atypical presentations of MM is not seldom in clinical practice. The hidden signs of the disease may cause late diagnosis and clinicians should be suspicious and aware for this entity. However in some rare cases these signs may really be invisible.

Case Description: A 55 yo woman presented with confusion, oliguria and elevated creatinine level of 18.2 mg/dl. Hemodialysis was started acutely. Renal ultrasonography revealed normal size kidneys without hydronephrosis. Renal biopsy was compatible with acute tubulointerstitial nephritis.



Kappa and lambda light chain staining was negative. 1 mg/kg methylprednisolone therapy was initiated and given for 1 month. No regression was observed and hemodialysis therapy was continued. After 2 months steroid therapy was reinitiated again but there was no clinical and biochemical response. On follow-up, after 7 months from renal biopsy hypercalcemia, anemia, high sedimentation rate, hyperglobulinemia and lytic bone lesions were detected. 16% monoclonal plasma cells were present in bone marrow. With further examinations MM diagnosis was made.

Discussion: Renal biopsies revealing acute tubulointerstitial nephritis pattern which are unresponsive to steroid therapy should always be deeply investigated for alternative diagnoses. MM may have obscure presentations.

PUB441

Sleep Disturbances in an ESRD Patient Soon After Initiation on Hemodialysis: An Atypical Presentation of ESRD-Related Sleep Disorders Desiree Garcia Anton, Franco H. Cabeza Rivera, Alexandre Abreu, Marco A. Ladino Avellaneda. *Nephrology, Univ of Miami, Miami, FL.*

Introduction: Sleep disorders including obstructive sleep apnea (OSA), restless leg syndrome (RLS) and insomnia are highly prevalent in ESRD patients undergoing dialysis, however, these remain stable or tend to improve after initiation of dialysis. There is scarce evidence of new-onset sleep complaints or disorders after initiation of dialysis.

Case Description: We present a case of a 64 year-old male with HTN, DM, ESRD and no previous sleep problems who developed insomnia, RLS, sleepwalking and other sleep disturbances within a month after initiation of continuous hemodialysis. He presented to the primary care clinic with secondary complications from uncontrolled diabetes (neuropathy, retinopathy and nephropathy); he had been followed by the nephrology service for 4 years before requiring dialysis for uremia and volume overload. Intermittent HD was well tolerated during first month of treatment, achieving good metabolic clearance and volume control; his KT/V was 1.16, phosphorus was controlled at 4.6 mg/dl and his anemia improved to a hemoglobin of 9.6 mg/dL; iron was 36 mcg/dl, ferritin 135 ng/ml, and transferrin saturation 15%. Despite clinical and laboratory improvement, disabling sleep symptoms were reported and he was referred to the Sleep clinic for further evaluation. On his initial actigraphy, a bedtime or rise time pattern was unable to be determined as it showed continuous movements 24 hours per day for the 14 days monitored. Overnight Polysomnography (PSG) revealed severe OSA and periodic limb movements (PLM); there was also evidence of insomnia with severely reduced sleep efficiency.

Discussion: New-onset sleep problems after initiation of dialysis in patients who previously had no sleep complaints are an atypical presentation. The role of RRT on sleep disturbances in the ESRD population is unknown. We propose PSG pre and post dialysis initiation on advanced CKD patients to assess for differences and identify how RRT may be a cause of sleep disturbances.

PUB442

Reduced Serum Anion Gap due to Lithium Overdose Tanmay Sahaj,¹ Josef Bautista,² ¹Internal Medicine, Roger Williams Medical Center, Providence, RI; ²Nephrology, Brown Univ/Rhode Island Hospital, Providence, RI.

Introduction: This case demonstrates the clinical presentation and corresponding laboratory results of lithium overdose as well as further discuss management of overdose with intermittent hemodialysis.

Case Description: A 32-year-old man with a history of bipolar disorder came to the hospital with altered mental status and worsening lethargy. He was subsequently intubated for airway protection. Patient's lithium level was > 20 mmol/L. CT head showed no injury. The rest of the toxicology screen was negative. His basic metabolic panel (including calcium and albumin) was within normal limits however his bicarbonate was 32 mmol/L and creatinine was elevated to 1.5 mg/dL. Calculated anion gap was 1 mmol/L. Serum osmolality was not measured at time of presentation. Patient was hemodynamically stable. Vigorous hydration with isotonic saline was initiated. Intermittent hemodialysis with high blood pump speed was initiated. Serum lithium level was checked 24 hours later and it fell to 2mmol/L. Intermittent hemodialysis was discontinued 24 hours later as patient was awake, alert and arousable with dramatic improvement in mental status. Creatinine also trended down to 0.9 after 48 hours. Patient was extubated 48 hours after initial presentation.

Discussion: Lithium has a narrow therapeutic window and therefore in cases of overdose or toxicity have many symptoms including altered levels of consciousness as seen in this patient. Low anion gap is a diagnostic clue to lithium intoxication however other causes include hyperkalemia, hypermagnesemia, and monoclonal gammopathies. Although serum osmolality was not measured in our patient, this can also be a helpful indicator noted in previous case reports. Elevated osmolar gaps with low anion gaps are useful in diagnosing lithium overdose. The standard management for lithium overdose is intermittent hemodialysis and maintaining water balance. The theory behind using intermittent hemodialysis versus continuous venovenous hemodiafiltration is that higher clearance of lithium can be achieved from faster blood flow rates in intermittent hemodialysis if it can be tolerated hemodynamically.

PUB443

Episodes of Hypertensive Crises in a Tetraplegic Dialysis Patient due to Catheter-Associated Endocarditis Martin Russwurm, Joachim Hoyer, Ivica Grgic. *Dept of Internal Medicine and Nephrology, Philipps-Univ Marburg, Marburg, Germany.*

Introduction: Hypertensive emergencies are a life-threatening condition associated with organ damage including acute heart failure, seizures and coma. Pre-existing arterial hypertension and non-adherence to anti-hypertensive treatment as well as volume overload particularly in dialysis patients are considered major triggers of HC. ESRD patients have a high prevalence (>70%) for hypertension and are at high risk for the development of cardiovascular disease and related complications. Early assessment and treatment of hypertensive states including HC is therefore imperative.

Case Description: Here, we report a case of a 34-year-old patient with sudden onset of repeated episodes of hypertensive emergencies on dialysis. The first episodes of spiking blood pressures of >240/120 mmHg occurred several weeks prior to admission and had become increasingly difficult to manage forcing early termination of dialysis sessions. The patient had been on hemodialysis, via tunneled catheter, for one year. Laboratory findings showed elevated inflammation parameters. Blood cultures were positive for gram-negative rods which were later identified as *Pseudomonas aeruginosa* (P.a.). We performed transesophageal echocardiography which showed echodense masses at the tip of the catheter and right cardiac atrium. Hemodialysis via an alternative vascular access instantly resulted in normal blood pressures during dialysis. Subsequently, the patient underwent heart surgery. The tunneled catheter and a large (5.2 x 3.5cm), P.a.-infected thrombus were removed from the right atrium and the patient put on a targeted antibiotics. Following recovery, a forearm fistula was created and used without major complications.

Discussion: To our knowledge, there is no report in the current literature of hypertensive crises in direct association with CVC infection. We speculate that initiation of dialysis via the infected catheter may have led to transient bacteremia triggering hypertensive episodes via an unclear mechanism. This case demonstrates that catheter-associated infections should be included in the differentials of causes and triggers of HC.

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PUB444

Adyptic Nephrogenic Diabetes Insipidus a Possibility? Nivin Haroon, Zeenat Yousuf Bhat. *Dept Nephrology, Wayne State Univ, Detroit, MI.*

Introduction: Adyptic diabetes insipidus (DI) is a rare syndrome where the patient has central DI and lack of thirst response due to presence of central lesion. We describe a patient who developed nephrogenic DI following a contrast exposure and acute kidney injury (AKI).

Case Description: The patient is a 47 yr old African American female with significant past medical history of mild diabetes mellitus. Her baseline kidney function was stable with creatinine (Cr) < 1 and non proteinuric. She had left sided progressive inflammatory breast cancer. She completed 2 cycles of paclitaxel and doxorubicin and cyclophosphamide. During this time she was admitted to the hospital following incision and drainage of a rectal abscess and treated with vancomycin and zosyn. Patient had received contrast exposure from computed tomography imaging for the abscess. Two days later the patient started to have rise in Cr with level going from 0.7 to 1.5. Nephrology was consulted for the same. There was no overt septic shock or blood pressure fluctuation. Urine microscopy was bland and ultrasound showed no pathology. Acute kidney injury was possible from the contrast exposure due to the time line of Cr bump within 48 to 72 hour period and lack of other overt evidence. Along with the AKI patient was found to have rise in sodium levels. She was having increased urine output in the range of over 4 Liters every day. Sodium was going up from baseline 140 up to 152. Interestingly patient was not having increased thirst response. She was given desmopressin (DDAVP) challenge test with no change in the urine output. An MRI imaging of brain was negative for pathology. She was instructed to drink water to match her urine out even if not thirsty. Initially the sodium leveled off and later trended down along with AKI.

Discussion: The case is very unique as the contrast injury resulted in nephrogenic DI. The patients lack of thirst response and rise in sodium was even more peculiar as the DI was clearly nephrogenic due to lack of response to DDAVP. It is still unclear why the thirst response in this patient was affected. More studies in future will unravel the complex relation between thirst response and osmolality.

PUB445

Frailty Modifies the Association Between Age and Dysnatremia in Community-Dwelling Adults Amanda Jean Miller,¹ Susan E. Howlett,² Kenneth John Rockwood,² Karthik K. Tennankore.¹ ¹*Nephrology, Dalhousie Univ, Halifax, NS, Canada;* ²*Geriatrics, Dalhousie Univ, Halifax, NS, Canada.*

Background: Frailty represents a state of increased risk to adverse health outcomes, reflecting some combination of increased damage and compromised repair processes. Dysnatremia is more common with age and can occur in many settings, suggesting that it may reflect not simply a specific renal problem, but a more general imbalance in damage and repair. The aims of this study were to establish whether frailty severity is associated with a higher rate of dysnatremia and to determine whether frailty explains the previously established association between age and dysnatremia.

Methods: The relationship between age, frailty severity and dysnatremia was investigated across the adult life course in 8898 respondents from the 2003-2004 and 2005-2006 cross-sectional National Health and Nutrition Examination Survey (NHANES) datasets. Respondents were assigned a frailty index (FI) and assessed for dysnatremia (a deviation of serum sodium from the 135-144 mmol/L normal range). The coefficient of variation in serum sodium was used as a systems measure of the response repertoire.

Results: In the overall population, there was a significant positive association between increasing frailty severity and the proportion of patients with dysnatremia (chi-square trend p < 0.001). Increasing frailty severity was also associated with more variability in serum sodium. There was a significant association between advancing age and dysnatremia (p < 0.001); however after stratifying by frailty (FI <0.100, 0.100-0.199, 0.200-0.299, 0.300-0.399, >=0.400), the association between increasing age and dysnatremia became non-significant in all categories.

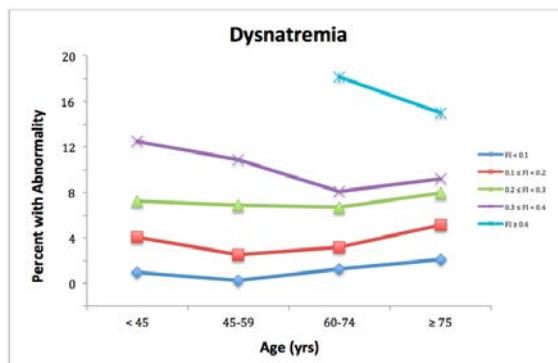


Figure 1: Proportion of dysnatremia with increasing age, stratified by frailty index

Conclusions: Increasing frailty severity is associated with dysnatremia and greater variability in serum sodium. Furthermore, frailty appears to modify the earlier association between age and dysnatremia.

PUB446

Approach to Hyponatremia in Congestive Heart Failure: A Survey of Canadian Physicians and Trainees Amanda Jean Miller,¹ Bonnie Kuehl,² Karthik K. Tennankore.¹ ¹*Nephrology, Dalhousie Univ, Halifax, NS, Canada;* ²*Research, Scientific Insights Consulting Group Inc., Mississauga, ON, Canada.*

Background: Hyponatremia is a complication of congestive heart failure (CHF) and is associated with reduced survival, however there are no consensus guidelines for the treatment of hyponatremia in CHF. The aim of this study was to determine the approach to hyponatremia in CHF amongst Canadian healthcare practitioners and trainees.

Methods: Respondents completed 15 multiple-choice style questions surrounding three cases of hyponatremia complicating CHF using an online survey on UKidney.com between December 2012-May 2013. Results were summarized as the proportion of correct/incorrect responses among Canadian Nephrologists, Cardiologists, Internists and trainees in each of two domains; pathophysiology and management. Management topics included use of diuretic therapy, hypertonic saline, oral urea tablets, vasopressin receptor antagonists (vaptans) and rate of sodium correction. Correct answers were determined by an expert panel of Canadian Nephrologists and Cardiologists.

Results: There were 1097 responses to survey questions among 455 Canadian respondents. Pathophysiology governing hyponatremia in CHF was correctly identified in 68.7% of responses (n = 380). Overall, hyponatremia was managed inappropriately in 43.6% of responses (n = 759). The proportion of incorrect responses among specialists and trainees is depicted in Figure 1. Importantly, an incorrect rate for sodium correction was selected 61.1% of the time (n = 211).

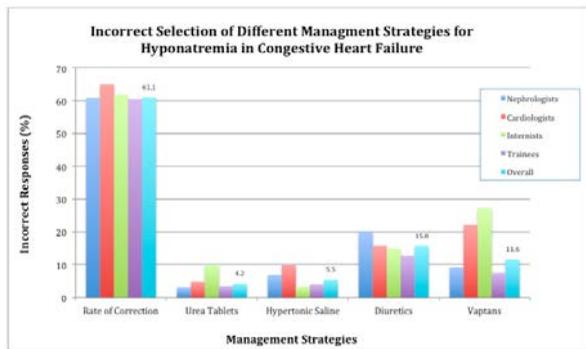


Figure 1: Proportion of Select Specialists and Trainees Choosing Incorrect Management Strategies for Hyponatremia in CHF

Conclusions: This study highlights knowledge gaps regarding pathophysiology and management of hyponatremia in CHF amongst Canadian specialist physicians and trainees. There is a need for further education to improve the management of hyponatremia in CHF at a national level.

PUB447

Sorafenib Induced Hyponatremia Elan Gorshein,¹ Catherine K. Wei,¹ Jasmeet S. Bajaj,² ¹Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; ²Critical Care Unit, Univ Medical Center of Princeton at Plainsboro, Plainsboro, NJ.

Background: Sorafenib treats unresectable hepatocellular carcinoma (HCC). It is a multi-targeted tyrosine kinase inhibitor (TKI), which prevents tumor cell proliferation. For those with inoperable disease, it prolonged median survival. Nevertheless, adverse reactions may limit its use. Sorafenib has been associated with hyponatremia, which may be related to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. We present a case of sorafenib induced hyponatremia.

Methods: A 58 year-old female presented with lethargy and edema. A patient was diagnosed with HCC 6 months earlier. She underwent transcatheter arterial chemoembolization and was noted on repeat imaging to have metastatic disease. Patient began sorafenib two weeks prior to admission, with a dose of 200 mg daily. A week later, the dose was increased to 200 mg twice daily. Three days later, the patient increased her dose to 400 mg in the AM and 200 mg in the PM. A day thereafter, patient became lethargic, with generalized swelling. The serum sodium was 106 mmol/L, with a baseline of 134 mmol/L three weeks prior to admission. Urine osmolality was 542 mOsm/kg, and the urine random sodium was less than 25 mEq/L. Patient's TSH was 6.82, with a normal FT4. AM cortisol was measured at 20.2. Her total protein and lipid profile were normal.

Conclusions: TKI agents have improved median survival in advanced HCC disease. Their use, however, has been limited by adverse events. Hyponatremia has been reported with a rate of up to 11% in patients treated for HCC. The pathophysiology may be related to SIADH. TKI agents may enhance the effects or increase the action of ADH. Time to onset of hyponatremia may be within ten days. Our patient took sorafenib for two weeks. Upon admission, her serum sodium was 106. With hypertonic saline and fluid restriction, her sodium reached 128. Other etiologies of hyponatremia were excluded. Sorafenib was discontinued, and attempts at patient follow-up have been unsuccessful. However, this report highlights that while sorafenib has had favorable impact on advanced HCC outcomes, clinicians should be mindful of its adverse effects.

PUB448

Current Trends in Etiologic Factors Responsible for the Development of Hyponatremia in Hospitalized Patients Sandar Win,¹ Maria V. DeVita,¹ Diana Dreyer,² Samuel J. Wahl,² Michael F. Michelis.¹ ¹Nephrology, NSLIJ/Lenox Hill Hospital, New York, NY; ²Pathology, NSLIJ/Lenox Hill Hospital, New York, NY.

Background: Hyponatremia remains the most common electrolyte disorder seen in hospitalized patients. The prevalence has been reported to vary from 5% to 15% and to be as high as 29.6% depending on the hospital setting.

Methods: New data were obtained on 2 separate days to evaluate the prevalence and etiologies of hyponatremia in hospitalized patients in a large metropolitan hospital. Hyponatremia was defined as less than 135mmol/L.

Results: Hyponatremia was recognized in 41 of 879 patients (4.6%). The mean serum sodium level in the hyponatremia group was 132.0+/-3.2 mmol/L. Eighty-five percent of the patients exhibited a serum sodium level of >130 mmol/L. Individuals aged 65 years old or greater made up 58.5% of the patients. Etiologic factors identified in the total number of hyponatremic patients included 9.7% with ESRD, 4.8% post op, 14.6% dehydration, 24.3% with pulmonary disorders, 26.8% with a diagnosis of cancer. The majority of patients were noted, however, to be receiving related drug therapies 63.4%. They were distributed between diuretic therapy (36.6%) and psychiatric drug therapy (26.8%).

Percent Distribution of Drug Therapies

Diuretics (36.6%)		CNS Drugs (26.8%)	
Diuretics Alone (17.1%)	Diuretics + CHF (19.5%)	SSRIs (17.1%)	Others (9.7%)

Conclusions: This study suggests that hyponatremia often is mild, is commonly associated with drug therapy, affects a significant number of younger patients, and now includes novel conditions such as patients receiving renal replacement therapy.

PUB449

Development of Metabolic Acidosis After Neobladder Replacement in Korea Shina Lee, Dong-Ryeol Ryu, Kyu Bok Choi, Duk-Hee Kang, Seung-Jung Kim. *Dept of Internal Medicine, School of Medicine, Ewha Womans Univ, Seoul, Republic of Korea.*

Background: Metabolic acidosis frequently develops in patients after neobladder replacement. However, the incidence of metabolic acidosis in patients with neobladder and the factors associated with the development of metabolic acidosis have not been well elucidated. We aimed to investigate the incidence and the potential predictors for the development of metabolic acidosis after neobladder replacement with intestinal segment.

Methods: We included all patients who underwent neobladder replacement using intestinal segment at Mokdong Hospital between January 1, 2005 and December 31, 2014. Metabolic acidosis was defined as serum tCO2 below 22 mEq/L at any visit during the follow up period. Patients' biologic data was presented using χ^2 test and student t test. Subgroups according to the time of metabolic acidosis occurrence was further analyzed in order to characterize predictors for metabolic acidosis by ANOVA tests and multiple regression.

Results: Metabolic acidosis was encountered in 79.4% of patients with neobladder during follow up period. When patients were divided into 2 groups according to anion gap (AG), total CO2 (18.9±2.1mEq/L vs. 20.0±1.3mEq/L, $p=0.001$) and chloride (106.6±4.9mEq/L vs. 109.4±3.6mEq/L; $p<0.001$) were significant different between groups with AG>12 and AG≤12 respectively. Furthermore, when patients were divided into 3 groups; patients with metabolic acidosis at post operative day 1; within a 14days; after 14days, there was significant difference of postoperative laboratory findings among the those subgroups.

Conclusions: Our study showed the rate of development of metabolic acidosis in patients underwent neobladder replacement and the difference between patients with metabolic acidosis and those without metabolic acidosis after neobladder replacement for the first time in Korea. In the future, well designed prospective study will be needed to prevent metabolic acidosis after neobladder replacement.

PUB450

Potassium Abnormalities and Acute Kidney Injury Are Common Complications After Colectomy Lindsay M. Smith,¹ Robert M. Perkins,² Andrea Lynn Berger,¹ H. Lester Kirchner,¹ Morgan Grams,³ Alex R. Chang.¹ ¹Geisinger Health System; ²Bayer Healthcare; ³Johns Hopkins Bloomberg School of Public Health.

Background: Patients undergoing colectomy may be predisposed to disturbed potassium homeostasis, since the colon has a role in potassium excretion, and volume depletion due to diarrhea occurs frequently after colectomy.

Methods: We examined the frequency of incident mild (>5 mmol/L) and severe hyperkalemia (>6 mmol/L), mild (<3.5 mmol/L) and severe (<2.5 mmol/L) hypokalemia, and inpatient AKI, stratified by estimated glomerular filtration rate (eGFR) using creatinine (inpatient only) and potassium (inpatient/outpatient) data from 1,762 patients who underwent colectomy surgery at Geisinger Health System between 2004-2013.

Results: Median age was 66 and mean baseline eGFR was 79 ml/min/1.73m². Colonic conditions included inflammatory bowel disease (8%), bowel obstruction (8%), ischemic bowel (2%), diverticulitis (23%), and colorectal cancer (20%). During the surgery hospitalization, post-operative AKI occurred in 32% of patients; mild and severe hyperkalemia occurred in 18% and 3% of patients. Over a median of 4.0 years post-discharge after colectomy, mild and severe hyperkalemia occurred at a rate of 13.4 events/100 person-years and 1.8 events/100 person-years; mild hypokalemia and severe hypokalemia occurred at a rate of 15.4 events/100 person-years and 0.7 events per person-years. Rates of inpatient AKI after discharge were high (9.1 events/100 person-years). Risks for AKI, mild and severe hyperkalemia increased as eGFR declined (p values<0.001; Table).

Conclusions: Patients who undergo colectomy are at high risk for hyperkalemia, hypokalemia, and AKI, particularly when eGFR is decreased. Comparison to a control group is needed to determine whether the high incidence of hyperkalemia is related to removal of the colon or frequent AKI episodes.

Table. Event Rates for Hyperkalemia, Hypokalemia, and AKI Events after Colectomy by Baseline eGFR Category

	Number of Events per 100 person-years				
	K>5	K>6	K<3.5	K<2.5	AKI
Baseline eGFR >=90 (n= 614)	9.9	1.1	13.6	1.0	7.3
Baseline eGFR 60-89 (n= 755)	11.6	1.5	15.0	0.6	8.3
Baseline eGFR 45-59 (n= 233)	26.7	2.7	17.6	0.6	13.6
Baseline eGFR 30-44 (n= 117)	32.0	4.4	22.0	0.8	16.0
Baseline eGFR < 30 (n= 43)	63.4	14.3	55.3	0	22.7

Funding: Private Foundation Support

PUB451

Identify the Causes of Chronic Hypokalemia: Importance of Urinary Sodium and Chloride Excretion Chih-chien Sung,^{1,2} Kun-Lin Wu,^{1,3} Chih-Jen Cheng,¹ Yu-Juei Hsu,¹ Sung-Sen Yang,^{1,2} Shih-Hua P. Lin.¹ ¹*Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan;* ²*Graduate Inst of Medical Science, National Defense Medical Center, Taipei, Taiwan;* ³*Dept of Medicine, Armed Forces Taoyuan General Hospital, Taoyuan, Taiwan.*

Background: Chronic hypokalemia with potassium (K⁺) wasting from kidney or gut is etiologically diverse. However, the correct diagnosis of the underlying causes is still fraught with challenge. To identify clinical and laboratory parameters helpful for the differential diagnosis of chronic hypokalemia.

Methods: The patients referred for evaluation of chronic hypokalemia in a medical center were enrolled prospectively for five years.

Results: Ninety-nine patients with chronic hypokalemia (serum K⁺ 2.8 ± 0.4 mmol/L, duration 4.1 ± 0.9 years) were enrolled. The major presentations were dizziness, fatigue, palpitation, abdominal fullness and muscle weakness/tetany. The plasma renin activities were increased in all patients along with normal-high serum aldosterone level. The main imaging findings were nephrocalcinosis/renal stones (n=25). Although Gitelman's/Barter's syndrome (n=32/13) and renal tubular acidosis (n=10) were major renal tubular disorders, forty-four patients were identified with anorexia/bulimia nervosa (n=24), surreptitious use of laxatives (n=10) and diuretics (n=10). The urinary K⁺ excretion rates in patients with renal versus non-renal tubular disorders were significantly overlapped for making the diagnosis alone. Of note, unparallelled urinary sodium (Na⁺) and chloride (Cl⁻) excretion with urinary Na⁺/Cl⁻ ratio are unique to non-renal tubular disorders. Furthermore, body mass index, serum bicarbonate and magnesium levels, and urine pH were also helpful for the differential diagnosis.

Conclusions: Chronic hypokalemia due to non-renal tubular disorders is emerging and often clinically indistinguishable from those with renal tubular disorders. The integrative interpretation of urine electrolytes excretion rates, especially Na⁺ versus Cl⁻, is important to make a prompt and accurate diagnosis.

Funding: Private Foundation Support

PUB452

Abstract Withdrawn

PUB453

PTHrP Induced Severe Hypercalcemia Secondary to Metastatic Neuroendocrine Tumor: A Case Report Azka Arif,¹ Ahmad Hassan,² Muhammad Awais Arif,² Agha syed Shabbir Ali,² Hafiz Armaghan Saeed,² Abdul Mateen Nagaria,¹ Talal A. Khan.¹ ¹*Freeman Health System;* ²*Rawalpindi Medical College.*

Background: Hypercalcemia is a common clinical problem. Most common etiology is hyperparathyroidism followed by malignancy. We report an interesting case of PTHrP induced severe hypercalcemia secondary to metastatic neuroendocrine tumor.

Methods: 49-year-old female with history of metastatic neuroendocrine tumor presented to the hospital with worsening mental status. On initial evaluation she was found to be severely hypercalcemic with serum calcium (Ca) of 19.6 mg/dL. Her ionized Ca was 2.45 mmol/liter. Her initial PTH level was 8.4 pg per mL. Her TSH level was 3.63 miu/ml & CK level was 66 U/L. She was not on Lithium, Thiazide diuretics. She had normal renal function. She was aggressively hydrated & started on intra muscular calcitonin. She was also given a dose of Intravenous bisphosphonates. Her serum calcium came down appropriately to 8.9 mg/dL, later her serum PTHrP was reported as 78 pg per mL. Her 25-hydroxy vitamin D level was low at 11 pg/mL, and her 1 25-hydroxy vitamin D level was 110 pg/mL. Her ACE level was 21 U/L. She was eventually transferred to hospice.

Conclusions: PTHrP is a normal gene product expressed in variety of neuroendocrine tumors. Gastrointestinal neuroendocrine tumors rarely excrete PTHrP, our case represents a severe form of malignant hypercalcemia secondary to hyper-secretion of PTHrP. Literature review showed that it was amongst the highest serum calcium reported, we did not proceed with renal replacement therapy initially as per family meeting. Hypercalcemia secondary to PTHrP production significantly increases mortality and morbidity.

PUB454

Carboplatin Induced Severe Hypomagnesemia and Concurrent Hypocalcemia: A Report of an Interesting Case to Elaborate Evaluation and Management of Hypomagnesemia: "The Forgotten Electrolyte" Azka Arif,¹ Ahmad Hassan,² Muhammad Awais Arif,² Agha syed Shabbir Ali,² Hafiz Armaghan Saeed,² Abdul Mateen Nagaria,¹ Talal A. Khan.¹ ¹*Freeman Health System;* ²*Rawalpindi Medical College.*

Background: Hypomagnesemia is commonly encountered in hospitalized patients. Renal wasting secondary to use of diuretics and persistent diarrhea are most important causes. It is one of the "forgotten" electrolytes. Many clinicians have limited awareness of how to accurately evaluate and manage hypomagnesemia. We report an interesting case of severe hypomagnesemia and hypocalcemia secondary to carboplatin administration with a view point of elaborating diagnostic approach to hypomagnesemia.

Methods: 62-year-old female with history of adenocarcinoma of the lung, developed severe hypomagnesemia with serum magnesium (Mg) levels reported as low as 0.5 mg/dL. She had concurrent severe hypocalcemia with serum calcium (Ca) of 5.1 mg/dL. Aggressive repletion was started & further workup was done. Her urine spot Mg level was reported as 381 mg, her fractional excretion of Mg was calculated & it was 9%. She received 3 cycles of carboplatin before hospitalization. She was not on any diuretics, PPIs & Aminoglycosides. She did not receive cetuximab as well; Urine calcium was less than 150mg, it was thought that she had carboplatin-induced distal nephron Mg wasting. Her serum PTH level was 245.5 pg/ml. Her hypercalcemia was thought to be secondary to PTH resistance mediated by severe hypomagnesemia. After aggressive repletion her serum Mg & Ca level normalized.

Conclusions: Hypomagnesemia can be due to multiple causes. Initial step in evaluation involves calculating FeMg, if less than 2.5%, it is likely secondary to GI loss. If FeMg is >2.5% then we measure 24hour urine calcium, if its more than 250mg it is likely due to TAL-Mg wasting which can be secondary to loop diuretics, nephrotoxins (Aminoglycosides) or Familial hypomagnesemia with hypercalciuria. If less than 150mg then it is likely due to distal nephron Mg wasting which can be secondary to thiazides & Gitelman's syndrome. Our case represents an interesting concurrent presentation of severe hypomagnesemia and hypocalcemia, which was successively treated.

PUB455

Effect of Arterial PH and Bicarbonate Level on Survival of Lactic Acidosis Patients Treated with Sodium Bicarbonate Dongyeol Lee,¹ Hansae Kim,¹ Eu Gene Jeong,³ Su Mi Lee,³ Sung Hyun Son,² Yong Ki Park,¹ Young Ki Son,³ Seong Eun Kim,³ Won Suk An.³ ¹*Internal Medicine, Bong Seng Hospital, Busan, Korea;* ²*Internal Medicine, Han Seo Hospital, Busan, Korea;* ³*Internal Medicine, Dong-A Univ, Busan, Korea.*

Background: Patients with lactic acidosis have high mortality rate, and higher lactate level is poor prognostic indicator. The correction of lactic acidosis with sodium bicarbonate is potentially harmful when sodium bicarbonate inappropriately was used. Therefore, we evaluated whether starting pH of sodium bicarbonate affect on the survival in lactic acidosis patients treated with sodium bicarbonate.

Methods: We conducted a single center analysis from May 2011 through April 2014. We retrospectively analyzed 230 patients with lactic acidosis treated with sodium bicarbonate. Patients were divided four groups according to starting arterial pH of sodium bicarbonate. We analyzed arterial blood gas analysis, lactate level about 6, 12, 24, 48 hours after using sodium bicarbonate.

Results: The mean age of patients was 62.8 ± 15.0 years, 174 patients (75.7 %) were died. The non-survivals had lower albumin, hemoglobin, and CRP (P < 0.001, P = 0.001, P = 0.003), higher SOFA and APACHE II scores (P < 0.001, P < 0.001), and higher blood lactate level at 6, 24, 48 hours, and maximum after checking the initial lactic acid levels (P < 0.001, P < 0.001, P < 0.001, P < 0.001). Patients with increased second lactate level showed high mortality (84.4 %). The mortality rate was 90 % in patients with sustained high lactate level at 48 hours. The mortality rate was not different according to starting point of sodium bicarbonate. In survival group, arterial bicarbonate level was slowly increased without fluctuation. However, arterial bicarbonate level showed fluctuation in non-survival group. The mortality rate was independently associated with arterial pH at 12 hours after sodium bicarbonate infusion.

Conclusions: Stably increased arterial bicarbonate without fluctuation and recovering arterial pH at 12 hours are important factors in patients survival treated with sodium bicarbonate. Therefore arterial pH and sodium bicarbonate level should be closely monitored especially till 48 hours, if sodium bicarbonate treatment with lactic acidosis.

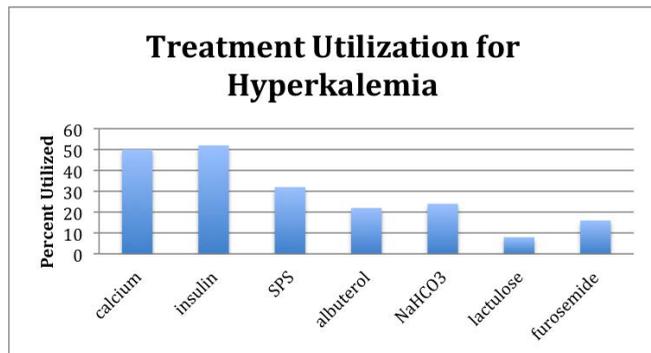
PUB456

Evaluation and Management of Hyperkalemia in an Academic Medical Center Jason K. Law,¹ Gaurav Ghosh,² Daniel Edmonston,¹ Saif A. Muhsin,¹ Yasin Hussain,³ Miriam Chung,^{1,2,4} Jeffrey I. Silberzweig.^{1,2,4} ¹*Dept of Medicine, New York-Presbyterian Hospital, New York, NY;* ²*Weill Cornell Medical College, New York, NY;* ³*Weill Cornell Medical College, Qatar, Doha, Qatar;* ⁴*Rogosin Inst, New York, NY.*

Background: Hyperkalemia (K > 6.0 mmol/L) is common among hospitalized patients but the approach to evaluation and management is highly varied. Patients are not routinely evaluated for clinical effects. Decisions regarding whether and how to treat are often based on individual physician judgments since few evidence-based guidelines exist. Since both hyperkalemia and its treatments can be associated with serious adverse consequences, we sought to evaluate the management in our institution.

Methods: Electronic medical records were reviewed for patients in our institution with potassium levels greater than 6.0 mmol/L between January 1, 2012 and December 31, 2014. Records were extracted for hyperkalemia associated symptoms and ECG findings, as well as interventions and outcomes.

Results: Only 2% of patients had clinical findings consistent with hyperkalemia. One-third of patients had ECGs performed and only 20% of those had findings consistent with hyperkalemia. Of patients with ECG findings consistent with hyperkalemia, only 15% had repeat tracings performed after treatment. At least 50% of patients were treated with insulin and dextrose and/or calcium. One-third of patients were treated with sodium polystyrene sulfonate (SPS), 25% with sodium bicarbonate and 10-15% were treated with lactulose or furosemide. Only 25% of patients had repeat potassium levels measured within six hours of treatment.



Conclusions: Management of hyperkalemia in our institution is far from systematic. Most patients receive treatment without evaluation for clinical effects of hyperkalemia. There is no standard treatment regimen and follow up measurements of potassium and ECGs were rarely done.

PUB457

Treatment of Hyperkalemia with Kayexalate in an Academic Medical Center Gaurav Ghosh,² Yasin Hussain,³ Jason K. Law,¹ Daniel Edmonston,¹ Saif A. Muhsin,¹ Miriam Chung,^{1,2,4} Jeffrey I. Silberzweig,^{1,2,4} ¹Dept of Medicine, New York-Presbyterian Hospital, New York, NY; ²Weill Cornell Medical College, New York, NY; ³Weill Cornell Medical College, Qatar, Doha, Qatar; ⁴The Rogosin Inst, New York, NY.

Background: Hyperkalemia ($K > 6.0$ mmol/L) is a potentially life-threatening condition; standard treatment has included sodium polystyrene sulfonate (Kayexalate) since its introduction in 1958. Recent literature has questioned the benefits of this treatment because of the lack of proven efficacy and the risk of serious adverse effects. We evaluated the effectiveness of Kayexalate for treatment of patients with hyperkalemia in our institution.

Methods: Electronic medical records were reviewed for all patients in our institution with potassium levels > 6.0 mmol/L between January 1, 2012 and December 31, 2014. Records were extracted for hyperkalemia treatment and outcomes. Hyperkalemia treatments included albuterol, diuretics, insulin, lactulose, sodium bicarbonate, and Kayexalate. Comparisons between hyperkalemia treatments with Kayexalate and without Kayexalate were made using t-tests.

Results: One-third of patients diagnosed with hyperkalemia were treated with Kayexalate. Post-treatment potassium values decreased by 14.8% in treatment with Kayexalate, compared to 17.4% reduction in treatment combinations without Kayexalate ($p = 0.46$). No patients suffered serious adverse effects from Kayexalate treatment.

Conclusions: In our population, treatment of hyperkalemia with Kayexalate was common. While no adverse events of treatment were noted, there was no significant difference in reduction of potassium levels with it. We conclude that there is insufficient evidence to support routine use of Kayexalate in our population.

PUB458

The Impact of Hyponatremia on Children: Prevalence and Consequences During Hospitalization Zachary Sartor, Poonam Thakore, Tetyana L. Vasylyeva. *Pediatrics, Texas Tech Univ Health Sciences Center, Amarillo, TX.*

Background: Hyponatremia in adults is associated with increased morbidity and mortality, but this association has not been explored in pediatrics. The aim of this study is to characterize the prevalence of hyponatremia and assess its impact on the course of hospitalization in pediatric patients.

Methods: Patients who were admitted to the TTUHSC pediatric service at Northwest Texas Hospital in Amarillo, TX from January through December 2012 were considered for retrospective chart review. Patients were divided into 3 diagnosis groups: bronchiolitis, asthma exacerbation, and gastroenteritis. Other diagnoses and patients without serum chemistries were excluded. Age, sex, and serum sodium levels were documented. The number of days admitted were also recorded. Hyponatremia was defined as mild if the sodium was 130-135 mEq/L, moderate if 125-129 mEq/L, or severe if < 125 mEq/L. Prevalence was calculated. Prevalence was determined to be statistically significance by comparing sodium levels between patients with hyponatremia and those with normal sodium levels. All patients were then grouped together, and length-of-stay (LOS) was compared between those with hyponatremia and those with normal sodium. The analysis for prevalence and LOS was performed using a two-tailed, unpaired t-test with a $p < 0.05$ used for significance.

Results: Overall, 416 patients were admitted to the inpatient service during the study period. After exclusion, 128 patients with bronchiolitis, 137 patients with asthma exacerbation, and 69 patients with gastroenteritis were available for analysis. There were 24 cases of hyponatremia in the bronchiolitis group (18.75% prevalence), 8 cases in the asthma exacerbation group (5.84% prevalence), and 18 cases in the gastroenteritis group (26.09% prevalence). There was one case of moderate hyponatremia in the bronchiolitis group, otherwise all other cases involved mild levels of hyponatremia. LOS was increased for patients with hyponatremia (2.33 ± 0.11 days versus 4.26 ± 0.71 days, $p = 0.01$).

Conclusions: Hyponatremia was prevalent at an overall rate of 15% during the study period. Hyponatremia was associated with increased hospitalization at a statistically significant level.

PUB459

Disorders of Plasma Sodium in Hospitalized Patients and Effect of Total Plasma Protein Concentration on Its Measurement Pedro J. Labrador, Silvia Gonzalez S, Santiago Polanco Candelario, Elena Davin Carrero, Jesús P. Marin, Ines Castellano, Juan R. Gomez-Martino. *Nephrology, San Pedro de Alcantara Hospital, Caceres, Spain.*

Background: The aim of the study was analysed the prevalence of hyponatremia in hospitalized patients, and the effect of total plasma protein (TPP) concentration on plasma sodium (Na) measurements.

Methods: We registered all biochemical analysis from in-hospital patients during one year. Data from age, sex, and department was recorded. Plasma Na was measured by an indirect ion selective electrode measuring system (Cobas 8000 analyzer, Roche Diagnostics). Hyponatremia was considered when plasma Na was lower than 135 mmol/L. Hyponatremia was classified based on plasma Na concentration. Mild hyponatremia was defined as 130-134 mmol/L, moderate as 125-129 mmol/L and profound as lower than 125 mmol/L. When TPP was measured, plasma Na concentration was corrected according to: a) Plasma Na = indirect Na $\times 93 / (99.1 - (0.7 \times \text{TPP concentration}))$; and b) Plasma Na = indirect Na $+ 0.7 \times (\text{TPP concentration} - 10)$.

Results: Our hospital is a 520 in-hospital beds. Plasma Na was measured in 26,904 biochemical analytics from 6,873 patients. Median age was 67 (IQR 50-79). 55.9% were men. Median plasma Na measurements was 5 (IQR 2-11). Hyponatremia was present in 1,514 patients (22%), mild hyponatremia 1,114 (16.2%), moderate 287 (4.2%) and profound 113 (1.6%). Plasma Na could be corrected to TPP in 3,122 patients, using the first formula hyponatremia was present in 29.4% (mild 19.6%, moderate 6.8% and profound 3%) while using the second one, 27.9% (mild 18.7%, moderate 6.4% and profound 2.8%). Kappa index for hyponatremia diagnostic between measured plasma Na and corrected to TPP was 0.7 and 0.74 ($p < 0.001$). Hyponatremia prevalence was increased in Onco-Haematology (49.7%), General surgery (42%), Nephrology (37.1), Pulmonary (35.1%), Urology (34.2%), Neonatology (32.8%), Digestology (32%), Orthopedic surgery (30.3%), and Internal medicine (28.4%).

Conclusions: Hyponatremia is present in one fifth of in-hospital patients. Correction of plasma Na concentration according to TPP concentration increase hyponatremia diagnostic up to 25%.

PUB460

An Unusual Cause of Hypokalemia Mohamad A. Hanouneh,¹ James F. Simon.² ¹Internal Medicine, Cleveland Clinic, Cleveland, OH; ²Glickman Urologic and Kidney Inst, Cleveland Clinic, Cleveland, OH.

Methods: A 59-year-old woman presented as a self-referral for a second opinion regarding hypokalemia. She had long-standing resistant hypertension currently treated with metoprolol, lisinopril and amlodipine. Four weeks ago she began experiencing hypotension. She claimed a history of edema treated with diuretics, including metolazone stopped one month prior and amiloride which was stopped one week prior. She denied taking any furosemide in the past 2 years. She complained of occasional orthostatic symptoms. Physical examination revealed orthostatic hypotension and no edema. Work-up revealed normal free serum cortisol, elevated plasma renin activity of 36.5 ug/L/hr (0.8-5.8 ug/L/hr) and serum aldosterone level of 76. ng/dL (3.1-35.4 ng/dL). Adrenal glands appeared normal on CT. 24-hour urine studies suggested renal potassium wasting (sodium 310 mmol/24 hour without a sodium load, potassium 38 mmol/24 hour, chloride 269 mmol/24 hour). Repeat chemistry done at the same time showed a serum creatinine of 2.2 mg/dL compared to 1 mg/dL 4 weeks prior, potassium level of 3.1 mmol/L. She was admitted for acute kidney injury. After receiving 2 liters of 0.9% saline IV, blood pressure stabilized and creatinine returned to 1mg/dL. She remained hypokalemic. Repeat labs after IVF showed plasma renin activity of 5.3 ug/L/hr and aldosterone of 15.0 ng/dL. Urine diuretic screen drawn while admitted was positive for furosemide, consistent with diuretic abuse. This patient's initial complaint of difficult to control hypertension and hypokalemia suggested a primary disorder of the renin-angiotensin system. However, hypotension upon presentation conflicted with this and was more consistent with a tubular wasting disorder such as Bartters or Gitelman syndrome or diuretic abuse, the last of which was most likely in this clinical situation. Suppression of both renin and aldosterone secretion after IVF confirmed the initial abnormalities were due to volume depletion.

Conclusions: Diuretic abuse should be considered when patients present with hypotension and hypokalemia. This case provides a rare insight into physiologic response of the renin-angiotensin system to diuretic abuse and volume resuscitation.

PUB461

Hypertnatremia During Hospitalization Is Associated with Increased Risk of Death: A Systematic Review and Meta Analysis Yorgi A. Azzi, Rabi Yacoub, Samira S. Farouk, Ioannis Konstantinidis, Girish N. Nadkarni, Steven G. Coca. *Icahn School of Medicine at Mount Sinai, NY.*

Background: While hyponatremia is the more common dysnatremia compared to hypertnatremia, and hyponatremia has been independently associated with mortality in several studies, some analyses have suggested that hypertnatremia portends a worse prognosis. Robust estimates regarding the excess hospital mortality associated with hypertnatremia across different inpatient settings are lacking. We sought to quantitatively synthesize the available evidence.

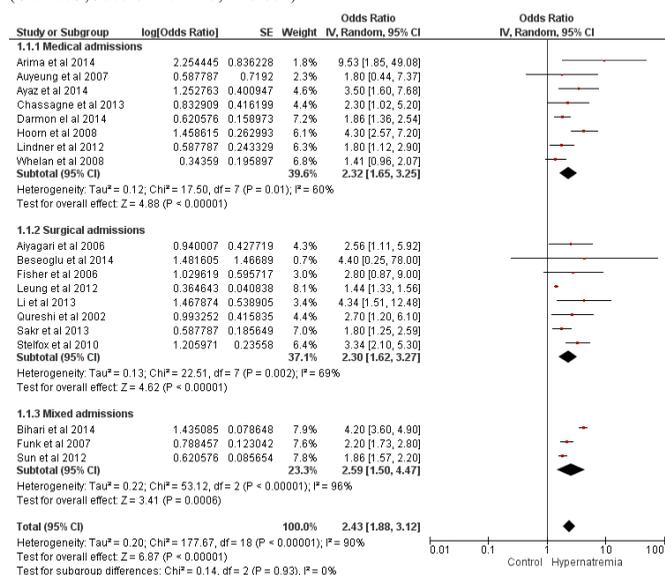
Methods: We systematically searched PubMed, EMBASE and Cochrane Central through May 2015, and selected studies using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. We analyzed studies reporting risk for

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

mortality adjusted for patients' characteristics and co-morbid conditions. We used random effects meta-analysis to derive pooled estimates of effect in medical, surgical and mixed admission settings.

Results: We evaluated 135 full text publications from 10,215 reviewed abstracts, of which 32 studies met the inclusion criteria (19, 13, and 5 reported aOR, proportion and both respectively). Patients with hyponatremia were at increased risk of hospital mortality (OR=2.59, 95% CI 1.5-4.47, P<0.001).



There was no difference in mortality risk between medical, surgical and mixed admission (P=0.9). Comparison of studies based on severity of hyponatremia revealed a small dose effect [(OR=2.23, 95% CI 1.64-3.04, P<0.001 for Na⁺145) and (OR=2.84, 95% CI 2.02-4, P<0.001 for ³150 mg/dl]. Analysis of proportion revealed higher odds of mortality (OR=5.48, 95% CI 3.66-8.21, P<0.001).

Conclusions: Admission with serum Na of ³145 mg/dl is significantly associated with twice the odds of hospital mortality. Protocols towards increasing awareness of hyponatremia and studies evaluating the efficacy of early intervention are warranted.

PUB462

Clinical Features of Reported Ethylene Glycol Exposures in the United States Meghan A. Jobson,¹ Susan L. Hogan,¹ Yichun Hu,¹ Gerald A. Hladik,¹ Ronald J. Falk,¹ Michael C. Beuhler,² William Franklin Pendergraft.¹ ¹Div of Nephrology and Hypertension, Dept of Medicine, UNC Kidney Center, Chapel Hill, NC; ²Carolinas Poison Center, Carolinas Medical Center, Charlotte, NC.

Background: Ethylene glycol is highly toxic and represents an important cause of poisonings worldwide. Toxicity can result in central nervous system dysfunction, cardiovascular compromise, elevated anion gap metabolic acidosis and acute kidney injury. Many states have passed laws requiring addition of the bittering agent, denatonium benzoate, to ethylene glycol solutions to reduce severity of exposures. The objectives of this study were to identify differences between unintentional and intentional exposures and to evaluate the utility of denatonium benzoate as a deterrent.

Methods: Using the National Poison Data System, we performed a retrospective analysis of reported cases of ethylene glycol exposures from January 2006 to December 2013. Outcome classification was summed for intentionality and used as a basis for comparison of effect groups.

Results: There were 45,097 cases of ethylene glycol exposures resulting in 154 deaths. Individuals more likely to experience major effects or death were older, male, and presented with more severe symptoms requiring higher levels of care. Latitude and season did not correlate with increased exposures; however, there were more exposures in rural areas. Denatonium benzoate use appeared to have no effect on exposure severity or number.

Conclusions: Deaths due to ethylene glycol exposure were uncommon; however, there were major clinical effects and more exposures in rural areas. Addition of denatonium benzoate was not associated with a reduction in exposures. Alternative means to deter ingestion are needed. These findings suggest the need to consider replacing ethylene glycol with alternative and less toxic agents.

PUB463

OTC Medication Leading to Chronic Salicylate Toxicity Muhammad Deen, Roohi Khan. Nephrology, CHI St. Luke's Health, Houston, TX.

Background: OTC medication containing salicylate leading to intoxication.

Methods: 60 YO F with PMH significant for chronic migraines, PUD s/p partial gastrectomy, presented to the ED with complains of nausea, vomiting, AMS, confusion and lethargy along with headaches, tinnitus and decreased bilateral hearing. Patient was found to be tachypnic, diaphoretic with respiratory alkalosis and anion gap metabolic acidosis with normal renal function.

Vitals: BP 114/67mmHg, Pulse 90/min, Temp 97.6 °F, RR 22/min and SpO2 100%.

Examination: Unremarkable examination except AMS.

Labs: Na 133mEq/L, K 3.1 mEq/L, Cl 103 mEq/L, CO2 12 mEq/L, BUN 10 mg/dl, Cr 0.8 mg/dl, venous lactate 8 mg/dl and ethanol <10 mg/dl. VBG: pH 7.5, pCO2 13 mmHg and pO2 49mmHg and HCO3 11 mmHg.

Imaging: CT head -NAF. Review of medication: Unremarkable for toxic medication. On further discussion with family, it was found that patient had been taking BC powder for her chronic headaches. Hence salicylate levels were drawn and found to be 75 mg/dl thus leading to the diagnoses of chronic salicylate toxicity.

Treatment: Medical management was initiated with IV fluid containing bicarb. In the following days patient's condition gradually improved and labs revealed salicylate level <8.

Conclusions: Chronic salicylate intoxication is most common in the elderly. Increased toxicity in older patient often appears due to inadvertent over dosage. Dual prescribing or additional use of non prescription OTC salicylates are some causes of unwitting long term toxicity. Chronic intoxication often poses a diagnostic dilemma with atypical presentation mimicking other disease states. The diagnosis of salicylate intoxication should be borne in mind when an older patient presents with recent deterioration in ADL with no known cause. Plasma salicylate concentration should be measured if salicylate intoxication is suspected, even if there is no documented history of salicylate ingestion. Chronic toxicity, which can occur even with marginally high salicylate concentrations is treated with drug withdrawal and supportive therapy. It can be averted by prescription of conservative doses of drugs, avoidance of concomitant use of different salicylate preparations, and therapeutic monitoring to guide dosage.

PUB464

Diagnostic Workup of Hyponatremia in Hospitalized Patients: Does Education Have an Impact? Faraj Kargoli, Ladan Golestaneh. Dept of Nephrology, Montefiore Medical Center, Bronx, NY.

Background: Hyponatremia is associated with poor outcomes. Studies show that hospitalized hyponatremic patients seldom get adequate diagnostic workups. This study tests the effects of a CME activity on physician's behavior in the diagnostic workup of hyponatremia.

Methods: This is a cross sectional analysis of patients admitted to the Internal medicine department at Montefiore Medical Center between 05/01/2014 and 12/01/2014. Demographic and clinical data were collected retrospectively. Patients were included if they were admitted under the service of 24 hospitalist attendings. These attendings were chosen based on their participation in a CME activity (lecture based). This activity was implemented to improve hyponatremia workup as defined by the frequency of the following orders: serum osmolality, urine osmolality, and urine sodium. Hyponatremia was defined as the earliest serum sodium less than 135 meq/dL. There was further subclassification into three groups based on the severity: mild: 130-135 meq/dL, moderate: 125-130 meq/dL and severe: less than 125 meq/dL. Frequency of the diagnostic orders was stratified to before and after the activity.

Results: There were 358 patients with hyponatremia: 176 hyponatremia admissions occurred before the live lectures and 182 occurred after. Average age was 63yrs ±17, average length of stay was 5.2 days ± 2.9. The severity of hyponatremia was 82%, 14% and 3.4% for mild, moderate and severe, respectively. Forty eight percent of all patients who had hyponatremia at admission were discharged with hyponatremia. There was an increase in serum sodium between admission and discharge with a mean difference of 3.06 (95%CI, 2.6-3.5mg/dL), (P<0.0001). The frequency of all 3 orders was 3.2%, 19% and 50% in the cohorts, (p value <0.001). This frequency was 6% in the pre-activity cohort versus 8% post. More of the severely hyponatremic patients were discharged with hyponatremia than the mild or moderate (p<0.005).

Conclusions: Hyponatremia was underinvestigated in our cohort despite a formal educational exercise addressing better diagnostic workup. Further research is warranted to investigate the effect of CME activity on the treating physician behavior and patients outcomes.

Funding: Pharmaceutical Company Support - Rockpointe LLC

PUB465

Characteristics and Initial Outcomes of a Multidisciplinary Renal Genetics Clinic (RGC) Andrew John Mallett,^{1,2,3} Helen G. Healy,^{1,2,3} Julie M. Mcgaughran,^{2,3,4} Melissa H. Little,^{3,5,6} Chirag Patel,^{2,3,4} ¹Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia; ²School of Medicine, The Univ of Queensland, Brisbane, QLD, Australia; ³Inst for Molecular Bioscience, UQ, Brisbane, QLD, Australia; ⁴Genetic Health Queensland, RBWH, Brisbane, QLD, Australia; ⁵Murdoch Children's Research Inst, Melbourne, VIC, Australia.

Background: Genetic Renal Disease (GRD) accounts for 10% of adults and 50% of children with end stage kidney disease. Advances in molecular genetic diagnostic testing and multidisciplinary renal clinic models suggest opportunities for clinical redesign. Here we describe the initial characteristics, experience and outcomes of the first Australian multidisciplinary RGC.

Methods: A retrospective audit was undertaken of the RBWH Adult Conjoint RGC (1st year of operation; Aug '13-Jul '14). Each encounter involved a nephrologist, clinical geneticist and genetic counselor.

Results: 27/48 patients (56%) encountered had a known GRD, 9/48 (19%) had a suspected GRD and 12/48 (25%) had an unknown GRD with positive family history (FHx). Patients were most commonly referred by nephrologists (66%). The most common GRD category & diagnosis were cystic kidney disease (49%) and Autosomal Dominant Tubulointerstitial Kidney Disease (25%). Extra-renal features were associated with GRD in 26/48 (54%). During consultations differential diagnoses were explored (54%), management

advice provided (83%) and genetic counseling undertaken (79%). A genetic test was requested in 58.3%, most commonly being indicated for combined diagnostic and genetic counseling reasons (78.6%). Of 12 returned genetic test results, 7 were positive and 1 was a variant of uncertain significance. Two negative results have prompted additional genetic testing. Of 27 patients referred with a known GRD, 6 now have a new suspected GRD. The majority of those referred with either a suspected (6/9) or unknown GRD diagnosis (10/12) now have a new suspected or confirmed GRD.

Conclusions: These findings demonstrate the early successful operation of this RGC model including diagnostic and genetic counseling benefit. Future assessment of clinical outcomes and expansion to telehealth and paediatric settings is anticipated.

PUB466

Characteristics and Clinicopathological Analysis of Japanese Nephronophthisis Patients Keisuke Sugimoto,¹ Tomoki Miyazawa,¹ Takuji Enya,¹ Hitomi Nishi,¹ Kohei Miyazaki,¹ Hidehiko Yanagida,² Mitsuru Okada,¹ Tsukasa Takemura.¹ ¹*Pediatrics, Kindai Univ Faculty of Medicine, Osakayama, Osaka, Japan;* ²*Pediatrics, Sakai Hospital, Kindai Univ Faculty of Medicine, Sakai, Osaka, Japan.*

Background: Nephronophthisis (NPHP) accounts for 4 to 5% of end-stage renal disease (ESRD) occurring in childhood. Disease subtypes include infantile NPH, which progresses to ESRD around the age of 5 years. Juvenile NPH, which develops from early childhood to school age and usually progresses to ESRD by an age of about 13 or 14 years; and adolescent NPH, with development of ESRD at an average age of 19 years. Juvenile NPH is reported to be the most common subtype.

Methods: We investigated clinical, histologic, and genetic features in 35 Japanese patients clinically and histologically suspected to have NPHP, aiming to promote early diagnosis. We studied many exons as many as 13 NPHP genes. Since such genetic analysis involves significant cost and time, we also screened biopsy specimens by immunohistologic methods employing antibodies against relevant peptides.

Results: NPHP occurred fairly uniformly throughout Japan irrespective of region or gender. In 3 families, NPHP affected siblings. The median age of patients was 12.5 years. Renal abnormalities attributable to NPHP discovered through mass screening, such as urine tests in school. However, NPHP accounted for less than 50% of children with abnormal findings, including incidentally discovered renal dysfunction during evaluation of extrarenal symptoms or during routine check-ups. Typical extrarenal manifestations led to discovery including anemia and delayed physical development. The urine often showed low gravity specific density and low-molecular-weight proteinuria. Frequent renal histologic findings included cystic dilation of tubules, mainly in the medulla, and irregularity of tubular basement membranes. Genetically abnormalities of *NPHP1* were not common, with large deletions frequently noted. Compound heterozygotes showing single abnormalities in each of *NPHP1*, *NPHP3*, *NPHP4* were observed.

Conclusions: Our findings resemble those reported in Western populations.

PUB467

The Functional Role of the ARHGAP32 L405V Mutation on Cytoskeleton Guisen Li, Li Wang. *Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China.*

Background: A site-directed mutagenesis for ARHGAP32 was developed to whether the mutation of ARHGAP32 has the effect on the related factors of cytoskeleton in vitro and to understand the functional role of ARHGAP32 in FSGS.

Methods: 1. (1) Blood DNA of 110 FSGS patients proved by renal biopsy were sequenced and screened for the mutation of ARHGAP32. (2) Total exons sequencing were performed in 28 DNA samples to find out whether mutation of ARHGAP32 and other genes were existed. 2. (1) site-directed mutagenesis primers of ARHGAP32 was designed and amplified by PCR, obtaining the mutations of ARHGAP32 plasmids. (2) Transform the wild type and mutant plasmids of ARHGAP32 into *Escherichia Coli* respectively, sequenced the plasmids to identify whether the site-directed mutagenesis of ARHGAP32 was successful constructed. (3) Transfected the mutant plasmid of ARHGAP32 into 293T cells and then verified by western blot and realtime RT-PCR. 3. (1) Detected the expression of ARHGAP32 in FSGS, IgAN, MN, minimal change disease and diabetic disease by IHC. (2) Detected the expression of CDC42 and β -catenin by realtime RT-PCR and western blot in 293T cells which were transfected with the wild type and mutant plasmids of ARHGAP32. (3) Observed the expression of F-actin by immunofluorescence in the wild plasmid of ARHGAP32 and mutant type in COS7 cells.

Results: 1. (1) No mutation of ARHGAP32 was detected while 6 candidate genes were selected by sequencing all exons. 2. (1) ARHGAP32 gene was expressed mainly in glomerular in kidney tissue in all different pathologic types by IHC. (2) The expression of CDC42 and β -catenin by realtime RT-PCR and western blot were no significant differences between the wild plasmid of ARHGAP32 and mutant type in 293T cells. (3) The distribution of F-actin was more significant in the wild type than that in mutant plasmid of ARHGAP32. It spreaded all the directions in wild type, while the distribution was scattered in mutant type.

Conclusions: 1 No mutation was detected in sporadic FSGS currently. 2 The mutation of ARHGAP32 had effect on the distribution of cytoskeletal protein of F-actin.

PUB468

Hyponatraemia and Fractured Neck of Femurs in a Geriatric Population: A Retrospective Analysis Tamer Rezk, Krish Patel, Ashish Karir, Sashinie Tennekoon Jayasundera, Christine Sarah Catley, Abdelgalil Abdelrahman Ali, Sumith Abeygunasekara. *MEHT, United Kingdom.*

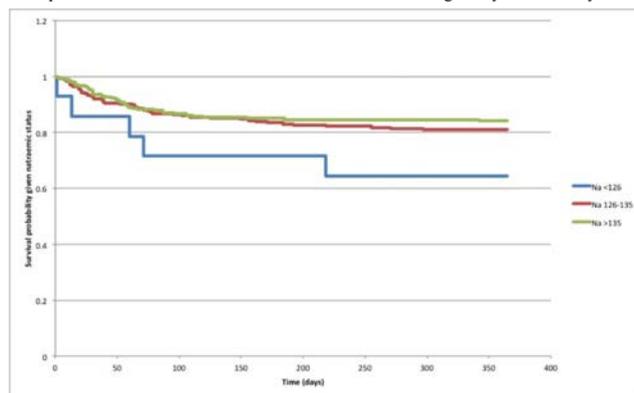
Background: Hyponatraemia is the commonest electrolyte abnormality found in elderly hospitalized patients defined as a serum sodium concentration <135 mmol/L with a mean prevalence of 5%. (NDT 2003; 18: 2486). It is a risk factor for fractures due to unsteady gait as well as osteoporosis and bone fragility. Fractured necks of femurs (NOF) are a significant cause of morbidity and mortality in the elderly with an estimated 24% mortality at 1 year (JAMA 2001; 285: 2736).

Methods: Retrospective analysis of 501 patients from fractured NOF database from 1/1/2014 to 31/12/2014 to identify the incidence and severity of hyponatraemia, Chronic Kidney Disease (CKD) Stage and mortality at 30 days and 1 year.

Results: Mean age was 83 years and M:F ratio of 1:3. Mild-moderate hyponatraemia was found in 48% of patients (serum sodium of 126-134mmol/L) with only 3% suffering with severe hyponatraemia (< 126mmol/L). 31% of patients had CKD Stage 3, 5% Stage 4 and 2% Stage 5. 30-day and 1-year mortality was 7% and 18% respectively. Patients were separated into 3 groups based on natraemic status

Natraemic status (mmol/L)	1 year survival (%)
<126 (severe)	0.643
126-134 (mild-moderate)	0.809
≥135 (normal)	0.841

Kaplan-Meier survival functions were calculated looking at 1-year mortality.



Those with hyponatraemia at the time of presentation appeared to have a worse 1-year survival. Log-rank test was performed. Using a chi-squared value of 3.521, a p value of 0.172 was obtained (not significant).

Conclusions: From our analysis it is clear that nearly half of patients on admission with fractured NOF have at least mild hyponatraemia with evidence to suggest reduction in 1-year survival. We propose more rigorous investigation of this subtle electrolyte disturbance in primary care which carries with it a significant morbidity and mortality.

PUB469

The Effect of Age on Mitochondrial Protein Levels in Rat Kidney Cortex and Medulla Marianna J. Zamlauski-Tucker, Natalya Mezenina, Cameron M. Behringer. *Physiology & Health Science, Ball State Univ, Muncie, IN.*

Background: The present study was undertaken to determine the effect of rat age on total protein levels in mitochondria from kidney cortex and medulla.

Methods: Young (3 months of age) and Old (22 months of age) female Lewis rats were used. The kidneys were harvested from anesthetized rats after being perfused with isotonic saline via a catheter in the abdominal aorta. The kidneys were separated into cortical and medullary sections and homogenized in isotonic saline. Differential centrifugation was used to isolate the mitochondrial pellet. The mitochondrial pellet was dissolved in distilled water and spun again at 10,000 rpm to isolate the mitochondrial protein pellet. The mitochondrial protein pellet was dissolved in 1 ml of 0.1 M sodium hydroxide. The protein concentration of the sodium hydroxide solution was measured using the Lowry Protein Assay. The protein concentration was expressed as mg protein/g kidney wet weight. Differences were evaluated using a Student's t test.

Results: A significant decrease in the total mitochondrial protein level was observed in kidney cortex from Old rats. The total mitochondrial protein level in kidney medulla from Old rats was not significantly decreased.

		Young (n=5)	Old (n=5)
Mitochondrial Protein	Cortex	2.02 ± 0.42	0.59 ± 0.30 *
mg/g kidney wet wt	Medulla	2.43 ± 0.42	1.11 ± 0.40

All data expressed as X ± SEM; * Significantly different from the Young

Conclusions: Total mitochondrial protein levels decrease in the cortex but not in the medulla of the rat kidney with age.

PUB470

Intradialytic Hemodynamic Stability and Functional Status Zubin T. Lathara, Aniko Szabo, Alexis Visotcky, Dawn F. Wolfgram. *Nephrology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Prior research suggests that functional status in ESRD patients declines after initiation of dialysis, implicating the dialysis process in contributing to functional decline. We evaluated a dialysis-specific risk factor of intradialytic change in blood pressure (BP) in relation to changes in physical performance, a component of functional status.

Methods: We enrolled 29 dialysis patients age ≥ 50 years. Participants completed a 4m timed walk to measure gait speed both pre and post dialysis and a Falls Efficacy Survey, a measure of concern for falls. Dialytic variables included BP measurements from pre, post and during dialysis along with ultrafiltration rate. Demographics and comorbid data was collected. Analysis evaluated for association between dialytic BP variables and change in gait speed and score on Falls Survey. Multivariate analysis was done to adjust for age, race, sex, diabetes and congestive heart failure.

Results: 28 participants completed the study. The mean age was 62.7 (12.3) years. The majority were male (70.4%) and hypertensive (86.2%). Diabetes was present in 55.2%. The mean (SD) change in gait speed from pre to post dialysis was -0.1(0.1) m/s. The mean (SD) change in systolic and diastolic BP from pre to post dialysis was -10.6(25.8) mmHg and -4.6(10.5) mmHg, respectively. Participants with diabetes had greater intradialytic hemodynamic changes with mean (SD) change of SBP+DBP of -26.9(23.5) and -7.9(11.3) respectively. Univariate analysis showed that every 10mmHg decrease in systolic BP and every 5mmHg decrease in diastolic BP was associated with a change in gait speed of -0.01m/s ($p = 0.02$) and -0.02m/s ($p = 0.01$), respectively. This association was no longer significant in multivariate analysis, likely due to correlation of change in BP with diabetes status. There was no association between BP change and Falls Survey score.

Conclusions: Decline in physical performance, as measured by gait speed, can be seen post dialysis and is associated with hemodynamic changes during dialysis. Patients with diabetes may be most susceptible to hemodynamic changes. Improving dialytic hemodynamic stability may be a way to reduce the significant functional impairment that occurs post-dialysis.

Funding: Private Foundation Support

PUB471

Sirtuin1 Expression in Kidney Tissue Specimens in Patients with IgA Nephropathy Cetin Ozener,² Izzet Hakki Arikan,² Ceren Ozcan,¹ Derya Guler,² Serhan Tuglular,² Deniz Filinte.³ ¹Internal Medicine, Marmara Univ Hospital, Istanbul, Turkey; ²Nephrology, Marmara Univ Hospital, Istanbul, Turkey; ³Pathology, Marmara Univ Hospital, Istanbul, Turkey.

Background: SIRT 1 immunexpression in renalbiopsy samples of the patients with IgA nephropathy were evaluated to identify the possible role of SIRT 1 on the pathogenesis of SIRT 1 in IgA nephropathy.

Methods: Twenty eight patients 28 patients (16 women, mean age 37 ± 13.8 years) were included. Biopsy specimens of the patients were reevaluated according to Oxford Classification. Immunexpression of SIRT 1, TNF- α , IL-10 and TGF- β were evaluated on kidney tissue specimens byimmunohistochemical staining.

Results: Older age, and higher serum creatinine and uric acid levels were the predictors of a greater decline of the kidney function. There was a positive correlation between mesangialhypercellularity and uric acid levels. TGF- β (nuclear) and IL-10 (cytoplasmic) expressions were shown in 20 (%71.4) and 25 (%89.3) of the patients, respectively. Expression of the IL-10 was higher in patients who had a high average mesangialscore. Tubular and weak (1+) SIRT 1 expression was present only in 7 patients.

Age	37 \pm 14
Gender(female/male)	16/12
BMI(kg/m2)	23.6 \pm 2.6
Creatinine(mg/dl)	1.6 \pm 1.5
Albumin(g/dl)	4.0 \pm 0.6
Uric acid(mg/dl)	6.0 \pm 2.2
Proteinuria(g/day)	2.4 \pm 1.9
GFR(CKD-EPI)(ml/min)	74.6 \pm 41.2
Hypertension,n(%)	13(46.6)
Macroscopic hematuria,n(%)	11(39.3)
Microscopic hematuria,n(%)	23(82.1)
Previous immunosuppressive therapy,n(%)	3(10.7)
Follow-up time (years)	4.8 \pm 2.7

Table 1. Baseline demographic and laboratory data of thepatients (n=28)

Conclusions: A positive correlation was shown between mesangial hypercellularity with serum uric acid levels in the first time. These results suggest that SIRT 1 does not play a direct role in the pathogenesis of IgA nephropathy.

Funding: NIDDK Support

PUB472

Response of Human Primary Renal Proximal Tubular Epithelial Cells to Different LPS Strains Hong Wang, Margaret M. O'Neill, Carine Boustany, Steven S. Pullen. *CardioMetabolic Diseases Research, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.*

Background: Toll-like receptors are expressed on leukocytes and renal tubular epithelial cells where they regulate immune responses. Recent evidence has implicated renal TLR4 signaling in the pro-inflammatory response in diabetic nephropathy. Ligands for TLR4 include lipopolysaccharide (LPS) and HMGB1. We sought to explore the response of renal proximal tubular epithelial cells (PTEC) to different strains of LPS and HMGB1 as well as modulation by TLR4 antagonists.

Methods: The HK-2 human proximal tubular cell line was stimulated with 3 strains of LPS (S. minnesota, E. coli K12, E. coli 0111:B4) and HMGB1. Primary human PTEC were stimulated with 5 strains of LPS (S. minnesota, E. coli 0111:B4, E. coli 055:B5, E. coli K12, S. typhosa) and HMGB1. Supernatants were harvested and IL-1 β , IL-6, IL-8, TNF α , and MCP-1 were detected. TLR4 antagonists EX 76233 and EX 76824 were tested for the ability to modulate cytokine production induced by LPS stimulation.

Results: In HK-2 cells, LPS from E. coli 0111:B4 induced IL-6 and IL-8 production, whereas, S. minnesota and E. coli K12 did not stimulate cytokine production. In PTEC, IL-6 and IL-8 production increased upon S. typhosa, and S. minnesota stimulation. Other strains of LPS did not stimulate production of IL-6 and IL-8 in PTEC. There was little detectable production of IL-1 β , TNF α or MCP-1 under the conditions tested in both PTEC and HK-2 cells. HMGB1 induced IL-8 production in PTEC whereas HK-2 cells did not produce any of the cytokines or chemokines tested upon HMGB1 stimulation. The TLR4 antagonists EX 76824 and EX 76233 blocked cytokine production stimulated by S. typhosa in PTEC. EX 76824 inhibited IL-6 and IL-8 production stimulated by E. coli 0111:B4 in HK-2 cells.

Conclusions: Primary PTEC have unique responses to different strains of LPS, and this response profile differs from that of the HK-2 cell line. HMGB1 induced IL-8 production in PTEC, whereas HK-2 cells did not respond to HMGB1 stimulation. These results highlight a limitation of using the HK-2 cell line in lieu of primary PTEC for interrogating the role of TLR4 in renal inflammation.

PUB473

Assessment of Serum Transforming Growth Factor-Beta 1 in Patients with Diabetic Nephropathy Om Prakash Kalra,¹ Avani Shukla,¹ Ashok Kumar Tripathi,² Alpna Raizada.¹ ¹Medicine, UCMS & GTB Hospital, Delhi, India; ²Biochemistry, UCMS & GTB Hospital, Delhi, India.

Background: Diabetes mellitus is the leading cause of chronic kidney disease (CKD) worldwide. The pathogenesis and initial molecular events leading to diabetic nephropathy are still elusive. Chronic low grade inflammation plays an important role in pathogenesis of diabetic nephropathy. Ubiquitous cytokines like transforming growth factor-beta (TGF- β) function in an autocrine or paracrine fashion to elicit extra cellular matrix (ECM) accumulation and cellular hypertrophy in several cell types. TGF- β may play an important role in the pathogenesis of diabetic nephropathy by influencing ECM accumulation.

Methods: This was a case control, cross sectional study. 75 subjects aged 30– 65 years of either sex were recruited and divided into three groups: Group I: healthy controls (n=25), Group II: patients of T2DM without nephropathy (n=25), Group III: patients of T2DM with nephropathy (n=25). Detailed history, complete physical examination, routine investigations, urine albumin creatinine ratio (ACR) estimation was done. Serum levels of hs-CRP and TGF-b1 were estimated by ELISA.

Results: A statistically significant difference in serum TGF-b1 and hs-CRP levels was observed between all the 3 groups ($p < 0.001$), where highest levels were found in group III and lowest in group I. A positive correlation was observed between serum TGF-b1 and duration of diabetes, FBS, PPBS, HbA_{1c} levels, serum creatinine, urinary ACR and serum hs-CRP. Similarly serum hs-CRP levels positively correlated with the duration of diabetes, FBS, PPBS, HbA_{1c} levels, serum creatinine, and urinary ACR. Serum TGF-b1 and serum hs-CRP showed negative correlation with eGFR.

Conclusions: Overall, TGF-b1 and hs-CRP levels were significantly higher in diabetics as compared to non-diabetic subjects. They were higher in diabetic subjects with nephropathy as compared to those without nephropathy. Serum TGF-b1 and hs-CRP levels in diabetic subjects appear to be dependent on duration of diabetes, glycemic control and degree of renal dysfunction. Thus cytokines like TGF- β may play a role in the etiopathogenesis of diabetic nephropathy.

PUB474

Daptomycin Antibiotic Lock Therapy for Hemodialysis Patients with Gram-Positive Bloodstream Infections following Use of Tunneled, Cuffed Hemodialysis Catheters. Retrospective Single Center Analysis Hung-Wen Yen, Szu-yuan Li. Dept of Medicine, Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Catheter-related blood stream infection (CRBSI) is a major complication in hemodialysis patients. We assessed the efficacy of systemic daptomycin (DPT) plus DPT antibiotic lock therapy (DPT-ALT) for catheter-salvage in patients with Gram-positive CRBSIs.

Methods: Study Design: Retrospective study of hemodialysis patients with tunneled, cuffed hemodialysis catheters. **Setting & Participants:** All patients were from a single institution in Taipei and received systemic DPT plus DPT-ALT for treatment of Gram-positive CRBSI. **Outcome:** Successful resolution of CRBSI. **Measurements:** Resolution of fever within 48 h, negative result of repeated blood cultures after resolution of fever, no clinical evidence of CRBSI relapse, and no need for catheter removal.

Results: Fifteen hemodialysis patients received DPT-ALT for CRBSI, 9 with coagulase-negative *Staphylococcus* (CONS), 2 with methicillin-resistant *Staphylococcus aureus* (MRSA), 3 with methicillin-sensitive *Staphylococcus aureus* (MSSA), and 1 with polymicrobial infections. Systemic DPT plus DPT-ALT cured 11 patients (73.3%). Treatment failed in all 3 MRSA cases (2 with MRSA and 1 with MRSA + *Enterococcus faecalis*).

Variable	Mean (range) or Number of patients (%)
Characteristics and outcomes of enrolled patients (n = 15)	
Age, years	76.20 (46-91)
Serum albumin, mg/dL	2.88 (1.5-3.7)
Males	9 (60.0%)
Comorbid disease	
Diabetes mellitus (DM)	8 (53.3%)
Coronary artery disease (CAD)	6 (40.0%)
Hematological neoplasia	1 (6.7%)
Autoimmune disease	1 (6.7%)
Metastatic infection	2 (13.3%)
Fever	15 (100.0%)
Microorganisms	
CONS	9 (60.0%)
MRSA	2 (13.3%)
MSSA	3 (20.0%)
Polymicrobial infection	1 (6.7%)
Outcome	
Success	11 (73.3%)
Relapse	0 (0%)
Failure	4 (26.7%)
Infection attributable mortality	4 (26.7%)
Success in Subgroup Analysis	
CONS	8 (88.9%)
MRSA	0 (0%)
MSSA	3 (100%)

Conclusions: Systemic DPT plus DPT-ALT appears to be a promising treatment for CRBSI from CONS and MSSA, but not for MRSA CRBSI. Systemic DPT plus DPT-ALT should be considered for patients with CRBSIs caused by certain species.

PUB475

The Association of the Type of Vascular Access and Erythropoietin Dose in Maintenance Hemodialysis Patients with Targeted Hemoglobin Level Fangping Lu.¹ ¹Nephrology, First Hospital of Tsinghua Univ, Beijing, China; ²Blood Purification, Beijing Chaoyang Hospital, Beijing, China; ³Nephrology, The Third Hospital of Beijing Hospital, Beijing, China.

Background: Both patients with central venous catheter(CVC) and higher doses of erythropoietin(EPO) are at increased risk of mortality in hemodialysis patients, but very limited studies involved the relationship. The present retrospective study aimed to investigate the association between the type of vascular access and EPO dose in MHD patients with targeted hemoglobin level.

Methods: We selected sixty-one patients among 711 MHD patients met inclusion criteria from January 2014 to June 2014 from three hospitals in Beijing, China and

compared the difference of EPO dose between arteriovenous fistula(AVF) and CVC group. Inclusion criteria: MHD treatment for >6 months with 3 sessions per week, at least 18 years of age, no malignant disease or obvious infection or active immunological disease, no gastrointestinal bleeding, no severe iron depletion, no blood transfusions within 3 months before inclusion, stable hemoglobin level(100-120g/L for consecutive 3 times within 6 months), and unchanged vascular access and EPO adjustment for 6 months.

Results: There were 32 AVF and 29 CVC patients. There were no difference of KT/V,serum ferritin, albumin, iPTH and CRP level between AVF and CVC patients. The mean total EPO dose (8793.10±2664.31 vs 7039.06±3651.79 iu/week,p=0.035). Standardised mean EPO dosage (IU/kg body weight/week)were significant higher in CVC patients compared with AVF patients(160.30±58.89 vs 118.02±70.06,p=0.013. It had been associated with increase in total weekly erythropoietin dose by 24.9% in CVC patients.

Conclusions: The findings of this study suggest that CVC patients need more EPO dose compared with AVF patients within targeted hemoglobin level. It is to further illustrate the importance of priority of AVF.

PUB476

Trans Radial Access for Percutaneous Treatment of Arteriovenous Fistula Thrombus – 2 Cases Cinthia Sobral Viegira,¹ Enio Ziemiecki Junior,² Eduardo Ferreira Medronha,² Heloisa Maria Chagas Rego,² Mauricio Da Silva Telles.¹ ¹Hemodialysis Unit, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil; ²Intervention Radiology Service, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

Background: Arteriovenous Fistula (AVF) is considered to be the preferential access for patients needing hemodialysis. It is called the “line of life” for these patients. Complications may occur even in autologous AVF or grafts (PTFE). Stenosis is the most frequent complication. Therefore thrombosis is the medical urgency. They are responsible for high morbidity, mortality, hospitalizations, interruption of the treatment and access loss. The patient must go to angiography study immediately. We want to show that endovascular percutaneous technique with transluminal angioplasty through trans radial access (TRA),results in quick recovery, particularly in AVF thrombus.

Methods: case 1: a 62 y.o. man with right medium radial AVF, for 3 y, started having AVF ache and missed the fistula thrill 48 h after dialysis. It took 45min. to realize the exam. **Case 2:** a 81 y.o man, with a left brachiocephalic AVF, for 5 m. visited the ER with gastroenteritis, dehydration and loss of fistula fremitus (less than 24 h).

Results: In these cases, TRA were used with implant of a 6Fr with high compliant balloon angioplasty (Conquest,Bard Peripheral Company). The AVF was recovered without early or later complications.

Conclusions: Besides the small number of subjects and a follow up of 4 months with AVF patency, the TRA technique shows to be a good alternative, promising and very useful for AVF recovery, even without fibrinolytics in south Brazil. Contraindications must be observed like: intra cardiac shunt R/L, pulmonary hypertension, infected access, surgery in the last 30 days. The most traditional techniques use thrombolysis by accessing directly the occluded vein, angioplasty or mechanical thrombectomy which demands more time of Rx and contrast exposition, higher costs and hospitalization. This procedure does not need hospitalization. The success is dependent of early diagnosis of AVF thrombus, by the Nephrology staff. There must be a close relationship between the staffs: Nephrology and Intervention Radiology.

PUB477

Incidence and Risk Factors for Catheter Related Infections (CRI) and Their Antibiograms in Haemodialysis Patients – A South Indian Study Shefali Gupta,¹ Shrikara P. Mallya.² ¹Microbiology, SGP GIMS, Lucknow, India; ²Microbiology, KMC, Mangalore, India.

Background: Bacterial infections particularly *Staphylococcus* species often complicate the vascular access in dialysis patients. This study was aimed to determine the incidence and associated risk factors for catheter related infections in patients on maintenance hemodialysis in a tertiary Hospital in South India.

Methods: Eighty-seven hemodialysis patients (56 M; 31 F) were enrolled in the study. After insertion of dual lumen catheter, patients were followed up till its removal. Nasal swabs were also collected before insertion. At each dialysis session, catheters were examined for any evidence of local infection or sepsis. In case of suspicion, local pus swab, blood culture samples and the catheter tip were sent to microbiology laboratory and patients were empirically administered vancomycin. Data obtained was examined for relationship of CRI with clinical and socio-demographic risk factors.

Results: Fifty-three catheters (61%) showed colonization(>15 CFU). Twenty four (45.2%) catheter tips were found to be colonized by *S. aureus*, 9 (17%) by *P. aeruginosa*, 5 (9%) by *Acinetobacter*, 4 (7.5%) by *Enterobacter*, 3 (5.6%) by *Klebsiella*, 2 (3.7%) each by *E. coli* and *Citrobacter* spp and one (1.9%) each by *S. epidermidis*, *S. maltophilia*, *S. marcescens* and *C. albicans*. Bacteremia was positive in 18(20.7%) patients and *P. aeruginosa* was the organism isolated in 7(38.8%) episodes. Staphylococcal nasal carriage was seen in 60 (69%) patients, and 36(41.4%) of these isolates were MRSA. Positive Statistically significant factors associated with CRI included history of bacteremia, presence of diabetes mellitus, long duration (>15 days) of catheterization and antibiotic use within 3 months (p < 0.05 for all). However, the age, gender and staphylococcal nasal carriage did not correlate with increased risk of infection.

Conclusions: *P. aeruginosa* is the most common organism in catheter related bacteremia which may have a bearing on our current antibiotic policy. Also, early initiation of hemodialysis through fistula may help reduce the CRI rate.

PUB478

Analysis of Risk Factors of Death in Patients of Maintenance Hemodialysis with Tunneled Cuffed Venous Catheter Li Zhou, Min Shi, Ping Fu. *Nephrology/Medicine, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.*

Background: To analyze the causes of death in patients of maintenance hemodialysis with tunneled cuffed catheter, and explore the risk factors of death.

Methods: All patients of maintenance hemodialysis with tunneled cuffed venous catheter starting hemodialysis from January 1, 2009 to December 1, 2014 in West China hospital were included and observed till June 1, 2015. The patients were divided into observation (death) and control group (survival). Multivariate logistic regression analysis was used.

Results: In total 94 hemodialysis patients who met the inclusion criteria, 24 cases died in the study period. The median age of dead patients was 73.4 years (51.5–96.4). The median time of hemodialysis was 19.20 months (3.17–56.27). Just 1 case replaced tunneled cuffed catheter for once. The main primary causes of renal disease were: diabetic kidney disease (DKD) 50.0%, chronic glomerulonephritis (CGN) 25.0%, hypertensive renal damage (HTN) 12.5%. The main causes of death were as following: infection 29.2%, cardiovascular diseases (CVD) 25.0%, cerebrovascular diseases 12.5%. The median age of survival patients was 64.9 years (20.8–95.4). Nineteen cases replaced tunneled cuffed catheter for twenty three times in total. The main primary causes of renal disease were: CGN 54.3%, DKD 25.7%, HTN 4.3%, polycystic kidney disease 4.3%. Multivariate logistic regression analysis showed that elder age, infection, low serum albumin were risk factors of death. Replacement of tunneled cuffed catheter was not the risk factors for death.

Conclusions: The main causes of death of patients with maintenance hemodialysis by tunneled cuffed venous catheter were cardiovascular and cerebrovascular diseases and infection. Elder age, infection, lower level of serum albumin were risk factors of death in patients of maintenance hemodialysis with tunneled cuffed venous catheter. Replacement of tunneled cuffed catheter was not the risk factors for death. Funds: the National Key Technology R&D Program of China (No. 2011BAI10B08), Cost and Evaluation System Study on payment revolution for patient in chronic hemodialysis with insurance of Chengdu City (Chengdu Municipal Medical Insurance Bureau).

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PUB479

Analysis of Vascular Access of Maintenance Hemodialysis Patients: A Single Center Retrospective Study Yuan Luo, Hong Ye. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Vascular access is life line for maintenance hemodialysis patients. The main options for vascular access for hemodialysis patients are arteriovenous fistulas (AVFs), arteriovenous grafts (AVGs), and tunneled cuffed central venous catheters. Proper vascular access is associated with lower complications and costs, which could improve the survival rate. The aim of our study is to analyze the characteristics of vascular accesses of maintenance hemodialysis patients in our hemodialysis center.

Methods: Patients underwent maintenance hemodialysis in the blood purification center of our hospital from January 2010 to December 2014 were enrolled in this study. The demographic characteristics, duration of dialysis, types of vascular access and blood flow volume, as well as the patency rate of AVFs of these patients were collected and analyzed.

Results: Sixty percent of the maintenance hemodialysis patients were male and the mean age was 57.89 ± 14.27 years old. More than 60% patients' initial vascular access was non-tunneled central venous catheters, only 20% applied AVFs as their initial vascular access. Vascular access types was as follows, 87.0% for AVFs, 3.5% for AVGs and 9.5% for tunneled cuffed central venous catheter. The cumulative patency rate of AVFs was 86.6%. The duration of primary patency was 29.00 (12.00, 68.00) months and the duration of the cumulative patency was 37.00 (12.75, 95.25) months. Fourteen patients applied AVG as their vascular access, of whom thromboembolism was the main complication. AVG thrombosis of three patients were treated using percutaneous interventions. Among the 294 patients applying non-tunneled central venous catheters, 5.4% have their catheters changed for more than 2 times and 66.7% have their catheters on the right internal jugular vein.

Conclusions: AVF is the leading type of vascular access in our dialysis center. The usage of tunnel cuffed central catheters is under 10%, while the usage rate of AVGs is increased. Non-tunneled central venous catheter is the main option for initial dialysis patients and the percentage of patients who prepared their AVFs ready before dialysis is still low.

Funding: Government Support - Non-U.S.

PUB480

Exchange Technique Using Over the Guidewire from Tunneled to Tunneled Hemodialysis Catheter Can Be Performed without Increasing Infection and Compromising Catheter Long Term Patency Hoon Suk Park, Min Seok Choi, Woo Jeong Kim, Sung Jun Kim, Byung Ha Chung, Hyung Wook Kim, Bum Soon Choi, Cheol Whee Park, Chul Woo Yang, Dong-Chan Jin. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ, Korea.*

Background: Exchange over the guidewire technique does not require time for hemostasis after removal and the temporary insertion of femoral HD catheter. It can also avoid additional new venipuncture that may be associated with the development of central vein stenosis later. However, some concerns of the increased risk of infection and bleeding after procedure cause to follow the de novo placement of the new tunneled catheter rather than exchanging over the guidewire.

Methods: From March in 2009 to March in 2013, 46 cases where the exchange from tunneled to tunneled catheter and 310 cases with de novo catheter placement were respectively assigned to exchange and de novo placement groups and these 2 groups were compared.

Results: Compared with the de novo placement group, the exchange group over the guidewire had a higher hemoglobin level (10.6 ± 1.7 g/dl vs. 9.5 ± 1.6 g/dl; $p < 0.001$), more females (69.6% vs. 48.1%; $p = 0.006$), more ESRD rather than AKI as a cause of catheter insertion (95.7% vs. 74.8%; $p = 0.002$). Both immediate complication rate including suturing at exit site for bleeding control (19.6% vs. 8.7%; $p = 0.02$) and late one including infection and catheter dysfunction (37.0% vs. 21.6%; $p = 0.02$) were higher in the exchange group. However, the catheter survival rates between two groups were comparable ($p = 0.58$) and multivariate Cox regression analysis for catheter survival showed the development of late complication was the only risk factor (odds ratio [OR] 1.391, 95% confidence interval [CI]: 1.017–1.901; $p = 0.039$) rather than the exchange procedure was not a risk factor (OR 0.878, 95% CI: 0.554–1.393; $p = 0.582$).

Conclusions: The exchange over the guidewire from a previous tunneled catheter to a new one should be positively considered and performed when the new tunneled catheter placement is required.

PUB481

The Exchange Technique Using Previous Venotomy Site Over the Guidewire from Non-Tunneled to Tunneled Hemodialysis Catheter Can Be Performed without Compromising Catheter Long Term Patency Woo Jeong Kim, Min Seok Choi, Hoon Suk Park, Sung Jun Kim, Byung Ha Chung, Hyung Wook Kim, Bum Soon Choi, Cheol Whee Park, Chul Woo Yang, Dong-Chan Jin. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ, Korea.*

Background: The exchange from non-tunneled HD catheter to tunneled one over the guidewire using previous venotomy does not require time for hemostasis for a new tunneled catheter insertion after its removal. It also does not require a new venipuncture so that it can prevent additional vessel wall injury. However, some concerns that it may be associated with the increased risk of infection and bleeding after procedure prevent its application.

Methods: From March in 2009 to March in 2013, 47 cases where the exchange from non-tunneled to tunneled catheter and 310 cases with de novo catheter placement were respectively assigned to exchange and de novo placement groups and these 2 groups were compared.

Results: Compared with the de novo placement group, the exchange group over the guidewire were younger (61 ± 16 years vs. 66 ± 14 years; $p = 0.04$), had a lower platelet count (171478 ± 115942 mm⁻³ vs. 207896 ± 100929 mm⁻³; $p = 0.03$), the lower incidence of DM (38.3% vs. 58.4%; $p = 0.01$), more AKI rather than ESRD as a cause of catheter insertion (42.6% vs. 25.2%; $p = 0.02$). The immediate complication rate including suturing at exit site for bleeding control was higher in the exchange group (19.1% vs. 8.7%; $p = 0.03$), but the late complication rate including infection and catheter dysfunction was higher in the de novo placement group (21.6% vs. 8.5%; $p = 0.04$). The catheter survival rates between two groups were comparable ($p = 0.35$). Multivariate Cox regression analysis for catheter survival showed the development of late complication was the only risk factor (odds ratio [OR] 1.495, 95% confidence interval [CI]: 1.045–2.139; $p = 0.028$) rather than the exchange procedure (OR 1.715, 95% CI: 0.991–2.968; $p = 0.054$).

Conclusions: The exchange over the guidewire from non-tunneled to tunneled catheter should be positively considered and performed when the catheter replacement of non-tunneled catheter with tunneled one is required.

PUB482

Analysis of Deep Venous Catheter-Related Infections in Hemodialysis Patients Yuan Zhang, Fei Deng, Daqing Hong, Li Wang. *Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Catheter-related infections are an ever-present risk in patients undergoing hemodialysis, and reports from Western countries have indicated their high prevalence. To analyze catheter-related infection rates in patients undergoing hemodialysis at the East Department of Sichuan Academy of Medical Science, Sichuan Provincial People's Hospital, Sichuan, China.

Methods: We cultured blood samples drawn from the catheters of 464 patients undergoing hemodialysis with deep venous catheters at our dialysis center between April 2011 and August 2013. We determined the type of pathogen, if present, and performed antimicrobial susceptibility tests. Data are presented as means ± standard deviation (SD). To analyze differences between two groups, we performed the χ^2 test. $P < 0.05$ was considered significant.

Results: Overall, 47 patients had catheter-related infections, including 41 patients with femoral venous catheters (9.9% of all patients with femoral venous catheters), and 6 had jugular venous catheters (12.0% of all patients with jugular venous catheters). There was no significant difference in infection rates between the two groups. Catheter blood cultures revealed 38 infections caused by Gram-positive bacteria, seven infections caused by Gram-negative bacteria, and two fungal infections. Three infections were caused by methicillin-resistant *Staphylococcus aureus*. Antimicrobial sensitivity tests revealed that Gram-positive bacteria were most sensitive to vancomycin, whereas Gram-negative bacteria were most sensitive to meropenem or imipenem.

Conclusions: The infection rates of patients with deep venous catheters undergoing hemodialysis were relatively high. Venous catheterization should be performed under strict sterile conditions, and arteriovenous fistulas should be established as early as possible.

PUB483

Utility of Arterio-Venous Fistula Flow and Doppler Ultrasound in the Prevention of Thrombosis of the Vascular Access Milagros Fernandez-Lucas, Fernando Caravaca-Fontan, Estefania Yerovi, Maria Delgado yagüe, Saul Enrique Pampa, Jose L. Teruel, Fernando Liano. *Nephrology, Hospital Univ Ramon y Cajal, Madrid, Spain.*

Background: A Multidisciplinary Unit for attention to the vascular access was established in our hospital in December 2010. The main role of the nephrologist consists in monitoring the functioning of the vascular access by determining the artery-venous flow (AVF) and undertaking the doppler ultrasound. The objectives for initiating this program were to reduce the thrombosis rate by diagnosis and treatment of a non clinically detected pathology and to decrease the percentage of patients with a tunnelled catheter.

Methods: The prevalence of haemodialysis patients on 31st December 2014 was 65 patients in the Hospital Unit and 90 patients in the Dialysis Center. In the Hospital Unit we supervise the functioning of the vascular access by measuring the AVF flow and we perform a Doppler ultrasound study if the flow is less than 500 ml/min, if there are significant decreases in comparison with previous controls or if there is any clinical dysfunction. The Dialysis Center uses first generation methods for monitoring (increase in venous pressure, pump flow decrease, recirculation) and requests the Hospital Unit to undertake a Doppler ultrasound study whenever there is any type of dysfunction.

Results: We have observed differences in the results between both centers: 1^o Incidence of patients with a tunnelled catheter was lower in the Hospital Unit (14 vs 22%). 2^o Thrombosis rate was 40% lower in the Hospital Unit (7,9 vs 12/100 patients-year). 3^o Doppler ultrasound detected 25 patients with haemodynamically significant stenosis, confirmed by radiologic study, which were successfully treated.

Conclusions: The combined use of AVF flow measuring and Doppler ultrasound studies for monitoring the vascular access is an efficient method for reducing the rates of thrombosis and the number of tunnelled catheters due to the early detection of stenosis and its preventive treatment.

PUB484

Females Have Less Arteriovenous Fistula and More Grafts Compared to Men: Data from the Slovenian Renal Replacement Therapy Registry Jadranka Buturovic-Ponikvar, Jakob Gubensek, Vanja Persic, Rafael Ponikvar. *Dept of Nephrology, Univ Medical Centre Ljubljana, Ljubljana, Slovenia.*

Background: The aim of our study was to compare prevalence of arteriovenous fistula (AVF) and graft in female and male chronic hemodialysis (HD) patients.

Methods: Data on vascular access in prevalent HD patients on December 31, from 2009-2013, were analyzed, in addition to sex, age, dry body weight and blood flow (QB) during HD, from database of the Slovenian Renal Replacement Therapy Registry. The use of preoperative ultrasonography mapping before AVF and graft construction in standard practice in the country.

Results:

Year	2013	2012	2011	2010	2009
All HD (No)	1375	1361	1346	1375	1397
Males No	831	837	824	818	827
Males age (years)	64±14	64±14	63±14	63±14	63±14
Males % AVF	82.8	81.8	83.5	85.0	84.6
Males % grafts	7.0	7.1	5.0	5.5	4.5
QB (ml/min)	287±35	287±39	290±39	290±44	295±44
Females No	544	524	522	557	570
Females age (years)	67±16	67±15	67±15	66±15	65±15
Females % AVF	72.1	72.3	72.4	76.5	75.1
Females % grafts	9.2	7.9	7.5	7.5	7.7
QB (ml/min)	273±35	274±38	275±38	271±40	277±41

The difference between percentage of AVF comparing females and males is persistent and highly significant during the observation period (p<0.001), with females having less AVF. Females had persistently slightly more grafts. Males had higher mean dry body weight (77.1±16 kg vs. 64.7±14.7 kg, end of 2013, p<0.001). Although absolute blood flow during HD was higher in males, females had higher blood flow when standardised to body weight (4.41±1.05 vs. 3.83±0.83 ml/min/kg, p<0.001, end of 2013).

Conclusions: Female chronic HD patients have significantly less arteriovenous fistula and slightly more grafts compared to males, with the difference being persistent during five years. Blood flow during HD, when standardised to body weight, was significantly higher in females than in males. Potential clinical consequence of higher blood flow during HD in females should be explored. Strategies to increase arteriovenous fistula prevalence in females should be explored, including potential acceptance of AVF providing lower blood flow during HD.

PUB485

Analysis of Early Arteriovenous Fistula/Graft Management and Coexistence of Dual Hemodialysis Accesses: Etiology and Clinical Implications of Waiting Too Long to Intervene Neena Jube, Peter J. Mattingly, Syed S. Haqqie, Arif Asif. *Albany Medical College, Albany, NY.*

Background: A number of patients with newly created arteriovenous fistulae (AVF) require tunneled dialysis catheter (TDC) for dialysis until their AVF is deemed mature. Although data have emphasized that the AVF maturation period is 4-6 weeks long, providers often wait up to 6 months hoping the AVF will eventually mature. During this maturation period if dialysis is required, patients frequently use TDC and can experience complications associated with these devices. This retrospective study evaluated 43 ESRD patients with a maturing AVF who were dialyzing with a coexisting TDC placed within 3 months of AVF creation. The patient population was divided based on dual access (DA) duration: DA <42 days (n=10), DA=42-90 days (n=13), and DA>90 days (n=20). An analysis of DA duration and follow-up visits were performed. All patients had surgical follow up at least once within the first 42 days of AVF placement regardless of DA duration. Additionally, patients with DA duration greater than 90 days were evaluated consistently by a surgeon during this period suggesting that prolonged DA is not due to lack of surveillance. Despite this, patient with DA period of greater than 42 days had increasing propensity to undergo avoidable exposure to the risks of prolonged TDC use (p<0.01). Specifically patients with DA<42 days, DA=42-90 days, and DA>90 days were unnecessarily exposed to the risks of dual access for an additional 2.5, 11.7, and 46 days, respectively (p<0.01). This discrepancy between regular surveillance and delayed TDC removal raises concerns that there is a lack of timely intervention after assessment. A more thorough documentation of reasons for prolonged TDC use and analysis of such data are required to verify this hypothesis and get a better idea of etiology of delayed TDC removal.

Methods: Retrospective collection of data from outpatient dialysis units on patients who have AVF/Graft and TDC.

Results: The delayed TDC removal in patients with AVF/Graft raises the risk of infection in these patients with both devices.

Conclusions: TDC should be removed at an appropriate period once AVF/Graft are mature enough to be used.

PUB486

Gene Methylation Profile of Human Vein Tissues Taken at the Time of Surgery: Correlation with AVF Maturation Begoña Campos, Sonia Bhati, Nikhil Grandhi, Mario Medvedovic, Amy Pflum, Timmy C. Lee, Rino Munda, Prabir Roy-Chaudhury. *Univ of Cincinnati.*

Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction and a major impediment to the Fistula First initiative. Despite the magnitude of the clinical problem, there are currently no effective therapeutic interventions for early AVF failure. In order to better understand the cellular and molecular mechanisms involved in early AVF failure we have evaluated the gene methylation profile of venous segment tissue samples obtained at the time of AVF creation. DNA methylation of CpG islands (regions of the genome that are rich in cytosine and guanine sequences), influences gene expression (turns off the gene). An increasing number of diverse factors are now known to epigenetically regulate genes, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD). In this study we compare the overall methylation profiles of non-maturing AVFs at 6 months as compared to AVFs that are able to support dialysis.

Methods: gDNA was isolated from venous segments collected at the time of AVF creation. Deep sequencing technologies were used to identify genes with the greatest differences in methylation between the two groups. Gene networks focused on inflammation, oxidative stress and endothelial dysfunction were evaluated. Standard bioinformatic techniques were used to identify/interrogate both the gene list and the network analyses.

Results: We were able to identify approximately 300 genes that were significantly different in the overall methylation profiles of non-maturing AVFs at 6 months as compared to AVFs that were able to support dialysis.

Conclusions: Our results suggest that epigenetic regulation (DNA methylation) could play an important role in AVF maturation, and also in the identification of novel druggable targets. This latter point could result in the development of novel therapies for dialysis vascular access dysfunction as a whole.

PUB487

Development of a Uremic Pig Model of Arteriovenous Fistula Stenosis (AVF): A Surgical Approach Begoña Campos,¹ Yang Wang,¹ Carissa Nicole Lester,¹ Krishnanath Gaitonde,³ Keith Louis Saum,¹ Sanjay Misra,² Prabir Roy-Chaudhury.^{1,3} *¹Univ of Cincinnati; ²Mayo Clinic; ³Cincinnati VA Medical Center.*

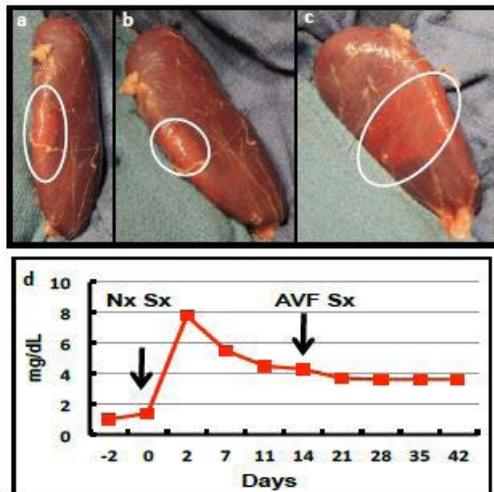
Background: AVF stenosis remains an important cause of hemodialysis vascular access dysfunction for which there are no truly effective therapies. We and others have previously described well characterized large animal models of AVF stenosis. An important flaw in these models is the lack of uremia, which increasingly has been shown to play an important role in the pathogenesis of AVF stenosis.

Methods: Chronic renal insufficiency was created by initially removing one of the kidneys through a midline incision. Following this the contralateral kidney underwent a dissection of the pelvis in order to expose the primary, secondary and if possible tertiary branches of the renal vasculature. A selective ligation of the renal vasculature in the pelvis,

which allowed for the viability of less than 20% of the renal mass on one side was then performed (upper figure = a, b and c). Of note the differential blanching/mottling of the kidney following ligation of vessels in the renal pelvis, allows us to perform a real time assessment in terms of the amount of viable renal tissue. BUN and creatinine estimations were then made biweekly for 6 weeks.

Results: The described surgical technique has allowed us to achieve a stable creatinine of 4 mg/dL over a four week period (lower figure = d). This stable period of uremia will allow us test out the impact of “downstream uremic vascular biology” on AVF maturation.

Conclusions: We have developed a unique, innovative and surgically created pig model of uremia with potential logistic and financial benefits. The availability of this animal model will put us in a unique position to be able to tease out the relative contributions of hemodynamics and uremia to AVF stenosis both in our experimental pig model and also in CKD and ESRD patients.



PUB488

Multimedia Education Tools for Dialysis Vascular Access Monitoring Tushar J. Vachharajani,¹ Claudia L. Poole,² Victoria L. Cash,² Joseph A. Vassalotti,³ ¹Nephrology, W. G. (Bill) Hefner VAMC, Salisbury, NC; ²Fistula First Catheter Last Workgroup Coalition, ESRD National Coordinating Center; ³Nephrology, Icahn School of Medicine at Mount Sinai & National Kidney Foundation, NY.

Background: From 2005 to 2012, the Fistula First Breakthrough Initiative (FFBI) of the Centers for Medicare & Medicaid Services focused on improving the arteriovenous fistula (AVF) rate in the hemodialysis (HD) patients. Since the transition to Fistula First Catheter Last (FFCL) in 2013, the workgroup has created multimedia tools to help dialysis facilities and clinicians reduce the use of central venous catheters (CVCs) and further increase AVF use. The key focus for FFCL remains access planning, access monitoring, and prevention of access infection. Access monitoring involves use of physical examination (PE) and interpreting the findings whereas access surveillance involves measuring access blood flow or venous pressure.

Methods: Why access monitoring? PE is cheap, reproducible and easy to perform and implement before each HD treatment. Evidence supports PE as an effective tool to accurately detect access dysfunction and infection. However, in practice, PE is underutilized due to inadequate training and perception of it being a labor-intensive evaluation method. Access monitoring tools: FFCL tools are created to educate the patient and the multidisciplinary dialysis care team (DCT) with the ultimate goal of maintaining a functional access.

Results: Two separate toolkits available on the FFCL website (<http://esrdncc.org/ffcl/>) highlight patient-level and DCT-level education. Practical teaching guides to implement the evidenced-based PE include “Check Before You Connect” for CVC and “One Minute Check” for AV access, which target the DCT and patients. The multimedia toolkits focus on a “look, listen and feel” concept, are interactive and are easily accessible from any mobile device. Poster/handout formats are also available. The impact of these educational tools will be evaluated once these resources are widely utilized in clinical practice.

Conclusions: The purpose of this presentation is to achieve wider dissemination of these tools to narrow the gap between evidence and clinical practice.

Funding: Other U.S. Government Support

PUB489

Multimedia Access Planning Tools to Attain Catheter Freedom Tushar J. Vachharajani,¹ Claudia L. Poole,² Victoria L. Cash,² Joseph A. Vassalotti,³ ¹W. G. (Bill) Hefner VAMC, Salisbury, NC; ²Fistula First Catheter Last Workgroup Coalition, ESRD National Coordinating Center; ³Icahn School of Medicine at Mount Sinai & National Kidney Foundation, NY.

Background: From 2005 to 2012, the Fistula First Breakthrough Initiative (FFBI) of the Centers for Medicare & Medicaid Services focused on improving the arteriovenous fistula (AVF) rate in hemodialysis (HD) patients. Since the transition to Fistula First Catheter Last

(FFCL) in 2013, the workgroup has created multimedia tools to help dialysis facilities and clinicians reduce the use of central venous catheters (CVCs) and further increase AVF use. The key focus for FFCL remains access planning, access monitoring (physical examination) and prevention of access infection.

Methods: Why the need for change? FFBI Change Concepts over the past decade resulted in an increase in the AVF rate in the prevalent HD population from 23% to 61% of eligible patients. The impact on the incident HD population has remained suboptimal, with >78% HD patients initiating dialysis with a tunneled CVC. Moreover, the percentage of patients in the prevalent HD population with CVCs in use for 90 days or longer has remained stagnant. Access planning tools: FFCL tools are created to educate the patient and the multidisciplinary dialysis care team (DCT) with the ultimate goal of achieving freedom from CVC. Two separate toolkits available on the FFCL website (<http://esrdncc.org/ffcl/>) highlight patient-level and DCT-level education.

Results: The multimedia toolkits are interactive and easily accessible from any mobile device. Conventional handout/poster formats are also available. The impact of these educational tools will be evaluated once these resources are widely utilized in clinical practice. The primary goal is to develop and disseminate tools to educate and create awareness to increase AV fistula utilization to 68% of appropriate patients, decrease the use of long term catheters (≥90 days) to <10%. FFCL is currently collecting metrics on professionals that are aware and using these tools.

Conclusions: The purpose of this presentation is to achieve wider dissemination of these tools and increase awareness among patients/professionals.

PUB490

Cardiac Implantable Electronic Device Infection and Ipsilateral Arteriovenous Fistula in End Stage Renal Disease: Avoidance and Management of Complications Stephanie Lanoiselee,¹ Francois Babinet,¹ Guillaume Seret,¹ Helene Loubiere,³ Achour Laradi.¹ ¹Centre ECHO Nephrologie Dialyse, Le Mans, France; ²Chirurgie Vasculaire, CH Le Mans, Le Mans, France.

Background: Cardiovascular implantable electronic devices (CIEDs) are frequently utilized for management of cardiac dysrhythmias in patients (pts) with End Stage Renal Disease (ESRD) and are associated with central venous stenosis resulting in adverse effects for existing or future arteriovenous fistula (AVF) with an increase risk of infection of both (CIEDs and AVF). We report the case of a pt with ESRD who experienced a potentially life-threatening complication related to his ipsilateral AVF and CIEDs.

Methods: We report the case of a 80 years-old male pt who developed a symptomatic unilateral left arm edema with skin lesions. He has past history of CIEDs four years ago and the ipsilateral implementation of an AVF 2 years after the CIEDs. He experienced 3 angioplasties on his AVF and a repeated surgery with a persistent post-anastomotic anastomosis with flow reduction of 180 ml/min. A left side chest blood collateral circulation was also present. A deep vein thrombosis related to the implementation of CIEDs was investigated and a left subclavian vein thrombosis was confirmed. On the meantime infection of the CIEDs was suspected but non confirmed. An attempt of a venous recanalization was unsuccessful. A closure of AVF with a plug of 14mm diameter leading to a complete occlusion of AVF.

Results: After the occlusion of AVF we noticed a complete regression of the huge left arm edema and a total recovery of the skin lesions. The pt underwent antibiotics therapy for life for the CIEDs infection with successful results two years after initiation of treatment.

Conclusions: Although the CIEDs can provide life-savings benefits, device associated complications needs careful management and should be placed by the epicardial approach as a first option for pts with ESRD. It remind us that the AVF is still the Achilles' heel of dialysis.

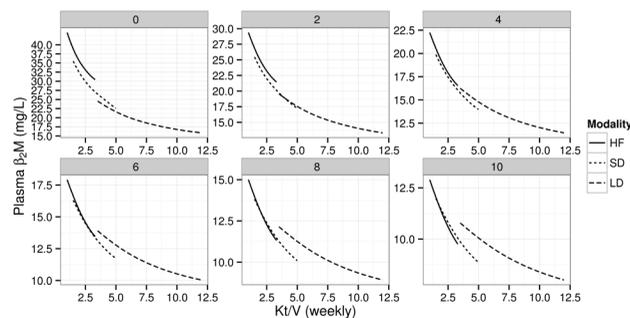
PUB491

Weekly Beta 2 Microglobulin (B2M) Kt/V, Residual Renal Function and Middle Molecule Levels in Daily Dialysis Christos Argyropoulos, Maria-Eleni Roumelioti, Mark L. Unruh. *Internal Medicine, Div of Nephrology, UNM-HSC, Albuquerque, NM.*

Background: B2M and residual renal function (RRF) are predictors of cardiovascular morbidity, mortality and LVH in ESRD. Daily dialysis leads to higher B2M removal and has been associated with improvements in LVH and mortality in randomized trials. It is not known whether kinetic measures of middle molecule adequacy are applicable to daily dialysis.

Methods: We adopted a population kinetic model (PKM) for the intraindividual variability in generation, distribution and extrarenal removal of B2M (ASN 2014, SA-PO969). We used the PKM to simulate B2M concentrations in 10000 patients dialyzed with HF membranes. We examined the intervention protocols for Short (SD), Long Daily (LD) and thrice weekly HF dialysis utilized in the FHN trials. Weekly B2M Kt/V was calculated as the sum of the Kt/V in each session. The impact of Kt/V relative to residual renal function (RRF) on B2M was examined across the three dialysis modalities averaging over the intra-individual variability of kinetic parameters and dialysis prescription.

Results: B2M was lower in SD and LD relative to HF irrespective of RRF. Given the variability in dialysis prescriptions there was a substantial overlap in the average Kt/V values between HF and SD.



There was a steep relationship between weekly Kt/V and B2M in all three modalities. The steepness of this relationship was similar between HF and SD across RRF values, but differed for RRF > 4 ml/min in LD. At any given level of Kt/V the B2M level depended on RRF and dialysis modality.

Conclusions: Weekly B2M Kt/V, a simple measure of middle molecule dialysis adequacy, tracks middle molecule exposure in conventional and daily dialysis. The interpretation of a given Kt/V value requires knowledge of RRF in all dialysis modalities. Future studies should determine whether RRF, dialytic Kt/V or both are predictors of survival in daily dialysis.

PUB492

A Test Battery to Establish Changes in Physical Performance and Protein Energy Wasting in Nocturnal Hemodialysis: The DiapriFIT Study

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¹Nutrition and Dietetics, VU Univ Medical Center, Amsterdam, Netherlands;
²Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; ³Nephrology, Spaarne Gasthuis, Hoofddorp, Netherlands.

Background: Nocturnal hemodialysis (NHD) improves volume control and phosphate and middle molecule removal. Observational data show increases in body weight and protein intake upon switching to NHD. Other aspects of protein energy wasting (PEW) remain underexposed and also little is known about functional outcomes, such as physical performance and muscle strength. Therefore, the aim of this study is to investigate whether physical performance improves and PEW decreases in patients who change from conventional hemodialysis (CHD) to NHD, compared to patients who continue their treatment on CHD.

Methods: The DiapriFIT study plans to include 25 patients on CHD (2-4x/wk, 3-4 hours) and 25 patients on CHD who switch to NHD (3-4x/wk, 8 hours) with 1-year physical performance and PEW as endpoints. They were submitted to a Visual Appetite Score (VAS), Handgrip Strength (HGS), upper arm circumference (UAC), Short Physical Performance Battery (SPPB) and 6 minute walk test (6MWT), baseline results are reported here. As in NHD weight increases, we tested associations of the outcome parameters with dry weight.

Results: At present, 23 patients were included, aged 58.3±16.0 years, 30.4% males, with a dry weight of 87.6±17.2 in males and 74.3±17.2 in females. Mean VAS was 7.3±2.3, HGS 22.7±9.8 kg, UAC 31.9±5.6 cm, SPPB 8.0±1.96 and 6MWT 576±328 meters. Only HGS and UAC were correlated with HD dry weight (r 0.43, p<0.05 for HGS, r 0.79, p<0.001 for UAC).

Conclusions: The DiapriFIT Study measures a great variety of parameters regarding physical performance and PEW. As some, but not all parameters correlate with HD dry weight, we expect them to differentiate between CHD and NHD during follow-up of the study. Other results of physical performance and PEW, such as subjective global assessment, physical activity-, sleep-, and QOL-questionnaires, activity monitoring, body composition measurement, nutritional diary, DEXA and lab tests will provide additional information on these patient-relevant outcomes of NHD.

Funding: Pharmaceutical Company Support - Baxter U.S.

PUB493

Anti-Thymocyte Serum Nephritis Rats Develops Augmented Circadian Rhythm of the Intrarenal Renin-Angiotensin System

Shinsuke Isobe, Naro Ohashi, Sayaka Ishigaki, Hideo Yasuda. *Internal Medicine I, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.*

Background: We reported the disturbed circadian rhythm of urinary angiotensinogen (AGT) excretion levels might lead to renal damage, hypertension and diurnal BP variation. Our purpose is to clarify the circadian rhythm of intrarenal renin-angiotensin system (RAS) components and its contribution to renal damage, hypertension and BP variation and to evaluate whether administration of RAS dependent or independent antihypertensive drug contributes to circadian rhythm of intrarenal RAS components.

Methods: Anti-thymocyte serum (ATS) nephritis rats were made as chronic progressive glomerulonephritis models (A group) and compared with control rats (C group). Other rats with ATS nephritis received olmesartan [angiotensin II (AngII) type 1 receptor (AT1R) blocker] (AO group) or hydralazine (vasodilatory drug) (AH group), respectively. Rats were sacrificed every 6 hour and the levels of the intrarenal RAS components were evaluated.

Results: The protein expression levels of intrarenal AGT, AngII and AT1R were increased in A group and peaked at the same time point as the peak of BP and urinary protein excretion during the rest phase. The amplitude of circadian fluctuation of these

proteins was increased in A group compared with C group and attenuated in AO and AH group (Peak to trough ratio of AGT in C: 1.13, A 1.47, AO 1.24, AH 1.17, AngII in C: 1.03, A: 1.26, AO: 1.14, AH: 1.17 and AT1R in C: 1.36, A: 1.51, AO: 1.37, AH: 1.26). However, renal function, proteinuria and augmentation of intrarenal RAS components were attenuated only in AO group. The protein expression levels of intrarenal renin and prorenin were the same tendency as AGT, AngII and AT1R, though fluctuation of them was augmented in AO group. The protein expression levels and fluctuation of angiotensin converting enzyme and (pro)renin receptor were not different among groups.

Conclusions: Intrarenal AGT, AngII and AT1R proteins were increased and the amplitude of oscillations of these proteins was augmented in ATS nephritis rats. Furthermore, renal damage may be linked to the activation of the intrarenal RAS independent of amplitude of its oscillation and BP.

PUB494

Do KCNQ1 Channels Contribute to Control of Arterial Vascular Tone?

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Background: Recent data suggest that the KCNQ family of voltage activated K⁺ (K_v) channels represents a new therapeutic target in cardiovascular disease. We used *Kcnq1*^{-/-} mice to determine whether KCNQ1 (K_v7.1) play a role in the regulation of arterial tone.

Methods: Wire-myography, pharmacology approach and patch-clamp technics were used.

Results: We found that R-L3 produces similar concentration-dependent relaxations (EC₅₀ ~1.4 μM) in wild-type (*Kcnq1*^{+/+}) and *Kcnq1*^{-/-} arteries pre-contracted with either phenylephrine or 60 mM KCl. This relaxation was not affected by 10 μM chromanol-B293, 10 μM HMR1556, 30 μM XE991 or 500 μM 4-aminopyridine. Chromanol-B293 and HMR1556 did not affect the anti-contractile effects of perivascular adipose tissue (PVAT). The anti-contractile effects of PVAT were normal in *Kcnq1*^{-/-} arteries. Whole-cell recordings showed normal peak K_v currents, capacity and their blockade by XE991 in *Kcnq1*^{-/-} VSMCs. The pan KCNQ2-5 opener retigabine lead to a similar relaxations in *Kcnq1*^{-/-} and wild-type vessels.

Conclusions: We conclude that KCNQ1 channels are apparently not involved in the control of arterial tone by α₁ adrenergic vasoconstrictors and PVAT. R-L3 is an appropriate pharmacological tool for studying the function of native vascular KCNQ1 channels in mice.

PUB495

The Role of Renal AT1 Receptor-Associated Protein in Salt-Sensitive Blood Pressure Regulation

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Background: The intrarenal renin-angiotensin system plays a role in the regulation of renal hemodynamics and the maintenance of water electrolyte balance, and is also involved in the pathophysiology of hypertension and target organ damages. We previously identified an angiotensin II type 1 receptor-associated protein (ATRAP), which interacts with the C-terminal domain of angiotensin II type 1 receptor (AT1R) and attenuates AT1R-mediated pathological responses. The present study was designed to investigate the putative functional role of ATRAP in the blood pressure regulation by high salt loading in vivo.

Methods: We generated transgenic mice expressing ATRAP dominantly in renal tubules on a C57BL/6J background. Renal ATRAP transgenic mice and their wild-type littermate mice on a normal salt diet at baseline were subjected to dietary high salt loading for 7 days.

Results: In renal ATRAP transgenic mice, the development of high blood pressure in response to high salt loading was suppressed, concomitant with a significant increase in urinary sodium excretion, as compared to wild-type mice.

Conclusions: These results demonstrate that renal tubule-dominant overexpression of ATRAP suppresses the salt-sensitive blood pressure elevation provoked by high salt loading, thereby suggesting ATRAP to be an interesting target in hypertension.

Funding: Private Foundation Support, Government Support - Non-U.S.

PUB496

Carbonic Anhydrase II Inactivation Confers Salt Appetite and Elicits Salt Sensitive Hypertension Mujan Varasteh kia,¹ Sharon L. Barone,² Saeed Alshahrani,¹ Marybeth Brooks,¹ Kamyar A. Zahedi,^{1,2} Jie Xu,¹ Manoocher Soleimani.^{1,2} ¹Center on Genetics of Transport, Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; ²Research Services, VA Medical Center; Cincinnati, OH.

Background: Salt appetite or salt intake in excess of physiological needs is a major health problem and a risk factor in the pathogenesis of hypertension, which consequently can lead to heart disease and stroke. Few genetic factors are implicated in the pathogenesis of salt appetite.

Methods: Wild-type and CAII null mice were given a choice of regular water or 140mM NaCl dissolved in their drinking water. Balance studies were performed and blood pressure was measured via the CODA tail cuff system. Western blots and Northern Hybridizations were performed.

Results: Our results indicate that CAII null mice display significant salt appetite as judged by their preference for salted water (140 mM NaCl) over regular water, when both options are provided. In age and gender matched mice (n=4 per each group), daily salted water intake was 2.89 ml in WT vs. 5.71 ml in CAII null mice, while daily regular water intake was 5.05 ml in WT and 3.6 ml in CAII null mice. Kidney renin expression and blood creatinine concentration were comparable in WT and CAII null mice. When given only salted water, CAII null animals showed a robust increase in their daily salt intake (12.21ml in CAII null vs. 7.80ml in WT mice) and urine volume (4.62ml/day in CAII null vs. 2.62ml/day in WT mice). Expression of sodium and water absorbing channels, ENaC and AQP-2, increased by ~100 to 200% in both cortex and medulla in CAII null vs. WT mice in response to salt intake for 10 days. Consequently, CAII null mice developed hypertension (systolic BP of 155 +/- 3.9 in CAII null vs. 138 +/- 3.2 in WT, p<0.003). The protein expression levels of ENaC in taste buds were not different between the two genotypes. Male CAII null mice exhibited a remarkable propensity toward salted water intake vs. regular water intake as compared to female null mice.

Conclusions: We propose that CAII plays an important role in regulating salt intake and its inactivation can cause salt appetite, specifically in male animals, and provoke salt sensitive hypertension.

Funding: Veterans Administration Support

PUB497

Ambulatory Blood Pressure in Chronic Kidney Disease: An International Collaborative Study Paul E. Drawz,¹ Luca De Nicola,² Naohiko Fujii,³ Francis B. Gabbai,⁴ Jennifer J. Gassman,⁴ Satoshi Iimuro,³ Roberto Minutolo,² Robert A. Phillips,⁴ Luis M. Ruilope,⁵ Raymond R. Townsend,⁶ Mahboob Rahman.⁶ ¹Div of Renal Diseases & Hypertension, Univ of Minnesota; ²Italian Cohort; ³CKD-JAC; ⁴AASK; ⁵Spanish Cohort; ⁶CRIC.

Background: In chronic kidney disease (CKD), ambulatory blood pressure (BP) is a better measure of hypertension related risk for cardiovascular disease and ESRD than clinic BP. The International Ambulatory Blood Pressure in Chronic Kidney Disease Collaborative Group is a collaboration among investigators from different countries interested in ambulatory BP in patients with CKD. The main aims of the research facilitated by this collaboration will be to evaluate: 1) the clinical and demographic characteristics associated with elevated ambulatory BP, 2) the prognostic role of ambulatory BP on cardiovascular and renal outcomes, and 3) ethnic and geographic differences in these associations.

Methods: This group will establish a large database derived from individual databases in the various countries to allow for powerful individual participant data meta-analyses of the relationship between clinical and demographic characteristics, CKD severity, ambulatory BP, and clinical outcomes.

Results: Investigators from 5 cohort studies have already agreed to participate. Characteristics of the cohorts are shown below.

	Italy	Spain	AASK	CRIC	CKD-JAC
Subjects	489	4434	617	1492	1075
Age (years)	64.4	69.3	60.3	63.1	60.7
Male/Female	290 / 199	2630 / 1804	382 / 235	833 / 659	682 / 393
eGFR	44.8	45.5	43.5	46.1	28.8
Proteinuria	63% ^a	16% ^b	30% ^c	42% ^c	86% ^b
Diabetics	176 (36%)	1385 (31%)	63 (10%)	626 (42%)	381 (35%)

a. Urine protein >0/15g/day; b. Urine alb/Cr >30mg/g; c. Urine prot/Cr >0.22mg/mg.

Conclusions: This multi-national collaboration will provide greater insights than possible from within-country analyses into the etiology and consequences of high risk ambulatory BP profiles. This information will be instrumental in helping us design prospective international large scale multicenter trials aimed at reducing renal and cardiovascular events in patients with CKD.

PUB498

Clinical Study of Pregnancy Related Kidney Injury Yumei Liu,¹ Ying Fan,¹ Yang Fei,¹ Hongda Bao,¹ Yajuan Huang,² Niansong Wang.¹ ¹Nephrology and Rheumatology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; ²Obstetrics and Gynecology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.

Background: The diagnosis and treatment of pregnancy related kidney injury is a complicated clinical problem for obstetricians and nephrologists. However, information regarding this topic in China is insufficient.

Methods: Totally 18589 women hospitalized between August 2004 and January 2013 from Obstetric and Nephrology Department in Shanghai Jiao Tong University Affiliated Sixth People's Hospital were screened. 569 women were enrolled for the pregnancy related kidney injury, including 494 cases from 2008 to 2013 and 75 cases from 2004 to 2007. The inclusive criteria was women with a history of kidney disease or Scr >= 70mmol/L or proteinuria >= 0.3g/24hour before the termination of pregnancy, or the diagnosis of kidney disease made during or after 6-month delivery.

Results: The prevalence of pregnancy related kidney injury was 3.1%. The incidence of kidney injury caused by obstetric disease was 3.1%, with the most common reason for pre-eclampsia (88.9%). The incidence of chronic kidney disease women with pregnancy is 0.74%, with the most common reason for chronic glomerular nephritis (36.2%). The incidence of kidney disease onset related to pregnancy was 1.5%. The incidence of proceeding to end stage renal disease for pregnancy was 0.21%. Kidney injury in pregnant women with obstetric disease may be more severe than that in pregnant women with kidney disease (with higher maternal blood pressure and proteinuria, lower birth weight and higher proportion of pre-term babies, P<0.05). Most women with pregnancy related kidney injury underwent cesarean section (>60%). Their proportion of stillbirth, pre-term and low birth weight babies were higher than healthy parturient, and the proportion of follow-up was low (9.9%). Neonatal death rate was 0.63% and pare-natal death rate was 2.1% in all.

Conclusions: Prevalence of pregnancy related kidney injury increases due to the foundation of Shanghai First-Aid Center for High-risk Pregnant Women in 2007. Serum creatinine, proteinuria and blood pressure have different indication for maternal condition and pregnancy outcome.

Funding: Government Support - Non-U.S.

PUB499

A New Vasculo-Renal Marker Enhances Accuracy of Hypertensive Nephropathy Recognition Arkadiusz Lubas,¹ Robert Ryzczek,² Grzegorz Kade,¹ Stanislaw Niemczyk.¹ ¹Dept of Internal Diseases, Nephrology and Dialysis, Military Inst of Medicine, Warsaw, Poland; ²Dept of Cardiology, Military Inst of Medicine, Warsaw, Poland.

Background: Latent and slow beginning of chronic kidney disease (CKD) coexisting with well tolerated, usually not recognized previously hypertension makes difficult to recognize hypertensive nephropathy (HN) from CKD of others origins. The aim of the study was to investigate the best marker helpful in differentiating HN from other causes of CKD.

Methods: Forty patients (4 F; 36 M; age 52.7 ±15.4) with stable CKD (CKD-EPI 53.1 ±27.6 ml/min/1.73m²) and a history of hypertension (26 with HN) were enrolled in the study. Serum Creatinine (Cre), Cystatin C (Cys), NT-pro brain natriuretic peptide (NTproBNP), Troponin I (TNI) and urinary albumin to creatinine ratio (UACR) were tested. Renal function was estimated according to Cre and Cys based CKD-EPI formula. Echocardiographic examination, carotid Intima-Media Thickness (IMT), ABPM, Renal Resistive Index (RRI) were performed. Vasculo-Renal Index (VRI) was calculated as IMT to UACR ratio.

Results: Groups with HN and CKD of other origins did not differ in renal function (CKD-EPI 46.2 vs 57.1 ml/min/1.73m²; p=0.22), RRI, NTproBNP, TNI, left ventricular (LV) ejection fraction, LV mass index and mean arterial pressure. Patients with HN were older (56.4 ±15.1 vs 45.9 ±14.1; p =0.039), had lower UACR (0.264 ±0.484 vs 0.814 ±0.564 mg/mg; p<0.001), but higher IMT (0.858 ±0.217 vs 0.652 ±0.180; p=0.009) and VRI (m. 28.8 [0.36; 1030.00] vs m. 0.78 [0.34; 12.50] p<0.0001). In ROC analysis VRI ≥ 1.91, UACR ≤ 0.199, and IMT ≥ 0.87 could recognize HN with sensitivity of 85%, 73% and 62% respectively, specificity of 79%, 93% and 86%, and accuracy of 82.5%, 80% and 70% (AUC 0.874, 0.849 and 0.749; p>0.05).

Conclusions: A new Vasculo-Renal Index recognizes HN more accurately, but UACR and IMT are not significantly worse.

Funding: Government Support - Non-U.S.

PUB500

Association of Percentage of Global Sclerosis with Nocturnal Blood Pressure and Sodium Excretion in Patients with Chronic Kidney Disease
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Background: In patients with chronic kidney disease (CKD), impaired urinary sodium excretion (UNa) may cause nocturnal hypertension and pressure natriuresis to compensate for daytime sodium retention. The aim of this study was to determine the renal histological lesions which associated with nocturnal blood pressure (BP) and UNa in patients with CKD.

Methods: We analyzed 64 patients biopsied in our institutions from Sep 2010 to Apr 2014 (Forty IgA nephropathy, 6 Purpura nephritis, 4 membranous nephropathy and 14 the others). During the same hospitalization period of renal biopsy, ambulatory BP monitoring and evaluation of UNa were performed simultaneously. The association of histological findings such as global sclerosis (%GS), arteriolar hyalinosis (%hyaline), and interstitial fibrosis (IF), with nocturnal BP and night/day ratio of UNa were assessed using linear regression analysis.

Results: Twenty three patients were male, mean age was 40.5 ± 15.9 years, and mean estimated glomerular filtration rate (eGFR) was 79.0 ± 28.9 mL/min/1.73m². Both nocturnal BP and night/day ratio of UNa positively associated with %GS, %hyaline, and IF, and negatively associated with eGFR. Multiple regression analysis adjusted for age, sex, eGFR, and usage of antihypertensive drugs showed that %GS was significantly associated with nocturnal systolic BP (β = 0.38, p = 0.012), nocturnal diastolic BP (β = 0.34, p = 0.031), and night/day ratio of UNa (β = 0.52, p = 0.005).

Conclusions: We found that night/day ratio of UNa and nocturnal BP closely related to the percentage of global sclerosis. These findings could be the morphological evidence that decrease in the number of functioning glomeruli causes increase in nocturnal UNa to compensate for daytime sodium retention resulting in elevation of nocturnal BP in patients with CKD.

PUB501

A Brief Intervention to Assign Once Daily Antihypertensive Medications to Morning versus Evening Dosing – A Pilot Study to Assess Feasibility and Efficacy in Chronic Kidney Disease Patients
 Julia Chernyakov, Lisa A. Hillman, Paul E. Drawz. *Univ of Minnesota.*

Background: Hypertension is a major risk factor for cardiovascular and renal disease. Evening dosing of antihypertensive medications lowers nighttime blood pressure and, at least in one large randomized trial, reduced risk for cardiovascular outcomes. However, whether evening dosing reduces adverse outcomes in patients with chronic kidney disease (CKD) is unknown. The purpose of this pilot study was to assess the efficacy of a brief pharmacist based intervention on patient adherence to an assigned time of day to take antihypertensive medications and the feasibility of a pragmatic randomized controlled trial.

Methods: Patients with moderate to severe CKD taking ³¹ antihypertensive medication once daily were randomized to take one once daily antihypertensive in the morning or the evening. After a nephrology clinic visit, a student pharmacist reviewed participants' antihypertensive medications with a focus on the one once daily study antihypertensive medication assigned to the morning or evening dosing arm. Study participants were contacted by phone three to six weeks after the clinic encounter to assess adherence.

Results: Of 99 potentially eligible patients approached in the nephrology clinic, 18 declined to participate, 2 had medication changes that made them ineligible, and 79 were randomized (39 to morning dosing, 40 to evening dosing). Average (SD) age was 56.5 (14) years, 68% were male, and average (SD) estimated glomerular filtration rate was 36.6 (8.9) mL/min/1.73m². Adherence, defined as taking the once daily medication at the time indicated at least 6 times in the last 7 days and not taking it at any other time during the day was 91% in the morning arm and 95% in the evening arm (P=0.57). The average (SD) time spent by the pharmacy student with each participant was 9.9 (6.1) minutes.

Conclusions: This pilot demonstrates the feasibility of a pragmatic randomized trial evaluating the effect of once daily nighttime dosing of antihypertensive medications on adverse outcomes in CKD patients. Patients were willing to participate in the study and adherence to the assigned timing was high in both the morning and evening dosing arms.

PUB502

Bedtime Dosing Regimen Drug Therapy for Chronic Kidney Disease (CKD) Patients with Hypertension: A Meta-Analysis of RCTs
 Caixia Wang,¹ Xun Liu,¹ Zhenda Zheng,² Linsheng Lv,³ Shaomin Li,¹ Tan-qi Lou.¹ ¹Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; ²Dept of Cardiology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; ³Operation Room, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong.

Background: Chronotherapeutic formulations are defined as the purposeful timing of medications. Bedtime dosing regimen drug therapy on blood pressure control is used widely, but its clinical benefits and protection for target organs in chronic kidney disease (CKD) patients is not known.

Methods: Randomized controlled trials (RCTs) were searched in PUBMED, EMBASE, ASN-ONLINE, the Cochrane Library and the reference articles of published papers. We identified five RCTs, including 3706 CKD patients with hypertension. Risk ratio (RR), weighted mean difference (WMD) with 95% confidence intervals (CIs) were pooled using fixed or random-effects models.

Results: In our analysis, a significant decrease was observed in bedtime mean SBP by -3.76 mmHg (MD, 95% CI, [-6.81, -0.71]), while there was a significant increase in awake time mean SBP by 1.16 mmHg (MD, 95% CI, [0.10, 2.21]) in the bedtime dosing group. Compared with the routine administration drug therapy, chronotherapy resulted in a larger decrease by 3.55% (MD, 95% CI, [0.22, 6.88]) in the sleep-time relative decline of SBP. Besides, a higher decline of non-dipper BP patterns was found in the chronotherapy group by 0.60 (RR, 95% CI, [0.43, 0.84]). No significant differences were noted for controlled BP, 24h mean SDP and DBP, awake time mean DBP and sleep-time mean decline in DBP and HB. Evidence was insufficient in CVE and proteinuria.

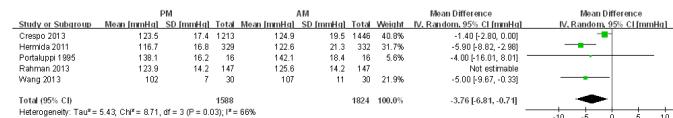


Figure1. Meta-graph of bedtime mean SBP

Conclusions: This meta-analysis suggests that the bedtime dosing regimen drug therapy benefits CKD patients in terms of hypertension especially those with non-dipper BP pattern.
Funding: Government Support - Non-U.S.

PUB503

The Impact of Glomerular Collapse in Hypertensive Emergency Patients
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Background: The prognosis of kidney disease with hypertensive emergency (malignant glomerulosclerosis) is still worse compared with benign nephrosclerosis. Here, further to assess the reasons of worse prognosis and to reconsider more appropriate therapy for malignant nephrosclerosis, we compared pathological parameters between malignant and benign nephrosclerosis.

Methods: 8 patients diagnosed as hypertensive emergency with acute renal failure were performed renal biopsies from October 2005 to May 2015. We selected all patients with pure benign nephrosclerosis (n=20), who were performed renal biopsies during same period, as controls. We compared changes in clinical and pathological data using the paired t-test and the Mann-Whitney U-test.

Results: All 8 patients with hypertensive emergency had characteristic pathological changes of malignant hypertension, such as fibrinoid necrosis, onion-skin thickening and edematous-appearing matrix in arterioles. These changes were never observed in benign nephrosclerosis. The rates of global sclerosis and segmental sclerosis had no statistical differences between these two groups. Interestingly, when glomerular collapsing rate was counted by GCR (GCR=number of glomerular collapse/ total number of glomeruli), GCR scores were much higher in hypertensive emergency cases compared with those in benign nephrosclerosis cases (42.9 ± 23.8 vs. 6.5 ± 7.4 %; p < 0.05). These patient's clinical characteristics showed a high level of plasma renin activity (PRA) (14.9 ± 5.8) and hypokalemia (3.5 ± 2.8). Two of 8 patients reached to end stage kidney disease requiring dialysis.

Conclusions: Glomerular collapse and hyper-renin mean glomerular hypoperfusion. Therefore, if therapy accelerate this glomerular hypoperfusion, it might affect renal prognosis. We should reconsider the way of therapy, such as the selection of anti-hypertensive drugs, and the speed of declining blood pressure and volume control by thinking glomerular hypoperfusion.

PUB504

A Study of Early Treatment with Benazepril in SHR at Different Doses
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Background: To investigate whether early treatment with super high dosage ACEI can reverse glomerulosclerosis in SHR.

Methods: 30 SHR were randomized and divided into three groups(n=10): model control group(M group), 10 mg·kg⁻¹·d⁻¹ Benazepril treatment(HT group),50 mg·kg⁻¹·d⁻¹ Benazepril treatment(SHT group),10 Wistar-Kyoto rats were studied as normal control group(N group), placebo , 10 mg·kg⁻¹·d⁻¹ Benazepril and 50 mg·kg⁻¹·d⁻¹ Benazepril were given through intragastric administration starting from 0 week of the experiment, rats were killed until 12 week of the experiment. Blood pressure(Bp), 24 hours urinary protein(24hUpr) and serum creatinine(Scr) were detected in the 0, 4, 8, 12 week of the experiment. Renal pathology damage was evaluated with paraffin wax section of kidney tissue through HE, MASSON stain; the protein levels for TGF-β1 and PAI-1 were tested through immunohistochemicalstaining method.

Results: Compared with model control group, Bp, 24hUpr of HT and SHT groups decreased obviously (P<0.05), the protein levels for TGF-β1 and PAI-1 in kidney tissue of HT group and SHT group were inhibited(P<0.05), glomerular collagen deposition of HT group and SHT group reduced evidently (P<0.05).

Conclusions: This study shows that high dosage ACEI and super high dosage ACEI all can decrease blood pressure, reduce proteinuria, depress the expressions of TGF- β and PAI-1 protein in SHR, and delay glomerulosclerosis. But super high dosage ACEI can not reverse glomerulosclerosis in SHR.

PUB505

Hemolytic Uremic Syndrome Associated with Scleroderma Renal Crisis: The Challenge for Timely and Accurate Diagnosis Amro Elshoury, Syed S. Haqqie, Daniel Sedhom, Arif Asif. *Albany Medical Center, Albany, NY.*

Background: Scleroderma renal crisis (SRC) is a rare cause of atypical hemolytic uremic syndrome (aHUS) and differentiating it from other causes of thrombotic microangiopathies can be challenging. A 53-year old Caucasian male, with no past medical history was found unresponsive. BP was elevated to 207/141 mm Hg. Skin examination showed diffuse telangiectasia and edema of his extremities with bilateral sclerodactyly (Figure 1). Fundoscopy revealed bilateral retinal hemorrhage and exudates. Labs showed a hemoglobin=5gm/dl, platelet=25x10³/uL, creatinine=6mg/dl, LDH=1122IU/L, bilirubin=1.6mg/dl, haptoglobin<5%, reticulocytic count=10.4% and schistocytes. ANA and anti-RNA Polymerase III antibody were positive (C3 and C4, coagulation profile, fibrinogen were normal; Coombs negative). CT head showed severe microvascular changes throughout the white matter of the cerebrum and MRI showed evidence of punctuate chronic micro-hemorrhages in the left thalamus and cerebellar tonsils. The presence of MAH, acute renal failure and thrombocytopenia raised suspicion for possible aHUS/TTP. Serum ADAMTS 13 was ordered. Because of the possibility of SRC, the patient was started on capropril. A dramatic improvement in BP, hemoglobin and platelets count along with the normalization of LDH and schistocytes disappearance was observed. However, there was no improvement in kidney function requiring hemodialysis. ADAMT-13 activity returned at 40% (cut-off for TTP is <5%). Patient did not pursue eculizumab therapy. A significant portion of patients with Scleroderma can develop aHUS. In this case, hypertension might have served as a complement amplifying condition.



Methods: Clinical presentation/course of the patient.

Results: Despite therapy with ACE inhibitors patient ended up on RRT.

Conclusions: Patient presenting with Malignant HTN and MAH was found to be in scleroderma crisis.

PUB506

The Impact of Neck Irradiation on Baroreceptor Reflex and Hypertension Amro Elshoury, Syed S. Haqqie, Daniel Sedhom, Rahim Dhanani, Arif Asif. *Albany Medical College.*

Background: Only a few studies with a very limited sample size have evaluated the impact of neck irradiation on baroreceptor reflex failure and blood pressure (BP) abnormalities. We investigated 60-patients, with head/neck cancer, who received neck irradiation between 2005 to 2010. IRB approval was obtained. Median for age was 61.5 years (range 24-90 years). We used the same cohort of patients, before the received neck irradiation, as a control for BP. Mean systolic BP before neck irradiation was 129.1 \pm 2.646 mm Hg, 1-months post-neck irradiation was 121.4 \pm 2.178 mm Hg (P=0.02), 3-months post-neck irradiation was 121.9 \pm 2.180 mm Hg (P=0.04), 6-months post-neck irradiation was 125.2 \pm 2.933 mm Hg (P=0.27), 1-year post-neck irradiation was 123.4 \pm 4.087 mm Hg (P=0.32), 2-years post-neck irradiation was 122.7 \pm 3.655 mm Hg (P=0.06) and 5-years post-neck irradiation was 124.8 \pm 2.833 mm Hg (P=0.35). Mean diastolic BP before neck irradiation was 76.28 \pm 1.802 mm Hg, 1-month post-neck irradiation was 69.88 \pm 1.585 mm Hg (P=0.009), 3-months post-neck irradiation was (72.84 \pm 1.764 mm Hg (P=0.17), 6-months post-neck irradiation (71.00 \pm 1.957 mm Hg, P=0.07), 1-year post-neck irradiation was 72.22 \pm 2.341 mm Hg (P=0.17), 2-years post-neck irradiation was 74.09mmHg \pm 1.757 mmHg (P=0.47), 5-years post-neck irradiation was 70.17mmhg \pm 3.131 mm Hg (P=0.16). Patients with head/neck cancer did not have clinically significant change in their BP after neck irradiation. These data do not support either acute fulminant hypertensive crisis or a chronic labile hypertension after neck irradiation. The study suggests that carotid baroreceptors might not have been damaged by radiation or baroreceptors in other locations might have been able to control BP.

Methods: Retrospective study of blood pressure in patients with neck radiation for cancer.

Results: Blood pressure before and after radiation showed no increase.

Conclusions: The study suggests that carotid baroreceptors might not have been damaged by radiation or baroreceptors.

PUB507

Sympathetic Nervous System Activity Reflected by Renalase and Catecholamines in Different Aged Patients with and without Chronic Kidney Disease Edyta Zbroch,¹ Dominika Maciorkowska,¹ Ewa Koc-Zorawska,² Jolanta Malyszko.¹ ¹2-nd Dept of Nephrology and Hypertension with Dialysis Centre, Medical Univ, Bialystok, Poland; ²1st Dept of Nephrology and Transplantation, Medical Univ, Bialystok, Poland.

Background: Sympathetic nervous system activity is elevated in patients with chronic kidney disease (CKD) as well as in older persons. It contributes to hypertension and cardiovascular diseases. It is due to a reduction of catecholamines clearance and in elderly also to an increased sympathetic discharge from different organs. Renalase may play a role in the catecholamines degradation. The aim of the study was to assess the sympathetic nervous system activity, according to serum renalase and catecholamines concentration in a cohort of 211 patients with hypertension and with or without chronic kidney disease.

Methods: The study group was divided according to age below and above 65 years. The older persons (61) was also divided into group with (75%) and without CKD stage 5. The serum renalase, dopamine and norepinephrine concentration as well as pressure control, residual renal function rate and echocardiography were assessed.

Results: The older group had higher renalase (p=0,02) and dopamine (p<0,001) concentration and it was elevated in patients with CKD comparing to those without. They also had advanced abnormalities in echocardiography, like thicker interventricular septum (p=0,03) and lower ejection fraction (p<0,001) as well as CKD patients comparing to those without CKD – pronounced left ventricular hypertrophy (p=0,007) and lower ejection fraction (p=0,004). They more often suffered from coronary artery disease. The residual renal function was less in older patients with CKD. The main used hypotensive drugs in studied group were beta-blockers. There was the significant correlation between age and renalase, norepinephrine and dopamine concentration.

Conclusions: The advanced aged especially combined with chronic kidney disease is associated with elevated renalase and dopamine level. It may reflect the sympathetic nervous system hyperactivity due to impaired kidney function and reduction of residual diuresis. It may have an impact on the development of cardiovascular complications.

PUB508

Heart Rate Variabilities During Day and Night Can Alter the Circadian Blood Pressure (BP) Rhythm Toshiyuki Miura,¹ Michio Fukuda,¹ Yoshiaki Ogiyama,¹ Ken Kiyono,² Yoshiharu Yamamoto,³ Junichiro Hayano,¹ Nobuyuki Ohte.¹ ¹Nagoya City Univ, Japan; ²Osaka Univ, Japan; ³Tokyo Univ, Japan.

Background: We previously reported in patients with chronic kidney disease (CKD) that the circadian rhythms of BP and urinary sodium excretion (U_{Na}V) were both impaired into non-dipper pattern as renal function deteriorated. Elevated salt-sensitivity of BP and inappropriate activation of the renin-angiotensin-aldosterone system and the sympathetic nerve system play important roles in high BP and the high incidence of cardiovascular diseases in patients with CKD.

Methods: In 39 patients with CKD, we analyzed HRV in 24-h electrocardiography, BP monitoring and urine collection, separately for daytime and nighttime. Patients, who took antihypertensive agents, were excluded. We evaluated the relationship between systolic blood pressure (SBP) and λ , HF, or U_{Na}V. The non-Gaussianity index of HRV (I_{25%}), which reflects the probability of intermittent large deviations of heart rate (HR) from the trend, and the power of high frequency (HF, 0.15–0.40 Hz), obtained by frequency domain analysis of HRV, was used as a marker of sympathetic cardiac overdrive, and as vagal nerve activity, respectively.

Results: As renal function deteriorated, 24-h λ and daytime λ increased, 24-h-SBP showed significant relationships with daytime λ (r=0.40, p=0.01) and night-time HF (r=-0.37, p=0.02). Night/day ratios of SBP and U_{Na}V were also elevated as GFR was reduced. Night/day ratios of SBP correlated inversely with night-time HF (r=-0.36, p=0.02). When analyzed by stepwise multiple regression analysis, the main determinants of 24-h-SBP were 24-h-U_{Na}V, daytime λ , and night-time HF. Night/day SBP ratios was determined by night/day ratio of U_{Na}V, rather than any HRVs.

Conclusions: Our study clearly demonstrated that as renal function deteriorated, sympathetic nerve activity is activated during the day, and vagal activation was impaired during the night, both of which can contribute to high BP in patients with CKD. However, non-dipper type of circadian BP rhythm was associated with the circadian U_{Na}V rhythm rather than sympathetic or vagal nerve activity, even though the sympathetic activity can stimulate tubular sodium reabsorption.

PUB509

The Effects of the Insight Meditation Practice on Blood Pressure Reduction in Buddhist Exemplary People Jutamas Vareesangthip,¹ Kriengsak Vareesangthip.² ¹Dhamma Communication Div, Graduate School, Mahachulalongkornrajavidyalaya Univ, Bangkok, Thailand; ²Renal Div, Dept of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.

Background: Hypertension (HTN) is a leading risk factor for preventable cardiovascular disease, with over one in five adults affected worldwide. Lifestyle modification is a key strategy for the prevention and treatment of HTN. Stress has been associated with greater cardiovascular risk, and stress management is a recommended intervention for hypertensives. For many patients, maximal medical therapy is insufficient

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

1005A

to adequately treat refractory hypertension. Lifestyle modification remains an important approach in management. Buddhist meditation encompasses a variety of meditation techniques that aim to develop mindfulness, concentration and insight.

Methods: We aimed to study whether Buddhist Insight Meditation (IM) Practice, composing of Walking Meditation and Sitting Meditation, could reduce the level of blood pressure in Buddhist Exemplary People. 65 exemplary people were divided into 3 groups according to the schedule they performed IM Practice. Group 1 (n=25) performed 30 minutes of the Walking and 30 minutes of the Sitting Meditation, group 2 (n=20) performed 45 minutes in each Meditation and group 3 (n=20) performed 60 minutes in each Meditation. Their blood pressures (BP), pulse pressures (PP) and pulses (P) were measured before and after Walking and Sitting Meditations.

Results: The results clearly showed that systolic BP, PP and P were significantly decreased after the Walking Meditation at 30-45-60 minutes. After IM Practice schedule, an arterial pulse has been significantly decreased in all 3 groups, PP has been significantly decreased in group 2 and systolic BP has been significantly reduced in group 3.

Conclusions: In conclusion, the Buddhist IM Practice could meaningfully reduce the sympathetic activities including systolic BP, PP and P. Therefore, this Buddhist Practice should be added to be one modality of the standard hypertensive treatments.

PUB510

ENaC as a Novel Mechanism for Hypertension and Volume Expansion in Type 2 Diabetes Mark L. Unruh,¹ V. Shane Pankratz,¹ Evan C. Ray,² Rebecca P. Hughey,² Thomas R. Kleyman.² ¹Div of Nephrology, Univ of New Mexico; ²Renal-Electrolyte Div, UPMC.

Background: Renal Na retention and extracellular fluid volume expansion are hallmarks of nephrotic syndrome. There is evidence that this occurs even in the absence of activation of hormones that are known to stimulate renal Na transporters. Recent studies suggest that plasmin-dependent activation of ENaC may be responsible for renal Na retention in the setting of nephrotic syndrome. We hypothesized that the ENaC inhibitor amiloride would be an effective therapeutic agent in inducing a natriuresis and lowering blood pressure in individuals with macroscopic proteinuria.

Methods: We conducted a pilot double-blind randomized cross-over study comparing the effects of daily administration of either oral amiloride (10 (low dose) followed by 20 (high dose) mg/d) or HCTZ (Na,Cl co-transporter inhibitor) to patients with type 2 diabetes and macroscopic proteinuria. We examined safety and feasibility of amiloride by monitoring kidney function, adherence, blood pressure, weight, urinary Na excretion and serum electrolytes during diuretic administration.

Results: 9 subjects were enrolled in the trial. Systolic blood pressure (SBP) decreased in both treatment groups, but there was not a significant difference between HCTZ and amiloride (p=0.53). Amiloride treatment was associated with a 1.1±0.4 kg greater decline in weight (p=0.02), and a 0.78 ± 0.18 mmol/L greater increase in serum potassium (p=0.002) over the low dose portion of the study. 2 subjects developed acute kidney injury and hyperkalemia when treated with amiloride. 5 subjects had readily detectable levels of urinary plasminogen/plasmin, and 4 did not. Among those receiving amiloride, the low plasmin group experienced a change of 1.1±4.6 mmHg in SBP and the high plasmin group experienced a change of -13.9±8.7 mmHg, although there was insufficient evidence to conclude that there were differential treatment effects by high/low plasminogen status (p=0.113).

Conclusions: Among patients with type 2 diabetes, normal renal function, and proteinuria, there was suggestion of increased natriuresis for those treated with amiloride vs. HCTZ, however, acute kidney injury and severe hyperkalemia was a safety concern.

Funding: Private Foundation Support

PUB511

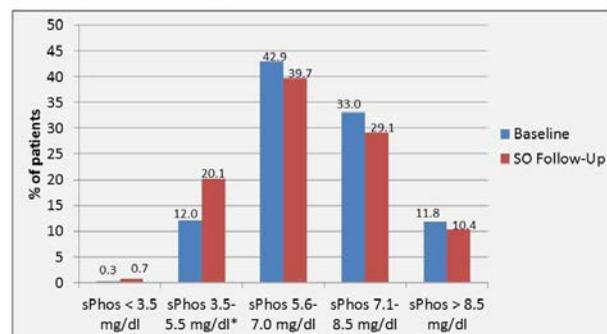
Serum Phosphorus Control and Reduced Phosphate Binder Pill Burden Among Hemodialysis Patients Who Switched from Sevelamer to Suroferic Oxyhydroxide Vidhya Parameswaran, Lin Ma, Linda H. Ficociello, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America, Waltham, MA.*

Background: Clinical management of hyperphosphatemia among hemodialysis (HD) patients (pts) can present challenges. A retrospective database analysis was conducted to study the effectiveness of suroferic oxyhydroxide (SO) among in-center HD pts who switched from sevelamer to SO as part of routine clinical care.

Methods: Pts who switched from sevelamer and had ³¹P serum phosphorus (sPhos) measured during SO treatment were included. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and pill burden were assessed at baseline (3-months prior to SO) and at follow-up (3-months during SO treatment).

Results: Pts (n=1487) were, on average, 54 years old, with dialysis vintage of 4.4 years and hyperphosphatemia (baseline sPhos=6.94 mg/dl). Figure shows sPhos distribution at baseline and follow-up. Pts with in-range sPhos (3.5-5.5 mg/dl) increased from 12% to 20.1% (68% increase). Mean sPhos decreased from 6.94 to 6.7 mg/dl (p<0.001) and mean sCa decreased from 9.3 to 9.25 mg/dl (p<0.001). There was a significant decrease (4.7 pills/day, p<0.001) in pill burden (8.5 to 3.7 pills). No significant change in iPTH levels was observed (626.1 to 637.6 pg/ml). TSAT and FER significantly increased (p<0.001) from 33.7% to 35.5% and 983.5 to 1051.4 ng/ml, respectively. In pts not receiving IV iron (n=149), there were no significant changes in TSAT (36.3% to 35.9%) or FER (1221.5 to 1177.4 ng/ml).

Distribution of sPhos during baseline compared to suroferic oxyhydroxide (SO)-treated follow-up for HD patients who switched from sevelamer (N=1487)



*Change in %in-range and %out of range baseline compared to SO Follow-up, p<0.001

Conclusions: HD patients who switched from sevelamer to suroferic oxyhydroxide as part of routine clinical care had decreased serum phosphorus (0.24, p<0.001). There was a 68% increase in the number of patients with in-range serum phosphorus (p<0.001). Patients were prescribed 4.7 fewer pills per day (p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB512

An Investigation of the Inverse Relationship Between Fractional Excretion of Phosphate and the Tubular Maximum for Phosphate per Volume of Filtrate Kenneth R. Phelps,^{1,2} Darius Mason.^{1,2,3} ¹Stratton VAMC, Albany, NY; ²Albany Medical College, Albany, NY; ³Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: The serum P concentration ($[P]_s$) is the sum of urinary excretion and tubular reabsorption rates of P per volume of filtrate (E_p/C_{cr} and TR_p/C_{cr}). The two ratios also determine fractional excretion of P (FE_p) [Clin Nephrol 83:167], and E_p/C_{cr} is approximately proportional to the concentration of P ($[P]_f$) in the cortical distal nephron (CDN) [Clin Nephrol 82:191]. Maximal TR_p/C_{cr} (i.e. Tm_p/GFR) exceeds actual TR_p/C_{cr} when FE_p is < 20%; as FE_p falls, Tm_p/GFR and ($Tm_p/GFR - TR_p/C_{cr}$) rise [Clin Chim Acta 26:15]. We investigated these phenomena.

Methods: We measured $[cr]$ and $[P]$ in fasting serum (s) and urine (u), and $[PTH]_{1-84}$ (Scantibodies) and intact $[FGF23]$ (Immutopics) in plasma from 28 subjects without renal or parathyroid disease. We calculated E_p/C_{cr} as $[P]_u/[cr]_u$, TR_p/C_{cr} as $[P]_s - E_p/C_{cr}$, and FE_p as $[P]_u/[cr]_u/[P]_s$. We then determined Tm_p/GFR from the Walton-Bijvoet nomogram. We performed simple linear regressions (y on x) as indicated in the table.

Results: All y-variables correlated inversely with FE_p . Tm_p/GFR correlated directly with TR_p/C_{cr} but was unrelated to E_p/C_{cr} . Other y-variables correlated inversely with E_p/C_{cr} but were unrelated to TR_p/C_{cr} . None of the y-variables correlated with $[PTH]$ or $[FGF23]$.

y	x	FE_p , %		E_p/C_{cr} mg/dL		TR_p/C_{cr} mg/dL	
		R ²	P	R ²	P	R ²	P
Tm_p/GFR , mg/dL		0.39	< 0.001	0.04	0.34	0.89	< 0.001
$(Tm_p/GFR)/[P]_s$		0.83	< 0.001	0.76	< 0.001	0.05	0.27
$(Tm_p/GFR) - TR_p/C_{cr}$, mg/dL		0.69	< 0.001	0.56	< 0.001	0.10	0.10
$(Tm_p/GFR)/(TR_p/C_{cr})$		0.62	< 0.001	0.64	< 0.001	0.01	0.60

Conclusions: Correlations of y-variables with FE_p ultimately reflect correlations with E_p/C_{cr} , TR_p/C_{cr} , or both [Clin Nephrol 83:167]. As expected, Tm_p/GFR was closely associated with TR_p/C_{cr} . The other y-variables, which depicted comparisons of Tm_p/GFR to TR_p/C_{cr} , were inversely related to E_p/C_{cr} , a specific indicator of P influx and a surrogate for $[P]_f$ in the CDN. As $[P]_f$ fell in the CDN, the difference rose between actual and maximal P reabsorption in the proximal nephron. We did not identify an endocrine mediator of this interaction.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

PUB513

Observational Study at the Mexican Institute for Social Security and Services for State Worker's National Medical Center 20 de Noviembre Nephrology Department Outpatient Clinic Using Cinacalcet as Renal Replacement Therapy for Secondary Hyperparathyroidism Caused by Chronic Kidney Disease *Elvira González, Jesús Alejandro Nava Martínez, Juvenal Torres Pastrana. Nephrology, CMN 20 Noviembre, Mexico, D.F, Mexico; Nephrology, CMN 20 de Noviembre, Mexico, D.F., Mexico; Nephrology, CMN 20 de Noviembre, Mexico, D.F., Mexico.*

Background: Secondary hyperparathyroidism is a highly prevalent clinical condition in persons with advanced chronic kidney disease (CKD). It can be seen in the early stages of the disease and consists of disorders in bone metabolism.

Methods: A descriptive, retrospective observational study was done using patient records from the Institute for Social Security and Services for State Worker's (ISSSTE) National Medical Center 20 de Noviembre Nephrology outpatient clinic, located in Mexico City, Mexico. 50 cases of adult patients with advanced chronic kidney disease were reviewed in renal replacement treatment, peritoneal dialysis and/or hemodialysis who were managed with Cinacalcet for Secondary Hyperparathyroidism, with PTHi >300 pg/ml.

Results: The baseline level of serum parathyroid hormone of the 42 patients was 1371.6 pg/ml prior to the use of cinacalcet, with a percentage reduction of 33% per month and 6 months of treatment 55% with a mean of 1133 pg/ml and 615.48 pg/ml respectively. A total of 42 patients; 19 (45%) achieved targets at the end of the 6-month study. 36 patients underwent to scintigraphy of parathyroid gland, because they did not obtain parathyroid hormone decreased over 30% at the 3rd month of treatment; 5 patients showed hyperplasia and 11 parathyroid adenoma.

Conclusions: Cinacalcet combined with conventional treatment succeeds in reaching goals compared to standard treatment only. Hypocalcemia is a common side effect however when administered together with calcium salts and / or vitamin D or its analogues decrease side effects According to previous studies cinacalcet it increases the achievement of goals in mild hyperparathyroidism. In our study was more important for the response time in the RRT than the severity of hyperparathyroidism.

Funding: Government Support - Non-U.S.

PUB514

"Binder Reminders" for Persistent Hyperphosphatemia in Hemodialysis Patients: A Fellow's Quality Improvement Project *Divakar Jammalamadaka, N. Stanley Nahman, John Jason White. Medicine, Georgia Regents Univ, Augusta, GA.*

Background: Despite regular quality improvement (QA) processes, control of mineral metabolism remains poor. One root cause is patient non-adherence to phosphate (Pho) binders. Evolving data suggest SMS/text reminders improve medication adherence in a wide range of chronic illnesses. Here, we report our initial experience with text reminders on Pho control in HD patients.

Methods: 40 patients with Pho > 5.5 mg/dL for 2 of last 3 months, and possessing cell-phones with texting capabilities were studied. We randomly assigned 20 to receive the phrase "Binder Reminder" at mealtimes x 7 days prior to their monthly lab draw. The remaining 20 received usual care. Group assignment and messaging was performed by a nephrology fellow, not part of the multidisciplinary team. Patients were excluded if they declined participation, missed any dialysis sessions during the 7 day period, or if they were unable to obtain their binders. Pho level after intervention was the primary outcome.

Results: After exclusions, 13 patients received the intervention and were compared to 14 controls. Pre-intervention Pho levels were 6.81 +/- 0.88 and 6.60 +/- 0.93 mg/dL (Mean +/- SD) in the control and intervention groups respectively. After intervention, Pho levels declined in the intervention group to 6.00 +/- 1.2 mg/dL (P = 0.10). Pho also declined in the control group to 6.19 +/- 0.76 mg/dL. Hence there was no difference between the groups (P = 0.76). Each group had 8 patients with improved Pho levels, and 5 patients at goal.

Conclusions: Our initial QA project utilizing SMS/text messaging appears to have no effect on short-term Pho control in a group of HDs patients with chronic hyperphosphatemia. A major drawback is the small number of patients and the number excluded (33%). However, this study does provide useful preliminary data for the planning of a larger pilot project, highlights the importance of contemporary control groups in QA to exclude the Hawthorne effect, and, given its simplicity, may be a model for fellow-driven QA projects and education.

Funding: Clinical Revenue Support

PUB515

Niacin Improves Cardiac Function in Alport Mice with Progressive Chronic Kidney Disease and Hyperphosphatemia *Kelly Ambler,¹ Evgenia Dobrinskikh,¹ Veronica A. Hogg-Cornejo,¹ Xiaoxin Wang,¹ Yuhuan Luo,¹ Jason R. Stubbs,² Moshe Levi.¹ ¹Univ of Colorado Denver; ²Univ of Kansas Medical Center.*

Background: Increase in serum phosphate (Pi) level (hyperphosphatemia) is a common clinical problem in chronic kidney disease (CKD). Systemic Pi homeostasis is balanced through three major mechanisms: intestinal uptake, retention or release from bone, and renal reabsorption. Sodium-phosphate co-transporter type 2b (NaPi2b) is a major phosphate transporter in the small intestine. Alport syndrome is a genetic disorder characterized by CKD, hearing loss and cardiac dysfunction.

Methods: By 9-10 weeks of age Alport mice, which have a mutation in a COL4A3 gene on the SvEv129 background, develop signs of CKD and hyperphosphatemia.

Results: We have found by western blot that there is an increase in intestinal NaPi-2b protein abundance and Everted Sac studies showed increased NaPi transport in the Alport Ileum compared to the WT littermate controls. Cardiac echo studies revealed that Alport mice have decreased ejection fraction (EF: 67±2% compared to 75±3% in the WT littermate) and diastolic dysfunction (mitral Doppler flow E/A ratio: 1.2±0.1 compared to 1.6±0.1 in the WT littermate, p<0.05), which could be corrected by treatment with Niacin (intestinal phosphate uptake inhibitor). In the treated Alport mice EF increased to 78±2% (p<0.05) and E/A ratio improved to 1.3±0.1 (p<0.05). In addition, there were significant decreases mRNA relative expression in β-MHC (0.08±0.02 in control vs. 2.19±0.34 in Alport, p<0.001, vs. 0.2±0.001 in Alport+Niacin, p<0.05), PAI-1 (0.12±0.01 in control vs. 1.05±0.15 in Alport, p<0.05, vs. 0.15±0.05 in Alport+Niacin, p<0.05), and TGF-β (0.03±0.01 in control vs. 0.77±0.23 in Alport, p<0.01, vs. 0.07±0.23 in Alport+Niacin, p<0.01), markers of heart failure and cardiac fibrosis.

Conclusions: Inhibition of intestinal phosphate transport with Niacin therefore improves systolic and diastolic cardiac dysfunction in CKD.

Funding: Pharmaceutical Company Support - Daiichi Sankio

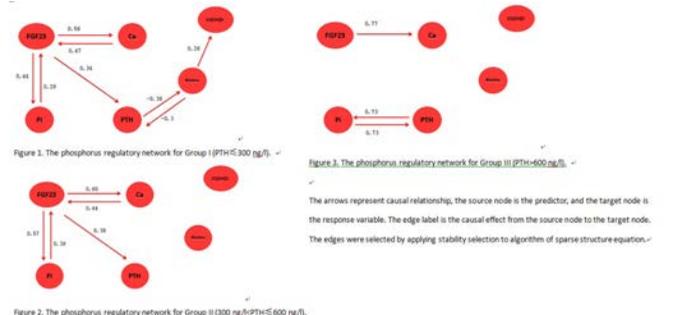
PUB516

Establishing Regulatory Networks of Phosphorus Metabolism in HD Patients – A New Path of Treating Hyperphosphatemia *Mengjiing Wang,¹ Panpan Wang,² Yulin Zhang,¹ Li Ni,¹ Minmin Zhang,¹ Jing Chen.¹ ¹Nephrology, Huashan Hospital, Shanghai; ²MOE Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan Univ, Shanghai.*

Background: The clinical efficiency of current treatment of hyperphosphatemia in HD varies widely on different patients. We assume that it is due to phosphorus regulation in vivo. In physiological conditions, phosphorus is regulated by a biological network consisting of interacting hormones and minerals. In HD, the networks change dramatically and affect serum phosphorus. This study aims to establish the regulatory networks of phosphorus in HD and identify the key factors that may have a causal effect on circulating concentrations of phosphorus.

Methods: 30 MHD patients were enrolled and divided into three groups (n=10, PTH≤300 ng/l; n=10, 300 ng/l<PTH≤600 ng/l; n=10, PTH>600 ng/l). Predialysis blood samples were obtained on the mid-week dialysis day for detection of PTH, FGF23, 25(OH)D3, Klotho, and Ca every week for 12 weeks every patient. Causal inference, a widely used process of concluding a causal connection, was adopted to establish the regulatory networks of phosphorus metabolism within different PTH levels.

Results: The networks show that when PTH<600 ng/l, FGF23 can stimulate the increase of serum Pi, Ca, and PTH, in turn, serum Ca and Pi can also stimulate the increase of FGF23. When PTH>600 ng/l, FGF23 becomes the stimulator of only serum Ca, and serum Pi has a positive causal effect on PTH, besides, the rise of PTH increases serum Pi level, too. So, serum Pi is affected by FGF23 when PTH<600 ng/l and by PTH when PTH>600 ng/l. Since FGF23 promotes the increase of PTH when PTH<600 ng/l, FGF23 becomes the key factor in disorders of phosphate metabolisms. The figures also shows that Klotho and 25(OH)D3 may be not important in the therapy of hyperphosphatemia.



Conclusions: Reducing FGF23 levels might contribute to the control of phosphorus.

PUB517

Evolution of Renal Calcium Excretion Throughout Chronic Kidney Disease *Carmen Gonzalez Corvillo,¹ Paula Batalha-Caetano,¹ Silvia Ros-Ruiz,² Fernando Vallejo Carrión,³ José G. Hervás,⁴ Mercedes Salgueira Lazo.¹ ¹Nephrology, Hospitales Virgen Macarena-Rocio, Sevilla, Spain; ²Nephrology, Hospital Regional, Malaga, Spain; ³Nephrology, Hospital Puerto Real, Cadiz, Spain; ⁴Nephrology, Universidad, Granada, Spain.*

Background: Chronic kidney disease(CKD)patients have a normal serum calcium(Ca) concentration until the end of renal disease(ESRD).The decrease of VitaminD levels,and that a percentage of patients develops hypocalcemia at ESRD,lead us to think that our patients have a negative Ca balance,this could justify the treatment with Ca supplements. Objective:analyze renal Ca excretion at different stages of CKD and the effect of the treatments.

Methods: Observational multicenter,retrospective and transversal study,with the participation of 5hospitals.63patients were included,in different stages of the disease(66,7%men,mean age 66years).None on renal replacement therapy. Variables:blood,urine analysis and treatment.The sample was stratified by stage of the disease and urine Ca(>or<100 mg/d).

Results: Sample: 6,3%CKD1, 4,8%CKD2, 28,6%CKD3, 38,1%CKD4 and 22,2%CKD5. Mean serum Ca: 9,47 mg/dl, mean serum phosphate (P): 3,77mg/dl. PTH level 174pg/dl, VitD 27ng/ml. Mean Ca excretion: 126mg/day. Mean P excretion: 477mg/d. 47% was on Ca based binders, 22,2% on calcifediol, 12,7% on calcitriol and 28,6% on paricalcitol. 70% of the sample had Ca excretion <100mg/d. When classifying by stages of the disease, increases the amount of patients with Ca excretion <100 mg/d (CKD1 25%, CKD2 50%, CKD3 50%, CKD4 80%, CKD5 83%), decreasing the mean Ca excretion. The subgroup of patients with lower Ca excretion had a higher PTH level (155 vs 111pg/dl) $p=0,05$. 94% of patients treated with Ca based binders had a Ca excretion <100mg/d with no difference in serum Ca. Patients on calcifediol, paricalcitol or calcitriol had lower Ca excretion than those without treatment.

Conclusions: According to our results, patients within CKD show a decrease in renal Ca excretion that become exacerbated as the renal disease progresses. Supplementation with hypercalcemic drugs is not balanced out with the expected increase of renal Ca excretion. Therefore, we think that CKD patients are exposed to a chronic Ca overload, sometimes underestimated, with the resulting negative impact in morbidity and mortality.

PUB518

Effect of Parathyroid Hormone on Serum Magnesium Level: The Neglected Relationship in Hemodialysis Patients with Secondary Hyperparathyroidism
Bing Tang, Li Fang, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Chronic kidney disease–mineral and bone disorder (CKD–MBD) is an important complication in patients with end-stage kidney disease which is associated with cardiovascular morbidity and mortality. Since recent studies have shown that serum magnesium play an important role in secondary hyperparathyroidism, vascular calcification and cardiovascular mortality, the interest on magnesium (Mg) has grown.

Methods: This cross-sectional study was conducted on 111 patients with end-stage renal disease on maintenance hemodialysis who was hospitalized for secondary hyperparathyroidism. The interventional study was conducted on 23 patients underwent total parathyroidectomy.

Results: In our study, hypermagnesaemia (>2.5mg/dl) occurs in up to 44% of cases and hypomagnesemia did not present. No significant correlations were found between serum magnesium and parathyroid hormone ($r=-0,143$, $p=0,134$). Correlation analysis and logistic regression analysis suggested that the derangement of magnesium homeostasis was correlated with the derangement of calcium/phosphate homeostasis. After parathyroidectomy, serum magnesium levels dropped immediately and reached the lowest level at one day after surgery; however, it gradually restored three days later. The changes of serum magnesium after surgery was positive correlated with the changes of serum phosphate ($r=0,558$, $p=0,003$).

Conclusions: The effect of PTH on magnesium metabolism could not be neglected, especially in hemodialysis patients with secondary hyperparathyroidism. The role of magnesium metabolism and therapeutic strategies to achieve optimum serum magnesium levels in CKD-MBD should take into account the varying stages of disease development.

Funding: Government Support - Non-U.S.

PUB519

Calciophylaxis in Patient with Chronic Renal Disease Not Dialytic and Multiple Myeloma
Patricia Junqueira Freitas, Aline Lourenco Baptista, Clovis Antonio Lopes Pinto, Joubert Araujo Alves, Pedro Caruso, Benedito Jorge Pereira, Fernanda Lemos Moura, Marina Harume Imanishe, Luis Andre Andrade, Germana Alves Brito. *Nephrology, AC CAMARGO, Sao Paulo, Brazil.*

Background: Calciophylaxis, also known as calcifying uremic arteriopathy, is a rare medical condition, which is normally diagnosed in patients with terminal CKD who are already in renal replacement therapy (RRT). Objective: report the presence of calciophylaxis in CKD, in patient with oncologic disease.

Methods: Female patient, 71 years old, caucasian, conducted to AC Camargo Hospital for etiologic investigation of injuries in lower limbs associated with renal failure, hypercalcemia, anemia and asthenia. Has history of hypertension and obesity. Physical examination: poor general state, dyspneic, respiratory and cardiovascular systems without changes, ulcerated lesions of necrotic center in lower limbs (FIGURE). Laboratory tests: Creatinine 8.8 mg/dL; Urea 169 mg/dL; K 4.1 mEq/L; HCO₃: 16.3 mmol/L; pH 7.29; Cai: 1:58 mmol/L; PTH: 295 pg/ml; : 3.6mg/dL; total Ca: 12,9mg/dL; albumin 1.8g/dL. Renal US: regular. Parathyroid US: regular. Held biopsy (Bx) of skin: chronic inflammatory process sharpened with necrosis and calcification dystrophic in dermis and hypodermis. Bx of Bone marrow: neoplastic infiltration of plasma cells. The patient was transferred to ICU due septic shock of cutaneous focus, performed antibiotic therapy, hemodialysis (HD) with Calcium (Ca) 2.5, initiated sodium thiosulfate three times a week and cinacalcet, presenting improvement of the injuries.



Conclusions: The calciophylaxis is a complex clinical entity and pathogenesis not fully elucidated, what makes the treatment still not uniform. It is characterized by dermal ischemic necrosis, of acute and progressive installation. It must be paid attention to its presence even in non dialytic stages of CKD as happened in the described case.

PUB520

Calcium Binders Are They All Equal? Comparison Calcium Acetate (CA) versus Carbonate Calcium (CC) in CKD 5D: Multicentric Study
Philippe Brunet,¹ David Attaf,² Laurent Juillard,³ *¹Nephrology - Dialyse, Conception Hospital, Marseille, Bouches-du-Rhône, France; ²Dialyse, Fresenius, Paris, IDF, France; ³Nephrology - Dialysis, Edouard Herriot Hospital, Lyon, Rhone, France.*

Background: CA's phosphate binder is available since 2010 in France. A monocentric study indicates that CA is equivalent to CC based on phosphatemia reduction **while reducing calcium intake by 60%**. This study compare CA to CC in different dialysis centers i.e different CKD MBD protocols.

Methods: 28 hemodialysis centers are involved. CC is switched to CA at M₀ with 6 months follow up (M₀-M₆). We compared M₀'s biologic datas with M₆'s datas.

Results: 293 patients (70+/-14 y) in 28 centers. At M₀ CA dosage was 3.8 +/- 2 pills/day. Demographic characteristics are consistent with our National French registry. At M₆ mineral values are similar to M₀: Ph mM (1,54 +/- 0,55 vs 1,52 +/- 0,65, NS), Ca mM (2,23 +/- 0,17 vs 2,21 +/- 0,15, NS), PTH pg/ml (221 +/- 204 vs 262 +/- 217, NS), Vit. D nM (75 +/- 32 vs 79 +/- 24, NS), % pts with non calcium binder (43 vs 49, NS), % pts w. Ca > 2,6 mM (2 vs 1, NS), % pts w. Ph > 1,5 mM (39 vs 38, NS). **The only difference is related to a decrease of Calcium Intake (g/d) from M₀ (1,51 +/- 1,13) to M₆ (0,63 +/- 0,31, P<0,05).**

Conclusions: At M₆ Calcium intake is reduced by 57% vs M₀ while Ph. is similar vs M₀. Mean serum calcium is not altered. The frequency of Ca > 2,60 mM and Ph > 1,5 mM are not modified at M₆/M₀. A M₆ PTH and 25-OH vit D are stable. **This multicenter study (ie different therapeutic strategies) confirm that CA is equivalent to CC with a reduced Ca Intake.**

Funding: Private Foundation Support

PUB521

Hemodynamic Changes in Maintenance Hemodialysis Patients with Hypotension After Parathyroidectomy
Meijuan Meng, Bing Tang, Hong Ye, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Parathyroidectomy (PTX) is applied to treat secondary hyperparathyroidism in hemodialysis patients. Some patients suffered from hypotension after PTX although hypocalcemia was corrected. The aim of this study was to demonstrate the hemodynamic changes in hemodialysis patients after PTX.

Methods: Twelve patients were included in this study. Among them 4 have hypotension after PTX (Group 1) and the other have their blood pressure remained after PTX (Group 2). Before PTX, systolic blood pressures (SBP) of all the 12 patients were above 90 mmHg. Noninvasive hemodynamic evaluation was performed before, during and after dialysis.

Results: Comparing with group 2, cardiac index (CI) was higher (P=0.252) while systemic vascular resistance index (SVRI) was lower (P=0.05) in group 1. The mean thoracic fluid capacity (TFC) of the two groups were similar (P=0.424) before dialysis. Serum Ca, PTH, ALP, ventricular ejection fraction and vascular calcification score of thoracic aorta, abdominal aorta and heart valve before PTX, as well as the weight of the removed parathyroid glands, serum Ca, ALP, hemoglobin after PTX of the patients were determined. No statistical differences were found. However, the phosphorus level was lower in group 1 both before and after PTX. CI, SVRI and TFC were similar in both groups during hemodialysis.

Conclusions: Patients with hypotension after PTX have a lower systemic vascular resistance index and a higher cardiac index, which might be associated with serum phosphorus level.

Funding: Government Support - Non-U.S.

PUB522

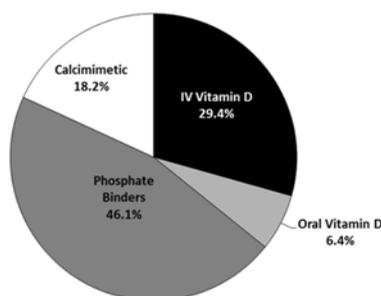
Cost of Medications Used in the Management of Secondary Hyperparathyroidism (SHPT) in Patients with End Stage Renal Disease (ESRD) Mark E. Bensink,¹ Leigh Darryl Quarles,² Vasily Belozeroff,¹ Kerry Cooper,¹ Jonathan D. Campbell,³ ¹Amgen Inc., Thousand Oaks, CA; ²Univ of Tennessee, Memphis, TN; ³Univ of Colorado, Aurora, CO.

Background: Management of SHPT associated with ESRD is complex, typically requiring combinations of medications. Eighty-two percent of the ESRD population is covered by Medicare with detailed drug expenditures reported annually by the US Renal Data System. For the remaining 18% covered by commercial health plans, drug expenditure information is unknown. The purpose of this study is to estimate the cost of medications used in the management of SHPT in ESRD patients from the US commercial health plan perspective.

Methods: Economic analysis with one-year time horizon to estimate per-member-per-month (PMPM) cost for SHPT related medications: calcium and non-calcium-based phosphate binders, calcitriol or active vitamin D analogs, and calcimimetics. Input parameters include: prevalence of ESRD in commercial health plans (MarketScan®); medication utilization and non-adherence (IMS Health for oral medications and Outcomes Plus for intravenous [IV] medications); and medication wholesale acquisition costs (WAC) (AnalySource.com) with one-way sensitivity analysis.

Results: The total PMPM (2014 US Dollars) cost of SHPT-related medications is \$0.34: cinacalcet \$0.06, phosphate binders \$0.16, oral vitamin D \$0.02, and IV vitamin D \$0.10.

Figure 1. Total PMPM Cost Breakdown



Results are most sensitive to variation in ESRD prevalence and cinacalcet WAC parameters.

Conclusions: Results indicate that the collective cost of medications for the management of SHPT in commercial health plans is substantial with the cost of cinacalcet being lower compared to phosphate binders and IV vitamin D, but higher compared to oral vitamin D.

Funding: Pharmaceutical Company Support - Amgen Inc.

PUB523

Medullar Compression by Bone Tumor: Case Report Cynthia Sobral Vieira, Nicole D.T. Carvalho. *Nephrology Unit- Clinefro, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.*

Background: The presentation of vertebral tumors may have different kinds of manifestation. They can mimic neoplastic, inflammatory and congenital diseases. The following report is about a patient with a lytic bone lesion in the thoracic spine causing medullar compression symptoms.

Methods: A 66 years old masculine patient, with chronic renal disease in hemodialysis for 5 years, non-adherent to treatment or diet, had his levels of phosphor, calcium/phosphor, alkaline phosphatase and parathyroid hormone (PTH) elevated in the last year. He did not take the medication prescription: Calcitriol and Sevelamer. The patient came to the ER of a general hospital referring constipation and abdominal distention. During the hospitalization he started to refer paresthesia in inferior members with progressive march dysfunction. The neurological exam showed ataxic/calcaneal gait and strength reduction (4+/5+) in the inferior members.

Results: At first, an angiotomography study of the mesenteric vessels were made, thinking of the possibility of mesenteric ischemia, but the exam showed multiple lytic lesions in the corps of lumbar vertebrae and in the hipbones, mimicking secondary implants. The spine MRI demonstrated one lytic bone lesion at the level of D6 and D7 causing medullar compression. The bone scintigraphy was suggestive of a metabolic bone disease and the parathyroid scintigraphy showed a hyperfunctioning tissue, in the parathyroid left pole. The patient was submitted to a compressive laminectomy, the biopsy revealed a Brown Tumor. Then, it was indicated a parathyroidectomy. The pathological result showed no evidence of malign disease. Nowadays, the patient is still in hemodialysis, receiving calcium and under physiotherapy to recover muscle strength, already walking.

Conclusions: Brown Tumor or osteoclastoma is a rare bone lesion, an incidence of 1,4 to 13% in chronic renal patient due to a secondary hyperparathyroidism and less than 5% in primary hyperparathyroidism. It is more frequent in women. The vertebra involvement is uncommon. This case report has its importance for calling attention to importance to include brown tumor as a differential diagnosis in compressive spines lesions especially in chronic renal patients.

PUB524

Rescue-Therapy with Lanthanum-Carbonate (LC) in Uncontrolled Hyperphosphoremia in Dialysis Nicola Giotta, Angela maria Marino. *Dept of Medicine, Nephrology and Dialysis Unit, Cardinal Massaia Hospital, Asti, AT, Italy.*

Background: Control of hyperphosphatemia in hemodialysis provides an approach based on changes in diet, dialysis efficiency improvement, and use of phosphate binders. The latter, however, in some patients do not prove effective, conditioning the indirect increase of mortality and morbidity of the subject on dialysis. The objective of this study was to evaluate the difference in efficacy of a regimen of lanthanum carbonate plus standard therapy (LTS) compared to standard therapy alone (TS) in the treatment of patients with persistent hyperphosphatemia, as rescue-therapy.

Methods: We conducted an observational study of data on consecutive patients in hemodialysis who have presented more than four phosphorus values greater than 6 mg/dL in three months. Patients treated with TS, have varied therapeutic scheme introducing LC. Patients treated with sevelamer have outstanding this therapy and were treated with LC. The data analysis has been done considering a retrospective phase (FR) of three months and a prospective phase (FP) of six months, for each subject analyzing the effectiveness of therapy before and after enrollment.

Results: In a cohort of 163 patients on hemodialysis, we have selected for the study, 14 patients who had a mean age of about 65 years and length of dialysis than 6 years. The combination of LC plus TS produced a significant increase in the proportion of patients achieving the therapeutic targets as defined by the K/DOQI Guidelines. Reduction of 2.12 mg / dL (-32.7%) than the average of the P phase prospective (4.55 mg/dL) than the retrospective phase (6.77 mg/dL), was statistically significant (p <0.001), is associated with the reduction of 19.21 mg2/dl2 (-32.9%) of the average value of CaxP in the prospective phase (39.07 mg2/dl2) compared to the retrospective phase (58.28 mg2/dl2), also statistically significant (p <0.001). The patients at target at the end of FP accounted for 92.31% for P and 100% for the CaxP, respectively vs. the 7.14% and 50% of FR.

Conclusions: The introduction of the LC-as rescue therapy in the treatment of hemodialysis patients with uncontrolled hyperphosphatemia resulted very effective allowing more easily reach the therapeutic objectives.

PUB525

Glucocorticoid-Induced Osteoporosis in Renal Patients Gabrielle Goldet,¹ George Greenhall,² Alan D. Salama.² ¹Basildon and Thurrock Univ Hospital; ²Royal Free Hospital, London; ³Royal Free Hospital, London.

Background: Glucocorticoid-induced osteoporosis (GIO) is associated with severe morbidity due to fragility fractures as well traumatic fractures and 30-50% of patients on long term steroids are affected by GIO. GIO is relevant in the renal context as steroids are widely used to treat renal disease and as part of immunosuppression in transplant. Also, renal patients are already at higher risk of fractures in association with renal bone disease.

Methods: We designed and undertook an audit to assess screening and management of GIO in nephrology outpatients in a university hospital in London, using national guidelines as a benchmark for our performance. We then presented the results at a local meeting, produced posters and leaflets on GIO to be placed in the outpatient waiting area for patients so as to raise awareness of this issue and provided a simple algorithm to be followed by clinicians in all the clinic rooms. We then re-audited after 6 months.

Results: 100 patients were audited in each audit cycle. Measures audited were a) whether all patients over 65 were treated with bone-sparing agents (BSA); b) whether all patients with documented fragility fracture were treated with BSA; c) whether all patients under 65 without fragility fracture underwent DXA scan; d) whether all patients with T-score below -2.5 were treated with BSA; e) whether all patients with T-score 0 to -1.5 underwent repeat DXA within 3 years; f) whether BSA was prescribed for all patients where indicated; g) whether all patients are managed according to national guideline (cycle 1: 29%; cycle 2: 41%). See table for breakdown of results.

Audit measure	Audit 1 percentage (%)	Audit 2 proportion of patients meeting target	Audit 2 percentage (%)	Audit 2 proportion of patients meeting target
a	11	1/9	9	1/11
b	0	0/0	0/1	0
c	56	48/86	61	50/82
d	13	1/8	43	3/7
e	40	8/20	75	15/20
f	19	5/26	26	8/31
g	29	29/100	41	41/100

Conclusions: Our intervention has improved performance as measured against national guidelines, though the rate of GIO screening remains low. Many patients could potentially benefit from bone protection, though larger studies would be needed to demonstrate an effect on fracture incidence.

Funding: Government Support - Non-U.S.

PUB526

The Kidney Stone and Increased Water Intake Trial in Steel Workers: Results from a Pilot Study Hakam Gharbi,¹ Yair Lotan,² Jodi Antonelli,² Inmaculada Buendia Jimenez,¹ Allison Ahrens Beaver,¹ Aphrih Dennis-Barrie,¹ Dendra K. Von merveldt,¹ Suzie Carter,¹ Adam B. Cohen,¹ John Poindexter,³ Orson W. Moe,³ Margaret S. Pearle.² ¹Danone Research, Palaiseau, France; ²Urology, Univ of Texas Southern Medical Center, Dallas, TX; ³Mineral Metabolism, Univ of Texas Southern Medical Center, Dallas, TX.

Background: Preventing dehydration in subjects at risk may provide a means of primary prevention of kidney stones. The purpose of this pilot study was to assess the hydration status of an at-risk group of steel plant workers based on end-of-shift (‘post-shift’) spot urine osmolality and 24-hour urinary stone risk parameters.

Methods: 100 volunteers were recruited from Gerdaul Midlothian steel mill in Texas on 11/14/14 and 12/5/14. Clinical data was recorded and a post-shift spot urine sample was obtained for measurement of urine osmolality. In addition, participants were invited to submit a 24-hr urine sample within 4 weeks of enrollment.

Results: Mean age was 41 and 95% were men. The majority of subjects were white (75%), followed by 10% Hispanic and 9% Black. Mean body mass index was 30.1 kg/m² and overall 16% had past history of stone disease. Mean post-shift urine spot osmolality was 704.5 mOsm (169-1165 mOsm) and was >800 mOsm and >700 mOsm in 39% and 57%, respectively. Among 59 24-hour urines samples, mean volume was 1.89 ± 0.92 l/day, with 56% <2 liters and 17% <1 liter. Elevated levels of urinary analytes were found in 29% of subjects for calcium (>250mg/TV), 39% for uric acid (>700 mg/TV), 25% for oxalate (>45mg/TV) and 50% for sodium (>200 meq/TV).

Conclusions: The prevalence of stone disease in this population of steel workers is higher than the published prevalence of stone disease in the general population. A significant number of workers had concentrated post-shift and 24-hour urines and elevated levels of urinary analytes.

PUB527

Chronic Renal Pain in Medullary Sponge Kidney Giovanni Gambaro,¹ Jackie Hirsch,² Rocco Baccaro,¹ Nicole Topilow,² Matteo Bargagli,¹ David S. Goldfarb,² Pietro Manuel Ferraro.¹ ¹Nephrology, Catholic University, Rome, Italy; ²NY Univ, School of Medicine, New York, NY.

Background: MSK usually occurs with recurrent stones; less frequently it is asymptomatic; very rarely the main manifestation is severe chronic flank pain. Often these pts are accused of seeking pain medications. Because of the rarity of such a presentation it is not known if pain is due to intense lithogenic activity or is independent of it, something like a form of the ‘loin pain hematuria syndrome’. Three Facebook support groups exist for North American patients with MSK and chronic pain. Their cooperation allowed us to investigate chronic pain in MSK.

Methods: An ad hoc questionnaire and the Brief Pain Inventory were administered through a dedicated web site; 92 patients (89 females) participated after verification of the diagnosis of MSK (imaging and diagnosis certified by a nephrologist or urologist).

Results: Mean age of patients was 39.8y, (range 24-66). Age at onset of manifestations and MSK diagnosis were 23y (4-47) and 31y (7-57), respectively. Manifestations at onset were: flank pain (31%), reno-ureteral colic (RUC) (26%), hematuria (19%), cystitis (14%), pyelonephritis (10%). 71% of pts have daily pain, 76.5% have taken painkillers in the previous week and 69.1% needed them at the time of questionnaire administration; 58% take them ³1 time/day. The strong pain (5.4 in a scale from 0 to 10), jeopardizes general activities, mood and sleep. Only 4.6% of pts have RUC like pain; in 52.9% it is non-radiating flank pain with manifestations of possible UTI or stone passage (painful micturition, urgency, frequent urination, hematuria, fever); in 42.5% it is non-radiating lumbar pain without other manifestations (however only in 3 cases the pain was a unilateral flank pain). Pain is frequently associated with stone (67%) or sand passage (46%), hydronephrosis (42%), hematuria (42.4%).

Conclusions: Although in these MSK pts the chronic pain -that dominates the clinical manifestations - is usually associated with some of the typical symptoms of stone passage, in a fraction of pts this is not the case and pain is not associated with lithogenic activity. The etiology of this pain syndrome remains uncertain and merits investigation.

Funding: Government Support - Non-U.S.

PUB528

Difference in Vitamin D Level Between Older and Younger Kidney Transplant Recipients Mohamed Amin Elesnawi, Abdullah Hamad, Fadwa S. Al-Ali. Nephrology, Fahd Bin Jasim Kidney Center, Hamad General Hospital, Doha, Qatar.

Background: Vitamin D deficiency is more common in older than younger people. In kidney transplant recipients, vitamin D deficiency has a high prevalence of up to 80 % according to recent studies. We compared vitamin D status in older versus younger patients with kidney transplant.

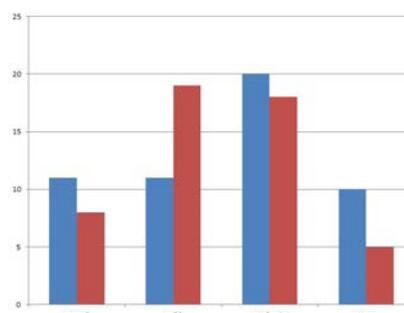
Methods: We reviewed all available record of kidney transplant recipients that came to our clinic at Hamad General Hospital in Qatar between September 1st 2013 and March 1st 2014. We recorded background data and laboratory tests. Patients divided into 2 groups younger and older (below and above 60 years old respectively). All patients were receiving vitamin D supplement.

Results: 102 patients were included. 52 patients in the younger group and 50 patients in the older. Age was 68.8±/5.9 years in the older versus 41.9±/10.4 years in the younger

group. Table (1) compare laboratory values between the two groups. Vitamin D status was classified(normal above 30, mild 20-29, moderate 10-19 and severe below 10 ng/mL) figure (1).

	Younger (<60 Years) n=52	Older (>60 years) n=50
Male/Female	25/27	42/8
vitamin d	21.2+/-16.8 ng/mL	21+/-9.93 ng/mL
calcium	2.3+/-0.16 mmol/L	2.27+/-0.12 mmol/L
phosphorus	1.14+/-0.29 mmol/L	1.22+/-0.2 mmol/L
alkaline phosphatase	90+/-39.2 u/L	74.1+/-41 u/L
intact parathyroid hormone	126+/-142 pg/mL	140.8+/-223 pg/mL

Vitamin D status in elderly versus young kidney transplant patients



Conclusions: In a comparative study, we found that older transplant recipient group had more male patients (pValue<0.05), lower alkaline phosphatase and higher intact parathyroid hormone (not statistically significant) but similar vitamin D, calcium and phosphorus level. There was a trend towards milder vitamin D deficiency in the older group that could be due to better compliance with vitamin D supplement. Despite vitamin D supplement protocol and long sunny days in Qatar we still found high rate of vitamin D deficiency in transplant recipients (81.4%).

PUB529

Efficacy of Low Dose, Alternate Day Cinacalcet for Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients: A Randomized Controlled Trial Pongsathorn Gojaseeni, Dolnapa Pattarathitinan, Kolasorn Pakchotanon, Anutra Chittinandana. Medicine, Bhumibol Adulyadej Hospital, Royal Thai Air Force, Bangkok, Thailand.

Background: Secondary hyperparathyroidism (SHPT) is common in hemodialysis patients and has been associated with increased mortality. Cinacalcet, a modulator of calcium-sensing receptor, effectively reduced serum parathyroid hormone (PTH) in clinical studies. We tested whether prescription of low dose, alternate day cinacalcet could be an option for treatment of SHPT.

Methods: An open-labeled, randomized controlled trial enrolled hemodialysis patients with severe secondary hyperparathyroidism (intact PTH > 585 pg/ml). Patients were randomized to received low-dose cinacalcet (25 mg alternate day) or standard-dose (25 mg daily) for 16 weeks. At 8 weeks, doses of cinacalcet could be increased to achieve KDIGO PTH target of less than 585 pg/ml. The primary outcome was the difference in percentage of patients achieving KDIGO target at 16 weeks. The changes of serum iPTH, other biochemical data were also tested.

Results: Between July 2014 and January 2015, a total of 30 hemodialysis patients (15 females, 15 males) were randomly assigned to a treatment group: 16 to low-dose and 14 to standard-dose. Baseline iPTH in low-dose and standard-dose group was 1,065.9 ± 477.7 and 1,211 ± 466.5 pg/ml respectively (p = 0.409). During study period, 4 patients (2 from each group) were dropout from study due to adverse events. Intention to treat analysis showing that the percentage of patients who achieving KDIGO PTH target was not different (38.5% in low-dose group compared with 30.8% in standard-dose group, p = 1.0). Serum iPTH reduction during 16 weeks of study period in low-dose and standard-dose group was 253.5 ± 316.1 and 330.6 ± 698.2 respectively (p = 0.731). The adverse events were not different between both groups except hypocalcemia that tend to be higher in standard-dose (38.5% vs 13.3%, p = 0.274).

Conclusions: Among patients with SHPT, cinacalcet 25 mg alternate day may be sufficient effectively decrease serum iPTH levels with low incidence of hypocalcemia. The role of low dose cinacalcet in SHPT should be determined in large-scale, adequately powered randomized controlled trials.

Funding: Government Support - Non-U.S.

PUB530

Parathormone Stability in Hemodialyzed Patients: Comparison on Non-Centrifuged EDTA and Serum Samples with 2nd and 3rd Generation Assays Marie Dohet,¹ Pierre Delanaye,² Etienne Cavalier.¹ ¹Clinical Chemistry, Univ of Liege, CHU Sart-Tilman, Liege, Belgium; ²Nephrology, Univ of Liege, CHU Sart-Tilman, Liege, Belgium.

Background: PTH stability is of importance. Many studies have shown divergent results between EDTA and serum, mainly linked to differences in protocols or cut-offs used to decipher whether PTH remained stable or not. No studies have yet compared PTH as measured by 2nd and 3rd generation assays on the same samples in hemodialyzed (HD) patients.

Methods: Five pairs of samples (EDTA and gel tubes) were obtained in 10 HD patients before session. One pair was centrifuged and run immediately to establish the "T0". Two pairs were kept at +4°C and +25°C. They were centrifuged after 4 and 18 hours. Supernatant was kept at -80°C for one week. Then, all samples were measured in a single batch, on Roche Cobas and DiaSorin XL 2nd and 3rd generation PTH assays. Samples were considered as stable if 90% of subjects had a decrease lower than a total change limit (TCL) that takes both analytical and biological variability into consideration. All determinations were run in duplicates.

Results: At T0, no difference was observed between plasma and serum for any of the methods. PTH decreased in all samples and degradation was the same with 2nd or 3rd generation assays, whatever the method used. Percentages of decrease were systematically lower in EDTA plasma compared to serum and none of our subjects presented a decrease higher than the TCL with EDTA plasma. In serum, PTH was not considered as stable, but only when kept at 25°C for 18 hours.

Conclusions: PTH stability is of paramount importance for correct interpretation of the results. Many studies have tried to evaluate this stability but are not free from criticisms, mainly due to a poorly defined T0 and questionable acceptance limits. In this study, we used an unfrozen T0 and decision limits based on analytical and biological variations. Moreover, we tested 2nd and 3rd generation PTH on two automated platforms. Our results show that, if PTH is basically more stable in EDTA plasma than in serum, this advantage is only clinically significant when samples are stored for a long period (18h) at +25°C.

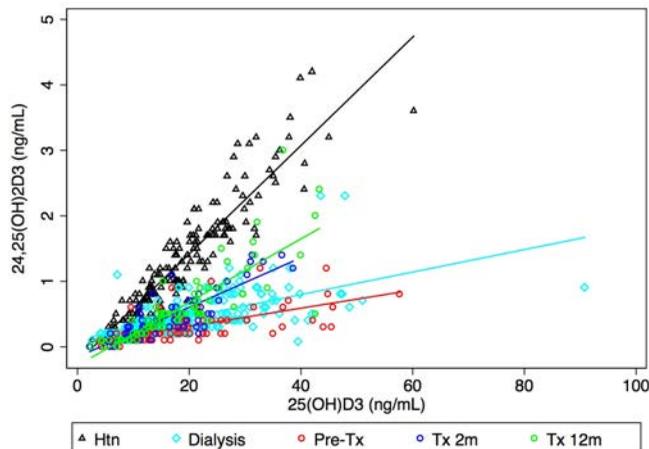
PUB531

Vitamin D Metabolism Is Incompletely Restored After Kidney Transplantation Thomas F. Hiemstra,² Stephen M.S. Ting,¹ Ragada El-Damanawi,² Kenneth Lim,³ Martin Kaufmann,⁴ Glenville Jones,⁴ Daniel Zehnder.¹ ¹Univ of Warwick, United Kingdom; ²Univ of Cambridge, United Kingdom; ³Massachusetts General Hospital, Boston; ⁴Queen's Univ, Kingston, Canada.

Background: Vitamin D deficiency is widely reported in patients with renal impairment and is associated with adverse outcomes. The extent and rate of recovery of vitamin D metabolism after kidney transplantation is uncertain.

Methods: We enrolled 175 dialysis patients (HD) listed for kidney transplantation, and 85 hypertensive but otherwise healthy controls (HTN). We determined blood markers of mineral metabolism including intact FGF23 and vitamin D metabolites at entry (or immediately pre-transplantation), 2 and 12 months. As a surrogate for vitamin D deficiency, we assessed the 25(OH)D3: 24,25(OH)2D3 ratio (D-ratio, normal 5-25).

Results: Of 175 dialysis patients, 76 were transplanted (TxR) during the study. TxR were younger with a lower BMI than controls. FGF23 was higher in HD patients than HTN at baseline, but normalised after 12 months (p=0.13). At baseline, vitamin D insufficiency (defined as 25(OH)D <30 ng/mL) was present in 82% of subjects and did not differ between groups. However, vitamin D deficiency (defined as 25(OH)D <10 ng/mL) was more common in dialysis (15% versus 4%, p=0.49). The baseline D-ratio was higher in HD (48, IQR 27-67) than in HTN (16, IQR 14-18, p<0.0001) patients. Transplantation resulted in significant reduction in D-ratio after 2 and 12 months compared to HD (p=0.0008 and p=0.005 respectively). The slope of D-ratio vs 25(OH)D3 increased after transplantation, but remained lower than for HTN controls, suggesting reduced expression or activity of the catabolic CYP24A1 (25-OH-D3-24-hydroxylase) in kidney failure.



Conclusions: Vitamin D insufficiency is highly prevalent in patients on dialysis and in hypertensive controls, and only partially resolves after kidney transplantation.

PUB532

Low Time-Averaged Serum Intact Parathyroid Hormone Level Is an Independent Risk Factor for Overall Mortality and Major Adverse Cardiac and Cerebrovascular Events in Incident Dialysis Patients Sul A Lee,¹ Mi Jung Lee,¹ Kyoung Sook Park,¹ Jong Hyun Jhee,¹ Jae Eun Um,² Meiyun Wu,² Hyung Jung Oh,¹ Jung Tak Park,¹ Seung Hyeok Han,¹ Shin-Wook Kang,^{1,2} Tae-Hyun Yoo.¹ ¹Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; ²Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Chronic kidney disease-mineral bone disorder (CKD-MBD) is known as a major risk factor for cardiovascular disease in end-stage renal disease (ESRD) patients. CKD-MBD is classified into low turnover and high turnover bone disease according to the bone dynamics, both of which are related with vascular calcification in ESRD. To evaluate the prognostic value of abnormal serum parathyroid hormone (PTH) levels on ESRD patients, we investigated the effects of time-averaged serum intact PTH (TA-iPTH) levels on overall mortality and major adverse cardiac and cerebrovascular events (MACCEs) in incident dialysis patients.

Methods: In this prospective observational study, 413 patients who started dialysis between January 2005 and September 2010 at Yonsei University Health System were enrolled. Patients were divided into three groups according to TA-iPTH levels during the 12 months after initiation of dialysis (group 1: <65pg/ml, group 2: 65 to 300 pg/ml, group 3: >300pg/ml). Cox regression analysis was performed to determine the prognostic value of TA-iPTH on overall mortality and MACCEs.

Results: The mean age was 56.5±14.5 years and 222 patients (53.8%) were male. During a median follow-up of 50.8 months, 49 patients (11.9%) were dead and MACCEs were occurred in 55 patients (13.3%). Multivariate Cox regression analysis demonstrated that low TA-iPTH level was an independent risk factor for both overall mortality [group 2 as reference; group 1, hazard ratio (HR)=2.08, 95% confidence interval (CI)=1.12-3.85, P=0.02] and MACCEs (HR=1.88, 95% CI=1.04-3.40, P=0.04) in incident dialysis patients after adjusting confounding factors.

Conclusions: This study demonstrates that low TA-iPTH is an independent risk factor for overall mortality and MACCEs in incident dialysis patients.

PUB533

Combined Analysis of Hypercalcemia and PTH Levels as Clue to Unveil Persistent Transplant Hyperparathyroidism Melani Custodio,^{1,2} Maria Julia C. L. N. Araujo,^{1,2} Wagner Dominguez,¹ Rosa M.A. Moyses,^{1,3} Elias David-Neto,¹ Vanda Jorgetti.¹ ¹Nephrology Div, Univ de Sao Paulo; ²Transplant Unit, Univ de Sao Paulo; ³UNINOVE, Sao Paulo, Brazil.

Background: Mineral and bone metabolism disorders in chronic kidney disease (CKD-MBD) are not always corrected after kidney transplantation (TxR). The persistence of hyperparathyroidism may have a negative impact on patient and graft outcome. Our objective was to evaluate the evolution off CKD-MBD and the incidence of hyperparathyroidism after 12 months of TxR.

Methods: In this study, we included all consecutive patients submitted to a TxR during the period between Jan 2010 and Dec 2014 in a University based center. We excluded patients with a PTH <300 pg/ml before TxR, multi-organ transplants, patients with an eGFR<30mL/min and those who underwent parathyroidectomy after TxR. Twelve-month eGFR, plasma levels of total calcium (Ca), phosphorus (P), alkaline phosphatase (AlkP), magnesium (Mg), parathormone (PTH), and 25-hydroxy vitamin D (25-OH vit D) were compared to baseline values. A PTH >100pg/mL and a total calcium >10.2mg/dL were considered abnormal. We defined high PTH, with or without hypercalcemia as the primary endpoints for the analysis.

Results: During the observation period, 408 patients were evaluated. There was a significant increase in eGFR and in calcium levels 12 months after the TxR. Compared to the baseline, PTH, AlkP, and P significantly decreased. 25-OH Vit D did not change during the period. Fifteen percent of patients presented both PTH and Ca above the reference levels, while 37% presented isolated high PTH and 8% hypercalcemia only. Multivariate analysis disclosed that post-TxR hyperparathyroidism was dependent on pre-transplant PTH (OR 1.001; CI 95%: 1.001-1.002) and Ca (OR 1.233; CI 95%: 1.036-1.468).

Conclusions: Monitoring Ca and PTH before and after TxR may be important to detect patients at high risk of persistent hyperparathyroidism, and to identify patients in need of treatment to prevent its complications.

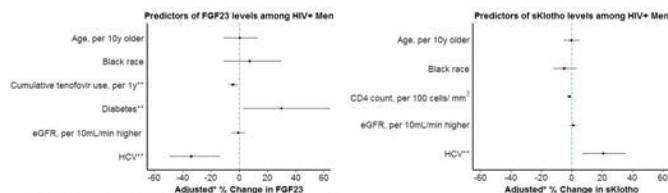
PUB534

Predictors of FGF23 and Soluble Klotho in HIV Infection Ruibin Wang,¹ Michael Shlipak,² Joachim H. Ix,³ Michelle M. Estrella.¹ ¹Johns Hopkins Univ; ²UCSF; ³UCSD.

Background: In the general population, FGF23 and its co-receptor, soluble klotho (sKlotho), have been implicated in the aging process. HIV+ individuals are at higher risk of age-related comorbidities compared with HIV- persons. We evaluated whether FGF23 and sKlotho levels differed by HIV status and determined clinical factors associated with each hormone in HIV+ men.

Methods: 384 HIV+ and 225 HIV- men in the Multicenter AIDS Cohort Study (MACS) were randomly selected for FGF23 and sKlotho measurements from samples stored in 2008-2010. We compared FGF23 and sKlotho levels by HIV status, adjusted for age and race. Multivariable linear regression models were used to determine predictors of FGF23 and sKlotho levels among HIV+ men.

Results: Mean age was 53y; 34% were black; and median eGFR was 90mL/min. 99% of HIV+ men were antiretroviral-treated. FGF23 and sKlotho were not significantly correlated (r=0.09). In adjusted analyses, HIV was associated with 11% (p=0.002) higher sKlotho but not FGF23 levels (-1%; p=0.84). Among HIV+ men, diabetes was associated with 30% (95% CI: 3-65%) higher FGF23, whereas HCV (-34%; 95% CI: -14%, -49%) and cumulative tenofovir (TDF) exposure (-4%/year; 95% CI: -1%, -7%) were associated with lower FGF23 levels. In contrast, only HCV was associated with higher sKlotho (21%; 95% CI: 7%, 36%). [Figure] Neither CD4 count nor HIV RNA were associated with FGF23 or sKlotho concentrations.



* Adjusted for covariates listed in the figures for FGF23 and sKlotho, respectively
 ** Factors with p<0.05

Conclusions: HIV+ individuals had similar FGF23 but higher sKlotho levels compared to HIV- counterparts. Among HIV+ men, clinical predictors associated with FGF23 differed from those associated with sKlotho. Mechanisms by which HIV treatment and co-morbid conditions may impact these hormone levels need further study.

Funding: NIDDK Support, Other NIH Support - NIAID, NCI, NHLBI, NIDCD

PUB535

Response of Fibroblast Growth Factor 23 to Sodium Interventions in Diabetic Nephropathy and Arterial Hypertension Jelmer K. Humalda,¹ Sarah Seiler,² Arjan J. Kwakernaak,¹ Marc G. Vervloet,³ Gerjan Navis,¹ Gunnar H. Heine,² Martin H. De Borst.¹ ¹Nephrology, Univ Medical Center Groningen, Groningen, Netherlands; ²Nephrology and Hypertension, Saarland Univ Medical Center, Homburg, Germany; ³Nephrology, VU Medical Center, for NiGrAm, Amsterdam, Netherlands.

Background: Fibroblast growth factor 23 (FGF23) rises progressively in chronic kidney disease (CKD) and is associated with adverse cardiorenal outcomes. Both CKD patients with diabetic nephropathy (DN) and patients with hypertension are vulnerable to the effect of excess sodium on volume status. FGF23 putatively induces sodium retention by up-regulating the sodium-chloride cotransporter (NCC). We studied whether, conversely, intervention in sodium status affects FGF23 levels.

Methods: We performed a post-hoc analysis of a randomized controlled 2x2 cross-over trial in 45 DN patients on background ACE-inhibition (ACEi) with four 6-week treatment periods with add-on hydrochlorothiazide (HCT) or placebo, combined with regular (RS) or low sodium (LS) diet. Plasma C-terminal FGF23 was measured by ELISA (Immutopics). Additionally, FGF23 was measured in 12 patients with arterial hypertension but without overt CKD before and after 4 hours of intravenous administration of 2 liters sodium-chloride 0.9%. Changes in FGF23 were assessed by Friedman's test and Wilcoxon Signed Rank test as appropriate.

Results: DN patients were 65±9 years old (mean±SD). During ACEi+RS eGFR was 65±25 mL/min/1.73m², HbA1c 7.1±0.8% and albuminuria 649 mg/d median [1st-3rd quartile: 230-2008 mg/d]. FGF23 levels were 94 [73-141] RU/mL. FGF23 did not change significantly after adding either HCT (99 [74-148] RU/mL) or low sodium diet (99[75-135 RU/mL]) or both HCT and low sodium diet (111 [81-160] RU/mL), P=0.15. The patients with arterial hypertension were 45±13 years old with an eGFR of 101±18 mL/min/1.73m². Sodium-chloride infusion did not affect FGF23 (before: 68 [58-97] RU/mL, after: 67 [57-77] RU/mL, P=0.4).

Conclusions: Chronic and acute changes in sodium status did not materially change FGF23 in DN and hypertensive patients, respectively. Our data thus do not support a direct feedback loop between volume status and FGF23 in diabetic nephropathy or hypertension.

PUB536

Hypocalcaemia Management Post Parathyroidectomy in Renal Patients – Our Experience and Change in Practice Rajkumar Chinnadurai, Maharajan Raman, Constantina Chrysochou, Smeeta Sinha. Dept of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom.

Background: Hypocalcaemia is common post parathyroidectomy in renal patients with secondary hyperparathyroidism due to hungry bone syndrome with an incidence as high as 51%. Hypocalcaemia can be prevented by effectively preloading patient with Vitamin D supplements and close monitoring of calcium levels post operatively. Currently there is no clear guidance on the preloading dose of One-alpha-calcidol in literature. Our current practice is to preload all patients with 2 mcg one-alpha-calcidol for 5 days pre operatively. Our aim was to study the management of hypocalcaemia post parathyroidectomy in renal patients and factors influencing length of hospital stay (LOS). To identify if any changes in current practice could improve outcome.

Methods: Retrospective observational study of all renal patients who underwent parathyroidectomy under a single surgeon over 6 years (April 2008 to September 2014). Data was collected from the Electronic Patient Record. Data were analysed using Stats direct and Fisher Exact test was used for testing statistical significance.

Results: 72% of our sample (n = 25) were male with a mean age of 54. Of the 25 there were 13 transplant, 9 haemodialysis and 3 CKD patients. The mean hospital stay was 5 days shorter than quoted in the literature (5.6 Days). 3 of 25 patients were not preloaded. 40% of our patients needed intravenous calcium replacements which was the main cause for increased LOS (p=0.0002). Haemodialysis patients had longer LOS than CKD and Transplant patients (p=0.0002), this group were more likely to not have received pre-loading. Those undergoing total parathyroidectomy had increased LOS compared to subtotal parathyroidectomy (p=0.0009). There were no surgical complications contributing to a delay in discharge.

Conclusions: Insufficient preloading was identified as a major risk factor for hypocalcaemia, which significantly increased LOS. Further to consensus between renal and surgical teams we have increased the preloading dose of one-alpha-calcidol to 5 mcg for 5 days pre operatively. A follow up study is planned in 12 months to observe the outcome of this change.

PUB537

Links Between Urinary Phosphate Handling, FGF23 and Klotho: An Australian Single-Centre Cross-Sectional Study Sven-Jean Tan,^{1,2} Edward Robert Smith,¹ Stephen G. Holt,^{1,2} Tim Hewitson,^{1,2} Nigel David Toussaint.^{1,2} ¹Nephrology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia; ²Medicine (RMH), The Univ of Melbourne, Melbourne, Victoria, Australia.

Background: Aim: To examine the links between measured phosphate parameters and regulators of phosphate homeostasis (fibroblast growth factor-23 [FGF23] and soluble α -klotho [sKl]). Background: FGF23, via the FGF-Receptor/Klotho complex, reduces expression of sodium-phosphate co-transporters thereby inhibiting tubular phosphate reabsorption. Chronic kidney disease (CKD) leads to FGF23 excess and deficiency of sKl. Elevated serum phosphate (sPi) results as remaining functioning nephrons are unable to compensate for reduction in total phosphate excretion. Complex relationships between these parameters in health and disease, and the impact on phosphate handling, are not fully understood.

Methods: Blood samples and spot and 24-hour urine were collected from patients with CKD (Stages 1-5) and healthy volunteers. Serum and urine biochemistry, intact FGF23 and sKl were analysed. FGF-23 and sKl were log-transformed (Ln). Fractional excretion of phosphate (FEPi) and maximal tubular phosphate reabsorption (TmP) were calculated. Pearson correlation coefficients were used to assess correlation between phosphate handling and regulatory hormones.

Results: 116 participants (77 CKD and 39 controls) were recruited. 74 (63.8%) were male. Median (IQR) age of all participants was 61 (49-71) years. FGF23 and FEPi were higher, while sKl and TmP were lower, in CKD compared to controls (all p<0.005). Adjusting for eGFR, LnFGF23 correlated with FEPi (R=0.222, p=0.026) and sPi (R=0.268, p=0.007) while LnKlotho displayed robust relationships with TmP (R=0.336, p=0.001) and sPi (R=0.309, p=0.002). There was no association between LnFGF23 and LnKlotho.

Conclusions: Disruption of phosphate regulatory mechanisms is characteristic of CKD. In this small cohort, we established that FGF23 contributes to phosphate excretion. However, sKl may provide insight into a greater physiological role of Klotho in regulating TmP at a cellular level. Causal relationships should be explored further *in vitro*.

Funding: Private Foundation Support

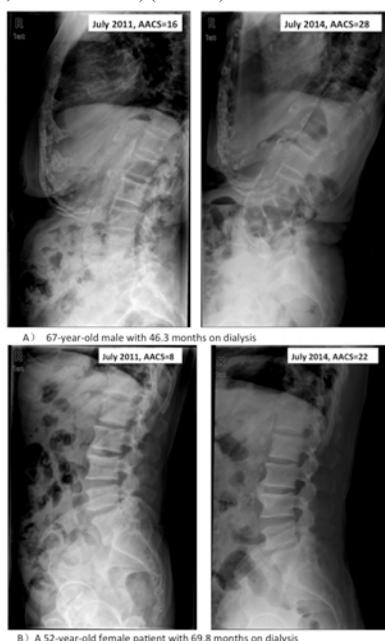
PUB538

Fibroblast Growth Factor 23 Can Predict the Progress of Aortic Artery Calcification in Dialysis Patients Zijin Chen,¹ Xiaonong Chen,¹ Xiaobo Ma,¹ Bei Ding,² Huawei Ling,² Nan Chen.¹ ¹Nephrology, Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China; ²Radiology, Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China.

Background: To investigate the factors associated with progress of aortic artery calcification in maintenance haemodialysis (MHD) patients and to determine whether plasma FGF23 level is related to progress of aortic artery calcification.

Methods: MHD patients from Ruijin Hospital from July 1st 2011 to July 31st 2011 were involved in our study. Follow up 36 months. Aortic artery calcification (AAC) was detected by a lateral lumbar X-ray plain and read by two radiologists.

Results: 120 MHD patients were enrolled and followed up for 36 months. To July 2014, a total of 67 MHD patients finished the study. Among 67 patients, 32 were male, mean age 53.9±13.1 years old, mean dialysis vintage 44.1±38.1 months, median FGF23 level 48052 (11372-35750.4)Ru/ml, LgFGF23 3.79±0.83. In July 2011, 53.7% of patients had visible calcification in the abdominal aorta and mean involved segment was 1.42 with mean AAC scores(AACS) 3.96. In July 2014, 73.1% had AAC and mean involved segment was 2.34 with mean AACS 10.7. There are significant differences between two AAC involved segments and AACS (both P<0.001). Age, dialysis vintage and FGF23 level had significant difference between AAC progress group and no AAC progress group (P = 0.007, <0.001 and 0.020, separately). Logistic analysis showed that the independent parameters associated with AAC progress were age (OR=1.114, CI:1.045-1.186) and Lg FGF23 (OR=3.848, CI:1.429-10.346) (P<0.001).



Conclusions: The severity of vascular calcification progress yearly in maintain hemodialysis patients. Age and FGF23 are independently associated with the progress of AAC. FGF23 level could predict the progress of AAC in MHD patients.

Funding: Government Support - Non-U.S.

PUB539

Could FGF23 Be a Regulator of Hecpudin in Liver Cells? Justine Bacchetta, Nathalie Demoncheaux, David Durantel. Hospices Civils de Lyon and INSERM, Univ Claude Bernard Lyon 1, Lyon, France.

Background: Hecpudin is a 25-amino-acid protein synthesized in hepatocytes and macrophages that acts as a post-translational inhibitor of ferroportin, the only receptor known to export iron from intracellular compartments to systemic circulation. Thus, higher hecpudin levels are associated with greater intracellular sequestration of iron, and increased risk of anemia. Vitamin D is an inhibitor of hecpudin expression; the working hypothesis is that FGF23 could be an ‘inverse’ regulator of iron metabolism in comparison to vitamin D, with a stimulation of hecpudin expression, an increase of intracellular ferritin and an inhibition of ferroportin expression on the cell membrane, leading to a further intracellular sequestration of iron.

Methods: Three different types of liver cells were used: HepG2, HepaRG and primary human hepatocytes (PHH). Cells were exposed to FGF23 (1, 10 et 100ng/mL), at different time points (H6, H24, H48). Cultures were performed in triplicates, and QRT-PCR in duplicates (StepOne Plus Real-Time PCR). Western Blots were also performed (Erk and Akt phosphorylation pathways, FGFR1, FGFR3, ferritin).

Results: In HepG2, even though FGFR-1 expression was found by Western blot analysis, FGF23 did not modify hecpudin expression by QRT-PCR, and Erk/Akt pathways were not activated by FGF23. In HepaRG cells, hecpudin expression was modified with FGF23 by QRT-PCR, i.e. increased at 6 hours and decreased at 24 hours,

Fold change of hecpudin mRNA expression in comparison to PBS	FGF23, 1 ng/mL	FGF23, 10 ng/mL	FGF23, 100 ng/mL
6 hours	1.34±0.22 *	1.53±0.18 *	1.17±0.01*
24 hours	0.68±0.12 *	0.73±0.08*	0.90±0.04

* p<0.05; Western blot analyses demonstrated the presence of FGFR1 and FGFR3, with an activation of the Erk pathway at 30 and 60 minutes with FGF23. However, there was no modification of ferritin by Western blots analysis with FGF23. In the only batch of PHH that was available, hecpudin expression increased at 6 and 24 hours.

Conclusions: FGF23 does not appear to play a crucial role in iron regulation in liver cells, even though its potential role in PHH deserves further studies.

Funding: Private Foundation Support

PUB540

Prevalence of Hyperparathyroidism and Its Correlates in a Large Cohort of Hemodialysis Patients Pasquale Esposito,¹ Fabio Malberti,² Elena Caramella,¹ Marta Calatroni,¹ Edoardo La Porta,¹ Marina Foramitti,² Rosanna Coppo,³ Antonio Dal Canton.¹ ¹Nephrology, Fondazione IRCCS, Pavia, Italy; ²Nephrology, Istituti Ospitalieri di Cremona, Cremona, Italy; ³Nephrology, Regina Margherita Children’s Hospital, Turin, Italy.

Background: Beyond experimental setting of randomized trials, little is known about the occurrence of mineral bone disorders (MBD) in the real-life clinical practice of hemodialysis (HD). This is the reason why we designed this observational study to define the prevalence of hyperparathyroidism (HPT) and its correlates in a large cohort of HD patients.

Methods: We enrolled HD prevalent patients from 38 Dialysis Units collecting data on: clinical information, dialysis parameters, biochemical and instrumental evaluations and pharmacological therapy. According to the KDIGO guidelines we divided the patients in: patients affected by HPT (i.e. PTH>9 the upper reference limit of each laboratory) vs patients on target.

Results: Out of 495 patients, 34 (6.8%- 59.9±15.5 years, 53%M) presented HPT with mean PTH of 1064±536 pg/ml, while 461 patients resulted OT (93.2%- 66.9±13.7 years, 66%M), mean PTH 242±151 pg/ml (p<0.0001). HPTs were younger than OT (59.9±15 vs 69.9±13.7 years, p=0.008), with a longer HD history (126.2±125 vs 64.3±69.4 months, p=0.0003). There were not significant differences in both clinical and dialysis parameters. Similarly, there were not differences in laboratory examination except from serum ALP that resulted higher in HPTs (194.8±142 vs 144.1±108 U/l OT, p=0.01). Moreover, there were not differences in the use of phosphate binders, whereas a significantly higher percentage of HPTs was taking paracalcitol and calcimetics and the prescribed vitamin D doses (both as calcitriol and paracalcitol) were significantly higher in HPT patients.

Conclusions: The prevalence of HPT in our population was surprisingly lower, compared to that reported in previous studies. This finding could be due to the general application of KDIGO guidelines, which recommend more permissive PTH levels compared with the previous K-DOQI guidelines, such as to the availability of effective drugs, probably used more appropriately than in the past.

PUB541

Effect of Vitamin D Receptor Activators on Glomerular Filtration Rate: A Meta-Analysis and Systematic Review Qian Zhang, Jing Chen. Div of Nephrology, Huashan Hospital, Fudan Univ, Shanghai, China.

Background: Vitamin D receptor activators (VDRAs) can protect against mineral bone disease, but they may also elevate serum creatinine and reduce glomerular filtration rate (GFR).

Methods: We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) to evaluate the effect of VDRAs on kidney function and adverse events. MEDLINE, EMBASE, the Cochrane Controlled Trials Register were searched for RCTs that evaluate vitamin D receptor activators (alfacalcidol, calcitriol, doxercalciferol, falecalcitriol, maxacalcitol and paricalcitol) up to March 2015.

Results: We included 31 studies, all of which were performed between 1976 and 2015, which enrolled 2621 patients. Patients receiving VDRAs had lower eGFR (weighted mean difference WMD -1.29 mL/min/1.73 m², 95% CI -2.42--0.17) and elevated serum creatinine (WMD 7.03 μmol/L, 95% CI 0.61–13.46) in sensitivity analysis excluding studies with dropout rate more than 30%. The VDRAs and control groups had no significant differences in all-cause mortality (relative risk RR 1.41, 95% CI 0.58–3.80), cardiovascular disease (RR 0.84, 95% CI 0.42–1.71), and severe adverse events (RR 1.15, 95% CI 0.75–1.77). Episodes of hypercalcemia (RR 3.29, 95% CI 2.02–5.38) were more common in the VDRAs group than in the control group.

Conclusions: Although administration of VDRAs slightly reduced the eGFR, all-cause mortality and severe adverse events were comparable between the groups. Future RCTs with larger sample sizes are needed to assess whether the mild reduction of eGFR is of clinical significance.

PUB542

Low Dose Cholecalciferol Supplementation on Serum Inflammatory Markers in Hemodialysis Patients with Hypovitaminosis D Yeon Joo Lee,¹ Insun Kim,¹ Eunyoung Lee,² Joo-Hark Yi,² Hee Joon Baek,³ Sang-Woong Han,² Sang sun Lee.¹ ¹Food and Nutrition, Hanyang Univ, Seoul, Korea; ²Internal Medicine, Hanyang Univ Guri Hospital, Guri, Korea; ³Nutrition, Hanyang Univ Seoul Hospital, Seoul, Korea.

Background: Vitamin D deficiency is common in hemodialysis(HD) patients and has been reported to be associated with mortality due to cardiovascular disease and an inflammatory response. The aim of this study was to investigate the hypothesis that low dose cholecalciferol supplementation improves serum 25(OH)D and 1,25(OH)₂D levels, and reduces inflammatory markers. Moreover, it was to analyze the association of FGF-23 and 25(OH)D levels.

Methods: This study was an one-year intervention study for hemodialysis patients with hypovitaminosis D (25(OH)D <30 ng/mL). During the first six months, the patients received 3,000 IU of cholecalciferol after each hemodialysis (9,000 IU/week), thereafter, they stopped taking supplements. Serum levels of 25(OH)D, 1,25(OH)₂D, and other biological variables were measured every 3 months for one year. We investigated the effects of cholecalciferol supplementation on the biological variables and inflammatory markers. In addition, the effective factors on the levels of 25(OH)D and 1,25(OH)₂D after cholecalciferol supplementation were assessed by multivariate regression analysis.

Results: Twenty-nine patients with hypovitaminosis D participated in our study. During cholecalciferol supplementation, the 25(OH)D and 1,25(OH)₂D concentration significantly increased from baseline to six months [9.9 to 34.3 ng/mL (p<0.001) and 19.7 to 22.9 pg/mL (p<0.05), respectively]. At 6 months, 65.5% of the patients had 25(OH)D levels within the target range [30 ng/mL] with a low dose of cholecalciferol supplementation. Also serum calcium and phosphorus levels did not increase above the normal range. However, the inflammation markers, hsCRP, e-selectin, VEGF-A, were not shown significant improvements after taking cholecalciferol supplements. The effective factors on serum 25(OH)D levels were BMI, baseline 1,25(OH)₂D and 6 months FGF-23 concentration by multivariate regression analysis.

Conclusions: The low dose cholecalciferol supplementation was effective in correcting serum vitamin D deficiency or insufficiency and safe for hemodialysis patients. However, 6 months of low dose cholecalciferol supplementation in these patients did not improve the levels of inflammatory markers.

Funding: Government Support - Non-U.S.

PUB543

The Effects of sKlotho on Left Ventricular Mass and Echocardiographic Changes in Patients with Chronic Kidney Disease Marc-Sebastian Baier,¹ Lucie Bauer,¹ Franziska Sandermann,¹ Insa E. Emrich,¹ Kathrin Untersteller,¹ Sarah Seiler,¹ Vincent Brandenburg,² Danilo Fliser,¹ Gunnar H. Heine.¹ ¹Internal Medicine IV - Nephrology and Hypertension, Saarland Univ Medical Center and Saarland Univ Faculty of Medicine, Homburg, Saarland, Germany; ²Dept of Internal Medicine I – Cardiology, Univ Hospital of the RWTH Aachen, Aachen, Nordrhein-Westfalen, Germany.

Background: Recently experimental data suggest that elevated circulating levels of soluble Klotho (sKlotho), which is the beyond FGF-23, may directly induce myocardial damage. In our prospective CARE FOR HOME study we analyzed the effect of serum sKlotho levels on patients with left ventricular hypertrophy at baseline and on echocardiographic changes during five years of follow-up.

Methods: The ongoing CARE FOR HOME study recruits chronic kidney disease G2-G4 patients. At baseline serum FGF-23 (c-terminal; Immuntopics; San Clemente; CA) and serum sKlotho (Immuno-Biologic Laboratories, Fujiokashi, Gunma, Japan) were measured in all patients. Cardiovascular and renal risk factors were evaluated by a questionnaire. The present analysis includes 398 patients with an echocardiography at baseline. 94 patients received an echocardiography after five years of follow-up according to the American Society of Echocardiography guidelines. Moreover the echocardiography was done by one physician.

Results: At baseline 155 patients (40%) had a normal ventricular geometry, 134 patients (34%) had an apparently concentric remodelling, 61 patients (16%) had a concentric hypertrophy and 39 patients (10%) had an eccentric hypertrophy. At the beginning of our study, left ventricular mass (LVMI) correlated with the following parameters: glomerular filtration rate (eGFR; r = -0.19; p < 0.001), serum FGF-23 (r = 0.18; p < 0.001), age (r = 0.18; p < 0.001) and pulse pressure (r = 0.15; p < 0.001). LVMI was not correlated with sKlotho (r = -0.07; p = 0.183) and mean blood pressure (r = 0.10; p = 0.052).

Conclusions: In contrast to recent animal data our results show neither an association of sKlotho with prevalent left ventricular hypertrophy nor with LVMI changes in patients with chronic kidney disease.

PUB544

Cost-Minimization Analysis of Sucroferic Oxhydroxide and Sevelamer Carbonate in Patients on Dialysis with Secondary Hyperparathyroidism in Germany Joris Van Stiphout,¹ Matthias Schwenkglenks,¹ Peter Braunhofer,² Thomas Szucs,¹ Viatcheslav Rakov,² Patricia R. Blank.¹ ¹Univ of Basel, European Center of Pharmaceutical Medicine, Univ of Basel, Basel, Switzerland; ²Vifor Pharma, Glattpark, Zurich, Switzerland.

Background: Many patients with chronic kidney disease (CKD) on dialysis require vitamin D (Vit.D) agents for managing secondary hyperparathyroidism (SHPT). It has been shown that the concomitant administration of oral phosphate binders (sucroferic oxhydroxide, SFOH or sevelamer carbonate, SEV) and Vit.D therapies might impair the therapeutic effect of the Vit.D due to drug-drug interaction. Based on clinical trials (NCT01324128/ NCT01464190), this cost-minimization analysis assessed the economic impact of using SFOH compared to SEV treatment with Vit.D agents from a German third-party payer perspective.

Methods: Costs of patients with serum phosphate concentrations ≥ 6.0 mg/dL receiving either SFOH (1.5g/day [3 tablets/day]) or SEV (6.4g/day [8 tablets/day]) were assessed. Due to lack of interaction, it was assumed that patients on SFOH were treated exclusively with oral Vit.D (calcitriol, 0.28mg/day), whereas SEV patients received intra-venous Vit.D agents (paricalcitol, 1.84mg/day). Costs for the administration of paricalcitol and for adverse events were not included. Drug acquisition costs were calculated on the basis of the German standard pharmacy prices (Rote Liste 2015). Uncertainties were addressed in one-way sensitivity analyses.

Results: Over an observation period of one year, costs for SFOH or SEV resulted in EUR 3'416 or EUR 3'592, respectively. Annual Vit.D therapy costs yielded in EUR 209 for calcitriol and EUR 3'306 for paricalcitol, respectively. SFOH treatment with calcitriol versus SEV with paricalcitol resulted in an annual cost-saving of EUR 3'273 per patient. The variation of drug prices by $\pm 25\%$ did not change the conclusion of the base-case.

Conclusions: This study provide evidence that SFOH treatment with calcitriol has an economic benefit compared to SEV with paricalcitol to treat German CKD patients with SHPT. Economicsavings might be substantial for the German health care system, but real world data will be needed to confirm these findings.

Funding: Pharmaceutical Company Support - Vifor Pharma. Research funding by Vifor Pharma via employment institution.

PUB545

Effect of Intravenous Saccharated Ferric Oxide on FGF23 Metabolism in Dialysis Patients Masahiro Koizumi,¹ Hirota K Komaba,¹ Yoko Takeda,² Masafumi Fukagawa.¹ ¹Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan; ²Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine.

Background: Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone, secreted from the bone. It has been well known that the reduction in serum phosphate occurs following intravenous administration of saccharated ferric oxide. A recent clinical study showed that both production and degradation of FGF23 is enhanced in the setting of iron deficiency (M Wolf. *J Bone Miner Res* 2013). These findings suggest that iron may be a key regulator of FGF23. However, its precise mechanism remains to be elucidated.

Methods: We previously reported that intravenous saccharated ferric oxide further increase in elevated serum FGF23 levels in hemodialysis patients with iron deficiency anemia, using the intact FGF23 assay that only detects the full-length protein (*Am J Nephrol* 2011). In this study, we additionally examined the FGF23 levels by the C-terminal FGF 23 assay which detects both the full-length protein and C-terminal fragments, and compared the results of these two assays (N = 27).

Results: We previously reported that intravenous saccharated ferric oxide further increase in elevated serum FGF23 levels in hemodialysis patients with iron deficiency anemia, using the intact FGF23 assay that only detects the full-length protein (*Am J Nephrol* 2011). In this study, we additionally examined the FGF23 levels by the C-terminal FGF 23 assay which detects both the full-length protein and C-terminal fragments, and compared the results of these two assays (N = 27).

Conclusions: Collectively, in hemodialysis patients with iron deficiency anemia, substantial amounts of C-terminal fragments of FGF23 accumulate by increase in both the production and the degradation. The administration of saccharated ferric oxide suppresses both the production and degradation, leading to increase in values by Intact FGF23 assay and decrease in those by C-terminal assay. Specific preparations of iron for intravenous use may regulate both the production and degradation of FGF23.

PUB546

Serum Levels of Sclerostin (SOST) in Renal Transplantation (Tx) Marzia Pasquali, Lida Tartaglione, Silverio Rotondi, Maria Luisa Muci, Sandro Mazzaferro. *Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, Sapienza Univ, Rome, Italy.*

Background: SOST, by inhibiting the Wnt pathway, suppresses osteoblasts activity and stimulates their apoptosis. Recent evidence has shown a role of SOST in alterations of bone metabolism in CKD. In CKD patients SOST serum levels are higher than in the general population and in HD patients SOST correlate negatively with histomorphometric parameters of bone turnover. Little is known about serum levels of SOST in Tx. Aim of our study was to evaluate serum SOST levels in Tx in whom few data are available.

Methods: We performed a cross sectional study in 80 Tx (55±10 y.o.;49M/31W) with CKD stage 2-4 (eGFR 47±16 ml/min). 30 healthy subjects (34±12y.o.;eGFR95±19 ml/min) were the control group. We evaluated in all patients SOST, Ca, Pi, PTH, FGF23 and Alkaline Phosphatase (AP).

Results: SOST was not different between Tx and controls (27,6±10,3vs31,0±6,0 pmol/l, p: n.s). The table shows the mean values of the parameters evaluated With mild vitamin D insufficiency (25D:26±11ng/ml), TX had normal 1,25D values, mild increment of PTH and Ca, and normal values of P.

Sclerostin, pmol/l	Cas, mg/dl	Ps, mg/dl	A.P. U/l (80-275)	PTH, pg/ml	25D, ng/ml	1,25D, pg/ml	FGF23, pg/ml
27.6± 10.3	10.1± 0.8	3.0± 0.7	178± 65	59± 51	26± 11	42± 15	47.3± 28.8

Serum levels of FGF23 were increased compared to controls (47,3±28,8 vs 30,0±19,0 pg/ml, p<.05). SOST showed a negative correlation with AP (r=-.375; p<.05) and a positive correlation with FGF23 (r=.236; p<.05) and 25D (r=.238; p<.05). No correlation existed with others parameters

Conclusions: eGFR does not seem to affect serum levels of SOST in Tx. The negative correlation whit AP indicates that SOST maintains its modulatory role of osteoblastic activity in this population. The correlation with FGF23, which is in agreement with low FGF23 in SOST null mice, suggests modulatory effects of both proteins on osteoblasts: direct, through Wnt inhibition, for SOST; indirect, through effects on 1,25D levels, for FGF23. Serum SOST may be an additional marker of bone metabolism, useful to understand metabolic pathways in normal subjects and in CRF.

PUB547

Comparison of Cholecalciferol Supplementation Dosing with a Bolus Dose Versus Daily Administration in Chronic Hemodialysis Patients
 Pablo Molina, Belen Vizcaino, Mercedes Gonzalez Moya, Sandra Beltrán, Marco Montomoli, Cristina Castro, Jose L. Gorriz, Luis M. Pallardo. *Nephrology, Dr Peset Univ Hospital, Valencia, Spain.*

Background: The aims of this study were to assess the safety profile of bolus cholecalciferol supplementation and compare its effectiveness to daily oral administration in hemodialysis (HD) patients.

Methods: This 6-month prospective, intervention study enrolled 60 stable HD patients with 25-hydroxyvitamin D [25(OH)D levels] <30ng/ml, who received cholecalciferol 25,000 IU once or twice monthly (n=30) or 700 IU daily (n=30). Differences in biochemical parameters, including 25(OH)D, calcium, phosphorous, parathyroid hormone(PTH), alkaline phosphatase and C-reactive protein levels, were analyzed monthly. Primary outcome was 25OH(D) level at 6 months. For safety purposes, in the subgroup of patients receiving the bolus regimen, biochemical parameters were also assessed on days 2,4 and 7 after the first bolus dose.

Results: At baseline, patient and biochemical characteristics were similar in both groups. No changes were observed in calcium, phosphorus and 25OH(D) levels in the first week after the first bolus dose. Throughout the 6-month follow-up, similar responses in 25OH(D) levels and other biochemical parameters were observed in both groups.

Parameter	Fortnightly 25,000 IU cholecalciferol (n=30)			Daily 700 IU cholecalciferol (n=30)			p-value between groups at month 6
	Baseline	Month 6	Pre-post p-value	Baseline	Month 6	Pre-post p-value	
25(OH)D (ng/ml)	10.5 ± 6.5	22.0 ± 6.5	<0.001	11.4 ± 5.2	24.8 ± 10.0	<0.001	0.195
25(OH)D status (n,%)							
Sufficiency (≥20ng/ml)	4 (13%)	18 (60%)	0.001	4 (13%)	20 (67%)	<0.001	0.395
Deficiency (<10ng/ml)	15 (50%)	30 (100%)	<0.001	13 (43%)	29 (97%)	<0.001	0.500
iPTH (pg/ml)	257 (128-318)	281 (151-354)	0.107	193 (130-266)	187 (132-315)	0.778	0.176
Ca _{adj} (mg/dl)	9.1 ± 0.6	9.1 ± 0.5	0.571	9.0 ± 0.6	8.9 ± 0.6	0.943	0.199
Phosphorous (mg/dl)	4.0 ± 1.4	3.8 ± 1.2	0.465	4.0 ± 1.3	3.8 ± 0.6	0.031	0.417

Conclusions: Supplementation of 25,000 IU fortnightly or monthly oral cholecalciferol seems to be safe, being equally effective for raising 25(OH)D levels than 700 IU daily cholecalciferol administration.

PUB548

The Prevalence of Vitamin D Deficiency Among IgA Nephropathy: A Cross-Section Study from One Center
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Background: Low serum vitamin D concentrations have been reported in chronic kidney disease (CKD). Very few studies concerns vitamin D deficiency of IgA nephropathy (IgAN) in Chinese patients. Our aim is to assess the deficiency of serum 25(OH)D concentrations in patients with IgAN, and to explore the possible correlated factors contributing to Vitamin D deficiency.

Methods: 283 patients who were come from north China and were not receiving vitamin D supplementation were included in this study from February 2013 and April 2014. We collected blood samples to determine levels of Scr, BUN, UA, serum phosphate (P) and calcium (Ca), iPTH, albumin, as well as urinary excretion of creatinine, protein, P and Ca within 24h. Electrochemiluminescence immunoassay measured total 25-hydroxyvitamin D. Vitamin D deficiency should be defined as a 25(OH) D of < 15 ng/ml.

Results: All of the 283 patients, 25(OH)D concentration was 10.25±6.94 ng/ml. Only 18.82% of the patients had a circulating 25(OH) D level greater than 15ng/ml. The prevalence of deficiency(<15ng/ml) were 87.2%, 72.9%, 75.0%, 85.45%, 93.1%(P=0.000) at different CKD stages.All the 120 IgAN patients were divided into 4 groups according to eGFR. The prevalence of vitamin D deficiency were higher in CKD stage 1 and 4-5(P=0.000), but there is no difference of average 25(OH) D concentration according to eGFR(P=0.059). The 25(OH)D concentration was higher in IgAN patients than MN and DN patients. But, 24UPR in IgAN patients was lower than MN and DN patients. In different age, gender, season, BMI or iPTH group, 25(OH)D levels were not affected, but 25(OH)D level was lower in ³5g/24h group.

Conclusions: For the IgAN patients in north China, kidney function might be related to vitamin D deficiency, and 24UPR may play a very important role in maintaining 25(OH) D serum concentrations.

PUB549

Utility of Whole Exome Sequencing in the Diagnosis of a Family with Apparent Mineralocorticoid Excess
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Background: Apparent Mineralocorticoid Excess (AME) is a rare familial disorder with hypertension, hypokalemia, metabolic alkalosis and low plasma renin and aldosterone due to mutations in the 11-β-hydroxysteroid dehydrogenase-2 (HSD11B2) gene. Five siblings of a third degree consanguineous family with unaffected parents were evaluated for hypertension of juvenile onset. They had varying degrees of hypokalemia, medullary nephrocalcinosis, concentric left ventricular hypertrophy and renal dysfunction. Plasma renin and aldosterone levels were low. Given the clinical picture and autosomal recessive inheritance pattern, a provisional diagnosis of AME was made. 24 hour urinary cortisol and cortisone estimation was unavailable. We decided to confirm the diagnosis using next generation gene sequencing.

Methods: Whole blood was collected from the parents and the affected members after informed consent. 50 ng of the isolated high quality DNA was used to prepare library and exome capture. Sequencing was performed using v3 reagents to generate over 49.48 million paired end reads of 101bp. The reads were aligned to the Human genome (hg19 build, UCSC) and was further filtered for read duplicates, recalibrated and realignment was performed around well-annotated Indels from the 1000 genome project using GATK and Picard tools. Variations were called using the GATK Unified Genotyper and analysed using ANNOVAR and annotated ClinVar.

Results: Analysis revealed the presence of homozygous variation p.R337C in HSD11B2 gene annotated to be pathogenic in ClinVar and predicted to be deleterious using PROVEAN in the affected siblings. The variant was further validated using Sanger sequencing of the amplicons, confirming the diagnosis. Both parents were heterozygous for the variation. This variation has been reported to be associated with the similar phenotype in two independent studies on native American populations.

Conclusions: A homozygous mutation (p.R337C variation) in the 11HSD2 gene was demonstrated in the family using whole-exome sequencing. This is the first genetically characterized report of AME from Indian population. Our study underscores the utility of using next generation sequencing in the diagnosis of rare inherited diseases.

Funding: Government Support - Non-U.S.

PUB550

Genetics of Thrombotic Microangiopathies – The Viennese TMA Cohort
 Christof Aigner,¹ Martina M. Gaggl,¹ Zoltan Prohaszka,² Raute Sunder-Plassmann,³ Gere Sunder-Plassmann,¹ Alice Schmidt.¹ ¹Dept of Medicine III, Div of Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria; ²IIrd Dept of Internal Medicine, Research Laboratory, Semmelweis Univ, Budapest, Hungary; ³Dept of Laboratory Medicine, Laboratory for Molecular Diagnostics, Medical Univ of Vienna, Vienna, Austria.

Background: Thrombotic microangiopathies (TMA) classified as hemolytic uremic syndrome (HUS) are characterized by acute kidney injury (AKI), mechanical hemolysis and thrombocytopenia, caused by an excessively activated alternative pathway of the

complement system. This is a result of either genetic alterations within complement factors and regulatory proteins or secondary causes. The aim of this study was to systematically investigate our cohort of patients with TMA regarding genotype and triggers of disease episodes.

Methods: Data were analyzed by means of patient records: Demographic and laboratory data, results of kidney biopsies, results of genetic sequencing of complement regulatory proteins, CFB, thrombomodulin (THBD) and C3, and medical history for triggering factors were analyzed.

Results: Out of 92 patients with TMA we classified 30 as atypical HUS (aHUS), 1 as typical HUS, and 61 as secondary HUS. At onset of disease patients with aHUS had a mean age of 25 years (range: 1-47), 20 were female (67%), and 13 (43%) were kidney transplant recipients. First presentation of 24 patients was AKI, 3 showed hemolysis, 2 had pre-eclampsia and 1 HELLP-syndrome. Distinct triggering factors in 20 patients were: infection (n=10), pregnancy (n=5), hypertension (n=2), surgery, diarrhea and renal transplantation (each n=1). Thirteen and 3 showed a CFH-H3 and a MCPggaac risk haplotype, respectively; potentially disease-causing mutations were identified in 22 patients (7 CFH, 6 CD46, 5 CFI, 4 C3, 2 CFB, 1 THBD; 4 of them with more than 1 mutation); 7 showed wild-types and no data existed for 1 patient.

Conclusions: In our cohort of TMA patients we identified 30 cases of aHUS. In 22 patients (74%) we identified a mutation within genes of the complement regulatory proteins or C3, whereas 7 subjects showed wild-type sequences despite presenting with a classic phenotype of aHUS.

PUB551

Under-Diagnosis of Alport Syndrome in First-Degree Relatives of Affected Individuals Clifford E. Kashtan,^{1,2} Theresa F. Cassidy,^{1,2} Michelle N. Rheault,^{1,2} ¹*Pediatrics, Univ of Minnesota, Minneapolis, MN;* ²*Alport Syndrome Treatments and Outcomes Registry (ASTOR).*

Background: Alport syndrome (AS) is an important inherited cause of progressive renal disease. Hematuria, the cardinal feature of AS, is highly penetrant in affected individuals. Urinalysis is a sensitive method for detecting AS in relatives of AS patients. This report describes a cohort of at-risk individuals (first-degree relatives of known AS patients) who underwent a first urinalysis as part of a clinical trial feasibility study.

Methods: For a study entitled "Multi-center Controlled Clinical Trials in Alport Syndrome - A Feasibility Study" (R21 DK91480, Clinicaltrials.gov #NCT01696253) conducted during 2013-14, first morning urine collection kits were sent to 104 people registered with ASTOR who carried a diagnosis of AS or were first-degree relatives of people known to have AS. 45/104 participants (43%) had been classified as unknown because a urinalysis had not been performed previously.

Results: 17/45 unknowns did not return the urine kit. Of the 28 who returned a urine kit, 11 had hematuria and 17 had normal urinalyses. Of the 11 who were reclassified from unknown to affected, 6 were siblings of a known affected child, 3 were sons of a known affected mother and 2 were mothers of known affected children. 3/11 had microalbuminuria (urine microalbumin:creatinine ratio > 30 mg/g); none had overt proteinuria.

Conclusions: The results are consistent with the following conclusions: 1) it is not unusual for first-degree relatives of known AS patients to have never been screened by urinalysis; 2) screening of first-degree relatives of known AS patients frequently identifies affected individuals (39% [11/28] of those who returned urine kits) who may benefit from early intervention. Early initiation of ACE-inhibitor therapy appears to slow renal disease progression in AS (Gross et al, *Kidney Int* 2012). It is recommended that treatment be initiated in AS patients as soon as they develop overt proteinuria (Kashtan et al, *Pediatr Nephrol* 2013; Savage et al, *JASN* 2013). Screening urinalyses should be performed in all first-degree relatives of AS patients in order to identify those who are or may become candidates for treatment.

Funding: NIDDK Support

PUB552

Urinary Biomarkers (UBio) Predict Renal Damage in Primary Hyperoxaluria (PH) Gauri Bhutani,¹ Lisa E. Vaughan,² Felicity T. Enders,² Samuel Edeh,¹ Andrea G. Cogal,¹ Nick Voskoboev,¹ Dawn S. Milliner,¹ John C. Lieske.¹ ¹*Nephrology, Mayo Clinic, Rochester, MN;* ²*Biostatistics, Mayo Clinic, Rochester, MN.*

Background: PH often results in kidney stones and CKD/ESRD. We investigated diverse UBio for correlations with urinary chemistries (UChem) and as predictors of GFR decline.

Methods: UBio (Table1) were measured in biobanked urine from PH cases and healthy controls. Clinical details and outcomes for PH cases were obtained from the Rare Kidney Stone Consortium Registry, including 24 hour UChems oxalate (Uox), calcium (UCa), citrate (UCit) and calculated CaOx supersaturation (CaOx SS) and proximal tubular Ox (PTOx= (UOx* serum Cr* 4)/ UCr). Univariate and multivariate models were used to compare UBio with UChem and outcomes.

Results: Urine was available from 30 cases (114 samples) and 47 controls (47 samples). Significant correlations were present between UChem and UBio including: U RBP, NGAL, MCP1, L-FABP with U Ca; U MCP1, L-FABP with U CaOx SS; L-FABP, H-FABP with PTOx (all P<0.05). Compared to controls NGAL was increased and OPN decreased in PH cases. Both NGAL and OPN independently predicted subsequent eGFR (P<0.001).

Log (n) of Cr-corrected Urinary Biomarker	Cases v/s Controls		eGFR prediction for cases (coefficient [95% CI; p-value])	
	Odds Ratio (95% CI)	P-value (c-statistic)	Univariate	Multivariate
Retinol Binding Protein [RBP], ug/g	1.01 (0.62-1.64)	.97 (0.47)	2.96 (-1.16,7.08; 0.16)	
Clusterin, ug/g	0.63 (0.49-0.81)	<.001 (0.68)	1.38(-0.41,3.16; 0.13)	
Neutrophil Gelatinase-Associated Lipocalin [NGAL], ug/g	4.70 (2.76-8.00)	<.001 (0.90)	1.85 (0.3,3.4; 0.02)	2.94 (1.47,4.41; <0.001)
8 isoprostane [8 IP], ng/g	3.33 (1.44-7.69)	.005 (0.64)	2.93 (-2.01, 7.86; 0.25)	
Monocyte Chemoattractant Protein [MCP1], ng/g	0.59 (0.40-0.87)	.007 (0.61)	1.55 (-0.47, 3.58; 0.13)	
Liver-type fatty acid binding protein [L-FABP], ug/g	1.11 (0.69-1.81)	.66 (0.57)	-3.53 (-7.61,0.54; 0.09)	
Osteopontin [OPN], ug/g	0.38 (0.22-0.66)	.001 (0.84)	2.20 (0.79,3.6; 0.002)	2.82 (1.25, 4.40; <0.001)
Heart-type fatty chain binding protein [H-FABP], ng/g	0.33 (0.18-0.59)	<.001 (0.74)	0.85 (-3.13,4.83; 0.68)	

Conclusions: In PH, specific UBio correlate with UChem and provide renal prognostic information. These likely reflect ongoing intrarenal pathology.

Funding: Pharmaceutical Company Support - OxThera

PUB553

Whole Exome Sequencing Identifies Advillin Mutation as a Novel Single-Gene Cause of Nephrotic Syndrome Jia Rao,¹ Shazia Ashraf,¹ Svetlana Lovric,¹ Weizhen Tan,¹ Merlin Airik,¹ Eugen Widmeier,¹ Heon Yung Gee,¹ Richard P. Lifton,^{3,4} Friedhelm Hildebrandt.^{1,4} ¹*Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA;* ²*Dept of Pediatric Nephrology, Faculty of Medicine Univ of Istanbul, Istanbul, Turkey;* ³*Dept of Genetics, Yale Univ School of Medicine, New Haven, CT;* ⁴*Howard Hughes Medical Inst, Chevy Chase, MD.*

Background: Identification of single-gene causes of steroid resistant nephrotic syndrome (SRNS) has furthered the understanding of its pathogenesis. However, many genes and disease mechanisms remain unknown. To identify additional genes that if mutated cause SRNS, we combined homozygosity mapping (HM) and whole human exome sequencing (WES) in a consanguineous families with NS.

Methods: An individual of consanguineous parents from Turkey with SRNS, deafness, cataract, microcephaly, and mental retardation histologically exhibited diffuse mesangial sclerosis. HM yielded >11 segments of homozygosity by descent with cumulative homozygous segments of ~200 Mb. We performed WES in this individual to identify the underlying single-gene disease-causing mutation.

Results: We identified a homozygous missense mutation (p.Leu425Met) in the AVIL (advillin) gene in an amino acid residue conserved since *Ciona intestinalis*. The mutation segregated with the affected status in this family and was absent from >6,500 European controls in the Exome Variant Server. AVIL (advillin) is a member of the gesolin superfamily of actin binding protein. AVIL (advillin) is known to be involved in neurite outgrowth and morphogenesis via interaction with the cytoplasmic domain of the Type F scavenger receptor, SREC-I.

Conclusions: We identified mutation of AVIL (advillin) as a novel single-gene cause of SRNS. Further genetic and functional studies will shed light on the gesolin superfamily of actin binding proteins in the pathogenesis of NS and will provide further understanding of the disease mechanism.

PUB554

Adult-Onset Familial Thrombotic Microangiopathy and Pulmonary Arterial Hypertension Related to Cobalamin C Deficiency Steven Grange,¹ Elise Artaud-Macari,¹ Soumeiya Bekri,³ Arnaud Francois,⁴ Christophe Girault,¹ Fabienne Tamion,¹ Dominique Guerrot.² ¹*Intensive Care Unit, Rouen Univ Hospital, France;* ²*Nephrology Dept, Rouen Univ Hospital, France;* ³*Dept of Metabolic Biochemistry, Rouen Univ Hospital, France;* ⁴*Dept of Pathology, Rouen Univ Hospital, France.*

Background: Cobalamin C (cblC) deficiency is the most frequent inherited disease of vitamin B12 metabolism, related to mutations in the MMACHC gene. The presentation in adults is dominated by neuro-psychiatric symptoms, and usually constitutes a diagnostic conundrum. We describe a unique presentation of cblC deficiency in 2 brothers, with the association of renal thrombotic microangiopathy (rTMA), atypical glomerulopathy, and pulmonary arterial hypertension (PAH).

Methods: An 18 year-old patient was referred for dyspnea. The investigations revealed stage 5 CKD, nephrotic syndrome, haemolytic anemia, and PAH. Renal histology showed major stenosing fibroproliferative myxoid lesions in the interlobular arteries. The glomeruli presented an ischemic appearance, with thickened and ribbon-like glomerular basement membranes. Immunofluorescence showed granular glomerular deposits of IgM,

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

without IgG or C3. Metabolic analyses showed an elevation of plasma homocysteine, methylmalonic acid, and propionylcarnitine concentrations. Genetic analyses found a compound heterozygosity in MMACHC gene, with c.271dupA and c.82-9delTTC mutations. The patient's brother died at the age of 17. Autopsy revealed pulmonary capillary hemangiomatosis, while the kidney histology showed similar lesions to those of his brother.

Conclusions: This is the first report of late-onset rTMA, atypical glomerulopathy, and PAH associated with cblC deficiency. We suggest that the association of rTMA and/or glomerular proteinuria with PAH in children and young adults should prompt metabolic investigations to identify cblC deficiency, and provide early specific management including hydroxycobalamin, folic acid, and betaine.

PUB555

The DS3 Scores and Quality of Life in Japanese Patients with Fabry Disease Nobuhito Hirawa,¹ Keisuke Yatsu,² Sanae Saka,¹ Gen Yasuda,¹ Satoshi Umemura.² ¹Dept of Nephrology and Hypertension, Yokohama City Univ Medical Center, Yokohama, Kanagawa, Japan; ²Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.

Background: Fabry disease (FD) is the lysosomal storage disorder, caused by the deficiency of lysosomal hydrolase α -galactosidase A activity. Various symptoms associated with renal disease, heart lesion and cerebrovascular disease occur in Fabry disease patients. Thus, the quality of life (QoL) would be altered with the disease progressed. We evaluated the clinical severity and the QoL in a sample of Japanese patients with Fabry (FD) disease using the Disease Severity Scoring System (DS3) and the SF-36 survey in male and in female.

Methods: Observational cross-sectional study. The DS3 and SF-36 survey was administered to the patients of the hospitals, which belong to the research group of Kanagawa enzyme replacement therapy. Participants were treated with agalsidase-alpha or agalsidase-beta. Disease activity was assessed by the Disease Severity Scoring System (DS3). The QoL was measured by Short form-36 (SF-36) and the Kidney Disease QoL Short Form version 1.3 (KDQoL).

Results: Fifteen patients were included in the study. Mean age was 45 years (M/F=10/5), and all patients were receiving ERT. The mean serum Cr was 2.9 mg/dl. The DS3 scores were follows; mean assessment score: 26.5 +/- 10.1, average domains: 10.5 +/- 0.9. The renal domain and the cardiac domain showed relatively high score compared to PNS and CNS scores. The QoL scores of the FD patients were lower than those of general population, but the scores were better than the previous reports of FD from U.S. or EU. The mental component summaries of women were similar to those of the general population. The physical component summaries of QoL were negatively associated with the assessment score of DS3 ($r=-0.545$, $p<0.05$).

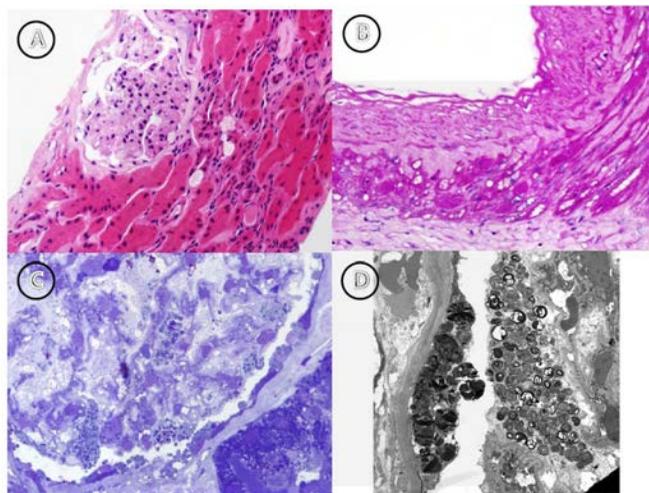
Conclusions: Japanese patients with FD receiving ERT had a relatively good QoL beyond anticipation. DS3 score is useful for assessing disease severity, and may predict some components of QoL.

PUB556

Two Cases of Fabry Disease in Women with Proteinuria Diagnosed by Molecular Analysis of α -Galactosidase A Gene and Kidney Biopsy Jong Oh Yang,¹ Eun-Young Lee.² ¹Internal Medicine, Soonchunhyang Univ, Cheonan, Chungcheongnam-do, Korea; ²Internal Medicine, Soonchunhyang Univ, Cheonan, Chungcheongnam-do, Korea.

Background: Fabry disease is a X-linked lysosomal storage disorder caused by deficiency of α -galactosidase A. This abnormality in enzyme results intracellular accumulation of globotriaosylceramide and leads to severe painful neuropathy with progressive renal, cardiovascular, and cerebrovascular dysfunction and early death. We report 52 and 55 year-old women with proteinuria and hematuria, which were proven to be due to Fabry disease.

Methods: A 52 and 55 year-old women was admitted to the hospital due to proteinuria. They denied previous histories of hypertension, diabetes mellitus, pulmonary tuberculosis, and hepatitis. Their sister and cousin diagnosed fabry disease. Physical examination revealed nonspecific findings. On admission, blood pressure 110/60 mmHg, heart rate 64/min, respiratory rate 16/min, body temperature 36.5°. Lungs were clear and heart was normal. The extremities showed no edema, cyanosis or skin rashes. The laboratory data showed the WBC 5650/mm³, Hb 13.2 g/dL, Platelet 212,000/mm³, BUN 10.2 mg/dL, serum creatinine 0.7 mg/dL. Urinalysis showed pH 5.0 SG 1.023 protein 2+ RBC 5-9/HPF WBC 5-9/HPF. 24-hour urine protein was 533 mg. Abdomen & Pelvic CT and echocardiography were normal. The serologic study was normal. The kidney biopsy showed expansion of mesangial matrix and glomerular hypertrophy. The cytoplasm of podocytes was vacuolated, which consisted of multiple, variable-sized, concentric electron-dense lamellated structures, by electron microscopy.



The enzyme activity for α -galactosidase in serum was 0.59 nmol/min/mg protein.

Conclusions: The patients received enzyme replacement therapy every other week. They had reduction in proteinuria and normal renal function.

PUB557

Intradialysis Partial Parenteral Nutrition (IDPN) in Hemodialysis Patients (HDP) with Protein Caloric Malnutrition (PCM): Preliminary Results Susana Beatriz Asia,¹ Marcela Fabiana Munizaga.¹ ¹Servicio de Nefrologia, Hospital Nacional de Clinicas, Cordoba, Argentina; ²Servicio de Nefrologia, Hospital Nacional de Clinicas, Cordoba, Argentina.

Background: PCD is highly prevalence in HDP and predicts morbi-mortality. NPID is according Espen Guides (march2012) and the SMOFF formulé(soja,TG,olive oil and fish oil), improve inflammation and lipid status. Our goal is to define the evolution of nutritional parameters in HDP and characterize them for future interventions. **OBJECTIVE:** To evaluate if severe PCD in HDP, improve malnutrition and inflammation markers such as albumine,(Alb),cholesterol (Ch), reactive C protein(RCP).

Methods: Prospective and observational study that included 14 patients up this time, both sexes, age 27-80 years old, in maintenance HD from a University Hospital and Army Hospital. Patients signed informed consent. Patients received each HD session and during six months, SMOF lipids 4 grs/kg/d, by IV continuous infusion. We analyzed weight, Hematocrit, Alb, Ch, TG, creatinine, RCP and Global Subjective Valoration (GSV) in pre HD blood samples at the beginning, three and six months. Quantitative demographic variables (age, sex, biochemic parameters) were expressed as medium, SD and applied Student Wilcoxon Test and Chi Test ($p<0.10$).

Results: fourteen patients improved weight (63.1 +/- 3.3 vs 64.9 +/- 3.5, $p=0.351$), alb (gr/dl) (3.7 +/- 0.4 vs 3.9 +/- 0.1, $p=0.016$), TG (mg/dl) (190.1 +/- 26.9 vs 179.4 +/- 30.8, $p=0.03$) and RCP (mg) (28.9 +/- 6.7 vs 10.1 +/- 2.5, $p=0.009$). there were not statistical significance in Hto (gr/dl) (33.3 +/- 1.9 vs 33.7 +/- 1.9, $p=0.856$) CH (mg/dl) (163.9 +/- 15.9 vs 165.6 +/- 13, $p=0.846$), creatinine (mg/dl) (7.7 +/- 0.7 vs 7.4 +/- 0.5, $p=0.233$).

Conclusions: 1- NPID is a successful tool as partial supplementation in HDP with oral dietary intake. 2- In spite of our sample is small, the improvement of Nutritional and inflammatory status, applying International Guides was observed after three months of treatment. 3- Medical awareness about nutritional risks in HDP, is the best tool to prevent alteration of nutritional status. 4- We'll expand the sample.

PUB558

Association of Protein Energy Wasting with Income in Chronic Kidney Disease Stage 3 Patients Anita Saxena, Amit Gupta. Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, India.

Background: Protein energy wasting (PEW) is a major challenge in CKD. Purpose: Assessment of PEW in predialysis patients at first visit to a nephrologist.

Methods: Three day dietary intake of 484 CKD stage 3 patients. Patients were divided in to groups based on appetite and BMI.

Results: Male and female parameters: Serum albumin 3.7 ± 0.84 / 3.68 ± 0.81 g/dL, total protein 7.02 ± 1.27 / 6.94 ± 1.26 g/dL, creatinine 4.68 ± 4.19 / 3.74 ± 3.36 mg% creatinine clearance 33.22 ± 30.48 / 37.55 ± 33.87 ml/minute, BMI 22.60 ± 4.29 / 23.43 ± 4.77 kg/m² energy/kg 16.97 ± 0.65 / 16.8 ± 0.64, protein g/kg 0.65 ± 0.28 / 0.64 ± 0.30, carbohydrate g/kg 2.98 ± 1.54 / 2.98 ± 1.36, fat g/kg 2.98 ± 0.23 / 2.79 ± 0.22, respectively. As appetite decreased dietary protein and energy intake decreased significantly.

Variable/Sex	Normal N 1/126	Average N 70/20	Poor N 88/47	Anorexic N 64/36
Protein g/kg /Male	0.79±.23	0.58 ± .17	0.50 ± .20	0.27 ±.17
Protein g/kg / Female	0.79±.23	0.56 ±.16	0.48 ±.15	0.29 ±.20
Energy cal/kg / Male	21.57 ± 7.85	25± 3.70	12.36±4.26	6.92 ±4.36
Energy cal/kg / Female	21.19 ±5.81	14.67 ±3.09	12.79±3.92	7.25± 3.95

Appetite was average 14.46%/4.13% poor 9.7%/18.18%, anorexic 13.2%/ 7.4% in males and females. Income correlated with BMI (p.000), dietary protein (p.000) energy (p.000) and carbohydrate (p.000). Appetite correlated with creatinine (p 0.019), dietary energy, protein, carbohydrate and fat (p.000) intake. BMI correlated (p0.000) with fat, carbohydrate, energy and creatinine clearance. Anova showed significant difference between appetite groups in energy, protein, fat, carbohydrate, creatinine clearance (p0.000) and serum albumin (p 0.025). There was significant difference in protein (p0.026) energy intake (p 0.000) and creatinine clearance (p0.038) between BMI groups. Based on income there was significant difference between groups in BMI (0.000), energy (p0.019), protein (p 0.031), albumin (0.001).

Conclusions: With decline in renal function, appetite worsened and nutritional intake decreased. Energy intake was significantly deficient. 84% patients had reduced appetite and 69.2% had PEW. Low income is a risk factor for PEW in CKD.

PUB559

Study on Correlation Between Serum Creatinine, Cystatin-C, Urinary Albumin Creatinine Ratio and Body Composition Xuemei Li, Jie Ma. *Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: Based on an epidemiological survey in Peking, China, to study the correlation between serum creatinine, Cystatin-C and urinary albumin creatinine ratio (ACR)and body composition.

Methods: Residents over the age of 35 of the Beijing Pinggu District by random sampling method. Laboratory test: take morning ACR, blood samples were taken for blood routine, kidney function. Test body composition after emptying the bladder by using INBODY-720 machine. Use SPSS 17.0 software for data statistical analysis, count data were analysed by using multivariate linear regression.

Results: A total of 9283 people participated in the survey, which 4324 males, age 54.7±10.7 years, 4959 females, age 53.4±11.2 years. Male: 1) Human body cell mass (BCM) and ACR, Cystatin-C, no correlation, was positively correlated with height (B=0.43, P<0.01), and serum creatinine was that positive correlation (B=.01, P<0.01). 2) Lean body mass (FFM) and ACR, serum creatinine, Cystatin-C, no correlation. 3) Skeletal muscle content and ACR, serum creatinine, Cystatin-C, no correlation. 4) Body fat mass and ACR, no correlation, and Cystatin-C was positively correlated with (B=7.09, P < 0.01). Female: 1) Human body cell mass (BCM) with height and cystatin-C, no correlation, but positively correlated with serum creatinine (B=0.035, P<0.01), and ACR was negative correlation (B=-0.005, P<0.05). 2) Lean body mass (FFM) and ACR, Cystatin-C, no correlation, and serum creatinine were positively related (B=0.035, P<0.01). 3) Skeletal muscle content and ACR, Cystatin-C, no correlation, and was positively correlated with height (B=0.031, P<0.01), and serum creatinine were positively related (B=0.035, P<0.01). 4) Body fat mass and ACR was negative correlation (B=-0.01, P<0.05). Cystatin-C were positively correlated (B=12.3, P<0.01), and age were negatively correlated (B=-0.13, P<0.01), and serum creatinine was negative correlation (B=-0.092, P<0.01).

Conclusions: There was a positive correlation between serum creatinine and the human body cell mass (BCM), lean body mass (FFM) in men, and skeletal muscle content, body fat weight in women, but the correlation is not strong. The blood cystatin-C and body fat weight was positively correlated.

PUB560

Worsening Nutritional Status Assessed Is an Independent Predictor of All-Cause Mortality in Incident Dialysis Patients Jong Hyun Jhee, Young Eun Kwon, Tae-Hyun Yoo, Shin-Wook Kang. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Malnutrition is closely associated with mortality in end-stage renal disease (ESRD) patients. However, little is known whether improvement or deterioration of nutritional status after dialysis initiation affects clinical outcome. This study was aimed to elucidate the association between the changes of subjective global assessment (SGA) after dialysis initiation and mortality in ESRD patients.

Methods: Data were recruited from the Clinical Research Center for ESRD cohort. SGA score was measured by trained investigators at the time of dialysis initiation and after 12 months. Nutritional status was defined as well-nourished (SGA 6-7, A), mildly to moderately malnourished (SGA 3-5, B), or severely malnourished (SGA 1-2, C). Severely malnourished patients (SGA C) were excluded due to small sample size. The patients were divided into four groups according to the change of SGA; group 1, A to A; group 2, B to A; group 3, A to B; and, group 4, B to B.

Results: A total of 911 patients were enrolled. The mean age was 54.6±14.1 years, 554 patients (60.0%) were male. During a median follow-up duration of 30 months, 109 patients (12.0%) died. Survival rate of group 1 was the highest, and that of group 4 was the lowest (group 1, 91.2%; group 4, 71.4%; P<0.001). Worsening nutritional status was

a significant risk factor for mortality (group 3 vs. 1, HR=3.15, CI=1.51-6.54, P=0.002), while baseline nutritional status at dialysis initiation was not (group 1 vs. 2, P=0.063; group 3 vs. 4, P=0.107).

Conclusions: Improvement of nutritional status after dialysis initiation could be beneficial for patient outcomes regardless of baseline status, suggesting that intervention to improve nutritional status after dialysis initiation might be a strategy to reduce mortality in ESRD patients.

PUB561

Prophylactic Effect of Erythropoietin Injection to Prevent Acute Mountain Sickness: An Open-Label Randomized Controlled Trial Hyungjin Cho, Soon Bae Kim. *Div of Nephrology, Dept of Internal Medicine, Univ of Ulsan, College of Medicine, Asan Medical Center, Seoul, Republic of Korea.*

Background: This study was performed to evaluate whether increasing hemoglobin before ascent by prophylactic erythropoietin injections prevents acute mountain sickness (AMS).

Methods: This open label, randomized, controlled trial involved 39 healthy volunteers with hemoglobin \leq 15.5g/dL who were divided randomly into erythropoietin (n = 20) and control (n = 19) groups. Epoetin alpha 10,000 IU injections were given weekly for four consecutive weeks. On day 1, and 7 days after the last injection (day 29), oxygen saturation (SaO2), and hemoglobin were measured. The subjects departed Seoul on day 30 and arrived at Annapura base camp (ABC, 4,130 m) on day 34. AMS was diagnosed when headache and Lake Louise score (LLS) of \geq 3 were present. Immediate descent criteria followed US Army recommendations.

Results: Two groups differ in hemoglobin levels on day 29 (15.4 ± 1.1 vs 14.2 ± 1.0 g/dL, P = 0.001). At ABC, erythropoietin group had a significantly lower mean LLS, AMS incidence, and number of subjects who met immediate descent criteria. Multiple logistic regression analysis showed that SaO2 < 87% and control group, but not hemoglobin < 15.0 g/dL, independently predicted satisfaction of immediate descent criteria.

Criteria	EPO (n=20)	Control (n=19)
HACE(ataxia) plus HAPE (PR>110)		1
HACE(ataxia)	1	0
HACE(severe lassitude)		1
Severe AMS plus HAPE (PR>110)	1	1
Severe AMS alone		4
HAPE(PR>110)	1	3
Total	3	10
*p=0.019. HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema; AMS, acute mountain sickness; PR, pulse rate		

Erythropoietin-related adverse effects were not observed.

Conclusions: Erythropoietin-related adverse effects were not observed. In conclusion, erythropoietin may be an effective prophylaxis for AMS.

Funding: Pharmaceutical Company Support - CJ pharmaceutical

PUB562

Nutritional Assessment for the Chronic Dialysis Patients with/without Sarcopenia Miho Suzuki, Yuya Sakai, Ikuto Masakane. *Yabuki Hospital.*

Background: A recent arising problem of chronic dialysis patients is sarcopenia closely related to malnutrition. Muscle loss deteriorates daily activities of dialysis patients and ultimately worsens the QOL and prognosis of the patients. The aim of this study was to clarify the relationship between the nutritional status and sarcopenia and to analyze the status of nutrient intake in these patients.

Methods: 90 chronic hemodialysis patients were enrolled to the current study. (age 62.8yrs. Men were 76%, DM 41%).Skeletal muscle mass (SMM) was estimated by bioelectrical impedance analysis and a low muscle mass was defined by the SMM index (SMI: SMM [kg] / height [m]²) as > men: 7.0kg, women: 5.7kg).Muscle function was estimated by grip strength and walking speed as the Timed up and go test (TUG).A low grip strength was defined as less than 26 kg (men) or 18 kg (women). TUG less than 11 second was diagnosed as a low walking speed.Malnutrition was defined as by the Malnutrition-Inflammation Score(MIS)(\geq 6point), GNRI(<92) and the criteria of protein energy wasting (PEW).The dietary assessment was performed by the food frequency questionnaire.

Results: Sarcopenia was identified in 22% of the subjects. The sensitivity to detect sarcopenia was not sufficient as 35% in MIS, 50% in GNRI and 10% in PEW. In the patients with sarcopenia, the average of total energy intake and protein was significantly lower than those in non-sarcopenia, 1618±122kcal vs 2041±65kcal in energy; 52±4g vs 68±2g in protein. The intake of fishes and meats (110±15g vs 153±8g),beans (31±11g vs 61±6g),confectionery, beverages and sugar (126±77g vs 306±41g) were significantly lower in sarcopenia than non-sarcopenia.

Conclusions: Malnutrition-related sarcopenia was only 10-50% among sarcopenia. It is important to measure muscle mass and muscle function regularly for dialysis patients because it is not enough to screen sarcopenia only by nutritional measurements. Sufficient protein and energy intake are essential for the prevention of sarcopenia. If patients don't have appetite,confectionery or a beverage or sugar may beacceptable for the prevention of muscle loss.

PUB563

Stomach Acid Reducers May Predict Nutritional Deficiency in Dialysis Patients Klara Berta, Mihaly B. Tapolyai, Maria Faludi, Melinda Forró, Ákos Géza Peth?. *Dialysis, Fresenius Medical Care Semmelweis Univ, Budapest, Hungary.*

Background: Malnutrition is a major predictor of mortality among dialysis patients. Malnutrition markers are thus regularly monitored in order to intervene when the nutritional status may decline. We investigated whether taking stomach acid reducing medications may indicate nutritional risk.

Methods: This is a cross sectional study of 103 patients undergoing chronic hemodialysis in Budapest, Hungary at a university hospital based dialysis unit. The patients' nutritional indicators such as serum albumin, phosphorus, nPCR and whether they were receiving cholecalciferol replacement were examined among those who did and those who did not take an acid reducing agent, such as a Proton Pump Inhibitor (PPI) or H2 blocker.

Results: Six patients were excluded because data were incomplete or the patients had not been on dialysis for more than 2 months. Of the 96 patients 44.9% took an acid reducer on a regular basis. The serum albumin (3.78 ± 0.02 mg/dL vs. 3.56 ± 0.01 p:0.008), phosphate (1.88 ± 0.49 mmol/L vs. 1.64 ± 0.54 p:0.04) and nPCR (1.00 ± 0.20 vs. 0.91 ± 0.25 p: 0.06) were lower among PPI takers. PPI takers were much more likely to be taking cholecalciferol for measured 25-OH-vitamin-D deficiency (1.8% vs. 18.1% p:0.01). While PPI takers were older (59.7 ± 16.2 years vs. 65.7 ± 13.3 p:0.04), there was no difference in the two populations in the presence of an AV Fistula, delivered Kt/V, calcium or serum bicarbonate.

Conclusions: We conclude that taking PPI's or H2 Blockers in dialysis patients may be an indicator of being at risk for malnutrition.

PUB564

Impact of the Potassium Additives on the Total Content of This Element in Processed Foods Margareth Lage L. de Fornasari,^{1,2} Maria raquel Manhani,² Yvoty As Sens.^{1,2} *Post Graduation, Santa Casa of Sao Paulo School of Medical Sciences, Sao Paulo, SP, Brazil; ²Nutrition, Sao Judas Tadeu Univ, Sao Paulo, SP, Brazil.*

Background: The additives of potassium salts are allowed in processed foods to preserve, to inhibit mold, to emulsify products. Patients with chronic kidney disease need to control the intake of potassium, and are advised for doctors and dietitians to restrict fresh foods and those rich in potassium. The addition of potassium to processed foods is permitted but frequently not specified on food labels in Brazil. The purpose of this study was to determine the actual potassium content of a number of products often consumed by end-stage renal disease patients and to compare the actual content with that estimated in a reference source.

Methods: Twenty-five frequently processed products consumed in the diet of end-stage renal patients treated at the hemodialysis unit were analyzed. The processed foods were milk beverages, yogurt, a type of cream cheese, margarine, tomato sauce, salad dressing, powdered juices, and had potassium sorbate or others potassium salts. The concentration of potassium (mg K/100g of food) was determined by flame photometry according to the Adolfo Lutz Institute methodology, and in triplicate. The comparison of the potassium obtained with the expected potassium was based on two national reference tables.

Results: All products had potassium-containing additives listed among their ingredients. The medium values of potassium (mg for 100 g or mL) for the different foods were: milk beverages 102.6 to 125.3; type of cream cheese 80.3 to 194.4; margarine 21.6 to 37.3; tomato sauce 253.3 to 258.2; salad dressing 78.5 to 128.4; powdered juices 33 to 240.8. Processed food that had higher potassium values than the content expected from the food label were, milk beverages (1.6 to 2 times); type of cream cheese (0.9 to 2.1 times); salad dressing (1.6 to 2.6 times); margarine (1.4 to 2.5 times) and powdered juices (376 to 726 times). Tomato sauce had less potassium values than expected levels (0.6 times).

Conclusions: Processed foods with potassium additives contain higher levels of potassium than those listed in reference tables.

PUB565

Differences in Eating Patterns Between Maintenance Hemodialysis Patients from the U.S. and the UK Annabel Biruete,¹ Brandon Kistler,¹ Patrick Highton,² Kristin P. Wiens,³ Peter J. Fitschen,¹ Alice C. Smith,² Ken Wilund.¹ *¹Univ of Illinois; ²Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; ³Univ of Delaware.*

Background: Maintenance hemodialysis (HD) patients in the United States (US) have poorer nutritional status and higher mortality than European patients. Patient characteristics and clinical practices are hypothesized to contribute to these differences. Therefore, our aim was to compare eating patterns between HD patients from the US and the United Kingdom (UK).

Methods: HD patients (US=60, UK=29) were recruited. Four 24-hour diet recalls were collected, two dialysis days (DD) and two on non-dialysis days (NDD) using the USDA 5-pass method. Dietary information was entered and analyzed using diet analysis software and then grouped into eight food categories according to NHANES. Food security was assessed by the USDA 10-item survey. Statistical analysis was performed using independent samples t-test and Pearson's correlations.

Results: Patients from the UK consumed more energy on DD (24.9 ± 2.1 vs. 18.5 ± 1.1 kcal/kg/d; p=0.004) and NDD (24.5 ± 1.5 vs. 20.5 ± 1.2 kcal/kg/d; p=0.048) than US patients. Additionally, US patients had lower energy intake on DD than NDD (p=0.007), while there were no differences in UK patients (p=0.85). UK patients consumed more baked goods/breads, whereas US patients consumed more energy from beverages, entrees, and deli

(p<0.05 for all). Moreover, some degree of food insecurity was more frequently observed in the US (54.2% vs. 10.3) and was associated with younger age ($r^2=0.29$, p=0.033), higher BMI ($r^2=0.41$, p=0.005), higher dietary sodium ($r^2=0.29$, p=0.03) and sugar ($r^2=0.27$, p=0.05).

Conclusions: HD patients from the US had lower energy intake on DD and NDD compared to UK patients. Furthermore, US patients had lower dietary intake on DD. This may be in part due to US clinics' restrictive policy on eating during dialysis. Furthermore, there were differences in food pattern consumption and food insecurity. These differences may help explain global differences in nutritional status and outcomes. Further studies are needed to assess the contribution of eating patterns and socioeconomic status on clinical outcomes in HD patients.

PUB566

Is Reverse Epidemiology in BMI of Maintenance Hemodialysis Patients Adaptable to the Patients without PEW? Yuya Sakai, Miho Suzuki, Ikuto Masakane. *Yabuki Hospital.*

Background: Reverse epidemiology has been addressed in Body mass index (BMI) of chronic hemodialysis patients; the lowest mortality rate in BMI 24-26 as reported by the Japanese Society for Dialysis Therapy. The higher BMI the lower mortality as stated by the Dialysis Outcomes and Practice Patterns Study. However, because these survey subjects included lower BMI patients with malnutrition and chronic inflammation, the high BMI patients' mortality risk might have been relatively low. The optimal BMI derived from these epidemiological analysis may not be well indicated for the patients' who do not have malnutrition and inflammation. So, we aim to study the optimal BMI of maintenance hemodialysis patients without Protein Energy Wasting (PEW).

Methods: 183 patients on maintenance hemodialysis patients were enrolled in the current study. All subjects have over 2 years of dialysis vintage and are not applicable to PEW and don't have inflammation which was defined as CRP less than 0.3 mg/dL as of December 2009. The observation period is from December 2009 to December 2014. The subjects were classified into 4 groups on a BMI scale (n(<18.5 (13), 18.5<=22 (81), 22<=25 (47), 25<= (42)). The 5-year cumulative survival rate, the death risk factor, and each BMI groups' relative mortality risk for BMI 22<=25 group were examined.

Results: During the observation period, clinical deaths resulted in 19 patients, changing hospital or accidental death resulted in 22 patients. There was no significant difference in the crude 5-year cumulative survival rate of BMI groups. Age, diabetes mellitus, albumin were dependent risk factors for death. When the mortality risks were adjusted by these 3 parameters, the mortality risk of BMI <18.5 was significantly higher than each of the 3 BMI groups (HR 6.97, P=0.0417). The mortality risk of BMI <25 was relatively higher than BMI 22<=25 group but not significant.

Conclusions: In the maintenance hemodialysis patient without PEW syndrome and inflammation, the patients of BMI <18.5 have a higher risk of death so they require nutritional management to maintain and/or achieve a BMI \geq 18.5. Reverse epidemiology in BMI was not adaptable to the Japanese dialysis patients without PEW and inflammation.

PUB567

Body Weight and Proteinuria Determine Plasma Triglycerides via Hepatic Syndecan-1/Heparan Sulfate in Experimental Nephrosis Saritha Adepu,¹ Harry Van Goor,² Gerjan Navis,¹ Stephan J.L. Bakker,¹ Jacob van den Born.¹ *¹Nephrology, Univ Med Center, Groningen, Netherlands; ²Pathology, Univ Med Center, Groningen, Netherlands.*

Background: Dyslipidemia contributes to a high cardiovascular risk profile of proteinuric patients. Via its heparan sulphate (HS) side chains, hepatic syndecan-1 (syn-1) is a major uptake receptor of remnant lipoproteins. We hypothesized that proteinuria induces changes in hepatic syn-1/HS metabolism leading to dyslipidemia, which is reversed by caloric restriction (CR).

Methods: We used the hypertensive rat MWF proteinuria model. Male rats (22 wks) were uni-nephrectomized and fed ad libitum (AL) food (MWF-AL; n=14), or CR (MWF-CR; n=13, 60% of MWF-AL food intake). Wistar rats matched for sex, age, nephrectomy on AL food intake served as controls (W-AL; n=13). Sacrification is at 48 wks. Wistar control rats were sacrificed at 22 wks (Young W-AL; n=6). Body weight, blood pressure, plasma creatinine, cholesterol, triglycerides, and proteinuria were measured at 22 and 48 wks. Livers were used for qRT-PCR and immunostaining. Correlation analysis was done by linear regression analysis.

Results: Renal aging (W-AL vs Young W-AL) was associated by mild proteinuria and dyslipidemia (both p<0.05). Compared to W-AL rats, at 48 wks MWF-AL rats developed hypertension, proteinuria, reduced creatinine clearance (all p<0.05) and comparable dyslipidemia. CR reversed all these parameters in MWF-CR comparable to W-AL rats (p<0.05). Hepatic syn-1/HS profiling revealed striking increase in syn-1 protein and altered HS sulfation pattern in proteinuric W-AL and MWF-AL. CR normalized syn-1 protein levels and increased HS sulfation. Syn-1 appeared positively ($r=0.366$, p<0.02) and HS sulfation inversely ($r=-0.450$, p<0.005) associated with plasma triglyceride concentrations. Both associations were lost after adjustment for body weight or proteinuria.

Conclusions: CR normalized hypertension, renal function, proteinuria, dyslipidemia and syn-1/HS in MWF rats. Regression analysis suggests that body weight and proteinuria reduce hepatic HS sulfation, leading to hampered TRL binding and uptake and increased TG values.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PUB568

Obese Donors: The Multidisciplinary Approach in Improving Outcomes Giselle Guerra,¹ Ian Thomas,¹ Panagiotis Tryphonopoulos,² Linda J. Chen,² Gaetano Ciancio.² ¹Dept of Medicine, Miami Transplant Inst, Miami, FL; ²Dept of Surgery, Miami Transplant Inst, Miami, FL.

Background: Living donation appears safe over the years but concerns still exists long-term. Small analyses after unilateral nephrectomies have resulted in proteinuria and slight decrease in renal function (eGFR) if patient tended to be obese; thus raising a concern for accepting living kidney donors (LKD) with body mass index (BMI) greater than 30 but less than 35 Aim: Determine the outcomes of obese LKD with BMI greater than 30 but less than 35.

Methods: A single center retrospective analysis was performed at out transplant center from January 1, 2013 - November 30, 2014. LKD ages 18-65 were assessed: 1. Study Arm (SA): obese LKD with BMI>30 who were enrolled into a nutritional program and 2. Control arm (CA): non-obese living kidney donor candidates at the time of referral. Weight loss prior to surgery and afterwards, surgical complications, loss of kidney function (eGFR), and proteinuria (spot urine protein/spot urine creatinine ratio) after 6 months from donation were reviewed.

Results: Patient demographics - SA: 15 African Americans (AA), 13 Hispanics (H), 7 White, 1 Other, 3 Unknown versus CA: 55 H; 49 Whites; 20 AA; 5 Other [figure 1]. In the SA: 24/40 had BMI >35 at time of referral and placed in nutritional program; 8/24 dropped BMI to less than 35 prior to surgery and 3/24 pending surgery now; 4/24 ruled out due to medical issues & (9/24) were non-compliant. Surgical complications 1/8: Parasthesia. After donation in SA, blood pressure remained stable, 2/8 gained weight, kidney function at 6 months: 47% of obese donors had a decrease in eGFR at 6 months of 40% or greater. The mean decrease in eGFR was 33.9% in the study arm. In the control arm: 55 Hispanics; 49 Whites; 20 AA; 5 Other. 15% had a decrease in eGFR at 6 months 40% or greater and the mean decrease in eGFR was 28.9.

Conclusions: Obesity in living donors needs careful analysis especially in minority populations since there is a trend to have a greater loss in kidney function after donor nephrectomy. Donation is possible but strict nutritional and guidelines and medical evaluation need to persist for the wellness of these patients long-term.

PUB569

The Role of Renal Pharmacist in Prescribing Immunosuppressant Medication for Renal Transplant Patients to Improve Safety Israr Baig, Preetham Boddana. *Pharmacy Dept, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, Gloucestershire, United Kingdom.*

Background: This paper describes the safe and efficient repatriation of renal immunosuppressant prescribing from General Practitioners (GPs) to secondary care using hospital Pharmacist Independent Prescribers (PIPs).

Methods: From March 2015 the UK commissioner NHS England required all renal immunosuppressant medication, which was traditionally prescribed by GPs following nephrologists' advice, to be prescribed by hospital renal prescribers. Gloucestershire hospitals NHS Foundation Trust decided to use Pharmacist Independent Prescribers to implement this change and provide the ongoing service using commercial Homecare Companies. All Patients were initially sent detailed information about the changes and asked to consent. On receipt of the completed consent form the PIP wrote the initial homecare prescription which was then processed by the pharmacy homecare team. Patients continued to be reviewed at regular intervals by their nephrologists. Details of these consultations were documented using a central renal database which included graft function, drug levels and communication with GPs. The Pharmacist Prescribers subsequently reviewed the renal database prior to generating ongoing homecare prescriptions and, when necessary, contacted the nephrologist for clarification and interventions.

Results: This service reconfiguration has resulted in safe and robust pathway. The use of Pharmacist Independent Prescribers has insured the whole pathway is efficient and closely monitored. Patients are satisfied with the new homecare service and clinicians value the pharmacists' input. Pharmacist prescribers have made a number of interventions which have included patient compliance issues, changes to doses in response to serum drug levels and appropriate brand changes to improve cost effectiveness.

Conclusions: The use of Pharmacist Independent Prescribers to prescribe and manage the renal immunosuppressant homecare service at Gloucestershire Hospitals NHS Foundation Trust has been shown to be safe and efficient.

PUB570

Tools for Adverse Events Prevention in a Hemodialysis Facility: A Local Experience Cinthia Sobral Vieira,¹ Cassiana G. Prates.² ¹Nephrology Service, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil; ²Hospital Epidemiology and Manager Risks Service, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

Background: After the publication "To err is human" there has been a new approach to prevent risks in health system. According to the International Patient Safety Goals there are six steps to be followed like patient identification, proper communication, right surgery in the right side, fall prevention, high alert medication and infection prevention. The goal is to show how a hemodialysis unit, for ambulatory and hospitalized patients leads with adverse event prevention.

Methods: This experience happens in a hemodialysis unit with 101 patients, 3 shifts of 4 hours. It is located in a general hospital in Porto Alegre, south Brazil.

Results: Every patient has an id badge with colored marks according to the risk possibilities (falls, allergies, multi resistant germ, no access condition, hypoglycemic risk). There are no medication facilities. There are checklists for dialysis. The staff has continued medical education for patient safety. There is a map risk (adverse events possibilities) and its approach. If it happens, a notification formulary is filled and reported to the Hospital Epidemiology and Manager Risks Service, that analysis the root causes. The chosen tool is Ishikawa diagram resulting in a plan of action. Every month, one case (not only hemodialysis) is discussed together with a multidisciplinary group and the hospital high direction. The quality patient safety indicators are evaluated, as mortality incidence (21,33 % y); sera conversion to hepatitis C and B (0) and catheter infection (5,24% y).

Conclusions: Chronic renal patient is at high risk of advent events because of frequent treatment, comorbidities, many medication and the pathology consequences. Needle dislodgment, hematomas, lack of registration of weight and arterial pressure at the beginning of dialysis, more than 2 vascular access needle insertion attempts, dialysis interruption may occur, so the unit must be prepared to intervention. Health staff rarely reveals mistakes afraid of consequences and blame. It is necessary to promote the Safety Culture, stimulating to talk about bad events or even near miss to prevent other ones.

PUB571

Zinc Deficiency Correction and Phosphaturia in Children with CKD – A Pilot Study Vladimir Belostotsky,¹ Stephanie A. Atkinson,¹ Michelle N. Rasiah,¹ Steven Arora,¹ Ji Cheng,¹ Joanne Grimmer,² Guido Filler.² ¹Pediatrics, McMaster Children's Hospital, Hamilton, ON, Canada; ²Pediatrics, Children's Hospital, London Health Sciences Centre, London, ON, Canada.

Background: There are no guidelines for correction of Zinc (Zn) deficiency in Chronic Kidney Disease (CKD). Experimental data (Morishita 2001) suggests that Zn modulates the phenotype of Klotho deficient mice and this can potentially increase phosphaturia. Aims: To identify Zn deficiency and determine whether 3 months of oral Zn therapy normalizes Zn status in children with CKD. To assess feasibility of conducting a clinical trial similar to Morishita's in mice and gather information on clinical outcomes and relationship between Zn status and correction of Zn deficiency and phosphate (P) excretion.

Methods: 40 patients (pt) 4-18 yr with primary CKD and CKD due to declining graft function were enrolled from 2 tertiary pediatric nephrology centers. Plasma Zn was measured by High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry at baseline and 3 months with routine blood and urine parameters. Pt with Zn<11.5 mmol/L were treated for 3 months with Zn citrate tablets (10mg Zn/day for 4-8 yr and 20 mg/day for 9-18 yr). Statistical analysis was done using nonparametric methods and relative risk ratio.

Results: Of 21 pt (M-13, F-8) with completed data, Zn deficiency was found in 10. Stages of CKD were: 2-11 pt, 3-5 pt, 4-5 pt. One pt was hyperphosphatemic. 2 Zn deficient pt had abdominal discomfort whilst taking Zn. Plasma Zn improved in 8 out of the 10 treatment pt (4.4 times more frequently than in control pt) after 3 months of Zn therapy. Zn therapy over 3 months did not change serum P (median 1.23 mmol/L to 1.25 mmol/L) or its fractional excretion (median 24.08% and 21.71%).

Conclusions: Zn deficiency occurred in about 50% of CKD pt. Preliminary analysis indicates that 3 months of oral Zn supplementation is likely beneficial in Zn deficient pt but a larger sample size is required to evaluate the impact of correction of Zn deficiency on other metabolic parameters. Correction of Zn deficiency does not alter P excretion in pt with normal blood P. Similar studies are feasible to perform in hyperphosphatemic pt.

Funding: Private Foundation Support

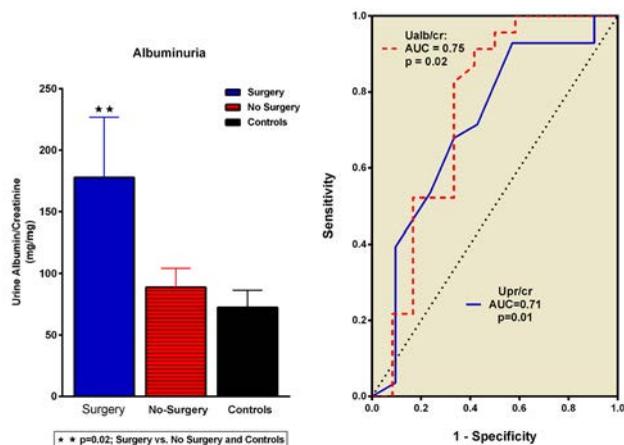
PUB572

Proteinuria as a Marker of Severe Unilateral Ureteral Obstruction in Infants Mariselis Rosa-Sanchez, Jayanthi Chandar, Wacharee Secherunvong, Chryso P. Katsoufis, George N. Sfakianakis, Rafael Gosalbez, Andrew Labbie, Gaston E. Zilleruelo, Carolyn L. Abitbol. *Pediatric Nephrology, Nuclear Medicine, Pediatric Urology, Holtz Children's Hospital/Univ of Miami, Miami, FL.*

Background: Unilateral ureteral obstruction (UO) is a common congenital anomaly in infants. Controversies remain regarding clinical indications for timely surgery. The objective was to compare the radiologic and laboratory parameters of a cohort presenting with significant unilateral hydronephrosis that were managed either conservatively or surgically.

Methods: This retrospective analysis included 81 infants during a 10 year period with high grade hydronephrosis designated by renal ultrasound. Further assessment included renal function by nuclear scintigraphy and proteinuria. Proteinuria was determined by random urine total protein to creatinine ratio (Upr/cr) and albuminuria by random urine albumin to creatinine ratio (Ualb/cr). Receiver operator characteristic (ROC) area under the curve (AUC) statistics were applied to Upr/cr and Ualb/cr ratios with determination of likelihood ratios (LR) for requiring surgery.

Results: In this cohort, 22/81 (27%) were operated, including 21 pyeloplasties and 1 nephrectomy for severe UO. Initial proteinuria was significantly greater in UO patients who underwent surgery compared to those without surgery (p=0.02). ROC-AUC demonstrated that both Upr/cr and Ualb/cr predicted the presence of severe UO requiring surgery (Upr/cr: AUC=0.71; p=0.01 and Ualb/cr: AUC=0.75; p=0.02). Upr/cr and Ualb/cr was similar in normal control infants and those with non-surgical UO.



Conclusions: Proteinuria and albuminuria were significantly elevated in UUO infants who required surgery compared to normal term infants and those with non-surgical UUO. Although both were sensitive markers of renal injury, albuminuria was superior in predicting the need for surgery in patients with UUO.

PUB573

High Prevalence of Glomerular Hyperfiltration in Obese Adolescents
 Anitha Ezekiel, Jennifer Therese Potonia, Pedro Anis Rahnemaye rabhani nourani, Samhar I. Al-Akash. *Driscoll Children's Hospital - Kidney Center, Corpus Christi, TX.*

Background: Glomerular hyperfiltration (GHF) has been described in diabetic and obese (O) adults, and usually precedes proteinuria or clinical disease, and may indicate underlying renal damage and chronic kidney disease (CKD). GHF is poorly studied in adolescent children (AC). We hypothesized that GHF is present in AC and that GFR correlates with the BMI.

Methods: We queried the electronic medical records from 6/2010 to 12/2013 to include AC 12-21 years of age with at least one serum creatinine (SCr) and BMI in the same encounter, and excluded pts with CKD, HTN, DM, proteinuria, or renal transplant. Pts were separated into 2 groups; Control (C) - BMI < 30 and O - BMI ≥ 30 kg/m². We used the original Schwartz formula (OSF) to calculate GFR as our lab uses the Jaffe method to measure SCr. We defined GHF as GFR > 150 ml/min/1.73m².

Results: Demographic data and results are shown in table 1.

	C (control) BMI < 30	O (obese) BMI ≥ 30	P-value
N (encounters)	730	246	
Mean age - years	18.5±0.8	15.5±2.0	<0.0001
Mean BMI - kg/m ²	21.7±4.1	38.4±6.8	<0.0001
Male	48%	49%	NS
Prevalence of GHF (GFR > 150)	3%	16%	0.0001 (OR 6.2)
- Male	0	28%	0.0001
- Female	4%		NS
		5%	
Mean GFR	A 89.6 (85-95)	B 128.2 (114-141) (BMI ≥ 30)	<0.0001
		C 120 (114-127) (BMI 30-34.9)	<0.0001 (A vs. B, C, D, E) 0.01 (C vs. E)
		D 130 (124-136) (BMI 35-39.9)	
		E 134 (128-141) (BMI ≥ 40)	
Prevalence of GFR > 130	20%	43%	<0.0001 (OR 6.9)
- Male	14%	62%	<0.0001 (OR 19.1)
- Female	12%	25%	<0.0291 (OR 2.5)

Conclusions: Using the OSF, we showed a higher prevalence of GHF in obese AC, and a showed that GFR correlated with BMI. Males have a greater risk of GHF. Due to the increased incidence of obesity in AC, special attention needs to be paid to renal function. In the absence of proteinuria or signs of clinical disease, GHF may be the earliest sign of renal disease, and should be assessed in obese AC. The choice of GFR estimation formula

specifically in the obese has not been well established. This study provides preliminary data for a prospective trial for comparison of standard GFR measurement with existing GFR estimation formulas to allow the use of the most appropriate formula in obese pts.

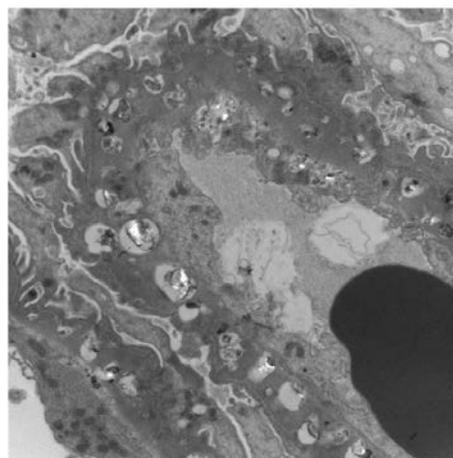
PUB574

Familial Lecithin-Cholesterol Acetyltransferase Deficiency Masquerading as Membranous Nephropathy in Childhood
 Ania B. Koziell, Katrina Soderquest. *Experimental Immunobiology, King's College London, London, United Kingdom.*

Background: Familial Lecithin-cholesterol acetyltransferase (LCAT) deficiency is a rare autosomal recessive disorder of lipid metabolism characterised by severely reduced HDL concentrations and impaired esterification of cholesterol. It is characterised clinically by glomerulopathy and mild haemolytic anaemia presenting in adulthood leading to ESRD by the fourth decade of life through the deposition of abnormal lipoproteins in the renal stroma. Paediatric cases are rarely described.

Methods: 2 siblings aged 8 and 11 years presented with asymptomatic non-nephrotic range proteinuria detected on routine testing. There was no family history of renal disease, although parents were consanguineous. Initial screens revealed normal renal function and normal serum albumin. Other investigations demonstrated raised lipid profiles but in keeping with nephrotic syndrome. A renal biopsy was performed in view of escalating protein and albumin creatinine ratios.

Results: Renal biopsy initially demonstrated light microscopic features of membranous nephropathy. However, electron microscopy demonstrated inclusions that were not typical of the adult form of the disease but clearly lipid filled (Figure 1). Confirmation of the diagnosis was by demonstration of significantly reduced HDL-cholesterol, and detection of a novel LCAT gene missense mutation G54V as well as reduced LCAT enzyme activity on assay.



Conclusions: LCAT deficiency may present with mild symptomatic proteinuria in childhood. Although rare, it should be considered in a differential in paediatric membranous nephropathy. The diagnosis was made on characteristic EM appearances, genetics and reduced enzyme activity. A trial of enzyme replacement is planned. Interestingly, the older sibling has higher lipids yet the younger worse renal disease opening up new hypotheses for how LCAT deficiency might cause renal pathology.

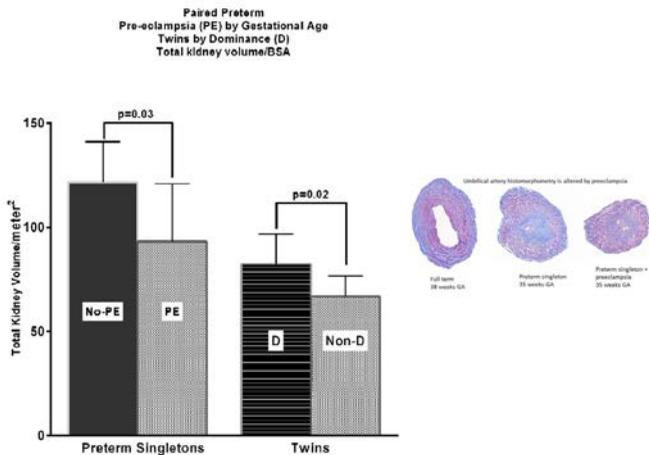
PUB575

Umbilical Artery Histomorphometry: Linking the Intrauterine Environment and Nephrogenesis
 Marissa J. Defreitas, Deepan Mathur, Wacharee Seherunvong, Shahnaz Duara, Salih Y. Yasin, Maria Matilde Rodriguez, Carolyn L. Abitbol. *Pediatric Nephrology, Pediatric Pathology, Neonatology, Perinatology, Univ of Miami/Holtz Children's Hospital, Miami, FL.*

Background: An adverse intrauterine environment is linked to the developmental origins of aortic stiffness, nephron deficit, and adult onset cardiovascular and renal disease. We hypothesized that umbilical artery histomorphometry(UAH), a direct extension of the central vascular tree, would provide insight into nephrogenesis across gestational age (GA) groups.

Methods: From 156 newborns enrolled in the Gerber Infant Kidney Study, a subcohort of 32 had umbilical cord specimens evaluated (7 term(T-S), 15 preterm singletons(PT-S) and 10 preterm twins(PT-T)).The umbilical cord was sectioned, stained with Trichrome and digitalized.Muscular(MA) and collagenous areas(CA) of the umbilical arteries were measured in pixels using the ImageJ1.48q software and converted to mm². The combined total kidney volume(TKV) was measured by ultrasound and factored by the infants' ponderal indices and BSAs.

Results: TKV/PI of T-S (6.9±1.8) and PT-S(7.5±1.9) were similar; while TKV/PI of PT-T was significantly less than either of the singleton groups (4.5±0.8;p<0.001). Among PT-S, 6(40%) were from pre-eclamptic (PE) mothers. When paired by GA to other PT-S not from PE mothers, they demonstrated stunted TKV/BSA (93±28 versus 122±19µm²/m²;p=0.02). Among twin pairs, there was also a discordance in TKV/BSA (68±10 versus 81±15 µm²/m²;p=0.04). UAH demonstrated a positive correlation with increasing %MA and a negative correlation with increasing %CA.



Conclusions: UAH links an adverse and/or competitive intrauterine environment with nephrogenesis independent of GA. An enhanced umbilical artery musculature area reflects an increased renal mass while increased vascular collagen parallels decreased renal mass in discordant twins and singletons of PE mothers.

Funding: Private Foundation Support

PUB576

Insulin-Like Growth Factor/Growth Hormone and Insulin-Like Growth Factor Binding Proteins in Normal Heighted and Short Children with CKD John D. Mahan,¹ Rose M. Ayoub,¹ Larry A. Greenbaum,² Amira Al-Uzri,³ Frederick J. Kaskel,⁴ Susan L. Furth,⁵ Bradley Warady.⁶ ¹Pediatrics, Nationwide Children's/OSU, Columbus, OH; ²Pediatrics, Emory Univ, Atlanta, GA; ³Pediatrics, Oregon Health & Science Univ, Portland, OR; ⁴Pediatrics, Albert Einstein COM, New York, NY; ⁵Pediatrics, Univ of Pennsylvania, Philadelphia, PA; ⁶Pediatrics, Children's Mercy Hospital, Kansas City, MO.

Background: Earlier reports indicated that children with chronic kidney disease (CKD) have 'normal' Growth Hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) levels, suggesting that intracellular resistance and increased IGF-1 Binding Proteins (BPs) account for the poor growth seen in 35% of these children. We explored key growth mediators in subjects with CKD enrolled in the Chronic Kidney Disease in Children (CKiD) study with either normal height or short stature to explore potential explanatory differences in these two subsets.

Methods: 232 children in CKiD (206 normal height: 26 short stature; none on GH therapy) were matched by gender, age and GFR. Short stature = Height Standard Deviation Score (SDS) < -1.88. GH, IGF-1, and IGFBP-1 and 3 were determined by chemiluminometer and ELISA.

Results: Normal height CKD children had higher serum IGF-1/GH, higher IGF-1/IGF-1 BP1 and similar IGF-1/IGF-1 BP3 compared to short CKD children.

	IGF-1/GH*	IGF-1/IGF-1 BP1*	IGF-1/IGF-1 BP 3*
Children height SDS < -1.88	356.7 [152.3, 1017.2]	0.0056 [0.0012, 0.0161]	37.91 [22.62, 56.97]
Children height SDS > -1.88	811.8 [168.2, 2360.0]	0.0136 [0.0055, 0.0582]	53.44 [35.34, 77.50]
P-value (Kruskal-Wallis ANOVA)	0.0002	0.02	0.07

* = (mean [IQR])

Height SDS correlated with IGF-1 in normal height children (r = 0.323), but not well in short children not on GH RX (r=0.046).

Conclusions: Differences in IGF-1, IGF-1/GH, and IGF-1/IGF-1BP1 may explain some variance in growth in CKD children. Height is more highly correlated to IGF-1 in normal height than short CKD children. Analyses in paired subjects may provide further insights in children naïve to and those on rGH to allow detection of critical thresholds that explain and/or predict growth in children with CKD.

Funding: NIDDK Support, Private Foundation Support

PUB577

Assessment of Cochlear Sensitivity of the Pediatric Chronic Kidney Disease and Hemodialysis Patients Rahime Renda,¹ Levent Renda,² Omer Tark Selçuk.² ¹Antalya Research and Training Hospital Pediatric Nephrology; ²Antalya Research and Training Hospital Otorhinolaryngology Dept.

Background: Abnormalities in auditory system are frequent in patients with chronic renal disease and hemodialysis. The aim of this study was to throw light on the relationship between cochlear sensitivity and chronic kidney disease with or without hemodialysis.

Methods: Children aged 6-18 years were evaluated in three groups; 36 nondialytic patients with chronic kidney disease, 16 end stage renal disease patients undergoing hemodialysis, and 30 age and sex-matched control subjects. Hearing outcomes were obtained by pure-tone audiometry and distortion product otoacoustic emissions measurements.

Results: No significant difference was found except in the both ears at 500 Hz frequencies between the study group and the control group. The signal/noise ratio levels and distortion product levels were significantly lower in the nondialytic and dialytic group at all frequencies. Patients with normal hearing were found to have significantly lower signal/noise ratios and distortion product levels than those observed in the healthy controls.

Conclusions: These results showed lower cochlear functions in the dialytic and nondialytic group regardless of hearing loss than in the control group. Patients with chronic renal disease with or without hemodialysis should be monitored periodically even if the hearing thresholds seem to be within normal limits.

Funding: Government Support - Non-U.S.

PUB578

Percutaneous Renal Biopsy at OPD Level Byoung-Soo Cho,¹ Yumi Choi,² Jin-Soon Suh.³ ¹The All Medical Hub Kidney Center, MIRAE ING Research Inst, Seoul, Republic of Korea; ²Dept of Pediatrics, Gwangmyeong Sung-Ae Hospital, Gwangmyeong-si, Gyeonggi-do, Republic of Korea; ³Dept of Pediatrics, College of Medicine, The Catholic Univ of Korea, Bucheon-si, Gyeonggi-do, Republic of Korea.

Background: Renal biopsy is a prerequisite procedure for the final diagnosis and to evaluate the treatment effect or to determine the prognosis, however due to serious complication of the procedure, should be done by nephrologist and has been performed at admission state.

Methods: Our center performed percutaneous renal biopsy 3,000 cases without major complications during last 30 years, when patients were admitted for 3days. During last 18 months, we performed percutaneous renal biopsy at OPD level under the ultrasound guide (LOGIQ E9).

Results: The youngest one is 1 year old male and the oldest was 64 years old. Mean age was 26 years old. Male to female ratio was 3:2 Mean glomeruli numbers were 31. We used disposable kidney biopsy needle (TSK ACECUT). We checked ultrasound 3 times after renal biopsy for checking AV fistula, hematoma formation during 6 hours hospital stay. Of the 100 case 8 cases received follow up biopsies. Among 100 samples renal medulla was not detected. Two patients(2%) among 100 biopsies showed small(less than 1cm) hematomas. No AV fistula were detected. All patients went home 6hours after renal biopsy without any problems. Renal biopsy results showed IgAN(23%), Nonspecific GN(21%), Diffuse mesangial proliferative GN (17%),HSPN (6.7%), MGN(5.6%),FSGS (5.6%),Others were Alport,Lupus nephritis,DM nephropathy,MPGN type I,Thin GBM nephropathy.

Conclusions: In conclusion, percutaneous renal biopsy under the ultra-sound guide at OPD level with 6 hour ABR is safe and effective if performed at renal cortex level.

PUB579

Acute Lymphocytic Leukemia with Bilateral Renal Masses Masquerading as Nephroblastomatosis Salim Aljabari, Poonam Thakore, Curtis W. Turner, Tetyana L. Vasylyeva. ¹Pediatrics, Texas Tech Univ Health Sciences Center, Amarillo, TX.

Background: While leukemia has a wide spectrum of presenting features, renal involvement at presentation of the disease is rarely seen. We are reporting a child with bilateral renal lesions resembling nephroblastic rests as the first and the only finding subsequently developing classic features of acute lymphocytic leukemia (ALL).

Methods: A 4 year old boy was presented with low grade fever and abdominal pain for few days. A complete blood count (CBC) and abdominal CT scan were done to rule out appendicitis. WBC of 8.1 K/UL,hemoglobin of 13.3 g/dL,Platelets of 170 K/UL, neutrophils 22%,Lymphocyte of 68.9% and absolute neutrophil count of 1.8 K/UL.CT scan showed bilateral renal enlargement with multiple hypodense lesions in the cortical and subcortical regions. Blood urea nitrogen of 7 mg/dl and creatinine of 0.38 mg/dl. The patient was diagnosed with viral gastritis and sent home on supportive treatment. CT scan was later interpreted as nephroblastomatosis by pediatric radiologist as an incidental finding advised to follow up with the pediatric nephrologist. After 14 days he again had low grade fever with abdominal pain. CBC showed WBC of 3.5 k/UL,Hemoglobin of 11.1 G/DL,platelets count of 21 K/UL,neutrophils 6% and lymphocyte 85%,absolute neutrophilic count was 351 and ESR of 71 mm/hr. The pediatric oncology service was consulted for possible malignancy. Peripheral blood smear showed the presence of abundant immature lymphoid cells representing 90% of the total white cells. Bone marrow aspirate and biopsy,flow cytometry and cytogenetic studies showed early B cell leukemia. Treatment was initiated following the guidelines of COG AALL0932. After one week of induction therapy,the CT scan showed a complete interval resolution of all renal hypodense lesions.

Conclusions: Renal involvement in leukemia is challenging to diagnose due to its variable presentation on imaging. On CT scan, it may present as enlargement of kidneys (unilateral or bilateral), or a low-attenuation focal parenchymal. These focal lesions can be difficult to distinguish from nephroblastomatosis which has a similar radiological picture on CT scan.

PUB580

Modality of Treatment of Pediatric Patients with Diarrheal HUS in Acute Renal Failure Does Not Affect Long Term Outcome and Survival
 Sonia Solomon, Julia W. Tzeng. *Pediatrics, Valley Children's Hospital, Madera, CA; Pediatrics, Univ of California, San Francisco - Fresno, Fresno, CA.*

Background: Diarrheal HUS is a disease process usually resulting from infection by *E. coli* H7:0157 and leading to the development of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Acute renal failure typically follows in five days from presentation, with about two-third of the patients requiring renal replacement therapy. Studies have demonstrated that these patients are at risk for long term renal insufficiency and end-stage renal disease. Indications to start dialysis and the mode of dialysis vary from institution to institution. There is no current study comparing which mode of dialysis, hemodialysis or peritoneal dialysis, has greater benefit and less complications. The aim of this study is to compare dialysis modalities and determine whether one modality will result in less complications and better outcomes.

Methods: This is single center, retrospective review. We studied a total of 102 patients from 1999 to 2014. We compared patients with dHUS started on PD or HD. We compared the number of complications and the types of complications from each modality. Long term outcomes were measured by each patient's CKD staging at least one year after diagnosis. EGFR was calculated using the Schwartz formula. Fisher's exact statistical test was used to assess statistical significance.

Results: No statistical significance was found between the modality of dialysis and associated complications ($p=0.4$). There was also no statistical significance between modality of dialysis and long term outcome ($p=0.9$). Complications of PD were catheter malfunction ($n=6$), peritonitis ($n=5$), and the need to switch to HD or CVVHDF ($n=3$). Complications of HD included central line infections ($n=1$).

Conclusions: PD and HD are equally effective in treating patients with dHUS in renal failure and have comparable long term outcome and risks for complications. An important complication to consider for patients on PD is the potential need to switch to HD or CVVHDF; this exposes the patient to an additional surgical procedure that may result in further complications.

PUB581

Self-Reported Health Care Transition Readiness Among Mexican Adolescents with Chronic or End-Stage Kidney Disease Guillermo Cantu,¹ Ana Catalina Alvarez-Elias,² Saul Valverde,² Maria E. Ferris,³ Mara Medeiros.²
¹Univ Panamericana, Mexico, DF, Mexico; ²Univ of North Carolina at Chapel Hill, NC; ³Hospital Infantil de México Federico Gómez, Mexico, DF, Mexico.

Background: 90% of pediatric patients with chronic disease live more than 20 years after being diagnosed. When pediatric patients are transferred to adult-focused health services, generally they do not have the skills and abilities to manage their disease. Adolescents tend to have poor adherence to treatment, and there is a period when there may be complications and increased morbi-mortality. Performance on self-reported health care transition readiness (HCTR) needs to be assessed in patients with chronic or end-stage kidney disease. The aim of the study was to measure self-reported HCTR using the STARx (Self-management and Transition to Adulthood with Rx=Treatment) Questionnaire1, among adolescents in the Nephrology Service at Hospital Infantil de Mexico Federico Gomez.

Methods: The Spanish version of the STARx Questionnaire was translated and back translated and applied to adolescents with chronic or end-stage kidney disease, in the outpatient nephrology department over a 9-month period. The 18-question tool diagnoses actions, knowledge and skills on chronic disease self-management, medications adherence and ability to find new health providers. Age was divided at 16 years. Student's T-tests were performed and p-values of < 0.05 were considered significant.

Results: We enrolled 68 adolescents (53% males) who had a mean age of 15.75 years (± 1.87). Patients who received hemodialysis in the past were 22 (34%). Females had significantly greater scores than males in the "action" category. Those who received hemodialysis in the past had greater knowledge about the disease ($p 0.013$).

Conclusions: The self-reported HCTR among Mexican adolescents with chronic or end-stage kidney disease differs by sex and treatment modality.

Funding: Government Support - Non-U.S.

PUB582

Italian Survey on Patients on Peritoneal Dialysis Treatment: ATENA Alessandro Possidoni,¹ Sara Di fino,¹ Flavia Caputo,² Carlo Crepaldi,³ Roberto Dell'Aquila,⁴ Emilio Giulio Galli,⁵ Anna Maria Costanzo,¹ Umberto Di luzzo paparatti,¹ Roberto Russo.⁶ ¹AbbVie Italy; ²H. Civico of Palermo; ³H. Civile San Bartolo; ⁴Bassano del Grappa; ⁵H. of Treviglio; ⁶H. of Bari.

Background: in Italy, there are few epidemiological data concerning the clinical management of patients (pt) on Peritoneal Dialysis (PD) and the impact of PD on clinical outcomes.

Methods: epidemiological, multicenter study with a retrospective phase (12 months) and a prospective phase (6 months) of subjects on PD. Primary objective: evaluate anaemia, hypertension and mineral metabolism compared to K-DIGO and K-DOQI guidelines (GL). Secondary objectives: comorbidities, hospitalizations, therapeutic strategies, mortality and quality of life (QoL).

Results: 377 consecutive pt. were enrolled (at baseline, CAPD 50.4%/APD 49.6%; Male 59%; mean age: 67 years; dialysis duration: 39.7 months). The most frequent comorbidities were hypertension (88%), cardiovascular diseases (CVD=56%), vascular diseases (25%), dyslipidaemia (25%) and diabetes II (20%). The main cause of hospitalization

was peritonitis (27%; no death associated), followed by CVD (20%). At 6 months, anaemia - not corrected or not adequately corrected (HbF 11g/dl) - occurred in 30% of pt. 73% received ESA. Systolic value >130 mmHg and diastolic value >80 mmHg occurred in 50% and 30% of pt, respectively. Left ventricular hypertrophy was observed in about 60% of echocardiograms. 25(OH)D levels were <10 ng/mL in 30% of executed tests. Secondary hyperparathyroidism (SHPT) occurred in 30% of pt. The drugs used to manage SHPT were calcitriol (36.3%), paricalcitol (29.2%), colecalciferol (23.6%) and cinacalcet (21.5%). Considering a group of pt under therapy for a year with similar basal PTH levels, a significant reduction of iPTH occurred with paricalcitol (1.05 mcg/day), but not with cinacalcet (39.4 mg/day) ($p < 0.001$ vs $p = 0.626$). No effect on Ca and P occurred in the paricalcitol group. At the end of the study, PD didn't modify the QoL significantly.

Conclusions: hypertension and CVD are the most common comorbidities of PD. Peritonitis is the main cause of hospitalization. Anaemia and SHPT are frequent and have to be treated and monitored carefully. There are significant differences in efficacy between different treatment options to treat SHPT.

PUB583

Advancements in Automated Peritoneal Dialysis Cyclers Technology Driving Improved Quality of Care Catherine Firanek, James A. Sloand. *Global Medical Affairs, Baxter Healthcare, Deerfield, IL.*

Background: Enhancements to APD technology directed at greater ease of use and health care professionals' (HCPs) oversight of patient status may help overcome barriers to home dialysis. Use of connectivity to enable remote patient monitoring (RPM) and prescription modification may facilitate patient management, increase HCP and patient communication, and improve outcomes. Advancements in design may also help simplify APD for patients. Objective is to understand and qualify importance of enhanced graphical user-interfaces (GUI), voice-guided instruction, and RPM embedded into APD cycler for HCPs and patients.

Methods: Forty-minute telephone interviews and web-based surveys, including cycler videos, were conducted with 214 nephrologists, 138 renal nurses, and 193 CKD patients from UK and US. HCPs included those in practice for >3 yrs, spending >75% of their time treating patients, and experience with use of conventional cyclers. Patients included those considered candidates for PD or those currently on dialysis, including incenter HD, home HD or PD. In double-blinded study, participants compared 2 conventional cyclers and a cycler with new technology with information screen, enhanced GUI and clinic connectivity.

Results: On a scale of 1-7 (7 the most important), cycler features rated most important to nephrologists, nurses, and patients include size and portability, GUI with voice-guided instructions, and data connectivity/RPM. When rating each cycler on favorability of attributes, the cycler with new technology scored highest. Attributes of 1st conventional cycler scored an average of 0.5 (on a scale of -3 to 3), while attributes of the cycler with new technology from the same manufacturer scored an average of 2.6 ($p < 0.0005$). The attributes of the 2nd conventional cycler compared to the cycler with new technology scored on average 1.15 and 2.3 ($p < 0.0005$), respectively.

Conclusions: HCPs and patients identified enhanced GUI, voice guidance, and data connectivity allowing RPM as favorable attributes to cycler usability and patient management. Technological enhancements that facilitate ease of cycler use and connectivity may increase PD acceptance by patients and HCPs.

PUB584

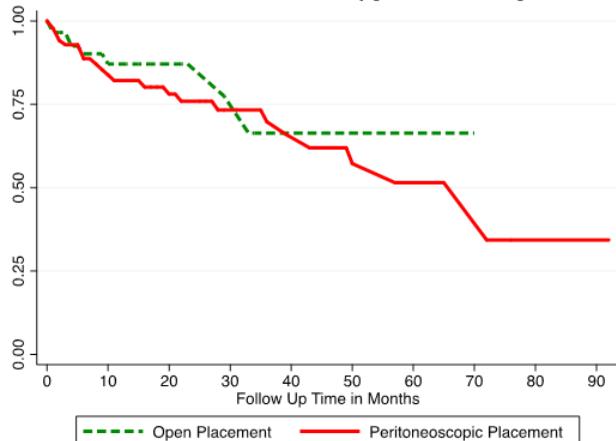
A Single Center Ten-Year Experience in PD Catheter Placement Yorg Al Azzi, Etti Deborah Zeldis, Girish N. Nadkarni, Harry Schanzer, Jaime Uribarri. *Nephrology, Mount Sinai Hospital - Icahn School of Medicine, New York, NY.*

Background: In our early implantation practice, curly tip catheters had better function and less migration when compared with straight catheters and as such, we for the past 10 years have implanted almost exclusively the curly catheters. This is in disagreement with some current literature that favors straight catheters. Due to this discrepancy, we decided to review our single center experience with PD catheters over the past 10 years.

Methods: PD catheters placed over the period of 2004-2014 at our hospital were reviewed. Demographics, comorbidities, operative note, type of catheter, surgical approach, complications and overall survival were collected.

Results: 170 PD catheters were inserted during 10 years (49.7% men, mean age 54.7 years, 167 curly catheters vs 1 straight intra-peritoneal, 63% placed by open surgical technique vs 37% by Y-Teck peritoneoscopy). Diabetes mellitus was the most common cause of ESRD. 60 peritonitis cases occurred during the period of observation (24 lost their catheter), 30 had exit site infection, 9 had a leak out of which 4 lost their catheter, 3 had primary non-function of their catheter, 4 had hernias (1 taken off PD). There was no difference in hazard ratios in catheter survival after adjusting for demographics; diabetes status and number of previous catheter placement for overall follow up. But, looking at 2-year catheter survival, open placement of catheters had a higher adjusted hazard ratio for catheter loss compared to peritoneoscopic placement (aHR 2.61; 95% CI 1.02-6.71; $p = 0.04$)

PD catheter cumulative survival stratified by placement technique



Conclusions: Our single-center experience demonstrated similar PD catheter survival rate and a better 2-year survival for catheters placed by peritoneoscopy. Our predominant use of the curly PD catheters suggests no significant difference in outcome compared to the straight catheters.

PUB585

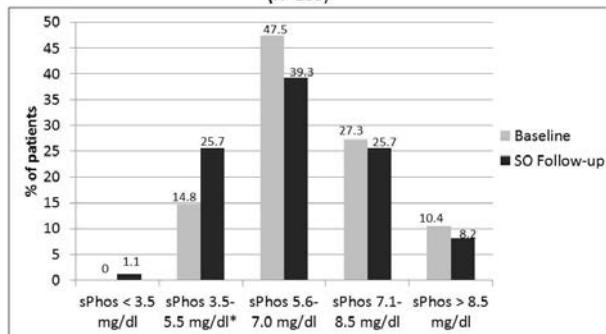
Peritoneal Dialysis Patients Who Switch Phosphate Binders from Sevelamer to Sucroferric Oxyhydroxide as Part of Routine Clinical Practice: A Retrospective Database Study Linda H. Ficociello, Vidhya Parameswaran, Phaneth Keo, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America (FMCNA), Waltham, MA.*

Background: A retrospective database study on the real-world effectiveness of sucroferric oxyhydroxide (SO), an iron-based phosphate binder (PB), in a cohort of adult peritoneal dialysis (PD) patients (pts) was conducted. This analysis examines PD pts from that cohort who switched from sevelamer (SEV) to SO (n=183).

Methods: All pts were prescribed SO as part of routine clinical practice at FMCNA clinics. Pts eligible for analysis had ³¹P serum phosphorus (sPhos) during SO and the most recent PB used during the 3 months before SO was SEV. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pills per day were assessed 3-months before starting SO (baseline) and 3-months during SO treatment (follow-up).

Results: Pts (n=183) were, on average, 53 years old with a dialysis vintage of 3.9 years. Pts with in-range sPhos increased from 14.8% to 25.7% (74% increase). There was a significant reduction in sPhos (6.8 to 6.5 mg/dl, p=0.005), sCa (9.2 to 9.1 mg/dl, p=0.02), and PB pills per day (8.4 to 3.8 pills, p<0.001). iPTH changed minimally (544.6 to 559.8 pg/ml, p=0.5). TSAT increased significantly (35.0 to 37.5%, p=0.02) but not FER (782.1 to 840.3 ng/ml) when pts treated with IV iron were included; there was minimal TSAT change (35.2 to 36.3%) and no increase in FER (823.2 to 732.9) in pts not treated with IV iron (n=77).

Distribution of serum phosphorus during baseline compared to sucroferric oxyhydroxide (SO)-treated follow-up for PD patients who switched from sevelamer (N=183)



*Change in %in-range and %out of range baseline compared to SO Follow-up, p=0.003.

Conclusions: In a cohort of PD patients who switched from sevelamer to sucroferric oxyhydroxide as part of routine clinic practice, an increase in patients with in-range serum phosphorus (74%, p=0.003) and significant decreases in serum phosphorus and calcium were observed. Phosphate pill burden was decreased by 4.6 pills (8.4 to 3.8 pills per day, p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB586

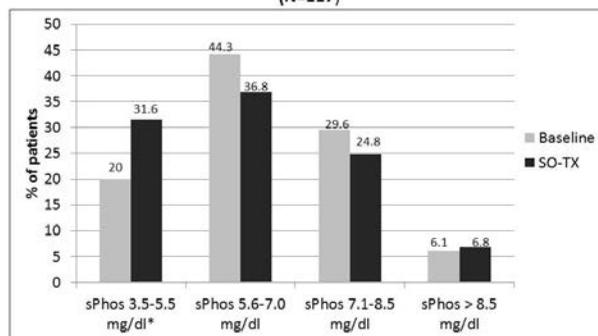
Improved Serum Phosphorus Control and Decreased Phosphate Binder Pill Burden Amongst African American Peritoneal Dialysis Patients Taking Sucroferric Oxyhydroxide Vidhya Parameswaran, Linda H. Ficociello, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America, Waltham, MA.*

Background: This study evaluated the real world effectiveness of sucroferric oxyhydroxide (SO) use among peritoneal dialysis (PD) patients (pts) who self-reported race as Black or African American (AA).

Methods: A retrospective database analysis was conducted on a cohort of AA PD pts who were prescribed SO as part of standard care at FMCNA clinics. Pts had ³¹P serum phosphorus (sPhos) measured while using SO and had been on sevelamer, calcium-based phosphate binders or had no phosphate binder specified prior to SO treatment. Differences in sPhos, pill burden (PB), serum calcium (sCa), ferritin, transferrin saturation (TSAT), and intact parathyroid hormone (iPTH) were noted between baseline (BL; 3 months prior to SO) and follow-up (SO-TX; 3 months during SO).

Results: 117 AA PD pts (mean age=50 years, dialysis vintage=4.2 years) were included. At BL, 37% were on sevelamer, 31% on calcium-based phosphate binders, 2% on dual therapy and 31% had no phosphate binder specified. Figure shows increase in pts who have in-range sPhos (20% to 31.6%; 58% increase). Mean sPhos decreased from 6.55-6.38 mg/dl (p=0.06). A significant decrease in PB was observed (4.5 pills/day, p<0.001) between BL (8.8 pills) and SO-TX (4.3 pills). No significant differences were observed between BL and SO-TX for sCa (BL=9.1 mg/dl, SO-TX=9.1 mg/dl), ferritin (BL=861.9 ng/ml, SO-TX=870 ng/ml), TSATs (BL=34.7%, SO-TX=36.8%) and iPTH (BL=729.5 pg/ml, SO-TX=696.4 pg/ml).

Distribution of serum phosphorus during baseline compared to sucroferric oxyhydroxide (SO)-treated follow-up among African American PD patients (N=117)



*Change in %in-range and %out of range baseline compared to SO-TX, p=0.006.

Conclusions: In a cohort of African American peritoneal dialysis patients who were prescribed sucroferric oxyhydroxide as part of routine clinical care, there was a 58% increase in the number of patients with serum phosphorus levels in-range (p=0.006). Furthermore, there was a significant reduction in pill burden (4.5 fewer pills, p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB587

Peritoneal Dialysis for Management of Refractory Heart Failure Girish Singhanja, Abhilash Koratala, Amir Kazory. *Nephrology, Univ of Florida, Gainesville, FL.*

Background: Refractory heart failure (RHF) is associated with significant morbidity and mortality. There is growing interest in the use of peritoneal dialysis (PD) for management of patients with RHF. In this study, we explored the currently available data on the safety and efficacy of PD in this setting.

Methods: A search of PubMed database using key words “peritoneal dialysis” and “heart failure” from 1985 to 2015 was performed by two of the authors independently and found 763 articles, from which those including at least 20 patients who had initiated PD for cardiac indication were selected. Relevant data on efficacy and safety such as changes in the quality of life and cardiac function as well as the rate of hospitalization were extracted and compared.

Results: Seven studies (4 prospective and 3 retrospective) met the inclusion criteria with a total of 398 patients and a mean age of 70.4 years. PD was associated with improvement in functional status (1 to 2 NYHA class reductions) in 5 of the 7 studies (not reported in 2) as well as an increase in the ejection fraction in 6 studies. A variety of PD regimens were used that in general showed efficacy in removal of fluid as suggested by notable reduction in patients’ weight in 6 studies by up to 8.3 kg (unavailable in 1). It was also shown to significantly reduce the number of days of hospitalization for acute HF in 6 studies by up to 90%. Five studies reported increase in responsiveness to diuretics as well as perceived improvement in the quality of life. The PD-related complications were found to be minimal in 6 studies while one reported 0.75 episode/patient/year of peritonitis.

Conclusions: Currently available evidence suggests that PD is an efficacious option for management of patients with RHF that can result in significant improvement in their functional status, hospitalization rate, and the quality of life. Based on the findings of these studies PD is safe in this population and its related morbidity does not replace HF-

associated morbidity. Larger controlled trials are warranted to explore the potential impact of PD on the mortality of patients with RHF and to define those subgroups most likely to benefit from this therapy.

PUB588

Procalcitonin, Is It a Useful Biomarker for Peritoneal Dialysis Peritonitis?
 Shinhan Song, Hyeon-Cheol Park, Jae Seok Kim, Jae Won Yang, Byoung Geun Han, Seung-Ok Choi. *Internal Medicine, Yonsei Wonju College of Medicine, Wonju, Korea.*

Background: Peritonitis is a common complication in peritoneal dialysis (PD). Procalcitonin is a peptide hormone which has been used as a biomarker for the diagnosis of bacterial infection. We aimed to investigate the usefulness of procalcitonin in the patients with PD peritonitis.

Methods: This study included 33 episodes of peritonitis in 27 patients for follow-up period of 450 days. In addition, we collected samples of PD effluents from 7 PD patients without peritonitis to compare with those of peritonitis. We investigated clinical characteristics, serum and PD effluent levels of procalcitonin at the time of initial visit and discharge.

Results: The mean value of dialysis vintage of patients with peritonitis was 1774 days, incidence of total peritonitis for period of PD maintenance; 4.3 times, interval from symptom onset to visit; 13.6 hours, duration of intraperitoneal antibiotic treatment; 8.2 days, and interval from clinical improvement to recurrence; 80.7 days. Initial serum procalcitonin increased to 0.97 ± 3.67 ng/mL (mean \pm standard deviation) compared with reference values (healthy <0.05 , PD patients <0.30 , PD peritonitis >0.50 ng/mL), and PD effluent procalcitonin also increased compared with in the subjects without peritonitis, but not significantly (0.07 ± 0.19 vs. 0.01 ± 0.01 ng/mL, $p=0.503$). The serum procalcitonin decreased to 0.33 ± 0.54 ng/mL with clinical improvement but not significantly ($p=0.308$), and the PD effluent procalcitonin also showed the decreased level of 0.03 ± 0.08 ng/mL but not the statistical significance ($p=0.360$). Pearson's correlation analysis showed that the serum and PD effluent procalcitonin did not have relationships with existing inflammatory markers such as ESR, CRP. Lastly, procalcitonin could not predict recurrence and mortality of peritonitis.

Conclusions: Collectively, procalcitonin showed the tendencies corresponding to the clinical course of PD peritonitis, but not statistical significance. We believe that procalcitonin is not superior biomarker in PD peritonitis compared with other existing markers.

PUB589

Epidemiological Survey of Maintenance Peritoneal Dialysis in China
 Xiang-Mei Chen, Xueying Cao, Delong Zhao, Guangyan Cai. *Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases.*

Background: To analysis epidemiology and trend of peritoneal dialysis during 2011 - 2014 in China.

Methods: Patient-reported outcome data from the peritoneal dialysis centers were collected online during the study.

Results: (1)By the end of 2014, there were 55373 cases of maintenance peritoneal dialysis patients in China, had increased by 17% per year over this time period. The annual incidence rate was 5.81/100 million people. The prevalence was 34.3/100 million. (2)The average age was 53 years. Male to female ratio was 1.2:1. The average age at initiation of dialysis was about 50 years old. The average residual renal function was 3ml/min. The average dialysis time was 2 years. The primary causes were primary glomerular disease 54%, diabetic nephropathy 16%, hypertensive renal damage 14%. (3)In 2014, DOR fell to 6.6%. TOT was 27.2 months. The death patients accounted for about 51.3% of exit patients. The average death age was 64.8 years. The average therapy time was more than 28.6 months. The cause of death was the cardiovascular and cerebrovascular events. (4) Peritoneal dialysis access was the two cuffs, no gooseneck, straight. 78% patients were the continuous ambulatory peritoneal dialysis patients. The therapeutic dose was 6L to 8L. High peritoneal transport type was the largest. (5)PD patients with hemoglobin 100g/L ratio was raised every year. The albumin level in plasma was greater than or equal to 35g/L with more than 50% patients. Serum calcium, phosphorus, parathyroid hormone level was improved year by year. The average Kt/V was maintained at 2.1/ weeks. Ccr could reach 62 L/1.73m²/ weeks.

Conclusions: There is a 17% annual increase in peritoneal dialysis patients. The incidence and prevalence was stable. DOR and TOT improved year by year. Anemia, plasma albumin, calcium, phosphorus metabolism and dialysis adequacy control were better than before.

Funding: Government Support - Non-U.S.

PUB590

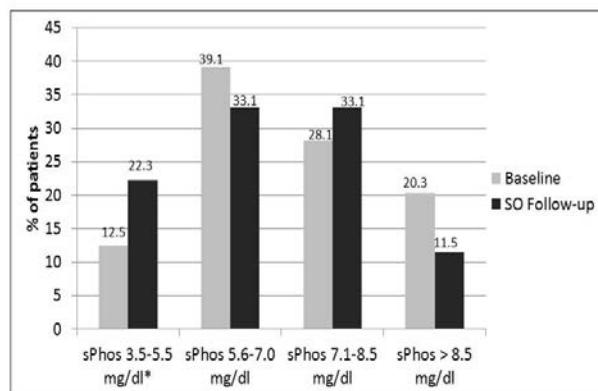
Peritoneal Dialysis Patients Who Switch from Calcium-Based Binders to Suroferric Oxyhydroxide as Part of Routine Clinical Practice: A Retrospective Database Study
 Linda H. Ficociello, Vidhya Parameswaran, Phaneth Keo, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America (FMCNA), Waltham, MA.*

Background: A retrospective database study on the real-world effectiveness of suroferric oxyhydroxide (SO), an iron-based phosphate binder (PB), was conducted in a cohort of adult peritoneal dialysis (PD) patients (pts). This analysis examines pts who switched from a calcium-based phosphate binder (CaPB); either calcium acetate (n=95) or calcium carbonate (n=35) to SO.

Methods: All pts were prescribed SO as part of routine clinical practice at FMCNA clinics, had ³¹ serum phosphorus (sPhos) measured during SO, and the most recent PB used was a CaPB. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), % transferrin saturation (TSAT), ferritin (FER), and PB pills per day were assessed 3-months before starting SO (baseline) and 3-months during SO treatment (follow-up).

Results: Pts who had in-range sPhos increased from 12.5% to 22.3% (78% increase) between baseline and follow-up (Figure). There were significant reductions in sPhos (7.1 to 6.8 mg/dl, $p=0.004$) and PB pills per day (7.4 to 3.6 pills, $p<0.001$). Minimal change in sCa (8.99 to 8.95 mg/dl, $p=0.5$) and iPTH (519.2 to 544.4 pg/ml, $p=0.4$) was observed. There was significant change in FER (708.5 to 788.3 ng/ml, $p=0.008$, but not TSAT (35.8 to 35.5%, $p=0.8$) when pts treated with IV iron were included. There was minimal increase in FER (733.6 to 735.0 ng/ml, $p=0.98$) or TSAT (38.0 to 39.1%, $p=0.6$) in pts not administered IV iron (n=43).

Serum phosphorus during baseline compared to suroferric oxyhydroxide (SO)-treated follow-up for patients who switched from calcium-based binders to SO (N=130)



*Change in %in-range and %out of range baseline compared to SO Follow-up, $p=0.003$.

Conclusions: In a cohort of PD patients who switch from calcium-based binders to suroferric oxyhydroxide as part of regular clinic practice, there was a 78% increase in patients achieving in-range serum phosphorus ($p=0.003$). Additionally, phosphate binder pill burden was lessened from 7.4 to 3.6 pills per day (3.7 fewer pills, $p<0.001$).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB591

Effects of Chlorhexidine-Impregnated Patches on Catheter Exit Site and Tunnel Infections in Peritoneal Dialysis Patients
 Chiaki Kawabata. *General Internal Medicine, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan.*

Background: Exit-site infections and tunnel infections are major causes of catheter loss in peritoneal dialysis (PD) patients. We studied the effects of chlorhexidine-impregnated patches (Biopatch), which are used as central-line dressings or drain site dressings, on PD catheter exit site infection and tunnel infections.

Methods: A retrospective review was conducted of 45 patients whose PD catheter exit site was made between January 2007 and December 2014. We compared acute exit site infections, chronic exit site infections, and tunnel infections of the two groups, (the Biopatch Group and the Non-Biopatch Group), 6 months after the exit site was created.

Results: The Biopatch was used until the exit site had healed perfectly. The mean time of using the Biopatch was 63 ± 26 days. The two groups had no significant differences in age [49.4 ± 12.0 years vs 52.3 ± 16.3 years], diabetes mellitus co-morbidity or pattern of peritoneal dialysis. There were no statistical differences in acute exit site infections [15.4% vs 6.1% ($p=0.27$)], chronic exit site infections [0% vs 9.1% ($p=0.28$)] or tunnel infections [15.4% vs 15.2% ($p=0.90$)] during the 6 months.

Conclusions: Using the Biopatch until the exit site has healed perfectly does not reduce either exit site infections or tunnel infections.

PUB592

The UK Peritoneal Dialysis Catheter Study (UK Cath): An Ancillary Study to the Peritoneal Dialysis Outcomes and Practice Patterns Study [Martin E. Wilkie](#),¹ Simon J. Davies,² Mark Lambie,² Francesca Tentori,³ Jeffrey Perl,⁴ ¹Sheffield Kidney Inst, Sheffield Teaching Hospitals NHS FT, Sheffield, United Kingdom; ²Keele Univ, Keele, United Kingdom; ³Arbor Research Collaborative for Health, Ann Arbor, MI; ⁴St. Michael's Hospital, Toronto, ON, Canada.

Background: Delivering high quality peritoneal dialysis (PD) access placement and outcomes is limited by lack of standardization of PD access definitions and events, variable reporting of outcomes, and a paucity of robust evidence regarding optimal PD catheter insertion pathway(s). The UK Renal Registry PD access audit (2013) demonstrated 82% catheter survival at 1 year, with considerable variation between centres. Moreover, catheter function at 3 months was poorer for a medical (percutaneous) compared to a surgical (open surgical) insertion pathway.

Methods: UK-Cath, a multi-centre prospective cohort study (1350 patients, 45 dialysis centres, 18 month recruitment window) will assess the outcomes associated with different pathways of catheter insertion, dialysis unit-level policy associated with pathway use, and patient-level factors (e.g. case-mix, urgent start). Health economic benefits of these pathways will be determined using the cohort data, enriched by additional information obtained from more long-term follow-up study in a subset of patients using Hospital Episode Summary (HES) data linkage. The study has received funding from the UK NIHR Research for Patient Benefit Programme, NIHR PB-PG-0613-31028. A subset of study 20 centres will contribute to International Peritoneal Dialysis Outcomes & Practice Patterns Study (PDOPPS) with the primary objective of understanding variations in PD technique failure.

Results: We will present information on study design, instrument development, governance mechanisms, and recruitment plan. We will discuss the impact of patient engagement on study design.

Conclusions: The UK Peritoneal Dialysis Catheter Study will inform dialysis units' decision to either focus their efforts on improving a single surgical pathway or to practise a mixture of surgical and medical insertions, with the ultimate goal to improve PD catheter survival, patient experience and optimise health economic efficiency.

Funding: Government Support - Non-U.S.

PUB593

Preparedness for Telemedicine in Outpatient Peritoneal Dialysis [Kana N. Miyata](#), Panida Ditsawanon, Tiane Dai, Sharon G. Adler, Ramanath B. Dukkkipati, Anuja P. Shah, Lili Tong, Anne A. Ugalde, Jenny I. Shen. *Nephrology, Harbor UCLA Medical Center, Torrance, CA.*

Background: Peritoneal dialysis (PD) is generally performed daily by patients at home, where questions may arise. Telemedicine has the potential to improve the delivery of healthcare services and outcomes for PD patients. We studied the preparedness for telemedicine of a PD clinic run by a large dialysis organization (LDO) serving an urban under-resourced population.

Methods: Adult PD patients cared for by the clinic were asked about their interest and ability to use VSEE® (HIPAA-compliant tool for video calls) to remotely manage clinical concerns about PD. We compared patient characteristics between interested and non-interested groups. We also assessed the clinic's ability to implement VSEE®.

Results: Initial barriers encountered were with the LDO. These included a firewall that prevented video products from being loaded onto clinic computers, consent issues, concerns regarding unequal care potentially being provided to patients with and without internet access, and lack of video equipment for on-call nurses. All of these barriers were overcome. We then assessed interest in 56 patients. Their age (mean±standard deviation) was 43±13 years, 63% were male, English was the primary language for 66%, and they had been on PD for 3.0±3.2 years. 34 patients (61%) showed some interest in telemedicine, 16 (29%) downloaded the software to their laptop, tablet, or cell phone, and downloading in process for the remaining 18 (32%). The most common reason for not being interested was "no device" or "no internet access at home", which was reported by 15 patients (27%). The only additional difference in characteristics between the interested and non-interested groups was that those interested lived further away from the clinic (12.9 vs 9.3 miles, p=0.03).

Conclusions: Multiple barriers to delivering telemedicine to PD patients exist, both on the clinic and patient side. 61% of patients were telemedicine-ready. Future evaluations will determine the impact on clinically significant outcome, patient satisfaction, and clinic workflow in this population.

PUB594

When to Remove the Peritoneal Dialysis (PD) Catheter After Renal Transplantation? (RT) [Saul Enrique Pampa](#),¹ Maitte Rivera,¹ Victor Burguera,¹ Fernando Caravaca-Fontan,¹ Estefanía Yerovi,¹ Nuria Rodriguez mendiola,¹ Sara Jimenez alvaro,¹ Cristina Galeano,¹ Fernando Liano.¹ ¹Nephrology, Hospital Univ Ramón y Cajal, Madrid, Spain; ²Urology, Hospital Univ Ramón y Cajal, Madrid, Spain.

Background: There seems to be consensus that the time of removal of the peritoneal catheter after RT may be delayed until renal function and the patient is stabilized, but there are few publications about it.

Methods: We analyzed retrospectively patients on Peritoneal Dialysis Unit (PD) who have received a RT between May 1995 and March 2015 gathering medical history data relating to the peritoneal catheter removal and complications.

Results: 108 patients transplanted from PD, 32 women/76 men with a mean age at the time of TR 50 +/- 13 years (range 16-80) were analyzed. Two patients received RT of living donor and 106 of cadaver. The catheter used in all was a straight Tenckhoff with two cuffs. If renal therapy substitution was needed posttransplantation all patients were treated with hemodialysis. The catheter was removed during surgery in nine patients (8%) due to exit or tunnel infection by Staphylococcus aureus or Pseudomonas aeruginosa. The withdrawal was delayed in 91 patients (84%) and 8 has not yet been removed. The average withdrawal time was 4.1 +/- 2.7 months. The indication of withdrawn was: stable renal function in 85 (93%), stable pancreatic and renal function in 4 and exit site infection in 2 (3%). Mean creatinine at the time of removal was 2.1 mg/dl +/- 1.8 mg/dl. All catheters were removed surgically under local anesthesia. The mean duration of hospitalization was 2.1 +/- 1.8 days (0-12). Four patients (3.7%) had complications during withdrawal (one hematoma, two hemorrhagic shock and one surgical wound infection). 15 (18%) patients suffered complications before withdrawal: 13 exit site infection, one peritonitis associated with urinary fistula and one spontaneous peritonitis.

Conclusions: In our experience the removal of the peritoneal catheter may be delayed until renal graft function were stabilize since the rate of complication is low compared with another studies.

Funding: Other NIH Support - Spanish Public Health Service

PUB595

Clinical Outcomes by Differences in Therapy Among Peritoneal Dialysis Patients [Hironori Nakamura](#), Anayama Mariko, Yasushi Makino, Masaki Nagasawa. *Dept of Nephrology, Shinonoi General Hospital, Nagano, Japan.*

Background: Studies evaluating the outcomes of peritoneal dialysis (PD) technique and patient survival, including those among patients who switch from PD to hemodialysis (HD), are scarce.

Methods: This retrospective study screened 120 patients in whom PD was initiated between January 1998 and December 2012 at our hospital. Of these, patients those who were transferred to another hospital, those who received transplantation, or those who did not have follow-up data were excluded. Fifty-two patients (age, mean ± SD: 69.2 ± 12.6 years) were included to investigate the time of survival based on PD technique and overall survival, including those patients who switched to HD, and to evaluate the correlation between survival time and pharmacotherapy at the initiation of PD.

Results: Time (in months) on PD, HD, and overall survival were 34.3 ± 30.0, 18.5 ± 43.4, and 52.6 ± 52.3, respectively. Comparison between the APD (n = 20) and non-APD patients (n = 28) showed that time on PD was 45.3 ± 34.4 vs. 31.3 ± 26.0 months, time on HD was 39.0 ± 40.6 (n = 8) vs. 81.8 ± 72.5 (n = 8) months, and overall survival time was 60.9 ± 49.9 vs. 54.7 ± 55.4 months, respectively. Comparison between groups with (n = 41) and without use of icodextrin (n = 7) showed time on PD was 10.8 ± 6.0 vs. 41.4 ± 30.1 months, time on HD was 49.6 ± 45.0 (n = 3) vs. 62.9 ± 65.3 (n = 13) months, and the survival time was 32.1 ± 41.7 vs. 61.6 ± 53.6 months. When analyzed by age groups of <60, 61-70, 71-80, and >81 years: time on PD (months) was 47.2 ± 38.4 (n = 14), 45.2 ± 23.4 (n = 15), 19.8 ± 27.0 (n = 10), and 21.2 ± 19.2 (n = 13), respectively. Time on HD was 22.8 ± 44.2 (n = 6), 14.6 ± 36.3 (n = 5), 8.7 ± 28.2 (n = 1), 26.3 ± 60.1 (n = 4), respectively; and survival time was 70.1 ± 52.8, 59.2 ± 41.9, 28.5 ± 39.7, and 46.7 ± 67.2 months.

Conclusions: The time on dialysis and survival time may be underestimated because of the exclusion of patients who are currently on dialysis. Compared with non-APD patients, APD patients had longer time on PD and overall survival time. Patients who needed icodextrin when commencing PD had shorter time on PD and overall survival time.

PUB596

Combined Markers of Protein-Energy Wasting and Inflammation Predict Clinical Outcomes in Incident Peritoneal Dialysis Patients [Chan Ho Kim](#),¹ Jung Tak Park,² Seung Hyeok Han,² Tae-Hyun Yoo,² Shin-Wook Kang,² ¹Internal Medicine, Catholic Kwandong Univ College of Medicine, Incheon, Korea; ²Internal Medicine, College of Medicine, Yonsei Univ, Seoul, Korea.

Background: Protein-energy wasting (PEW) and chronic inflammation are not only common but are known as predictors of adverse clinical outcomes in end stage renal disease (ESRD) patients. Whether the combined values of serum albumin, high sensitivity C-reactive protein (hs-CRP), and body mass index (BMI) have an additive impact on clinical outcomes compared to each variable by itself in incident peritoneal dialysis (PD) patients was evaluated.

Methods: A prospective cohort of 565 incident PD patients from the Clinical Research Center for ESRD in Korea was selected. Patients were divided into two groups based on the baseline levels of albumin (≥ and <3.8 g/dL), hs-CRP (≥ and <0.45 mg/dL), and BMI (≥ and <23 kg/m²). Primary outcome was the composite of all-cause mortality and unplanned hospitalization.

Results: The mean age was 51.4 years and 60.0% were male. During a median follow-up duration of 27 months, 50 patients (8.8%) died and unplanned hospitalization events occurred in 123 patients (21.8%). Univariate analysis revealed an increase in primary outcome risk with lower albumin and elevated hs-CRP compared to higher albumin and lower hs-CRP, respectively. A similar tendency was observed with lower BMI and primary outcome, although without statistical significance. Regarding the combination of these variables, Cox proportional hazards analysis revealed that patients with any two risk factors and all three risk factors exhibited significantly higher hazard ratios for primary outcome compared to patients without any single risk factor. The combination of these factors retained a significantly higher HR for predicting primary outcome, even after adjusting for other confounders.

Conclusions: The combination of serum albumin, hs-CRP, and BMI at the time of PD commencement was a significant independent risk factor for the composite outcome of all-cause death and unplanned hospitalization in incident PD patients.

Funding: Government Support - Non-U.S.

PUB597

Single Center Experience with a Peritoneal Dialysis Cyclor with Advanced Patient Interactive Screen: Impact on Patient Training Lili Chan,¹ Ma shelda Cabus-Fojas,¹ Marcia A. Duffoo,¹ Catherine Firanek,² James A. Sloand,² Jaime Uribarri.¹ ¹Mount Sinai; ²Baxter.

Background: Learning proper device use and clinical concepts of care must be internalized by patients to successfully perform PD at home. With increasingly diverse patients going on PD and increasing adoption of urgent start PD, there is a need for simpler devices. Enhancing the learning environment with methods including visual, graphical and voice will improve the educational experience leaving the patient with better understanding of the procedure.

Methods: Automated PD training was undertaken at a university based home dialysis program using a novel APD device (AMIA). 5 patients were trained on the device in a 1:1 nurse to patient ratio. The cyclor provided on screen instructions using a touch screen interface with voice guidance, text instructions and animation. Each patient was trained according to standardized outlines and sequential training progression from CAPD to APD techniques. Training included RN demonstration followed by patient direct interaction with the device. Instructions were displayed on a touch screen, along with verbal and graphical cues. Patient training completion required consistency of error free setup.

Results:

Patient	Age (years)	Gender	Etiology of renal disease	Incident (I)/ Prevalent (P)	Urgent (U)/ Routine (R)	Training Days
1	30	F	Hypertension/ NSAID	I	U	2
2	47	F	FSGS	I	U	3
3	49	F	Calcineurin Inhib Toxicity	P-HD	R	5
4	68	M	FSGS	P-HD	R	4
5	41	F	Lupus Nephritis	P-APD	R	4

5 patients aged 30-68 yrs (mean 47), 80% female with a minimum of HS education completed training. Device training ranged from 2-3 days for urgent start patients and 4-5 days in routine start patients.

Conclusions: From our experience, training times were similar or reduced using the AMIA cyclor and allowed the ability to efficiently train urgent start patients. Observed advantages of the new cyclor included: 1) less need for memorization 2) distinction of a beginner vs advanced mode 3) online alarm troubleshooting 4) presence of an air detector in patients' line 5) multiple prescription capability. The step by step instructions and online problem solving of the new device may impact positively the efficiency and understanding of these patients.

PUB598

Peritoneal Dialysis-Related Peritonitis in a Single Center: 10 Years Experience Patricia O. Costa, Carla M V Melo, Jordano P. Oliveira, Flavia A. Nobrega, Jandson P. Oliveira, Kleyton Andrade Bastos. *Dept of Medicine, Federal Univ of Sergipe, Aracaju, Sergipe, Brazil.*

Background: Peritonitis remains as the main Peritoneal Dialysis (PD)-related complication. It is estimated that it contributes directly to 20% of dropout and is related to 16% of all deaths. This study proposes to evaluate episodes of PD-related peritonitis and describe its incidence, causative organisms and possible predictors in patients belonging to a DP program from a reference center at Aracaju-Sergipe-Brazil.

Methods: Retrospective cohort study that evaluated 565 patients who stayed for at least 30 days in the technique, between 01/01/2003 and 12/31/2012, with a mean age of 54 ± 19 years, 55% male, 62% less than 8 years of regular study and 88% with monthly income less than 5 national minimum wages. They remained in DP by an average of 713.5 ± 714.2 days. Since 2011, was initiated daily use of gentamicin at the exit site of the peritoneal catheter.

Results: Most patients (59%) showed no peritonitis. The global index was 1 episode every 27.03 months. It was recorded the lowest rate in 2012 (1 episode every 45.6 months), while the highest were in 2003 and 2005 (1 episode every 23.2 and 22.2 months, respectively). *S. aureus* was the most prevalent germ (23%), followed by *E. coli* (9%) and *Alcaligenes sp* (6%). The culture was negative in 31% of cases. There was healing of peritonitis in 71% of cases, with better outcome in gram-positive bacteria (83%). Gram-negative healed in 61% of cases. It identified a higher risk of peritonitis in patients with history of exit site infection (relative risk = 1.24; 95% confidence interval = 1.02 - 1.50; p <0.05). There was no significant difference between the groups, with or without peritonitis, in terms of sociodemographic factors.

Conclusions: Despite the bad social indicators of the study population, the incidence of peritonitis follows the recommendations of the International Society for Peritoneal Dialysis (ISPD), with a reduction of rates along the years, especially after the introduction of gentamicin. Similar as described by other authors, exit site infection was recognized as a peritonitis' predictor, so it is extremely important to perform preventive strategies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PUB599

Placement of Peritoneal Dialysis Catheters: Not Limited to Operating Rooms Sijie Zheng,³ Todd Drasin,² Jeanne A. Darbinian,⁴ Paul Dybbro,² Neelam M. Bhalla.¹ ¹Nephrology, Kaiser Permanente Northern California, Hayward, CA; ²Interventional Radiology, Kaiser Permanente Northern California, Hayward, CA; ³Nephrology, Kaiser Permanente Northern California, Oakland, CA; ⁴Div of Research, Kaiser Permanente, Oakland, CA.

Background: As of December 2012, only 7% of ESRD patients in the USA utilize Peritoneal Dialysis (PD) for renal replacement therapy, despite many advantages of PD over hemodialysis (HD). One factor leading to low PD utilization is the lack of experienced surgeons available to place PD catheters in a timely manner. Interventional Radiologists (IR) can help with catheter placement. As of December 2014, Kaiser Permanente achieved a 23% PD rate among its ESRD population. One factor that contributed to the high percentage of PD utilization is a skilled IR service in the Greater Southern Alameda Area (GSAA) that facilitates the placement of PD catheters in a timely manner. We report a large number of PD catheters placed by GSAA IR physicians from January, 2011 to December, 2013 and compare to PD catheters placed by laparoscopic surgeons in the nearby East Bay Area (EBA) and Diablo Service Area (DSA) during the same time period.

Methods: We retrospectively analyzed KPNC electronic data base from 1/1/2011 – 12/31/2013. We extracted data from GSAA where IR placed PD catheters using an Advanced Image guided Percutaneous (AIP) technique. We also extracted data from the EBA and DSA where surgeons placed PD catheters using the Advanced Laparoscopic Surgical (ALS) technique.

Results: We identified 203 PD catheters placed by GSAA IR with the AIP technique and 316 PD catheters placed by EBA/DSA surgeons using the ALS technique. Overall, GSAA IR placed 39% of all PD catheters across the 3 areas during the study time period.

Conclusions: IR placed a significant percentage of overall PD catheters in 3 areas of our integrated health care system. In doing so, they overcame one of the barriers to high PD penetration in ESRD patients. In areas where there is a shortage of skilled surgeons, one can consider utilizing IR to solve this problem. Currently we are studying the outcomes of these two approaches.

Funding: Private Foundation Support

PUB600

Body Composition and Cardiovascular Outcomes Using Continuous Automated Peritoneal Dialysis – A Prospective Cohort Study Carlos Alberto Garza, Gabriela Leal, Bernardo Moguel. *Dept of Nephrology, National Inst of Cardiology, Mexico City, Federal District, Mexico.*

Background: Fluid overload (FO) due to compliance in Continuous Ambulatory Peritoneal Dialysis (CAPD) is common. Efforts to achieve dry weight and avoid cardiovascular outcomes (CO) are lessened from inaccurate body composition (BC) estimations despite best clinical assessment.

Methods: We'll follow BC, multiple frequency bioelectrical impedance (InBody S10, InBody Co), standard laboratories and CO, in all new patients to continuous Automated Peritoneal Dialysis (APD) previously in a CAPD. Measurements at baseline (CAPD), 1 month and every visit to the dialysis clinic thereafter (APD) for a 5 year period.

Results: These are the first data of BODY cohort study. Initial 10 subjects are described, 4 men and 6 women, median age 27 years (17-46), height 159.5cm (146-166), baseline and first follow up variables are in Table 1. Wilcoxon rank test for related samples was performed. We found that PD modality switch to APD, at 1 month, reflected a body composition transition with statistical significance (P <0.05), within the EBW/TBW ratio at expense of trunk compartment. Most likely from improved dialysis adherence

Variable	Unit	Baseline	30 days	P
Weight	Kilogram (K)	60.75(42.7-104.2)	58.65(45.2-108.4)	-
BMI	Kg/m ²	23.6(17.2-39.7)	23.4(18.6-41.3)	-
Systolic pressure	mmHg	152(110-175)	136(117-180)	-
Diastolic pressure	mmHg	97.5(64-108)	91(59-127)	-
Body water (TBW)	Liters(L)	31.95(22.2-45.3)	31.5(24.8-45.2)	-
Extracellular water (EBW)	L	12.5(9.3-17.9)	12.2(9.4-17.5)	-
Intracellular water (IBW)	L	19.4(12.9-27.4)	19.4(14.7-27.7)	-
EBW/TBW	Ratio	0.39(0.38-0.42)	0.38(0.38-0.41)	P<0.05
EBW/TBW Trunk	Ratio	0.39(0.38-0.42)	0.38(0.38-0.41)	P<0.05
Lean Muscle	K	43.5(30.1-60.6)	43(33.4-60.6)	-
Body Fat	K	15.5(3.3-43.6)	16.2(5.7-47.8)	-
Metabolic Rate (BMR)	Kcal/day	1310(1019-1679)	1298(1091-1678)	-
Dialysis	L	7L(2-10)	8L(8-12)	P<0.05

"-"not statistically significant

Conclusions: We consider that APD, on the ground of increased, uninterrupted and rigorously performed therapy, is an appropriate method to optimize FO and aim for dry weight in PD. Further recruitment of patients and follow up of the BODY Cohort study is expected to confirm this hypothesis.

Funding: Pharmaceutical Company Support - HiTec Medical

PUB601

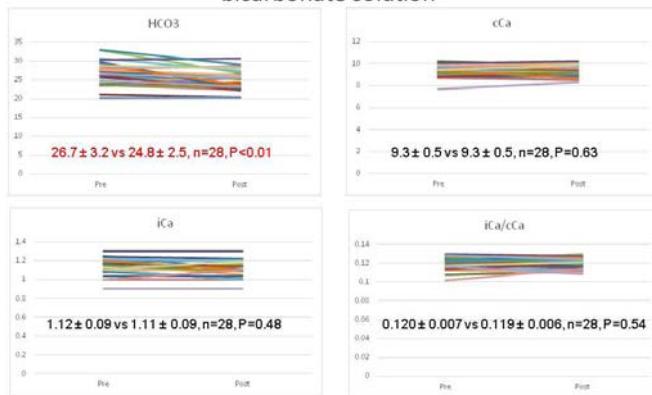
The Changes in Bicarbonate Level and Ionized Ca/ Corrected Ca Ratio of Patients Receiving Peritoneal Dialysis Using Bicarbonate/Lactate-Buffered Solution Emi Kimoto, Nanae Matsuo, Masamitsu Morishita, Mami Nakamura, Yukio Maruyama, Yasuyuki Nakada, Masatsugu Nakao, Yudo Tanno, Ichiro Ohkido, Hiroyasu Yamamoto, Keitaro Yokoyama, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Recently, PD solution which contains 25mEq/L bicarbonate and 10mEq/L lactate (Bicarbonate/Lactate-buffered peritoneal dialysis solution; B/L solution) is developed in Japan. Because of high concentration of lactate (40mEq/L) of conventional peritoneal dialysis (PD) solution, patients have generally higher serum bicarbonate level than those of patients receiving hemodialysis (HD). The new B/L solution is expected not only its biocompatibility but also improving excess correction of acidosis. Under the metabolic alkalosis environment, we reported that PD patients have lower levels of ionized Ca (iCa) at the same corrected Ca (cCa) levels. Thus, we hypothesized that iCa / cCa ratio increased after switching PD solution from Lactate-buffered to B/L solution.

Methods: We recruited 28 patients (55 ± 13 years, male 82%, PD duration 42 ± 21 months) who switched from Lactate-buffered to B/L solution, and investigated changes in serum bicarbonate, iCa, and cCa levels.

Results: After switching solution, serum bicarbonate decreased (26.7 ± 3.2 vs 24.8 ± 2.5, P<0.01), and cCa did not change (9.3 ± 0.5 vs 9.3 ± 0.5, P=0.63). Neither iCa nor iCa/cCa ratio increased significantly (1.12 ± 0.09 vs 1.11 ± 0.09, P=0.48; 0.120 ± 0.007 vs 0.119 ± 0.006, P=0.54, respectively).

Change of parameters before and after switching bicarbonate solution



Conclusions: Conversion to B/L solution from lactate solution was associated with lower serum bicarbonate. Unfortunately, iCa did not change. Further investigations are needed to confirm the utility of the monitoring of iCa for the management of chronic kidney disease - mineral and bone disorder (CKD-MBD) in PD patients.

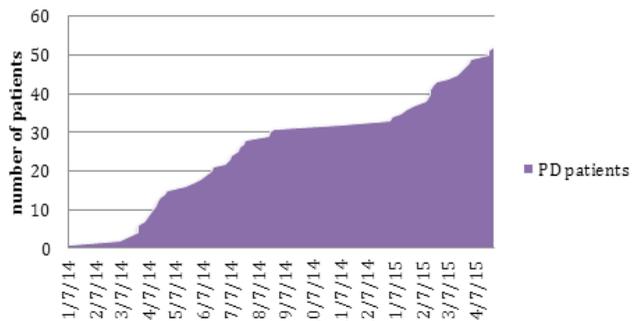
PUB602

Road to Success: One Academic Medical Center’s Experience Building a Peritoneal Dialysis Clinic Yazan M. Alia, William A. Schlueter, Erwin E. Morales, Maria A. Gavino, Shubhada N. Ahya, Robin E. Watson. *Nephrology, Northwestern Memorial Hospital, Chicago, IL.*

Background: Peritoneal Dialysis (PD) is an option for renal replacement therapy. The US Renal Data System 2012 Annual Report states that the annual per-patient HD cost is approximately \$87,500 whereas for PD it is \$66,750. In addition, studies have demonstrated that some aspects of quality of life are improved in PD patients compared with HD patients. Despite this, PD is underutilized in the US. Northwestern Medicine’s PD Program was initiated in 01/2014 with 4 nephrologists and 10 patients who transferred from a neighboring PD Unit. From 02/2014 to 04/2015, Northwestern’s Peritoneal Dialysis Clinic grew to 50 peritoneal dialysis patients.

Methods: We included all patients who started on PD (or transferred to PD) in PD Clinic between the periods of 2/14 and 4/15. Patients excluded from this analysis stopped PD within this period for the following reasons: switched to HD, expired, recovered kidney function, or underwent transplantation.

PD growth overtime



Results: From January 2014 to April 2015, PD Clinic grew to 50 patients. The age range is 22-86 years and mean age is 54.4 years. Thirty-one (62%) are men. Twenty-one (42%) are African American, 13 (26%) are Caucasian, 11 (22%) are Hispanic, and 5 are of Asian descent.

Conclusions: We describe a single, academic medical center experience on growth of PD Clinic from 0 to 50 patients within 14 months. Obstacles to PD Clinic growth included lack of availability of dialysate in mid 2014 and lack of experience with Urgent Start PD. However, with time, both nephrologist and surgeons and medical staff grew comfortable with this method of dialysis initiation. Features that facilitated successful and timely growth are: 1-realtime options training, 2-surgeon cooperation, 3-physical proximity to CKD Clinic and to inpatient floors, 4-continuity of care for patient-physician from outpatient CKD Clinic to inpatient setting to outpatient Home Dialysis Clinic.

PUB603

Peritoneal Membrane Transport Evaluation in Peritoneal Dialysis Using Traditional PET, Modified PET and Mini-PET Miguel C. Riella,⁴ Jacek Waniewski,² Bengt Lindholm,³ Marcelo Nascimento,¹ ¹Univ Federal do Parana, Curitiba, Parana, Brazil; ²Inst Biocybernetics and Biomedical Engineering, Warsaw, Poland; ³Baxter Novum and Renal Medicine, Karolinska Inst, Stockholm, Sweden; ⁴Pro-Renal Foundation, Curitiba, Parana, Brazil.

Background: Peritoneal equilibration test (PET) is widely used for evaluating peritoneal transport; however, additional methods have been described to facilitate and improve this evaluation. Here we compared traditional PET (PET) with two newer methods, mini-PET and modified PET (mod-PET), which are increasingly used to investigate ultrafiltration capacity and peritoneal membrane characteristics in patients undergoing peritoneal dialysis.

Methods: Twenty-one non-diabetic adult patients on peritoneal dialysis (PD) for >3 months underwent: PET (2.27%; 4 h), mini-PET (3.86%; 1 h) and mod-PET (3.86%; 4 h). Results of dialysate to plasma concentration ratios for creatinine (D/P Cr) and sodium (D/P Na), and dialysate to initial glucose concentration (D/D0 glucose) at the end of each test were compared by analysis of variance (ANOVA), Pearson correlation and Bland-Altman test.

Results: Whereas D/P Cr was not significantly different between PET and mod-PET (p=0.746) there were significant differences between mini-PET and both PET (p<0.001) and mod-PET (p<0.001). D/P Cr for PET correlated with D/P Cr for mod-PET (r=0.387; p=0.009) but not with D/P Cr for mini-Pet (r=0.088; p=0.241). Bland Altman test showed no significant bias of D/P Cr for PET vs mod-PET (-0.029; p=0.201) but a systematic difference (0.206; p<0.001) of D/P Cr for PET vs mini-PET. Whereas measurements of D/D0 glucose and D/P Na were in general not comparable nor significantly correlated, ultrafiltration during PET and mini-PET were weakly correlated (r= 0.260; p=0.009).

Conclusions: These results confirm that characterization of transport status based on D/P Cr may not necessarily differ between conventional PET and mod-PET.

Funding: Government Support - Non-U.S.

PUB604

Low Level of Albumin Is a Risk Factor for Short-Term Mortality of PD Patients Kenji Harada. *Kokura Memorial Hospital; Kokura Memorial Hospital.*

Background: Mortality of HD(hemodialysis) patients are reported, but few reports about PD(peritoneal dialysis) patients. This study aims to investigate clinical features of PD patients, their prognostic risk factors, and to establish a prognostic model for predicting their short-term mortality(1-2 years).

Methods: We investigated the mortality about PD patients(n=269, age:65 year old±13.7, male/female 173/96, PD vintage within 2 years, DM:121), and the influence of several parameters from 2009 to 2012. The dead and the transferred HD were excluded within 90 days. Finally 241 patients are remained. The survival rates for one year and two years were 91 % and 72 %. Infection was the most causes of death(53%). We investigated between death and several parameters(age, sex, blood pressure, albumin, hemoglobin, Ca, P, whole PTH, TC) by univariate analysis with JMP12, SAS. Those physical and laboratory data are measured at one month after PD started. Age and level of albumin were correlated with death. We hypothesized that low albuminuria and malnutrition influenced the rate of death. We divided three categories, from group A(albumin>3.3, n=82) and group B(2.8≤albumin<3.3, n=89), group C(albumin<2.7, n=73).Cox proportional hazards regression model was used to analyse prognostic risk factors and establish prognostic model.

Results: There were significant differences between group B and A (Hazard Ratio:2.611, p=0.0116, 95%CI:1.232-6.009), group B and C (Hazard Ratio:6.031, p<0.001, 95%CI:2.975-13.53), group C and A (Hazard Ratio:2.309, p=0.0029, 95%CI:1.33-4.09). In addition these groups were analysed by adjustment factor such as age, sex, blood pressure, hemoglobin, Ca, P, whole PTH, TC with multivariable analysis. The results proved that there were tended to be correlation between group B and A (Hazard Ratio:1.963, p=0.09, 95%CI:0.901-4.61). There were significant differences between group B and C (Hazard Ratio:4.00, p=0.003, 95%CI:1.866-9.35), group C and A (Hazard Ratio:2.037, p=0.0029, 95%CI:1.165-3.63).

Conclusions: Low level of albumin increases the mortality of PD patients gradually. Therefore we may decrease the mortality of PD patients by improving nutritional condition and infection control when PD patients are introduced.

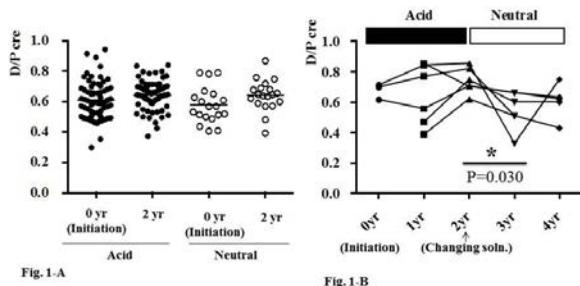
PUB605

The Effect of Neutral pH versus Conventional Peritoneal Dialysis Solutions on Peritoneal Permeability Atsushi Ueda, Kei Nagai, Toshiaki Usui, Joichi Usui, Kunihiro Yamagata, Chie Saito. *Univ of Tsukuba, Tsukuba, Japan.*

Background: Biocompatible peritoneal dialysis (PD) solutions have been anticipated to reduce oxidative stress more than conventional PD solutions, however, previous reports suggested peritoneal permeability have not been changed. This study was undertaken to investigate the peritoneal transport status from PD initiation, using biocompatible or conventional PD solutions.

Methods: We employed retrospectively 101 patients who started PD and divided into three groups. Acid group was consisted of 76 patients who used only conventional low pH solutions, and neutral pH group was consisted of 19 patients who used only biocompatible neutral pH solutions during the subsequent two years. The rest of six patients used low pH solutions at the initial phase of PD, then switched to neutral pH solutions. The ratios of dialysate to plasma creatinine concentration at 4 hour (D/Pcre) in peritoneal equilibration test were measured at every year. We evaluated D/Pcre levels at the initiation and two years after between acid and neutral pH groups, and also the D/Pcre movements before and after switching PD solutions of the six patients.

Results: There was no significant difference on the D/Pcre values between at the start and two years after in the acid and neutral pH groups respectively. D/Pcre change between at the start and two years after in the acid group was not significant different compared to that of the neutral pH group. However, D/Pcre declined significantly one year after switching PD solutions from acid to neutral pH.



Conclusions: It was not observed obvious beneficial effects of neutral pH solutions on peritoneal permeability within two years PD duration. However, the transient effect in decreasing peritoneal permeability was found, and suggested that biocompatible solutions may preserve peritoneal functions compared to conventional solutions in a long time period.

PUB606

Predictive Power of Serum Cystatin C Assessing Residual Renal Function in Patients on Peritoneal Dialysis Jong Man Park,¹ Sang Heon Song,¹ Eun Young Seong,¹ Harin Rhee,¹ Ihm Soo Kwak,¹ Il Young Kim,² Dong Won Lee,² Soo Bong Lee,² Woo Jin Jung,¹ Su Min Park,¹ Min Jung Kim,² Joo Hui Kim.² ¹Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea; ²Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea.

Background: Residual renal function (RRF) is of considerable importance for patient survival on peritoneal dialysis. In clinical practice, the RRF is usually measured by assessing the urine concentrations of urea and creatinine and total urine output and the process is cumbersome and time consuming. Cystatin C has proposed to be used in place of RRF measurement. This study aims to investigate the predictive power of cystatin C in peritoneal dialysis patients.

Methods: This study included 54 patients on peritoneal dialysis who had evaluated RRF, serum cystatin C and serum creatinine. RRF was measured using the 24-hour urea-creatinine clearance method and cystatin C based glomerular filtration rate (eGFRcysC) was estimated using the Hoek's formula. RRF and cystatin C were followed up for 6 months at least. The rate of RRF decline and slope of serum cystatin C were assessed by regression.

Results: Patients were on peritoneal dialysis for a median of 30 months and average serum concentrations of cystatin C was 5.41 ± 1.06 mg/L. Among the 54 patients, sixteen was anuric and seven became anuric during follow up. The patients with RRF had significantly lower cystatin C levels (p = 0.001). RRF was correlated with cystatin C (γ = -0.687, p < 0.01). In simple linear regression, RRF was associated with cystatin C (γ = 0.687, p < 0.001), eGFRcysC (γ = 0.741, p < 0.001) and creatinine (γ = 0.662, p < 0.001). The slope of serum

cystatin C was correlated with the rate of RRF decline (γ = 0.616, p < 0.001) during follow up. The overall loss of RRF group had a higher level of serum cystatin C at the point of dialysis initiation (p = 0.017).

Conclusions: Serum cystatin C level might be convenient parameter for estimating the RRF and serum cystatin C at the point of dialysis initiation might be a predictive marker of preservation of RRF. Further studies about the cystatin C based equations are required to replace creatinine/urea clearance measured RRF.

PUB607

Peritoneal Dialysis: A Decade Experience at a Reference Centre in Brazil Patricia O. Costa, Carla M.V. Melo, Flavia A. Nobrega, Jordano P. Oliveira, Jandson P. Oliveira, Kleyton Andrade Bastos. *Dept of Medicine, Federal Univ of Sergipe, Aracaju, Sergipe, Brazil.*

Background: Peritoneal Dialysis (PD) is underutilized in most countries. The Brazilian prevalence is around 9%. This study aims to describe the ten years experience on PD in a dialysis center in Northeast of Brazil (Aracaju-Sergipe). Unlike other national programs, negative selection for DP is not an attribute of this dialysis unit.

Methods: Retrospective cohort study that evaluated the sociodemographic and clinical profiles, comorbidities, peritonitis, hospitalizations and death causes of 565 patients who remained in PD for at least 30 days from 01/01/2003 to 12/31/2012.

Results: Patients were mostly men (55%), living outside Sergipe's capital (56%), had a mean age of 54 ± 19 years old when started on dialysis, were illiterate or had less than 4 school years (62%) and had a family income less than 5 national minimum wages per month (88%). The etiology of nephropathy was identified in 54% of cases, diabetic nephropathy (46%) and hypertensive nephrosclerosis (22%) were the most prevalent. Hypertension was the main comorbidity (76%). DP was the initial dialysis modality for 53% of patients, mainly as an emergency (58%), and only 9% of patients had undergone predialysis care for at least six months. Patients remained in PD by an average of 710.5 (± 714.2) days, and 61% of them also underwent hemodialysis (HD) at some point during their dialysis treatment. 676 peritoneal catheters were implanted (1.19/patient), 75% by trocar, by nephrologist, mostly Tenckhoff (58%). The main cause of dropout were infectious complications related to therapy (17%). The peritonitis index was 1 episode every 27.03 months, and S. aureus was the most prevalent etiological agent (22%). There were 1045 hospitalizations during follow up, most frequently due to infections (48%). The cause of death was identified in 64% of cases, mostly from cardiovascular diseases (50%).

Conclusions: In this study, patients had predominantly low socioeconomic status and did not have access to predialysis treatment, however, peritonitis rates and catheter complications are similar to those reported in other international series. HD and PD are shown as complementary techniques.

PUB608

Implementation of Clinical Practice Guidelines on Antimicrobial Prophylaxis in Peritoneal Dialysis Patients Denise Campbell,¹ Fiona Brown,² John F. Collins,³ Jonathan C. Craig,¹ Martin P. Gallagher,⁴ David W. Johnson,⁵ Geoffrey S. Kirkland,⁶ Subramanian K. Kumar,⁷ Wai Hon Lim,⁸ Dwarakanathan Ranganathan,⁹ Walaa W. Saweirs,¹⁰ Germaine Wong,¹ David Mudge.⁵ ¹School of Public Health, Univ of Sydney, Sydney, New South Wales, Australia; ²Nephrology, Monash Univ, Clayton, Victoria, Australia; ³Renal Medicine, Auckland City Hospital, Auckland, New Zealand; ⁴Renal and Metabolic Div, George Inst for Global Health, Sydney, New South Wales, Australia; ⁵Nephrology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; ⁶Nephrology, Royal Hobart Hospital, Hobart, Tasmania, Australia; ⁷Renal Unit, Gosford Hospital, Gosford, New South Wales, Australia; ⁸Renal Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; ⁹Nephrology, Royal Brisbane & Women's Hospital, Herston, Queensland, Australia; ¹⁰Renal Unit, Whangarei Hospital, Whangarei, New Zealand.

Background: Despite the existence of international guidelines, peritoneal dialysis (PD)-related infections vary widely across Australian and New Zealand units, with multiple units reporting suboptimal rates and variable practice.

Methods: The current practice and barriers to guideline uptake were evaluated in eight PD units located in Australia and New Zealand in 2011. A multifaceted intervention was developed which included case report forms, a patient diary, a 'Preventing Peritonitis Checklist', an Emergency Department flyer, a letter to the patient's general practitioner, a medical card, and a poster summarizing ISPD and KHA-CARI guidelines.

Results: At baseline (1 Jan-31 Dec 2011), exit-site infection (ESI) rates ranged from 0.06-0.53 episodes/patient-year; peritonitis from 0.31-0.86 episodes/patient-year; and fungal peritonitis from 0.00-0.08 episodes/patient-year. After implementation (9 Dec 2013-8 Dec 2014), the ESI rates were 0.00-0.22 episodes/patient-year; peritonitis was 0.29-0.49 episodes/patient-year; and fungal peritonitis was 0.00-0.14 episodes/patient-year.

Conclusions: Implementing the various tools resulted in improvement in the ESI and peritonitis rates but the difference was not statistically significant (P=0.15 and P=0.08). There was no statistically significant difference in the fungal peritonitis rate (P=0.64).

Funding: Government Support - Non-U.S.

PUB609

Survival Analysis of 326 Continuous Ambulatory Peritoneal Dialysis (CAPD) Patients Hao Zhang, Liu Li, Bin Yi, Wei Li. *The Third Xiangya Hospital, Central South Univ, Changsha, Hunan, China.*

Background: This study aimed to identify clinical outcomes and risk factors that may affect potential prognosis of ESRD (end-stage renal disease) patients who receiving continuous ambulatory peritoneal dialysis (CAPD) in Southern China.

Methods: ESRD patients who initiated CAPD between period Aug 1st 2002 to Mar 31st 2010 in The Third Xiangya Hospital, affiliated with Central South University were reviewed retrospectively. Demographic data including age at initiation, gender, body mass index (BMI), blood pressure, primary causes of ESRD and dialysis vintage, biochemical data including hemoglobin (HB), serum albumin (Alb), HDL (high-density lipoprotein), LDL (low-density lipoprotein), TL (total cholesterol), TG (triglyceride), immunoreactive parathyroid hormone (iPTH), serum phosphorus, serum calcium and residual renal function (eGFR) were collected from medical records. Outcome of death or technique failure from any causes were selected. All-cause mortality and survival rate were analyzed using variance analysis and COX regression.

Results: A total of 326 CAPD patients (199 male and 127 female) were identified in this study. The mean age was 50.73±14.99 years, median dialysis vintage was 46(2-144) months. Primary glomerulonephritis was the most common cause of ESRD (50.6%). The overall 1-, 3- and 5- patient survival rate were 95.4%, 79.3% and 46.2%, and 1-, 3- and 5- technique survival rate were 90.8%, 67.2% and 43.6%, respectively. Significant differences in age, BMI, hemoglobin, albumin, eGFR between groups were found. No statistical significances were found in gender and primary causes of ESRD. In multivariate cox regression analysis, patient technique survival were associated with BMI (HR=1.230(1.154-1.310), p=0.000), Alb (HR=0.913(0.882-0.945), p=0.000), HB (HR=0.981(0.971-0.992), p=0.000), eGFR (HR=0.818(0.750-0.884), p=0.000).

Conclusions: The results suggested that obesity, anemia, hypoalbuminemia, lower eGFR at the commencement were independent risk factors for technique survival in CAPD patients.

PUB610

Factors Influence the Baseline Peritoneal Transport Status Hao Zhang, Bin Yi, Cuiling Hou. *The Third Xiangya Hospital, Central South Univ, Changsha, Hunan, China.*

Background: Baseline peritoneal solute transport rate (PSTR) is an independent risk factor for total and cardiovascular (CV) mortality in the PD(peritoneal dialysis) population. The determinants of PSTR in incident PD patients are still under debate. Our objective was to explore the influence factors of baseline PSTR.

Methods: (1) 205 incident PD patients who had a standard peritoneal equilibration test (PET) within 1-3 months after commencing PD and without peritonitis history were enrolled. Pre-dialysis clinical parameters and biochemical indexes were assessed. 205 individuals were divided into two groups according to the baseline PET. High transport group: PET>0.65, Low transport group: PET < 0.65. (2) Pre-dialysis serum advanced oxidation protein products (AOPP) and dialysate AOPP, GPx, hsCRP, IL-1beta, TGF-beta1 of 59 patients among the enrolled 205 individuals were detected.

Results: (1) High baseline PET are more likely to be male (male: 77.3% vs 52.5%, p = 0.001), had lower serum albumin (34.0±4.40g/L vs 35.9±4.55g/L, p=0.005) and TG levels (1.11±0.62 mmol/L vs 1.28±0.57mmol/L, p=0.047) compared to the low baseline PET. Gender (r = 0.299, p = 0.299), serum albumin (r = 0.199, p = 0.199) and TG level (r = 0.140, p = 0.140) are correlated with the baseline PET respectively. Multiple stepwise linear regression analysis shows that gender (B = 0.085, p = 0.085), serum albumin (B = 0.005, p = 0.005) are associated with baseline PET independently. Multivariate Logistic analysis showed that men (OR = 3.314, p = 0.001), hypoalbuminemia (OR = 2.552, p = 2.552) are independent risk factors for high baseline PET. ROC curve display that when serum albumin < 35.8 g/L, it is likely to have a high baseline PET. (2) High baseline PET had a relatively high level of dialysate TGF-beta1 (1.58±0.33ng/ml vs 1.75±0.30 ng/ml, p=0.049) than the low transport status. No statistical differences were found in serum AOPP and dialysate AOPP, GPx, hsCRP, IL-1beta between groups. Dialysate TGF-beta1 (r = 0.336, p = 0.009) relative to the baseline PET independently.

Conclusions: (1) Male, hypoalbuminemia, high dialysate TGF-beta1 level are independent predictors of fast baseline PSTR. (2) When serum albumin < 35.8 g/L, it is likely to have a high baseline PSTR.

PUB611

Influence of Peritoneal Transport Rate in Diabetic Patients on Peritoneal Dialysis: A Single Center Experience in Saudi Arabia Naveed Aslam. *Nephrology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.*

Background: Measurement of the peritoneal membrane transport features is crucial for both the characterization of its functional state and for the prescription of the adequate dialysis dose. It has been reported that increased peritoneal transport rate (PTR) is associated with lower patient survival, but the influence of diabetes mellitus (DM) on the PTR is still controversial. The objective of this study is to describe the PTR and its correlation, in terms of technique and patient survival, in diabetic patients on peritoneal dialysis (PD).

Methods: In a retrospective, single-center study, we evaluated a total of 84 diabetic patients, newly started on PD between January 2004 and December 2010. Peritoneal equilibration test (PET) status was recorded and patients were classified as one of the

following four peritoneal transport types: high (H), high average (HA), low average (LA) and low (L) transporters. Inflammatory and nutritional markers along with routine renal parameters were assessed. Withdrawal from PD and death were recorded.

Results: The average age of patients starting PD was 76.3 ± 7.2 with a prevalence of male gender (70%). 80% of the patients showed high peritoneal transport rate (High: 28%, High-Average: 52%, Low-Average: 20%, Low: 2%). The 1, 3 and 5 year patient survival rates were 78%, 62% and 42% respectively. Technique survival rates were 64%, 52% and 24% respectively. Only 10% of the patients could perform their PD therapy without the assistance of any family member or nurses. Only 70% of the patients were on APD among high transporters. Albumin level and CRP were negatively associated with patient survival.

Conclusions: Our data suggest that diabetic PD patients tend to be significantly high peritoneal transporters with worse prognosis in terms of patient and technique survival. This result is similar to what several large studies had reported in the literature. For diabetic PD patients, PET should be carefully evaluated and accordingly the prescription of short dwells, which have found their natural application in APD, should be kept in mind as a treatment option. The high transport rate is a contributory factor in low serum albumin levels.

PUB612

Practical Experience with Acute Peritoneal Dialysis (PD) as Initial Dialysis Modality Jiri Vlasak. *FMC, Sokolov, Czech Republic.*

Background: Hemodialysis (HD) is the predominant renal replacement therapy (RRT) in new end-stage renal disease (ESDR) patients in the Czech Republic. One of many reasons for this situation is that roughly 40% patients with ESDR are "late referral". Due to the lack of predialysis education, these patients have limited knowledge about dialysis options. Usually, hemodialysis is performed after the central catheter placement.

Methods: Between November 2012 and April 2015, 15 patients with urgent need of dialysis were successfully initiated in our center on PD as the first option treatment.

Results: In two patients, we started PD immediately after the catheter insertion and on the second or third day in 13 patients. Exchanges were conducted in the out-patient dialysis center under the constant supervision of an experienced PD nurse in the modified mode-supine position, small volume solutions with 1.5% of glucose, 6-8 exchanges daily, using automated peritoneal dialysis (APD). Only one patient was treated in the local hospital because of severe uremia related symptoms. Exchanges were well tolerated. We did not observe any early complications (leak, malfunction of the catheter, infection, bleeding etc). All patients were educated 2-3 weeks after the start of acute PD regimen and we observed a strong adherence to PD method in all 15 patients.

Conclusions: Based on our experience, acute peritoneal dialysis can be successfully administered under the conditions of outpatient care in the majority of ESDR patients with the urgent need of dialysis if three preconditions are met. First, the team of well-educated staff in PD, especially in APD. Second, a close cooperation with surgeon experienced in laparoscopically assisted puncture technique of PD catheter. Third, the ability to introduce the PD catheter as urgent surgery.

PUB613

Cause of Failure in Chronic Peritoneal Dialysis Catheters Elizabeth Huerta calixto. *Nephrology, Hospital Angeles Puebla, Puebla, Mexico.*

Background: One of most common treatment of end stage kidney failure is peritoneal dialysis. Encapsulating peritoneal sclerosis is a complication in which the osmotic capacity of peritoneal barrier is lost, mainly due to infections. This pathology has different clinical presentations that oblige to use different diagnostic and therapeutic methods.

Methods: I was a survey conducted retrospective, descriptive and cross that included June 1, 2008 to May 30, 2014 in nephrology department of Angeles Hospital.

Results: Clinical and imagine presentation in three different patients, we analyze each separately as well as their solutions. These include delimitation of the affected zone, sterilization of the cavity and it's collapse, even the renal transplantation.

Conclusions: Different clinical presentations of the encapsulating peritoneal sclerosis oblige to design evaluation and treatment for each patient in particular, using all the imagine and laparoscopic methods.

PUB614

Take on Characteristics of Incident PD Patients in a Multicentre Multinational Integrated Care Setting Belen Marron,¹ Marietta Torok,² Delia Timofte,³ Janusz Ostrowski,⁴ Jose C. Divino-Filho.¹ *¹Diaverum Home Therapies, Medical Office, Diaverum, Munich, Germany; ²Szeged Diaverum Clinic, Diaverum, Szeged, Hungary; ³Sema Diaverum Clinic, Diaverum, Bucharest, Romania; ⁴Wloclawek Diaverum Clinic, Diaverum, Wloclawek, Poland.*

Background: Our institution as a Renal Service provider is committed to integrated care, offering all types of RRT and focusing in patient's choice. Objectives: To analyze HD and PD take on and its relationship with the type of previous referral and provided care.

Methods: Retrospective analysis of 547 incident patients starting dialysis in 23 HD/PD clinics in 2012. Early referral (ER) considered if patient known ≥ 3months in Nephrology, and scheduled initiation of dialysis with a permanent access was considered planned (P).

Results: Population: 30% diabetes, mean age 64 years, 84% with previous medical care of renal disease, 49 % late referral, 80% modality informed, 58 % unplanned start, 11% PD (3% early switch from urgent HD). PD therapy in non-planned start applied in 5/59 PD patients. No differences in HD/PD take on were observed for gender, diabetes, initial renal and predialysis follow up, at structured units or in elapsed time between early

follow up and dialysis start. PD patients (p=0.02) received more modality information than HD (92% vs. 78%) and were mainly under 50 years (p <0.001). PD incidence varied according with different studied groups

Studied groups: n (% vs.col.)	All patients n=547	HD n=488	PD n=59	p value
ER + P	168 (31)	133 (27)	35 (59)	< 0.001
Late referral + P	63 (12)	58 (12)	5 (9)	
ER + Unplanned start	113 (20)	104 (21)	9 (15)	
Late referral + Unplanned start	203 (37)	193 (40)	10 (17)	
Optimal care: ER + modality informed + P	121 (22)	96 (20)	25 (42)	

Conclusions: Despite commitment to offer PD/HD as complementary treatments, PD incidence is still low. Optimal care provision is important to improve outcomes but also to involve patients in their therapy choice.

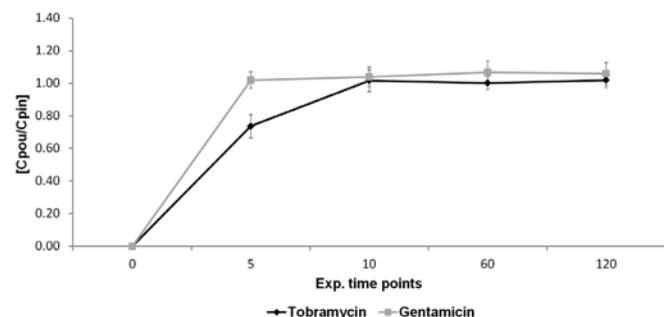
PUB615

The Adsorption Kinetics Profile of Aminoglycoside Antibiotics During Lixelle S-35 Cartridge Hemoperfusion Marco Sartori,^{1,2} Angela Casas,¹ Silvia De Rosa,¹ Mirella Zancato,² Leopolda Zampieri,¹ Davide Giavarina,¹ Claudio Ronco.¹ ¹International Renal Research Inst of Vicenza, St. Bortolo Hospital, Vicenza, Italy; ²Dept of Pharmaceutical and Pharmacological Sciences, Univ of Padua, Padua, Italy.

Background: The bactericidal activity against Gram(-)mo of Tobramycin(TOB)and Gentamicin(GEN)is concentration-dependent.It is therefore fundamental achieving the maximum drug plasma levels.Lixelle S-35 cartridge is a sorbent used in dialysis-related-amyloidosis which can modified the drug plasma levels.The aim of *in vitro* study was to evaluate the TOB and GEN adsorption removal by Lixelle S-35.

Methods: We performed mock direct hemoperfusion (DHP;Q₀=100ml/min;Bellco prototype dialysis machine)for 120 min using Lixelle S-35 cartridge.Human blood was diluted with fresh frozen plasma in order to achieve appropriate rheological characteristics(Hct 30%;650mL each bag;n=6).Blood was separately spiked with TOB(11.00±0.42 mg/L;n=3)and GEN(12.80±1.06mg/L;n=3)then it was circulated into the system.Samples were taken from arterial(C_{pin})and venous(C_{put})lines at 5,10,60 and 120 min.Sample levels were measured by TOBR and GENT Flex methods(Siemens Healthcare,Newark,NJ,USA)for TOB and GEN,rspectively.The adsorption kinetics profiles were calculated.

Results: At the of DHP TOB and GEN levels were 7.13±0.18 and 7.20±0.90mg/L. Ratio C_{put}/C_{pin} rose rapidly during the first 5 min then reach plateau for both antibiotics as shown Fig.On mass balance analysis,the total mass of antibiotics introduced into the system decreased from 5.12±0.25 to 3.22±0.50 and from 6.16±0.51 to 3.32±0.41mg for TOB and GEN,rspectively.The TOB mass adsorption was 37.20% whereas GEN was 46.20%.



Conclusions: Our *in vitro* study indicates an high adsorption rate for both aminoglycosides.This should be considered when TOB or GEN are used in pts treated with Lixelle S-35 cartridge.A supplemental dose may be needed to maximixed efficacy.

PUB616

Analysis of Some Aminoglycoside Antimicrobials in Human Plasma by HILIC-MS/MS Shinya Omiya,^{1,2} Xiao-Pen Lee,² Takeshi Kumazawa,² Keizo Sato,² Kiyoko Inui,¹ Tomoaki Miyazaki,¹ Yoshihiko Inoue,¹ Ashio Yoshimura.¹ ¹Dept of Medicine, Div of Nephrology, Showa Univ Fujigaoka Hospital, Kanagawa, Japan; ²Dept of Legal Medicine, Showa Univ School of Medicine, Tokyo, Japan.

Background: Aminoglycoside(AG) antimicrobials(AMBs) have been used for a treatment of bacterial infections,especially by acid-fast bacteria.However,their acute overdose or chronic abuse can cause serious side effects,such as difficulty in hearing, interstitial nephritis resulting in renal failure and even sudden death from anaphylactic shock.In such cases,there is a great need to identify and quantify AG AMBs in the blood from patients or cadavers.We earlier reported an analytical procedure for nine AG AMBs

in human serum by capillary HPLC/mass spectrometry(MS).Although this method works well for identification of the drug,it is semi-quantitative unless a suitable isotopic internal standard is used.

Methods: A simple,rapid,sensitive and quantitative method is presented for the analysis of six AG AMBs (streptomycin, ribostamycin, kanamycin, amikacin, dibekacin, arbekacin) in human plasma samples by hydrophilic interaction liquid chromatography(HILIC)-tandem MS(MS/MS).A small volume(150ul) of plasma spiked with six drugs was diluted with 350ml of acetonitrile containing 0.1% formic acid.After centrifugation,100ul of the clear supernatant extract was directly injected into the HILIC-MS/MS,without any solvent evaporation and reconstitution steps.The chromatographic separation of the AG AMBs was achieved on Unison UK-Amino HILIC column(50mm x 3mm i.d.,particle size 3um)with a linear gradient elution system composed of 0.1% formic acid and acetonitrile.

Results: All drugs showed base peaks due to [M+H]⁺ ions by HILIC-MS with positive ion electrospray ionization,and the product ions were produced from each [M+H]⁺ ion by HILIC-MS/MS.Quantification was made by selected reaction monitoring.The data obtained from actual determination of the AG antimicrobials in human plasma after their oral or intramuscular administration are also presented for validation of the methods.

Conclusions: This method would seem to be useful in clinical and forensic medicine because of its ability in both identification and quantification of the drugs.

PUB617

Prevalence of Chronic Musculoskeletal Pain Among Hemodialysis Patients Magdy M. Elsharkawy, Cherry Reda, Haitham Ezzat, Amr Mohab. *Nephrology Dept, Ain Shams Univ, Egypt.*

Background: Chronic musculoskeletal (MS) pain is common in patients with end stage renal disease (ESRD) undergoing hemodialysis; however information regarding its frequency and prevalence is relatively scarce.

Methods: A cross-sectional study was conducted on 100 ESRD patients on maintenance hemodialysis 3 times per week for at least 3 months. Chronic musculoskeletal pain was evaluated using the VON KROFF questionnaire for grading the severity of musculoskeletal pain. Correlation was done between chronic MS pain and physical findings of motor and sensory systems examination. In addition, correlation was also done between chronic MS pain and serum intact Parathormone (i-PTH), serum corrected calcium, serum phosphorus, serum alkaline phosphatase, serum albumin & hemoglobin level.

Results: Mean age was 57.46 years. Mean dialysis duration was 3.80 years. 42% were females and 58% males. In our study, 37% of the patients had low disability low intensity of pain i.e. little affection on the daily, social & work activity(grade 1),37% of the patients had low disability high intensity of pain (grade 2) while 26% of them had high disability high intensity of pain i.e. moderate limitation of the daily, social, recreational & work activities (grade 3). Chronic musculoskeletal pain showed positive correlation with muscle state, tenderness and power (p<0.001, p<0.001, p=0.001 respectively). Grade 3 disability patients had the highest level of serum Ca and i-PTH which were significantly different from grade 1 and 2 patients (p<0.001, p=0.013 respectively).While serum albumin level was lowest in grade 3 patients (p=0.025).

Conclusions: Chronic MS pain is common in ESRD patients.Disturbed mineral metabolism is strongly associated with chronic MS pain in long-term HD patients. Musculoskeletal system involvement remains a common problem that limits the physical function of patients with ESRD.

PUB618

Practice Patterns of United States Nephrologists in Blood Pressure Medication Use when Transitioning Patients to Dialysis Mary C. Mallappallil,¹ Steven Fishbane,² Rimda Wanchoo,² Andrea Roche-Recinos,¹ Subodh J. Saggi,¹ Moro O. Salifu.¹ ¹Internal Medicine- Div of Nephrology, SUNY Downstate School of Medicine, Brooklyn, NY; ²Internal Medicine -Div of Nephrology, Hofstra North Shore LIJ School of Medicine, Great Neck, NY.

Background: As there is no standard approach to transition a patient in chronic kidney disease (CKD)-5 to CKD5-Dialysis in regards to adjustment of diuretics, BP medication, optimal frequency of medication reconciliation (MR) and determination of dry weight (DW) we conducted a survey to determine how US nephrologists transition a patient from CKD5 to CKD5D in these aspects.

Methods: We designed an anonymous electronic survey with 39 questions and sent it to practicing nephrologists in the US after IRB approval.

Results: 120 US Nephrologists replied to the survey; 60% were in Nephrology for more than 10 years. Most (79%) used furosemide in CKD 5, (66%) used a combination of furosemide and metolazone. The first choice of diuretics in CKD5 was furosemide (79%), bumetinide (12%) and torsemide (9%) (p<0.005). In CKD5D, 45% used diuretics daily, 29% on non-dialysis days and 26% discontinued them(p=0.02). In CKD 5, 63% would continueACEI or ARB. In CKD5D, 84% of responders had at least 30% of patients on ACEI/ARB and most (64%) would not stop these medications despite hyperkalemia. The majority (79%) did not change ACEI to those that were not dialyzed out. The perceived most effective BP medication in CKD5D in decreasing order: Nifedipine/amlodipine (36%), ACEI/ARB(29%), beta blockers(17%), diuretics(13%) and others(4%); (p<0.0005). Most responders (70%) prescribed BP medication on non-dialysis days only and 88% thought that high BP in the first month could be controlled with ultrafiltration. The first MR in new CKD5D was monthly (78%), weekly (12%) and as needed only (8%). DW was determined in the first week(31%) and the first month(52%). Of those surveyed, 59% felt HTN in CKD5D hadt multiple causes.

Conclusions: Transitioning patients from CKD5 to CKD5D continues to remain challenging in terms of adjustment of BP medication. Variations in practice regarding the frequency of medication use may benefit from guidelines.

PUB619

First Dialysis Prescription and Access Use: A Survey of United States Nephrologists Mary C. Mallappallil,¹ Steven Fishbane,² Rimda Wanchoo,² Andrea Roche-Recinos,¹ Subodh J. Saggi,¹ Moro O. Salifu.¹ ¹Internal Medicine-Renal Div, SUNY Downstate School of Medicine, Brooklyn, NY; ²Div of Nephrology, Hofstra North Shore LIJ School of Medicine, Great Neck, NY.

Background: As there is no standard approach to initiate renal replacement therapy in CKD5patients in regard to location of first treatment, access and dialysis prescription we conducted a survey of US nephrologists to better identify current practice patterns.

Methods: We created an anonymous electronic survey with 39 questions that was validated then approved by the IRB. Aggregate data was analyzed using descriptive statistics, avoiding duplicate responses.

Results: 120 US nephrologists replied to the survey, 60% were in nephrology practice for more than 10 years. The first hemodialysis (HD) treatment was as inpatient (22%), outpatient (29%) or either (49.5%). At the first HD, most nephrologists (92%) used a blood flow (BF) <300 mL/minute; 65% would use lower than usual dialysate flow rates (DFR) and 47% would use a smaller dialyzer. Ninety six percent prescribed less time than usual, even with blood urea nitrogen less than 100 mg/dL. About 45% replied that only 10-50% of patients meeting criteria for peritoneal dialysis were actually started on this modality (p<0.005). Of the participants 47% noted that only 10-50% of patients who were eligible for transplant were listed, and the majority of responders (83%) noted that less than 10% of their patients got a preemptive transplant (p<0.0005). A patient educator was available to 64% of the participants. First dialysis with a permanent access was noted among 30-60% of patients by 43% of responders and in more than 60% of patients by 22% of responders. Of the participants 73% replied that the majority (>60%) of their patients got vein mapping before access creation. The time between vein mapping and access creation was one week to one month (61%) and more than one month (26%), (p<0.005). The number of angioplasties that were acceptable prior to primary access failure was noted as 2, (25%) 3 (25%) or more than 4(24%).

Conclusions: There is variation in practice in several areas in regard to the initial dialysis session in CKD5D which may benefit from guidelines.

PUB620

How to Dialyze a Patient with Left Ventricular Assist Device in a Chronic Dialysis Unit? A Practical Protocol Sadiq Ahmed,¹ Debbie Baker.² ¹Univ of Kentucky; ²Davita.

Background: To provide chronic HD treatments to ESRD patients with LVAD in a chronic unit in the community is a challenge and a relatively new experience for nephrologists. As LVADs have revolutionized the treatment of advance heart failure there are rising numbers of these patients developing ESRD with need for HD in the community. Development of a practical, simple and safe protocol is needed to dialyze these patients in the chronic units.

Methods: This protocol and safety check list is developed to provide routine HD treatment for patients with LVAD and successfully implemented in a chronic dialysis unit in the community setting. The special policy and procedure relevant to this protocol, safety check list and standing orders for the dialysis nurses were approved by the governing body before dialysis staffs were trained. The VAD coordinator is present during first training.

Results: This protocol is a step by step guidance for the dialysis staff. The whole process has 3 components. 1. A supplemental informed consent signed by the patient to cover for additional higher risk of HD with LVAD. 2. Guidance and check list for the dialysis staffs for assessments of LVAD patients with additional documentation before starting HD treatment. 3. Standing order to be followed by staff during dialysis of LVAD patient on top of regular dialysis orders. # 2 and 3 covers patient assessment, verification of LVAD equipment, power supplies and special hemodynamic monitoring of these patients during HD.

LVAD check list
Presence of support person who waits in lobby after power base is connected
Fully charged extra batteries for LVAD & backup system controller
Power base unit connected to electrical outlet & Patient connected to unit
Charge nurse to review LVAD log and trends
Document Pump Flow, Pump Speed & Pulsativity index for treatment and previous day
Obtain doppler, lubricant & sphygmomanometer for every 30 minute BP check
Initiate HD
Document LVAD assesment, doppler pressure, communications with MD and VAD coordinator
Review Post weight with charge Nurse if > 1 KG above TW notify MD

Conclusions: This protocol to provide incenter HD to patients with LVAD in a chronic unit is simple & safe. It can be implemented in a chronic HD unit.

PUB621

Association Among Calcium, Phosphorus, and Parathyroid Hormone with Aortic Ring Calcification in a Cohort of Hemodialysis Patients Arturo Reyes Marin. Nephrology, Hospital Juarez de Mexico, DF, Mexico.

Background: The prevalence of vascular calcification in dialytic therapy is 40-92%, values increased in serum levels of calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) have been associated with high calcification progression and cardiovascular mortality. It has been described association among serum levels of Ca, P, Ca-P product and PTH with aortic ring calcification in patients with chronic renal disease (CRD). We did an observational and descriptive study, in the nephrology department of Hospital Juarez de Mexico, with a cohort of 95 hemodialysis patients, the aim of study was to evaluate the association among aortic ring calcification by torax radiography with the serum levels of Ca, P and PTH.

Methods: Adult patients in hemodialysis were included, patients with severe malnutrition, cancer and mental abnormalities were excluded. We used 2 scales (torax radiography), in order to assessment the aortic ring calcification and we did correlation coefficient among Ca, P, PTH and 2 scales. We used Pearson correlation coefficient for analysis and Bland-Altman test for analysis of concordance among Ca, P, PTH and 2 scales.

Results: They were 95 adult patients: 50 (52%) men and 45 (48%) women, average age was 40.7 years old. We found weak negative correlation between Ca and PTH (r = -0.28, p > 0.05), weak positive association was found between P and PTH (r = 0.30, p > 0.05), correlation between PTH and CaxP (r = 0.36, p > 0.05), PTH and 2 scales (r = 0.5, p > 0.05). In the scales that we used to evaluate vascular calcification (torax radiography) showed high scores, however the intraclass correlation coefficient between scales and PTH, Ca and P (0.33) showed not statistical significance.

Conclusions: Despite that vascular calcification was high by torax radiography, the association among scales (torax radiography) and serum levels of Ca, P and PTH was not statistical significant. There are other important factors that can explain the progression of vascular calcification and the traditional markers for calcification: Ca, P and PTH are not enough for explain it.

Funding: Government Support - Non-U.S.

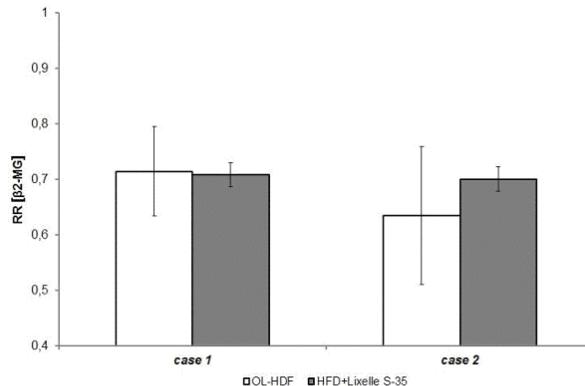
PUB622

β2-Microglobulin Removal: Comparison Between Lixelle S-35 Cartridge Coupled with High-Flux Dialysis versus Online-Hemodiafiltration Marco Sartori,^{1,2} Sara Samoni,¹ Federico Nalesso,¹ Alessandra Brendolan,¹ Mauro Neri,¹ Francesco Garzotto,¹ Silvia De Rosa,¹ Mirella Zancato,² Claudio Ronco.² ¹International Renal Research Inst of Vicenza, St. Bortolo Hospital, Vicenza, Italy; ²Dept of Pharmaceutical and Pharmacological Sciences, Univ of Padua, Padua, Italy.

Background: Lixelle is a sorbent used to treat dialysis-related amyloidosis due to β2-microglobulin(β2-MG) deposit. The aim of this study was to assess the impact of Lixelle S-35 coupled with High-Flux Dialysis(HFD)vs online Hemodiafiltration(OL-HDF)in 2 pts.

Methods: We enrolled 2 pts with β2-MG levels over 15mg/L, treated with OL-HDF. Case 1. Male, 57yrs old with BMI 35.5Kg/m². We collected samples previous and after pre/post-reinfusion OL-HDF(n=3). Then the pt was shifted to HFD+Lixelle S-35(n= 3; Q_b=380mL/min; Q_d=500mL/min; ΔBW=2.87±0.42Kg). Case 2. Male, 72yrs old, BMI 26.8Kg/m². We collected samples previous and after post-reinfusion OL-HDF(n=3). Then the pt was shifted to HFD+Lixelle S-35(n=3; Q_b=300mL/min; Q_d=500mL/min; ΔBW=3.1±0.53Kg). We compared the data obtained in each treatment.

Results: Case 1. Before and after pre/post-reinfusion OL-HDF and HFD+Lixelle S-35, β2-MG levels were 18.26±3.91 and 5.00±0.18, 27.34±1.45 and 7.96±0.77mg/L, respectively. There was no difference between pre/post-reinfusion OL-HDF(71.48%) and HFD+Lixelle S-35(70.90%)β2-MG removal rate[RR]. Case 2. Before and after post-reinfusion OL-HDF and HFD+Lixelle S-35 β2-MG levels were 13.68±4.10 and 4.66±0.24, 17.23±1.55 and 5.13±0.60mg/L, respectively. There was difference between post-reinfusion OL-HDF(63.44%) and HFD+Lixelle S-35(70.09%)β2-MG removal rate. We did not observe any adverse reactions and/or side effects potentially related to Lixelle S-35.



Conclusions: Our preliminary results indicate that HFD+Lixelle S-35 seems to be more efficient in β2-MG removal than post-reinfusion OL-HDF, whereas no differences have been found with pre/post-reinfusion OL-HDF. More studies are needed.

Funding: Private Foundation Support

PUB623

Does Dialysis Influence Treg Cells? A Meta-Analysis Carlotta Caprara,¹ Gilbert R. Kinsey,² Wenjun Xin,³ Jennie Z. Ma,³ Valentina Corradi,¹ Elisa Scalzotto,¹ Francesca K. Martino,¹ Mark D. Okusa,² Mitchell H. Rosner,² Fiorenza Ferrari,¹ Claudio Ronco.¹ ¹International Renal Research Inst Vicenza (IRRIV), Dept of Nephrology, Dialysis & Transplantation, St. Bortolo Hospital, Vicenza, Italy; ²Medicine, Univ of Virginia, Charlottesville; ³Public Health Sciences, Univ of Virginia, Charlottesville.

Background: The immunological state of patients with ESRD is dysregulated. Regulatory T (Treg) cells comprise a small proportion of the total lymphocyte population yet regulate key immune responses across a variety of disease settings. Contrasting results have been reported about the influence of dialysis on Treg cells. Our aim is to determine whether the available literature support a positive or negative influence of dialysis on Treg cells.

Methods: After screening 84 published studies (PubMed and Web of Science) we included 10 that evaluated Treg cells in ESRD patients. Of these, 5 studies that included comparable healthy controls (HCs) and hemodialysis (HD) patients and used similar criteria for determining the percentage of Treg cells in total CD4 T cells were subjected to a meta-analysis.

Results: A total of 99 HD patients and 88 age-matched HCs were included in these 5 studies. Using the fixed effect model a significant difference in the percentage of Treg cells in total CD4 T between HD and HCs was observed (P<0.001). The mean difference in Treg percentage was -2.34% in HD patients vs. HCs. Several discrepancies were noted between studies that may be due to the lack of consistent criteria for Treg cell identification and use of different type of dialysis membranes which was not specified in all articles.

Conclusions: The available literature comparing Tregs in HD patients and HCs suggest HD is associated with a reduction in Tregs. A limitation is that only a few articles consider uremic patients (ESRD not on dialysis) as a control group for HD. Furthermore, no studies have investigated Treg cells in the same patient before and then after initiating dialysis. This type of study will be critical to understanding the influence of dialysis on Treg cells. Furthermore, the clinical significance of these changes in Treg cell numbers will need to be elucidated.

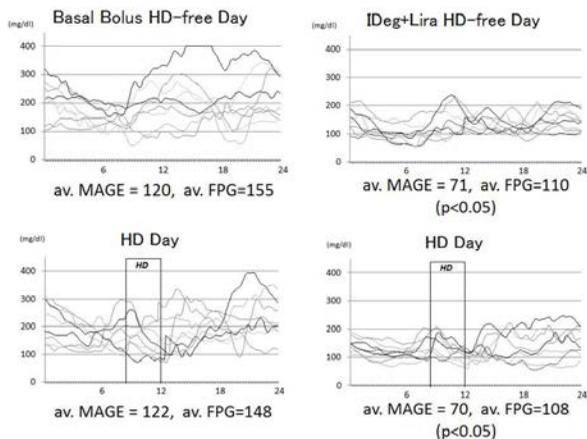
PUB624

Combination of Insulin Degludec (IDeg) and Liraglutide (Lira) (IDeg+Lira) Is Potentially Superior to Basal-Bolus Insulin Therapy (BB) in Hemodialysis (HD) Patients with Type 2 Diabetes (T2DM) – An Assessment by Continuous Glucose Monitoring (CGM) Satoshi Funakoshi,¹ Jyunichiro Hashiguchi,¹ Kenji Sawase,¹ Osamu Sasaki,¹ Hiroshi Ichinose,¹ Miwa Shirahama,¹ Miki Yano,¹ Yutaka Mori,³ Takuhisa Uchino,¹ Kazunori Utsunomiya,³ Yoko Obata,² Tomoya Nishino,² Takashi Harada.¹ ¹Nagasaki Kidney Center, Japan; ²Dept of Internal Medicine, Nagasaki Univ Graduate School of Medicine, Japan; ³Dept of Diabetology, Jikei Univ, Japan.

Background: During HD, plasma glucose (PG) level drops due to various factors including clearance gap between glucose and insulin, and then rebounds to hyperglycemic state after HD. Therefore, it may be difficult for conventional BB to control these complicated PG changes in HD patients with T2DM. Recently a free combination of any insulin and Lira has been approved in Japan.

Methods: Eight adults with T2DM, glycoalbumin (GA) of >20%, fasting C-peptide of >8 ng/ml and treated with BB including IDeg (5-74 units) + insulin lispro (5-30 units) were converted to daily injections of the free combination of same dose of IDeg and 0.9mg of Lira (IDeg+Lira), then IDeg was titrated to achieve an appropriate fasting plasma glucose level. Glycemic control was assessed by CGM and the mean amplitude of glycemic excursions (MAGE) was calculated before and after the conversion.

Results: As shown in figure 1, after 4-8 weeks of change from BB, mean both MAGE and PG were significantly decreased as shown in figure. Six out of 8 patients reported gastrointestinal adverse events, but these events were transient.



Conclusions: IDeg+Lira can potentially be superior compared with BB in controlling glycemic fluctuations in HD with T2DM.

Funding: Private Foundation Support

PUB625

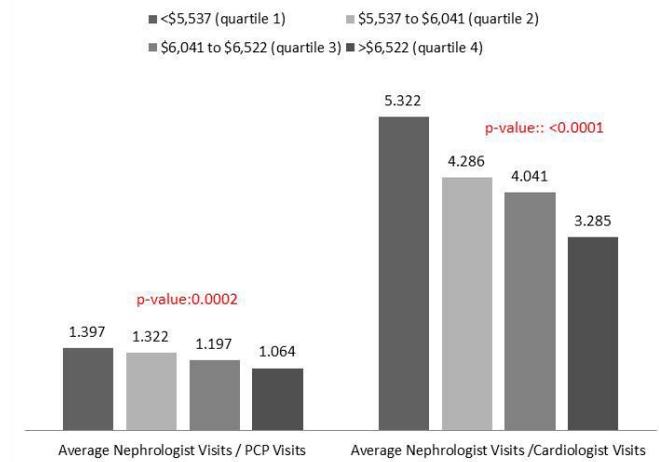
More Nephrologist Visits Are Associated with Lower Cost of Care for Dialysis Patients Hao Han, Jane Brzozowski, Sheetal Chaudhuri, John W. Larkin, Mahathi Mothali, Len A. Usvyat, Terry Ketchersid, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Medicare patients with end stage renal disease (ESRD) are treated by nephrologists, primary care providers (PCPs), cardiologists and other specialties on a regular basis. We investigated the relationship of visits to these providers and total costs of care.

Methods: Medicare 100% ESRD data for patients with evidence of dialysis at any time during January 1, 2010 through December 31, 2011 were analyzed. Nephrologist, PCP and cardiologist visits were determined by specialty codes of Part B claims (including both in- and out-patient visits). All data was aggregated at the Metropolitan Statistical Area level (MSA). We computed a ratio of nephrologist visits to PCP visits per MSA as well as nephrologist visits to cardiologist visits per MSA during the above period (visits were calculated on a per patient per month basis). Total costs of care (per member per month [PMPM]) were determined by aggregating Medicare Part A and B costs. Comparisons of ratios were performed using t-tests for quartiles of PMPM for two specialty visit ratios.

Results: Claims for 368,711 patients were analyzed. Patients in the lower quartiles of total cost had significantly more nephrology visits relative to PCPs and cardiologists.

Ratios by Quartiles of Total Cost



Conclusions: These results indicate that higher ratios of nephrologist visits to cardiologist/PCP visits are significantly associated with decreased cost on a MSA level. Taken that nephrologist visits tend to be constant (due to the monthly capitated payment), these results may be revealing a “sicker” and therefore more expensive population of patients on a MSA level that require more medical attention from a cardiologist or PCP, likely due to hospitalizations. Adjustments for underlying disease should be considered.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB626

Prediction of Non-Adherence to Hemodialysis Treatment Regimens Yue Jiao,¹ Daniel E. Geary,¹ Theresa J. Hetzel,¹ Sheetal Chaudhuri,¹ Mahathi Mothali,¹ Terry Ketchersid,¹ Dugan Maddux,¹ John W. Larkin,¹ Peter Kotanko,^{2,3} Brian Scott Ash,¹ Len A. Usvyat,¹ Franklin W. Maddux.¹ ¹Fresenius Medical Care North America, Waltham, MA; ²Renal Research Inst, New York, NY; ³Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Non-adherence with hemodialysis (HD) treatment regimens is known to be associated with increased morbidity and mortality. The aim of this project was to develop a predictive model (PM) to identify HD patients who will likely have unexcused no shows to routine dialysis treatments within the next week.

Methods: Using data between 1/1/2014 and 12/31/2014 from the Fresenius Medical Care Knowledge Center and 2014 weather data from the National Oceanic and Atmospheric Administration’s National Centers for Environmental Information, PMs were designed and developed for prediction of unexcused no shows in patients not residing in a nursing home. Various PMs were investigated and included the generalized linear model, partitioning and regression trees, artificial neural networks, and generalized additive model (GAM). In all, 1,554,833 records stratified in weekly intervals on 60 variables from 172,854 patients were utilized. Variables included data on the patient’s history of unexcused no shows, demographics, comorbidities, laboratories, holidays, sporting events, and weather. A multi-tier prediction process was performed with respect to the availability of data. The area under the curve (AUC), sensitivities and specificities were investigated to determine the model with the highest performance.

Results: Best performing model had AUC of 0.87 for the multi-tier PMs utilizing a 30% test dataset. A small pilot test on 860 patients for three weeks utilizing optimal Youden index as the cutoff value to predict the high probability of the unexcused no show events achieved an average sensitivity of 0.57 and specificity of 0.95.

Conclusions: This pilot test of the developed modeling demonstrates that PM can assist in identifying patients with a high probability for unexcused missed HD treatments. Additional studies are needed to further analyze the potential of predictions for and interventions associated with reducing unexcused no show events.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB627

Factors Influencing Residual Renal Function Decrease in Hemodialysis Treated Patients Fernando Caravaca-Fontan, Milagros Fernandez-Lucas, Jose L. Teruel, Saul Enrique Pampa, Estefania Yerovi, Maria Delgado yagüe, Fernando Liano. *Nephrology, Hospital Univ Ramon y Cajal, Madrid, Spain.*

Background: We have shown in previous studies that maintenance of residual renal function in hemodialysis treated patients is conditioned by the number of weekly sessions, and is better in patients who start treatment with a twice weekly schedule. The aim of this study is to analyse the influence of other variables in the preservation of residual renal function.

Methods: Of the 174 consecutive patients who started hemodialysis treatment in the hospital, 98 began with 2-weekly sessions (2HD group), and 76 with 3-weekly sessions (3HD group). Residual renal function was measured every two months (mean urea and creatinine clearance).

Results: Decrease in residual renal function was lower in the 2HD group (median 0.19 vs 0.46 ml/min/month, p=0.005). In both groups the residual renal function decrease was higher in the patients from the transplant program than in those from predialysis: 2HD group: median 0.93 vs 0.17 ml/min/month, p=0.003; 3HD group: median 0.76 vs 0.32 ml/min/month, p=0.005. Neither the initial schedule, sex or etiology of the renal disease influenced the decrease in residual renal function in either of the two groups of patients. Moreover we found no correlation between the decrease in residual renal function with age, the renal function at the start of dialysis or with the Charlson comorbidity index. Of the 98 patients who began with the 2HD schedule, 45 went on to dialysis three times a week when the residual renal function was less than 3 ml/min: these patients had a mean of 10±8 months on the 2HD schedule. The length of time on this model was not influenced either by age, sex, etiology of the nephropathy, comorbidity index, scheduled start or basal renal function.

Conclusions: The decrease in residual renal function in the patient treated with hemodialysis depends basically on the number of weekly sessions with which the dialysis treatment was started. Of all the variables analysed only the return to dialysis due to graft loss conditioned a higher decrease in residual renal function in both groups of patients.

PUB628

Circadian Blood Pressure Behaviour in Hemodialysis Patients Dimitrios Petras,¹ Kyriakos Dimitriadis,² Panagiota E. Giannou,¹ Eirini Andrikou,² Konstantinos Tsioufis.² *¹Nephrology Dept, Hippokraton Hospital, Athens, Greece; ²First Cardiology Clinic, Hippokraton Hospital Univ of Athens, Athens, Greece.*

Background: Blood pressure (BP) evaluation and management in haemodialysis (HD) patients is often a matter of debate. During HD hypotension as well as a paradoxical rise in BP may be documented. Intradialytic BP is also variable depending mostly from the weight gain between the HD sessions. We investigated circadian BP behavior in the setting of HD.

Methods: We studied 38 patients with ESRD (68% men, mean age 62±19 years, 52% hypertensive) that underwent HD three times a week in the HD unit of our hospital and were at their ideal dry weight. Ambulatory BP monitoring was applied one hour before an HD session and was set to measure BP every 30 minutes and until arrival for the next HD session, for a total of two subsequent 24-hour periods. Blood pressure dipping was defined as [(daytime systolic BP – nighttime systolic BP)/ daytime systolic BP]. Patients were defined as dippers if BP dipping was >10% and risers if BP dipping <0%.

Results: Body weight before and after the HD session was 78±28Kg and 75±27mmHg respectively. Ambulatory systolic/diastolic BP increased not significantly from 127±23/70±13mmHg to 130±19/71±11mmHg (p>0.05) from the first to the second 24-hour period. Mean dipping was 1.5±7.8% in the first day and further decreased to -0.94±6.8% in the second day. Accordingly, in the first 24-hour period, only 6 patients (16%) were dippers and reduced to 2 patient in the following day (5%). Sixteen patients (42%) and 18 patients (47%) were risers at the first and second 24-hour period respectively.

Conclusions: Daytime systolic BP does not substantially change during the 48-hour period extending from HD to HD session. Yet, prevalence of the non-dipper as well as the riser pattern is high and further increases during the interdialytic period. Patients with this BP pattern are at high risk for coronary artery disease, especially if other comorbidities coexist. Ambulatory BP monitoring in ESRD patients is a promising non invasive technique for the recognition of future heart disease.

PUB629

In Vitro Dialysability of SNF472, a Novel Inhibitor of Vascular Calcification, Using Conventional Hemodialysis and Hemodiafiltration Joan Perelló,¹ Miquel Gomez Umbert,² Nestor Yesid Rodriguez,² Carolina Salcedo,¹ Miquel D. Ferrer,¹ Juan Manuel Buades,³ Maria del mar Perez,³ Eva Martín Becerra,⁴ Francisco Maduell.² *¹Sanifit, Palma, Spain; ²Nephrol. and Renal Transpl., Hosp. Clinic, Barcelona, Spain; ³Nephrol., Hosp. Son Llàtzer, Palma, Spain; ⁴Kinrel, Madrid, Spain.*

Background: SNF472 is being developed for the treatment of calciphylaxis and cardiovascular calcification in end stage renal disease patients on hemodialysis. The intended use of SNF472 is intravenous infusion during dialysis; therefore our aim was to assess its possible dialyzability and its effects on calcium (Ca) chelation.

Methods: Dialysability of SNF472 was assessed using online hemodiafiltration (OL-HDF) and conventional hemodialysis (HD) systems. The interaction of SNF472 with the system was assessed under bypass conditions (dialysis in off-mode). One liter of heparinized fresh blood spiked with 8 mg/dl creatinine was introduced in a container maintained at 37 °C and a one hour dialysis session was simulated. 66.6, 30 and 10 mg/L SNF472 were infused during the first 20 minutes of dialysis. Samples were obtained at different time points and creatinine, total and ionized Ca and SNF472 levels were quantified.

Results: No dialyzability of SNF472 was detected at 30 and 66.6 mg/L neither in OL-HDF nor in HD systems. Dialyzability was measured at 10 mg/L SNF472 both in OL-HDF and in HD, with an estimated clearance (Cl) of 39 and 18 mL/min, respectively. Creatinine showed a Cl of 231 and 220 mL/min, respectively. In bypass conditions, blood Ca was chelated during the 20 minutes of SNF472 infusion when added at 66.6 mg/mL. However, when the system was switched to the dialysis mode, the Ca in the dialysis bath compensated the chelating effect of SNF472 and Ca levels remained unaltered.

Conclusions: SNF472 dialyses with a low Cl. SNF472 levels increase in blood during infusion and dialysis does not prevent from attaining potentially therapeutic levels. As SNF472 will be infused during the whole dialysis session, this low Cl is not expected to affect system exposure. The chelating effects of SNF472 on Ca are compensated by the Ca in the dialysis bath, so no hypocalcemia is expected. Supported by REDINREN RD012/0021 and RETOS COLABORACIÓN RTC-2014-2460-1 grants.

Funding: Pharmaceutical Company Support - Laboratoris Sanifit, Government Support - Non-U.S.

PUB630

A Simple and Cost Effective Approach to Ultra-Pure Dialysate Anthony M. Valeri,¹ Bobby C. Lee,² John Duffy,³ Robin Ferrer,⁴ Ronald Villota,⁴ Greg C. Riccardi,³ Edmond P. Wong.³ *¹Dept of Medicine, Columbia Univ, New York, NY; ²Dept of Pharmacy, New York-Presbyterian Hospital (Columbia), New York, NY; ³Dept of Biomedical Engineering, New York-Presbyterian Hospital (Columbia), New York, NY; ⁴Dept of Nursing, New York-Presbyterian Hospital (Columbia), New York, NY.*

Background: Ultrapure dialysate has been shown to reduce inflammation and improve nutritional and anemia parameters in patients on chronic maintenance hemodialysis. The Nephros[®] DSU (Dual Stage Ultrafilter, Nephros[®] Inc, River Edge, NJ) has been shown to reduce bacterial counts and endotoxin levels by at least a 5-log order of magnitude.

Methods: We performed an observational trial of this filter in a hospital-based acute dialysis facility in the USA.

Results: There were 23 chronic stable hemodialysis outpatients treated during the 6 months before and after the installation of the Nephros[®] filters. The mean age was 51 (range 12-91), 61% male, predominantly Hispanic (70% Hispanic, 17% African-American, 9% Caucasian, 4% Asian) and 30% diabetic. Comparing data from the 6 month period after the installation of the filters to the preceding 6 months, there was an increase in the mean hemoglobin level of 0.5 gms/dL (p=0.010) with a reduction in the mean weekly darbopoietin dose of 14.6 mcg or 40% (P<0.001) translating to a reduction in the ESA resistance index (weekly ESA dose/hemoglobin level) of 1.52 (p<0.001). During this time period, indirect inflammatory markers showed a reduction in the mean WBC count from 7,000 to 6,600 x 10³ /L (p=0.008) and an increase in serum albumin from 3.6 to 3.7 (p=0.024). The mean spKt/V was unchanged during the 2 time periods (from 1.609 to 1.607, p=0.30).

	Hemoglobin (gms/dL)		Darbopoietin dose (mcg/week)		ESA resistance index (ESA/Hgb)	
	Pre	Post	Pre	Post	Pre	Post
Mean	10.3	10.8	36.3	21.7	3.54	2.03
Interquartile Range	10.1-10.8	10.5-11.1	21.5-40.0	15.9-25.6	2.06-4.42	1.46-2.25
p-value (post vs. pre)		0.010		<0.001		<0.001

Conclusions: In conclusion, the use of the Nephros[®] DSU filter to further reduce endotoxin exposure in chronic hemodialysis patients can result in improved ESA responsiveness and a lower ESA dose.

PUB631

Care Delivery Models for End Stage Renal Disease: A Systematic Review

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Background: Reimbursement for dialysis care has led the way for the broader transition to a value-based payment model. As payment policy for dialysis evolves, a better understanding of the evidence around care delivery models that optimize outcomes and increase the value of care for dialysis patients is essential. Limited evidence exists about which care delivery models are most effective.

Methods: Multiple databases were searched for comparative studies of care delivery models for ESRD published between 2000 and 2014. The intervention had to include >5 dialysis patients over age 18 years and receiving treatment, >6 months follow up, and reported patient important outcomes i.e. mortality, important clinical outcomes, hospitalizations and quality of life. Data was abstracted by reviewer pairs; study quality was evaluated using Cochrane and Newcastle-Ottawa tools.

Results: 1841 abstracts were screened, 59 full-text articles were reviewed, and 23 studies with 87,281 patients were included for final analysis. The interventions included nutritional (n=4), multidisciplinary care (n=6), satellite programs (n=3), home dialysis (n=3), access monitoring (n=2), physician contact (n=4), and nocturnal dialysis (n=1). Most were observational studies of decent quality with representativeness and incomplete follow up being the main potential sources of bias. Two randomized studies on home dialysis and pharmacist care, had attrition as the main risk of bias. Most interventions showed positive effect raising concern of publication bias. Overall, hospitalizations were significantly lower in the intervention group despite large heterogeneity IRR: 0.824, 95% CI 0.781, 0.868, p<0.001, I²=95.6%.

Conclusions: Multiple interventions have the potential to improve the outcomes of dialysis patients but have not been compared in terms of safety and effectiveness. Limited evidence is available to inform dialysis practice redesign to adapt to new payment structures. Further studies are needed to define best delivery models for dialysis care.

PUB632

Symmetrical Dimethylarginine (SDMA) Is Poorly Cleared by Standard Hemodialysis

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Background: High SDMA levels have been associated with an increased risk for cardiovascular disease in patients with normal or reduced renal function. The effect of hemodialysis on SDMA has not been thoroughly studied.

Methods: We measured SDMA levels and its handling by hemodialysis and by the normal kidney in subjects with ESRD on chronic hemodialysis (n= 7) and in normal controls (n=6).

Results: The mean (SD) SDMA levels in ESRD were six times higher than in normal controls, 3.35(0.65) vs 0.53(0.25) μ M, p<0.001. For comparison pre-dialysis BUN levels was 44.1(23.1)mg/dl in ESRD, and 14.9(3.2) mg/dl in controls. The fractional reduction of SDMA was significantly lower than that of urea, 47.4(11.5)%, vs 76.7(4.7)%, p<0.001; and the volume of distribution was much higher 58.5(14.5)L vs 35.5(10.4)L for urea. Also the urinary clearance of SDMA [78.2 (33.5) ml/min] in normal individuals was higher than that of urea 55.2(13.7) ml/min. SDMA production rates were similar 46.7(9.4) vs 52.3 (13.9) mmoles/day, ESRD vs normals, p>0.05.

Conclusions: In summary, SDMA circulates at high levels in hemodialysis patients due at least in part to its relatively high clearance by the normal kidney, relative to urea, and its larger volume of distribution. The latter suggests that SDMA is likely to be localized in the intracellular compartment, and therefore less available for clearance by standard hemodialysis.

Funding: NIDDK Support, Private Foundation Support

PUB633

On-Line Hemodiafiltration Is Efficient for Inflammation and Phosphorus Control

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Background: High efficiency on-line hemodiafiltration is efficient to remove uremic toxins and phosphorus. Many studies had demonstrated the impact of this modality in mortality. The main objective of this study was to analyze the high efficiency on-line hemodiafiltration ability to remove phosphorus and reactive C protein.

Methods: This is a prospective study with end stage chronic kidney disease patients undergoing dialysis with high levels of phosphorus. High efficiency on-line hemodiafiltration, as described as a reposition volume higher than 22Lts, was used for a period of at least one year of follow-up. Beta-2- microglobulin, pre dialysis urea, post dialysis urea, reactive C protein, hemoglobin and phosphorus were collect from patients before starting on-line hemodiafiltration treatment and every month.

Results: Patients included in this study were 54.45±16.75 years old; they were on hemodialysis for at least for one year. 58% had hypertension or coronaryopathy. Hemodialysis dose as single pool Kt/V were significantly higher (1.21±0.20 vs 1.36±0.16; p<0.001) and this difference was kept for all follow-up. In six months of high efficiency hemodiafiltration we also found a decrease on phosphorus levels (7.9±2.4 vs 7.3±2.01 p<0.001) in one year follow up, phosphorus levels were still significantly lower than in the conventional

hemodialysis (7.3±2.01 vs 5.6±2.03 p=0.001). We also observed a decline in the need for erythropoietin doses in six months (p=0.04) associated with a higher hemoglobin levels (p<0.001). Reactive C protein showed significantly lower levels after six months of on-line hemodiafiltration (p=0.004).

Conclusions: High efficiency on-line hemodiafiltration is an efficient method of reduction of reactive C protein and may reduce costs due to reduced doses of erythropoietin analogues.

PUB634

On-Line Hemodiafiltration Filters a Comparative Study

Nadia Guimaraes- Souza, Adriano Luiz Ammirati, Thais Nemoto Matsui, Maria C.C. Andreoli, Fabiana Dias Carneiro, Ana C M S Ramos, Bento C. Santos. *Dialysis Center, Hospital Israelita Albert Einstein, Brazil.*

Background: High efficiency on-line hemodiafiltration is the best method for middle molecules and phosphorus remotion. Many studies had demonstrated the efficiency of this method in mortality reduction. The main objective of this study was to compare the three filters available for on-line HDF comparing the ability to remove urea, phosphorus and beta-2-microglobulin.

Methods: Prospective cross-over study including four patients and three available filters for hemodiafiltration. All section of on-line hemodiafiltration was made with high efficiency (23-25lt). Filters HDF 100, FX100 e HDF80COR were compared. Urea, phosphorus and beta-2 microglobulin were collected before and after first use of each filter A reduction ratio was calculated to compare the treatments.

Results: 76% of patients were man, the middle age (61.3±5), 76% of patients were diabetics and had peripheral neuropathy and 34% had coronaryopathy. FX100 filter showed significantly higher dialysis dose compared to FX80COR (p=0.03); the same was observed for urea reduction ratio (p=0.04). Beta-2-microglobulin and phosphorus reduction ratio were similar between all filters.

Conclusions: FX100 and HDF100 filter were similar for urea remotion ratio. There were no differences for other molecules.

PUB635

Satisfaction of Patients on Dialysis Unit

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Background: The assessment of the nsatisfaction of patients in Dialysis, is a useful tool to meet patient needs; axis on which the care serevice is based. In turn it allows to identify the deficient areas.

Methods: Objective 1) To know the views of patients about the service that is offered in each of the areas of focus. 2) To analyze the profile of satisfaction of patients they expressed their overall dissatisfaction. Prospective, descriptive study conducted at the Dialysis Unit of the Military Hospital Córdoba, conducted between 15/11/2014 to 15/12/2014. Inclusion criteria: All patients attending the service, wich received some form of dialysis (hemodialysis-DP) in the period. Exclusion criteria: a) diagnosos of cognitive dementia, b) Carryng less than three month of treatment c) not be psychological and physical conditions to answer the survey. A qualitative survey, structured arjar, applied voluntary and anonymous.

Results: 95 surveys of the total population comprised 111 patients were taken; of wich 85 are for patients undergoing henodialysis and 10 patients on CAPD. By studying the "General Satisfaction" in all aspect of the service that is offered to the patients responses they were largely positive, 80 % of the sample expressed feeling satisfied, while 20 % responded negatively. The results denote that carriers are those who receive the worst assessment by patients. The ambient temperatura for both dialysis room to the waiting room appears as an aspect also of disagreement. The most valued aspect is the power receidinguring treatment, both the quality and quantity as well as the attention of the professionals: technical, medical and social worked, in that order.

Conclusions: 1. As a management tool, it should be rated as positive aspects stimulate and work on correcting the negative aspects. 2. The level of dissatisfaction is directly related to dialysis treatment time of the patient, the longer, higher degree of dissatisfaction. 3. It is advisable conduct regular surveys on the degree of patient satisfaction Dialysis, and that will help improve their quality of life.

PUB636

Correlation Between Calcium Phosphorus Product and Hypertension in ESRD Patients on Maintenance Hemodialysis

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Background: Increased levels of serum calcium, phosphorus and product of serum calcium and phosphorus (Ca x P) in end stage renal disease (ESRD) patients has been shown to be associated with increased mean arterial blood pressure (MAP). The available data is limited and no study has been done in Pakistan. We conducted a cross sectional study to determine the correlation between mean arterial blood pressure (MAP) and serum calcium-phosphorus product in our ESRD patients on hemodialysis.

Methods: Blood Pressure of all the prevalent ESRD patients in a single dialysis center was recorded and mean arterial blood pressure (MAP) was calculated pre and post dialysis. All patients were clinically euvolemic. Serum calcium and phosphorus levels were measured and Calcium-phosphorus product (CaxP) was calculated. The product above 50 and the MAP above 93 were taken as high.

Results: Of the 60 ESRD patients, 35(58.3%) were males with mean age was 39.5±5 years. High CaxP product was seen in 18 (30%) patients with high pre-dialysis MAP in 8 (44%) and high post-dialysis MAP in 4 (22%) patients respectively. Of 42 (70%) patients with CaxP product below 50 high pre-dialysis MAP was seen in 31(73%) and high post dialysis MAP was seen in 29 (69%) patients.

Conclusions: This study showed that high CaxP product (>50) is not correlated with high pre and post-dialysis MAP. The results are not consistent with earlier studies done in developed countries. Larger studies are needed to re-evaluate these findings.

PUB637

Behaviour of Ankle-Brachial Index During Hemodialysis: Effect of Calcium Dialysate Concentration Zaida Noemy Cabrera Jimenez,¹ Rosa M.A. Moyses,^{1,2} Bruno C. Silva,¹ Luciene dos Reis,¹ Wagner Dominguez,¹ Fabiana Gracioli,¹ Rosilene M. Elias.¹ ¹Nephrology, Univ of Sao Paulo, Sao Paulo, SP, Brazil; ²Univ Nove de Julho- UNINOVE, Sao Paulo, SP, Brazil.

Background: Ankle-brachial index (ABI) is a simple way to access cardiovascular risk. Both low (<0.9) and high (>1.3) ABI are associated with increased mortality risk in patients on hemodialysis (HD). However, little is known regarding the acute variation of ABI (from pre to post hemodialysis), and also whether the calcium dialysate content [Ca] may interfere with this variability. We aimed to investigate the impact of [Ca] 3.5 vs. 2.5 on the variability of ABI during HD.

Methods: Incident patients on HD for up to 90days were included. ABI was evaluated pre- and post-HD in the midweek session of two consecutive weeks with [Ca] 3.5 and 2.5, respectively. Biochemical variables, electrical bioimpedance and non-invasive hemodynamic (Finapres®) were assessed.

Results: 17 patients (10 men) aged 42 ± 17 years were included. ABI pre- and post-HD with [Ca] 3.5 and 2.5 were 1.2 ± 0.1, 1.1 ± 0.1, 1.1 ± 0.2, and 1.2 ± 0.1, respectively. Although the mean ABI values were within normal range, there was a great variability in the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing classification while in 6 patients it increased using [Ca] 2.5 with 3 patients (18%) changing classification. A [Ca] 3.5 was associated with an increase in serum calcium and a decrease in parathyroid hormone, while during a [Ca] 2.5 occurred a more pronounced blood pressure drop and consequent raise of peripheral arterial resistance. As the ultrafiltration rate was similar with [Ca] 3.5 and 2.5, there was no difference in total, extra- and intracellular water removal. ABI correlated with pre HD serum aldosterone (r= -0.515, p=0.002). Multiple regression analysis revealed that pre HD aldosterone and also a [Ca] were independently associated with the delta of ABI during dialysis, even adjusting for cardiac debit and ultrafiltration rate.

Conclusions: ABI presents great variability during a conventional HD. However, whether an acute decrease in ABI by using a [Ca] 2.5 may impact the long-term mortality deserves further investigation.

PUB638

Variation in the Intracranial Pressure During Hemodialysis in a Patient with Subdural Hematoma on Propofol Rhea Bhargava,¹ Omkar U. Vaidya,^{1,2} ¹Dept of Internal Medicine, Univ of Missouri- Kansas City, Kansas City, MO; ²Dept of Nephrology and Hypertension, Univ of Missouri- Kansas City, Kansas City, MO; ³Dept of Critical Care, Saint Lukes Hospital, Kansas City, MO.

Background: Dialysis disequilibrium syndrome (DDS) is a rare but potentially serious complication of hemodialysis. Pathophysiology of this disorder is explained by the 'reverse urea effect'. This can be difficult to detect in patients in the neuro-intensive care unit given their compromised CNS status. However it is imperative to diagnose DDS especially in this population as intracranial pressure (ICP) instability during hemodialysis can lead to micro circulatory defects.

Methods: 60 y/o male with ESRD admitted for left frontal subdural hematoma, underwent evacuation with ventricular drain placement. He was intubated and sedated. BP 142/69 mmHg, Pulse 122 bpm, Temp of 37.3 °C, RR of 34 and SpO2 100%. The remaining physical examination was unremarkable. Hemodialysis (HD) was performed on 3 contiguous days. ICP and the changes in cerebral perfusion pressure (CPP) were monitored every 15 minutes during hemodialysis. Sedation with propofol which was started on Day1, was weaned off completely by the session on day three. The patient seized after the 3rd hemodialysis session. CT scan of the head was unremarkable. He was eventually discharged on day 14 and made full recovery.

Results: ICP and CPP during hemodialysis decreased in the first 30 minutes and maximum variation was between 45-120 minutes. Peak ICP pressure during HD: Day 1: 5 mmHg; Day 2: 15 mmHg and Day 3: 25 mm Hg. Maximum change in CPP from baseline during HD: Day1: 20 mm Hg; Day 2: 22mm Hg and Day 3: 47 mmHg.

Conclusions: ICP monitoring during hemodialysis is a useful modality to identify neurological complications in patients who have undergone neurosurgical interventions. Propofol along with being a sedative can lower ICP and hence prevent or mask the effects of hemodialysis on ICP. In the present case, net change in CPP could have led to seizure activity on the 3rd day of hemodialysis.

PUB639

Characterization of T Regulatory Type 1 (Tr1) Cells in Naïve and Transplanted Non-Human Primates Ruichao Yu, Makoto Tonsho, Philip Spencer, Sibylle Bernard-stoecklin, Gilles Benichou, Joren Madsen. *Center for Transplantation Sciences, Harvard Medical School, Massachusetts General Hospital, Boston, MA.*

Background: T regulatory Type 1 (Tr1) cells are peripheral CD4⁺FoxP3⁺ regulatory T cells expressing CD49b and LAG-3 in mice and humans. Mouse Tr1 cells inhibit antigen-presenting cell (APC) activation via secretion of IL-10 and TGF-β and via cell-contact dependent mechanisms mediated through their expression of programmed cell death (PD)-1. However, the phenotype and functions of Tr1 cells non-human primates are still unknown.

Methods: Mononuclear cells were isolated from the peripheral blood of cynomolgus monkeys (PBMCs). First, co-expression of CD49b and LAG-3 was compared among bona fide CD4⁺CD25^{hi}FoxP3⁺ Tregs and CD4⁺CD25^{lo}Foxp3⁺ using flow cytometry. Second, cytokines (IL-10, TGF-β, IFN-γ, IL-4, IL-17 etc.) were processed after polyclonal activation via anti-CD3/CD28 Ab-coated beads. Next, we compared PD-L1 and CD45RO expression by Tr1 cells collected from the PBMCs of naïve monkeys, monkeys undergoing rejection of kidney allografts and monkeys which have been rendered tolerant of kidney allografts via donor mixed hematopoietic chimerism induction and leukocyte costimulation blockade.

Results: In cynomolgus monkeys, CD49b and LAG-3 were co-expressed on CD4⁺CD25^{hi}Foxp3⁺ Tr1 lymphocytes but not on CD4⁺FoxP3⁺Tregs. After polyclonal activation via anti-CD3/CD28 Ab-coated beads, virtually all Tr1 cells secreted high levels of IL-10 anti-inflammatory cytokine but no pro-inflammatory IFN-γ or IL-17 cytokines. We observed a significant expansion of Tr1 cells expressing a memory phenotype (CD45RO) and the immunomodulatory receptor PD-L1 in tolerant but not other animals.

Conclusions: Our data show that the surface markers CD49b and LAG-3 can be used to distinguish Tr1 from "classical" FoxP3⁺ Tregs in cynomolgus monkeys. Tr1 cells are likely to inhibit T cell responses mediated by PD-1/PD-L1 interactions. The contribution of these activated Tr1 cells to induction and maintenance of organ allograft tolerance in non-human primates is under investigation.

Funding: NIDDK Support, Veterans Administration Support

PUB640

Urinary MicroRNA-25 as a Potential Biomarker for Detection of Renal Damage in Rats and Renal Transplant Patients Kumiko Nishihara,¹ Masayuki Kanki,¹ Moto Kajiwara,^{2,3} Kei Kurihara,⁴ Takahisa Yano,² Hidehisa Kitada,⁴ Satoshiro Masuda,² Akira Unami.¹ ¹Drug Safety Research Laboratories, Astellas Pharma Inc., Osaka, Japan; ²Dept of Pharmacy, Kyushu Univ Hospital, Fukuoka, Japan; ³Dept of Research and Development of Next Generation Medicine, Faculty of Medical Sciences, Kyushu Univ, Fukuoka, Japan; ⁴Dept of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Circulating microRNAs (miRNAs) were proposed as potential biomarkers of various biological functions and diseases in the kidneys. We have found that some urinary miRNAs were useful for detection of cisplatin-induced proximal tubular injury in rats (Kanki M et al., Toxicology. 324, 158, 2014). In this study, we examined the feasibility of miRNAs for renal damage in Japanese patients receiving kidney transplantation as well as rats.

Methods: Gentamicin (100 mg/kg) (model of tubular injury) was daily given for 7 days and puromycin (50 mg/kg) (model of glomerular injury) was given as a single injection to male SD rats. Seven days after the treatment, the urinary levels of 15 miRNAs were determined by real-time PCR. The receiver-operator characteristics (ROC) curve analysis for proximal tubular necrosis was performed including previous cisplatin study. Human urine samples were collected from 30 healthy volunteers and 11 renal transplant patients at 7 days and 2, 10, and 11 weeks after surgery. The levels of 4 miRNAs were determined.

Results: In gentamicin treated rats, the levels of miR-328, let-7a-1, miR-1839, miR-25, miR-140, and miR-378 were increased more than 2-fold with high values of the area under the ROC curve, which were the same or more than those of BUN and serum creatinine, while they were not changed in rats treated with puromycin. Among these miRNAs, miR-25, miR-140-3p, miR-328 and miR-378 were measured in the human urine samples. In human samples, miR-25 at postoperative day 7 in some patients exhibited higher levels than the highest value of those in the volunteers.

Conclusions: Urinary miR-25 but not other miRNAs might be available for detecting renal damage in the postoperative course of renal transplant patients as well as that in the rats with proximal tubular injury.

PUB641

Early Activation of Complement in Renal Ischemia/Reperfusion (I/R) Injury Is Mediated by Pentraxin 3 (PTX3) Synthesized by Peripherical Blood Mononuclear Cells (PBMCs) Giuseppe Castellano,¹ Chiara Divella,¹ Alessandra Stasi,¹ Paola Pontrelli,¹ Matteo Accettura,¹ Marco Fiorentino,¹ M. Rossini,¹ Vincenzo Montinaro,¹ G. Lucarelli,¹ M. Battaglia,¹ Loreto Gesualdo,¹ Giuseppe Grandaliano.² ¹Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, Italy; ²Dept of Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.

Background: PTX3 has been recently implicated in the promotion of vascular inflammation via the activation of Complement. Aim of this work was to investigate the possible involvement of PTX3 in renal I/R injury.

Methods: PBMCs were isolated from blood of patients with Delay graft function (DGF, n=10) and Early graft function (EGF, n=10) at T0 and T24h from transplant. Gene expression profiles of PBMCs from both groups were assessed by Affymetrix technologies. Results were evaluated by statistical analysis and functional pathway analysis and validated by confocal analysis on a swine model of I/R injury. Renal I was induced in 5 pigs by arterial clamping for 30 min and tissues were analyzed at different time points after R (T15', 30', 60').

Results: Microarray analysis (FDR<5% and a FC>1.5) revealed that the expression of PTX3 and C3 were downregulated in EGF compared to DGF patients. On the contrary, the gene CR1 was upregulated in DGF. Furthermore, in the pig model, confocal laser microscopy demonstrated PTX3 deposits already at 15' of R, localized at peritubular (7.7±1.1; p=0.005) and glomerular (8.2±2.5; p=0.03) capillary levels. We found a significant increase in infiltrating interstitial leucocytes such as CD163⁺/PTX3⁺ monocyte-macrophages (6.2±2.1; p=0.05) and SWC3a⁺/PTX3⁺ dendritic cells (3.7±0.5; p=0.05) compared to T0. Finally, we identified tubulo-interstitial FSP1⁺/PTX3⁺ myofibroblast (4.1±1.3; p=0.04). Co-localization between C5b-9/PTX3, PTX3/C1q and PTX3/MBL clearly demonstrated the activation of Classical and Lectin Complement pathways in presence of PTX3 deposits.

Conclusions: Our data would suggest a key role of PTX3 synthesized by peripheral blood mononuclear cells (PBMCs) during DGF leading to an early activation of complement in transplant kidney.

PUB642

The Effect of Combined Treatment of Dipeptidyl Peptidase IV Inhibitor and Metformin in Sirolimus-Induced Diabetes Mellitus Long Jin, Jian Jin, Sun Woo Lim, Byung Ha Chung, Chul Woo Yang. *Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: Optimal treatment of post-transplant diabetes mellitus is still controversial. This study was performed to evaluate whether the combined treatment of DPP IV inhibitor with metformin (MET) is effective in sirolimus (SRL)-induced diabetes mellitus.

Methods: SRL-induced diabetes mellitus was made by treating SRL (0.3 mg/kg) for 3 weeks in rats, and then started to treat DPP IV inhibitor (LC15-0444[LC], 5mg/kg), and/or MET (200 mg/kg) for further 3 weeks. The effect of combined treatment of LC and MET on SRL-induced diabetes mellitus was evaluated by IPGTT and islet size. The oxidative stress was evaluated by measuring 8-OHdG, 4-HHE, MnSOD, and catalase in samples. Insulin secretion capacity was evaluated by glucose-stimulated insulin secretion (GSIS) test using normal isolated rat islets treated with SRL, exendin-4 and/or MET.

Results: SRL treatment for 6 weeks decreased body weight and increased water intake and urine volume compared with vehicle group. SRL treatment significantly increased AUCg from the values obtained during the IPGTT, but LC or MET treatment recovered these value compared with the SRL treatment alone. Combined treatment with LC and MET has more significantly decreased blood glucose level than LC or MET treatment alone. Islet size which was significantly decreased in the SRL group was recovered with combined treatment of LC and MET. SRL treatment significantly increased intense nuclear expression and larger positive area for 8-OHdG and 4-HHE, but combined treatment LC and has significantly decreased expression of 8-OHdG and 4-HHE. The decreased expression of MnSOD and catalase in the SRL group was recovered with combined treatment with LC and MET. The result of GSIS also showed that combined treatment of LC and MET showed higher insulin level than exendin-4 or MET treatment alone.

Conclusions: Combined treatment with LC and MET exerts better glucose control by decreasing oxidative stress caused by SRL. This finding provides the rationale for the combined use of DPP IV inhibitor and MET in SRL-induced diabetes mellitus.

Funding: Government Support - Non-U.S.

PUB643

Incidence and Outcomes of Hyponatremia Early Post Lung Transplantation Ekamol Tantissattamo,¹ Aneesa A. Shetty,¹ Bing Ho,¹ John J. Friedewald,¹ Opas Traitanon,¹ Sangeeta Bhorade,² Alexander Haynes,² Amber Nieland,² Lorenzo G. Gallon.¹ *¹Div of Nephrology and Hypertension; ²Pulmonary and Critical Care, Dept of Medicine, Northwestern Univ Feinberg School of Medicine.*

Background: Outcomes of in-hospital hyponatremia in lung transplant recipients are unclear. The aim of this study is to describe the frequency of hyponatremia and outcomes associated with hyponatremia during the early postoperative period.

Methods: We performed a retrospective chart review of all lung transplant recipients at Northwestern Memorial Hospital since the first case performed in July 2014 until May 2015. The severity of hyponatremia was defined as mild, moderate, and severe with serum Na of <135, <130, and <125 mEq/L, respectively.

Results: A total of 13 lung transplant recipients were included. Age at the time of transplantation was 61.5±/2.2 (SEM) years and 69% was female. The most common indication for transplantation was severe COPD (54%). Serum creatinine at the time of transplantation and at hospital discharge was 0.8±/0.1 and 1±/0.2 mg/dL, respectively. Seven patients with postoperative acute kidney injury (AKI) had >2 times longer length of hospitalization (26.2±/4.8 vs. 10.0±/1.1 days; p 0.0046) and were more likely to develop postoperative hyponatremia (100% vs. 71%; p=0.151). Among 11 patients with postoperative hyponatremia, 7 were readmitted (5 with hyponatremia and 4 with AKI). At the time of transplant, 8% of the patients had hyponatremia but the incidence was up to 46% at the time of discharge (Table1). Almost half of the patients had persistent hyponatremia during 1 month follow-up.

Conclusions: Lung transplant recipients commonly develop hyponatremia during the immediate post operative period and are more likely to be readmitted with hyponatremia. The incidence of hyponatremia remains high up to 1 month post transplantation. AKI is also a risk for readmission and predicts longer length of hospital stay.

Degree of serum sodium	At transplant	3 days	7 days	At discharge	30 days	90 days	180 days
Normal	12(92%)	6(46%)	9(7%)	7(54%)	7(54%)	7	4
Mild	0	4(31%)	0	5(38%)	6(46%)	NA	1
Moderate	1(8%)	0	2(8%)	1(8%)	NA	NA	NA
Severe	0	1(8%)	2(8%)	0	NA	NA	NA
Hyponatremia	0	2(15%)	0	0	NA	NA	NA

PUB644

Motivations, Challenges, and Attitudes to Self-Management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies Nathan Jamieson,^{1,2} Camilla Sara Hanson,^{1,2} Michelle A. Josephson,³ Elisa J. Gordon,⁴ Jonathan C. Craig,^{1,2} Fabian Halleck,⁵ Klemens Budde,⁵ Allison Tong.^{1,2} *¹Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; ²School of Public Health, Univ of Sydney, Sydney, New South Wales, Australia; ³Dept of Medicine, The Univ of Chicago, Chicago, IL; ⁴Center for Healthcare Studies and Comprehensive Transplant Centre, Northwestern Univ Feinberg School of Medicine, Chicago, IL; ⁵Dept of Nephrology, Charité, Universitätsmedizin Berlin, Berlin, Germany.*

Background: Kidney transplantation offers superior life expectancy and quality of life outcomes compared to other renal replacement therapy modalities. However, the complex and ongoing medication and self-management regimens impose a treatment burden on patients, and non-adherence remains a leading cause of graft loss.

Methods: MEDLINE, Embase, PsycINFO, and CINAHL were searched from database inception to October 2014. We used thematic synthesis to analyse the findings.

Results: Fifty studies involving 1238 participants aged from 18 to 82 years across 19 countries were included. We identified five themes: *empowerment through autonomy* (achieving mastery, tracking against tangible targets, developing bodily intuition, routinising and problem-solving, adaptive coping), *prevailing fear of consequences* (inescapable rejection anxiety, aversion to dialysis, minimising future morbidity, trivialisation and denial, defining acceptable risks), *burdensome treatment and responsibilities* (frustrating ambiguities, inadvertent forgetfulness, intrusive side-effects, reversing ingrained behaviours, financial hardship), *over-medicalising life* (dominating focus, evading patienthood, succumbing to burnout), and *social accountability and motivation* (demonstrating gratitude towards medical team, indebtedness to donor, peer learning).

Conclusions: Self-efficacy and social accountability are motivators for self-management, but ongoing adherence can be mentally and physically taxing. Multi-component interventions that incorporate education, psychosocial support, decision aids, and self-monitoring tools may foster self-management capacity and improve transplant outcomes.

PUB645

Abstract Withdrawn

PUB646

Characteristics of Patients with Vitamin D Deficiency After Kidney Transplantation in Qatar Mohamed Amin Elesnawi, Abdullah Hamad, Fadwa S. Al-Ali. *Nephrology, Fahd Bin Jasim Kidney Center, Hamad General Hospital, Doha, Qatar.*

Background: Vitamin D deficiency is common among normal people and in patients with chronic kidney disease including dialysis patients. Vitamin D deficiency continues to be prevalent after kidney transplantation (studies showed prevalence of 50-80%) especially with immunosuppression use and sun protection needed for elevated risk of skin cancer. We studied characteristics of kidney transplant patients with vitamin D deficiency in Qatar.

Methods: We reviewed all available records of kidney transplant patients presented to our clinic at Hamad General Hospital in Doha, Qatar between 1/9/2013 and 1/3/2014 and have vitamin D level less than 30 ng/mL. Background data and laboratory tests of patients were obtained. All patients were receiving vitamin D supplements and prednisone within their immunosuppression per institution protocol.

Results: We studied 83 patients. Mean age was 55.5 ±/ 16 years. There were 55 males (66%) and 28 females (34%). Vitamin D deficiency was severe (level than 10 ng/mL) in 15 patients, moderate in 38 (10-19 ng/mL) and mild in 30 patients (20-29 ng/mL). Duration of transplant was 7.9 ±/ 2.5 years. Glomerular Filtration Rate was 65.5 ±/ 20.6 ml/min. We found no correlation between vitamin D and PTH levels or between vitamin D and GFR levels. Table 1 summarize bone mineral panel in our patients.

	Plasma Level +/- SD
Vitamin D	16.4+/-6.7 ng/ml
Calcium	2.28+/-0.14 mmol/L
Phosphorus	1.2+/-0.26 mmol/L
Alkaline Phosphatase	86.9+/-37.8 u/L
Intact Paath thyroid Hormone	146+/-2.1pg/mL

Conclusions: In a study of kidney transplant patients with vitamin D deficiency in Qatar we found that they were predominantly males, have normal calcium, phosphorus and alkaline phosphatase levels, while they have variable degree of elevated PTH with no correlation to vitamin D level. Most patients have mild to moderate vitamin D deficiency (82%) despite receiving vitamin D supplement although the supplement could have decreased the number of patients with severe vitamin D deficiency (18%). Further study could help to evaluate the role of vitamin D supplement in improving vitamin D level in kidney transplant recipients.

PUB647

Comparison of Vitamin D Deficiency Between Young and Elderly Kidney Transplant Recipients Mohamed Amin Elesnawi, Abdullah Hamad, Fadwa S. Al-Ali. *Nephrology, Fahd Bin Jasim Kidney Center, Hamad General Hospital, Doha, Qatar.*

Background: Vitamin D deficiency is common in normal population and in patients with chronic kidney disease including kidney transplant recipients. Elderly patients are vulnerable to vitamin D deficiency with less sun exposure and having multiple medical problems. We compared young versus elderly kidney transplant recipients with vitamin D deficiency in Qatar.

Methods: We reviewed all available records of kidney transplant recipients presented to our clinic at Hamad General Hospital in Qatar between 1/9/2013 and 1/3/2014. Background data and laboratory tests of patients were collected. All patients were receiving vitamin D supplements and prednisone per institution protocol.

Results: 83 patients were included. 41 patients in the young group (< 60 years old) and 42 in the elderly group (> 60 years old). There were 21 females versus 20 males in the young group and 35 males versus 7 females in the elderly group (pValue<0.05). Time on transplant was 9.1 +/- 4.93 years in the young group versus 8.6+/-2.7 in the elderly. Table 1 summarizes laboratory values for kidney transplant patients with vitamin D deficiency.

	Age over 60 years (n=42)	Age less than 60 years (n=41)
Vitamin D	17.7+/-6.4 ng/mL	15.1+/-6.7 ng/mL
Calcium	2.28+/-0.13 mmol/L	2.29+/-0.15 mmol/L
Phosphorus	1.22+/-0.18 mmol/L	1.16+/-0.3 mmol/L
Parathyroid Hormone	148.7+/-238.3 pg/mL	143.9+/-154.8 pg/mL
Alkaline Phosphatase	75.8+/-29 u/L	91.9+/-39.9 u/L
Glomerular Filtration Rate (GFR)	69.9+/-21.4 ml/min	61.2+/-19.2 ml/min

Conclusions: We compared vitamin D deficiency in young versus elderly kidney transplant recipients in Qatar. Although elderly patients have higher vitamin D levels, it was not statistically significant. This could be due to better compliance with vitamin D supplement in the elderly. Although duration on transplant, calcium, phosphorus and intact parathyroid hormone were similar, Glomerular Filtration Rate (GFR) was higher in the elderly. We explain it that almost all kidney transplants in Qatar are from live donors which lead to a higher GFR in the elderly as they are receiving kidneys from younger donors. There was statistically significant smaller number of females than males in the elderly group.

PUB648

Abstract Withdrawn

PUB649

The Current Status of Plasmapheresis Before Living Donor Kidney Transplantation in Japan Norio Hanafusa,¹ Tomoko Usui,¹ Akihiro Matsumoto,¹ Satoko Sakurai,¹ Eisei Noiri,¹ Hideo Yasunaga,² Masaomi Nangaku.¹ ¹Dept of Hemodialysis and Apheresis, The Univ of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan; ²Dept of Clinical Epidemiology and Health Economics, School of Public Health, The Univ of Tokyo, Bunkyo-ku, Tokyo, Japan.

Background: Plasmapheresis (PP) is utilized to remove alloantibodies before the living donor kidney transplantation (LDKT). The detailed practice patterns of PP before LDKT remains unknown. There also are concerns about the depletion of coagulation factors [Transfus Apher Sci 49: 254, 2013] by PP. We investigated the current status of PP before LDKT with use of the nationwide database.

Methods: The Japanese Diagnosis Procedure Combination Database includes all the patients discharged from hospitals participating in this program between July 2010

and March 2013. Those who received LDKT and PP before LDKT were included into this study. The modalities of PP, fresh frozen plasma (FFP) use, and albumin use were examined. We also investigated the relationship between modalities selected and outcomes such as the length and total costs of the hospital stay, or the amount of blood transfusion as the proxy of bleeding.

Results: In total 775 patients received PP before LDKT during the period. Among them 209 patients were treated only by simple plasma exchange (PE). Remaining 566 patients received double filtration plasmapheresis (DFPP), or cascade filtration. Interestingly, 274 patients treated by DFPP received also PE before transplantation. FFP was used during PP on 109, 180, and 42 patients treated by PE only, DFPP followed by PE, and DFPP only, respectively. Moreover, FFP was infused before the operation on 161 patients who were not used FFP during PP. As a whole 63.5% of total patients received FFP from the start of PP to the day of operation. DFPP followed by PE groups received less amount of blood transfusion (p=0.047), though the length of stay was longer and total costs were higher, compared to DFPP only group.

Conclusions: Many of the patients received FFP, which suggests concerns about the depletion of coagulation factors during PP. The practice patterns were quite heterogeneous and the standardization of the practice patterns is needed to maximize the benefits of PP.

Funding: Government Support - Non-U.S.

PUB650

Age as a Risk Factor for Acute Rejection in the Renal Transplant Patient Sarah Lamarche, Jean-Philippe Lafrance, Michel Vallee, Duy Tran. *Nephrology, Univ de Montréal, Montréal, QC, Canada.*

Background: It has previously been shown that younger age is associated with a higher risk of acute rejection post renal transplantation. However, those studies were undertaken in times with differing use of immunosuppressive therapies. We thus sought to examine if this trend was still relevant in a contemporary cohort of patients with a new prescription profile.

Methods: We retrospectively reviewed the charts of 217 patients who underwent renal transplantation between the years 2006-2012 at our institution. Baseline characteristics of donors and recipients were examined. Recipients were stratified according to age <30, 30-40, 40-55, 55-65 and >65 years old. Our primary endpoint was the incidence of acute rejection at one year post renal transplantation. Multivariate Cox regression models predicting acute rejection were also fitted to adjust for several confounders.

Results: Regarding baseline recipient characteristics, there was a significant difference in the leading cause of end-stage kidney disease among the groups (glomerulopathy in young recipients and diabetic nephropathy in old recipients). Also, hypertension, diabetes and coronary heart disease were more prevalent in older recipients. Overall, the incidence rate of acute rejection at 1 year in all groups was 19 per patient-year. Statistically significant differences in Kaplan-Meier estimates of rejection at one year were recorded (log rank p=0.03) and those differences were confirmed in multivariable Cox regression analyses. Indeed, individuals aged 30-40 years had a higher risk of developing acute rejection (HR 6.5, 95% CI: 1.9, 22.5) compared to the reference group (40-55). Other significant predictors of acute rejection at 1 year included PRA > 20% (HR 6.8), unrelated living donor (HR 10.2), donor after cardiac death (HR 3.7) and length of initial hospitalisation stay (HR 1.03).

Conclusions: In a contemporary cohort, we recorded a significant difference in patterns of acute rejection following renal transplantation according to age. Indeed, individuals aged 30-40 years were more prone to transplant rejection, even after adjusting for several covariates. This research should fuel additional investigations regarding the biology of this disease.

Funding: Clinical Revenue Support

PUB651

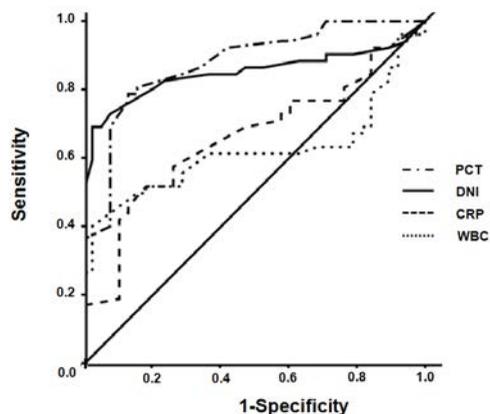
Delta Neutrophil Index as a Marker for Differential Diagnosis Between Acute Graft Pyelonephritis and Acute Graft Rejection Soyon Rhee, Eunjung Kim, Hee Jung Jeon, Ja-Ryong Koo. *Internal Medicine, Nephrology, Hallym Univ of College of Medicine, Seoul, Republic of Korea.*

Background: Acute graft pyelonephritis (AGPN) versus acute graft rejection is a frequently encountered diagnostic and therapeutic dilemma in renal transplant recipients, but little is known about the clinical usefulness of the delta neutrophil index (DNI) value in the differentiation of the two conditions.

Methods: We reviewed the medical records of 86 renal transplant recipients, 45 patients with 51 acute graft rejection episodes and 41 patients with 54 AGPN episodes, at the Kangdong Sacred Heart Hospital from January 2008 to February 2014. Of these episodes, 15 were excluded due to neutropenia (n=4), other infections (n=5), and no available data of procalcitonin levels (n=6). As a result, 72 renal transplant recipients with 90 episodes were enrolled in this study.

Results: AGPN group had significantly higher DNI values than acute graft rejection group (2.9% vs. 1.9%, P<0.001). The area under the ROC curve for DNI value was 0.85 (95% confidence interval [CI]; 0.76-0.92, P< 0.001).

Figure 1



A DNI value of 2.7% was selected as cut-off value for AGPN, and renal transplant recipients with a DNI $\geq 2.7\%$ were found to be at a higher risk of infection than those with a DNI $< 2.7\%$ (odds ratio [OR] 40.50; 95% CI 8.68-189.08; $P < 0.001$). In a multivariate logistic regression analysis, DNI was a significant independent factor for predicting AGPN after adjusting age, sex, log WBC count, log neutrophil count, log lymphocyte count, DNI value, CRP concentration and procalcitonin concentration (OR 4.32; 95% CI 1.81-10.34, $P < 0.001$).

Conclusions: The present study demonstrated that a DNI value above 2.7% was an independent predictive marker for AGPN and an effective marker to differentiate between AGPN and acute graft rejection. Thus, these findings suggest that DNI may be a useful marker in the management of these patients.

PUB652

Effect of Pre-Transplant Dialysis Modality on Outcomes of Living-Donor Kidney Transplantation Recipients Chiaki Kawabata. *General Internal Medicine, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan.*

Background: There are few studies on living-donor kidney transplantation that compare the outcomes after pre-transplant dialysis modality. We examined the short-term outcomes of living-donor kidney transplantation recipients after peritoneal dialysis (PD) and hemodialysis (HD), respectively.

Methods: 112 patients have undergone living-donor kidney transplantation procedures in our hospital between January 2001 and May 2014. We studied 40 patients, under 40 years of age, with dialysis durations of less than 5 years. We compared 13 PD patients with 27 HD patients and investigated the short-term outcomes.

Results: These two groups showed no significant differences as regards baseline characteristics including dialysis duration, body mass index, type of calcineurin inhibitor or ABO blood type incompatibility. The PD group was younger than the HD group as regards recipient age and donor age (22.5 ± 8.0 years vs 29.1 ± 6.0 years [$p = 0.005$]; and, 50.7 ± 8.2 years vs 56.9 ± 7.1 years [$p = 0.02$], respectively). There were no differences in early post-transplant complications, such as wound infection, bleeding, thrombosis, delayed graft function, or acute rejection. The PD group was better than the HD group in the estimated glomerular filtration rate (eGFR) at discharge (74.3 ± 27.3 ml/min/1.73 m² vs 48.3 ± 12.3 ml/min/1.73 m² [$p = 0.001$]) and eGFR 1 year post-transplantation (68.4 ± 21.8 ml/min/1.73 m² vs 45.6 ± 13.2 ml/min/1.73 m² [$p = 0.003$]).

Conclusions: In the case of younger and less than 5 years of dialysis duration, PD and HD demonstrated no differences in early post-operative complications. PD is significantly better than HD as regards eGFR up to 1 year post-transplantation.

PUB653

Bright Field Microscopy of the Unstained Urine Sediment: A Basic Tool to Identify Decoy Cells due to Polyomavirus BK on Kidney Allograft Recipients During Routine Urinalysis José A. Poloni,^{1,2,3} Gabriel Godinho Pinto,² Maria Giordani,¹ Elizete Keitel,^{1,2} Alessandro C. Pasqualotto,^{1,2} Liane Rotta,² ¹*Irmãdada de Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil;* ²*Univ Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil;* ³*Control Lab, Rio de Janeiro, RJ, Brazil.*

Background: Polyomavirus BK (BKV) is an important pathogen that can be reactivated in kidney allograft recipients, potentially leading to BKV nephropathy (BKVN), an important cause of graft loss. Decoy cells (DC), urothelial cells or renal tubular epithelial cells modified by the proliferation of BKV, are one of the hallmarks of BKV reactivation and it can be identified in the fresh urine sediment.

Methods: A cohort of 102 kidney transplant patients was followed during months 3 and 6 after the transplant procedure. Urine samples were obtained to detect the presence of DC in the fresh and unstained urine sediment under bright field microscopy (BFM) by two experienced analysts, as well as BKV viruria by qPCR.

Results: DC were found in 15 patients.

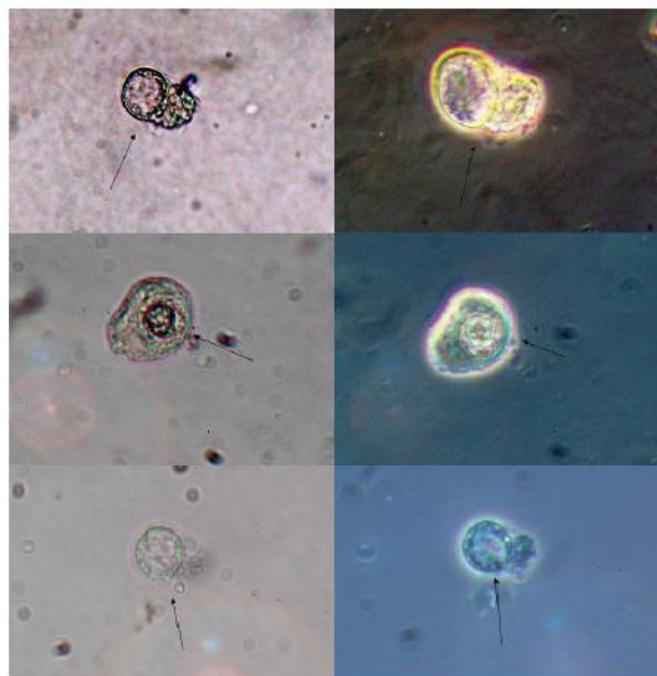


Figure 1 – Three decoy cells presented under bright field microscopy (left panel) and under phase contrast microscopy (right panel). Original magnification 400x.

Urine sediment analysis revealed a strong agreement ($P < 0.001$) between the microscopists to both qualitative and quantitative identification of DC. Also, the qualitative comparison of both microscopists to BKV viruria revealed agreement ($P < 0.001$). The positive predictive value, negative predictive value, specificity and accuracy of BFM were 80%, 75%, 97% and 75%, respectively. The sensitivity was 16%.

Conclusions: Despite its limited sensitivity, fresh and unstained urine sediment analysis under BFM is a method that can be used to identify DC due to BKV reactivation. The analysis procedure is fast, cheap and painless. The information obtained during routine urinalysis can lead to the early diagnosis of BKV reactivation helping on the clinical management of the patients. The ability of less trained observers to perform such diagnosis requires further validation.

PUB654

Intravenous Immunoglobulin in the Management of Pneumocystis Pneumonia: A Case Series Musab Elgaali, Muhammad Imran, Matthew Edey. *Hull Royal Infirmary, Hull, United Kingdom.*

Background: Pneumocystis pneumonia (PCP) is a well-recognized complication of renal transplantation. We present 2 cases of severe PCP treated successfully with intravenous immunoglobulin (IVIg), trimethoprim-sulfamethoxazole (TMP-SMX) and withdrawal of immunosuppression. Graft function was maintained despite a high baseline immunological risk.

Methods: Case A: A 32 year-old woman presented 2 years post-transplant with acute cellular rejection treated with steroids. 2 months later she was admitted with respiratory failure due to PCP. She required intubation and ultimately oscillatory ventilation. CMV DNA was detected at low levels in bronchoalveolar lavage (BAL) fluid. IVIg 30g on alternate days (10 doses) was added, in addition to withdrawal of immunosuppression and hydrocortisone replacement. She made a full recovery, with preservation of transplant function throughout. Case B: A 47 year-old woman received a second kidney transplant. Early post-transplant she developed acute antibody mediated rejection managed with plasma exchange then maintenance prednisolone, tacrolimus and mycophenolate. 9 months later she was admitted with respiratory failure and Pneumocystis jirovecii in BAL. She required invasive ventilation and inotropic support. She was treated with intravenous TMP-SMX, but her clinical condition deteriorated with acute kidney injury (AKI) requiring hemofiltration and escalating ventilator requirements. She received IVIg 25g/day for 5 days, replacement hydrocortisone and immunosuppression was withdrawn. Her AKI resolved and later she became ventilator-independent. Graft function was at baseline on discharge. Maintenance immunosuppression was recommenced.

Conclusions: It is understood that immunity against Pneumocystis jirovecii is both B- and T-cell mediated. Thus pooled immunoglobulin might be expected to have some anti-Pneumocystis activity. It is also recognized that IVIg has immunomodulatory properties. In both cases the administration of IVIg allowed withdrawal of immunosuppression apart from replacement steroid without graft rejection despite high immunological risk. Both patients survived life-threatening PCP. We suggest adjunctive therapy with IVIg be considered in severe PCP.

PUB655

Ethical Issues Related to Kidney Donation/Transplantation: Perspective of Indian Doctors Richard S. Fernandes Almeida,¹ Nirmala Almeida,² Karen Almeida,³ Alan F. Almeida.⁴ ¹Lifesupporters Inst of Health Sciences; ²Human Development, Nirmala Niketan College of Home Science; ³Psychology, Mumbai Univ; ⁴Nephrology, PD Hinduja Hospital, Mumbai, India.

Background: Dearth of kidneys for transplantation has provoked the need to evaluate new policies and practices. This spurred the current study which addressed the perspective of doctors regarding emerging ethical issues pertaining to kidney donation/transplantation.

Methods: The sample consisted of 140 doctors from Mumbai (Age Range=21-80 years, M=38.1, SD=17.95, Males=44.3%, Females=55.7%). A questionnaire, presenting ethical issues related to kidney donation/transplantation, in an agree/disagree format with supporting reasons was employed. The research design was exploratory; data was analyzed quantitatively and qualitatively.

Results:

Question	Agree%	Reasons (%)*	Dis-agree%	Reasons (%)*
Unrelated transplants should be promoted by the government	75.7	Saves lives (16.4) Remedies organ donor shortage(16.4)	24.3	Misuse of organs (7.1) Higher chances of mismatch/organ rejection(7.1)
Kidney selling should be made legal	22.9	Greater donor availability(7.9) Avoidance of malpractice(6.4)	77.1	May lead to illegal/unethical practices(41.4)
Handicapped should not be kidney donors	24.3	Should not burden them as already challenged health-wise(10.7)	75.7	If informed consent given(20) If kidneys effectively functioning(14.3)
Substance abusers should not be transplant recipients	50.7	Chose to bring deterioration in life(10) Might abuse the transplant(15.7)	49.3	All are entitled to be kidney recipients(22.1)
Younger individuals should be given transplantation preference	60	Longer life expectancy (20) Greater transplantation success (12.9) Higher productivity(12.9)	40	Need-based rather than age-based preference(11.4)
Families of cadaver donors should be given incentives	45.7	Motivates donation(22.9)	54.3	Would lead to commercialization and criminal activities(20.7)
Kidney donation should be made compulsory after death	44.3	Saves lives(26.4)	55.7	Donation is individual's choice, coercion is unethical(44.3)

*Representative

Conclusions: This study is relevant in view of the dearth of Indian research. Educating doctors about medico-ethical issues is the need of the hour.

PUB656

Cardiovascular Risk Management of Renal Transplant Patients Joseph C. Newton, Thalakunte M. Muniraju. *Dumfries and Galloway Royal Infirmary, Dumfries, United Kingdom.*

Background: There is a high burden of cardiovascular disease amongst renal transplant recipients, and it is the most common cause of death with a functioning graft. We have assessed the medical management of all transplant patients in our region by comparing regular monitoring of glycaemia, blood pressure and serum lipids, with appropriate prescription of medicines based on their cardiovascular risk.

Methods: Using the electronic health record information was collected on cardiovascular comorbidities, all current medications, frequency of clinic monitoring, BP and most recent biochemical results for glycaemia, proteinuria and lipid results for the local transplant cohort of 69 patients. Prescription of statins, antihypertensives and aspirin were audited against guidelines from the UK Renal Association (RA) and KDIGO. Cardiovascular risk was calculated using the Joint British Societies Guidelines (JBS2).

Results: Amongst hypertensive patients, 2/28 (7.1%) were not on antihypertensive therapy. Significant proteinuria (uPCR >50) was not common (6/68 = 8.8%), but of these only 2/6 (33.3%) were receiving an ACE inhibitor or ARB. Glycaemic control of diabetic patients was generally good, with 9/12 (75%) achieving target HbA1c of <48 mmol/mol. For non-diabetic patients, 11/56 (19.6%) were found to have a random glucose ≥7. Of these 4/11 (36.4%) had HbA1c checks, one of which confirmed new diabetes. The remaining 7 patients (63.6%) have not had a follow up HbA1c. 20/69 (29.0%) of patients were calculated as >20% cardiovascular risk on the basis of comorbidities or using JBS2. Of these only 12/20 (60%) were on statin therapy. Almost all (6/7 = 85.7%) of patients with vascular disease were taking regular aspirin.

Conclusions: We have identified room for improvement in the management of hypertension and proteinuria. Rates of statin prescription suggest that we often underestimate cardiovascular risk clinically, however, further analysis will be required to determine whether valid reasons exist to support decisions to omit statins or renin-angiotensin

blockade. These audit results will be discussed with local clinicians, and will be added to the electronic record to highlight areas where individual management differs from national guidelines.

PUB657

Preemptive Transplantation Is Associated with Improved Graft Survival: Results from the French Transplant Database Mathilde Reydit,^{1,2} Christian Combe,² Jerome Harambat,² Christian Jacquelinet,³ Pierre Merville,² Lionel Couzi,² Karen Leffondré.¹ ¹INSERM U897, Bordeaux School of Public Health, Bordeaux, France; ²Nephrology and Transplantation, Bordeaux Univ Hospital, Bordeaux, France; ³Agence de la Biomédecine, Paris, France.

Background: Kidney transplantation (KT) is the treatment of choice for end-stage renal disease. In France, preemptive kidney transplantation (PKT) should be considered when glomerular filtration rate is under 20 ml/min/1.73m² but European reports on the results of PKT are scarce. Our objective was to evaluate the impact of PKT on graft and patient survival.

Methods: We analyzed all first kidney-only transplants performed in adults in France between 2002 and 2012. A Cox multivariable model was used to study the impact of PKT on the hazard of graft failure defined as death, return to dialysis, or retransplant, whichever came first.

Results: Between 2002 and 2012, 22 288 patients received a first KT, including 3 112 (14%) who had a PKT. Mean recipient age at KT was 50.5 ± 13.4 years, 61.9% were men. Median time of follow-up was 4.7 years. In multivariable analysis, after adjustment for age and sex of recipients, primary kidney disease, donor type (living or deceased donor, expanded criteria donor or standard), HLA mismatches, cold ischemia time, center and year of transplantation, PKT was associated with a 43% reduction in the hazard of graft failure when compared with patients who were treated by dialysis before KT (Hazard ratio (HR) 0.57; IC95% 0.51-0.64). This reduction in the hazard of graft failure was greater after the first year of transplant (HR during the first year 0.69, IC95% 0.57-0.83; HR after the first year 0.51, IC95% 0.45-0.59) and the impact of PKT was also greater in living than in deceased donor recipients (HR in living donor 0.34, IC95% 0.19-0.55; HR in deceased donor 0.59, IC95% 0.52-0.66). Among the subgroup of patients registered on the waiting list before the initiation of dialysis, PKT was associated with a 29% reduction in the hazard of graft failure (HR 0.71; IC 95% 0.58-0.87).

Conclusions: In France, PKT is associated with better graft survival than KT performed after the initiation of dialysis. Nephrologists should prepare patients to PKT rather than to dialysis.

Funding: Private Foundation Support

PUB658

Novel Potential Theranostic Targets in Individuals with Kidney Allograft Dysfunction Roberto Bassi,^{1,2} Monika A. Niewczas,³ Stefania Bussolino,⁵ Valentina De Zan,² Giuseppe Paolo Segoloni,⁶ Antonio Secchi,² Anil K. Chandraker,⁴ Luigi Biancone,⁶ Paolo Fiorina.^{1,2} ¹Nephrology, Boston Children's Hospital, Boston, MA; ²Medicine, San Raffaele Scientific Inst, Milan, Italy; ³Section of Genetics and Epidemiology, Joslin Diabetes Center, Boston, MA; ⁴Transplantation Research Center, Brigham and Women's Hospital, Boston, MA; ⁵Internal Medicine, San Giovanni Battista Hospital, Turin, Italy; ⁶Univ of Torino.

Background: The lack of early diagnostic and therapeutic targets for chronic allograft dysfunction (CAD) is among the major determinants of poor long-term graft survival. Metabolic abnormalities in serum and kidney graft parenchyma may worsen allograft function, while alterations of urinary metabolites may be used as diagnostic biomarkers.

Methods: To explore this hypothesis, we recruited individuals with stable allograft function (n=20), chronic allograft dysfunction (n=20) and healthy controls (n=10), and analyzed their metabolomic profile by *ex vivo* liquid/gas chromatography-mass spectrometry (LC/GS-MS) of serum and urine and *in vivo* two dimensional correlated spectroscopy (2D-COSY) of the kidney graft.

Results: LC/GS-MS revealed serum and urinary abnormalities of amino acids, biogenic amines and acylcarnitines in individuals with worse allograft function (T3) compared to conserved graft function (T1). Particularly, CAD was associated with reduction of serum tryptophan and glutamine (T3 vs. T1, p<0.01) and of urinary histidine (T3 vs. T1, p<0.05). Derivatives of dimethylarginine (DMA; symmetric (S)DMA: T3 vs. T1, p<0.001; p<0.01) and short-chain acylcarnitines (C4; C12: T3 vs. T1, p<0.01; p<0.05) increased in serum, while dopa and dopamine (T3 vs. T1, p<0.01; p<0.001) together with DMA, SDMA and ADMA (T3 vs. T1, p<0.001, p<0.001, p<0.01) decreased in urine. *In vivo* 2D-COSY performed on the same patients revealed reduction (p<0.05) of the parenchymal content of choline, creatine, taurine and threonine in individuals with CAD. Notably, taurine was selectively reduced within the graft parenchyma and increased in serum and urine of individuals with CAD.

Conclusions: Novel potential theranostics targets have been identified with an unbiased *ex vivo* and *in vivo* metabolomic profiling of individuals with CAD.

Funding: Government Support - Non-U.S.

PUB659

Good Patient and Graft Survival in Recipients of Kidney Transplantation due to Diabetic Nephropathy Amgad E. El Agroudy. *Internal Medicine Dept, College of Medicine and Medical Sciences, Arabian Gulf Univ, Manama, Bahrain.*

Background: Compared with non-diabetic subjects, patients with type 2 diabetes and end-stage renal disease (ESRD) have seldom been selected for renal transplantation. The aim of this study is to compare patient and graft outcome in kidney transplant patients with diabetes mellitus.

Methods: We retrospectively studied 358 patients who underwent kidney transplantation between 1979 and 2014, including 88 with diabetic ESRD (DM group) (type 1, $n = 8$; type 2, $n = 80$) and 270 with non-diabetic ESRD (NDM group). Mean follow-up was 92 ± 9 (0.1–389) months.

Results: Mean age was higher in the DM group (52.8 vs 44.6 years; $P < .0001$), and there was no significant difference in recipient gender, donor age or donor source. At the end of follow-up, there was no differences between the groups in terms of blood pressure control (DM $139.3 \pm 16.7/81.7 \pm 7.6$ mmHg vs NDM $138.3 \pm 19.7/82.1 \pm 8.1$ mmHg, $P = 0.83/0.80$) and renal function (creatinine, 115.4 ± 47.1 vs 133.4 ± 80.2 $\mu\text{mol/l}$, $P = 0.18$; calculated creatinine clearance, 66 ± 24 vs 68.4 ± 24 ml/min/1.73 m², respectively, $P = 0.9$). In total, 26 patients had acute transplant rejections [8 patients with diabetes vs 18 patients without diabetes, $P = 0.11$]. There was no significant difference in post transplant surgical complications as wound dehiscence or infections. There was a significant high incidence of the urinary tract infection rate in DM group (17 vs 32 patients; $P = .012$). Four out of 22 patients died (18.2%) in the DM group and 10 out of 47 patients died (21.3%) in the NDM group died from cardiovascular disease ($P = 0.17$). The 1-, and 10-year patient survival rates in the DM and NDM groups were 97.5% vs 99% (ns), and 56.8% vs 58.8% (ns), respectively. The 1-, and 10-year graft survival rates were 97.5% vs 70.7% (ns) and 58.9% vs 66.1% (ns), respectively.

Conclusions: Renal transplantation in diabetic ESRD patients yields good results in terms of patient survival and complications, suggesting that renal transplantation can be performed in these patients and should become a more established treatment option.

PUB660

Impact of Pre-Transplant Peritoneal Dialysis Compared with Hemodialysis on the Incidence of Delayed Graft Function in Kidney Transplant Recipients with Lupus Gabriel Contreras, Javier Pagan, Antonio A. Armstrong, Jorge M. Diego, Ian Thomas, Patricia Marie Byers, Alberto J. Sabucedo, Jair Munoz Mendoza, David Roth. *Univ of Miami Miller School of Medicine.*

Background: Delayed graft function (DGF) increases the risk of allograft failure in recipients of kidney transplants.

Methods: In this study, we assessed the impact of pre-transplant peritoneal dialysis (PD) compared with hemodialysis (HD) on the risk of DGF in patients with lupus using logistic regression models.

Results: Three hundred-fifty three of 2513 (14 %) recipients transplanted between 3/22/1994 and 9/27/2006 with complete records in the United Network for Organ Sharing files had DGF. The incidence of DGF was lower in recipients who used PD (68/613 = 11.1%) compared with HD (285/1900 = 15%) prior to transplantation ($P = 0.013$). After adjusting for donor and recipient age, gender and race-ethnicity, type of donor, recipient education and insurance, time of dialysis prior to transplantation, panel reactive antibodies (PRA), human leukocyte antigen (HLA) mismatch, and ABO blood type compatibility, the lower risk for DGF associated with the use of PD compared with HD remained significant (Odds-ratio 0.70 [95% confidence interval 0.53-0.94]; $P = 0.015$). Donor age (1.01 [1.00-1.02] per 1 year), deceased donor transplantation (3.64 [2.59-5.12] living donor as reference), HLA mismatch (1.08 [1.01-1.15] per 1 antigen mismatch), and PRA (1.01 [1.00-1.01] per 1%) were also independently associated with DGF.

Conclusions: In lupus recipients of kidney transplants, the use of PD compared with HD is associated with lower risk of DGF after adjusting for important predictors.

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PUB661

Association Between Dipstick Proteinuria and Allograft Outcomes in Living Donor Kidney Transplant Recipients Joong-sung Park, Jong Wook Choi, Chang Hwa Lee, Gheun-Ho Kim. *Dept of Internal Medicine, Hanyang Univ College of Medicine, Seoul, Republic of Korea.*

Background: Proteinuria is one of the important factors suggestive of kidney function impairment. Previous epidemiologic studies had demonstrated that greater than trace amounts of protein on a casual urine dipstick may be an important predictor of long-term clinical outcomes in general population. In kidney transplant (KT) recipients, there were few data concerning it.

Methods: Thus, we retrospectively analyzed 238 living donor KT recipients to investigate impact of dipstick proteinuria on allograft outcomes. All KT recipients were divided into 2 groups according to dipstick proteinuria: control group ($n=190$), negative; case group ($n=48$), \geq trace. Cox's proportional hazard model with time-dependent covariates was used to encompass compounding effect of covariates that change over time, including vintage and allograft survival time.

Results: As compared with controls, the change of estimated glomerular filtration rate was prominent in recipients with dipstick proteinuria after 3-year post-KT (-1.5 ± 7.1 vs. -4.4 ± 7.4 mL·min⁻¹·1.73 m⁻²·year⁻¹, $P < 0.0174$). In Kaplan-Meier analysis, KT recipients in control group had a better dialysis-free survival as compared with cases (201 ± 6 vs. 164 ± 10 months; log-rank $P = 0.0118$). In Cox proportional hazard models, trace or more dipstick proteinuria was closely associated with long-term allograft loss (HR=1.964, 95% CI=1.152-3.348), and further adjustment for age and gender did not attenuate this association (HR=1.764, 95% CI=1.050-3.065).

Conclusions: Our results may suggest that presence of small amount protein in urine may be the first sign of deteriorating allograft renal function.

PUB662

Cytomegalovirus Exposure Is Associated with Immunological Sensitization in End-Stage Renal Disease Robert Lam,¹ Rita Suri,² Amitabh Singh,¹ Lakshman Gunaratnam.^{1,3} ¹Schulich Medicine & Dentistry, Western Univ, London, ON, Canada; ²Univ of Montreal, Montreal, QC, Canada; ³Matthew Mailing Center, London Health Sciences, London, ON, Canada.

Background: The presence of antibodies to Human Leukocyte Antigen (HLA) is associated with long transplant wait-times, acute rejection, and poor graft outcomes. While prior transplant, pregnancy, and blood transfusion can trigger HLA antibodies, many sensitized patients have none of these known risk factors. Previous infections have been proposed as a potential cause of "spontaneous" sensitization, but this has not been well studied. Because cytomegalovirus (CMV) is known to modulate the host's immune defenses to avoid identification and clearance, we hypothesized that prior CMV exposure would be associated with HLA sensitization.

Methods: We conducted a cross-sectional study of 150 patients aged ≥ 18 years attending a University Hospital renal pre-transplant assessment clinic over 16 months. Patients with prior transplant were excluded. Demographics, comorbidities, viral serology, peak combined Panel Reactive Antibody (cPRA), blood transfusions, and pregnancies were obtained by chart review; sensitizing events were confirmed by patient questionnaire. Logistic regression was used to identify potential risk factors associated with sensitization, defined as cPRA $> 20\%$.

Results: Mean age was 54.2 ± 12.5 yrs, 61% were male, and mean years on dialysis was 2.7 ± 4.2 . Fifty percent were CMV IgG positive and 32% had cPRA $> 20\%$. A cPRA $> 20\%$ was significantly associated with CMV positive IgG (adjusted odds ratio 2.8, 95%CI 1.3-6.6; $p = 0.012$), prior pregnancy (adj OR 4.0, 95%CI 1.7-9.4; $p = 0.002$), and blood transfusion (adj OR 3.9, 95%CI 1.7-8.7; $p = 0.001$), whereas age, sex, hypertension, diabetes, and years on dialysis were not. In the subgroup of 83 patients with no previous pregnancy or blood transfusion, the prevalence of cPRA $> 20\%$ was 24% in CMV positive patients, versus 12% in CMV negative patients (unadj OR 2.3, 95%CI 0.7-7.5; $p = 0.152$).

Conclusions: We identified previous CMV exposure as a novel independent risk factor strongly associated with the presence of HLA antibodies. Whether CMV infection triggers HLA sensitization requires further study in prospective longitudinal studies.

Funding: Government Support - Non-U.S.

PUB663

The Role of Plasmapheresis in the Treatment of Recurrent Focal Segmental Glomerulosclerosis Juliana Busato Mansur,^{1,3} Gustavo Ferreira da Mata,¹ Tainá Veras de sandes Freitas,³ Gianna Mastroianni-kirsztajn,^{1,3} Helio Tedesco Silva,^{1,3} J. Medina-Pestana.^{1,3} ¹Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil; ²Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil; ³Nephrology, Hospital do Rim, Sao Paulo, Brazil.

Background: Focal segmental glomerulosclerosis (FSGS) has a high recurrence rate after kidney transplantation (Tx). There is no established treatment, although plasmapheresis (PP), alone or with rituximab (RTX), is the most frequent therapeutic intervention. The purpose of this study was to evaluate the clinical-laboratorial profile and outcomes of patients diagnosed with rFSGS or with highly probable rFSGS submitted to PP.

Methods: Retrospective cross-sectional study involving patients with rFSGS submitted to PP between 2003-2014 at Hospital do Rim/UNIFESP.

Results: 70 patients (median age: 29 years, 5-62 years) were included. In 51%, FSGS was identified as the cause of ESRD. Proteinuria $> 0.5\text{g/g}$ and $> 3\text{g/g}$ was present, respectively, 15 and 64 days after kidney Tx; 70% of patients received a kidney from a deceased (DC) donor; cold ischemia time was 23 H (mean). Tacrolimus, prednisone, azathioprine/micophenolate were the most frequently used immunosuppressive drugs. Incidence of DGF was of 70% and of 19% in cases of DC and living donor's, respectively. The 1st biopsy was on the 24th day (mean) post-Tx and the most prominent diagnosis were acute cellular rejection (21.9%) and acute tubular necrosis (29.7%), with only 17% of rFSGS. Histological diagnosis was confirmed on the 124th day and the beginning of the PP was on the 77th day; 48% presented partial remission after 83 sessions; complete remission occurred in 22% of cases (means). Infectious episodes were the main complication during PP (69%). Part of the patients underwent methylprednisolone (80%) and RTX treatment (34%). The allograft survival in the 1st year was 70.8%, followed by 41.4% and 32.7% at 3 and 5 years respectively.

Conclusions: Laboratorial manifestations of rFSGS occurred early after renal Tx and preceded histological diagnosis. Treatment with PP was related to infectious episodes, low complete remission and important graft loss rates, which reinforces the need for further studies to determine a more efficient treatment.

Funding: Private Foundation Support

PUB664

Successful Treatment of BK Nephropathy with Tacrolimus and mTOR Inhibitors Natalia I. Polanco fernandez, Enrique Morales, Manuel Praga, Esther Gonzalez monte, Eduardo Gutierrez-martinez, Amado Andres. *Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.*

Background: BK nephropathy (BKN) is a relevant cause of graft dysfunction in kidney transplantation. mTOR inhibitors (mTORi) have been suggested as the best immunosuppression in BKN. However Tacrolimus-free therapy could increase risk of rejection. Since 2009 in patients with BKN we conducted a protocol discontinuing Mycophenolate and decreasing Tacrolimus (TAC) dose in association with mTORi, both with target levels of 5 ng/mL.

Methods: From 2007 to 2013 we diagnosed 22 BKN. Patients diagnosed since 2009 (n= 14, group 1) were treated beginning mTORi and decreasing TAC dose. The others 8 patients suffered significant reduction of immunosuppression (group 2). We analyze renal function, plasma quantitative BK PCR, antiHLA antibodies, rejections and dialysis or dead at final follow-up.

Results: 22 patients were identified. The BKN was diagnosed at 7th month after transplantation (range 2-55). The medium duration of follow-up was 53 months (6-85). Baseline characteristics and evolution are listed in table 1.

	Group 1 (n= 14)	Group 2 (n= 8)
Serum Creatinine at baseline (mg/dl)	1.3 ± 0.36	1.68 ± 0.57
AntiHLA antibodies positives at BKN diagnosis	43% (6)	12.5% (1)
Serum Creatinine at BKN diagnosis (mg/dl)	1.93 ± 0.37	2.4 ± 0.63
Serum Creatinine at final follow-up (mg/dl)	1.6 ± 0.7	3.2 ± 2.2
Dialysis at final follow-up	7.1% (1)	12.5% (1)
Plasma BK viral load at diagnosis (copies/ml)	84369 (10035-8234680)	20674 (10715-1543440)
Patients with negative plasma BK viral load at final follow-up	78.6% (11)	75% (6)
Acute rejection after BKN	0%	12.5% (1)

Although group 1 had a greater immunologic risk and a higher plasma BK viral load at diagnosis, the renal function during follow-up was more favorable than patients from group 2. No rejection episodes were diagnosis in group 1. Only one patient in each group started chronic dialysis at the end of the follow-up (52 and 85 months after BKN diagnosis).

Conclusions: An immunosuppression regimen based in TAC and mTORi is an effective and safety treatment in patients with BKN. This treatment reduces viral load and increases graft survival without increases the rejection risk.

PUB665

A Rare Case of Guillain-Barré Syndrome Associated with Cytomegalovirus Disease in a Renal Transplant Patient Jessica Bian, George P. Bayliss. *Medicine, Rhode Island Hospital, Providence, RI.*

Background: While cytomegalovirus (CMV) infection is associated with Guillain-Barré syndrome (GBS) in the general population, there are few reports of GBS associated with CMV disease in the renal transplant patients. We describe the case of one renal transplant patient who developed GBS after treatment for documented CMV disease.

Methods: The patient is a 62 year-old woman with ESRD from polycystic kidney disease status post deceased donor renal transplant (CMV donor positive/recipient seronegative) on tacrolimus and prednisone. She completed 6 months of CMV prophylaxis with valgancyclovir. Fourteen days after stopping valgancyclovir, she presented with fevers, myalgias, and headache. Tacrolimus level was 6.6 ng/mL on admission. She was diagnosed with CMV disease (serum CMV PCR 2200 copies; CSF CMV PCR undetectable) and started on treatment-dose valgancyclovir. Ten days later, she returned with numbness of her hands and feet. CSF studies were notable for albuminocytologic dissociation. MRI brain and spine was normal. Electromyography showed diffuse sensory motor polyneuropathy consistent with GBS. She developed ascending motor weakness, sensory loss, and areflexia without progression to respiratory compromise, improving with IVIG therapy. She was discharged to rehabilitation.

Results: She returned 7 days later with compartment syndrome of her right arm due to deep venous thromboses of her right subclavian, axillary, and brachial veins with associated hematomas requiring emergent fasciotomy and hematoma evacuation. This was attributed to recent IVIG therapy, as thromboses may occur even in the absence of other risk factors (US boxed warning). She was bridged to warfarin prior to discharge. Of note, she maintained excellent allograft function throughout this complicated course.

Conclusions: This vignette details a case of CMV-associated GBS after renal transplantation. The case is notable for the development of CMV disease shortly after cessation of valgancyclovir prophylaxis in a CMV donor positive/recipient negative renal transplant despite only being on a two-drug immunosuppressive regimen. This may support a longer course of CMV prophylaxis in donor positive/recipient negative transplants.

Funding: Clinical Revenue Support

PUB666

A Prolonged Warm Ischemia Time Is Associated with Graft Failure and Mortality After Kidney Transplantation Karthik K. Tennankore,¹ Joseph Kim,² Ian P. Alwayn,³ Bryce A. Kiberd.¹ ¹Medicine, Div of Nephrology, Dalhousie Univ, Halifax, NS, Canada; ²Medicine, Div of Nephrology, Univ of Toronto, Toronto, ON, Canada; ³Dept of Surgery, Multi-Organ Transplant Program, Dalhousie Univ, Halifax, NS, Canada.

Background: Warm ischemia time is a potentially modifiable insult to transplanted kidneys, but little is known about its effect on long term patient and graft survival. The purpose of this study was to determine if a prolonged warm ischemia time was associated with death and graft failure after kidney transplantation.

Methods: We conducted a cohort study of adult kidney transplant recipients in the Scientific Registry of Transplant Recipients between 1/1/2000 and 12/31/2013. Warm ischemia time was defined as the time of organ removal from cold storage to reperfusion with warm blood, including surgical anastomosis time. Times were categorized as 0-10, 10-20, 20-30, 30-40, 40-50, 50-60 and ≥60 minutes. Acknowledging that times of <10 minutes were potentially attributed to coding error, 10-20 minutes was chosen as the reference group. The primary outcome was all-cause mortality and graft failure adjusted for recipient, donor, immunological and surgical factors.

Results: Overall, 131,677 patients were included and there were 35,901 events. Relative to patients with warm ischemia times of 10-20 minutes, a longer warm ischemia time was associated with an increased relative hazard for death or graft failure (table 1). The association between warm ischemia time and the composite outcome persisted after stratification by donor type (living versus deceased donor) and delayed graft function status.

Conclusions: Warm ischemia time is associated with long term patient and graft survival after kidney transplantation. Strategies to reduce warm ischemia time should be an important consideration for future study.

Table 1. Adjusted Cox survival analysis for death or graft failure

Warm Time (Minutes)	Death or graft failure Relative Hazard [95% CI]	Death censored graft Failure Relative Hazard [95% CI]
	Events: 35,901	Events: 20,032
0-<10	1.17 [1.09-1.26]	1.15 [1.04-1.27]
10-<20	Ref	Ref
20-<30	1.07 [0.99-1.15]	1.04 [0.94-1.14]
30-<40	1.13 [1.06-1.22]	1.13 [1.03-1.24]
40-<50	1.17 [1.09-1.26]	1.17 [1.06-1.29]
50-<60	1.20 [1.12-1.30]	1.23 [1.11-1.36]
≥60	1.23 [1.15-1.33]	1.25 [1.13-1.37]

Adjusted for donor type (living, standard, expanded criteria), donor race, donor sex, donor diabetes status, donor body mass index categories, number of human leukocyte antigen mismatches, panel reactive antibody categories, induction type, cold ischemia time, and recipient characteristics (age, sex, gender, cause of end-stage renal disease, dialysis vintage, diabetes, coronary artery disease, hypertension, cerebrovascular disease, peripheral vascular disease, chronic lung disease, prior malignancy, previous kidney transplant, body mass index categories)

Funding: Private Foundation Support

PUB667

Clinical Significance of Pre-Transplant 25-Hydroxyvitamin D Levels on Post-Transplant Clinical Outcome Tae Hyun Ban,^{1,2} In-Ae Jang,^{1,2} Bum Soon Choi,^{1,2} Cheol Whee Park,^{1,2} Chul Woo Yang,^{1,2} Yong-Soo Kim,^{1,2} Byung Ha Chung.^{1,2} ¹Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea; ²Transplant Research Center, Seoul St. Mary's Hospital, Seoul, Korea.

Background: It is well known that vitamin D shows immune modulating effects in various immunologic disorders and infectious disease. The aim of this study is to investigate the clinical significance of 25(OH)D levels on acute rejection or infection in kidney transplant recipients.

Methods: We included 174 kidney transplant recipients with low immunologic risk between 2011 and 2013. We measured 25(OH)D levels right before transplantation, and investigated whether the level of 25(OH)D predicts the development of acute rejection or infectious complications.

Results: During the first year after the KT, a total 27 cases of biopsy proven acute rejection was detected. 25(OH)D levels showed significant association with the development of acute rejection within the first year from KT. In the high tertile, the rate of acute rejection was 6.9 % (p=0.012). It was significantly lower incidence toward the high tertile. There was significant distinction between each tertile (low and second, p=0.032; second and high, p=0.002). For the prediction of infectious complications, after the 1 year predictive values of 25(OH)D levels were dissipated. During 1 year after KT, a total of 82 (47.1%) cases of infectious complications were detected. Most common causes were 23 (13.2%) cases of CMV and UTI respectively. 25(OH)D levels did not show significant association with either the overall or different types of infectious complications.

Conclusions: Pre-transplant serum 25(OH)D levels are independent predictor of acute rejection in the first year from kidney transplantation. However, they were not associated with infectious episode.

PUB668

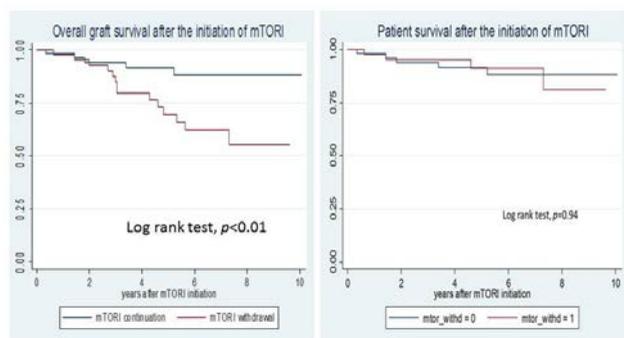
Mammalian Target of Rapamycin Inhibitors Withdrawal in Kidney Transplant Recipients: Risk Factors and Related Transplant Outcomes

Lee-Moay Lim,¹ Mei-Chuan Kuo,^{1,2} Hung-Tien Kuo.^{1,2} ¹*Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan;* ²*Faculty of Renal Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.*

Background: With its antiproliferative and antineoplastic properties, Mammalian Target of Rapamycin Inhibitors (MTORi) potentially have important long-term therapeutic consideration in kidney transplantation. Treatment cessation frequently occurs following its unique adverse effects. The objective of this study was to investigate the risk factors for MTORi withdrawal and its impacts on transplant outcomes.

Methods: This retrospective observational study consisted of kidney transplant recipients followed up from January 1999 till May 2015. We examined the risk factor for MTORi withdrawal using multivariate logistic regression analysis. The impacts of MTORi withdrawal on transplant outcomes were analyzed using multivariate Cox regression and logistic regression. $P < 0.05$ was considered as statistically significant.

Results: A total of 111 kidney transplant recipients who received MTORi treatments were included, with 46 patients withdrew (41.0%). The risk factors for mTORi withdrawal included initial proteinuria (adjusted OR= 4.61, $P=0.007$), higher initial serum creatinine (per 1 mg/dl increment, adjusted OR=2.73, $P=0.035$), and glomerulonephritis as primary renal disease (adjusted OR=5.00, $P=0.035$). MTORi withdrawal was associated with an increased risk of graft failure (adjusted HR=3.79, $P=0.027$), but not with patient survival (adjusted HR=0.61, $P=0.595$).



Conclusions: MTORi withdrawal is a strong risk factor for renal graft failure. Proteinuria, poor initial graft function and primary renal disease of glomerulonephritis are predictors for MTORi withdrawal. Earlier identification of risk factors may assist physician to decide the best candidate for MTORi conversion in order to optimize transplantation outcomes.

PUB669

Impact of Donor Age on Longterm Outcomes in Living Donor Kidney Transplants: A Propensity Score Matched Analysis Using Multicenter Cohort

Kyung Don Yoo,¹ Jung Nam An,¹ Jang-Hee Cho,³ Chan-Duck Kim,² Su-Kil Park,³ Dong-Wan Chae,¹ Yun Kyu Oh,¹ Chun Soo Lim,¹ Yon Su Kim,¹ Young hoon Kim,³ Jung Pyo Lee.¹ ¹*Seoul National Univ College of Medicine;* ²*Kyungpook National Univ Hospital;* ³*Asan Medical Center and Univ of Ulsan College of Medicine.*

Background: Recently, kidney transplantation from elderly living donor has been increasing. However, the impact of donor age on outcomes in kidney transplantation recipients has not been well established in Asian.

Methods: This multicenter cohort study included 2,595 adult kidney transplant recipients admitted to 5 major tertiary hospitals in Korea between 1997 and 2012. Patient survival, allograft survival, and biopsy-proven acute rejection (BPAR) were compared between the elderly donors (≥ 50 years) and young donors (18–49 years) by the propensity score matched (PSM) analysis.

Results: The proportion of donor with over 50 years was 21.2% ($N=553$). The mean age in the elderly donor was 54.9 ± 4.3 years old. Despite of difference of donor age, mean recipient age was similar between the groups. Elderly donors were more likely to donate to unrelated recipients. The proportions of recipients with diabetes mellitus (22.8%), serum creatinine and BMI of donor were significantly higher in the elderly donor group than in the young donor-age group. In elderly donor group, recipients' patient survival was worse than younger age group before PSM ($p=0.014$). After PSM, donor age did not affect the recipient's survival ($p=0.305$) and allograft survival ($p=0.077$), however, BPAR was frequently occurred in the allograft from elderly donor ($p=0.019$). In the multivariate Cox regression analysis, elderly donor affected the BPAR-free survival ($p=0.01$, hazard ratio 1.52, 95% confidence interval 1.07-2.17).

Conclusions: Kidney transplantation from elderly donor needs more meticulous management, because donor age could affect acute rejection.

PUB670

Long-Term Outcome of Randomized Trial Comparing Cyclosporine and Tacrolimus Therapy with Steroid Withdrawal in Living-Donor Renal Transplantation: 10-Year Follow-Up

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Background: The use of steroid withdrawal protocols after kidney transplantation has been increasing because of well-known adverse effects of steroids and the introduction of new effective immunosuppressants. Long-term efficacy and safety of tacrolimus plus mycophenolate mofetil (TAC group) compared with cyclosporine A plus MMF (CsA group) for 10 years were analyzed in renal transplantation patients with low immunologic risk who underwent steroid withdrawal at 6 months after operation.

Methods: Overall 10-year follow-up data of patients who underwent their first living-donor renal transplantation at Samsung Medical Center between September 2000 and August 2003 were retrospectively analyzed. Patients were randomized to CsA or TAC groups and underwent steroid withdrawal at 6 months after renal transplantation. End points were patient and graft survival, and the incidence of acute rejection and post-transplant de-novo comorbidity such as diabetes mellitus.

Results: A total of 117 patients who successfully discontinued steroid treatment were included (55 in CsA group vs. 62 in TAC group). The 10-year patient survival was 96.2% in the CsA group and 98.4% (61/62) in the TAC group ($p=0.495$). The 10-year graft survival rate did not differ between groups (81.3% in CsA vs 91.2% in TAC; $p=0.412$). The cumulative incidence of acute rejection for 10 years after transplantation was 24.5% and 15.6% in the CsA and TAC groups, respectively ($p=0.201$). The incidence of post-transplantation diabetes mellitus was higher in the TAC group compared to the CsA group (10.0% vs 23.3%, respectively; $p=0.046$).

Conclusions: Long-term graft and patient survival, and the incidence of acute rejection were similar between CsA- and TAC-based regimens combined with MMF in low immunologic risk patients who underwent steroid withdrawal 6 months after kidney transplantation.

PUB671

Dysregulation of Circulating Immunoglobulins in Renal Transplant Recipients

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Background: Peripheral levels of serum immunoglobulin reflect humoral immunity. Gross derangements in the immunoglobulin levels might occur in the post-transplant period.

Methods: Peripheral venous blood was periodically collected from patients before (pre-Tx) and after kidney transplantation at 1Month, 3 Months, 6 Months, 12 Months and at the time of Rejection. Serum was isolated from clotted blood after brief centrifugation at 3000g for 10 minutes. Serum level of IgM, IGA, IgG, IgG1, IgG2, IgG3 and IgG4 were quantified by Nephelometry (MiniNeph™, UK).

Results: This study includes 75 first kidney transplant recipients who were divided into two groups: Rejection group (R, $n=35$) and Non Rejection group (NR, $n=35$). Rejection group was further segregated as cellular ($n=25$) and antibody mediated ($n=9$). Thirty five age and sex matched healthy donors were recruited as control. No differences in the levels of IgG, IgA and IgM were noted in the pre-tx sera and healthy donor sera. Post-transplantation, there is an early decrease in serum IgG and IgA levels in both R and NR groups between 1-3 months and the rate of decrease is higher in patients with rejecting grafts. IgG3 and IgG4 are significantly reduced during rejection ($p < 0.0001$ and 0.0006 respectively). IgG3 levels correlated with cellular rejection, while the rate of decrease of IgG2 and IgG4 was higher in antibody mediated rejection.

Conclusions: Post-transplantation: there is a fall in serum levels of IgA, IgG and its subtypes in both non rejecters and rejecters, more so in the later. Low serum levels of IgG3 and IgG4 could be a pointer to rejection. Significant correlation of IgG3 with cellular rejection embarks that IgG subtypes are dysregulated in cell-mediated rejection.

PUB672

Impact of Kidney Transplantation on Arterial Stiffness in Patients with ESRD

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Background: Arterial stiffness is closely associated with cardiovascular mortality in end-stage renal disease (ESRD) patients. We investigated whether kidney transplantation (KT) can improve arterial stiffness in patients with ESRD.

Methods: We enrolled 171 KT recipients and we measured brachial-ankle pulse wave velocity (baPWV) and ankle-brachial blood pressure index (ABI) before KT, and post KT baPWV and ABI was assessed in a subgroup of 84 patients. First, we investigated cardiovascular (CV) events risk and established influence factors. Second, these patients divided into improvement and non-improvement groups based on change of baPWV after KT which was very strong marker of CV disease prediction. We also compared risk factors which affect arterial stiffness between two groups.

Results: 10 CV events occurred in the overall group, and 7 events in the post KT baPWV subgroup. Risk factors affected CV events of these group were diabetes, high body mass index(BMI) and high baPWV. Overall arterial stiffness measured by baPWV after KT showed significant improvement (1417.5 ± 234.5 cm/s) compared to those of before KT (1503.5 ± 255.2 cm/s) ($p < 0.05$ vs after KT). 55 out of 79 patients (69.6%) showed improvement of baPWV after KT, but 24 patients did not. Between two groups, improvement group showed higher pre-transplant baPWV than no-improvement group (1561.0 ± 263.9 vs. 1371.6 ± 177.1), and multivariate analysis revealed that gender and BMI, degree of decrement of calcium level were an independent risk factor of change of baPWV.

Conclusions: We could expect CV event risk in KT recipients by diabetes, BMI and baPWV, and these were very strong prediction marker of CV event. Arterial stiffness in ESRD patients improves after transplantation, and lower BMI, the amount of calcium decreased, gender affected the improvement of baPWV. PUB673

The Correlation of Donor:Recipient Body-Mass Index (BMI) Ratio and 6-Month Post-Transplant Kidney Function in Known End-Stage Renal Disease (ESRD) Patients Joseph Justin Hipolito Regalado. *Internal Medicine, Cardinal Santos Medical Centre (CSMC), San Juan, Metro Manila, Philippines.*

Background: Kidney Transplant (KT) is the preferred treatment for ESRD. The challenge rests in finding appropriate donors. Donor-recipient size mismatch was shown to correspond to donor-recipient nephron supply mismatch, affecting prognosis. Matching nephron supply to recipient needs was proposed to improve outcomes. Patients with a higher BMI relative to their donors were shown to have poorer post-KT graft function. Determining whether measures such as BMI are valid predictors of outcomes is a legitimate area of study. This research sought to determine the association and correlation between Donor-Recipient BMI Ratio and the 6-month post-KT creatinine (crea).

Methods: A review of patients who underwent KT in 2005-2014 at the CSMC was done. Inclusion criteria were Filipinos aged 18 years and above with a graft, coming from a Living Donor, functioning for at least 6 months post-KT (25 Donor-Recipient pairs). Association using Chi-Square and correlation using Multiple Regression Analysis between Donor-Recipient BMI and renal function based on 6 months post-KT crea were determined.

Results: Data showed no statistically significant association ($p = 0.64$) and correlation ($p = 0.77$) between Donor-Recipient BMI ratio and post-KT crea. Statistically significant correlations ($p < 0.10$) were noted between the post-KT crea and the recipient and donor BMI (strong correlation, $r = 0.78$), with a $22.51 \mu\text{mol/L}$ increase in post-KT crea per 1 point increase in the donor BMI, and a $13.51 \mu\text{mol/L}$ decrease in post-KT crea per 1 point increase in recipient BMI.

Conclusions: The data support two schools of thought on donor-recipient selection in improving outcomes. First, recipients are to lose weight to improve BMI before KT due to the increased risk of graft damage from hyperfiltration and lipotoxicity. Second, donors with larger BMI's are better due to a higher nephron reserve. It could be surmised from the study that the donor and recipient BMI's influence the 6-month post-KT crea. The appropriate mathematical instrument defining the relationship between these measures predicting KT outcomes more accurately, however, is yet to be universally established.

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Incidence of Malignancies in Kidney Transplant Patients – Report from Eastern Province of Saudi Arabia Abdul Razack Amir.¹ *Nephrology, Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Eastern, Saudi Arabia;* ²*Internal Medicine, Univ of Dammam, Dammam, Eastern, Saudi Arabia.*

Background: Renal transplant patients have a higher incidence of malignancies due to the use of immunosuppressive medications and concomitant infections.

Methods: Based on the follow up of a single center in Saudi Arabia, the incidence of malignancies patients who underwent kidney transplantation was analyzed.

Results: During the 15 years study period, a total of 221 patients underwent renal transplantation. Eleven patients developed post-transplant malignancies with an average incidence of 4.9%. Two patients had Kaposi sarcoma (0.9%) and two developed Non-Hodgkins lymphoma (0.9%). One case was reported to have transitional cell carcinoma of urinary bladder (0.45%), one had breast cancer (0.45%), one had cervical cancer (0.45%), one developed angiosarcoma (0.45%), and one had hepatocellular carcinoma (0.45%). In addition, two patients developed renal cell carcinoma, one in the native kidney (0.45%), and the other in the transplanted kidney (0.45%). The duration to cancer development ranged from 6-120 months. Mortality rate in renal transplant patients with cancer was higher (55%) than those who did not develop cancer. Risk factors that determined cancer development included patient age, gender, duration of the transplantation and type of immunosuppression. Type of transplant was not found to be a determining factor of cancer development.

Conclusions: The incidence of malignancies in post renal transplant patients in the Kingdom of Saudi Arabia is evidently comparable to that reported in literature. In addition, the data highlights the importance of long term close follow up of renal transplant patients.

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Left Ventricular Global Longitudinal Strain as Early Detection of Subclinical Myocardial Dysfunction in Renal Transplant Recipients Secundino Cigarran,¹ Jose Lomban,³ Ana Maria Sanjurjo Amado,¹ Diego Coronel,¹ Sheila Casas,³ Juan Latorre,¹ M^a Milagros López Hernández,¹ Jesus Calvino.² *¹Nephrology, Hospital Da Costa, Burela, Lugo, Spain; ²Nephrology, Hospital Lucus Augusti, Lugo, Spain; ³Cardiology, Hospital Da Costa, Burela, Lugo, Spain.*

Background: Echocardiographic global longitudinal strain (GLS) is recognised as a technique to detect subtle changes in left ventricular function. As in CKD pts, kidney transplant recipients (TXKR) has an increased mortality risk by CV events. Early detection of CV risk is the utmost importance in the TXKR outcomes. The aim of this cross sectional study is to assess the grade of myocardial dysfunction in TXKR without previous CV events & normal left ventricular ejection fraction (LVEF).

Methods: 37 TXKR following >1 yr were included. 44.4% F, 24.5% DM, age 55.4 ± 12.12 yo, GFR-EPI 51.93 ± 23.2 ml/min/m², No previous CV events & LVEF >55%. All of them on stable treatment with ACEI/ARB, CCHB, diuretics added to immunosuppressive drugs (TAC, CSA). Echocardiography 2D Vivid 9 (GE Vigmed Ultrasound, Horten, Norway), was performed: GLS, LAVI (ml/bsa), E/e', E/A, LVEF following recommendations of American Society of Echocardiography. Body composition analysis were performed by BIVA and serum biomarkers of inflammation, anaemia, mineral bone disease, renal function (GFR-EPI) and CV risk markers. Normal GLS (<-20%) LAVI 24 ml/m² were considered as published for general population Rev Esp Cardiologia 2014;67:651-8.

Results: Mean GLS was $-18.6 \pm 3.78\%$, LVEF $70.8 \pm 8.7\%$, LAVI 30.16 ± 20.4 ml. GFR correlated negatively with GLS ($r = -0.338$, $P < 0.016$) and LAVI ($r = 0.372$, $p = 0.14$). GLS progressed positive as GFR decline (P adjusted 0.025). E/e' 13.06 ± 6.48 ; E/A 0.93 ± 0.28 . Multivariate analysis was significant the relationship between GLS with ACR ($\beta = -0.151$, $p = 0.43$) e P excretion index ($\beta = -0.377$; $p = 0.14$). LAVI correlated with age ($\beta = 0.467$, $p = 0.004$), net acid load ($\beta = 0.345$; $p = 0.23$) and AGEs ($\beta = 0.314$; $p = 0.35$). No other correlations were met.

Conclusions: 66% TXKR show GLS > -20% and 41.6% LAVI > 24 ml/m². GLS & LAVI echocardiography derived are two valuable measures to assess early subclinical myocardial damage in TXKR. GLS appears more sensitive predictor than LVEF. Studies on TXKD pts are required.

Funding: Other NIH Support - SERGAS

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Seronegative Invasive Gastro-Intestinal Cytomegalovirus Disease in Renal Allograft Recipients – A Diagnostic Dilemma! Tissue PCR the Saviour? Anupama Kaul, Dharmendra Bhaduria, Narayan Prasad, Amit Gupta, Raj K. Sharma. *Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.*

Background: CMV as opportunistic infection affecting the gastrointestinal tract is the most common cause for tissue invasive CMV disease occurring in 10-30% of organ transplant recipients. Gastrointestinal CMV disease can be diagnosed in presence of clinical suspicion along with histopathological findings (CMV inclusions) and presence of mucosal lesion(s) on endoscopic examination with collaborative evidences via molecular technique.

Methods: Few cases of CMV infection affecting the gastrointestinal tract show no evidences of dissemination despite use of highly sensitive molecular techniques.

Results: We countered 6 cases where in despite strong clinical suspicion of Gastrointestinal CMV disease there were seronegative and endoscopic negative evidences for CMV, blind tissue biopsy yielded positive results for CMV disease with excellent improvement with antiviral therapy.

Conclusions: Blind biopsy specimen for tissue PCR could serve as saviour in an immunocompromised individual who has a strong clinical symptomatology for GI-CMV disease in absence of viremia, normal endoscopy and histopathology, so that the early therapeutic interventions could help in excellent patient and graft survival.

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Allograft Outcome After Desensitization with IVIg: A Single Center Experience Nitender Goyal, Phanicharan Sistla, Anshul Bhalla, Wendy Mccallum, Richard Rohrer, Ronald D. Perrone. *Tufts.*

Background: The presence of antibodies to donor human leukocyte antigens (HLA) is a significant barrier to transplantation. High dose intravenous Ig (IVIg) is widely used for desensitization. There is no general consensus on the best approach for desensitization, and long-term data on efficacy of IVIg are unknown.

Methods: We reviewed kidney transplants done from Jan, 2010 to Dec, 2014 at Tufts. Sensitization was defined as PRA >20% and/or presence of donor specific antibody (DSA). Patients who were desensitized with IVIg were identified as cases; those without desensitization served as controls. No attempt was made to desensitize patients awaiting deceased donor kidneys. Baseline characteristics and follow up data were collected at months 3, 6, 12 and 24. A sensitivity analysis was done for patients who received a living donor kidney.

Results: There were 19 patients in the desensitized group and 37 patients in the control group. Mean age at transplant in two groups was 47 ± 12 and 49 ± 12 respectively. In the desensitized group, there were more patients with prior transplant (37% vs 22%), receipt of living donor (95% vs 54%) and positive DSA (89% vs 22%). One patient developed severe side effects from IVIg, requiring discontinuation. Leukopenia and BK viremia were

seen more in non-desensitized patients at 3 months, but significance was not sustained after 3 months (Table). The leukopenia effect was not significant when adjusted for steroid. There was no difference in eGFR in either group, however mean eGFR was higher in those desensitized. Incidence of rejection was very low in both groups (5% vs 8%). When living donor recipients from both groups were compared, the eGFR and leukopenia effect was similar in both groups, and there was no significant difference in BK Viremia.

	No desensitization	Desensitization	p-value
Leukopenia			
3 month	18(49%)	4(21%)	0.04
12 month	5(18%)	5(36%)	0.22
Mean eGFR(sd)			
3 month	61.2(19.5)	68.7(24.8)	0.26
12 month	63.7(20.2)	72.2(25.1)	0.29
BK Viremia			
3 month	7(19%)	0	0.04
12 month	3(12.5%)	1(8%)	0.65

Conclusions: Desensitization with IVIg appears to be safe and effective. The lower incidence of leukopenia in desensitized group can be explained by greater use of steroids.

PUB678

Results of Chinese Renal Transplant Recipients with Post-Transplantation Malignancies Lihui Qu, Hong Jiang, Jianghua Chen. *The Kidney Disease Center, The First Affiliated Hospital, Medical College, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Malignancies are a severe complication of immunosuppressive therapy among renal transplant recipients, representing an important cause of long-term morbidity and mortality.

Methods: A retrospective study of 2700 recipients who underwent renal transplantation between July 1977 and July 2013 was carried out. 51 patients developed the following malignancies at a mean of 55.2 months (range = 1-207) after kidney transplantation. According to the regimen of immunosuppressive agents, all the recipients occurred malignancies were divided into azathioprine group (Aza group, n=21) and mycophenolate mofetil group (MMF group, n=30). The recipient age, gender, interval from renal transplantation to tumor development, long term survival of patient and graft and the ratio of converting to rapamycin of patients were made a comparison in detail between two groups.

Results: 29 patients survived without a recurrence including 28 with graft function (Survival group, n=29), and 22 patients died of malignancies including 21 with graft function (Death group, n=22). In the survival group, only one patient lost the graft after 26 months after immunosuppressant adjustment due to chronic rejection. Renal graft function remained stable in all other patients from diagnosis throughout follow-up. Moreover, 10 patients in the survival group were switched from calcineurin inhibitor-based immunosuppression to rapamycin after the diagnoses of malignancy, otherwise no patient in death group switched to rapamycin. At a mean follow-up of 34.0 months (range = 4-74), all the 10 patients are cancer-free and survived with functional graft. The incidence of death was similar in the Aza group and MMF group.

Conclusions: Our results demonstrate that the incidence of malignancy in renal allograft recipients is much higher than normal population, closely related to the long term use of immunosuppressant. Treating cancer thoroughly and maintaining the function of the transplanted kidney can decrease the risk of death with functional graft. Rapamycin-based immunosuppression blocks the recurrence of nonmetastatic tumors.

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Basiliximab Induction Therapy, Graft and Patient Survival Sergio Santiago Pedroza-Orozco, Paloma Arleth Zavalza-Camberos, Benjamin Gomez-Navarro. *Nephrology and Transplantation, Inst Mexicano del Seguro Social, CMNO, Guadalajara, Jalisco, Mexico.*

Background: Basiliximab is widely used in clinical practice for induction therapy of renal transplant recipients, expecting to reduce the incidence of acute rejection and improved graft function without increasing adverse events. We evaluate the impact of induction therapy using Basiliximab on relevant clinical outcomes: graft and patient survival, incidence of acute rejection (AR) and incidence of infectious or malignancy complications.

Methods: This retrospective study included all renal allograft recipients who were transplanted between January 2010 and April 2014 and who received Basiliximab as induction therapy. We collected the baseline characteristic of recipients, type of donor, donor's age, HLA matches and immunosuppression at the time of transplantation. The clinical outcomes were evaluated at the first year of transplantation and include: AR incidence, infectious or malignancy complications, serum creatinine and estimated glomerular filtration rate (eGFR) using the 4-variable MDRD formula, as well as graft and recipient survivals.

Results: The demographic characteristics of recipients and donors are in Table 1. Among 662 renal transplant recipients including in this study, only 10.6% (n=70) experienced AR during the first year follow up. The incidence of infectious complications

in the first year after transplantation was 32.3%, mostly urinary tract infection (82%). No episode of malignancy was reported. Graft and patient survival rates were 96.9% and 98.5% respectively.

Recipients mean age (year ± DE): 26 ± 10
HLA matching number: 4 IQR 1
Type of donor: Living related 89% Living unrelated 7% Deceased 4%
Donor's mean age (year ± DE): 38 ± 11
eGFR year 1 (mL/min/1.73m2): 82 ± 26 sCr year 1 (mg/dl): 1.2 ± 0.4

Conclusions: Our findings support previous studies, with similar incidence of AR episodes during the first year posttransplant, accompanied by a similar incidence of infectious and malignant complications, and similar patient and graft survivals at 1 year follow up. We can conclude that basiliximab is associated with excellent graft and patient survival and low rates of AR episodes.

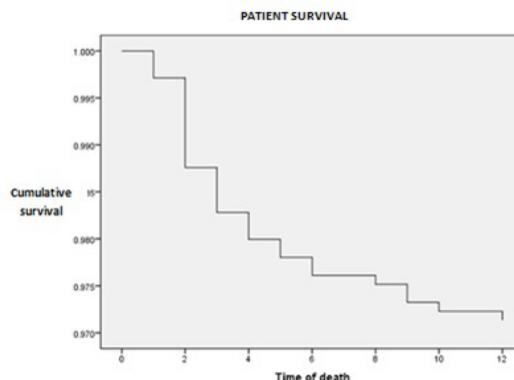
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Death within the First Year After Kidney Transplantation Paloma Arleth Zavalza-Camberos, Sergio Santiago Pedroza-Orozco, Benjamin Gomez-Navarro. *Nephrology and Transplantation, Inst Mexicano del Seguro Social, CMNO, Guadalajara, Jalisco, Mexico.*

Background: A successful kidney transplant improves the quality of life and reduces the risk of death in most patients when compared with staying on dialysis, however, the survival of transplant patients is lower than general population patients of the same age. This study was performed to evaluate mortality and characteristics of the dead patients.

Methods: It was a retrospective observational study that included all kidney transplant patients between January 1, 2010 to April 30, 2014, at HE-CMNO, IMSS, Guadalajara, Jalisco, Mexico. The follow-up time was one year. Mortality was calculated, the causes of death and characteristics of deceased patients were identified.

Results: During this time 1,047 transplants were performed. 30 deaths (2.86%) were recorded during the first year after transplantation. Regarding the type of donor: 12/102 (11.76%) patients with brain death donor died, and 18/945 (1.9%) patients with living donor died. The causes of death were 20 (66.66%) infections, 6 (20%) cardiovascular events, 2 (6.66%) related to graft rejection event and 2 (6.66%) unknown. The average time of transplantation to death was 2 months 27.4 days with a SD of ± 2 months 29.1 days; 70% of deaths occurred in the first 3 months after transplantation. The average time in dialysis was 5 years, with a SD ± 3 years 4.4 months; 83.3% of patients had more than two years on dialysis. Most patients who died had thymoglobulin induction, but patients were older, had more comorbidities, more time on dialysis, increased immunological risk and they had a brain death donor. Finally, 76.7% of patients who died had functional graft.



Conclusions: In our hospital, 1 year mortality postkidney transplantation is low, but there are many individual patient factors that contribute to the risk of mortality increases significantly in them and there we could intervene.

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Granzyme B Level and Acute Kidney Allograft Rejection: Impact on One Year Survival in Mexican Population Perla Edith Simancas Ruiz,¹ Caridad Aurea Leal,² Benjamin Gomez-Navarro.¹ *¹Nephrology and Transplant, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; ²Surgical Research, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.*

Background: Exposure to insufficient levels or discontinuation of immunosuppressants often increases the risk of rejection. Creatinine is the most useful test to monitor graft function. However, it is a poor predictor of rejection and often raises only after significant damage has occurred to the graft, so the identification of early biomarkers is mandatory. Granzyme B has been tested as a marker of acute rejection, with high specificity and sensitivity in different types of sample and has also enabled the identification of subclinical

rejection. The elevation of both the mRNA and protein has been associated with a worse prognosis of allograft. **OBJECTIVE:** Explore the association between serum levels of Granzyme B and acute rejection after one year post-transplant.

Methods: Kidney recipients transplanted between January 2008 and March 2009. Donors (n=38) and healthy subjects (n=6) were also included. The relation of granzyme B levels determined by ELISA with graft function and rejection was studied.

Results:

Receptor age (n=94)	26 ± 10 yr
Induction therapy:	
Basiliximab	46%
Daclizumab	39%
Thymoglobulin	2%
CMV	
High	21%
Moderate	72%
Low	7%
One year creatinine	1.66 mg/dL
Rejection:	46%
Borderline	31%
Banff 1A	56%
Banff ≥1B	14%
Chronic nephropathy	46%

Granzyme level in patients (n = 43) was 12.5 pg/ml while the reference group (n = 6) was 1.5 pg/ml (p <0.001). Comparison between patients with rejection (n = 14) and non-rejection (n = 20) was not statistically significant, nor the development of interstitial fibrosis year. The correlation between creatinine, GFT and granzyme level showed a trend to significance (n = 66, r = 0.30, p = 0.06).

Conclusions: The level of granzyme B was not associated with one year post-transplant rejection. However immune system activation is suggested by the higher level of granzyme in patients vs control group. Continuous analysis of patients.

PUB682

Epidemiological Analysis of Post Transplant Glomerulonephritis *Pratik Das, Santosh Kumar, Rohit Rungta. Nephrology and Transplantation, Rabindranath Tagore International Inst of Cardiac Sciences, Kolkata, West Bengal, India.*

Background: Post-transplant glomerulonephritis is an important cause of graft dysfunction and consequent graft loss. Aim of the study is to identify the incidence and outcome of glomerulonephritis in post-transplant patients.

Methods: We retrospectively evaluated all the patients who underwent renal allograft biopsy between January 2010 to January 2014, for graft dysfunction, proteinuria or active urinary sediments. All protocol biopsies were excluded from the study. Graft biopsies were evaluated by light microscopy and indirect immunofluorescence study. Out of 285 graft biopsies 242 biopsies were taken into study. Biopsies showing evidences of glomerulonephritis were further evaluated for incidence of individual types of glomerulonephritis and their outcome at the end of one year post diagnosis.

Results: Based on biopsy findings among 242 renal allograft biopsies taken in study 42(17.35%) had post-transplant glomerulonephritis. Further the incidence of individual glomerulonephritis were 14(33.3%) for focal segmental glomerulosclerosis, 13(31%) for IgA nephropathy, 8(19%) for membranoproliferative glomerulonephritis, 4(9.6%) for pauci-immune crescentic GN, 2(4.8%) for anti-glomerular basement membrane disease and 1(2.3%) for membranous nephropathy. On follow up for one year 30(71.4%) patients lost their graft and became dialysis dependent irrespective of treatment. When compared to this outcome with other causes of graft dysfunction (rejection or infection), results are inferior in terms of graft and patient loss.

Conclusions: We conclude that post-transplant glomerulonephritis is strongly associated with poor kidney allograft survival. Therefore, optimal management of recurrent or *de novo* glomerulonephritis should be the critical focus of post-transplant care.

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Impact of Hemoglobin Concentration on Mortality After Renal Transplantation *Vitoria C. Vilela,¹ Marcos A. Meniconi,¹ J. Medina-Pestana,¹ Miguel Cendoroglo Neto,^{1,2} Miguel A Goes.^{1,2} ¹Nephrology Div, Federal Univ of Sao Paulo, Sao Paulo, Brazil; ²Nephrology Div, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.*

Background: Kidney transplant recipients have chronic anemia, irrespective of the time from transplantation. Objective: To assess the impact of hemoglobin concentration on mortality after renal transplantation.

Methods: A total of 233 patients who underwent renal transplantation at one center (Hospital do Rim) were prospectively analyzed. Follow-up time was 6 years, from January 2008 through December 2014. Data on demographics, ESRD etiology, pre-transplantation dialysis, transplant characteristics, and immunosuppression regimen. Two-sample t test were used to compare differences between two groups (mortality versus non-mortality groups) and χ^2 to analyze categorical variables. Binary logistic regression was used to determine the impact of factors on outcome-mortality.

Results: The main causes of ESRD were diabetes (35%) and hypertension (20%). Transplants from living donors occurred in 59%. During the entire follow-up period, there were 24 (10%) deaths within 3+1 yr after renal transplantation. 7 (29%) from cardiovascular

disease and 17 (71%) died from infection. We observed that mortality group were older (p<0.001) and longer time on dialysis (4+2.5, 2.5+2.0 yr; p=0.006). Hemoglobin (Hb) concentration was lower in mortality (10.7+2.3) than non-mortality (12.0+2.42; p=0.01) group. Patients who used mycophenolate had lower mortality (p = 0.04). There is no correlation between Age and Hb (r=-0.02; p=0.8). Age (p = 0.01) and Hb concentration (p =0.02) were independent predictors of mortality.

Conclusions: This study shows that a lower Hb concentration is an independent predictor of mortality in renal transplant patients.

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Prediction of Recipients Survival in Deceased Donor Kidney Transplant Using Korean Network for Organ Sharing Database *Kyung Don Yoo,¹ Junhyug Noh,² Hajeong Lee,¹ Dong Ki Kim,¹ Chun Soo Lim,¹ Young hoon Kim,³ Yon Su Kim,¹ Gunhee Kim,² Jung Pyo Lee.¹ ¹Seoul National Univ College of Medicine; ²Seoul National Univ College of Engineering; ³Univ of Ulsan.*

Background: The Korean Network for Organ Sharing (KONOS) was founded in 2000 for organ allocation in Korea. It has been allows medical doctors and researchers to fully access the national population-based raw data about KT recipients. We propose a novel prediction approach of recipient survival based on machine learning techniques using KONOS data.

Methods: Our dataset is collected from 2000 to 2014 by the KONOS. We design a novel prediction model that uses all of the follow-up recipients' data including censored ones, on which estimated death risks are weighted accordingly. We compare this approach with the baseline model that uses only uncensored data by the CART (Classification And Regression Trees) modeling.

Results: We analyze 5,430 recipients' records with more than 31 attributes, among which we choose 15 independent attributes to learn our models. The proposed weighted algorithm leads a better performance when predicting survival rates of transplant recipients within 6 years, but fails to show any significant difference from the baseline for those more than 7 years after transplantation. Using the decision-tree models, we find that the inotropic agent usage of donor management is the most important predictor, which estimates in 51.3% of 10-year mortality. In the age ≥51.5 group, non-diabetes recipients, waiting period < 4years, and donor age < 23.5 years show significant associations with better 10YRS. The results are consistent with our hypothesis that poor donor status, recipients' longer waiting time and advanced age are associated with poor prognosis.

Year after transplantation	1	3	5	7	9
Baseline model AUC	0.644	0.665	0.759	0.832	0.862
Weighted Model AUC	0.653	0.678	0.777	0.822	0.794

Conclusions: In this study, we show that the proposed machine learning based models with weights of estimated-death risks can present more accurate and flexible than baseline models for predicting in long-term survival rates of kidney transplant recipients.

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Perforin Expression in Renal Allograft Biopsies *Michele T. Rooney,¹ Ping L. Zhang,² Dilip Samarapungavan,³ Randolph Alexander Hennigar.⁴ ¹Incyte Diagnostics, Spokane, WA; ²Anatomic Pathology, William Beaumont Hospitals, Royal Oak, MI; ³Nephrology, William Beaumont Hospitals, Royal Oak, MI; ⁴Nephropathology Associates, Little Rock, AR.*

Background: Perforin is a cytotoxic protein in effector lymphocytes that facilitates targeted cell killing and it has an established role in allograft rejection. A diagnostic value has not been delineated. We examined perforin expression in renal transplant biopsies by immunohistochemistry (IHC) and found that positive lymphocytes are confined largely to the microvasculature in cases of active cellular rejection (ACR). The goal of this study is to investigate whether perforin IHC is a useful metric in identifying and classifying acute rejection in renal transplant biopsies.

Methods: Renal transplant biopsies accessioned over a one-year period were selected to include cases showing no acute rejection, acute tubular injury, BK nephritis, ACR types 1 and 2, and C4d+ antibody-mediated rejection (AMR), according to the 2013 revised Banff Classification. IHC using a mouse monoclonal anti-perforin antibody was performed on each case. Perforin positive cells/10 high power (400X) fields (hpf) were counted from slides identified by number only.

Results: Most rejection-negative cases had < 10 perforin-positive cells/10 hpf. Biopsies showing type 1A ACR, excluding one outlier, did not exhibit a significant increase in perforin-positive cells relative to rejection-negative cases. In contrast, cases of type 1B and 2 ACR, and C4d+ AMR displayed significantly increased perforin-positive cells (p = 0.0001) with most showing > 40/ 10 hpf. Cases of AMR contained the highest number of perforin-positive cells (p = .0352). Cases of BK nephritis varied widely from < 10 to > 50/ 10 hpf. 2 of 3 cases with > 50 had a recent history of ACR developing BK infection upon increasing immunosuppression, raising the possibility of coexisting BK and rejection.

Conclusions: Further study is needed, but our data suggests that increased numbers of perforin-positive lymphocytes correlate with more aggressive forms of rejection, and that perforin IHC may be a useful ancillary test for acute allograft rejection of type 1B or higher.

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Is It Safe to Transplant Sensitized Patients? Analysis of 1,002 Consecutive Kidney Transplants *Anna Rita Aguirre, Patricia Soares Souza, Fabiana Agena, Daisa R.S. David, Flavio Jota Paula, Elias David-Neto, Maria Cristina R. Castro. Renal Transplant Service, Hospital das Clinicas - Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: From 2009-13, 24% of kidney recipients in our center had antiHLA antibodies(aHLA abs). Obj: To compare the risks of rejection, patient and graft survival when transplants(Tx) were performed with or without aHLA abs and with or without DSAs. To compare mortality between patients transplanted with aHLA abs to mortality in the waiting list.

Methods: Retrospective study, which included all isolated kidney Tx in patients older than 18yo, performed between jan09 and dec13(N1002). We analysed the incidence of TCMR and ABMR in the 1st year after Tx. Median follow-up time was 32mo. Graft and patient survival were evaluated by Kaplan Meyer estimates.

Results: In 741 Tx(74%), no aHLA abs were detected(ARP=0) and 261(26%) had PRA>0. Among Tx with PRA=0, 658(89%) did not have rejection in the 1st year, 77(10.4%) had TCMR and 6(0.81%) had ABMR. Among Tx with PRA>0 without DSAs(149), 129(86.6%) did not have rejection, 16(11%) had TCMR and 7(4.7%) had ABMR. In Tx with PRA>0% with DSA(91), 58(62.4%) did not have rejection, 7(7.5%) had TCMR and 31(33.4%) had ABMR. ABMR was more frequent when there was a DSA(p<0.0001). Graft survival did not differ according to ARP or DSA in groups with no rejection, TCMR and ABMR. There were more graft losses in the whole sample when a DSA was detected(p<0.0001) or when RAMA occurred, in comparison to no rejection(p<0.0001) and TCMR(p 0.0143). Regarding patient survival, there was no influence of aHLA abs and DSAs, nor influence of TCMR or ABMR. In recipients with aHLA abs, mortality was 11% in 32mo, or 4.12% per year, smaller than in the waiting list in our state, which was 5.61% in the same period.

Conclusions: There was no difference in patient survival after 32 mo between patients with or without aHLA abs or DSAs, or even between patients with or without ABMR. However, there were more graft losses in recipients with aHLA abs and with ABMR. Mortality after Tx among sensitized patients hasn't been larger than in the waiting list. We conclude that transplanting the sensitized patient does not increase mortality risk.

PUB687

Response of Anti Blood Group Antibodies to Desensitization Procedures and Kidney Transplantation *Bharat V. Shah, Zaheer Amin Virani, Prashant J. Rajput. Inst of Renal Sciences, Global Hospitals, Mumbai, Maharashtra, India.*

Background: ABO-incompatible (ABOi) kidney transplantation (KT) is option for overcoming the shortage of organ donors. Before performing ABOi transplant, it is important to reduce anti-blood group antibody titers (ABGAT) by desensitization. The aim of our study was to determine: 1) Baseline ABGAT in patients undergoing ABOi KT, 2) Response of ABGAT to desensitization and 3) Behavior of ABGAT after KT.

Methods: Nineteen (13 male and 6 female) ABO-I patients (6-O, 8-A and 5-B blood groups) studied. The IgG and IgM ABGAT were determined using column agglutination technique (CAT). Desensitization was attempted if baseline IgG ABGAT > 1:32. For desensitization, besides rituximab, Plamapheresis (PP) and/or Glycosorb was used. Desensitization considered successful if IgG ABGAT dropped to < 1:32. ABGAT monitored daily or alternate days for 1 week after transplant, twice a week in the 2nd week and weekly for next 2 weeks.

Results: The baseline IgG antibody titres ranged from 1:4 to > 1:512 (median 1:64) while IgM antibody titres ranged from 1:2 to > 1:512, (median 1:32). In one case with baseline titre <1:4 no desensitization was done. In 15 cases, PP alone was attempted. In 3 of these cases (with baseline titre > 1:512), the titres could not be reduced to < 1:32 and transplant was not done. Based on this experience, we used Glycosorb with or without PP in next 3 cases with titres > 1:512. All of these 3 cases could be desensitized. Of the 16 patients who were transplanted, the titres remained < 1: 64 (median 1:8) after transplant in 15. None of them required PP or Glycosorb treatment after transplant. In one patient, IgG ABGAT rose to > 1:128 in the first week after KT. Biopsy was suggestive of acute antibody mediated rejection and was treated with PP, Rituximab and Bortezomib.

Conclusions: Majority of our patients have low baseline ABGAT. In cases with low ABGAT, Rituximab (2 doses of 200 mg weekly) and 2 to 3 sessions of PP bring down titres to < 1:32. For baseline titres > 1:512, use of Glycosorb may be required. After KT titres remain < 1:64 in most and this is not associated with any graft dysfunction. One may consider an allograft biopsy if IgG ABGAT is > 1:128 in the first 2 weeks.

PUB688

Temporal Characteristics of End Stage Renal Disease due to Tuberous Sclerosis in United States, 2001- 2010 *Donna J. Claes,¹ Sarah J. Kizilbash,¹ Hassan N. Ibrahim,² Robert N. Foley,² Scott Reule.² ¹Pediatrics, Nephrology, Univ of Minnesota, Minneapolis, MN; ²Internal Medicine, Nephrology, Univ of Minnesota, Minneapolis, MN.*

Background: Tuberous sclerosis (TS) is an autosomal dominant, multisystem disorder characterized by hamartomas in various organs with renal involvement occurring in approximately 50 to 80% of patients. Although renal involvement may result in end-stage renal disease (ESRD), studies examining the characteristic of ESRD in patients with TS are limited.

Methods: Census data was combined with data from the USRDS for all patients diagnosed with ESRD from 2001-2010 (n=1,072,161). A total of 367 patients with ESRD

due to TS were identified. Incidence rates and standardized incidence ratios (SIR) were computed using Poisson distribution and standardized using 2001-2002 as reference. Hazards ratios adjusting for age, sex, race and ethnicity (AHR) were calculated for outcomes.

Results: In 2001-2002, the overall incidence rate of ESRD due to TS was 1 per 10 million person years (PMPY) and the SIR remained largely unchanged over the observation period. Those with ESRD due to TS were more likely to be < 40 years (23.2% vs. 9.2%), white ethnicity (81.5% vs. 65.5%), and lack diabetes (81.2% vs. 48.1%). Compared to those with ESRD due to other causes, odds ratios adjusted for age, sex, race and ethnicity (AOR) were highest for females (1.83) and those with eGFR > 15ml/min (1.31). Factors associated lower AOR included age 40-64 years (0.29), age ≥ 65 years (0.25), and black race (0.33). Over the study period, 53.7% of TS patients died, 27.3% were listed and 10.6% were transplanted. The AHR for outcomes demonstrated those < 40 years of age were more likely to be listed for renal transplant, receive renal transplant and survive.

Conclusions: The incidence of ESRD due to TS remained largely unchanged from 2001 through 2010. Our results indicated gender and racial differences in the odds of ESRD due to TS.

PUB689

The Impact of Hepatitis C Virus Infection on the Clinical Course, Short-Term and Long-Term Outcome in Renal Transplant Recipients – A Retrospective Study *Pratik Das, Rohit Rungta, Santosh Kumar. Nephrology and Transplantation, Rabindranath Tagore International Inst of Cardiac Sciences, Kolkata, West Bengal, India.*

Background: Hepatitis C infection is common in patients of end stage renal disease with increased morbidity and mortality post-transplant. The aim of the study was to find out the impact of HCV infection on graft and patient outcome and compare it with the non HCV infected post-transplant cohort.

Methods: We retrospectively analysed patient and graft survival of HCV infected (after virological remission) post renal transplant patients from 2008 to 2014 with a median follow up of 24 months and compared them with our HCV negative statistically matched cohort.

Results: Outcome analysis was done at 6, 12, 18 and 24 months in terms of liver dysfunction, acute rejections, infections, hospitalization and death. Results were further tabulated as shown.

VARIABLES	HCV positive patients	hcv negative patients	P value
1. Patients(n)	51	1381	
2. Induction with ATG	26(50%)	700(50.68%)	NS
3. Tacrolimus	34(66.67%)	1196(86.9%)	<0.05
4. Cyclosporin	17(33.3%)	185(13.1%)	<0.05
5. Infection	05(9.8%)	117(8.5%)	NS
6. Abnormal LFT	08(15.6%)	NA	-
7. 1 year patient survival	96.1%	97%	NS
8. 2 year patient survival	92%	93.2%	NS
9. Hospitalization	24 episodes	621 episodes	NS

Results were found not to be statistically different from non HCV infected renal allograft recipients.

Conclusions: HCV infected end stage renal disease patients may undergo renal transplantation safely after virological remission and outcome is not different from other renal transplant recipients.

PUB690

Patient and Graft Survival in Pediatric Kidney Transplantation: A Single-Center Experience According to Transplant Era *Marta Monteverde,¹ Juan Carlos Lopez,¹ Gerardo Nyman,¹ Liliana Briones.¹ ¹Nephrology Unit, Hospital JP Garrahan, Buenos Aires, CABA, Argentina; ²Urology Unit, Hospital JP Garrahan, Buenos Aires, CABA, Argentina.*

Background: Improvements in the management of kidney transplantation has improved in the last 20 years. However the long term results in terms of graft survival and morbidity still require more research.

Methods: We evaluated 744 pediatric renal transplants (RTX), 551 with deceased donor (DD) and 222 with living-related donor (LRD), between 1988- 2015. We divided this time in 2 periods: 1988-2000 and 2001-2015. Patient and graft survival were calculated for each period for LD and DD recipient. We analyzed causes of mortality, causes of graft failure and risk factors for graft loss. Mean age at RTX was 11.6 y (r: 3.7-19.5). Median time of follow-up was 54.5 months (IQR: 22.4-90.1) months.

Results: Patient and graft survival for DD have significantly increased in the recent era (p=0.0002; p=0.0013 resp). Chronic rejection was the first cause of graft loss in both eras (61.9% vs 61.11%); Vascular thrombosis decreased (14.9% vs 5.5%; p= <0.001), and also Death with a Functioning Graft (15.8% vs 8.3%; p=<0.001). Acute rejection during the first 30 days post RTX + relapse of the original disease increased (0% vs 9.7%). First cause of death in both eras was bacterial infection (77% vs 66%). No death due to PTLD were seen in 2001-2015. Independent Risk factors for graft loss for DD recipients were: FSGS

as cause of ESRD (HR: 3.1; CI 95%: 2-4.8), DGF (HR: 2.8; CI 95%: 2-4) and Receiving no induction therapy (HR: 2.1; CI 95% 1.3-3.5). For LRD recipients: DGF (HR: 5.2; CI: 2.9-9.3) and Age at RTX > 12y (HR: 2.2; CI95%: 1.2-3.9).

Conclusions: Patient and graft survival has significantly improved for DD in the recent era. Chronic rejection remains a the major cause of graft failure. No death from malignancy were observed in the recent era.

Graft Survival	1y (%SE)	3y (%SE)	5y (%SE)	7y (%SE)	10y (%SE)
LD(1988-2000)	97 (0.001)	90.5 (0.02)	85 (0.03)	78.2 (0.03)	65.3 (0.04)
LD(2001-2015)	96 (0.02)	90 (0.03)	87 (0.03)	80.6 (0.06)	76.1 (0.07)
DD(1988-2000)	83.2 (0.03)	74.5 (0.03)	67.9 (0.03)	62.6 (0.03)	51 (0.04)
DD(2001- 2015)	94.7 (0.01)	86.8 (0.02)	82.7 (0.02)	74.5 (0.03)	58.6 (0.07)

PUB691

Impact of Rituximab Induction on Short Term Outcome of Kidney Transplant Recipients Bharat V. Shah, Prashant J. Rajput, Zaheer Amin Virani. *Inst of Renal Sciences, Global Hospitals, Mumbai, Maharashtra, India.*

Background: Acute graft rejection remains a major problem in kidney transplant (KT) recipients. Induction with Thymoglobulin or Basiliximab is a KDIGO recommendation to minimize the risk of acute rejection. However, these induction agents do not eliminate the risk of antibody mediated rejection. Recent studies of ABO incompatible (ABOi) transplant using Rituximab, in addition to standard induction and maintenance immunosuppression (IS) have shown better outcome than ABO compatible (Kohei N, Tanabe K Am J Transplantation 2012; 12: 469-476) transplants. Therefore our aim was to study efficacy and safety of Rituximab induction in addition to single dose Thymoglobulin induction in living donor (LD) KT patients.

Methods: The study included 53 adult LD KT recipients transplanted between 3/1/14 and 2/28/15 and followed for at least 3 months after KT. Of these, 39 were (ABOc) transplants and 14 were (ABOi) transplants. Rituximab 200 mg was given within a week before transplant. ABOi recipients received an additional 200 mg Rituximab on the day of transplant. Thymoglobulin 1 mg/kg was used only on the day of transplant. Maintenance immunosuppression included Tacrolimus, MMF and tapering doses of prednisolone in all. All patients received valgancyclovir and cotrimoxazole prophylaxis. The short term outcome of these patients (Ritux group) was compared to that of 53 historic controls (control group) who received only thymoglobulin 1 mg/kg on the day of KT.

Results: There was no difference in characteristics (age, sex, etiology of CKD, donor characteristics, HLA mismatch) of patients in the 2 groups. Six patients in the Ritux group developed acute rejection (5, cellular and 1 antibody mediated). Six patients in the control group developed acute rejection (2 cellular and 4 antibody mediated). The patient and graft survival at 3 months was 100% in Ritux group. The patient survival was 100% in control group. One graft was lost from antibody mediated rejection in control group. Infections within 3 months after KT were similar in both groups.

Conclusions: Rituximab induction is safe in KT. It reduces the risk of antibody mediated rejection without increasing infectious complications in the early period after KT.

PUB692

Epo Use in Pregnant Renopancreas Transplant Patients Amelia R. Heguilen, Alicia M. Lapidus, Liliana Susana Voto, Ricardo M. Heguilen. *Medicine, Hospital Juan A. Fernandez, Buenos Aires, Argentina.*

Background: Pancreas-kidney transplantation (Tx) improves life and reproductive function. Anaemia (AN) is common in this population. Prenatal counselling address potential fetal complications; as well as worsening anaemia, hypertension, preeclampsia, gestational diabetes, acute rejection or graft loss. The aim of this study was to evaluate the use of Erythropoietin (rHuEpo) during pregnancy in Tx recipients.

Methods: Four double Tx (cadaveric donor) recipients, underwent successful pregnancies after a complex medical history of diabetes in their childhood with retinopathy & polyneuropathy, two with hypothyroidism, and end stage renal disease. They were all switched into a pregnancy-friendly schedule with azathioprine, tacrolimus and low prednisone dose. Iron supplements (IS) and rHuEpo were prescribed because of anaemia progression. Because of hypo-responsiveness to rHuEpo, doses were increased to 8000 U/week in the 4 pt.in the third trimester.

Results: Serum creatinine (mg/dL) remained initially stable (1.28 ± 0.1); increased near delivery (36.2 wks) to 1.45 ± 0.1 and remained (1.32 ± 0.09) mg/dl postpartum. Blood pressure also increased near term without need of medication, serum uric acid rose to 6.2 ± 0.6 mg/dl and mild proteinuria (550 ± 155 mg/d) developed. They were all normoglycemic, with normal pancreatic and hepatic function throughout pregnancy and postpartum. rHuEpo and IS were stable mothers H⁺ (24.7%) and HB (8.2 g/dl) with normal ferric parameters and reticulocytes. Fetal heart rate was normal. One pt developed preterm premature rupture of membranes; all pt delivered vaginally healthy babies, weight: 2100 ± 320 g. (IUGR) with no evidence of congenital anomalies. There was no postpartum hypertension and they continued with stable renal and HCT parameters. Three months later serum creatinine returned to baseline and no proteinuria was detected. rHuEpo need to be decreased in all pt. postpartum, newborns outcome was uneventful.

Conclusions: According to our study the administration of human recombinant erythropoietin has a beneficial effect in pregnancy without side effects. Preterm delivery, IUGR and low birth weight are common in this population probably due to other drug adverse effects.

PUB693

Acute Rejection Incidence in Deceased Kidney Transplant Recipients with Delayed Graft Function After Single Dose Thymoglobulin Igor Gouveia Pietrobom, Laila Almeida Viana, Cinthia Montenegro Teixeira, Andre Caires Alvino Lima, Mayara Ivani de paula, Geovana Basso, Tainá Veras de sandes Freitas, J. Medina-Pestana, Helio Tedesco Silva. *Hospital do Rim, Federal Univ of Sao Paulo, São Paulo, Brazil.*

Background: Thymoglobulin (rATG) induction has proven efficacy. However, it remains unclear what is the best dosing regimen.

Methods: From August 8th, 2014 immunosuppression protocol was changed at our institution to induction with single dose thymoglobulin to all deceased donor kidney transplant recipients. This retrospective study evaluated the incidence of acute rejection (AR) in deceased kidney transplant recipients with delayed donor graft function (DGF) before and after the adoption of a new induction protocol.

Results: Pre-protocol Group 1 - 96 patients transplanted between 12/31/2013 and 08/08/2014; Standard criteria deceased donors (SCD) (without induction, tacrolimus 0.1 mg/kg/dose, prednisone and azathioprine) or expanded criteria deceased donors (ECD) (induction with thymoglobulin 6mg / kg, tacrolimus 0.05 mg/Kg/dose, prednisone and mycophenolate sodium) versus Group 2 (new protocol) , 87 patients transplanted between 08/08/2014 and 03/31/2015, subdivided in the same way, receiving the same maintenance therapy and thymoglobulin induction 3mg/kg single dose. In both groups, the population was overwhelmingly male (63% vs. 55%), young (47 vs. 46 years) and low immunological risk. The incidence of AR in G1 vs. G2, SCD subgroup was 13%, vs. 4% (p = 0.09). When compared ECD recipients, the incidence of rejection was similar between G1 vs. G2 (15% vs. 14%, p = 1.0), respectively.

Conclusions: In the SCD kidney transplant recipients, the incidence of AR was numerically lower in the group that received induction with single dose rATG 3mg / kg and induction with a reduced dose of rATG was not inferior in the ECD group.

PUB694

Cardiovascular Changes After Kidney Donation Fernando H. Margulic. *Nefrología y Trasplante Renal, Hospital General de Agudos Cosme Argerich, CABA, Buenos Aires, Argentina.*

Background: The aim of our study was to investigate the changes in cardiovascular structure and endothelial function after donation in kidney donors.

Methods: Fourteen living kidney donors (both genders) without history of kidney disease, diabetes, cardiovascular events or hypertension, who participated in the donor screening protocol with subsequent donation, were included. Office blood pressure (OBP), ambulatory blood pressure monitoring (ABPM), left ventricular mass index (LVMI), arterial stiffness (AS) and endothelial function (EF) were measured before and one year after the donation. AS was assessed from the left index finger using a digital photoplethysmograph (Pulse Trace; Micro Medical), that uses a simplified analysis of the digital volume pulse wave, to assess endothelium dependent arterial vasodilation, 400 ug of salbutamol was given by inhalation. Data were expressed as mean ± SD or median and IR. Student t test and Wicoxon test were used for data with normal and nonparametric distribution respectively, p<0.05 were considered to be statistically significant.

Results: The mean age of the cohort was 47 ± 8 (range, 30 – 56) years. At one year after donation the mean BMI (27.1 ± 2.6, P<0.006), median OBP (89 (86, 92), P<0.023) and median serum creatinine (1.14 (0.99, 1.42), P<0.001) were significantly increased as compared to baseline (26.4 ± 3; 85 (76, 92) and 0.78 (0.74, 0.97), respectively). The estimated glomerular filtration rate levels by MDRD 4 formula at 1 year (57.4 ± 12ml/min/1.73 m², P<0.0001) were significantly decreased as compared to baseline (82.2 ± 10 ml/min/1.73 m²). We did not find significant differences in mean 24hs ABPM (84 ± 8 mmHg, P=0.940), mean LVMI (96.6 ± 17 g/m², P=0.727), mean AS (7.78 ± 2.3 m/s, P=0.210) and median EF (5.1% (0.8, 13.3), P=0.374) compared to baseline (85 ± 7 mmHg; 99.8 ± 31.6 g/m²; 9.03 ± 2.3 m/s and 10% (-1.6, 34.6), respectively).

Conclusions: Our study demonstrated that after an year, reduced nephron mass because of kidney donation was not associated with changes in cardiovascular structure and endothelial function.

Funding: Government Support - Non-U.S.

PUB695

A Rare Case of Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) After Kidney Transplantation Maria C. Bermudez, Mayurkumar Gohel, Ali Javed, Michael F. Schultz. *Nephrology, Geisinger Medical Center, Danville, PA.*

Background: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described inflammatory condition of the central nervous system. To date 50 cases have been reported in the literature, however none have been reported following renal transplantation.

Methods: 47 year old Hispanic male, status post diseased donor kidney transplant in 2008, with history of hypertension and diabetes, presented to our clinic with several months of progressive dizziness, unsteady gait and right facial numbness that progressed to diplopia and right facial palsy. An MRI of the brain with gadolinium revealed a 1.3 cm mass with a ring-like target appearance in the right brachium pontis and dorsal pons. MR spectroscopy revealed mild elevation of choline, suggesting demyelinating disease versus lymphoma or other high-grade malignancy. Given his long term immunosuppression, malignancy or an infectious process were considered as the main diagnostic possibilities. An extensive evaluation included serial lumbar punctures for cytology and a variety of

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

viral, fungal and bacterial cultures. Cytologic and serologic studies were unremarkable. Flow cytometry analysis of the spinal fluid showed no evidence of lymphoma. A brain biopsy was performed revealing non-specific perivascular lymphoplasmocytic infiltrate with no evidence of lymphoma or infection. Additionally, myelin stain was positive ruling out demyelinating disease. Our patient was started on high-dose steroids with remarkable improvement of his symptoms. Diagnosis of CLIPPERS was made.

Conclusions: CLIPPERS is a rare and poorly recognized CNS inflammatory condition. To our knowledge, this is the first case reported after renal transplantation. More studies are needed to determine the pathophysiology of CLIPPERS in immunosuppressed patients and whether it could represent a pre-malignant state. Duration of treatment and follow up is yet to be determined. In this case, treatment with steroids has let to symptomatic improvement over a month and close follow-up continues.

PUB696

The Impact of Post-Transplant Hemoglobin and Creatinine Level on Renal Allograft Survival Luiz Fernando Christiani, Fernanda Paula Feres Rios Da Costa, Ana Flavia Baldoni, Alicia Imada, Kelly Rodrigues, Maria Izabel Neves de Holanda Barbosa, G ssika Marcelo Gomes, Cl udia Fagundes. *Nephrology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil.*

Background: Anemia is a common finding after kidney transplantation. The roll and the prevalence of Posttransplantation anemia (PTA) in predicting renal allograft outcomes still vary between different studies. In this study, we aim to assess the prevalence of anemia at one and six months post transplant and its correlation with 1 year renal allograft survival.

Methods: Anemia was defined by an absolute level of hemoglobin less than 11 g/dL. Hemoglobin and creatinine level were assessed at one, six and twelve-month after transplantation.

Results: We included 261 consecutive patients who underwent renal transplant from January/2010 to June/2012. Mean recipient age was 42±10 years and 56% were male. Prevalence of anemia was 42% at 1 month, 16% at 6 months and 9% at 12 months. Hemoglobin and creatinine level at first month of transplantation were 11.2±2 and 1.8±1.0 for patients with functional allograft vs. 9.4±2.1 and 4.8±3.4 for those who return to dialysis within 12 months (p<0.001 for both comparisons). Overall patient and graft survival was 8% and 10%, respectively. On multivariate analysis, creatinine and hemoglobin level were independently associated with poor graft survival at 12 months. The best cut-off selected by receiver operating characteristic curve analysis was 10.8 g/dL for Hemoglobin level, (AUROC 0.74 (0.63-0.86), p<0.001), and 2.25 mg/dL, for serum creatinine (AUROC 0.77 (0.62-0.91), p<0.001). Combining the best points of those two variable could identify patients at risk of graft loss. Patients who met both criteria (Hb < 10.8 g/dL and Creatinine > 2.25 mg/dL) had 59% graft survival at 1-year, whereas allograft survival was 98.5% for patients without any criteria (Hb > 10.8 g/dL and Creatinine < 2.25 mg/dL).

Conclusions: Prevalence of anemia was high in the first month after transplant and persisted in a substantial proportion of functioning kidney transplant recipients. Early (1-month) hemoglobin and creatinine level can predict 1 year-graft survival.

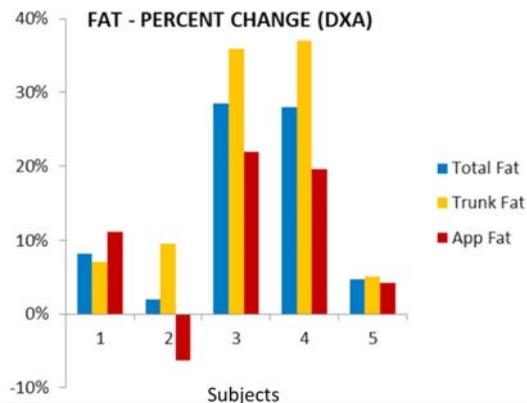
PUB697

Examining Adverse Weight Gain After Kidney Transplantation Biruh Workeneh,¹ Linda W. Moore,² William E. Mitch.¹ *¹Medicine/Nephrology, Baylor College of Medicine, Houston, TX; ²Transplant Medicine, Houston Methodist Hospital, Houston, TX.*

Background: Between 15,000-17,000 patients with end-stage renal disease (ESRD) receive a kidney transplant in the United States every year. Among the most consequential complications to these patients are adverse weight gain and the development of diabetes, commonly termed New-Onset Diabetes After Transplantation (NODAT) with consequent CV mortality. However, there is no consensus about the exact nature of the weight gain that routinely occurs after kidney transplantation (i.e., relative changes in fat vs. muscle vs. fluid volume) and how this relates to insulin resistance. We wish to test the hypothesis that weight gain is primarily due to an increase in fat mass.

Methods: We are conducting a longitudinal study in ESRD patients anticipating receiving a live donor kidney transplant. We are studying subjects before kidney transplant, at 12 weeks and 1 year after they have received living donor kidney transplant to measure changes body composition and other indices. Body composition was characterized by DEXA as well as total body potassium (a gold standard measure of muscle mass).

Results: Results from 5 subjects who completed baseline assessment and 3 months post-transplant reveals there is significant gain in adipose weight gain in all cases.



Additionally, we discovered there is significant loss in skeletal muscle mass (p=0.032) measured by total body potassium.

Conclusions: We have not studied enough to conclude whether changes in energy expenditure and diet contribute to adipose weight gain and whether there is acute nitrogen (muscle) loss perioperatively. Ultimately, methods to identify patients at high risk for adverse weight gain and related metabolic disorders before transplant are greatly needed.

Funding: Private Foundation Support

PUB698

Effect of Mycophenolate Mofetil Dose on BK Virus Infection in Kidney Transplant Recipients Vedran Pasara,¹ Danica Galesic Ljubanovic,² Mladen Knotek.¹ *¹Dept of Medicine, Renal Div, Univ of Zagreb Medical School, Merkur Hospital, Zagreb, Croatia; ²Dept of Pathology, Univ of Zagreb Medical School, Dubrava Univ Hospital, Zagreb, Croatia.*

Background: Intensity of overall immunosuppression is a risk factor for BK virus infection (BKVI). However, the exact impact of exposure to tacrolimus and mycophenolate mofetil (MMF) to BKVI is unclear. The aim of this study was to determine if BKVI in kidney transplant (KT) recipients (KTR) is associated with drug exposure to MMF.

Methods: This prospective randomised controlled clinical trial (NCT01860183) included 36 KTR who underwent KT from May 2013 to February 2015 at Clinical Hospital Merkur. Immunosuppression consisted of basiliximab induction, with tacrolimus, MMF+steroid maintenance. KTR were randomized in two groups, with respect to MMF dose (2g or 3 g daily). Urine cytology for decoy cells was performed at prespecified time-points posttransplant. KTR were followed up to 12 months post KT. Graft biopsy was performed per protocol at 2, 6 and 12 months, or in case of graft dysfunction. Kaplan-Meier analysis with log-rank test was used to assess graft survival. A Cox regression was used to determine variables associated with graft survival.

Results: 13 (37.1%) KTR had decoy cells in urine, 4 (11.4%) KTR had biopsy-proven BK virus-associated nephropathy (BKVAN). The mean time-to-occurrence was 4.8 months for decoy cells and 4.3 months for BKVAN. Cumulative one-year overall graft survival was 93.5%. Incidence of decoy cells, BKVAN, or acute rejection was similar in the two MMF groups. Rejection was not a risk factor for decoy cell positivity or for BKVAN.

Conclusions: MMF dose may not increase risk for BKVI after kidney transplantation.

Funding: Government Support - Non-U.S.

PUB699

Malignancy following Renal Transplantation Lourdes de la Vara Iniesta,¹ Francisco Llamas Fuentes,² Inmaculada Lorenzo Gonzalez,² Carmen Gomez Roldan.² *¹Virgen de la Luz Hospital, Cuenca; ²Univ Hospital of Albacete, Albacete.*

Background: There is retrospective experience in many reports about the association between the intensity of immunosuppression and the higher frequency of malignancy. Objective: Analyse and describe our centre's experience.

Methods: 275 transplant patients were analyzed. A record was made of the frequency, anatomic-pathological diagnostics, location, the mean interval between transplantation and diagnostics (latency time), follow-up time, use of antilymphocyte-antibodies, affection by cytomegalovirus, rejection and immunosuppressive therapy.

Results: Of 273 patients, 9.52%(26) were diagnosed of cancer. The majority, 93.43%(24), corresponded to De novo malignancy, 7.7%(2) were recurrences of pre-existing disease. The mean age at diagnosis was 63.19±7.24years. The latency time was 63.65months (11-114), although there is a notable but unexplained reduction over the last five year (33,50vs63,65 months). The average follow-up time was 97.54months. The most frequent malignancies were skin cancers, predominantly Basal-cell and Squamous-cell carcinomas. The incidence of other tumors was similar to the general population. The most common causes of chronic renal failure was the glomerular and interstitial disorders. The risk of neoplasm was 0.36%, 4,36% and 9,52% at one, five and ten years after the kidney transplant. No association was detected with use of antilymphocyte-antibodies, CMV infection, rejection episodes or different immunosuppressive therapy. At the time of analysis, 84.60%(22) of patients had functioning graft, 7.70%(2) had returned to dialysis and 7.70%(2) had died, both due to the cancer.

Conclusions: Our experience is similar to what is reported in the literature. The incidence of cancer is higher than expected in the general population and increases according to the duration of the immunosuppression. Skin cancers were the most frequent malignancies. Unlike other studies, there was a low incidence of lymphoproliferative disorder and Kaposi's sarcoma, and the incidence of other solid malignancies being similar to that of the general population. To reduce the development of malignancies must be one of our objectives.

PUB700

Lipidapheresis in 3 Sisters with Familial Hypercholesterolemia Christina Taylan,¹ Andrea Schlune,² Thomas Meissner,² Lutz Thorsten Weber.¹ ¹*Pediatric Nephrology, Univ Hospital of Cologne, Cologne, Germany;* ²*Dept of Pediatrics, Neonatology and Cardiology, Univ Hospital of Duesseldorf, Duesseldorf, Germany.*

Background: Familial hypercholesterolemia (FH) is the most common monogenic form of hypercholesterolemia. It carries the risk of premature coronary heart disease. As the atherosclerotic burden is dependent on the degree and duration of exposure to raised LDL-cholesterol levels, early diagnosis and effective treatment are imperative. Statins are the mainstay in the management of these patients. Lipoprotein-apheresis becomes recently more established in patients with severe dyslipidemia. Together these treatments improve the prognosis of FH. Most children fail to attain targeted lipid goals owing to persistent shortcomings in diagnosis and treatment.

Methods: Three siblings with a LDLR mutation (p.Trp577Arg) being on statins (20 mg/d Atorvastatin) and Ezetimib (10 mg/d) for 12 months with still LDL-C plasma concentrations of above 300-500 mg/dl started once weekly a double filtration plasmapheresis (DFPP) with a single plasma volume to be treated.

Results: After each LDL-apheresis LDL-C concentration of 100-150 mg/dl could be reached. (66-70% reduction). After 6 months plasma volume to treat was doubled because of a rebound within 7 days with LDL-C concentration up to 300-350 mg/dl. But though after each session LDL-C concentration decreased to 50-100 mg/dl the rebound was still evident after 7 days of therapy pause. With a treatment regime with twice plasma volume every 3-4 days the children finally attained a stable pre-treatment LDL-C concentration of 120-170 mg/dl. Another 2 months later statin therapy was stopped because of underlying mutation with assumed non receptor function. Neither the effectiveness of each apheresis nor the LDL-C concentration after 4 days showed any change.

Conclusions: In pediatric FH patients with high levels of LDL-cholesterol plasma concentration it might be necessary to treat instead of conservative medication with apheresis in high frequency and with high plasma volumes to reach a durable decrease in LDL-cholesterol plasma concentration. The use of cholesterol uptake-inhibitors should be considered.

PUB701

Thrombomodulin Up-Regulation in Preeclamptic Nephropathy Is Associated with Parietal Cell Activation Rosanne Jane Turner,¹ Maria Elisabeth Penning,¹ Malu Zandbergen,¹ Eliyahu V. Khankin,² S. Ananth Karumanchi,³ Jan A. Bruijn,¹ Kitty Bloemenkamp,³ Hans J. Baelde.¹ ¹*Pathology, LUMC, Leiden, Netherlands;* ²*Howard Hughes Medical Inst and Dept of Medicine, Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA;* ³*Obstetrics, LUMC, Leiden, Netherlands.*

Background: Preeclampsia is a pregnancy-specific syndrome characterized by angiogenic imbalance and endothelial dysfunction. This endothelial dysfunction leads to kidney damage, i.e. glomerular endotheliosis, increased podocyte turnover and proteinuria. Thrombomodulin (TM) facilitates maintenance of glomerular endothelium by inhibiting coagulation, inflammation and apoptosis. In preeclampsia, levels of soluble thrombomodulin in the circulation are increased. We hypothesize that glomerular thrombomodulin expression is increased in preeclampsia and set out to correlate thrombomodulin expression with endothelium and podocyte damage.

Methods: A nationwide, ethics committee-approved search of the Dutch Pathology Registry (PALGA) was conducted; this revealed renal autopsy material from 11 women with preeclampsia according to the ISSHP definition, from 22 normotensive pregnant controls and from 14 hypertensive non-pregnant controls. Kidneys from 13 sFLT-1 transfected mice and controls were collected. Samples were stained for TM and fibrin and markers of endothelium and podocyte damage were investigated.

Results: TM expression was increased in glomeruli from preeclampsia patients (82%) compared to pregnant, (41%, P=0.03) and hypertensive controls (21%, P=0.004). In sFLT-1 transfected mice TM expression was the same as in controls. TM expression correlated with activation of parietal epithelial cells (P=0.023), but not with endotheliosis or endothelial fibrin deposits (P>0.05).

Conclusions: TM expression in the kidney is increased in preeclampsia. This is associated with parietal cell activation and not with endothelial damage or fibrin deposits. TM apparently exerts cytoprotective and not anticoagulant effects in the kidney in preeclampsia. Glomerular damage induced by sFLT-1 did not increase TM expression in a mouse model; this indicates that the increased TM expression in humans is probably not caused by this anti-angiogenic factor alone.

PUB702

Cadmium Induces Matrix Metalloproteinase-9 Expression via NADPH Oxidase/ROS-Dependent EGFR Signals in Human Endothelial Cells Nam ho Kim. *Internal Medicine, Chonnam Natuinal Univ Hospital, Gwangju, Korea.*

Background: Cadmium, a widespread cumulative pollutant, is a known human carcinogen, associated with inflammation and tumor. Matrix metalloproteinase-9(MMP-9) plays a pivotal role in inflammatory reaction and tumor metastasis, however, the mechanisms underlying MMP-9 expression induced by cadmium remains obscure in human endothelial cells.

Methods: Here, cadmium elevated MMP-9 expression and enzyme activity, as well as MMP-9 promoter-driven luciferase activity, in a dose and time dependent manner in ECV304 human endothelial cells. Moreover, cadmium activated phosphorylation of EGFR, Akt, Erk1/2, JNK1/2, p38MAPK and promoted NF-κB and AP-1 binding.

Results: Specific inhibition and mutagenesis study shows that EGFR, Akt, Erk1/2, JNK1/2 and transcription factor NF-κB and AP-1 were related to cadmium-induced MMP-9 expression in ECV304 cells. Akt and MAPKs (Erk1/2 and JNK1/2) functioned as upstream signaling molecules in the activation of NF-κB and AP-1, respectively. Furthermore, Cadmium increased ROS production and the ROS-producing NADPH oxidase. Cadmium translocates p47phox, a key subunit of NADPH oxidase, to the cell membrane. The exogenous H₂O₂ increased MMP-9 mRNA expression. And that, inhibition of ROS by ROS scavenger (NAC) or NADPH oxidase inhibitor (DPI) attenuated EGFR, Akt, MAP(Erk1/2, JNK1/2, p38MAPK) activation, and MMP-9 expression. Likewise, inhibition of EGFR phosphorylation prevented the activation of AKT, MAPKs (Erk1/2, p38MAPK). Finally, ECV304 cells treated with cadmium displayed markedly invasiveness, which was partially abrogated by MMP-9 neutralizing antibodies.

Conclusions: These results demonstrated that cadmium induces MMP-9 expression via NADPH oxidase/ROS-dependent EGFR/Akt/NF-κB and EGFR/MAPKs (Erk1/2, JNK1/2)/AP-1 signaling pathways and, in turn, stimulates invasiveness in human endothelial ECV304 cells. These findings provide further insight into the molecular mechanisms in the carcinogenesis effect of cadmium.

PUB703

Exosomes from Activated Kidney Fibroblast Have Ambivalent Potential Effect on Atherosclerosis Fumitoshi Nishio, Noritoshi Kato, Yoshio Funahashi, Takuji Ishimoto, Tomoki Kosugi, Naotake Tsuboi, Shoichi Maruyama, Seichi Matsuo. *Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi-Pref, Japan.*

Background: Exosomes are small (50-140nm) membrane vesicles of endosomal origin that contain host cell's proteins, mRNAs, and microRNAs (miRNAs). The body of evidence revealed that these contents were biologically active, and had roles in intracellular communication. Especially tumor-derived exosomes has been intensively exploited and proven to be associated with distant metastasis. On the other hand, it is well known that CKD patients are at risk of cardiovascular diseases, but the mechanism of this distant organ crosstalk is not fully understood. Under the hypothesis that exosomes are involved in cardio-renal syndrome (CRS), the aim of this study is to explore the role of exosomes from kidney fibroblasts, which are activated in diseased kidney, on vascular endothelial cells.

Methods: We isolated Exosomes from culture media of TGF-β stimulated rat kidney fibroblasts cell line (NRK-49f) by ultracentrifugation technique. Cultured vascular endothelial cells (RAOEC; Rat Aortic Endothelial Cells) were stimulated by these exosomes or exosomes from unstimulated fibroblast. Then we evaluated the expression of genes, which associated with atherosclerosis by qPCR.

Results: RAOEC stimulated with exosomes from TGF-β activated kidney fibroblast (RAOEC-T) showed higher expression of PIGF and lower expression of Flt-1, ABCA-1 than control (RAOEC-C). This expression pattern is compatible with atherosclerotic change. On the other hand, RAOEC-T showed reduced expression of adhesion molecules such as ICAM-1/VCAM-1 and E-selectin compare with RAOEC-C.

Conclusions: So far, CRS is supposed to be caused by uremic factor, RAS system, chronic inflammation, and so on. From this study, we showed that exosomes from activated kidney fibroblasts have ambivalent roles in atherosclerosis by modulating the expression of adhesion molecules, metabolic factor, and VEGF system on endothelial cells. Further studies are needed to elucidate the contribution level of exosomes on CRS.

PUB704

Prevalence of Metabolic Syndrome in Patients with End Stage Renal Disease: Relevance of Biomarkers Vinod K. Bansal,¹ Jennifer Saluk,² Debra Hoppensteadt,² Daneyal Syed,² Schuhaarazad Abro,² Jawed Fareed.² ¹*Nephrology, Loyola Univ Medical Center, Maywood, IL;* ²*Pathology, Loyola Univ Medical Center, Maywood, IL.*

Background: Since the metabolic syndrome (MetS) and chronic kidney disease (CKD) share many of the same risk factors and similar inflammatory pathogenesis, many studies have suggested a correlation between CKD and MetS, and shown that patients with MetS are more likely to develop CKD. The purpose is to investigate metabolic biomarker levels in ESRD patients to evaluate their relevance to ESRD and to provide insight into the pathogenic ESRD processes and the development of associated comorbidities.

Methods: Plasma samples were retrospectively collected from 89 ESRD patients prior to maintenance hemodialysis. Normal human plasma samples (female & male, 18-35 years old) were purchased from George King Biomedical Inc. (Overland Park, KS). Samples

were stored at -80°C . Biochips were purchased from RANDOX (Co. Antrim, Northern Ireland) to test C peptide, ferritin, IL-6, resistin, insulin, TNF α , IL-1 α , leptin, PAI-1. These biomarkers were tested on 82 ESRD and 17 normal samples.

Results: All biomarkers, except insulin, were significantly elevated in Patients with ESRD compared to normal (p values are 0.05 - .0001). MetS patients with ESRD, as compared to non-MetS Patients with ESRD, had significantly elevated Leptin ($P=0.002$), and the correlation between MetS and Leptin levels was significant ($P<0.0001$, $r=0.43$). All other biomarkers showed no significant difference between ESRD+MetS and ESRD-MetS patients. Furthermore, when leptin levels for Patients with ESRD were broken down into ESRD+MetS and ESRD-MetS, ESRD+MetS vs. normal was significant ($P=0.0003$), but ESRD-MetS vs. normal was not ($P=0.6$).

Conclusions: Elevated biomarkers suggest an ongoing inflammatory process in ESRD patients. Insulin levels were not significantly elevated in ESRD patients, possibly attributed to the high Leptin levels, which can interfere with insulin secretion and signaling. ESRD+MetS and ESRD-MetS populations are not statistically different for all other biomarkers. This suggests that biomarker elevation is due to ESRD pathogenesis, rather than due to MetS as a comorbidity.

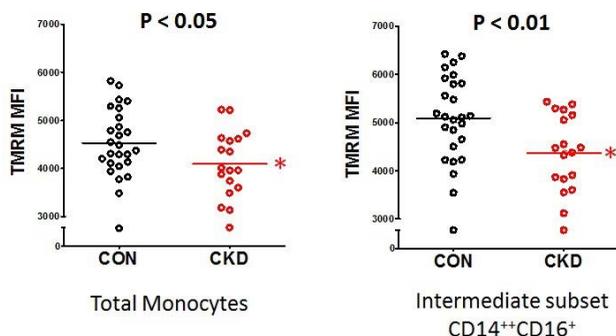
PUB705

Decreased Mitochondrial Membrane Potential in Monocyte Subsets from Patients with Chronic Kidney Disease Ying Wang,¹ Eric Joseph Lai,¹ Annie Febus,¹ Yuan Zhang,² Linda Vernocchi,¹ Anjali Ganda.¹ ¹Div of Nephrology, Dept of Medicine, Columbia Univ Medical Center, New York, NY; ²Dept of Biostatistics, Mailman School of Public Health, Columbia Univ, New York, NY.

Background: Particular monocyte subsets are associated with future cardiovascular events in patients with chronic kidney disease (CKD), and the underlying mechanisms require further investigation. Previous studies have suggested impaired mitochondrial function in patients on dialysis, while little is known about mitochondrial functionality in monocyte subsets from non-dialyzed patients with CKD. Given that mitochondrial dysfunction has been linked to atherosclerosis, we hypothesized that non-dialyzed patients with CKD would have mitochondrial dysfunction in monocyte subsets which could accelerate atherosclerosis in patients with CKD.

Methods: Monocyte subsets from 18 adult CKD patients (eGFR <30 ml/min/1.73 m²) and 26 matched controls (eGFR ≥ 60 ml/min/1.73 m²) were freshly analyzed by flow cytometry. Mitochondrial membrane potential (DYm), as a measure of mitochondrial functionality, was determined by the mean fluorescence intensity (MFI) of TMRM (tetramethylrhodamine methyl ester).

Results: DYm was significantly reduced by 10% in patients with CKD vs. controls in total monocytes ($P<0.05$). Interestingly, the intermediate monocyte subset (CD14⁺CD16⁺), which has the highest DYm among all the monocyte subsets and has been shown to predict future cardiovascular events in CKD patients, had the most pronounced reduction in DYm (14% lower, $P<0.01$) in patients with CKD vs. controls.



Conclusions: Patients with CKD demonstrate mitochondrial dysfunction in total monocytes and monocyte subsets. Mechanistic and prospective studies are needed to examine the relationship between monocyte mitochondrial dysfunction, atherosclerosis, and future cardiovascular events in CKD patients.

Funding: NIDDK Support, Private Foundation Support

PUB706

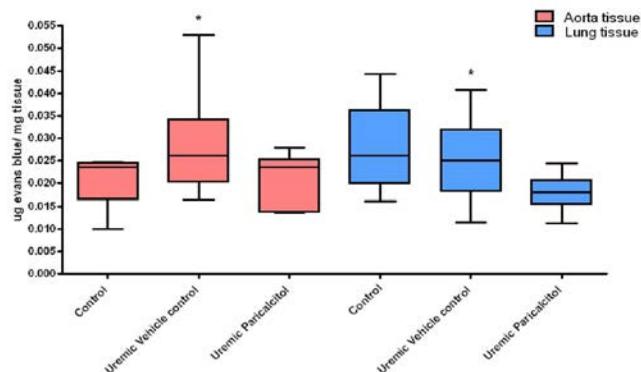
Paricalcitol Upregulates Renal Klotho and Restores Uremia-Induced Endothelial Integrity Disruption Marc Vila cuenca,¹ Robert H.j. Beelen,¹ Marc G. Vervloet,² ¹Molecular Cell Biology & Immunology, VU Univ Medical Center, Amsterdam, Netherlands; ²Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

Background: Klotho deficiency in chronic kidney disease (CKD) is associated with the disruption of the endothelial integrity. Active vitamin D induces klotho expression. Hence, active vitamin D may limit endothelial layer disruption.

Methods: Male wistar rats were assigned into one of four groups: Control; Vitamin D deficiency, induced with Vitamin D deficient diet; Uremic, developed after 3/4 nephrectomy; Uremic + Vitamin D deficiency. Animals were treated with Paricalcitol or vehicle control during 7 weeks. Serum samples were analyzed for 25D and 1,25D. Evans Blue was injected

for estimation of the endothelial thoracic aorta and lung permeability and quantified using spectrophotometry. To determine the levels of Klotho, qPCR and WesternBlot was performed in kidney tissue.

Results: Average 25D levels were 9.83 nmol/L while 1,25D levels were below the detection levels (20pmol/L) after the induction Vitamin D deficiency. mRNA and protein levels of Klotho in the Kidney were decreased in Vitamin D deficient and uremic rats and restored after Paricalcitol treatment. Aortic Evans blue leakage increased in all uremic rats regardless of vitamin D level, compared with the control group and restored after Paricalcitol treatment ($p=0.03$). Uremia did not induce pulmonary leakage, but paricalcitol lowered it compared to control and uremic condition ($p=0.04$). Figure shows uremic with/without D-deficiency together.



Conclusions: CKD induces aortic endothelial leakage, while the deficit of vitamin D on its own did not. Paricalcitol completely rescued endothelial leakage induced by CKD. In parallel, Klotho expression increased upon this treatment and may mediate the beneficial effect on the endothelium. To explain the difference between aortic and pulmonary tissue, additional studies are required.

Funding: Pharmaceutical Company Support - Abbvie

PUB707

Altered Intra-Aortic Expression of the Renin-Angiotensin System Is Associated with Arterial Aging in Mice Hye Eun Yoon,^{1,2} Eun Nim Kim,¹ Min Young Kim,¹ Ji Hee Lim,¹ Cheol Whee Park,¹ Bum Soon Choi.¹ ¹Internal Medicine, The Catholic Univ of Korea, Seoul, Korea; ²Internal Medicine, Incheon St. Mary's Hospital, Incheon, Korea.

Background: Aging is the major risk factor of cardiovascular disease and results in progressive decline in physiological function and structural abnormalities of vasculature. The renin-angiotensin system (RAS) is the key player in cardiovascular diseases. This study evaluated whether the change in the RAS is associated with arterial aging.

Methods: Histologic changes and expressions of angiotensin, angiotensin converting enzyme 1 (ACE1), angiotensin II type 1 receptor (AT₁R), angiotensin II type 2 receptor (AT₂R), and antioxidant enzymes, superoxide dismutase 1 (SOD1) and superoxide dismutase 2 (SOD2), were measured in the thoracic aortas from 2-month-old, 12-month-old, and 24-month-old C57/BL6 mice.

Results: Twenty-four-month-old mice showed significantly increased aortic media thickness compared to 2-month-old mice (1.6-fold). The aortic expression of angiotensin was increased in 12-month-old (1.2-fold) and 24-month-old mice (1.3-fold) compared to 2-month-old mice. Similarly, the expression of ACE1 was increased in 12-month-old (1.2-fold) and 24-month-old mice (3-fold) compared to 2-month-old mice. The AT₁R/AT₂R ratios were increased in 12-month-old (1.3-fold) and 24-month-old mice (1.5-fold) compared with 2-month-old mice. The expressions of SOD1 and SOD2 were decreased in 12-month-old (0.8-fold and 0.6-fold, respectively) and 24-month-old mice (0.6-fold and 0.5-fold, respectively) compared with 2-month-old mice.

Conclusions: Age-related intra-aortic activation of the RAS was associated with reduced antioxidant enzymes and hypertrophy of the aorta. These results suggest that the altered expression of the RAS contributes to the increased susceptibility to vascular injury in the elderly population.

Funding: Government Support - Non-U.S.

PUB708

Upregulation of Microparticles, Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease Vinod K. Bansal,¹ Daneyal Syed,² Debra Hoppensteadt,² Jawed Fareed.² ¹Nephrology, Loyola Univ Medical Center, Maywood, IL; ²Pathology, Loyola Univ Medical Center, Maywood, IL.

Background: End stage renal disease (ESRD) represents the final stage of chronic kidney disease characterized by kidney failure (GFR <15 mL/min/1.73 m²). To understand the pathophysiology of ESRD, we measured the circulating levels of microparticles (MP), tissue factor (TF), adhesion molecules, such as p-selectin (P-Sel), soluble ICAM (s-ICAM), nitric oxide (NO) and adiponectin (AD).

Methods: Plasma samples were collected from 119 ESRD patients undergoing maintenance hemodialysis to profile various inflammatory biomarkers. 100 normal plasma samples were collected from healthy individuals. MP levels were measured using an annexin

binding method (Hyphen Biomedical, Paris, France). NO was measured using a kit from R&D systems (Minneapolis, Minnesota) and ELISA methods for TF, P-Selectin and adiponectin were obtained from R&D systems. A chromogenic substrate method was used to measure heparin.

Results: MP levels were elevated in the ESRD group (28.1nm + 6.1nm vs. the control 8.9nm +1.3nm). Tissue factor levels were found to be increased in the ESRD group (20.4±6.1pg/ml) vs the control (11.9±2.8pg/ml). The nitric oxide level was markedly higher in the ESRD group (32±17uM) vs the controls (7±3uM). The p-selectin levels were elevated in the ESRD group (46±20ng/ml) vs the control (31±3ng/ml). The soluble ICAM levels were higher in the ESRD group (250±112ng/ml) vs the control (180±19ng/ml). Interestingly, the adiponectin levels were also increased in the ESRD group (19.2±9.3ug/ml) vs the control (11.2±4.1ug/ml). Detectable levels of heparin (.05 – 0.20 U/ml) were measured in the ESRD group.

Conclusions: These studies suggest that MP, TF, NO, p-selectin and s-ICAM levels are increased in the ESRD patient. It is of interest to note that despite that a significant number of ESRD patients were diabetic; the AD levels were increased. These results also suggest that while ESRD represents a pro-inflammatory/hypercoagulable state, the repeated administration of heparin and other drugs may contribute to the regulation of the hemostatic process and inflammatory balance.

PUB709

Coronary Artery Calcification and All-Cause Mortality in RRT Patients with Diabetes: 5 Year Survival Analysis Ramin Tolouian,¹ Sean M. Connery,² Kyari Sumayin Ngamdu,² ¹Internal Medicine, Eastern Virginia Medical School, Norfolk, VA; ²Internal Medicine, Texas Tech Univ HSC El Paso, El Paso, TX.

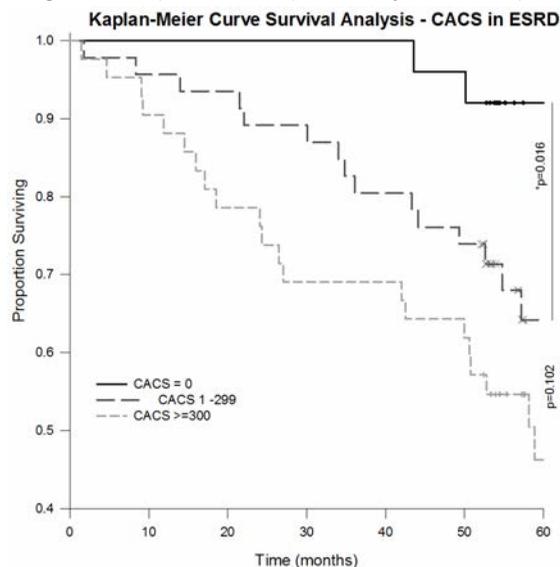
Background: Vascular calcification is a significant sequela of ESRD. A Coronary Artery Calcification (CAC) Agatston score ≥ 300 has been associated with adverse cardiovascular events & increased mortality. The purpose was to evaluate all-cause mortality rates in ESRD with diabetes.

Methods: 113 diabetic pts undergoing RRT had CAC scoring by sub-second gated helical CT standard Agatston scoring system, slice thickness 3mm. Patients were categorized into 3 groups according to CAC score: 0, 1-299, ≥ 300 (Low, Medium, High Risk). Survival of 3 groups was calculated using Kaplan-Meier curves for all-cause mortality for 5 year period after CAC. Unadjusted and risk-factor adjusted for age & length of time on dialysis Cox proportional hazard modeling was used to estimate time to all-cause mortality.

Results: 5 year survival was 92%, 60%, 46% for Low, Medium, High Risk CAC groups.

	Low (n=25)	Medium (n=46)	High (n=42)
Age, yrs	47 ±11	57 ±11*	61 ±9**
Months on Dialysis	40 ±35	23 ±20	40 ±35□
Mean ±SD, p<0.05 *Low vs Medium, **Medium vs High, □Medium vs High ANOVA			

There was a statistically significant difference between survival curves, Gehan-Breslow p = 0.031, but no difference between Medium & High Risk curves pairwise multiple comparison procedures Holm-Sidak method (p=0.1). Adjusting for covariates of age & length of time on dialysis at time of scan did not make a significant difference in survival curves, Age HR = 1.034 (0.99-1.07 95% CI), time on dialysis HR = 1.004 (0.99-1.01 95%).



Mortality in Medium & High groups was 40% & 50% while only 8% in low group.

Conclusions: Any level of CAC, regardless of severity, in HD pts with diabetes has a significant impact on survival. CAC might be useful predicting mortality in this population.

PUB710

Elevated Toll Like Receptor 4 Expression and Macrophage Infiltration Is Found in High Dose Vitamin D-Induced Non-Uremic Vascular Calcification Jianheng Zhou,^{1,2} Yuan Min Wang,¹ Helen Williams,³ Anne M. Durkan,¹ Geoff yu Zhang,¹ Huiling Wu,⁴ Andrew Sawyer,¹ Stephen I. Alexander,¹ David C. Harris,² Vincent W.S. Lee.² ¹Centre for Kidney Research, Children's Hospital at Westmead, Sydney, NSW, Australia; ²Centre for Transplantation and Renal Research, Univ of Sydney at Westmead Millennium Inst, Westmead, Sydney, NSW, Australia; ³Vascular Biology Research Centre, Surgery, Univ of Sydney, Westmead Hospital, Sydney, NSW, Australia; ⁴Transplant Research Group, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia.

Background: Vascular calcification is strongly associated with cardiovascular morbidity and mortality. Several studies have suggested that monocytes/macrophages are involved in arterial vascular calcification, while the involvement of the TLR4 pathway in vascular calcification has also been proposed.

Methods: Male C57BL/6 mice aged 8 weeks were injected with a high dose of vitamin D (50000IU/kg/day) subcutaneously for 3 days at 0, 24 and 48 hours. All mice were sacrificed 3 days after the final administration of vitamin D. Kidneys were assessed histologically. Whole aortas were dissected. Macrophage infiltration and TLR4 expression was assessed by immunohistochemistry and histology and vascular calcification by Von Kossa staining.

Results: High dose vitamin D treatment did not induce kidney fibrosis or injury in C57BL/6 mice within the short time frame, as assessed by GT fibrosis score and PAS tubular damage score. High dose vitamin D treated mice demonstrated significantly higher calcium deposition in the aortic arteries (17.45% of vessel area) compared to controls (1.2% p<0.05). This was accompanied by a greater level of macrophage infiltration and TLR4 expression in these arteries compared to controls.

Conclusions: Accelerated vascular calcification was induced in mice with high dose vitamin D treatment. These data also identify a potential role for macrophages and the TLR4 pathway in vascular calcification.

PUB711

Lack of Correlation of Pyrophosphate Levels with Survival and Coronary Artery Calcification in Hemodialysis Patients Ramin Tolouian,¹ Sean M. Connery,² ¹Internal Medicine, Div of Nephrology, Eastern Virginia Medical School; ²Internal Medicine, Texas Tech Univ HSC El Paso.

Background: Vascular calcification is an important predictor of cardiovascular mortality in ESRD. Decreased levels of inorganic pyrophosphate (PPI) are thought to increase vascular calcification. The purpose of this study was to evaluate the association of PPI & coronary calcification scores in maintenance HD patients and all-cause mortality over 5 years.

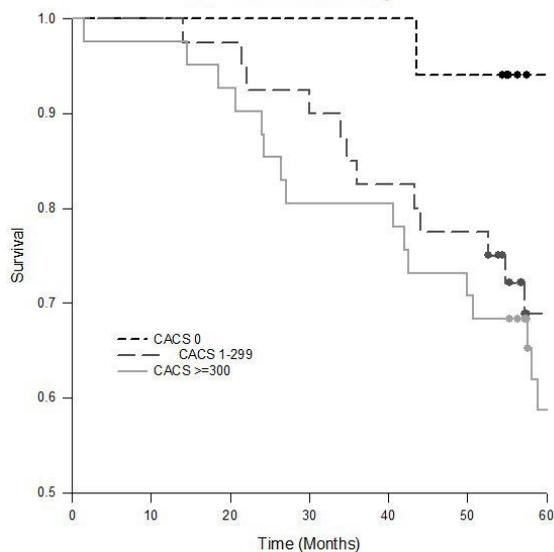
Methods: 98 maintenance HD patients were studied (mean ±SD): Age (yr.) 57 ±10.7, HD vintage (month) 36 ±37.6. Platelet free plasma PPI was measured by radiometric, enzymatic method as described by Tolouian. Coronary arterial calcification score (CACS) was measured by sub-second gated helical computed tomography with an Imatron C-150 XL ultra fast CT scanner using a standard protocol for vascular calcification. Patients were categorized into 3 groups according to their CAC score: 0, 1-300, and > 300.

Results:

	CACS 0 (n=17)	CACS 1-299 (n=40)	CACS ≥300 (n=41)
PPI (µM)	1.49 ±0.37	1.60 ±0.56	1.56 ±0.46
Age (yrs)	51 ±11.0	58 ±11.3	60 ±9.0*
Months on HD	32 ±27.2	25 ±21.5	47 ±49.5 ‡
* p<0.5 Low vs High, ‡Medium vs High ANOVA, Dunnett T3			

The covariate PPI had no significant effect on the hazard rate, log rank p=0.61. After adjusting for covariates of PPI, age, length of time on HD at time of measurement the log rank statistic for the survival curves is not great enough to exclude the possibility that the difference is due to random sampling variability; there is not a statistically significant difference (P = 0.614).

Kaplan-Meier Survival Analysis All-Cause Mortality



Conclusions: The difference in 5 year survival rate in dialysis patients based on the severity of vascular calcification is not influenced by pyrophosphate levels. This supports the multi-factorial nature of vascular calcification.

PUB712

Aortic Artery Calcification and Cardiac Valve Calcification Is Associated with Mortality in Chinese Hemodialysis Patients: A 3.5 Year Follow-Up
 Xiaonong Chen,¹ Zijin Chen,¹ Xiaobo Ma,¹ Bei Ding,² Huawei Ling,² Zhongwei Shi,³ Nan Chen.¹ ¹*Nephrology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ, Shanghai, China;* ²*Radiology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ, Shanghai, China;* ³*Cardiology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ, Shanghai, China.*

Background: Aim to investigate the relationship among aortic artery calcification(AAC), cardiac valve calcification(CVC) and mortality in maintenance haemodialysis(MHD) patients.

Methods: The study included 110 MHD patients. All MHD patients were treated in Shanghai Ruijin Hospital in July 2011. Follow-up these patients for 42 months.

Results: Totally 110 MHD patients were involved in this study. 64(58.2%) patients were male, and the mean age was 55.2±15.0 years old, the mean dialysis duration was 41.7±38.1 months. 25.5% patients had cardiac valve calcification, while 61.8% had visible calcification. After 42 months follow-up, 26(22.7%) patients died, including 16 cases death from cardiovascular events, 5 cases respiratory failure, 3 cases tumor metastasis, 1 case deep venous thrombosis and 1 case abandon treatment. Kaplan-Meier analysis showed that patients with AAC or CVC had a significant greater number of all-cause and cardiovascular deaths than those without. In multivariate analyses, the presence of AAC was a significant factor associated with all-cause mortality (HR 3.149, P=0.025) in addition to lower albumin level and lower 25(OH)D level. The presence of CVC was a significant factor associated with cardiovascular mortality (HR 3.800, P=0.029) in addition to lower albumin level and lower 25(OH)D level.

Table1. multivariate Cox proportional hazards analysis for all-cause mortality

Cox proportional hazards model			
	Hazard Ratio	95% Confidence Interval	P
Sex (male vs female)	1.673	0.634-4.417	0.299
Age (/1 y)	1.034	0.992-1.078	0.112
ALB (/1g/L)	0.820	0.725-0.927	0.002
25(OH)D (/1nmol/L)	0.981	0.965-0.998	0.024
CVC (presence vs absence)	1.563	0.637-3.836	0.330
AAC (presence vs absence)	3.149	0.889-11.159	0.025

Table2. multivariate Cox proportional hazards analysis for cardiovascular mortality

Cox proportional hazards model			
	Hazard Ratio	95% Confidence Interval	P
Age (/1 y)	1.008	0.975-1.062	0.757
ALB (/1g/L)	0.847	0.728-0.984	0.030
25(OH)D (/1nmol/L)	0.962	0.941-0.984	0.001
CVC (presence vs absence)	3.800	1.150-12.558	0.029
AAC (presence vs absence)	2.391	0.631-9.060	0.200

Figure1. The Kaplan-Meier analysis of all-causemortality (P=0.002 and P=0.001)

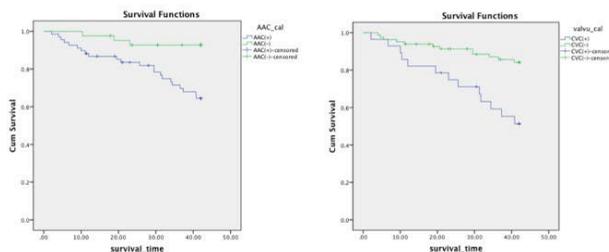
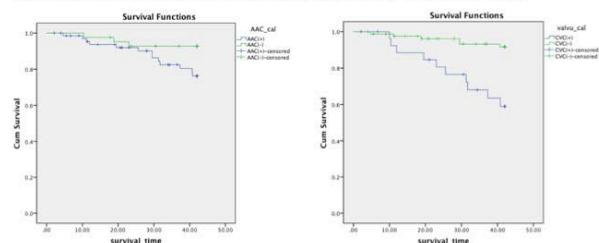


Figure2. The Kaplan-Meier analysis of cardiovascular mortality (P=0.049 and P<0.001)



Conclusions: The presence of AAC and CVC were independently associated with mortality in MHD patients. Regular follow-up by X-ray and echocardiography could be useful method to stratify mortality risk in MHD patients.

Funding: Government Support - Non-U.S.

PUB713

Beneficial Effect of the Vasopressin AV1a and AV2 Receptor Blocker Conivaptan (C) on the Renal Alterations Resulting from Mild Heat-Induced Dehydration (MHID) and Rehydration with a 10% Fructose (F) Beverage
 L. Gabriela Sanchez-Lozada,¹ Fernando E. Garcia-arroyo,¹ Monica Gabriela Blas-Marron,¹ Jose Pedraza-chaverri,² Cecilia Zazueta,³ Magdalena Cristobal,¹ Edilia Tapia.¹ ¹*Renal Physiopathology, INCICH, Mexico City, DF, Mexico;* ²*Biology, UNAM, Mexico City, DF, Mexico;* ³*Cardiovasc BioMed, INCICH, Mexico City, DF, Mexico.*

Background: The aims of this study were: 1. To define a possible synergistic effect between fructose and vasopressin during MHID, and 2. To evaluate the potential therapeutic benefit of C (3mg/kg BW) on this condition.

Methods: Six groups of male Wistar rats were MHID (37°C/ 1 h/day) and rehydrated with the selected beverage during 30 days: Water (W)+Veh, W+C, F+Veh, F+C, Stevia (S)+Veh and S+C. A group of normal control (NC) rats was studied as reference. After 30 days plasma and urine parameters were evaluated, renal cortex mitochondria were isolated and respiratory control rate (RCR) was evaluated with malate/glutamate (M/G) and succinate/rotenone (S/R) substrates.

Results:

Group/parameter	POsm (mOsm/kg)	PCr (mg/dL)	PCo-peptin (ng/mL)	RenalOx-Prot (nM/mg prot)	Urine NAG	RCR M/G	RCR S/R
NC	295± 4	0.7± .1	0.03± .01	5± 4	0	4.4± 0.2	3.4± 0.2
W+V	303± 4	0.8± 0.1	24± 3	16± 3	0.51± 0.03	3.9± 0.3	3.2± 0.1
W+C	301± 4	0.8± 0.1	24± 2	14± 1	0.41± 0.02	3.9± 0.2	3.4± 0.2
F+V 317± 4 1.1± 0.1 85± 7				49± 3	1.1± 0.1	3.6± 0.3	2.5± 0.2
F+C	308± 3 ^{oo}	0.8± 0.1 ^{ooo}	85± 4	33± 3 ^{oooo}	0.72± 0.3 ^{oooo}	3.6± 0.3	3.4± .3 ^{oooo}
S+V	303± 3	0.7± 0.1	16± 2	11± 1	0.42± 0.04	4.0± 0.3	3.1± 0.2
S+C	304± 4	0.8± 0.1	16± 2	12± 2	0.41± 0.02	4.0± 0.2	2.9± 0.2
BEVERAGE	****	****	***	****	****	**	**
TX	*			****	****		****
INTERACTION	*	***		****	****		****

Oxprot= oxidized proteins; °p<0.05 vs V; °°p<0.01 vs V; °°°p<0.001 vs V; °°°°p<0.0001 vs V.

Conclusions: These data suggest a crosstalk between F and vasopressin on this particular condition. In addition, C treatment prevented renal and mitochondrial alterations induced by rehydration with F.

Funding: Pharmaceutical Company Support - Danone Nutricia Research

PUB714

Lack of Aquaretic Effects of the Kappa Opioid Agonist Nalbuphine following Multiple Ascending Oral Doses in Healthy Volunteers Amale Hawi,¹ Thomas Sciascia,² Vandana S. Mathur.³ ¹Hawi Consulting, Ridgefield, CT; ²Trevi Therapeutics, New Haven, CT; ³Mathur Consulting, Woodside, CA.

Background: Nalbuphine is a mixed μ-antagonist and κ-agonist opioid drug that may suppress itch in hemodialysis patients with pruritus following oral administration of nalbuphine HCl extended release (ER) tablets. However, as a class, kappa opioid agonists have aquaretic effects in both animals and humans, which can be treatment-limiting. In this Phase 1 study, the potential of nalbuphine to induce aquaretic effects was explored in healthy subjects.

Methods: Healthy male and female subjects (n=9) were administered oral doses of nalbuphine escalated every 2-3 days from 30 mg QD on Day1 to 30 mg BID, 60 mg BID, 120 mg BID, and 180 mg BID over a 2-week period. Urine output and vital signs were measured pre-treatment and at multiple time points on Days -1 through 14.

Results: Repeated measurements of urine volume with progressively higher nalbuphine doses over the 6-fold dose range showed no evidence of increased urine output related to dose or duration of time on nalbuphine. Urine specific gravity remained within the normal range (1.001-1.03) and did not decline in any subject during treatment. None of the subjects developed hypernatremia nor was there a trend of rising serum sodium with all values remaining within the normal range. There were no dose-related reductions in blood pressure and none of the subjects developed hypotension. The mean systolic blood pressure remained consistently in the 108–128 mmHg range. Likewise, heart rate remained normal throughout the study with no HR >73 beats per minutes.

Conclusions: There was no evidence of an aquaretic effect at nalbuphine oral doses up to 180 mg BID in healthy subjects, the most sensitive population in which such effects may be observed.

Dose (mg) AM/PM	Study Day	24-hour Urine Volume (L)	Serum Na (mEq/L)
0	-1	-	139.8 (1.56)
30/0	1	2.7 (1.5)	-
30/60	4	3.1 (1.6)	-
60/60	6	3.0 (2.0)	-
60/120	7	-	140.7 (1.41)
120/120	9	3.2 (1.6)	-
180/0	13	3.4 (2.3)	-
0	14	-	141.0 (1.60)

Dosing from 30 mg QD Day1 to BID 30 mg (Day2) to 60 mg (Day4, PM) to 120 mg (Day7, PM) to 180 mg (Day10, PM) to 180 mg QD on Day13

PUB715

Urinary Excretion Pattern of Exosomal Aquaporin-2 in Nephronophthisis Mice Hiroko Sonoda, Nobuyuki Mikoda, Sayaka Oshikawa, Masahiro Ikeda. *Veterinary Pharmacology, Univ of Miyazaki, Miyazaki, Japan.*

Background: Nephronophthisis (NPHP), an inherited disorder, is the most frequent genetic cause of end-stage renal failure in children. So far, twenty responsible genes have been identified, including the *NPHP3*. The pcy mouse with missense mutation in *Nphp3* gene orthologous to human *NPHP3* is an animal model of NPHP. So far, renal aquaporin-2 water channel (AQP2) expression in pcy mice has been shown to be up-regulated, accompanied by both polyuria and urinary concentrating defect. Urinary exosomes, known to be released into urine from epithelial cells in all nephron segments, have been reported to selectively contain renal functional proteins, including AQP2. In this study, we examined whether the level of urinary exosomal AQP2 excretion was altered in pcy mice.

Methods: Urine samples were collected for 20 hrs from either pcy mice or the control DBA/2 mice, at 7, 16, and 21 weeks of age, respectively. Urinary exosomes were isolated by differential centrifugation. The levels of urinary exosomal and renal protein were analyzed by immunoblotting.

Results: Although urinary volume in pcy mice was not altered at 7 weeks of age, those were significantly increased at 16 and 21 weeks of age in comparison with age-matched control mice. Urine osmolality was significantly decreased in pcy mice at all ages examined in this study. Urinary exosomal AQP2 protein levels in pcy mice were dramatically increased at 16 weeks of age, whereas those at 7 and 21 weeks of age were not significantly increased. Similarly, a transient increase in urinary excretion of exosomal tumor susceptibility gene 101 protein (TSG101), frequently used as an exosome marker protein, was observed in pcy mice at 16 weeks of age. The levels of renal AQP2 protein in pcy mice at 16 weeks of age or older were significantly higher than those in the control mice.

Conclusions: Urinary exosomal AQP2 protein excretion was transiently increased in pcy mice and this increase appeared to be related to both the number of exosomes excreted into the urine and its renal abundance.

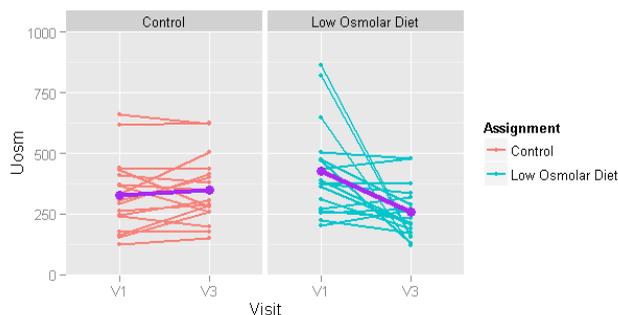
PUB716

Low Osmolar Diet and Adjusted Water Intake for Vasopressin Suppression in ADPKD Osama W. Amro,^{1,2} Jessica K. Paulus,² Farzad Noubary,³ Ronald D. Perrone.^{1,2} ¹Nephrology, Tufts Medical Center; ²Tufts Univ School of Medicine.

Background: Autosomal dominant polycystic kidney disease (ADPKD) affects 12.5 million persons worldwide and accounts for 10% of patients with end-stage renal disease in the United States. Vasopressin is a known detrimental factor in disease progression and cyst enlargement.

Methods: This randomized controlled trial examined the effect of a novel approach of combining low osmolar diet and adjusted water intake on vasopressin, measured by change in urinary osmolality, and total daily urinary solute in 34 patients with early ADPKD. Participants were randomized to receive a low osmolar diet (low sodium (1500 mg/day), low protein (0.8 gram/kg body weight) diet) followed by adjusted water intake to achieve a urine osmolality of 280 mOsm/kg versus no intervention for two weeks duration, with equal (1:1) allocation. Permuted block randomization was performed within strata of age and sex.

Results: Baseline characteristics of the two groups were similar. Compared with baseline, the mean urine osmolality significantly declined from 426 (±193) to 258 (±110) mOsm/kg (P=0.007) but not in the control group. At 2 weeks, levels significantly differed between groups (P=0.04).



Total urinary solute decreased only in the low osmolar diet group and significantly differed between groups at 2 weeks (P=0.03). The two week adherence rate to diet and adjusted water intake was 70% with a mean water prescription of 2.6 liters/daily.

Conclusions: We identified a novel step wise dietary intervention that led to significant reduction in vasopressin as measured by reduction in 24 hour urine osmolality in patients with early ADPKD. Furthermore, this dietary intervention led to significant reduction in water required for vasopressin suppression. Long-term studies are needed to evaluate diet and adjusted water intake adherence, and determine if the reduction in vasopressin slows ADPKD progression.

Funding: NIDDK Support

PUB717

CRISPR-Cas9-Mediated Deletion of Myosin Light Chain Kinase in Cultured Collecting Duct Cells Kiyoshi Isobe, Viswanathan Raghuram, Pablo Sandoval, Chin-Rang Yang, Chung-Lin Chou, Mark A. Knepper. *Systems Biology Center, NHLBI, NIH.*

Background: Regulation of osmotic water transport in the renal cortical collecting duct by vasopressin is in part dependent on membrane trafficking of aquaporin-2 (AQP2) to the apical plasma membrane of the principal cells. It is known that trafficking of AQP2 is in part dependent on changes in AQP2 phosphorylation. We previously proposed that AQP2 trafficking is dependent on the protein kinase Myosin Light Chain Kinase (MLCK; gene symbol: *Mylk*). Here, we test the role of MLCK in AQP2 phosphorylation and trafficking, utilizing CRISPR-Cas9 generated mutations in MLCK in cultured mouse mpkCCD cells.

Methods: We used CRISPR-Cas9 genome-editing to mutate the catalytic region of the *Mylk* gene. Clones were generated with 4 different guide RNAs and were characterized by genomic sequencing and immunoblotting. Effects of the deletions were assessed by immunoblotting and immunofluorescence immunocytochemistry of AQP2.

Results: Multiple clones with mutations in the catalytic domain of MLCK were generated. Western blots showed absence of MLCK protein in MLCK-deleted clones. Controls were clones that express MLCK without mutations in the catalytic domain, but may contain off-target modifications. AQP2 protein abundance varied over a broad range, among all MLCK-deleted (n=4) and control (n=4) lines, but, on average, was not affected by the deletion. Immunocytochemistry showed that vasopressin stimulates redistribution of AQP2 to the apical plasma membrane in both control cells and MLCK-deleted cells. Vasopressin-dependent phosphorylation of AQP2 at Ser256 and Ser269 was not significantly reduced in MLCK-deleted cells.

Conclusions: The results demonstrate the feasibility of CRISPR-Cas9-mediated genome editing in mouse mpkCCD cells. Our experiments in mouse cultured collecting duct cells provide evidence that vasopressin-induced phosphorylation of AQP2 and redistribution of AQP2 to the apical plasma membrane can occur independently of myosin light chain kinase.

Funding: Other NIH Support - NHLBI Intramural

PUB718

The PDZ Domain-Containing Protein Harmonin Is a Binding Partner of Sodium-Coupled Monocarboxylate Transporter 2 Nobuyuki Onizawa,^{1,2} Naoyuki Otani,¹ Promsuk Jutabha,¹ Motoshi Ouchi,¹ Hajime Hasegawa,² Naohiko Anzai.¹ ¹*Dept of Pharmacology and Toxicology, Dokkyo Medical Univ School of Medicine, Mibu, Tochigi, Japan;* ²*Dept of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical Univ, Kawagoe, Saitama, Japan.*

Background: Lactate is freely filtered and extensively reabsorbed in the proximal tubule to prevent the loss of this valuable metabolite from the body. Sodium-coupled monocarboxylate transporter SMCT2 (SLC5A12) mediates the transport of pyruvate, nicotinate and lactate (Gopal et al., *BBA*. 2007). In contrast to its well characterized transport properties, less information is available on the regulatory mechanism of SMCT2. The C-terminal domain of SMCT2 is exposed to the cytoplasmic compartment and contains the PDZ motif, one of the famous protein-protein interaction modules, suggesting that it may interact with PDZ proteins.

Methods: We used the yeast two-hybrid screening to investigate the putative SMCT2-associated proteins that modulate its transport function. Using the SMCT2 C-terminal tail (SMCT2-CT) as bait, we performed a yeast two-hybrid screen of a cDNA library constructed from the human adult kidney. Next, to further confirm the interaction between SMCT2 and harmonin, we performed a co-immunoprecipitation study using anti-harmonin antibodies.

Results: In the yeast two-hybrid screening, 34 positive clones were obtained from a total of 1.2×10^7 independent colonies screened. Of these, 8 yielded an identical sequence encoding the gene for the PDZ protein PDZK1 (manuscript in preparation), and 1 yielded an identical sequence encoding the gene for the PDZ protein Harmonin. Deletion of C-terminal PDZ motif abolished the interaction with harmonin in the yeast two-hybrid system. Furthermore, co-immunoprecipitation studies revealed that the SMCT2 interacted directly with harmonin.

Conclusions: Harmonin was identified as the binding partner for SMCT2. The elucidation of these interactions may further our understanding of the function and regulation of monocarboxylate (e.g., lactate) transport in the human kidney.

PUB719

Stimulation of V1a Receptor Increases Renal Uric Acid Clearance via ABCG2 Transporter – Insight into Hypouricemia in SIADH Kei Taniguchi, Yoshifuru Tamura, Shigeru Shibata, Shunya Uchida. *Dept of Internal Medicine, Teikyo Univ School of Medicine, Itabashi, Tokyo, Japan.*

Background: Hypouricemia seen in the subjects with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is pathognomonic but the mechanism of hypouricemia remains to be clarified. V2 receptor agonist ‘desmopressin’ induced hyponatremia but not hypouricemia in human unlike SIADH (G Decaux, *JASN*, 1996). Therefore, we hypothesized that V1 receptor but not V2 receptor may play a role in inducing hypouricemia. In the present study, we examined the changes in serum uric acid, urinary uric acid excretion and expression of uric acid transporters in response to V1a receptor agonist ‘terlipressin’.

Methods: Terlipressin was subcutaneously infused by osmotic mini pump to 7-week-old male Wistar rats (n = 9). Control rats were infused with normal saline (n = 9). The rats were sacrificed to obtain renal cortical tissues at 3 days.

Results: Serum uric acid significantly decreased and the excretion of urinary uric acid significantly increased in the terlipressin group. Thus, fractional excretion of uric acid increased from $1.20 \pm 0.28\%$ to $3.10 \pm 0.56\%$ ($P < 0.001$). The expression of ATP-binding cassette transporter, sub-family G, member 2 (ABCG2) significantly increased in the terlipressin group. Other uric acid transporters did not significantly change.

Conclusions: These results suggest that stimulation of V1a receptor increases renal uric acid clearance probably via upregulation of ABCG2, leading to hypouricemia seen in SIADH patients.

PUB720

Fluorescein Angiography and the Kidney: Friend or Foe? Mohamed E. Elraggal,¹ Ahmed Fathy Elkerai,² Ahmed M. Abdelhadi,³ Ashraf Nabil Abdalla.⁴ ¹*Nephrology, Kidney and Urology Center, Alexandria, Egypt;* ²*Nephrology, Alexandria Univ, Alexandria, Egypt;* ³*Ophthalmology, Alexandria Univ, Alexandria, Egypt;* ⁴*Pharmacology, Umm Al-Qura Univ, Saudi Arabia.*

Background: Fluorescein angiography (FA) is an indispensable tool for diagnosis and management of diabetic retinopathy (DR). However, safety of fluorescein sodium on renal functions is not fully understood.

Methods: 100 type 2 diabetic patients presenting to the ophthalmology outpatient clinic at Alexandria main university hospital were included in our study. Serum creatinine and cystatin-C were measured just before and 2 days after FA. Urinary NGAL as a tubular biomarker was measured also before and 4 hours after FA. Renal injury was defined as 25% increase in serum creatinine or cystatin-C.

Results: The mean of serum creatinine was 0.99 ± 0.36 mg/dl and 1.0 ± 0.36 mg/dl before and after FA respectively with no statistically significant change ($P=0.061$). Only one patient (out of 100) experienced more than 25% rise in serum creatinine from baseline. Serum Cystatin-C and urinary NGAL increased significantly after FA ($P>0.001$). Mean of serum Cystatin-C was 0.89 ± 0.34 mg/l and 0.95 ± 0.36 mg/l before and after FA respectively. 11 patients experienced more than 25% rise in serum cystatin-C from baseline. Mean of urinary NGAL was 21.78 ± 23.90 ng/ml and 27.15 ± 28.17 ng/ml before and after FA respectively.

Conclusions: Using ordinary renal biomarkers as serum creatinine, FA was thought to be kidney friendly. Nevertheless, using more sensitive early biomarkers as serum cystatin-C and urinary NGAL, FA is not as innocent as previously thought. A creatinine negative, biomarker positive change may implicate a form of subclinical AKI.

PUB721

Transcultural Adaptation and Validation of the Mexican Version of the Kidney Disease Questionnaire KDQOL-SF36 Version 1.3 Edgar Dehesa Lopez,¹ Ricardo Correa-Rotter,² David Olvera,³ Carlos Gonzalez Parra,⁴ Rafael Baizabal.⁵ ¹*Dept of Nephrology, Research and Teaching Center in Health Sciences (CIDOCS), Culiacan, Sinaloa, Mexico;* ²*Dept of Nephrology, National Inst of Medical Sciences and Nutrition Salvador Zubiran, Mexico, D.F, Mexico;* ³*Dept of Nephrology, Hospital ISSSTE, Ciudad Valles, San Luis Potosí, Mexico;* ⁴*Department of Nephrology, Christus Murgueza UPAEP, Puebla, Mexico;* ⁵*Dept of Nephrology, Hospital ISSSTE, Xalapa, Veracruz, Mexico.*

Background: The evaluation of health-related quality of life through the application of efficient, reliable and simple instruments is a relatively new concept in the practice of nephrology. The aim of the study was to translate the Kidney Disease Quality of Life Short Form 36 KDQOL-SF36 v1.3 questionnaire into the Spanish language, to adapt it culturally and to validate it in the Mexican population.

Methods: The translation, transcultural adaptation and validation of the Mexican version of KDQOL-SF36 was performed according to the recommendations of RAND Health. The validity was evaluated using Cronbach's α . The test-retest reliability was evaluated using interobserver and intraobserver intraclass correlation coefficients (ICCs).

Results: The questionnaires were applied to 194 Mexican patients with end stage chronic kidney disease in chronic hemodialysis. The average age was 54 ± 16 years, and 54.6.1% were males. The Mexican version proved reliable with intra- and interobserver ICCs ≥ 0.7 in most of the dimensions evaluated, with a range between 0.5 and 0.9. The validity of the questionnaire was acceptable, with an internal items-dimensions consistency between 0.4 and 0.9, dimensions-total of 0.725 and items-total of 0.921.

Table 1. Reliability and construct validity of the Mexican version of KDQOL-SF36 v1.3.

Scales	ICC (n=18) Interobserver	ICC (n=18) Intraobserver	Cronbach α (n=194)
KDQOL component			
Symptom/problem list	0.882	0.878	0.818
Effects of kidney disease	0.793	0.926	0.736
Burden of kidney disease	0.850	0.886	0.736
Work status	0.853	0.895	0.445
Cognitive function	0.733	0.845	0.669
Quality of social interaction	0.781	0.731	0.479
Sexual function	0.930	0.853	0.886
Sleep	0.719	0.916	0.636
Social support	0.829	0.600	0.846
Dialysis staff encouragement	0.641	0.693	0.811
Patient satisfaction	0.687	0.900	-
SF36 component			
Physical functioning	0.888	0.892	0.937
Role physical	0.964	0.975	0.884
Pain	0.742	0.930	0.812
General health	0.502	0.628	0.638
Emotional well-being	0.865	0.937	0.821
Role emotional	0.761	0.631	0.701
Social function	0.715	0.865	0.609
Energy/fatigue	0.798	0.932	0.762

ICC = Intraclass Correlation Coefficient.

Conclusions: The psychometric properties evaluated in the Mexican version of the KDQOL-SF36 v1.3 demonstrated that it is a valid and reliable instrument, with psychometric results similar to the original version.

PUB722

Urinary Neutrophil Gelatinase Associated Lipocalin Beyond AKI, Relation to Renal and Patient Survival Ahmed Fathy Elkeraie,¹ Mohammed Megahed,² Ahmed Elkhodary,² *¹Nephrology, Alexandria Univ, Alexandria, Egypt; ²Critical Care, Alexandria Univ, Alexandria, Egypt.*

Background: Neutrophil gelatinase-associated lipocalin (NGAL) has been postulated as an early, sensitive, non-invasive biomarker for acute kidney injury (AKI). The aim of this study was to evaluate urinary NGAL levels as a predictor of early AKI (first 5 days) in severely traumatized patients associated with hemorrhagic shock.

Methods: This is a prospective observational study on 57 adult trauma patients presented with severe trauma (ISS ≥ 16) and hemorrhagic shock to the units of Critical Care Medicine Department in Alexandria Main University Hospital and Mostafa Kamel Armed Forces Hospital. Urinary NGAL was measured upon admission and 48 hrs after trauma. Presence of AKI was defined by Acute Kidney Injury Network (AKIN) criteria.

Results: Using AKIN criteria, a total of 13 patients were identified with AKI (incidence of 37.14%). Those who subsequently developed AKI had a striking rise in urinary NGAL early after trauma and a sustained increase over next 48 hrs. The urinary NGAL levels of the AKI group (group A) were significantly higher than non AKI (group B) both on admission and 48 hrs later. For cut-off point >29 ng/mL, urinary NGAL 48 hrs after trauma sensitivity, specificity, positive and negative predictive values were 84.62, 95.45, 91.67 and 91.30, respectively. In the analysis of urinary NGAL (on admission) performance for predicting clinical outcomes; Using a cutoff value of 30 ng/mL the area under the receiver-operating characteristic curve for in-hospital mortality and the need for RRT during the first week was 0.768, 0.903 respectively. Odds of in-hospital mortality increased by 12.7% for every 30ng/ml increase in urinary NGAL on admission, confirming the usefulness of NGAL in predicting clinical outcomes.

Conclusions: Urinary NGAL is an early and reliable predictive marker of AKI in severely traumatized patients presented with hemorrhagic shock and also a predictor of adverse clinical outcomes. The important clinical utility of this biomarker in patient care, might facilitate early renal protective interventions with the hope of improvement in the renal and patient outcomes.

PUB723

Epidemiology and Prognosis of Community Acquired Acute Kidney Injury versus Hospital Acquired Acute Kidney Injury Edgar Dehesa Lopez,¹ Melissa Rodriguez,² Rodolfo Radames Salas Zazueta,² Daniel Antonio Hernandez Quintero,² Hector Guillermo Peña Peredia,² Berenice Tamayo Garcia,² *¹Dept of Nephrology, Research and Teaching Center in Health Sciences (CIDOCS), Culiacan, Sinaloa, Mexico; ²Research and Teaching Center in Health Sciences (CIDOCS), Culiacan, Mexico.*

Background: The epidemiological characteristics and prognosis of patients with community acquired acute kidney injury (C-AKI) vs hospital acquired acute kidney injury (H-AKI) have not been thoroughly studied.

Methods: A total of 192 patients admitted to internal medicine service were studied. AKI was diagnosed and classified at time of admission (C-AKI) or posteriorly during hospitalization. AKI was defined according to the Acute Kidney Injury Network (AKIN) and serum sCr. The etiology, severity and evolution of the AKI episodes were compared among patients with C-AKI and H-AKI.

Results: C-AKI incidence was 22.4% (n=43) and H-AKI was 5.7% (n=11), giving an overall incidence of 28.1%. AKIN 1 stage was present in 51.7%, AKIN 2 in 12.9% and AKIN 3 in 35.4%. Renal factors were the most frequent etiology of AKI in 55.6%, prerenal in 38.9% and obstructive in 5.6%. Oliguric AKI was observed in 25.9%.

Hemodialysis was required in 9.3% of cases. The recovered AKI was observed in 75.9% at the time of hospital discharge. The length of hospital stay (9±9 vs 7±6 days; p<0.05) and mortality (18.5 vs 7.2%; p=0.02) were greater in patients with AKI compared with patients without AKI. Patients with H-AKI had a longer hospital stay (15±12 vs. 8±8; p<0.05) and a statistical trend to higher mortality (36.4% vs 14%; p=0.08) in relation to patients with C-AKI.

Table 1. Clinical and prognostic differences between C-AKI vs H-AKI

	C-AKI		H-AKI		P
	n=42	%	n=11	%	
AKI severity					
Stage 1	17	39.5%	2	18.2%	NS
Stage 2	5	11.6%	5	45.5%	0.03
Stage 3	21	48.8%	4	36.4%	NS
Etiology of AKI					
Prerenal	15	34.9%	3	27.3%	
Renal	25	58.1%	8	72.7%	0.54
Postrenal	3	7.0%	0	0.0%	
Oliguria	8	18.6%	6	54.5%	0.01
Hemodialysis	5	11.6%	0	0.0%	0.23
Discharged with recovered AKI	33	76.7%	8	72.7%	0.78
Etiology of renal AKI:					
Acute tubular necrosis	19	76.0%	6	75.0%	
Glomerulonephritis	6	24.0%	2	25.0%	0.95
Nephrotoxic drugs	0	0.0%	0	0.0%	
AKI days	5±4		5±3		NS

AKI= Acute kidney injury; C-AKI = Community acquired acute kidney injury; H-AKI= Hospital acquired acute kidney injury

Conclusions: AKI was a frequent diagnosis on hospital admission or during hospitalization. C-AKI and H-AKI added a negative effect on the prognosis. H-AKI episodes were more severe and were associated with a longer hospital stay and an statistical trend in mortality in comparison with C-AKI.

PUB724

Drug Utilization Patterns and Factors Associated with Acute Kidney Injury in an Intensive Care Unit at a Brazilian Public Hospital – A Prospective Cohort Study Danielly Botelho Soares,¹ Gabriela Rebouças Botelho,¹ Flávia Fialho Girundi,¹ Fernando Antonio Botoni,² Maria Auxiliadora Parreiras Martins,¹ *¹School of Pharmacy, Univ Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; ²School of Medicine, Univ Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.*

Background: Acute kidney injury (AKI) is associated with a significant increase in morbidity, mortality and health care costs. In intensive care units (ICU), the cause of AKI is commonly associated with multiple factors, among which the use of potentially nephrotoxic drugs is often neglected as a preventable cause of AKI.

Methods: This is a prospective cohort study that evaluated the AKI as a primary outcome in ICU patients at a teaching hospital in Belo Horizonte, Brazil. Length of stay greater than 24 hours and hospital stay lower or equal to 7 days were evaluated for potential eligibility. To be enrolled, patients should not present kidney dysfunction at the time of ICU admission.

Results: Data collection was performed from October 2014 to February 2015, including 122 patients, mostly originated from the surgical department (46.7%). An average of 22.0 ± 9.4 drugs was prescribed and 2-24 potentially nephrotoxic drugs were used per patient. Mechanical ventilation was required for 67.2% of patients and at least one vasoactive drug was used in 68.0% of cases. An incidence of AKI was observed in 23.8% of patients, among them 34.5% required dialysis, 24.1% reached the third stage of AKI and 31.8% were referred to additional treatment after ICU discharge. Eleven (9%) patients died and 63.6% of them developed AKI. The bivariate analysis showed that age (p = 0.006) and APACHE II score (p = 0.003) had higher median among patients who developed AKI compared to those who did not develop AKI. In the logistic regression, the number of medications (OR: 1.15; 95% CI: 1.05 to 1.26) presented a statistically significant correlation with the development of AKI.

Conclusions: These results demonstrate that the identification of factors associated with AKI in ICU patients is very important for the early identification of renal dysfunction induced by drugs, providing conditions for appropriate prevention and treatment of the extent of kidney damage.

PUB725

Clinical, Dialytic and Laboratorial Factors Associated with Poor Health Related Quality of Life in Mexicans Hemodialysis Patients

Edgar Dehesa Lopez,¹ David Olvera,² Carlos Gonzalez parra,³ Rafael Baizabal.⁴

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Background: The evaluation of health related quality of life (HRQOL) in hemodialysis patients has recently gained great importance because it has proven to be an independent predictor of clinical outcomes.

Methods: Cross-sectional study. The validated Mexican version of the KDQOL-SF36 v1.3 questionnaire were applied to 194 adult patients with ESRD on hemodialysis in different regions of Mexico. According to the global score of questionnaire, patients were grouped in: patients with poor HRQOL (global score below the median) and patients with good HRQOL (global score greater than the median). Logistic regression was used to investigate the effects of clinical, dialytic and laboratorial factors on HRQOL.

Results: The average age was 54+16 with 54.6.1% male. Comorbidities were: hypertension in 86.6%, diabetes mellitus 2 in 57.2% and dyslipidemia in 7.2%. The vascular access was a catheter in 55.2% and fistula in 44.8% of the cases. Diabetes mellitus and the use of catheters as vascular access were more frequent in patients with poor quality of life. On the other hand, phosphorus >5.5 mg/dl and albumin >4g/dl were more frequent in patients with good quality of life. There were no differences in age, KtV, hemoglobin and calcium between groups. Table 1 shown the clinical, dialytic and laboratorial factors studied in the multivariate logistic analysis.

Table 1-Multivariate logistic regression analysis of clinical, dialytic and laboratorial factors associated with poor HRQOL.

Variables	OR	CI 95%		p
		Lower	Upper	
Age (years)	1.02	0.99	1.05	0.23
Gender (male vs female)	0.87	0.40	1.89	0.73
Diabetes mellitus (yes/no)	1.35	0.56	3.24	0.50
Vascular access (catheter vs fistula)	3.03	1.30	7.09	0.01
Hemoglobin (<9 g/dl vs >9 g/dl)	1.23	0.46	3.26	0.68
Albumin (< 4 g/dl vs > 4 g/dl)	3.30	1.37	7.98	0.01
KtV (<1.4 vs >1.4)	1.02	0.40	2.60	0.97
Calcium (<8.5 mg/dl reference)				
Calcium (8.5-10 mg/dl)	1.56	0.65	3.78	0.32
Calcium (>10 mg/dl)	0.55	0.18	1.65	0.28
Phosphorus (<4.5 mg/dl reference)				
Phosphorus (4.5-5.5 mg/dl)	2.45	0.30	19.77	0.40
Phosphorus (>5.5 mg/dl)	1.15	0.14	9.28	0.90
Hemodialysis stay (months)	1.02	1.00	1.04	0.03

OR=odds ratio, CI=Confidence interval, HRQOL: Health related quality of life

Conclusions: The associated factors with poor HRQOL in Mexicans hemodialysis patients were: the time spent in hemodialysis, serum albumin <4 g /dl and use of catheter for vascular access.

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Mahmud, Farid H.	PUB305	Mammen, Cherry	SA-PO221		FR-PO441, SA-OR003, SA-OR006,	Marumo, Takeshi	FR-OR079
Mahnken, Jonathan D.	FR-PO753	Mamuya, Fahmy	SA-OR116		SA-OR019, SA-PO724	Maruyama, Hiroki	SA-PO043
Maia, Pedro	TH-OR060, FR-PO718	Mancia, Giuseppe	FR-OR043	Mariappan, Meenalakshmi M.		Maruyama, Noriaki	TH-PO650,
Maia, Sara	PUB194, PUB196	Mancini, Elena	FR-PO663		TH-PO297, SA-PO473		SA-OR029, SA-PO930
Maier, Barbara	TH-OR044	Mancini, Erika J.	FR-OR048	Mariat, Christopher R.	TH-PO730	Maruyama, Shoichi	TH-OR036,
Maier, Carolin	TH-PO832	Manda, Krishna K.R.	SA-PO081	Marier, J.F.	SA-PO854		TH-PO790, TH-PO912, FR-OR039,
Maier, Paula S.	FR-PO526	Mandai, Shintaro	TH-PO441,	Mariko, Anayama	TH-PO1020,		TH-PO217, FR-PO248, FR-PO870,
Maillard, Marc P.	TH-PO427		TH-PO605, SA-PO018		PUB595		FR-PO970, FR-PO999, FR-PO1024,
Maillard, Nicolas	TH-PO730	Mandart, Lise	TH-PO207, SA-OR031	Marin, Ethan P.	TH-PO222		SA-OR091, SA-PO411, SA-PO430,
Maio, Raffaele	TH-PO608	Mandayam, Sreedhar A.	TH-PO814,	Marin, Jesús P.	TH-PO053, PUB459		PUB703
Maisel, Alan S.	TH-PO081, PUB031		FR-PO014, FR-PO024, FR-PO1108	Marinaki, Anthony	FR-OR054	Maruyama, Toru	FR-PO536, SA-PO250
Majewska, Ewa	FR-PO538	Mandel, Ernest I.	SA-OR077	Maringer, Katherine V.	TH-PO046	Maruyama, Yukio	PUB329, PUB601
Majithia, Richa S.	TH-PO027	Mandelbrot, Didier A.	FR-PO1100	Marinho, Amadeu	PUB430	Maryan, Tracy	SA-PO786, PUB171
Major, Melissa	TH-PO653		SA-PO1055	Marino, Angela Maria	PUB524	Masajitis-zagajewska, Anna	TH-PO575
Mak, Robert H.	TH-PO554, FR-PO311	Mane, Gerta	TH-PO1043	Marino, Francesco	FR-PO588	Masakane, Ikuto	TH-PO946,
Makanjuola, David	TH-PO874,	Manfredi, Silvia Regina	FR-PO842, FR-PO843	Marino-Vazquez, Luvia A.	SA-PO959		TH-PO961, FR-PO807, FR-PO846,
	FR-PO724			Maristany, Daniela	TH-PO414		PUB329, PUB562, PUB566
Makary, Raafat Farag	SA-PO983	Mangier, Melanie	PUB069	Mark, Patrick B.	TH-PO888,	Masaki, Takao	TH-PO494,
Makino, Hirofumi	PUB156	Manhani, Maria Raquel	PUB564		TH-PO919, FR-PO747, FR-PO1045,		TH-PO817, TH-PO904, FR-PO133,
Makino, Yasushi	TH-PO1020, PUB595	Manickavasagam, Venkataraman			PUB297		FR-PO809, PUB129
Maki-Petaja, Kaisa	TH-PO423		TH-PO062	Marko, Lajos	FR-PO272	Masand, Anjali	SA-PO1071, PUB405
Makita, Minoru	PUB262	Manllo, John	SA-PO1079, SA-PO1080	Markossian, Talar	TH-OR117,	Masani, Naveed N.	TH-PO1053
Makita, Yuko	TH-PO735, FR-PO973,	Mann, Michelle C.	TH-PO914, PUB327		SA-PO725, SA-PO730	Mascio, Heather M.	SA-PO153
	FR-PO974	Manne, Madhuri	SA-PO081	Markowska, D.	PUB340	Maseki, Mari	TH-PO551, TH-PO950
Makri, Giouli	FR-PO960	Mannella, Valeria	TH-PO185	Marks, Stephen D.	SA-OR021,	Masengu, Agnes	TH-PO864
Makris, Angela	FR-PO730	Manning, Kelly E.	SA-PO596,		SA-OR022	Maser, Robin L.	TH-PO198
Malagoli, Andrea	PUB157		SA-PO597	Marlais, Matko	SA-OR021, SA-OR022,	Masereeuw, Rosalinde	TH-PO021
Malagrino, Pamela Araujo	SA-PO573	Manns, Braden J.	TH-PO924,		TH-OR038,	Masharani, Umesh	FR-PO651
Malas, Mohammed Said	FR-PO392		FR-PO634, FR-PO889, SA-OR101,		TH-PO032, TH-PO649, TH-PO936,	Mashhadian, Ardavan	TH-PO1039
Malat, PharmD, Gregory	SA-PO1075		SA-PO732		SA-PO537, SA-PO800, SA-PO824	Mashiba, Shinichi	TH-PO585
Malberti, Fabio	PUB540	Manns, Michael P.	FR-PO499	Marquardt, Andi	TH-PO367	Maskey, Dipak	TH-PO201, TH-PO223
Malbousson, Luiz M.	SA-PO192	Manoustathopoulou, Sotiria	TH-PO773	Marques, Igor	SA-PO563	Masola, Valentina	FR-PO1074,
Malcomson, Roger D.	FR-PO454	Manrique, Joaquin	FR-PO667, PUB140	Marques, Maria Guedes	TH-OR060,		SA-PO472
Malha, Line	FR-PO767, SA-PO910,	Mansfield, Nicholas D.	FR-PO413		FR-PO718	Mason, Darius	FR-PO916, FR-PO917,
	PUB359	Mansilla, M. Adela	FR-OR057	Marques, Rita D.	TH-PO426		PUB512
Malheiro, Jorge	PUB151	Manson, Lynn	SA-PO047	Marquis, Karine	PUB338	Mason, Sara	FR-OR057
Malheiros, Denise M.	TH-PO140,	Manson, Scott R.	TH-PO228, FR-PO274,	Marra, Amanda N.	FR-OR092,	Mason, Thomas G.	SA-PO901
	TH-PO146, TH-PO149, TH-PO166,		FR-PO951, SA-PO248		FR-PO190	Masoudi, Frederick A.	TH-PO613
	TH-PO167, TH-PO244, TH-PO761,	Mansour, Sherry	TH-PO1026,	Marron, Belen	TH-PO678, PUB118,	Massengill, Susan F.	TH-PO468,
	TH-PO762, FR-PO116, SA-PO443,		SA-PO136		PUB614		PUB144
	PUB424	Mansour, Wissam	SA-OR032,	Marschner, Julian A.	SA-OR074,	Massie, Allan	FR-OR072, FR-PO1050
Malhotra, Ashwani	TH-PO154,		SA-PO156		PUB080	Massy, Ziad	FR-PO1014, SA-OR006,
	TH-PO233, TH-PO234, TH-PO238,	Mansur, Juliana Busato	PUB202,	Marsh, Graham	TH-PO412		SA-PO726
	TH-PO245, TH-PO289, TH-PO290,		PUB663	Marshall, Mark R.	SA-PO833	Mast, Chris	TH-PO667
	TH-PO300, TH-PO304, TH-PO310,	Manunta, Paolo	TH-PO077,	Marshall, Sally M.	FR-PO635	Mastroianni-Kirsztajn, Gianna	
	FR-PO340, FR-PO421, FR-PO978,		TH-PO816, FR-PO078, FR-PO519,	Martens, Lisa P.	TH-PO196		SA-PO019, SA-PO1081, PUB202,
	SA-PO290, SA-PO291, SA-PO292,		FR-PO947, SA-PO500	Marti, Hans-Peter	TH-OR018,		PUB663
	SA-PO315, SA-PO325, PUB087	Mao, Juan	PUB195		SA-PO495, SA-PO515	Masuda, Masashi	TH-PO501
Malhotra, Atul	TH-PO081, SA-PO642,	Mao, Michael A.	TH-PO065,	Martin Alemany, Nadia	SA-PO603	Masuda, Satoshi	SA-PO549, PUB640
	PUB031		SA-PO094	Martin Moreno, Paloma L.	SA-PO195,	Masuda, Takahiro	SA-PO382,
Malhotra, Deepak K.	TH-PO447,	Mao, Xiaoyi	FR-PO277		PUB057, PUB059		SA-PO908
	PUB058	Mao, Xing	SA-PO309, PUB011	Martin, Aline	SA-PO942	Masutani, Kosuke	TH-PO791,
Malhotra, Rajeev	FR-OR028	Mapplebeck, Sarah	TH-PO618	Martin, Blanche	TH-PO337, PUB007		TH-PO793, FR-PO006, FR-PO758,
Malhotra, Rakesh	TH-PO1045,	Maquigussa, Edgar	FR-PO296,	Martin, Claire E.	FR-PO343		SA-PO1051, SA-PO1058, PUB500
	FR-PO894, PUB062		FR-PO841, FR-PO843	Martin, Finian	SA-PO332	Matar, Dany	SA-PO1079, SA-PO1080
Malhotra, Varun	PUB251	Mara, Kristin C.	FR-PO949	Martin, John	SA-PO485	Matas, Arthur J.	FR-OR069,
Mali, Padmavathi	FR-PO085, PUB186	Marahatta, Ramesh	TH-PO1120,	Martin, Josefina	PUB034, PUB041		SA-PO1018, SA-PO1020
Malicdan, May Christine V.	TH-PO248		FR-PO027, SA-PO092	Martin, Laurent	PUB112	Matesanz, Laura	SA-PO626
Malieckal, Deepa A.	FR-PO946	Maraj, Paul P.	SA-PO069	Martin, Michelle T.	SA-PO1066	Matharu, Tervinder S.	TH-PO1095
Malik, Marek	PUB339	Maranhão, Raul Cavalcante	FR-PO814	Martin, N.	FR-PO1026	Mathavakkannan, Suresh	FR-PO428,
Malik, Talat H.	TH-PO128	Maranon, Rodrigo	FR-PO552	Martin, Paul	FR-PO779, SA-PO1059		SA-PO786, PUB171
Mallamaci, Francesca	TH-PO608,	Maranzano, Valentina	FR-PO988	Martin, Pierre-Yves F.	FR-OR011,	Matheny, Michael Edwin	FR-PO502
	TH-PO626, FR-OR043, FR-PO588,	Marayati, Firas	PUB206		FR-PO485	Matheron, Sophie	SA-PO670
	SA-PO649	Marcante, Stefano	PUB037, PUB096	Martin, Teresa	SA-PO214	Matheson, Matthew	TH-PO469,
Mallappallil, Mary C.	TH-PO1123,	Marcelli, Daniele	TH-PO952,	Martina, Maria Noel	TH-PO027		SA-OR023, SA-PO733
	FR-PO759, SA-PO022, SA-PO091,		FR-OR013, FR-PO734, FR-PO766,	Martinez Moreno, Julio Manuel			FR-OR047
	PUB618, PUB619		PUB198		TH-PO490, TH-PO500	Mathew, Anna V.	TH-PO801, TH-PO951,
Mallat, Marko	SA-PO1063	March, Keith	FR-PO234	Martinez, Elisa	TH-PO667		FR-PO849, FR-PO865
Mallett, Andrew John	TH-OR044,	Marchbank, Kevin J.	FR-PO454	Martinez, Petra	TH-PO776	Mathew, Sijo	FR-OR095
	FR-OR056, FR-PO529, PUB465	Marchelek-Mysliwicz, Malgorzata		Martinez, Robert V.	FR-PO314	Mathieson, Peter W.	SA-PO344,
Mallipattu, Sandeep K.	TH-PO305		TH-PO564	Martinez-Alonso, Montserrat	TH-PO623		PUB086, PUB109, PUB286
Malluche, Hartmut H.	FR-OR021,	Marchetto, Paolo	SA-PO638	Martinez-Arias, Laura	TH-PO485	Mathisen, Ulla Dorte	FR-OR045
	FR-OR023, SA-PO569	Marciano, Denise K.	FR-PO920	Martin-Gómez, Laura	SA-PO986,	Mathur, Deepan	PUB575
Mallya, Shrikara P.	PUB477	Marciszyn, Allison L.	SA-PO261		PUB393	Mathur, Vandana S.	TH-PO956,
Malone, Andrew F.	FR-PO161	Marcuccilli, Morgan E.	PUB375	Martini, Sebastian	TH-PO723,		PUB113, PUB114, PUB714
Malta Cerqueira, Debora	FR-OR089	Marculescu, Rodrig	FR-OR023		FR-PO326, SA-OR054, SA-PO347	Matias, Patricia	SA-OR028
Malvar, Ana	TH-PO767, TH-PO768,	Marcus, Richard J.	FR-PO1065,	Martino, Francesca K.	TH-PO495,	Matignon, Marie	SA-OR011
	TH-PO777		SA-PO712, SA-PO1057		PUB623	Matos, Larissa R.	SA-PO284
Malyszko, Jacek S.	TH-PO576	Marcussen, Niels	FR-PO187	Martins, Janaina Silva	SA-PO573,	Matozaki, Takashi	SA-PO436
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Matsell, Douglas G.	SA-PO1027, SA-PO1031	Mayer, Gert J.	TH-OR024, PUB297	Mcintyre, Natasha Juliette	TH-PO534, TH-PO592	Mejia-Vilet, Juan M.	TH-OR022
Matsubara, Chieko	TH-PO551, TH-PO950	Mayeux, Philip R.	TH-PO023	McKay, Gareth J.	SA-PO491	Mekahli, Djilila	SA-PO891
Matsubara, Hidehito	FR-PO617	Maynard, Sharon E.	TH-PO067, SA-PO046, SA-PO135	Mckenney, Mikaela Lee	SA-PO585	Melamed, Michal L.	TH-PO091, FR-PO773, SA-OR036, SA-OR037
Matsuda, Akihiko	PUB225	Mayo, Martha	TH-OR035, TH-PO658, SA-PO924	Mckinney, Seth D.	TH-PO029	Melandri, Marco	TH-PO816, PUB344
Matsuhashi, Tetsuro	FR-PO236	Mayoux, Eric W.	SA-PO385	McKnight, A.J.	SA-PO491, SA-PO518	Melanson, Taylor A.	SA-PO705
Matsui, Isao	TH-PO479, TH-PO497, FR-PO932, SA-PO594	Mazdyasni, Sheila	TH-PO933	Mckusick, Michael A.	FR-PO212	Melderis, Simon	FR-OR067
Matsui, Katsuomi	TH-PO550, TH-PO615	Mazer, Murray J.	TH-PO1047	McLeish, Kenneth R.	TH-PO132, FR-PO304	Melendo, Maria	FR-PO106
Matsui, Masaru	TH-OR010, FR-PO507, PUB036	Mazzaferro, Sandro	PUB546	McLeod, Lorraine L.	FR-PO584	Melis, Patrizia	SA-PO050
Matsui, Noriaki	TH-PO1075	Mazzone, Patrizio	PUB344	McMahon, Andrew P.	FR-OR088, FR-OR098, FR-OR107	Melnick, Joel Z.	TH-PO641
Matsui, Thais Nemoto	SA-PO759, PUB325, PUB381, PUB633, PUB634	Mazzonetto, Ricardo P.	TH-PO167	McMahon, Blaitthin A.	FR-OR098, FR-OR107	Melo, Carla M.V.	PUB598, PUB607
Matsui, Yuki	FR-PO443, FR-PO1102, SA-PO998	McAdams-DeMarco, Mara	TH-PO982, FR-PO1053, SA-PO717	McMahon, Jill A.	FR-OR098, FR-OR107	Melo, Fernando de Assis Ferreira	PUB051
Matsukane, Ai	TH-PO918	McAfee, Nancy	FR-OR035	McMahon, Kelly	SA-PO221	Melsom, Toralf	TH-PO544, TH-PO567, TH-PO570, TH-PO598, FR-OR045, FR-PO638
Matsukuma, Yuta	TH-PO793, TH-PO898, FR-PO006, FR-PO758	Mcarthur, Eric	FR-PO567, SA-OR101, SA-PO205, SA-PO215	McMenamin, Maggie	TH-PO151	Meltzer, Grant	PUB040
Matsumoto, Akihiko	FR-PO1096, PUB649	Mcburney, Conor	TH-PO675	McMorrow, Tara	TH-PO291, PUB108	Mena, Maria del Cielo	FR-PO667
Matsumoto, Kei	FR-PO300	Mccafferty, Kieran	TH-PO744, FR-PO794, SA-PO683, PUB255, PUB383	McMullan, Ciaran Joseph	TH-PO529, FR-OR046, SA-PO633, SA-PO634, SA-PO635, SA-PO660, SA-PO662	Mencarelli, Francesca	TH-PO379, TH-PO634
Matsumoto, Mayumi	PUB370	Mccall, Abraham Scott	FR-OR061	McPherson, Laura J.	FR-PO1034, SA-PO1006	Mencke, Rik	TH-PO502
Matsumoto, Tatsuki	TH-PO005, TH-PO781, FR-PO273, FR-PO503, SA-PO267	Mccall, Kelly D.	TH-PO172	McPherson, Sterling	TH-OR005	Mendelssohn, David C.	TH-PO400, FR-PO681
Matsumoto, Yoshihiro	TH-PO753	Mccallum, Wendy	PUB677	Mcritchie, Susan	FR-PO531	Mendes, Artur P.	TH-PO400, FR-PO618
Matsumura, Daisuke	TH-PO708	Mccann, Eileen C.	SA-PO673	Meaney, Calvin J.	SA-PO542, SA-PO543	Mendes, Filipa Brito	FR-PO618, SA-PO399, PUB298, PUB299
Matsumura, Hideki	TH-PO1106, SA-PO105, PUB404	Mccarroll, Francis	FR-PO480, SA-PO233	Meca, Renata	TH-PO202	Mendes, Natali	PUB051
Matsumura, Kazuya	TH-PO461	McCarthy, Deborah J.	SA-PO352	Medaura, Juan Antonio	FR-PO018, PUB435	Mendes, Teresa	TH-OR060
Matsumura, Kiyoshi	PUB500	McCarthy, Ellen T.	FR-PO320, FR-PO352	Medeiros, Mara	TH-PO468, SA-PO540, PUB581	Mendez, Armando	SA-OR054
Matsuo, Akihiro	FR-PO236	McCarthy, Kevin J.	SA-PO352	Medina-Pestana, J.	FR-PO1059, SA-PO1049, SA-PO1081, PUB663, PUB683, PUB693	Mendez, Celia	SA-OR0720
Matsuo, Nanae	TH-PO1001, SA-PO060, PUB601	Mccarty, Midori L.	TH-PO610	Medjeral-Thomas, Nicholas R.		Mendiluce, Alicia	PUB034, PUB041
Matsuo, Seiichi	TH-OR028, TH-OR036, TH-PO790, TH-PO912, FR-OR039, FR-PO248, FR-PO970, FR-PO999, SA-OR091, PUB156, PUB376	McClellan, William M.	FR-PO702	Medronha, Eduardo Ferreira	PUB476	Mendley, Susan R.	TH-PO469, SA-OR023, SA-PO733
Matsuoka, Tetsuhei	SA-PO663	Mcclellon, Anita M.	FR-PO522	Medvedovic, Mario	TH-PO841, PUB486	Mendoza Cabrera, Salvador	FR-PO495
Matsusaka, Taiji	TH-PO224, TH-PO225, TH-PO230, TH-PO246, FR-PO125, PUB280	Mcclellon, Daniel R.	FR-PO522	Meehan, Daniel T.	SA-OR048	Mendoza, Carmen E.	FR-PO419
Matsushita, Kunihiro	TH-OR013, TH-PO095, TH-PO535, TH-PO630, FR-OR068, SA-OR007, SA-PO607, SA-PO923, PUB136	Mcclellon, Jeanette N.	SA-PO587	Meek, Alicia	FR-PO942	Mendoza, Melissa	FR-PO774
Matta, Valeria	SA-PO050	Mcclellon, Raymond	SA-PO182	Meek, Rick L.	TH-OR005, TH-PO332	Mendu, Mallika L.	TH-PO070
Mattana, Joseph	TH-PO395, TH-PO1053, SA-PO095, SA-PO709, SA-PO742, PUB199, PUB200	Mcclore, Leslie	FR-OR044	Megahed, Mohammed	PUB722	Meneghini, Maria	FR-PO1031, FR-PO1039
Matteo, Maria	TH-OR030	Mccomsey, Grace	TH-PO528, FR-PO524	Meganathan, Karthikeyan	TH-PO068	Menez, Steven	SA-PO607
Matteucci, Maria Chiara	TH-PO634	Mccormack, Mark	SA-PO516	Meggs, Leonard G.	TH-PO238, FR-PO340, SA-PO315	Menezes, Luis F.	TH-OR048
Matthay, Michael	TH-PO085	Mccormack, Siobhan	FR-PO280, SA-PO884	Megyesi, Judit	TH-PO033	Meng, Chan Choong	PUB223
Mattiazzi, Adela D.	FR-PO1069, SA-PO1059	Mccormick, Brendan	TH-PO984	Mehling, Heidrun	TH-OR031	Meng, Meijuan	PUB334, PUB521
Mattingly, Peter J.	PUB485	Mccormick, James A.	TH-OR081, TH-OR082	Mehrotra, Anita	SA-PO714	Meng, Ting	FR-PO959
Mattinzoli, Deborah	FR-PO1031, FR-PO1039	Mccormick, Joseph B.	SA-PO688	Mehrotra, Purvi	TH-PO029, FR-PO229, FR-PO233, FR-PO234, PUB014	Mengel, Michael	TH-OR074, FR-PO1093
Mattoo, Aprajita	PUB426	Mccorriston, Debra J.	FR-PO521	Mehrotra, Rajnish	TH-OR005, TH-PO801, TH-PO1025, FR-OR033, FR-PO637, FR-PO1007, FR-PO1008, SA-PO721, SA-PO835, SA-PO845	Meniconi, Marcos A.	FR-PO1059, PUB683
Mattoo, Tej K.	PUB149	Mccoyle, Ian	TH-PO1055	Mehrotra, Rajnish	TH-PO801, TH-PO1025, FR-OR033, FR-PO637, FR-PO1007, FR-PO1008, SA-PO721, SA-PO835, SA-PO845	Menini, Stefano	TH-PO353
Mattson, David L.	FR-PO117, SA-PO305	Mccoyle, Rozalina G.	FR-PO793	Mehrotra, Anita	SA-PO714	Menne, Jan	FR-PO446
Mau, Wilfried	TH-PO996	Mccuaig, Laura Elisabeth	FR-PO533	Mehrotra, Purvi	TH-PO029, FR-PO229, FR-PO233, FR-PO234, PUB014	Menon, Madhav C.	TH-PO275, FR-PO325, FR-PO1038, SA-PO1053
Mauer, Michael	TH-OR002, FR-PO165, FR-PO613, FR-PO643	Mcculloch, Charles E.	TH-PO612, FR-PO741, FR-PO1018, SA-PO685	Mehrotra, Rajnish	TH-OR005, TH-PO801, TH-PO1025, FR-OR033, FR-PO637, FR-PO1007, FR-PO1008, SA-PO721, SA-PO835, SA-PO845	Menon, Mini	FR-PO051
Maurer, Anita	SA-PO560	Mccullough, Keith	TH-PO885, TH-PO940	Meggs, Leonard G.	TH-PO238, FR-PO340, SA-PO315	Menoyo, Jose A.	TH-PO955, SA-PO927
Maurer, Johannes	TH-PO378	Mccurley, Amy T.	TH-PO031, TH-PO032	Megha, Nitesh R.	TH-PO455	Meola, Mario	SA-PO258
Maursetter, Laura J.	TH-PO1122, SA-PO132	Mcdermott, Paul	TH-PO837	Mehta, Rahul	PUB002	Meoni, Lucy A.	TH-PO825, TH-PO900, TH-PO902, TH-PO903, TH-PO906, TH-PO907, SA-PO607, PUB136
Mavani, Gaurang P.	PUB304, PUB425	Mcdonald, Stephen P.	FR-OR034, FR-PO509, SA-PO721, SA-PO1088	Mehta, Rajil B.	SA-PO975	Meran, Soma	FR-PO290, SA-PO485
Mavragani, Clio	FR-PO410	McDonough, Alicia A.	TH-PO445, SA-OR070	Mehta, Ramila A.	FR-PO949	Meraz-Munoz, Alejandro Y.	TH-PO584
Mavrakanas, Thomas A.	FR-PO728, FR-PO729	McDougall, Kathryn A.	FR-PO688, FR-PO689	Mehta, Ravindra L.	TH-OR034, TH-PO088, TH-PO124, FR-PO457, FR-PO458, FR-PO459, FR-PO460, FR-PO461, FR-PO462, FR-PO463, SA-PO193, SA-PO229, PUB062	Mercadal, Lucile	TH-PO820, SA-OR031
Mavridis, Dimitris	TH-PO765	McEniery, Carmel M.	TH-PO423	Mehta, Rohan V.	SA-PO612, PUB002	Mercado-Garcia, Adriana	SA-PO644
Mawad, Habib	SA-PO1074	McEvoy, Caitriona M.	FR-PO418	Mehta, Rupal	TH-OR124	Merchant, Michael	TH-PO294, FR-PO304, FR-PO613, FR-PO918, SA-PO805
Mawad, Hanna W.	SA-PO569	Mcevoy, Kevin M.	SA-PO1107	Mehta, Shikha	FR-PO064	Merchen, Todd D.	TH-PO266
Maxwell, Alexander P.	TH-PO864, SA-PO491, SA-PO518	Mcfadden, Christopher B.	TH-PO102	Mehta, Suchita J.	TH-PO1049	Mercier, Kelly	FR-PO531
Maxwell, Kyle D.	TH-PO283	Mcfadden, Molly	SA-PO810, PUB368	Mei, Changlin	TH-PO015, TH-PO190, TH-PO191, FR-PO288, SA-PO279, SA-PO409	Mercurio, Carmela	SA-PO626
May, Carl J.	TH-PO301	McGaraughey, Steve	SA-PO364	Mei, Janet Yanqing	FR-PO122	Merdegia, Girliie Singian	FR-PO011
Mayer, Bernd	FR-PO606	Mcgaughran, Julie M.	PUB465	Mei, Shuqin	TH-PO015	Merello, Jose Ignacio	TH-PO833
		McGill, Rita L.	TH-PO863, FR-PO701	Meier-Kriesche, U.	SA-OR064	Merfeld-Clauss, Stephanie	FR-PO234
		McGrath, Martina M.	TH-PO1031	Meijer, Esther	TH-PO213, SA-PO851, PUB260	Merino, Julio Israel	SA-PO162
		McGregor, JulieAnne G.	TH-PO135, TH-PO683, TH-PO1108, FR-PO408, FR-PO964, FR-PO979, SA-PO1110	Meijers, Bjorn	TH-PO819, FR-PO858, FR-PO859, FR-PO860, SA-PO848	Merkel, Peter A.	SA-PO555
		McGuinness, Dagmara	SA-PO311, SA-PO526	Meijles, Daniel N.	TH-OR103	Merkulova, Maria	FR-PO887
		McHugh, Kirk M.	TH-PO477, TH-PO478	Meisels, Ira S.	FR-PO001	Mernaugh, Glenda	FR-OR095
		McIntyre, Christopher W.	TH-PO534, TH-PO592, TH-PO899	Meisner, Allison	SA-PO197	Merouani, Aicha	TH-PO1073
				Meissner, Thomas	PUB700	Merscher, Sandra M.	FR-PO326, FR-PO349, SA-OR054, SA-PO347, SA-PO348, SA-PO349
				Mejia, Carlos H.	PUB162	Mertens, Luc	PUB305
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Messaggio, Elisabetta	TH-PO816, SA-PO500	Mimura, Imari	SA-PO425	Miyazaki, Makoto	SA-PO598	Molina, Alvaro	TH-PO823
Messana, Joseph M.	TH-PO943, FR-PO789, FR-PO799	Mimura, Toshihide	TH-OR021, TH-PO686	Miyazaki, Mariko	TH-PO525, PUB303	Molina, Pablo	PUB547
Messchendorp, A. Lianne	TH-PO169, SA-PO851, SA-PO881	Min, Hye Sook	TH-PO138, TH-PO139, TH-PO656, SA-PO372, SA-PO374	Miyazaki, Ryoichi	SA-PO029	Molina, Patrick A.	FR-PO098
Metalidis, Christoph	TH-PO819	Min, Ji Won	SA-PO962	Miyazaki, Shigeaki	TH-PO354	Molitoris, Bruce A.	TH-PO031, TH-PO032, SA-PO397
Metcalfe, Wendy	SA-PO047	Min, Kelly	SA-PO731	Miyazaki, Shigeru	FR-PO898, SA-PO827	Mollae, Mehri	FR-PO438
Meteoglu, Ibrahim	SA-PO044, SA-PO107, PUB440	Min, Kyungok	FR-PO985, FR-PO1041	Miyazaki, Teruo	FR-PO893	Mollet, Geraldine	TH-PO431, FR-OR050, FR-PO157, FR-PO341
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Metz, Christine N.	FR-PO872	Minatoguchi, Shun	TH-PO865, FR-PO596, PUB356	Miyazaki, Toru	TH-PO020, FR-PO974	Molnar, Miklos Zsolt	TH-OR016, TH-OR115, TH-PO095, TH-PO536, TH-PO539, TH-PO546, TH-PO637, TH-PO638, FR-OR041, FR-PO439, FR-PO650, FR-PO1007, FR-PO1008, SA-OR009, SA-OR010, SA-OR055, SA-OR089, SA-PO619, SA-PO648, SA-PO790, SA-PO795, SA-PO845
Metzger, Gregory J.	TH-PO829	Miner, Jeffrey H.	TH-OR057, TH-PO228, FR-OR084, FR-PO154, FR-PO161, FR-PO315, SA-OR045, SA-OR046, SA-PO350, SA-PO351	Miyazaki, Yoichi	TH-PO230, TH-PO711, SA-PO653	Molnec, Tom Eirik	SA-PO535, SA-PO536
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Meuer, Stefan	FR-OR076, FR-PO1077, SA-PO1089	Minnema, Renae A.	SA-PO170	Miyazawa, Tomoki	PUB466	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meusen, Bas	FR-PO374	Minnings, Kailey	PUB159	Miyazawa, Yasuharu	SA-PO908	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meuwese, Christian L.	SA-PO610	Minovic, Isidor	FR-PO1035	Miyoshi, Sosuke	SA-OR044	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, James Otto	TH-PO299	Mintz, Rachel Lauren	FR-PO872	Miyoshi, Taku	TH-PO1084, TH-PO1113, SA-PO270	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, Klemens B.	TH-PO863, FR-PO701	Minutolo, Roberto	TH-OR014, FR-PO576, PUB301, PUB497	Mizia-Stec, Katarzyna T.	SA-PO622	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, Matthias C.	FR-PO984	Minz, Mukut	PUB671	Mizobuchi, Masahide	TH-PO512, TH-PO923	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, Nicole M.	TH-PO528	Minz, Ranjana Walker	PUB671	Mizumoto, Teruhiko	SA-PO270	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, Nicole	SA-OR017	Mion Junior, Decio	SA-PO621	Mizuno, Masashi	FR-OR039, SA-OR091	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, Nuala J.	TH-PO001	Mir, Saiful A.	TH-PO030	Mizuno, Shinichi	PUB311	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer, Timothy W.	FR-PO654, FR-PO773, SA-OR036, SA-OR037, SA-PO154, PUB632	Miranda Munoz, Gabriela	TH-PO696	Mizuno, Tomohiro	FR-PO975, SA-PO430	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyers, Kevin E.C.	TH-PO632	Miranda, Catherine	TH-PO1116, FR-PO034, SA-PO176, SA-PO956	Mjoeen, Geir	TH-PO888	Molnec, Tom Eirik	SA-PO535, SA-PO536
Meyer-Schwesinger, Catherine	FR-OR062, FR-PO346, FR-PO981, FR-OR051	Mironova, Elena V.	TH-PO433, SA-OR067	Mo, Hongyan	TH-PO306	Molnec, Tom Eirik	SA-PO535, SA-PO536
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Michaud, Jennine	TH-PO1033, TH-PO1069	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moe, Sharon M.	TH-PO560, FR-PO392, FR-PO840, SA-PO585, SA-PO587, SA-PO793	Molnec, Tom Eirik	SA-PO535, SA-PO536
Michea, Luis F.	TH-PO448, FR-OR026, FR-PO114	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moeckel, Gilbert W.	FR-PO058, FR-PO260	Molnec, Tom Eirik	SA-PO535, SA-PO536
Michel, Pierre-Antoine	SA-OR011	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moeller, Marcus J.	FR-PO334	Molnec, Tom Eirik	SA-PO535, SA-PO536
Michelis, Michael F.	SA-OR007, PUB304, PUB848	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moes, Arthur David	SA-PO629	Molnec, Tom Eirik	SA-PO535, SA-PO536
Michihata, Tetsuo	TH-PO585	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moffat, Jason	SA-PO340	Molnec, Tom Eirik	SA-PO535, SA-PO536
Michos, Odysse	FR-OR088	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mogalar, Indraneel	TH-PO1072	Molnec, Tom Eirik	SA-PO535, SA-PO536
Middleton, John Paul	TH-PO610	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mogili, Hari Krishna Reddy	SA-PO054	Molnec, Tom Eirik	SA-PO535, SA-PO536
Midgley, Adam	FR-PO290	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moguel, Bernardo	PUB600	Molnec, Tom Eirik	SA-PO535, SA-PO536
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Mielke, Michelle M.	PUB177	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohamed, Maha A.	FR-PO085, FR-PO1100, SA-PO1055	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mierzicki, Piotr	TH-PO520	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohamed, Mohamed Yahya	PUB348	Molnec, Tom Eirik	SA-PO535, SA-PO536
Miettinen, Marja H.	FR-PO740	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohamed, Muner	SA-PO114	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mifflin, Theodore E.	SA-OR004	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohammed, Saleh	TH-OR072	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mihaylova, Borislava N.	SA-PO729	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohammed-Ali, Zahraa	SA-PO456	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mihout, Fabrice	SA-OR011	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohan, Chandra	FR-PO710	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mikhaeel, Mary	SA-OR034	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohan, Sumit	FR-OR070, FR-PO1034, FR-PO1046, FR-PO1054, FR-PO1085, FR-PO1089, SA-PO020, SA-PO948, SA-PO949, SA-PO1002, SA-PO1030	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mikami, Daisuke	TH-PO1110	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohandas, Rajesh	SA-PO636, SA-PO656	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mikhail, Ashraf I.	SA-PO814	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	MohdNazri, Shah	SA-PO189	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mikkelsen, Margit K.	FR-OR041	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohler, Emile	PUB321	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mikoda, Nobuyuki	PUB715	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohorko, Evelina	PUB147	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mikulak, Joanna	FR-PO421	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohottige, Dinushika	PUB153	Molnec, Tom Eirik	SA-PO535, SA-PO536
Milan Manani, Sabrina	TH-PO695, TH-PO1016, FR-PO824, FR-PO825, PUB076	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mohsin, Nabil	PUB347	Molnec, Tom Eirik	SA-PO535, SA-PO536
Milanesi, Samantha	TH-PO391	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moineddin, Rahim	PUB305	Molnec, Tom Eirik	SA-PO535, SA-PO536
Milani, Payvand	SA-PO1073	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moinuddin, Irfan K.	PUB209, PUB213	Molnec, Tom Eirik	SA-PO535, SA-PO536
Miles, Colin	SA-PO874, PUB281	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moissl, Ulrich	SA-OR033	Molnec, Tom Eirik	SA-PO535, SA-PO536
Miles, Jonathan Alexander	SA-PO974, SA-PO1078	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Mola, Maria Grazia	SA-OR117	Molnec, Tom Eirik	SA-PO535, SA-PO536
Mil-Homens, Clara	SA-OR028	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moldawer, Lyle L.	TH-PO408	Molnec, Tom Eirik	SA-PO535, SA-PO536
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Miller, Edgar R.	TH-OR119, SA-OR004, SA-PO711	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Moledina, Dennis G.	TH-PO614, SA-OR099	Molnec, Tom Eirik	SA-PO535, SA-PO536
Miller, Loan N.	PUB085	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349	Molin, Nicole	FR-PO243, PUB004	Molnec, Tom Eirik	SA-PO535, SA-PO536
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Milo Rasouly, Hila	FR-PO324	Mitrofanova, Alla	FR-PO326, SA-PO348, SA-PO349			Molnec, Tom Eirik	SA-PO535, SA-PO536
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Sriskandarajah, Sanjeevan	FR-PO406	Stephens, Mark	PUB314	Surae, Satnam	SA-PO332	Sural, Saubhik	FR-PO931
Srisung, Weeraporn	TH-PO1079, FR-PO022, SA-PO076	Stephens-Shields, Alisa J.	SA-PO617	Sureshkumar, Kalathil K.	FR-PO1065, SA-PO712, SA-PO1057	Suri, Guga	SA-PO973
Srivastava, Anand	PUB172	Stappich, Julia	TH-PO839	Surowiecka- Pastewka, Agnieszka	FR-PO501	Suri, Rita	SA-PO846, PUB662
Srivastava, Priya S.	SA-PO145	Stern, Edward	FR-PO448	Susa, Koichiro	TH-PO442, SA-PO116	Susantitaphong, Paweena	TH-PO644, TH-PO670
Srivastava, Shalabh	SA-PO874, PUB281	Stern, Gunnar	TH-PO506	Susanto, Christopher	PUB120	Susomboon, Teerada	TH-PO644
Srivastava, Swayam Prakash	TH-PO371	Sternlicht, Hillel	FR-PO008	Sussman, Amy Nicole	PUB209, PUB213	Sussman, Caroline R.	TH-PO210
Srivastava, Tarak	FR-PO320, FR-PO352	Stevens, Brian K.	TH-PO012	Susztak, Katalin	TH-PO001, TH-PO247, FR-PO624, SA-OR086, SA-PO494, SA-PO496	Suthanthiran, Manikkam	SA-PO1071
Srivatana, Vesh	SA-PO918, PUB405	Stevens, Kathryn K.	FR-PO747	Sutliff, Roy L.	SA-OR068	Suwa, Junya	TH-OR021, TH-PO686
Srivaths, Poyyapakkam	TH-PO651	Stevens, Megan	FR-PO348	Suwabe, Tatsuya	FR-PO622, FR-PO626, SA-PO870, PUB260	Suwanichkul, Adisak	FR-PO969
Sroya, Hafiz Ali	FR-PO072	Stevens, Todd M.	FR-PO064	Suwelack, Barbara M.	FR-PO1067, FR-PO1071	Suzuki, Atsushi	SA-PO417, SA-PO941
Srugies, Fabian	SA-PO435	Stevenson, Andra S.	SA-OR071	Suzuki, Hiroyuki	SA-PO223	Suzuki, Hiroyuki	SA-PO223
St. Clair, E. William	SA-PO555	Stewart, Ian J.	SA-OR102				
Stack, Austin G.	FR-PO573, FR-PO732, FR-PO733	Stewart, Laura M.	FR-PO776				
Stadler, Krisztian	TH-PO308, FR-OR083	Stewart, Tyrus	TH-PO458				
Stahl, Jessica L.	SA-PO1019	Stienstra, Rinke	SA-PO412				
Stahl, Rolf A.	FR-OR062, FR-OR066, FR-OR067, FR-PO346, FR-PO403, FR-PO984, FR-PO1071, FR-PO1075, FR-PO1078, SA-OR015, SA-OR063, SA-PO978	Stijnen, Theo	PUB125				
Stallone, Giovanni	TH-OR030, TH-OR073, TH-PO798, SA-PO847	Stijman, Isaac Ely	TH-PO1055, PUB176				
Stanescu, Horia	TH-PO744, PUB250	Stilp, Adrienne M.	SA-PO499				
Stanifer, John W.	PUB153	Stiphout, Joris Van	PUB544				
Stannard, Jasmine N.	TH-PO133	Stites, Erik	SA-PO979				
Stanton, Tony	FR-OR025	Stiith, Sarah	SA-PO1010, SA-PO1026, SA-PO1028				
Stapleton, Caragh P.	SA-PO516	St-Jules, David E.	FR-PO904				
Staplin, Natalie	TH-OR020, FR-PO564	Stockand, James D.	TH-PO433, SA-OR067				
Star, Robert A.	TH-PO019, TH-PO258, SA-PO239, SA-PO257, SA-PO437, SA-PO455, PUB389	Stockler-Pinto, Milena Barcza	TH-PO287, FR-PO862, SA-OR098, SA-PO798, PUB100, PUB104				
Starkey, Jonathan Michael	SA-PO688	Stone, John H.	SA-PO555				
Starmer, Joshua	TH-PO683	Stoneback, Jason W.	SA-PO559				
Starost, Matthew F.	TH-PO248	Stoop, Reinout	PUB290				
Staruschenko, Alexander	FR-PO339	Storey, Ben	TH-OR116				
Stasi, Alessandra	SA-PO462, PUB641	Storhaug, Hilde Merete	TH-PO598				
Stasiv, Yuri	TH-OR035, TH-PO658, SA-PO924	Storr, Markus	TH-PO913, FR-OR029, FR-PO668				
Stauber, Jonathan	SA-PO402	Storsley, Leroy J.	SA-PO717				
Stavros, Fiona	SA-PO927	Stott, Daniel	FR-PO510				
Stea, E.D.	SA-PO507	Stoudmann, Candice	SA-PO575				
Steadman, Robert	FR-PO290, SA-PO485	Stoumpos, Sokratis	FR-PO484				
Steegh, Floortje	TH-PO329	Stover, Cordula M.	PUB005				
Steel, Jennifer L.	SA-PO744	Stowe, Tim	SA-PO333				
Steele, Maggi	TH-PO874, FR-PO724	Strandgaard, Svend	SA-PO600				
Stefanska, Anna Maria	SA-PO298	Street, Jonathan	TH-PO019, TH-PO258, SA-PO239, SA-PO257, SA-PO437, SA-PO455, PUB095, PUB389				
		Streets, Andrew J.	TH-PO199, PUB275				

Suzuki, Hitoshi	TH-PO730, TH-PO734, TH-PO735, FR-PO973, FR-PO974, FR-PO976	Taguchi, Kensei	FR-PO134	Tamura, Kouichi	TH-PO390, FR-PO129, FR-PO130, SA-PO363, PUB495	Tano, Jean-Yves	PUB494
Suzuki, Hodaka	SA-PO502	Taguma, Yoshio	TH-PO880, PUB311	Tamura, Kristen P.	SA-PO085, SA-PO843	Tanoue, Michael T.	TH-PO1102
Suzuki, Keiko	TH-PO1075	Tahir, Khalid	TH-PO828	Tamura, Masahito	FR-PO828	Tanphaichitr, Natthavat	SA-PO082
Suzuki, Koichi	PUB253	Tai, Reibin	FR-PO868, SA-PO620, SA-PO909	Tamura, Yoshifuru	PUB719	Tantillo, Ilaria	TH-PO1016, FR-PO824, FR-PO825
Suzuki, Masashi	SA-PO417, SA-PO941	Taine, Marion	TH-PO635	Tan, Chieh-suai	TH-PO870	Tantisattamo, Ekamol	FR-PO074, FR-PO1072, SA-PO061, SA-PO062, SA-PO117, SA-PO118, PUB421, PUB643
Suzuki, Miho	FR-PO846, PUB562, PUB566	Taira, Takayasu	TH-PO390	Tan, Chunyan	SA-PO468	Tantravahi, Jogiraju V.	SA-PO656
Suzuki, Norio	FR-PO541, SA-PO246	Taiwo, Adetokunbo A.	SA-PO154	Tan, Dean D.	FR-PO599	Tao, Jianling	TH-PO691
Suzuki, Satoshi	TH-PO794	Tajima, Takaya	FR-PO878	Tan, Hui Zhuan	PUB223	Tao, Shixin	FR-PO262
Suzuki, Sayuri	PUB253	Takae, Keita	FR-PO574	Tan, Joseph-Anthony Tapia	FR-OR010	Tao, Xia	FR-PO655
Suzuki, Takehiro	FR-PO236, PUB093	Takahara, Shiro	FR-PO015, SA-OR044, SA-PO961	Tan, Roderick J.	TH-OR089, TH-PO049, FR-OR102, SA-OR084, SA-PO421	Tao, Yuhong	FR-PO255
Suzuki, Yasuhiro	FR-OR039, SA-OR091	Takahashi, Daiei	TH-PO442	Tan, Ru Yu	SA-PO1025	Taotao, Tang	TH-PO011, FR-PO144 PUB713
Suzuki, Yasunori	SA-PO084	Takahashi, Daisuke	PUB329	Tan, Sih Min	TH-PO130	Tapolyai, Mihaly B.	FR-PO720, PUB563
Suzuki, Yoshiki	FR-PO610, FR-PO886, FR-PO898	Takahashi, Hisahide	PUB266	Tan, Si-Yen	FR-PO1090	Tarbell, John	FR-PO228
Suzuki, Yusuke	TH-PO734, TH-PO735, FR-PO973, FR-PO974	Takahashi, Kazue	FR-PO994	Tan, Sven-Jean	FR-OR025, SA-PO424, PUB537	Tardi, Nicholas J.	TH-OR094, TH-PO231
Svara, Frantisek	TH-PO520	Takahashi, Kazuo	TH-PO549, FR-PO975, SA-PO430, SA-PO718	Tan, Thida	TH-PO979, FR-PO432	Tarng, Der-Cherng	FR-PO245, FR-PO383, FR-PO562
Svarstad, Einar	TH-OR018, TH-PO792, FR-PO165, SA-PO515	Takahashi, Kota	SA-PO961	Tan, Timothy L.	FR-PO599	Tarrant, Carolyn	SA-PO746
Svelto, Maria	FR-OR038, FR-PO611	Takahashi, Naoki	TH-PO1110	Tan, Weizhen	FR-OR052, FR-PO150, FR-PO151, FR-PO152, FR-PO176, PUB553	Tartaglione, Annunziata	FR-PO663
Svensson, Ann-Marie	FR-PO631	Takahashi, Nobuyuki	TH-PO319, TH-PO148	Tan, Yi Liang	TH-PO870	Tartaglione, Lida	PUB546
Svensson, Katherine	SA-PO644	Takahashi, Ryo	TH-PO551, TH-PO950	Tan, Zhi	SA-OR101, SA-PO727	Tarzi, Ruth M.	FR-PO413
Svensson, Maria	FR-PO631	Takahashi, Shunsuke	FR-PO239, SA-PO320	Tanabe, Kazunari	TH-PO737, SA-PO961, SA-PO977, SA-PO1037, SA-PO1051, SA-PO1058, SA-PO1085	Tashiro, Yoshihito	TH-PO384, FR-PO539
Sverrisson, Kristinn	SA-PO451	Takahashi, Teisuke	TH-PO344	Tanaka, Hirofumi	TH-PO630	Tasian, Gregory Edward	SA-OR078
Svetkey, Laura P.	TH-PO610	Takahashi, Yasuhito	PUB329	Tanaka, Hitomi	PUB055	Tasic, Velibor	FR-OR048, FR-PO176 FR-PO176
Swain, Elizabeth	TH-PO531, SA-PO850	Takahashi, Yukina	TH-PO229	Tanaka, Keiko	TH-PO559, PUB390	Tateoka, Ryoko	FR-PO864
Swain, Kawan A.	FR-PO017	Takahashi, Yukina	TH-PO229	Tanaka, Kenji	TH-OR112	Tato, Ana M.	TH-PO985
Swaminathan, Sethuraman	TH-PO470, TH-PO509	Takahashi, Yusuke	SA-PO1016	Tanaka, Kenji	TH-OR112	Tatsukawa, Hideki	SA-PO430
Swaminathan, Sundaraman	TH-PO044, SA-PO238	Takahata, Akiko	FR-PO973, FR-PO974	Tanaka, Ryojiro	TH-PO787	Tatsumi, Norifumi	TH-PO523
Swan, Joshua Taylor	FR-PO471	Takaichi, Kenmei	FR-PO622, FR-PO626, SA-PO583, SA-PO870	Tanaka, Shigeru	TH-PO791, TH-PO793, TH-PO803, TH-PO822, TH-PO920, FR-PO758, PUB500	Tatsumi, Sawako	TH-PO503
Sweat, Michael D.	SA-OR008	Takamura, Takeyuki	TH-PO1124, FR-PO614	Tanaka, Shinji	SA-PO252	Tatsumoto, Narihito	FR-OR022
Sweeney, Michael	TH-PO609, TH-PO666	Takanami, Erika	TH-PO718, SA-OR017	Tanaka, Tetsuhiro	SA-PO252	Tauc, Michel	SA-PO932
Sweeney, William E.	TH-PO204	Takane, Koki	PUB329	Tanaka, Yasuko	FR-PO100, FR-PO105	Tavajoh, Saeideh	FR-PO682
Sweigert, Patrick	PUB317	Takano, Tomoko	FR-PO343, SA-OR053	Tanaka, Yuka	PUB225	Tavares, Gesiane Fernandes	PUB184
Swenson-Fields, Katherine	TH-PO206	Takaori, Kaori	FR-PO004	Tanaka, Yuri	TH-PO918	Tavares, Nelson	SA-PO399
Swetlik, Carol	FR-PO943, FR-PO944	Takaori, Koji	TH-OR098	Tanbo, Yuki	TH-PO734	Tavares-Brum, Alexandre	SA-PO1074
Swietochowska, Anita	PUB137	Takasato, Minoru	TH-OR044	Tang, Bing	PUB518, PUB521	Tavasoli, Mahtab	SA-PO353
Swinkels, Dorine W.	TH-PO021, SA-PO548	Takase, Osamu	FR-PO183, FR-PO208	Tang, Dang	TH-PO336	Tawada, Mitsuhiro	FR-OR039, SA-OR091
Syed, Daneyal	PUB317, PUB704, PUB708	Takayama, Shuichi	SA-OR039	Tang, Hairong	TH-PO771, PUB236	Tayama, Yosuke	PUB271
Syed, Fahd	PUB116	Takayanagi, Kaori	PUB225, PUB271	Tang, Hong	FR-PO967	Taylan, Christina	FR-PO839, PUB700
Syed, Huzaefah J.	PUB211	Takechi, Hanako	FR-PO617	Tang, Hui	FR-PO211, FR-PO295, SA-PO222, SA-PO658	Taylor, Brent C.	SA-PO677
Syed, Kunzah Aleem	PUB279	Takeda, Asami	SA-PO1084	Tang, Ignatius Yun-Sang	FR-PO1062, SA-PO999, SA-PO1066	Taylor, Carrie Turich	TH-PO271
Sykes, Brian William	SA-PO666	Takeda, Kyoko	SA-PO679	Tang, Jie	FR-PO710	Taylor, Dominic	TH-PO942
Synodinou, Irene	FR-PO1012	Takeda, Tetsuro	FR-PO641	Tang, Li	SA-PO381	Taylor, Eric N.	FR-PO941, SA-OR077
Szabo, Aniko	PUB470	Takeda, Yoko	PUB545	Tang, Mila	FR-PO517	Taylor, Eric	TH-PO292
Szabo, Zoltan	TH-PO095	Takehara, Eriko	SA-PO018	Tang, Qizhi	SA-PO968	Taylor, Maria E.	TH-PO125, FR-PO029
Szalai, Alexander J.	TH-OR095	Takehara, Seiya	TH-PO072	Tang, Ri-ning	PUB295	Taylor, Patricia B.	TH-PO935
Szamosfalvi, Balazs	SA-PO919	Takei, Takashi	TH-PO724, TH-PO775, TH-PO789, SA-OR018	Tang, Sydney C.W.	TH-PO357, SA-PO452, SA-PO508, SA-PO509, PUB286	Taylor, Veronica A.	SA-PO1036
Szamoslaska, Katarzyna	FR-PO501	Takei, Yoshifumi	FR-OR039, SA-OR091	Tang, Yuka	FR-PO507, SA-PO508, SA-PO509, PUB286	Tazaki, Miyako	SA-PO1016
Szczech, Lynda	TH-OR039, TH-PO646, TH-PO647, TH-PO648	Takemoto, Minoru	FR-PO186, SA-PO434	Tang, Ying	TH-OR096	Teboul, Isaac	TH-PO395
Szerlip, Harold M.	SA-PO016	Takemoto, Reika	SA-PO043	Tangri, Navdeep	TH-PO927, FR-PO584, FR-PO784, SA-PO689, SA-PO717, SA-PO727	Tedeschi, Silvana	FR-PO447
Szeto, Cheuk-Chun	SA-PO738, PUB350	Takemura, Koji	TH-PO813	Tangwonglerit, Theerasak	TH-PO094	Tedla, Fasika M.	FR-PO091, FR-PO1055
Szeto, Daphne	SA-OR071	Takemura, Tsukasa	PUB466	Taniguchi, Kei	PUB719	Tee, James B.	FR-PO1063
Szeto, Hazel H.	TH-OR087, TH-PO326, FR-OR101	Takenaka, Tsuneo	FR-PO308	Taniguchi, Keiichi	FR-PO936	Teehan, Geoffrey S.	PUB212
Szeto, Stephen G.	TH-PO315, FR-PO278	Taketani, Yutaka	TH-PO501	Taniguchi, Masatomo	TH-PO803, TH-PO822, TH-PO920, FR-PO758, FR-PO902	Teh, Rachel	SA-PO362
Szpiro, Adam	TH-PO613	Taki, Fumika	FR-PO077, SA-PO158, SA-PO799, SA-PO914, PUB139	Taniguchi, Yoshinori	TH-PO005, TH-PO781, FR-PO273, FR-PO503, SA-PO267	Tei, Ritsukou	TH-PO650
Szpiro, Wladimir M.	FR-PO408	Taki, Yasuhiro	SA-PO762	Tanimoto, Hitomi	TH-PO551, TH-PO950	Teixeira, Cynthia Montenegro	FR-PO693
Szucs, Thomas	PUB544	Takiyama, Yumi	TH-PO338	Taniuchi, Yuta	FR-PO935	Teixeira, Vicente De Paulo Castro	FR-PO1000
Taal, Maarten W.	TH-PO534, TH-PO592, PUB197	Takizawa, Keiichi	TH-PO457, FR-PO005, FR-PO092	Tanna, Anisha	FR-PO407, FR-PO409, FR-PO413	Teixeira-Pinto, Armando	TH-PO915
Tabada, Grace Hsu	TH-PO613	Talaksi, Farouk	SA-PO022, SA-PO091, PUB395	Tanno, Yudo	TH-PO737, TH-PO1001, FR-PO071, FR-PO081, SA-PO060, SA-PO977, PUB601	Tejedor Jorge, Alberto	FR-PO106, SA-PO626
Tabari, Azadeh	TH-OR053	Talbot, Ben	SA-PO1033			Tejedor, Marta	FR-PO106
Tabatabaieifar, Mansoureh	FR-PO157	Talsma, Ditmer	TH-PO131			Tejedor, Sandra	FR-PO492
Taber, Tim E.	FR-PO1049, SA-PO958, SA-PO1022, SA-PO1032	Tam, Chun-Hay	TH-PO774			Tel, Francesca	TH-PO082, FR-PO447, FR-PO852, SA-PO638
Tada, Norimasa	TH-PO457, FR-PO005, FR-PO092	Tam, Frederick W.K.	FR-PO154, FR-PO386, FR-PO409			Telles, Mauricio Da Silva	PUB476
Tagawa, Miho	TH-OR010, TH-PO824, FR-PO507, PUB036	Tamai, Hiroshi	TH-PO1106, SA-PO105, PUB404			Tellez-Rojo, Martha M.	SA-PO644
Taglienti, Mary E.	FR-PO184, FR-PO330	Tamaki, Masanori	FR-PO141, FR-PO850, PUB075			Ten Dam, Marc A.G.J.	TH-PO673, SA-PO186
		Tamaki, Toshiaki	PUB101			Teng, Beina	TH-PO303, TH-PO307, TH-PO328
		Tamam, Zeinab M.	SA-PO012			Teng, Jiamin	SA-PO359, SA-PO457
		Tamashiro, Kadee-Kalia	TH-PO215				
		Tamion, Fabienne	PUB554				
		Tamma, Grazia	SA-OR117				
		Tamponi, Elisabetta	SA-PO050				
		Tam-Tham, Helen	TH-PO924, SA-PO719				

Teng, Jie	TH-PO007, TH-PO111, FR-PO467	Thijssen, Stephan	TH-PO960, FR-PO370, FR-PO655, FR-PO674, FR-PO734, FR-PO774, FR-PO874, SA-PO826, SA-PO910, PUB068	Titan, Silvia M.	PUB184, PUB185	Torresani, Ermínio	TH-PO082
Teng, Yoe Kie Onno	TH-PO688, TH-PO766	Thiri, Myo	SA-PO502	Titeca Beauport, Dimitri	FR-PO1014	Tortorici, Amanda R.	FR-PO845, FR-PO900
Tennankore, Karthik K.	FR-PO764, PUB445, PUB446, PUB666	Thodima, Pradeep Reddy	PUB439	Titze, Jens	TH-PO419, TH-PO422, TH-PO832, FR-OR009	Torvik, Laura Rassmussen	SA-PO497
Tentori, Francesca	TH-PO846, TH-PO939, TH-PO940, TH-PO957, FR-OR032, FR-PO738, SA-PO724, PUB592	Thom, Tatiana A.	TH-PO1121	Tobar, Ana	TH-PO359	Tostivint, Isabelle	FR-PO179
Tentori, Stefano	TH-PO816, FR-PO078, PUB344	Thomas, Alison	SA-PO178	Tobe, Sheldon W.	SA-PO780	Toth-Manikowski, Stephanie M.	TH-PO903
Teo, Boon Wee	TH-PO617, FR-PO544	Thomas, Chandra Mary	SA-PO719	Tobita, Seiji	SA-PO425	Toto, Robert D.	SA-PO220
Tepel, Martin	SA-PO479	Thomas, Christie P.	TH-PO718, FR-OR057, SA-OR017, SA-PO317	Toblili, Jorge E.	TH-PO713	Touceda, Luis Alberto	PUB231
Ter Wee, Pieter M.	TH-PO921, FR-PO856, FR-PO857, FR-PO925, SA-PO570	Thomas, Fridtjof	TH-PO536, SA-OR009, SA-OR010, SA-PO619, SA-PO648	Toda, Takayuki	TH-PO1075	Touchard, Guy	TH-PO725
Terabayashi, Takeshi	SA-OR091	Thomas, George	TH-OR119	Todorov, Vladimir T.	TH-PO129, PUB021	Touchberry, Chad D.	TH-PO486
Terada, Yoh	FR-PO936	Thomas, Ian	FR-PO1103, SA-PO1054, PUB568, PUB660	Todros, Tullia	FR-PO594	Touret, Jerome	SA-PO670
Terada, Yoshio	TH-PO005, TH-PO781, FR-PO273, FR-PO503, SA-PO267	Thomas, Jason Peter	PUB210	Toelen, Jaan	TH-OR042	Toussaint, Nigel David	FR-OR025, SA-PO130, PUB537
Terai, Kazuhiro	FR-PO936	Thomas, Karlene	TH-PO882	Togawa, Hiroko	TH-PO787, PUB266	Touyz, Rhan	TH-PO339
Teran, Federico Jose	FR-PO113, FR-PO995	Thomas, Leslie F.	TH-PO1042, TH-PO1065, PUB054	Toida, Tatsunori	TH-PO896	Touze, Antoine	SA-PO1063
Teran, Richard A.	PUB188	Thomas, Nicola	SA-PO840	Tokadome, Gorou	PUB329	Townsend, R.	SA-OR064
Terao, Akira	FR-PO910	Thomas, Sandhya S.	FR-PO543	Tokunaga, Masanori	TH-PO822, FR-OR022, FR-PO902, SA-PO588	Townsend, Raymond R.	TH-OR118, TH-OR119, TH-PO396, TH-PO612, TH-PO632, FR-PO741, SA-PO617, SA-PO747, PUB497
Terawaki, Hiroyuki	FR-PO827	Thomas, Sheela V.	SA-OR112	Tokunaga, Katsushi	SA-PO502	Toyama, Tadashi	TH-PO622, FR-PO571
Tereshchenko, Larisa	TH-PO825, TH-PO900, TH-PO902	Thomas, Tina	FR-PO079	Tokuyama, Hirobumi	TH-PO317, FR-OR878, SA-PO021, SA-PO414	Trachtman, Howard	TH-PO459, TH-PO723, PUB144
Terker, Andrew	TH-OR081, TH-OR082	Thomas, Ijpelaar, Daphne	SA-PO395	Tolba, Hoda	TH-PO811	Traina, Tiffany A.	PUB412
Teruel, Jose L.	PUB483, PUB627	Thomasova, Dana	TH-OR093, SA-OR040, SA-PO283	Tolbert, Evelyn	TH-PO159, SA-PO459, PUB392	Traitanon, Opas	FR-PO1072, PUB643
Tesar, Vladimir	TH-OR026, TH-OR031, FR-PO407	Thompson, Barbara	FR-PO428	Tolkoff-Rubin, Nina E.	PUB178	Traktuev, Dmitry O.	FR-PO234
Tessitore, Nicola	TH-PO850	Thompson, Boyd Taylor	TH-PO085	Tolmie, Elizabeth P.	PUB347	Tran, Duy	PUB650
Testa, Sara	TH-PO082, FR-PO447, FR-PO852, SA-PO638, SA-PO891	Thompson, Jennifer	FR-PO069	Tolosano, Emanuela	PUB083	Tran, John	SA-PO419
Testagrossa, Leonardo Abreu	TH-PO761, TH-PO762, PUB424	Thompson, Samantha J.	SA-PO132	Tolouian, Ramin	PUB709, PUB711	Tran, Nam	PUB023
Testani, Jeffrey M.	TH-PO614	Thompson, Stephanie E.	TH-PO924, PUB353	Tolvani, Tuomas Alekski	TH-PO366	Tran, Pamela Vivian	TH-PO192
Teulon, Jacques	FR-PO178	Thompson, Suzette	FR-PO848	Tolwani, Ashita J.	TH-PO125, FR-PO025, SA-OR105, SA-PO532	Tran, Quynh	PUB032
Textor, Stephen C.	TH-OR065, FR-PO211, FR-PO212, SA-PO222, SA-PO658	Thomsen, Lise	TH-PO358	Tomas, Patricia	FR-PO492	Tran, Tiffany	SA-PO642
Tey, C.S. Jason	TH-PO878	Thomsen, Rikke Lindgaard	PUB293	Tomida, Mamoru	TH-PO072	Tran, Uyen	TH-OR050, TH-PO201, SA-PO878
Tezenas du Montcel, Sophie	TH-PO820, SA-OR031	Thomson, Benjamin R.	TH-PO321, TH-PO420	Tomii, Yuji	TH-PO457, FR-PO005	Tran, Wen-Ching	PUB273
Tezuka, Yuta	PUB216	Thomson, Denise J.	SA-PO059	Tominaga, Naoto	SA-PO929	Trasande, Leonardo	TH-PO459
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- apoptosis**..... TH-OR088, TH-PO015, TH-PO017, TH-PO018, TH-PO036, TH-PO049, TH-PO181, TH-PO205, TH-PO221, TH-PO263, TH-PO264, TH-PO361, TH-PO365, TH-PO387, FR-OR085, FR-OR089, FR-PO218, FR-PO219, FR-PO231, FR-PO258, FR-PO306, FR-PO354, FR-PO523, FR-PO828, FR-PO969, SA-PO240, SA-PO243, SA-PO273, SA-PO279, SA-PO286, SA-PO287, SA-PO293, SA-PO296, SA-PO301, SA-PO303, SA-PO304, SA-PO305, SA-PO307, SA-PO311, SA-PO312, SA-PO313, SA-PO359, SA-PO365, SA-PO409, SA-PO867, PUB022, PUB066, PUB076, PUB471
- arteries**..... TH-PO257, FR-PO127, FR-PO194, SA-PO055, PUB694
- arteriosclerosis**..... TH-PO381, TH-PO386, TH-PO390, TH-PO406, TH-PO416, TH-PO888, TH-PO889, TH-PO891, TH-PO897, TH-PO971, FR-PO004, FR-PO545, FR-PO625, FR-PO863, SA-PO314, SA-PO592, PUB187, PUB201, PUB705
- arteriovenous access**..... TH-OR062, TH-PO536, TH-PO842, TH-PO851, TH-PO858, TH-PO869, TH-PO870, TH-PO873, FR-PO382, FR-PO693, FR-PO694, FR-PO703, FR-PO713, SA-PO845, PUB486, PUB488
- arteriovenous fistula**..... TH-OR059, TH-PO334, TH-PO838, TH-PO839, TH-PO841, TH-PO842, TH-PO843, TH-PO846, TH-PO851, TH-PO855, TH-PO859, TH-PO860, TH-PO862, TH-PO864, TH-PO866, TH-PO869, TH-PO871, TH-PO874, TH-PO875, TH-PO876, FR-PO693, FR-PO697, FR-PO716, FR-PO717, FR-PO720, FR-PO723, SA-PO055, SA-PO147, SA-PO165, SA-PO576, PUB475, PUB476, PUB479, PUB483, PUB484, PUB485, PUB486, PUB487, PUB489, PUB490
- arteriovenous graft**..... TH-PO850, TH-PO855, TH-PO859, TH-PO866, TH-PO879, FR-PO693, PUB484, PUB485
- arteriovenous shunt**..... TH-PO854
- Bartter syndrome**..... TH-OR076, TH-PO425, FR-PO011, FR-PO040, SA-PO904
- blood pressure**..... TH-OR020, TH-OR084, TH-PO019, TH-PO423, TH-PO432, TH-PO451, TH-PO470, TH-PO546, TH-PO586, TH-PO612, TH-PO659, TH-PO665, TH-PO674, TH-PO804, TH-PO808, TH-PO827, TH-PO837, TH-PO883, TH-PO949, TH-PO970, TH-PO1022, FR-OR041, FR-OR047, FR-PO089, FR-PO113, FR-PO121, FR-PO137, FR-PO141, FR-PO142, FR-PO146, FR-PO227, FR-PO368, FR-PO528, FR-PO565, FR-PO631, FR-PO650, FR-PO673, FR-PO741, FR-PO744, FR-PO745, FR-PO1012, SA-OR009, SA-OR066, SA-OR067, SA-OR068, SA-OR069, SA-PO456, SA-PO497, SA-PO616, SA-PO618, SA-PO619, SA-PO620, SA-PO627, SA-PO629, SA-PO630, SA-PO638, SA-PO639, SA-PO640, SA-PO644, SA-PO648, SA-PO650, SA-PO651, SA-PO652, SA-PO653, SA-PO668, SA-PO702, PUB146, PUB367, PUB494, PUB502, PUB568, PUB618, PUB628, PUB637, PUB638
- cadaver organ transplantation**..... FR-OR070, FR-PO1003, FR-PO1004, FR-PO1061, SA-OR056, SA-PO069, SA-PO948, PUB655
- calcium**..... TH-OR115, TH-PO003, TH-PO243, TH-PO299, TH-PO312, TH-PO351, TH-PO352, TH-PO394, TH-PO516, TH-PO521, TH-PO562, TH-PO820, TH-PO824, TH-PO840, TH-PO905, TH-PO906, TH-PO1058, TH-PO1060, TH-PO1103, TH-PO1107, FR-OR001, FR-OR027, FR-OR030, FR-PO001, FR-PO029, FR-PO033, FR-PO041, FR-PO054, FR-PO067, FR-PO328,

- calcium (continued)**.....FR-PO331, FR-PO358, FR-PO755, FR-PO901, FR-PO903, FR-PO919, FR-PO920, FR-PO921, FR-PO922, FR-PO923, FR-PO924, FR-PO925, FR-PO926, FR-PO943, FR-PO944, FR-PO947, FR-PO953, FR-PO955, SA-OR047, SA-OR049, SA-PO016, SA-PO065, SA-PO413, SA-PO458, SA-PO575, SA-PO581, SA-PO590, SA-PO591, SA-PO592, SA-PO595, SA-PO597, SA-PO929, PUB023, PUB417, PUB438, PUB453, PUB454, PUB517, PUB519, PUB520, PUB533, PUB536, PUB601, PUB629, PUB636, PUB637
- calcium receptor**..... TH-PO517, TH-PO523
- calcium switch**..... FR-PO263
- calcium-sensing receptor**..... TH-PO369, TH-PO516, TH-PO520, FR-PO919, SA-PO565, SA-PO574, PUB529
- cancer**..... TH-OR073, TH-PO114, TH-PO185, TH-PO256, TH-PO291, TH-PO670, TH-PO752, TH-PO926, TH-PO966, TH-PO1029, TH-PO1034, TH-PO1077, TH-PO1103, TH-PO1121, FR-PO039, FR-PO056, FR-PO261, FR-PO381, FR-PO406, FR-PO587, FR-PO589, SA-PO024, SA-PO056, SA-PO059, SA-PO084, SA-PO104, SA-PO111, SA-PO113, SA-PO142, SA-PO516, SA-PO918, SA-PO1086, SA-PO1087, SA-PO1088, SA-PO1090, PUB108, PUB150, PUB161, PUB253, PUB378, PUB385, PUB394, PUB408, PUB412, PUB436, PUB506, PUB519, PUB579, PUB674, PUB678, PUB699
- cardiovascular**..... TH-OR120, TH-PO051, TH-PO100, TH-PO101, TH-PO152, TH-PO393, TH-PO486, TH-PO594, TH-PO596, TH-PO617, TH-PO620, TH-PO625, TH-PO634, TH-PO833, TH-PO837, TH-PO889, TH-PO890, TH-PO897, TH-PO910, TH-PO911, TH-PO914, TH-PO919, FR-OR028, FR-OR046, FR-PO468, FR-PO546, FR-PO635, FR-PO705, FR-PO725, FR-PO746, FR-PO751, FR-PO752, FR-PO805, FR-PO915, FR-PO1011, FR-PO1014, SA-OR006, SA-OR034, SA-OR097, SA-PO627, SA-PO707, SA-PO809, SA-PO894, PUB025, PUB127, PUB131, PUB299, PUB333, PUB337, PUB509, PUB620, PUB694
- cardiovascular disease**..... TH-OR110, TH-OR111, TH-OR122, TH-PO081, TH-PO375, TH-PO379, TH-PO388, TH-PO389, TH-PO391, TH-PO407, TH-PO410, TH-PO414, TH-PO458, TH-PO463, TH-PO479, TH-PO480, TH-PO481, TH-PO482, TH-PO483, TH-PO484, TH-PO512, TH-PO540, TH-PO576, TH-PO579, TH-PO586, TH-PO588, TH-PO593, TH-PO595, TH-PO607, TH-PO613, TH-PO618, TH-PO622, TH-PO623, TH-PO626, TH-PO628, TH-PO633, TH-PO639, TH-PO798, TH-PO816, TH-PO817, TH-PO824, TH-PO885, TH-PO896, TH-PO898, TH-PO899, TH-PO901, TH-PO907, TH-PO908, TH-PO909, TH-PO918, TH-PO922, FR-OR045,
- cardiovascular disease (continued)**.. FR-PO119, FR-PO145, FR-PO276, FR-PO469, FR-PO504, FR-PO530, FR-PO670, FR-PO726, FR-PO727, FR-PO731, FR-PO733, FR-PO747, FR-PO748, FR-PO749, FR-PO754, FR-PO756, FR-PO834, FR-PO902, FR-PO925, FR-PO933, FR-PO1026, FR-PO1101, SA-OR029, SA-OR060, SA-OR103, SA-OR107, SA-PO142, SA-PO197, SA-PO308, SA-PO311, SA-PO399, SA-PO595, SA-PO606, SA-PO614, SA-PO630, SA-PO654, SA-PO725, SA-PO822, PUB031, PUB038, PUB133, PUB136, PUB137, PUB138, PUB139, PUB140, PUB182, PUB321, PUB322, PUB327, PUB330, PUB335, PUB339, PUB490, PUB497, PUB538, PUB582, PUB629, PUB656, PUB672, PUB706, PUB709
- cardiovascular events**..... TH-OR010, TH-OR115, TH-OR123, TH-OR124, TH-PO072, TH-PO084, TH-PO537, TH-PO549, TH-PO550, TH-PO585, TH-PO589, TH-PO598, TH-PO599, TH-PO604, TH-PO605, TH-PO606, TH-PO609, TH-PO610, TH-PO612, TH-PO615, TH-PO619, TH-PO627, TH-PO799, TH-PO803, TH-PO805, TH-PO886, TH-PO893, TH-PO912, TH-PO923, TH-PO1007, TH-PO1017, FR-PO069, FR-PO126, FR-PO477, FR-PO486, FR-PO502, FR-PO533, FR-PO636, FR-PO715, FR-PO730, FR-PO734, FR-PO736, FR-PO738, FR-PO739, FR-PO740, FR-PO741, FR-PO743, FR-PO753, FR-PO755, FR-PO855, FR-PO1021, FR-PO1029, SA-PO180, SA-PO655, SA-PO775, SA-PO925, PUB025, PUB130, PUB320, PUB324, PUB329, PUB332, PUB344, PUB345, PUB532, PUB543, PUB600, PUB675, PUB712
- cell and transport physiology**..... TH-OR075, TH-PO163, TH-PO294, TH-PO331, TH-PO439, TH-PO444, TH-PO488, FR-PO101, FR-PO110, FR-PO124, FR-PO203, FR-PO329, FR-PO955, SA-OR068, SA-OR073, SA-OR115, SA-PO285, SA-PO575, SA-PO935, PUB718
- cell ablation**..... TH-PO417, FR-OR106
- cell activation**..... TH-PO161, TH-PO255, TH-PO383, FR-PO619, SA-PO316, SA-PO565
- cell adhesion**..... TH-PO045, TH-PO303, TH-PO415, FR-PO283, FR-PO312, FR-PO322, FR-PO362, FR-PO829, FR-PO835, SA-PO340, SA-PO352, SA-PO413
- cell biology and structure**..... TH-OR099, TH-PO196, TH-PO199, TH-PO215, TH-PO222, TH-PO247, TH-PO292, TH-PO302, TH-PO313, FR-PO161, FR-PO177, FR-PO207, FR-PO226, FR-PO252, FR-PO298, FR-PO321, FR-PO325, FR-PO328, FR-PO825, FR-PO961, SA-PO290, SA-PO306, SA-PO314, SA-PO334, SA-PO339, SA-PO403, SA-PO485, SA-PO942, PUB085, PUB087, PUB099, PUB471
- cell death**..... TH-OR093, TH-OR099, TH-PO003, TH-PO008, TH-PO039, TH-PO161, TH-PO218, TH-PO247, TH-PO251, TH-PO300, TH-PO695, TH-PO835, TH-PO839, TH-PO1016, FR-PO265, FR-PO540, FR-PO824, SA-PO260, SA-PO263, SA-PO275, SA-PO283, SA-PO288, SA-PO291, SA-PO292, SA-PO294, PUB068
- cell signaling**..... TH-OR049, TH-OR053, TH-OR067, TH-OR096, TH-OR109, TH-OR111, TH-PO005, TH-PO023, TH-PO026, TH-PO137, TH-PO147, TH-PO150, TH-PO158, TH-PO162, TH-PO163, TH-PO181, TH-PO184, TH-PO188, TH-PO189, TH-PO233, TH-PO256, TH-PO283, TH-PO290, TH-PO291, TH-PO295, TH-PO307, TH-PO310, TH-PO311, TH-PO321, TH-PO332, TH-PO345, TH-PO347, TH-PO363, TH-PO381, TH-PO408, TH-PO447, TH-PO448, TH-PO483, TH-PO484, TH-PO489, FR-OR053, FR-OR067, FR-OR081, FR-OR102, FR-OR105, FR-PO127, FR-PO182, FR-PO237, FR-PO238, FR-PO240, FR-PO253, FR-PO264, FR-PO273, FR-PO285, FR-PO292, FR-PO293, FR-PO295, FR-PO298, FR-PO305, FR-PO335, FR-PO340, FR-PO345, FR-PO358, FR-PO810, FR-PO918, FR-PO971, FR-OR976, SA-OR081, SA-OR086, SA-OR095, SA-OR117, SA-PO253, SA-PO291, SA-PO296, SA-PO297, SA-PO303, SA-PO307, SA-PO310, SA-PO316, SA-PO319, SA-PO323, SA-PO325, SA-PO327, SA-PO331, SA-PO333, SA-PO343, SA-PO353, SA-PO356, SA-PO371, SA-PO406, SA-PO410, SA-PO420, SA-PO457, SA-PO464, SA-PO475, SA-PO476, SA-PO478, SA-PO484, SA-PO757, SA-PO983, PUB095, PUB096, PUB101, PUB284
- cell survival**..... TH-OR032, TH-OR096, TH-PO050, FR-PO230, FR-PO236, FR-PO279, FR-PO828, SA-PO305, SA-PO400, PUB020, PUB067
- cell transfer**..... FR-PO248, FR-PO817, PUB079
- cell volume**..... TH-PO835
- cell volume regulation**..... TH-PO443
- cell-matrix-interactions**..... TH-PO031, TH-PO298, FR-PO220, FR-PO278, FR-PO290, SA-PO359, SA-PO461, SA-PO472, SA-PO489
- chemokine**..... TH-PO335, TH-PO403, TH-PO663, FR-PO270, FR-PO327, FR-PO403, FR-PO522, FR-PO617, SA-PO323, SA-PO988, SA-PO992, PUB233
- chemokine receptor**..... TH-OR031, TH-PO024, TH-PO277, TH-PO306, TH-PO663, TH-PO664, FR-OR067
- chemotherapy**..... TH-PO076, TH-PO092, TH-PO093, TH-PO668, TH-PO1053, TH-PO1074, TH-PO1102, FR-PO040, FR-PO261, FR-PO482, SA-PO007, SA-PO045, SA-PO094, SA-PO228, PUB054, PUB385, PUB394, PUB412, PUB454

children TH-PO379, TH-PO380, TH-PO453, TH-PO462, TH-PO463, TH-PO464, TH-PO467, TH-PO469, TH-PO509, TH-PO633, TH-PO733, TH-PO1106, FR-PO430, FR-PO838, FR-PO852, SA-OR021, SA-OR024, SA-PO105, SA-PO232, SA-PO638, SA-PO643, SA-PO644, SA-PO741, SA-PO1016, PUB046, PUB220, PUB404, PUB576, PUB581, PUB700

chronic allograft failure..... TH-OR074, FR-PO1009, FR-PO1035, SA-OR059, SA-PO967, SA-PO981, PUB658

chronic allograft nephropathy FR-PO044, FR-PO289, FR-PO1070, FR-PO1079, SA-PO062, SA-PO479, SA-PO981, SA-PO983, SA-PO987, SA-PO991, SA-PO998, PUB046, PUB698

chronic allograft rejection TH-OR068, FR-PO1049, SA-PO969

chronic diabetic complications..... FR-PO572, FR-PO607, SA-PO390, PUB380

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chronic glomerulonephritis TH-OR070, TH-PO145, TH-PO225, TH-PO787, FR-PO439, SA-PO358, SA-PO1076, PUB247

chronic graft deterioration..... TH-PO273, TH-PO521, FR-PO1024, SA-PO989, SA-PO997, SA-PO1040, SA-PO1076

chronic heart failure TH-PO540, TH-PO576, TH-PO920, FR-PO685, PUB341

chronic hemodialysis TH-OR063, TH-PO405, TH-PO495, TH-PO671, TH-PO806, TH-PO807, TH-PO808, TH-PO822, TH-PO837, TH-PO873, TH-PO878, TH-PO904, TH-PO920, TH-PO935, TH-PO971, FR-PO652, FR-PO681, FR-PO705, FR-PO760, FR-PO777, FR-PO912, SA-PO152, SA-PO156, SA-PO168, SA-PO182, SA-PO566, SA-PO787, SA-PO800, SA-PO906, SA-PO925, PUB112, PUB313, PUB337, PUB349, PUB363, PUB365, PUB396, PUB633

chronic hypoxia TH-OR030, SA-PO414, PUB346

chronic inflammation... TH-OR060, TH-OR109, TH-PO191, TH-PO391, TH-PO489, TH-PO568, TH-PO591, TH-PO597, TH-PO666, TH-PO834, TH-PO972, TH-PO1068, FR-OR104, FR-PO116, FR-PO144, FR-PO527, FR-PO663, FR-PO766, FR-PO847, FR-PO862, FR-PO887, FR-PO897, FR-PO989, FR-PO1026, FR-PO1035, SA-OR075, SA-PO328, SA-PO399, SA-PO572, PUB100, PUB104, PUB288, PUB482, PUB610, PUB633, PUB634

chronic kidney disease TH-OR005, TH-OR008, TH-OR011, TH-OR014, TH-OR017, TH-OR035, TH-OR036, TH-OR038, TH-OR039, TH-OR040, TH-OR066, TH-OR085, TH-OR086, TH-OR090, TH-OR098, TH-OR108, TH-OR109, TH-OR113, TH-OR117, TH-OR118, TH-OR119, TH-OR120, TH-OR123, TH-PO029, TH-PO030, TH-PO053, TH-PO060, TH-PO062, TH-PO068, TH-PO069, TH-PO107, TH-PO140, TH-PO147, TH-PO149, TH-PO157, TH-PO159, TH-PO165, TH-PO167, TH-PO207, TH-PO236, TH-PO244, TH-PO258, TH-PO260, TH-PO287, TH-PO322, TH-PO368, TH-PO377, TH-PO378, TH-PO379, TH-PO380, TH-PO385, TH-PO388, TH-PO396, TH-PO402, TH-PO407, TH-PO410, TH-PO452, TH-PO453, TH-PO454, TH-PO461, TH-PO469, TH-PO476, TH-PO478, TH-PO482, TH-PO490, TH-PO491, TH-PO492, TH-PO496, TH-PO497, TH-PO499, TH-PO505, TH-PO506, TH-PO507, TH-PO513, TH-PO525, TH-PO527, TH-PO529, TH-PO530, TH-PO532, TH-PO533, TH-PO536, TH-PO537, TH-PO538, TH-PO540, TH-PO541, TH-PO543, TH-PO546, TH-PO547, TH-PO550, TH-PO551, TH-PO552, TH-PO554, TH-PO555, TH-PO556, TH-PO557, TH-PO558, TH-PO559, TH-PO564, TH-PO565, TH-PO566, TH-PO572, TH-PO574, TH-PO575, TH-PO580, TH-PO583, TH-PO584, TH-PO585, TH-PO588, TH-PO589, TH-PO591, TH-PO595, TH-PO599, TH-PO600, TH-PO601, TH-PO602, TH-PO603, TH-PO605, TH-PO606, TH-PO607, TH-PO610, TH-PO611, TH-PO614, TH-PO615, TH-PO617, TH-PO618, TH-PO622, TH-PO631, TH-PO633, TH-PO636, TH-PO638, TH-PO639, TH-PO640, TH-PO641, TH-PO643, TH-PO645, TH-PO646, TH-PO648, TH-PO649, TH-PO650, TH-PO651, TH-PO652, TH-PO654, TH-PO656, TH-PO658, TH-PO659, TH-PO670, TH-PO671, TH-PO674, TH-PO677, TH-PO707, TH-PO715, TH-PO719, TH-PO756, TH-PO793, TH-PO838, TH-PO883, TH-PO901, TH-PO1030, TH-PO1060, TH-PO1064, TH-PO1065, TH-PO1069, TH-PO1088, FR-OR011, FR-OR021, FR-OR022, FR-OR025, FR-OR026, FR-OR045, FR-OR105, FR-OR110, FR-OR112, FR-OR114, FR-PO018, FR-PO068, FR-PO116, FR-PO119, FR-PO132, FR-PO142, FR-PO175, FR-PO214, FR-PO215, FR-PO223, FR-PO224, FR-PO226, FR-PO246, FR-PO266, FR-PO273, FR-PO275, FR-PO276, FR-PO280, FR-PO288, FR-PO296, FR-PO300, FR-PO311, FR-PO323, FR-PO356, FR-PO380, FR-PO383, FR-PO384, FR-PO385, FR-PO388, FR-PO393, FR-PO429, FR-PO466, FR-PO484, FR-PO501, FR-PO503, FR-PO507, FR-PO509, FR-PO510, FR-PO516, FR-PO517, FR-PO519,

chronic kidney disease (continued)..... FR-PO523, FR-PO524, FR-PO528, FR-PO529, FR-PO533, FR-PO534, FR-PO536, FR-PO537, FR-PO539, FR-PO544, FR-PO545, FR-PO549, FR-PO550, FR-PO551, FR-PO552, FR-PO553, FR-PO554, FR-PO556, FR-PO558, FR-PO559, FR-PO560, FR-PO562, FR-PO571, FR-PO575, FR-PO579, FR-PO586, FR-PO591, FR-PO592, FR-PO593, FR-PO594, FR-PO596, FR-PO597, FR-PO601, FR-PO606, FR-PO612, FR-PO614, FR-PO624, FR-PO633, FR-PO640, FR-PO646, FR-PO649, FR-PO722, FR-PO843, FR-PO851, FR-PO858, FR-PO862, FR-PO863, FR-PO864, FR-PO868, FR-PO873, FR-PO883, FR-PO884, FR-PO885, FR-PO886, FR-PO888, FR-PO891, FR-PO893, FR-PO925, FR-PO932, FR-PO982, FR-PO1000, SA-OR002, SA-OR010, SA-OR023, SA-OR043, SA-OR074, SA-OR075, SA-OR076, SA-OR080, SA-OR081, SA-OR082, SA-OR084, SA-OR085, SA-OR086, SA-OR094, SA-OR097, SA-OR101, SA-OR102, SA-PO128, SA-PO137, SA-PO147, SA-PO151, SA-PO158, SA-PO159, SA-PO162, SA-PO169, SA-PO170, SA-PO173, SA-PO210, SA-PO225, SA-PO231, SA-PO245, SA-PO251, SA-PO253, SA-PO268, SA-PO288, SA-PO309, SA-PO326, SA-PO330, SA-PO346, SA-PO360, SA-PO367, SA-PO390, SA-PO412, SA-PO423, SA-PO425, SA-PO428, SA-PO432, SA-PO437, SA-PO445, SA-PO446, SA-PO452, SA-PO456, SA-PO460, SA-PO465, SA-PO467, SA-PO468, SA-PO469, SA-PO474, SA-PO494, SA-PO496, SA-PO499, SA-PO520, SA-PO521, SA-PO533, SA-PO537, SA-PO546, SA-PO552, SA-PO553, SA-PO561, SA-PO563, SA-PO576, SA-PO577, SA-PO587, SA-PO591, SA-PO593, SA-PO597, SA-PO599, SA-PO603, SA-PO618, SA-PO620, SA-PO641, SA-PO653, SA-PO663, SA-PO672, SA-PO674, SA-PO675, SA-PO676, SA-PO679, SA-PO683, SA-PO685, SA-PO686, SA-PO687, SA-PO688, SA-PO689, SA-PO691, SA-PO695, SA-PO696, SA-PO698, SA-PO699, SA-PO700, SA-PO701, SA-PO702, SA-PO703, SA-PO705, SA-PO709, SA-PO713, SA-PO716, SA-PO718, SA-PO720, SA-PO723, SA-PO724, SA-PO727, SA-PO728, SA-PO730, SA-PO731, SA-PO732, SA-PO735, SA-PO740, SA-PO741, SA-PO742, SA-PO743, SA-PO752, SA-PO754, SA-PO755, SA-PO760, SA-PO761, SA-PO762, SA-PO763, SA-PO764, SA-PO765, SA-PO778, SA-PO781, SA-PO833, SA-PO871, SA-PO883, SA-PO885, SA-PO894, SA-PO914, SA-PO924, SA-PO934, SA-PO997, SA-PO1022, SA-PO1052, PUB034, PUB039, PUB041, PUB064, PUB075, PUB080, PUB093, PUB100,

- chronic kidney disease (continued)**.....PUB110, PUB111, PUB116, PUB119, PUB121, PUB126, PUB128, PUB129, PUB130, PUB132, PUB138, PUB139, PUB141, PUB142, PUB145, PUB146, PUB150, PUB153, PUB156, PUB158, PUB159, PUB161, PUB163, PUB164, PUB165, PUB166, PUB169, PUB170, PUB172, PUB173, PUB177, PUB180, PUB181, PUB183, PUB186, PUB187, PUB188, PUB192, PUB196, PUB197, PUB199, PUB200, PUB205, PUB219, PUB225, PUB244, PUB246, PUB303, PUB325, PUB452, PUB473, PUB477, PUB497, PUB498, PUB499, PUB502, PUB507, PUB508, PUB515, PUB523, PUB538, PUB548, PUB558, PUB571, PUB573, PUB576, PUB577, PUB578, PUB581, PUB613, PUB614, PUB657, PUB704, PUB706
- chronic kidney failure**..... TH-OR105, TH-OR122, TH-PO120, TH-PO137, TH-PO539, TH-PO637, TH-PO695, TH-PO793, TH-PO857, TH-PO889, TH-PO948, FR-PO221, FR-PO531, FR-PO567, FR-PO989, SA-PO293, SA-PO422, SA-PO584, SA-PO686, SA-PO719, SA-PO734, SA-PO791, PUB137, PUB603
- chronic metabolic acidosis**..... TH-PO491, SA-PO894, PUB449
- chronic nephropathy**..... TH-PO217, FR-PO957, SA-PO164, SA-PO360
- chronic rejection**..... TH-OR069, FR-PO1086, SA-PO959, SA-PO971
- chronic renal disease**..... TH-OR015, TH-OR018, TH-OR034, TH-OR043, TH-OR077, TH-PO173, TH-PO467, TH-PO487, TH-PO553, TH-PO576, TH-PO578, TH-PO579, TH-PO581, TH-PO590, TH-PO596, TH-PO609, TH-PO612, TH-PO613, TH-PO727, TH-PO773, TH-PO1018, FR-OR009, FR-PO173, FR-PO274, FR-PO299, FR-PO302, FR-PO485, FR-PO599, FR-PO682, FR-PO842, FR-PO899, SA-PO190, SA-PO248, SA-PO483, SA-PO600, SA-PO681, SA-PO714, SA-PO730, SA-PO746, SA-PO749, SA-PO798, SA-PO814, SA-PO854, SA-PO876, PUB147, PUB191, PUB393, PUB500
- chronic renal failure**..... TH-OR006, TH-OR015, TH-OR107, TH-PO153, TH-PO582, TH-PO833, FR-OR019, FR-PO538, FR-PO567, FR-PO665, SA-OR008, SA-OR033, SA-PO450, SA-PO551, SA-PO565, SA-PO606, SA-PO717, SA-PO719, SA-PO926, PUB014, PUB179, PUB396, PUB567, PUB612, PUB618
- chronic renal insufficiency**..... TH-PO392, TH-PO676, FR-PO470, FR-PO556, FR-PO569, FR-PO661, FR-PO916, FR-PO917, PUB125, PUB163, PUB557
- cisplatin**..... TH-PO049, FR-PO236, FR-PO247, FR-PO261, FR-PO270, SA-PO275, SA-PO287, PUB029
- cisplatin nephrotoxicity**..... TH-PO033, TH-PO039, TH-PO153, FR-PO235, FR-PO257, FR-PO260, FR-PO872, SA-PO206, SA-PO221, SA-PO243, SA-PO262, SA-PO266, SA-PO268, SA-PO270, SA-PO273, SA-PO527, SA-PO554, PUB009
- clinical epidemiology**..... TH-OR124, TH-PO063, TH-PO459, TH-PO529, TH-PO539, TH-PO546, TH-PO574, TH-PO580, TH-PO594, TH-PO791, TH-PO942, TH-PO955, TH-PO956, TH-PO957, TH-PO965, FR-OR041, FR-PO436, FR-PO505, FR-PO529, FR-PO548, FR-PO573, FR-PO586, FR-PO587, FR-PO591, FR-PO599, FR-PO634, FR-PO680, FR-PO725, FR-PO753, FR-PO763, FR-PO768, FR-PO769, FR-PO783, FR-PO856, FR-PO1017, SA-OR019, SA-OR078, SA-PO195, SA-PO515, SA-PO619, SA-PO632, SA-PO648, SA-PO659, SA-PO679, SA-PO722, SA-PO724, SA-PO726, SA-PO729, SA-PO754, SA-PO755, SA-PO790, SA-PO794, SA-PO854, SA-PO872, PUB049, PUB118, PUB124, PUB125, PUB155, PUB159, PUB310, PUB657
- clinical hypertension**..... SA-PO119, SA-PO632, SA-PO642, SA-PO654
- clinical immunology**..... TH-PO670, TH-PO742, FR-OR061, FR-PO047, FR-PO986, FR-PO1036, SA-PO068, SA-PO535, SA-PO536, SA-PO957, SA-PO958, SA-PO967, SA-PO1069, PUB425, PUB686
- clinical nephrology**..... TH-PO096, TH-PO098, TH-PO517, TH-PO547, TH-PO744, TH-PO1040, TH-PO1068, TH-PO1097, TH-PO1115, FR-OR008, FR-OR073, FR-PO014, FR-PO032, FR-PO050, FR-PO051, FR-PO053, FR-PO075, FR-PO393, FR-PO408, FR-PO456, FR-PO495, FR-PO566, FR-PO599, FR-PO666, FR-PO688, FR-PO689, FR-PO767, FR-PO1016, FR-PO1045, SA-OR005, SA-OR032, SA-PO012, SA-PO020, SA-PO030, SA-PO079, SA-PO130, SA-PO140, SA-PO188, SA-PO196, SA-PO211, SA-PO613, SA-PO817, SA-PO821, SA-PO896, SA-PO905, SA-PO1000, PUB026, PUB057, PUB059, PUB143, PUB147, PUB216, PUB227, PUB229, PUB247, PUB250, PUB252, PUB264, PUB269, PUB442, PUB465, PUB514, PUB527, PUB602
- clinical trial**..... TH-OR023, TH-OR033, TH-OR034, TH-OR040, TH-PO125, TH-PO460, TH-PO506, TH-PO615, TH-PO639, TH-PO652, TH-PO654, TH-PO661, TH-PO667, TH-PO675, TH-PO677, TH-PO739, TH-PO742, TH-PO804, TH-PO915, TH-PO921, TH-PO938, FR-OR008, FR-OR016, FR-OR030, FR-PO446, FR-PO651, FR-PO907, FR-PO908, FR-PO928, FR-PO945, FR-PO950, SA-OR076, SA-PO174, SA-PO550, SA-PO572, SA-PO662, SA-PO745, SA-PO849, SA-PO865, SA-PO924, SA-PO927, SA-PO953, SA-PO1037, PUB111, PUB113, PUB114, PUB115, PUB116, PUB265,
- clinical trial (continued)**..... PUB357, PUB383, PUB501, PUB571, PUB610, PUB714, PUB716
- Cockcroft-Gault**..... PUB162
- collapsing FSGS**..... TH-PO1026, SA-PO1078
- collecting ducts**..... TH-PO433, TH-PO434, FR-OR093, FR-OR107, FR-PO094, FR-PO102, FR-PO107, FR-PO108, FR-PO185, FR-PO200, FR-PO209, SA-PO282, SA-PO379, SA-PO935, SA-PO944, PUB095, PUB717
- complement**..... TH-PO129, TH-PO130, TH-PO460, TH-PO679, TH-PO680, TH-PO682, TH-PO718, TH-PO726, TH-PO1062, TH-PO1063, TH-PO1085, TH-PO1087, TH-PO1093, TH-PO1096, FR-OR065, FR-PO012, FR-PO062, FR-PO169, FR-PO293, FR-PO446, FR-PO447, FR-PO450, FR-PO451, FR-PO452, FR-PO454, FR-PO483, FR-PO512, FR-PO660, FR-PO957, FR-PO958, FR-PO959, FR-PO960, FR-PO994, SA-PO027, SA-PO036, SA-PO042, SA-PO511, SA-PO535, SA-PO536, SA-PO979, SA-PO1082, PUB005, PUB028, PUB046, PUB074, PUB226, PUB416, PUB437
- congestive heart failure**..... TH-PO081, TH-PO539, TH-PO631, TH-PO637, TH-PO638, FR-PO1100, SA-PO052, PUB040, PUB137, PUB587
- coronary artery disease**..... TH-OR117, TH-PO052, TH-PO065, TH-PO532, TH-PO591, FR-PO474, FR-PO725, FR-PO731, FR-PO732, FR-PO1021, SA-PO189, SA-PO212, PUB125
- coronary calcification**..... TH-PO600, TH-PO904, FR-PO1101, SA-OR094, SA-PO601, SA-PO602, PUB139, PUB140, PUB344, PUB621, PUB711
- cortisol**..... FR-PO004, FR-PO027, SA-PO105
- creatinine**..... TH-PO089, TH-PO611, TH-PO666, FR-PO070, FR-PO259, FR-PO460, FR-PO471, FR-PO506, FR-PO521, FR-PO869, SA-OR099, SA-PO121, SA-PO189, SA-PO193, SA-PO205, SA-PO232, SA-PO767, SA-PO772, SA-PO1046, PUB012, PUB033, PUB160, PUB300, PUB696
- creatinine clearance**..... FR-PO365, FR-PO1018, SA-PO153, SA-PO193, SA-PO681, SA-PO1022, PUB058, PUB062, PUB162, PUB541
- cyclic AMP**..... TH-PO210, SA-PO946, PUB268
- cyclic GMP**..... TH-PO235, FR-PO241
- cyclosporine**..... TH-PO299, FR-OR001, FR-PO1083, SA-PO541, PUB081
- cyclosporine nephrotoxicity**..... TH-PO175, TH-PO691
- cystic kidney**..... TH-OR048, TH-OR051, TH-OR054, TH-OR056, TH-PO153, TH-PO176, TH-PO181, TH-PO182, TH-PO185, TH-PO186, TH-PO191, TH-PO194, TH-PO195, TH-PO218, TH-PO222, TH-PO420, FR-OR090, FR-PO103, FR-PO164, FR-PO174, FR-PO381, FR-PO927, SA-PO505, SA-PO847, SA-PO852, SA-PO853, SA-PO874, SA-PO876,

- cystic kidney (continued)**..... SA-PO882, SA-PO884, SA-PO887, SA-PO891, SA-PO1087, PUB267, PUB276
- cytokines**..... TH-OR097, TH-PO006, TH-PO018, TH-PO022, TH-PO041, TH-PO048, TH-PO151, TH-PO160, TH-PO172, TH-PO278, TH-PO288, TH-PO319, TH-PO356, TH-PO394, TH-PO395, TH-PO415, TH-PO892, FR-OR058, FR-OR059, FR-PO117, FR-PO163, FR-PO247, FR-PO400, FR-PO831, FR-PO837, FR-PO842, FR-PO896, FR-PO952, FR-PO988, FR-PO1000, SA-PO028, SA-PO222, SA-PO235, SA-PO280, SA-PO300, SA-PO319, SA-PO323, SA-PO373, SA-PO378, SA-PO407, SA-PO433, SA-PO486, SA-PO488, SA-PO589, SA-PO930, PUB096, PUB174, PUB233, PUB295, PUB471, PUB472
- cytomegalovirus**..... TH-PO277, TH-PO1050, FR-PO064, SA-PO1068, PUB061, PUB662, PUB665, PUB676
- cytoskeleton** TH-PO038, TH-PO302, TH-PO401, TH-PO425, FR-PO266, FR-PO267, FR-PO319, FR-PO332, FR-PO336, FR-PO359, SA-OR045, SA-OR046, SA-PO297, PUB467
- daily hemodialysis** SA-PO162, SA-PO838, SA-PO839, SA-PO841, PUB491
- delayed graft function**..... TH-PO263, TH-PO264, FR-PO1038, FR-PO1042, FR-PO1046, FR-PO1058, FR-PO1059, FR-PO1100, SA-PO249, SA-PO947, SA-PO952, SA-PO953, SA-PO986, SA-PO996, SA-PO1028, PUB660
- dementia**..... TH-OR015, TH-OR017, TH-PO829, FR-PO383, FR-PO1099, SA-PO631, PUB367
- Dent disease** FR-OR051, SA-PO053
- depression** TH-OR016, TH-PO997, TH-PO1024, FR-PO600, FR-PO667, FR-PO800, FR-PO1037, SA-PO168, SA-PO739, SA-PO742, SA-PO743, SA-PO744, SA-PO747, SA-PO759, PUB350, PUB372
- diabetes**..... TH-OR001, TH-OR009, TH-OR012, TH-OR032, TH-PO241, TH-PO270, TH-PO324, TH-PO344, TH-PO382, TH-PO384, TH-PO475, TH-PO622, TH-PO805, TH-PO904, TH-PO965, FR-OR074, FR-PO380, FR-PO569, FR-PO584, FR-PO631, FR-PO635, FR-PO637, FR-PO648, FR-PO793, FR-PO894, FR-PO948, FR-PO1105, SA-OR006, SA-OR093, SA-OR095, SA-PO299, SA-PO301, SA-PO348, SA-PO367, SA-PO379, SA-PO385, SA-PO386, SA-PO392, SA-PO400, SA-PO403, SA-PO406, SA-PO611, SA-PO687, SA-PO866, SA-PO1020, PUB129, PUB295, PUB310, PUB380, PUB611, PUB642, PUB697, PUB709
- diabetes insipidus** FR-OR003, FR-OR004, FR-PO030, FR-PO109, SA-OR116, SA-PO010, PUB444
- diabetes mellitus** TH-OR016, TH-PO068, TH-PO176, TH-PO354, TH-PO362, TH-PO446, TH-PO653, TH-PO879, TH-PO932, TH-PO1059, FR-PO092, FR-PO530, FR-PO561, FR-PO602, FR-PO604, FR-PO605, FR-PO606, FR-PO618, FR-PO620, FR-PO621, FR-PO628, FR-PO633, FR-PO639, FR-PO644, FR-PO646, FR-PO650, FR-PO685, FR-PO1017, FR-PO1019, FR-PO1064, FR-PO1104, FR-PO1107, SA-OR008, SA-PO158, SA-PO326, SA-PO363, SA-PO382, SA-PO384, SA-PO388, SA-PO389, SA-PO401, SA-PO418, SA-PO503, SA-PO528, SA-PO875, PUB156, PUB197, PUB283, PUB298, PUB299, PUB305, PUB307, PUB624
- diabetic glomerulopathy** TH-PO320, TH-PO326, TH-PO328, TH-PO353, FR-PO627, SA-PO289, SA-PO416, PUB094, PUB300
- diabetic glomerulosclerosis**..... TH-PO249, TH-PO319, TH-PO1123, SA-PO381, SA-PO410, PUB435
- diabetic nephropathy** TH-OR003, TH-OR005, TH-OR006, TH-OR007, TH-OR010, TH-OR033, TH-OR034, TH-OR087, TH-PO168, TH-PO169, TH-PO238, TH-PO242, TH-PO243, TH-PO244, TH-PO250, TH-PO280, TH-PO297, TH-PO314, TH-PO316, TH-PO318, TH-PO321, TH-PO323, TH-PO325, TH-PO327, TH-PO329, TH-PO330, TH-PO331, TH-PO332, TH-PO333, TH-PO334, TH-PO336, TH-PO338, TH-PO339, TH-PO340, TH-PO341, TH-PO342, TH-PO343, TH-PO344, TH-PO346, TH-PO347, TH-PO348, TH-PO349, TH-PO352, TH-PO355, TH-PO356, TH-PO358, TH-PO359, TH-PO360, TH-PO363, TH-PO364, TH-PO367, TH-PO369, TH-PO370, TH-PO371, TH-PO372, TH-PO581, TH-PO663, TH-PO664, TH-PO669, FR-OR078, FR-OR079, FR-OR081, FR-OR082, FR-OR085, FR-OR087, FR-OR114, FR-PO219, FR-PO222, FR-PO287, FR-PO310, FR-PO386, FR-PO555, FR-PO572, FR-PO586, FR-PO603, FR-PO605, FR-PO608, FR-PO609, FR-PO611, FR-PO612, FR-PO613, FR-PO614, FR-PO615, FR-PO616, FR-PO617, FR-PO619, FR-PO622, FR-PO623, FR-PO626, FR-PO630, FR-PO632, FR-PO643, FR-PO645, FR-PO647, FR-PO995, SA-OR040, SA-OR044, SA-OR054, SA-PO271, SA-PO299, SA-PO313, SA-PO315, SA-PO324, SA-PO354, SA-PO362, SA-PO363, SA-PO364, SA-PO365, SA-PO366, SA-PO368, SA-PO369, SA-PO370, SA-PO371, SA-PO372, SA-PO373, SA-PO374, SA-PO375, SA-PO377, SA-PO378, SA-PO382, SA-PO383, SA-PO387, SA-PO391, SA-PO393, SA-PO394, SA-PO395, SA-PO396, SA-PO398, SA-PO402, SA-PO403, SA-PO405, SA-PO407, SA-PO409, SA-PO412, SA-PO415, SA-PO416,
- diabetic nephropathy (continued)**..... SA-PO501, SA-PO503, SA-PO504, SA-PO528, SA-PO690, SA-PO692, SA-PO1044, PUB085, PUB171, PUB283, PUB284, PUB285, PUB286, PUB287, PUB288, PUB289, PUB293, PUB294, PUB297, PUB301, PUB302, PUB303, PUB305, PUB306, PUB308, PUB472, PUB473, PUB510, PUB535, PUB659
- dialysis**..... TH-OR062, TH-PO051, TH-PO052, TH-PO058, TH-PO070, TH-PO100, TH-PO101, TH-PO102, TH-PO103, TH-PO105, TH-PO106, TH-PO109, TH-PO111, TH-PO112, TH-PO113, TH-PO119, TH-PO125, TH-PO374, TH-PO392, TH-PO419, TH-PO493, TH-PO518, TH-PO558, TH-PO560, TH-PO564, TH-PO620, TH-PO745, TH-PO805, TH-PO810, TH-PO814, TH-PO820, TH-PO829, TH-PO831, TH-PO870, TH-PO887, TH-PO890, TH-PO893, TH-PO908, TH-PO911, TH-PO912, TH-PO921, TH-PO925, TH-PO926, TH-PO927, TH-PO931, TH-PO937, TH-PO939, TH-PO942, TH-PO943, TH-PO944, TH-PO945, TH-PO946, TH-PO952, TH-PO959, TH-PO965, TH-PO967, TH-PO973, TH-PO974, TH-PO977, TH-PO978, TH-PO979, TH-PO986, TH-PO988, TH-PO1013, TH-PO1048, TH-PO1124, FR-OR028, FR-OR029, FR-OR030, FR-OR037, FR-PO019, FR-PO046, FR-PO066, FR-PO078, FR-PO080, FR-PO086, FR-PO367, FR-PO371, FR-PO372, FR-PO373, FR-PO374, FR-PO392, FR-PO457, FR-PO458, FR-PO462, FR-PO463, FR-PO465, FR-PO474, FR-PO475, FR-PO484, FR-PO499, FR-PO501, FR-PO558, FR-PO562, FR-PO581, FR-PO652, FR-PO659, FR-PO664, FR-PO672, FR-PO680, FR-PO692, FR-PO709, FR-PO722, FR-PO732, FR-PO740, FR-PO741, FR-PO743, FR-PO748, FR-PO749, FR-PO754, FR-PO757, FR-PO762, FR-PO765, FR-PO766, FR-PO769, FR-PO770, FR-PO773, FR-PO776, FR-PO777, FR-PO783, FR-PO784, FR-PO787, FR-PO794, FR-PO796, FR-PO799, FR-PO800, FR-PO801, FR-PO802, FR-PO804, FR-PO838, FR-PO852, FR-PO856, FR-PO857, FR-PO880, FR-PO890, FR-PO901, FR-PO905, FR-PO907, FR-PO908, FR-PO1001, FR-PO1034, FR-PO1056, SA-OR032, SA-OR035, SA-OR037, SA-OR096, SA-OR104, SA-PO011, SA-PO091, SA-PO113, SA-PO163, SA-PO529, SA-PO530, SA-PO537, SA-PO564, SA-PO577, SA-PO602, SA-PO605, SA-PO640, SA-PO769, SA-PO774, SA-PO777, SA-PO780, SA-PO781, SA-PO788, SA-PO789, SA-PO794, SA-PO799, SA-PO805, SA-PO807, SA-PO819, SA-PO820, SA-PO825, SA-PO830, SA-PO833, SA-PO836, SA-PO838, SA-PO843, SA-PO908, SA-PO910, SA-PO919, SA-PO1006, PUB028, PUB055, PUB076, PUB118, PUB120, PUB154, PUB307, PUB324, PUB327, PUB330,

- dialysis (continued)** PUB332, PUB347, PUB348, PUB353, PUB360, PUB364, PUB367, PUB369, PUB371, PUB378, PUB388, PUB524, PUB531, PUB545, PUB562, PUB563, PUB566, PUB580, PUB584, PUB589, PUB605, PUB629, PUB631, PUB635, PUB660, PUB662, PUB708
- dialysis access** TH-OR063, TH-PO171, TH-PO393, TH-PO408, TH-PO841, TH-PO843, TH-PO851, TH-PO855, TH-PO859, TH-PO863, TH-PO868, TH-PO874, TH-PO877, TH-PO879, TH-PO984, TH-PO985, TH-PO994, TH-PO995, FR-OR032, FR-OR035, FR-PO084, FR-PO581, FR-PO668, FR-PO691, FR-PO692, FR-PO698, FR-PO701, FR-PO707, FR-PO716, FR-PO719, FR-PO722, FR-PO724, SA-PO102, SA-PO710, SA-PO1005, PUB358, PUB422, PUB476, PUB480, PUB481, PUB485, PUB488, PUB489, PUB592, PUB594, PUB599, PUB612
- dialysis related amyloidosis** TH-PO946, PUB405
- dialysis volume** TH-PO807, TH-PO834, TH-PO935, TH-PO949, FR-PO687, FR-PO720, FR-PO767, FR-PO848, SA-OR034, PUB341, PUB491
- dialysis withholding** TH-PO969, SA-PO704, SA-PO721, SA-PO786, SA-PO793, PUB426
- distal tubule** TH-OR079, TH-OR083, TH-PO436, TH-PO451, FR-OR007, FR-OR092, FR-PO133, FR-PO178, FR-PO191, FR-PO192, FR-PO921, FR-PO927, FR-PO930, SA-PO937
- diuretics** TH-PO109, TH-PO435, TH-PO658, FR-OR008, FR-OR010, FR-OR036, FR-PO137, FR-PO140, FR-PO801, SA-OR108, SA-OR109, SA-OR114, SA-OR116, SA-PO657, SA-PO668, SA-PO745, SA-PO893, SA-PO917, PUB451, PUB460, PUB618
- drug excretion** TH-PO740, SA-PO011, SA-PO533, SA-PO927
- drug interactions** TH-PO1059, FR-PO567, FR-PO644, SA-PO021, SA-PO172, SA-PO1066, PUB262, PUB563, PUB692
- drug metabolism** TH-PO669, TH-PO774, TH-PO958, TH-PO1039, FR-PO016, FR-PO069, FR-PO323, SA-OR001, SA-PO006, SA-PO171, SA-PO538, SA-PO540, SA-PO548, SA-PO551, SA-PO552, PUB429, PUB616
- drug nephrotoxicity** TH-PO062, TH-PO086, TH-PO088, TH-PO089, TH-PO091, TH-PO258, TH-PO584, TH-PO1038, TH-PO1051, TH-PO1063, TH-PO1093, TH-PO1099, FR-PO030, FR-PO069, FR-PO098, FR-PO105, FR-PO203, FR-PO490, FR-PO570, FR-PO995, FR-PO1069, SA-OR005, SA-OR039, SA-PO023, SA-PO025, SA-PO089, SA-PO093, SA-PO108, SA-PO203, SA-PO206, SA-PO229, PUB001, PUB056, PUB061, PUB235, PUB258, PUB411, PUB429, PUB436, PUB616, PUB724
- drug transporter** SA-PO385, SA-PO549, SA-PO553
- dyslipidemia** TH-PO585, TH-PO987, TH-PO1084, SA-PO415, SA-PO608, PUB134, PUB230, PUB345
- echocardiography** TH-PO626, TH-PO636, TH-PO817, TH-PO893, TH-PO917, FR-PO670, FR-PO745, FR-PO853, FR-PO1015, FR-PO1029, SA-OR029, PUB123, PUB135, PUB675
- economic analysis** TH-PO059, TH-PO117, TH-PO877, FR-PO505, FR-PO685, FR-PO768, FR-PO1066, SA-PO149, SA-PO150, SA-PO708, SA-PO727, PUB167, PUB314, PUB522, PUB544, PUB625
- economic impact** TH-OR064, TH-PO989, FR-PO691, FR-PO692, FR-PO791, SA-PO149, SA-PO150, SA-PO636, SA-PO703, SA-PO708, SA-PO729, SA-PO793, SA-PO830, SA-PO1043, PUB154, PUB170
- electrolytes** TH-OR080, TH-OR081, TH-PO426, TH-PO444, TH-PO446, TH-PO451, TH-PO605, TH-PO606, TH-PO610, TH-PO1046, FR-OR001, FR-OR010, FR-PO010, FR-PO022, FR-PO032, FR-PO039, FR-PO043, FR-PO050, FR-PO063, FR-PO1043, FR-PO1058, SA-PO490, SA-PO579, SA-PO650, SA-PO652, SA-PO901, SA-PO903, SA-PO904, SA-PO912, SA-PO915, SA-PO917, SA-PO920, SA-PO922, SA-PO925, SA-PO926, SA-PO927, SA-PO928, SA-PO940, SA-PO941, SA-PO942, PUB127, PUB412, PUB428, PUB431, PUB446, PUB451, PUB456, PUB457, PUB463, PUB464
- electron microscopy** TH-PO471, TH-PO680, TH-PO697, FR-PO315
- electrophysiology** FR-PO754, FR-PO920, FR-PO930, SA-PO1047, PUB339
- ENaC** TH-PO431, TH-PO432, TH-PO433, FR-PO102, FR-PO136, SA-OR066, PUB496, PUB510
- endocytosis** TH-PO302, TH-PO331, TH-PO449, FR-PO180, FR-PO336, FR-PO360, FR-PO361, FR-PO610, SA-OR052
- endoplasmic reticulum** TH-OR066, TH-OR076, TH-PO228, TH-PO335, TH-PO367, FR-PO145, FR-PO541, SA-PO269, SA-PO312, SA-PO335, SA-PO338, SA-PO888
- endothelial cells** TH-OR112, TH-PO017, TH-PO018, TH-PO046, TH-PO321, TH-PO364, TH-PO373, TH-PO386, TH-PO399, TH-PO400, TH-PO402, TH-PO595, TH-PO1083, FR-PO121, FR-PO213, FR-PO230, FR-PO249, FR-PO344, FR-PO617, FR-PO924, FR-PO969, FR-PO980, SA-OR038, SA-PO252, SA-PO320, SA-PO354, SA-PO482, SA-PO484, SA-PO998, PUB015, PUB019, PUB128, PUB295, PUB703
- endothelium** TH-OR059, TH-OR061, TH-PO274, TH-PO371, TH-PO378, TH-PO380, TH-PO382, TH-PO384, TH-PO389, TH-PO396, TH-PO404, TH-PO412, TH-PO418, TH-PO420, TH-PO486, FR-OR103, FR-PO120, FR-PO139, FR-PO224, FR-PO228, FR-PO229, FR-PO234, FR-PO300,
- endothelium (continued)** FR-PO718, FR-PO834, SA-PO298, SA-PO342, SA-PO353, SA-PO660, SA-PO662, SA-PO665, SA-PO979, SA-PO990, PUB021, PUB708
- eosinophilia** SA-PO099, PUB214, PUB398
- epidemiology and outcomes** TH-OR002, TH-OR004, TH-OR018, TH-OR019, TH-PO057, TH-PO071, TH-PO207, TH-PO518, TH-PO543, TH-PO544, TH-PO561, TH-PO567, TH-PO614, TH-PO624, TH-PO626, TH-PO632, TH-PO636, TH-PO684, TH-PO745, TH-PO748, TH-PO797, TH-PO849, TH-PO857, TH-PO861, TH-PO885, TH-PO903, TH-PO932, TH-PO940, TH-PO946, TH-PO947, TH-PO954, TH-PO963, TH-PO969, TH-PO1025, FR-OR014, FR-OR068, FR-OR108, FR-OR109, FR-OR113, FR-PO418, FR-PO432, FR-PO457, FR-PO458, FR-PO459, FR-PO460, FR-PO461, FR-PO462, FR-PO463, FR-PO467, FR-PO472, FR-PO478, FR-PO491, FR-PO497, FR-PO503, FR-PO504, FR-PO551, FR-PO557, FR-PO565, FR-PO568, FR-PO577, FR-PO580, FR-PO584, FR-PO589, FR-PO595, FR-PO613, FR-PO677, FR-PO678, FR-PO728, FR-PO735, FR-PO738, FR-PO739, FR-PO743, FR-PO756, FR-PO779, FR-PO780, FR-PO781, FR-PO784, FR-PO795, FR-PO797, FR-PO825, FR-PO838, FR-PO849, FR-PO933, FR-PO940, FR-PO941, FR-PO1045, FR-PO1087, FR-PO1093, SA-OR007, SA-OR057, SA-OR077, SA-OR107, SA-PO190, SA-PO191, SA-PO197, SA-PO230, SA-PO513, SA-PO579, SA-PO607, SA-PO625, SA-PO639, SA-PO641, SA-PO676, SA-PO682, SA-PO684, SA-PO688, SA-PO693, SA-PO694, SA-PO698, SA-PO705, SA-PO709, SA-PO720, SA-PO732, SA-PO740, SA-PO751, SA-PO756, SA-PO760, SA-PO802, SA-PO824, SA-PO850, SA-PO876, SA-PO923, SA-PO1000, SA-PO1009, SA-PO1015, SA-PO1042, SA-PO1075, PUB042, PUB051, PUB126, PUB127, PUB132, PUB141, PUB144, PUB209, PUB227, PUB234, PUB238, PUB296, PUB297, PUB347, PUB450, PUB459, PUB534, PUB589, PUB602, PUB607, PUB673
- epidermal growth factor** TH-PO347, TH-PO719, FR-PO039, FR-PO101, FR-PO297, FR-PO528, FR-PO547, SA-OR003, SA-PO215, SA-PO317, SA-PO477
- epithelial** TH-PO286, TH-PO477, TH-PO478, FR-PO252, FR-PO287, FR-PO351, SA-PO944
- epithelial sodium channel** TH-PO436
- epithelial sodium transport** TH-OR075, TH-OR076, TH-OR077, TH-OR105, SA-OR112, SA-PO386, PUB510
- epoetin** FR-OR012, FR-OR017, FR-OR031, SA-PO830, PUB276, PUB314

erythropoietin TH-OR038, TH-OR039, TH-OR091, TH-PO175, TH-PO373, TH-PO384, TH-PO646, TH-PO648, TH-PO649, TH-PO960, FR-OR011, FR-OR013, FR-OR015, FR-PO242, FR-PO538, FR-PO539, FR-PO541, FR-PO801, FR-PO889, SA-PO217, SA-PO322, SA-PO444, SA-PO463, SA-PO801, SA-PO803, SA-PO806, SA-PO808, SA-PO820, SA-PO821, SA-PO824, SA-PO825, SA-PO828, SA-PO1005, PUB110, PUB143, PUB288, PUB315, PUB318, PUB336, PUB561

ESRD (end-stage renal disease) TH-OR009, TH-OR064, TH-PO169, TH-PO373, TH-PO376, TH-PO387, TH-PO416, TH-PO456, TH-PO458, TH-PO480, TH-PO510, TH-PO535, TH-PO536, TH-PO537, TH-PO551, TH-PO561, TH-PO573, TH-PO653, TH-PO678, TH-PO758, TH-PO782, TH-PO809, TH-PO810, TH-PO813, TH-PO822, TH-PO825, TH-PO827, TH-PO829, TH-PO845, TH-PO848, TH-PO849, TH-PO852, TH-PO870, TH-PO877, TH-PO885, TH-PO897, TH-PO900, TH-PO902, TH-PO903, TH-PO917, TH-PO919, TH-PO922, TH-PO925, TH-PO931, TH-PO932, TH-PO943, TH-PO948, TH-PO956, TH-PO959, TH-PO963, TH-PO966, TH-PO967, TH-PO968, TH-PO974, TH-PO981, TH-PO982, TH-PO992, TH-PO995, TH-PO1016, TH-PO1037, TH-PO1042, TH-PO1098, TH-PO1104, FR-OR018, FR-OR031, FR-OR068, FR-OR109, FR-OR113, FR-PO029, FR-PO063, FR-PO067, FR-PO074, FR-PO084, FR-PO090, FR-PO139, FR-PO507, FR-PO515, FR-PO521, FR-PO532, FR-PO557, FR-PO576, FR-PO581, FR-PO585, FR-PO655, FR-PO656, FR-PO662, FR-PO671, FR-PO679, FR-PO682, FR-PO698, FR-PO702, FR-PO742, FR-PO744, FR-PO745, FR-PO756, FR-PO759, FR-PO762, FR-PO763, FR-PO764, FR-PO765, FR-PO767, FR-PO782, FR-PO791, FR-PO793, FR-PO797, FR-PO798, FR-PO799, FR-PO804, FR-PO848, FR-PO855, FR-PO861, FR-PO894, FR-PO909, FR-PO1099, SA-PO060, SA-PO092, SA-PO161, SA-PO169, SA-PO170, SA-PO176, SA-PO179, SA-PO491, SA-PO501, SA-PO503, SA-PO515, SA-PO582, SA-PO586, SA-PO595, SA-PO607, SA-PO613, SA-PO697, SA-PO709, SA-PO710, SA-PO713, SA-PO714, SA-PO721, SA-PO722, SA-PO751, SA-PO753, SA-PO768, SA-PO775, SA-PO776, SA-PO779, SA-PO789, SA-PO790, SA-PO791, SA-PO802, SA-PO813, SA-PO823, SA-PO833, SA-PO841, SA-PO845, SA-PO957, SA-PO958, SA-PO1000, SA-PO1001, SA-PO1002, SA-PO1003, SA-PO1004, SA-PO1005, PUB039, PUB103, PUB106, PUB117, PUB118, PUB136, PUB170, PUB199, PUB200, PUB313, PUB317, PUB345, PUB347, PUB353, PUB357, PUB359, PUB360, PUB361, PUB373, PUB377,

ESRD (end-stage renal disease) (continued) PUB379, PUB388, PUB403, PUB441, PUB443, PUB470, PUB490, PUB532, PUB560, PUB593, PUB598, PUB607, PUB614, PUB623, PUB625, PUB626, PUB630, PUB631, PUB688, PUB704, PUB708

ethnic minority TH-PO526, TH-PO531, TH-PO934, TH-PO978, TH-PO1004, FR-OR071, FR-OR074, FR-PO494, FR-PO671, FR-PO796, FR-PO1002, FR-PO1025, SA-PO137, SA-PO159, SA-PO497, SA-PO669, SA-PO695, SA-PO696, SA-PO698, SA-PO711, SA-PO715, SA-PO727, SA-PO779, SA-PO784, SA-PO785, SA-PO793, SA-PO1010, SA-PO1026, PUB166, PUB169

ethnicity TH-OR115, TH-PO526, TH-PO637, TH-PO638, TH-PO1012, FR-PO416, FR-PO677, FR-PO794, SA-OR009, SA-PO164, SA-PO504, SA-PO523, SA-PO670, SA-PO776, PUB166

expression TH-OR030, TH-PO035, TH-PO405, FR-PO111, SA-OR040

extracellular matrix TH-OR047, TH-OR060, TH-PO120, TH-PO183, TH-PO878, FR-OR061, FR-OR084, FR-OR095, FR-PO195, FR-PO277, FR-PO283, FR-PO286, FR-PO289, FR-PO290, FR-PO291, FR-PO307, FR-PO312, FR-PO313, FR-PO314, FR-PO401, FR-PO809, SA-OR041, SA-OR051, SA-OR084, SA-PO272, SA-PO289, SA-PO300, SA-PO350, SA-PO351, SA-PO457, SA-PO459, SA-PO473, SA-PO479, SA-PO485, SA-PO977, PUB392

Fabry disease TH-PO1027, FR-PO165, FR-PO166, SA-PO004, SA-PO043, PUB555, PUB556

familial nephropathy FR-OR057, FR-PO112, PUB276, PUB551

family history SA-PO514, SA-PO523

fibroblast TH-PO499, FR-PO291, FR-PO292, FR-PO303, SA-OR079, SA-OR083, SA-PO420, SA-PO424, SA-PO458, SA-PO464, SA-PO485, SA-PO486, PUB539, PUB703

fibronectin TH-PO286, FR-PO819, SA-PO461

fibrosis TH-OR074, TH-OR098, TH-OR122, TH-PO142, TH-PO167, TH-PO204, TH-PO278, TH-PO279, TH-PO283, TH-PO284, TH-PO319, TH-PO356, TH-PO357, TH-PO358, TH-PO370, TH-PO371, TH-PO421, TH-PO715, TH-PO781, TH-PO1067, FR-OR039, FR-OR103, FR-OR105, FR-PO015, FR-PO163, FR-PO196, FR-PO213, FR-PO246, FR-PO259, FR-PO262, FR-PO272, FR-PO275, FR-PO276, FR-PO282, FR-PO285, FR-PO289, FR-PO290, FR-PO299, FR-PO300, FR-PO309, FR-PO311, FR-PO313, FR-PO314, FR-PO379, FR-PO518, FR-PO537, FR-PO554, FR-PO623, FR-PO809, FR-PO811, FR-PO813, FR-PO814, FR-PO815, FR-PO816, FR-PO817, FR-PO818, FR-PO819, FR-PO820, FR-PO822, FR-PO823, FR-PO826, FR-PO829, FR-PO836, FR-PO991, FR-PO1074,

fibrosis (continued) FR-PO1080, SA-OR044, SA-OR059, SA-OR081, SA-OR085, SA-OR086, SA-OR087, SA-PO074, SA-PO253, SA-PO277, SA-PO288, SA-PO298, SA-PO304, SA-PO328, SA-PO329, SA-PO330, SA-PO331, SA-PO332, SA-PO373, SA-PO378, SA-PO416, SA-PO422, SA-PO423, SA-PO433, SA-PO444, SA-PO461, SA-PO463, SA-PO465, SA-PO468, SA-PO471, SA-PO472, SA-PO477, SA-PO479, SA-PO480, SA-PO483, SA-PO486, SA-PO487, SA-PO488, SA-PO490, SA-PO496, SA-PO593, SA-PO884, SA-PO984, SA-PO999, PUB014, PUB015, PUB067, PUB089, PUB178, PUB389, PUB391, PUB392, PUB393, PUB420

focal segmental glomerulo-sclerosis TH-OR043, TH-OR094, TH-PO174, TH-PO224, TH-PO240, TH-PO398, TH-PO465, TH-PO701, TH-PO1106, TH-PO1108, FR-OR049, FR-OR051, FR-OR052, FR-OR053, FR-OR060, FR-PO021, FR-PO059, FR-PO152, FR-PO153, FR-PO155, FR-PO175, FR-PO308, FR-PO316, FR-PO322, FR-PO326, FR-PO327, FR-PO335, FR-PO342, FR-PO349, FR-PO356, FR-PO433, FR-PO437, FR-PO513, FR-PO986, SA-OR020, SA-OR045, SA-OR053, SA-OR054, SA-PO002, SA-PO017, SA-PO093, SA-PO100, SA-PO295, SA-PO347, SA-PO442, SA-PO512, SA-PO1079, SA-PO1080, PUB072, PUB077, PUB078, PUB203, PUB245, PUB257, PUB467

gastrointestinal complications TH-OR013, FR-PO061, FR-PO590, FR-PO804, PUB397, PUB676

gastrointestinal medications TH-OR114, TH-PO655, FR-PO878, SA-PO547

gender difference TH-PO212, TH-PO553, TH-PO863, TH-PO933, FR-PO395, FR-PO701, SA-PO542, PUB190, PUB198, PUB610

gene expression TH-OR041, TH-OR042, TH-OR047, TH-OR048, TH-OR049, TH-PO030, TH-PO154, TH-PO172, TH-PO186, TH-PO187, TH-PO189, TH-PO197, TH-PO230, TH-PO256, TH-PO261, TH-PO276, TH-PO279, TH-PO304, TH-PO325, TH-PO408, TH-PO485, TH-PO492, TH-PO508, TH-PO522, TH-PO683, TH-PO707, TH-PO798, FR-OR003, FR-OR076, FR-OR078, FR-PO094, FR-PO183, FR-PO397, FR-PO421, FR-PO813, FR-PO818, FR-PO827, FR-PO954, FR-PO978, FR-PO1077, SA-OR095, SA-PO171, SA-PO274, SA-PO282, SA-PO393, SA-PO492, SA-PO494, SA-PO504, SA-PO510, SA-PO512, SA-PO587, SA-PO858, SA-PO982, SA-PO984, SA-PO997, SA-PO1089, PUB097, PUB389

gene therapy TH-PO357, FR-PO221, FR-PO822, SA-OR072, SA-PO488

- gene transcription** TH-PO135, TH-PO208, TH-PO229, TH-PO238, TH-PO245, TH-PO348, TH-PO349, TH-PO363, TH-PO502, TH-PO1105, FR-OR080, FR-OR093, FR-PO399, SA-PO494
- genetic renal disease**.....
 TH-OR044, TH-OR052, TH-OR053, TH-OR055, TH-PO127, TH-PO162, TH-PO209, TH-PO216, TH-PO217, TH-PO233, TH-PO234, TH-PO247, TH-PO251, TH-PO398, TH-PO457, TH-PO786, TH-PO980, TH-PO1027, TH-PO1035, TH-PO1044, TH-PO1055, TH-PO1062, TH-PO1096, FR-OR005, FR-OR048, FR-OR049, FR-OR050, FR-OR052, FR-OR054, FR-OR055, FR-OR056, FR-PO005, FR-PO013, FR-PO015, FR-PO021, FR-PO023, FR-PO092, FR-PO112, FR-PO152, FR-PO153, FR-PO155, FR-PO156, FR-PO158, FR-PO160, FR-PO164, FR-PO167, FR-PO168, FR-PO169, FR-PO172, FR-PO174, FR-PO175, FR-PO176, FR-PO179, FR-PO180, FR-PO220, FR-PO323, FR-PO341, FR-PO388, FR-PO398, FR-PO946, FR-PO1022, FR-PO1047, SA-OR017, SA-OR026, SA-OR048, SA-PO002, SA-PO053, SA-PO142, SA-PO291, SA-PO427, SA-PO498, SA-PO499, SA-PO501, SA-PO505, SA-PO506, SA-PO507, SA-PO509, SA-PO513, SA-PO519, SA-PO522, SA-PO523, SA-PO527, SA-PO849, SA-PO869, SA-PO874, SA-PO878, SA-PO882, SA-PO889, SA-PO890, SA-PO891, PUB087, PUB105, PUB192, PUB261, PUB264, PUB269, PUB272, PUB274, PUB428, PUB465, PUB466, PUB549, PUB550, PUB551, PUB552, PUB553, PUB554
- genetics and development**..... TH-OR041, TH-PO077, TH-PO188, TH-PO218, TH-PO455, TH-PO1027, FR-OR056, FR-OR057, FR-OR094, FR-OR096, FR-PO172, FR-PO181, FR-PO183, FR-PO189, FR-PO199, FR-PO208, FR-PO388, FR-PO947, FR-PO976, SA-OR002, SA-OR027, SA-PO511, SA-PO512, PUB282, PUB467
- gentamicin**..... SA-OR039, PUB615, PUB640
- geriatric nephrology**..... TH-OR017, TH-OR035, TH-PO066, TH-PO590, TH-PO845, TH-PO979, FR-PO166, FR-PO762, FR-PO868, FR-PO892, FR-PO1054, FR-PO1092, SA-PO264, SA-PO298, SA-PO642, SA-PO677, SA-PO680, SA-PO749, SA-PO752, SA-PO756, SA-PO758, SA-PO761, SA-PO762, SA-PO766, SA-PO767, SA-PO768, SA-PO769, SA-PO770, SA-PO773, SA-PO777, SA-PO778, SA-PO909, PUB325, PUB364, PUB388, PUB468, PUB469, PUB470
- Gitelman syndrome**.....FR-PO178, SA-PO904, SA-PO905, PUB428
- glomerular disease**..... TH-OR022, TH-OR089, TH-PO128, TH-PO129, TH-PO132, TH-PO134, TH-PO139, TH-PO145, TH-PO158, TH-PO242, TH-PO248, TH-PO250, TH-PO253, TH-PO255, TH-PO305, TH-PO398, TH-PO452, **glomerular disease (continued)**.....TH-PO693, TH-PO696, TH-PO700, TH-PO716, TH-PO722, TH-PO724, TH-PO735, TH-PO751, TH-PO755, TH-PO760, TH-PO769, TH-PO782, TH-PO786, TH-PO1071, TH-PO1072, TH-PO1077, TH-PO1086, TH-PO1112, FR-OR066, FR-PO149, FR-PO150, FR-PO154, FR-PO157, FR-PO159, FR-PO160, FR-PO164, FR-PO206, FR-PO315, FR-PO318, FR-PO321, FR-PO330, FR-PO333, FR-PO348, FR-PO352, FR-PO362, FR-PO363, FR-PO419, FR-PO426, FR-PO436, FR-PO440, FR-PO441, FR-PO449, FR-PO450, FR-PO451, FR-PO514, FR-PO964, FR-PO966, SA-OR013, SA-OR025, SA-OR047, SA-OR048, SA-OR053, SA-PO028, SA-PO036, SA-PO038, SA-PO081, SA-PO083, SA-PO088, SA-PO157, SA-PO297, SA-PO343, SA-PO350, SA-PO427, SA-PO436, SA-PO438, SA-PO505, SA-PO508, SA-PO509, SA-PO538, PUB050, PUB082, PUB084, PUB089, PUB146, PUB209, PUB210, PUB213, PUB214, PUB216, PUB222, PUB232, PUB236, PUB238, PUB256, PUB399, PUB553, PUB554, PUB574, PUB682
- glomerular endothelial cells** TH-PO273, TH-PO298, TH-PO315, TH-PO346, TH-PO369, SA-PO353, SA-PO466, PUB091, PUB701
- glomerular epithelial cells** TH-OR085, TH-PO366, TH-PO1031, FR-PO324, FR-PO328, FR-PO329, SA-PO335
- glomerular filtration barrier** TH-PO239, TH-PO246, TH-PO303, FR-PO154, FR-PO162, FR-PO324, FR-PO334, FR-PO337, FR-PO341, FR-PO352, SA-OR038, SA-PO351, SA-PO448, SA-PO451, SA-PO454, PUB081, PUB091, PUB094
- glomerular filtration rate**..... TH-OR001, TH-OR013, TH-OR037, TH-PO019, TH-PO047, TH-PO055, TH-PO095, TH-PO461, TH-PO544, TH-PO568, TH-PO630, TH-PO660, TH-PO665, TH-PO666, TH-PO675, TH-PO705, TH-PO712, TH-PO739, TH-PO740, TH-PO771, FR-OR068, FR-OR114, FR-PO070, FR-PO132, FR-PO149, FR-PO227, FR-PO375, FR-PO378, FR-PO526, FR-PO544, FR-PO550, FR-PO551, FR-PO557, FR-PO578, FR-PO583, FR-PO628, FR-PO633, FR-PO638, FR-PO645, FR-PO847, FR-PO853, FR-PO1003, FR-PO1018, FR-PO1023, FR-PO1062, SA-OR010, SA-OR043, SA-OR063, SA-PO257, SA-PO258, SA-PO455, SA-PO545, SA-PO642, SA-PO672, SA-PO673, SA-PO674, SA-PO675, SA-PO676, SA-PO677, SA-PO680, SA-PO737, SA-PO740, SA-PO765, SA-PO767, SA-PO773, SA-PO856, SA-PO877, SA-PO892, SA-PO1011, SA-PO1022, SA-PO1025, PUB044, PUB119, PUB124, PUB133, PUB160, PUB161, PUB162, PUB177, PUB180, PUB189, PUB190, PUB193, PUB194, PUB195, PUB300, PUB377, PUB661
- glomerular hyperfiltration**TH-PO372, TH-PO705, FR-PO122, FR-PO320, FR-PO605, SA-PO345, PUB088, PUB573
- glomerulonephritis**..... TH-OR024, TH-OR072, TH-OR093, TH-PO126, TH-PO160, TH-PO237, TH-PO252, TH-PO254, TH-PO683, TH-PO689, TH-PO703, TH-PO709, TH-PO713, TH-PO725, TH-PO736, TH-PO747, TH-PO749, TH-PO761, TH-PO788, TH-PO794, TH-PO797, TH-PO1078, TH-PO1080, TH-PO1100, TH-PO1109, TH-PO1117, TH-PO1119, TH-PO1120, FR-OR067, FR-PO017, FR-PO024, FR-PO346, FR-PO386, FR-PO403, FR-PO408, FR-PO410, FR-PO414, FR-PO424, FR-PO427, FR-PO442, FR-PO449, FR-PO452, FR-PO453, FR-PO970, FR-PO971, FR-PO972, FR-PO973, FR-PO976, FR-PO979, FR-PO981, FR-PO984, FR-PO992, FR-PO993, FR-PO996, FR-PO998, SA-OR014, SA-PO014, SA-PO019, SA-PO033, SA-PO035, SA-PO039, SA-PO040, SA-PO041, SA-PO064, SA-PO068, SA-PO076, SA-PO078, SA-PO104, SA-PO109, SA-PO110, SA-PO111, SA-PO123, SA-PO349, SA-PO426, SA-PO440, SA-PO441, SA-PO534, SA-PO647, SA-PO687, SA-PO1055, PUB074, PUB077, PUB101, PUB208, PUB215, PUB221, PUB241, PUB254, PUB255, PUB258, PUB407, PUB408, PUB410, PUB415, PUB435
- glomerulopathy** TH-PO138, TH-PO230, TH-PO700, TH-PO718, TH-PO726, TH-PO762, TH-PO1043, FR-PO425, FR-PO957, FR-PO958, SA-OR017, SA-OR050, SA-PO003, SA-PO027, SA-PO042, SA-PO059, SA-PO344, SA-PO359, SA-PO454, SA-PO457, SA-PO522, SA-PO1081, PUB069, PUB074
- glomerulosclerosis** TH-OR088, TH-OR092, TH-PO235, TH-PO309, TH-PO750, FR-OR101, FR-PO286, FR-PO302, FR-PO338, FR-PO352, FR-PO353, FR-PO435, FR-PO438, FR-PO512, FR-PO534, FR-PO582, FR-PO623, FR-PO624, SA-OR052, SA-OR103, SA-PO051, SA-PO121, SA-PO360, SA-PO427, SA-PO983, PUB246, PUB290, PUB409, PUB504, PUB663
- glomerulus** TH-PO133, TH-PO232, TH-PO338, FR-PO187, FR-PO189, FR-PO193, FR-PO304, FR-PO317, FR-PO339, FR-PO359, FR-PO396, FR-PO960, FR-PO996, SA-OR046, SA-PO336, SA-PO339, SA-PO345, SA-PO352, SA-PO355, SA-PO388, SA-PO453, PUB083, PUB090, PUB092, PUB282, PUB293
- glycation**..... TH-PO248, FR-PO963, SA-PO397, SA-PO692
- Goodpasture syndrome**..... TH-PO1122, FR-PO407, FR-PO962, FR-PO965, SA-PO022

- health status** TH-PO667, TH-PO922, FR-PO393, FR-PO577, FR-PO764, FR-PO883, SA-PO704, SA-PO717, SA-PO723, SA-PO730, SA-PO737, SA-PO763, SA-PO764, SA-PO782, SA-PO1029, SA-PO1036, PUB120, PUB273, PUB386, PUB540
- heart disease** TH-OR110, TH-PO180, TH-PO382, TH-PO470, TH-PO486, FR-PO078, FR-PO465, FR-PO739, FR-PO1006, FR-PO1013, SA-PO1048, PUB386, PUB543
- heart failure** TH-OR118, TH-PO593, TH-PO614, TH-PO621, TH-PO917, TH-PO979, FR-PO502, FR-PO735, FR-PO1029, SA-OR035, SA-PO063, SA-PO187, SA-PO423, SA-PO674, PUB031, PUB319, PUB338, PUB543, PUB620
- heme oxygenase** TH-PO016, FR-PO960, SA-PO259, SA-PO525, PUB083, PUB084
- hemodialysis** TH-PO066, TH-PO079, TH-PO103, TH-PO108, TH-PO114, TH-PO115, TH-PO116, TH-PO118, TH-PO119, TH-PO386, TH-PO494, TH-PO519, TH-PO625, TH-PO627, TH-PO644, TH-PO678, TH-PO798, TH-PO799, TH-PO800, TH-PO801, TH-PO802, TH-PO809, TH-PO810, TH-PO811, TH-PO812, TH-PO814, TH-PO815, TH-PO816, TH-PO817, TH-PO819, TH-PO824, TH-PO827, TH-PO828, TH-PO830, TH-PO836, TH-PO848, TH-PO854, TH-PO857, TH-PO860, TH-PO865, TH-PO867, TH-PO883, TH-PO884, TH-PO886, TH-PO888, TH-PO891, TH-PO892, TH-PO894, TH-PO895, TH-PO898, TH-PO899, TH-PO905, TH-PO913, TH-PO914, TH-PO916, TH-PO918, TH-PO923, TH-PO924, TH-PO929, TH-PO930, TH-PO933, TH-PO934, TH-PO938, TH-PO940, TH-PO941, TH-PO949, TH-PO951, TH-PO953, TH-PO956, TH-PO957, TH-PO958, TH-PO961, TH-PO964, TH-PO968, TH-PO970, TH-PO976, TH-PO1013, FR-OR013, FR-OR014, FR-OR020, FR-OR029, FR-OR037, FR-PO016, FR-PO042, FR-PO054, FR-PO071, FR-PO078, FR-PO365, FR-PO369, FR-PO370, FR-PO371, FR-PO372, FR-PO391, FR-PO635, FR-PO637, FR-PO639, FR-PO653, FR-PO655, FR-PO656, FR-PO658, FR-PO662, FR-PO666, FR-PO667, FR-PO670, FR-PO672, FR-PO675, FR-PO679, FR-PO683, FR-PO687, FR-PO688, FR-PO689, FR-PO694, FR-PO697, FR-PO699, FR-PO715, FR-PO717, FR-PO719, FR-PO724, FR-PO727, FR-PO734, FR-PO738, FR-PO746, FR-PO747, FR-PO751, FR-PO758, FR-PO761, FR-PO768, FR-PO771, FR-PO772, FR-PO773, FR-PO775, FR-PO778, FR-PO785, FR-PO786, FR-PO790, FR-PO795, FR-PO803, FR-PO805, FR-PO806, FR-PO807, FR-PO842, FR-PO844, FR-PO846, FR-PO848, FR-PO849, FR-PO865, FR-PO866, FR-PO867, FR-PO870, FR-PO874, FR-PO881, FR-PO882,
- hemodialysis (continued)** FR-PO885, FR-PO898, FR-PO902, FR-PO903, FR-PO904, FR-PO937, FR-PO1007, FR-PO1008, SA-OR036, SA-OR098, SA-PO012, SA-PO013, SA-PO063, SA-PO156, SA-PO175, SA-PO176, SA-PO177, SA-PO178, SA-PO180, SA-PO184, SA-PO202, SA-PO234, SA-PO570, SA-PO582, SA-PO615, SA-PO739, SA-PO759, SA-PO784, SA-PO795, SA-PO798, SA-PO801, SA-PO803, SA-PO804, SA-PO809, SA-PO811, SA-PO812, SA-PO814, SA-PO815, SA-PO816, SA-PO817, SA-PO818, SA-PO822, SA-PO831, SA-PO832, SA-PO834, SA-PO835, SA-PO836, SA-PO837, SA-PO839, SA-PO840, SA-PO842, SA-PO844, SA-PO846, PUB056, PUB113, PUB114, PUB115, PUB311, PUB312, PUB315, PUB316, PUB320, PUB321, PUB322, PUB323, PUB325, PUB328, PUB331, PUB333, PUB340, PUB343, PUB344, PUB346, PUB348, PUB351, PUB354, PUB355, PUB356, PUB357, PUB358, PUB361, PUB366, PUB370, PUB372, PUB374, PUB379, PUB381, PUB382, PUB400, PUB422, PUB441, PUB474, PUB475, PUB477, PUB479, PUB482, PUB492, PUB516, PUB520, PUB522, PUB529, PUB530, PUB542, PUB547, PUB565, PUB570, PUB595, PUB621, PUB624, PUB627, PUB628, PUB711, PUB721, PUB725
- hemodialysis access** TH-OR061, TH-OR064, TH-PO845, TH-PO847, TH-PO852, TH-PO853, TH-PO862, TH-PO864, TH-PO874, FR-PO666, FR-PO694, FR-PO710, FR-PO711, FR-PO714, FR-PO721, PUB443, PUB478, PUB480, PUB481, PUB482, PUB488, PUB619
- hemodialysis adequacy** TH-PO803, TH-PO807, TH-PO815, TH-PO826, TH-PO947, FR-PO652, FR-PO653, FR-PO654, FR-PO660, FR-PO661, FR-PO663, FR-PO684, FR-PO686, FR-PO707, FR-PO714, FR-PO752, SA-OR032, SA-PO831, SA-PO838, PUB349, PUB352, PUB359, PUB491, PUB634
- hemodialysis biocompatibility** TH-PO815, TH-PO835, TH-PO961, FR-PO053, FR-PO660, FR-PO662, FR-PO663, FR-PO669, FR-PO807, SA-PO122
- hemodialysis hazards** FR-PO372, FR-PO708, FR-PO736, SA-PO184, SA-PO831, PUB577, PUB630, PUB638
- hemodynamics and vascular regulation** TH-PO122, TH-PO174, TH-PO833, TH-PO911, FR-PO071, FR-PO233, FR-PO234, FR-PO366, FR-PO661, FR-PO742, SA-PO640, SA-PO649, PUB124, PUB331, PUB334, PUB620, PUB637
- hemolytic uremic syndrome** TH-PO082, TH-PO127, TH-PO460, TH-PO983, TH-PO1028, TH-PO1050, TH-PO1062, TH-PO1093, TH-PO1096, FR-PO012, FR-PO048, FR-PO168, FR-PO169, FR-PO444, FR-PO446, FR-PO447, FR-PO483, FR-PO487, FR-PO961, SA-PO037, SA-PO082, SA-PO120, SA-PO228, SA-PO507, SA-PO535, SA-PO536, SA-PO1081, SA-PO1082, PUB052, PUB060, PUB259, PUB423, PUB433, PUB437, PUB505, PUB550, PUB580, PUB632
- hemoperfusion** TH-PO116, TH-PO123, TH-PO124, SA-PO792, PUB615, PUB622
- hemoxygenase** TH-PO040
- Henoch-Schonlein purpura** TH-PO728, TH-PO1089
- hepatitis** TH-PO667, FR-PO475, FR-PO560, FR-PO561, FR-PO779, FR-PO780, FR-PO1065, SA-OR057, SA-PO021, SA-PO169, SA-PO181, SA-PO211, SA-PO681, SA-PO1056, SA-PO1057, SA-PO1059, SA-PO1060, SA-PO1066, SA-PO1072, PUB112, PUB188, PUB689
- Heymann nephritis** PUB081
- histopathology** TH-OR027, TH-PO002, TH-PO320, TH-PO685, TH-PO701, FR-OR075, FR-PO318, SA-PO398, SA-PO445, SA-PO978, PUB209, PUB235
- HIV nephropathy** TH-OR083, TH-PO154, TH-PO234, TH-PO245, TH-PO304, TH-PO757, TH-PO1125, FR-PO291, FR-PO421, FR-PO437, FR-PO481, FR-PO524, FR-PO978, SA-PO075, SA-PO290, SA-PO292, SA-PO325, SA-PO670, SA-PO671, PUB157, PUB188, PUB194, PUB196, PUB399
- HOMA-IR** TH-PO823
- homocysteine** TH-PO351, PUB196
- hospitalization** TH-OR011, TH-OR062, TH-PO056, TH-PO677, TH-PO927, TH-PO944, TH-PO951, TH-PO975, TH-PO977, TH-PO993, TH-PO1012, FR-PO471, FR-PO476, FR-PO478, FR-PO601, FR-PO688, FR-PO689, FR-PO781, FR-PO782, FR-PO793, FR-PO1020, SA-PO226, SA-PO732, SA-PO787, PUB141, PUB151, PUB337, PUB459, PUB582, PUB587, PUB649
- human genetics** TH-OR026, FR-PO150, FR-PO159, FR-PO926, SA-PO311, SA-PO491, SA-PO518, SA-PO526
- hyaluronidase** FR-PO097
- hypercalciuria** TH-PO243, TH-PO515, FR-OR002, FR-PO919, FR-PO953, SA-PO005, SA-PO053, SA-PO574, SA-PO937, PUB438
- hypercholesterolemia** TH-PO434, TH-PO467, PUB574, PUB700
- hyperfiltration** TH-PO567, FR-OR045, SA-PO442, SA-PO455, PUB157, PUB285
- hyperglycemia** TH-OR008, TH-OR009, TH-PO290, TH-PO315, FR-PO629, SA-PO394, SA-PO1018, PUB291, PUB302, PUB400

- hypernatremia** TH-PO1066, FR-PO028, FR-PO030, SA-PO911, SA-PO920, PUB444, PUB445, PUB461
- hyperparathyroidism** TH-PO507, TH-PO516, TH-PO517, TH-PO518, TH-PO519, TH-PO523, TH-PO524, TH-PO641, TH-PO644, FR-OR022, FR-PO068, FR-PO665, FR-PO1108, SA-PO016, SA-PO091, SA-PO562, SA-PO577, SA-PO584, SA-PO603, SA-PO1014, PUB335, PUB409, PUB522, PUB523, PUB529, PUB533
- hyperphosphatemia** TH-PO113, TH-PO410, TH-PO479, TH-PO500, TH-PO504, TH-PO511, TH-PO821, TH-PO950, TH-PO1000, FR-PO576, FR-PO627, FR-PO902, FR-PO905, FR-PO906, FR-PO912, FR-PO913, FR-PO914, FR-PO915, FR-PO932, FR-PO936, PUB511, PUB524, PUB571, PUB585, PUB586, PUB590, PUB621, PUB633, PUB634
- hypertension** TH-OR036, TH-OR079, TH-OR080, TH-OR105, TH-OR119, TH-PO029, TH-PO071, TH-PO212, TH-PO257, TH-PO422, TH-PO431, TH-PO440, TH-PO441, TH-PO442, TH-PO444, TH-PO530, TH-PO542, TH-PO569, TH-PO608, TH-PO624, TH-PO634, TH-PO635, TH-PO674, TH-PO711, TH-PO780, TH-PO816, TH-PO910, TH-PO1115, FR-OR042, FR-OR043, FR-OR044, FR-OR046, FR-OR069, FR-PO009, FR-PO114, FR-PO115, FR-PO117, FR-PO118, FR-PO120, FR-PO122, FR-PO123, FR-PO124, FR-PO126, FR-PO128, FR-PO131, FR-PO134, FR-PO138, FR-PO143, FR-PO144, FR-PO145, FR-PO197, FR-PO268, FR-PO338, FR-PO466, FR-PO508, FR-PO552, FR-PO556, FR-PO673, FR-PO744, FR-PO1015, FR-PO1030, SA-OR008, SA-OR031, SA-OR033, SA-OR065, SA-OR071, SA-OR078, SA-OR090, SA-OR102, SA-PO059, SA-PO380, SA-PO391, SA-PO447, SA-PO500, SA-PO617, SA-PO620, SA-PO621, SA-PO623, SA-PO624, SA-PO626, SA-PO631, SA-PO633, SA-PO634, SA-PO635, SA-PO637, SA-PO638, SA-PO641, SA-PO643, SA-PO645, SA-PO647, SA-PO649, SA-PO656, SA-PO658, SA-PO659, SA-PO660, SA-PO661, SA-PO662, SA-PO664, SA-PO665, SA-PO666, SA-PO667, SA-PO669, SA-PO711, SA-PO712, SA-PO715, SA-PO731, SA-PO828, SA-PO879, SA-PO917, SA-PO1045, SA-PO1049, PUB088, PUB169, PUB187, PUB290, PUB342, PUB443, PUB493, PUB496, PUB497, PUB498, PUB499, PUB500, PUB501, PUB503, PUB507, PUB508, PUB509, PUB549, PUB636
- hypertrophy** TH-PO317, TH-PO350, TH-PO711, FR-PO184, FR-PO385, SA-OR060, SA-PO289, SA-PO316, SA-PO336, SA-PO366
- hypoalbuminemia** TH-PO747, TH-PO748, TH-PO801, TH-PO1018, FR-PO590, FR-PO865, SA-PO200, PUB063, PUB356
- hypokalemia** FR-PO009, FR-PO010, FR-PO027, FR-PO040, SA-PO010, SA-PO087, SA-PO285, PUB419, PUB451, PUB549
- hyponatremia** TH-PO952, TH-PO953, TH-PO1049, FR-OR033, FR-PO004, FR-PO022, FR-PO025, FR-PO028, FR-PO031, FR-PO035, FR-PO063, FR-PO077, FR-PO106, SA-OR109, SA-PO020, SA-PO914, SA-PO916, SA-PO918, SA-PO919, SA-PO920, SA-PO921, SA-PO931, PUB373, PUB431, PUB439, PUB445, PUB447, PUB448, PUB452, PUB458, PUB459, PUB464, PUB468, PUB643
- hypotension** TH-PO059, TH-PO808, TH-PO830, FR-PO510, FR-PO659, FR-PO729, FR-PO742, SA-PO058, SA-PO122, SA-PO166, SA-PO632, SA-PO636, PUB323, PUB331, PUB334, PUB470, PUB521
- hypoxia** TH-OR091, TH-PO007, TH-PO008, TH-PO293, TH-PO375, TH-PO377, TH-PO445, TH-PO936, FR-OR091, FR-PO211, FR-PO212, FR-PO281, FR-PO305, FR-PO527, SA-PO217, SA-PO225, SA-PO272, SA-PO276, SA-PO322, SA-PO425, SA-PO443, SA-PO908, PUB075, PUB086, PUB341, PUB411
- ICD-9-CM codes** PUB256
- idiopathic nephrotic syndrome** TH-PO744, TH-PO750, TH-PO751, FR-PO430, FR-PO431, SA-OR012, SA-OR018, PUB257
- IgA** TH-PO734, TH-PO782, TH-PO786, SA-PO106
- IgA deposition** TH-PO253, TH-PO682, TH-PO684, TH-PO1117, FR-PO974, FR-PO975, SA-PO1084
- IgA nephropathy** TH-OR027, TH-OR028, TH-OR029, TH-PO136, TH-PO137, TH-PO253, TH-PO661, TH-PO679, TH-PO685, TH-PO714, TH-PO730, TH-PO732, TH-PO734, TH-PO735, TH-PO783, TH-PO784, TH-PO785, TH-PO787, TH-PO788, TH-PO789, TH-PO790, TH-PO792, TH-PO793, TH-PO795, TH-PO796, TH-PO1089, FR-PO223, FR-PO394, FR-PO515, FR-PO516, FR-PO959, FR-PO973, FR-PO977, SA-PO067, SA-PO075, SA-PO430, SA-PO439, SA-PO508, SA-PO509, SA-PO510, SA-PO511, SA-PO863, SA-PO1077, PUB030, PUB067, PUB073, PUB102, PUB205, PUB216, PUB222, PUB227, PUB234, PUB254, PUB399, PUB548
- immune complexes** TH-PO136, TH-PO730, TH-PO1077, TH-PO1078, TH-PO1117, TH-PO1120, FR-OR064, FR-PO014, FR-PO969, FR-PO971, FR-PO973, SA-PO040, SA-PO064, PUB102, PUB213
- immune deficiency** TH-OR073, PUB097
- immunohistochemistry** TH-PO227, TH-PO257, TH-PO478, TH-PO691, TH-PO703, TH-PO704, TH-PO726, TH-PO746, TH-PO1033, FR-PO162, FR-PO207, FR-PO433, FR-PO632, SA-PO569, SA-PO1033, PUB389, PUB390, PUB685
- immunology** TH-OR071, TH-PO012, TH-PO013, TH-PO022, TH-PO023, TH-PO027, TH-PO042, TH-PO044, TH-PO131, TH-PO164, TH-PO165, TH-PO167, TH-PO219, TH-PO252, TH-PO272, TH-PO289, TH-PO295, TH-PO316, TH-PO387, TH-PO389, TH-PO415, TH-PO422, TH-PO732, TH-PO781, TH-PO783, TH-PO818, TH-PO891, FR-OR058, FR-OR059, FR-OR064, FR-OR066, FR-PO033, FR-PO075, FR-PO115, FR-PO118, FR-PO147, FR-PO269, FR-PO881, FR-PO962, FR-PO965, FR-PO970, FR-PO972, FR-PO979, FR-PO981, FR-PO987, FR-PO993, FR-PO994, FR-PO998, FR-PO999, FR-PO1028, SA-PO254, SA-PO264, SA-PO330, SA-PO476, SA-PO952, SA-PO962, SA-PO964, SA-PO968, SA-PO970, PUB014, PUB069, PUB070, PUB191, PUB228, PUB241, PUB542, PUB623
- immunology and pathology** TH-OR070, TH-PO011, TH-PO028, TH-PO170, TH-PO477, TH-PO688, TH-PO707, TH-PO710, TH-PO730, TH-PO746, TH-PO781, TH-PO1044, TH-PO1064, TH-PO1069, TH-PO1070, FR-OR060, FR-OR077, FR-PO083, FR-PO255, FR-PO257, FR-PO810, FR-PO832, FR-PO964, FR-PO966, FR-PO967, FR-PO968, FR-PO975, FR-PO982, FR-PO983, FR-PO995, SA-PO003, SA-PO041, SA-PO048, SA-PO073, SA-PO263, SA-PO302, SA-PO426, SA-PO430, SA-PO435, SA-PO436, SA-PO489, SA-PO966, SA-PO1090, PUB001
- immunosuppression** TH-OR025, TH-OR072, TH-OR095, TH-PO014, TH-PO029, TH-PO698, TH-PO753, TH-PO754, TH-PO778, TH-PO785, TH-PO1122, FR-OR076, FR-PO048, FR-PO049, FR-PO052, FR-PO057, FR-PO079, FR-PO405, FR-PO406, FR-PO413, FR-PO431, FR-PO443, FR-PO453, FR-PO568, FR-PO598, FR-PO784, FR-PO929, FR-PO958, FR-PO1062, FR-PO1064, FR-PO1065, FR-PO1067, FR-PO1068, FR-PO1071, FR-PO1072, FR-PO1073, FR-PO1075, FR-PO1076, FR-PO1077, FR-PO1078, FR-PO1079, FR-PO1080, FR-PO1081, FR-PO1082, FR-PO1084, FR-PO1086, FR-PO1089, FR-PO1090, SA-OR013, SA-OR018, SA-OR020, SA-OR063, SA-OR064, SA-PO024, SA-PO038, SA-PO047, SA-PO057, SA-PO077, SA-PO277, SA-PO526, SA-PO540, SA-PO544, SA-PO629, SA-PO960, SA-PO961, SA-PO973, SA-PO1008, SA-PO1014, SA-PO1027, SA-PO1031, SA-PO1052, SA-PO1058, SA-PO1062, SA-PO1070, SA-PO1073, SA-PO1089, PUB098, PUB203, PUB207, PUB361, PUB414, PUB569, PUB654, PUB664, PUB665, PUB670, PUB677, PUB678, PUB679, PUB693, PUB695, PUB698

- insulin resistance** TH-PO330, TH-PO366, TH-PO419, TH-PO987, FR-OR086, FR-PO438, FR-PO543, FR-PO880, FR-PO893, FR-PO1083, FR-PO1106, SA-OR090, SA-OR097, SA-PO370, SA-PO376, SA-PO400, SA-PO401, SA-PO418, PUB289, PUB292, PUB624
- interstitial fibrosis** TH-OR066, TH-PO140, TH-PO149, TH-PO217, TH-PO566, TH-PO717, TH-PO719, TH-PO723, TH-PO727, TH-PO784, TH-PO1110, FR-OR101, FR-PO015, FR-PO262, FR-PO281, FR-PO284, FR-PO287, FR-PO288, FR-PO297, FR-PO298, FR-PO306, FR-PO308, FR-PO547, FR-PO582, FR-PO622, FR-PO624, FR-PO627, FR-PO643, SA-OR080, SA-OR083, SA-PO434, SA-PO437, SA-PO460, SA-PO476, SA-PO482, SA-PO981, SA-PO996, PUB176, PUB225, PUB237, PUB271, PUB291, PUB390, PUB616
- interventional nephrology** TH-PO731, TH-PO868, TH-PO869, TH-PO875, FR-PO020, FR-PO707, FR-PO711, FR-PO718, SA-OR011, SA-PO124, PUB478
- intestine** TH-PO013, TH-PO165, TH-PO548, FR-PO532, FR-PO566, FR-PO858, FR-PO859, FR-PO860, FR-PO866, FR-PO878, FR-PO895, FR-PO928, FR-PO988, SA-OR073, SA-PO077, SA-PO172, SA-PO900, PUB003
- intoxication** TH-PO097, TH-PO116
- intracellular pH** FR-PO124, SA-PO901
- intracellular signal** TH-PO159, TH-PO492, PUB639
- intralipid** TH-PO1048
- intrauterine growth** TH-PO474, TH-PO635, FR-PO197, FR-PO198, SA-PO624, PUB692
- intravenous** FR-PO490, FR-PO1081, SA-PO800
- intravenous immunoglobulin** FR-PO088
- intrinsic renal cell** FR-OR064
- ion channel** TH-OR051, TH-OR082, TH-PO176, TH-PO221, TH-PO430, TH-PO449, FR-OR051, FR-PO121, FR-PO930, SA-OR071, SA-PO243, SA-PO574, PUB006
- ion transport** TH-PO426, TH-PO427, TH-PO435, TH-PO439, TH-PO442, TH-PO450, FR-PO111, FR-PO112, FR-PO922, FR-PO929, FR-PO936, SA-OR068, SA-OR073, SA-OR113, SA-PO384, SA-PO941, SA-PO944, SA-PO946, PUB496
- ischemia** TH-PO098, FR-PO477, SA-OR088, SA-PO202, SA-PO948, SA-PO950, SA-PO951, PUB023
- ischemia-reperfusion** TH-OR095, TH-OR096, TH-OR097, TH-OR101, TH-OR102, TH-OR103, TH-PO002, TH-PO011, TH-PO013, TH-PO014, TH-PO017, TH-PO020, TH-PO024, TH-PO031, TH-PO032, TH-PO035, TH-PO036, TH-PO043, TH-PO044, TH-PO045, TH-PO046, TH-PO049, TH-PO131, TH-PO164, TH-PO417, TH-PO445, FR-OR098, FR-OR099, FR-OR102, FR-OR103, FR-PO225, FR-PO226,
- ischemia-reperfusion (continued)** FR-PO227, FR-PO229, FR-PO230, FR-PO231, FR-PO248, FR-PO250, FR-PO251, FR-PO254, FR-PO258, FR-PO259, FR-PO266, FR-PO267, FR-PO271, FR-PO272, FR-PO364, FR-PO400, FR-PO994, SA-OR087, SA-PO225, SA-PO244, SA-PO247, SA-PO249, SA-PO251, SA-PO256, SA-PO263, SA-PO265, SA-PO269, SA-PO271, SA-PO274, SA-PO276, SA-PO279, SA-PO421, SA-PO462, SA-PO472, SA-PO949, PUB003, PUB004, PUB005, PUB012, PUB016, PUB018, PUB320
- ischemic renal failure** TH-PO004, TH-PO080, SA-PO119, SA-PO127, SA-PO219, SA-PO277, PUB008, PUB075, PUB413
- kidney** TH-PO047, TH-PO148, TH-PO430, FR-PO111, FR-PO210, FR-PO349, FR-PO376, FR-PO954, SA-OR070, SA-PO097, SA-PO124, SA-PO141, SA-PO144, SA-PO166, SA-PO188, SA-PO257, SA-PO302, SA-PO336, SA-PO348, SA-PO389, SA-PO406, SA-PO664, SA-PO936, SA-PO948, SA-PO1030, PUB005, PUB006, PUB009, PUB022, PUB186, PUB528, PUB646, PUB647
- kidney anatomy** FR-PO375, FR-PO595
- kidney biopsy** TH-OR002, TH-OR004, TH-PO168, TH-PO320, TH-PO471, TH-PO685, TH-PO687, TH-PO688, TH-PO704, TH-PO721, TH-PO736, TH-PO737, TH-PO767, TH-PO768, TH-PO770, TH-PO776, TH-PO1040, TH-PO1041, TH-PO1063, TH-PO1065, TH-PO1092, TH-PO1104, TH-PO1109, FR-PO006, FR-PO065, FR-PO085, FR-PO165, FR-PO304, FR-PO507, FR-PO603, FR-PO613, SA-PO031, SA-PO044, SA-PO049, SA-PO107, SA-PO954, SA-PO976, SA-PO993, SA-PO1033, SA-PO1076, PUB256, PUB434, PUB435, PUB440, PUB556, PUB578, PUB641
- kidney cancer** TH-PO291, TH-PO1081, FR-PO051, SA-PO495
- kidney development** TH-OR041, TH-OR045, TH-OR046, TH-OR050, TH-PO046, TH-PO733, FR-OR088, FR-OR089, FR-OR091, FR-OR094, FR-OR097, FR-PO172, FR-PO182, FR-PO184, FR-PO186, FR-PO187, FR-PO188, FR-PO196, FR-PO200, FR-PO202, SA-OR027, SA-PO519, SA-PO528, PUB279, PUB282
- kidney disease** TH-PO032, TH-PO344, TH-PO502, TH-PO514, TH-PO552, TH-PO1092, FR-OR020, FR-OR107, FR-PO090, FR-PO244, FR-PO269, FR-PO343, FR-PO386, FR-PO390, FR-PO445, FR-PO877, SA-PO301, SA-PO332, SA-PO487, SA-PO491, SA-PO534, SA-PO538, SA-PO550, SA-PO559, SA-PO583, SA-PO684, SA-PO772, SA-PO937, PUB087, PUB151, PUB154, PUB242, PUB608, PUB626
- kidney donation** TH-PO073, TH-PO261, FR-OR057, FR-OR069, FR-OR071, FR-OR072, FR-PO1002, FR-PO1051, FR-PO1060, SA-PO1011, SA-PO1015, SA-PO1018, SA-PO1020, SA-PO1024, SA-PO1025, SA-PO1029, SA-PO1032, SA-PO1037, SA-PO1039, SA-PO1043, SA-PO1045, PUB382, PUB568, PUB655, PUB669, PUB684
- kidney dysfunction** TH-OR101, TH-PO019, TH-PO064, TH-PO337, TH-PO548, TH-PO577, TH-PO1058, FR-OR069, FR-PO098, FR-PO103, FR-PO573, FR-PO574, FR-PO1022, SA-PO072, SA-PO194, SA-PO214, SA-PO624, SA-PO756, SA-PO890, PUB182, PUB183, PUB205, PUB275, PUB305
- kidney failure** TH-OR019, TH-PO005, TH-PO048, TH-PO563, TH-PO983, FR-PO168, FR-PO1085, SA-OR103, SA-PO026, SA-PO051, SA-PO084, SA-PO113, SA-PO117, SA-PO126, SA-PO302, SA-PO610, PUB047, PUB049, PUB120, PUB541, PUB550
- kidney stones** TH-PO177, TH-PO515, TH-PO1032, TH-PO1035, TH-PO1095, FR-OR005, FR-PO081, FR-PO176, FR-PO177, FR-PO179, FR-PO579, FR-PO920, FR-PO940, FR-PO941, FR-PO942, FR-PO943, FR-PO944, FR-PO945, FR-PO947, FR-PO948, FR-PO950, FR-PO951, FR-PO952, FR-PO953, FR-PO955, SA-OR072, SA-OR074, SA-OR075, SA-OR076, SA-OR077, SA-OR078, SA-PO101, SA-PO126, SA-PO987, PUB526, PUB527, PUB552
- kidney transplantation** TH-OR073, TH-PO273, TH-PO521, TH-PO737, TH-PO1002, TH-PO1035, TH-PO1045, TH-PO1111, FR-OR074, FR-OR075, FR-PO048, FR-PO056, FR-PO062, FR-PO082, FR-PO088, FR-PO091, FR-PO522, FR-PO585, FR-PO876, FR-PO1001, FR-PO1004, FR-PO1010, FR-PO1020, FR-PO1024, FR-PO1033, FR-PO1034, FR-PO1043, FR-PO1044, FR-PO1048, FR-PO1049, FR-PO1051, FR-PO1057, FR-PO1062, FR-PO1064, FR-PO1067, FR-PO1069, FR-PO1070, FR-PO1071, FR-PO1072, FR-PO1075, FR-PO1076, FR-PO1081, FR-PO1082, FR-PO1088, FR-PO1095, FR-PO1096, FR-PO1098, FR-PO1104, FR-PO1107, SA-OR055, SA-OR061, SA-OR062, SA-OR064, SA-PO069, SA-PO090, SA-PO249, SA-PO560, SA-PO563, SA-PO567, SA-PO947, SA-PO949, SA-PO952, SA-PO954, SA-PO959, SA-PO961, SA-PO965, SA-PO967, SA-PO969, SA-PO972, SA-PO975, SA-PO978, SA-PO984, SA-PO987, SA-PO990, SA-PO991, SA-PO999, SA-PO1001, SA-PO1002, SA-PO1003, SA-PO1006, SA-PO1010, SA-PO1011, SA-PO1012, SA-PO1013, SA-PO1014, SA-PO1026, SA-PO1028, SA-PO1031, SA-PO1047, SA-PO1048, SA-PO1050, SA-PO1053, SA-PO1054, SA-PO1057, SA-PO1059, SA-PO1060, SA-PO1063, SA-PO1066, SA-PO1067, SA-PO1068,

kidney transplantation

(continued)..... SA-PO1070, SA-PO1071, SA-PO1072, SA-PO1074, SA-PO1075, SA-PO1078, SA-PO1079, SA-PO1085, SA-PO1086, SA-PO1087, PUB421, PUB533, PUB644, PUB647, PUB652, PUB655, PUB659, PUB663, PUB667, PUB670, PUB671, PUB673

kidney tubule..... TH-OR081, TH-OR121, TH-PO003, TH-PO050, TH-PO262, TH-PO336, TH-PO442, TH-PO448, TH-PO691, TH-PO716, FR-OR010, FR-PO114, FR-PO136, FR-PO397, FR-PO922, SA-OR041, SA-OR110, SA-PO270, SA-PO281, SA-PO414, SA-PO1037

kidney volume..... TH-PO203, FR-PO525, SA-PO855, SA-PO859, SA-PO860, SA-PO877, SA-PO879, SA-PO880, SA-PO881, SA-PO883, SA-PO885, PUB262, PUB271

LDL cholesterol..... TH-OR116, FR-PO564, PUB700

lean body mass..... TH-PO556, TH-PO676, FR-PO861, FR-PO882, SA-PO757, PUB492

left ventricular hypertrophy..... TH-OR111, TH-OR118, TH-PO388, TH-PO483, TH-PO484, TH-PO509, TH-PO562, TH-PO601, TH-PO602, TH-PO634, TH-PO902, TH-PO915, FR-OR042, FR-PO1106, SA-OR029, SA-PO707, PUB135

leptospirosis..... SA-PO284

life-threatening dialysis

complications..... TH-PO958, SA-PO180, PUB598, PUB638

lipids..... TH-PO246, TH-PO308, TH-PO359, TH-PO368, TH-PO395, TH-PO404, TH-PO416, TH-PO465, TH-PO564, TH-PO587, TH-PO896, TH-PO898, TH-PO933, TH-PO1114, FR-OR083, FR-PO167, FR-PO326, FR-PO805, FR-PO863, FR-PO896, FR-PO1102, SA-OR054, SA-PO260, SA-PO329, SA-PO347, SA-PO376, SA-PO396, SA-PO725, SA-PO994, PUB177, PUB274, PUB291, PUB310, PUB333, PUB342, PUB567

liver cysts..... FR-PO307, SA-PO864, SA-PO868, SA-PO869, SA-PO873, SA-PO877, SA-PO888, PUB260, PUB270

liver failure..... TH-PO010, TH-PO048, TH-PO105, TH-PO1106, FR-PO046, FR-PO499, FR-PO521, FR-PO583, SA-PO058, SA-PO061, SA-PO109, SA-PO117, SA-PO118, SA-PO192, SA-PO1053, SA-PO1054, SA-PO1056, PUB040

lupus nephritis..... TH-OR021, TH-OR022, TH-OR072, TH-PO148, TH-PO288, TH-PO687, TH-PO688, TH-PO689, TH-PO694, TH-PO697, TH-PO706, TH-PO709, TH-PO713, TH-PO717, TH-PO721, TH-PO758, TH-PO759, TH-PO760, TH-PO761, TH-PO762, TH-PO763, TH-PO764, TH-PO765, TH-PO766, TH-PO769, TH-PO772, TH-PO775, TH-PO777, TH-PO778, TH-PO779, TH-PO1070, TH-PO1110,

lupus nephritis (continued)..... TH-PO1124, FR-OR058, FR-OR059, FR-PO216, FR-PO514, FR-PO703, FR-PO985, FR-PO991, SA-PO038, SA-PO073, SA-PO167, SA-PO430, SA-PO556, SA-PO1004, PUB220, PUB223, PUB231, PUB233, PUB237, PUB244, PUB259, PUB410, PUB660

lymphocytes..... TH-OR069, TH-OR070, TH-PO012, TH-PO014, TH-PO027, TH-PO157, TH-PO271, TH-PO749, TH-PO1017, TH-PO1036, TH-PO1075, FR-OR075, FR-PO678, FR-PO841, FR-PO843, FR-PO982, FR-PO983, FR-PO998, SA-PO439, SA-PO969, SA-PO1069, PUB069, PUB623, PUB641, PUB685, PUB695

macrophages..... TH-OR031, TH-OR065, TH-OR067, TH-PO024, TH-PO041, TH-PO129, TH-PO142, TH-PO144, TH-PO156, TH-PO162, TH-PO206, TH-PO219, TH-PO288, TH-PO381, TH-PO391, TH-PO395, TH-PO403, TH-PO407, TH-PO485, TH-PO727, FR-OR082, FR-OR104, FR-PO146, FR-PO147, FR-PO256, FR-PO307, FR-PO877, FR-PO884, FR-PO896, FR-PO952, FR-PO956, FR-PO992, SA-OR091, SA-PO280, SA-PO395, SA-PO438, SA-PO440, SA-PO441, SA-PO489, SA-PO490, PUB097

malfolding proteins..... TH-OR086

malnutrition..... TH-PO476, TH-PO836, TH-PO886, TH-PO952, TH-PO964, FR-PO788, FR-PO856, FR-PO857, FR-PO868, FR-PO869, FR-PO870, FR-PO885, FR-PO888, FR-PO892, FR-PO897, SA-OR089, SA-PO588, SA-PO757, SA-PO909, PUB362, PUB492, PUB557

MCP-1 (monocyte chemoattractant protein 1)..... TH-PO160, TH-PO280, FR-PO448, SA-OR091, SA-PO395, SA-PO690, SA-PO851, PUB294

MDCK (Madin-Darby canine kidney)..... TH-PO313

MPGN (membranoproliferative glomerulonephritis)..... TH-PO226, TH-PO1083, TH-PO1085, TH-PO1087, TH-PO1113, FR-PO006, FR-PO014, FR-PO452, FR-PO454, FR-PO956, SA-PO019, SA-PO042, SA-PO064, SA-PO109, SA-PO123, PUB226

membranous nephropathy..... TH-PO690, TH-PO704, TH-PO710, TH-PO714, TH-PO720, TH-PO722, TH-PO741, TH-PO743, TH-PO744, TH-PO745, TH-PO747, TH-PO748, TH-PO749, TH-PO751, TH-PO752, TH-PO753, TH-PO754, TH-PO755, TH-PO756, TH-PO757, TH-PO759, TH-PO761, TH-PO1044, TH-PO1052, TH-PO1054, TH-PO1070, FR-OR062, FR-OR063, FR-PO010, FR-PO344, FR-PO354, FR-PO387, FR-PO423, FR-PO511, FR-PO966, FR-PO967, FR-PO968, SA-OR011, SA-OR012, SA-OR014, SA-OR015, SA-OR025, SA-PO004, SA-PO006, SA-PO032, SA-PO034, SA-PO081, SA-PO085, SA-PO104,

membranous nephropathy

(continued)..... SA-PO426, SA-PO502, SA-PO965, SA-PO1085, PUB155, PUB202, PUB206, PUB215, PUB245, PUB247, PUB250, PUB418

mesangial cells..... TH-PO297, TH-PO368, FR-OR084, FR-PO974, FR-PO975, SA-OR048, SA-PO309, SA-PO327, SA-PO343, SA-PO357, SA-PO368, SA-PO410, PUB102

metabolism..... TH-PO009, TH-PO041, TH-PO185, TH-PO203, TH-PO272, TH-PO409, TH-PO430, TH-PO499, TH-PO559, TH-PO597, TH-PO702, FR-PO181, FR-PO285, FR-PO301, FR-PO384, FR-PO531, FR-PO537, FR-PO543, FR-PO597, FR-PO847, FR-PO864, FR-PO879, FR-PO880, FR-PO891, FR-PO1103, SA-OR040, SA-OR090, SA-OR096, SA-PO185, SA-PO281, SA-PO337, SA-PO383, SA-PO386, SA-PO408, SA-PO417, SA-PO446, SA-PO573, SA-PO893, SA-PO993, PUB105, PUB147, PUB292, PUB335, PUB516, PUB658, PUB704

microalbuminuria..... TH-OR007, TH-PO463, TH-PO464, TH-PO577, FR-PO608, FR-PO618, FR-PO630, FR-PO636, FR-PO648, SA-PO363, SA-PO645

mineral metabolism..... TH-OR083, TH-OR106, TH-OR113, TH-OR124, TH-PO487, TH-PO491, TH-PO494, TH-PO495, TH-PO496, TH-PO500, TH-PO501, TH-PO503, TH-PO561, TH-PO596, TH-PO600, TH-PO616, TH-PO640, TH-PO828, TH-PO930, TH-PO939, TH-PO1000, TH-PO1019, TH-PO1057, FR-OR023, FR-OR024, FR-OR025, FR-PO068, FR-PO592, FR-PO798, FR-PO867, FR-PO900, FR-PO903, FR-PO913, FR-PO914, FR-PO927, FR-PO928, FR-PO931, FR-PO932, FR-PO934, FR-PO935, FR-PO937, FR-PO1031, FR-PO1039, SA-PO227, SA-PO558, SA-PO559, SA-PO560, SA-PO566, SA-PO568, SA-PO570, SA-PO573, SA-PO578, SA-PO580, SA-PO584, SA-PO585, SA-PO605, SA-PO614, SA-PO712, PUB002, PUB111, PUB298, PUB299, PUB338, PUB375, PUB409, PUB417, PUB511, PUB513, PUB514, PUB518, PUB535, PUB537, PUB540, PUB546, PUB582, PUB585, PUB586, PUB590

mitochondria..... TH-OR051, TH-OR100, TH-PO006, TH-PO010, TH-PO261, TH-PO292, TH-PO336, TH-PO340, TH-PO702, FR-OR083, FR-PO038, FR-PO110, FR-PO151, FR-PO177, FR-PO237, FR-PO238, FR-PO240, FR-PO241, FR-PO301, FR-PO616, FR-PO830, FR-PO840, FR-PO891, FR-PO893, SA-OR002, SA-PO002, SA-PO267, SA-PO337, SA-PO341, SA-PO342, SA-PO375, SA-PO405, SA-PO442, SA-PO481, SA-PO658, SA-PO750, PUB105, PUB107, PUB469, PUB705

- molecular biology** TH-PO279, TH-PO401, TH-PO475, TH-PO683, FR-PO211, FR-PO309, FR-PO387, FR-PO530, FR-PO824, FR-PO951, SA-OR117, SA-PO261, SA-PO318, SA-PO366, SA-PO440, SA-PO449, SA-PO539, PUB013, PUB391
- molecular genetics** TH-PO204, TH-PO216, TH-PO350, FR-OR092, FR-PO156, FR-PO161, FR-PO190, FR-PO191, FR-PO193, FR-PO399, SA-PO493, SA-PO847, PUB281
- mortality**..... TH-OR121, TH-PO053, TH-PO069, TH-PO084, TH-PO414, TH-PO494, TH-PO587, TH-PO613, TH-PO629, TH-PO672, TH-PO799, TH-PO800, TH-PO803, TH-PO834, TH-PO894, TH-PO912, TH-PO918, TH-PO925, TH-PO939, TH-PO947, TH-PO953, TH-PO957, TH-PO982, TH-PO1008, TH-PO1014, TH-PO1049, FR-OR014, FR-OR037, FR-PO265, FR-PO457, FR-PO459, FR-PO468, FR-PO476, FR-PO534, FR-PO575, FR-PO578, FR-PO640, FR-PO675, FR-PO708, FR-PO731, FR-PO734, FR-PO737, FR-PO748, FR-PO749, FR-PO757, FR-PO759, FR-PO782, FR-PO792, FR-PO794, FR-PO845, FR-PO855, FR-PO875, FR-PO900, FR-PO1000, FR-PO1009, FR-PO1033, FR-PO1053, FR-PO1097, FR-PO1098, SA-OR035, SA-PO234, SA-PO596, SA-PO614, SA-PO677, SA-PO708, SA-PO771, SA-PO774, SA-PO775, SA-PO779, SA-PO783, SA-PO790, SA-PO796, SA-PO829, SA-PO835, SA-PO875, SA-PO902, SA-PO907, SA-PO918, SA-PO922, SA-PO1056, PUB038, PUB043, PUB138, PUB164, PUB182, PUB224, PUB321, PUB330, PUB336, PUB349, PUB356, PUB373, PUB461, PUB560, PUB680, PUB683
- mortality risk**..... TH-OR008, TH-PO058, TH-PO456, TH-PO549, TH-PO558, TH-PO586, TH-PO592, TH-PO598, TH-PO631, TH-PO809, TH-PO920, TH-PO926, TH-PO928, TH-PO935, TH-PO936, TH-PO941, TH-PO980, TH-PO999, TH-PO1025, FR-OR033, FR-OR036, FR-OR041, FR-PO016, FR-PO392, FR-PO480, FR-PO489, FR-PO573, FR-PO577, FR-PO637, FR-PO650, FR-PO674, FR-PO681, FR-PO690, FR-PO728, FR-PO730, FR-PO761, FR-PO763, FR-PO781, FR-PO839, FR-PO874, FR-PO899, FR-PO933, FR-PO1007, FR-PO1008, FR-PO1035, FR-PO1055, FR-PO1057, SA-OR009, SA-OR010, SA-PO195, SA-PO214, SA-PO215, SA-PO233, SA-PO616, SA-PO619, SA-PO648, SA-PO706, SA-PO755, SA-PO761, SA-PO769, SA-PO800, SA-PO911, SA-PO1083, PUB055, PUB057, PUB059, PUB132, PUB296, PUB329, PUB346, PUB362, PUB381, PUB566, PUB570, PUB604, PUB631, PUB684, PUB711
- mRNA**..... TH-PO197, TH-PO374, FR-OR090, FR-PO094, FR-PO205, FR-PO519, SA-PO449
- multiple myeloma**..... TH-PO1072, TH-PO1079, TH-PO1101, FR-PO496, SA-PO049, SA-PO051, SA-PO088, SA-PO115, PUB217, PUB311, PUB440
- mycophenolate mofetil**..... TH-OR022, TH-PO774, FR-PO450, PUB211, PUB239
- myeloma**..... TH-PO076, TH-PO668, TH-PO1091, SA-PO029
- sodium (Na) transport** TH-OR077, TH-OR078, TH-OR079, TH-OR114, TH-PO424, TH-PO425, TH-PO429, TH-PO437, TH-PO438, TH-PO440, TH-PO445, TH-PO447, TH-PO655, TH-PO832, FR-OR009, FR-PO120, FR-PO139, FR-PO140, FR-PO923, SA-OR031, SA-OR069, SA-OR118, SA-PO380, SA-PO382, SA-PO466, SA-PO500, SA-PO547, SA-PO549, SA-PO629, SA-PO691, SA-PO919, PUB535, PUB718
- NADPH oxidase**..... TH-PO339, FR-PO815, SA-PO306, SA-PO374, SA-PO405, PUB010, PUB702
- nephrectomy** TH-PO030, TH-PO055, FR-PO201, FR-PO1095, SA-OR042, SA-PO422, SA-PO455, SA-PO651, SA-PO890, SA-PO1024, PUB003, PUB449
- nephrin**..... TH-PO141, TH-PO328, FR-OR086, FR-PO324, FR-PO345, FR-PO423, SA-PO324, PUB099
- nephritis**..... TH-PO152, TH-PO1040, TH-PO1071, TH-PO1102, FR-PO343, FR-PO456, SA-PO019, SA-PO045, PUB204
- nephrology** TH-PO574, TH-PO642, TH-PO724, FR-OR031, SA-PO133, SA-PO135, SA-PO136, SA-PO137, SA-PO138, SA-PO139, SA-PO149, SA-PO150, SA-PO155, SA-PO174, SA-PO649, SA-PO714, SA-PO753, SA-PO781, PUB383, PUB384, PUB387, PUB625
- nephron** TH-OR045, TH-PO705, FR-OR007, FR-OR089, FR-OR092, FR-PO182, FR-PO190, FR-PO191, FR-PO192, SA-PO026, SA-PO447, PUB280
- nephropathy**..... TH-PO172, TH-PO268, TH-PO269, TH-PO1104, FR-PO085, FR-PO602, SA-PO062, SA-PO080, SA-PO299, PUB020, PUB230, PUB406, PUB653
- nephrotic syndrome** TH-PO301, TH-PO431, TH-PO466, TH-PO472, TH-PO662, TH-PO708, TH-PO720, TH-PO723, TH-PO742, TH-PO753, TH-PO780, TH-PO787, TH-PO796, TH-PO1029, TH-PO1034, TH-PO1036, TH-PO1043, TH-PO1074, TH-PO1083, TH-PO1084, TH-PO1113, TH-PO1123, FR-OR050, FR-OR052, FR-OR062, FR-PO008, FR-PO021, FR-PO059, FR-PO064, FR-PO125, FR-PO150, FR-PO151, FR-PO152, FR-PO154, FR-PO155, FR-PO156, FR-PO157, FR-PO159, FR-PO420, FR-PO423, FR-PO427, FR-PO428, FR-PO429, FR-PO432, FR-PO434, FR-PO435, FR-PO439, FR-PO441, FR-PO443, FR-PO451, FR-PO511, FR-PO514, FR-PO555, FR-PO588, SA-OR011, SA-OR015, SA-OR016, SA-OR019, SA-OR050,
- nephrotic syndrome (continued)**..... SA-PO003, SA-PO008, SA-PO017, SA-PO018, SA-PO032, SA-PO050, SA-PO056, SA-PO070, SA-PO078, SA-PO105, SA-PO108, SA-PO115, SA-PO116, SA-PO121, SA-PO502, PUB040, PUB070, PUB078, PUB099, PUB109, PUB203, PUB206, PUB210, PUB212, PUB215, PUB219, PUB239, PUB240, PUB395, PUB401, PUB404, PUB414, PUB415, PUB416, PUB553
- nephrotoxicity**..... TH-PO009, TH-PO054, TH-PO083, TH-PO088, TH-PO090, TH-PO094, TH-PO096, TH-PO151, TH-PO673, TH-PO1053, TH-PO1098, FR-PO038, FR-PO042, FR-PO204, FR-PO425, FR-PO481, FR-PO485, FR-PO500, SA-PO044, SA-PO186, SA-PO229, SA-PO275, SA-PO294, SA-PO446, SA-PO895, PUB007, PUB035, PUB063, PUB153, PUB158, PUB462, PUB642, PUB720, PUB724
- nitric oxide** TH-PO323, TH-PO337, FR-OR043, SA-PO247, SA-PO451, SA-PO546, SA-PO892, PUB007
- nocturnal hypoxemia** TH-PO976, FR-PO771, FR-PO772
- nutrition** TH-OR014, TH-PO080, TH-PO086, TH-PO112, TH-PO200, TH-PO501, TH-PO525, TH-PO555, TH-PO619, TH-PO801, TH-PO887, TH-PO930, TH-PO941, FR-OR109, FR-OR111, FR-PO123, FR-PO198, FR-PO199, FR-PO535, FR-PO590, FR-PO596, FR-PO651, FR-PO676, FR-PO758, FR-PO760, FR-PO787, FR-PO844, FR-PO846, FR-PO851, FR-PO852, FR-PO862, FR-PO865, FR-PO867, FR-PO874, FR-PO877, FR-PO882, FR-PO883, FR-PO886, FR-PO888, FR-PO890, FR-PO892, FR-PO894, FR-PO897, FR-PO898, FR-PO904, FR-PO906, FR-PO941, FR-PO948, FR-PO1030, FR-PO1107, SA-OR077, SA-OR089, SA-OR092, SA-OR093, SA-OR096, SA-OR104, SA-PO122, SA-PO411, SA-PO646, SA-PO711, SA-PO715, SA-PO735, SA-PO864, PUB104, PUB142, PUB180, PUB307, PUB350, PUB365, PUB372, PUB558, PUB559, PUB560, PUB562, PUB563, PUB564, PUB565, PUB566, PUB697
- obesity**..... TH-OR014, TH-OR058, TH-PO317, TH-PO359, TH-PO452, TH-PO454, TH-PO593, TH-PO853, TH-PO1008, FR-OR112, FR-OR113, FR-PO625, FR-PO638, FR-PO639, FR-PO640, FR-PO641, FR-PO732, FR-PO845, FR-PO849, FR-PO850, FR-PO853, FR-PO861, FR-PO876, FR-PO884, FR-PO1015, FR-PO1047, SA-OR094, SA-PO226, SA-PO362, SA-PO376, SA-PO392, SA-PO401, SA-PO408, SA-PO411, SA-PO414, SA-PO418, SA-PO611, SA-PO643, SA-PO666, SA-PO1021, PUB287, PUB304, PUB573, PUB697

- obstructive nephropathy**..... TH-OR067, TH-PO078, TH-PO285, TH-PO474, TH-PO1060, TH-PO1067, FR-OR090, FR-PO037, FR-PO052, FR-PO294, FR-PO295, FR-PO306, SA-OR082, SA-PO435, SA-PO475, SA-PO478, PUB058, PUB421
- obstructive uropathy**..... TH-PO1068, PUB526, PUB572
- organ transplant**..... FR-PO492, FR-PO929, FR-PO1041, SA-PO020, SA-PO1032
- organic anion transporter** FR-PO110, SA-PO432
- osmolality**..... TH-PO422, TH-PO1049, TH-PO1056, TH-PO1066, FR-OR003, FR-PO096, SA-PO934, PUB439, PUB442, PUB716
- osteopontin**..... TH-PO144, SA-PO588
- outcomes**..... TH-OR028, TH-OR037, TH-PO082, TH-PO107, TH-PO466, TH-PO590, TH-PO592, TH-PO681, TH-PO710, TH-PO725, TH-PO758, TH-PO769, TH-PO773, TH-PO777, TH-PO778, TH-PO779, TH-PO792, TH-PO861, TH-PO915, TH-PO921, TH-PO931, TH-PO943, TH-PO945, TH-PO951, TH-PO960, TH-PO962, TH-PO973, TH-PO981, TH-PO989, TH-PO1006, TH-PO1009, FR-OR070, FR-OR071, FR-PO166, FR-PO429, FR-PO470, FR-PO476, FR-PO477, FR-PO480, FR-PO487, FR-PO495, FR-PO512, FR-PO516, FR-PO548, FR-PO594, FR-PO598, FR-PO601, FR-PO609, FR-PO681, FR-PO686, FR-PO695, FR-PO706, FR-PO733, FR-PO735, FR-PO752, FR-PO769, FR-PO775, FR-PO777, FR-PO799, FR-PO802, FR-PO832, FR-PO857, FR-PO871, FR-PO1033, FR-PO1038, SA-OR003, SA-OR028, SA-OR056, SA-PO132, SA-PO139, SA-PO148, SA-PO153, SA-PO162, SA-PO201, SA-PO205, SA-PO212, SA-PO218, SA-PO231, SA-PO233, SA-PO234, SA-PO235, SA-PO560, SA-PO578, SA-PO615, SA-PO710, SA-PO716, SA-PO763, SA-PO810, SA-PO845, SA-PO868, SA-PO949, SA-PO1013, SA-PO1018, SA-PO1020, SA-PO1029, SA-PO1030, SA-PO1075, SA-PO1078, PUB027, PUB113, PUB114, PUB148, PUB249, PUB340, PUB343, PUB348, PUB363, PUB366, PUB368, PUB376, PUB509, PUB592, PUB596, PUB619, PUB659, PUB668, PUB690
- oxidative stress**..... TH-OR061, TH-OR088, TH-PO026, TH-PO037, TH-PO042, TH-PO235, TH-PO268, TH-PO269, TH-PO281, TH-PO282, TH-PO283, TH-PO287, TH-PO300, TH-PO306, TH-PO337, TH-PO341, TH-PO343, TH-PO390, TH-PO396, TH-PO447, TH-PO459, TH-PO473, FR-PO271, FR-PO309, FR-PO354, FR-PO536, FR-PO554, FR-PO665, FR-PO806, FR-PO816, FR-PO827, FR-PO840, FR-PO872, SA-OR098, SA-PO209, SA-PO236, SA-PO238, SA-PO245, SA-PO246, SA-PO294, SA-PO345,
- oxidative stress (continued)**..... SA-PO375, SA-PO381, SA-PO394, SA-PO411, SA-PO412, SA-PO586, SA-PO749, SA-PO815, PUB100, PUB103, PUB104, PUB106, PUB107, PUB117, PUB174, PUB275, PUB308, PUB713
- p38 mitogen-activated protein kinase**..... TH-PO345, FR-PO254
- pancreas transplantation**..... FR-PO056
- parathyroid hormone**..... TH-PO487, TH-PO510, TH-PO511, TH-PO514, TH-PO520, TH-PO522, TH-PO820, TH-PO1037, FR-PO054, FR-PO901, FR-PO916, FR-PO918, FR-PO1108, SA-PO399, SA-PO566, SA-PO571, SA-PO573, SA-PO580, SA-PO581, PUB453, PUB518, PUB519, PUB521, PUB530, PUB532
- pathology**..... TH-OR058, TH-OR090, TH-PO471, TH-PO533, TH-PO682, TH-PO687, TH-PO700, TH-PO708, TH-PO721, TH-PO734, TH-PO791, TH-PO1026, TH-PO1073, TH-PO1110, TH-PO1125, FR-PO131, FR-PO376, FR-PO442, FR-PO618, FR-PO619, FR-PO625, SA-PO004, SA-PO029, SA-PO154, SA-PO157, SA-PO445, SA-PO980, SA-PO1065, PUB078, PUB082, PUB155, PUB178, PUB246, PUB252
- pathophysiology of renal disease and progression**..... TH-OR003, TH-OR068, TH-PO146, TH-PO149, TH-PO166, TH-PO231, TH-PO267, TH-PO333, TH-PO501, TH-PO538, TH-PO578, TH-PO581, TH-PO692, TH-PO693, TH-PO756, TH-PO763, FR-OR086, FR-PO162, FR-PO260, FR-PO308, FR-PO358, FR-PO389, FR-PO389, FR-PO448, FR-PO545, FR-PO642, FR-PO988, SA-PO077, SA-PO262, SA-PO368, SA-PO421, SA-PO438, SA-PO443, SA-PO448, SA-PO467, SA-PO626, SA-PO965, PUB254, PUB257, PUB277, PUB305, PUB391, PUB416, PUB418, PUB503, PUB701
- patient satisfaction** TH-PO990, TH-PO996, TH-PO1024, SA-PO153, SA-PO158, SA-PO160, SA-PO177, SA-PO178, SA-PO748, SA-PO832, SA-PO837, SA-PO1001, SA-PO1046, PUB115, PUB165, PUB168, PUB383, PUB635
- patient self-assessment**..... TH-PO468, TH-PO924, TH-PO929, TH-PO996, FR-PO498, FR-PO774, FR-PO785, FR-PO1034, SA-PO161, SA-PO675, SA-PO720, SA-PO724, SA-PO728, SA-PO731, SA-PO746, SA-PO1003, SA-PO1023, PUB144, PUB163, PUB165
- pediatric intensive care medicine**..... TH-PO099, TH-PO983
- pediatric kidney transplantation** TH-PO456, FR-PO005, FR-PO092, FR-PO1005, FR-PO1063, FR-PO1085, FR-PO1106, SA-PO963, SA-PO1017, SA-PO1019, SA-PO1023, SA-PO1027, SA-PO1036, PUB690
- pediatric nephrology** TH-OR042, TH-OR056, TH-PO099, TH-PO121, TH-PO385, TH-PO457, TH-PO458, TH-PO465, TH-PO466, TH-PO472, TH-PO477, TH-PO496, TH-PO554, TH-PO632, TH-PO651, TH-PO728, TH-PO776, TH-PO849, TH-PO909, TH-PO962, TH-PO992, TH-PO1073, FR-OR097, FR-PO002, FR-PO005, FR-PO151, FR-PO173, FR-PO369, FR-PO431, FR-PO432, FR-PO455, FR-PO478, FR-PO487, FR-PO579, FR-PO593, FR-PO628, FR-PO839, FR-PO938, FR-PO939, SA-OR023, SA-OR024, SA-OR025, SA-OR027, SA-OR072, SA-PO131, SA-PO167, SA-PO221, SA-PO520, SA-PO521, SA-PO524, SA-PO540, SA-PO558, SA-PO644, SA-PO666, SA-PO733, SA-PO886, SA-PO887, SA-PO891, SA-PO903, SA-PO963, SA-PO1023, PUB160, PUB318, PUB466, PUB575, PUB580
- pediatrics**..... TH-PO054, TH-PO074, TH-PO099, TH-PO454, TH-PO464, TH-PO468, TH-PO473, TH-PO1021, FR-OR035, FR-PO368, FR-PO369, FR-PO986, SA-OR023, SA-OR100, SA-PO557, SA-PO974, SA-PO1031, PUB210, PUB458, PUB579
- peritoneal dialysis**..... TH-PO118, TH-PO121, TH-PO312, TH-PO495, TH-PO625, TH-PO678, TH-PO858, TH-PO962, TH-PO984, TH-PO985, TH-PO987, TH-PO988, TH-PO989, TH-PO991, TH-PO992, TH-PO993, TH-PO994, TH-PO997, TH-PO998, TH-PO999, TH-PO1001, TH-PO1003, TH-PO1004, TH-PO1005, TH-PO1006, TH-PO1007, TH-PO1008, TH-PO1011, TH-PO1013, TH-PO1014, TH-PO1015, TH-PO1018, TH-PO1019, TH-PO1020, TH-PO1021, TH-PO1022, TH-PO1023, TH-PO1025, TH-PO1042, FR-OR033, FR-OR034, FR-OR039, FR-OR040, FR-PO060, FR-PO075, FR-PO090, FR-PO751, FR-PO755, FR-PO761, FR-PO789, FR-PO790, FR-PO792, FR-PO809, FR-PO811, FR-PO812, FR-PO816, FR-PO817, FR-PO818, FR-PO820, FR-PO821, FR-PO822, FR-PO823, FR-PO825, FR-PO826, FR-PO829, FR-PO830, FR-PO832, FR-PO833, FR-PO834, FR-PO835, FR-PO836, FR-PO837, FR-PO839, SA-PO021, SA-PO060, SA-PO099, SA-PO102, SA-PO112, SA-PO129, SA-PO143, SA-PO161, SA-PO477, SA-PO738, SA-PO829, SA-PO836, SA-PO846, SA-PO906, PUB103, PUB106, PUB116, PUB117, PUB135, PUB350, PUB358, PUB397, PUB430, PUB583, PUB584, PUB588, PUB589, PUB591, PUB593, PUB594, PUB595, PUB596, PUB597, PUB598, PUB599, PUB600, PUB605, PUB606, PUB607, PUB611, PUB612, PUB614

- peritoneal membrane**.....TH-PO1001, TH-PO1002, TH-PO1010, TH-PO1015, TH-PO1020, FR-OR039, FR-PO808, FR-PO810, FR-PO811, FR-PO812, FR-PO813, FR-PO814, FR-PO819, FR-PO820, FR-PO821, FR-PO823, FR-PO824, FR-PO827, FR-PO831, FR-PO833, SA-PO060, SA-PO112, PUB107, PUB397, PUB603, PUB605, PUB611, PUB613
- pharmacokinetics**..... TH-PO090, TH-PO125, TH-PO1023, FR-PO066, FR-PO378, FR-PO396, SA-OR039, SA-PO529, SA-PO530, SA-PO531, SA-PO532, SA-PO533, SA-PO537, SA-PO541, SA-PO542, SA-PO543, SA-PO544, SA-PO545, SA-PO552, SA-PO553, SA-PO556, PUB615
- phosphate binders**..... TH-PO498, TH-PO642, TH-PO643, TH-PO828, TH-PO937, TH-PO1000, FR-OR015, FR-PO061, FR-PO895, FR-PO905, FR-PO907, FR-PO908, FR-PO909, FR-PO910, FR-PO911, FR-PO912, FR-PO913, FR-PO914, FR-PO915, SA-PO172, SA-PO174, SA-PO813, PUB322, PUB368, PUB375, PUB511, PUB520, PUB524, PUB544, PUB585, PUB586, PUB590
- phosphate uptake**..... TH-OR106, TH-OR114, TH-PO504, TH-PO560, TH-PO623, TH-PO640, TH-PO655, TH-PO1057, FR-PO906, FR-PO916, FR-PO917, FR-PO935, FR-PO936, SA-OR088, SA-PO547, SA-PO581, PUB128, PUB512, PUB516
- platelets**..... TH-PO224, TH-PO811, FR-PO053, FR-PO080, FR-PO083, FR-PO803, SA-PO224
- podocyte**..... TH-OR003, TH-OR021, TH-OR086, TH-OR087, TH-OR092, TH-OR094, TH-PO168, TH-PO225, TH-PO226, TH-PO228, TH-PO229, TH-PO230, TH-PO232, TH-PO233, TH-PO234, TH-PO236, TH-PO238, TH-PO239, TH-PO240, TH-PO248, TH-PO249, TH-PO251, TH-PO290, TH-PO299, TH-PO300, TH-PO301, TH-PO303, TH-PO304, TH-PO305, TH-PO306, TH-PO307, TH-PO308, TH-PO309, TH-PO324, TH-PO325, TH-PO326, TH-PO327, TH-PO328, TH-PO329, TH-PO330, TH-PO334, TH-PO345, TH-PO351, TH-PO352, TH-PO354, TH-PO366, TH-PO686, TH-PO733, TH-PO1030, FR-OR049, FR-OR050, FR-OR053, FR-OR062, FR-OR080, FR-OR085, FR-PO153, FR-PO157, FR-PO165, FR-PO187, FR-PO193, FR-PO206, FR-PO315, FR-PO316, FR-PO318, FR-PO320, FR-PO321, FR-PO322, FR-PO326, FR-PO331, FR-PO332, FR-PO333, FR-PO335, FR-PO336, FR-PO337, FR-PO340, FR-PO341, FR-PO343, FR-PO345, FR-PO346, FR-PO347, FR-PO349, FR-PO350, FR-PO351, FR-PO353, FR-PO355, FR-PO359, FR-PO360, FR-PO361, FR-PO363, FR-PO402, FR-PO420, FR-PO421, FR-PO422, FR-PO424, FR-PO428, FR-PO437, FR-PO978, SA-OR016,
- podocyte (continued)**....SA-OR045, SA-OR046, SA-OR047, SA-OR049, SA-OR051, SA-PO029, SA-PO286, SA-PO290, SA-PO292, SA-PO295, SA-PO309, SA-PO325, SA-PO334, SA-PO338, SA-PO340, SA-PO342, SA-PO348, SA-PO351, SA-PO352, SA-PO361, SA-PO369, SA-PO370, SA-PO372, SA-PO453, SA-PO1040, PUB082, PUB084, PUB085, PUB086, PUB088, PUB090, PUB280, PUB294, PUB701
- polycystic kidney disease**..... TH-PO179, TH-PO180, TH-PO184, TH-PO188, TH-PO190, TH-PO198, TH-PO201, TH-PO203, TH-PO204, TH-PO206, TH-PO208, TH-PO209, TH-PO212, TH-PO213, TH-PO214, TH-PO215, TH-PO216, TH-PO223, TH-PO657, TH-PO692, FR-OR042, FR-PO020, FR-PO104, SA-PO850, SA-PO857, SA-PO865, SA-PO866, SA-PO867, SA-PO868, SA-PO869, SA-PO870, SA-PO878, SA-PO883, SA-PO886, PUB266, PUB268, PUB273, PUB715
- polymorphisms**..... TH-PO441, TH-PO1061, SA-PO500, SA-PO507, SA-PO513, SA-PO516, SA-PO518, SA-PO554, SA-PO555, SA-PO988, PUB052
- potassium (K) channels**.....TH-PO157, TH-PO434, TH-PO435, TH-PO436, SA-PO923, PUB450, PUB494
- primary glomerulonephritis**..... TH-PO741, PUB232
- progression of chronic renal failure**..... TH-OR006, TH-OR016, TH-PO202, TH-PO244, TH-PO526, TH-PO534, TH-PO535, TH-PO541, TH-PO554, TH-PO557, TH-PO560, TH-PO571, TH-PO572, TH-PO587, TH-PO603, TH-PO665, TH-PO948, FR-OR044, FR-OR063, FR-OR108, FR-PO268, FR-PO282, FR-PO422, FR-PO515, FR-PO518, FR-PO546, FR-PO558, FR-PO565, FR-PO583, FR-PO638, FR-PO642, FR-PO795, FR-PO845, FR-PO878, FR-PO900, SA-OR003, SA-OR004, SA-OR007, SA-OR019, SA-PO520, SA-PO678, SA-PO716, SA-PO721, SA-PO735, SA-PO796, SA-PO851, SA-PO922, PUB184, PUB185, PUB193, PUB194, PUB523
- progression of renal failure**..... TH-OR027, TH-PO538, TH-PO580, TH-PO664, FR-PO163, FR-PO394, FR-PO559, FR-PO626, SA-OR026, SA-PO210, SA-PO220, SA-PO469, SA-PO492, SA-PO545, SA-PO569, SA-PO754, SA-PO872, SA-PO875, PUB027, PUB223, PUB272, PUB303, PUB552
- proliferation**..... TH-PO178, TH-PO179, TH-PO182, TH-PO190, TH-PO255, FR-OR102, FR-PO107, FR-PO260, FR-PO277, FR-PO316, FR-PO317, SA-OR080, SA-OR085, SA-PO295, SA-PO300, SA-PO357, PUB021, PUB092
- proteinuria**..... TH-OR021, TH-OR094, TH-PO132, TH-PO141, TH-PO147, TH-PO148, TH-PO227, TH-PO232, TH-PO241, TH-PO242, TH-PO327, TH-PO353, TH-PO354, TH-PO557, TH-PO565, TH-PO599, TH-PO645, TH-PO656, TH-PO696, TH-PO699, TH-PO764, TH-PO780, TH-PO1011, TH-PO1034, TH-PO1038, TH-PO1043, TH-PO1055, TH-PO1072, TH-PO1086, TH-PO1092, TH-PO1101, TH-PO1114, TH-PO1118, FR-PO047, FR-PO149, FR-PO325, FR-PO329, FR-PO344, FR-PO346, FR-PO356, FR-PO360, FR-PO387, FR-PO404, FR-PO424, FR-PO425, FR-PO433, FR-PO434, FR-PO440, FR-PO442, FR-PO449, FR-PO466, FR-PO510, FR-PO576, FR-PO607, FR-PO608, FR-PO612, FR-PO615, FR-PO629, FR-PO630, FR-PO996, FR-PO1012, SA-OR016, SA-OR026, SA-OR050, SA-OR062, SA-PO030, SA-PO032, SA-PO035, SA-PO043, SA-PO098, SA-PO100, SA-PO310, SA-PO334, SA-PO339, SA-PO341, SA-PO349, SA-PO367, SA-PO448, SA-PO452, SA-PO453, SA-PO456, SA-PO498, SA-PO521, SA-PO628, SA-PO664, SA-PO678, SA-PO679, SA-PO706, PUB131, PUB134, PUB152, PUB175, PUB184, PUB185, PUB192, PUB206, PUB207, PUB212, PUB214, PUB219, PUB222, PUB236, PUB258, PUB275, PUB283, PUB301, PUB304, PUB309, PUB556, PUB567, PUB572, PUB574, PUB663
- proximal tubule**..... TH-PO038, TH-PO163, TH-PO292, TH-PO294, TH-PO317, TH-PO349, TH-PO370, TH-PO446, TH-PO504, TH-PO686, FR-OR079, FR-OR099, FR-PO007, FR-PO113, FR-PO125, FR-PO180, FR-PO184, FR-PO192, FR-PO239, FR-PO396, FR-PO542, FR-PO570, FR-PO610, FR-PO629, FR-PO641, FR-PO918, FR-PO949, SA-OR082, SA-PO237, SA-PO267, SA-PO307, SA-PO317, SA-PO318, SA-PO328, SA-PO333, SA-PO383, SA-PO385, SA-PO397, SA-PO417, SA-PO932, SA-PO933, SA-PO936, SA-PO941, PUB152, PUB640, PUB718
- pulse wave velocity**..... TH-PO542, TH-PO553, TH-PO616, TH-PO630, TH-PO884, TH-PO903, TH-PO906, FR-PO546, SA-PO600, SA-PO653, PUB338
- pure red cell aplasia**..... FR-PO091
- pyelonephritis**..... TH-PO462, FR-PO389, FR-PO871, FR-PO990, SA-OR024, PUB651
- quality of life**..... TH-PO800, TH-PO924, TH-PO934, TH-PO996, TH-PO999, TH-PO1024, TH-PO1079, FR-PO658, FR-PO671, FR-PO679, FR-PO774, FR-PO786, FR-PO807, FR-PO870, FR-PO942, FR-PO1001, FR-PO1040, SA-OR030, SA-OR098, SA-PO134, SA-PO717, SA-PO719, SA-PO734, SA-PO736, SA-PO737, SA-PO739, SA-PO744, SA-PO746, SA-PO747, SA-PO748, SA-PO752, SA-PO758, SA-PO759, SA-PO774, SA-PO776,

- quality of life (continued)** SA-PO777, SA-PO778, SA-PO782, SA-PO784, SA-PO785, SA-PO786, SA-PO787, SA-PO791, SA-PO837, SA-PO844, SA-PO871, SA-PO1006, SA-PO1019, SA-PO1050, PUB121, PUB144, PUB355, PUB369, PUB370, PUB386, PUB555, PUB581, PUB587, PUB617, PUB635, PUB644, PUB721, PUB725
- RAGE (receptor for AGEs)** TH-PO894, FR-PO134, SA-PO943
- randomized controlled trials** TH-PO080, TH-PO505, TH-PO662, TH-PO673, TH-PO985, FR-OR017, FR-PO673, FR-PO713, FR-PO770, FR-PO909, FR-PO934, SA-OR064, SA-PO764, SA-PO816, SA-PO950, SA-PO951, PUB313, PUB353, PUB366
- reactive oxygen species** TH-OR103, TH-PO037, TH-PO308, TH-PO309, TH-PO318, TH-PO339, TH-PO406, TH-PO578, TH-PO840, FR-OR083, FR-PO104, FR-PO144, FR-PO245, FR-PO264, FR-PO339, SA-PO250, SA-PO260, SA-PO281, SA-PO310, SA-PO451, SA-PO867, PUB004, PUB010, PUB098
- rejection** TH-PO266, TH-PO274, TH-PO276, TH-PO1031, TH-PO1045, FR-PO082, FR-PO1038, FR-PO1054, FR-PO1070, FR-PO1075, FR-PO1078, FR-PO1105, SA-OR057, SA-PO960, SA-PO962, SA-PO964, SA-PO978, SA-PO979, SA-PO990, SA-PO992, SA-PO1016, SA-PO1046, SA-PO1051, SA-PO1067, SA-PO1082, PUB667, PUB671, PUB681
- renal ablation** TH-PO146, TH-PO166, TH-PO548, TH-PO910, FR-PO142, FR-PO850, SA-PO443, SA-PO622, PUB342
- renal artery stenosis** TH-PO620, TH-PO672, TH-PO773, TH-PO1047, FR-PO143, SA-PO007, SA-PO119, SA-PO222, SA-PO658, SA-PO667, PUB201
- renal autoregulation** TH-PO152, SA-OR042, SA-PO258
- renal biopsy** TH-OR010, TH-OR069, TH-PO679, TH-PO681, TH-PO694, TH-PO703, TH-PO706, TH-PO713, TH-PO714, TH-PO716, TH-PO729, TH-PO731, TH-PO746, TH-PO1036, TH-PO1055, TH-PO1064, TH-PO1082, FR-OR066, FR-PO058, FR-PO072, FR-PO076, FR-PO626, SA-OR099, SA-PO043, SA-PO154, SA-PO165, SA-PO166, SA-PO495, SA-PO647, SA-PO1085, PUB176, PUB208, PUB249, PUB252, PUB255, PUB425, PUB578, PUB682
- renal carcinoma** TH-PO738, TH-PO1120, FR-PO072, SA-PO090, SA-PO661, PUB108, PUB253
- renal cell biology** TH-OR042, TH-PO214, TH-PO295, TH-PO313, TH-PO448, FR-OR097, FR-PO264, FR-PO319, SA-PO338, SA-PO356, SA-PO361, SA-PO874
- renal development** TH-PO179, TH-PO210, TH-PO457, FR-OR095, FR-PO018, FR-PO170, FR-PO171, FR-PO181, FR-PO189, FR-PO195, FR-PO208, PUB278, PUB279, PUB280, PUB575
- renal dialysis** TH-PO110, TH-PO115, TH-PO672, TH-PO1001, FR-PO367, SA-OR105, SA-PO143, SA-PO531, SA-PO532, PUB065, PUB312
- renal dysfunction** TH-OR028, TH-PO089, TH-PO427, TH-PO475, TH-PO785, FR-PO256, SA-PO001, SA-PO015, SA-PO221, SA-PO235, SA-PO943, PUB217
- renal epithelial cell** TH-OR052, TH-OR075, TH-PO015, TH-PO221, TH-PO294, TH-PO439, FR-PO178, FR-PO200, FR-PO397, FR-PO990, SA-PO396, SA-PO487, PUB108
- renal failure** TH-PO098, TH-PO275, TH-PO1026, TH-PO1123, FR-OR073, FR-PO173, FR-PO631, FR-PO871, FR-PO1098, SA-OR005, SA-OR020, SA-PO058, SA-PO194, SA-PO199, SA-PO205, SA-PO689, PUB433, PUB466
- renal fibrosis** TH-OR065, TH-PO032, TH-PO144, TH-PO156, TH-PO258, TH-PO260, TH-PO280, TH-PO281, TH-PO282, TH-PO285, TH-PO401, TH-PO474, TH-PO669, FR-PO135, FR-PO199, FR-PO254, FR-PO271, FR-PO274, FR-PO278, FR-PO279, FR-PO280, FR-PO292, FR-PO293, FR-PO296, FR-PO303, FR-PO305, FR-PO310, FR-PO542, FR-PO691, SA-OR088, SA-PO248, SA-PO276, SA-PO364, SA-PO419, SA-PO420, SA-PO421, SA-PO435, SA-PO459, SA-PO462, SA-PO464, SA-PO470, SA-PO484, SA-PO492
- renal function** TH-PO418, TH-PO428, TH-PO455, TH-PO621, TH-PO697, TH-PO739, TH-PO740, TH-PO762, TH-PO767, FR-PO235, FR-PO375, FR-PO644, FR-PO682, FR-PO1067, FR-PO1071, FR-PO1076, FR-PO1078, SA-OR062, SA-OR063, SA-PO164, SA-PO220, SA-PO247, SA-PO364, SA-PO380, SA-PO384, SA-PO447, SA-PO645, SA-PO667, SA-PO694, SA-PO835, SA-PO866, SA-PO1016, PUB157, PUB175, PUB183, PUB190, PUB559, PUB568, PUB606
- renal function decline** TH-OR002, TH-PO527, TH-PO568, TH-PO569, TH-PO573, TH-PO1011, FR-PO243, FR-PO508, FR-PO574, FR-PO598, FR-PO602, FR-PO603, FR-PO647, FR-PO1096, SA-PO026, SA-PO073, SA-PO218, SA-PO859, SA-PO860, SA-PO1039, SA-PO1049, PUB119, PUB175, PUB296, PUB627, PUB715
- renal hemodynamics** TH-PO110, TH-PO404, TH-PO711, FR-PO527, FR-PO699, SA-OR042, SA-PO258, SA-PO355, SA-PO634
- renal hypertension** FR-PO133, SA-OR065, SA-OR066, SA-PO623
- renal injury** TH-PO023, TH-PO034, TH-PO036, TH-PO040, TH-PO072, TH-PO081, TH-PO083, TH-PO091, TH-PO122, TH-PO151, TH-PO155, TH-PO219, TH-PO259, TH-PO342, TH-PO527, TH-PO570, TH-PO589, TH-PO619, TH-PO1080, TH-PO1118, FR-PO065, FR-PO209, FR-PO244, FR-PO250, FR-PO265, FR-PO274, FR-PO455, FR-PO461, FR-PO462, FR-PO463, FR-PO526, FR-PO547, FR-PO879, FR-PO954, SA-OR004, SA-OR099, SA-PO197, SA-PO213, SA-PO216, SA-PO248, SA-PO265, SA-PO415, SA-PO424, SA-PO432, SA-PO554, PUB009, PUB013, PUB026, PUB031, PUB148, PUB406, PUB407, PUB410, PUB462, PUB498, PUB640, PUB713, PUB720, PUB724
- renal ischemia** TH-PO031, TH-PO1047, FR-OR104, FR-PO212, FR-PO214, FR-PO236, FR-PO240, FR-PO251, FR-PO256, FR-PO268, SA-PO240, SA-PO246, SA-PO254, SA-PO280, PUB047, PUB096, PUB225, PUB413
- renal morphology** FR-PO377, FR-PO993, SA-PO855
- renal osteodystrophy** TH-PO1037, FR-OR021, FR-OR022, FR-OR023, FR-PO023, FR-PO592, SA-PO091, SA-PO557, SA-PO561, SA-PO562, SA-PO564, SA-PO569, SA-PO578, SA-PO579, SA-PO582, SA-PO583, PUB525, PUB636
- renal pathology** TH-PO128, TH-PO224, TH-PO254, TH-PO281, TH-PO282, TH-PO706, TH-PO723, TH-PO729, TH-PO788, TH-PO1075, TH-PO1122, FR-PO044, FR-PO197, FR-PO582, FR-PO622, SA-PO033, SA-PO068, SA-PO072, SA-PO089, SA-PO429, SA-PO431, SA-PO637, SA-PO996, SA-PO1021, PUB253, PUB293, PUB500
- renal progression** TH-OR020, TH-PO559, TH-PO565, TH-PO566, FR-PO517, FR-PO520, FR-PO533, SA-PO213, SA-PO683, SA-PO701, SA-PO706, SA-PO854, PUB034, PUB173, PUB174, PUB186, PUB201
- renal protection** TH-OR087, TH-OR100, TH-PO033, TH-PO044, TH-PO085, TH-PO086, TH-PO127, TH-PO158, TH-PO173, TH-PO326, TH-PO547, TH-PO673, FR-OR101, FR-PO224, FR-PO225, FR-PO609, SA-OR071, SA-PO186, SA-PO238, SA-PO246, SA-PO255, SA-PO428, SA-PO429, SA-PO617, SA-PO726, PUB016, PUB035
- renal proximal tubule cell** TH-OR057, TH-OR106, TH-PO011, TH-PO246, TH-PO259, TH-PO335, TH-PO342, TH-PO361, TH-PO365, FR-OR087, FR-OR098, FR-PO023, FR-PO103, FR-PO203, FR-PO207, FR-PO237, FR-PO238, FR-PO253, SA-PO266, SA-PO272, SA-PO273, SA-PO303, SA-PO319, SA-PO320, SA-PO397, SA-PO424, SA-PO431, SA-PO549, PUB148, PUB472

- renal stem cell** TH-OR046, TH-PO237, TH-PO259, TH-PO311, FR-OR091, FR-OR100, FR-OR107, FR-PO195, FR-PO202, FR-PO208, FR-PO209, FR-PO210, FR-PO215, FR-PO235, FR-PO239, FR-PO242, FR-PO327, FR-PO342, SA-PO315, SA-PO976
- renal transplantation** TH-OR068, TH-OR074, TH-PO274, TH-PO1098, FR-OR076, FR-PO044, FR-PO045, FR-PO049, FR-PO057, FR-PO072, FR-PO076, FR-PO079, FR-PO081, FR-PO087, FR-PO436, FR-PO1003, FR-PO1005, FR-PO1017, FR-PO1019, FR-PO1021, FR-PO1023, FR-PO1027, FR-PO1028, FR-PO1031, FR-PO1040, FR-PO1046, FR-PO1052, FR-PO1055, FR-PO1061, FR-PO1074, FR-PO1077, FR-PO1084, FR-PO1090, FR-PO1094, FR-PO1099, FR-PO1101, FR-PO1105, SA-OR059, SA-OR060, SA-PO103, SA-PO125, SA-PO467, SA-PO526, SA-PO576, SA-PO606, SA-PO844, SA-PO953, SA-PO964, SA-PO970, SA-PO971, SA-PO985, SA-PO986, SA-PO992, SA-PO1009, SA-PO1025, SA-PO1030, SA-PO1034, SA-PO1055, SA-PO1058, SA-PO1061, SA-PO1064, SA-PO1080, SA-PO1088, SA-PO1089, SA-PO1090, PUB546, PUB569, PUB649, PUB650, PUB651, PUB656, PUB668, PUB669, PUB672, PUB673, PUB676, PUB678, PUB681, PUB695
- renal tubular acidosis** TH-PO1105, SA-PO895, PUB050
- renal tubular epithelial cells** TH-OR047, TH-OR102, TH-OR103, TH-PO001, TH-PO035, TH-PO150, TH-PO155, TH-PO222, TH-PO284, TH-PO357, TH-PO426, TH-PO432, TH-PO438, FR-OR095, FR-PO128, FR-PO190, FR-PO205, FR-PO263, FR-PO272, FR-PO284, FR-PO443, FR-PO611, SA-OR087, SA-PO287, SA-PO305, SA-PO306, SA-PO312, SA-PO433, SA-PO939, SA-PO945, PUB284, PUB390
- renin angiotensin system** TH-OR007, TH-OR035, TH-PO154, TH-PO245, TH-PO310, TH-PO428, TH-PO437, TH-PO461, TH-PO530, TH-PO658, TH-PO659, TH-PO661, TH-PO692, TH-PO791, TH-PO923, FR-PO114, FR-PO115, FR-PO123, FR-PO129, FR-PO130, FR-PO131, FR-PO132, FR-PO296, FR-PO520, FR-PO562, FR-PO643, SA-OR067, SA-OR070, SA-PO223, SA-PO321, SA-PO388, SA-PO391, SA-PO419, SA-PO428, SA-PO600, SA-PO635, SA-PO637, SA-PO879, SA-PO892, SA-PO914, SA-PO924, PUB032, PUB101, PUB181, PUB332, PUB419, PUB493, PUB495, PUB707
- rhabdomyolysis** SA-OR102, SA-PO046, SA-PO097, SA-PO236, SA-PO250, SA-PO259, PUB248
- rheumatology** FR-PO417, FR-PO448, SA-PO017, SA-PO039, SA-PO069, SA-PO167, PUB133, PUB189, PUB211, PUB434, PUB617
- risk factors** TH-OR005, TH-OR011, TH-OR018, TH-PO056, TH-PO061, TH-PO063, TH-PO074, TH-PO077, TH-PO104, TH-PO405, TH-PO455, TH-PO468, TH-PO473, TH-PO528, TH-PO533, TH-PO543, TH-PO544, TH-PO569, TH-PO572, TH-PO582, TH-PO701, TH-PO792, TH-PO856, TH-PO888, TH-PO927, TH-PO928, TH-PO944, TH-PO945, TH-PO993, TH-PO1005, TH-PO1021, FR-OR032, FR-OR034, FR-OR035, FR-OR036, FR-OR063, FR-OR111, FR-PO461, FR-PO464, FR-PO469, FR-PO470, FR-PO473, FR-PO489, FR-PO494, FR-PO508, FR-PO526, FR-PO544, FR-PO552, FR-PO553, FR-PO559, FR-PO569, FR-PO589, FR-PO636, FR-PO642, FR-PO675, FR-PO730, FR-PO737, FR-PO757, FR-PO875, FR-PO879, FR-PO1011, FR-PO1093, SA-OR001, SA-OR004, SA-OR093, SA-OR101, SA-PO186, SA-PO200, SA-PO201, SA-PO213, SA-PO216, SA-PO362, SA-PO646, SA-PO652, SA-PO670, SA-PO688, SA-PO689, SA-PO690, SA-PO770, SA-PO795, SA-PO822, SA-PO902, SA-PO908, SA-PO928, SA-PO1008, SA-PO1013, SA-PO1042, SA-PO1048, SA-PO1063, SA-PO1065, PUB027, PUB033, PUB123, PUB131, PUB151, PUB153, PUB198, PUB301, PUB381, PUB407, PUB526, PUB570, PUB596, PUB609, PUB656, PUB668, PUB680, PUB681, PUB725
- signaling** TH-OR054, TH-OR092, TH-PO004, TH-PO136, TH-PO142, TH-PO143, TH-PO146, TH-PO182, TH-PO190, TH-PO231, TH-PO278, TH-PO284, TH-PO289, TH-PO297, TH-PO305, TH-PO413, TH-PO443, TH-PO450, TH-PO480, TH-PO481, TH-PO488, TH-PO508, TH-PO563, FR-OR088, FR-PO252, FR-PO269, FR-PO331, FR-PO333, FR-PO351, FR-PO355, FR-PO836, FR-PO924, SA-PO240, SA-PO274, SA-PO318, SA-PO337, SA-PO340, SA-PO357, SA-PO361, SA-PO407, SA-PO452, SA-PO459, SA-PO469, SA-PO473, SA-PO481, SA-PO589, SA-PO858, SA-PO943, PUB392
- statins** TH-OR116, TH-OR117, TH-PO045, TH-PO083, TH-PO084, TH-PO085, TH-PO173, TH-PO588, TH-PO656, TH-PO988, FR-PO564, FR-PO647, FR-PO937, SA-PO725, SA-PO857, PUB066
- stem cell** TH-OR043, TH-OR044, TH-OR045, TH-PO362, TH-PO668, FR-OR055, FR-OR094, FR-OR106, FR-PO065, FR-PO143, FR-PO201, FR-PO204, FR-PO206, FR-PO210, FR-PO214, FR-PO216, FR-PO217, FR-PO218, FR-PO219, FR-PO220, FR-PO221, FR-PO222, FR-PO223, FR-PO243, FR-PO245, FR-PO247, FR-PO248, FR-PO249, FR-PO250, FR-PO275, FR-PO364, FR-PO621, FR-PO840, SA-OR038, SA-OR061, SA-PO265, SA-PO315, SA-PO563, SA-PO678, PUB019, PUB278
- survival** TH-PO104, TH-PO107, TH-PO519, TH-PO525, TH-PO624, TH-PO813, TH-PO854, TH-PO862, TH-PO887, TH-PO892, TH-PO1005, TH-PO1006, TH-PO1007, TH-PO1009, TH-PO1012, FR-OR032, FR-OR034, FR-PO408, FR-PO416, FR-PO472, FR-PO473, FR-PO486, FR-PO488, FR-PO497, FR-PO585, FR-PO657, FR-PO667, FR-PO677, FR-PO678, FR-PO680, FR-PO683, FR-PO695, FR-PO750, FR-PO759, FR-PO760, FR-PO764, FR-PO765, FR-PO875, FR-PO1019, FR-PO1068, FR-PO1092, SA-OR030, SA-OR105, SA-PO230, SA-PO244, SA-PO516, SA-PO570, SA-PO608, SA-PO789, SA-PO797, SA-PO1002, SA-PO1009, SA-PO1068, SA-PO1083, PUB045, PUB051, PUB112, PUB221, PUB340, PUB352, PUB377, PUB455, PUB584, PUB595, PUB609, PUB661, PUB666, PUB679, PUB699, PUB709
- systemic lupus erythematosus** TH-OR023, TH-PO254, TH-PO709, TH-PO717, TH-PO763, TH-PO767, TH-PO768, TH-PO770, TH-PO771, TH-PO774, TH-PO775, TH-PO776, TH-PO777, TH-PO1014, TH-PO1124, FR-PO012, FR-PO017, FR-PO984, FR-PO997, SA-PO009, PUB211, PUB237, PUB251, PUB423
- systolic blood pressure** FR-OR044, SA-PO622, SA-PO873
- tacrolimus** TH-PO268, TH-PO269, TH-PO270, TH-PO440, TH-PO662, TH-PO766, TH-PO775, FR-PO434, FR-PO435, FR-PO1074, FR-PO1083, FR-PO1086, FR-PO1103, SA-OR012, SA-PO006, SA-PO541, SA-PO542, SA-PO543, SA-PO544, SA-PO1086, PUB207, PUB664
- target organ damage** TH-PO174, SA-PO468, SA-PO497
- TGF-beta** TH-PO250, TH-PO285, TH-PO286, TH-PO301, TH-PO324, TH-PO350, TH-PO358, TH-PO399, FR-PO278, FR-PO284, FR-PO286, FR-PO294, FR-PO295, FR-PO310, FR-PO542, FR-PO887, FR-PO977, SA-PO331, SA-PO332, SA-PO371, SA-PO434, SA-PO475, SA-PO478, SA-PO480, PUB393, PUB473, PUB504
- theophylline** PUB029
- thrombosis** TH-PO267, TH-PO397, TH-PO718, TH-PO847, TH-PO850, TH-PO867, TH-PO882, TH-PO1047, FR-PO080, FR-PO088, FR-PO419, FR-PO439, FR-PO440, FR-PO511, SA-OR017, SA-PO009, SA-PO054, SA-PO170, PUB054, PUB354, PUB408, PUB413, PUB483, PUB554
- tolerance** TH-PO043, FR-PO658, SA-OR061
- transcription factors** TH-OR046, TH-PO164, TH-PO293, TH-PO364, FR-OR098, FR-PO186, FR-PO205, FR-PO257, FR-PO330, FR-PO835, FR-PO980, PUB702

- transcription regulation**.....FR-OR078, FR-OR079, FR-OR080, FR-PO185, FR-PO282, FR-PO330, SA-PO439, SA-PO493
- transcriptional profiling** TH-OR054, TH-PO001, TH-PO133, TH-PO134, TH-PO229, TH-PO275, TH-PO316, TH-PO738, TH-PO772, FR-PO108, FR-PO385, FR-PO837, SA-OR113, SA-PO495, SA-PO496, SA-PO939, SA-PO982
- transgenic mouse**..... TH-OR056, TH-OR084, TH-OR085, TH-PO128, TH-PO215, TH-PO226, TH-PO227, TH-PO361, TH-PO365, FR-OR081, FR-OR087, FR-PO183, FR-PO185, FR-PO325, FR-PO355, FR-PO399, SA-OR067, SA-PO335, SA-PO344, SA-PO471
- transplant nephrectomy** FR-PO1052, SA-PO985, SA-PO1021
- transplant outcomes**.....TH-PO276, FR-OR070, FR-PO045, FR-PO047, FR-PO055, FR-PO059, FR-PO073, FR-PO587, FR-PO790, FR-PO1005, FR-PO1006, FR-PO1011, FR-PO1012, FR-PO1013, FR-PO1028, FR-PO1032, FR-PO1037, FR-PO1040, FR-PO1041, FR-PO1042, FR-PO1046, FR-PO1047, FR-PO1048, FR-PO1049, FR-PO1051, FR-PO1052, FR-PO1053, FR-PO1054, FR-PO1056, FR-PO1059, FR-PO1060, FR-PO1061, FR-PO1063, FR-PO1065, FR-PO1066, FR-PO1085, FR-PO1089, FR-PO1090, FR-PO1091, FR-PO1092, FR-PO1093, FR-PO1094, FR-PO1100, SA-OR021, SA-OR055, SA-OR058, SA-PO024, SA-PO080, SA-PO101, SA-PO518, SA-PO734, SA-PO954, SA-PO955, SA-PO956, SA-PO959, SA-PO971, SA-PO975, SA-PO988, SA-PO1007, SA-PO1017, SA-PO1019, SA-PO1033, SA-PO1042, SA-PO1055, SA-PO1057, SA-PO1060, SA-PO1061, SA-PO1071, SA-PO1072, SA-PO1073, SA-PO1080, SA-PO1081, SA-PO1083, SA-PO1084, PUB123, PUB202, PUB594, PUB643, PUB650, PUB664, PUB666, PUB677, PUB679, PUB680, PUB683, PUB684, PUB686, PUB687, PUB689, PUB691, PUB693, PUB696
- transplant pathology**..... TH-PO267, TH-PO680, TH-PO1061, FR-PO081, FR-PO093, FR-PO380, FR-PO1094, SA-PO086, SA-PO956, SA-PO961, SA-PO973, SA-PO974, SA-PO976, SA-PO977, SA-PO980, SA-PO982, SA-PO985, SA-PO998, SA-PO999, SA-PO1044, SA-PO1084, PUB243, PUB653, PUB682
- transplantation** TH-OR032, TH-OR071, TH-PO262, TH-PO266, TH-PO270, TH-PO271, TH-PO731, TH-PO942, TH-PO1050, TH-PO1058, TH-PO1089, FR-PO041, FR-PO051, FR-PO058, FR-PO064, FR-PO083, FR-PO085, FR-PO566, FR-PO1007, FR-PO1008, FR-PO1014, FR-PO1018, FR-PO1022, FR-PO1025, FR-PO1026, FR-PO1030, FR-PO1032, FR-PO1036, FR-PO1039, FR-PO1042, FR-PO1050, FR-PO1056, FR-PO1059, FR-PO1063, FR-PO1066,
- transplantation (continued)**..... FR-PO1073, FR-PO1080, FR-PO1087, FR-PO1089, FR-PO1097, FR-PO1102, FR-PO1108, SA-OR022, SA-OR055, SA-OR056, SA-PO057, SA-PO061, SA-PO065, SA-PO086, SA-PO100, SA-PO101, SA-PO117, SA-PO118, SA-PO125, SA-PO192, SA-PO610, SA-PO747, SA-PO758, SA-PO766, SA-PO846, SA-PO950, SA-PO951, SA-PO955, SA-PO958, SA-PO962, SA-PO968, SA-PO974, SA-PO995, SA-PO1007, SA-PO1008, SA-PO1032, SA-PO1035, SA-PO1038, SA-PO1039, SA-PO1040, SA-PO1045, SA-PO1049, SA-PO1051, SA-PO1052, SA-PO1062, SA-PO1071, PUB202, PUB292, PUB339, PUB382, PUB528, PUB531, PUB639, PUB641, PUB642, PUB646, PUB654, PUB665, PUB674, PUB675, PUB687, PUB691, PUB694, PUB699
- tubular epithelium**.....TH-PO020, TH-PO028, TH-PO293, TH-PO450, TH-PO689, TH-PO1030, FR-OR093, FR-PO204, FR-PO294, FR-PO297, FR-PO401, SA-OR110, SA-PO431, SA-PO893, SA-PO942, PUB653
- tubule cells** TH-PO156, TH-PO159, TH-PO184, TH-PO200, TH-PO206, TH-PO236, TH-PO289, TH-PO1069, FR-PO099, FR-PO267, FR-PO279, FR-PO401, FR-PO921, SA-OR069, SA-PO261, SA-PO283, SA-PO409, SA-PO425, SA-PO429, SA-PO434, SA-PO437, SA-PO471, SA-PO525, SA-PO905, PUB020
- ultrafiltration**..... TH-PO802, TH-PO806, FR-PO074, FR-PO334, FR-PO373, FR-PO659, FR-PO729, FR-PO737, FR-PO808, FR-PO814, FR-PO830, SA-PO355, PUB319, PUB323, PUB359, PUB619
- uninephrectomy**..... FR-PO519
- USRDS (United States Renal Data System)**.....TH-OR019, TH-PO531, TH-PO863, TH-PO966, TH-PO968, TH-PO978, FR-PO690, FR-PO701, FR-PO746, FR-PO789, FR-PO791, FR-PO796, FR-PO1055, SA-OR034, SA-PO705, SA-PO713, SA-PO722, SA-PO783, SA-PO850, PUB364, PUB688
- urea**..... TH-PO695, FR-PO026, FR-PO096, FR-PO373, FR-PO672, SA-OR109, SA-PO594, SA-PO842, PUB632
- urea modeling**..... FR-PO684
- uremia**..... TH-OR120, TH-PO287, TH-PO374, TH-PO392, TH-PO397, TH-PO871, TH-PO1016, FR-OR023, FR-PO046, FR-PO119, FR-PO531, FR-PO535, FR-PO536, FR-PO540, FR-PO550, FR-PO655, FR-PO841, FR-PO866, FR-PO873, FR-PO895, FR-PO989, FR-PO1014, SA-OR001, SA-OR036, SA-OR091, SA-PO308, SA-PO561, PUB068, PUB093, PUB098, PUB374, PUB487, PUB603, PUB632
- ureteric bud**..... FR-PO198
- urokinase**.....TH-PO231, FR-PO513, PUB072
- vascular** TH-PO047, TH-PO318, TH-PO399, TH-PO409, TH-PO412, TH-PO417, TH-PO418, TH-PO908, TH-PO971, TH-PO1118, FR-PO137, FR-PO213, FR-PO228, FR-PO232, FR-PO299, FR-PO350, FR-PO376, FR-PO377, FR-PO708, SA-OR070, SA-PO072, SA-PO327, SA-PO483, SA-PO656, PUB047, PUB279, PUB317, PUB499, PUB575
- vascular access**..... TH-OR058, TH-OR059, TH-OR063, TH-PO070, TH-PO376, TH-PO838, TH-PO840, TH-PO841, TH-PO842, TH-PO843, TH-PO846, TH-PO848, TH-PO853, TH-PO856, TH-PO858, TH-PO861, TH-PO865, TH-PO866, TH-PO867, TH-PO871, TH-PO872, TH-PO875, TH-PO878, TH-PO880, TH-PO882, FR-PO084, FR-PO368, FR-PO695, FR-PO697, FR-PO699, FR-PO700, FR-PO704, FR-PO706, FR-PO709, FR-PO711, FR-PO712, FR-PO715, FR-PO716, FR-PO719, FR-PO720, FR-PO721, FR-PO798, SA-PO054, SA-PO147, SA-PO815, PUB474, PUB476, PUB477, PUB478, PUB479, PUB480, PUB481, PUB484, PUB486, PUB487, PUB489
- vascular calcification**..... TH-PO400, TH-PO500, TH-PO562, TH-PO603, TH-PO604, TH-PO627, TH-PO632, TH-PO884, TH-PO895, TH-PO905, TH-PO906, TH-PO907, FR-OR026, FR-OR027, FR-OR028, FR-PO934, FR-PO1031, FR-PO1039, SA-PO408, SA-PO585, SA-PO586, SA-PO587, SA-PO588, SA-PO589, SA-PO590, SA-PO591, SA-PO592, SA-PO593, SA-PO594, SA-PO596, SA-PO598, SA-PO599, SA-PO602, SA-PO603, SA-PO604, SA-PO605, SA-PO607, SA-PO608, SA-PO609, SA-PO612, SA-PO613, PUB129, PUB538, PUB672, PUB710, PUB712
- vascular disease** TH-OR060, TH-PO378, TH-PO385, TH-PO397, TH-PO400, TH-PO402, TH-PO403, TH-PO413, TH-PO459, TH-PO901, TH-PO907, TH-PO909, FR-OR025, FR-PO211, FR-PO212, SA-PO054, SA-PO222, SA-PO314, SA-PO585, SA-PO596, SA-PO601, SA-PO610, SA-PO786, SA-PO986, PUB140, PUB176, PUB200, PUB326, PUB328, PUB707
- vascular endothelial growth factor** TH-PO315, TH-PO375, TH-PO419, TH-PO421, FR-OR084, FR-PO348
- vasculitis**..... TH-OR024, TH-OR025, TH-OR026, TH-PO126, TH-PO135, TH-PO145, TH-PO1076, TH-PO1085, TH-PO1121, FR-PO006, FR-PO055, FR-PO404, FR-PO405, FR-PO411, FR-PO412, FR-PO413, FR-PO415, FR-PO417, FR-PO979, SA-PO031, SA-PO033, SA-PO047, SA-PO052, SA-PO078, SA-PO096, SA-PO106, SA-PO127, SA-PO555, PUB218, PUB224, PUB228, PUB424

vasopressin..... TH-PO213, TH-PO795,
TH-PO1056, FR-PO028, FR-PO031,
FR-PO095, FR-PO097, FR-PO100,
FR-PO106, FR-PO108, SA-OR111,
SA-OR112, SA-OR113, SA-OR114,
SA-OR115, SA-OR116, SA-PO010,
SA-PO379, SA-PO852, SA-PO853,
SA-PO857, SA-PO863, SA-PO880,
SA-PO916, PUB095, PUB713, PUB717,
PUB719

VEGF TH-PO016, TH-PO241, FR-PO148,
FR-PO350, FR-PO831, SA-PO116,
SA-PO215, SA-PO317

vesico-ureteral reflux TH-PO462, TH-PO737,
FR-PO018, FR-PO455

virology..... TH-PO1031, FR-PO052, FR-PO332,
FR-PO778, SA-PO106, SA-PO181,
SA-PO1058, SA-PO1062, SA-PO1063,
SA-PO1064, SA-PO1065, SA-PO1069,
PUB689

vitamin B1..... FR-PO596

vitamin C.... TH-PO1095, FR-PO890, SA-PO807

vitamin D.... TH-PO394, TH-PO485, TH-PO488,
TH-PO505, TH-PO506, TH-PO507,
TH-PO508, TH-PO510, TH-PO511,
TH-PO512, TH-PO513, TH-PO514,
TH-PO515, TH-PO522, TH-PO523,
TH-PO524, TH-PO601, TH-PO623,
TH-PO641, TH-PO645, TH-PO822,
TH-PO914, TH-PO1019, FR-PO029,
FR-PO034, FR-PO229, FR-PO311,
FR-PO615, FR-PO696, FR-PO800,
FR-PO815, FR-PO841, FR-PO926,
FR-PO943, FR-PO944, FR-PO1009,
SA-OR028, SA-PO016, SA-PO065,
SA-PO365, SA-PO398, SA-PO558,
SA-PO580, SA-PO597, SA-PO611,
SA-PO633, SA-PO635, SA-PO660,
SA-PO743, SA-PO1067, PUB073, PUB525,
PUB528, PUB531, PUB540, PUB542,
PUB544, PUB547, PUB548, PUB646,
PUB647, PUB667

water channels..... FR-OR038, FR-PO096,
FR-PO098, FR-PO099, FR-PO100,
FR-PO101, FR-PO102, FR-PO104,
FR-PO105, FR-PO109, FR-PO140,
FR-PO611, FR-PO945, SA-OR115,
SA-OR117, SA-OR118, SA-PO285,
SA-PO928, SA-PO972, PUB268,
PUB715, PUB717

water transport..... FR-OR004, FR-OR038,
FR-PO095, FR-PO107, FR-PO109,
FR-PO808, SA-OR118, PUB714

water-electrolyte balance..... TH-OR082,
TH-OR084, TH-PO120, TH-PO423,
TH-PO428, TH-PO832, TH-PO1056,
FR-OR004, FR-OR009, FR-PO007,
FR-PO026, FR-PO050, FR-PO097,
FR-PO099, FR-PO100, FR-PO106,
FR-PO118, FR-PO122, FR-PO506,
FR-PO923, SA-OR110, SA-OR111,
SA-OR112, SA-PO257, SA-PO417,
SA-PO657, SA-PO902, SA-PO903,
SA-PO906, SA-PO907, SA-PO909,
SA-PO913, SA-PO916, SA-PO932, PUB362,
PUB431, PUB446, PUB600

HI-OR01

Empagliflozin and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Chronic Kidney Disease Christoph Wanner,¹ John M. Lachin,² David H. Fitchett,³ Silvio E. Inzucchi,⁴ Maximilian von Eynatten,⁵ Michaela Matheus,⁵ Odd Erik Johansen,⁶ Hans-Juergen Woerle,⁵ Uli Christian Broedl,⁵ Bernard Zinman,^{7,8} ¹Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; ²The Biostatistics Center, The George Washington Univ, Rockville, MD; ³St Michael's Hospital, Div of Cardiology, Univ of Toronto, Toronto, Canada; ⁴Section of Endocrinology, Yale Univ School of Medicine, New Haven, CT; ⁵Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; ⁶Boehringer Ingelheim Norway KS, Asker, Norway; ⁷Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, Canada; ⁸Div of Endocrinology, Univ of Toronto, Toronto, Canada.

Background: Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) are at high risk of cardiovascular (CV) events and premature death. Empagliflozin is a sodium glucose co-transporter (SGLT)-2 inhibitor used in the treatment of T2D.

Methods: In EMPA-REG OUTCOME®, we explored long-term CV outcomes with empagliflozin vs placebo when added to standard of care in 7020 T2D patients with established CV disease. Inclusion criteria included eGFR ≥ 30 mL/min/1.73m². Patients (mean age 63 years, male 71%, mean HbA1c 8.1%) were randomized 1:1:1 to empagliflozin 10 mg, 25 mg or placebo.

Results: Most patients had impaired kidney function (52.2% stage 2, 17.8% stage 3a, 7.7% stage 3b CKD) while 28.7% and 11.0%, respectively, had moderately (30-300mg/g) or severely (>300 mg/g) increased urine albumin to creatinine excretion. After a median follow-up of 3.1 years, the primary outcome (first occurrence of non-fatal myocardial infarction, non-fatal stroke, or CV death) occurred in a lower percentage of patients on empagliflozin (10.5%) than placebo (12.1%) (HR 0.86 [0.74-0.99]; p=0.04). This result was driven by a 38% reduction in CV death vs placebo (HR 0.62 [0.49-0.77]; p<0.001), with no difference in the risk of heart attack or stroke. Empagliflozin reduced hospitalization for heart failure by 35% (HR 0.65 [0.50-0.85]; p=0.0017). Pre-defined subgroup analyses on CV outcomes in patients with T2D and CKD will be presented.

Conclusions: Empagliflozin reduces CV morbidity and mortality in patients with T2D and various degrees of CKD.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim and Eli Lilly and Company

HI-OR02

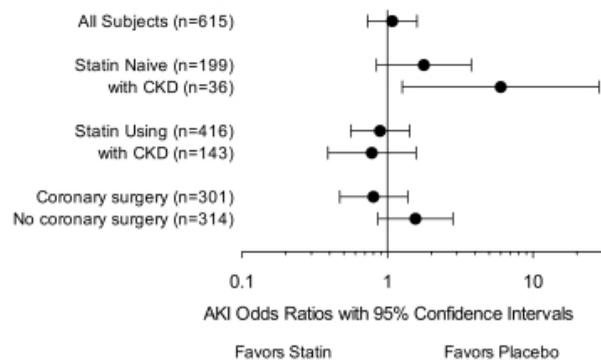
High Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery Frederic Tremaine Billings, Chad E. Wagner, Patty Hendricks, Yaping Shi, Michael R. Petracek, Nancy J. Brown. *Vanderbilt Univ, Nashville, TN.*

Background: Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins) affect several mechanisms underlying acute kidney injury (AKI), a common and dangerous complication after cardiac surgery. We hypothesized that short-term high-dose perioperative atorvastatin would reduce AKI following cardiac surgery.

Methods: We randomized elective cardiac surgery patients, stratified by chronic kidney disease (CKD), to atorvastatin or matching-placebo starting the day prior to surgery until hospital discharge in pre-study statin naïve subjects or until the day after surgery in pre-study statin-using subjects. Our primary endpoint was AKI by AKIN criteria.

Results: The study was stopped on recommendations of the DSMB after 653 of 820 subjects completed the study due to futility and an increased incidence of AKI among statin-naïve subjects with CKD randomized to atorvastatin. AKI occurred in 20.8% of subjects randomized to atorvastatin versus 19.5% randomized to placebo (P=0.75). Among statin-naïve subjects (n=199), however, AKI occurred in 21.6% randomized to atorvastatin versus 13.4% randomized to placebo (p=0.14), and 52.9% vs. 15.8%, P=0.03, in patients with CKD (n=36). Serum creatinine concentrations increased a median of 0.11 (-0.11 – 0.56) versus 0.05 (-0.12 – 0.33) mg/dl in statin-naïve patients randomized to atorvastatin versus placebo (P=0.007), and this effect was magnified among those with CKD, where serum creatinine concentrations increased by 0.26 (-0.22 – 0.94) versus -0.06 mg/dl (-0.16 – 0.41), P=0.04.

Effect of Treatment on AKI



Conclusions: High-dose perioperative atorvastatin treatment does not reduce AKI following cardiac surgery and may increase risk in patients with CKD who are naïve to statin treatment. Perioperative continuation or short-term withdrawal of statin treatment in statin-using patients does not affect AKI.

Funding: Other NIH Support - K23GM102676; K12ES015855; UL1RR024975

HI-OR03

Effect of Methylprednisolone on Acute Kidney Injury in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass Amit X. Garg,¹ Richard P. Whitlock,² ¹Western Univ, London, Canada; ²McMaster Univ, Hamilton, Canada and the Population Health Research Inst; for the SIRS Investigators.

Background: Acute kidney injury is a common complication of the 20 million cardiac surgeries performed worldwide each year. We conducted a substudy of the Steroids In cardiac Surgery (SIRS) trial to determine whether methylprednisolone alters the risk of acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass [substudy protocol BMJ Open 2014 Mar 5;4(3): e004842].

Methods: This was a randomized clinical trial of 7,286 high-risk patients undergoing cardiac surgery with cardiopulmonary bypass from 79 centres in 18 countries between June 2007 and December 2013. Patients were assigned to take intravenous methylprednisolone (250 mg at anesthetic induction and 250 mg at initiation of cardiopulmonary bypass) or placebo. Patients, care givers and outcome-assessors were blinded to allocation. Acute kidney injury was defined as $\geq 50\%$ or ≥ 26.5 mmol/L (≥ 0.3 mg/dL) increase in the postoperative serum creatinine concentration from the preoperative concentration in the 14 days following surgery, or new dialysis in the 30 days following surgery.

Results: Methylprednisolone (n=3,647) versus placebo (n=3,639) did not alter the risk of acute kidney injury (40.9% versus 39.5%, respectively; relative risk 1.03 [95% CI, 0.96 to 1.11]). Results were consistent with multiple alternate continuous and categorical definitions of acute kidney injury, and in the subgroup with baseline chronic kidney disease.

Conclusions: Amongst patients undergoing cardiac surgery with cardiopulmonary bypass, the use of corticosteroids in the perioperative period did not alter the risk of acute kidney injury. Trial Registration: NCT00427388

	Number of Events (%)		Relative Risk (95% CI)
	Methylprednisolone n = 3647	Placebo n = 3639	
AKI	1490 (40.9%)	1439 (39.5%)	1.03 (0.96 to 1.11)
Alternative Definitions			
AKI or death	1513 (41.5%)	1463 (40.2%)	1.03 (0.96 to 1.11)
\geq stage 2 AKI	362 (9.9%)	359 (9.9%)	1.01 (0.87 to 1.16)
\geq stage 3 AKI	145 (4.0%)	162 (4.5%)	0.89 (0.71 to 1.12)
Acute dialysis	95 (2.6%)	88 (2.4%)	1.08 (0.81 to 1.43)

Funding: Government Support - Non-U.S.

HI-OR04

The NEFIGAN Trial: NEFECON, a Novel Targeted Release Formulation of Budesonide, Reduces Proteinuria and Stabilizes eGFR in IgA Nephropathy Patients at Risk of ESRD Bengt C. Fellstrom,¹ Rosanna Coppo,² John Feehally,³ Jürgen Floege,⁴ Johan W. De Fijter,⁵ Alan G. Jardine,⁶ Francesco Locatelli,⁷ Bart D. Maes,⁸ Alex Mercer,⁹ Fernanda Ortiz,¹⁰ Manuel Praga,¹¹ Søren Schwartz Sørensen,¹² Vladimir Tesar,¹³ ¹Uppsala Univ Hospital; ²Univ Turin; ³Univ Leicester; ⁴RWTH Univ Aachen; ⁵Leiden Univ Medical Center; ⁶Univ Glasgow; ⁷Ospedale A Manzoni, Lecco; ⁸AZ Delta Roeselare; ⁹Pharmalink; ¹⁰Helsinki Univ Hospital; ¹¹Hospital 12 de Octubre, Madrid; ¹²Rigshospitalet, Copenhagen; ¹³Charles Univ, Prague.

Background: IgA nephropathy (IgAN) is the most prevalent primary chronic glomerular disease. Despite RAS blockade, >25% of patients progress to ESRD within 20 years. This study evaluated a novel budesonide formulation (NEFECON) targeted for release in the distal ileum, where Peyer's patches reside, in patients at risk of ESRD despite optimized RAS blockade.

Methods: Double-blind, placebo-controlled study in 150 patients (62 sites, 10 EU countries) with primary IgAN, proteinuria (UPCR ≥ 0.5 g/g OR urine protein ≥ 0.75 g/d) and eGFR CKD-EPI ≥ 45 mL/min/1.73m² randomized to 8 or 16 mg/d NEFECON or placebo (1:1:1), after 6 mo run-in phase to optimize RAS blockade. Primary endpoint: reduction in UPCR at 9 mo of treatment; secondary: mean percentage change in eGFR.

Results: Baseline data were similar across groups; BP was 127-128/78-80 mmHg, UPCR 0.76-0.83 g/g, and eGFR 72-85 mL/min/1.73m². Primary endpoint was met at the pre-specified interim analysis. Mean UPCR decreased by 24% (NEFECON 8+16 mg/d) vs 3% increase (placebo) at 9 mo (p=0.007); reduction in the 16 mg/d group was 27% (p=0.009). At final analysis, mean change in eGFR was -4.7 mL/min/1.73m² for placebo compared with 0.32 and 1.95 mL/min/1.73m² for NEFECON 8 and 16 mg/d, respectively; difference in mean percentage change in eGFR achieved statistical significance for 8 mg/d (p=0.006) and 16 mg/d (p=0.003). Adverse event rates were higher in NEFECON groups (88-94%) than placebo (84%). Two serious adverse events were assessed as possibly related to NEFECON; deteriorated renal function (in follow-up) and deep vein thrombosis.

Conclusions: NEFECON reduced UPCR and maintained eGFR in patients with primary IgAN at risk of progression to ESRD despite optimized RAS blockade. Treatment was generally well-tolerated.

Funding: Pharmaceutical Company Support - Pharmalink AB

Underline represents presenting author/disclosure.

HI-OR05

Randomized Trial on Efficacy of Mycophenolate Mofetil versus Tacrolimus in Maintaining Remission in Children with Steroid Resistant Nephrotic Syndrome Aditi Sinha, Arvind Bagga. *All India Inst of Medical Sciences, New Delhi, India.*

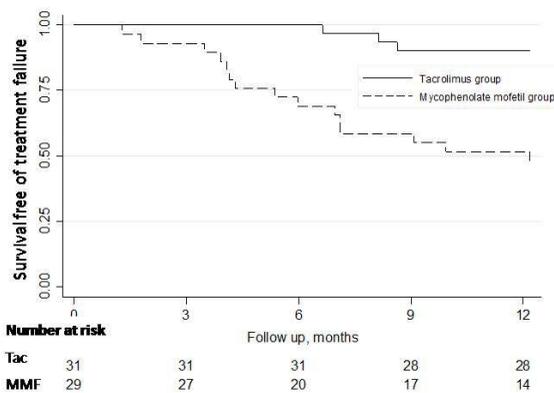
Background: Since prolonged therapy with tacrolimus (Tac) causes nephrotoxicity, this RCT examined non-inferiority of mycophenolate mofetil (MMF) to Tac in maintaining remission in patients with steroid resistant nephrotic syndrome (SRNS). CTRI/2012/03/00247

Methods: Following approvals, 84 patients with SRNS (1-18 yr; minimal change 48, FSGS 36) & eGFR >60 ml/min/1.73m² received Tac (0.15 mg/kg/d; trough 4-8 ng/ml) for 6-months. Stratifying for histology & type of response, patients with complete (Up/Uc <0.2 mg/mg) or partial remission (Up/Uc 0.2-2, albumin >2.5 g/dl) were randomized to continue Tac or receive MMF (0.75-1 g/m²/d), prednisone & enalapril. Primary outcome, at 12-mo, was proportion with remission or infrequent relapses. Therapy failure was recurrent SRNS, frequent relapses or >1 SAE. Enrolment was closed after interim intention-to-treat analysis of outcome in 1/3 sample.

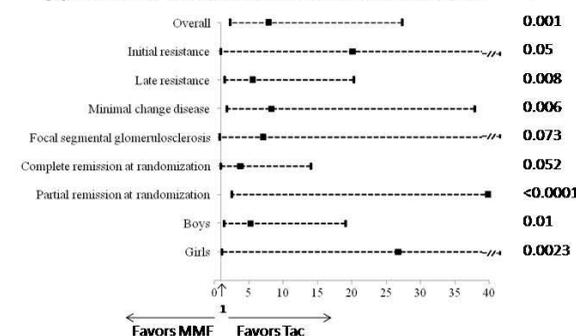
Results: Baseline features were similar. Therapy with MMF led to significantly higher treatment failure, prednisone dose & SAE; eGFR change was similar. On multivariate regression, hazards of treatment failure were high with MMF (HR 9.7, adjusted for histology, type of resistance & remission; P<0.0001).

Baseline	Tac, N=31	MMF, N=29
Minimal change/FSGS	17/16	17/12
Initial resistance	15	13
Age months	76±46	77±46
Complete/partial remission	19/12	18/11
Albumin g/dl	4.2±0.5	4.3±0.5
OUTCOMES		
Satisfactory remission [^]	28, 90%	13, 48%
Complete/partial remission	17	12
Infrequent relapses	11	1
Treatment failure [^]	3	16
Frequent relapses	3	8
Steroid resistance	0	8
Relapse/yr	0.8±1.0	1.3±1.3
Prednisone mg/kg/d [^]	0.3±0.2	0.5±0.4
Change eGFR ml/min/1.73m ²	-6±35	-19±31
P<0.0005; [^] 0.028		

(a) Survival free of treatment failure (Log rank P=0.0002)



(b) Hazards of treatment failure with MMF versus Tac



Conclusions: Therapy with MMF is inferior to Tac in maintaining Tac induced remission in patients with SRNS

HI-OR06

Prevention of Bone Mineral Density Loss in De Novo Kidney Transplant Recipients with Twice-Yearly Denosumab: A Randomized Controlled Trial (ClinicalTrials.gov number NCT01377467) Rudolf P. Wuthrich,¹ Diana P. Frey,² Jens Gunther Brockmann,³ Thomas Fehr,¹ Thomas F. Mueller,¹ Lanja Saleh,⁴ Arnold Von Eckardstein,⁴ Nicole Graf,⁵ Marco Bonani.¹ ¹Div of Nephrology; ²Div of Rheumatology; ³Div of Visceral and Transplantation Surgery; ⁴Inst of Clinical Chemistry, Univ Hospital, Zurich, Switzerland; ⁵Graf Biostatistics, Winterthur, Switzerland.

Background: Kidney transplantation is associated with bone loss and an increased risk of fracture. Since current therapeutic options to prevent bone loss are limited we assessed the efficacy and safety of Receptor Activator of Nuclear Factor κB Ligand (RANKL) inhibition with denosumab to improve bone mineralization in the first year after kidney transplantation.

Methods: We enrolled 108 kidney transplant recipients and randomized 90 patients two weeks after surgery in a 1:1 ratio to receive denosumab (subcutaneous injections of 60 mg denosumab at baseline and after 6 months) or no treatment. The primary endpoint was the percentage change in bone mineral density (BMD) measured by DXA at the lumbar spine at 12 months.

Results: After 12 months, the primary outcome of total lumbar spine BMD increased by 4.6% (95% CI 3.3-5.9%) in 46 patients in the denosumab group and decreased by -0.5% (95% CI -1.8-0.9%) in 44 patients in the control group (between-group difference 5.1%, 95% CI 3.1-7.0%, p<0.0001). Denosumab also significantly increased BMD at the total hip by 1.9% (95% CI, 0.1 to 3.7%; p=0.035) over that in the control group at 12 months. HR-pQCT in a subgroup of 24 patients showed that denosumab also significantly increased BMD and cortical thickness at the distal tibia and radius (p<0.05). Biomarkers of bone resorption (β-CTX, urine deoxypyridinoline) and bone formation (P1NP, BSAP) markedly decreased with denosumab (p<0.0001). Episodes of cystitis and asymptomatic hypocalcemia occurred more often with denosumab, whereas graft function, rate of rejections and incidence of opportunistic infections were similar.

Conclusions: Antagonizing RANKL with denosumab effectively increased BMD in de novo kidney transplant recipients, but was associated with more frequent episodes of urinary tract infection and decreased calcemia.

Funding: Government Support - Non-U.S.

HI-OR07

Randomized, Double-Blind, Placebo-Controlled, Parallel, 3-Arm Study of Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Hemodialysis Patients with Uremic Pruritus Vandana S. Mathur,¹ Jayant Kumar,³ Paul W. Crawford,³ Howard Hait,⁴ Thomas Sciascia.² ¹MathurConsulting; ²Trevi Therapeutics; ³Research by Design; ⁴Edenridge Consulting; ³Renal Medical Associates.

Background: Uremic pruritus (UP) is associated with decrements in quality of life and sleep and higher mortality. UP pathogenesis may involve endogenous κ/μ opioid ligand ratio imbalance. Nalbuphine ER tablets (NAL) are a κ-opioid agonist/μ-opioid antagonist being developed for chronic pruritic conditions.

Methods: 373 hemodialysis patients (HDP) with mean baseline numerical rating scale score (NRS) ≥ 4.5 for worst itching (0 [no itch] -10 [worst possible itching]) were randomized 1:1:1 to NAL 60 mg (n = 128), NAL 120 mg (n=120), or placebo (n = 125) and treated for 8 weeks.

Results: Demographics, dialysis adequacy and vintage, phosphorus, parathyroid hormone, pruritus duration, and antihistamine use were similar in the 3 arms at baseline. The primary efficacy endpoint was the change from Baseline to the Evaluation Period (Weeks 7 and 8) in the NRS for each dose of NAL, with pre-specified hierarchical ordering – the 120 mg vs. placebo comparison was performed first. The mean (SD) NRS in the NAL 120 mg group declined from 6.94 (1.46) to 3.51 (2.11), with an LS mean decline vs. placebo = -0.73 (0.31), p = 0.017. The mean NRS in the NAL 60 mg group declined from 6.87 (1.40) to 4.95 (2.10), with an LS mean decline vs. placebo = -0.24 (0.31), p = 0.432. A statistically significant mean reduction for NAL 120 compared to placebo was observed as early as one week following titration. The most common adverse events were nausea, vomiting, dizziness and somnolence with incidence rates of these events quickly approaching that of placebo after the first week of titration. Among subjects with NRS ≥7 (post-hoc analysis), NAL 120 reduced NRS by 4.48 (SD) vs. 3.16 (SD) vs. placebo (p=0.007) with sleep quality (Itch MOS sleep scale) improved significantly (p=0.006).

Conclusions: Nalbuphine ER tablets at a dose of 120 mg BID were safe and significantly reduced itching intensity.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

HI-OR08

The Omega-3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease (FAVOURED) Study: A Randomised Placebo-Controlled Trial Ashley B. Irish.^{1,2} ¹Nephrology, Fiona Stanley Hospital, Perth, Western Australia, Australia; ²Australasian Kidney Trials Network, Univ of Queensland, Brisbane, Queensland, Australia.

Background: Increasing the use of arteriovenous fistulae (AVF) to improve haemodialysis access is limited by early thrombosis and maturation failure. Omega-3 polyunsaturated fatty acids (w3FA) may prevent these complications by inhibition of platelet aggregation, vasoconstriction, intimal hyperplasia and inflammation.

Underline represents presenting author/disclosure.

Methods: This international, randomised, double-blind, placebo-controlled trial examined whether 3 months therapy with w3FA (4g/day) reduced primary AVF failure at 12 months after AVF creation. AVF failure was defined as AVF thrombosis and/or abandonment and/or cannulation failure. A subset of patients received aspirin (100mg/day) or matching placebo in addition to w3FA or placebo in a factorial design (n=388).

Results: The 567 randomised participants had a mean age of 55 years, 63% were male and 46% diabetic. AVF failure occurred in 128/270 (47%) participants assigned to w3FA compared with 125/266 (47%) assigned to placebo (relative risk adjusted for aspirin use [RR] 1.03, 95% confidence interval [CI] 0.86-1.23, p=0.78). Regarding each component of AVF failure, w3FA did not reduce the risk of thrombosis (22% vs 23%, RR 0.98, 95% CI 0.72-1.34, p=0.90), AVF abandonment (19% vs 22%, RR 0.87, CI 0.62-1.22, p=0.43) or cannulation failure (40% vs 39%, RR 1.03, 0.83-1.26, p=0.81). A subgroup difference was observed for diabetes mellitus (interaction p=0.038; RR 1.30 vs 0.78; diabetics vs non-diabetics) but not for age, gender, AVF site, dialysis modality and cardiovascular disease. There was no difference in any serious adverse event (AE), 9.2% vs 13.0%, p=0.14; bleeding, 8.1% vs 10.9% p=0.26, or gastrointestinal AE, 4.9% vs 5.4%, p=0.86. The risk of AVF failure was similar (45% vs 43%, RR 1.05, 95% CI 0.84-1.31) in the subset of participants randomised to aspirin or placebo-aspirin as part of the factorial design.

Conclusions: Three months of w3FA intake was ineffective in reducing primary AVF failure at 12 months. Aspirin may be similarly ineffective. There was no increased risk of bleeding. Neither w3FA nor aspirin increased the proportion of useable de novo AVF.

Funding: Other NIH Support - NHMRC Project Grant, Pharmaceutical Company Support - AMGEN Australia

SA-PO1091

The Remote Ischemic Preconditioning in Cardiac Surgery Trial (Remote IMPACT) Michael Walsh.^{1,2} ¹McMaster Univ; ²Population Health Research Inst.

Background: Cardiac surgery is frequently complicated by ischemia-reperfusion injury which can lead to kidney and myocardial injury. Preoperative Remote Ischemic Preconditioning (RIPC), cycles of brief ischemia to a limb alternating with reperfusion, may reduce the frequency or severity of organ injury after cardiac surgery.

Methods: We randomly allocated 258 patients at high risk for death after cardiac surgery to receive either RIPC or a sham procedure immediately after induction of anesthesia. RIPC consisted of 3 cycles of thigh tourniquet inflation to 300 mmHg for 5 minutes followed by 5 minutes reperfusion. The sham group tourniquets were inflated to 15 mmHg. Patients and care providers were blinded. The main clinical outcomes were change in creatinine over the first 4 postoperative days and the peak CK-MB within 24 hours of surgery. Other outcomes were assessed to 30 days after randomization. Analyses were performed according to the intention-to-treat principle.

Results: We randomized 128 patients to RIPC and 130 to sham. No patients were lost to follow-up. There was no significant between group differences in postoperative change in creatinine (p=0.79) or peak CK-MB (p=0.18) (Figure 1). We found no significant differences in the frequency of acute kidney injury (34% vs 31%), myocardial injury (24% vs 19%), stroke (4% vs 3%) or mortality (6% vs 5%) at 30 days.

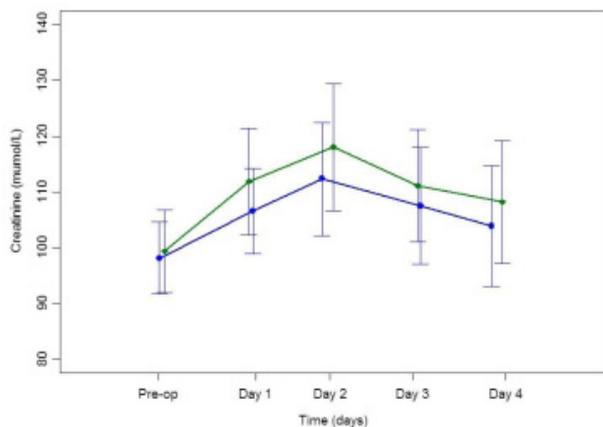


Figure 1. Mean and 95% confidence intervals of creatinine over time for the RIPC (green diamonds) and sham (blue circles) groups.

Conclusions: In this trial RIPC did not affect markers of kidney and myocardial injury. These results fail to provide proof-of-concept that RIPC may impact clinically important outcomes in the cardiac surgery setting.

SA-PO1092

Nephrotoxicity of Invasive and Noninvasive Coronary Angiography: Randomized Controlled Study of Intracoronary and Intravenous Contrast Agent Administration Eva Schöninger,¹ Patricia D. Bady,² Peter Martus,³ Elke Zimmermann,² Michael Laule,⁴ Marc Dewey.² ¹Anesthesiology, Charité, Berlin, Germany; ²Radiology, Charité, Berlin, Germany; ³Inst für Clinical Epidemiology and Applied Biostatistics, Eberhard Karls Univ, Tübingen, Germany; ⁴Cardiology, Charité, Berlin, Germany.

Background: Iodinated contrast agents can have nephrotoxic effects. It is unknown whether nephrotoxicity is more likely following intracoronary or intravenous contrast agent administration.

Methods: We randomly assigned patients with suspected coronary disease to either intracoronary contrast agent for invasive coronary angiography (ICA) or intravenous administration for coronary computed tomography angiography (CTA). The same low-osmolar nonionic contrast agent with a concentration of 350 mg iodine per milliliter was used for ICA and CTA. Blood samples were taken before and at two time points after ICA and CTA (18 to 24 hours and 46 to 50 hours) to identify contrast-induced acute kidney injury defined according to the most commonly used definition as an increase in creatinine of at least 0.5 mg per deciliter or 25%.

Results: We enrolled 340 patients of whom 10 and 4 dropped out from the ICA and CTA group, respectively, leaving 161 and 165 patients who underwent ICA and CTA until September 8, 2015. Baseline creatinine levels in the ICA (0.85±0.19) and the CTA group (0.87±0.21 mg per deciliter) were similar (P=0.34). Follow-up creatinine was not available in 3 and 5 patients in the ICA and CTA group, respectively. Twenty-one of the 158 patients in the ICA group (13%) had an increase in creatinine of at least 0.5 mg per deciliter or 25%, as compared with 9 of the 160 patients in the CTA group (6%; P<0.05). In patients without coronary disease on ICA or CTA, such a creatinine increase was found in 17 of the 134 patients in the ICA group (13%) and 6 of the 139 patients in the CTA group (4%; P<0.05). No patient without coronary disease in the CTA group had an increase in creatinine according to the KDIGO definition of at least 0.3 mg per deciliter or 50%, but 6 of the 134 patients in the ICA group (4%; P<0.05).

Conclusions: Nephrotoxicity may be more likely after intracoronary than after intravenous contrast agent administration.

Funding: Government Support - Non-U.S.

SA-PO1093

Efficacy and Safety of Bosutinib in Autosomal Dominant Polycystic Kidney Disease: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Kazimierz Ciechanowski,¹ Vladimir Tesar,² York P. Pei,³ Irina Barash,⁴ Megan Shannon,⁵ Ruifeng Li,⁶ Jason Williams,⁷ Matteo Levisetti,⁸ Steven Arkin,⁶ Andreas L. Serra,⁹ ¹Pomeranian Medical Univ, Szczecin, Poland; ²Charles Univ, Prague, Czech Republic; ³Univ Health Network, Toronto, Ontario, Canada; ⁴Icahn School of Medicine at Mount Sinai, New York, NY; ⁵Pfizer Inc, San Diego, CA; ⁶Pfizer Inc, Cambridge, MA; ⁷Sanofi US, Bridgewater, NJ; ⁸Roche Pharma Research and Development, Basel, Switzerland; ⁹Inst für Allgemeine Innere Medizin und Nephrologie, Suisse ADPKD Hirslanden, Zurich, Switzerland.

Background: Src overactivation has been linked to the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). We assessed efficacy and safety of bosutinib (BOS), an oral dual Src/Abl tyrosine kinase inhibitor, in ADPKD patients (pts).

Methods: In this phase 2, multicenter study (NCT01233869), ADPKD pts with estimated glomerular filtration rate ≥ 60 mL/min/1.73 m² and magnetic resonance image (MRI)-confirmed total kidney volume (TKV) ≥ 750 cc were randomized 1:1:1 to placebo (PBO), 200 mg/d, or 400 mg/d of oral BOS for £24 mo. The primary endpoint was annualized TKV % change. Pts treated for ≥ 2 wk who had an MRI after a 30-d washout period were in the modified intent-to-treat (mITT) analysis.

Results: 169 of 172 enrolled pts received ≥ 1 dose of treatment. 24 pts who initially received 400 mg/d BOS were later reduced to 200 mg/d BOS per protocol. 88 pts (52%) were in the mITT population (200 mg/d, n=27; 400 mg/d, n=7; 400 to 200 mg/d, n=21; PBO, n=33) after discontinuations (unrelated to study drug, 27%; study drug-related adverse events, 17%; consent withdrawal, 14%). Annual rate of kidney enlargement was significantly reduced for pooled BOS vs PBO (0.84% vs 4.74%, respectively, 95% CI for difference in annualized rates [2.02-5.74]; p<.0001) and was 65.2% lower for BOS 200 mg/d vs PBO (1.63% vs 4.74%, respectively, 95% CI [0.93 to 5.23]; p=.005). Gastrointestinal (GI) effects were dose-dependent for BOS; the overall safety profile, including GI toxicities, was consistent with the known profile of BOS.

Conclusions: BOS reduced the annual rate of kidney enlargement vs PBO in ADPKD pts, and the safety profile was consistent with the BOS label.

Funding: Pharmaceutical Company Support - Pfizer Inc

SA-PO1094

Low Osmolar Diet and Adjusted Water Intake for Vasopressin Suppression in ADPKD: A Randomized Controlled Trial Osama W. Amro,^{1,2} Jessica K. Paulus,^{1,2} Farzad Noubary,^{1,2} Ronald D. Perrone.^{1,2} ¹Nephrology, Tufts Medical Center, Boston, MA; ²Tufts Univ School of Medicine.

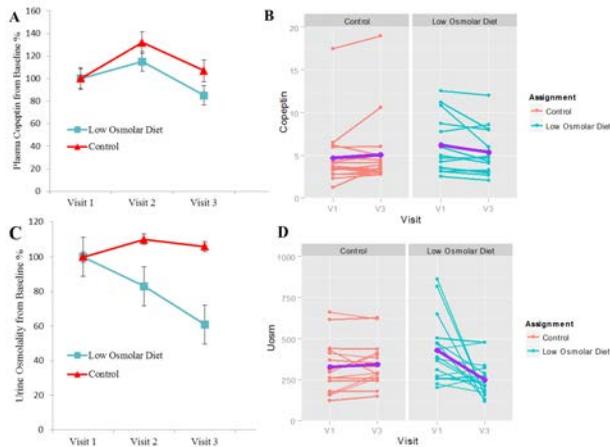
Background: Autosomal dominant polycystic kidney disease (ADPKD) affects 12.5 million persons worldwide. Vasopressin promotes disease progression.

Methods: This randomized trial examined the effect of combining a low osmolar diet and adjusted water intake on vasopressin as measured by change in plasma copeptin, and

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urinary osmolality in 34 ADPKD patients. Participants were randomized to receive a low osmolar diet (low sodium (1500 mg/day), low protein (0.8 gram/kg body weight) diet) followed by adjusted water intake to achieve a urine osmolality of ≤ 280 mOsm/L versus no intervention for two weeks.

Results: Change from baseline to two weeks between intervention and control groups was statistically significant for the primary outcome of copeptin and urine osmolality (-0.86 ± 1.3 pmole/L versus $+0.39 \pm 1.2$ pmole/L ($p=0.009$) and -167 ± 264 mOsm/L versus $+20 \pm 80$ mOsm/L (0.007) respectively). Mean plasma copeptin and urine osmolality declined from 6.2 ± 3.05 to 5.3 ± 2.5 pmole/L ($p=0.3$) and from 426 ± 193 to 258 ± 117 mOsm/L ($p=0.003$) respectively in the intervention group compared to a non-significant increase from 4.7 ± 3.6 to 5.07 ± 4 pmole/L ($p=0.7$) and from 329 ± 159 to 349 ± 139 mOsm/L ($p=0.6$) in the control group.



Total urinary solute decreased only in the intervention group and significantly differed between groups at week one ($p=0.03$) reducing mean water prescription from 3.2 to 2.6 liter/day.

Conclusions: we developed a step wise dietary intervention that led to significant reduction in vasopressin in ADPKD patients. Furthermore, this intervention led to reduction in water required for vasopressin suppression. Long-term studies are needed to determine if vasopressin suppression slows ADPKD progression.

Funding: Other NIH Support - Dr. Amro is supported by NIH 5T32DK007777 institutional training grant. This project was performed and Dr. Perrone were supported in part by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), Grant Number UL1 TR001064.

SA-PO1095

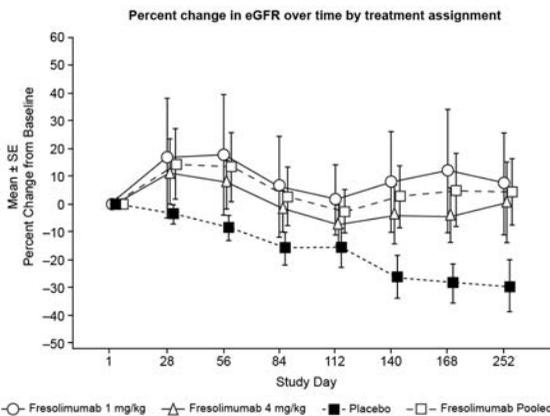
A Phase 2, Double-Blind, Randomized Study of Fresolimumab or Placebo in Patients with Steroid-Resistant Primary Focal Segmental Glomerulosclerosis

James A. Tumlin,¹ Flavio Vincenti,² Fernando C. Fervenza,³ Kirk N. Campbell,⁴ Montserrat M. Diaz Encarnacion,⁵ Manuel Praga,⁶ Denyse Thornley-Brown,⁷ Francisco Verissimo Veronese,⁸ Beverly Accomando,⁹ Sara Engstrand,¹⁰ Steven R. Ledbetter,¹⁰ Julie Lin,¹⁰ John F. Neylan.¹⁰ ¹UT Coll. of Med., Chattanooga, TN; ²UCSF, San Francisco, CA; ³Mayo Clinic, Rochester, MN; ⁴Icahn Sch. of Med. at Mt. Sinai, New York, NY; ⁵Fundacion Puigvert, Barcelona, Spain; ⁶Hosp. Univ 12 de Oct., Madrid, Spain; ⁷Univ of Alabama at Birmingham, AL; ⁸Hosp. de Clinicas de Porto Alegre, Brazil; ⁹Sanofi, Cambridge, MA; ¹⁰Formerly Genzyme, Sanofi.

Background: Steroid-resistant primary FSGS confers substantial risk of morbidity & progressive kidney failure. Fresolimumab (freso), a neutralizing mAb to all 3 isoforms of TGF- β , is a potential new treatment.

Methods: 36 pts with biopsy-proven nephrotic-range FSGS randomized to freso 1mg/kg ($n=14$) v 4mg/kg ($n=12$) v placebo (PL) ($n=10$) for D112, allowed immunosuppressives after D112 & followed up double-blind for D252. 1^o outcome: proteinuria remission; 2^o outcomes included changes in Up/c & eGFR.

Results: Pts: 53% male; median 41 y; 17% Black, 31% Hisp. Baseline (BL) median Up/c: 6.19mg/mg; eGFR, 63 ml/min/1.73 m². 72% pts received prior CNI. Durable partial remission ($>50\%$ Up/c decrease from BL to <3 mg/mg): 3 pts, 1mg/kg; 2 pts, 4mg/kg; 1 pt, PL; 1 additional pt on 1mg/kg had steep & consistent Up/c decline from 17-4mg/mg. All 7 freso responders were Black/Hispanic. Mean Up/c changes at D112: -18.5% (1mg/kg, $P=0.008$), +10.5% (4mg/kg, $P=0.52$), +9.0% (PL, $P=0.91$). eGFR showed nonsignificant trend for stability in freso v decline in PL. Freso was generally well tolerated with no significant difference in AEs in low v high doses.



Number of Patients							
Fresolimumab 1 mg/kg	14	14	14	14	14	14	14
Fresolimumab 4 mg/kg	12	12	12	12	12	11	11
Placebo	10	10	10	10	10	10	9
Fresolimumab Pooled	26	26	26	26	26	25	25

Conclusions: In steroid-resistant FSGS, freso may be associated with proteinuria remission. Black & Hisp pts may have higher response rates. Freso merits continued evaluation in FSGS.

Funding: Pharmaceutical Company Support - Genzyme-Sanofi

SA-PO1096

Effects of Sustained-Release Beraprost Sodium in Patients with Primary Glomerular Disease or Nephrosclerosis: The CASSIOPEIR Study

Toshiro Fujita,¹ Xueqing Yu,² Suhnggwon Kim,³ Hidetomo Nakamoto,⁴ Hideki Origasa,⁵ Hajimu Kurumatani,⁶ Takashi Kiriya.⁷ ¹The Univ of Tokyo, Tokyo, Japan; ²The First Affiliated Hospital, Sun Yat-sen Univ, Guangzhou, Guangdong, China; ³Seoul National Univ Hospital, Seoul, Korea; ⁴Saitama Medical Univ, Saitama, Japan; ⁵The Univ of Toyama, Toyama, Japan; ⁶Toray Industries, Inc, Tokyo, Japan; ⁷Astellas Pharma Inc., Tokyo, Japan.

Background: No single treatment, except RAS inhibitors, can delay progression of CKD. TRK-100STP, a sustained-release tablet of an orally-active prostacyclin analogue, beraprost sodium, is suggested to suppress worsening of renal filtration function. We aimed to demonstrate superiority of TRK-100STP over placebo in patients with CKD, either as primary glomerular disease or nephrosclerosis; determine the recommended dose of TRK-100STP; and evaluate its safety profile.

Methods: We performed a randomized, double-blind, placebo-controlled, parallel-group comparative study at 160 sites in seven Asian-Pacific countries and regions (CASSIOPEIR: CRF Asian Study with Oral PGI₂ Derivative for Evaluating Improvement of Renal Function). Patients entered a run-in period with oral administration of placebo twice daily for two to eight weeks. Patients meeting the inclusion/exclusion criteria at the end of the run-in period ($n=892$) were randomized to TRK-100STP 120 mg, TRK-100STP 240 mg, or placebo for a treatment period of two to four years. The primary efficacy endpoint was the time to first occurrence of a renal composite endpoint: doubling of Scr or occurrence of end-stage renal disease. ClinicalTrials.gov identifier : NCT01090037.

Results: No significant differences were evident observed in renal composite endpoints between TRK-100STP and placebo (2-sided 5% significance level, $P=0.5674$). The overall incidence of adverse events and adverse drug reactions was comparable between the treatment arms.

Conclusions: TRK-100STP did not demonstrate superiority over placebo, and the recommended therapeutic dose for patients with CKD either primary glomerular disease or nephrosclerosis was not determined. However, no findings raised safety concerns in the comparison between TRK-100STP and placebo.

Funding: Pharmaceutical Company Support - Toray Industries, Inc., Astellas Pharma Inc.

SA-PO1097

Corticosteroid Monotherapy versus Combined Immunosuppression in IgA Nephropathy: Insights from the STOP-IgA Trial

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Background: In high-risk IgA nephropathy (IgAN) the value of immunosuppression is controversial.

Methods: We recently reported a randomized, controlled trial in IgAN patients (STOP-IgA trial). Following 6 months of optimized supportive treatment 162 trial participants, who still displayed a proteinuria >0.75 g/d, entered a 3 year study phase and were randomized to continue on supportive therapy (SUP) or to receive additional immunosuppression (IMM). IMM-patients with an eGFR >60 ml/min/1.73m² received a 6-month corticosteroid monotherapy ("Poizzi-protocol"). Patients with an eGFR of 30 to

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59 ml/min/1.73m² received cyclophosphamide for 3 months, followed by azathioprine, plus oral prednisolone ("Ballardie protocol"). Primary endpoints were (i) full clinical remission (proteinuria < 0.2 g/g and eGFR loss of < 5 ml/min) and (ii) eGFR loss >15 ml/min from baseline to trial end.

Results: Here we report a secondary analysis of the two IMM subgroups versus corresponding SUP patients matched for eGFR. The intention-to-treat (ITT) analysis assuming a worst-case scenario at 3 years is shown in the table.

Endpoint	GFR >60 ml/min/1.73m ² IMM vs. SUP (n = 55 vs. 54)	GFR 30-59 ml/min/1.73m ² IMM vs. SUP (n = 27 vs. 26)
Full clinical remission	OR 5.23 (95%-CI 1.29-21.15), p=0.020	OR 2.77 (95%-CI 0.38-32.29), p=0.319
eGFR loss >15 ml/min	OR 0.65 (95%-CI 0.27-1.56), p=0.333	OR 1.62 (95%-CI 0.49-5.61), p=0.428

Patients treated with the Pozzi protocol had a transient decrease in proteinuria after 12 months and significantly less microhematuria at trial end compared to matched SUP patients. In the group with the low eGFR range, there were no significant differences between both arms. Compared to supportive care, more patients receiving immunosuppression developed severe infections, impaired glucose tolerance and weight gain in year one.

Conclusions: Our secondary analyses provide little evidence for a stabilization of renal function with immunosuppression in the group with an eGFR >60 ml/min and no evidence for a benefit in patients with a lower eGFR.

Funding: Government Support - Non-U.S.

SA-PO1098

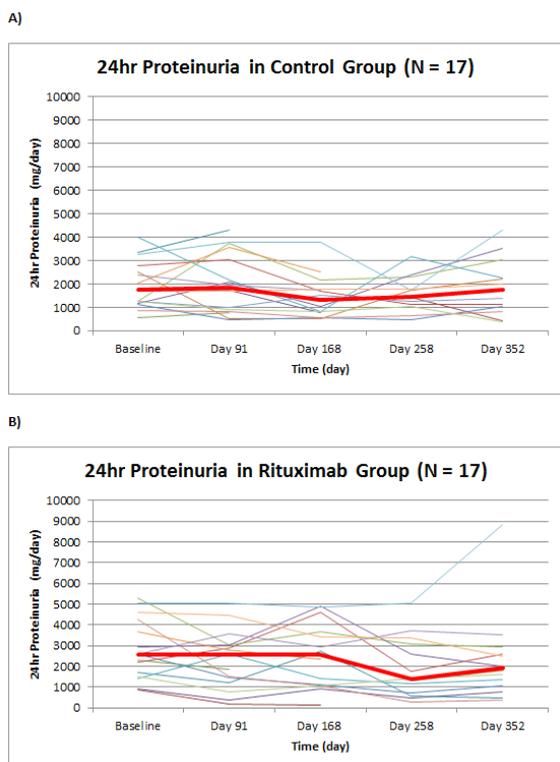
A Randomized Trial of Rituximab in Advanced IgA Nephropathy
Richard A. Lafayette,¹ Pietro A. Canetta,² Brad H. Rovin,³ Gerald B. Appel,² Marie C. Hogan,⁴ Stephen B. Erickson,⁴ Fernando C. Fervenza.⁴ ¹Stanford Univ, Stanford, CA; ²Columbia Univ, New York, NY; ³Ohio State Univ, Columbus, OH; ⁴Mayo Clinic, Rochester, NY.

Background: IgA nephropathy (IgAN) frequently leads to progressive renal dysfunction. Present immunosuppressive treatment remains uncertain in terms of benefit and risks side effects. B cells are an attractive target in IgAN so we performed a pilot trial of rituximab in subjects at high risk of progression.

Methods: Patients with biopsy proven IgAN, more than 1 g/d of proteinuria despite RAASI (or ³0.5 g/d if on dual RAASI), well controlled blood pressure (BP) and eGFR <90ml/min were randomized to 1 year of rituximab therapy (4g total) vs ongoing BP control, fish oil and use of RAASI. They were followed for B cell depletion, effects on proteinuria and changes in eGFR. Safety signals were also followed.

Results: 34 patients were randomized. Baseline serum creatinine was 1.5±0.5 mg/dl and proteinuria was 2.1, 0.6-5.5 g/d. There was no change in BP during the study. Treatment with rituximab resulted in significant B cell depletion and was generally well tolerated. There was no change in renal function during the study in either group. Rituximab treatment had no significant effect on proteinuria compared to baseline or control patients, and 3/17 patients in each group experienced a ≥ 50% reduction in proteinuria during the study.

Figure 1: Proteinuria in (A) Control vs. (B) Rituximab Groups. The heavy weight red line represents median data.



Underline represents presenting author/disclosure.

Conclusions: In this small study, rituximab therapy had no influence on renal function or proteinuria in subjects with advanced disease due to IgA nephropathy. There were numerically greater reductions in proteinuria, but this did not reach significance. Few patients had substantial responses in either group. These results do not support the use of rituximab as treatment for patients with IgA nephropathy.

Funding: Pharmaceutical Company Support - Roche, Inc.

SA-PO1099

Establishing Endpoints for Lupus Nephritis Clinical Trials: Progress by the Kidney Health Initiative/Lupus Nephritis Trials Network Collaboration
Brad H. Rovin,¹ Meggan Mackay,² Joanna Stein,² Maria Dall'Era,⁴ Kenneth Kalunian,³ Martin L. Lesser,² Melissa West.⁵ ¹Ohio State Univ; ²Feinstein Inst; ³Univ Calif San Diego; ⁴Univ Calif San Francisco; ⁵American Society of Nephrology.

Background: There are no universally accepted endpoints for lupus nephritis (LN) clinical drug trials. To obtain approval of new therapies a uniform endpoint that can be applied to future LN trials is needed. The optimal endpoint is a short-term measurement that accurately reflects long-term kidney survival. The present work was undertaken to define LN trial endpoints.

Methods: Clinical data at LN flare (baseline) and during serial follow-up (minimum 22 months) from 751 patients were analyzed. Clinical variables at baseline and after 6 and 12 months were tested as predictors of adverse long-term renal outcomes, in this case time to new chronic kidney disease (CKD), defined as a sustained increase in serum creatinine (SCr) ³30%. Multivariable Cox regression analysis was used to model time to CKD.

Results: After accounting for missing data 507 patients were included in the final analysis. This cohort was 89% female, 56% White, 20% Asian and 14% Black. The average baseline SCr was 1.2±0.7 mg/dl, proteinuria was 4.1±3.4 g/d, and eGFR by CKD^{EP} was 81±35 ml/min. Median follow-up was 42 months (range: 22-147 months). By univariate analysis urine RBCs, race, complement C3, SCr, eGFR and proteinuria were potential significant predictors of time to CKD. By multivariate modeling the significant predictors of future CKD were: SCr at 12 months (p=0.0005, Hazard Ratio (HR) 1.8 (95%CI: 1.3-2.5)); proteinuria at 12 months (p<0.0001; HR 1.6 (1.3-1.8)); and an increase in eGFR>10% from baseline to 12 months compared to no change in eGFR (p<0.0001; HR 0.4 (0.3-0.6)).

Conclusions: We have identified 3 highly significant predictors of time to CKD in LN patients that can be measured during the first 12 months of treatment for flare. These can be developed into a composite endpoint for future LN therapeutic trials. Unexpectedly, small improvements in eGFR appear to predict renal survival. Also, because urine RBCs do not appear to predict time to CKD, it may be possible to exclude urinalysis as an endpoint component in future clinical trials.

Funding: Private Foundation Support

SA-PO1100

Grazoprevir (GZR)/Elbasvir (EBR) Treatment of Hepatitis C Virus (HCV) Infection in Patients with Chronic Kidney Disease Stage 4/5: Final Results of the C-SURFER Phase 3 Study
David Roth,¹ Annette Bruchfeld,² Paul Martin,¹ David R. Nelson,³ Marcelo Silva,⁴ Howard Mounour,⁵ Laurent Alric,⁶ Shuyan Wan,⁷ Beth Jackson,⁷ Bach-Yen Nguyen,⁷ Janice Wahl,⁷ Eliav Barr,⁷ Wayne L. Greaves.⁷ ¹Univ of Miami, Miami, FL; ²Karolinska Inst, Stockholm, Sweden; ³Univ of Florida, Gainesville, FL; ⁴Hospital Univ Austral, Pilar, Buenos Aires, Argentina; ⁵Houston Methodist Hospital, Houston, TX; ⁶Hôpital de Purpan, Toulouse, France; ⁷Merck & Co., Inc., Kenilworth, NJ.

Background: Limited options are available for treating HCV infection in patients with advanced kidney disease. C-SURFER is the first randomized, placebo-controlled phase 3 study to evaluate an all-oral, ribavirin-free regimen in CKD 4/5 patients.

Methods: 224 patients with HCV genotype (G)1 and CKD 4/5 ± hemodialysis (HD) were randomized to GZR/EBR 100/50mg (Immediate Treatment Group, ITG; n=111) or placebo for 12 weeks. Placebo subjects (deferred treatment group, DTG; n=113) received GZR/EBR after placebo therapy. 11 additional subjects received GZR/EBR with intensive pharmacokinetic (PK) sampling. The primary safety comparison was GZR/EBR vs. placebo. The primary efficacy endpoint, sustained virologic response (SVR) 12 weeks post-therapy in the ITG+PK group, was reported previously. Here we report the final results, including data from subjects who received GZR/EBR after placebo.

Results: In the placebo-controlled phase, serious adverse events (AEs) occurred in 16 (14%) GZR/EBR and 17 (15%) placebo subjects; discontinuation due to an AE in GZR/EBR and placebo subjects was 0% and 4%. SVR12 in all subjects who received GZR/EBR was 94.6% (ITG+PK, 94.3% [115/122]; DTG after placebo, 95.0% [96/101]). 12 subjects failed to attain SVR12: virologic relapse, n=3; discontinuation for AE, n=1; admin reason, n=8. Excluding subjects who discontinued for reasons unrelated to study drug, overall SVR12 was 98.6% (211/214). PK data indicate no need for dose adjustment in HD patients (geometric mean ratio [HD/non-HD] ranged from 0.67-0.85 for GZR and 1.43-1.67 for EBR).

Conclusions: Once-daily GZR/EBR for 12 weeks was highly effective with a low rate of adverse events in patients with advanced kidney disease and HCV G1 infection.

Funding: Pharmaceutical Company Support - Merck Sharp & Dohme Corp.

SA-PO1101

Long-Term (52-Week) Efficacy and Safety of ZS-9 in the Treatment of Hyperkalemia: Interim Results From a Phase 3 Open-Label, Multi-Center, Multi-Dose Maintenance Study James A. Tumlin,¹ Mikhail Kosiborod,² Pablo E. Pergola,³ Wajeh Y. Qunibi,⁴ David K. Packham,⁵ Simon D. Roger,⁶ Edgar V. Lerma,⁷ Steven Fishbane,⁸ Henrik S. Rasmussen,⁹ Bruce S. Spinowitz.¹⁰ ¹U of Tennessee College of Medicine, TN; ²Saint Luke's Mid America Heart Inst., MO; ³Renal Associates PA, TX; ⁴U of Texas Health Science Center, TX; ⁵Melbourne Renal Research Group, Australia; ⁶Renal Research, Gosford, Australia; ⁷U of Illinois, IL; ⁸North Shore U. Hospital, NY; ⁹ZS Pharma, Inc., TX; ¹⁰Weill Medical College, NY.

Background: Hyperkalemia (HK) is a common and potentially lethal electrolyte disorder, often induced with the use of renin-angiotensin-aldosterone inhibitors (RAASi). Currently, the use of RAASi is prevented by HK and thus the potential for cardiac and renal protective effects of these agents is limited. In previous studies, ZS-9 (sodium zirconium cyclosilicate), a selective K⁺ trap, significantly lowered serum K⁺ and maintained normokalemia (NK) for up to 28 days. We present the results to date of the largest ever phase 3 trial examining the efficacy of ZS-9 in treating HK patients for up to 52wks.

Methods: ZS-005 (target N=750) is a multicenter, ongoing, open-label study evaluating ZS-9 treatment for 52wks in ambulatory pts with HK (K⁺ ≥ 5.1 mEq/L) with or without concurrent RAASi therapy. In the acute phase (AP), pts with HK received 10g ZS-9 TID over a 24-72hr period until NK (K⁺ 3.5-5.0 mEq/L) was achieved. Pts achieving NK were enrolled in a 52wk maintenance phase (MP) starting with 5g ZS-9 QD. There were no restrictions on diet and ZS-9 could be titrated to maintain NK. Primary outcomes were proportion of pts with mean K⁺ ≤ 5.1 mEq/L during MP and safety of ZS-9.

Results: To date, 583 pts with a mean baseline K⁺ of 5.6 mEq/L (15% ≥ 6.0 mEq/L) entered the study. Overall, 575 (99%) normalized K⁺ in AP and transitioned to the MP. To date, K⁺ was maintained at ≤ 5.1 and < 5.5 mEq/L in 87% and 99% of patients, respectively. The incidence and severity of adverse events were similar to that of previous studies.

Conclusions: ZS-9 acutely reduced K⁺ levels in pts with HK and maintained NK for up to 52wks irrespective of RAASi use. ZS-9 may control HK, both emergent and long-term, while allowing continued use of cardio- and reno-protective RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

SA-PO1102

Interleukin-1 Inhibition and Vascular Function in Patients with Chronic Kidney Disease (CKD): A Randomized Controlled Trial Kristen L. Nowak,¹ Michel Chonchol,¹ Talat Alp Ikizler,² Heather Farmer,¹ Natjalie Salas,² Rafia I. Chaudhry,² Wei Wang,¹ Gerard John Smits,¹ Adriana Hung.^{2,3} ¹Univ of Colorado Denver; ²Vanderbilt Univ; ³VA Tennessee Valley Healthcare System.

Background: Vascular endothelial dysfunction and increased arterial stiffness contribute to increased cardiovascular risk in CKD patients who exhibit chronic systemic inflammation. As chronic inflammation is a key mechanism contributing to vascular dysfunction, blocking inflammation may reduce cardiovascular risk in CKD.

Methods: In a two-site, double-blind trial, n=42 patients with stage 3-4 CKD were randomized to receive either the interleukin-1 (IL-1) trap rilonacept (subcutaneous injection; loading dose of 320 mg followed by 160 mg/wk) or placebo for 12 weeks. All patients were receiving optimal treatment of hypertension, diabetes, and/or hypercholesterolemia, with 64% and 62% receiving a statin and an ACE inhibitor or ARB, respectively. The co-primary endpoints were change in brachial artery flow-mediated dilation [FMD_{BA}] and aortic pulse-wave velocity [aPWV] after 4, 8 and 12 weeks using mixed effects models. Secondary endpoints were change in high-sensitivity C-reactive protein (hsCRP), ΔFMD_{BA} following an acute infusion of ascorbic acid known to inhibit superoxide production (n=23), and vascular endothelial cell protein expression of NADPH oxidase (n=13).

Results: Participants were 63±11 (mean±s.d.) years of age, 24% female and 24% Black, with eGFR 38±13 ml/min/1.73m². Rilonacept improved FMD_{BA} (baseline: 3.8±3.1%, 12 wks: 4.9±3.2%) compared to placebo (baseline: 3.4±2.1%, 12 wks: 2.5±2.3%; p<0.01), without changing aPWV (p=0.52). Rilonacept also reduced hsCRP levels (baseline: 4.6 (1.9, 8.22) [median (interquartile range)], 12 wks: 2.16 (0.96, 7.38) mg/L; p<0.01), and endothelial cell NADPH oxidase expression (p<0.05). Acute infusion of ascorbic acid tended to improve FMD_{BA} in the placebo (p=0.07) but not the rilonacept group (p=0.56), indicating reduced vascular oxidative stress. Overall, rilonacept was well tolerated.

Conclusions: 12 weeks of treatment with an IL-1 trap improved FMD_{BA} without changing aPWV in patients with stage 3-4 CKD. This was associated with a reduction in systemic inflammation and vascular oxidative stress.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Regeneron Pharmaceuticals, Inc, Private Foundation Support

SA-PO1103

Abstract Withdrawn

SA-PO1104

Impact of Vitamin D Supplementation on Endothelial and Vascular Function in Patients with Chronic Kidney Disease: A Randomized, Double Blind, Placebo-Controlled Trial Vivek Kumar,¹ Ashok Kumar Yadav,¹ Vinod Sharma,¹ Manphool Singhal,² Anupam Lal,² Debasish Banerjee,³ Vivekanand Jha.¹ ¹Nephrology, Postgraduate Inst of Medical Education and Research, Chandigarh, Chandigarh, India; ²Radiodiagnosis, Postgraduate Inst of Medical Education and Research, Chandigarh, Chandigarh, India; ³Nephrology, St. George's Univ Hospitals NHS Foundation Trust, London, London, United Kingdom.

Background: Vitamin D deficiency is associated with mortality in CKD patients. We investigated the effect of Vitamin D supplementation on endothelial and vascular function in patients with non-diabetic CKD stage 3-4.

Methods: In a prospective, randomized, double blind, placebo-controlled trial, 120 patients with non-diabetic CKD stage 3-4 and vitamin D deficiency [serum 25(OH)D <20ng/ml] aged 18-70 years were randomized (1:1) to receive either two directly observed oral doses of 300,000 IU of cholecalciferol at 0 and 8 weeks or matching placebo. The pre-specified primary outcome was 40% change in endothelium dependent brachial artery flow mediated dilatation (FMD) at 16 weeks. Secondary outcome measures included changes in pulse wave velocity (PWV), augmentation index (AI), and serum biomarkers.

Results: Baseline FMD was identical in both arms (7.65±2.24% vs 7.85±2.34%). Intervention arm showed a significant increase in serum 25(OH)D (+24.9 ng/ml, 95% CI: 21.8 to 28.06, p<0.0001), and the number of subjects meeting the primary end point (70% vs 5%, p<0.0001). FMD change was 5.42% (95% CI: 4.44 to 6.40%) in the intervention arm and -0.07% (95% CI, -0.70 to 0.58%) in placebo arm. Intervention led to favorable changes in PWV (-0.94 m/s, 95% CI: -1.30 to -0.58, p<0.0001), E-selectin (-3.68 ng/ml, 95% CI: -8.1 to 0.7 p=0.028), IL-6 (-2.0 pg/ml, 95% CI: -2.96 to -0.8 p=0.001), FGF-23 (-14.7 pg/ml, 95% CI -28.5 to -1.0 p=0.036) and 1,25(OH)₂D (+15.5 pg/ml, 95% CI: 5.4 to 25.5, p=0.003). These did not change significantly in the control group. No changes were observed in AI, vWF and hs-CRP in either group.

Conclusions: In non-diabetic patients with stage 3-4 CKD and vitamin D deficiency, vitamin D supplementation leads to improvement in endothelial function, markers of inflammation and arterial stiffness.

Funding: Government Support - Non-U.S.

SA-PO1105

Effect of Cholecalciferol versus Calcitriol on Vascular Endothelial Function in CKD: A Randomized Active-Controlled Trial Jessica B. Kendrick,^{1,2} Gerard John Smits,¹ Emily Decker,¹ Heather Farmer,¹ Michel Chonchol.¹ ¹Univ of Colorado School of Medicine, Aurora, CO; ²Denver Health Medical Center, Denver, CO.

Background: Epidemiological studies have shown that vitamin D is associated with decreased cardiovascular morbidity and mortality, but the effects of vitamin D administration on patient outcomes in chronic kidney disease (CKD) are lacking. We conducted a prospective, double-blinded, randomized trial to determine the effects of oral cholecalciferol vs. calcitriol on vascular endothelial function over 24 weeks in patients with CKD stage 3-4.

Methods: 128 patients with CKD stage 3-4 (estimated GFR 15-44 ml/min/1.73m²) with vitamin D deficiency, defined as serum 25-hydroxyvitamin D level (25(OH)D) < 30 ng/mL, were randomly assigned to receive either cholecalciferol (4000 IU daily x 4 weeks then 2000 IU daily x 20 weeks) or calcitriol (0.25 mcg daily x 4 weeks then 0.5 mcg daily x 20 weeks). The primary endpoint was change in brachial artery flow mediated dilation (FMD_{BA}) over 24 weeks. Secondary endpoints included changes in parameters of mineral bone disease and plasma concentrations of inflammatory cytokines (C-reactive protein and interleukin-6).

Results: 115 patients completed the study. The mean (SD) age and eGFR was 58.1 ± 12.4 years and 33.1 ± 10.2 ml/min/1.73m², respectively. In the cholecalciferol group, mean 25(OH)D levels increased from 22.7 ± 7.5 ng/mL to 33.5 ± 7.9 ng/mL. There was no change in 25(OH)D levels in the calcitriol group. Parathyroid hormone levels decreased significantly in the calcitriol group compared to the cholecalciferol group (p=0.001). At 24 weeks, the change in FMD_{BA} did not differ significantly between treatment groups (cholecalciferol group -0.72%, 95% CI -1.97 to 0.54 vs. calcitriol group 0.29%, 95% CI -0.72 to 1.29, p=0.44). There was no significant change in C-reactive protein or interleukin-6 concentrations between the two groups. Episodes of hypercalcemia were more frequent in the calcitriol group (n=4) compared with the cholecalciferol group (n=1).

Conclusions: Twenty-four week therapy with cholecalciferol or calcitriol did not improve vascular endothelial function or reduce inflammation in patients with CKD.

Funding: NIDDK Support

SA-PO1106

Vitamin D Receptor Activation and Dietary Sodium Restriction to Reduce Residual Albuminuria in Chronic Kidney Disease Martin H. De Borst,¹ Charlotte A. Keyzer,¹ Fenna van Breda,² Marc G. Vervloet,² Gozewijn Dirk Laverman,³ Marc H. Hemmelder,⁴ Wilbert M. Janssen,⁵ Hiddo Jan Lambers Heerspink,¹ Stephan J.L. Bakker,¹ Gerjan Navis.¹ ¹UMC Groningen; ²VUmc Amsterdam; ³ZGT Almelo; ⁴MC Leeuwarden; ⁵Martini Hospital Groningen, Netherlands.

Background: Reduction of residual albuminuria during single-agent RAAS-blockade is associated with improved cardiorenal outcomes in CKD. Both vitamin D receptor activators (VDRA) and dietary sodium restriction reduce residual albuminuria. Previous data suggested that sodium restriction is not required for optimal albuminuria reduction by VDRA. We studied the individual and combined effects of paricalcitol and sodium restriction on residual albuminuria during optimally dosed ACEi in CKD.

Methods: In a multi-center, randomized, placebo-controlled cross-over trial, 45 patients with non-diabetic CKD stage 1-3 and residual albuminuria >300 mg/24h despite ramipril 10 mg/d and BP <140/90 mmHg were treated during four 8-week periods with paricalcitol (PARI, 2 µg/day) or placebo (PLAC), each combined with a low (LS, 2.5 gr Na⁺/d) or regular sodium (RS, 4 gr Na⁺/d) diet, in random order. Linear mixed-effect models for repeated measurements were used to determine treatment effect.

Results: In the *intention-to-treat* analysis, albuminuria was 1,060 [778 to 1,443] (geometric mean [95% CI]) mg/24h during RS+PLAC. During RS+PARI, albuminuria was 990 [755 to 1,299] mg/24h (-12.5% [-26.0% to 26.3%] vs. RS+PLAC, *P*=0.2). LS+PLAC reduced albuminuria to 717 [512 to 1,005] mg/24h (-25.4% [-52.6% to -2.3%] vs. RS+PLAC, *P*<0.001). LS+PARI provided the strongest albuminuria reduction to 683 [502 to 929] mg/24h (-31.7% [-55.0% to -0.9%], *P*<0.001 vs. RS+PLAC), although the additional reduction by PARI beyond the effect of LS was non-significant (*P*=0.6). However, in a *per protocol* analysis (≥95% compliance, N=34) PARI did reduce residual albuminuria beyond the effect of LS (*P*=0.04).

Conclusions: The combination of paricalcitol and moderate dietary sodium restriction provided the strongest reduction of residual albuminuria during optimal ACEi; the effect was mainly driven by sodium restriction. Our findings underline the relevance of sodium restriction, possibly combined with paricalcitol, to optimize albuminuria reduction.

SA-PO1107

Vascular Function and Uric Acid Lowering via Allopurinol in Stage III CKD: Results of a Double-Blinded Randomized Placebo-Controlled Study Diana I. Jalal,¹ Emily Decker,¹ Loni J. Perrenoud,¹ Nina Bispham,² Tapan Mehta,¹ Gerard John Smits,¹ Richard J. Johnson.¹ ¹Medicine/ Renal Div, UC AMC, Aurora, CO; ²Integrative Physiology, UC Boulder, Boulder, CO.

Background: Observational studies suggest that asymptomatic hyperuricemia associates with vascular disease in chronic kidney disease (CKD). A recent study suggested that lowering serum urate with allopurinol improves endothelial function in elderly adults with stage III CKD. It remains unknown if lowering serum urate improves endothelial function in adult subjects with stage III CKD.

Methods: 80 adult subjects (18-70) years of age with stage III CKD and asymptomatic hyperuricemia (≥7 mg/dL in men and ≥6 mg/dL in women) were randomized to receive placebo or allopurinol (100 mg tablets) for 12 weeks. The study was double-blinded and subjects were instructed to take 1 tablet for 1 week, 2 tablets for another week, and 3 tablets thereafter. Changes (from baseline) between both groups were compared by Wilcoxon rank-sum test.

Results: No significant differences existed between both groups at baseline. After 12 weeks, allopurinol lowered serum urate significantly. FMD increased in the allopurinol group compared to placebo; but this was not statistically significant. NMD increased with allopurinol but decreased with placebo; *p* value = 0.14. These data are shown in Table 1. There were no significant differences between allopurinol and placebo for systolic or diastolic blood pressure, markers of inflammation, or markers of oxidative stress. 10 subjects withdrew from the study. A few adverse events were noted in both groups including 1 gout attack in each group. 1 subject died during the study due to a cardiac event.

Variable	Placebo	Allopurinol	P value
Serum Urate(mg/dL)	0.05(1.54)	-3.24(1.35)	<0.0001
FMD(%change)	0.16(4.05)	0.91(3.9)	0.47
NMD(%change)	-1.29(5.33)	0.93(6.05)	0.14

Conclusions: Allopurinol effectively and safely lowered serum urate in adults with stage III CKD and asymptomatic hyperuricemia but this did not improve endothelial function significantly. There was tendency towards improved NMD suggesting that hyperuricemia may negatively impact vascular smooth muscle function in stage III CKD.

Funding: NIDDK Support

SA-PO1108

Podocyturia Is an Earlier and Superior Predictor of Cardiovascular Outcomes Than Is Albuminuria Assaad Antoine Eid,¹ Robert Habib,² Kamal F Badr.² ¹Anatomy, Cell Biology and Physiological Sciences, American Univ of Beirut - Faculty of Medicine, Beirut, Lebanon; ²Internal Medicine, American Univ of Beirut - Faculty of Medicine, Beirut, Lebanon.

Background: Increased urinary albumin excretion rate (AER), a predictor of cardiovascular events, results from abnormally increased albumin filtration accompanying injury to glomerular endothelial and epithelial cells (“podocytes”). Since AER is modified by renal proximal tubule albumin retrieval, we hypothesized that urinary podocyte shedding, podocyturia, would be a more relevant and earlier biomarker of endothelial injury (and CVD) than moderate albuminuria.

Methods: 106 Type II diabetic subjects (mean age: 46/60 men/women) with normal AER [<2.26 mg/mmol (20 µg/mg) creatinine] and free of overt cardiovascular disease (CVD) were enrolled. AER and podocyte-specific proteins (podocin and nephrin) mRNA were measured at baseline (visit 1), 3-4 years later (visit 2) and at 7 years (visit 3). Development of cardio vascular diseases VD - defined as coronary disease, cerebrovascular disease and/or peripheral vascular disease (can be removed to fit words counting)- was collected as outcome. 7-year Kaplan-Meier time-to-event (log rank) data were compared in baseline biomarker tercile groups (low, intermediate, high).

Results: All three biomarkers increased significantly between visits (*P*<0.001). AER terciles exhibited similar time to CVD (*p*=0.127), which was in contrast with the step-wise and substantial increase in CVD events with increasing podocin and nephrin levels (*P*<0.001). Considering all three biomarkers as continuous factors, the covariate-adjusted hazard ratios (95% confidence intervals) [HR] were highest for podocin mRNA [HR=15.9 (6.1-41.8); *p*<0.001], intermediate for nephrin mRNA [HR=7.61 (3.75-15.5); *p*<0.001] and lowest for AER [HR=1.17 (1.01-1.36); *p*=0.041].

Conclusions: Compared to traditional AER, podocyturia predicts more accurately and at an earlier time point the presence of silent systemic vascular injury, that manifests as overt cardiovascular events.

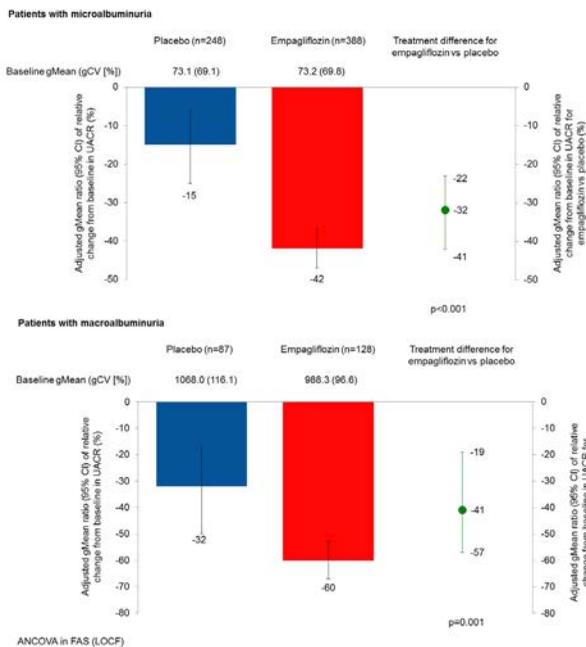
SA-PO1109

Empagliflozin Reduces Microalbuminuria and Macroalbuminuria in Patients with Type 2 Diabetes David Cherney,¹ Soren Søgaard Lund,² Bruce A. Perkins,³ Per-Henrik Groop,^{4,5} Mark E. Cooper,⁵ Stefan Kaspers,² Susanne Crowe,² Hans-Juergen Woerle,² Maximilian von Eynatten.² ¹Toronto General Hospital, Univ of Toronto, Canada; ²Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; ³Mount Sinai Hospital, Univ of Toronto, Canada; ⁴Univ of Helsinki and Helsinki Univ Hospital, Folkhälsan Research Center, Helsinki, Finland; ⁵Baker IDI Heart and Diabetes Inst, Melbourne, Australia.

Background: Reductions in HbA1c, systolic blood pressure (SBP), and weight with the highly selective SGLT2 inhibitor empagliflozin in patients with type 2 diabetes (T2D) may favorably impact albuminuria.

Methods: Using data pooled from 5 Phase III, randomized clinical trials, we assessed the effect of empagliflozin 10 or 25 mg for 24 weeks on urine albumin to creatinine ratio (UACR) in patients with T2D and prevalent microalbuminuria (UACR 30–300 mg/g; n=636) or macroalbuminuria (UACR >300 mg/g; n=215) at baseline.

Results: Empagliflozin reduced UACR vs placebo in patients with T2D and microalbuminuria (-32%; *p*<0.001) or macroalbuminuria (-41%; *p*=0.001) after controlling for baseline log (UACR), HbA1c, SBP, estimated glomerular filtration rate (MDRD), region, study and treatment (Figure). Adjusted mean (SE) changes in HbA1c, weight, SBP and diastolic BP with empagliflozin vs placebo were -0.50 (0.07) %, -1.6 (0.2) kg, -4.4 (1.1) mmHg and -2.3 (0.6) mmHg, respectively, in patients with microalbuminuria (all *p*<0.001), and -0.53 (0.13) %, -1.8 (0.4) kg, -6.3 (2.0) mmHg and -2.2 (1.1) mmHg, respectively, in patients with macroalbuminuria (all *p*<0.05). Linear regression analyses showed that changes in HbA1c, weight and SBP accounted for a maximum of half the UACR-lowering effect.



Conclusions: SGLT2 inhibition with empagliflozin reduced UACR by >30% in patients with T2D and prevalent microalbuminuria or macroalbuminuria, independent of its known metabolic and hemodynamic effects.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim and Eli Lilly and Company

SA-PO1110

Vadadustat, a Novel Oral Treatment for Anemia of Chronic Kidney Disease, Maintains Stable Hemoglobin Levels in Dialysis Patients Converting from Erythropoiesis-Stimulating Agents Volker H. Haase,¹ Charlotte S. Hartman,² Bradley J. Maroni,² Ramin Farzaneh-Far,² Peter A. McCullough,³ ¹Div of Nephrology and Hypertension, Vanderbilt Univ Medical Center, Nashville, TN; ²Akebia Therapeutics, Inc., Cambridge, MA; ³Baylor Univ Medical Center, Dallas, TX.

Background: Vadadustat is a novel, oral agent that stimulates erythropoiesis by stabilizing hypoxia-inducible factor (HIF). Prior studies in patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) have shown that vadadustat results in controlled, dose-dependent increases in hemoglobin (Hb) and enhances iron mobilization and utilization. Here we present data from a Phase 2 trial of vadadustat in hemodialysis patients.

Methods: A multi-center, open-label, 16-week trial was designed to assess Hb response, safety, and tolerability of vadadustat. The trial enrolled 94 hemodialysis patients (Hb 9 - 12 g/dL), who were maintained on erythropoiesis-stimulating agents (ESAs) prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD; or 450 mg three times weekly (TIW). The primary efficacy analysis was to evaluate mean Hb changes from baseline at weeks 7/8, and weeks 15/16. From week 8, dose could be adjusted as needed to maintain Hb. All patients were iron replete at baseline and throughout the study; IV iron use was allowed.

Results: Vadadustat maintained stable Hb levels in all 3 dose cohorts during the 16 week treatment period following conversion from ESA.

Mean Hb levels (g/dL) in Modified Intent-To-Treat (MITT) population			
Dose Cohort	Baseline	Week 7/8	Week 15/16
300mg QD	10.4	10.4	10.3
450mg QD	10.6	10.3	10.5
450mg TIW	10.5	10.2	10.4

One subject in the 300mg QD cohort had a single Hb excursion to 13.1 g/dL. Adverse events were balanced across the 3 cohorts. Serious adverse events (SAEs) were reported in 13 subjects (13.8%), which was within the expected range (13 - 17 subjects). No drug-related SAEs, nor deaths, were reported.

Conclusions: Vadadustat safely and effectively maintained Hb levels in dialysis patients who were converted from injectable ESAs.

Funding: Pharmaceutical Company Support - Akebia Therapeutics Inc., Cambridge, MA, United States

SA-PO1111

Autologous Erythropoietin Production by the TARGT Gene Therapy Platform Maintains Stable Hb for 6-12 Month in ESRD Patients without the Need for ESA Administration Shany Blum,¹ Nir Shapir,¹ Reem Miari,¹ Shai Efrati,³ Pablo E. Pergola,⁴ Garry A. Neil,² ¹Medgenics Medical Israel Ltd., Misgav, Israel; ²Medgenics Inc, Wayne, PA; ³Research & Development and Nephrology Units, Assaf-Harofeh Medical Center, Zerifin, Israel; ⁴Renal Associates PA, San Antonio, TX.

Background: Recombinant human erythropoietin (rHuEPO) administration to iron replete patients corrects anemia in most patients with ESRD, but doses result in supra-physiological peak serum concentration (C_{max}) of EPO that may cause thromboembolic complications. The Transduced Autologous Restorative Gene Therapy system (TARGT™) is an ex-vivo gene therapy, providing autologous, continuous protein therapies at physiological ranges that was used encoding for the human erythropoietin gene (TARGT_{EPO}) for these studies. Patient dermal tissue biopsies (MOs) are transduced with a Helper-Dependent Adenoviral Vector containing the EPO gene and then re-implanted subcutaneously to deliver the required EPO dose.

Methods: We present initial results from 3 ongoing open label ascending dose studies of TARGT_{EPO} in patients with anemia due to CKD undergoing either Hemo or Peritoneal Dialysis.

Results: Thus far 14 patients were enrolled in all protocols. Follow up is ongoing with the first implanted patient being followed with stable EPO secretion and stable Hb for over 14 months from a single implantation without the need for rHuEPO or blood transfusion. Results obtained suggest that treatment with TARGT_{EPO} stabilize serum EPO levels at the physiological range of £20 mIU/ml resulting in Hb levels between 9-12 g/dL. Comparative analysis of serum EPO levels revealed significantly lower C_{max} with TARGT_{EPO} compared to rHuEPO and an order of magnitude less overall EPO exposure as calculated by Area Under the Curve which may confer significant clinical benefit. No treatment related serious adverse events have been reported.

Conclusions: TARGT_{EPO} is a promising novel therapy for the treatment of anemia of CKD and potentially for other protein deficient diseases.

Funding: Pharmaceutical Company Support - Medgenics Inc.

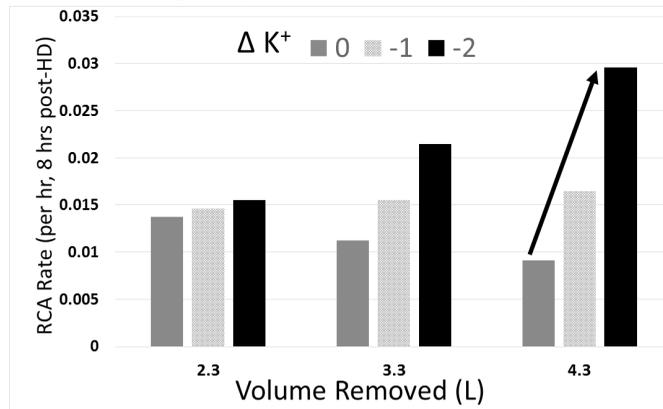
SA-PO1112

Monitoring in Dialysis (MiD) Study: Exploring the Timeline and Etiology of Increased Arrhythmias in Hemodialysis (HD) Patients Prabir Roy-Chaudhury,¹ Don E. Williamson,² James A. Tumlin,³ Vijay K. Kher,⁴ Vikranth Reddy,⁵ Kowdle Chandrasekhar Prakash,⁶ David M. Charytan,⁷ Suresh Chandra Tiwari,⁸ Saurabh Pokhariyal,⁹ Amber S. Podoll,¹⁰ ¹Univ of Arizona, Tucson; ²Nephrology Associates, Augusta; ³Univ of Tennessee, Chattanooga; ⁴Medanta Medicity; ⁵CARE Hospital, Hyderabad; ⁶Apollo Hospitals-Chennai; ⁷Brigham and Women's Hospital; ⁸Fortis-Vasant Kunj, Delhi; ⁹Fortis, Gurgaon; ¹⁰Univ of Texas, Houston.

Background: Sudden cardiac death (SCD), likely due to cardiac arrhythmias (CA) is the most important cause of mortality in the HD population. We herein present data on the timeline and potential etiology of CA in HD patients (pts).

Methods: The MiD study (n=66) characterized the type and frequency of CA in 3x/wk HD pts over 6 mths, using an implanted loop recorder (Medtronic Reveal). Reviewer confirmed arrhythmias (RCA; all documented CA) and clinically significant arrhythmias (CSA; brady/asystole/VT/ symptomatic), were linked to the dialysis cycle, pt wt and pre/post-session electrolytes, using negative binomial mixed effects regression analyses.

Results: Mean age was 56.3±12.2; 64% diabetic; 70% male; HD vintage 4.3±5.1 yrs. 97% and 67% of pts had a RCA/CSA. Most CSA occurred during the intradialytic period of the first weekly HD and then decreased in subsequent sessions. Univariate analyses identified increased pre and post wt, high pre HD potassium (K) and drop in K as risk factors for RCA. Multivariate analyses (adjusted for DM, yrs on HD, pre-wt), identified higher pre HD K levels as a predictor for increased RCA. The highest risk of arrhythmia occurred in pts with high K drops AND substantial volume removal (p=0.03).



Underline represents presenting author/disclosure.

Conclusions: These data establish linkages between intra-dialytic CSA and the long interdialytic period, and also identify a unique interaction between fluid removal and K in the generation of RCA. This suggests for the first time, that future data driven targeting of these parameters might reduce CA and potentially SCD in HD pts.

Funding: Pharmaceutical Company Support - Medtronic

SA-PO1113

The Occurrence of Cardiac Arrhythmias in Hemodialysis Patients is Linked to the Hemodialysis Procedure and to Electrolyte Abnormalities as Recorded by Implantable Loop Recorders Christian Combe,^{1,2} Antoine Benard,^{1,2} H  l  ne Savel,^{1,2} F. Sacher.^{1,2} ¹CHU & Univ. Bordeaux, Bordeaux, France; ²Rythmodial Study Group.

Background: Sudden cardiac death (SCD) is the most common mode of death among hemodialysis (HD) patients (pts). Little is known about the terminal arrhythmic events in these pts. Our objective was to identify the mechanisms which may lead to SCD in HD pts using an implantable loop recorder (ILR, Reveal XT  , Medtronic).

Methods: Pts from 9 HD centers have been included in the study. Continuous monitoring of the cardiac rhythm has been performed using the remote monitoring capability of the ILR device (Carelink  ). Clinical, biological, and technical HD parameters and medications have been recorded for at least 1 year. General joint frailty model for recurrent event data were used to analyze associations between these parameters and the occurrence of cardiac rhythm events.

Results: 72 pts (65.1  8.6 yrs, 52M) have been included. Causes of ESRD were diabetes (n=32) and hypertension (n=19). 22 pts had an ischemic cardiomyopathy. In multivariate analyses, the occurrence of conduction abnormalities (n=64) was associated to high potassium (K⁺) concentrations (K⁺>5mM, RR=5.22, p<10⁻⁴) and to body weight (bw) variation during HD (RR per %bw/h 3.22, p<10⁻²). There was no association with serum calcium, hemoglobin, HD bath ions, blood pressure. Ventricular arrhythmias >150/min (n=11) were associated only to high K⁺ levels (K⁺>5mM, RR=13.35, p<0.05), to low K⁺ levels (K⁺<4 mM, RR=24.48, p<0.01), and to high phosphate levels (Pi>45mg/L, RR=5.64, p<0.04). Atrial fibrillation was the most frequent event (n=255), with less clear associations with patient-dependent and HD-dependent variables. In 6 SCD patients, ILR tracings demonstrated progressive bradycardia followed by asystole.

Conclusions: Our data show that the various types of arrhythmias and conduction abnormalities occurring in HD pts are linked to different pathophysiological mechanisms, with a central role of serum K⁺ levels, levels lower than 4 mM or higher than 5 mM being deleterious. Rapid body weight variations were linked to ventricular arrhythmias. Therapeutic strategies aimed at controlling these factors can be drawn from our study.

Funding: Pharmaceutical Company Support - Medtronic, Government Support - Non-U.S.

SA-PO1114

Abstract Withdrawn

SA-PO1115

Comparison of the Efficacy and Safety of Intravenous (IV) Etelcalcetide (AMG 416) and Oral Cinacalcet (CIN) in Patients on Hemodialysis (HD) with Secondary Hyperparathyroidism (sHPT) Kevin J. Martin,¹ Geoffrey A. Block,² Sunfa Cheng,³ Bastian Dehmel,³ Reshma Kewalramani,³ David M. Spiegel,⁴ Hao Wang,³ Glenn Matthew Chertow.⁵ ¹St Louis Univ SOM, St. Louis, MO; ²Denver Neph, Denver, CO; ³Amgen; ⁴Relypsa; ⁵Stanford Univ SOM, Palo Alto, CA.

Background: This is a randomized, active controlled, double-blind, double dummy study comparing the efficacy and safety of a novel IV calcimimetic, AMG 416, with CIN.

Methods: Patients receiving HD with PTH >500 pg/ml, albumin-corrected calcium (cCa)   8.3 mg/dL, and no CIN use for 3 months were randomized 1:1 to AMG 416 IV/oral placebo or oral CIN/IV placebo for 26 weeks (wks). Doses were titrated at wks 5, 9, 13, 17 based on the prior wk's PTH and cCa. AMG 416 was started at 5mg and titrated by 2.5 or 5mg up to 15mg 3 times weekly with HD. CIN was started at 30mg and titrated up to 180mg daily per label. Target PTH was   100 and   300 pg/ml. Primary endpoint was noninferiority on >30% reduction in PTH during wks 20-26. Secondary endpoints were >30% reduction in PTH (superiority analysis), >50% reduction in PTH, mean days of nausea or vomiting (n/v) (patient reported outcome) per wk in the first 8 wks.

Results: 683 subjects were randomized (340 AMG 416, 343 CIN), 553 completed the trial (84% AMG 416, 86% CIN). AMG 416 was noninferior to CIN on the primary endpoint. AMG 416 was superior on >30% reduction in PTH (68% AMG 416, 58% CIN, p=0.004) and >50% reduction in PTH (52% AMG 416, 40% CIN, p=0.001). Mean days of n/v in the first 8 wks did not differ (0.4 AMG 416, 0.3 CIN, NS). The most common adverse event (AE) in either group was blood calcium decreased (69% AMG 416, 60% CIN), mostly mild to moderate severity. Heart failure related AEs were reported in 10 (3.0%) AMG 416 subjects and 2 (0.6%) CIN subjects, of which 5 and 1, respectively, were serious. 9 (3%) subjects receiving AMG 416 and 6 (2%) receiving CIN had fatal treatment-emergent AEs – all unrelated to study drug.

Conclusions: AMG 416 achieved a >50% and a >30% reduction in PTH in more subjects compared to CIN. Hypocalcemia was seen more often with AMG 416. Nausea and vomiting did not differ. IV AMG 416 is more efficacious than oral CIN for the treatment of sHPT in patients on HD.

Funding: Pharmaceutical Company Support - Amgen

SA-PO1116

A Trial Assessing Use of a Wearable Artificial Kidney (WAK) in Patients Undergoing Maintenance Hemodialysis Victor Gura,¹ Matthew B. Rivara,² Raj P. Munshi,² Scott D. Bieber,² Masoud Beizai,³ Carlos J. Ezon,³ Larry Kessler,² Jonathan Himmelfarb.² ¹Cedars Sinai- UCLA, Los Angeles, CA; ²Univ of Washington, Seattle, WA; ³Blood Purification Technologies Inc, Beverly Hills, CA.

Background: Current stationary dialysis machines hinder mobility and limit activities of daily life during dialysis treatments. There is a critical need for new technologies to increase patient autonomy, enhance quality of life, and allow for increased patient rehabilitation.

Methods: This is the first FDA-approved human trial of the WAK, a miniaturized, wearable hemodialysis machine based on dialysate-regenerating sorbent technology (NCT02280005). We aimed to determine the safety and efficacy of the WAK in maintaining euvoolemia and achieving solute clearance and electrolyte homeostasis over 24 hours.

Results: All patients remained hemodynamically stable, and there were no serious adverse events. Serum electrolytes and hemoglobin remained stable over the treatment period for all subjects. Six out of seven patients ambulated while receiving WAK treatment. Fluid removal was consistent with prescribed ultrafiltration rates. Mean blood flow was 42    24 and dialysate flow was 43  20 ml/min with no laboratory evidence of hemolysis. Mean BUN, creatinine, and phosphorus clearances were 21    13, 20    11, and 22    12 ml/min respectively during the first hour of treatment. In one subject, treatment was discontinued due to clotting after 4 hours. In a second subject, treatment was discontinued due to discoloration of dialysate observed after 10 hours. The trial was stopped after the 7th subject due to device-related malfunctions. These included excessive CO2 bubbles in the dialysate, variable blood and dialysate flows, and tubing leaks during the priming phase. Redesign and re-manufacturing of the WAK prototype will be required prior to additional human studies.

Conclusions: Treatment with the WAK was well tolerated, resulted in effective uremic solute clearance and maintenance of electrolyte and fluid homeostasis. These results serve as proof-of-concept of the WAK as a viable novel dialysis technology.

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SA-PO1117

CR845, a Novel Kappa Opioid Receptor Agonist Reduces Moderate-to-Severe Pruritus and Improves Quality of Life in Chronic Kidney Disease Patients Undergoing Hemodialysis Robert Spencer,¹ Vandana S. Mathur,² James A. Tumlin,³ Joseph W. Stauffer,¹ Frederique Menzaghi,¹ ¹Cara Therapeutics, Inc., Shelton, CT; ²Mathur Consulting, San Francisco, CA; ³Univ of Tennessee, Chattanooga, TN.

Background: Approximately 40% of US hemodialysis (HD) patients experience moderate-to-severe itching, which negatively affect their mental and physical health (e.g., sleep loss, depression, higher antibiotic and erythropoietin use and increased mortality). The etiology of this condition is likely multi-factorial, including immune system dysfunction and imbalance of mu/kappa endogenous opioids. CR845 is a novel and well-tolerated kappa opioid receptor (KOR) agonist with limited central nervous system entry, thereby preferentially activating KOR on peripheral neurons and immune cells.

Methods: In this Phase 2 double-blind, randomized (1:1), placebo-controlled clinical study, 65 prevalent US HD patients with persistent (~ 5 years) moderate-to-severe pruritus (baseline VAS ~68 mm, 0=no itch; 100 mm =worst itch) were treated with 1 mcg/kg intravenous CR845 or placebo following each HD session for 2 weeks. Antihistamines were discontinued 1 week prior to the study.

Results: The primary endpoint was met (VAS change in worst itch intensity from baseline to Days 12-15), with a significant difference in itch intensity between placebo and CR845-treated patients (p=0.016). CR845-treated patients had a 50% mean reduction in itch intensity from baseline. The 1st secondary endpoint was also met with a significant improvement in Skindex-10, a validated patient-reported outcome measure of pruritus-related quality of life (p =0.031). Furthermore, a trend for a sleep improvement was observed (SLP9).

Conclusions: Short-term treatment with CR845 significantly reduced itch intensity and improved quality of life in HD patients with moderate-to-severe pruritus. Thus, CR845 appears to have substantial potential to alleviate the symptoms and consequences of this frequently incapacitating condition for which existing treatments have often provided little or no relief. These data also support the opioid/immune etiology of this condition.

Funding: Pharmaceutical Company Support - Cara Therapeutics, Inc.

Underline represents presenting author/disclosure.

SA-PO1118

The ASSertID Study: Feasibility Randomised Controlled Trial of Drug Treatment for Depression in Patients on Haemodialysis Ayman Guirguis,^{1,2,3} Michael K. Almond,⁴ Joseph Chilcot,⁵ Andrew Davenport,⁶ Clara Day,⁷ Naomi Fineberg,^{2,3} Karin Friedli,² Benjamin Spencer,⁵ David Wellsted,² Ken Farrington,^{1,2} ¹East & North Hertfordshire NHS Trust, United Kingdom; ²Univ of Hertfordshire, United Kingdom; ³Hertfordshire Partnership Univ NHS Trust, United Kingdom; ⁴Southend Univ Hospitals NHS Trust, United Kingdom; ⁵King's College London, United Kingdom; ⁶Royal free London NHS Trust, United Kingdom; ⁷Univ Hospitals Birmingham NHS Trust, United Kingdom.

Background: Major Depressive Disorder (MDD) is common in patients on Haemodialysis (HD) but there is little evidence of benefit from antidepressants. Hence we undertook a multicentre feasibility Randomised Controlled Trial (RCT) of sertraline versus placebo.

Methods: A screening phase identified patients with Beck Depression Inventory (BDI-II) score ≥ 16 . Those meeting eligibility criteria, underwent psychiatric assessment (Mini International Neuropsychiatric Interview). Consenting patients with mild to moderate MDD and Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 18 were randomised to sertraline or placebo. Follow-up by study psychiatrist; week 2, month 2, 4 and 6 and monthly by study nurses. Initial dose was 50 mg with titration to 100 mg if required.

Results: Of 1355 patients approached, 715 consented for screening. BDI-II ≥ 16 was present in 231 (32.3%), 58 (25.1%) were ineligible due to current treatment for MDD. Sixty-three underwent psychiatric assessment. MDD was diagnosed in 37; 30 consented to the RCT (mean age 61 \pm 15; 71% male; 60% white). Twenty-one (70%) completed the trial, 8 (of 15) on sertraline and 13 (of 15) on placebo. Over 6 months, BDI-II and MADRS scores decreased ($t(17) = -6.3$, $p < 0.001$ and $t(20) = -11.3$, $p < 0.001$ respectively). There was no reliable difference between the sertraline and placebo groups. Fewer on sertraline completed (6 withdrawals and one death versus 2 withdrawals on placebo [$C2 = 3.97$, $p = 0.046$]). There was a trend towards a greater fall in MADRS scores by month 2 on sertraline (effect size 0.37; lower bound > 0).

Conclusions: This feasibility study is the largest RCT investigating the use of antidepressants in HD patients with MDD. Similar significant improvement in MDD occurred over 6 months in both groups. Recovery may have been quicker on sertraline.

SA-PO1119

Randomised Controlled Trial to Determine the Appropriate Time to Initiate Peritoneal Dialysis after Insertion of Catheter to Minimise Complications Helen G. Healy,¹ George T. John,¹ Edward Yeoh,¹ Nicola Williams,¹ Thin M. Han,² Lakshmanan Jeyaseelan,³ Kavitha Ramanathan,³ Dwarakanathan Ranganathan,¹ ¹Renal Dept, Royal Brisbane & Women's Hospital, Brisbane, Queensland, Australia; ²Renal Dept, Rockhampton Hospital, Rockhampton, Queensland, Australia; ³Dept of Statistics, Christian Medical College, Vellore, India.

Background: The optimal time for the commencement of peritoneal dialysis (PD) after PD catheter insertion is not well known. If dialysis is started too soon after insertion, dialysate leaks and infection may occur. However by starting PD earlier, morbidity and costs can be reduced through less need for haemodialysis. This is the first randomised controlled trial to determine the safest and shortest interval to commence PD after catheter insertion.

Methods: All consecutive patients undergoing PD catheter insertion at the Royal Brisbane and Women's Hospital and Rockhampton Hospital from 1st March 2008 to 31st May 2013, and who met the inclusion and exclusion criteria were invited to participate in the study. Participants were randomised to one of three groups. Group 1 (G₁) commenced PD at one week, group 2 (G₂) at two weeks and group 3 (G₃) at four weeks after Tenckhoff catheter insertion. The groups were stratified by hospital and the presence of diabetes. Primary outcomes were the incidence of peritoneal fluid leaks or PD related infection during the 4 weeks after commencement of PD.

Results: 122 participants were recruited, with 39, 42 and 41 randomised to groups G₁, G₂ and G₃ respectively. The primary outcome of either catheter leaks or infection was significantly different in both intention to treat (ITT) and per protocol (PP) analyses ($p = 0.016$ and 0.006 respectively). Multiple pairwise comparison showed a significant difference between G₁ and G₃ in PP analysis (p -value = 0.010) but not in the ITT analysis.

Conclusions: Overall complications were higher in patients commencing PD one week after catheter insertion compared with the other two groups.

Funding: Pharmaceutical Company Support - Baxter Medical

SA-PO1120

The Effects of Normal Saline and an Acetate-Buffered Crystalloid Solution on Hyperkalemia in Deceased Donor Renal Transplantation: A Randomized Blinded Trial Laura Elisabeth Harris, Peter F. Mount, Francesco L. Ierino, David A. Story, Glenn M. Eastwood, Larry Mcnicol, Rinaldo Bellomo, Laurence Weinberg. *Austin Health, Melbourne, Victoria, Australia.*

Background: Perioperative administration of 0.9% normal saline (NS) in deceased donor renal transplantation is associated with hyperchloremic metabolic acidosis, but the effect of NS on the risk of hyperkalemia or delayed graft function is unknown. We compared the effect of NS to an acetate buffered crystalloid solution (Plasmalyte-148) (PL), on the incidence of hyperkalemia, acid base status, and delayed graft function in deceased donor renal transplant patients.

Methods: Blinded randomized single-centre trial conducted in a renal transplant unit of a tertiary hospital. Patients were randomized to NS or PL for perioperative fluid management. The primary outcome was hyperkalemia (≥ 5.5 mM) within the first 48 h postoperatively. Secondary outcomes were acid base disturbances; delayed graft function and hospital length of stay.

Results: Forty-nine patients were randomized: 25 to NS and 24 to PL. Baseline characteristics were similar in both groups. The median [IQR] total volume of fluid administered was 6446mL [4807,8075] for NS and 7776mL [5140,9080] for PL ($p = 0.3$). The incidence of hyperkalemia in the first 48 hours postoperatively was higher in the NS group: 20 patients (80%) vs. 12 patients (50%) in the PL group ($p = 0.04$). Sixteen patients (64%) in the NS group required treatment for hyperkalemia compared to 5 patients (21%) in the PL group ($p = 0.003$). The peak serum potassium in the 48 h postoperative period was higher in the NS group (6.1 ± 0.8 vs. 5.4 ± 0.9 mM, $p = 0.009$). Patients receiving NS were more acidotic ($pH: 7.32 \pm 0.06$, vs. 7.39 ± 0.05 , $p = 0.001$) and had higher serum chloride (107 mM vs. 101 mM, $p < 0.001$) at the end of surgery. There were no significant differences in delayed graft function or hospital length of stay.

Conclusions: Deceased donor renal transplant patients that received NS developed hyperchloremic metabolic acidosis with an increased incidence of hyperkalemia when compared to PL. This study supports the use of acetate buffered crystalloid solutions for perioperative fluid management in patients undergoing deceased donor renal transplantation.

Funding: Pharmaceutical Company Support - Baxter Healthcare Pty Ltd

SA-PO1121

Abstract Withdrawn

SA-PO1122

Eculizumab in Prevention of Acute Antibody-Mediated Rejection in Sensitized Deceased-Donor Kidney Transplant Recipients: Updated 12-Month Outcomes D. Glotz,¹ G. Russ,³ Lionel Rostaing,³ Christophe M. Legendre,³ Steven J. Chadban,³ J. Grinyo,³ Nizam Mamode,³ Gunnar Tufveson,³ Lionel Couzi,³ P. Riggoti,³ Y. Lebranchu,³ S. Sandrini,³ W. Marks,² ¹Hôpital Saint-Louis, Paris, France, Metropolitan; ²Alexion Pharmaceuticals, Inc., Cheshire, CT; ³The International Eculizumab Transplant Study Group.

Background: Complement activation by preformed DSA is the major mechanism of acute antibody-mediated rejection (aAMR) in sensitized, kidney transplant recipients (SKTR). In a previous interim study report, the C5 inhibitor eculizumab (Ec) appeared effective in preventing aAMR in deceased donor (DD) SKTR compared to historical controls. We now report 12-mo efficacy and safety data from a Sept 2015 update of this ongoing, open-label, single-arm trial.

Methods: SKTR defined as current DSA > 3000 MFI detected by SAB; or B- or T-cell flow cytometric crossmatch ≥ 300 and ≤ 500 mean channel shift; or historical positive complement-dependent cytotoxicity crossmatch to donor HLA. All recipients received Ec 1200mg postoperative day (POD) 0 prior to reperfusion, 900mg on POD 1, 7, 14, and 28, and 1200mg at wks 5, 7, and 9. Recipients received Rabbit ATG for induction and corticosteroids, tacrolimus, and mycophenolate for maintenance immunosuppression. Plasmapheresis was not allowed through Post-transplant week 9. The primary composite endpoint was clinically significant, biopsy (bx)-proven aAMR grade II/III (Banff 2007, based on centrally read bx), graft loss, death, or loss to follow-up at 9wks. Graft and patient (pt) survival were estimated by K-M.

Results: 80 pts were transplanted (48 F, 32 M); median age 52y (range, 24–70). 7 of 80 SKTR had aAMR (8.8%) compared to 30% expected for historical controls. 11/80 SKTR met the 9wk composite primary endpoint based on local bx (13.8% [95% CI 7.1–23.3]). Graft survival at 6 and 12mo was 93.7% and 88.7%, respectively; pt survival at 6 and 12mo was 97.4%. SCr levels (mg/dL) at baseline, 1 and 12mo were 7.43 (± 2.51), $n = 79$; 1.86 (± 1.07), $n = 74$; and 1.63 (± 0.76), $n = 69$. No new safety concerns were identified.

Conclusions: Ec appeared to be effective in reducing aAMR in SKTR. Pt and graft survival and kidney function at 12mo were similar to those expected for non-sensitized KTR. Ec was well tolerated.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

SA-PO1123

Impact of De Novo Donor Specific Antibodies on Graft Outcomes in Kidney Transplant Recipients following Early Switch from Calcineurin Inhibitor to Everolimus: Analysis of the ELEVATE Trial Johan W. De Fijter, Hallvard Holdaas, Patricia M. Lopez, Peter Bernhardt, Zailong Wang, Frans Claas, Wolfgang Arns, Josep M. Cruzado, Markus van der Giet. *For the ELEVATE Study Group.*

Background: Development of *de novo* donor specific HLA-antibodies (dnDSA) after kidney transplantation (KTx) is associated with an increased risk of antibody-mediated rejection (AMR) and graft failure. The ELEVATE study evaluated the impact of early conversion from CNIs to everolimus (EVR) after KTx and prospectively explored the status and development of DSAs.

Methods: In this 24 month (M), multicentre study KTx recipients were randomized at 10–14 weeks post-Tx to convert from CNI to EVR ($n = 360$: C0 6–10 ng/mL) or continue CNI ($n = 357$: C0, tacrolimus 5–10 ng/mL, cyclosporine 100–250 ng/mL); all received enteric-coated mycophenolate sodium (MPS) + corticosteroids. Blood samples were collected at

baseline, randomization (RND), M12 and M24 or at time of rejection episodes and analysed by Lumindex/SAB assay in one central lab. dnDSA was defined by a MFI value ≥ 500 any time post-RND in patients with MFI < 500 at RND.

Results: Baseline characteristics were comparable between groups. Incidence of preformed DSA (MFI ≥ 500 at baseline) against HLA class-I or -II was low (table A). Overall, incidence of dnDSA HLA class-I was higher with EVR/MPS treatment vs CN1/MPS at M12 and M24. The incidence of dnHLA Class-II antibodies was dominated by anti-DQ in the CsA/MPS [Irm]group (table B). No association between *de novo* (either HLA class-I or -II) antibodies and a diagnosis of AMR or tBPAR was evident in this population up to M24 (table C, D).

Conclusions: Early conversion to EVR at 3M post-Tx did not increase the risk of dnDSA formation vs CN1 continuation. Moreover, no association was observed between development of dnDSA and AMR or tBPAR, even with the lowest detection thresholds.

TABLE 3: DSA outcomes

A) Incidence of pre-formed DSA

HLA Class I	EVR	Baseline			HLA Class II	EVR	Baseline			
		Total	TRC	CIA			Total	TRC	CIA	
MFI ≥ 500	HLA A	3.4	3.9	4.4	2.8	HLA DR	0.8	4.1	4.5	3.3
	HLA B	4.5	4.9	5.7	3.5	HLA DQ	0.7	7.1	8.3	3.4
MFI < 500	HLA A	2.5	1.7	2.0	3.3	HLA DR	2.5	1.0	1.5	0.0
	HLA B	2.2	2.5	2.4	2.4	HLA DQ	4.2	1.2	0.0	0.7

B) Incidence of de novo DSA (%)

HLA Class I	EVR	M12			M24			HLA Class II	EVR	M12			M24					
		Total	TRC	CIA	Total	TRC	CIA			Total	TRC	CIA	Total	TRC	CIA			
MFI ≥ 500	HLA A	6.3	2.8	4.1	0.0	0.4	2.3	3.1	0.0	HLA DR	3.4	0.0	0.0	0.0	3.4	1.7	2.3	0.0
	HLA B	4.5	2.7	3.9	0.0	2.7	0.7	1.0	0.0	HLA DQ	10.7	6.0	0.0	0.0	14.3	0.4	23.5	0.0
MFI < 500	HLA A	3.2	0.7	1.0	0.0	0.3	0.7	0.0	0.0	HLA DR	1.1	0.0	0.0	0.0	1.1	0.0	0.0	0.0
	HLA B	0.9	0.7	1.0	0.0	0.0	0.0	0.0	0.0	HLA DQ	5.6	0.0	0.0	0.0	23.5	2.8	10.7	0.1

C) AMR in patients with de novo DSA (%)

HLA Class I	EVR	M12			M24			HLA Class II	EVR	M12			M24						
		Total	TRC	CIA	Total	TRC	CIA			Total	TRC	CIA	Total	TRC	CIA				
MFI ≥ 500 at time of onset and < 500 at RND	HLA A	6/0	4/0	4/0	0/0	0/0	3/1	3/1	0/0	MFI ≥ 500 at time of onset and < 500 at RND	HLA DR	3/1	0/0	0/0	0/0	3/0	3/1	3/1	0/0
	HLA B	5/1	4/0	4/0	0/0	3/0	1/0	1/0	0/0	HLA DQ	4/0	3/0	2/0	5/0	3/0	3/0	3/0	4/0	4/0

D) tBPAR in patients with de novo DSA (%)

HLA Class I	EVR	M12			M24			HLA Class II	EVR	M12			M24						
		Total	TRC	CIA	Total	TRC	CIA			Total	TRC	CIA	Total	TRC	CIA				
MFI ≥ 500 at time of onset and < 500 at RND	HLA A	6/0	4/1	4/1	0/0	0/0	3/2	3/2	0/0	MFI ≥ 500 at time of onset and < 500 at RND	HLA DR	3/0	0/0	0/0	0/0	3/0	3/1	3/1	0/0
	HLA B	5/0	4/0	4/0	0/0	3/0	1/0	1/0	0/0	HLA DQ	4/0	3/1	2/0	5/1	3/0	3/1	3/0	4/1	

*% number of patients with corresponding DSA category, n=number of patients that developed AMR

Funding: Pharmaceutical Company Support - Novartis

SA-PO1124

Donor-Derived Cell-Free DNA in Plasma Increases with Rejection and Decreases after Treatment in Kidney Transplant Recipients
 Marica Grskovic,¹ Brian Christie,¹ David Hiller,¹ Robert Woodward,¹ Jim Yee,¹ Flavio Vincenti.² ¹CareDx, Inc., Brisbane, CA; ²UCSF, San Francisco, CA.

Background: Donor-derived cell-free DNA (dd-cfDNA) is an emerging biomarker of acute cellular rejection in organ transplant recipients. The utility of determining plasma levels of dd-cfDNA aimed at diagnosing rejection and evaluating treatment response was assessed in kidney transplant recipients in a longitudinal observational trial.

Methods: Clinical status, biopsy grade (performed in response to elevated serum creatinine) and plasma were collected at 326 routine surveillance visits from 101 patients. Samples from nine patients assigned a biopsy grade I, II or III (NIH criteria) were classified as rejection (R). Samples from seventeen patients assigned a biopsy grade 0 were classified as quiescent (Q). cfDNA extracted from plasma was amplified at targeted SNPs and analyzed using a sensitive and accurate Next Generation Sequencing assay to quantify dd-cfDNA levels without the need to separately genotype the donor. Standard statistical measures of significance were used.

Results: dd-cfDNA levels were significantly higher (p=0.029) in patients with biopsy-confirmed rejection (R, mean 4.23%) compared to quiescent patients (Q, mean 0.96%). Creatinine levels were not significantly different between R and Q patients (p=0.69; mean 4 and 3.1 mg/dL, respectively). Longitudinal sample analysis from 15 patients showed increased dd-cfDNA levels following transplant (mean 2.8%) with reduction to levels below 1% by two weeks post transplantation. In 3 cases with clinically treated biopsy-confirmed rejection and 2 serial samples following the rejection, levels of dd-cfDNA decreased following rejection treatment.

Conclusions: dd-cfDNA shows promise as a biomarker of rejection that may be used for non-invasive surveillance of kidney allograft status and treatment response. The ongoing measurement of cfDNA may allow clinicians to better personalize care and improve patient outcomes.

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